PRECISION OF MINIMALLY INVASIVE SURGERY FOR INTRACEREBRAL HEMORRHAGE TREATMENT

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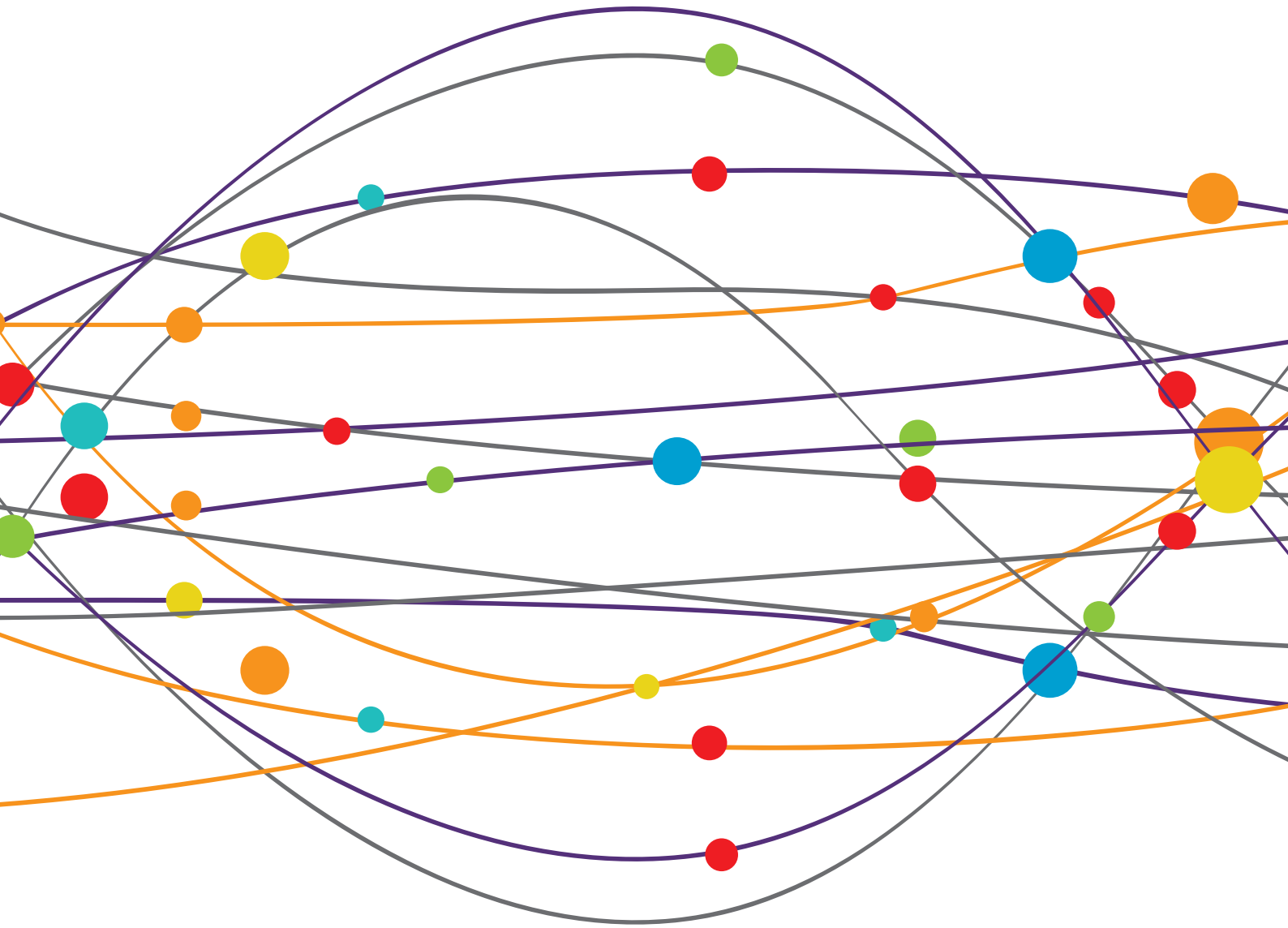

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PRECISION OF MINIMALLY INVASIVE SURGERY FOR INTRACEREBRAL HEMORRHAGE TREATMENT

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Editorial: Precision of minimally invasive surgery for intracerebral hemorrhage treatment

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intracerebral hemorrhage, minimally invasive treatment, hematoma removal, treatment, precision

Editorial on the Research Topic
Precision of minimally invasive surgery for intracerebral hemorrhage treatment

Intracerebral hemorrhage (ICH) is a life-threatening disease and has the clinical characteristics of high incidence, long treatment cycle, and bleak prognosis, which cause a global health burden. Following the initial irreversible tissue injury, a secondary brain injury induced by hematoma is closely associated with severe neurological deficit. Therefore, early evacuation of the hematoma plays a critical role in alleviating the severity of neurological impairment following ICH. Craniotomy, the traditional surgical option, is traumatic and tends to result in inevitable damage to normal brain tissue. Furthermore, it has neither improved functional prognosis nor lowered the mortality rate when compared with conservative treatment (1, 2). Meanwhile, minimally invasive surgery (MIS), a new operative procedure for ICH, has developed rapidly. MIS is expected to reduce mortality and improve the prognosis of patients with ICH. As professional scholars in the field of ICH research, Prof. Zhouping Tang, John Zhang, Qiang Dong, Guofeng Wu, Yu Hasegawa, and Christopher Paul Kellner were invited to curate the Research Topic "*Precision of Minimally Invasive Surgery for Intracerebral Hemorrhage Treatment*" for *Frontiers in Neurology*.

This Research Topic focuses on recent advances in the precision of MIS for ICH treatment. Twenty-seven manuscripts were submitted and twelve were accepted. A brief description of these research findings follows.

Jiang et al. established an *in vitro* blood clot model to examine the dissolution effect, focusing on the optimal concentration and action time of alteplase (rt-PA) in arterial blood clots derived from patients with ICH. They suggest that a low concentration of rt-PA produces a better dissolution effect and that it

functions in a time-dependent manner, reaching a peak at 90 min. This provides new insights into the therapeutic optimization of patients with ICH undergoing MIS.

Hou et al. through meta-analysis, show that the MIS technique could independently reduce the death rate in both a short- and long-term follow-up. In addition, further analysis found that the MIS technique appears to be beneficial when compared to conservative medication. However, the authors did not conduct any subgroup analyses based on different hemorrhage locations. Two in three spontaneous ICH are deep ICH and the remaining third are lobar ICH. Evidence-based medical studies by Akram et al. reveal that no statistical difference was observed between surgery and medical treatment for lobar ICH. Therefore, future studies with larger sample sizes are needed to determine the actual effect of MIS in lobar ICH.

There are two main approaches to MIS: stereotactic hematoma puncture and drainage, and endoscopic hematoma removal. No widely accepted standard is currently available, although various methods of stereotactic aspirations have been established. Wang H. et al. present their single-center experience in the application of an easy, fast, and effective procedure for hematoma evacuation in a total of 45 patients with spontaneous ICH. With the assistance of a location sticker and a brain surgery head frame, the operator could design personalized puncture routes based on the different hematoma locations and volumes. However, because of the limited number of enrolled patients and the lack of a control group, a prospective randomized controlled study was needed to further validate the safety and effectiveness of this approach. Regarding endoscopic evacuation, Hsu et al. share over a decade of experience and outline the progress of MIS for ICH treatment. This is expected to promote the specialization of ICH surgery in the field of MIS. They suggest that MIS, under the guidance of an endoscope for ICH evacuation, is safe and effective. The rehemorrhage ratio and mortality rates are shown to be lower than those of craniotomy. Furthermore, through a retrospective review of 53 patients with ICH undergoing neuroendoscopic surgery, Wu et al. suggest that robot-assisted neuroendoscopic hematoma evacuation, when combined with intracranial pressure monitoring, could improve the curative effect of patients with ICH. This is superior to single neuroendoscopic hematoma evacuation in terms of safety and effectiveness. MIS, when combined with the use of medications, might lessen secondary brain injury following ICH. Ren et al. find that a combination treatment of MIS and deferoxamine could increase perihematomal Claudin-5 and ZO-1 expression levels, reduce blood-brain barrier permeability in the ICH rat model, and improve neurological function. These outcomes may thus prevent secondary brain damage after ICH.

Intraventricular hemorrhage (IVH) adds to the morbidity and mortality of ICH and is an independent predictor of worse outcomes. Zheng et al. in their extensive review, introduce pharmacological catheter- and mechanical-based minimally invasive approaches for ICH and IVH. They firmly believe more clear evidence is expected in the near future to support the use of MIS for ICH treatment. Primary brainstem hemorrhage (PBSH) is the most fatal form of ICH and has a consistently worse prognosis. The management of PBSH is mainly subjected to conservative treatment and surgical procedures are generally not recommended based on current clinical evidence. Chen D. et al. summarize the common prognostic factors and four main surgical options of PBSH. Inconsistent with existing viewpoints, the authors argue that PBSH patients with a score of 2–3 points by a novel grading scale, entitled "the new primary pontine hemorrhage (PPH) score," seemed to benefit from surgery, although this claim has yet to be demonstrated.

Shen et al. in their original paper, discover that higher levels of fasting blood glucose, neutrophil to lymphocyte ratio, thrombin time at admission, and NIHSS score after surgery were related to symptomatic ICH after endovascular treatment of large vessel occlusion stroke. Moreover, hematoma expansion (HE) indicates a poor prognosis after spontaneous ICH. Hematoma shape-related signs, including the blend sign, spot sign, and island sign, are identified as imaging markers for determining potential individuals who have a high risk of HE among ICH patients (3). In the original paper contributed by Chen Y. et al., the authors assert that the attenuation value of the non-hypodense region of hematoma could also predict HE and the attenuation value of <64 HU was proved to be an appropriate cut-off value of early HE. Post-operative rehemorrhage is one of the most serious complications in patients with ICH undergoing MIS and predicts a more pessimistic prognosis. Postoperative rehemorrhage is therefore seen as an obvious target for medical intervention. Irregular-shaped hematoma (ISH) is a dependable predictor of HE (4). However, few studies have assessed the correlation of ISH with postoperative rehemorrhage in patients with ICH following MIS. To demonstrate the relationship between them, Wang L. et al. carry out a binary logistic regression analysis, which indicates that ISH served as an independent prognostic factor of rehemorrhage after MIS.

Collectively, the current Research Topic provides valuable information on, and insights into, the precision of MIS for ICH treatment. More work is needed to deepen our understanding and grasp of this technology. The use of MIS for ICH treatment should be guided by "stratified decrease of intracranial pressure, liquefaction and drainage of hematoma, and transformation of large hematoma into small one" (5), and eventually lead to the precise treatment of patients with ICH. It is critical to continue to focus on the next steps in promoting the standardization, quantification, precision, and personalization of MIS to facilitate the application of this technology in clinical practice.

Author contributions

All authors equally contributed to the drafting and writing of the editorial. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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REVIEW
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Primary Brainstem Hemorrhage: A Review of Prognostic Factors and Surgical Management

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Primary brainstem hemorrhage (PBSH) is the most fatal subtype of intracerebral hemorrhage and is invariably associated with poor prognosis. Several prognostic factors are involved, of which the two most predominant and consistent are the initial level of consciousness and hemorrhage size. Other predictors, such as age, hyperthermia, and hydrocephalus, are generally not dependable indicators for making prognoses. Scoring systems have now been developed that can predict mortality and functional outcomes in patients suffering from PBSH, which can thus guide treatment decision-making. A novel grading scale, entitled "the new primary pontine hemorrhage (PPH) score," represents the latest approach in scoring systems. In this system, patients with a score of 2–3 points appear to benefit from surgical management, although this claim requires further verification. The four main surgical options for the treatment of PBSH are craniotomy, stereotactic hematoma puncture and drainage, endoscopic hematoma removal, and external ventricular drainage. Nevertheless, the management of PBSH still primarily involves conservative treatment methods and surgery is generally not recommended, according to current practice. However, the ongoing clinical trial, entitled Safety and Efficacy of Surgical Treatment in Severe Primary Pontine Hemorrhage Evacuation (STIPE), should provide additional evidence to support the surgical treatment of PBSH. Therefore, we advocate the update of epidemiological data and re-evaluation of PBSH treatment in a contemporary context.

Keywords: primary brainstem hemorrhage, prognostic factors, scoring system, surgical management, surgical options

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INTRODUCTION

Primary brainstem hemorrhage (PBSH) is a type of spontaneous brainstem hemorrhage that is particularly relevant to chronic hypertension but is not associated with definite or objective lesions such as cavernomas and arteriovenous malformations. PBSH is the most fatal subtype of intracerebral hemorrhage (ICH) and invariably has a bleak prognosis (1–3). It has the clinical

characteristics of sudden onset, rapid evolution, and high morbidity and mortality (4, 5). Multiple studies have investigated the correlation between the prognosis of PBSH and its clinical features, neuroradiological presentation and neurophysiological properties (6–8). The identification of prognostic factors contributes to the development of a specific scoring system for PBSH, and a fast and accurate prognostic assessment in the emergency room plays a key role in the selection of reasonable therapeutic strategies (9). The new primary pontine hemorrhage (PPH) score represents the very latest approach in scoring systems, which will be explained below (3). It is suggested to spare medical resources for patients with a maximum score (3). However, the availability of the new PPH score for determining the surgical indications needs to be further investigated.

Actually, PBSH is currently mainly subjected to conservative treatment, and the efficacy of surgical procedures such as hematoma clearance remains questionable (4, 10–13). However, surgical interventions promise to become attractive options to manage PBSH with growing knowledge of safe entry zones into the brainstem and advances in new technologies as well as equipment in the fields of neuroimaging, microsurgery, neuronavigation, neuroendoscopy, intraoperative monitoring, and neurological rehabilitation. In this review, we aimed to analyze the identification of prognostic factors and scoring systems in PBSH and to discuss the current status and future prospects of controversial surgical management. Specifically, because PPH accounts for the vast majority (60–80%) of PBSH (5), both of these terms are used in our review, depending on the actual situation.

EPIDEMIOLOGY

According to different localization of bleeding, ICH falls into two types-supratentorial and infratentorial ICH. Supratentorial ICH mainly involves basal ganglion and spontaneous infratentorial hemorrhage consists primarily of spontaneous cerebellar ICH and PBSH. PBSH occurs most frequently in the region of pontine, constituting 6 to 10% of ICH with an incidence of about 2 to 4 in 100,000 people per year and a mortality rate varying between 30 and 90% in different reports (4, 6, 14–16). PBSH occurs most often in patients aged 40 to 60, showing trends toward younger age compared with supratentorial and cerebellar ICH (17, 18). The incidence is higher in men than in women, probably because of personal living habits and health conditions prior to their illness. Hypertension is the most important risk factor of PBSH and other relative factors include anticoagulation therapy, amyloid angiopathy, etc. (16).

PROGNOSTIC FACTORS

Researches, that carried out multivariate logistic regression analysis to identify independent predictors for PBSH, were shown in **Table 1**.

Demographic Factors

The incidence of ICH continues to increase as people age (4, 23). Age plays a vital prognostic role in ICH and is an important part of the ICH score (23, 24). Furthermore, previous studies showed that ICH appears to be more common in men, while women show better survival (23, 25). However, whether age or sex affects patients with PBSH remains an unresolved problem. Patient age was found to independently affect 30-day mortality or functional outcomes by Morotti et al. and Ding et al. by multivariate logistic regression analysis (1, 22). Intriguingly, no study has demonstrated that sex is a predictor of the outcomes of PBSH.

Clinical Presentations

Coma is one of the typical symptoms of PBSH. In previous studies, depressed and poor initial levels of consciousness were usually described as "coma on admission" or measured by different GCS score critical thresholds in the range of <4 to ≤ 9 (3, 9, 16, 20, 21). In agreement, both of these descriptions could independently and reliably predict death and an unfavorable functional outcome of PBSH (6). According to **Table 1**, the initial level of consciousness has been identified as an independent predictor in 9 different studies, which presents the most consistent and influential predictor for PBSH. The initial level of consciousness is also simple to judge and has the potential to be part of a future PBSH-related scoring system.

Central hyperthermia is a complication after PBSH that is characterized by a core temperature of $\geq 39°C$ and is unresponsive to conventional antipyretic treatments due to an unchanged thermoregulatory setpoint (26–28). Central hyperthermia was proven to be independently related to death in PPH by Matsukawa et al., but was not identified as an independent predictive factor of 30-day outcomes after PBSH in another study (20, 22). Although central hyperthermia associated with PBSH is supposed to be injurious to patients, it remains unknown whether a positive pursuit of a normal body temperature contributes to a more favorable clinical prognosis in the absence of evidence. Therefore, future studies of patients suffering from PBSH-related central hyperthermia are absolutely essential to reveal its mechanism and preventive and treatment measures.

Additionally, patients with severe PBSH present with a high risk of neurological complications and in desperate need of measures to protect the airway, especially within the acute phase. A study revealed that early tracheostomy (≤ 7 days after admission) was significantly associated with a favorable 30-day functional outcome (prognostic benefits) and was also able to reduce the length of hospitalization and intensive care unit stay (financial benefits) (22). However, there are potential risks that should not be neglected when performing a tracheostomy, such as skin breakdown, tracheomalacia and so on (29).

In addition, other factors, such as tachycardia (>110 beat/min), absence of a pupillary light reflex, the necessity for mechanical ventilation, and pupillary abnormalities, systolic blood pressure <100 mmHg, intact motor function, and a history of diabetes mellitus, have also been identified to significantly affect death or functional outcomes after PBSH (9, 16, 28, 30).

Laboratory Evaluation

In a retrospective study enrolling 225 patients with PBSH, Fan et al. found that elevated platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and admission blood glucose level were

TABLE 1 | Researches that used multivariate logistic regression analysis to identify independent predictors for PBSH.

				Functional outcome				
Author	**Year**	**Design**	**Sample size**	**N death (duration to death)**	**N good functional outcomes**	**Follow-up**	**Independent predictors for mortality**	**Independent predictors for functional outcomes**
Dziewas et al. (14)	2003	R	39	27 (mean 16 days)	6 (mRS, 0–2)	2–8 years	Coma on admission; Hemorrhage localization; Hemorrhage size	NA
Jung et al. (19)	2007	R	35	13 (in-hospital)	12 (subjective)	Mean 13.9 months	GCS score	NA
Jang et al. (10)	2011	R	281	110 (30 days)	27 (mRS, 0–3)	90 days	Coma on admission; Dilated pupils; Respiration; Blood pressure; Hydrocephalus; Treatment modality	Coma on admission; Motor function; History of hypertension or diabetes mellitus; Eye movement; Hemorrhage size; Ventricular hemorrhage; Ventricle size
Matsukawa et al. (20)	2015	R	118	66 (follow-up period)	NA	Median 51 days	GCS score; Hyperthermia; Hemorrhage size; Hematoma extension	NA
Ye et al. (21)	2015	P	76	3 (30 days)	NA	NA	Coma on admission; Hemorrhage size; Hemorrhage localization Hemorrhage localization	NA
				56 (3 years)	NA	NA	Coma on admission; Hemorrhage size	NA
Meguro et al. (9)	2015	R	101	59 (30 days)	NA	NA	GCS score; Pupillary light reflex; Blood glucose	NA
Morotti et al. (1)	2016	R	49	30 (30 days)	NA	NA	Age; GCS score; Hemorrhage size	NA
				28 (in-hospital)	NA	NA	GCS score	NA
Huang et al. (3)	2017	R	171	68 (30 days)	74 (mRS, 0–3)	90 days	GCS score; Hemorrhage size	NA
		P	98	33 (30 days)	50 (mRS, 0–3)	90 days	NA	NA
Fan et al. (8)	2018	R	225	7 (90 days)	113 (GOS≥4)	90 days	NA	NLR; PLR; ABG; NLR-PLR-ABG
Ding et al. (22)	2020	R	136	7 (in-hospital)	30 (mRS, 0–3)	30 days	NA	Hemorrhage size; GCS score; Age; Tracheostomy
Chen et al. (7)	2021	P	31	19 (30 days)	NA	90 days	(delta + theta)/(alpha + beta) ratio (DTABR)	NA

N, number; R, retrospective; P, prospective; NA, not available; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ABG, admission blood glucose level; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; mRS, modified Rankin Scale.

independently correlated with unfavorable 90-day functional outcomes of PBSH, with critical thresholds defined as 59.3, 6.65, and 7.81 mmol/L, respectively (8). Moreover, a combination of the aforementioned three factors showed a better predictive value than a single factor (8). In another study, plasma glucose with a threshold value ≥180 mmol/L (10 mmol/L) was identified to independently predict 30-day mortality in patients with PPH (9). Hyperglycemia reflects a stress-response level in the setting of the acute phase of PBSH, which could result in heightened susceptibility to complications connected with hospitalization and ultimately lead to unfavorable outcomes (31, 32).

Radiological Evaluation

MRI findings are less relevant to prognosis after PBSH and only certain case report-level evidences have examined the potential relationship between functional prognosis after PBSH and findings derived from diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) (33–35). Instead, CT scanning is routinely deemed the method of preference for assessing PBSH owing to its general accessibility and rapid availability. Moreover, some CT findings closely correlate with prognosis in PBSH.

1) Hemorrhage size. In view of the small size of the brainstem, the average hemorrhage size of PBSH is less than that of supratentorial hemorrhage but might be more fatal (36). Hemorrhage size is a reliable and significant independent prognostic factor for PBSH, of which the threshold values are found to fluctuate between 4–5 ml and 20–31.5 mm for hemorrhage volume and transverse diameter, respectively (6, 37). Hemorrhage size is another most important predictor besides the initial level of consciousness, which has been demonstrated as an independent predictor in 7 different studies in **Table 1**. Given the importance of hemorrhage size, inaccurate data might exert a certain adverse influence on the judgment of the prognosis. Therefore, it is probably pertinent to discuss studies on the measurement of hemorrhage volume. Computer-assisted volumetric analysis and 3D slices are typically viewed as the "gold standard" to measure hemorrhage volume (38, 39). However, the calculation process is time-consuming and tedious, hindering their clinical application. Among the formula methods, 1/2ABC is the most common and convenient way to calculate hemorrhage volume of ICH in clinical work. Nevertheless, as it may underestimate or overestimate the volume of irregularly shaped hemorrhage and small hemorrhage in the brainstem, some researchers began to question its accuracy (38, 40, 41). Through a review of 147 CT results of patients with infratentorial hemorrhage, Yang et al. found that 2/3SH was more accurate than 1/2ABC for the volume calculation of brainstem hemorrhage and irregular hemorrhage (42). As for formula 2/3SH, S represents the area of largest axial hemorrhagic slice and H represents the height of hematoma which is derived from the number of slices times the slice thickness. Overall, a more precise and simple method to measure brainstem hemorrhage size remains to be developed.

2) Hemorrhage classification, localization, extension and hydrocephalus. There is currently no unified classification for PBSH (5). PBSH can be divided into three subtypes of medullary hemorrhage, pontine hemorrhage, and midbrain hemorrhage in clinical practice (43). Among them, pontine hemorrhage is the most frequent type, and isolated medullary and midbrain hemorrhages have a lower incidence (44). The medullary type may lead to ataxic respiration and cause rapid death (45). In addition, based on the axial CT findings of the exact anatomical location and spread direction, various sorts of classifications have been established (4). All of the studies are consistent with the view that unilateral tegmental hemorrhage is related to a good outcome, while massive hemorrhage (located in bilateral basal and anterior segments) is closely associated with the most unfavorable outcomes (6, 10, 14, 16, 20, 21, 26–46). For patients with neuroradiological results that fall between the two, it is difficult to predict the survival outcome according to CT findings alone (4). Intraventricular extension is an important predictive factor in ICH but is not an independent determinant of early death for PBSH patients (6, 24, 47). Jang et al. ascribed this phenomenon to the active use of external ventricular drainage (EVD), which could be conducive to the reduction of mortality and short-term prognosis in ICH (10, 48). Moreover, hemorrhage vertically extending from the pontine to the midbrain and/or thalamus could predict adverse outcomes (20). According to a systematic review, 30.3% of patients developed hydrocephalus after PPH (6). However, only one study has identified it as an independent prognostic factor of mortality for PBSH (6, 10).

3) Hemorrhage expansion. In recent years, hematoma expansion has attracted wide attention in clinical practice and has been identified to independently predict mortality and functional prognosis in patients with ICH (49, 50). Hematoma shape-related signs, such as the CTA spot sign and some non-contrast computed tomography markers, have been demonstrated to be potential markers for screening out patients at high risk of hematoma expansion among ICH patients (51–53). Nevertheless, few studies have focused on hematoma expansion and relevant signs in PBSH. Even so, due to the small size but vital role of the brainstem, hematoma expansion at this site was presumed to wreak havoc on survival and prognosis. Therefore, it is an indicator to which we should attach importance in patients with PBSH. Hematoma expansion and CTA spot signs also exist in patients with PPH. In this retrospective analysis of forty-nine PPH cases, Andrea et al. found that the spot sign showed good accuracy for the prediction of in-hospital mortality (61%) and 30-day mortality (57%) but was not an independent predictor (1). In addition, the presence of spot signs was not significantly associated with hematoma expansion rates (1). However, the lack of statistical significance is ascribed to a deficient number of cases, and a clear association between spot signs and hematoma expansion rates remains uncertain.

Different from the hemorrhage size and localization, hematoma expansion has a characteristic of preventability to a certain extent. Virtual measures to restrict hematoma expansion seem beneficial to PBSH patients due to their function in reducing the ultimate hemorrhage size. Patients with PBSH are often in an urgent and high-risk state, and only a routine CT scan could be acquired. Moreover, because CTA is not available routinely in many emergency departments, the application of spot signs to predict early hematoma expansion is subject to certain restrictions (54). Under such circumstances, NCCT

markers, such as the island sign (55), satellite sign (56), black hole sign (57), and blend sign (58), seem to have a clear advantage. However, as patients with PBSH are excluded from almost all relevant studies, the application value of these markers in PBSH remains unclear and needs further verification. Furthermore, the definite correlation on between hematoma expansion and PBSH and the exact mechanisms of hematoma expansion remain to be clarified. Future studies with large sample sizes are also needed to determine whether there are differences in the incidence of hematoma expansion between supratentorial hemorrhage and PBSH.

Electrophysiological Evaluation

Although neuromonitoring is generally deemed a predictive tool for functional recovery in stroke patients, few articles have focused on the same topic in patients with PBSH (59, 60). In an analysis of 31 consecutive comatose patients with acute severe brainstem hemorrhage, Chen et al. found that a quantitative electroencephalography parameter [i.e., (delta + theta)/(alpha + beta) ratio, DTABR] could independently predict 90-day mortality, whereas no transcranial Doppler (TCD) variables showed prognostic value (7). However, that study only focused on mortality and did not attach importance to the correlation between neurophysiological parameters and functional recovery. An abnormal brainstem auditory evoked potentials (BAEPs) may predict hearing loss in PBSH as well as a poor prognosis (61). Furthermore, Seong et al. confirmed that using somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) in combination was a reliable predictor for functional recovery in PBSH patients (62). In summary, the potential of neurophysiological parameters for predicting functional recovery still needs to be fully tapped in patients with PBSH, who often have a tendency toward severe disability.

Scoring System

A scoring system plays an important role in the risk stratification of patients with brainstem hemorrhage, which also contributes to a consensus on their management (3, 9, 36, 63). Therefore, we discuss the development and present status of scoring systems for brainstem hemorrhage in detail.

The ICH score and its modified version are reliable and convenient and have been extensively used to predict mortality and functional recovery in ICH (24, 64). Subsequently, Del Brutto et al. revealed that both the original and modified ICH scores proved accurate for predicting the risk of 30-day mortality in PPH (63). Nevertheless, there are still some concerns. First, in the cohort used for the development of the original ICH, less than one-tenth (15 of 152, 9.87%) of all subjects were diagnosed with brainstem hemorrhage (24). Second, in light of its content, the original and modified ICH scores lead to infratentorial hemorrhage being regarded as an independent predictor of a poor outcome. Third, the cut-off value of hemorrhage size and GCS score should be different in the scoring systems for ICH and PPH. Last, a comparative study conducted by Huang et al. revealed that the original ICH score lacked discrimination and ought to be revised specifically for PPH (36). Taken together, the original and modified ICH scores may not apply well to PPH.

To solve this problem, Meguro et al. proposed the first specific grading scale (entitled the PPH score) for predicting 30-day mortality of PPH and validated it in a retrospective review of a cohort of 101 consecutive patients with PPH (9). However, the study had several flaws. The researchers did not carry out external validation and did not take into account early do not resuscitate orders (DNRs). As demonstrated by Zahuranec et al., an illusion of model accuracy may be generated when DNRs are ignored (65). Consequently, Huang et al. established and validated a new PPH score for predicting short-term outcome (30-day mortality) and long-term outcome (90-day functional prognosis) in PPH patients and demonstrated that it had a higher discrimination (area under the curve for 30-day mortality was 0.902 and that for 90-day good outcome was 0.927) and calibration than the original ICH score and the PPH score in their study cohort (3). This is the largest study with the best evidence for scoring systems to date, including a total of 269 cases (171 cases as the training set for scale development and the other 98 cases as the prediction set for external validation) (3). The detailed grading standards of these two scoring systems are shown in **Table 2**. Significantly, variables in the new PPH score are precisely the two most influential predictors we proposed above.

In terms of registered clinical studies, an ongoing trial based on the application of radiomics methods, entitled "a new prognostic scoring system for patients with primary pontine hemorrhage: medical records-based study" (URL: http://www.chictr.org.cn. Unique identifier: ChiCTR2100042705) aims to construct a new grading scale for PPH to determine the prognosis and guide therapeutic decisions.

The next step for research in scoring systems will focus on the question whether the existing system is applicable to determine the surgical indications, thereby stratifying patients and guiding treatment decision-making.

SURGICAL MANAGEMENT

Guidelines

Chinese researchers developed and issued the first guideline for brainstem hemorrhage in 2020 (5). However, there are no definite specifications focusing exclusively on the diagnosis and treatment of PBSH in widely recognized guidelines issued by the American Heart Association/American Stroke Association (AHA/ASA) and European Stroke Organization (66, 67). The AHA/ASA guidelines are explicitly against surgical interventions for brainstem hematomas (66). Moreover, conservative treatment of PBSH is widely accepted, whereas surgical management remains questionable because the complex anatomical structures and critical functions of the brainstem have potential risks during surgery (4, 10–13). However, conservative treatment may do little to prevent fatal outcomes in many cases and with new surgical and neuroimaging technological advances, surgical procedures are expected to be more optimistic options for the treatment of PBSH. Therefore, it is meaningful to discuss the controversial but promising surgical management of PBSH in further detail below based on the available evidence.

TABLE 2 | Grading standards of the PPH score and the new PPH score.

The PPH score (9)			The new PPH score (3)		
Variables	**Range**	**Points**	**Variables**	**Range**	**Points**
GCS score	≤6	1	GCS score	3–4	2
	>6	0		5–7	1
Pupillary light reflex	Absence	1		8–15	0
	Presence	0	Hemorrhage volume	>10 ml	2
Blood glucose	≥180 mg/dL	1		5–10 mL	1
	<180 mg/dL	0		<5 ml	0
Reference values			**Reference values**		
Scores	30-day mortality rates (%)		Scores	30-day mortality rates (%)	
0	7.7		0	2.7	
1	33.3		1	31.6	
2	78.9		2	42.7	
3	100		3	81.8	
			4	100	

Potential Indication of Surgical Interventions

Identifying optimal candidates for surgery is an essential question. Surgical prognostic factors after PBSH conduce to the identification of ideal candidates for PBSH. Through analyses of prognostic factors, Tao et al. concluded that patients with a smaller hematoma (>5 ml and <10 ml), a greater GCS score (>6 and <8), age <65 years, unilateral tegmental hemorrhage, and without extrapontine extension might benefit from surgical treatment (2). Furthermore, based on their experience with five severe cases of surgical treatment, Shrestha et al. proposed their indication for surgery: (1) hemorrhage volume >5 ml (concentrated relatively), (2) GCS score <8 with progressive neural dysfunction, (3) unstable basic vital signs, especially for patients who require mechanical ventilation, (4) location of the hematoma <1 cm from the brainstem surface, and (5) time of hemorrhage <24 h (68).

The indicator by Tao et al. is the equivalent of 2 points in the new PPH score. Four cases in the study by Shrestha et al. scored 2 or 3 points. All the 4 cases survived during their hospital stay and one of them even could go about all daily tasks and walk with minimal help after surgery. According to the findings of Huang et al., a score of 4 points in the new PPH score is the contraindication for both surgery and medical treatments (3). Also, Huang et al. suggested sparing medical resources for patients with a score of 4 points (3). Notably, prompt evacuation of hematoma remains contraindicated in the absence of all brainstem reflexes (68). To sum up, we made the assumption that PBSH patients with a score of 2–3 points in the new PPH score might benefit from surgical management. However, because surgery is not recommended for PBSH based on the current evidence, the assumption requires further verification and should be treated with caution.

As a result of the entirely different anatomical features, blood supply system and the possible distinct cell reactions to hemorrhages (69, 70), the findings and experience of the timing of surgery for supratentorial ICH could not be applied to PBSH directly. Pathological changes observed in animal experiments show that brain edema and arterial necrosis generally appear 6 h after PBSH onset (71). Therefore, in theory, surgery carried out in the super early phase (within a 6 h time window) seems to be the best choice. According to a study by Lan et al., patients with PBSH in the early operative group (≤6 h) had a better neurologic recovery than those in the late operative group (>6 h), and this difference was statistically significant ($P = 0.02$) (72). However, based on their experience with 52 cases of surgical treatment, Chen et al. proposed that 12–48 h after ictus may be the optimal surgical timing for PBSH (73).

Overall, as with supratentorial ICH, the exact indicators and the optimal surgical timing for PBSH remain controversial and undetermined (74).

Anatomical Considerations for Surgery

The ideal surgical approaches often depend on the location and size of the hematoma. The two-point rule by Brown et al. (namely, one point at the center of the hematoma and the other at the point on the brainstem surface to which the hematoma is closest) is frequently used as a means to enter a brainstem hematoma while minimizing disruption of the normal structure (75). However, with the widening knowledge of the anatomy of the brainstem, safe entry zones are considered to have an advantage over the simple two-point rule (76). Various safe entry zones and surgical approaches for the brainstem have been designed to reduce, as much as possible, damage to any eloquent or essential structures. Yang et al. identified 21 different safe entry zones according to the existing literature and endowed each of them with an evidence level (**Table 3**) (76). Endoscopic endonasal transclival approach (EETA) is a useful approach for endoscopic hematoma removal to provide adequate exposure of the ventral brainstem structure (77). The routine surgical approaches for microsurgery in different brainstem divisions are shown in **Table 3** (68).

TABLE 3 | Safe entry zones into the brainstem and common surgical approaches (68, 76).

Brainstem division	Safe entry zones			Surgical approaches
	Case report (case number ≤5)	Limited evidence (5 <case number <25)	Credible evidence (case number ≥25)	
Midbrain	Intercollicular region Inferior brachial triangle Interpeduncular fossa zone	Lateral mesencephalic sulcus Anterior mesencephalic zone	Supracollicular/infracollicular zones	Occipital transtentorial approach Subtemporal tentorial approach
Pons	Superior fovea zone Median sulcus zone Area acustica zone Floccular peduncle	Supratrigeminal zone Peritrigeminal zone Lateral pontine zone	Suprafacial zone Infrafacial zone	Suboccipital midline approach Subtemporal tentorial approach Suboccipital retrosigmoid approach
Medulla Oblongata	Posterior intermediate sulcus Posterior lateral sulcus zone Anterolateral sulcus zone	Lateral medullary zone Olivary zone	Posterior median sulcus	Suboccipital midline approach Far lateral approach

TABLE 4 | Comparison of advantages and disadvantages among the four surgical options of PBSH.

	Craniotomy	Stereotactic hematoma puncture and drainage	Endoscopic hematoma removal	External ventricular drainage
Advantage	Definite hemostasis effect; concurrent decompression could be performed	Short operation time and easy operation; minimal invasiveness; particularly useful for old and feeble patients 3D-printed navigation (78, 79): high individualized; local anesthesia	Concurrent surgical management of hydrocephalus could be performed (80). EETA: improved direct visualization; adequate exposure of the ventral brainstem structure; minimal brain or neurovascular retraction; a natural surgical corridor with sufficient illumination (77, 81)	A rescue surgical procedure for PBSH in primary hospitals; dynamically monitoring and managing intracranial pressure after the surgery (82)
Disadvantages	Extensive surgical trauma and the possibility of an aggravation of the condition	Special stereotactic equipment The accuracy of 3D print-assisted puncture is slightly lower than that of conventional stereotactic technology (78)	Cerebrospinal fluid leak (83); possible thermal injury to nearby tissues (84); lack of enough experience and high-quality evidence to support EETA in PBSH; a longer learning curve for doctors (77, 84)	A weak therapeutic effect in patients without IVH or hydrocephalus

CSF, cerebrospinal fluid; EETA, endoscopic endonasal transclival approach; IVH, Intraventricular hemorrhage; PBSH, primary brainstem hemorrhage.

Surgical Options

Patients with PBSH should be given proper type of surgical options based on the concrete states. Craniotomy is a classic surgical procedure used for PBSH, with advantage of definite hemostasis effect; stereotactic hematoma puncture and drainage is particularly useful for patients who are reluctant to accept craniectomy or are old and feeble; endoscopic hematoma removal could provide adequate exposure of the ventral brainstem lesion when used in a special approach; EVD could be used in emergency medical treatment especially in primary hospitals. We discuss these four main surgical options below and summarize their advantages and disadvantages in **Table 4**. Major milestones for research on the surgical management of PBSH are presented in **Figure 1**.

1) **Craniotomy**

Since suboccipital craniectomy was first used for brainstem hematoma clearance by Hong et al. (85), craniotomy has become one of the most important surgical treatments for PBSH. Lan et al. conducted a case-control study including 286 patients with severe PBSH (GCS ≤8), and 46 patients underwent craniotomy under microscope for hematoma clearance (72). Compared with the conservative group, the surgical group had a lower mortality rate (30.4% vs. 70.45%) and a higher good recovery rate (13.1% vs. 5.9%) at the expense of a higher rate of a vegetative state (4.3% vs. 2.5%), severe disability (32.6% vs. 13.3%), and moderate disability (19.6% vs. 7.9%) (72). Ichimura et al. reported the surgical results of five patients with relatively mild PBSH (patients without low initial consciousness and bilateral pupil dilation) (86). All of them had ameliorations in consciousness, motor performance, and mRS grades after surgery (86). Moreover, the authors suggested that the half-sitting position could greatly lower the risk of injury to normal tissue in surgical treatment of brainstem lesions (86). With growing knowledge of safe entry zones and continuing advances in microsurgical techniques (87), satisfactory results could be obtained in a minimally invasive way. Empirical evidence from 52 patients with PBSH indicated that minimally invasive microsurgery for hematoma clearance was very rapid, effective, and safe and was especially suitable for patients with hemorrhage volume <10 ml (73).

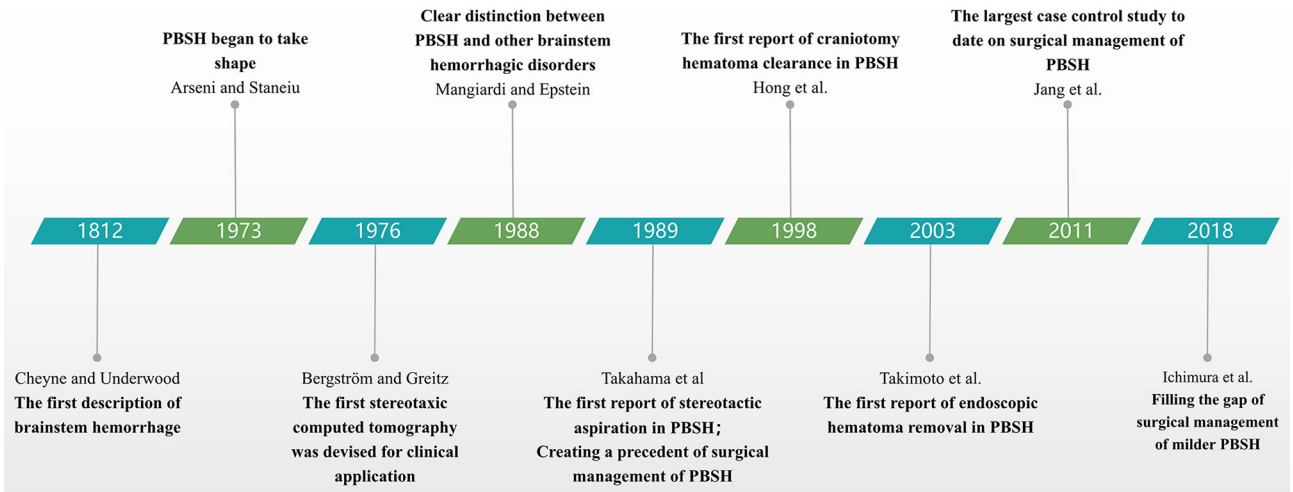

FIGURE 1 | Timeline diagram depicting major milestones for surgical management of PBSH. PBSH, primary brainstem hemorrhage.

2) **Stereotactic hematoma puncture and drainage**

Stereotactic hematoma puncture and drainage was the earliest surgery performed to treat PBSH by Takahama et al. (12). This surgical procedure is easy to perform and has many advantages, such as minimally invasive characteristics and a short surgery time. With the use of stereotactic equipment, anticoagulant urokinase, and rt-PA, it is endowed with high precision and a high hematoma clearance rate. A study by Shitamichi et al. of 45 patients with PPH showed that CT-guided stereotaxic aspiration could improve the prognosis, especially for severe cases (88). In another study enrolling 37 PPH patients, Hara et al. found that 72% (13 of 18) of subjects undergoing CT-guided stereotaxic aspiration showed a dramatic improvement, whereas only 42% (8 of 19) of subjects treated conservatively did (11).

The application of three-dimensional (3D) printing technology is achieving great success in various medical fields, including surgical intraoperative navigation (89, 90). Recently, Wang et al. successfully tested the application of a 3D-printed navigation template for puncture drainage in patients with severe brainstem hemorrhage (78). The actual puncture end was located precisely in the hematoma cavity in all cases, and the postoperative outcomes were satisfactory in all 7 included patients (78). 3D print-assisted hematoma puncture and drainage provides a highly promising new modality for the surgical treatment of PBSH and achieves precision medicine in a completely personalized manner.

With the application of various advanced stereotactic techniques, such as the ROSA (Robotized Stereotactic Assistant) device, stereoscopic virtual reality system, and augmented reality interactive neuronavigation, the surgical procedure would be increasingly safe and precise (91–93).

3) **Endoscopic hematoma removal**

Takimoto et al. were the first to evacuate a pontine hemorrhage with the aid of neuroendoscopy, which provided a new method for the surgical treatment of PBSH (80). However, ventrally located brainstem lesions are still surgically challenging due to their inaccessibility through traditional transcranial approaches. With several advancements, the EETA of neuroendoscopy has gradually become a feasible alternative to treat well-selected ventral brainstem lesions with the advantages of direct visualization and less injury (77). Both Essayed et al. and Weiss et al. proposed the potential feasibility and surgical limitations of EETA to remove ventral brainstem lesions based on cadaveric anatomical studies, and the combination of fiber dissection and 7T-MRI neuronavigation may help us to better understand the clear internal anatomical structure of the brainstem to enter the site of the lesion in a safer manner (94, 95). Topczewski et al. conducted a single-center study of 5 patients undergoing endoscopic endonasal surgery and concluded that EETA could provide enough access to the ventral brainstem (83). Adept operative techniques, the assistance of neuronavigation and intraoperative neurophysiological monitoring are critical for achieving better surgical results. Liu et al. reported a successful case of EETA used in the surgical treatment of a man with severe PBSH (77). An immediate improvement was found in his spontaneous respiration, and his GCS score improved significantly from 3 to 11 1 month after surgery (77). However, there are no other reports of EETA for PBSH. Therefore, EETA used in PBSH remains a surgical challenge that requires further verification of feasibility and surgical limitations based on a large sample.

4) **EVD**

Intraventricular hemorrhage occurs as a rupture of a hematoma into the ventricular system in approximately 39.5% of PBSH patients (6), and it is very frequently involved in elevated intracranial pressure and acute obstructive hydrocephalus due to its physical effect and

mass effect (96, 97). EVD is conducive to the clearance of intraventricular blood and the normalization of intracranial pressure (82). Currently, EVD has been used extensively to rescue acute obstructive hydrocephalus and prevent the potential risk of brain herniation induced by high intracranial pressure in the setting of PBSH because no special equipment is required (82, 98). Intraventricular thrombolytics are widely used to dissolve the casting of a hematoma, whereas the recent CLEAR III trial failed to prove a significant improvement in functional outcome with irrigation with alteplase in adult intraventricular hemorrhage (5, 99).

Clinical Registration Research

Due to the low incidence of PBSH (accounting for 6–10% of spontaneous ICH cases), it is difficult to collect large sample size surgical data within a short time (4). Moreover, in consideration of the high risk, various complications, high treatment costs and uncertain efficacy, the current treatment of PBSH is still mainly conservative. As a consequence, almost all of these previous studies were performed retrospectively with a small sample size, and no high-level evidence is available to support surgical management of PBSH to date.

One ongoing clinical trial, entitled Safety and Efficacy of Surgical Treatment in Severe Primary Pontine Hemorrhage Evacuation (STIPE) (URL: https://clinicaltrials.gov. Unique identifier: NCT04647162), is designed to fill this gap. The STIPE trial is sponsored by West China Hospital and is currently recruiting with an estimated enrollment of 345 participants. Furthermore, it is a multicentric, prospective, randomized, controlled, open-label, clinical study with the objective of evaluating the safety and efficacy of surgical treatment in patients with primary severe PPH (defined as GCS <8 and hemorrhage volume ≥ 5 ml, the equivalent of 2–4 points in the new PPH score). Patients in the experimental group will receive surgical intervention, such as craniotomy, stereotactic hematoma puncture and drainage or endoscopic hematoma removal, and the control group will only receive conservative medical treatment. The primary outcome measures include the mortality rate and intracranial infection rate at 30 days as well as the rebleeding rate within 3 days after the operation. The secondary outcome measures included the mRS and EQ-5D-5 L questionnaire results at 90, 180, and 365 days after surgery. The study started on January 1, 2021, and the estimated completion date is May 2025.

CONCLUSIONS AND EXPECTATIONS

In conclusion, PBSH has a low incidence but high mortality compared to other forms of ICH in which various prognostic factors are involved. Initial level of consciousness and hemorrhage size are the two most important and consistent predictors and present the two variables in the new PPH score. The new PPH score represents the latest developments in scoring systems and patients with a score of 2–3 points might benefit from surgical management. Therefore, the future direction of scoring systems should verify the availability of the new PPHl score for determining the surgical indications. However, conservative treatment still plays a major role in the management of PBSH and surgery is not recommended for PBSH based on the current evidence. PBSH is always excluded from previous surgical intervention trials for spontaneous ICH, such as the MISTIE III trial, the ICES trial, and the STICH I-II trials (100–103). Besides, in consideration of the complex structures and critical functions of the brainstem, more attention should be paid to potential risks during surgery. Because the number of cases is insufficient, there remains a lack of high-level evidence to prove the efficacy and safety of surgical intervention. The ongoing STIPE trial may fill this gap and provide additional evidence for the surgical treatment of PBSH.

From another point, the plight of clinical studies highlights that animal studies of brainstem hemorrhage are also essential to understand pathophysiological mechanism of PBSH and provide some reference to determining surgical timing, exploring surgical approaches and evaluating surgical efficacy. Though rat models of PPH by autologous blood or collagenase infusion have been established successfully (104–106), there is insufficient evidence to determine whether the pathophysiological difference between supratentorial ICH and PBSH exists. Furthermore, scant attention has been given to PBSH based on the perspective of translational stroke research (106). More efforts should be made in the future to explore pathophysiological features of PBSH and for better translational research.

In summary, we advocate the establishment of a worldwide registry and expert cooperative group to update the epidemiological data (incidence, mortality, etc.), re-evaluate prognostic factors, and re-investigate the surgical indication and timing. Prevention of PBSH also cannot be ignored. Recognizing and controlling risk factors actively are recommended to prevent PBSH.

AUTHOR CONTRIBUTIONS

DC, YiT, HN, and PZ conceived the review. DC wrote the paper, with major contributions from WW, QD, GW, MX, YuT, and WL. CP and ZT take responsibility for the manuscript as a whole. All authors contributed to the article and approved the submitted version.

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Effect of Robot-Assisted Neuroendoscopic Hematoma Evacuation Combined Intracranial Pressure Monitoring for the Treatment of Hypertensive Intracerebral Hemorrhage

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Objective: This study aimed to investigate the clinical efficacy of robot-assisted neuroendoscopic hematoma evacuation combined intracranial pressure (ICP) monitoring for the treatment of hypertensive intracerebral hemorrhage (HICH).

Patients and Methods: A retrospective analysis of 53 patients with HICH undergoing neuroendoscopic hematoma evacuation in our department from January 2016 to December 2020 was performed. We divided the patients into two groups: the neuroendoscopic group ($n = 32$) and the robot-assisted neuroendoscopic combined ICP monitoring group ($n = 21$). Data on clinical characteristics, treatment effects, and outcomes were retrospectively reviewed and analyzed between these two groups.

Results: The operation time of the procedure of the neuroendoscopic group was significantly longer than that of the robot-assisted neuroendoscopic combined ICP-monitoring group (mean time 153.8 ± 16.8 vs. 132.8 ± 15.7 min, $P < 0.001$). The intraoperative blood loss was significantly less in the robot-assisted neuroendoscopic combined ICP-monitoring group than in the neuroendoscopic group (215.4 ± 28.3 vs. 190.1 ± 25.6 ml, $P = 0.001$). However, the patients undergoing neuroendoscopic had a comparable hematoma clearance rate with those undergoing robot-assisted neuroendoscopic combined ICP monitoring (85.2 ± 4.8 vs. 89.2 ± 5.4%, $P = 0.997$). The complications rate was greater in the endoscopic group (25%) than in the robot-assisted neuroendoscopic combined ICP-monitoring group (9.5%) but without significant difference ($P = 0.159$). We also found that the dose of used mannitol was significantly less in the ICP monitoring group (615.2 ± 63.8 vs. 547.8 ± 65.3 ml, $P < 0.001$) and there was a significant difference in modified Rankin scale (mRS) score at discharge, patients with less mRS score in the robot-assisted neuroendoscopic combined ICP monitoring group than in the neuroendoscopic group (3.0 ± 1.0 vs. 3.8 ± 0.8, $p = 0.011$). Patients undergoing robot-assisted neuroendoscopic combined ICP monitoring had better 6-month functional outcomes, and there was a significant difference between the two groups ($p = 0.004$). Besides, multivariable analysis shows younger age, no

complication, and robot-assisted neuroendoscopic combined ICP monitoring were predictors of 6-month favorable outcomes for the patients with HICH.

Conclusion: Robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring appears to be safer and more effective as compared to the neuroendoscopic hematoma evacuation in the treatment of HICH. Robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring might improve the clinical effect and treatment outcomes of the patients with HICH.

Keywords: hypertensive intracerebral hemorrhage, neuroendoscopic hematoma evacuation, intracranial pressure monitoring, Remebot robot, clinical effect

INTRODUCTION

Hypertensive intracerebral hemorrhage (HICH) is a common serious cerebrovascular disease with high mortality and morbidity rate, which frequently occurs in the middle-aged and elderly population, with a peak incidence in winter and spring (1–3). Due to the influence of long-term hypertension, it can cause arteriosclerosis in the brain, decrease the elasticity of the blood vessel wall, increase the brittleness, cause cellulose necrosis, and promote the formation of a miliary aneurysm. Once the blood pressure rises, the aneurysm will rupture and cause cerebral hemorrhage. Owing to the harmfulness and the risks of HICH, the patients should get timely and effective treatment (4, 5).

At present, surgical treatment and conservative medical methods are the two main options for patients with HICH, but there is no uniform standardized treatment method. The surgical methods mainly include conventional craniotomy, small-bone window craniotomy, stereotactic aspiration, neuroendoscopic hematoma evacuation, and so on (6, 7). The principle of operation is to clear the hematoma and promote the recovery of neurological function. With the recent advances in endoscopic technique, neuroendoscopes have been used for the treatment of intracranial cysts and hydrocephalus and as an adjunct during microsurgical tumor removal. Meanwhile, neuroendoscopic hematoma evacuation has been applied widely in the treatment of patients with HICH, which is less invasive than craniotomy and can also easily achieve hemostasis of the bleeding vessels (8, 9). However, neuroendoscopic hematoma evacuation also has its inherent shortcomings such as a narrow surgical window results in a low-removal rate, sometimes cannot reach the designated position accurately and rapidly, and should be performed by a skilled surgeon. To the best of our knowledge, there have been several reports on the use of robotic devices in neuroendoscopic surgery. Zimmermann et al. (10) demonstrated their preliminary experience with robot-assisted navigated endoscopic third ventriculostomies, the authors proved for the first time that robot assistance allows highly exact and repeatable positioning of a rigid endoscope with an accuracy of 50 mm, a very smooth and slow insertion of the endoscope within the brain tissue. According to this, neuro-navigation and robotic technologies have been developed and used in surgical procedures to reduce brain injury and improve clinical outcomes and prognosis of patients with HICH (11).

In the meantime, patients still have many complications after the operation, including rehemorrhage, brain swelling, and cerebral ischemia that can cause increased intracranial pressure (ICP), thus, ICP monitoring in the treatment of patients with HICH is of great importance for preventing the occurrence of complications. Many scholars have reported that ICP monitoring was associated with a good prognosis (12, 13). In our study, we retrospectively reviewed 53 patients with HICH undergoing neuroendoscopic hematoma evacuation in the Tongji Hospital, the purpose of this study was to investigate the clinical efficacy of robot-assisted neuroendoscopic hematoma evacuation and ICP monitoring for the treatment of HICH.

MATERIALS AND METHODS

Patient Population

This retrospective study was permitted and sponsored by the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. January 2016 to December 2020, we reviewed 53 patients who underwent neuroendoscopic hematoma evacuation at the Department of Neurosurgery, Tongji Hospital. The patients were divided into two groups according to the surgical strategy: the neuroendoscopic group ($n = 32$) and the robot-assisted neuroendoscopic combined ICP monitoring group ($n = 21$). The clinical data regarding patient age, sex, neuroimaging features, outcomes, postoperative complications, and the duration of the operation procedure and hospitalization were retrospectively analyzed. The inclusion criteria were as follows: patients with HICH were confirmed by CT scan with hematoma volume > 30 ml; the past medical history of hypertension; disease onset within 24 h and GCS score ≥ 4. The exclusion criteria were as follows: hemorrhage caused by aneurysm, trauma, tumor, arteriovenous malformation, venous sinus thrombosis; preoperative administration of antiplatelet or anticoagulant drugs; patients with severe systematic comorbidities.

Surgical Techniques

All the surgeries were performed by the same neurosurgeon, Professor Kai SHU, Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, who performed 300 operations of robotic surgery every year. Thirty-two patients underwent neuroendoscopic hematoma evacuation, and 21 patients

underwent robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring. All the patients underwent CT angiography to exclude arteriovenous malformation and aneurysm before surgery. We used the Glasgow Coma Scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS) to assess the neurological function of patients with HICH at admission. The Coniglobus formula was used to estimate the hematoma volumes, that is, volume = (length × width × thickness)/2. And the hematoma clearance rate =100- (postoperative volume)/(preoperative volume) × 100. All the patients were followed up for 6 months.

For the neuroendoscopic hematoma evacuation procedures, after skin disinfection, a burr hole was made on the skull nearest to the hematoma for patients with lobar hemorrhage or the forehead at the site 1.5 cm inside the hairline and 2.5–3.5 cm from the midline for the patients with basal ganglia hemorrhage. A small-bone window was opened with a size of 3 cm diameter by using the milling cutter. Then, a sheath with stylet inside was inserted after the dura matter was incised. Based on the location and volume of the hematoma, the depth and orientation of the sheath were determined by the experience of the surgeon. The stylet was removed and an endoscope with 0 or 30 degrees was inserted once the sheath reached the hematoma. The hematoma was removed under neuroendoscope. The hematoma cavity was filled with absorbable hemostatic gauze, and a monopolar electrocautery probe was used for hemostasis when artery bleeding was seen. After the hematoma was evacuated, the drainage tube was inserted into the hematoma cavity and we sutured and disinfected the wound.

