Surgical interventions for spontaneous supratentorial intracerebral haemorrhage: a systematic review and network meta-analysis

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eClinicalMedicine 2025;79: 102999
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102999

Summary

Background Surgical interventions for spontaneous supratentorial intracerebral haemorrhage (ICH) include conventional craniotomy (CC), decompressive craniectomy (DC), and minimally invasive surgery (MIS), with the latter encompassing endoscopic surgery (ES) and minimally invasive puncture surgery (MIPS). However, the superiority of surgery over conservative medical treatment (CMT) and the comparative benefits of different surgical procedures remain unclear. We aimed to evaluate the efficacy and safety of various surgical interventions for treating ICH.

Methods In this systematic review and network meta-analysis, we searched PubMed, Cochrane Central Register of Controlled Trials, Embase, and ClinicalTrials.gov from inception to June 16, 2024. Eligible studies were randomised controlled trials (RCTs) comparing surgery (i.e., CC, ES, MIPS, or DC) with CMT or comparing different types of surgeries in patients with spontaneous supratentorial ICH. Paired reviewers independently screened citations, assessed the risk of bias of included trials, and extracted data. Primary outcomes were good functional outcome and mortality at 6 months. Secondary outcomes were good functional outcome and mortality at different follow-up times, complications (rebleeding, brain infection, pulmonary infection), and hematoma evacuation rate. The frequentist pairwise and network meta-analysis (NMA) were performed. The GRADE approach was used to evaluate the certainty of evidence. This study is registered with PROSPERO, CRD42024518961.

Findings Of the 8573 total records identified by our searches, 31 studies (6448 patients) were eligible for the systematic review and network analysis. Compared with CMT, moderate certainty evidence showed that surgery improved good functional outcome (risk ratio [RR] 1.31, 95% CI 1.13–1.52; risk difference [RD] 9.1%, 95% CI 3.8 to 15.3; I^2 = 36%) and reduced mortality (RR 0.82, 95% CI 0.71–0.95; RD −5.1%, 95% CI −8.2 to −1.4; I^2 = 14%). Moderate certainty evidence from NMA suggested that compared with CMT, both ES (RR 1.51, 95% CI 1.18–1.93; RD 9.4%, 95% CI 3.3–17.1) and MIPS (RR 1.48, 95% CI 1.24–1.76; RD 15.7%, 95% CI 7.9–24.9) improved good functional outcome at 6 months, and both ES (RR 0.66, 95% CI 0.52–0.85; RD −17.0%, 95% CI −24.0 to −7.5) and CC (RR 0.75, 95% CI 0.60–0.94; RD −6.3%, 95% CI −10.1 to −1.5) reduced mortality at 6 months, whereas MIPS and DC showed a trend, although not statistically significant, towards a reduction in mortality. ES and MIPS also reduced pulmonary infection risk (ES RR 0.39, 95% CI 0.23–0.69; MIPS RR 0.35, 95% CI 0.20–0.60; RD −5.3%, 95% CI −6.6 to −3.3). ES showed higher hematoma evacuation than CC (MD: 7.03, 95% CI: 3.42–10.65; I^2 = 94%). No difference in rebleeding or brain infection was found between CC and MIS.

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Interpretation Current moderate certainty evidence suggested that surgical intervention of spontaneous supratentorial ICH, may be associated with improved functional outcomes and a reduced risk of death at 6 months. The advantages of surgical haematoma removal are particularly pronounced when MIS including ES and MIPS are employed. ES could improve functional outcomes, reduce the risk of mortality and pulmonary infection, and have a high hematoma evacuation rate, suggesting that it might be an optimal surgical treatment.

Funding National Natural Science Foundation of China, National Science Fund for Distinguished Young Scholars, Fundamental Research Funds for the Central Public Welfare Research Institutes, and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University.

Keywords: Intracerebral haemorrhage; Surgical intervention; Systematic review; Network meta-analysis

Research in context

Evidence before this study

In the preliminary search of PubMed, Embase, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov, we scoped the existing evidence on the surgical interventions for spontaneous supratentorial intracerebral haemorrhage from inception through December 2023, with a restriction to English-language publications. Our search terms included "intracranial haemorrhage OR cerebral haemorrhage" AND "surgery OR craniotomy OR endoscopy OR minimally invasive surgical procedures OR decompressive craniectomy". We updated the search on June 2024. We identified a number of studies on surgical interventions for spontaneous supratentorial intracerebral haemorrhage. A systematic review and network meta-analysis published in 2020 on the topic included 20 randomised clinical trials. It included three types of surgical interventions (craniotomy, endoscopy, and minimally invasive surgical procedures), and integrated data from different follow-up time points.

Added value of this study

This study used a comprehensive search including both database specific subject headings and elaborated key words, an additional surgical intervention (decompressive craniectomy), and added recently published peer-reviewed publications from 2020 to 2024. This updated systematic review included 31 randomised trials, of which five were not included in the most recent systematic review on this topic in 2020, and six were published after the 2019 search, resulting in 11 additional included trials. We found that surgical intervention could improve functional and survival outcomes at 6 months in patients with spontaneous supratentorial intracerebral haemorrhage, with greater functional improvements for patients undergoing surgery within 24 h. We also observed that endoscopic surgery and minimally invasive puncture surgery could improve functional outcomes, while endoscopic surgery and craniotomy could improve survival benefits. Endoscopic surgery and minimally invasive puncture surgery also reduced pulmonary infection risk. In addition, endoscopic surgery has a high hematoma evacuation.

Implications of all the available evidence

Findings from this study demonstrate that for patients with spontaneous supratentorial intracerebral haemorrhage, surgical interventions, especially endoscopic surgery and minimally invasive procedure surgery, could be considered in clinical practice, and craniotomy may be used as a life-saving measure. While surgical intervention is most beneficial when performed within the first 24 h post-onset, it retains clinical significance even when performed up to 72 h after the onset of symptoms. Nonetheless, these findings still need to be verified by future well-designed and rigorously conducted clinical trials. Additionally, individual meta-analyses should elucidate the impact of various factors, such as the location of the hematoma, its volume, and the level of patient consciousness, on patient outcomes and the selection of surgical strategies.

Introduction

Intracerebral haemorrhage (ICH) represents a significant global health concern, resulting in high rates of morbidity and mortality.[1,2] The 30-day mortality rate can reach 40%,[3] with survivors suffering from functional and cognitive impairments.[4,5] The primary treatment for ICH is conservative medical treatment (CMT), which, however, has limited efficacy.[6,7] Surgical intervention has garnered attention for its potential to reduce hematoma volume, alleviate mass effects, and potentially improve patient prognosis.[8] Despite these potential benefits, the efficacy of surgical treatment of ICH remains controversial. While the American Stroke Association (ASA) and European Stroke Organization (ESO) guidelines recommend surgery as a lifesaving strategy in certain contexts, its impact on improving functional outcomes remains uncertain.[6,7]

Surgical interventions for spontaneous supratentorial ICH include decompressive craniectomy (DC),

conventional craniotomy (CC), and minimally invasive surgery (MIS), with the latter encompassing endoscopic surgery (ES) and minimally invasive puncture surgery (MIPS). In contrast to previous RCTs that failed to show the functional benefits of surgical interventions like CC and MIS,[9–12] the recent ENRICH (Early Minimally-Invasive Removal of Intracerebral Haemorrhage) trial represents a pivotal advancement, demonstrating that minimally invasive surgery within 24 h of ICH onset improves functional recovery at 6 months.[13] Additionally, a recent trial conducted the first comparison of DC with CMT,[14] sparking interest in evaluating the efficacy and safety of different surgical procedures with CMT or in comparison to each other.

Several factors, such as the surgical time window,[15] hematoma size,[16,17] and postoperative complications,[18] crucially impact surgical outcomes and prognosis. Delayed surgery, averaging 27–58 h post-ICH onset, has shown limited functional improvement in previous trials.[9–12] Hematoma expansion occurring in 20% of patients within 3 h can worsen outcomes significantly, with a 3 mL increase tripling death and disability risks.[17,19,20] Therefore, addressing the importance of a comprehensive understanding of the surgical time window is crucial.[15] Larger hematomas pose higher risks due to mass effect and intracranial pressure,[16,21] and the efficacy of surgery for different sizes remains debated. Additionally, research on complications like post-operative bleeding and infection is scarce but essential.