For the robot-assisted neuroendoscopic hematoma evacuation combined ICP monitoring procedures, markers were attached to the temple and forehead of the patient, and then CT scans were performed before operation. All images were copied to the Remebot robot system (developed by Beijing Baihuiweikang Technology Company, and approved by the National Medical Products Administrations, China), and then the entry point, the range of hematoma, and optimal trajectory were carefully planned by the surgeon. The head of the patient was immobilized in a Mayfield clamp after general anesthesia. After accurate registration, a burr hole was drilled based on preoperative planning. After the dura matter was incised, a sheath with stylet inside was inserted into the hematoma cavity with the assist of a Remebot robot. The methods of removing and aspirating hematoma, hemostasis, and suturing were the same as the treatment in the neuroendoscopic hematoma evacuation group. And we inserted a drainage tube with the Codman ICP monitoring probe to the ventricle or hematoma cavity (**Figure 1**). The drainage tube with the Codman ICP monitoring probe was inserted into the ventricle for patients who were complicated with ventricular hemorrhage. The drainage tube with the Codman ICP monitoring probe was inserted into the hematoma cavity for patients with HICH with no involvement of the ventricular system. Management of different dosages of mannitol was guided by ICP changes: for the patients with ICP higher than 25 mmHg, 125 ml of 20% mannitol every 6 h was used to decrease ICP to maintain ICP lower than 15 mmHg, also emergent CT scan would be performed if necessary; for ICP between 15 and 25 mmHg, 125 ml of 20% mannitol compound was intravenously injected every 8–12 h; and for ICP between 0 and 15 mmHg, it would be considered as normal.

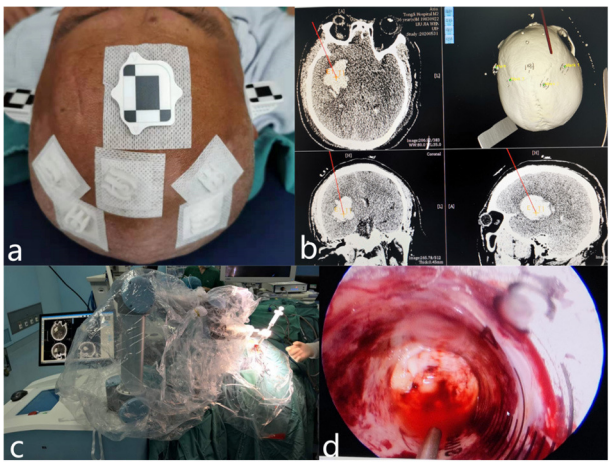

FIGURE 1 | Representative images of robot-assisted neuroendoscopic hematoma evacuation combined ICP monitoring surgical workflow. **(a)** Markers were attached to the temple and forehead of the patient, and then CT scans were performed before the operation. **(b)** The entry point, the range of hematoma, and optimal trajectory were carefully planned by the surgeon. **(c)** After the dura matter was incised, a sheath with stylet inside was inserted into the hematoma cavity with the assist of a Remebot robot. **(d)** The hematoma was removed under neuroendoscope.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 22.0 (IBM Corporation, USA). Data are described as $\bar{x} \pm s$. The intergroup comparison was performed using the Student's *t*-test and the chi-squared test. Predictors of 6-month favorable outcomes were identified by using multiple-variable logistic regression (variables with statistical significance in univariate analysis were entered into a multivariate analysis). $p < 0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics are all shown in **Table 1**. A total of 53 patients were identified, with 34 men (64.2%) and 19 women (35.8%). The mean age of the population was 56.5 ± 9.1 years. There were no significant differences in patient age, sex, the GCS score, systolic pressure admission, the NIHSS score, localization of hematoma, hematoma volume, or midline shift between the neuroendoscopic group, and the robot-assisted neuroendoscopic hematoma evacuation combined ICP monitoring group.

The operation time of the procedure of the neuroendoscopic group was significantly longer than that of the robot-assisted neuroendoscopic combined ICP-monitoring group (mean time 153.8 ± 16.8 vs. 132.8 ± 15.7 min, $P < 0.001$). The intraoperative blood loss was significantly less in the robot-assisted neuroendoscopic combined ICP-monitoring group than in the neuroendoscopic group (215.4 ± 28.3 vs. 190.1

TABLE 1 | Summary of the baseline clinical characteristics of the patients.

Parameters	Neuroendoscopic group ($n = 32$)	Robot-assisted neuroendoscopic combined ICP monitoring group ($n = 21$)	χ^2/*t*-value	*P*-value
Age (mean ± SD), years	56.2 ± 9.3	57.3 ± 8.9	0.195	0.577
Sex ratio (male/female)	21:11	13:8	0.076	0.782
GCS score	7.1 ± 2.1	7.8 ± 2.4	1.122	0.866
Systolic pressure admission (mmHg)	175.4 ± 17.3	178.9 ± 19.8	0.680	0.750
NIHSS score	11.2 ± 2.9	10.5 ± 2.7	−0.883	0.191
Left side	14	9	0.004	0.949
Hematoma volume (ml)	45.8 ± 15.4	46.9 ± 16.8	0.245	0.596
Location	0.707			0.699
Lobar	10	8		
Basal ganglia region	15	10		
Cerebellum	3	2		
Intraventricular extension	4	1		
Midline shift (mm)	8.1 ± 1.9	8.4 ± 1.8	0.574	0.716

± 25.6 ml, $P = 0.001$). However, the patients undergoing neuroendoscopic had a comparable hematoma clearance rate with those undergoing robot-assisted neuroendoscopic combined ICP monitoring (85.2 ± 4.8 vs. 89.2 ± 5.4%, $P = 0.997$). The complications rate was greater in the endoscopic group (25%) than in the robot-assisted neuroendoscopic combined ICP-monitoring group (9.5%) but without significant difference ($p = 0.159$). Complications occurred in eight cases of the neuroendoscopic group, including four patients with pulmonary infection, two with digestive tract hemorrhage, one with bleeding recurrence, and one who experienced a seizure. In the robot-assisted neuroendoscopic combined ICP monitoring group, one patient experienced pulmonary infection and one patient with digestive tract hemorrhage. The postoperative duration of hospitalization of the neuroendoscopic group was significantly longer than the robot-assisted neuroendoscopic combined ICP monitoring group (mean 13.8 ± 3.3 vs. 11.1 ± 2.8 days, $P = 0.016$).

We also used the modified Rankin scale (mRs) to evaluate the neurological function recovery state of the patients. We found that the dose of used mannitol was significantly less in the ICP monitoring group (615.2 ± 63.8 vs. 547.8 ± 65.3 ml, $P < 0.001$), and there was a significant difference in mRS score at discharge, patients with less mRS score in the robot-assisted neuroendoscopic combined ICP monitoring group than in the neuroendoscopic group (3.0 ± 1.0 vs. 3.8 ± 0.8, $p = 0.011$). Moreover, there was no significant difference in mortality rate between the two groups. The patients were followed up for 6 months, and we utilized Glasgow Outcome Scale to assess the clinical outcome of the patients. In the endoscopic group, 16 patients had a good recovery, 13 patients had moderate disability, one patient was with a vegetative state, and two patients died. In the robot-assisted neuroendoscopic combined ICP-monitoring group, 15 patients had a good recovery, four patients had moderate disability, one patient was with a vegetative state, and one patient died. Patients undergoing robot-assisted neuroendoscopic combined ICP monitoring had better 6-month functional outcomes, and there was a significant difference between the groups ($P = 0.004$). These results are all summarized in **Table 2**. **Table 3** summarizes the results from single and multiple logistic regression of Predictors of 6-month favorable outcomes. On single-variable logistic regression, younger age, less hematoma volume, not deep location, no complication, and robot-assisted neuroendoscopic hematoma combined with ICP monitoring were independent predictors of 6-month favorable outcomes. Sex, GCS score, systolic pressure admission, NIHSS score, the bleeding side of brain hemisphere, midline shift, operation time, intraoperative blood loss, hematoma clearance rate, a dose of mannitol, and postoperative duration of hospitalization were not significant prognostic factors for survival ($P > 0.05$). Multivariable analysis identified younger age, no complication and robot-assisted neuroendoscopic hematoma combined with ICP monitoring were predictors of 6-month favorable outcomes. There are four typical examples of the robot-assisted neuroendoscopic combined ICP-monitoring group in **Figure 2**.

DISCUSSION

With the current social improvement of living standards, more and more people are suffering from hypertension, and there are ∼200 million patients with hypertension in China according to the latest epidemiological data (14). HICH is one of the most serious complications of hypertension because of its high morbidity and mortality rate, which accounts for 70–80% of a spontaneous cerebral hemorrhage. The mass effect of hematoma can cause primary brain injury in a short time and perihematoma edema is the main source of secondary cerebral damage (15). Therefore, surgical treatment has become an effective treatment for HICH patients because it can release the compression of the hematoma rapidly and reduce ICP at an early stage. A traditional craniotomy is not widely applied because of its disadvantages

TABLE 2 | Comparison of postoperative data and clinical outcomes in the two groups of patients.

Parameters	Neuroendoscopic group ($n = 32$)	Robot-assisted neuroendoscopic combined ICP monitoring group ($n = 21$)	χ^2/t-value	*P*-value
Operation time (min)	153.8 ± 16.8	132.8 ± 15.7	−4.566	<0.001*
Intraoperative blood loss (ml)	215.4 ± 28.3	190.1 ± 25.6	−3.303	0.001*
Hematoma clearance rate, %	85.2 ± 4.8%	89.2 ± 5.4%	2.824	0.997
Dose of mannitol (ml)	615.2 ± 63.8	547.8 ± 65.3	−3.727	<0.001*
Complications rate	8/32	2/21	1.984	0.159
Postoperative duration of hospitalization, days	13.8 ± 3.3	11.1 ± 2.8	−3.088	0.016*
mRS score at discharge	3.8 ± 0.8	3.0 ± 1.0	−3.223	0.011*
Mortality rate	2	1	0.053	0.819
Glasgow outcome scale after 6 months	3.86 ± 1.18	4.48 ± 1.16	1.927	0.033*

**Statistically significant.*

TABLE 3 | Predictors of 6-month favorable outcomes.

Independent variable	Single variable logistic regression			Multiple logistic regression		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Age	0.001*	0.92	[0.86, 0.99]	0.013*	0.95	[0.91, 0.98]
Sex	0.256	1.59	[0.68, 3.62]			
GCS score	0.082	7.93	[3.63, 20.46]			
Systolic pressure admission	0.333	9.77	[1.76, 54.23]			
NIHSS score	0.452	4.88	[2.08, 18.32]			
The bleeding side of brain hemisphere	0.437	0.49	[0.28, 0.87]			
Hematoma volume	0.010*	5.69	[1.51, 10.69]	0.354	2.34	[0.91, 3.58]
Midline shift	0.378	1.01	[0.96, 1.06]			
Location	0.008*	6.91	[1.23, 10.21]	0.493	1.75	[0.69, 5.49]
The operative type	0.013*	5.34	[2.57, 18.58]	0.021*	2.69	[1.86, 4.06]
Operation time	0.476	0.23	[0.06, 0.39]			
Intraoperative blood loss	0.396	1.01	[0.96, 1.06]			
Hematoma clearance rate	0.358	0.96	[0.92, 1.03]			
Dose of mannitol (ml)	0.254	0.95	[0.86, 1.06]			
Complication	0.009*	0.16	[0.03, 0.72]	0.042*	0.36	[0.16, 1.68]
Postoperative duration of hospitalization	0.264	0.94	[0.83, 1.07]			

**Statistically significant.*

of severe trauma and postoperative complications. Currently, minimally invasive puncture drainage, small bone-window craniotomy, and neuroendoscopic hematoma evacuation are widely recognized by neurosurgeons. Because they have their advantages and limitations, experts and scholars have not reached a unified consensus about which of these surgical treatments is the most effective until now (16–18).

Nowadays, neuroendoscopic hematoma evacuation has been widely applied in the treatment of patients with HICH owing to its advantages of a clear operative field, short time, less bleeding, and injury (8, 9, 11, 19). However, there are also some limitations of the neuroendoscopic procedures, such as a narrow surgical window results in a low removal rate, sometimes cannot reach the designated position accurately and rapidly, and should be performed by a skilled surgeon. Hayashi et al. (11) reported that the surgeons should have experience doing the endoscopic procedure to achieve a good removal rate. Atsumi et al. (20) showed that the navigation system is beneficial for avoiding a burr hole exactly above the transverse and sigmoid sinus confirming the direction of hematoma extension in the neuroendoscopic surgery. For these reasons, we introduced the Remebot robot to improve clinical outcomes and prognosis of patients with HICH. The Remebot robot system has been successfully used in a variety of surgical methods that were designed and produced in China. We have examined the accuracy of the Remebot robot in several applications such as stereotactic brain biopsy and have shown it to be accurate (21). In addition, Wang et al. (14) showed that robot-assisted surgery using a Remebot is a safe and effective treatment method for hematoma removal and tube drainage in patients with HICH, and the target error is <1 mm. To the best of our knowledge, this is the first report to perform robot-assisted neuroendoscopic hematoma

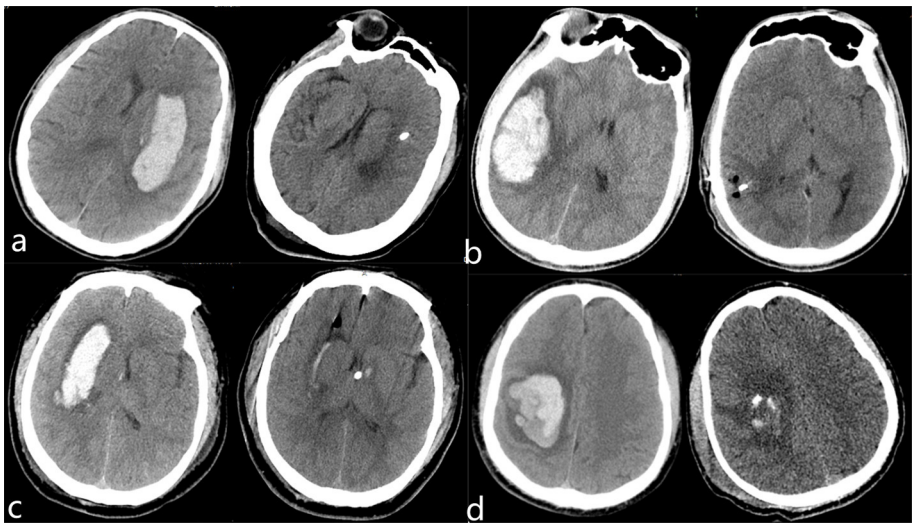

FIGURE 2 | Preoperative and postoperative CT images in robot-assisted neuroendoscopic hematoma evacuation combined ICP monitoring of representative patients with HICH **(a–d)**. **(a)** A 62-year-old female was presented with a headache and right hemiplegia for 4 h. The hematoma was removed completely and the symptoms of headache were improved obviously. Continuous rehabilitation training was given to the patient after discharge. **(b)** A 54-year-old male presented with a headache for 10 h. Preoperative CT shows right temporal lobe hemorrhage that has been evacuated totally. **(c)** A 65-year-old male was presented with consciousness disturbance for 5 h. Preoperative CT scan shows right basal ganglia hemorrhage, which has been evacuated and we inserted a drainage tube with the Codman ICP monitoring probe to the ventricle. **(d)** A 73-year-old male was presented with left hemiplegia for 3 h. Preoperative CT shows right parietal lobe hemorrhage, which has been evacuated and we inserted a drainage tube with the Codman ICP monitoring probe to the hematoma cavity. Continuous rehabilitation training was given to the patient after they were discharged.

evacuation combined with ICP monitoring for patients with HICH. In this study, we found that the operation time of the procedure of the neuroendoscopic group was significantly longer than that of the robot-assisted neuroendoscopic combined ICP monitoring group (mean time 153.8 ± 16.8 vs. 132.8 ± 15.7 min, $P < 0.001$) and the intraoperative blood loss was significantly less in the robot-assisted neuroendoscopic combined ICP monitoring group than in the neuroendoscopic group (215.4 ± 28.3 vs. 190.1 ± 25.6 ml, $p = 0.001$). The Remebot robot navigation system has several benefits. First, because a supine lateral position and other positions can lead to disorientation, the robot system could help us to confirm whether the selection of the site of the burr hole was satisfactory. Second, it could help us better confirm the direction of hematoma extension and the depth to complete the hematoma extraction, which can reduce the number of punctures and trauma of most puncture wounds.

Moreover, postoperative management has important value for the recovery of patients with HICH. As is well-known, ICP monitoring has been widely used in the field of head trauma and neuro-critical care. MacLaughlin et al. (22) found that ICP monitoring was associated with a significant decrease in mortality rate through a retrospective analysis of 123 patients with severe traumatic brain injury. Many researchers also showed that ICP monitoring is crucial in the postoperative management of patients with HICH because it can improve postoperative treatment and prognosis by detecting the information of any abnormal increase of ICP in time (13). The application of mannitol drugs could reduce ICP of the patients with HICH after surgery and reduce the risk of rehemorrhage and brain edema. However, excessive use of mannitol drugs increases the risk of complications such as electrolyte disturbances, the imbalance of body fluid, and acute renal failure that can result in rapid clinical deterioration and increase the length of recovery. Without ICP monitoring, we made the postoperative treatment decisions that depends on clinical signs and imaging methods. In our study, we found that the postoperative duration of hospitalization of the neuroendoscopic group was significantly longer than the robot-assisted neuroendoscopic combined ICP-monitoring group (mean 13.8 ± 3.3 vs. 11.1 ± 2.8 days, $p = 0.016$), the dose of used mannitol was significantly less in the ICP monitoring group (615.2 ± 63.8 vs. 547.8 ± 65.3 ml, $p < 0.001$). In the meantime, there was no significant difference in mortality rate between the two groups, but there was a significant difference in mRS score at discharge, patients with less mRS score in the robot-assisted neuroendoscopic combined ICP-monitoring group than in the neuroendoscopic group (3.0 ± 1.0 vs. 3.8 ± 0.8, $p = 0.011$). The results showed that ICP monitoring could significantly reduce the postoperative duration of hospitalization and mannitol use because it can help the clinicians to initiate intervention timely before the irreversible cerebral damage. The complications rate was greater in the endoscopic group (25%) as compared with the robot-assisted neuroendoscopic combined ICP-monitoring group (9.5%) but without significant difference ($p = 0.159$). This could be explained by the limited number of patients.

Furthermore, patients undergoing robot-assisted neuroendoscopic combined ICP monitoring had better 6-month functional outcomes, and there was a significant difference between the groups ($P = 0.004$). Besides, multivariable

analysis shows younger age, no complication, and robot-assisted neuroendoscopic combined ICP monitoring were predictors of 6-month favorable outcomes for the patients with HICH. The results are in accordance with those of previous literature. Che et al. (12) reported that a good 6-month functional recovery was associated with ICP monitoring. Ferrete-Araujo et al. (23) performed a prospective observational study of 186 patients with severe ICH, which showed that ICP monitoring and early operation were predictors of longer survival and better functional outcomes. For these reasons, we proposed that robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring should be used for patients with HICH. Because it has the advantages of less operation time and intraoperative blood loss, less mannitol use and postoperative duration of hospitalization, and better functional recovery.

There are several limitations of our study. The primary limitations are its retrospective design and the number of patients enrolled was still not large enough, which limits the power of statistical tests. Moreover, the findings are limited by the presence of selection bias, as described previously, and the lack of multicenter participation. Therefore, a prospective, randomized controlled trial is needed to further evaluate the effect of robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring for the treatment of HICH.

CONCLUSION

Robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring appears to be safer and more effective than neuroendoscopic hematoma evacuation in the treatment of HICH. Robot-assisted neuroendoscopic hematoma evacuation combined with ICP monitoring might improve the clinical effect and treatment outcomes of the patients with HICH.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethical Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KS contributed to the conception and design of this study. SW and HW contributed to data analysis and wrote the manuscript. WJ and TL contributed to the data analysis and to modify the article. FH and JW contributed to the data collection and data interpretation. All authors read and approved the final manuscript.

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Minimally Invasive Surgery in Patients With Intracerebral Hemorrhage: A Meta-Analysis of Randomized Controlled Trials

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Background: Minimally invasive surgery for intracerebral hemorrhage (ICH) has been evaluated in clinical trials. Although meta-analyses on this topic have been performed in the past, recent trials have added important information to the results of the comparison. However, little work has been done to compare the effect of MIS and conventional treatment on patient prognosis, especially mortality.

Methods: PubMed, EMBASE, Web of Science, Ovid, China National Knowledge Infrastructure, and ClinicalTrials.gov were searched on May 1, 2021, for randomized controlled trials of MIS for spontaneous ICH. The primary outcome was defined as death at follow-up, while the secondary outcome was defined as death in different comparisons between MIS and craniotomy (CT) or medication (Me).

Results: The initial search yielded 12 high-quality randomized controlled trials involving 2,100 patients. We analyzed the odds ratios (ORs) for MIS compared with conventional treatment, including Me and conventional CT. The OR and confidence intervals (CIs) of the primary and secondary outcomes were 0.62 (0.45–0.85) for MIS vs. conventional treatment. We also conducted subgroup analyses and found that the ORs and CIs for MIS compared with that of conventional treatment in the short-term follow-up were 0.58 (0.42–0.80), and, in the long-term follow-up, was 0.67 (0.46–0.98); and found that ORs were 0.68 (0.48–0.98) for MIS vs. CT and 0.57 (0.41–0.79) for MIS vs. Me.

Conclusions: This meta-analysis demonstrates that certain patients with ICH benefit in short- and long-term follow-up from MIS over other treatments, including open surgery and conventional Me.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/.

Keywords: minimally invasive surgery, intracerebral hemorrhage, meta-analysis, death, craniotomy

INTRODUCTION

Spontaneous intracerebral hemorrhage is the second most common subtype of stroke and is a critical disease with high mortality 2-6-fold higher than ischemic stroke (1, 2). Clot volume is the best predictor of outcomes regardless of the hemorrhage location (2, 3). Surgical therapies, including open craniotomy and stereotactic therapy, with or without thrombolysis, are beneficial

in hemorrhage evacuation (4). However, in many patients, the surgical approach causes trauma to the surrounding brain in negating the benefit of hematoma evacuation. Thus, minimally invasive surgery (MIS) is the most promising surgical strategy for patients with ICH. MIS refers to surgery accomplished with a smaller incision and minimal surgical stress, and was first introduced in 1987, which performed the first laparoscopic cholecystectomy in history (5). The MIS for ICH can be performed using an endoscope or needle through a smaller incision, and a bone hole to suck the clot from the brain. Recently, randomized controlled trials (RCTs) have been performed to evaluate MIS in comparison to either medical therapy or conventional craniotomy with different surgical techniques (6). However, the conclusions are controversial; some studies showed the net benefit of MIS, while, in others, no benefit of MIS was observed. This may be due to the different study designs and ICH definitions (7, 8). Ongoing RCTs include two industry-sponsored trials: (1) the Early Minimally Invasive Removal of ICH trial sponsored by NICO Corporation, and (2) the Minimally Invasive Endoscopic Surgical Treatment with Apollo/Artemis in Patients with Brain Hemorrhage trial sponsored by Penumbra (9). Previous meta-analyses focused on the benefits of MIS over other therapies (10, 11), and found that MIS independently seems to decrease the rate of moderate-to-severe functional impairment and death at long-term follow-up. However, the selected data in these studies were doubtful, and the comparisons of mortality between patients who underwent MIS and those who underwent craniotomy were insufficient (10). Our study aimed to investigate the impact of MIS on ICH prognosis.

MATERIALS AND METHODS

Study Design

We performed a systematic review and study-level meta-analysis of RCTs evaluating the ICH treatment according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (12) (see **Supplementary Table 1**). Details of the protocol for this analysis were registered (CRD42021283433) on the online database, International Prospective Register of Systematic Reviews. We only included RCTs evaluating MIS approaches for spontaneous ICH to minimize the selection and confounding biases of prospective observational studies. The study groups were defined by randomized assignment to either MIS for ICH evacuation or non-MIS, including medical therapy and conventional craniotomy. We reviewed the methodology of each study to determine which MIS technique was used. If surgery was defined as minimally invasive by the authors, it was included in the MIS group. If an endoscope was used during the evacuation, the technique was categorized as MIS (endoscopic surgery). If a device or catheter was stereotactically placed for infusion of a thrombolytic agent and drainage of the hematoma beyond the time of the operative procedure, the technique was categorized as MIS (stereotactic thrombolysis). The pre-specified primary outcomes were death, defined as a modified Rankin Scale score of 6 or Barthel Index of <30 when the modified Rankin Scale was not available. The analyzed outcome measures were those used in the original studies, with some variability in the scale used to dichotomize the good from the poor outcomes. The modified Rankin Scale and the Barthel Index have high reproducibility and are commonly used to assess neurological outcomes in the ICH.

Study Selection

PubMed, EMBASE, Web of Science, Ovid, China National Knowledge Infrastructure, and ClinicalTrials.gov were searched for related studies that were either published or established before May 1, 2021. Terms related to "minimally invasive surgery," "minimally endoscopic surgery," "minimally stereotactic surgery," etc., were also searched; no language restriction was applied. The exact search strategy and rationale are shown in **Supplementary Material**. We obtained additional articles using the reference lists of the articles which were identified in the initial searches. The inclusion criteria were: (1) computed tomography-confirmed diagnosis of spontaneous ICH, and (2) RCTs comparing MIS techniques with other treatment options, including conventional medical treatment and craniotomy. The exclusion criteria were: (1) traumatic brain injury, hemorrhagic tumor, coagulopathy, intracranial aneurysm, cerebral arteriovenous malformation, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage, or pituitary apoplexy; (2) infratentorial ICH, including cerebellar hemorrhage or brain stem hemorrhage; and (3) a total study quality assessment score of < 2. The quality assessment of the study was based on the Cochrane criteria: (1) random sequence generation (yes $= 2$, unclear $= 1$, and no $= 0$); (2) allocation concealment (yes $= 2$, unclear $= 1$, and no $= 0$); (3) blinding of outcome assessment (yes $= 2$, unclear $= 1$, and no $= 0$); and (4) incomplete outcome data reported (yes $= 1$ and no $= 0$) (see **Supplementary Table 2**).

Study Assessments

Two authors independently identified the articles using the inclusion and exclusion criteria, and the study quality assessment scores were assigned. Any disagreements were resolved by consensus with a third investigator (Dr. Wu).

First, we compared the outcomes between MIS and other treatments. Second, we performed subgroup analyses according to the follow-up duration. We also conducted subgroup analyses focusing on short-term or long-term outcomes, as well as the different interventions.

Statistical Analysis

The primary outcome of the study was analyzed as categorical variables, with the effectiveness of different treatment methods evaluated and interpreted using a summary odds ratio (OR) and the corresponding 95% confidence interval (CI). Classic χ^2 test, Q^2, and I^2 statistics were used to assess the existence and the magnitude of the between-study heterogeneity. The

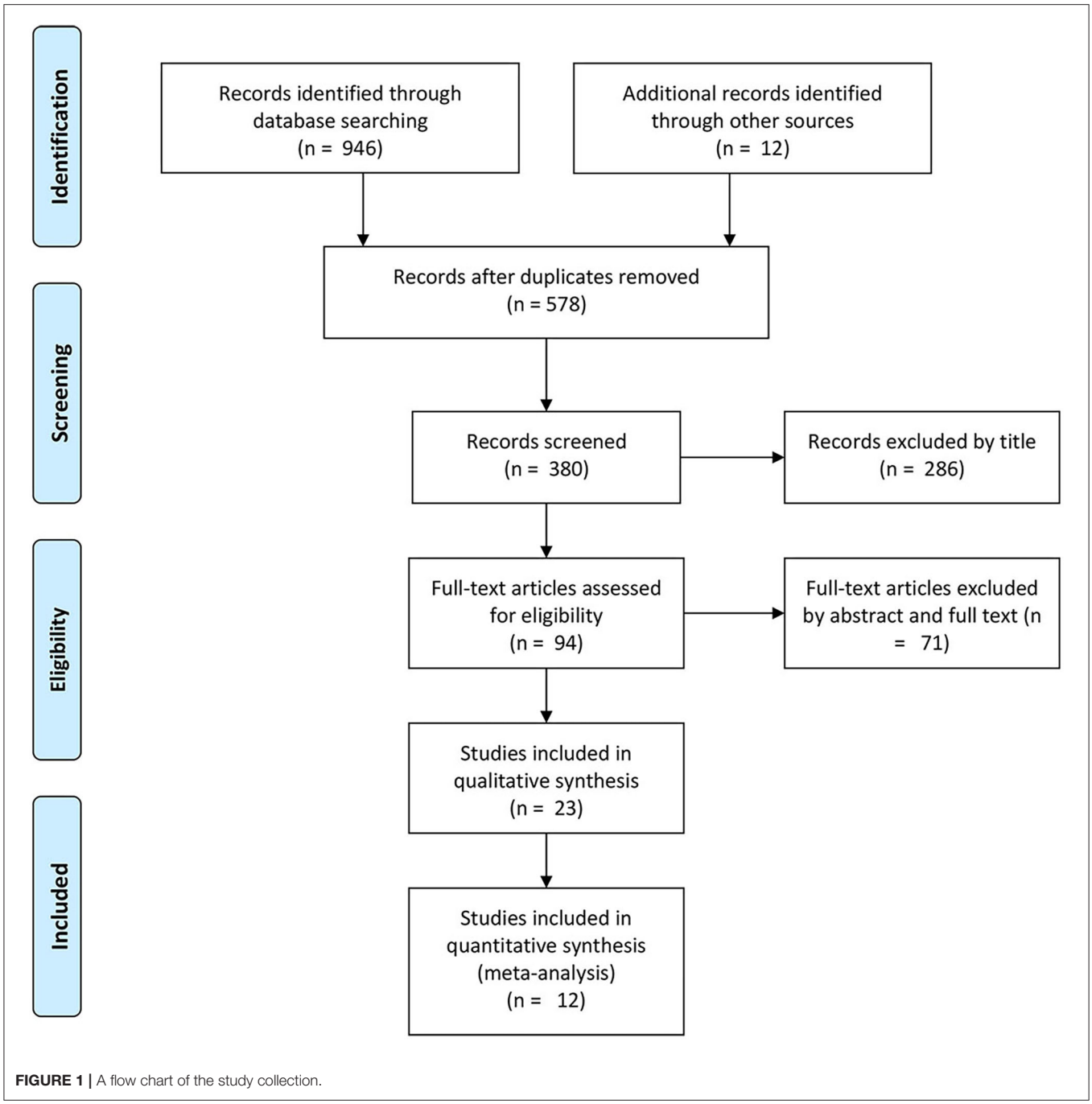

FIGURE 1 | A flow chart of the study collection.

significance level was set at $p < 0.05$. We used a random-effects model in the analysis. We assumed *a priori* that the meta-analysis could be affected by study-level variability determined by different inclusion criteria across RCTs, which is more appropriately addressed by a random-effects model over a fixed-effects model.

Inverted funnel plots and a regression test were used to assess the potential presence of publication bias. All data analyses were conducted and verified by both R (Version 4.0.0) and RevMan5.4 (Cochrane Information Management System, London, UK).

RESULTS

Literature Research

The initial comprehensive literature search identified 946 potentially relevant articles from the databases. A total of 578 studies were excluded as duplicates, leaving a total of 380 studies. Based on the inclusion and exclusion criteria, 286 articles were excluded. Next, we reviewed the full text of the remaining 94 studies, and 71 studies were eliminated after reading the abstracts and full texts. Finally, 11 studies were included in this meta-analysis (see **Figure 1** and **Table 1**).

TABLE 1 | Characteristics of the related studies including RCTs and cohorts.

References	Duration	Trial type	Disease type	Treatment methods				Hematoma volume (ml)		Hematoma volume changes (%)		Outcome		
				MIS	Data	Conservative therapy	Data	MIS	Conservative therapy	MIS	Conservative therapy	Outcome	MIS numbers	Conservative therapy numbers
Hanley et al. (8)	2006–2013	RCT	ICH	MIS+ rtPA	54	Standard	42	48.2	43.1	–	–	180-day mRS	14	11
Wang et al. (13)	2003–2004	RCT	ICH	MIS	195	Medication	182	33.8	31.3	–	–	3-month BI	19/181	22/165
Auer et al. (14)	1983–1986	RCT	ICH	Endoscopy	50	Medication	50	>50ml: 22; <50ml: 28	>50ml: 24; <50ml: 26	–	–	6-month mRS	42%	70%
Zhou et al. (15)	2005–2008	RCT	ICH	MIS	90	Craniotomy	78	30–100	30–100	–	–	1-year fatality	17	19
Sun et al. (16)	2003–2005	RCT	ICH	Craniopuncture +urokinase	159	Craniotomy	145	52.3	51.7	–	–	90-day BI	29	26
Kim and Kim (17)	2001–2009	RCT	ICH	Stereotactic	204	Craniotomy	183	24	21	–	–	6-month mortality	11	7
Hattori et al. (18)	1998–2000	RCT	ICH	Stereotactic	121	Conservative	121	–	–	–	–	Mortality	11.8%	23.5%
Zuccarello et al. (19)	1994–1996	RCT	ICH	Stereotactic	4	Medication	11	35	30	44%	0	3-month BI	0	3
Vespa et al. (20)	2009–2012	RCT	ICH	Endoscopy	14	Medical	39	38	40	25	3	30-day mortality	2	9
Vespa et al. (20)	2009–2012	RCT	ICH	Surgery	13	Medical	26	38	40	25	3	1-year mortality	15%	40%
Teernstra et al. (21)	1996–1999	RCT	ICH	Surgery	36	Non-surgery	34	66	52	17.9	7	180-day mRS	20	20
Yang et al. (22)	2012–2014	RCT	ICH	MIS	78	Craniotomy	78	–	–	45	75	12^{th} week BI	3	19
Feng et al. (23)	2006–2013	RCT	ICH	Keyhole	93	Craniotomy	91	–	–	–	–	6-month ADL	6	8
Sun et al. (16)	2015–2016	Cohort	ICH	Keyhole	46	Craniotomy	43	–	–	95%	82%	6-month mortality	4.3%	4.7%

RCT, randomized controlled trial; ICH, intracerebral hemorrhage; MIS, minimally invasive surgery; mRS, modified Rankin scale; BI, Barthel index; rtPA, recombinant tissue plasminogen activator; ADL, activity of daily living.

Comparisons Between the MIS and Control Groups for Mortality and Rebleeding Morbidity

In 12 RCTs (8, 13–23) involving 2,100 patients, the MIS group had decreased the short-term or long-term mortality (OR = 0.62, 95% CI 0.45–0.85; $I^2 = 30\%$, $P = 0.15$) compared to the control group (i.e., medication or open surgery). This suggests that MIS can effectively reduce the postoperative death rate (see **Figure 2**). For rebleeding after the treatment, we included five RCTs (Sun H, Teernstra O, Wang W, Hanley D, and Vespa P) into the analysis and found no significant differences between the MIS and the control groups (OR = 1.86, 95% CI 0.47–7.36; $I^2 = 78\%$, $P = 0.001$, see **Supplementary Figure 5**). We then removed the data from Vespa, which probably caused heterogeneity from the original analysis, performed the statistical analysis again (not shown), and found that the heterogeneity of the data did not decrease significantly ($I^2 = 83\%$, $P = 0.004$; OR = 1.93, 95% CI 0.42–8.91), which suggests that the determining factor leading to heterogeneity is not the presence or the absence of the study by Vespa but, probably, the different internal designs of each study.

Subgroup Analysis Between the MIS and the Control Groups for Long-Term Mortality

In five RCTs involving 974 patients, the MIS group had decreased the long-term (6-month or 1-year) mortality (OR = 0.67, 95% CI 0.46–0.98; $I^2 = 32\%$, $P = 0.20$) compared to the control group (i.e., medication or open surgery). This suggests that MIS can effectively reduce the long-term postoperative death rate (see **Figure 3**).

Subgroup Analysis Between the MIS and Control Groups for Short-Term Mortality

In eight RCTs involving 1,126 patients (**Figure 3**), the MIS group had decreased the short-term (3-month) mortality (OR = 0.58, 95% CI 0.42–0.80; $I^2 = 37\%$, $P = 0.14$) compared to the control group (i.e., medication or open surgery). This suggests that MIS can effectively reduce the short-term postoperative death rate. Thus, MIS is beneficial for both long-term and short-term prognoses.

Comparisons Between the MIS and Control Groups for Hematoma Evacuation

As most studies did not report hematoma clearance rates, this comparison is limited to the data reported in five studies. In these five RCTs involving 404 patients, the MIS group had no significant effect on mortality compared to the control group (OR = 0.36, 95% CI 0.06–2.13; $I^2 = 91\%$, $p < 0.00001$) as shown in **Figure 4**.

Subgroup Analysis Between the MIS and Craniotomy Groups for Mortality

We divided the control group into two subgroups: one for patients undergoing craniotomy and one for those treated with conventional drugs. We analyzed the two subgroups separately. In five RCTs involving 1,139 patients, the MIS group had insignificantly decreased the short-term or long-term mortality compared to open craniotomy as shown in **Figure 5**. The OR was 0.68 (95% CI 0.48–0.98) with large heterogeneity ($I^2 = 59\%$, $P = 0.04$).

Subgroup Analysis Between the MIS and Medication Groups for Mortality

In eight RCTs involving 961 patients, the MIS group had decreased the short-term or long-term mortality compared to conservative medication (OR = 0.57, 95% CI 0.41–0.79; $I^2 = 0\%$, $P = 0.49$), as shown in **Figure 5**.

Publication Bias and Egger's Test

Egger's test results for mortality between the MIS and the control groups ($z = -0.4950$, $P = 0.6206$) in the general population suggested that the publication bias across the included studies was unlikely.

DISCUSSION

In this systematic review and meta-analysis, we have incorporated recent data to reevaluate the total effect of MIS in treating ICH, as well as the effect on mortality by using the MIS techniques, including endoscopic surgery and stereotactic thrombolysis. We found that MIS techniques have independently decreased the rate of death at the short-term follow-up. In addition, we performed subgroup analyses focusing on different control groups, demonstrating that MIS techniques is potentially beneficial compared with conservative medication and open craniotomy. However, another subgroup analysis focusing on different follow-up durations demonstrated that MIS techniques seem beneficial at the 3-month follow-up and at the 6-month or 1-year follow-up.

Study design, including the primary and secondary outcome measures and the subgroup analyses, were modeled after previous meta-analyses on this topic, as performed by Prasad, Zhou et al. (11), and Scaggiante et al. (10) to permit several comparisons, including the comparison of MIS and conventional surgical efficacy, comparisons between different populations, Glasgow coma scale (GCS) scores, and different hematoma volumes. Previous studies have demonstrated that "patients with supratentorial ICH may benefit more from MIS than other treatment options. The most likely candidates to benefit from MIS are both sexes, those aged between 30 and 80 years with superficial hematoma, a GCS score of $\geq$ 9, hematoma volume between 25 and 40 ml, and MIS performed within 72 h after the onset of symptoms" (11), and "endoscopic surgery and stereotactic thrombolysis seemed to independently decrease the rate of moderate to severe functional impairment and death at the long-term follow-up" (10). The main aim of this study was to investigate the relationship between MIS techniques on the short-term, long-term, and overall prognosis of patients with ICH, as well as to observe the effect of MIS vs. massively invasive surgery, and MIS vs. conventional drug treatment on the overall prognosis.

The effect of MIS and craniotomy on overall prognosis (mortality) was not statistically significant, meaning that the size of the surgical trauma did not determine the mortality of

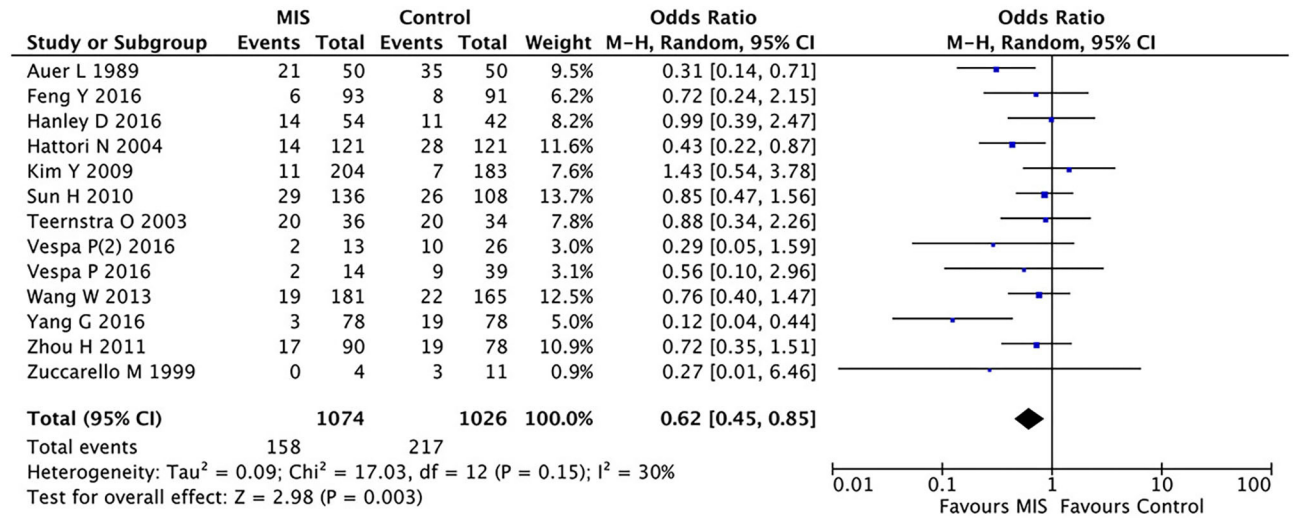

FIGURE 2 | A forest plot of the minimally invasive surgery and control groups for overall mortality.

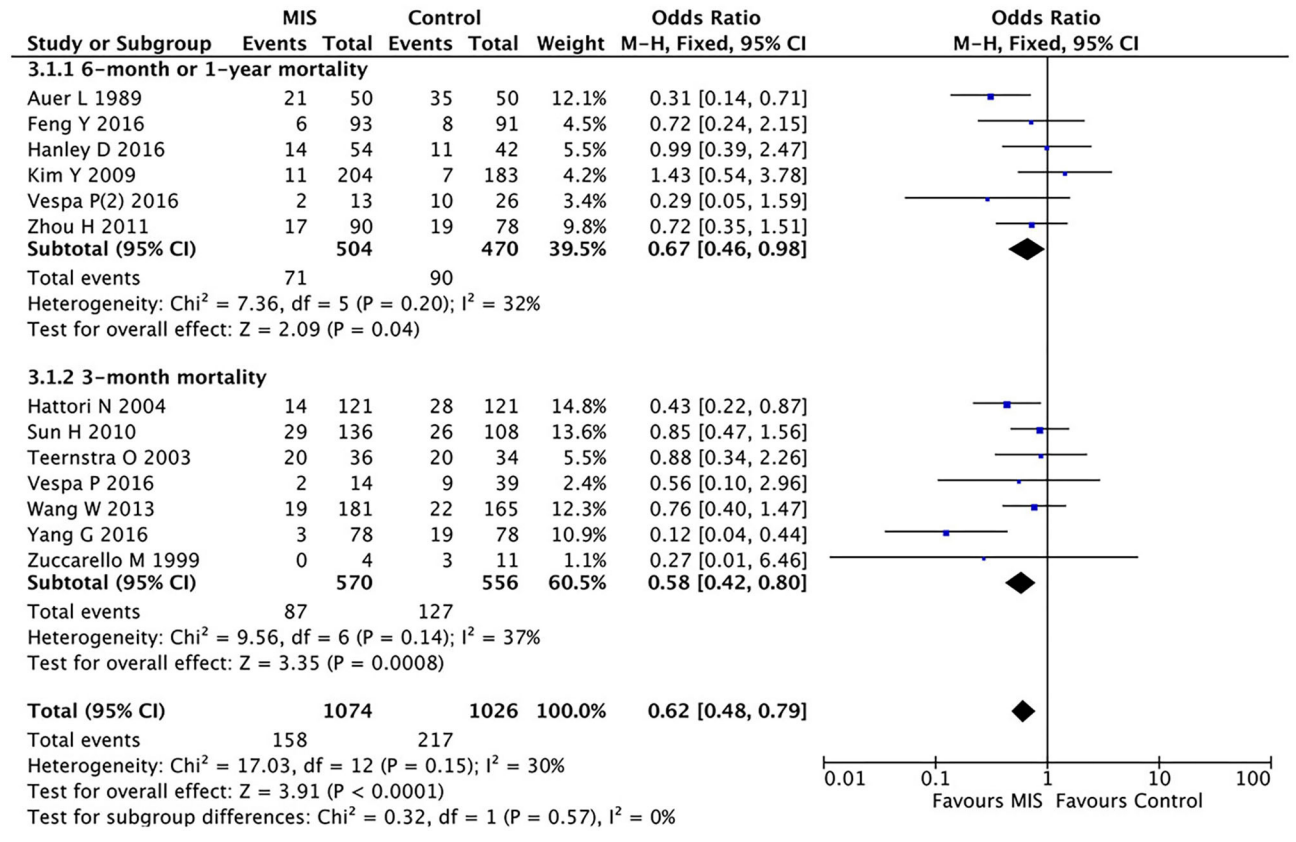

FIGURE 3 | A forest plot of the subgroup analysis of the minimally invasive surgery and control groups for long-term (6-month or 1-year) and short-term (3-month) mortality.

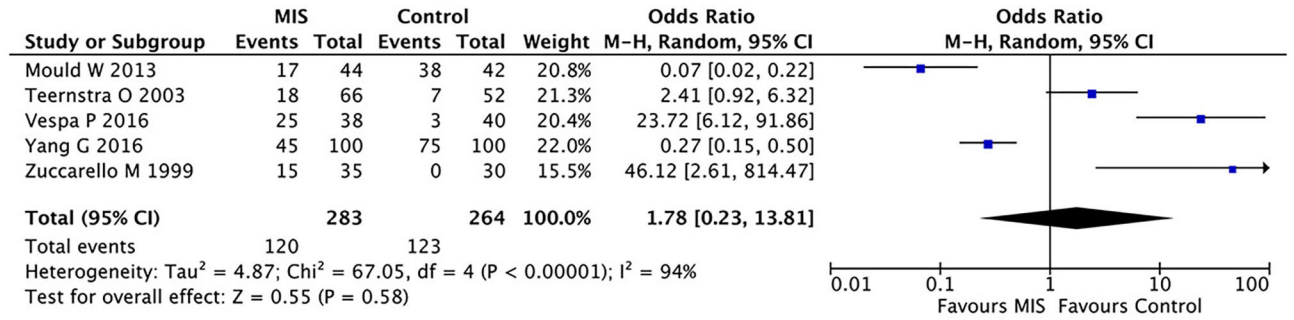

FIGURE 4 | A forest plot of the hematoma evacuation rate.

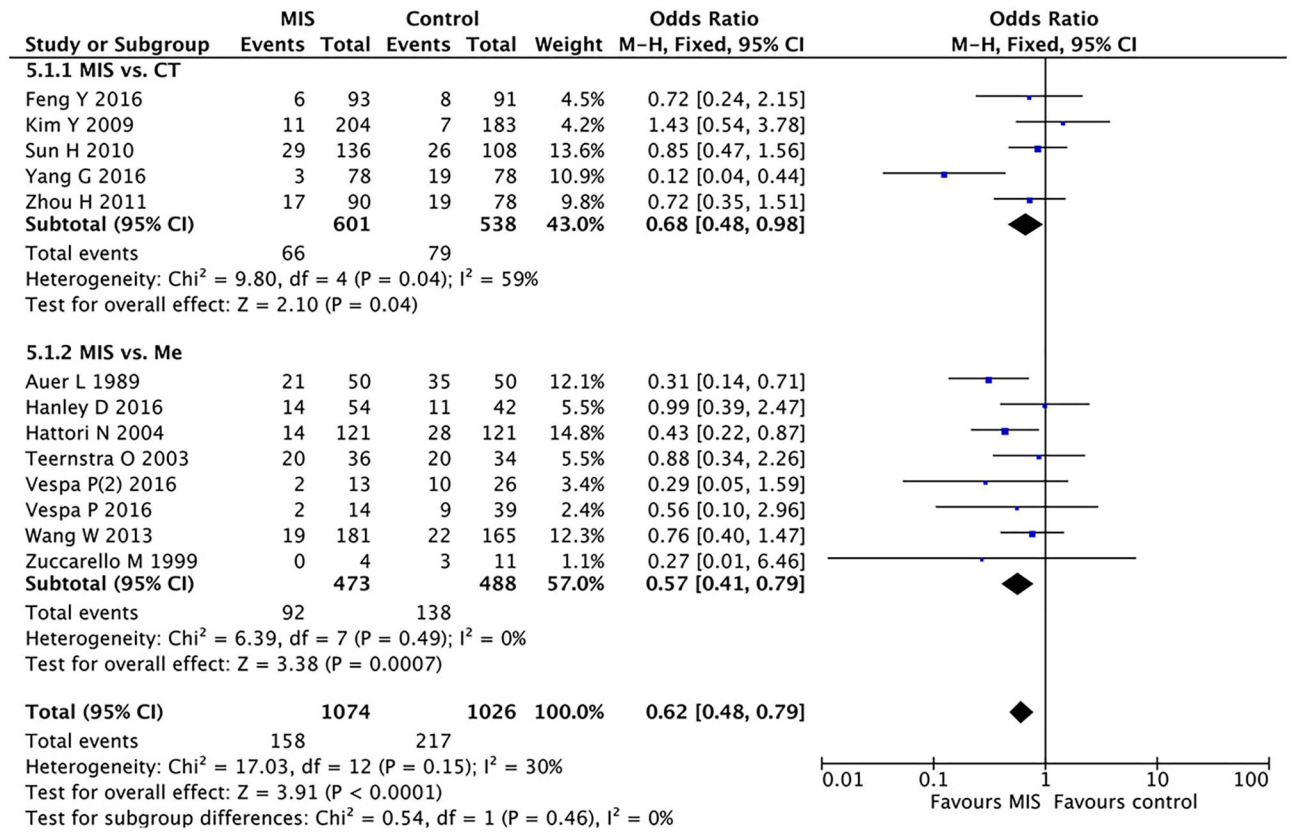

FIGURE 5 | A forest plot of the subgroup analysis of the minimally invasive surgery (MIS) and craniotomy and MIS and medication groups for overall mortality.

the patient, a point that has rarely been studied. However, MIS reduces overall mortality in patients with ICH compared with massively invasive surgery, suggesting that MIS has advantages. Hanley et al. (8) studied the postoperative complications in patients with ICH and found that the combination of the MIS and a thrombolytic drug therapy was not effective in reducing the risk of postoperative infection and rebleeding when compared with standard drug therapy. In addition, Mendelow et al. (6) studied the age, GCS score, size, and location of the hematoma before surgery and found no advantage of an early massively invasive surgery over conventional drug therapy in these areas. Zhou et al. found the superiority of MIS techniques in the abovementioned areas to improve the prognosis of the patient (11). Advanced age (>80 years), low GCS score, and hematoma volume > 30 ml are all key factors that exacerbate the prognosis of patients with ICH (1).

Our results also suggest that MIS effectively reduces mortality at 6-month or 1-year follow-up when compared with non-MIS treatment, and it was also effective in reducing the mortality at a 3-month follow-up. This suggests that MIS mainly affects

the short-term and long-term prognosis of patients. Owing to the lack of sufficient data, no statistical significance was found when comparing the MIS technique with debridement surgery in terms of hematoma clearance rates. Our study illustrates, to some extent, the impact of MIS on the prognosis of patients with ICH, mainly affecting the short-term prognosis, and that this impact of MIS on prognosis may be accomplished by selecting the appropriate population for treatment.

Meta-analyses are classically limited by the heterogeneity of the inclusion and exclusion criteria of the examined studies, as well as the variability of the outcome measures. In these studies, the evaluations of death varied, such as in Zhang et al. in which death was defined as a modified Rankin Scale score of 6, and in Yang and Shao (22) in which functional outcomes were defined using the Barthel Index. In certain cases, the outcomes for both primary and secondary outcomes were not available. Therefore, the conclusions of this meta-analysis are limited by the quality and the heterogeneity of the data. Although not perfectly homogenous, many studies permit quantitative analyses that may inform future trial design and clinical practice.

CONCLUSIONS

We found that MIS techniques independently decreased the death rate at short-term and long-term follow-ups. In addition, we performed subgroup analyses, demonstrating that MIS techniques seem beneficial compared with conservative medication.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

QD, DW, and YT designed this project and proofread and reviewed the manuscript. DH and YL reviewed the articles and collected data. DH, DW, and YT analyzed data. DH drafted the manuscript and polished the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.789757/full#supplementary-material

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Surgical vs. Conservative Management for Lobar Intracerebral Hemorrhage, a Meta-Analysis of Randomized Controlled Trials

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Background: Outcomes regarding the conventional surgical and conservative treatment for the lobar intracerebral hemorrhage (ICH) have not been previously compared. The current meta-analysis was designed to review and compile the evidence regarding the management of patients with lobar intracerebral hemorrhage.

Methods: Online electronic databases, including PubMed, Embase, Medline, Cochrane Library, and Google Scholar, were searched for randomized controlled trials (RCTs). Studies were selected on the basis of the inclusion and exclusion criteria. Trials with CT-confirmed lobar intracerebral hemorrhage patients of which treatment regimen was started within 72 h following the stroke were included. Low quality trials were excluded. Death or dependence was defined as primary outcome and death at the end of the follow up was the secondary outcome.

Results: One hundred five RCTs were screened and 96 articles were excluded on the basis of abstract. Nine articles were assessed for the eligibility and 7 trials were included that involved 1,102 patients. The Odds ratio (OR) for the primary outcome was 0.80 (95% CI, 0.62–1.04, $p = 0.09$) and for the secondary outcome was 0.79 (95%CI, 0.60–1.03, $p = 0.09$).

Conclusion: Our findings suggested that surgical treatments did not significantly improve the functional outcome as compared with the conservative medical management for patients with lobar ICH.

Keywords: intracerebral hemorrhage, surgical management, conservative management, randomized controlled trial, meta-analysis

INTRODUCTION

Stroke is a major public health concern contributing 10% to all deaths worldwide and 5% loss to disability-adjusted life-years (1). Stroke accounts for high levels of morbidity and mortality even in treated patients (2). Intracerebral hemorrhage (ICH) causes more loss to disability-adjusted life-years than ischemic stroke (3). Stroke is the second most prevalent cause of death in China, contributing one-third of total deaths worldwide (4, 5). As one of the fatal types of stroke,

spontaneous intracerebral hemorrhage (ICH) has an incidence of 24.6 per 100,000 person-years and mortality rate of 40% at 1 month in adults (6). The incidence of ICH varies among populations (7). Cerebral amyloid angiopathy (CAA) associated vasculopathies lead to lobar intracerebral hemorrhage—a subtype of intracranial hemorrhage (8). CAA is the second most common cause leading to ICH following hypertension. The incidence of CAA-related lobar ICH in elderly has been increasing (8–10). About two-third of cases of spontaneous ICH are deep ICH, and lobar ICH accounts for the remaining one-third. Lobar ICH involves the cortical and subcortical areas, and follows a lobar pattern across one or multiple brain lobes (10). The rate of recurrence in lobar hemorrhagic patients is as high as 4% per patient-year (11).

The management techniques for ICH have remained controversial. Many studies have compared the surgical procedures, including minimally invasive surgery, endoscopic surgery, stereotactic aspiration, keyhole surgery, craniotomy, and craniopuncture with conservative medical management for ICH (12). Wang et al. reported that minimally invasive surgery (MIS) had improved functional outcomes compared to the conservative medical management for patients with intracerebral hemorrhage (13). Contrary to the above findings, the results of two research studies have shown that MIS had no advantage over medical management (14, 15). Moreover, another study explored that MIS procedure had significantly better results for ICH than other procedures like open surgery and conservative medical management (16). Minimally invasive procedures have evolved into different novel surgical techniques for Intracerebral hemorrhage (13, 16–19).

Image guided MIS plus alteplase in intracerebral hemorrhage evacuation (MISTIE II) procedure seems safe in patients with ICH, but with cautionary findings of increased asymptomatic bleeding (20). MISTIE III trials showed that MIS procedure was safe in patients with ICH, but showed no improvement in the functional outcome for moderate to large ICH compared to standard medical care (21).