Recently, several pivotal RCTs on the efficacy and safety of different surgical interventions have been published,[13,14,22–25] providing an important opportunity to determine the impact of surgical interventions in patients with ICH. Therefore, we performed a systematic review and network meta-analysis of RCTs to assess the effect of surgical interventions on ICH and identify the optimal surgical treatment.

Methods

Search strategy and study selection

This was a prospectively registered systematic review and network meta-analysis (PROSPERO CRD42024518961) that followed the reporting guideline of PRISMA for systematic reviews.[26] Changes from protocol are presented in supplement materials (Appendix 1). Two reviewers (JH and YM) independently screened titles/abstracts and full texts for eligibility, assessed the risk of bias, and collected data from each eligible study using a standardized template. Any disagreements were resolved by discussion, if needed, by consulting a third reviewer (LL).

Eligible studies were English-language RCTs comparing surgery (i.e., CC, ES, MIPS, or DC) with CMT or comparing different types of surgeries in patients with spontaneous supratentorial ICH. The included studies had to have a minimum follow-up period of three months and report at least one outcome of interest (see below). The primary outcomes were: (1) good functional outcome at 6 months; (2) death at 6 months. The secondary outcomes were: (1) good functional outcome at 3 months, 12 months, and the end of follow-up; (2) death at 7 days, 1 month, 3 months, 12 months, and end of follow-up; (3) rebleeding; (4) pulmonary infection; (5) brain infection; (6) hematoma evacuation rate.

PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to identify relevant RCTs from inception to June 2024. ClinicalTrials.gov was also searched to identify potentially eligible RCTs (Appendix 2). The reference lists of the included articles and relevant reviews were checked to ensure all relevant articles were included in the final analysis.

Data analysis

The following information was collected from each eligible RCT: 1) Study characteristics: year of publication, the first author, sample size, duration of follow-up, region, centre; 2) Interventions and controls: type of surgical intervention, type of control group, specific treatment received by patients in the intervention and control groups, time from symptom onset to surgery (surgical time window); 3) Patient's characteristics: age, sex (male proportion), ICH location, and ICH volume; 4) Outcomes: number of events, patients included for analyses in each group, mean and standard deviation of results for continuous outcomes.

We defined "good functional outcome" in the study based on the criteria commonly used in previous research.[27,28] The following benchmarks was considered to determine a good functional outcome: a modified Rankin Scale (mRS) score of 0–2, a Glasgow Outcome Scale (GOS) score of 4–5, an extended Glasgow Outcome Scale score (eGOS) score of 5–8, or a Barthel Index (BI) score of ≥60. Additionally, any alternative or self-defined criteria used in the RCTs were included if they aligned with the overall criterion of "no severe disability". For outcomes with multiple follow-up time points documented in the eligible studies, data were extracted for each specified follow-up time point.

Statistical analyses were performed with R version 4.3.2. We synthesized dichotomous outcomes as relative risks (RRs) and risk differences (RDs) accompanied by their 95% confidence intervals (CIs), whereas for continuous outcomes we used mean differences (MD). We used the following formula: RD = baseline risk*(RR–1),[29] baseline risk was considered the rate of occurrence of the event of interest in control group. To assess the presence of statistical heterogeneity among the included studies, we employed both the Q statistic and the I^2 statistic. Considering the inevitable heterogeneity across studies, we employed random effects models for data pooling. For instances where ten or more studies were compared,

publication bias was evaluated by funnel plot inspection and Egger's test.

Conventional pairwise meta-analysis was employed to compare the role of all surgical types with conventional medical treatment (*meta* package, version 6.5-0). A frequentist network meta-analysis (NMA) was then performed to compare different surgical approaches (*netmeta* package, version 2.8-2). The assumption of transitivity was assessed to ensure that the included studies comparing different surgical treatments shared the necessary similarity to generate credible indirect evidence. This involved examining the distribution of variables—including age, sex (male proportion), ICH volume, and sample size—that could influence outcomes across treatment comparisons. The node-splitting method was used to examine the consistency assumption between direct and indirect evidence. Potential inconsistency within the network was quantified by calculating the ratio of direct to indirect estimates, accompanied by their respective 95% CIs, and by determining the *P* value for inconsistency.