In recent years, many treatment techniques, including stereotactic aspiration, MIS, endoscopic surgery, and craniotomy have been widely used for ICH treatment. The purpose of this study was to pool all the randomized controlled trials (RCTs) determining the effects of surgical and conservative management for the patients with lobar ICH. The literature does not highlight any definite technique, and explicitly focuses on lobar intracerebral hemorrhage. These results may help clinicians to choose evidence-based treatment for lobar ICH.

METHODS

Data Extraction and Search Strategy

A literature search was performed on the electronic databases, including PubMed, Embase, Medline, Cochrane Library, and Google Scholar from 1980 to 2020. The combination of the following keywords was used to locate the related research articles: "surgery" or "craniotomy" or "minimally invasive procedure" or "endoscopic" and "conservative" or "medical management" or "non-surgical" and "lobar hemorrhage" or "intracerebral hemorrhage" or "supratentorial" or "subcortical" or "hematoma." Searched studies were selected based on the inclusion and exclusion criteria (**Supplementary Table 1**).

Eligibility Criteria

The inclusion criteria for the studies were as follows: (1) CT- or MRI-confirmed diagnosis of patients with lobar intracerebral hemorrhage, (2) treatment regimen of the patients was started within 72 h following the stroke, (3) RCTs comparing the surgical treatment with the conservative medical management, and (4) age $\geq$ 18 years. Exclusion criteria were as follows: (1) intracerebral hemorrhage caused by ruptured aneurysms, arteriovenous malformation (AVM), vascular anomaly, brain tumors, traumatic brain injury, or coagulopathy; and (2) studies who included patients with infratentorial hemorrhage.

Types of Intervention

The interventions used for the treatment purpose comprised the surgical treatment (endoscopic surgery, open craniotomy, stereotactic aspiration, and endoscopic surgery + stereotactic aspiration) and conservative management (pharmacological, non-surgical). Decision regarding the inclusion of the studies was made independently by the authors.

Main Measurements Examined

Reported data showed that studies utilized different outcome measures in order to determine the results. The mainly used outcome measures were Glasgow Outcome Scale (GOS), The Barthel Index, and The Modified Rankin Scale (14, 22–27). An unfavorable outcome was considered as a primary outcome in the current study. Vegetative state or death and severe disability according to the GOS reflected unfavorable outcomes. In the absence of the GOS, the modified Rankin scale equal to or greater than 3 ($\geq$3) or a Barthel index score of 90 represented the unfavorable outcome. Whereas, in the Surgical Treatment for Ischemic Heart Failure (STICH) and STITCH II studies, Extended Glasgow Outcome Scale (GOSE) was used to determine the level of independence of the patients (25, 26). Being independent in performing activities outside the home was considered a favorable outcome. The prognostic score for these studies was calculated by the "10 × GCS – Age - 0.64 × Volume," giving a cutoff value of 27.672 to divide the outcome in favorable and unfavorable.

Quality and Risk of Bias Assessment

Quality of the studies was assessed using the Cochrane criteria, comprising four aspects, namely, (1) random sequence generation, (2) allocation concealment, (3) blinding of outcome assessment, and (4) incomplete outcome data reported. The first three points were scored as "No = 0, Unclear = 1, Yes = 2" and the fourth was scored as "No = 0, Yes = 1." All the studies with a score >2 were included in the data synthesis and the rest were regarded as low-quality studies. All the studies were sorted based upon inclusion and exclusion criteria and assessed for quality by the authors. Statistical analysis was performed using RevMan5 Software. Fixed effects meta-analysis was used to pool the events rate across the studies. Funnel plot

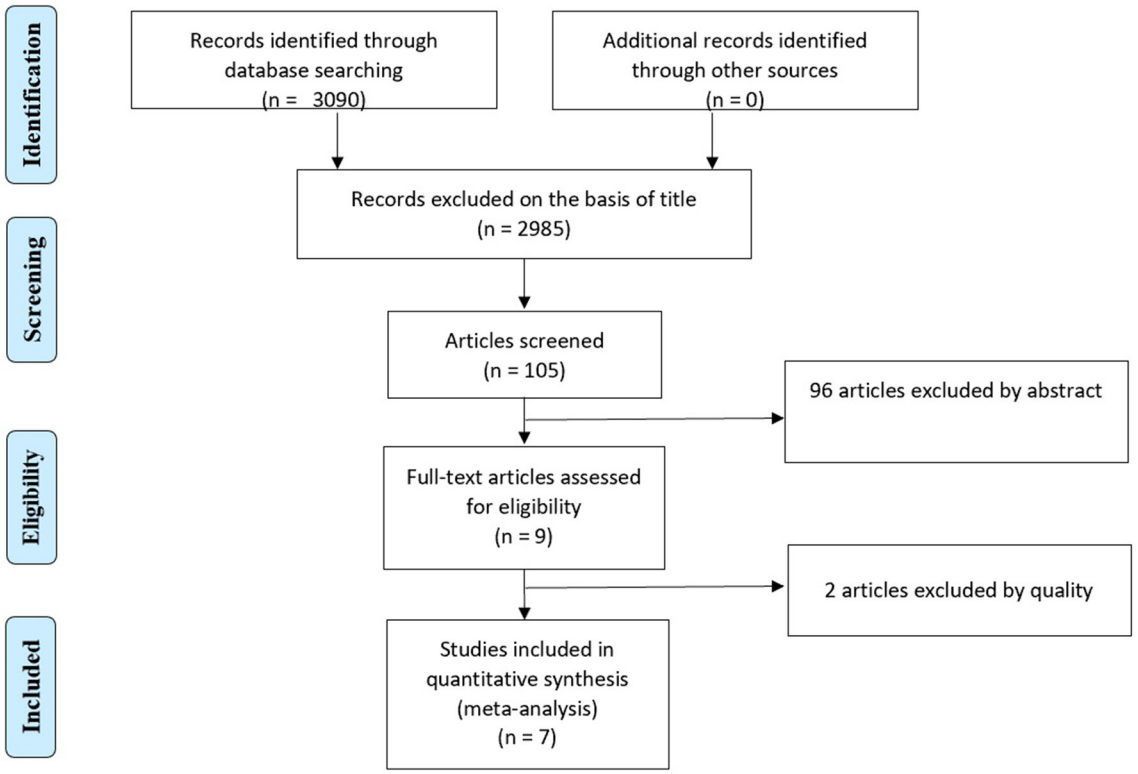

FIGURE 1 | PRISMA Flow chart of study selection.

was used to indicate the presence of specific publication bias (**Supplementary Figure 1**). I^2 statistics was used to determine the heterogeneity of the studies. Risk of bias summary of the study was analyzed (**Supplementary Figure 2**).

RESULTS

Study Selection

There were 3,090 studies initially retrieved. Two thousand nine hundred eighty-five studies were excluded on the basis of dissimilarity in the title. The remaining 105 studies were screened in total, out of which, 96 studies were excluded on the basis of abstract. Nine remaining articles were assessed for the quality based upon the Cochrane eligibility criteria. As a cut off score of <2 was a set point value for the low-quality study, 2 studies were excluded on quality basis. Thus, seven trials were considered eligible for the inclusion in the study (**Figure 1**).

Main Outcomes Description

Among seven studies comparing the surgical treatment with the conservative management for lobar ICH, three studies involved endoscopic surgery and stereotactic aspiration, two studies involved the open craniotomy, one study endoscopic surgery, and another study involved only stereotactic aspiration. The other treatment group in seven studies received the conservative medical management.

Table 1 shows the details of included studies, treatment protocols, timing of the surgery, and the quality of the studies. The clinical characteristics and outcomes of included studies are described in **Table 2**. The total number of the patients with lobar ICH was 1,102. Among them, 552 were in the surgical group and 550 in the conservative group. All the studies provided data regarding death or dependence at the end of the follow up (**Figure 2**). Mendelow et al. included the maximum number of the patients as compared to other studies. The overall results showed a non-significant trend toward better prognosis in the surgical group (OR 0.80, 95% CI 0.62–1.04; $p = 0.09$).

Secondary outcome was recorded for 410 patients with lobar intracerebral hemorrhage. Auer and Mendelow contributed the most cases of the patients, 45 and 38, respectively, to the meta-analysis. No significant difference (OR 0.79, 95% CI 0.60–1.03, $p = 0.09$) was observed in the secondary outcome between surgical and conservative medical management group.

DISCUSSION

The current meta-analysis included seven articles without any conflict or controversial findings. It was intended to determine the best possible effects of two treatments, surgical and conservative, for lobar patients with ICH. The management for intracerebral hemorrhage has remained controversial and depends greatly on the patient and baseline clinical

TABLE 1 | Baseline summary of included studies.

Trials	Treatments		Surgery timings	Quality of literature				
				Randomized generation	Outcome blinding	Incomplete data	Allocation concealment	Total
Ludwig M. Auer	Endoscopic surgery	Conservative medical	<48	1	0	1	0	2
Seppo Juvela	Open craniotomy	Conservative medical	<24	2	0	1	0	3
L. B.Morgenstern	Open craniotomy	Conservative medical	<12	2	1	1	2	6
Zuccarello	Stereotactic aspiration	Conservative	<24	2	0	1	2	5
O. P. M.Teernstra	Stereotactic aspiration	Conservative medical	<72	2	0	1	2	5
Mendelow	Endoscopic surgery + Stereotactic aspiration	Conservative medical	<24	2	2	1	2	7
A. David Mendelow	Endoscopic surgery + Stereotactic aspiration	Conservative medical	<48	2	2	1	2	7

TABLE 2 | Main characteristics and outcomes of included studies.

References	No. of ICH cases	SG	CG	Lobar SG	Lobar CG	Total lobar cases	Lobar hematoma %	Primary outcome	Secondary outcome
Auer et al. (14)	100	50	50	24	21	45	45	6 mo. Outcome (11/24:15/21)	6 mo. Death (8/21:12/18)
Juvela et al. (22)	52	26	26	5	3	8	15	6 mo. Outcome (4/5:0/3)	6 mo. Death (3/3:0/3)
Morgenstern et al. (27)	34	17	17	1	7	8	24	6 mo. Outcome (1/1:5/7)	NR
Zuccarello et al. (23)	20	9	11	5	5	10	50	3 mo.BI (3/5:2/5)	3 mo. Death (1/3:1/3)
Teernstra et al. (24)	70	36	34	24	14	38	54	6 mo. mRS (22/24:11/14)	6 mo. Death (15/16:7/9)
Mendelow et al. (25)	1,033	503	530	196	214	410	40	6 mo. BI (121/181:146/195)	6 mo. Death (66/112:90/128)
Mendelow et al. (26)	601	307	294	297	286	583	97	6 mo. Outcome (190/297:194/286)	6 mo. death (174/297:178/286)
Total	1,910	948	962	552	550	1,102	58		

SG, surgical group; CG, conservative group; NR, not reported.

characteristics, including GCS score, volume, and location of the hematoma. The results of current meta-analysis were consistent with the included researches and showed no significant differences between surgical and conservative medical management of the patients with lobar ICH.

A limited number of randomized controlled trials have focused on the management of lobar intracerebral hemorrhage. Mendelow et al. performed the trials focusing the lobar intracerebral hemorrhage management. STICH AND STITCH II have demonstrated the treatment priorities, considering the surgical or conservative treatments in detail, and the studies stated no significant differences between the percentage of favorable outcomes in the conservative and medical management groups (25, 26). The remaining data included in our study is extracted from literature that included other sub-types of hematoma, including thalamic, basal ganglia, and putaminal.

Patients involving only lobar hematoma were considered and outcomes were analyzed for patients with lobar intracerebral hemorrhage (14, 22–24, 27). Moreover, the specific data, including GCS score, volume of hematoma, and age of the

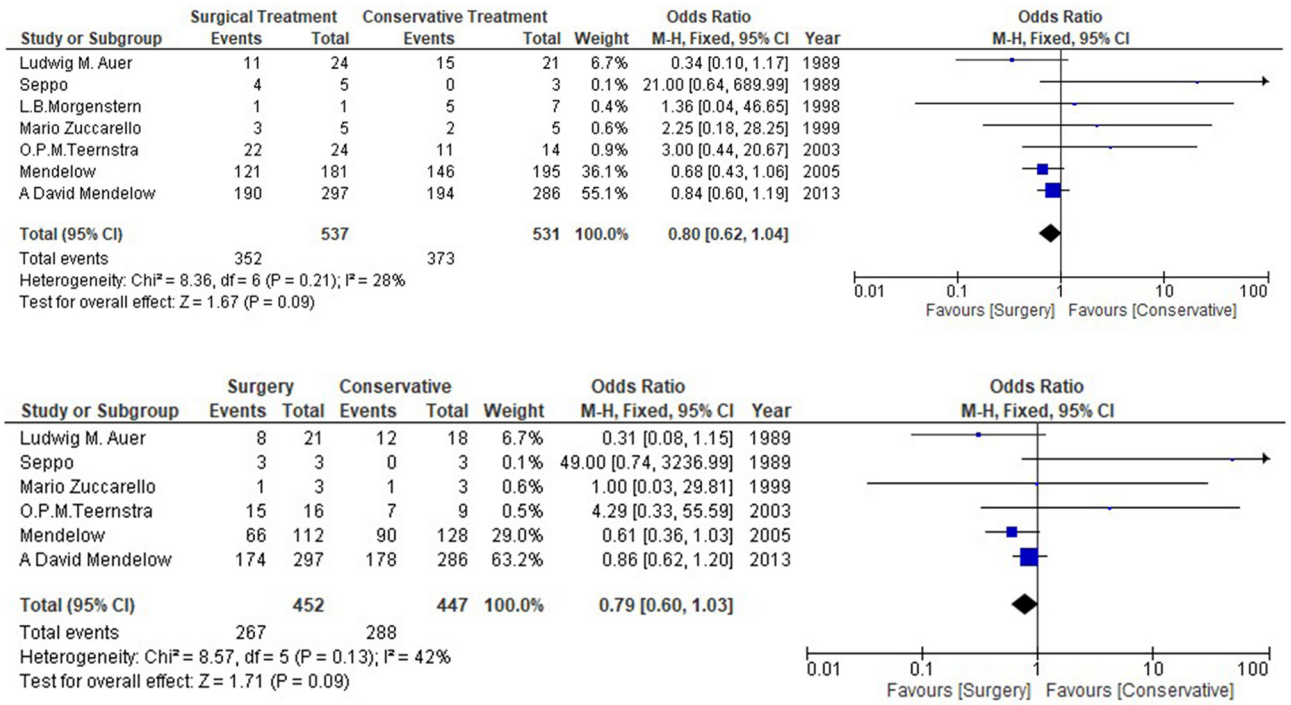

FIGURE 2 | Overall analysis of surgical vs. conservative medical management.

patients, was lacking for the patients with lobar intracerebral hemorrhage. Most of the studies have described overall GCS scores and hematoma volume for intracerebral hemorrhage (14, 22, 27). Surgical evacuation failure in ICH has attributed to the high levels of morbidity related to surgical techniques (28).

The current meta-analysis showed lower heterogeneity ($p = 0.09$, $I^2 = 28\%$) for the primary outcome and it was higher for the secondary outcome ($p = 0.09$, $I^2 = 42\%$) (**Figure 2**). Prognosis-based outcome analysis indicated that there was no significant evidence that supports surgical method has better outcome comparing with conservative medical management in patients with lobar intracerebral hemorrhage. STITCH II trial has suggested that conscious patients with lobar hematomas have greater survival advantage when the prognosis is poor (Glasgow Coma Scale Score 9-12) and patients are assigned randomly within 21 h (26). This marginal benefit is lost when the patients have better prognosis because they are mostly operated when the condition is deteriorated. RCTs, except the STITCH II trials, have not reported the specific GCS score for lobar intracerebral hemorrhagic patients. Thus, the results can differ if the GCS is known for the other studies.

The results may also change if open surgery and minimally invasive surgery are separately considered, but the lack of effect of surgical treatment is the consequence of surgery being beneficial in some patients while not in others. Moreover, the minimally invasive techniques may be beneficial for intraventricular hemorrhages and deep clots, which require more trials.

Other surgical approaches, including craniectomy and minimally invasive surgery with thrombolysis in ICH evacuation comparing with the conservative management for the lobar intracerebral hemorrhage, should be investigated. The included studies have used different statistical approaches so the analysis have been done with caution.

CONCLUSION

Our study suggested that there was no significant difference between the surgical and the conservative medical treatment for patients with lobar ICH. Future trials with larger sample sizes and standardized procedures are needed to determine the treatment effect of minimal invasive surgery in lobar ICH.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

QL and MA contributed to the study concept and design. MA contributed in the statistical analysis. MA, RZ, and QL contributed to the drafting of the manuscript. QL, MA, PX, and L-BZ contributed to the critical revision of the manuscript

for important intellectual content. QL obtained funding. QL, PX, and L-BZ contributed to the study supervision. All authors contributed to the acquisition of data, analysis, and interpretation of data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.742959/full#supplementary-material

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Prognosis and Predictors of Symptomatic Intracranial Hemorrhage After Endovascular Treatment of Large Vessel Occlusion Stroke

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Background: Symptomatic intracranial hemorrhage (sICH) is a devastating complication of endovascular treatment (EVT) in patients with acute ischemic stroke (AIS) and is associated with high risk of disability and mortality. This study intended to evaluate the predictors of sICH after EVT in patients with large vessel occlusion (LVO)-induced AIS.

Methods: We conducted a retrospective review on consecutive AIS patients who underwent EVT in our University hospital between January 2019 and August 2020. The patients were classified into two groups based upon the occurrence of sICH. The main outcomes were the occurrence of sICH using the Heidelberg Bleeding Classification and functional condition at 90 days. Multivariate logistic regression analysis and receiver operating characteristics (ROC) curves were used to identify independent predictors of sICH after EVT.

Results: Three hundred and 69 patients were enrolled in the study, of which 16.8% ($n = 62$) developed sICH. Favorable neurological outcome was lower in patients with sICH than in patients without sICH (6.5 vs. 43.3%; $P < 0.001$), with the overall mortality being 112 (30.4%) at 90 days post- EVT. Results from univariate analysis showed significant differences between the two groups in the prevalence of diabetes, initial Alberta Stroke Program Early CT Score (ASPECTS) score, National Institutes of Health Stroke Scale (NIHSS) score after operation, the levels of fasting blood glucose (FBG), neutrophil to lymphocyte ratio (NLR), platelets (PLT), and thrombin time (TT) at admission. Multivariate logistic regression analysis showed that FBG $\geq$ 7.54 mmol/L (OR: 2.765; 95% confidence interval [CI]: 1.513–5.054), NLR $\geq$ 5.48 (OR: 2.711; 95% CI: 1.433–5.128), TT at admission $\geq$ 16.25 s (OR: 2.022; 95% CI: 1.115–3.667), and NIHSS score within 24 h after the operation $\geq$ 10 (OR: 3.728; 95% CI: 1.516–9.170) were independent predictors of sICH. The combination of NLR $\geq$ 5.48, FBG $\geq$ 7.54 mmol/L, TT at admission $\geq$ 16.25 s, and NIHSS score within 24 h after the operation $\geq$ 10 generated an optimal prediction model (AUC: 0.723).

Conclusion: Higher levels of FDG, NLR, TT at admission, and NIHSS score after operation were associated with sICH after EVT in patients with LVO-induced AIS.

Keywords: acute ischemic stroke, large vessel occlusion, endovascular treatment, symptomatic intracranial hemorrhage, predictors

INTRODUCTION

Stroke is the second and the third most common cause of death and disability, respectively, globally (1). Acute ischemic stroke (AIS) arises from large vessel occlusion (LVO) has serious effects on the survival and quality of life of patients since it is associated with high risks of disability and mortality. Currently, reperfusion therapies are the most effective therapeutic strategies for AIS (2). Endovascular treatment (EVT) with or without intravenous thrombolysis (IVT) has become the standard of care for AIS caused by anterior circulation large-vessel occlusions based on findings from several randomized controlled trials (3–7).

Despite the success associated with endovascular treatment, complications of EVT such as symptomatic intracranial hemorrhage (sICH) can reduce the benefit-risk ratio of the treatment (8). However, there is limited data available regarding the predictors and clinical relevance of sICH after EVT in patients with LVO-induced AIS. In addition, the reported risk factors vary by country and region. Therefore, it is of great significance to identify the risk factors for sICH after EVT for the prevention of sICH and the improvement of the efficacy of this new treatment strategy.

The propose of our study was to identify the potential predictors of sICH after EVT in individuals with LVO-induced AIS by analyzing clinical data collected from our center. This will help guide the development of appropriate management strategies against the sICH.

SUBJECTS AND METHODS

Patients

We conducted a single-center retrospective cohort study of patients who were treated with EVT for AIS between January 1, 2019, and August 3, 2020, at Xuanwu Hospital of Capital Medical University, China.

Patients were included in the study if (1) patients were diagnosed with AIS; (2) large vessel occlusion (LVO) was identified as the cause of AIS using computed tomography angiography (CTA), brain magnetic resonance angiography (MRA), and/or cerebral digital subtraction angiography (DSA); (3) they received endovascular recanalization therapy (including intra-arterial thrombolysis, mechanical thrombectomy with or without stenting).

Exclusion criteria: patients (1) had no follow-up brain imaging (Computed tomography or Magnetic resonance imaging) at 24 h or when neurological deterioration occurred; (2) only received DSA without further treatment; and (3) had no modified Rankin Scale (mRS) at 3 months.

Clinical Data Collection

The electronic medical records were reviewed and analyzed for data such as baseline demographic data (age and gender), Body Mass Index (BMI), vascular risk factors (smoking, drinking, hypertension, hyperlipidemia, diabetes, atrial fibrillation, previous stroke, and coronary heart disease), blood pressure at admission (systolic and diastolic), pre-stroke mRS, stroke severity, stroke subtype, radiographic features [Alberta Stroke Program Early CT Score (ASPECTS), the site of the occluded arteries], and information concerning EVT (procedure process time, treatment methods and recanalization). Additional data that was analysed include Fasting blood glucose (FBG), white blood cell (WBC), platelets (PLT), thrombin time (TT), neutrophil to lymphocyte ratio (NLR), albumin, total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL). NLR was defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count.

The stroke severity of the patients at admission was estimated using the National Institutes of Health Stroke Scale (NIHSS). The stroke subtype was classified according to Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria (9). The site of the occluded arteries was identified using CTA, MRA, and/or cerebral DSA reports, and included internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), vertebral artery (VA), and basilar artery (BA). Anterior circulation lesions were defined using ASPECTS and posterior circulation lesions were evaluated using pc-ASPECTS.

The procedure process time involved symptom onset-to-door time (OTD), door-to-groin puncture time (DTP), and puncture-to-final recanalization time (PTR). Patients in our study received endovascular treatment, which included intra-arterial thrombolysis, thrombectomy with stent retrievers, thromboaspiration, intracranial angioplasty and stent implantation, or a combination of these approaches at the discretion of the treatment surgeon.

Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3 (10). The modified Rankin scale (mRS) was conducted at 3 months by a stroke neurologist during a scheduled post-stroke follow-up visit, or *via* a phone interview. Functional outcome was evaluated according to mRS as complete recovery (mRS = 0–1); partial recovery, independent (mRS = 2); dependent (mRS = 3–5); and death (mRS = 6). Favorable and unfavorable outcomes were defined as mRS of 0–2 and > 2 (3–6), respectively.

Evaluation of sICH

Symptomatic Intracranial Hemorrhage (sICH) was classified based on the Heidelberg Bleeding Classification (11). The diagnosis of sICH was based on the association of ICH with any of the following conditions: (1) Increase in NIHSS score

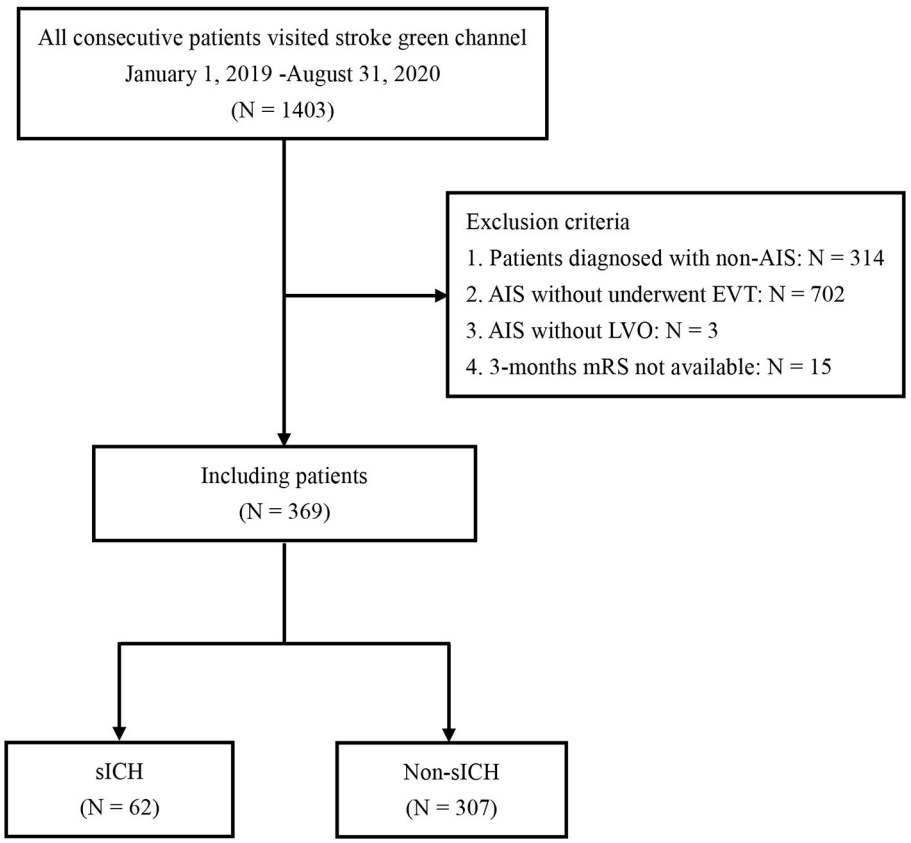

FIGURE 1 | Flowchart of patient selection. AIS, acute ischemic stroke; LVO, large vessel occlusion; EVT, endovascular treatment; sICH, symptomatic intracranial hemorrhage.

by >4 points compared to the score before ICH; (2) Increase in NIHSS score by >2 points in one category; (3) deterioration leading to intubation, hemicraniectomy, external ventricular drain placement, or any other major interventions. It is also necessary that the symptom deteriorations cannot be explained by causes other than the observed ICH (11). For hemorrhage classified as parenchymal hematoma 2 (PH 2, hematoma occupied ≥ 30% of the infarct volume, with an obvious mass effect), even if the neurological function deteriorations could be attributed to infarction, the hemorrhage would be defined as sICH.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 25.0 software (IBM, Armonk, NY, USA). Baseline characteristics were compared between patients with sICH and patients without sICH. Continuous variables are shown as medians (interquartile ranges, IQRs) according to the type of non-normal distribution, while categorical variables are presented as frequencies (percentages). Mann-Whitney *U* tests were used for continuous variables, and χ^2 tests or Fisher exact tests were adopted for categorical variables. For the functional outcome, an ordinal logistic regression analysis was performed to evaluate the effect of sICH across the entire range of mRS scores. Then, we used the binary logistic regression analysis to evaluate independent predictors for sICH, with the adjusted ORs and corresponding 95% CIs being reported. Receiver operating characteristic (ROC) curve analysis was used to evaluate the optimal cutoff value for predicting sICH and to establish optimal cutoff points at which the sum of the specificity and sensitivity was the highest.

Results of univariate analyses with $P < 0.1$ were involved in the multivariate logistic regression. The overall ROC analysis was used to valuate the overall discriminative ability of the five-items model to predict sICH after EVT. A two-tailed value of $P < 0.05$ was considered to be significant.

RESULTS

Clinical Characteristics of the Patients

Out of the 1,403 patients who visited the emergency department at Xuanwu Hospital during the study period, we excluded 1,034 patients based on the inclusion and exclusion criteria. A total of 369 patients with AIS due to large vessel occlusion treated with EVT and were enrolled in this study. A study population flowchart is shown in **Figure 1**.

Among the 369 patients, the median age for the cohort was 66 (57, 74) years, and 67.8% were male. The median baseline NIHSS

TABLE 1 | Baseline characteristics of patients with sICH and without sICH.

No.	Total Patients (n = 369)	sICH group (n = 62)	Non-sICH group (n = 307)	P-value
Age (y)	66 (57, 74)	68 (59, 75)	65 (57, 74)	0.224
Gender, male, *n* (%)	250 (67.8)	38 (61.3)	212 (69.1)	0.233
BMI (kg/m^2)	24.91 (22.86, 27.34)	24.75 (22.05, 27.19)	24.97 (23.03, 27.34)	0.347
Medical history, *n* (%)				
Smoking	115 (31.2)	16 (25.8)	99 (32.2)	0.318
Drinking	102 (27.6)	14 (22.6)	88 (28.7)	0.329
Hypertension	252 (68.3)	42 (67.7)	210 (68.4)	0.919
Hyperlipemia	95 (25.7)	13 (21.0)	82 (26.7)	0.346
Diabetes	108 (29.3)	28 (45.2)	80 (26.1)	0.003
Atrial fibrillation	97 (26.3)	21 (33.9)	76 (24.8)	0.137
Previous stroke	109 (29.5)	21 (33.9)	88 (28.7)	0.412
Coronary heart disease	89 (24.1)	17 (27.4)	72 (23.5)	0.505
Blood pressure at admission (mmHg)				
SBP	150 (135, 167)	159 (136, 171)	150 (135, 165)	0.182
DBP	85 (78, 92)	86 (80, 93)	84 (78, 92)	0.525
Related scores				
Pre-stroke mRS score	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.195
ASPECTS score at admission	8 (7, 9)	8 (7, 9)	8 (7, 10)	0.008
NIHSS score at admission	15 (12, 19)	16 (12, 20)	15 (12, 19)	0.198
Laboratory data				
FBG (mmol/L)	7.2 (6.0, 9.3)	8.1 (7.0, 12.7)	7.1 (5.9, 9.0)	<0.001
WBC ($\times 10^9$/L)	8.9 (7.1, 11.0)	9.0 (6.8, 11.3)	9.2 (7.3, 11.1)	0.973
NLR	5.95 (3.38, 9.68)	6.48 (4.02, 9.36)	5.80 (3.08, 10.08)	0.038
PLT ($\times 10^9$/L)	212 (172, 252)	199 (159, 246)	223 (181, 264)	0.033
TT (s)	16.0 (15.3, 17.0)	16.4 (15.4, 17.2)	15.9 (15.2, 16.5)	0.013
Albumin (g/L)	40.3 (38.0, 42.7)	40.8 (39.1, 42.9)	40.8 (38.5, 43.1)	0.458
TC (mmol/L)	4.44 (3.69, 5.09)	4.61 (3.83, 5.27)	4.43 (3.65, 5.06)	0.740
TG (mmol/L)	1.19 (0.79, 1.81)	1.18 (0.73, 2.05)	1.19 (0.80, 1.83)	0.934
LDL (mmol/L)	2.78 (2.07, 3.46)	2.94 (2.22, 3.67)	2.77 (2.07, 3.46)	0.799
Stroke subtype: TOAST, *n* (%)				0.411
LAA	257 (69.6)	40 (64.5)	217 (70.7)	
CE	95 (25.7)	20 (32.3)	75 (24.4)	
Other subtype	17 (4.6)	2 (3.2)	15 (4.9)	

sICH, symptomatic intracranial hemorrhage; BMI, Body Mass Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; mRS, modified Rankin scale; APSECTS, Alberta Stroke Program Early Computed Tomography score; NIHSS, National Institutes of Health Stroke Scale; FBG, Fasting blood glucose; WBC, White blood cell; NLR, Neutrophil to lymphocyte ratio; PLT, Platelets; TT, Thrombin time; TC, Total cholesterol; TG, Triglyceride; LDL, Low-density lipoprotein; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LAA, Large-artery atherosclerosis; CE, Cardioembolism.

and ASPECTS scores were 15 (12, 19) and 8 (7, 9), respectively. According to the TOAST classification, 257 patients were defined as large-artery atherothrombotic (69.6%), 95 as cardioembolic (25.7%), and 17 (4.6%) as other subtypes of stroke.

The sites of artery occlusion included ICA (118, 32%), MCA (156, 29.5%), ICA + MCA (2, 0.5%), VA (18, 4.9%), and BA (75, 20.3%). Occlusion of the anterior circulation was recorded in 74.8% (276/369) of the patients. The median time from symptom OTD, DTP, OTP, and PTR were 233 (127, 344) min, 130 (105, 162) min, 366 (279, 492) min, and 40 (29, 58) min, respectively.

Thrombectomy with stent retrievers and aspiration (a) was performed in 256 patients (69.4%), intracranial angioplasty and stent implantation (b) in 22 patients (6.0%), and a combination of a and b in 78 patients (21.1%). In addition, 11 patients (3%) were treated with intra-arterial thrombolysis, whereas two patients (0.5%) were treated with both intra-arterial thrombolysis and stent implantation. A total of 80 patients (21.7%) underwent IVT before EVT. Successful reperfusion was reported in 87.3% of the patients and the median NIHSS score within 24 h after EVT was 13 (8, 19). Demographic, clinical, and Laboratory data are shown in **Table 1**, while radiological characteristics, procedure process time, and therapy are shown in **Table 2**.

Correlation Between sICH and mRS at 90 Days

The patients with sICH who reached a favorable functional outcome (mRS, 0–2) at 90 days were less than patients without sICH who had favorable functional outcome (6.5 vs. 43.3%; P

TABLE 2 | Procedural and treatment of patients with sICH and without sICH.

No.	Total Patients ($n = 369$)	sICH group ($n = 62$)	Non-sICH group ($n = 307$)	*P*-value
Site of artery occlusion, *n* (%)				0.665
ICA	118 (32)	23 (37.1)	95 (30.9)	
MCA	156 (29.5)	28 (45.2)	128 (41.7)	
ICA + MCA	2 (0.5)	0 (0.0)	2 (0.7)	
VA	18 (4.9)	2 (3.2)	16 (5.2)	
BA	75 (20.3)	9 (14.5)	66 (21.5)	
Lesion site, *n* (%)				0.138
Anterior circulation lesions	276 (74.8)	51 (82.3)	225 (73.3)	
Posterior circulation lesions	93 (25.2)	11 (17.7)	82 (26.7)	
Procedure process time (min)				
OTD	233 (127, 344)	220 (120, 347)	229 (127, 334)	0.982
DTP	130 (105, 162)	125 (99, 182)	130 (107, 161)	0.826
OTP	366 (279, 492)	366 (283, 469)	369 (274, 493)	0.951
PTR	40 (29, 58)	39 (27, 54)	40 (29, 58)	0.638
Therapy, *n* (%)				0.957
Thrombectomy with stent retrievers + aspiration (a)	256 (69.4)	45 (72.6)	211 (68.7)	
Intracranial angioplasty + stent implantation (b)	22 (6.0)	3 (4.8)	19 (6.2)	
a + b	78 (21.1)	12 (19.4)	66 (21.5)	
Intra-arterial thrombolysis	11 (3.0)	2 (3.2)	9 (2.9)	
Intra-arterial thrombolysis + stent implantation	2 (0.5)	0 (0.0)	2 (0.7)	
Intra-arterial tirofiban, *n* (%)	92 (24.9)	11 (18.0)	81 (26.4)	0.169
IVT + EVT, *n* (%)	80 (21.7)	13 (21)	67 (21.8)	0.881
mTICI at end of procedure, *n* (%)				0.966
0-2a	47 (12.7)	9 (6.6)	38 (16.4)	
2b-3	322 (87.3)	54 (87.1)	268 (87.3)	
NIHSS score after operation	13 (8, 19)	16 (12, 25)	13 (8, 18)	<0.001

sICH, symptomatic intracranial hemorrhage; ICA, intracranial carotid artery; MCA, middle cerebral artery; VA, Vertebral artery; BA, Basilar artery; OTD, symptom onset to door time; DTP, door to groin puncture time; OTP, symptom onset to groin puncture time; PTR, puncture to final recanalization time; MT, mechanical thrombectomy; IVT, intravenous thrombolysis; EVT, endovascular treatment; mTICI, Modified Treatment in Cerebral Ischemia Scale; NIHSS, National Institutes of Health Stroke Scale.

TABLE 3 | Functional outcome at 90 days in sICH and non-sICH groups.

	Total	sICH group ($n = 62$)	Non-sICH group ($n = 307$)	*P*-value
mRS at 90 d				< 0.001
mRS 0–2	137 (37.1)	4 (6.5)	133 (43.3)	
mRS 3–6	232 (62.9)	58 (93.5)	174 (56.7)	
mortality	112 (30.4)	34 (54.8)	78 (25.4)	< 0.001

sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale.

< 0.001). The overall mortality was 112 (30.4%) at 90 days after EVT, with the mortality being higher for patients with sICH (54.8 vs. 25.4%, $P < 0.001$) (**Table 3**). The overall distribution of 90-day mRS scores in the sICH and non-sICH groups is shown in **Figure 2**.

Comparison Between Patients With and Without sICH

Sixty-two patients (16.8%) were diagnosed with sICH within 72 h after EVT. The characteristics of patients with sICH are shown in **Tables 1**, **2**.

In the univariate analysis, the prevalence of diabetes was higher in sICH group than in non-sICH group (45.2 vs. 26.1%, $P = 0.003$). The initial ASPECTS scores after EVT were lower in patients with sICH compared to the patients without sICH [8 (7, 9) vs. 8 (7, 10), $P = 0.008$]. In addition, there were significant differences in FBG ($P < 0.001$), NLR ($P = 0.038$), PLT ($P = 0.033$), and TT at admission ($P = 0.013$) between the two groups of patients. However, there were no significant differences in WBC counts, albumin, TC, TG, or LDL ($P > 0.05$) at admission between the two groups. The NIHSS score within 24 h after EVT was higher in the patients with sICH than in the patients without sICH [16 (12, 25) vs. 13 (8, 18), $P < 0.001$].

Univariate logistic regression analysis revealed that ASPECTS score at admission, FBG, NLR, PLT, TT, and NIHSS score after the operation were associated with sICH after EVT. ROC analyses were performed to identify the optimal cutoff values of ASPECTS score at admission, FBG, NLR, PLT, TT, and NIHSS score after operation for predicting sICH. The optimal cutoff value for ASPECTS scores at admission FBG, NLR, PLT, TT, and NIHSS score after the operation was ≤ 6, ≥ 7.54 mmol/L, ≥ 5.48, $\leq 478 \times 10^9$/L, ≥ 16.25 s, and ≥ 10, respectively.

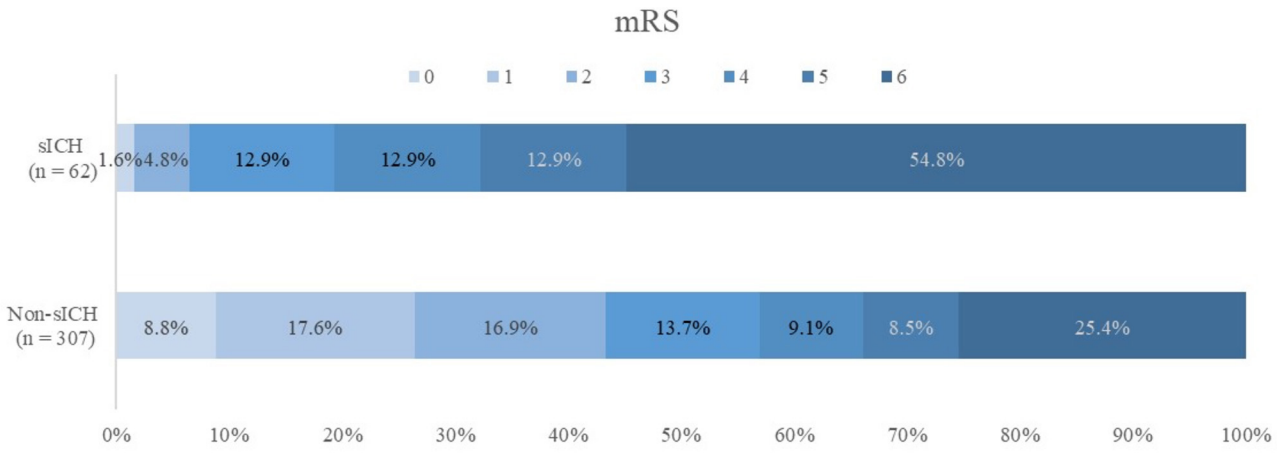

FIGURE 2 | Modified Rankin Scale (mRS) scores at 90 d in patients with and without symptomatic intracranial hemorrhage (sICH). There was a statistically significant difference between two groups in the overall distribution of mRS scores in an analysis with univariable ordinal regression (common odds ratio, 0.23; 95% confidence interval, 0.957–2.020), indicating a shift toward poor functional outcome, with non-sICH patients as reference group.

TABLE 4 | Multivariate analysis of predictors of sICH after EVT.

Characteristics	OR	95% CI	*P*-value
ASPECTS score at admission ≤ 6	1.021	0.332–3.144	0.971
FBG ≥ 7.54 mmol/L	2.765	1.513–5.054	0.001
NLR ≥ 5.48	2.711	1.433–5.128	0.002
PLT ≤ 478 $\times 10^9$/L	2.739	0.196–38.235	0.454
TT ≥ 16.25 s	2.022	1.115–3.667	0.021
NIHSS score after operation ≥ 10	3.728	1.516–9.170	0.004

sICH, symptomatic intracranial hemorrhage; EVT, endovascular treatment; OR, Odds ratio; 95% CI, 95% confidence interval; APSECTS, Alberta Stroke Program Early Computed Tomography score; FBG, Fasting blood glucose; NLR, Neutrophil to lymphocyte ratio; PLT, Platelets; TT, Thrombin time; NIHSS, National Institutes of Health Stroke Scale.

After adjusting for all potential confounders, FBG ≥ 7.54 mmol/L [adjusted odds ratio (OR): 2.765; 95% confidence interval (CI): 1.513–5.054], NLR ≥ 5.48 (OR: 2.711; 95% CI: 1.433–5.128), TT at admission ≥ 16.25 s (OR: 2.022; 95% CI: 1.115–3.667), and NIHSS score after operation ≥ 10 (OR: 3.728; 95% CI: 1.516–9.170) were identified as independent predictors for sICH after EVT ($P < 0.05$). **Table 4** shows the results of the multivariate logistic regression model used to determine predictors of sICH after EVT.

Figure 3 shows the results of ROC analysis for determining the prognostic value of the model to predict sICH. The area under the curve for the model was 0.723, which indicates that the model has a good overall discriminative ability. **Figure 4** shows the calibration curve for the model to predict sICH. The calibration curve for the model showing the calibration ability of the model. Hosmer-Lemeshow $\chi^2 = 6.924$, $P = 0.549 > 0.05$.

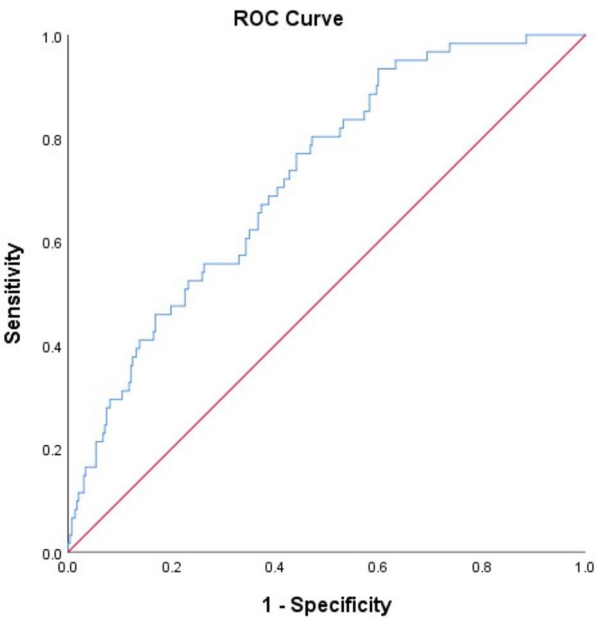

FIGURE 3 | Receiver operating characteristic (ROC) curve for the value of model to predict sICH. The ROC curves showing the predictive ability of the model (including ASPECTS score at admission, NIHSS score after operation, FBG, NLR, PLT, and TT levels). Area under the curve of the model: 0.723.

DISCUSSION

In our study, we explored the predictors of sICH after EVT in patients with large vessel occlusion (LVO)-induced AIS. We demonstrated that higher levels of FDG, NLR, TT at admission, and NIHSS score after operation were associated with sICH after EVT in LVO-induced AIS patients.

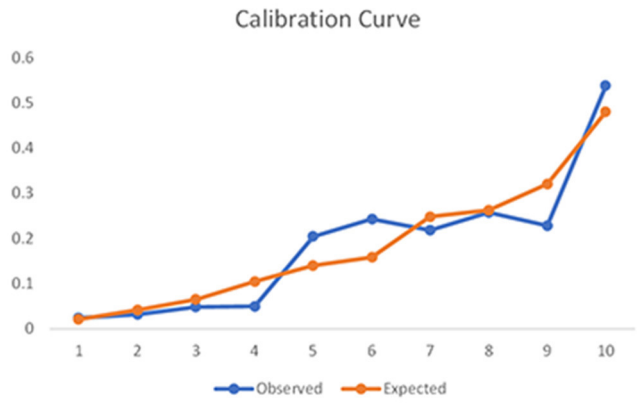

FIGURE 4 | Calibration curve for the model to predict sICH. The calibration curve for the model showing the calibration ability of the model. Hosmer-Lemeshow $\chi^2 = 6.924$, $P = 0.549 > 0.05$.

In our study, the occurrence of sICH was higher (16.8%) than that reported in randomized controlled trial studies (4.4%) (12) and the North American Solitaire Acute Stroke study (9.9%) (13), but was similar to the ACTUAL study (16%) in China (14). Previous studies (14) have indicated that a longer time from symptoms onset to puncture might be associated with sICH, while in our study no differences were found between procedure process time and type of treatment. This was possibly due to the retrospective nature of our study which better reflects the realities in clinical practice such as expanded indications, unfavorable treatment conditions, or insufficient practices that may result in a higher risk of sICH. In addition, the study was conducted in a national referral center with grievous cases of cerebral vascular disease, which could have introduced a selection bias that did not fully represent the actual conditions of AIS patients after EVT. Similar to reports from previous studies, sICH after EVT was associated with poor functional outcomes and mortality (8). Findings from our study revealed that patients with sICH showed poorer functional outcomes (93.5% of cases) compared to patients without sICH, with a mortality of 54.8%. This was an indication that sICH is a fatal complication that greatly affects the prognosis of patients and should be taken seriously.

In our study, high levels of FBG (≥ 7.54 mmol/L) were the strongest predictor of sICH after EVT. FBG scores higher than 7.54 mmol/L in patients with LVO-induced AIS were associated with increased risk of sICH after EVT, which was consistent with previous studies (15–19). It is well known that hyperglycemia often coexists with AIS and is associated with poor functional outcomes (15). High levels of blood glucose have been reported as a related factors of sICH in patients undergone intravenous thrombolysis (IVT) (16) or intra-arterial thrombolysis (17). A study indicated that patients with a serum glucose level ≥of 160 mg/dl had an extremely higher risk of sICH compared to patients with normal blood glucose levels (18). Furthermore, another study revealed that postoperative glucose values were independent predictors of sICH in patients with anterior circulation LVO treated with stenting. The addition of postoperative glucose values to the basic risk factors model could improve the risk prediction for sICH after EVT (19). Leon et al. observed a linear relationship and an overall significant association between glucose and the probability of sICH and poor functional outcome for patients with glucose levels between 6 mmol/L and 9 mmol/L on admission (20). Several mechanisms underlying the relationship between ICH and hyperglycemia have been proposed. Hyperglycemia has been shown to increase the activity of matrix metalloproteinase (MMP)-9 and MMP-3 in the ischemic region (21), exacerbate blood-brain barrier dysfunction and hemorrhagic transformation after recanalization (22).

Our results also shown that high NLR is a strong predictor of sICH after EVT. The study of Lee et al. (23) and Forget et al. (24) reported a mean NLR of 1.65 and a median NLR of 1.65 in the adult healthy population, respectively. In a previous cohort of 143 AIS patients with LVO in the anterior circulation, NLR measured at admission predicted ICH after endovascular thrombectomy, with a cut-off value of 3.89 (25). Hence, our study expands the existing literature by analyzed the relationship between NLR on admission and sICH after EVT in patients with LVO-induced AIS. Our study identified a cut-off of five. Forty-eight (72.1% sensitivity and 50.5% specificity), and a median NLR of 6.48 for the sICH group, which is much higher than that in the healthy individuals. NLR refers to the Neutrophil-to-Lymphocyte Ratio and has gained interest in the recent years as a biomarker of inflammation. Previous studies have indicated that NLR is a predictor for unfavorable functional outcome after AIS and ICH, but the underlying mechanisms remain indefinite (26–28). The occurrence of AIS results in an increase in neutrophil counts (an activation of neutrophils), and a decrease in lymphocyte counts due to the post-stroke immunodepression (29), activated by the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (30). The subsequent increase in the secretion of MMP-9 causes disruption of the neurovascular unit, which explains the occurrence of ICH in AIS patients with higher NLR. The role of neutrophils is even more complex as pro-inflammatory N1 neutrophils are involved in brain neurotoxicity, whereas anti-inflammatory N2 neutrophils have been found to prompt neuronal survival and successful brain reconstruction (31).

In our study, we observed that TT at admission predicted sICH after EVT, with a cut-off value of 16.25s. As far as we know, our research is the first study to evaluate the relationship between TT at admission and sICH in AIS patients after EVT. We therefore made inferences using findings from studies on the relationship between cerebral hemorrhage and coagulation. TT is prolonged with low levels of fibrinogen, dysfunctional fibrinogen, or when inhibitors of thrombin are present, indicating a decrease in coagulation function. A study found that coagulation function was associated with cerebral microbleeds (CMBs) and confirmed that activated partial thromboplastin time (APTT) was an independent predictor for CMBs (32). In addition, low circulating fibrinogen levels were associated with post-thrombolysis hemorrhage in patients with AIS (33). Zsuzsa Bagoly et al. investigated the thrombin generation test in AIS patients before IVT and found that sICH was significantly

correlated with low endogenous thrombin potential (ETP) and thrombin peak levels (33). Therefore, we speculated that the thrombin generation test may be a useful tool for predicting outcomes and safety of recanalization therapy in prospective studies.

The conclusions regarding the relationship between NIHSS and ICH are inconclusive due to inconsistent results reported from different studies. Some research shown that the baseline NIHSS score was independently associated with sICH (34, 35), While another IVT study showed that baseline NIHSS score was not independently associated with sICH after adjustment for the aforementioned covariates (36). In contrast to previous studies, we evaluated the NIHSS score at admission and within 24 h after EVT, and found that only postoperative NIHSS is statistically significant. This may indicate that the higher NIHSS score within 24 h after EVT may be related to ischemic cerebral hemorrhage in clinical practice. In the future, further researches are still needed to verify.

There were some potential limitations to our study due to its retrospective design and use of data from a single-center. In addition, the relatively small sample size and incomplete evaluation index may not fully determine a causal connection. On the other hand, differences in genetic background and design may have contributed to the inconsistencies observed between our results and findings from published studies. The practical implications of these unsolved findings will need future validation. Despite these limitations, the findings from this study give insight into the influence of laboratory results on ICH and prognosis before thrombectomy, to facilitate early management.

CONCLUSION

In this single-center study, the incidence of sICH after EVT is higher than previously reported. Incidence of unfavorable functional outcome and mortality is higher for AIS patients with sICH after EVT than those without sICH. High levels of FDG, NLR, TT at admission, and NIHSS score after operation may increase the risk of sICH after EVT in patients with LVO-induced AIS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XH and HSo responsible for research conception and methodological design, wrote the original manuscript, and prepared to review and editing. QM, LJ, FC, SX, JL, and ZL assisted with participant recruitment and data entry. HSh assisted with data analysis and interpretation. All authors have read and approved the final version of the manuscript.

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ORIGINAL RESEARCH
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Dissolution Effect of Alteplase on Arterial Blood Clot Model of Hypertensive Intracerebral Hemorrhage Patients *in vitro*

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Objective: To explore the dissolution effect of alteplase (rt-PA) on arterial blood clots of patients with hypertensive cerebral hemorrhage *in vitro* and analyze the optimal concentration and action time of rt-PA for intracranial hematomas.

Methods: The arterial blood of 35 patients with confirmed hypertensive cerebral hemorrhage were collected, centrifuged, and the serum was aspirated to prepare the blood clot model. The 0.125, 0.25, 0.5, 1, 2, and 3 mg t-PA, 20,000 U, and 40,000 U urokinase (u-PA) were taken for the corresponding blood clot for dissolution test. The blood clot volume and dissolution volume was measured at 0, 30, 60, 90, 120, and 150 min.

Results: Without intervention, the blood clot volume of men was higher than that of women at 0, 30, 60, and 90 min ($P < 0.05$). Without intervention, hematocrit (HCT) was correlated with blood clot volume and the correlation decreased with time. The 30, 60, and 90 min dissolution curves of each group showed an upward trend ($P < 0.05$), and the dissolution curves tended to be flat at 120 min and 150 min. The dissolution volume of.125 mg/3 ml, 0.25 mg/3 ml, 0.5 mg/3 ml rt-PA, 20,000 U, 40,000 U u-PA was higher than that of 1, 2, 3 mg/ml rt-PA ($P < 0.05$). The dissolution volume of.125 mg/3 ml, 0.25 mg/3 ml, 0.5 mg/3 ml rt-PA was not significantly different from 20,000 and 40,000 U u-PA ($P > 0.05$). Gender differences did not affect the effects of the above drugs.

Conclusion: *In vitro*, low-concentration rt-PA has a better dissolution effect, and it shows a time-dependent effect, reaching the highest effect in 90 min.

Keywords: alteplase, urokinase, hypertensive cerebral hemorrhage, arterial blood, dissolution

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INTRODUCTION

Hypertensive intracerebral hemorrhage has a high incidence, a long treatment period, and a poor prognosis, which causes a large burden on the family and society (1–3). At present, traditional craniotomy is traumatic and causes inevitable damage to normal brain tissue, and the prognosis does not show obvious advantages over conservative treatment (4, 5). Phase II and Phase III clinical trials of minimally invasive surgery plus alteplase (rt-PA) for intracerebral hemorrhage evacuation

(MISTIE) confirmed that minimally invasive puncture and drainage of the hematoma and injection of rt-PA into the hematoma could effectively relieve the hematoma occupying effect and secondary damage (5).

The main component of rt-PA is glycoprotein which can bind to fibrin through lysine residues and activate plasminogen bound to fibrin to turn it into plasmin, thereby dissolving blood clots or thrombus. Rt -PA is a third-generation thrombolytic drug with the characteristics of safety, efficiency, and convenience (6). However, studies have observed that rt-PA had dose-related neurotoxicity and overdose could cause edema around the lesion and destroy the blood-brain barrier, which was not conducive to the prognosis (7–12). Therefore, the drug concentration and action time of rt-PA used in the treatment of intracranial hematoma have become a research hotspot. In this study, the arterial blood of patients with hypertensive cerebral hemorrhage was collected and the blood clot model *in vitro* was prepared, and different doses of rt-PA intervention were given to observe the relationship between rt-PA and dissolution effect. This study aimed to provide theoretical support to further optimize the treatment of hypertensive intracerebral hemorrhage.

MATERIALS AND METHODS

Patients

Thirty-five patients with hypertensive cerebral hemorrhage diagnosed from 2020-2-6 to 2020-6-30 in the Department of Neurosurgery of Rudong Hospital Affiliated with Nantong University and Haimen District People's Hospital were selected as the research objects. Inclusion criteria: (1) meet the diagnostic criteria for hypertensive intracerebral hemorrhage; (2) the hematoma was located in the basal ganglia, thalamus, or brain lobe; (3) consciousness disorder, hemiplegia, aphasia, limb numbness, and other neurological disorders; (4) the time from onset to hospitalization did not exceed 48 h; (5) normal cardiopulmonary function, normal blood coagulation function. Exclusion criteria: (1) age <18 years; (2) cerebral hemorrhage caused by other causes; (3) those with a history of surgery within one month; (4) abnormal blood coagulation function; (5) The time from onset to hospitalization exceeded 48 h; (6) oral anticoagulants; (7) drug users; (8) pregnant women; (9) severe heart, lung, kidney, and liver function abnormalities. Among the 35 patients with hypertensive intracerebral hemorrhage, 27 were males and 8 were females, ranging in age from 28 to 81 years old, with an average of 64.14 ± 13.00 years old. The average systolic blood pressure at admission was 171.34 ± 25.24 mmHg, and the average diastolic blood pressure was 96.91 ± 11.66 mmHg. There were 5 cases with a history of stroke; 3 cases with a history of diabetes; 13 cases with a history of hypertension were clearly stated, only 4 cases with a history of regular use of antihypertensive drugs; 2 cases with a history of smoking; 4 cases with a history of drinking. The studies involving human participants were reviewed and approved by the Ethics Committee of Rudong County People's Hospital and Haimen District People's Hospital. The patient's family provided written informed consent to participate in this study.