We conducted two prespecified subgroup hypotheses and assessed the credibility of any apparent subgroup effects (i.e., the *P*-value of interaction test ≤0.05) with the Instrument for the Credibility of Effect Modification Analyses (ICEMAN criteria)[30]: time window between symptom onset and surgery (<24 h vs. <72 h; larger effect in trials involving patients undergoing surgery within 24 h), and haemorrhage volume at baseline (<50 mL vs. ≥50 mL; larger effect in trials involving patients with haemorrhage volume <50 mL). As the data available at 6 months were limited and insufficient to support subgroup analyses, we used the data at the end of the follow-up for our analyses. Given the heterogeneity of different scales used in the studies, we conducted three sensitivity analyses for the good functional outcome by only including studies that reported mRS 0 to 2, mRS 0 to 3 and mRS 0 to 4. We also conducted four sensitivity analyses using odds ratio (OR) and excluding studies with high risk of bias. To investigate the impact of small studies effect, we omitted those having sample size less than 50. Additionally, to assess temporal differences, we excluded studies published more than 20 years ago.

We assessed the risk of bias of included studies using the revised Cochrane risk of bias tool for RCTs (RoB 2.0),[31] which includes randomization process, deviations from the intended interventions, missing outcome data, measurement of outcome, and selection of the reported result. Each domain was answered with 'low risk of bias', 'some concerns', or 'high risk of bias'. A trial was considered to be at high risk of bias overall if any domain was at high risk of bias. Then a web application was used to generate risk of bias assessment figures.[32]

The certainty of the evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[33,34] RCTs begin as high-quality evidence and can be rated down by risk of bias, imprecision, inconsistency, indirectness, and publication bias. We adopted the minimally contextualized framework to rate the imprecision and draw conclusions from an NMA.[35]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The data were available to all authors on request. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of 8573 potentially relevant records identified, 31 trials involving 6448 patients with a mean age of 60 years met our inclusion criteria (Fig. 1). Additionally, 12 ongoing trials were identified (eTable 1). Three of the 31 trials were three-arm RCTs[25,36,37] and the remaining 28 were two-arm RCTs.[9–14,22–24,38–56] The sample size of the included trials ranged from 10 to 1033. Six were multinational,[9–14] eight were multicentral within a single region,[24,25,37,41,42,46–48] and the remaining 17 were limited to a single institutional setting.[22,23,36,38–40,43–45,49–56] Nine studies focused on deep ICH,[14,23,36,42,45–47,53,56] one study[10] focused on lobar ICH, and the remaining 21 studies included both lobar and deep ICH.[9,11–13,22,24,25,37–41,43,45,48–52,54,55] 27 studies reported baseline haemorrhage volume,[9–14,22–25,36,37,39–47,49,50,52,53,55,56] with mean ICH volumes ranged from 23 mL to 65 mL. Of the 24 studies reported maximum time window from ICH onset to surgery,[9–14,22,23,25,36–43,45–47,49,50,52,55] all patients underwent surgery within 72 h of ICH onset, whereas 29 (7.5%) of patients in the Kim[45] study underwent surgery within 7 days (Table 1).

Detailed procedures of surgical intervention were provided in all studies except the one by Juvela et al.,[39] and we summarized the details of surgeries and CMT for each study in the Appendix (eTable 2). CC were performed in 19 studies,[9,10,22,23,25,36,37,39,40,43,47–49,51–56] ES in ten studies,[22,23,25,36,38,44,49–51,54] MIPS in 15 studies,[11–13,24,25,36,37,41,42,45–48,53,55] and DC in two studies.[14,56] The procedure of CC was similar among studies, and typically involves opening the skull, removing the blood clot, and controlling bleeding. Similarly, the procedure for DC was consistent across the studies, involving the removal of a portion of the skull to facilitate brain tissue expansion, with hematoma excision typically not being part of this procedure. The ES procedure exhibited a notable degree of uniformity across the studies, with the procedure typically included minimal incisions, burr hole, insertion of sheath, endoscope-guided hematoma removal and coagulation. Cather placement in the cavity after colt removal was conducted in some of the trials.[36,38,44,51,54] In the MIPS for ICH, there were variations among studies in terms of the surgical tools used and the thrombolytic agents administered. Some studies