Samples and Model

A total of 40 ml of arterial blood was drawn from each patient and randomly injected into 10 blood collection tubes (4 ml/tube), centrifuged, then the serum was aspirated to prepare the blood clot model, and divided into the standard group, control group, 0.125 mg/3ml, 0.25 mg/3ml, 0.5 mg/3ml, 1 mg/3ml, 2 mg/3ml, 3 mg/3ml rt-PA groups, 20,000 U, and 40,000 U urokinase (u-PA) groups. No intervention in the standard group for checking blood clot volume, the control group was added with 3 ml saline, then 0.125 mg/3 ml, 0.25 mg/3 ml, 0.5 mg/3 ml, 1 mg/3 ml, 2 mg/3 ml, 3 mg/3 ml rt-PA groups were added with the corresponding dose of the rt-PA (Boehringer-Ingelheim, Germany), and the 20,000 and 40,000 U u-PA groups were added with the corresponding dose of the u-PA (NDPHARM, China). Then, the tube was placed in a 37°C electric-heated thermostatic water bath (Wuxi Yierda, China), and the corresponding dissolved volume or blood clot volume was measured 30, 60, 90, 120, and 150 min after the intervention with a pipette gun (Eppendorf, Germany).

Statistical Analysis

The SPSS 21.0 data software (IBM, NY, USA) package was used for the statistical analysis of the data obtained in this study. The measurement data obtained in the study was verified by the Shapiro-Wilk test to conform to the normal distribution, expressed by mean±SD, and the independent-test or ANOVA was used for comparison between groups. The relationship between blood clot volume and the blood test indexes of patients was analyzed with Spearman correlation analysis. $P < 0.05$ was considered the difference to be statistically significant.

RESULTS

The Relationship Between Blood Clots of the Standard Group and Clinical Data

The blood clot volume of males was bigger than that of females at 0, 30, and 90 min ($P < 0.05$), and the difference was not statistically significant at 120 min, 150 min. There was no statistically significant difference between the subgroups of other clinical factors at any time point. The results were shown in **Table 1**.

Hematocrit (HCT) was correlated with blood clot volume and the correlation decreased with time ($P < 0.05$). There was no correlation between other relevant blood test indexes and blood clot volume ($P > 0.05$). The results were shown in **Table 2**.

Effect of Time on the Hemolytic Efficiency of Drugs

The dissolution volume of each group gradually increased at 30, 60, and 90 min ($P < 0.05$). The dissolution volume at 120 and 150 min in the 20,000 and 40,000 U u-PA groups was similar to that at 90 min. Although the dissolution volume of the other groups continued to increase at 120 min, there was no statistically significant difference compared with 90 min ($P > 0.05$). The dissolution volume at 150 min in all groups was similar to that at 120 min (**Figure 1**).

TABLE 1 | The relationship between blood clot of standard group and clinical data.

	n	0 min	30 min	60 min	90 min	120 min	150 min
Gender							
Male	27	1.53 ± 0.16	1.34 ± 0.18	1.25 ± 0.22	1.21 ± 0.23	1.17 ± 0.24	1.17 ± 0.24
Female	8	1.36 ± 0.16	1.15 ± 0.13	1.08 ± 0.13	1.03 ± 0.12	1.01 ± 0.12	1.01 ± 0.12
t		2.59	2.73	2.14	2.12	1.87	1.87
P		***0.01***	***0.01***	***0.04***	***0.04***	0.07	0.07
Age							
≥60	25	1.51 ± 0.17	1.30 ± 0.19	1.21 ± 0.23	1.18 ± 0.24	1.14 ± 0.24	1.14 ± 0.24
< 60	10	1.45 ± 0.20	1.28 ± 0.18	1.20 ± 0.18	1.14 ± 0.18	1.11 ± 0.17	1.11 ± 0.17
t		0.84	0.37	0.14	0.50	0.30	0.30
P		0.41	0.72	0.89	0.62	0.77	0.77
History of stroke							
No	30	1.51 ± 0.18	1.31 ± 0.20	1.21 ± 0.23	1.17 ± 0.24	1.13 ± 0.24	1.13 ± 0.24
Yes	5	1.37 ± 0.09	1.25 ± 0.07	1.21 ± 0.08	1.16 ± 0.08	1.13 ± 0.08	1.13 ± 0.08
t		1.71	0.65	0.05	0.05	0.06	0.06
P		0.10	0.52	0.97	0.96	0.95	0.95
Medication history							
No	21	1.49 ± 0.17	1.30 ± 0.18	1.21 ± 0.22	1.16 ± 0.23	1.13 ± 0.25	1.13 ± 0.25
Yes	14	1.49 ± 0.19	1.29 ± 0.21	1.21 ± 0.21	1.17 ± 0.21	1.14 ± 0.20	1.14 ± 0.20
t		0.05	0.29	0.00	0.09	0.14	0.14
P		0.96	0.77	1.00	0.93	0.89	0.89
Smoking history							
No	33	1.48 ± 0.18	1.29 ± 0.19	1.20 ± 0.21	1.15 ± 0.22	1.12 ± 0.22	1.12 ± 0.22
Yes	2	1.65 ± 0.08	1.47 ± 0.04	1.42 ± 0.01	1.39 ± 0.02	1.36 ± 0.03	1.36 ± 0.03
t		1.27	1.37	1.42	1.47	1.51	1.51
P		0.21	0.18	0.17	0.15	0.14	0.14
Drinking history							
No	31	1.49 ± 0.18	1.29 ± 0.19	1.20 ± 0.22	1.16 ± 0.22	1.12 ± 0.23	1.12 ± 0.23
Yes	4	1.47 ± 0.22	1.31 ± 0.20	1.27 ± 0.19	1.24 ± 0.18	1.20 ± 0.21	1.20 ± 0.21
t		0.23	0.18	0.59	0.73	0.62	0.62
P		0.82	0.86	0.56	0.47	0.54	0.54
History of diabetes							
No		1.50 ± 0.18	1.31 ± 0.18	1.23 ± 0.21	1.18 ± 0.22	1.15 ± 0.23	1.15 ± 0.23
Yes		1.43 ± 0.04	1.11 ± 0.16	1.03 ± 0.18	0.99 ± 0.17	0.97 ± 0.17	0.97 ± 0.17
t		0.59	1.91	1.53	1.48	1.29	1.29
P		0.56	0.07	0.14	0.15	0.21	0.21

Bold and italic values indicate P < 0.05.

TABLE 2 | The relationship between blood clot of standard group and blood test indexes.

	0 min	30 min	60 min	90 min	120 min	150 min
WBC (10∧9/L)	0.074	0.195	0.192	0.18	0.149	0.149
Neu (10∧9/L)	0.063	0.169	0.156	0.146	0.111	0.111
PT(s)	−0.037	0.075	0.119	0.14	0.146	0.146
INR	0.09	0.021	−0.062	−0.047	−0.092	−0.092
PLC (10∧9/L)	−0.066	−0.023	−0.009	0.01	0.017	0.017
FG (g/L)	−0.238	−0.213	−0.182	−0.206	−0.166	−0.166
DD (ug/L)	0.063	−0.061	−0.11	−0.134	−0.132	−0.132
FDP (ug/ml)	0.152	−0.107	−0.213	−0.214	−0.221	−0.221
HCT (%)	0.648**	0.628**	0.493**	0.488**	0.453**	0.453**

*DD, D-dimer; FDP, fibrinogen degradation product; FG, Fibrinogen; HCT, hematocrit; INR, international standardized ratios; Neu, neutrophil count; PLC, platelet count; PT, prothrombin time; WBC, white blood cell count. **P < 0.01.*

Effect of Concentration on the Hemolytic Efficiency of Drugs

The dissolution volume of different doses of rt-PA and u-PA was higher than that of the control group ($P < 0.05$). Among them, the dissolution volume of 0.125 mg/3 ml, 0.25 mg/3ml, and.5 mg/3 ml rt-PA was not significantly different from that of 20,000 and 40,000 U u-PA ($P > 0.05$). The dissolution volume of.25 mg/3 ml rt-PA was slightly higher than that of.125 mg/3 ml and.5 mg/3 ml rt-PA, but the difference was not statistically significant ($P > 0.05$). The dissolution volume of.125 mg/3 ml, 0.25 mg/3 ml, 0.5 mg/3 ml rt-PA, 20,000 U, 40,000 U u-PA was higher than that of 1 mg/3 ml, 2 mg/3 ml, and 3 mg/3 ml rt-PA ($P < 0.05$). The dissolution volume of 1 mg/ml rt-PA was higher than the dissolution volume of 2 mg/3 ml and 3 mg/3 ml rt-PA ($P < 0.05$). There was no significant difference in the dissolution volume of 2 mg/3 ml and 3 mg/3 ml rt-PA ($P > 0.05$) (**Figure 1**; **Table 3**). Gender differences had no effect on the effects of the above drugs (**Table 4**).

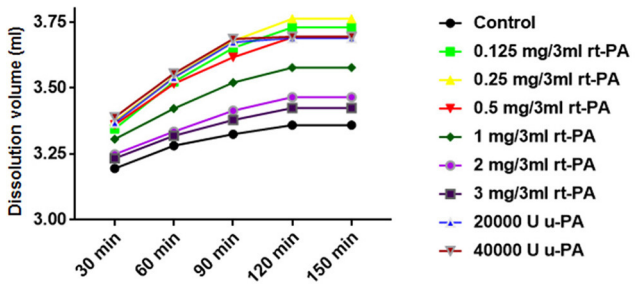

FIGURE 1 | Effect of time or concentration on the hemolytic efficiency of drugs. The 30, 60, and 90 min dissolution curves of each group showed an upward trend ($P < 0.05$), and the dissolution curves tended to be flat at 120 and 150 min. The dissolution volume of 0.125 mg/3 ml, 0.25 mg/3 ml, 0.5 mg/3 ml rt-PA, 20,000 U, 40,000 U u-PA was higher than that of 1 mg/3 ml, 2 mg/3 ml, 3 mg/3 ml rt-PA volume ($P < 0.05$).

DISCUSSION

In this study, the arterial blood of patients with hypertensive intracerebral hemorrhage was used to create a blood clot model *in vitro* to explore the effect of fibrinolytic drugs on the hematoma. Because hypertensive cerebral hemorrhage intracranial hematoma is formed by arterial blood coagulation after arterial rupture, the experimental blood clot model was closer to the clinic, and the results were more credible. The method of constructing the blood clot model was scientific and reliable (13). In addition, we found that due to the separation effect of serum, the rt-PA and u-PA solutions could not interact with blood clots in the preliminary experiment, after the serum was separated by centrifugation, the experiment proceeded smoothly.

The results showed that the concentration of rt-PA was critical to the dissolution effect, and the dissolution efficiency of rt-PA on arterial blood clots was negatively correlated with the drug concentration. The dissolution efficiency of u-PA or rt-PA was the best in the 30–90 min after the intervention, and the plateau period was obvious after 90 min. U-PA and rt-PA were added to arterial blood clots *in vitro*, and the dissolution efficiency of u-PA was the best at 90 min, the dissolution efficiency of rt-PA was slightly lower than that of u-PA. However, u-PA is more likely to cause bleeding when used in the body, and it is prone to pollution during production. It has been banned by the US Food and Drug Administration (14), so rt-PA was studied in this study. The results also showed that the dissolution efficiency of low-concentrations rt-PA (0.125, 0.25, and 0.5 mg groups) was higher than that of the high-concentration group (1, 2, and 3 mg groups), which was close to or reached the dissolution efficiency of the u-PA groups, and there was no statistically significant difference between the low concentration groups. The results suggest that the dissolution efficiency of rt-PA does not have a positive correlation with the concentration, which may be related to the enzymatic reaction, that is, when the substrate concentration is constant, the increase in the enzyme concentration is not positively related to the reaction speed, and even inhibition occurs. Clinical related reports also pointed out that when the concentration of rt-PA was too high, it was

TABLE 3 | Effect of drugs concentration on the hemolytic efficiency.

Group	30 min	60 min	90 min	120 min	150 min
Control	3.20 ± 0.15	3.28 ± 0.21	3.32 ± 0.21	3.36 ± 0.22	3.36 ± 0.22
0.125 mg/3 ml rt-PA	3.35 ± 0.20*	3.52 ± 0.26*	3.65 ± 0.29*	3.73 ± 0.30*	3.73 ± 0.30*
0.25 mg/3 ml rt-PA	3.37 ± 0.20*	3.54 ± 0.26*	3.68 ± 0.28*	3.76 ± 0.30*	3.76 ± 0.30*
0.5 mg/3 ml rt-PA	3.36 ± 0.24*	3.52 ± 0.27*	3.62 ± 0.28*	3.69 ± 0.28*	3.69 ± 0.28*
1 mg/3 ml rt-PA	3.31 ± 0.21*@	3.42 ± 0.23*@	3.52 ± 0.26*@	3.58 ± 0.26*@	3.58 ± 0.26*@
2 mg/3 ml rt-PA	3.25 ± 0.18*@#	3.34 ± 0.19*@#	3.41 ± 0.23*@#	3.47 ± 0.22*@#	3.47 ± 0.22*@#
3 mg/3 ml rt-PA	3.23 ± 0.18*@#	3.32 ± 0.18*@#	3.38 ± 0.19*@#	3.42 ± 0.18*@#	3.42 ± 0.18*@#
20,000 U u-PA	3.37 ± 0.24*@#^	3.54 ± 0.26*@#^	3.67 ± 0.29*#^	3.69 ± 0.30*#^	3.69 ± 0.30*#^
40,000 U u-PA	3.39 ± 0.26*#^	3.55 ± 0.28*#^	3.69 ± 0.30*#^	3.70 ± 0.30*#^	3.70 ± 0.30*#^

*rt-PA, alteplase; u-PA, urokinase. * VS. Control group, $P < 0.05$; @ VS. 0.125 mg/3ml, 0.25 mg/3 ml, and 0.5 mg/3 ml rt-PA groups, $P < 0.05$; # VS. 1 mg/3 ml rt-PA group, $P < 0.05$; ^ VS. 2 mg/3 ml, and 3 mg/3 ml rt-PA groups, $P < 0.05$.*

TABLE 4 | Effect of drugs concentration on the hemolytic efficiency between male and female.

Group	Gender	30 min	60 min	90 min	120 min	150 min
Control	Male	3.19 ± 0.14	3.28 ± 0.21	3.32 ± 0.22	3.36 ± 0.23	3.36 ± 0.23
	Femal	3.21 ± 0.17	3.29 ± 0.20	3.33 ± 0.20	3.35 ± 0.20	3.35 ± 0.20
0.125 mg/3ml rt-PA	Male	3.33 ± 0.21	3.51 ± 0.28	3.64 ± 0.31	3.72 ± 0.32	3.72 ± 0.32
	Femal	3.39 ± 0.18	3.56 ± 0.20	3.68 ± 0.22	3.76 ± 0.22	3.76 ± 0.22
0.25 mg/3ml rt-PA	Male	3.37 ± 0.21	3.53 ± 0.27	3.68 ± 0.30	3.77 ± 0.32	3.77 ± 0.32
	Femal	3.40 ± 0.18	3.57 ± 0.20	3.68 ± 0.20	3.75 ± 0.21	3.75 ± 0.21
0.5 mg/3ml rt-PA	Male	3.35 ± 0.25	3.51 ± 0.28	3.62 ± 0.30	3.69 ± 0.30	3.69 ± 0.30
	Femal	3.39 ± 0.21	3.53 ± 0.24	3.62 ± 0.23	3.69 ± 0.23	3.69 ± 0.23
1 mg/3ml rt-PA	Male	3.30 ± 0.22	3.42 ± 0.24	3.52 ± 0.27	3.58 ± 0.27	3.58 ± 0.27
	Femal	3.32 ± 0.20	3.43 ± 0.22	3.51 ± 0.24	3.57 ± 0.23	3.57 ± 0.23
2 mg/3ml rt-PA	Male	3.24 ± 0.19	3.33 ± 0.18	3.41 ± 0.23	3.47 ± 0.23	3.47 ± 0.23
	Femal	3.27 ± 0.18	3.35 ± 0.21	3.41 ± 0.21	3.45 ± 0.22	3.45 ± 0.22
3 mg/3ml rt-PA	Male	3.23 ± 0.18	3.31 ± 0.18	3.38 ± 0.19	3.43 ± 0.18	3.43 ± 0.18
	Femal	3.25 ± 0.18	3.33 ± 0.20	3.38 ± 0.20	3.41 ± 0.20	3.41 ± 0.20
20,000 U u-PA	Male	3.36 ± 0.25	3.54 ± 0.28	3.68 ± 0.30	3.69 ± 0.31	3.69 ± 0.31
	Femal	3.39 ± 0.19	3.55 ± 0.23	3.66 ± 0.24	3.68 ± 0.26	3.68 ± 0.26
40,000 U u-PA	Male	3.38 ± 0.27	3.55 ± 0.29	3.69 ± 0.31	3.70 ± 0.31	3.70 ± 0.31
	Femal	3.41 ± 0.20	3.57 ± 0.25	3.68 ± 0.26	3.69 ± 0.27	3.69 ± 0.27

rt-PA, alteplase; u-PA, urokinase.

easy to induce neuroinflammation and aggravate edema (9, 13, 15, 16). Therefore, we speculate that low concentrations of rt-PA may be safer and more effective in clinical applications. It is not recommended to use rt-PA with a concentration higher than.5 mg/3 ml for the treatment of intracranial hematoma. Since our experiment was an *in vitro* experiment, it cannot completely simulate the intracranial environment. The optimal concentration needs to be confirmed by further animal models or human clinical experiments.

The results of this experiment also observed that time were an important factor for the dissolution effect. Ninety min after adding the rt-PA, the dissolution effect of the rt-PA increased with time, showing a positive correlation, and the slope of the dissolution curve was large; after 90 min, the slope of the dissolution curve tended to be flat; after 120 min, there was no change in the slope of the dissolution curve. It is inferred that 90–120 min after adding the medicine is the ideal time to drain the liquefied hematoma, and the clamping time of the drainage tube should not exceed 120 min in the clinical application of rt-PA for intracranial hematoma. However, our data were the results of *in vitro* experiments and the related animal experiment or should clinical experiments be explored in the following days; it should be determined whether to add rt-PA in time based on the residual situation of the hematoma examined by the head CT and the improvement of clinical symptoms; the sample size of patients is small, especially the sample size of female patients is small, but this is roughly the same as the ratio of male to female patients with hypertensive intracerebral hemorrhage in China. The results of gender subgroup analysis showed that gender differences had no effect on the effects of the above drugs.

In summary, *in vitro*, low-concentration rt-PA has a better dissolution effect, and it shows a time-dependent effect, reaching the highest effect in 90 min, which maybe provides theoretical support to further optimize the treatment of hypertensive intracerebral hemorrhage.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Rudong County People's Hospital and Haimen District People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REVIEW
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Minimally Invasive Surgery for Intracerebral and Intraventricular Hemorrhage

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Spontaneous intracerebral hemorrhage (ICH), especially related to intraventricular hemorrhage (IVH), is the most devastating type of stroke and is associated with high mortality and morbidity. Optimal management of ICH remains one of the most controversial areas of neurosurgery and no effective treatment exists for ICH. Studies comparing conventional surgical interventions with optimal medical management failed to show significant benefit. Recent exploration of minimally invasive surgery for ICH and IVH including catheter- and mechanical-based approaches has shown great promise. Early phase clinical trials have confirmed the safety and preliminary treatment effect of minimally invasive surgery for ICH and IVH. Pending efficacy data from phase III trials dealing with diverse minimally invasive techniques are likely to shape the treatment of ICH.

Keywords: intracerebral hemorrhage, intraventricular hemorrhage, minimally invasive surgery, mechanical-based approach, pharmacological catheter-based approach

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is the most serious public health issue and impinges ∼2 million people in the world each year (1–3). The incidence of ICH has been increasing because of an aging population and increased use of anticoagulation and antiplatelet agents for thromboembolic diseases. Although ICH accounts for 6.5–19.6% of strokes, it is related to the high rate of mortality and morbidity; the 30-day mortality rate is in the range of 35–52% and only 20% of survivors live independently (4). When ICH involves intraventricular hemorrhage (IVH), the outcome is even worse, with an estimated mortality rate of between 50 and 80% (3). Since most cases occur in working adults in a large number of people in low- and middle-income countries, ICH has a huge social and economic impact due to the loss of productive life years (5).

Risk factors for ICH include hypertension, anticoagulation, and amyloid angiopathy. Most patients (50–70%) with ICH suffer from hypertension (6). Hypertensive hemorrhage is inclined to occur in the external capsule (42%), pons (16%), thalamus (15%), cerebellum (12%), and white matter (10%) (7). Evidence from studies indicates that the incidence of ICH is reduced due to improved control of hypertension (8, 9). Anticoagulation-related ICH is more severe and associated with more extensive hemorrhage and a higher mortality rate in comparison with non-anticoagulation-related ICH and has risen in incidence over the past decade (10, 11). Cerebral amyloid angiopathy (CAA) is associated with 12–15% lobar ICH, particularly in the elderly (12, 13).

CAA-related ICH usually occurs in people aged > 60 years. Compared with other causes of ICH, CAA-related ICH has a lower mortality rate, but an increased rate of recurrence (14).

Unfortunately, there has been no beneficial medical treatment for ICH and surgery lacks definitive evidence and is still in debate. Theoretically, hematoma evacuation could remove the neurotoxic blood products, reduce the mass effect and intracerebral pressure (ICP), and control cerebral perfusion pressure, helping to prevent brain edema and secondary brain injury. Open surgery, however, may make damage to the normal brain tissue and affect functional outcomes, especially for patients with deep hemorrhage. The International Surgical Trial in ICH (STICH) and STICH II were the two largest prospective randomized clinical studies to evaluate the efficacy of open surgery for ICH. These clinical trials did not find a significant benefit in functional outcomes between patients who underwent surgery and patients who were medically treated (15, 16). The failure of traditional surgical treatment to improve the prognosis of patients with supratentorial ICH is because, in many patients, the damage of surrounding brain tissues caused by surgical methods neutralizes the benefits of hematoma clearance. This makes minimally invasive surgery (MIS) the most promising surgical strategy for patients with ICH. Because of the shorter operation time, the possibility of bedside treatment, and less damage to the brain tissue, minimally invasive treatment is more attractive than conventional craniotomy in the treatment of ICH (17).

In this review, we discuss different minimally invasive techniques for ICH and IVH, emphasizing clinical trials (**Table 1**) for this condition.

MINIMALLY INVASIVE SURGERY FOR ICH

The use of MIS for ICH evacuation started in the 1960s (32). The endoscope was used to evacuate the clot after ICH (33). Since then, several improvements have been made to the method to improve the efficiency of hematoma removal (34). In the late 1980s, mechanically-assisted thrombolysis by using ultrasound techniques was explored and favorable outcomes were described (35). MIS continues to evolve with the advancement of technology. Generally, MIS approaches can be divided into two categories: primarily pharmacological catheter based and primarily mechanically based. The pharmacological catheter-based approach involves the placement of a drainage catheter under the guidance of images and gentle aspiration for hematoma, followed by the infusion of the catheter with a thrombolytic agent to prevent clogging, facilitating passive drainage of the hematoma over several days. This requires intermittent imaging to confirm the catheter position and to monitor the progress of hematoma drainage. Mechanical methods for hemorrhage evacuation involve the surgical removal of the hematoma in a single procedure without leaving a drainage catheter and by using a thrombolytic agent. The evacuation of the hematoma is performed with either an endoscope or other devices. These two approaches have their own advantages and disadvantages, which may or may not contribute to functional outcomes in patients with ICH.

Pharmacological Catheter-Based MIS for ICH

Matsumoto and Hondo reported that they performed CT-guided stereotactic evacuation of hypertensive intracerebral hematoma in 51 patients. First, they inserted one silicon tube into the center of the hematoma and then, the hematoma was aspired with a syringe, followed by the administration of urokinase until the hematoma was completely evacuated. Of 51 patients, 38 patients had functional outcomes (36). This method was also used in the posterior fossa hematoma. In one study, the aspiration and administration of urokinase were performed in 11 patients (9 patients with cerebellar hematoma and 2 patients with pontine hematoma) and 7 patients had functional outcomes (37). Thereafter, the recombinant tissue-type plasminogen activator (rt-PA) was used for clot thrombolysis and it was well tolerated and more effective in evacuating hematoma (26, 38). In addition, sonothrombolysis, in combination with pharmacological thrombolysis, has been used for clot evacuation. Newell et al. reported that rt-PA and 24 h of continuous ultrasound were delivered to the clot in 33 patients with ICH and they found that the combination of sonothrombolysis and rt-PA was more effective than rt-PA alone in hemorrhage lysis (39). Recently, Sun and Liu developed a new catheter-based MIS technology called cubic oriented stereotactic aspiration (40) and invented associated devices. This technology combines brain anatomy with solid geometry (**Figure 1**). Luo et al. confirmed the safety and efficacy of the technology (41) (**Figure 2**). At present, this technology has been used for supratentorial and infratentorial ICH in China (42–44).

These preliminary studies have shown that pharmacological catheter-based MIS can effectively remove hematomas. However, there is no unified standard for the selection of patients, the timing of MIS, and the proportion of hematoma evacuated. More importantly, the clinical benefit is still unclear. Therefore, it is essential to conduct randomized controlled trials (RCTs) to evaluate the effect of the pharmacological approach of MIS.

YL-1 Craniopuncture

Wang et al. randomized 377 patients with 25–40 ml basal ganglion hematoma in a multicenter controlled study into conservative medical treatment or the stereotactic craniopuncture and aspiration with YL-1 puncture needle followed by infusion of urokinase. Although there were significantly more complications in the craniopuncture group, the case fatality in these two groups was not significantly different and MIS led to a significant reduction of dependence at the end of the third month, compared with the conservative treatment (40.88 vs. 63.03%) (23). Moreover, other two RCTs were performed to evaluate and compare the effect of YL-1 craniopuncture plus urokinase with craniotomy with a small bone flap or conventional surgery in patients with ICH. Compared with craniotomy with a small bone flap and conventional surgery, the MIS had fewer complications and had a trend to improve long-term outcomes (25, 27). These

TABLE 1 | Randomized controlled trials of MIS for ICH and IVH.

References	Treatment		Included patients (MG/OG)	Age* (years) (MG/OG)	Hematoma location	Volume* (ml) (MG/OG)	Onset to surgery (hours)	Outcomes	Follow-up (months)
	MG	OG							
Auer et al. (18)	ES	CMT	100 (50/50)	30–80	Subcortical, putaminal, or thalamic	≥10	Within 48	①②③	6
Naff et al. (19)	EVD with urokinase	EVD with saline	12 (7/5)	49.6/55.2	IVH with or without supratentorial ICH	ICH: 5.3/13.2 IVH: 72.8/41.54	NA	②③④⑤	1
Teernstra et al. (20)	SA with urokinase	CMT	71 (36/35)	67/69	Supratentorial	66/52	Within 72	①②	6
Zhang et al. (21)	ES with EVD	EVD with urokinase	42 (20/22)	31-75	IVH with or without Supratentorial ICH	ICH < 30	Within 48	①②	2
Kim and Kim (22)	SA	CMT	387 (204/183)	64.3/67.1	Basal ganglia and thalamus	24.3/21.0	NA	①②③	6
Wang et al. (23)	CP with urokinase	CMT	377 (195/182)	56.6/56.9	Basal ganglion	33.9/31.3	4–72	①②③	3
Chen et al. (24)	ES with EVD	EVD	48 (24/24)	65.54/62.17	IVH with thalamic hemorrhage	ICH:10.5/11.5	NA	①②⑤	3
Sun et al. (25)	CP with urokinase	CC with small bone flap	304 (159/145)	56.9/55.2	Basal ganglion	52.3/51.7	Within 72	①②③	3
Naff et al. (26)	EVD with rt-PA	EVD with placebo	48 (26/22)	54.1/56.6	IVH with or without supratentorial ICH	ICH: 7.2/7.9 IVH:54.8/50.1	≤12	②③④	1
Zhou et al. (27)	CP with urokinase	CC with large bone flap	168 (90/78)	57.6/59.2	Basal ganglion or brain lobe	30–100 ml	6–24	①②③	12
Hanley et al. (28)	SA with rt-PA	CMT	96 (54/42)	60.7/61.1	Lobar or deep	48.2/43.1	NA	①②③	12
Vespa et al. (29)	ES	CMT	24	59/62	Supratentorial	36.4/41.4	Within 48	①②③	12
Hanley et al. (30)	EVD with rt-PA	EVD with saline	500 (249/251)	59/59	IVH with or without supratentorial ICH	ICH:8.3/7.2 IVH:21.2/22.4	≤12	①②③④⑤	6
Hanley et al. (31)	SA with rt-PA	CMT	506 (255/251)	62/62	Basal ganglia or lobar region	42.7/41.5	NA	①②③	12

CC, conventional craniotomy; CMT, conservative medical treatment; CP, craniopuncture; ES, endoscopic surgery; EVD, external ventricular drainage; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MG, minimally invasive surgery group; NA, not available; OG, other treatment options group; SA, stereotactic aspiration. ① good functional outcome; ② death; ③ rehemorrhage; ④ ventriculitis; ⑤ ventriculoperitoneal shunt.

**Age and volume are usually expressed as mean or median. If there was no such information in literatures, a range would be given.*

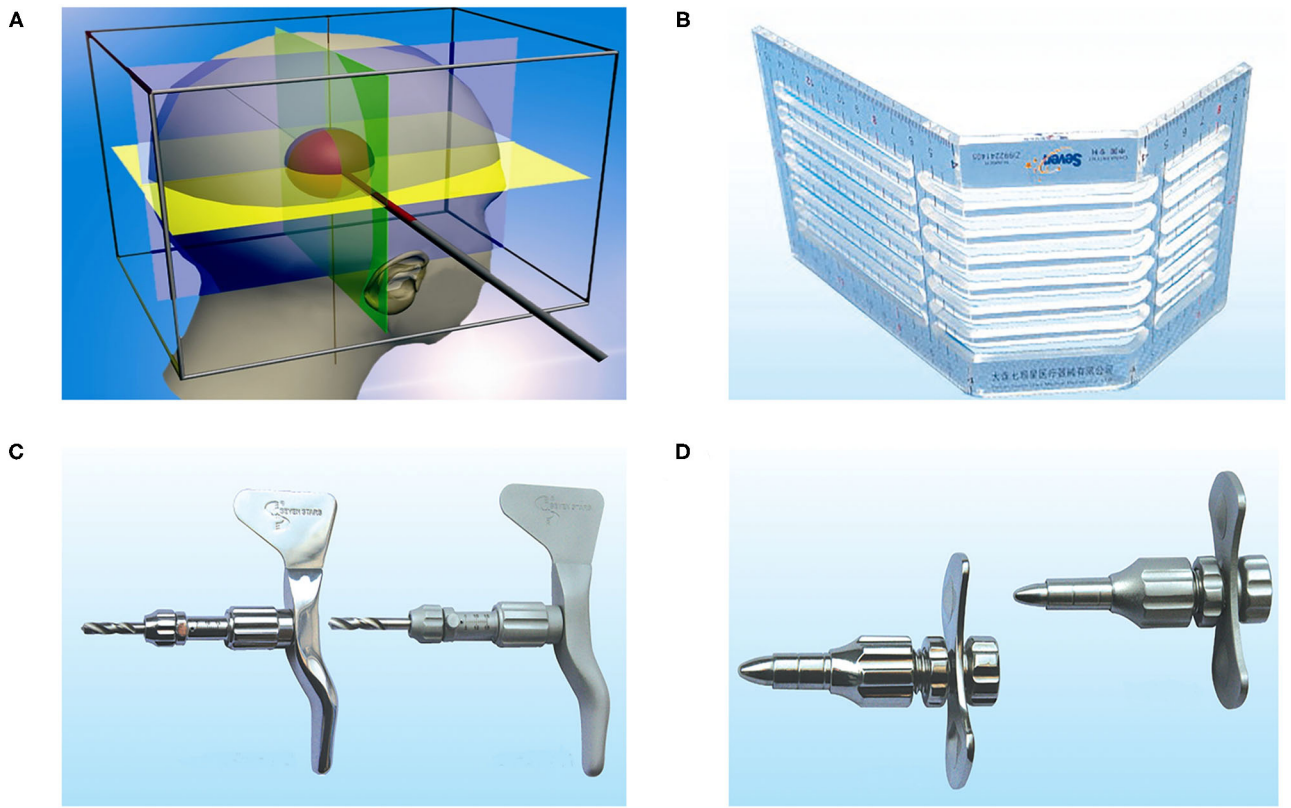

FIGURE 1 | The principle and devices of cubic oriented stereotactic aspiration technology. **(A)** The principle of cubic oriented stereotactic aspiration: according to the principle of solid geometry, the position of any point in space can be determined by the three-dimensional directional coordinate system. Combining this principle with cranial anatomy, the "quasi-circular" head is "framed" in cube space. According to the principle that three mutually perpendicular planes intersect to form a three line and a point in a cube, a horizontal plane, a coronal plane, and a sagittal plane passing through the point can be made, respectively, to form a three-dimensional directional coordinate system with this point as the origin. According to the parameters of CT scanning, the vertical projection lines and planes in the forehead, temporal part, and top and occipital parts were determined. Then, the center of the hematoma was determined according to the intersection of the three planes. The straight line formed by the intersection of any two planes in the three mutually perpendicular planes can be used as the puncture path and the position of the other plane can determine the puncture depth. This allows accurate access to the center of the hematoma. The stereotactic ruler **(B)**, skull drill **(C)**, and skull keyhole tool **(D)** are used in cubic oriented stereotactic aspiration.

studies suggest that minimally invasive craniosurgery combined urokinase is safe and might improve independent survival in patients with ICH. Nonetheless, the YL-1 needle is sharp and rigid, which may induce damage to brain tissues and rebleeding. Therefore, large-scale RCTs are needed to evaluate the safety and efficacy of YL-1 craniopuncture with thrombolytic agents.

Stereotactic Treatment of Intracerebral Hematoma by Means of a Plasminogen Activator (SICHPA)

The SICHPA trial was a multicenter RCT to investigate the efficacy of stereotactic treatment of ICH with the use of a plasminogen activator. This trial enrolled 71 patients with ICH volume $\geq$ 10 ml and randomly assigned them to surgery with catheter placement and urokinase infusion or medical treatment. The SICHPA significantly reduced the ICH volume. However, the rebleeding rate and mortality at 180 days were similar in these two groups (20). This study suggests that stereotactic aspiration is safe and effective for reducing the ICH volume. Nevertheless, the number of patients enrolled in this trial is small and, thus, the results should be interpreted carefully.

Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator in Intracerebral Hemorrhage Evacuation (MISTIE)

The MISTIE was an international, randomized, open-label, phase II study that enrolled 96 patients with ICH from 26 hospitals and randomized them into medical care or MIS with alteplase. According to the MISTIE protocol, a rigid cannula was inserted into the hematoma under the image guidance and then one soft drainage cannula was placed. The administration of rt-PA in a dose of 0.3 or 1.0 mg was carried out every 8 h until 9 doses were given or until the volume of remaining hematoma was $\leq$ 15 ml or until a clinically significant rebleeding occurred. MIS plus alteplase decreased the number of patients with the modified Rankin Scale (mRS) $\geq$ 3 in 1-year follow-up and significantly decreased the perihematoma edema volume. In addition, 30-day mortality,

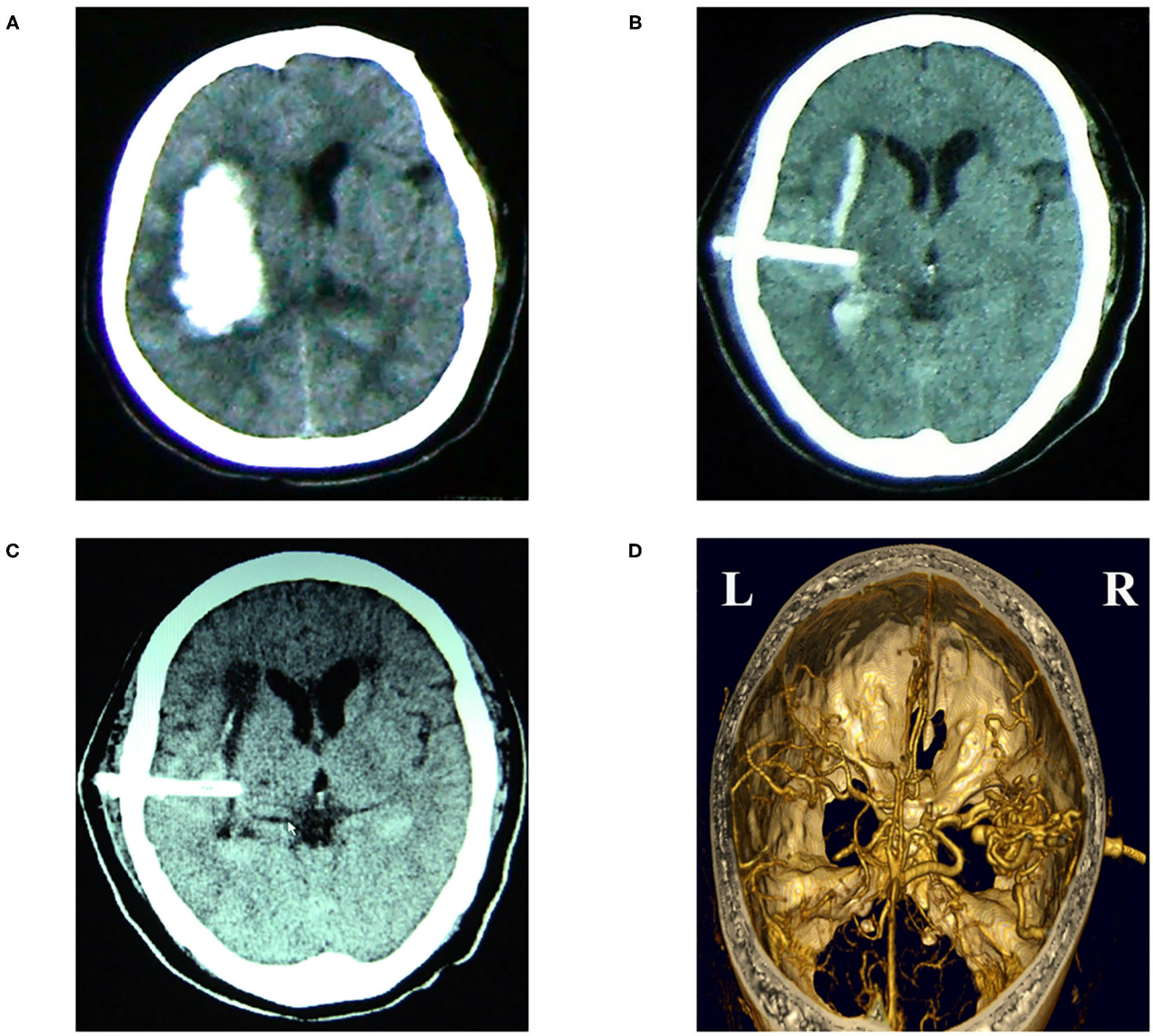

FIGURE 2 | Images from a 65-year-old patient with the hypertensive right temporal hemorrhage who received cubic oriented stereotactic aspiration. **(A)** Preoperative CT image of the head. **(B)** A post-operative CT image of the head was carried out immediately, which showed that the soft drainage tube was inserted into the hematoma and the volume of the hematoma was reduced after aspiration. **(C)** CT image at 4 days after operation displayed that the hematoma was almost completely evacuated. **(D)** The post-operative CT angiography image of the head showed that the soft tube did not lead to the damage of vessels.

infection, and symptomatic bleed were not significantly different between MIS plus alteplase and the conservative groups. Moreover, the volume of hematoma remaining was statistically significantly correlated with functional outcomes when other variables were controlled. These results suggest that MIS plus alteplase is safe to effectively evacuate hematoma and may improve functional outcomes through reducing clot volume (28). However, the sample size is relatively small and the objective of this study is to detect the threshold of safety not efficacy. In addition, the wide range of benefits estimated in intention-to-treat analyses makes it difficult to draw conclusions about benefits.

To test the conclusion of the MISTIE II and ensure its generalizability, the MISTIE III was performed in 78 centers. Appropriate patients were $\geq$ 18 years with supratentorial hemorrhage more than 30 ml plus the Glasgow Coma Scale (GCS) $\leq$ 14 or the National Institutes of Health Stroke Scale (NIHSS) score $\geq$ 6 and the hematoma remained stable (growth $<$ 5 ml) for at least 6 h after diagnostic CT. A total of 506 patients were enrolled in this study. The process for cannula placement and rt-PA injection was the same as described in the MISTIE II, except that the dose of rt-PA was different and limited to 1.0 mg. The mean reduction in hematoma size was 69% in the MISTIE group vs. 3% in the standard medical care group. Nonetheless,

only 58% of patients met the preset goal that the hematoma was <15 ml after surgical treatment and the functional outcome between these two groups did not significantly different. In addition, the safety events rates were not significantly different between the two groups (31). The main conclusion of this clinical study is that the MISTIE is safe and effective for ICH evacuation, but it cannot improve the prognoses of patients. Therefore, it cannot be recommended as an intervention to improve the functional outcome of all the patients with ICH. However, the MISTIE may improve functional outcomes when the protocol-defined surgical aim can be achieved (residual hematoma smaller than 15 ml) (31). In an exploratory analysis, reduction of hematoma volume to ≤15 ml associated with a good functional outcome (mRS 0–3) and reducing the hematoma volume by 70% or more increased the chance of achieving a good outcome, i.e., if the reduction exceeded the 15 ml threshold, the probability of good results would increase by 10% for every additional 1 ml of hematoma removed. The failure to achieve ≤15 ml goal evacuation was significantly associated with initial hematoma volume, history of hypertension, irregular-shaped hematoma, number of alteplase doses given, surgical protocol deviations, and catheter manipulation problems. Additionally, greater surgeon/site experience was associated with avoiding poor hematoma clearance. Taken together, the results indicate that surgical performance may determine the outcomes of patients with ICH. Enhanced surgical performance may improve the prognosis of patients.

Mechanically-Based Approaches for ICH

Endoport-Mediated Evacuation

The endoport system for clearing ICH originates from the computer-aided stereotactic method for resection of deep and central intracranial tumors. The system aims to effectively remove the hematoma and minimize damage to adjacent tissues. The endoport-mediated evacuation involves a small craniotomy with dura opening, stereotactic placement of an endoport to the hematoma (typically along the longest axis of the hematoma), and removal of hematoma with traditional surgical tools or special devices. Compared with the pharmacological catheter-based approach, this technique allows direct access to the hematoma cavity with irrigation, suction, and cautery instruments and clears more hematoma at once. It, however, needs craniotomy and may increase brain damage along the endoport path.

Currently, the most commonly used device is the NICO endoport system (Indianapolis, Indiana, USA). The NICO endoport system, consisting of the Myriad handpiece and the BrainPath sheath (**Figure 3**), is cleared by the United States Food and Drug Administration for the removal of tissue and visualization of the surgical field during neurosurgery (45). Ding et al. presented a case report about the use of NICO endoport system to evacuate a large basal ganglia hematoma (46). And then, they performed a retrospective study of 11 patients with ICH (9 with supratentorial hemorrhage and 2 with infratentorial hemorrhage and the volume of ICH from 8 to 168 ml) and used the same technique to evacuate the hematoma. They found that the ICH volume was reduced by 87% and 36% of patients were functionally independent (mRS 0–2) at 90 days (47).

Minimally Invasive Subcortical Parafascicular Access for Clot Evacuation (MISPACE)

A multicenter study to evaluate the safety and feasibility of the MISPACE by using the NICO endoport system was conducted in 11 centers in the United States and Canada. A total of 39 patients with ICH (ICH volume from 27 to 65 ml) were enrolled. The result of this study showed that hematoma volume was reduced by more than 90% in 72% of patients and 52% of patients had good functional outcomes with the mRS ≤ 2 at 90 days (48). The authors concluded that this method was safe and feasible to remove the clot. However, the sample size of this study is small and it is a retrospective, uncontrolled study. RCTs are still needed to assess the safety and effectiveness of the MISPACE.

Early MiNimally-Invasive Removal of Intracerebral Hemorrhage (ENRICH)

The ENRICH is a multicenter randomized controlled study comparing early (<24 h) surgical hematoma evacuation by using minimally invasive parafascicular surgery (MIPS) with the NICO endoport system with standard medical management in the treatment of acute spontaneous supratentorial ICH. This study is based on the solid foundation supplied by the results from the multicenter study for the MISPACE and other clinical studies by using the NICO system. The ENRICH is designed to enroll 300 patients with ICH and was started in 2016. It is still in progress.

Endoscope Evacuation

The ICH evacuation by an endoscope with the use of a single burr hole was first reported by Auer et al. (49). Thereafter, the same group performed a single-center randomized controlled study that compared endoscopic evacuation vs. medical treatment in patients with ICH. A total of 100 patients with supratentorial hematoma more than 10 ml and neurological or consciousness impairment were enrolled and assigned randomly. The clearance rate of hematoma in most patients was 50–70%. The mortality rate in the surgical group was significantly lower than the medical treatment group 6 months after hemorrhage (42 vs. 70%). The rate of better outcomes was higher in the surgical group than in the medically treated group (40 vs. 25%). However, these results were restricted in patients under 60 years old and with hematoma smaller than 50 ml (18). Since these promising results were obtained by the first generation of endoscopy, it is difficult to transfer the findings to the clinical situation of today. A more recent retrospective analysis of 68 patients with supratentorial ICH treated with endoscope-assisted ICH evacuation showed that rebleeding, morbidity, and mortality rates were low and long functional outcome was favorable when compared with the traditional craniotomy (50). Moreover, another retrospective analysis of 43 patients with putamen hematoma (volume > 31 ml), cerebellar ICH (hematoma > 3 cm in diameter), or thalamic ICH (hematoma volume > 20 ml) and acute hydrocephalus treated with endoscopic surgery and craniotomy procedure demonstrated higher evacuation rate and the higher GCS score at day 7 in the group of

FIGURE 3 | The NICO BrainPath System consists of a 13.5 mm diameter sheath with an internal dilator. The sheath and dilator have different lengths.

endoscopic surgery (51). However, the safety and efficacy of endoscopic surgery for ICH evacuation should be evaluated in RCTs.

Intraoperative Stereotactic CT-Guided Endoscopic Surgery (ICES) Trial

The ICES trial was a randomized arm of the MISTIE trial. In this study, 24 patients with hematoma volume more than 20 ml from different hospitals were randomized 3:1 to endoscopic surgery or standard medical management. The result showed that endoscopic surgery led to a 71.2% reduction of ICH with an associated 12% increase in good functional outcomes defined as the mRS score from 0 to 3 at 1 year (29). Although the number of patients involved in this preliminary study was small, the result of the study suggests that the endoscopic technique can be performed by different surgeons in a different location and can produce valuable results worthy of further evaluation in the phase III study.

Apollo System and the Minimally Invasive Endoscopic Surgical Treatment With Apollo in Patients With Brain Hemorrhage (INVEST)

There are some promising tools used for endoscopic ICH evacuation and the Apollo System (Penumbra Incorporation, Alameda, California, USA) is one of them. The Apollo System is a nonclogging aspiration–irrigation system designed to fit down the working channel of a three-port neuroendoscope (**Figure 4**). The aspiration–irrigation system can be connected with the Apollo wand through a flexible tube. The wand is equipped with an internal stirrer line that vibrates at ultrasonic frequency and impregnates the clot material to keep the system unobstructed during the suction process. The aspiration–irrigation system provides the ability of suction and continuous saline flushing and transmits vibration energy to the internal agitator elements in the wand. The advantage of the Apollo device in increasing the emptying of the endoscope is that it allows more directional suction and can extend beyond the end of the endoscope in a controlled way. Spiotta et al. performed a retrospective analysis of 29 patients with ICH who underwent ICH evacuation with the Apollo system at 4 centers. The mean ICH volume decreased from 45.4 ± 30.8 to 21.8 ± 23.6 ml after evacuation (52). Fiorella et al. presented case reports of 3 patients with supratentorial ICH who underwent hematoma evacuation by using the Apollo System with combined neuronavigation, neuroendoscopy, and cone-beam CT. The volume of hematoma was reduced from 93.4 to 15.6 ml and 11.2 to 0.9 ml after evacuation. Moreover, no complications occurred for the procedure (53). More clinical data are needed to determine the extent of hematoma removal to improve clinical symptoms and whether it can achieve more complete blood product emptying, thereby offsetting the disadvantages of large channels.

The INVEST trial is a multicenter single-arm phase II trial, which is evaluating the safety and efficacy of the minimally invasive hemorrhage evacuation with Apollo device compared with medical management. The study has initiated enrollment in 2016.

Other Mechanically-Based MIS Approach

Kim et al. performed a prospective study, which enrolled 387 patients with ICH volume $\leq$ 30 ml limited to the basal ganglia and thalamus and randomized them into either MIS by using an Archimedes aspirator or to medical management. If the remaining hematoma exceeded 10 ml after surgical evacuation, the instillation of urokinase in the hematoma cavity was considered. In the MIS group, patients had better functional outcomes with higher mean of the Barthel Index scores (90.9 vs. 62.4) and the lower mRS scores (1.2 vs. 3.0) at 180 days.

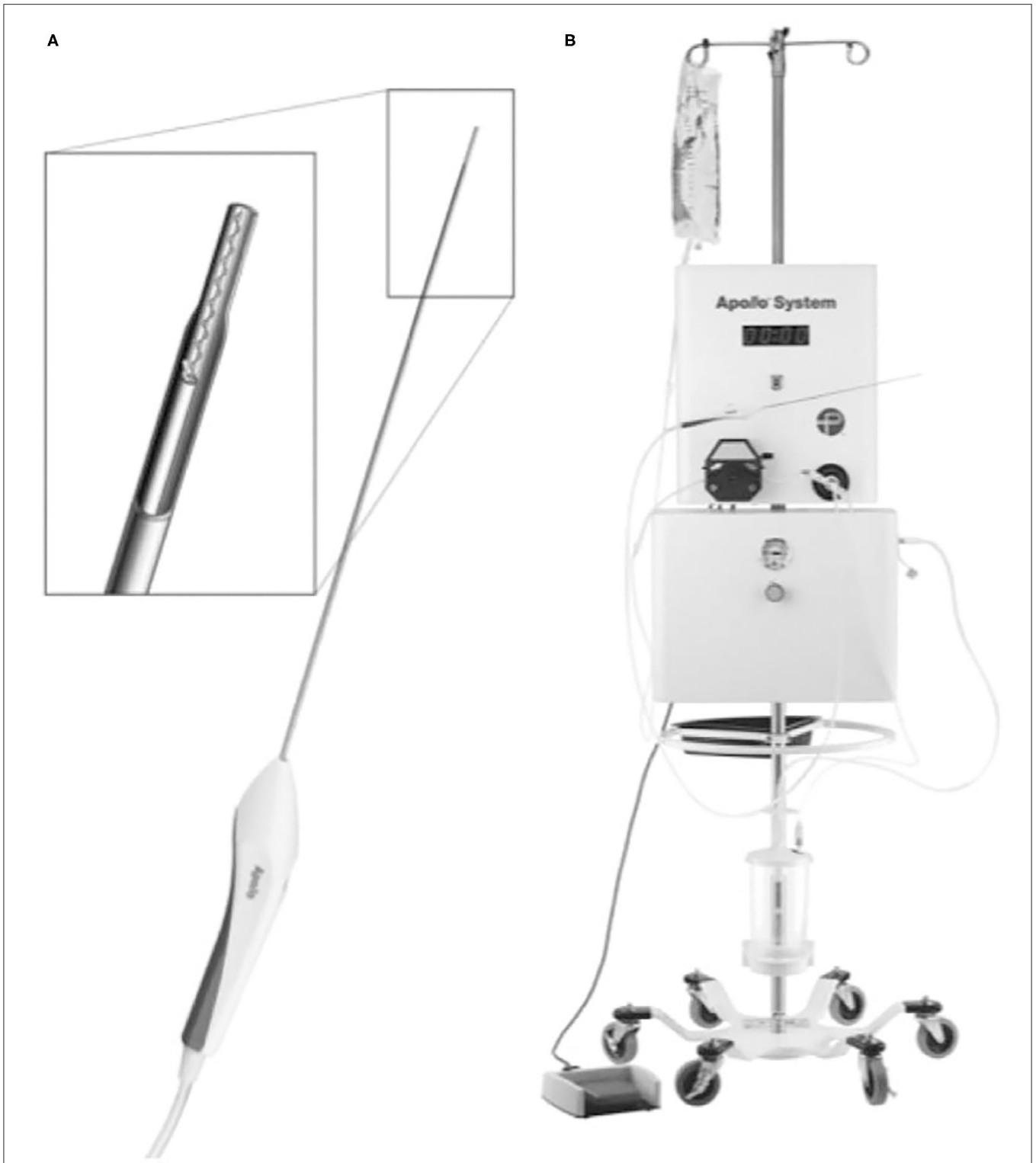

FIGURE 4 | The Apollo System consists of a suction-irrigation system that can be connected to the Apollo wand through a soft tube. The wand **(A)** can be placed through the working channel of a neuroendoscope. The wand is equipped with an internal stirrer line that vibrates at ultrasonic frequency and impregnates the clot material to keep the system unobstructed during suction. The wand is connected to a stand-alone suction-irrigation system **(B)** [from Fiorella et al. (45) with permission].

Meanwhile, the mortality was not significantly different between the MIS and medical treatment groups (22).

MINIMALLY INVASIVE SURGERY FOR IVH

Usually, IVH is a complication of spontaneous ICH. However, it sometimes occurs without an identifiable cause. The extension of ICH into the ventricular is an independent risk factor for poor prognosis (54). In addition, the volume of IVH is related to the clinical outcomes (54, 55).

The application of MIS in the treatment of IVH is based on the hypothesis that the reduction of hematoma volume and the restoration of cerebrospinal fluid circulation can reduce secondary brain tissue damage. Like ICH, MIS for IVH includes pharmacological catheter-based and mechanically-based approaches. The pharmacological catheter-based method involves the injection of fibrinolytic drugs (urokinase or rt-PA) through external ventricular drainage (EVD) tube. The mechanically-based approach involves the direct movement of intraventricular hematoma with the endoscopy. These methods have their disadvantages. The disadvantages of the pharmacological catheter-based method include the risk of infection from the repeated injection of a lytic agent through EVD, potential hematoma expansion induced by the lytic agent, a relatively long period for adequately clearing IVH, and risk of failure to reduce the volume of intraventricular hematoma (56). The mechanically-based approach is more invasive and needs craniotomy with a small bone flap.

Pharmacological Catheter-Based Treatment for IVH

Injection of fibrinolytic drugs through EVD has been proved to be safe and effective in animal studies (57–59). And then, this result has been confirmed in small clinical case series (60–62). Nieuwkamp et al. conducted one systemic review of 343 patients with severe IVH caused by extension from subarachnoid hemorrhage or ICH from 18 observational studies and these patients received conservative treatment, EVD or EVD with fibrinolytic agents. They found that the case fatality rate was significantly lower in patients receiving EVD combined with fibrinolytic agents. The poor outcome rate was also lower for EVD with fibrinolytic agents compared with conservative treatment or EVD. Treatment with EVD combined with fibrinolytic agents may improve the outcome of patients with severe IVH (63). Furthermore, Khan et al. conducted a meta-analysis to investigate the impact of intraventricular fibrinolytic therapy on mortality, functional outcome, ventriculitis, shunt dependence, and rehemorrhage. The meta-analysis enrolled 24 studies and demonstrated the benefit of intraventricular fibrinolytic on mortality and good functional outcome. In addition, intraventricular fibrinolytic decreased the rate of shunt dependence and was not associated with increased rates of ventriculitis or rehemorrhage (64). This meta-analysis concluded that intraventricular fibrinolytic was safe and could be an effective strategy for the treatment of IVH. Nonetheless, those results are from observational or small randomized studies and randomized clinical trials are needed. Then, a randomized, double-blind, controlled, multicenter, pilot study was performed to assess the safety and efficacy of intraventricular thrombolysis. A total of 12 patients with IVH associated with supratentorial ICH of <30 ml were enrolled in this study and randomized to receive intraventricular injections of normal saline solution or urokinase at 12-h intervals. Compared with treatment with EVD alone, intraventricular thrombolysis with urokinase speeded the resolution of intraventricular blood clots and the frequency of adverse events did not differ significantly between the two groups (19). The number of patients enrolled in this study, however, is small and the findings need to be validated in a large study.

Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR-IVH)

The pilot study led to the CLEAR-IVH trial which was a phase II trial and was to evaluate the safety and efficacy of using multiple injections of low-dose rt-PA to accelerate lysis and evacuation of IVH. In this study, 48 patients with IVH were randomized into treatment with rt-PA and placebo. The administration of rt-PA could accelerate the clearance of IVH clots. Although the symptomatic bleeding rate in patients treated with rt-PA was higher than that in patients receiving placebo, a trend to improve clinical outcomes at 30 days was observed. Moreover, the rate of IVH clot resolution was significantly correlated with early clinical improvement (26). This phase II trial optimized the dose effect of rt-PA and demonstrated a trend toward improved clinical outcome at 30 days in patients treated with rt-PA, promoting a more definitive phase III trial.

The CLEAR III was an investigator-initiated, phase III, randomized, multicenter, double-blind, placebo-controlled study comparing the use of EVD combined with rt-PA with EVD plus saline (placebo) for the treatment of IVH. A total of 500 patients with IVH and obstructive hydrocephalus in 73 centers were enrolled and assigned 1:1 to the alteplase group and the saline group. Alteplase (1 mg) or 0.9% saline was given up to 12 doses, 8 h apart through EVD. The administration of alteplase was stopped when 3rd and 4th ventricles open, intraventricular hemorrhage mass effect relieved, 80% of clot removed, or 12 doses were given. The study showed that intraventricular rt-PA did not affect the primary efficacy outcome, but there were less frequent adverse events and a lower case fatality at 180 days in the alteplase group. In addition, clot removal was significantly related with both the mRS $\leq$ 3 and case fatality (30). These results suggest that by using alteplase through EVD is safe, but it cannot improve functional outcomes at the mRS 3 cutoff compared with by using saline through EVD. However, the benefits of alteplase may be possible if greater clot removal can be achieved. Unfortunately, only 30% of patients treated with alteplase achieved the goal of 80% blood clot reduction, which may be one of the reasons that alteplase treatment cannot effectively improve functional outcomes.

Mechanically-Based MIS for IVH Treatment

Several case series and case reports showed the safety and efficacy of endoscopy to treat IVH. Longatti et al. reported 13 patients with spontaneous primary or secondary IVH who

underwent endoscopy treatment and they found that endoscopy management was safe and effective to remove the intraventricular blood clot. Compared with other more conventional treatments, endoscopy may improve the clinical outcome of patients with IVH (65). Basaldella et al. performed a comparative retrospective analysis of 96 patients with massive IVH (48 patients treated with endoscopy surgery and 48 patients treated with EVD alone) to assess the efficacy of endoscopy surgery on IVH. The analysis demonstrated that endoscopy treatment combined with EVD reduced the shunting rate by 34% compared with EVD alone. However, endoscopy treatment did not significantly affect the outcome at 1 year as determined by using the mRS (66). In addition, Rienzo et al. presented a retrospective analysis of the two groups of patients with cast IVH who received endoscopy-assisted surgery or EVD and found that endoscope-assisted evacuation reduced ICU staying and cerebrospinal fluid (CSF) clearance times. Moreover, endoscopy seemed to improve neurological outcomes, but without affecting the need for permanent shunt (67). However, these are just experience from small case serials and RCTs are needed to evaluate the safety and efficacy of endoscopy treatment for IVH. Zhang et al. conducted a prospective and randomized study that enrolled 42 patients with IVH and these patients were randomly assigned to the endoscopic group and the EVD group. In the endoscopic group, EVDs were placed after the procedure and if the remaining IVH volumes were > 10 ml, injection of urokinase into the ventricle through EVD was performed. In patients allocated to receive an EVD alone, a lytic solution was also administered through the drain. The authors found that more patients in the endoscopic group got the high Glasgow Outcome Scores at 2 months. The mortality rate was not significantly different between these two groups (21). Chen et al. randomized 48 patients with IVH from thalamic hemorrhage (1:1) into the EVD group and endoscopic surgery followed by the EVD group. In the endoscopic surgery group, a standard suction tube was placed side by side with the endoscope through a hard sheath to evacuate blood from the ventricular system ipsilateral to the thalamus hemorrhage. The endoscopic surgery significantly reduced the length of the intensive care unit (ICU) stay and the rate of the shunt (47.62 vs. 90.48%) compared with EVD alone. Nonetheless, the 30- and 90-day mortality rates and the GCS scores were not significantly different between the EVD and endoscopic surgery groups (24).

Several small randomized and observational studies of endoscopic surgery, EVD alone, or EVD with intraventricular fibrinolysis studies in IVH were assessed in a meta-analysis conducted by Li et al. of 680 patients from 11 studies. This meta-analysis demonstrated that compared with EVD with intraventricular fibrinolysis, endoscopic surgery with EVD significantly reduced mortality and shunt rates and increased hematoma evacuation rate. Therefore, the authors suggested that endoscopic surgery with EVD may be better than EVD with intraventricular fibrinolysis in the management of IVH (68).

In brief, the available evidence suggests that mechanically-based techniques can safely and effectively evacuate IVH. Mechanically-based techniques have the potential to improve functional outcomes in some patients with IVH, but more evidence is needed. Zhu et al. are performing a prospective, randomized, controlled, multicenter clinical trial to compare the prognosis of patients undergoing endoscopic surgery vs. those undergoing EVD for moderate-to-severe IVH. This clinical trial will enroll 956 patients with moderate-to-severe IVH who will be randomly assigned 1:1 to the endoscopic surgery group or the EVD group and recruitment began in 2020 (69). The results from this trial will provide high-quality evidence for mechanically-based MIS treatment for IVH.

From the abovementioned clinical studies concerning the pharmacologically- or mechanically-based MIS for ICH and IVH, it is clear that MIS is safe and effective in removal of hematoma compared with conventional surgery and medical treatment. However, MIS is not suitable for patients with unstable hematoma. Additionally, phases II and III clinical trials do not supply definitive evidence that MIS can improve the prognoses of patients. There are several explanations for this. First, extended clot dissolution time offsets the main goal to minimize secondary injury induced by ICH, which begins only a few hours after bleeding and progresses over time. Second, removing the bleeding foci by dissolving the blood clot without properly managing the suspected blood vessel may lead to further expansion of the hematoma. Third, each MIS method lacks standardization and, thus, it is difficult to teach technology and generalize the results. Last but not least, surgical performance may be different during MIS. Catheter manipulation problems, surgical protocol deviations, and greater surgeon/site experiences influence hematoma evacuation, while the volume of residual hematoma is associated with functional outcomes. Therefore, generalization of optimal performance with hematoma evacuation will require focused surgeon education, emphasizing technical nuances, better demonstration of experience, and a rigorous definition of benchmarks for successful tasks. Future research should focus on the best way to achieve this goal and case selection may need to be customized separately for various technologies. Besides, since ultra-early surgery results in a higher rate of rebleeding, the timing of surgery may be an important part of the effectiveness of MIS and this factor should be included in the trial design.

NEW MIS TECHNOLOGIES

Three-Dimensional Printing Technology

In the recent years, 3D printing technology has become a hot field of biomedical research; it is a rapid prototyping technology based on the digital model file, which is used to print solid objects with complex geometry through layered processing. For ICH, 3D printing technology is based on the original Digital Imaging and Communications in Medicine (DICOM) data of CT. This technology can help to analyze the shape and location of the hematoma of the patient and design surgical approaches that avoid important areas such as the venous sinuses, functional areas, and frontal sinuses. In addition, during hematoma puncture, the puncture angle and puncture position can be fixed by 3D-printed guide holes to reduce tissue damage caused by inaccurate positioning and repeated punctures. Zhang et al. retrospectively analyzed 12

patients with basal ganglia hemorrhage who underwent 3D-printed model-guided endoscopic evacuation for hematoma. They found that the average evacuation rate of hematoma was 97.2% and all the patients had good outcomes evaluated by functional independence measure scores at 6 months, which suggested that 3D-printed model-guided endoscopic evacuation was effective and safe (70). Additionally, Wang et al. applied a 3D-printed navigation mold in puncture drainage for brainstem hemorrhage and found that 3D-printed technology made the puncture drainage more individualized and precise (71).

Diffusion Tensor Imaging and MIS

Diffusion tensor imaging has been used to assess the integrity of the white matter tract and predict motor functional outcomes in patients with ICH (72, 73). Wu et al. found that the changes of the cortical spinal tract could be observed intuitively through DTI in patients with ICH and MIS can reduce the damage to the cortical spinal tract led by hematoma and even could restore the cortical spinal tract, which was oppressed and displaced by hematoma (74). Moreover, preoperative DTI can help doctors to clarify the positional relationship between hematoma and white matter tracts and, thereafter, to determine the MIS approach and surgical trajectory. Therefore, DTI may be combined with different MIS technologies to optimize MIS approaches and explore the efficacy of MIS.

Robot for Neurosurgery

The robot for neurosurgery has been used in clinical studies. It establishes 3D coordinates based on CT or MRI. Then, the mapping relationship between the computer and actual images is established through positioning marks and stereotactic surgery is planned and operated virtually. Finally, the auxiliary positioning and navigation by multisensor intelligent mechanical arms are realized. In addition, the robot can display 3D visualization of cerebral vessels based on multimodal image infusion, which could help to accurately locate the hematoma and plan the hematoma puncture trajectory, avoiding vessels. Wang et al. retrospectively analyzed 17 patients with hypertensive ICH who received robot-assisted frameless stereotactic MIS. They found that the average positioning error was 1.28 ± 0.49 mm and the functional outcome of patients was improved at 3 months (75).

Xiong et al. conducted a systematic review to assess the safety and efficacy of robotic surgery for ICH and suggested that compared with conventional surgery or conservative treatment, robotic surgery is safer and more effective (76).

CONCLUSION

Spontaneous ICH, especially those related to IVH, is still one of the most fatal and disabling diseases, causing a high-cost burden on society. Extensive practice mode, vague practice standard, lack of proven therapy, and persistent adverse results cast a shadow on its management. So far, it has not been clearly shown that neurosurgical interventions can improve the prognosis of patients with ICH. However, new emerging results of MIS for ICH and IVH have been very encouraging: MIS can reduce the secondary injury after ICH and IVH, thus potentially reducing mortality and dependence. During the process of MIS, surgical performance is important, since it is associated with the outcomes of patients. Additionally, new technologies could improve the accuracy and safety of MIS. Currently, trials of several new minimally invasive approaches for ICH and IVH evacuation are being evaluated and more clear evidence is expected in the near future. Moreover, ongoing clinical trials are expected to change clinical practice by optimizing case selection and surgical tasks and integrating these new tools into treatment.

AUTHOR CONTRIBUTIONS

ZZ and QW contributed to the literature review and wrote the manuscript. JL contributed to writing and modifying the manuscript. SS read and checked the manuscript. All authors contributed to the article and approved the submitted version.

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Minimally Invasive Surgery for ICH Evacuation Combined With Deferoxamine Treatment Increased Perihematomal Claudin-5 and ZO-1 Expression Levels and Decreased BBB Permeability in Rabbits

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Objective: To investigate the role of minimally invasive surgery (MIS) in intracerebral hemorrhage (ICH) evacuation combined with deferoxamine (DFX) treatment on perihematomal tight junction protein (claudin-5 and ZO-1) expression levels and blood-brain barrier (BBB) permeability in rabbits.

Methods: We randomly assigned 65 male rabbits (weight: 1.9–2.6 kg) to a normal control group (NC group, 13 rabbits), hemorrhage model group (HM group, 13), DFX treatment group (DFX group, 13 rabbits), MIS group (MIS group, 13 rabbits), or MIS combined with DFX treatment group (MIS + DFX group, 13 rabbits). ICH was established in all of the groups except the NC group. MIS was performed to evacuate the hematoma 6 h after the ICH model was created in the MIS and MIS + DFX groups. The DFX and MIS + DFX groups were treated with DFX (100 mg/kg, dissolved in 2 mL of 0.9% saline solution, administered intramuscularly) at 2 h, and then every 12 h for 7 d. The same dose of 0.9% saline solution was administered to the NC, HM, and MIS groups at the same time points. Sixty-five rabbits were divided into 5 groups, and 13 rabbits in each group. Neurological deficit (i.e., Purdy's score) was recorded in all rabbits before euthanasia (N total = 65). In each group, 2 rabbits were used for iron concentration measurement (N total = 10), 2 rabbits were used for brain water content measurement (N total = 10), 3 rabbits were used for BBB permeability measurement (N total = 15), 3 rabbits were used for claudin-5, ZO-1 expression detection by Western Blotting (N total = 15), and 3 rabbits were used for claudin-5, ZO-1 mRNA detection by real-time PCR (N total = 15). On day 7, the rabbits were sacrificed and the perihematomal brain tissue was harvested to test the iron concentration, brain water content (BWC), tight junction proteins (claudin-5 and ZO-1) expression, and BBB permeability.

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Results: Purdy's score, iron concentration, and BWC were lower in the MIS and MIS + DFX groups compared to the HM and DFX groups. The MIS + DFX group showed a significant decrease in these indicators. The use of MIS to evacuate the hematoma led to increased expression levels of claudin-5 and ZO-1, as well as decreased BBB permeability. The MIS + DFX group exhibited a remarkable increase in claudin-5 and ZO-1 expression levels and a significant decrease in BBB permeability.

Conclusions: MIS combined with DFX treatment could increase the expression levels of perihematomal tight junction proteins (claudin-5 and ZO-1) expression, reduce BBB permeability, and improve the neurological function. MIS combined with DFX treatment may also prevent secondary brain damage following ICH.

Keywords: intracerebral hemorrhage, minimally invasive surgery, deferoxamine, tight junction proteins, blood-brain barrier permeability

INTRODUCTION

Intracerebral hemorrhage (ICH) has the highest mortality rate of any type of stroke; 46% of patients die or still have severe disability 1 year after the ICH. ICH is the most common cause of death and disability among Chinese residents. The severe impact on patients and society has made China the country with the heaviest burden of ICH worldwide (1–3). Nevertheless, there are no effective treatments for ICH, the clinical outcome remains poor and many challenges remain (4). Craniotomy for ICH evacuation is an aggressive treatment option that may lead to iatrogenic injury in some patients. A recent randomized clinical trial from China reported that a minimally invasive craniopuncture technique can improve the independent survival rates of ICH patients compared to conservative treatment. Minimally invasive craniopuncture appears safe and effective for ICH treatment (5, 6).

After ICH onset, red blood cells (RBCs) infiltrate the brain tissue and continuously lyse to release hemoglobin. Hemoglobin/iron deposit-induced oxidative damage leads to neuronal ferroptosis and poor neurological outcomes. Iron, a heme degradation product, plays an important role in ICH-induced brain injury. RBC disintegration leads to brain iron overload following ICH. Iron overload is closely related to poor outcome in ICH patients (7–9). Peroxidation catalyzed by iron is an important cause of brain damage. Iron damages the endotheliocytes and pericytes, which constitute the blood brain barrier (BBB), thereby degrading tight junction (TJ) proteins (claudin-5 and ZO-1), destroying the BBB integrity, and causing secondary brain injury (10).

Minimally invasive surgery (MIS) is an effective treatment option that may have superior benefit for ICH patients compared to other treatment options (11, 12). However, MIS does remove all RBCs, iron, and other neurotoxic substances, which extravasate into the perihematomal brain tissue (13–16). MIS alleviates secondary brain damage, but has limitations. Hematoma evacuation with MIS combined with the use of medications may alleviate secondary brain injury during ICH treatment (13, 17).

DFX, an iron chelator, rapidly penetrates the BBB and accumulates in the brain tissue at a significant concentration after intramuscular or subcutaneous injections (18, 19). DFX can prevent damage caused by iron overload and iron-mediated toxicity after ICH (20). DFX treatment reduces iron deposition and brain edema, and improves neurologic outcomes after ICH (21–23). Similar to MIS, DFX use also has limitations. In particular, DFX treatment did not improve outcomes in a collagenase-induced ICH rat model compared to the use of a whole-blood model (24). To explore the effect of DFX treatment in ICH and determine whether MIS combined with DFX treatment may be appropriate for ICH treatment, we evaluated the effect of MIS in hematoma evacuation combined with intramuscular DFX treatment on secondary brain damage in an ICH rabbit model.

MATERIALS

Main Reagents

Urethane (Hefei BASF Bio-technology Co., Ltd., Anhui, China), penicillin (Harbin Pharmaceutical Group, Harbin, China), urokinase (Wuhan Renfu Pharmaceutical Co., Ltd., Wuhan, China), deferroamine mesylate (Novartis Pharma GmbH, Weil, Germany), iron determination kit (Nanjing Jiancheng Institute of Bioengineering, Nanjing, China), 4% paraformaldehyde (Sinopharm Chemical Reagents Co., Ltd., Shanghai, China), PBS phosphate buffer (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China), claudin-5, ZO-1 rabbit polyclonal antibody (Boolsen Biotechnology Co., Ltd., Beijing, China), and PrimeScript™ RT reagent Kit with gDNA Eraser and HiScript II One Step QRT-PCR SYBR Green Kit (Nanjing Novus Biotechnology Co., Ltd., Nanjing, China) were used for the experiments. The following reagents were purchased from Kangwei Century Company, Beijing, China: Protease inhibitor, BCA protein quantitative Kit, WB (HRP) Kit (rabbit), WB (HRP) Kit (mouse), Ultrapure RNA Kit, Goat anti-rabbit. claudin-5 and ZO-1 (Boolsen Biotechnology Co., Ltd., Beijing, China), GAPDH and β-actin (Jing Tiancheng Biotechnology Co., Ltd., Beijing, China), formamide (Shanghai Aladdin Biochemical Technology

Co., Ltd., Shanghai, China), and Evans Blue (Beijing Solebo Technology Co., Ltd., Beijing, China) were purchased from the respective manufacturers.

Main Instruments

A ZH-Lanxing B-Type rabbit stereotaxic apparatus (Huaibei Zhenghua Biological Instrument & Equipment Co. Huaibei, Anhui, China), UV-visible Spectrophotometer (Beijing Universal Analysis Instrument Co., Ltd., Beijing, China), Real-time Fluorescence Quantifier (RT-PCR) (Step One Plus TM, Applied Biosystems, Foster City, CA, USA), low-temperature centrifuge (Hunan Xiangyi Experimental Instrument Factory, Hunan, China), electrophoresis apparatus (Shanghai Tieneng Technology Co., Ltd., Shanghai, China), electronic balance (Shimadzu Co., Ltd., Kyoto, Japan), and a constant temperature drying oven (Tianjin Tester Co., Ltd., Tianjin, China) were used for the experiments.

METHODS

Experimental Groups

The study protocols were approved by the Animal Care and Use Committee of Guizhou Medical University, China, and performed according to the criteria of satisfactory laboratory practice for drugs. A total of 65 rabbits (1.9–2.6 kg) were provided by the Experimental Animal Center of Guizhou Medical University. The rabbits were kept at 10–25°C by a special animal breeder. Rabbits were fed animal fodder and water. Rabbits were randomly divided into a normal control group (NC group, 13 rabbits), a hemorrhage model group (HM group, 13 rabbits), a DFX medication group (DFX group, 13 rabbits), a MIS group (MIS group, 13 rabbits), and a MIS combined with DFX treatment group (MIS + DFX group, 13 rabbits). ICH was induced in all of the groups except NC group. The rabbits were sacrificed under anesthesia on day 7 after the relevant treatment.

ICH Model Preparation

The methods used in this study for establishing the ICH model were similar to those used in our previous studies (25, 26). First, rabbits were anesthetized using injections of 20% urethane (2 mL/kg) into the marginal ear vein. The anesthetized rabbit was fastened to a stereotaxic apparatus, and the skin in the operative area was disinfected with povidone iodine. The skin was incised (3 cm) to expose the bregma and lambdoid demarcations. The head was adjusted to position the bregma to be 1.5 mm higher than the lambdoid demarcation. The bregma cross-suture junction was used as a reference point; the puncture point was selected 6 mm to the left along the coronal plane and 1 mm parallel to the sagittal plane. The skull was drilled using a dental drill (1 mm in diameter) at the puncture point, and 0.5 mL of autologous arterial blood was extracted from the central ear artery using an insulin syringe. The syringe was connected to a size-7$^{\#}$ needle with a flat tip. The size-7$^{\#}$ needle was quickly inserted vertically into the puncture point in the skull up to a depth of 12 mm, and 0.3 mL of autologous arterial blood (similar to a 30 mL basal ganglia hematoma in humans) was slowly injected into the basal ganglia. The injection lasted for at least 3 min. The needle was retained in the same position for 8 min after injection, followed by slow removal of the needle. The drill hole was sealed with bone wax to prevent pneumocephalus.

The rabbits were sent back to the experimental animal center and fed as usual for 7 d. Animals received an intramuscular injection of penicillin (400,000 U) once daily for 3 d to prevent infection.

All of the rabbits were underwent pathological analysis of brain tissue at day 7. Neurological deficit scores >2 (recorded before euthanasia) or basal ganglia hematoma, with no empirical evidence of damage or lateral ventricle hematoma, was required for the ICH model to succeed (**Figure 1C**). Exclusion criteria during and after MIS included backflow along the needle track, blood in the ventricle, and death.

MIS Procedures

According to our previous studies, the optimal time of MIS is 6–12 h after ICH (27). MIS was performed to evacuate the hematoma 6 h after the ICH model was established. The rabbits were anesthetized again and placed in the stereotaxic apparatus. A size-7# needle with a flat tip was inserted into the hematoma along the same drill hole, and an insulin syringe was connected to the needle; 0.1 mL/5000 U of urokinase (urokinase 100,000 U dissolved in 2 mL of 0.9% saline solution; 0.1 mL = 5000 U) was injected into the hematoma. The needle was kept inside the hematoma for 1 h, followed by withdrawal of the needle while slowly aspirating the hematoma. The skin was disinfected and sutured. The rabbits in the NC group were treated using the same procedures (i.e., 0.3 mL of 0.9% saline solution was injected into the puncture region, and 0.1 mL of 0.9% saline solution was infused into the same area again at 6 h). In the HM and DFX groups, a sham MIS was performed 6 h after the ICH model was established, by infusing 0.1 mL of 0.9% saline solution into the hematoma at 6 h. The rabbits in the DFX group were given the DFX solution intramuscularly (100 mg/kg, dissolved in 2 mL of 0.9% saline solution) at 2 h, followed by repeat administration every 12 h for 7 d. In the MIS+DFX group, MIS was used to evacuate the hematoma, followed by intramuscular injection of the same amount of DFX solution. The rabbits were sacrificed on day 7 after the corresponding procedures. Histopathological analysis was performed to evaluate the effectiveness of MIS (**Figure 1E**).

Brain Tissue Preparation

The methods used for preparation of brain tissue were the same as those used in our previous studies (25, 26). We injected 20% urethane (2 mL/kg) to anesthetize the rabbits. The brain was placed on ice. With the hematoma placed at the center, brain tissues around the hematoma were sliced and divided into four parts: anterior, posterior, left, and right. A total of 5 mm of brain tissues surrounding the hematoma were harvested from each part to measure the iron content, brain water content (BWC), expression levels of claudin-5 and ZO-1, and BBB permeability.

Neurological Deficit Score (Purdy's Score) Evaluation

Neurological deficit was recorded after the rabbit awoke from anesthesia and 2 h before euthanasia on day 7 after the corresponding treatments were performed. A neurological deficit

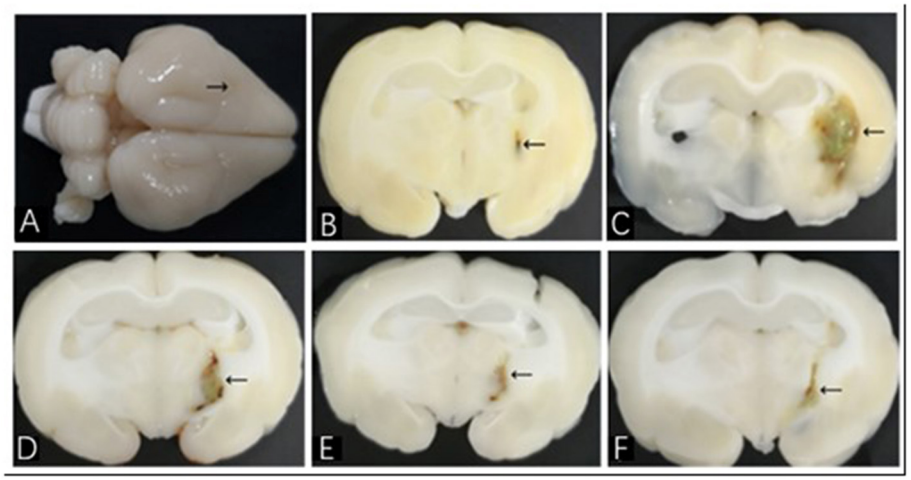

FIGURE 1 | Brain histological sections of ICH model in rabbit. **(A)** The whole brain specimen of rabbit; the arrow shows the puncture point; **(B–F)** show histological sections of NC, HM, DFX, MIS, and MIS + DFX groups, respectively. The arrows show hematoma.

scale (Purdy's score) (28) was used to compare the neurological function among the experimental groups. Tests were performed by two researchers who were blinded to the treatments. The tests included an evaluation of the motor function (score of 1–4), conscious level (score of 1–4), head turning (score of 0–1), circling (score of 0–1), and hemianopsia (score of 0–1). A score of 11 indicated maximum impairment (comatose or death), whereas a score of 2 indicated normal examination.

Iron Concentration Measurement

The double steaming water colorimetry method was used to measure perihematomal iron concentration. The perihematomal brain tissues were weighed to determine the iron concentration [weight (g): volume (mL) = 1:9]. Therefore, saline was added at a volume 9 times the weight of the brain tissue. Mechanical homogenization was performed under ice-water bath condition; the homogenate was centrifuged for 10 min at 2,500 rpm. The supernatant was obtained and tested to determine the iron concentration using the Iron Determination Kit (Nanjing Jiancheng Institute of Bioengineering, Nanjing, China).

BWC Measurement

The dry- and wet-weight method was used to measure the BWC. Brain tissues surrounding the hematoma were used to measure the BWC. First, the wet tissues were weighed, and the samples were placed in an oven at 100°C for 48 h. The dried samples were also weighed (with an accuracy of 0.1 μg). BWC was calculated as follows: (wet weight—dry weight)/wet weight × 100%.

BBB Permeability Measurement

Evens Blue (EB) was applied as a tracer to estimate the BBB permeability. Two h before brain harvesting, EB solution (2 mL/kg) was injected into the ear vein of the rabbits. Brain tissues surrounding the hematoma were quickly obtained and weighed on an electronic balance (with an accuracy of 0.1 mg). The samples were placed in a test tube with 4 mL of formamide.

TABLE 1 | Sequences for primers.

Gene name		Primer sequences	Product (bp)
claudin-5	Forward	5′-TCCAGTGCAAAGTCTTCGAC-3′	243
	reverse	5′-TGTTGCCATACCATGCTGTG-3′	
ZO-1	Forward	5′-AGGGGCAGCTACAGGAAAAT-3′	173
	reverse	5′-TGGTTCAGGATCAGGACGAC-3′	
GAPDH	Forward	5′-CATGTTTGTGATGGGCGTGA-3′	244
	reverse	5′-GGAGGCAGGGATGATGTTCT-3′	

The test tube was capped and placed into a 54°C constant-temperature water bath for 24 h for EB staining. The test tube was centrifuged at 2,400 rpm for 5 min. The supernatant was absorbed using a pipette, and the absorbance was measured using a spectrophotometer (λ = 632 nm). Formamide solution was applied as a blank control. EB content was measured from the standard curve, as described in our previous studies (25, 26). The formula used was as follows: EB content in brain tissues (μg/g wet brain) = B × formamide (mL)/wet weight (g); where B is the sample EB content (μg/mL) obtained from the linear regression equation base of the standard curve.

Real-Time PCR for Claudin-5, ZO-1 mRNA Detection

Brain tissues surrounding the hematoma were obtained. An electronic balance (∼30 mg, with an accuracy of 0.1 mg) was used to weigh the brain tissues. The brain tissues were pulverized, and total RNA was separated using a Trizol Reagent box. Total RNA was used to produce cDNA using a PrimeScript™ RT reagent Kit with gDNA Eraser. Data were normalized to those of GAPDH. Primer sequences used for claudin-5, ZO-1, and GAPDH are listed in **Table 1**.

Western Blotting for Claudin-5, ZO-1 Expression Detection

Brain samples were homogenized and centrifuged to determine the protein concentrations. Proteins were separated using 10% sodium dodecyl sulfonate- polyacrylamide gel (SDS-PAGE) electrophoresis and transferred to a nitrocellulose film. The protein concentrations were determined by marking and using one-step fast WB kit (HRP). Antibodies used for incubation were as follows: primary antibody β-actin 1:500, goat anti claudin-5 polyclonal antibody 1:100, mouse anti ZO-1 monoclonal antibody 1:500, and secondary antibody 1:400. The antibodies were incubated overnight at 4°C and rinsed for chemiluminescence, followed by film exposure. Gel-Pro analyzer 4 image analysis software was used to measure the gray values of each band, and the results were expressed as the ratio of integral optical density value for claudin-5/β-actin and ZO-1/β-actin.

Statistical Analysis

SPSS software (version 19.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data are presented as mean ± standard deviation (X ± SD). ANOVA was used to compare the groups. The groups were compared using the Fisher's (F) test when the variances were equal. An F test (Welch test) was used when the variances were not equal. Multiple comparisons with the means were checked using Dunnett's T3 (unequal variances) tests. *P*-values < 0.05 were considered to be statistically significant.

RESULTS

ICH Model Preparation

After the injection of autologous arterial blood into the basal ganglia, the rabbits manifested with contralateral hemiplegia and were unable to walk or crawl. Neurological deficit scores > 2 demonstrated that the ICH model in this study was successful. A total of 72 rabbits were used in this study, of which 65 underwent the ICH model successfully according to the experimental requirements. Seven rabbits died accidentally. The brains of dead rabbits were dissected and examined, and results showed that two rabbits in the MIS group had died of intracranial infection. One rabbit died due to overdose of anesthetic agents in the NC group. Two rabbits in the MIS+DFX group died of unclear causes. One rabbit in the HM group died of status epilepticus, and one died of lung infection. These seven rabbits were excluded from the study. The other 65 rabbits were included in the experiments. There were 13 rabbits in each group. All of the rabbits tolerated ICH and MIS. They survived until the experiment was terminated.

Brain Histological Sections of the ICH Model in Rabbits

The rabbits were sacrificed on day 7 after the corresponding interventions were performed. The whole brain was observed with the naked eyes (**Figure 1A**), and the brain was sliced along the coronal puncture point. Analysis of the brain tissues from the NC group revealed clearly discernible, bilaterally symmetrical brain structure; a slight injury focused on the puncture point (**Figure 1B**). In the HM group, an oval hematoma was observed along with brownish-yellow margins in the left basal ganglia. The midline structures were not displaced and there was severe edema around the hematoma (**Figure 1C**). Compared with the HM group, the hematoma volume in the DFX group (**Figure 1D**), MIS group (**Figure 1E**), and MIS + DFX group (**Figure 1F**) were smaller and there was less hemosiderin deposition around the hematoma. The MIS + DFX group exhibited excellent results compared to the DFX and MIS groups.

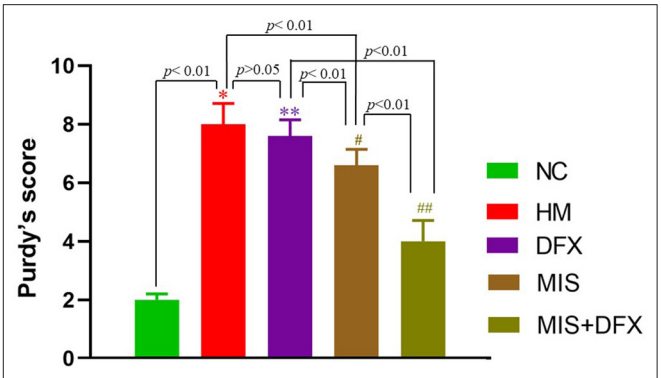

FIGURE 2 | Changes in neurological deficit (Purdy's score). MIS combined with DFX treatment was superior to both MIS and DFX treatment alone. Evaluating the neurological deficit by Purdy's score. $*p < 0.01$ vs. NC group; $**p > 0.05$ vs. HM group; $\#p < 0.01$ vs. HM and DFX groups; $\#\#p < 0.01$ vs. DFX and MIS groups. Data are presented as mean ± SD.

Neurological Deficit Score (Purdy's Score) Changes

The neurological function scores were significantly higher in the HM group compared to the NC group ($p < 0.01$), suggesting that ICH was associated with impaired neurological function. There was no significant difference in neurological deficit between the DFX and HM groups ($p > 0.05$). The MIS group exhibited lower neurological function scores compared to those in the HM and DFX groups ($p < 0.01$). Following MIS combined with DFX treatment, the neurological function scores were significantly decreased compared to those in the DFX or MIS group ($p < 0.01$), suggesting that MIS combined with DFX treatment was superior to only MIS or DFX treatment (**Figure 2**).

Perihematomal Iron Concentration

Iron concentration around the hematoma in the HM group was significantly higher than that in the NC group ($p < 0.01$), suggesting that hemoglobin was released due to RBC lysis after ICH. In the MIS and DFX groups, iron concentration was decreased compared to that in the HM group ($p < 0.01$), suggesting that both MIS and DFX treatments could decrease the iron concentration. Additionally, MIS combined with DFX treatment significantly decreased the iron concentration compared to that in the MIS and DFX groups ($p < 0.05$) (**Figure 3**).

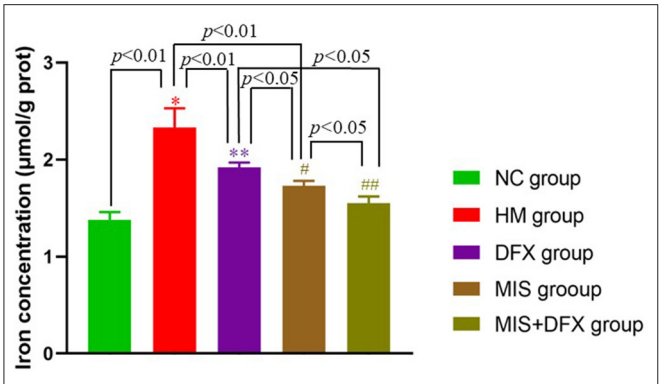

FIGURE 3 | Changes in perihematomal iron concentration. MIS combined with DFX treatment was found to reduce iron overload surrounding hematoma. Testing the iron concentration by double steaming water colorimetry. $^{*}p < 0.01$ vs. NC group; $^{**}p < 0.01$ vs. HM group; $^{\#}p < 0.01$ vs. HM group; $^{\#}p < 0.05$ vs. DFX group; $^{\#\#}p < 0.05$ vs. DFX and MIS groups. Data are presented as mean ± SD.

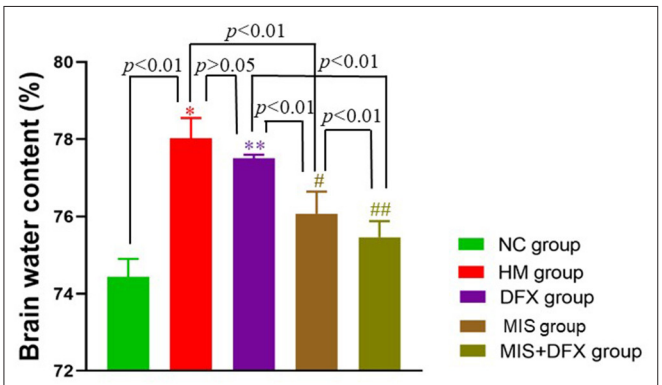

FIGURE 4 | Changes in perihematomal BWC. MIS combined with DFX treatment was found to decrease perihematomal BWC. Evaluating BWC by dry- and wet-weight method. $^{*}p < 0.01$ vs. NC group; $^{**}p > 0.05$ vs. HM group; $^{\#}p < 0.01$ vs. HM and DFX groups; $^{\#\#}p < 0.01$ vs. DFX and MIS groups. Data are presented as mean ± SD.

Perihematomal BWC

BWC in the HM group was significantly higher compared to that in the NC group ($p < 0.01$), suggesting that ICH-induced impaired BBB permeability resulted in brain edema. There was no significant difference in the BWC between the DFX and HM groups ($p > 0.05$). The MIS group had decreased BWC compared to that in the HM group ($p < 0.01$). Following MIS combined with DFX treatment, the BWC was significantly decreased compared to those in the DFX and MIS groups ($p < 0.01$), suggesting that MIS combined with DFX therapy was superior to MIS or DFX treatment alone (**Figure 4**).

Perihematomal BBB Permeability

The perihematomal EB content in the HM group was significantly higher compared to that in the NC group ($p < 0.01$), suggesting that the BBB was severely damaged after ICH. Although there was no significant difference in perihematomal BBB permeability between the DFX and HM groups ($p > 0.05$), the MIS group showed lower BBB permeability compared to that in the HM group ($p < 0.01$). The MIS + DFX group had superior outcomes compared to those in the MIS and DFX groups ($p < 0.01$). These results demonstrated that MIS to evacuate the ICH reduced the ICH-induced BBB damage, and MIS combined with DFX treatment was superior to decrease BBB permeability (**Figure 5**).

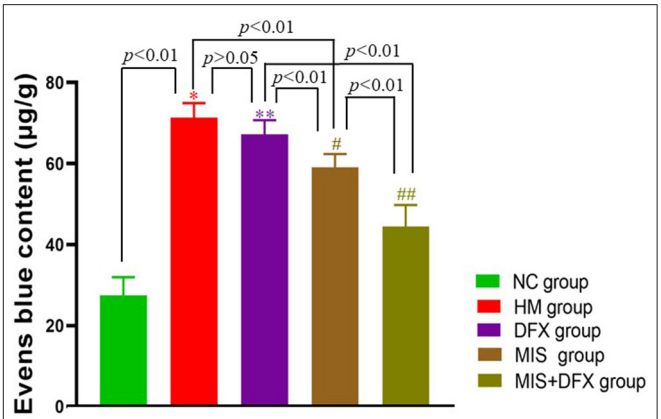

FIGURE 5 | Changes in perihematomal BBB permeability. MIS combined with DFX treatment was found to decrease perihematomal BBB permeability. Evens Blue was applied as a tracer to estimate the BBB permeability. $^{*}p < 0.01$ vs. NC group; $^{**}p > 0.05$ vs. HM group; $^{\#}p < 0.01$ vs. HM and DFX groups; $^{\#\#}p < 0.01$ vs. DFX and MIS groups. Data are presented as mean ± SD.

Perihematomal Claudin-5 and ZO-1 Proteins

Real-time PCR and western blotting were used to determine the TJ proteins claudin-5 and ZO-1 levels. Claudin-5 and ZO-1 mRNA and protein expression levels were significantly lower in the HM group compared to the NC group, suggesting that the BBB was damaged due to the ICH. Although there was no significant difference in claudin-5 or ZO-1 levels between the DFX and HM groups ($p > 0.05$), claudin-5 and ZO-1 mRNA and protein expression levels were higher in the MIS group than in the HM and DFX groups ($p < 0.01$). The MIS group was superior to the DFX treatment group. The MIS+DFX group had better results compared to the MIS group or DFX group ($p < 0.01$). These outcomes suggested that MIS to evacuate the hematoma increased the TJ protein levels (claudin-5 and ZO-1). MIS was superior to DFX therapy alone and MIS combined with DFX treatment was most effective for ICH-induced BBB damage (**Figure 6**).

DISCUSSION

ICH is a stroke sub-type and represents a major public health problem worldwide. ICH is associated with poor outcomes

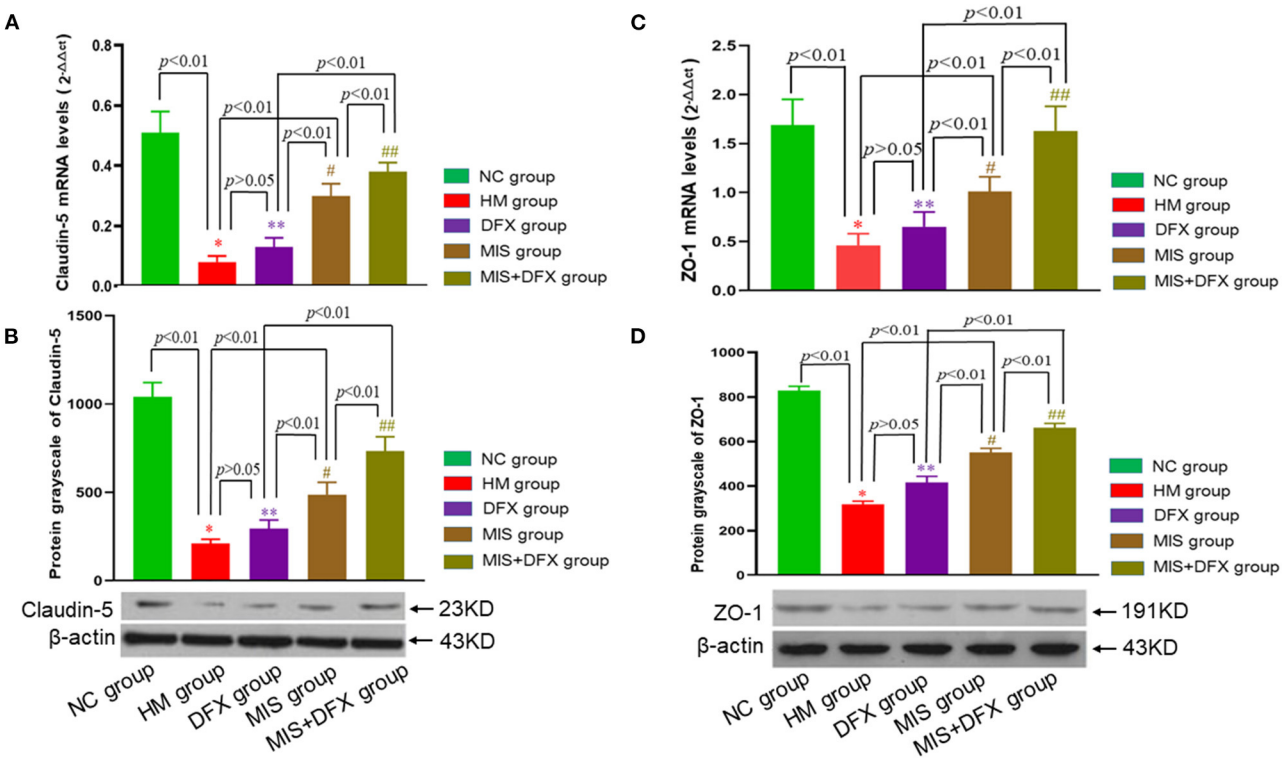

FIGURE 6 | Changes in perihematomal claudin-5 and ZO-1 expression levels. Real-time PCR and Western blotting were used to determine the claudin-5 and ZO-1 expression levels. MIS combined with DFX therapy was found to increase perihematomal claudin-5 and ZO-1 expression levels. **(A,C)** Claudin-5 mRNA and ZO-1 mRNA levels. $^{*}p < 0.01$ vs. NC group; $^{**}p > 0.05$ vs. HM group; $^{\#}p < 0.01$ vs. HM and DFX groups; $^{\#\#}p < 0.01$ vs. DFX and MIS groups. **(B,D)** Claudin-5 and ZO-1 protein expression levels. $^{*}p < 0.01$ vs. NC group; $^{**}p > 0.05$ vs. HM group; $^{\#}p < 0.01$ vs. HM and DFX groups; $^{\#\#}p < 0.01$ vs. DFX and MIS groups. Data are presented as mean ± SD.

and high morbidity, disability, and mortality (29). There are no effective treatment options for ICH (30). In recent years, MIS has been used as an alternative to craniotomy due to its improved survival rate and lower complication rate (31). Several experimental studies have reported that MIS is effective for ICH treatment (25, 32). Although MIS can remove most of the hematoma, thereby reducing its size and alleviating the mechanical brain injury due to compression, neurotoxic substances (e.g., thrombin, hemoglobin, and iron) are not removed because they are extravasated into the surrounding brain tissues. Therefore, the effect of MIS on secondary brain injury is limited.

Brain edema, BBB destruction, and neuronal death are manifestations of secondary brain injury, which may be observed in the perihematomal region. ICH-induced BBB disruption is a key pathophysiological process in brain injury (33). The TJ protein (claudin-5 and ZO-1) expression levels are associated with BBB integrity and are major biomarkers of ICH-induced brain injury (34). Hemoglobin, heme, and iron are released after RBC lysis, which aggravate ICH-induced BBB destruction (35). Iron damages the endotheliocytes and pericytes, destroying the BBB integrity (10). Therefore, MIS for hematoma evacuation followed by treatment with the iron chelator DFX may prevent secondary brain injury.

In the HM group of our study, the hematoma-occupying effects persisted and the neurotoxic substances extravasated into the perihematomal brain tissues, which manifested as iron overload, reduced expression levels of claudin-5 and ZO-1, severe BBB disruption, brain edema, and increased neurological function scores compared to the NC group. These results suggest that after ICH, iron is released from the lysed RBCs, which damages the BBB integrity, leading to secondary brain injury and neurological dysfunction.

In the DFX group, although the iron concentration was significantly decreased, the BWC and BBB permeability were only slightly decreased, and neurological function showed slight improvement. There were no significant differences between the HM and DFX groups. These results suggest that DFX use alone does not significantly improve the neurological outcome.

In the MIS group, MIS to evacuate the hematoma reduced the mass effect and prevented the release of iron and other neurotoxic substances from the RBCs, which manifested as decreased iron content, increased claudin-5 and ZO-1 expression levels, reduced BBB permeability, improved brain edema and neurological

function compared to the HM group. These results indicated that MIS could alleviate secondary brain injury after ICH. Previous studies reported that MIS significantly reduced the damage to the internal capsule fibers and improved neurological function in a dog ICH model (36). Moreover, MIS effectively reduced matrix metalloproteinase-9 (MMP-9) expression and BBB permeability (32). A meta-analysis showed that MIS treatment improved the outcome in ICH patients compared to the conservative treatment (37). Our results were consistent with those of previous studies.

Additionally, some studies found that DFX treatment significantly reduced iron overload after ICH, but it did not improve the outcome in a collagenase-induced ICH rat model (24, 38). A recent multicenter, randomized, placebo-controlled, double-blind phase 2 trial showed that DFX treatment was safe for ICH patients, but it was not associated with a favorable clinical outcome (i.e., modified Rankin Scale score of 0–2) at day 90 (39). These results were similar to those of our study. DFX use only significantly decreased iron accumulation, but it did not significantly improve neurological function. The reasons may be related to the delayed removal of the hematoma and to the continuous release of neurotoxic substances. Therefore, combined treatment may be the optimal choice for ICH patients.

In the MIS + DFX group, iron concentration, BBB permeability, and BWC were significantly reduced, and neurological function was markedly improved compared to the MIS and DFX groups. MIS for intracerebral hematoma removal combined with DFX treatment increased the perihematomal claudin-5 and ZO-1 expression levels, as well as decreased the BBB permeability in rabbits. MIS combined with the DFX strategy may be the ideal option for ICH patients.

In conclusion, MIS combined with DFX treatment could relieve the mechanical compression of brain tissue by the hematoma, significantly reduce iron overload around the hematoma, decrease BBB permeability, alleviate brain edema, and improve neurological function. Our findings could offer a novel strategy for ICH treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving animals were reviewed and approved by the Animal Ethics Committee of Guizhou Medical University, China.

AUTHOR CONTRIBUTIONS

SR, SH, and GW drafted the manuscript, conception, design, and data analysis. LW revised the manuscript for content and analysis. YH and JW supervised or coordinated the experiment. All authors contributed to the article and approved the submitted version.

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Irregular-Shaped Hematoma Predicts Postoperative Rehemorrhage After Stereotactic Minimally Invasive Surgery for Intracerebral Hemorrhage

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Background and Purpose: Minimally invasive surgery (MIS) is performed to treat patients with intracerebral hemorrhage (ICH) with favorable results. However, postoperative rehemorrhage is a significant risk. The present study retrospectively analyzed the association of irregular-shaped hematoma with postoperative rehemorrhage following stereotactic MIS (sMIS).

Methods: We enrolled 548 patients with spontaneous ICH who underwent sMIS. Based on the hematoma shape, the patients were assigned to the regular-shaped hematoma group (RSH group; 300 patients) or irregular-shaped hematoma group (ISH group; 248 patients). Logistic regression analysis was performed to identify the predictors of postoperative rehemorrhage after sMIS for ICH evacuation. The functional outcome was assessed using the modified ranking scale (mRS) score at discharge. A receiver operating characteristic (ROC) curve was used to confirm the results.

Results: Among 548 patients with ICH who underwent sMIS, 116 developed postoperative rehemorrhage. Postoperative rehemorrhage occurred in 30.65% of patients with ISH and 13.30% with RSH ($P < 0.01$), with a significant difference between the ISH and RSH groups. Among 116 patients with postoperative rehemorrhage, 76 (65.52%) showed ISH on CT scan. In 432 patients without postoperative rehemorrhage, only 39.81% displayed ISH. The logistic regression analysis demonstrated that ISH could independently predict postoperative rehemorrhage. The sensitivity, specificity, positive predictive value, and negative predicative value were 0.655, 0.398, 0.655, and 0.602, respectively. The ROC analysis confirmed the value of ISH in predicting postoperative rehemorrhage with an area under the curve of 0.629.

Conclusions: Irregular-shaped hematoma was an independent predictor of postoperative rehemorrhage after sMIS.

Keywords: intracerebral hemorrhage, stereotactic minimally invasive surgery, regular-shaped hematoma, irregular-shaped hematoma, postoperative rehaemorrhage

INTRODUCTION

Spontaneous intracerebral hemorrhage (sICH) is associated with high mortality and disability worldwide. There are few established treatment strategies for sICH that improve neurological outcomes (1, 2). Hematoma volume is a major determinant of outcome in patients with ICH (3). Previous studies have demonstrated that the extent of ICH-mediated brain injury is directly related to ICH volume and duration of exposure of brain tissue to blood. Smaller postoperative ICH volumes are associated with improved outcomes and maximum removal of blood predicts a good outcome (4). However, a multicenter randomized surgical trial of ICH did not show an overall advantage of early surgery compared to the initial conservative treatment (5). Early conventional surgery only provided benefits for patients with superficial sICH (6). In recent decades, newer surgical techniques for ICH management, called minimally invasive surgery (MIS), have been evaluated in several large clinical trials (7). The minimally invasive craniopuncture technique is a safe and practical technique that improves the independent survival of patients with small basal ganglia hemorrhage. In addition, stereotactic MIS (sMIS) for ICH evacuation is associated with significantly reduced ICH volume and intraoperative hemorrhage. Catheter-based evacuation of ICH is followed by the administration of recombinant tissue plasminogen activator and causes rapid hematoma lysis and drainage with minimal major adverse events (8). A preliminary study, MISTIE III, showed consistent rates of hematoma evacuation despite technical challenges with the surgical approaches (9). MIS plus alteplase appears to be safe in patients with ICH and may be added to the surgical management of ICH (10). In a recently published study, although MIS did not increase the proportion of patients who achieved a good outcome 365 days after ICH, reduction of the hematoma size to 15 ml or less was associated with improved modified ranking scale (mRS) scores at 365 days in stabilized patients (11). However, postoperative rehemorrhage is a significant challenge in clinical practice. A recent study found that the MIS increased the risk of asymptomatic bleeding (12). Other studies found that the rate of postoperative rehemorrhage or rebleeding was almost 26.19% in patients with ICH who underwent MIS and 40% in patients with ICH during the early stage after open surgery (13). The prevention of postoperative rehemorrhage is a possible target for medical intervention because postoperative rehemorrhage is associated with poor outcome in patients with ICH after surgery (14).

Several imaging markers, such as the spot sign, blend sign, and island sign, predict hematoma expansion (HE) (15). The spot sign is a strong predictor of postoperative rehemorrhage after endoscopic surgery for ICH. The blend and black-hole signs on the initial CT scan are associated with postoperative rehemorrhage in patients with ICH following sMIS, which may affect the outcome of patients (16).

Hematoma expansion or growth strongly predicts a worse outcome and can potentially be prevented if high-risk patients are identified and treated early. Previously published studies have demonstrated that irregular-shaped hematoma (ISH) is a strong predictor of HE (17). ISH was independently associated with poor outcomes after ICH, albeit with limited predictive values of an irregular shape (18).

However, few studies have evaluated the correlation of ISH with postoperative rehemorrhage in patients with ICH following sMIS. In the present study, we evaluated whether ISH may be associated with postoperative rehemorrhage following sMIS for ICH evacuation.

METHODS AND PROCEDURES

We conducted a retrospective clinical observation study, which was approved by the ethics committee and institutional review board of the Affiliated Hospital of Guizhou Medical University, China. All patients provided informed consent. The study was performed in compliance with the WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Study Design

We retrospectively collected data from the medical records of patients with ICH treated between January 1, 2018, and December 20, 2020. The study included patients aged over 18 years who had a history of hypertension or had hypertension observed upon admission. The patients had symptoms and signs suggestive of ICH, with supratentorial spontaneous ICH in the basal ganglia, thalamus, subcortex, or cerebral lobe with an ICH volume over 30 ml on a non-enhanced CT scan. The patients were surgical candidates with no contraindications for surgery, and their authorized representatives provided consent for the surgery.

The exclusion criteria were similar to those used in our previously published studies (19). Patients with ICH due to trauma, arteriovenous malformations, aneurysms, anticoagulation therapy, and antiplatelet therapy were excluded. Patients with brainstem, cerebellum, or supratentorial ICH with volumes less than 30 ml, or those patients whose authorized representative did not provide consent for surgery were also excluded.

The patients were diagnosed with ICH using a baseline CT scan performed within 1 h of admission, and the surgery was performed within 24 h after admission. All eligible patients underwent sMIS and were divided into two groups based on their hematoma shape.

Imaging Analysis

Hematoma Shape Assessment

The initial and follow-up CT scans (General Electric Medical Systems, Milwaukee, WI, USA) were performed using standard clinical parameters (axial 3-mm-thick sections, current of 225 mA, window level of 39, and window width of 120). The images were stored for further evaluation. Irregularity of the hematoma shape was rated using the scale established by Barras (20). The scale ranges from grade I (most regular shape) to grade V (most irregular shape). The total rating $<$ grade III indicates shape-regular hematoma. Otherwise, if the total rating $\geq$ grade III, it indicates the hematoma was irregular (**Figure 1**).

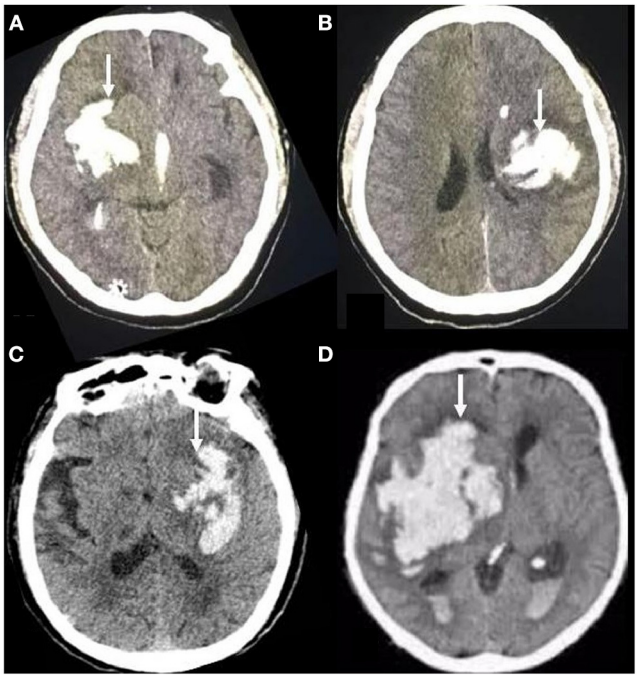

FIGURE 1 | Brain transverse CT section showing examples of hematoma shape. On the transverse CT scans of the brain, the irregular shape of hematoma showed different features, corresponding to grades III **(A, B)** or IV-V **(C, D)** of the Barras scale.