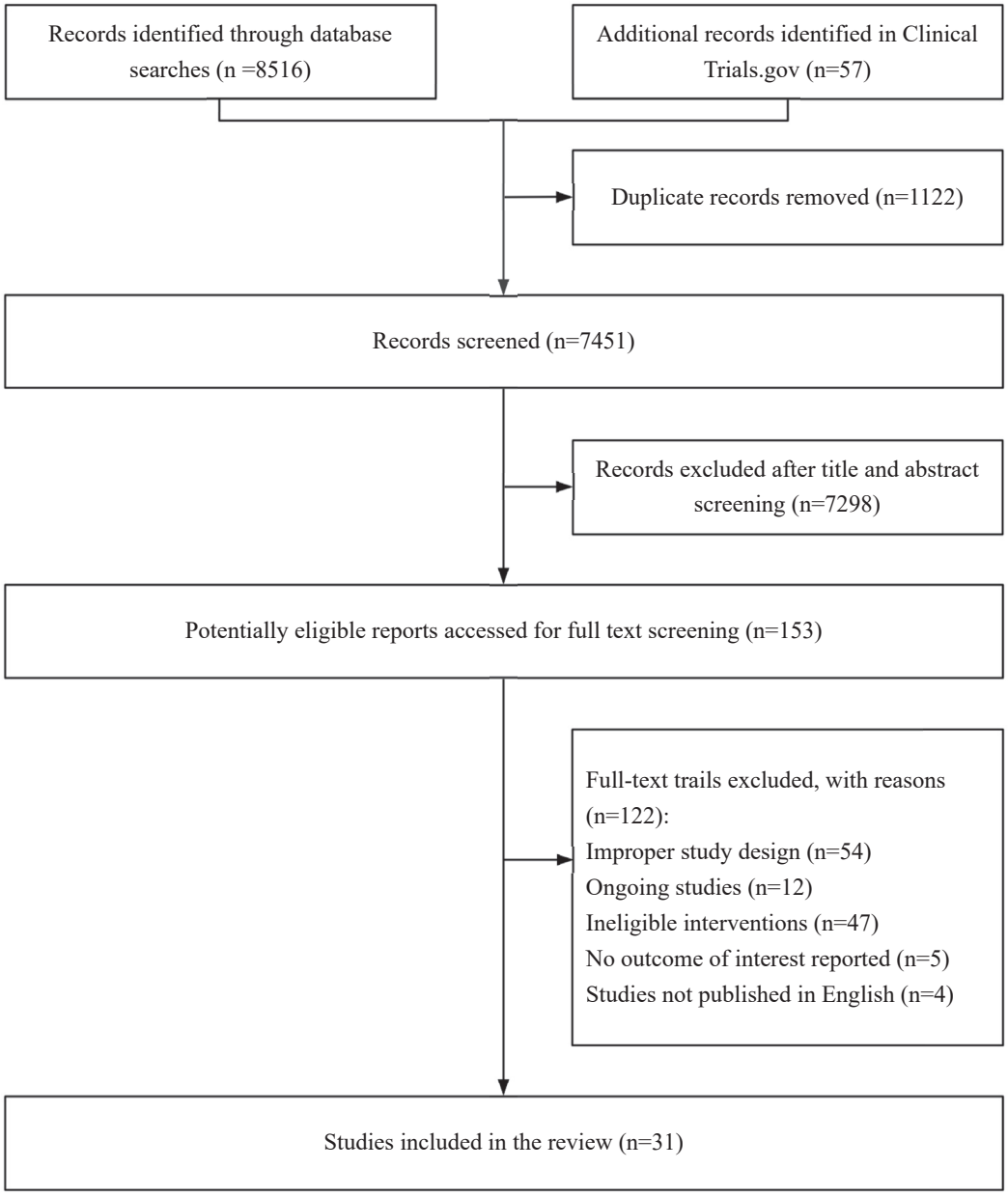


Fig. 1: **Flowchart of study selection**.

employed needles, while others utilized soft catheters. Additionally, the types of thrombolytic drugs and their methods of administration, such as dosages and times, varied. CMT was based on guideline-directed standard therapy or what was referred to as the best treatment in the studies, encompassed a range of basic treatments to maintain vital signs, including maintenance of blood pressure, fluid management, intracranial pressure monitoring, thromboprophylaxis, airway management, and nutritional support, etc.