Two experienced neuroimaging experts who were blinded to the clinical information of the patients independently evaluated the hematoma shape by visual inspection (21).

Discrepancy Settlement

Discrepancies between the readers about the hematoma shape were settled by discussion. The hematoma shape was determined on the basis of a CT scan repeated before surgery. Surgery was performed after the repeat CT scan, which was performed within 24 h (6–24 h) after admission.

Hematoma Volume Calculation

If the CT image slice with the largest hematoma area showed a round or approximately round hematoma shape, the hematoma volume was estimated based on the ABC/2 formula ($t = \pi/6 \times l \times s \times$ slice) (22). If the hematoma shape was irregular, the volume was calculated using the following formula: $V = 2/3Sh$ (23), where S indicates the area of the largest axial ICH slice on the CT and H indicates the height or depth of the ICH.

CT Angiography

If the hematoma on routine CT was suspected to be due to aneurysm or arteriovenous malformation, CT angiography was performed.

Treatment of the Patients

ICH Evacuation by SMIS

The methods used to perform the sMIS procedures were similar to those used in our previous studies (24). Briefly, we fixed a stereotactic instrument on the patient's skull and performed a repeat CT scan to locate the ICH before surgery. After the blood pressure was controlled to a suitable level, we punctured the skull using a 3-mm-diameter needle (with a drill integrated into the needle guard) under the guidance of the stereotactic instrument. After the drill was replaced by a tip-blunt plastic-needle core, the LY-1-type puncture-needle set was slightly advanced into the hematoma. Following the removal of the plastic-needle core, the liquid part of the hematoma was aspirated using a 10-ml syringe and a plastic tube connected to the needle guard. Aspiration was stopped when the first resistance was encountered, and the needle guard connected to a plastic tube was retained in place for several days for drainage. After removing the location framework and stereotactic apparatus, the patients were transferred to the intensive care unit. Then, 50,000 units of urokinase (diluted in 2 ml of normal saline) were slowly injected every 8 h into the residual hematoma to dissolve the solid component of the hematoma. The needle system was closed for 2 h before reopening to allow spontaneous drainage. The first postoperative follow-up CT scan was performed on the day after the surgery, and the second postoperative CT was performed on the third day after surgery. Some patients required a third or even a fourth postoperative follow-up CT scan. The LY-1-type puncture-needle system was removed after the ICH was either completely or nearly completely removed. A repeat CT scan was performed at any time after surgery if the patients showed neurological deterioration.

Medications

All the patients in our study received standard medical management based on the guidelines for the treatment of hypertensive ICH (25), including management of coagulopathy, blood pressure, secondary brain injury, and intracranial pressure. In addition, patients received supportive treatment, including prevention of deep venous thrombosis, control of temperature and blood glucose, nutritional support, and prevention of other complications.

Criteria for Postoperative Rehemorrhage

Postoperative rehemorrhage was defined as the reappearance of the hematoma or hyperdensity in the hematoma region on any follow-up CT scan after it was completely removed (**Figure 2**), as confirmed by the previous CT scan (26). An increase in the hematoma volume of >33% or 12.5 ml (27) compared to the ICH volume determined using the previous CT scan minus the ICH volume removed by the operation was also considered postoperative rehemorrhage.

Statistical Analysis

On the basis of the assumption that 38% of the patients with ICH would have an mRS score of 0–3 following sMIS (28), we estimated that 180 participants would provide 95% statistical power at an α level of 0.05. The permissible error β was 0.1, and the inspection efficiency was 0.9. The sample size was calculated using the following formula:

$$N = \frac{z_{\alpha}^{2} p(1-p)^{2}}{\delta}$$

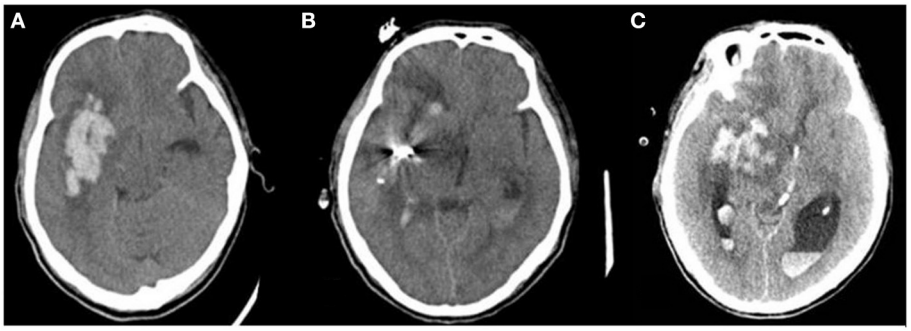

FIGURE 2 | Postoperative rehemorrhage in patients with ISH following sMIS. Postoperative rehemorrhage occurred in patients with irregular-shaped hematoma. **(A)** hematoma before surgery; **(B)** Hematoma size significantly decreased on the first postoperative follow-up CT scan; **(C)** Hematoma size increased on the second follow-up CT scan compared to the previous CT scan, suggesting postoperative rehemorrhage.

A commercially available software package (version 22.0; SPSS Statistical software; IBM Corp., Armonk, NY, USA) was used to perform the statistical analyses. Categorical data are shown as a number (percentage) and continuous data as $\bar{x}\pm S$ or median and interquartile range (IQR, 25th−75th percentile). Demographic, clinical, and radiological characteristics were compared using Student's *t*-tests (for normal distribution) or a non-parametric test (if the data were not normally distributed). Predictors of postoperative rehemorrhage were evaluated using a univariable logistic regression model, and possible predictors with a p-value < 0.05 were included in the multivariable analysis for assessment of independent predictors. Receiver operating characteristic curve (ROC) analysis was performed to assess the value of ISH in predicting postoperative rehemorrhage. The interobserver reliability of ISH and regularity was assessed by calculating the κ values. The κ values were categorized as previously reported (29). A κ value of 1 indicated total agreement between the observers. A p-value < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Participants

Between January 1, 2018, and December 30, 2020, 1,304 patients with sICH were admitted to the Affiliated Hospital of Guizhou Medical University. Among them, 548 patients underwent sMIS, 39 underwent craniotomy for ICH clearance, 25 refused surgery, and the remaining 692 received standard medical management (**Figure 3**).

A total of 548 patients fulfilled the inclusion criteria. Complete data were available for all patients. Among the 548 patients, 300 fulfilled the criteria for hematoma shape grade I–II, rated by the scale created by Barras (20), and were classified as the regular–shaped hematoma (RSH) group. The remaining 248 patients with hematoma shape grade ≥ III were assigned to the ISH group (**Figure 1**).

Interobserver Agreement in Hematoma Shape

Among the 548 included patients, 248 had an irregularly-shaped hematoma on repeat preoperative CT. The remaining 300 patients had hematoma with a regular shape. Discrepancies were observed in only 13 patients between the two neuroimaging experts, which were settled by discussion (a κ value was 0.962, $P < 0.001$). The interobserver agreement for identifying the hematoma shape was excellent.

Baseline Data of the Included Patients

Between January 1, 2018, and December 30, 2020, 1,034 patients were assessed for eligibility and 548 fulfilled the inclusion criteria. Among the 548 participants, 392 were men and 156 were women. The ages ranged from 33 to 90 years (average: 58.65 ± 12.36) and 344 patients had a history of hypertension. The time from symptom onset to baseline CT was 5.5 (range: 2–11) h. The admission GCS score was 10.08 ± 3.49 and the NIHSS score was 17.27 ± 5.16.

Based on the hematoma shape, patients were categorized in the ISH (248 patients) or the RSH (300 patients) group. No significant differences were noted between the two groups in terms of age, history of smoking, alcohol use, hypertension, preoperative ICH volume, anticoagulant use, GCS score at admission, NIHSS score at admission, time from symptom onset to baseline CT, or time from symptom onset to surgery (**Table 1**).

Changes in ICH Volume After Surgery and Postoperative Rehemorrhage

No difference in the ICH volume was noted between the ISH and RSH groups before the surgery. A significant difference in the residual ICH volume after surgery was observed between the two groups ($p = 0.001$), showing that the hematoma shape influenced ICH removal (**Table 2**). Among the 548 patients who underwent sMIS, 116 (21.16%) had postoperative rehemorrhage.

ISH and Postoperative Rehemorrhage

In 300 patients with RSH, 40 (13.33%) patients developed postoperative hemorrhage. In 248 patients with ISH, 76

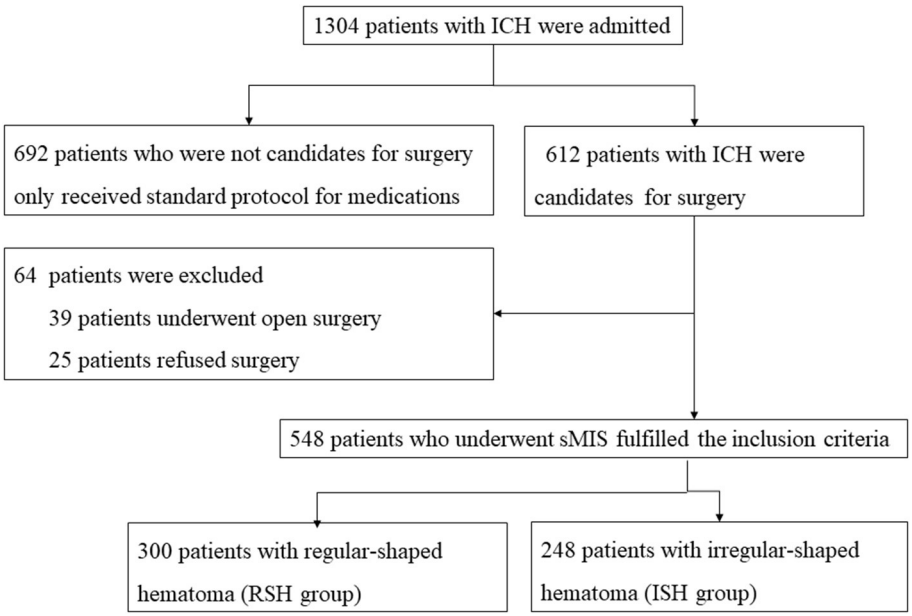

FIGURE 3 | Flowchart of patients' inclusion. During the study period, 1,034 patients with ICH were admitted to the Affiliated Hospital of Guizhou Medical University. Among them, 548 patients underwent stereotactic minimally invasive surgery for ICH evacuation. The irregular-shaped hematoma was found in 248 patients and regular-shaped hematoma in 300 patients.

TABLE 1 | Comparison of baseline data between regular-shaped and irregular-shaped hematoma groups.

Factors	ISH group (248)	RSH group (300)	χ^2/F	*P*-value
Ages (years, x±s)	58.35 ± 12.30	58.06 ± 12.87	−0.27	0.79
Gender (male,%)	171 (68.95%)	221 (73.67%)	1.48	0.22
History of smoking (*n*,%)	117 (47.18 %)	146 (48.67%)	0.12	0.72
History of drinking (*n*,%)	103 (41.53%)	131 (43.67%)	0.25	0.62
History of hypotension (*n*,%)	153 (61.69%)	191 (63.67%)	0.23	0.63
History of DM	11 (4.44%)	13 (4.33%)	0.83	0.66
Anticoagulants ($n = 253$,%)	4 (4.11%)	3 (1.92%)	1.08	0.30
Hematoma volume (ml, IQR)	35.81 ± 20.25	36.65 ± 20.43	−0.48	0.63
Systolic pressure (mmHg, x±s)	171.79 ± 30.93	172.38 ± 27.75	−0.24	0.81
Diastolic pressure (mmHg, x±s)	100.17 ± 20.04	100.58 ± 19.33	−0.24	0.55
GCS on admission (points, IQR)	11 (8, 13)	11 (8, 13)	−1.32	0.19
NIHSS on admission (points, IQR)	15 (12.25, 18)	15 (12, 18.75)	27.04	0.71
Time for baseline CT (h, IQR)	5.75 (3, 10)	5 (2, 11)	−0.41	0.68
Time from onset to surgery (h, IQR)	17 (10, 35)	17.5 (10, 31.5)	−1.37	0.17
Duration of surgery (h, IQR)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	−0.18	0.86
Time for removing the tube (days, IQR)	4.53 ± 3.01	4.70 ± 2.33	−2.52	0.01
ICH ruptured into the venrticles (*n*, %)	83 (33.47%)	107 (35.67%)	0.29	0.59
Postoperative rehaemorrhage (n,%)	76 (30.65)	40 (13.33)	24.38	0.00
Poor functional outcome (n, %)	173 (69.76)	55 (18.33)	51.50	0.00

ISH, irregular-shaped hematoma; RSH, regular-shaped hematoma; GCS, glasgow coma scale; NIHSS, national institute of health stroke scale.

(30.65%) patients showed postoperative rehemorrhage (**Table 1**). The proportion of postoperative hemorrhage was remarkably increased in the ISH group. A significant difference was observed between the ISH and RSH groups ($p < 0.001$). On the other hand, in 116 patients with postoperative rehemorrhage, 76 (65.52%) patients showed ISH on CT scan. However, in 432 patients without postoperative rehemorrhage, only 172 (39.81%) patients displayed ISH (**Table 3**). These results suggested that patients with ISH were prone to developing postoperative rehemorrhage. To determine the relationship between ISH

TABLE 2 | Changes in hematoma volume before and three days after surgery.

Group	Preoperative ICH volume (ml, IQR)	Postoperative Residual ICH volume (ml, IQR)	Time for removing the tube (days, IQR)
SIH group($n = 248$)	33 (20–47)	3 (1–6.25)[&]	5.29 ± 2.86
SRH group ($n = 300$)	33 (22.25–47)	2 (1–4)	4.68 ± 2.46
Z (*P*-value)	−0.42 (0.68)	−3.24 (0.001)	−2.667 (0.01)

[&] *compared with the RSH group, P < 0.05 (RSH group: regular-shaped hematoma group, ISH group: irregular-shaped hematoma group).*

TABLE 3 | Univariate analysis of predictors related to postoperative rehaemorrhage who underwent stereotactic minimally invasive surgery.

Factors	Postoperative rehaemorrhage positive ($n = 116$)	Postoperative rehaemorrhage negative ($n = 432$)	χ^2/F	*P*-value
Ages (x±s)	57.46 ± 13.32	58.39 ± 12.41	0.71	0.48
Gender (male, %)	87 (75.00%)	305 (70.60%)	0.87	0.35
History of smoking (*n*,%)	61 (52.59%)	202 (46.76%)	1.24	0.27
History of drinking (*n*,%)	59 (50.86%)	175 (40.51%)	4.01	0.045
History of hypertension (*n*,%)	62 (53.45%)	282 (65.28%)	5.48	0.02
Anticoagulants (*n*,%) $n = 253$	2 (4.23%)	5 (2.41%)	4.32	0.51
History of diabetes (*n*,%)	5 (4.31%)	19 (4.40%)	0.27	0.87
Systolic pressure (mmHg, x±s)	172.64 ± 28.788	171.94 ± 29.346	0.22	0.83
Diastolic pressure (mmHg, x±s)	101.97 ± 23.182	99.97 ± 18.579	0.97	0.33
GCS on admission (points, IQR)	11 (8, 14)	11 (8,13)	18.11	0.80
NIHSS on admission (points, IQR)	15 (12.18.75)	15 (12,18)	35.88	0.45
Time from onset to baseline CT (h, IQR)	3.5 (2.0–9.375)	5.0 (3.0–11.75)	1.56	0.12
ICH volume on admission (ml, IQR)	34.49 ± 21.77	36.75 ± 19.93	1.06	0.29
Hematoma ruptured into ventricles (*n,* %)	40 (34.48%)	150(34.72%)	0.00	0.96
Time from onset to surgery (h, IQR)	23 (10–42)	17 (10–30)	1.61	0.11
Duration of surgery (h, IQR)	1.45 (1.0–1.65)	1.5 (1.0–2.0)	4.45	0.65
Irregular hematoma (n,%)	76 (65.52%)	172 (39.81%)	24.38	0.00
Time for removing the drainage tube	4.87 ± 3.06	4.98 ± 2.56	3.39	0.70
Residual ICH volume	3.0 (2.0–7.5)	2.0 (1.0–5.0)	3.96	0.00
Poor functional outcome	87(75.00%)	141(32.64%)	12.53	0.00

TABLE 4 | Binary logistic regression for predictors of postoperative rehemorrhage.

Variables	B	Wald	OR	95%CI	*P*
Irregular-shaped hematoma	1.08	23.77	2.94	1.91–4.54	0.00
History of drinking	0.52	5.60	1.68	0.93–2.39	0.10
History of hypertension	−0.55	6.17	0.58	0.38–0.89	0.01

and postoperative rehemorrhage, we performed a univariate analysis followed by a binary logistic regression. The results showed that ISH was an independent predictor of postoperative rehemorrhage following sMIS (**Tables 3**, **4**). At the same time, a receiver operating characteristic curve (ROC) was used to confirm the value of irregular-shaped hematomain, predicting postoperative rehemorrhage following sMIS with an area under the curve of 0.629 ($p < 0.05$, **Figure 4**). However, the history of hypertension was protective from postoperative rehaemorrhage (OR = 0.580, $P = 0.013$). The sensitivity, specificity, and positive and negative predictive values of ISH for predicting postoperative rehemorrhage were 0.655, 0.398, 0.655, and 0.602, respectively (**Table 5**).

ISH and Poor Outcome

Patients in the ISH group had worse outcomes compared with those in the RSH group ($p < 0.001$). Poor outcomes were seen in 173 patients (69.76%) in the ISH group and 55 patients (18.33%) in the RSH group (**Table 1**). Among 228 patients with poor outcomes, 166 (72.81%) had ISH and only 62 (27.19%) had RSH.

DISCUSSION

In the present study, out of 548 patients who underwent sMIS, 116 (21.17%) had postoperative rehemorrhage on follow-up CT scan, which was consistent with previously published studies (30). However, patients with ISH had a significantly higher

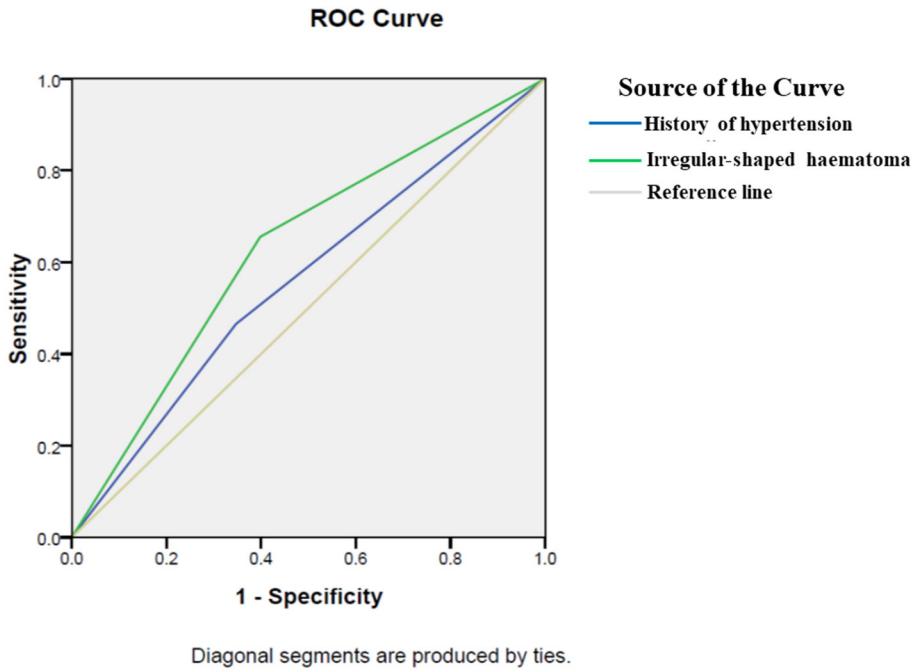

FIGURE 4 | A receiver operating characteristic for predictors of postoperative rehemorrhage. A receiver operating characteristic (ROC) curve was used to confirm the value of irregular-shaped hematoma and history of hypertension in predicting postoperative rehemorrhage following sMIS. The area under the curve of history of hypertension was 0.559($p = 0.05$). Therefore, a history of hypertension cannot predict postoperative rehemorrhage. However, ROC curve analysis confirmed the value of ISH in predicting postoperative rehemorrhage in patients after sMIS, with an area under the curve of 0.629 ($p < 0.05$).

TABLE 5 | A receiver operating characteristic for predictors of postoperative rehemorrhage.

Variables	Sensitivity predictive values	Specificity predictive values	Positive predictive values	Negative predictive values	AUC	95%CI	*P*
Irregular-shaped hematoma	0.655	0.398	0.655	0.602	0.629	0.572–0.685	0.000

proportion of postoperative rehemorrhage (30.65%) compared with RSH patients (13.33%). Postoperative rehemorrhage was a severe complication in patients with ICH following surgery, possibly leading to severe secondary damage to the surrounding brain and other medical complications. Patients with postoperative rehemorrhage had a higher rate of poor outcome and increased length of hospital stay. The present study showed that 75.0% of patients with postoperative rehemorrhage had a poor outcome. To confirm the relationship between ISH and postoperative rehemorrhage, we conducted a binary logistic regression analysis, which showed that ISH was an independent predictor of postoperative rehemorrhage after sMIS. Hematoma volume is an important determinant of clinical outcome (3). In patients with ICH who undergo surgery, the outcome is closely associated with postoperative ICH volume (4). Reduction in hematoma size to 15 ml or less was associated with improved mRS scores in stabilized patients. However, hematoma evacuation by open craniotomy has not been found to have beneficial effects in large, randomized trials (13). MIS, including stereotactic catheter aspiration and clearance of ICH with recombinant tissue plasminogen activator, holds promise for the improvement of outcomes of supratentorial brain hemorrhage (29). Sixteen studies, including 1,912 patients, demonstrated that MIS was effective and safe for the treatment of hypertensive ICH, and was associated with decreased mortality and a significantly improved outcome and quality of life in patients compared to other treatment strategies (30). However, postoperative rehemorrhage remains a significant challenge. It is associated with poor outcomes in patients with ICH after surgery (4). Patients with ISH are prone to develop postoperative rehemorrhage, leading to a poor outcome. In the present study, the proportion of patients with poor outcomes was increased in the ISH group compared with the RSH group. Preoperative identification of factors related to postoperative rehemorrhage may be used to guide medical interventions in clinical practice.

Several imaging markers, such as density heterogeneity, blend sign, black hole sign, and margin irregularity on non-contrast CT scans, are associated with hematoma expansion at 24 h. However, the relationships between imaging markers and postoperative rehemorrhage following sMIS remain poorly understood. Previously published studies showed that the CT blend sign and black hole sign are associated with postoperative

rehemorrhage (14, 19). However, it is unclear whether ISH is associated with postoperative rehemorrhage. In the present study, we found that patients with ISH are prone to develop postoperative rehemorrhage after sMIS. ISH independently predicts postoperative rehemorrhage in patients who undergo sMIS, and patients with ISH have an increased risk of poor outcomes. The present study also demonstrated that the hypertension history might be protective from postoperative rehemorrhage. Patients with a hypertension history showed a lower percentage of postoperative rehemorrhage (19). In another study, hypertension was not independently associated with postoperative rehemorrhage (31). Combined with these studies, we could postulate that the hypertension history might protect patients with ICH from postoperative rehemorrhage after MIS. However, the present study focused on the effects of irregular-shaped hematoma on the postoperative rehemorrhage after MIS. So, the influence of hypertension history on postoperative rebleeding has not been analyzed in detail.

The outcome of patients with ICH is significantly dependent on the complications (32, 33). Stereotactic aspiration of ICH improves the general condition of patients, but these may induce rehemorrhage (34). In the present study, postoperative rehemorrhage occurred in both RSH and ISH groups. However, the rate of postoperative rehemorrhage in the ISH group was higher than that in the RSH group. Therefore, patients at an increased risk of rehemorrhage should be identified and preoperative measures should be taken to prevent bleeding, such as the application of hemostatic drugs.

In conclusion, ISH increases the risk of postoperative rehemorrhage and leads to a poor outcome in patients with ICH after sMIS. ISH could be used as an independent predictor of postoperative rehemorrhage in patients with ICH who undergo sMIS.

This retrospective study had some limitations. Clinical data were obtained from the medical records; therefore, errors due to the subjective influences of treating physicians could not be completely excluded. Although the ABC/2 formula has been validated to be reliable for ICH volume estimation, it possibly overestimates some irregular shapes of intracerebral hematoma volume. In addition, we were unable to obtain long-term outcomes. These limitations should be addressed in our subsequent study. Certainly, the evaluation of the ICH shape features and rehemorrhage were reliable as they could be identified easily by the naked eye.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available from the corresponding author by reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University approved this retrospective study. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GW and QY conceived the study, participated in the study design, coordinated the study, and drafted the manuscript. SL, SR, and LW conducted the clinical study. LW performed the statistical analyses and drafted the manuscript. HY and GS are responsible for guiding the analysis of the hematoma shape. All authors read and approved the final manuscript.

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ORIGINAL RESEARCH
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The Attenuation Value Within the Non-hypodense Region on Non-contrast Computed Tomography of Spontaneous Cerebral Hemorrhage: A Long-Neglected Predictor of Hematoma Expansion

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Background and Purpose: The ability of attenuation value of the non-hypodense region of hematoma in non-contrast computed tomography (NCCT) for predicting hematoma expansion (HE) remains unclear. Our purpose is to explore this relationship.

Methods: Two cohorts of patients were collected for analysis. The region where we measured hematoma attenuation values was limited to the non-hypodense region that was not adjacent to the normal brain tissue on NCCT. The critical attenuation value was derived *via* receiver operating characteristic (ROC) curve analysis in the derivation cohort and its predictive ability was validated in the validation cohort. Independent relationships between predictors, such as critical attenuation value of the non-hypodense region and HE were analyzed using the least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic analysis.

Results: The results showed that the attenuation value <64 Hounsfield units (HU) was independently associated with HE [odds ratio (*OR*), 4.118; 95% confidential interval (*CI*), 1.897–9.129, $p < 0.001$] and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the curve (AUC) for predicting HE were 36.11%, 81.71%, 1.97, 0.78, 44.8%, 75.7%, and 0.589, respectively.

Conclusions: Our research explored and validated the relationship between the attenuation value of the non-hypodense region of hematoma and HE. The attenuation value < 64 HU was an appropriate indicator of early HE.

Keywords: attenuation value, non-hypodense region, hematoma expansion, Hounsfield units, non-contrast computed tomography, spontaneous intracerebral hemorrhage

INTRODUCTION

Hematoma expansion (HE) occurs in approximately one-third of patients with spontaneous intracerebral hemorrhage, and it is an independent risk factor for the worsening prognosis and early death (1). Early recognition of HE is considered as one of the potential therapeutic goals to improve prognosis (2, 3). In addition to the spot sign and its density on contrast CT (4), the presence of hypodense areas within the hematoma on non-contrast computed tomography (NCCT) is an important factor in assessing the inefficient clot contraction and the instability of intracerebral hematomas with a high discriminating ability (5). However, the hypodense foci on NCCT do not always match the location of the spot sign suggestive of contrast leakage on contrast CT (6), which may be implicated in the relatively low sensitivity of the NCCT signs in predicting HE (7–9). Minimally invasive surgery appeared to reduce the poor prognosis of patients at high risk of hematoma expansion, yet this difference was not significant for reasons that cannot be ruled out due to the inability to accurately identify the actual hematoma that will undergo expansion (10). In our clinical work, we have noticed that some homogeneous hematomas dilated (>6 ml or 33% increase compared with baseline volume) without any hypodensity foci but with overall low attenuation value, some dilated heterogeneous hematomas (those with a swirl sign, black hole sign, or blend sign) with relatively low attenuation value within the non-hypodense region, while some non-dilated heterogeneous hematomas have relatively high attenuation values within the non-hypodense region (**Figure 1**), prompting us to wonder that whether low attenuation value of the non-hypodense region is a risk factor for HE. Therefore, this study aims to investigate the clinical significance of the attenuation value within the non-hypodense region for predicting HE.

MATERIALS AND METHODS

Patients

Patients with spontaneous intracerebral hemorrhage admitted to our three hospital branches from January 2013 to June 2021 were selected for this retrospective study. Inclusion criteria for eligible patients were (1) the first NCCT examination was performed within 6 h after onset and (2) one or more NCCT re-examinations were performed within 72 h after onset. Exclusion criteria were (1) patient age <18 years old; (2) intracerebral hemorrhage secondary to arteriovenous malformation, aneurysm, trauma, tumor, Moya-Moya disease, or other diseases; (3) multiple cerebral hemorrhages or primary ventricular hemorrhage; (4) any form of neurosurgery performed before the first NCCT re-examination; (5) patients with axial layers <3 on the first NCCT scan (aiming to eliminate partial volume effects when extracting hematoma attenuation values); and (6) baseline hematoma volume <1 ml.

Abbreviations: NCCT, non-contrast computed tomography; HE, hematoma expansion; ROC, receiver operating characteristic; LASSO, least absolute shrinkage and selection operator; HU, Hounsfield units; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; AUC, area under the curve; IQR, interquartile range.

Derivation Cohort

Eligible patients admitted in the main hospital site from January 2013 to August 2015 were included as a derivation cohort according to the inclusion and exclusion criteria described above. Attenuation value within the non-hypodense region of the hematoma was examined retrospectively for suitability to predict HE, and a cutoff value was determined by an ROC analysis based on the maximum Youden index.

Validation Cohort

Patients admitted in the main hospital site between September 2015 and June 2021 ($n = 119$) and two other branch sites (October 2015 to June 2021, $n = 70$; November 2017 to June 2021, $n = 58$) who met the above criteria were included as a validation cohort. A validating analysis was performed to investigate whether a critical attenuation value of the non-hypodense region could predict HE in this cohort. The studies involving human participants were reviewed and approved by the local ethics committee. Written informed consent was not required for this study due to the de-identified retrospective data.

Clinical Information

Clinical information for each patient is collected from the electronic medical records, such as demographic characteristics, medical history, physical examination items, and potentially relevant laboratory tests at the time of admission (**Table 1**).

Imaging Characteristics

Non-contrast computed tomography images of the patients were obtained by standard clinical protocols (120 kV, axial section 5–7.5 mm thick). Baseline hematoma volume was calculated *via* the Tada formula ABC/2. The NCCT image data with DICOM format of each patient were used to measure the attenuation value of the non-hypodense region of the hematoma in the Picture Archiving and Communication System (PACS). The non-hypodense region was restricted to any layer within the highest density region of the heterogeneous hematoma as well as the core region of the homogeneous hematomas. When the standard deviance of the mean HU value in the region of interest of the non-hyperdense region is ≤6, this part of the hematoma is considered to be homogeneous. The layer used to measure the attenuation value was limited to the core axial section of the hematoma, and the upper and lower layers adjacent to the normal brain tissue were not used for measurement (**Figure 2**). The attenuation value of the hematoma was assessed independently by two experienced raters (YC and DC) who were unaware of the outcome of patient. The midline shift distance was defined as the maximum lateral vertical displacement distance of brain tissue structures in the horizontal plane from the mid-axis sagittal plane of the NCCT scan. The definitions of irregular sign, satellite sign, island sign, swirl sign, black hole sign, and blend sign were conformed to the standards that were proposed by Andrea Morotti et al. (11). HE or dilated hematoma was defined as a >33% or >6 ml increase of hematoma volume or new intraventricular hematoma development on the NCCT re-examination (**Figure 3**) (12).

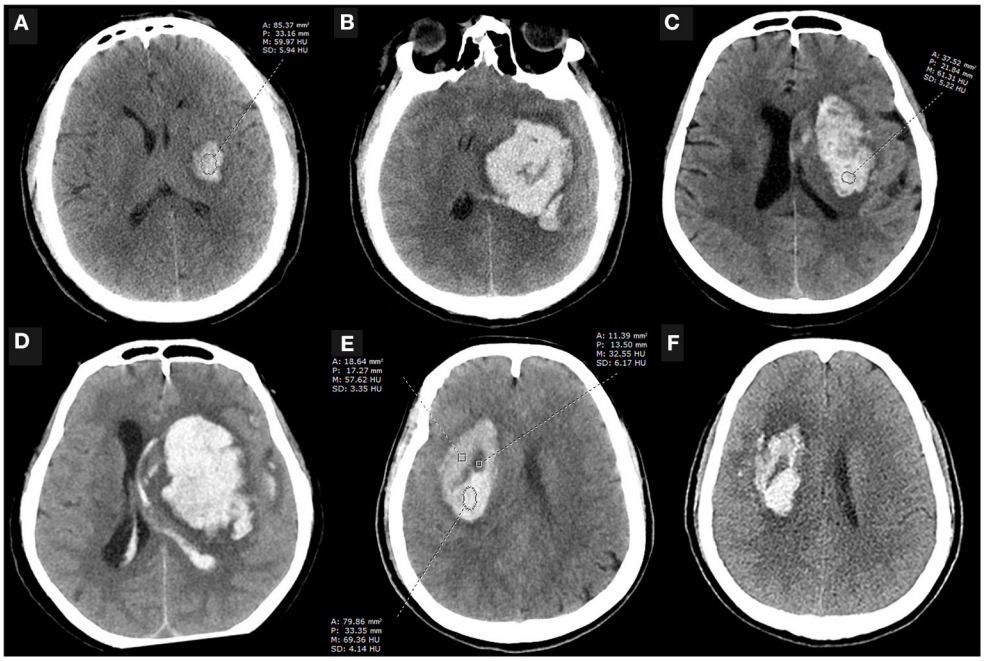

FIGURE 1 | Case examples. **(A,B)** An initial NCCT scan performed 3.5 h after the onset of symptoms showed a small, regular shape hematoma with an attenuation value of 61.72 HU at the internal capsule, which enlarged 10 h later. The patient eventually died. **(C,D)** An NCCT scan performed 0.5 h after symptom onset showed a basal ganglia hematoma that was heterogeneous with an attenuation value of 63.86 HU within the non-hypodense region and appeared significantly expansion 12 h later. **(E,F)** NCCT scan performed 1 h after onset showed a heterogeneous basal ganglia hematoma with an attenuation value of more than 64 HU in the non-hypodense region, and the patient did not present with HE despite the presence of the black hole sign on the initial NCCT examination. A, area; P, perimeter; M, mean; SD, standard deviance; HU, Hounsfield units; NCCT, non-contrast computed tomography.

Statistical Analysis

Statistical analyses were performed with R software (version 4.0.5, http://www.Rproject.org) and the SPSS package (version 24.0, IBM Corporation, Armonk, NY). Categorical variables were expressed as percentages (%) and continuous variables were expressed as means [±standard deviation (SD)] or medians (interquartile range, IQR). Cohen's κ-test was used to determine inter- and intra-rater agreement referring to the NCCT signs and attenuation value level. A univariate analysis was performed using chi-square test, Fisher's exact test, two-tailed Student's *t*-test, or univariate logistic analysis, as appropriate. An ROC curve analysis with Delong's test was used to obtain cutoff for attenuation value within the non-hypodense region of the hematoma and to obtain the sensitivity, specificity, PPV, NPV, PLR, NLR, and AUC values. Considering the possible collinearity between variables, the least absolute shrinkage and selection operator (LASSO) regression was first used to screen the potential predictors of HE (13), and then variables with non-zero coefficients were further included in the multivariate model. The model was visualized using the nomogram and the discrimination and calibration of the prediction were observed by the use of Harrell's concordance index (C-index)/AUC of ROC analysis and calibration plot. The decision curve analysis and clinical impact curve analysis were used to observe the performance of the attenuation value within the non-hypodense region in the terms of improving the predictive power of the model. A two-tailed test of $p < 0.05$ was considered statistically significant.

RESULTS

Clinical and Radiological Characteristics and Outcomes of Two Cohorts

In the primary and validation cohorts, 31 of 132 patients (23.5%) and 72 of 247 patients (29.1%) experienced HE. The median attenuation value of the non-hypodense region of hematoma was 66.2 HU [IQR, 63.1–69.3 HU] in the derivation cohort and 67.6 HU [IQR, 64.4–70.8 HU] in the validation cohort. **Supplementary Figure 1** shows the patient selection process for both cohorts. The clinical and radiological characteristics and the outcomes of two cohort patients are shown in **Table 1**.

Factors Associated With the Attenuation Value of the Non-hypodense Region of the Hematoma in the Validation Cohort

The correlation matrix heatmap for continuous variables are shown in **Supplementary Figure 2**. In homogeneous hematomas, the attenuation value within the core region was relatively low in those with HE compared with those without HE, and without a significant increasing trend over time (**Figure 4A**). In heterogeneous density hematomas, there was

TABLE 1 | Comparison of clinical and radiological characteristics and the outcome of derivation and validation cohort patients.

Variables	Derivation cohort ($n = 132$)	Validation cohort ($n = 247$)	*P*
Clinical characteristics			
Age, years, mean (SD)	55.0 (11.1)	57.6 (12.4)	0.039
Sex, male (%)	88 (66.7)	162 (65.6)	0.922
Hypertension (%)	81 (61.4)	171 (69.2)	0.152
Diabetes (%)	13 (9.85)	21 (8.50)	0.804
Current smoker (%)	50 (37.9)	46 (18.6)	<0.001
Current alcohol drinker (%)	36 (27.3)	42 (17.0)	0.026
Stroke history (%):			0.812
No	117 (88.6)	210 (85.0)	
Hemorrhage	6 (4.55)	17 (6.88)	
Infarction	8 (6.06)	17 (6.88)	
Hemorrhage and infarction	1 (0.76)	3 (1.21)	
Antiplatelets or anticoagulants therapy (%)	5 (3.79)	11 (4.45)	0.969
Systolic pressure on admission (mmHg), median [IQR]	162 [146; 178]	160 [144; 180]	0.807
Diastolic pressure on admission (mmHg), mean (SD)	92.4 (16.9)	92.9 (15.5)	0.795
Baseline GCS score (%):			0.519
12–15	51 (38.6)	109 (44.1)	
9–11	52 (39.4)	84 (34.0)	
3–8	29 (22.0)	54 (21.9)	
RBC count (*10^{12}/L), median [IQR]	4.64 [4.37; 4.95]	4.62 [4.28; 5.00]	0.447
Hemoglobin (g/L), median [IQR]	140 [129; 150]	139 [129; 151]	0.475
Hematocrit (%), median [IQR]	41.6 [38.7; 43.7]	41.2 [38.7; 44.3]	0.700
MCV (fl), median [IQR]	89.1 [86.7; 91.4]	89.9 [87.0; 92.5]	0.237
MCH (pg), median [IQR]	30.3 [29.5; 31.2]	30.5 [29.2; 31.4]	0.917
MCHC (g/L), median [IQR]	338 [330; 348]	338 [328; 345]	0.311
RDW (%), median [IQR]	13.0 [12.5; 13.7]	12.9 [12.2; 13.6]	0.186
Platelet count (*10^{9}/L), median [IQR]	196 [158; 227]	206 [171; 249]	0.082
Platelet distribution width (%), median [IQR]	13.9 [12.2; 15.8]	12.7 [11.1; 14.3]	<0.001
Prothrombin time (seconds), median [IQR]	13.4 [13.0; 13.9]	13.3 [12.9; 13.8]	0.060
Activated partial thromboplastin time (seconds), median [IQR]	34.2 [32.0; 36.8]	34.5 [32.2; 37.2]	0.434
International normalized ratio, median [IQR]	1.03 [1.00; 1.08]	1.02 [0.97; 1.06]	0.020
Total cholesterol (seconds), median [IQR]	4.27 [3.65; 5.04]	4.33 [3.70; 4.94]	0.806
Serum glucose (mmol/L), median [IQR]	6.72 [5.56; 8.43]	6.84 [5.80; 8.33]	0.640
Time from first NCCT scan to onset (hours), median [IQR]	3.00 [1.88; 4.12]	3.00 [1.50; 4.00]	0.472
Radiological characteristics			
Hematoma location (%):			<0.001
Thalamus	28 (21.2)	43 (17.4)	
Basal ganglia	101 (76.5)	157 (63.6)	
Brain stem or cerebella	0 (0.0)	11 (4.5)	
Cerebral lobe	3 (2.3)	36 (14.6)	
Baseline hematoma volume (ml), median [IQR]	19.6 [9.25; 34.7]	16.8 [8.69; 30.6]	0.187
Largest hematoma width/length ratio on axial section (>0.6), (%)	65 (49.2)	119 (48.2)	0.929
Midline shift distance (>0.5 cm), (%)	41 (31.1)	51 (20.6)	0.033
Subarachnoid hemorrhage (%)	7 (5.30)	15 (6.07)	0.940
Intraventricular hemorrhage (%)	48 (36.4)	62 (25.1)	0.029
Swirl sign (%)	19 (14.4)	44 (17.8)	0.479
Black hole sign (%)	10 (7.58)	26 (10.5)	0.454
Blend sign (%)	12 (9.1)	49 (19.8)	0.011
Irregular sign (%)	51 (38.6)	95 (38.5)	1.000
Satellite sign (%)	39 (29.5)	68 (27.5)	0.768

(Continued)

TABLE 1 | Continued

Variables	Derivation cohort ($n = 132$)	Validation cohort ($n = 247$)	*P*
Island sign (%)	13 (9.85)	23 (9.31)	1.000
Attenuation value of non-hypodense region (HU), median [IQR]	66.2 [63.1; 69.3]	67.6 [64.4; 70.8]	0.011
Outcome			
HE (%)	31 (23.5%)	72 (29.1%)	0.289
3 months mRS score (4∼6), (%)	60 (45.5%)	128 (51.8%)	0.283

SD, standard deviation; IQR, interquartile range; GCS, Glasgow coma scale; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; NCCT, non-contrast CT; HU, Hounsfield units; HE, hematoma expansion; mRS, modified Rankin scale.

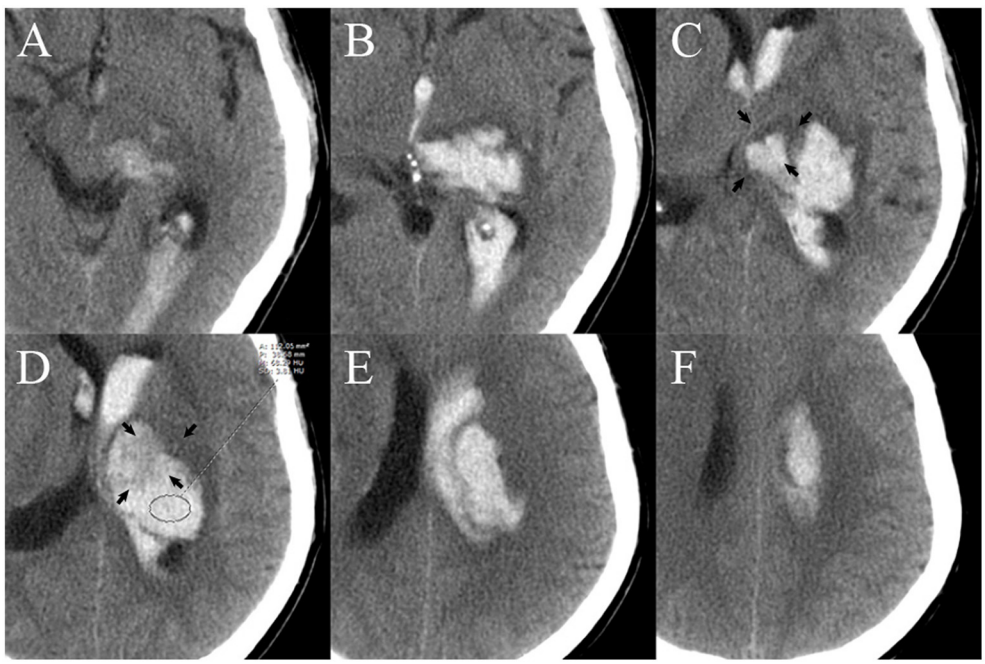

FIGURE 2 | Measurement of the attenuation value of the region of interest (ROI) of the non-hyperdense region of the hematoma. There are six layers of hematoma on axial NCCT images. The upper **(A,B)** and lower layers **(E,F)** are not suitable for measurement because they are adjacent to normal brain tissue. The core two layers **(C,D)** are selected as the best layer for measurement. The area of layer **(D)** (black arrow) that is adjacent to normal tissue [layer **(C)**, black arrow] may cause partial volume effects that affect the accuracy of the measurement and is therefore excluded from the ROI. A, area; P, perimeter; M, mean; SD, standard deviance; HU, Hounsfield units; NCCT, non-contrast computed tomography.

no significant correlation between the attenuation value within the non-hypodense region of the hematoma and the time from the first NCCT scan to onset, irrespective of the occurrence of HE (**Figure 4A**). NCCT attenuation value was generally lower within the non-hypodense region of expanded hematomas, and this difference was more pronounced in the brainstem or cerebellar locations (**Figure 4B**). A positive correlation existed between attenuation value within the non-hypodense region and hemoglobin level (**Figure 4C**), and a negative correlation existed referring to the red blood cell distribution width, regardless of whether the hematoma was expanded (**Figure 4D**).

Derivation of the Critical Attenuation Value of Hematoma to Predict HE

An ROC curve analysis showed that the cutoff of attenuation value within non-hypodense region for predicting HE was <64 HU, and its sensitivity, specificity, PLR, NLR, PPV, NPV, and AUC were 67.74% (95% *CI*, 48.6–83.3%), 82.18% (95% *CI*, 73. 3–89.1%), 3.8 (95% *CI*, 2.3–6.2), 0.39 (95% *CI*, 0.2–0.7), 53.8% (95% *CI*, 41.8–65.4%), 89.2% (95% *CI*, 83.2–93.3%), and 0.722 (95% *CI*, 0.600–0.844, $p < 0.001$), indicating its suitability for predicting HE (**Figure 5A**). A total of 40 hematomas had an attenuation value of <64 HU within the non-hypodense region and there were 31 heterogeneous hematomas. Among them, 8 of 9 hematomas with regular morphology and homogeneous density and suffered HE, and had a density value of < 64 HU ($p < 0.001$). Seven of the 11 patients with irregular morphology, homogeneous density, and dilatation had an attenuation value < 64 HU ($p = 0.028$). Among the heterogeneous hematomas, 6 of the 9 hematomas with a non-hypodense region attenuation value of <64 HU and only 5 of the 22 hematomas with a non-hypodense region attenuation value of >64 HU that eventually expanded ($p = 0.02$).

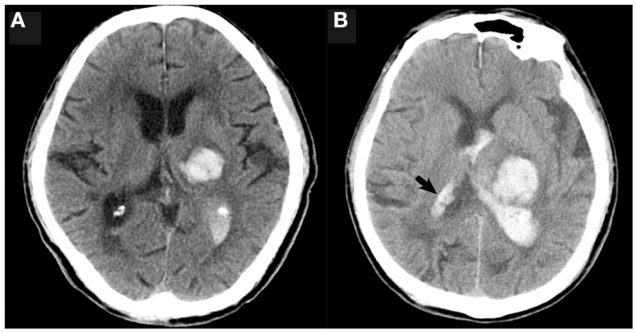

FIGURE 3 | The initial NCCT showed that the thalamic hematoma broke into the ipsilateral ventricle only **(A)**; a follow-up NCCT **(B)** showed new hematoma formation in both the ipsilateral and contralateral ventricles (black arrow).

Validation of the Association Between Attenuation Value < 64 HU and HE

There was good inter-rater (rater 1, $\kappa = 0.967$; rater 2, $\kappa = 0.956$) and intra-rater ($\kappa = 0.945$, rater 1 vs. rater 2) agreement for the measurement of attenuation value <64 HU. A univariate logistic analysis showed that attenuation value within non-hypodense region <64 HU was associated with HE, both unadjusted and after adjusting for other factors (**Table 2**). An ROC analysis showed that the sensitivity, specificity, PLR, NLR, PPV, NPV, and AUC of the attenuation value <64 HU for HE prediction were 36.11% (95% *CI*, 25.1–48.3%), 81.71% (95% *CI*, 75.2–87.1%), 1. 97 (95% *CI*, 1.3–3.1), 0.78 (95% *CI*, 0.6–0.9), 44.8% (95% *CI*, 34.4–55.8%), 75.7% (95% *CI*, 72.0–78.9%), and 0.589 (95% *CI*, 0.526–0.652, $p = 0.005$) (**Figure 5B**). There were 89 heterogeneous hematomas and there were 58 hematomas that had attenuation value < 64 HU within the non-hypodense region. Of the 14 hematomas with regular morphology, homogenous density and subsequent expansion, 9 had attenuation value <64 HU ($p < 0.001$). Out of 22 patients with irregular morphology, homogeneous density and who underwent expansion, 11 had attenuation value <64 HU ($p = 0.041$). Among heterogeneous hematomas, expansion occurred in the 6 of 12 hematomas with attenuation value <64 HU in the non-hypodense region and in 30 of 77 hematomas with attenuation value >64 HU in the non-hypodense region of the hematoma ($p = 0.683$).

A LASSO analysis was applied to screen for predictors without the collinearity of HE (**Figures 6A,B**). The multivariate model showed that an attenuation value < 64 HU remained an independent predictor [odds ratio (*OR*), 4.118; 95% *CI*, 1.897–9.129, $p < 0.001$] after adjusting for male sex, time from the first NCCT scan to onset, baseline hematoma volume, blend sign, and irregular sign (**Figure 6C**, **Supplementary Table 1**).

Based on the multivariate model, the nomogram was constructed (**Figure 7A**) and its discriminating and calibrating ability was favorable with a C-index/AUC of 0.806 (**Supplementary Figure 3**) and good calibration (**Figure 7B**). In addition, the model showed good discrimination ability in derivation cohort and combined cohorts with the C-indexes of 0.883 and 0823. A decision curve analysis showed that an attenuation value < 64 HU significantly improved the predicted net benefit when the probability of HE varied in the range of ∼0.3–0.6 (**Figure 7C**). The clinical impact curve showed that the predicted and actual number of HE was close when the threshold risk of HE exceeded ∼0.5 (**Figure 7D**).

DISCUSSION

The attenuation value of intracerebral hematoma on the NCCT is one of the indicators that have received much attention in recent years for it can be used to predict HE which seriously affects the prognosis of a patient (14–16). Studies had shown that the difference of attenuation value between high-density and low-density areas that had a clear margin within hematoma >18 HU (7, 17–19), and the minimal attenuation value of the hematoma ≤ 31 HU were independent risk factors for predicting HE (20). Here, according to our study, the attenuation value within the non-hypodense region of the hematoma is also an independent predictor associated with HE, and an attenuation value <64 HU is a potential cutoff.

There is no doubt that the hemostatic status of the bleeding site of the ruptured vessel is the fundamental cause of whether the hematoma will enlarge. In the early stages of intracerebral hemorrhage, the density of fresh hematoma is ∼+30 to 45 HU (21). Then, it gradually increases during the initial ∼48 h and then decreases again after reaching the peak value (5, 22, 23). The increased attenuation value of the hematoma is mainly due to the formation of a meshwork of fibrin fibers, globin molecules, and early clot contraction events after bleeding (5, 24), therefore hypodense foci within the hematoma may be the result of repeated bleeding from the primary bleeding site or poor clot contraction and hence the evidence of the potential HE (7, 9, 17). However, the exact site of hemorrhage, whether it is a primary hemorrhagic vessel (25), or a secondary hemorrhagic vessel (26), is not always within the hypodense foci, but may also be located within the non-hypodense region and appear as a spot sign on contrast CT (6, 27). Therefore, the role played by the attenuation value within the non-hypodense region in determining the hemostatic status of the bleeding site is not negligible.

The attenuation value of the hyperdense area of hematoma has been taken into count sparsely in assessing the probability of HE. In the acquirement of the mean attenuation value of hematoma by Jeong et al., both the hypodense and non-hypodense regions of hematoma were measured in a *post-hoc* analysis, though the mean density of the hematoma with and without hypodense foci was not statistically significant, the mean density of the dilated hematoma was significantly lower (5). Nevertheless, their study failed to account for the proportion of high-density and low-density regions in each hematoma, so the unique role of the non-hypodense regions in hematoma expansion cannot be accurately determined. In contrast, our study confirmed that the non-hypodense regions of the expanded hematoma do possess a lower attenuation value. To the best of our knowledge, there is no clearly reported indicator regarding NCCT hematoma density that can be used as a predictor of secondary expansion of homogeneous hematomas. Since the existing hypodensity sign,

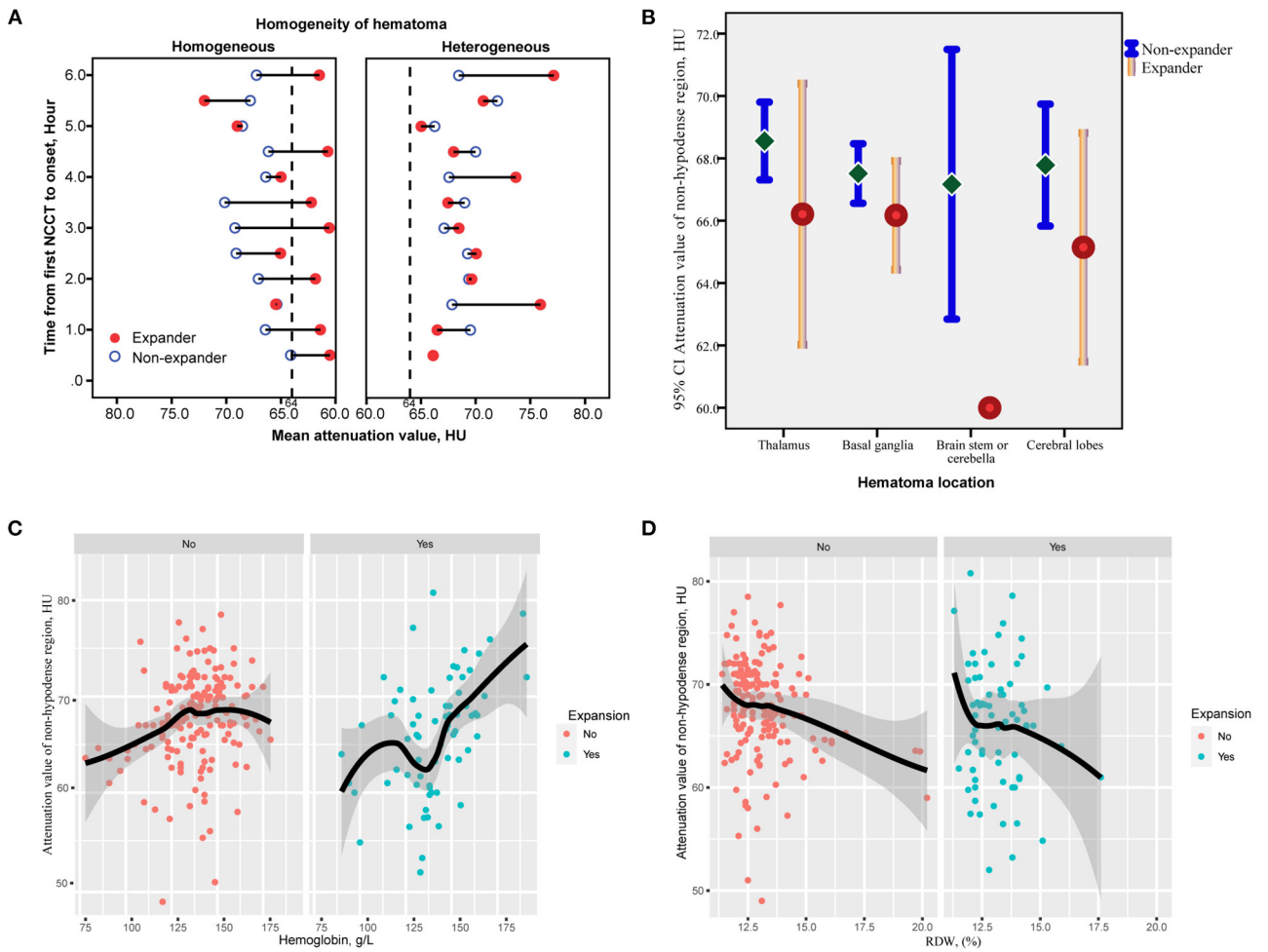

FIGURE 4 | Correlation of the attenuation value of non-hypodense region and time from the first NCCT to onset between hematomas with or without hypodensities. **(A)** The attenuation value of the non-hypodense region of most expanded hematomas remains lower irrespective of time prolonging, whereas no trend exists between the time and non-hypodense region attenuation value of heterogeneous hematomas. **(B)** The mean value and 95% *CI*s of the attenuation value of the non-hypodense region at different cerebral locations. The attenuation value of the non-hypodense region of the cerebellar and brainstem hematomas is the lowest and differs most significantly between expanders and non-expanders. **(C,D)** Loess analysis of attenuation value and hemoglobin and RDW between expanders and non-expanders. The attenuation value increases with a higher hemoglobin level, but with a lower RDW. HU, Hounsfield units; RDW, red blood cell distribution width.

swirl sign, black hole sign, and blend sign are based on hypodense regions to determine the risk of HE, the attenuation value within the non-hypodense region of the hematoma provides an option to determine whether a homogeneous hematoma is at high risk. In addition, heterogeneous hematomas with this feature may have a greater likelihood of expansion. This feature does not intersect with the hematoma morphology and low-density markers that predict HE, and quantifies the density values of the high-density areas independently of the low-density areas within the hematoma, avoiding the influence of the proportion of low-density areas in the calculation of mean density value and thus having independent diagnostic value.

The multifactor model incorporated predictors involving the attenuation value level within the non-hypodense region that was determined by LASSO regression and was presented in the form of a nomogram, allowing for a clearer understanding of the role played by each predictor. The nomogram is simple and feasible, applicable to individual patients and practitioners in daily clinical practice, and the data are easily accessible (28, 29). The discriminative power of our model is good compared with previous reports (29, 30), with a cutoff nomogram score of about 126 and a corresponding prevalence of about 0.3 of expansion, the patient has a high probability of HE. A decision curve analysis can be used to visually and graphically evaluate the ability of each component to improve the model and has been highly recommended in recent years (31, 32). Our model shows that the net benefit of treatment is higher when the risk of hematoma varies between 0.3 and 0.6, thus taking into account the magnitude of the attenuation value within the non-hypodense region may be more helpful (Net Reclassification Improvement = 0.4336, $p = 0.001$; Integrated Discrimination Improvement = 0.0483, $p = 0.002$) in making

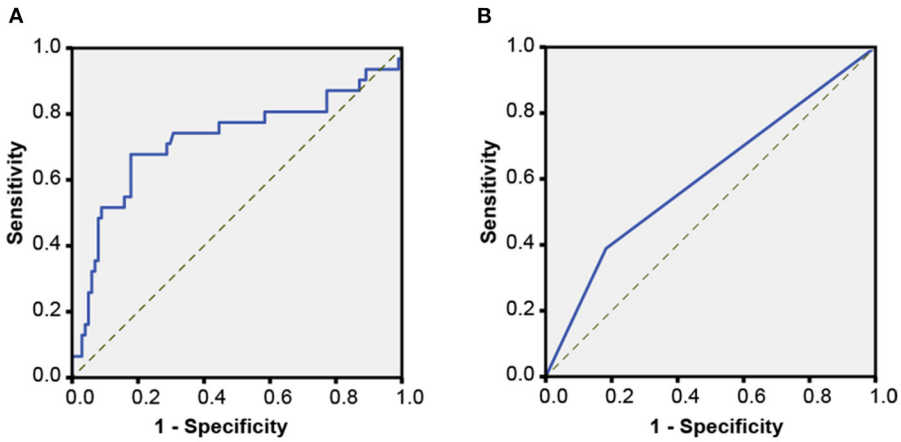

FIGURE 5 | Receiver operating characteristic (ROC) curves. **(A)** An ROC analysis for determining the critical attenuation value of the non-hypodense region of hematoma in the derivation cohort. **(B)** An ROC analysis of the attenuation value <64 HU for predicting HE in the validation cohort.

TABLE 2 | Variables with statistical significance for predicting HE analyzed by univariate logistic regression.

Variables	Crude			Model 1			Model 2			Model 3		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Sex, male	2.056	1.103–3.834	0.023	2.033	1.028–4.022	0.041	2.235	0.948–5.272	0.066	3.140	1.129–8.734	0.028
Time from first NCCT scan to onset, hour	0.764	0.632–0.925	0.006	0.751	0.618–0.914	0.004	0.673	0.532–0.850	0.001	0.611	0.462–0.809	0.001
Baseline GCS score	1.562	1.100–2.219	0.013	1.644	1.140–2.373	0.008	1.470	0.966–2.236	0.072	1.297	0.762–2.208	0.338
Baseline hematoma volume, ml	1.023	1.010–1.037	0.001	1.024	1.011–1.038	<0.001	1.022	1.006–1.038	0.008	1.014	0.993–1.037	0.200
Blend sign	2.980	1.559–5.695	0.001	2.860	1.462–5.595	0.002	3.916	1.793–8.552	0.001	3.471	1.326–9.038	0.011
Irregular sign	3.223	1.825–5.691	<0.001	3.578	1.957–6.540	<0.001	3.554	1.739–7.263	0.001	2.911	1.021–8.304	0.046
Island sign	1.727	1.118–2.668	0.014	1.948	1.219–3.115	0.005	2.227	1.303–3.808	0.003	2.079	0.954–4.527	0.065
Attenuation value of non-hypodense region, HU	0.935	0.886–0.986	0.014	0.926	0.876–0.979	0.007	0.912	0.854–0.974	0.006	0.845	0.770–0.928	<0.001
Attenuation value of non-hypodense region <64 HU	2.140	1.111–4.122	0.023	3.072	1.577–5.986	0.001	4.337	1.885–9.978	0.001	10.252	3.306–31.788	<0.001

Variables that were statistically significant in the univariate analysis were adjusted again to observe whether there was a significant change of OR for the coexistence of other factors.
Model 1: Adjusted for age, sex, co-existing diseases (hypertension, diabetes, current smoker, current alcohol drinker, and stroke history), and antiplatelets or anticoagulants therapy.
Model 2: Adjusted for Model 1, physical examination results (systolic pressure, diastolic pressure, and baseline GCS score) and laboratory findings (RBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelet count, platelet distribution width, prothrombin time, activated partial thromboplastin time, international normalized ratio, total cholesterol, and serum glucose).
Model 3: Adjusted for Model 2, time from the first NCCT scan to onset, and hematoma features on NCCT scan (location, baseline hematoma volume, hematoma width/length ratio on axial section, midline shift distance > 0.5 cm, subarachnoid hemorrhage, intraventricular hemorrhage, swirl sign, black hole sign, blend sign, irregular sign, satellite sign, and island sign).
HE, hematoma expansion; OR, odds ratio; CI, Confidence interval; NCCT, non-contrast CT; GCS, Glasgow coma scale; HU, Hounsfield units; RBC, red blood count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width.

the right clinical decisions when the risk of HE determined by assessment methods is within this range. Besides, the prediction will be more accurate if the threshold of HE is >0.5 according to the clinical impact curve.

The study has some limitations. First, the relatively small number of subjects may have produced some selective bias. In addition, the attenuation of the non-hypodense region was not suitable for predicting intracerebral hematomas with volume <1 ml, which means that most hematomas located in the midbrain, pons, and medulla may not be applicable. The study also excluded multiple intracerebral hemorrhages, although some of these hematomas may have the same etiology, the non-hypodense region attenuation value, and associated model may not be suitable for these hematomas. Again, although the model performed well in our dataset, a follow-up replication study is necessary to validate it as the new metric that has not been studied in other literature. Finally, the optimal cutoff of the new predictor may need to be modified to reach higher accuracy.

CONCLUSIONS

In conclusion, our study explored and validated the attenuation value of the non-hypodense region of hematoma that was independently associated with early HE in patients with spontaneous cerebral hemorrhage. The critical attenuation value < 64 HU was shown to be an appropriate indicator of possible subsequent HE and was able to significantly improve the predictive power of the multifactor model.

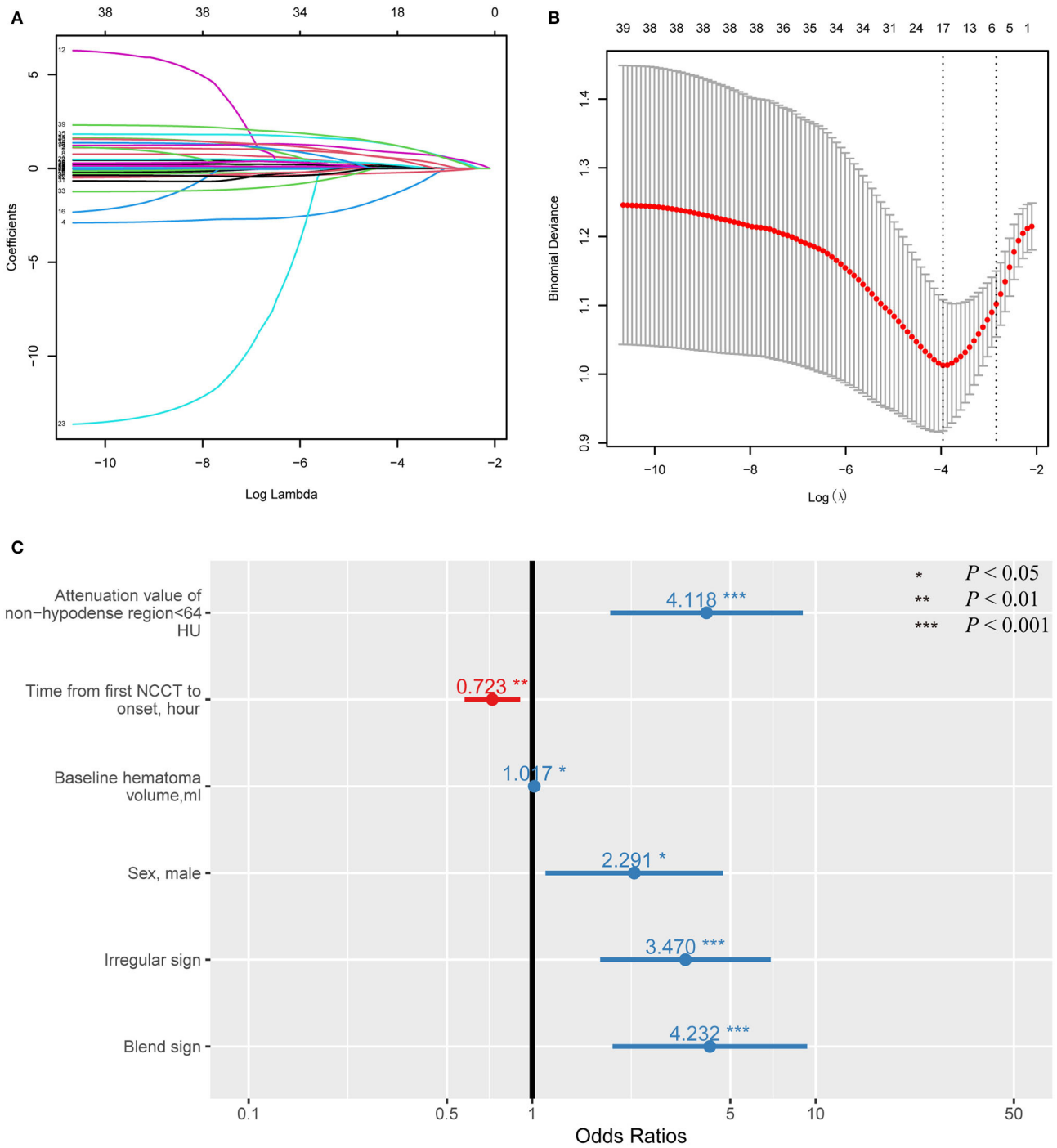

FIGURE 6 | Forest plot showing the results of multivariate analysis. The potential predictors included in the multivariate analysis were first screened by the least absolute shrinkage and selection operator (LASSO) regression. **(A)** LASSO coefficient curves for 39 variables, such as age, sex, time of onset, radiological characteristics of the hematoma, medical history, physical examination, and laboratory parameters. **(B)** Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the one-standard error of the minimum criteria (the 1-SE criteria). Six variables with non-zero coefficients (attenuation value of non-hypodense region <64 HU, time from the first NCCT scan to onset, baseline hematoma volume, sex, irregular sign, blend sign) were identified. **(C)** Forest plot of all six variables identified by LASSO regression that have $p < 0.05$.

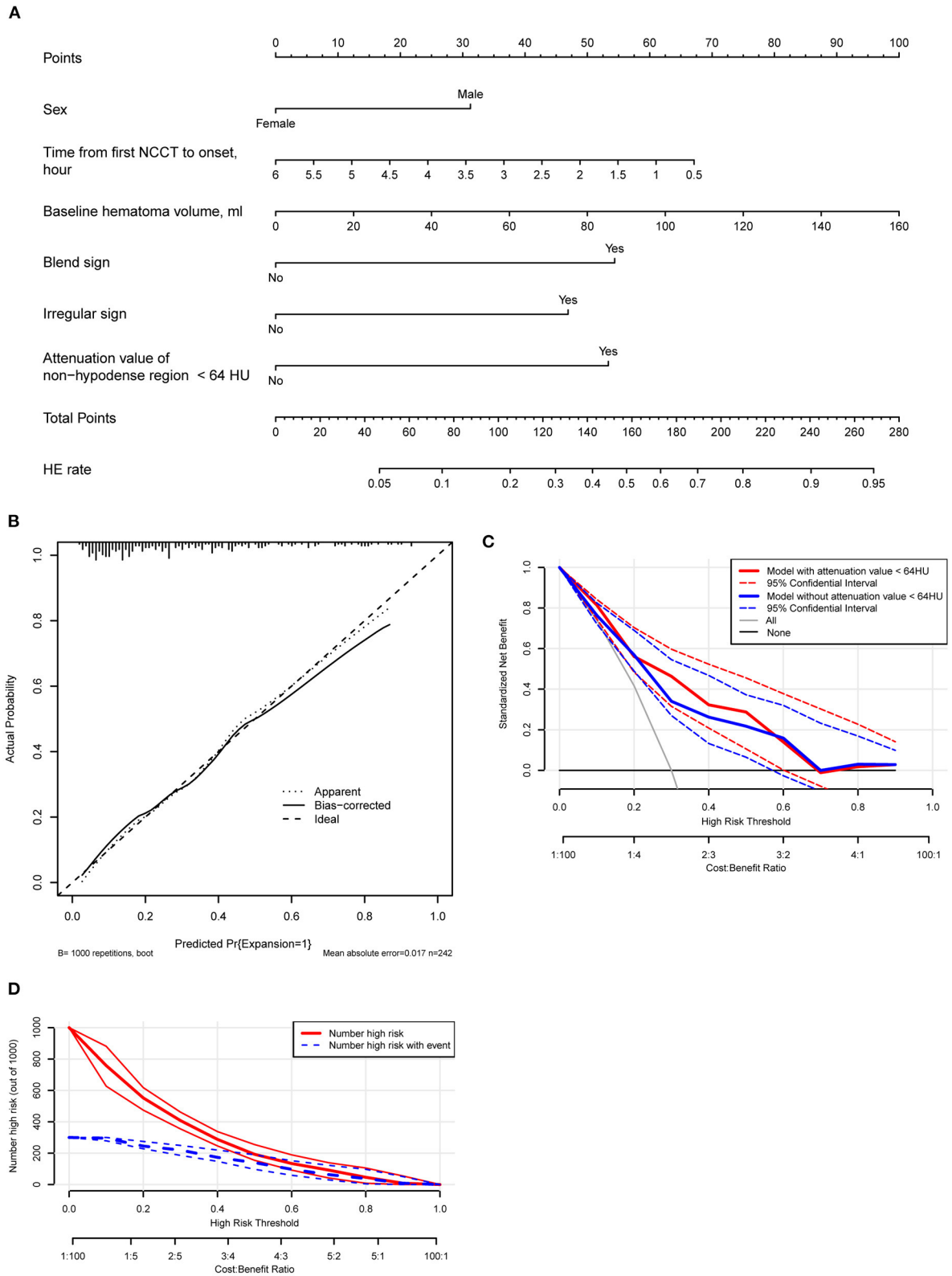

FIGURE 7 | (A) A nomogram is derived from the multivariate analysis. **(B)** Calibration plot of the nomogram model. **(C)** A decision curve analysis of the model with or without incorporation of the attenuation value of the non-hypodense region of hematoma. The model with six variables has a higher net benefit when the expansion risk threshold varies between 0.3 and 0.6. **(D)** Clinical impact curve analysis. The actual events and the predicted events are close while the risk of threshold exceeds about 0.5.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available on request to the corresponding author, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YC contributed to the study conception and design. Material preparation, data collection, and analysis were performed by YC, DC, X-LM, and Z-QG. The first draft of the manuscript was written by YC and reviewed by Y-BO, YH, XC, and JC. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.785670/full#supplementary-material

Supplementary Figure 1 | Flowchart for the patient selection of two patient cohorts.

Supplementary Figure 2 | Correlation heatmap of the potential predictors (continuous variables) of hematoma expansion (HE). The hemoglobin, hematocrit, and MCHC are the positively related factor of HU, whereas the RDW is the negatively related factor that with statistical significance. SBP, systolic pressure; DBP, diastolic pressure; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, RBC distribution width; PLT, platelet; PDW, platelet distribution width; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; TC, total cholesterol; SG, serum glucose; BV, baseline hematoma volume; HU, Hounsfield units.

Supplementary Figure 3 | The receiver operating characteristic (ROC) analysis of the multivariate model. The C-index/area under the curve (AUC) is 0.806. The corresponding nomogram score for cutoff is 126 (asterisk).

Supplementary Table 1 | Multivariate analysis of the predictors of HE identified by LASSO regression.

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Experience of Using a New Brain Surgery Head Frame and Location Sticker for Treating Spontaneous Intracranial Hematoma

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Objectives: Various stereotactic aspirations have been accepted; however, no standard stereotactic aspiration has been established for the treatment of spontaneous intracerebral hemorrhage (ICH). The authors explored an easy, fast, and effective procedure by using a new brain surgery head frame and location sticker for the removal of spontaneous hematoma.

Patients and Methods: A retrospective database review was performed from January 2018 to March 2020 to identify patients with ICH who were treated with puncture and drainage for hematoma by using a new brain surgery head frame and location sticker for positioning and guidance.

Results: A total of 45 patients with spontaneous ICH were enrolled in our study. The mean (± *SD*) surgical time was 29.3 ± 4.1 min. The average hematoma evacuation rate was 72.2%. The mean (± SD) preoperative Glasgow Coma Scale (GCS) score was 9.58 ± 2.92; the mean GCS score increased to 11.55 ± 2.59 ($p = 0.006$) and 12.86 ± 2.04 ($p < 0.001$) at 1 week after surgery and at the time of discharge, respectively. The mean (± *SD*) preoperative muscle force score was 1.25 ± 1.51; the mean muscle force score had improved to 2.20 ± 1.64 ($p = 0.009$) and 2.88 ± 1.64 ($p < 0.001$) at 1 week after the operation and the time of discharge, respectively. Out of these, one patient experienced postoperative rebleeding, however, no further hematoma expansion was found after the second aspiration and thrombolysis.

Conclusion: Using this brain surgery, head frame and location sticker combined with urokinase infusion appears simple, safe, and effective for the removal of hematoma for patients with spontaneous ICH. However, randomized controlled trials are necessary to provide more concrete evidence-based results.

Keywords: intracerebral hemorrhage, brain surgery head frame, location sticker, evacuation, stroke

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INTRODUCTION

Currently, intracerebral hemorrhage (ICH), a serious and common cerebrovascular disease, is associated with high mortality and adverse clinical outcomes, especially in the elderly (1). Around 10% of strokes and 30% of cerebrovascular diseases are caused by ICH, which affects ∼4,000,000 people per year worldwide, with 40% mortality at 1 month (2–4). Meanwhile, 40% of survivors

are severely disabled, and only 12% of them can live independently, having a huge impact on families and society (5, 6). Surgery is the most common treatment of ICH, and it has been greatly improved with the accumulation of surgical experience and progress in scientific research (7). However, there are different surgical procedures with varying prognoses (8, 9). Craniotomy is the traditional surgical treatment, and good effects for hematoma removal and neurocognitive function improvement have been reported in many studies. However, craniotomy always damages normal brain tissues in the area around the hemorrhage, subsequently affecting the efficacy of craniotomy for the treatment of patients with ICH (10–12). Meanwhile, the appearance of minimally invasive endoscopic techniques and their promising application perspectives have been demonstrated (13). There are two primary kinds of minimally invasive surgery, such as endoscopic evacuation and stereotactic aspiration, for removing the hematoma. In endoscopic evacuation, the endoscope is placed into the hematoma by creating a small bone window, and suction and irrigation are then used to remove the hematoma. For stereotactic aspiration, a catheter is inserted into the center of the hematoma, and then the hematoma is suctioned using different image guidance. The catheter can also be left in the center of the hematoma to repeatedly instill thrombolytic drugs to prevent any residual hematoma. Currently, although various stereotactic aspirations have been accepted and show differing results, no standard stereotactic aspiration technique has been established for the treatment of spontaneous ICH (14). Here, we present our single-center experience with applying an easy, fast, and effective procedure for the removal of hematoma in 45 consecutive patients with spontaneous ICH.

MATERIALS AND METHODS

We conducted a retrospective study involving 45 patients treated from January 2018 to March 2020 at the Department of Neurosurgery, Tangshan Gongren Hospital. All the patients with ICH were treated with puncture and drainage for cerebral hematoma by using a new brain surgery head frame and location sticker for positioning and guidance. Computed tomography (CT) scans revealed that the volume of intracranial supratentorial hemorrhage was more than 20 ml and subtentorial hemorrhage was more than 10 ml. These patients required surgical treatment. The incidence of hematoma evacuation and rebleeding, operative time, Glasgow Coma Scale (GCS) score, and muscle force at 1 h preoperatively, 1 week postoperatively, and discharge time were analyzed.

Ethics

This trial was approved by the Medical Ethical Committee of Tangshan Gongren Hospital. Signed consent forms were obtained from all the patients before the operation or from an immediate family member, if the patient was unable to do so.

Inclusion and Exclusion Criteria

Patients were included in our study, if they met the following preplanned criteria: (I) diagnosed with spontaneous supratentorial hemorrhage from 20 to 50 ml or subtentorial hemorrhage from 10 to 15 ml; (II) age between 25 and 80 years; (III) spontaneous ICH occurring within 72 h; (IV) GCS score $\geq$ 5; and (V) normal coagulation function.

The exclusion criteria were as follows: (I) ICH caused by intracranial aneurysm, traumatic brain injuries, or cerebrovascular malformation; (II) coagulation dysfunction; (III) serious heart, renal, or lung functional failure; (IV) neurological deficits or cerebrovascular events before ICH; and (V) incomplete or missing consent form.

Brain Surgery Head Frame and Location Sticker

The brain surgery head frame (patent number: ZL 201621187091.5) and the location sticker (patent number: ZL 201720977420.4) are based on the theory of "three points on one line" (**Figures 1A,B**) The three points are the hematoma center site, scalp puncture point, and scalp reference point. One line refers to the straight line formed by these points, namely, the surgical puncture route (**Figures 1C,D**).

Intervention

Before admission to the operation room, all the patients underwent a CT scan to confirm the appearance of an intracranial hemorrhage requiring evacuation (**Figure 2A**). The waiting time before the operation in all the patients was set for at least 6 h after onset owing to most rebleeding appearing within 6 h after onset according to several publications (15–17). Then we made the preoperative surgical plans. Based on the location and volume of the intracranial hematoma observed on the preoperative CT scan, we roughly located the hematoma center site and puncture route on the largest slice of the hematoma seen on the CT image (**Figures 2B–E**) and then marked the puncture point and reference point of the hematoma on the scalp where the location sticker would be attached (**Figure 2F**). A CT scan with 1 mm for each layer was performed to locate an optimal slice of the hematoma to measure the precise drilling and puncture depth and to obtain a puncture point and reference point that would appear in the location sticker by using the PISP (Philips IntelliSearch Portal v5.0.2.10010 or v7.0.6.40181) system and then mark them on the scalp before surgery (**Figures 3A,B**). The best puncture route should generally meet the following conditions: (I) avoid the important functional areas and large blood vessels; (II) along the hematoma axis as much as possible; and (III) as short as possible. We adjusted the brain surgery head frame before it was fixed on the scalp to be perpendicular to the puncture path (**Figures 3C–F**). The two ends of the brain surgery head frame were accurately fixed at the puncture point and reference point to place the puncture point, reference point, and hematoma center point on the puncture path. Aspiration of the hematoma was conducted after drilling through the skull and arriving at the puncture site according to the preset depth on the second CT scan (**Figure 4**). If the resistance increased, the hematoma aspiration was stopped, and a drainage tube was inserted into the cavity of the hematoma combined with a urokinase drip for several days (50,000 IU every 8 h) in 3 ml of normal saline through the hematoma catheter to remove the

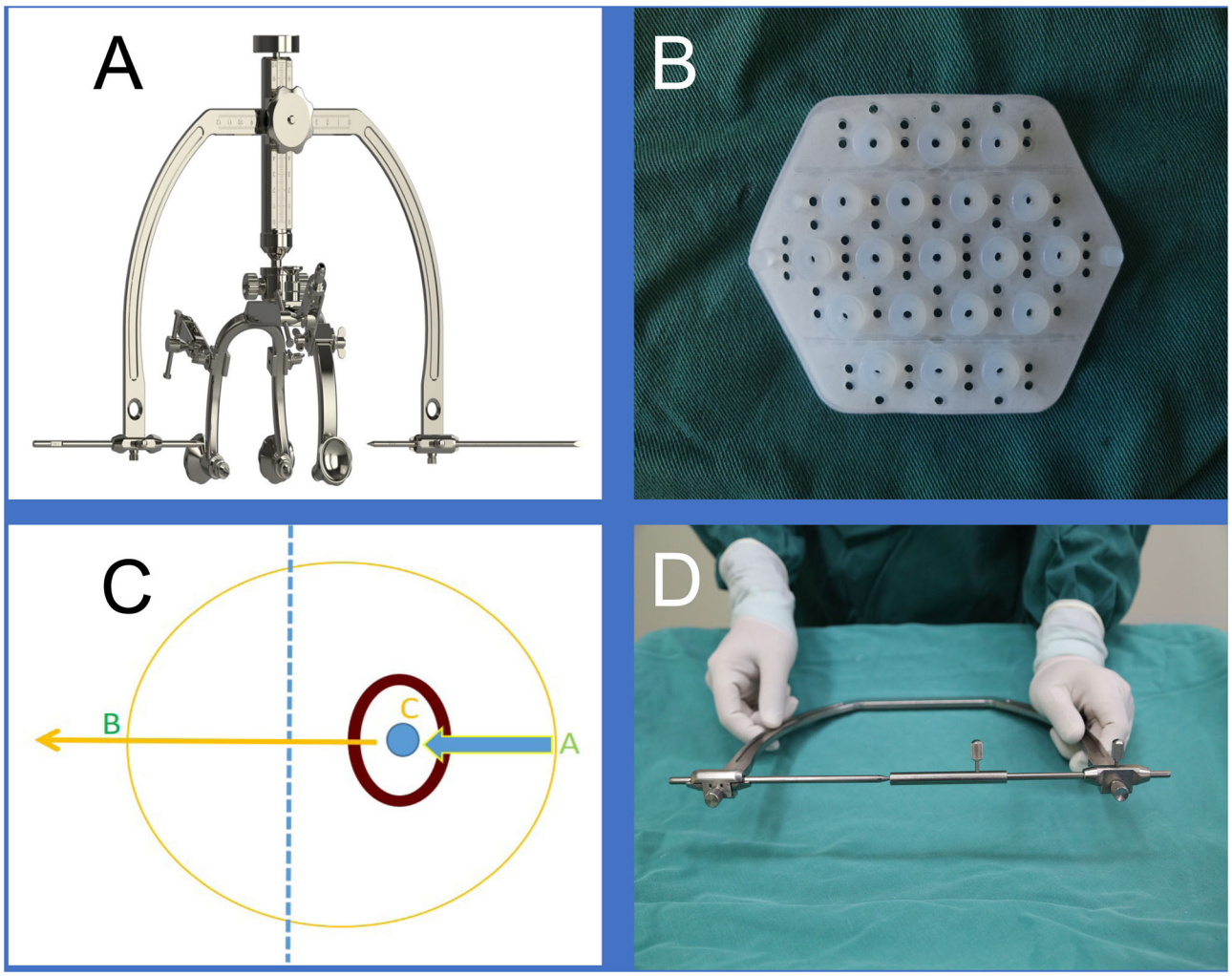

FIGURE 1 | (A) is the brain surgery head frame, **(B)** is the location sticker, **(C and D)** shows that our design was based on the theory of "three points on one line," where the three points are the scalp puncture site, the hematoma center site, and the reference point, and the one line refers to the straight line formed by the three points.

remaining hematoma. If a multitarget puncture was required, we conducted the hematoma aspiration according to the method described above with several catheters.

Total intravenous anesthesia (TIVA) was used during the surgery. Anesthesia induction: intravenous midazolam 0.04–0.06 mg/kg, propofol 1.5–2.5 mg/kg, sufentanil 0.3–0.5 μg/kg, and rocuronium 0.6 mg/kg. Mechanical ventilation was performed after anesthesia induction and endotracheal intubation. The tidal volume was 6–8 ml/kg, the ventilation frequency was 12 times/min, the inhalation-exhalation ratio was 1.0:2.0, the inhalation oxygen concentration was 40–60%, and the oxygen flow was 2 L/min. The anesthesia maintenance drugs were relifentanil 0.1–0.3 μg/kg·min and propofol 4–6 mg/kg/h. Rocuronium bromide was intermittently given with a dosage of 0.15 mg/kg, bispectral index (BIS) was maintained between 40 and 60, and vasoactive drugs were given when necessary to maintain the blood pressure and heart rate within the normal range.

In addition, early intensive hypotension is safe and effective and can significantly improve patient outcomes. If there is a preoperative systolic blood pressure of 150–220 mm Hg and no contraindications for acute antihypertensive therapy, it should be reduced to <140 mm Hg based on a good cerebral perfusion. The target value of decompression for patients with more than 220 mmHg should be based on the patient's history of hypertension and basic blood pressure, but it can be reduced to below 160 mmHg. The intraoperative and postoperative blood pressure should be under 140 mmHg based on a good cerebral perfusion.

Hematoma Volume Calculations

The hematoma volumes were calculated using the ABC/2 formula, where A and B are the perpendicular maximal diameters of the lesion, and C is the total length in the vertical plane [equation: V = (length ×width ×thickness)/2]. All diameters and

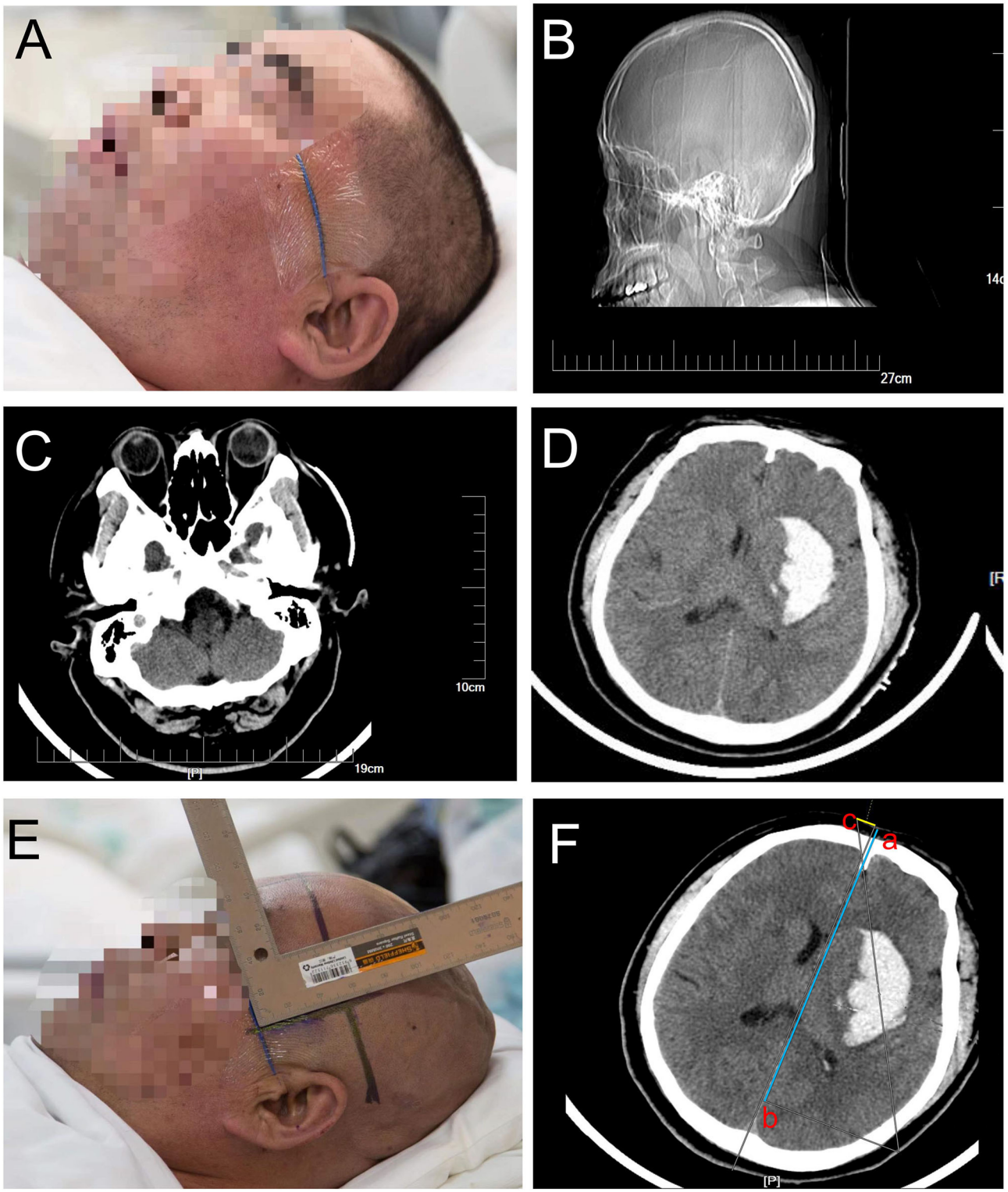

FIGURE 2 | (A) shows that the orbitomeatal line is the preparation before the CT scan for patients with suspected cerebral hemorrhage, **(B)** confirms that the orbitomeatal line was precisely attached to the scalp, **(C)** represents the slice marked by the orbitomeatal line as the first slice of the CT scan, intracranial hemorrhage was confirmed in **(D)**, and the punctured plane was measured based on the distance between the first slice and the largest slice of the hematoma in **(E)**. **(F)** represents how to determine the position of the location stickers on the CT image by measuring and marking their positions on the scalp.

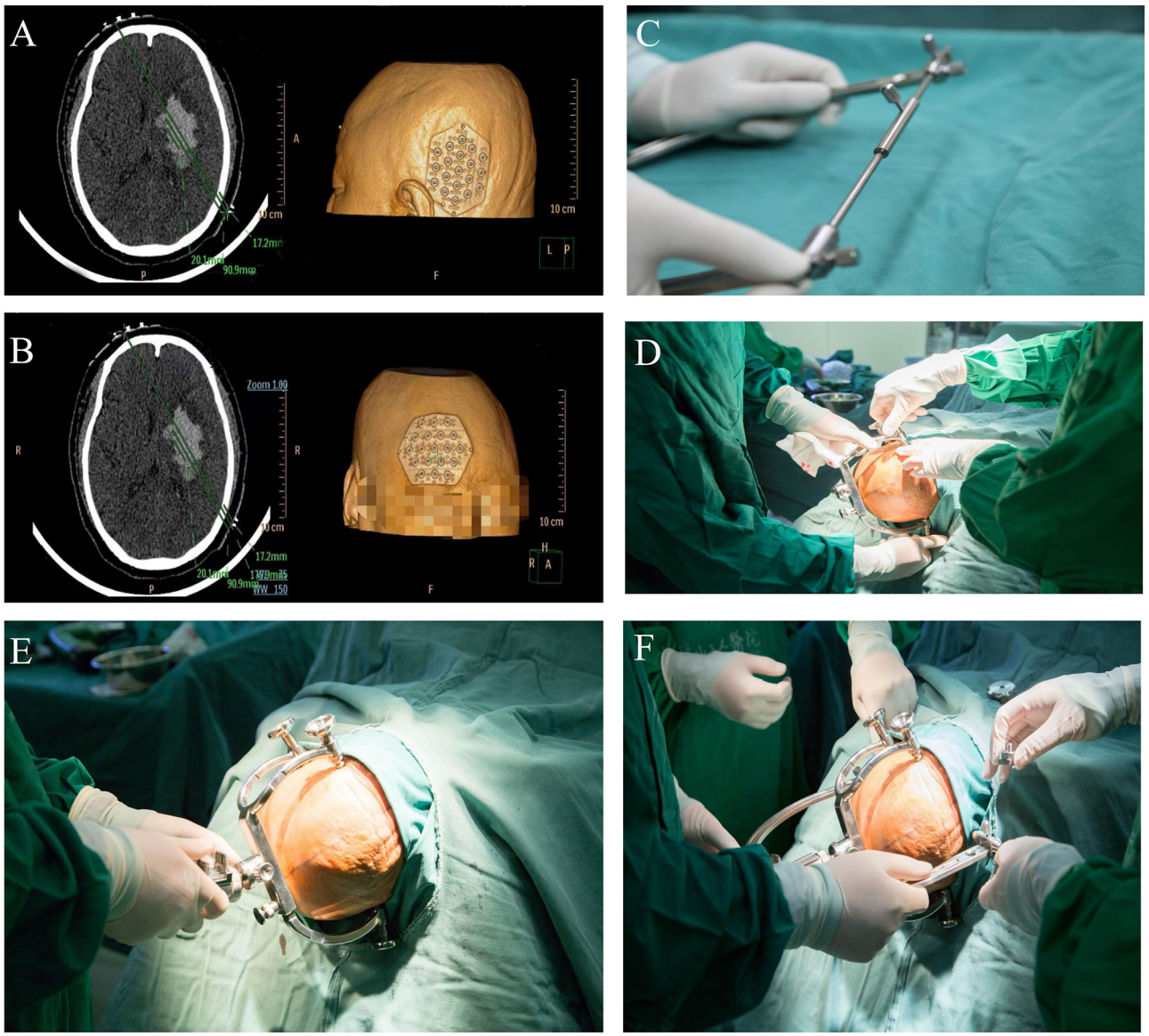

FIGURE 3 | (A,B) show that the accurate puncture site, reference point, puncture route, puncture depth, and drill depth are located on the skin by performing a CT scan with 1 mm for each layer using the PISP (Philips IntelliSearch Portal v5.0.2.10010) system. The brain surgery head frame is correct in **(C)**, and **(D–F)** is the fixation process of the head frame.

lengths were obtained from the CT scans taken just before the operation (18).

Imaging Follow-Up

Cranial CT was conducted 2 h after the drainage tube was removed, and the incidence of hematoma evacuation was calculated by the same person blinded to all treatment and outcomes using Slicer software (19).

Statistical Analysis

We used SPSS statistical software (version 19.0, IBM Corp.) to conduct our analyses, and a $p < 0.05$ was considered to reveal a significant difference. We used the paired Wilcoxon test to compare the preoperative hematoma volume and time of tube removal. For patients with supratentorial ICH, the Kruskal–Wallis test was used to compare the preoperative initial GCS score, GCS score at 1 week after the operation, and discharge time, and multiple comparisons in one-way analysis of variance (ANOVA) were used to compare the preoperational muscle power, 1 week after the operation, and at the discharge time.

RESULTS

Total forty-five patients with spontaneous ICH were enrolled in our study, including 30 cases of putamen hemorrhage, 5 cases of

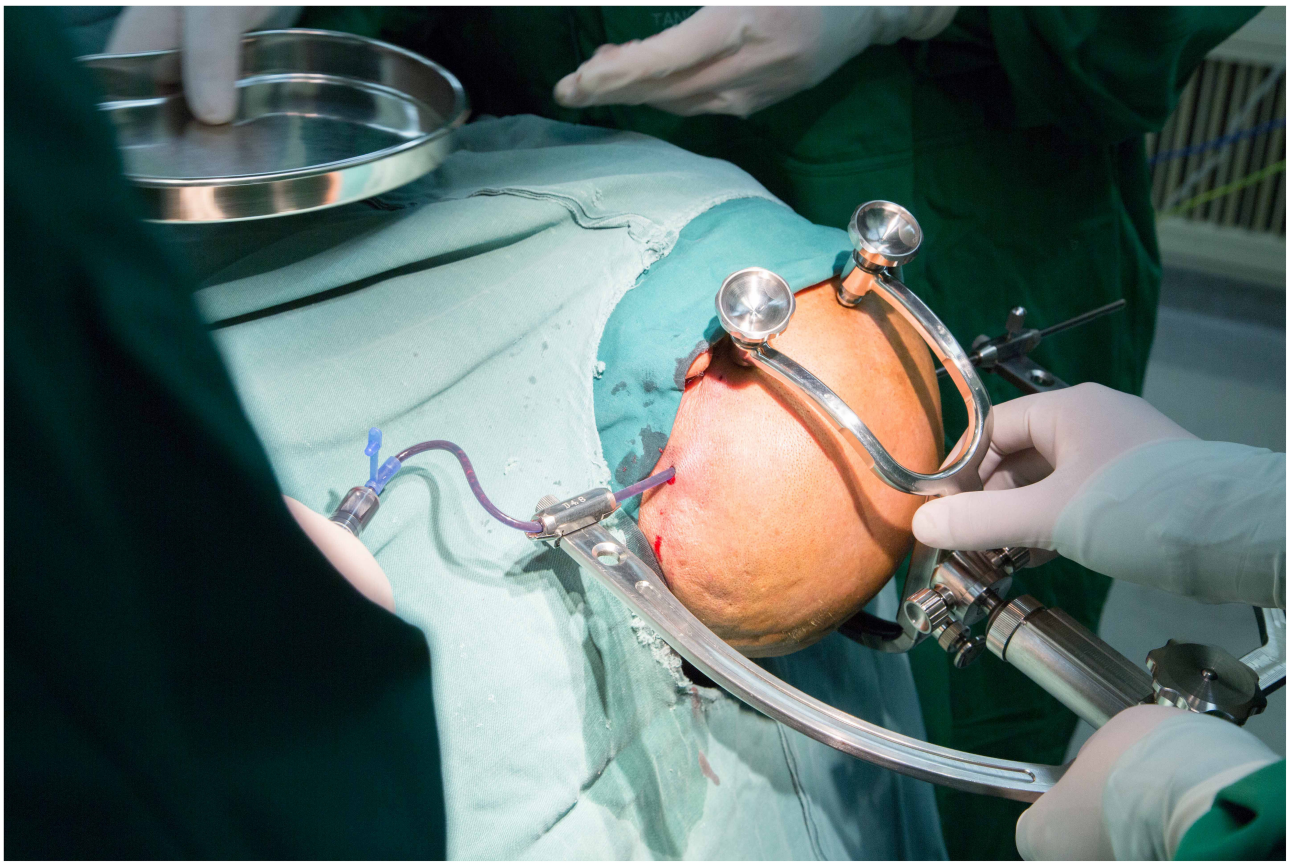

FIGURE 4 | Puncture and aspiration of the hematoma.

thalamic hemorrhage, 5 cases of lobar hemorrhage, and 5 cases of cerebellar hemorrhage. The mean age of the patients was 57.13 ± 10.29 years, and there were 33 men and 12 women. Out of these, thirty-one patients (71.11%) had a prior history of hypertension, and 26 were being treated with medications. More details of the patients' clinical and demographic characteristics are shown in **Table 1.** The brain surgery head frame combined with a location sticker was used to ensure that the optimal puncture was made and that the soft drainage tube reached the center of the hematoma in all cases. Although not all hematomas were initially removed, all patients eventually achieved satisfactory removal of the hematoma.

The time from symptom onset to the first aspiration was more than 6 h in all cases. The mean hematoma volume was 32.27 ± 10.63 ml before the operation, while the average left hematoma volume was 6.08 ± 2.27 ml until the drainage tube was removed ($p < 0.001$, **Figure 5**), showing a mean evacuation rate of 72.20%. The soft drainage catheter was inserted for a median duration of 2.76 days.

For patients with supratentorial ICH, the average initial GCS score was 9.58 ± 2.92, and the mean GCS score at 1 week after the operation and discharge time were 11.55 ± 2.59 ($p = 0.006$) and 12.86 ± 2.04 ($p = 0.000$, **Figure 6**), respectively. The average preoperative muscle power was 1.25 ± 1.51, and the mean muscle power at 1 week after the operation and at the discharge time were 2.20 ± 1.64 (statistically significant improvement, $p = 0.009$) and 2.88 ± 1.64 (statistically significant improvement, $p < 0.001$, **Figure 7**), respectively. Meanwhile, mRS and GOS scores were assessed preoperatively and at 6 months postoperatively. The results showed that the majority of patients improved significantly in neurological function based on the mRS (mean 4.244 reduced to mean 2.689, $p < 0.001$) and GOS scores (man 2.765 increased to mean 4.200, $p < 0.001$). More details were shown on **Table 1**.

General anesthesia was used for all cases. The mean (± *SD*) surgical time was 29.3 ± 4.1 min. Preoperative surgical plans, such as designing an accurate puncture site, reference point, puncture route, puncture depth, and drill depth data processing, were completed within ∼5 min, and the median time from the initial head frame fixation to its removal was 20–30 min for the patients needing a single tube for aspiration, while it was 30–40 min for patients needing two tubes. There was no intracranial infection or systemic hemorrhage in any of the patients. No patient died before being discharged from the hospital. Although

TABLE 1 | Demographic and clinical characteristics of the 45 patients in the study.

Case No.	Age	Gender	H, D, or C History	MH	Side	Location	Pre mRS	3 M mRS	Six M mRS	Pre GOS	Six M GOS	TSOHA	Vol(ml)	Rv(ml)	ICD	Operation Time	LOS
1	57	male	H&C	No	Left	Putamen	4	3	3	3	4	13	25.6	5.8	3	27 mins	20
2	48	male	H&D	No	Left	Putamen	4	2	2	3	5	12	32	6	3	26 mins	25
3	67	male	H&D	Anti-P	Left	Parietooccipital	4	3	3	3	4	10	48.36	7.2	3	35 mins	25
4	42	female	H	No	Left	Putamen	4	2	2	3	5	13	37.4	4.5	2	27 mins	16
5	54	male	H	No	Right	Putamen	4	2	1	3	5	8	31.5	3.5	2	28 mins	18
6	52	male	H	No	Right	Putamen	4	3	3	3	4	9	30.7	8	4	27 mins	17
7	49	male	H	No	Left	Temporoparietal	3	2	2	4	5	8	31	8.5	4	29 mins	16
8	72	female	No	No	Left	Occipital	3	2	2	4	5	7	46	6.7	4	28 mins	30
9	47	male	H	No	Left	cerebellum	4	2	2	3	5	8	12.3	3.18	2	26 mins	18
10	76	female	H	No	Left	Putamen	5	4	4	2	3	10	46	11.3	2	35 mins	35
11	39	male	H	No	Left	Thalamus	5	3	3	2	4	8	23.6	3.6	3	27 mins	21
12	51	male	No	No	Left	Putamen	4	3	3	3	4	8	28.5	4.6	3	25 mins	23
13	42	male	H	No	Right	Putamen	4	3	3	3	4	8	39.5	6.6	3	28 mins	24
14	65	male	H	No	Right	Putamen	5	4	4	2	3	9	48.9	4.6	4	37 mins	23
15	63	female	H	No	Left	Putamen	5	3	2	2	5	9	26.5	3.96	3	26 mins	18
16	56	male	H	No	Left	Putamen	5	4	4	2	3	10	46.6	9.7	2	35 mins	23
17	44	male	H	No	Left	Temporal	4	1	1	3	5	7	22	5	2	23 mins	18
18	55	male	H	No	Left	Putamen	5	2	1	2	5	16	31	7.4	4	27 mins	30
19	58	female	H	No	Left	Putamen	4	3	3	3	4	10	26	4.27	3	27 mins	18
20	51	male	H	No	Left	Putamen	4	3	3	3	4	7	32.5	6.8	3	30 mins	21
21	65	male	H	No	Right	cerebellum	3	2	2	4	5	8	13.5	3.5	3	26 mins	18
22	60	female	H	No	Left	Thalamus	5	4	4	2	3	9	22.4	4.5	4	28 mins	21
23	77	male	H	No	Left	Putamen	5	4	4	2	3	8	45.6	8.6	4	34 mins	28
24	52	male	H	No	Left	Putamen	4	3	2	3	5	8	33.1	5.8	2	25mins	23
25	42	male	H	No	Left	Putamen	4	3	3	3	4	13	37.41	2.3	3	35 mins	22
26	51	male	H	No	Right	Putamen	4	3	2	3	5	12	44.5	5.7	3	37 mins	20
27	51	male	No	No	Left	Putamen	4	3	2	3	5	10	33.1	3.8	2	29 mins	18
28	45	male	H	No	Right	cerebellum	3	1	1	4	5	13	12.5	3.8	3	28 mins	21
29	54	male	No	No	Left	Putamen	4	3	3	3	4	8	29.5	5.3	3	25 mins	18
30	51	male	H	No	Right	Putamen	4	3	2	3	5	9	33.7	5.6	4	28 mins	22
31	67	male	H	No	Right	Temporoparietal	4	3	2	3	5	8	45.21	8.5	4	37 mins	25
32	56	male	H&D	No	Right	Putamen	5	4	4	2	3	7	33.9	7.7	3	26 mins	30
33	62	female	No	No	Left	Putamen	4	3	2	3	5	8	30.6	7.2	4	26 mins	18
34	70	female	H	No	Right	cerebellum	3	2	1	4	5	10	11.5	2.2	3	28 mins	20
35	50	female	No	No	Left	Putamen	4	3	3	3	4	8	43	8	4	33 mins	20
36	45	male	H&D	No	Right	Putamen	5	3	3	2	4	8	43.29	10.7	4	32 mins	28
37	71	male	No	No	Right	Putamen	5	4	4	2	3	8	44.2	9.8	3	37 mins	26

(Continued)

TABLE 1 | Continued

Case No.	Age	Gender	H, D, or C History	MH	Side	Location	Pre mRS	3 M mRS	Six M mRS	Pre GOS	Six M GOS	TSOHA	Vol(ml)	Rv(ml)	ICD	Operation Time	LOS
38	72	female	No	Anti-P	Left	Putamen	5	4	4	2	3	9	31.5	5	3	29 mins	18
39	50	female	H	Anti-P	Right	Thalamus	5	4	4	2	3	9	22.6	5.7	3	28 mins	30
40	65	male	H	No	Right	Putamen	4	3	3	3	4	10	46.6	10.8	3	35 mins	18
41	60	male	H&D	No	Right	cerebellum	4	2	2	3	5	7	13.1	3.8	3	25 mins	31
42	71	female	H	No	Right	Putamen	5	4	3	2	4	16	37.9	6.9	3	36 mins	27
43	69	male	H	No	Left	Thalamus	5	4	3	2	4	10	23.6	6.6	3	24 mins	35
44	55	male	H	No	Right	Putamen	4	3	3	3	4	7	31.7	5.64	2	27 mins	25
45	66	male	H	No	Right	Thalamus	5	4	4	2	3	8	22.4	5.3	3	28 mins	36

ICD, Indwelling catheter days; TSOHA, time from symptom onset to hematoma aspiration; LOS, length of stay; Pre, Previous; H, hypertension; D, diabetes; C, coronary heart disease; MH, medication history; Anti-P, antiplatelet; M, months; mRS, Modified Rankin Scale; GOS, Glasgow Outcome Scale.

there was one patient who experienced postoperative rebleeding, no further hematoma expansion was found after the second aspiration and thrombolysis.

Illustrative Cases

Case 1: A Cerebellar Hemorrhage

A 65-year-old man with a history of 2 years of hypertension was admitted to our hospital for sudden headache, dizziness, and vomiting. Cranial CT revealed a right cerebellar hemorrhage (**Figure 8A**). An optimal image for attaching the patches was available based on the distance between the orbitomeatal line and the largest area of the hematoma seen on the CT image. Based on the vertical distance of 45.90 mm (puncture point) from the centerline and a parallel distance of 64.96 mm (reference point) along the centerline (**Figure 8B**), we achieved a location sticker on the patient's head (**Figures 8C–F**). We performed a CT scan of 1 mm for each layer to reveal the accurate puncture site, reference point, puncture route, puncture depth (50.1 mm), and drill depth (20.7 mm) by using the PISP (Philips IntelliSearch Portal v7.0.6.40181) system before surgery (**Figures 9A,B**). We fixed the positioning and guided the brain surgery head frame on the head perpendicular to the puncture trajectory, and then 5 ml hemorrhage was suctioned by using a drainage tube inserted in the hemorrhage for 3 days combined with urokinase administration. The cranial CT conducted the next day demonstrated close to complete evacuation of the hematoma (**Figure 9C**).

Case 2: A Basal Ganglia Hemorrhage

A 54-year-old man with a history of 5 years of hypertension was admitted to our center after a sudden confusion of consciousness and left limb paralysis. Emergency brain CT scans showed a right basal ganglia hemorrhage (**Figure 10A**). The distance between the orbitomeatal line and an optimal section of the hematoma shown in the CT image was 4.5 cm. Two location stickers were attached on the scalp at a vertical distance of 9.58 mm (reference point) from the centerline and a parallel distance of 179.97 mm (puncture point) along the centerline (**Figure 10B**). The PISP system (Philips IntelliSearch Portal v5.0.2.10010) was used to show the accurate puncture site, reference point, puncture route, puncture depth (113.0 mm), and drill depth (9.4 mm) by performing a CT scan of 1 mm for each layer before the surgery (**Figures 10C,D**). Cranial CT conducted the next day revealed the hematoma was almost completely evacuated (**Figure 10E**). MR diffusion tensor imaging showed that the drainage tube was placed beside the corticospinal tract to remove the hematoma, quickly relieving the pressure on the corticospinal tract, promoting the recovery of the limbs (**Figure 10F**).

DISCUSSION

The role of minimally invasive surgery, such as neuroendoscopic evacuation or stereotactic aspiration, has gained wide acceptance for the treatment of ICH in recent years owing to the benefit of surgical clot evacuation with less tissue damage, a shorter time required for surgery, and an increased possibility of using local anesthesia (20–22). A multicenter study involving

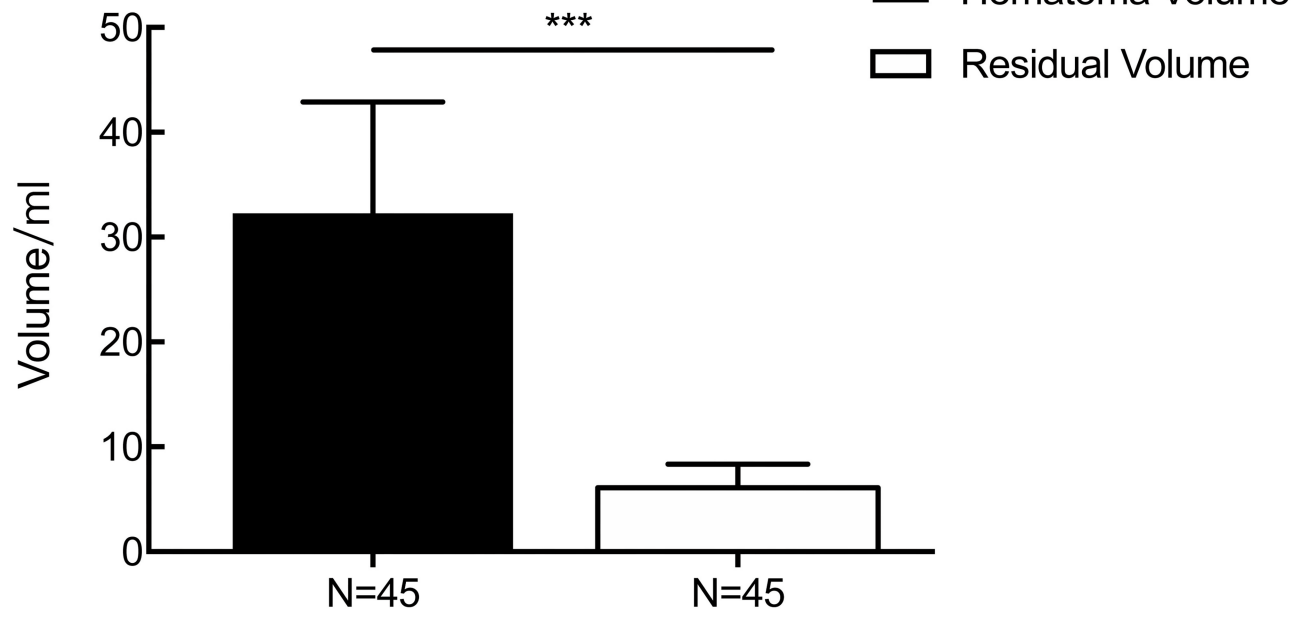

FIGURE 5 | The result of changes in the volume of the hematoma perioperatively. The mean hematoma volume was 32.27 ± 10.63 ml before the operation, while the average left hematoma volume was 6.08 ± 2.27 ml until the drainage tube was removed ($p < 0.001$). ***$p < 0.001$.

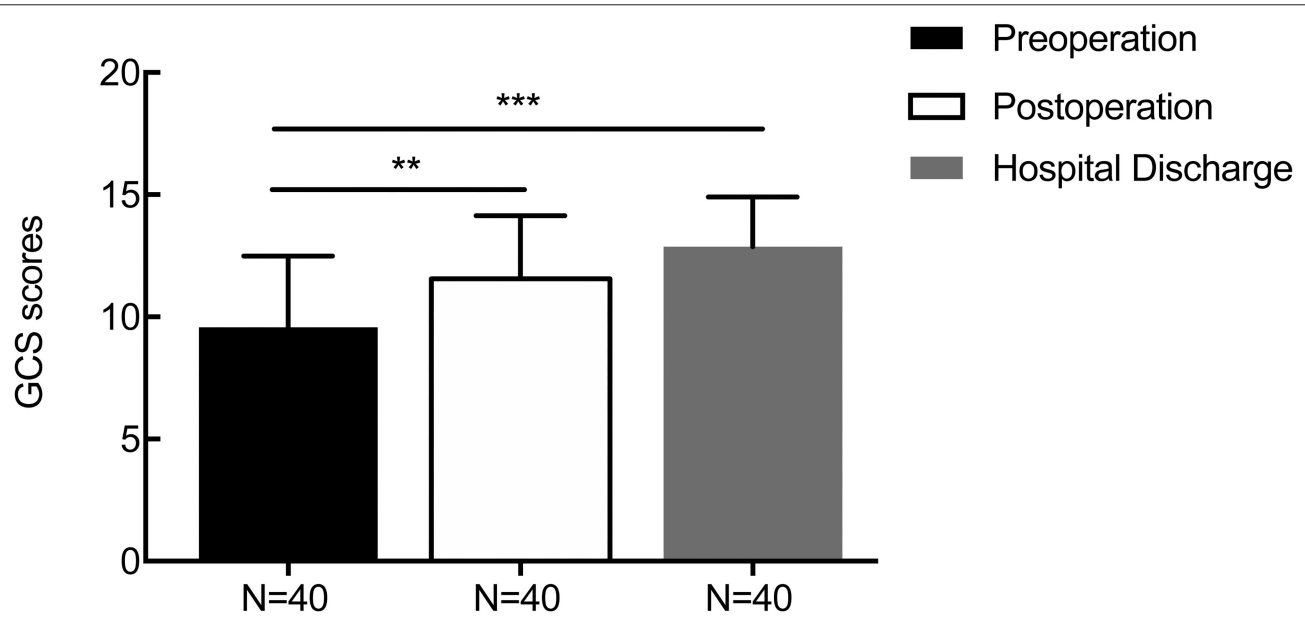

FIGURE 6 | The result of changes in the perioperative GCS score. The average initial GCS score was 9.58 ± 2.92, and the mean GCS scores at 1 week after the operation and at discharge were 11.55 ± 2.59 ($p = 0.006$) and 12.86 ± 2.04 ($p = 0.000$), respectively. **$p < 0.01$ and ***$p < 0.001$.

135 hospitals, including 841 patients with a basal ganglia hemorrhage, demonstrated that puncture suction is the optimal treatment when the volume of the hematoma was <50 ml (23). However, localization of the hematoma is always based on the experience of the surgeons, according to most published studies of endoscopic hematoma evacuation, causing instability, unreliability, and issues with quality control (24, 25). Although hematoma localization could be based on neuronavigation, which can accurately locate the desired position, the thinnest scan layers of CT data are necessary (26). In addition, there is a drawback to neuronavigation due to its time-consuming preparation (27). Therefore, the debate remains regarding how

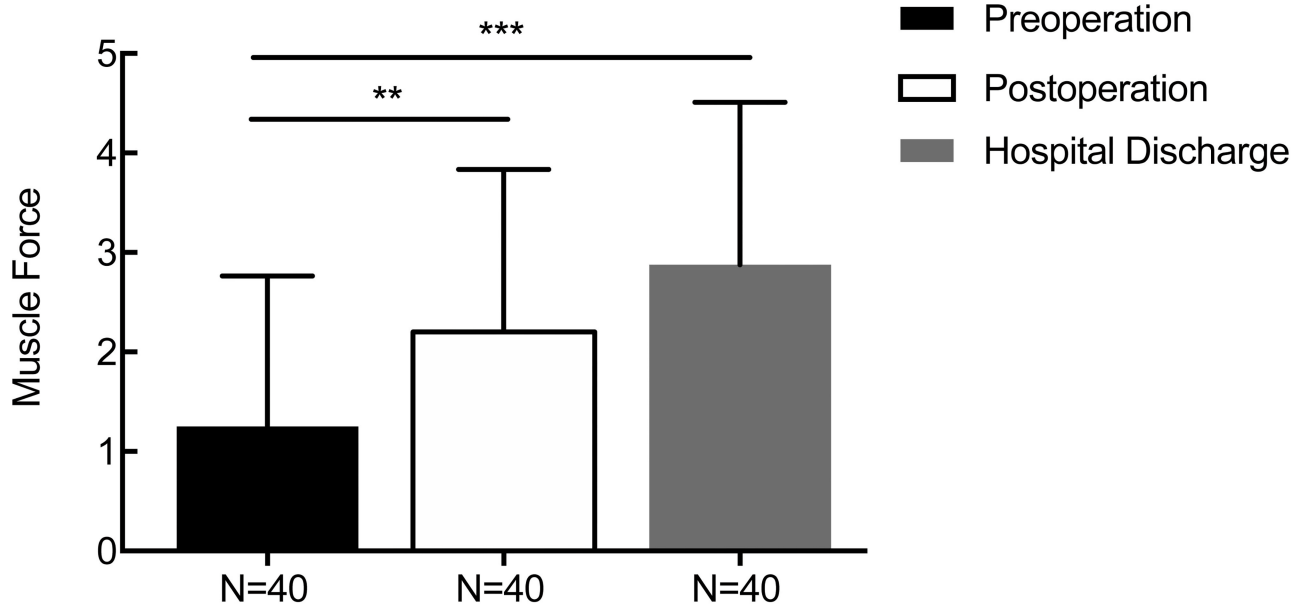

FIGURE 7 | Changes in the perioperative muscle force score. The average preoperative muscle power was 1.25 ± 1.51, and the mean muscle power at 1 week after the operation and discharge time were 2.20 ± 1.64 ($p = 0.009$) and 2.88 ± 1.64 ($p < 0.001$), respectively. $^{**}p < 0.01$ and $^{***}p < 0.001$.

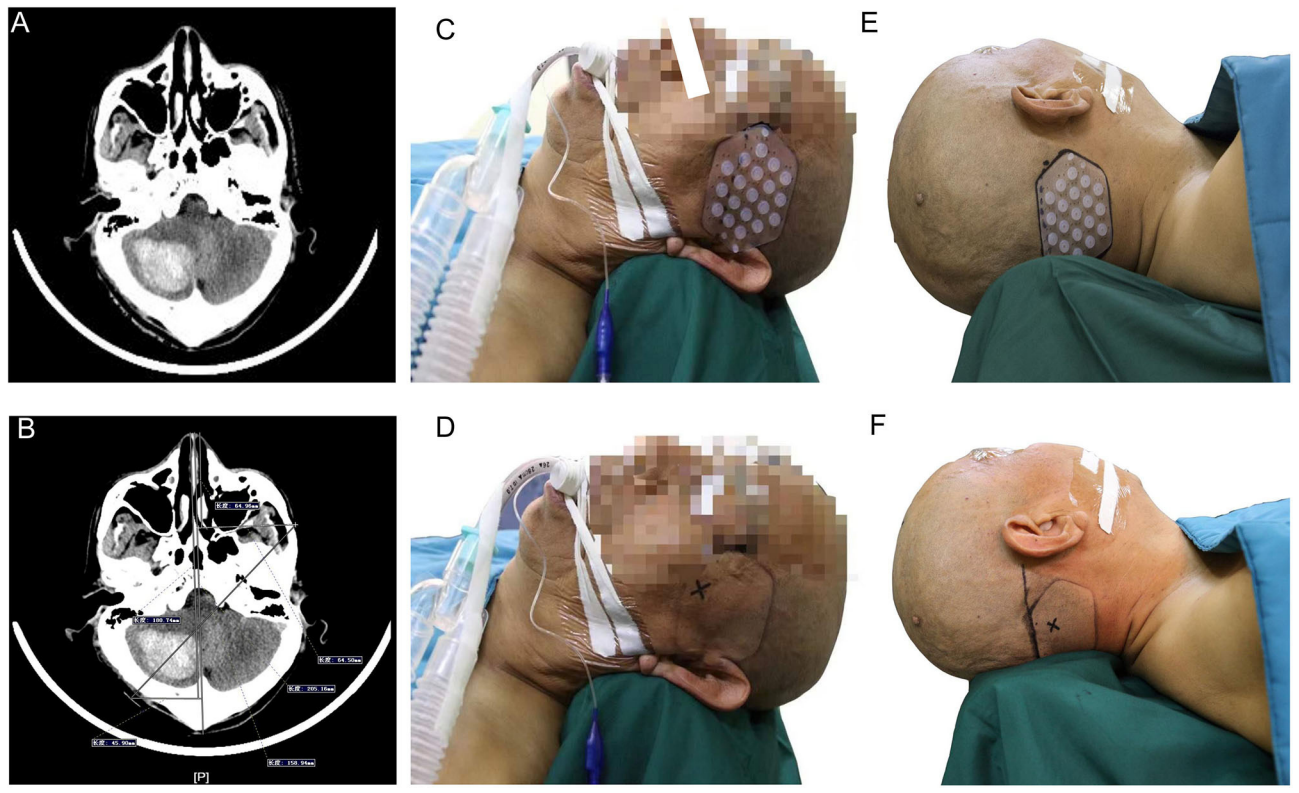

FIGURE 8 | Right cerebellar hemorrhage shown in **(A)**. A vertical distance of 45.90 mm (puncture point) from the centerline and a parallel distance of 64.96 mm (reference point) along the centerline are shown in **(B)** to locate the location sticker in **(C–F)**.

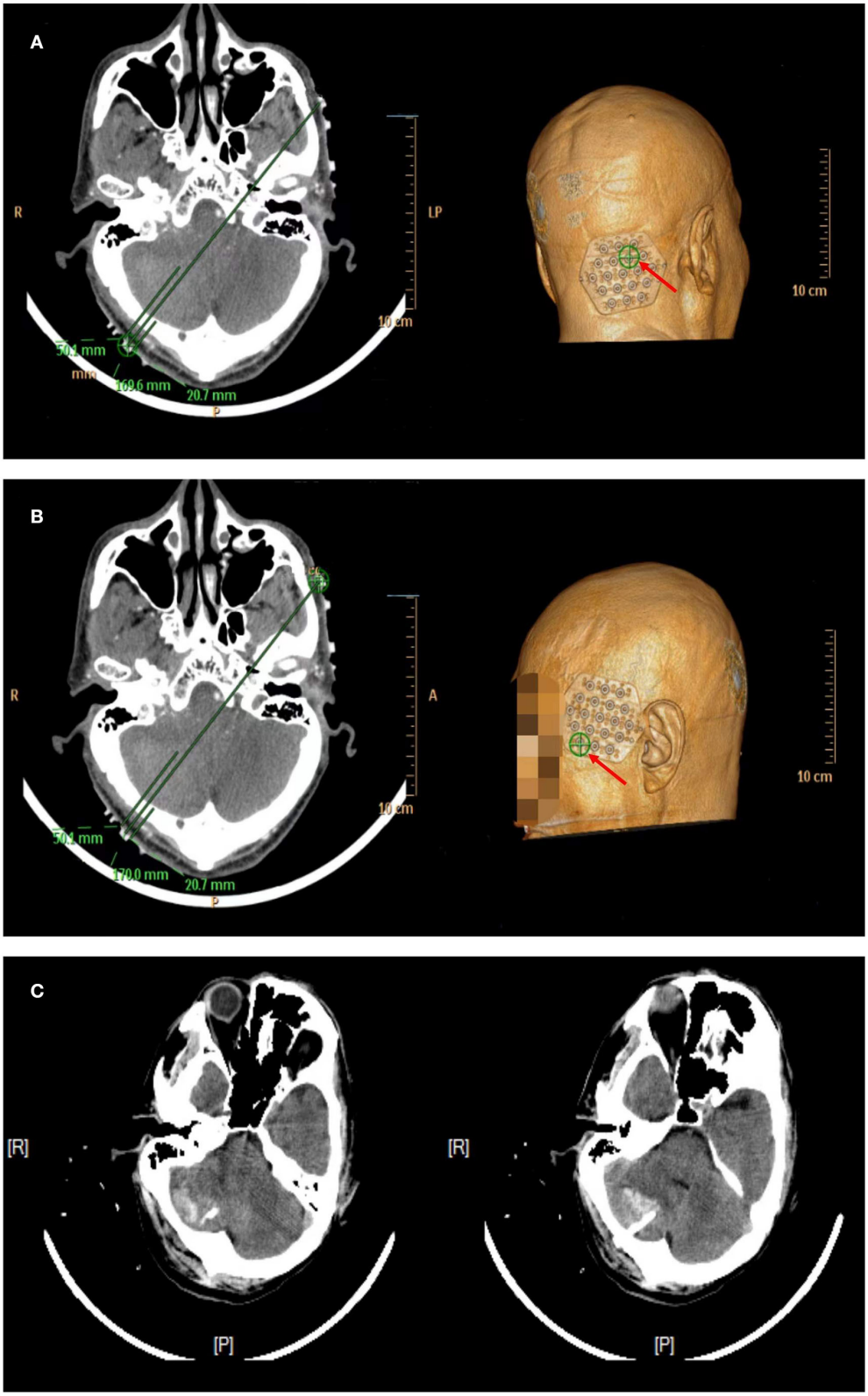

FIGURE 9 | The accurate puncture site, reference point, puncture route, puncture depth (50.1 mm), and drill depth (20.7 mm) are shown in **(A,B)** when using the PISP system. **(C)** shows the good clinical outcomes.

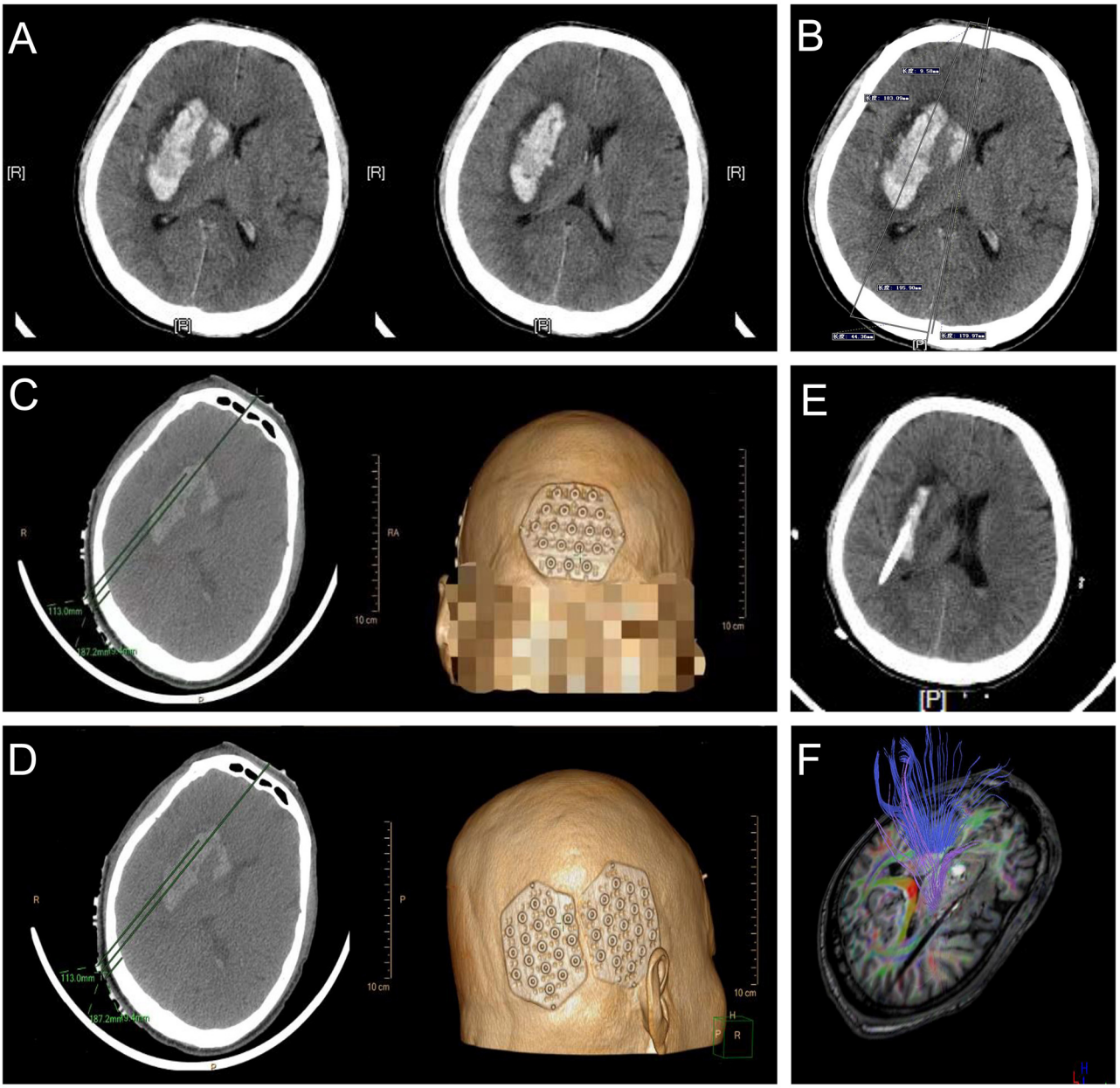

FIGURE 10 | Basal ganglia hemorrhage appears in **(A)**, with a vertical distance of 9.58 mm (reference point) from the centerline and a parallel distance of 179.97 mm (puncture point) along the centerline in **(B)** used to locate the location sticker in **(C,D)**. **(E,F)** represent good clinical outcomes.

to select an adequate method of hematoma localization to obtain a mass proportion effect (28, 29). Here, we show our single-center experience with applying an easy, fast, and economical brain surgery head frame combined with a location sticker for the removal of hematomas from 45 consecutive patients with ICH.

Because the hematoma was removed through puncture, accurately guiding the drainage tube to the center of the hematoma is the key to optimal evacuation. Using our method, the operator could successfully locate the body of the hematoma and quickly introduce the drainage tube to the pre-established point by using this easy, fast, effective, and economical procedure. Therefore, the amplitude of swinging of the puncture tube was reduced, and procedure-related adverse effects on brain tissue were also minimized. The time required for preoperative surgical planning was ∼5 min, and the hematoma evacuation time was 20–40 min depending on the number of required tubes. Wound closure is not necessary for our procedure.

Thus, the total procedure time was <40 min. Concerning the optimal start time, traditionally, early surgery can improve the prognosis *via* decreasing secondary insults, however, achieve a lower hematoma evacuation rate. Jang et al. (30) performed a study involving 35 patients to compare the aspirated volume during surgery based on the surgical timing from symptom onset. Surgery after 120 h revealed the highest efficiency in terms of hematoma aspiration compared with the time period within 12 h, between 12 and 24 h and between 24 and 120 h. Additionally, the STICH II trial uncovered that patient undergoing an operation before 21 h from ictus had a trend toward getting a better outcome (29). Therefore, the optimal start time plays a key role in affecting the rebleeding risks and secondary brain injuries. In this study, the average time from symptom onset to hematoma aspiration was 9.356 h (at least 6 h and at most 16 h). Similarly, Tang et al. (31) performed a meta-analysis revealed that, within 24 h, minimal invasive surgery was associated with a low mortality rate and rebleeding rate, as well as a significant improvement of the prognosis and the quality life of patients when compared with conservative medical treatment or craniotomy. The amount of intraoperative blood loss was within 10 ml in all cases owing to the small procedural wound and less brain tissue injury, achieving a mean evacuation rate of 72.20%. Simultaneously, the average GCS score at 1 week after surgery and at the time of hospital discharge were 11.55 ± 2.59 and 12.86 ± 2.04, and the muscle power was 2.20 ± 1.64 and 2.88 ± 1.64, respectively, which shows a statistically significant improvement compared with preoperational.

Although stereotaxic devices are acceptable for the puncture of intracerebral hematoma, there are many disadvantages to the procedure. The installation of the framework of the stereotactic apparatus is necessary before the operation by screwing the head nails into the skull, causing significant pain. General anesthesia or basic intravenous anesthesia is always unavoidable because patients with cerebral hemorrhage usually appear restless and have difficulty cooperating with the installation process. CT data should be imported into the computer workstation to make an operation plan after performing a thin slice CT scan, which extends the whole operation time. In contrast, the installation of an apparatus is not necessary before the operation in our study, and the preoperative surgical planning can be completed quickly and accurately by using the PISP system, which uses the work station of the CT machine and could precisely locate the puncture route, puncture depth, and drill depth to avoid important brain functional areas, large blood vessels, and the sinus, and it is available in most of the hospitals.

Multiple types of targeting and puncture routes could be designed with the assistance of a brain surgery head frame and a location sticker to select the best operative plan based on the different locations and volumes of the hematoma. For hematomas in the basal ganglion region, high-occipital puncture along the long axis of hematoma is frequently used. Placing the lateral pore of the drainage tube at the center to aspirate, dissolve and drain the hematoma, then eliminating the compression to the corticospinal tract can preserve the neurological functions.A high-occipital puncture route is a safe way to drain the thalamic hemorrhage because it avoids functioning regions and large blood vessels. For cerebellar and brain stem hematoma, an accurate puncture could avoid craniotomy to reduce the operative time and trauma. For lobe hemorrhage, the route of puncturing is different based on the exact location. For large volumes of intracranial hematoma, multiple punctures from different layers could be performed. The drainage tube in the lower layer is placed in the front, while the high layer is placed at the back to aspirate the hematoma simultaneously. The gravity effect could drive the liquefied hematoma to flow into the lower tube after injecting urokinase so that the hematoma could be eliminated.

In this study, the drainage tube was soft with a blunt tip and a large lateral pore. The blunt tip of the drainage tube could push the encountering vessels aside without cutting the vessels during the puncture. The tube could move during the restoration of the brain tissue without cutting it during the hematoma reduction.

Our research also has some limitations that should be considered. Although the results of using a brain surgery head frame and location sticker combined with urokinase infusion for spontaneous ICH seems encouraging, the number of patients involved in our study was limited and it lacked a control group. A prospective randomized controlled study is necessary to compare the safety and effectiveness of this approach with the conventional aspiration of spontaneous ICH.

CONCLUSION

Using this brain surgery head frame and location sticker combined with urokinase infusion appears simple, safe, and effective for the removal of hematoma from patients with spontaneous ICH. However, RCTs are necessary to provide more concrete evidence-based results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of Tangshan Gongren Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HW, WX, and JC designed the study, acquired the data and drafted the article, analyzed and interpreted the data, and revised the article critically for important intellectual content together. All authors contributed to the article and approved the submitted version.

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Minimally Invasive Neurosurgery for Spontaneous Intracerebral Hemorrhage—10 Years of Working Progress at National Taiwan University Hospital

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Intracerebral hemorrhage (ICH) is a life-threatening disease with a global health burden. Traditional craniotomy has neither improved functional outcomes nor reduced mortality. Minimally invasive neurosurgery (MIN) holds promise for reducing mortality and improving functional outcomes. To evaluate the feasibility of MIN for ICH, a retrospective analysis of patients with ICH undergoing endoscopic-assisted evacuation was performed. From 2012 to 2018, a total of 391 patients who underwent ICH evacuation and 76 patients who received early (<8 h) MIN were included. The rebleeding, mortality, and morbidity rates were 3.9, 7.9, and 3.9%, respectively, 1 month after surgery. At 6 months, the median [interquartile range (IQR)] Glasgow Coma Scale score was 12 (4.75) [preoperative: 10 (4)], the median (IQR) Extended Glasgow Outcome Scale score was 3 (1), and the median (IQR) Modified Rankin Scale score was 4 (1). The results suggested that early (<8 h) endoscope-assisted ICH evacuation is safe and effective for selected patients with ICH. The rebleeding, morbidity, and mortality rates of MIN in this study are lower than those of traditional craniotomy reported in previous studies. However, the management of intraoperative bleeding and hard clots is critical for performing endoscopic evacuation. With this retrospective analysis of MIN cases, we hope to promote the specialization of ICH surgery in the field of MIN.

Keywords: functional outcome, intracerebral hemorrhage, minimally invasive neurosurgery, mortality, early surgery

INTRODUCTION

The optimal treatment for intracerebral hemorrhage (ICH) remains among the most controversial topics in neurosurgery. ICH is associated with high morbidity and mortality rates and imposes a substantial economic burden worldwide. Recent studies have reported that compared with traditional craniotomies, minimally invasive treatments resulted in more favorable outcomes (1–3). These treatments include minimally invasive clot evacuation with stereotactic or endoscopic

aspiration with or without thrombolytic usage. Minimally invasive treatments cannot only reduce mortality but also improve neurological recovery in selected patients (3–5), which is rarely observed and encouraging for the treatment of ICH.

Taiwan has a highly dense population and many hospitals. Patients with ICH can arrive at the hospital shortly after ictus. This is especially true in Taipei City, the capital of Taiwan, where our hospital, National Taiwan University Hospital (NTUH), is located. The majority of surgeries were performed within 4 h after ictus (6). We have performed minimally invasive neurosurgery (MIN) under endoscopic guidance for ICH evacuation since 2008. For more than 10 years, we have been continuously refining the surgical technique, equipment, protocol, and workflow in the pursuit of clinical excellence and improved outcomes. With the paradigm shifting toward minimally invasive surgery, we share our experience in this retrospective analysis.

MATERIALS AND METHODS

Study Design

This retrospective study was conducted at NTUH after obtaining the approval from the Ethical Review Board of our institute. We extracted and analyzed clinical data from the medical charts of patients with spontaneous supratentorial ICH who received early MIN (within 48 h after ictus) from 2012 to 2018. This study was performed in compliance with applicable local regulations and the ethical principles of the Declaration of Helsinki. All the experimental protocols were approved by the Institutional Review Board of NTUH. Because of the retrospective nature of this study, the requirement of informed consent was waived. Informed consent for surgery was obtained from each patient per routine practice.

Patient Selection

A series of experiences presented in this study represents the working progress of 6 years following a previously published series of our experiences from 2008 to 2011 (6). Between 2012 and 2018, a total of 391 patients underwent ICH evacuation at NTUH. We included patients with spontaneous supratentorial ICH who received early MIN (within 48 h after ictus). A cutoff of <48 h was selected on the basis of the finding of a meta-analysis that patients who underwent MIN within 72 h were two times more likely to achieve functional independence (7). In this experience, ICH evacuation after 48 h of ictus may lead to significant brain edema and massive blood clots that favor decompressive craniectomy as the primary treatment instead of MIN.

We excluded patients with etiology related to structural lesions or nonprimary lesions (cerebral aneurysm, arteriovenous malformation, and cavernous malformation), cerebellar hemorrhage, traumatic ICH, tumor bleeding, hemorrhagic transformation after ischemic stroke or postoperative bleeding, or primary intraventricular hemorrhage (IVH). In addition, we excluded patients who underwent traditional craniotomy, external ventricular drainage, or decompressive craniectomy as the primary treatment.

We carefully reviewed the medical records of the remaining 88 patients who underwent minimally invasive endoscope-assisted ICH evacuation. Furthermore, we excluded 12 patients because they had incomplete medical records ($n = 4$), did not undergo postoperative follow-up imaging ($n = 5$), or were lost to long-term follow-up ($n = 3$). Finally, 76 patients were included in this study (**Figure 1**).

Rationale for Surgical Management of Patients With Intracerebral Hemorrhage

Currently, we have four attending neurosurgeons in the NTUH ICH team, which is the only dedicated ICH team in the country. This specialized team aims to improve functional outcomes, quality of care, and quality of life for patients. The minimally invasive endoscopic-assisted ICH evacuation was performed in approximately 70% of our surgical cases. On the basis of our extensive experience and the literature review, we have developed guidelines for the optimal treatment of patients with ICH in NTUH. Recent studies have suggested that early surgery for ICH is associated with satisfactory functional outcomes and low mortality (8–12). This finding is concordant with our practice at NTUH where we performed surgery in more than 80% of patients with ICH within 4 h after ictus (6). We prefer the endoscopic-assisted evacuation over stereotactic thrombolytic therapy because of its earlier decompression, high hematoma clearance rate, and cost-effectiveness (13).

The selection of the surgical method depended on our clinical experience and the literature review. MIN was mostly performed for deep-seated early ICH (such as the basal ganglia and thalamus, with ICH volume ranging from 20 to 80 ml). For superficial (subcortical or lobar) ICH, minicraniotomy using microscopic evacuation or endoscopic-assisted MIN was both feasible. For delayed cases (>72 h after ictus), craniectomy with ICH evacuation was preferred because such cases usually have substantial brain edema and massive blood clots that favor decompressive craniectomy as the primary treatment instead of MIN.

Surgical Procedure

Various MIN techniques have been developed for ICH evacuation (14). We adopted the endoscopic-assisted approach where suction is applied on the side of the endoscope inside a 10–12-mm port or sheath that creates the working space (also known as the port-based approach). By contrast, the pure endoscopic approach [e.g., the stereotactic intracerebral hemorrhage underwater blood aspiration (SCUBA) technique] uses the aspiration device inside the endoscope (through its working channel) with a 19-F peel-away sheath.

Clot evacuation could be smoothly performed with one hand holding the endoscope and the other hand holding a suction device. We used 8-Fr suction to remove the clot because suction with a smaller caliber would lead to the ineffective removal of ICH. In the presence of a hard clot, the alligator punch was used to pass through the sheath for piecemeal removal. In extreme cases, we used the cavitron ultrasonic surgical aspirator (CUSA) to remove the hard clot. The CUSA is a surgical device used in neurosurgical procedures. The CUSA is coupled with low-frequency ultrasound that helps operators to dissect or fragment tissues or pathologies. The CUSA was used to manage ICH cases with hard clots that could not be removed with suction only.

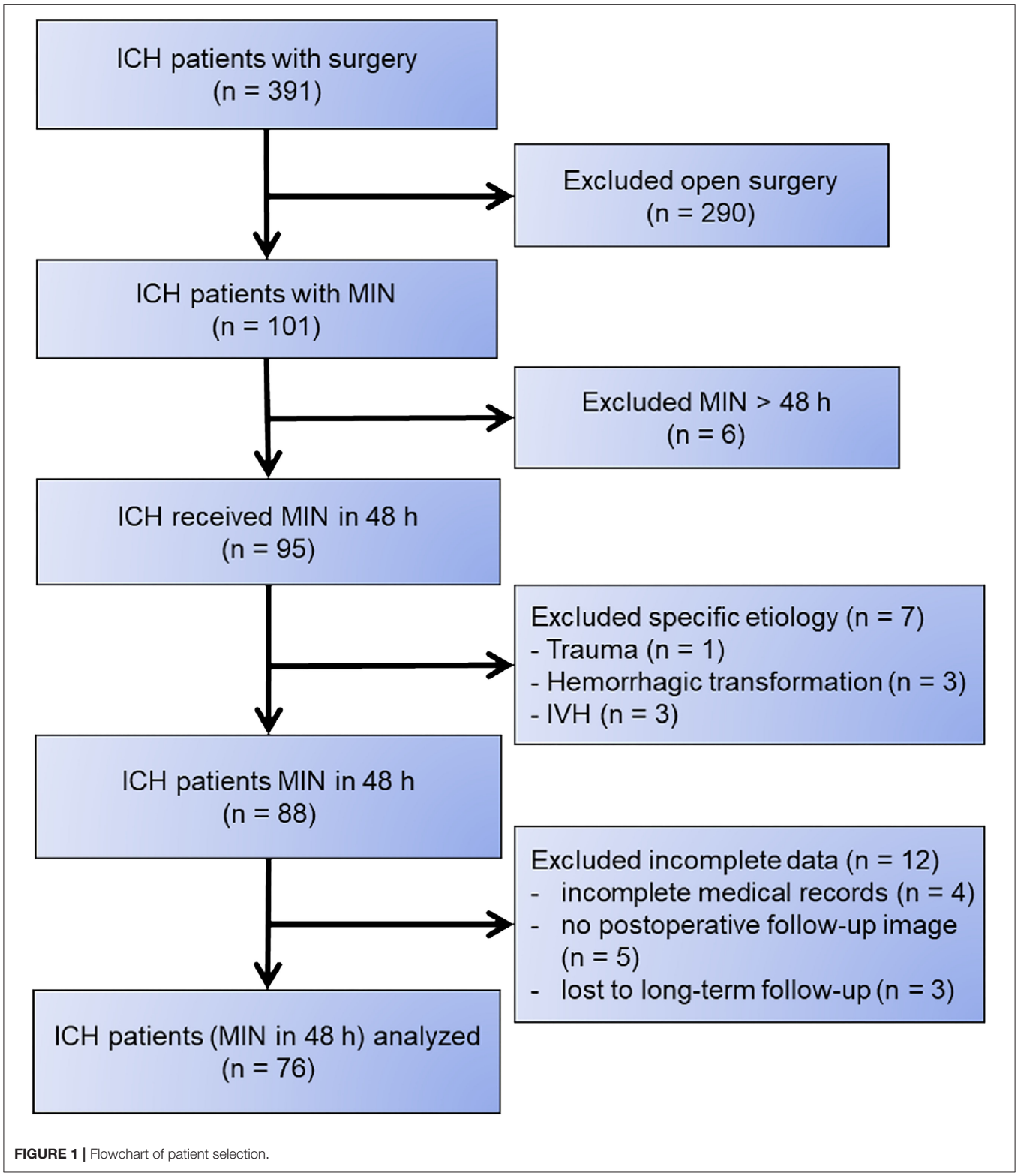

FIGURE 1 | Flowchart of patient selection.

Apollo, Artemis, and Myriad are not available in Taiwan; thus, we have no experience in using these devices.

Regarding hemostasis during surgery, we initially used an endoscopic bipolar or a suction coagulation device; however, these techniques were time-consuming. Moreover, achieving hemostasis by using these techniques was difficult. Later, we used local hemostatic agents that remarkably reduced the time of hemostasis, with a low rebleeding rate. In our experience,

no active bleeding requiring coagulation was noted in more than 90% of cases and local hemostatic agents [e.g., FLOSEAL Hemostatic Matrix (Baxter Healthcare Corporation, Fremont, California, USA), a gelatin–thrombin matrix] yielded satisfactory hemostasis (15).

When an active bleeder was encountered during surgery, we suctioned out blood, used irrigation to identify the active bleeder, contacted it with the suction tip, and performed cauterization by using a metallic suction tube. The importance of a balanced suction irrigation technique in the minimally invasive surgery of ICH was described in detail in a previous study (16). After hemostasis, we placed an external ventricular drain if the frontal horn was entered during surgery; otherwise, we inserted an intracranial pressure (ICP) monitor [fiber optic devices (e.g., Camino ICP Monitor) and strain gauge devices (e.g., Codman Microsensor and Raumedic Neurovent-P ICP sensor)] through the surgical corridor created by the trocar under direct vision in the perihematoma zone of the brain parenchyma. A surgical biopsy of the brain parenchyma was performed, if amyloid angiopathy was suspected (17).

In terms of surgical techniques, we recommend using the penetrating technique (Huang's technique) instead of the circumferential technique used in our previous studies (6, 8) for ICH removal because it prevents collateral brain damage when using the trocar or port inside the normal brain tissue. For typical basal ganglia ICH, we used modified Kocher's point (1 cm lateral to Kocher's point). A 2.5-cm incision was vertically made on modified Kocher's point, creating a 1.5–2.0-cm burr hole. After dural opening, either the trans-sulcal or transcortical approach was used. The intraoperative Aloka burr-hole type ultrasound was selectively used to verify the trajectory and depth of ICH before puncturing with the trocar (we used a transparent trocar with an outer diameter of 12 mm and length of 10 cm for putaminal ICH) (6). For thalamic ICH, we used a considerably different surgical approach. Initially, our team used an aggressive approach involving the use of the endoscopic technique to remove thalamic ICH in the brain parenchyma. However, the surgical outcome was poor and most of the patients remained comatose after evacuation. Therefore, our current goal was to relieve hydrocephalus and remove IVH to minimize shunt dependency. We only dived into thalamic ICH in the brain parenchyma when we observed the rupture side during endoscopic surgery. The first step was to determine whether to use the frontal or occipital approach; we occasionally used the contralateral approach (18). The rupture side could be determined through preoperative CT performed to choose the surgical approach. The thalamostriate vein was required to be carefully preserved to prevent iatrogenic infarction.

We applied the concepts of the SCUBA technique in our MIN for ICH evacuation. The SCUBA technique differs from minimally invasive ICH intervention because it combines two separate neuroendoscopic strategies in two phases: the first is using dry-field conditions and the second is using a wet-field strategy (19). This prevents the collapse of the hematoma cavity and allows for complete clot removal. This technique is useful for bleeder identification. During the procedure, balancing suction and irrigation is crucial for bleeder identification and hemostasis (16).

For brain access, most neurosurgeons used the 12-mm outer diameter transparent trocar. The peel-away sheath was occasionally used by neurosurgeons who were comfortable with ventriculoscopic techniques (6). In our experience, only 10%−15% of the cases had intraoperative bleeding requiring hemostasis and most of the small arterial bleeding from thalamostriate perforators could be stopped using local hemostatic agents (8). During surgery, similar to the SCUBA technique, we alternated between air and water phases; we found this technique to be useful for preventing the hematoma cavity from collapsing with resultant residual ICH and for identifying the bleeder (19). Cauterization was required in <5% of cases and was easily performed using traditional suction at the bleeding point (vessel) with unipolar cauterization touching the handle of the sucker (poor man's suction bipolar). Alternatively, commercialized suction bipolar devices can be used (6). If all these attempts failed, the next step was to change to a larger trocar (Vycor, with a diameter of >2 cm used for traditional bipolar cauterization). We rarely converted to craniotomy, which was only performed in three out of more than 400 ICH cases.

Perioperative Care

In the perioperative period, we observed that dexmedetomidine substantially reduced blood pressure fluctuations. This reduction is associated with a decreased rebleeding rate, as demonstrated in various experiences and other major surgeries (20). The effect of dexmedetomidine on patients with ICH was reported in a clinical trial (21). For cases with a high risk of rebleeding, we may consider tranexamic acid and recombinant factor VIIa (NovoSeven) (22). Currently, we routinely perform CT within 24 h after surgery to confirm the residual hematoma and the degree of evacuation.

Cognitive enhancers and neural stimulants were reported to improve cognitive and behavioral impairments in patients with putaminal ICH and traumatic brain injury (23). We used methylphenidate in patients with ICH who were comatose before the surgery to improve neurological outcomes. In our experience of 58 patients, methylphenidate was safe and effective and was associated with faster consciousness recovery, greater chance of successful extubation, and shorter intensive care unit (ICU) stay. However, a study reported the rare side effects of methylphenidate, such as serotonin syndrome, in patients with ICH (24).

Data Collection

We collected data on the following characteristics of the patients: hematoma location and volume, presence of IVH, sex, age, time of operation, operative blood loss, and hematoma evacuation rate. All the patients underwent preoperative head CT and a follow-up head CT within 1 week after surgery. The estimated hematoma volume was calculated using the ABC/2 method (A: maximum length in the axial cut of CT, B: width perpendicular to A on the same CT cut, and C: the number of slices multiplied by the slice thickness).

TABLE 1 | Characteristics of patients.

	Putaminal ($n = 56$)	Thalamic ($n = 9$)	Subcortical ($n = 11$)	All
Male, *n* (%)	42 (75.0)	5 (55.6)	6 (54.5)	53 (69.7)
Age (year), median (IQRs)	58 (17.25)	66 (6)	62 (32)	59 (18)
ICH score, median (IQRs)	2 (1)	3 (1)	2 (1.5)	2 (1)
IVH, *n* (%)	26 (46.4)	6 (66.7)	4 (36.4)	36 (47.4)
Anticoagulants and antiplatelets, *n* (%)				
Antiplatelet agents	6 (10.7)	1 (11.1)	3 (27.3)	10 (13.2)
Anticoagulant agents	1 (1.8)	0 (0)	0 (0)	1 (1.3)
Both	2 (3.6)	0 (0)	0 (0)	2 (2.6)
Operative time (min), median (IQRs)	108 (50.25)	109 (63)	104 (34.5)	107 (50.25)
Preoperative ICH volume (ml), median (IQRs)	45 (28.75)	35 (15)	50 (20)	42.5 (25)
Operative blood loss (ml), median (IQRs)	50 (12.5)	50 (0)	50 (0)	50 (0)
ICU length of stay (day), median (IQRs)	16 (14.5)	13.5 (15.25)	19 (3)	16 (13)
Hospital length of stay (day), median (IQRs)	30 (23.5)	29 (25.25)	37 (21)	28 (11.5)

IVH, intraventricular hemorrhage; IQR, interquartile range; ICU, intensive care unit; ICH, intracerebral hemorrhage.

Clinical Outcome

Outcome measures included the hematoma evacuation rate, rebleeding, mortality rate, morbidity rate, the preoperative and postoperative Glasgow Coma Scale (GCS) scores, the postoperative Extended Glasgow Outcome Scale (GOSE) scores, the Modified Rankin Scale (mRS), length of ICU stay, and the length of hospital stay. The hematoma evacuation rate was calculated as [(preoperative volume – postoperative volume)/(preoperative volume) × 100 (%)]. Mortality was defined as all-cause death occurring within 30 days after surgery. Rebleeding and morbidity rates were examined 1 month after surgery. Rebleeding was defined as a postoperative hematoma volume greater than the preoperative volume or a difference of <5 ml between preoperative and postoperative hematoma volume. Morbidity included wound dehiscence and surgical site infection, including meningitis, ventriculitis, and brain abscess. Postoperative outcomes included the GCS scores at 1 and 6 months and the GOSE and the mRS scores at 6 months.

Statistical Analysis

Descriptive statistics were used to present categorical data in numbers and percentages and continuous data in numbers, medians, and interquartile ranges (IQRs). The surgical and functional outcomes were analyzed using the Kruskal–Wallis test. A *P*-value of <0.05 was regarded as statistically significant. Statistical analyses were performed using SPSS (version 25, Chicago, Illinois, USA).

RESULTS

Demographics and Baseline Characteristics

Table 1 summarizes the demographics of the patients. We divided the patients into three groups according to the hematoma location: putaminal ($n = 56$), thalamic ($n = 9$), and subcortical ($n = 11$). The male predominance of approximately 69.7% was noted and IVH was found in 47.4% of the patients. Most of the enrolled patients were aged from 57 to 60 years, except for those with thalamic ICH (median age: 66 years). The median operative time ranged from 104 to 108 min. The ICH score (median: 2) and operative blood loss (median: 50 ml) were similar among the different types of ICH. The patients with putaminal ICH had the highest preoperative ICH volume (median: 45 ml).

Most of the patients (97%) underwent MIN within 4 h after ictus. Only two patients underwent surgery on the second day of ictus because of hematoma expansion. Our hospital defines three classes for emergent operation. The duration between notifying the operation room to the start of operation is limited to 30 min, 2 h, and 4 h for first-class, second-class, and third-class emergent operations, respectively. ICH is classified as a third-class surgery, which is mostly performed within 4 h.

Postoperative Outcomes

Table 2 summarizes the surgical and functional outcomes, with no significant difference noted between the groups. The median (IQR) hematoma evacuation rate was 85.7% (16.7%) and the median (IQR) postoperative ICH volume was 5 (5) ml. According to the Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation III (MISTIE III) study, a reduction in clot size to ≤15 ml is associated with improvement in functional outcomes (4). In our series, 64 (84.2%) patients reached the goal of a residual hematoma volume of <15 ml. The overall rebleeding rate at 1 month after surgery was 3.9%. Three patients experienced rebleeding in the first postoperative follow-up [2 (3.6%) in the putaminal group and 1 (11.1%) in the thalamic group]. Six patients died eventually (the overall mortality rate: 7.9%): two patients died from pneumonia and sepsis, two patients died from postoperative central nervous system infection, and two patients died because their family members decided to withdraw life support owing to the lack of clinical improvement. The morbidity rate at 1 month after surgery was 3.9%; one patient developed

TABLE 2 | Outcomes.

	Putaminal ($n = 56$)	Thalamic ($n = 9$)	Subcortical ($n = 11$)	*P*-Value	All ($n = 76$)
Rebleeding, *n* (%)	2 (3.6)	1 (11.1)	0 (0)		3 (3.9)
Mortality, *n* (%)	5 (8.9)	0 (0)	1 (9.1)		6 (7.9)
Morbidity, *n* (%)	3 (5.4)	0 (0)	0 (0)		3 (3.9)
Hematoma evacuation rate (%), median (IQRs)	86.6 (11.9)	75.0 (19.0)	80.0 (20.8)	0.170	85.7 (16.7)
Postoperative ICH volume (ml), median (IQRs)	5 (5)	10 (5)	10 (12.5)		5 (5)
Postoperative hematoma volume <15 ml, *n* (%)	48 (85.7)	8 (88.8)	8 (77.8)		64 (84.2)
GCS, median (IQRs)					
Pre-op	10 (4)	8 (3)	11 (3.5)	0.343	10 (4)
Post-op 1 month	11 (4)	12 (5)	13 (4)	0.508	12 (4)
Post-op 6 months	12 (4)	14 (6)	14 (3)	0.659	12 (4.75)
GOSE, median (IQRs)					
Post-op 6 months	3 (1)	4 (2)	4 (1.5)	0.666	3 (1)
mRS, median (IQRs)					
Post-op 6 months	4 (1)	4 (2)	4 (1)	0.997	4 (1)
mRS 0–2, *n* (%)	7 (12.5)	1 (11.1)	3 (22.2)		11 (14.5)
mRS 0–3, *n* (%)	21 (37.5)	4 (44.4)	3 (22.2)		28 (36.8)

GCS, Glasgow coma scale; GOSE, Glasgow outcome scale extended; ICU, intensive care unit; mRS, modified rankin scale; OP, operation; IQR, interquartile range; ICH, intracerebral hemorrhage.

scalp wound dehiscence, one patient developed meningitis and ventriculitis, and one patient developed brain abscess.

Functional outcomes improved after surgery, with no significant differences observed between the groups (**Table 2**). The median (IQR) preoperative GCS score was 10 (4), which was numerically increased to 12 (4) at 1 month and 12 (4.75) at 6 months. The median (IQR) GOSE score at the 6-month follow-up was 3 (1). The median (IQR) mRS score at the 6-month follow-up was 4 (1). Satisfactory outcomes (mRS score: 0–3) were noted in 36.8% of the patients.

DISCUSSION

The prevalence of ICH is especially high in Asia-Pacific regions, where ICH accounts for approximately 30%−40% of all stroke cases. In the United States, ICH accounts for approximately only 15% of all stroke cases (25). Each year in China alone, more than 150,000 patients receive minimally invasive treatment for ICH (8). Race and ethnicity appear to explain some of the variation in clinical characteristics and outcomes after acute ICH; for example, Caucasian patients with ICH are more likely to be older, have a larger ICH volume, and have a higher mortality rate than Asian patients (26).

The operation rate considerably varies worldwide, ranging from 2 to 74% (27). In the United States, the early operation rate was previously 16% and decreased to 6% in 2005, presumably due to the results of the Surgical Treatment for Ischemic Heart Failure (STICH) trial (28, 29). With the current increasing interest in surgical treatment, the operation rate has increased to approximately 20% (1, 30). In the Asia-Pacific region, the operation rate ranges from 30 to 40% and the MIN method, either stereotactic aspiration or endoscopic-assisted evacuation, is widely used (27).

Clinical Outcomes Compared With Prior Minimally Invasive Neurosurgery Reports

In our series, early MIN within 48 h after ICH ictus resulted in a low rebleeding rate (3.9%), low mortality rate (7.9%), and low morbidity rate (3.9%); moreover, 36.8% of the patients exhibited satisfactory functional outcomes (mRS score: 0–3) 6 months after MIN. Although the overall median GOSE score indicated that the patients still required assistance to perform the activities of daily living (GOSE = 3) 6 months after MIN, the patients with thalamic or subcortical ICH could occasionally be at home independently (GOSE = 4) and their overall GCS score improved over time. Compared with those of patients included in other MIN studies, the postoperative outcomes of our patients appeared to be more favorable. In the MISTIE III study (4), 44% of patients achieved the mRS score of 0–3, 39% of patients had the GOSE score of ≥4 at 12 months, and the mortality rate at 6 months was 15%. In the MISTIE III study, 33.4% of patients achieved the mRS score of 0–3 and the mortality rate within 30 days was 14.8% (31). In the intraoperative stereotactic CT-guided endoscopic surgery (ICES) trial including six patients, 24% of patients achieved the mRS score of 0–3 and no patient died within 30 days after surgery (3).

Literature Support for Minimally Invasive Neurosurgery Over Traditional Craniotomy for Intracerebral Hemorrhage Evacuation

In patients with supratentorial ICH, compared with medical management alone, surgery in addition to medical management reduced functional dependency and mortality more effectively

(1, 32). Moreover, two meta-analyses have demonstrated that selected patients benefited from MIN over other treatments (7, 33). The first meta-analysis of five randomized trials and nine prospective studies observed a significant difference in the mortality rate between patients receiving MIN and those receiving traditional craniotomy [odds ratio (OR), 0.76, 95% CI, 0.60–0.97] as well as a lower rate of rebleeding and a higher rate of satisfactory neurological recovery for the MIN approach (33). The second meta-analysis of 15 randomized controlled trials reported that patients with ICH who received MIN within 24 h of ictus were 2.8 times more likely to achieve functional independence, whereas patients who received MIN within 72 h were two times more likely to reach functional independence (7).

Traditional craniotomy requires brain retraction and is highly invasive and traumatic. The problem with retraction in neurosurgery should be emphasized and is often avoided, especially in deep-seated ICH, such as putaminal ICH (28, 34). In our experience, retraction may lead to rebleeding. The rebleeding rate in open craniotomy using retraction was 15%−40% (35) and was significantly higher than that of 0%−3.3% in the MIN group (6, 8, 12, 16, 36). Moreover, long-term brain atrophy after brain retraction is alarming because retraction is associated with the chronic local thinning of the neocortex (37).

Early Minimally Invasive Neurosurgery for Clot Evacuation, Hemostasis, and Low Rebleeding Rate

Rebleeding is the primary concern in MIN and usually occurs within 4 h of ictus. The American Heart Association/American Stroke Association Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in 2015 indicated that ultra-early craniotomy (within 4 h of ictus) was associated with an increased risk of rebleeding. These data were from a study that performed ultra-early craniotomy in 24 patients and the rebleeding rate was 40% (35). Because of the concern of a high rebleeding rate of ultra-early craniotomy, randomized prospective trials have reported a timeframe for surgery that ranges from 6 to 24 h postictus. By contrast, early endoscopic ICH evacuation has been performed in many patients, with low rebleeding rates of 0%−3.3% (6, 8, 12, 16, 36), suggesting that MIN reduces the high rebleeding rate. In our previous study, 84% of cases were operated within 4 h after ictus, resulting in a rebleeding rate of 1.5% (6). In this study, we included the patients using antiplatelet and anticoagulative agents and observed a rebleeding rate of 3.9%. Similarly, Chen et al. (12) treated seven patients within 5 h after ICH and observed no postoperative rebleeding. Nakagasaka treated 23 patients at a median time of 4 h and noted no postoperative rebleeding (16). Nishihara treated 82 patients within 3 h after ICH and observed no postoperative rebleeding (11). Miki et al. treated 127 patients with early (<8 h) endoscopic-assisted ICH evacuation and reported a postoperative rebleeding rate of 7.1% (38).

A meta-analysis of eight studies including 2,186 patients demonstrated the improved functional outcome of surgery performed within 8 h of ictus (10). These findings indicated that early ICH evacuation using MIN may reduce the rebleeding rate in ICH and improve surgical outcomes (9). This finding is in contrast to the notion that early craniotomy for ICH leads to a high rebleeding rate (9, 35). These facts may cause a paradigm shift for neurosurgeons to perform early MIN decompression to reduce secondary brain injuries associated with ICH (e.g., perihematomal edema).

Many studies have enrolled patients with stable clots shown on the CT scan performed 6 h post-onset, including the MISTIE III study, the International Verapamil-Trandolapril Study (INVEST), and the ICES trial (3, 9). The main reason for setting the selection criteria is because a previous study reported that ultra-early surgery within 4 h after ictus was associated with high rebleeding rates (35). However, we must be aware that the majority (25%) of patients with ICH deteriorate within the first few hours of ictus and may require clot evacuation within 4 h after ictus, especially for patients with a spot sign or black hole sign (39).

All the studies have reported that MIN performed within 8 h after ictus reduced the rebleeding rate (**Supplementary Table 1**). Therefore, we suggest that minimally invasive surgical trials for ICH should not exclude patients operated within 4–6 h; instead, these are the patients with the most favorable functional outcome per our experience of more than 400 patients with MIN. Similarly, a single-arm surgical evaluation in 39 patients with ICH indicated that 52% of the patients achieved functional independence at follow-up and no mortality was noted (40). If surgical evacuation is performed early, secondary injury from ICH may be avoided. Moreover, if early clot evacuation can reduce the rebleeding rate and mass effect, MIN will most likely benefit patients when it is performed early. In short, we strongly recommend early MIN (8 h postictus) for ICH because patients will likely to be benefited from such surgery, especially in terms of functional outcomes.

The ideal approach to surgically treat ICH is to maintain a balance among minimal invasiveness, completeness of clot removal, and secure hemostasis. In our experience, the vital questions are: (1) whether ICH volume can be reduced to < 15 ml, which may lead to improved functional outcomes (4); (2) whether intraoperative bleeding is manageable (if traditional cauterization is necessary, if the working space is adequate for hemostasis, and if the trocar or probe needs to be changed to a larger one); and (3) whether progressive brain edema occurs after ICH removal.

Limitations

This retrospective study has several limitations. First, this single-center study analyzed the data of 76 patients only. These study results lack generalizability and can be applied only to a narrow population or in a very specific situation; therefore, we suggest that MIN should be considered in early deep-seated ICH with volume ranging from 30 to 80 ml. On the basis of the findings of previous studies, MIN should be considered for deteriorating patients with ICH with a clot volume of > 25 ml (33, 41). In our experience, a clot volume of > 80 ml is more difficult to treat minimally invasively. Second, this study did not include the control group to detect the difference between MIN and traditional

craniectomy or medical treatment. Third, the patient cohort with a small sample size was heterogeneous with different clinical decision-making among the four different surgeons. Finally, the lack of data integrity is inherent due to the nature of the retrospective study. We did not manage missing data because it reflected a real-world setting. Because of these limitations, these study outcomes should be interpreted with caution. These promising preliminary results warrant further large-scale and well-controlled investigations.

CONCLUSION

Early endoscope-assisted ICH evacuation is a safe and effective treatment for selected patients with ICH. The rebleeding, morbidity, and mortality rates of our technique were lower than the reported outcomes of traditional craniotomy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of National Taiwan University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AH contributed to conceptualization, methodology, and formal analysis. C-HH and S-CC investigated the study. L-TK, S-JH, S-HY, and D-ML contributed to resources. C-HH wrote the original draft and writing, reviewing, and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.817386/full#supplementary-material

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