The risk of bias was assessed separately for good functional outcome, mortality and other secondary outcomes. Among the 29 RCTs reporting good functional outcome, seven studies (24.1%) had a high risk of bias due to randomization process[37,44] or deviations from intended interventions[39,46,47,52,55] and seven studies[9–14,25] (24.1%) had a low risk of bias (eFig. 1). Among the 31 RCTs reporting mortality, two studies[37,44] (6.5%) had a high risk of bias due to the randomization process and seven studies[9–14,25] (22.6%) had a low risk of bias

Study	Sample size, n	Region	Center	Intervention	Age, mean	Male, n (%)	ICH location	ICH volume, mean mL	Time to surgery, hrs	Follow up, mons
Auer 1989[38]	100	Austria	Single	ES/CMT	NA	61 (61)	Lobar and Deep	NA	<48	6
Juvela 1989[39]	52	Finland	Single	CC/CMT	52	30 (58)	Lobar and Deep	61	<48	12
Morgenstern 1998[40]	34	USA	Single	CC/CMT	54[a]	22 (65)	Lobar and Deep	46[b]	<12	6
Zuccarello 1999[37]	20	USA	Multi	CC/MIPS/CMT	62	11 (55)	Lobar and Deep	42	<24	3
Teernstra 2003[41]	70	Netherlands	Multi	MIPS/CMT	68	40 (57)	Lobar and Deep	59	<72	6
Hattori 2004[42]	242	Japan	Multi	MIPS/CMT	61	148 (61)	Deep	44	<24	12
Mendelow 2005[9]	1033	Multinational	Multi	Surgery (75% CC)/CMT	62[a]	591 (57)	Lobar and Deep	38[b]	<72	6
Pantazis 2006[43]	108	Greece	Single	CC/CMT	61	60 (56)	Lobar and Deep	56	<8	12
Cho 2006[36]	90	China	Single	CC/MIPS/ES	56	60 (67)	Deep	43	<24	3
Miller 2008[44]	10	USA	Single	ES/CMT	59	9 (90)	Lobar and Deep	48	NA	3
Kim 2009[45]	387	Korea	Single	MIPS/CMT	66	289 (75)	Deep	23	<168	6
Wang 2009[46]	377	China	Multi	MIPS/CMT	57	236 (63)	Deep	33	<72	3
Sun 2010[47]	304	China	Multi	CC/MIPS	56	196 (64)	Deep	52	<72	3
Zhou 2011[48]	168	China	Multi	CC/MIPS	58	109 (65)	Lobar and Deep	NA	NA	12
Mendelow 2013[10]	601	Multinational	Multi	Surgery (98% CC)/CMT	64	340 (57)	Lobar	41	<72	6
Zhang 2014[49]	51	China	Single	CC/ES	61	38 (75)	Lobar and Deep	60	<24	6
Hanley 2016[11]	96	Multinational	Multi	MIPS/CMT	61	63 (66)	Lobar and Deep	46	<72	12
Vespa 2016[50]	56	USA	Single	ES/CMT	61[a]	37 (66)	Lobar and Deep	40	<72	12
Feng 2016[51]	184	China	Single	CC/ES	68	114 (62)	Lobar and Deep	NA	NA	6
Bhaskar 2017[52]	61	India	Single	CC/CMT	55	37 (61)	Lobar and Deep	65	<72	6
Ge 2018[53]	196	China	Single	CC/MIPS	59	118 (60)	Deep	44	NA	3
Rasras 2018[56]	30	Iran	Single	DC/CC	59	43 (13)	Deep	47	NA	6
Hanley 2019[12]	506	Multinational	Multi	MIPS/CMT	62[a]	305 (60)	Lobar and Deep	42[b]	<72	12
Gui 2019[54]	126	China	Single	CC/ES	53	75 (60)	Lobar and Deep	NA	NA	3
Luan 2019[55]	80	China	Single	CC/MIPS	57	43 (54)	Lobar and Deep	43	<72	3
Deng 2022[24]	78	China	Multi	MIPS/CMT	62	48 (62)	Lobar and Deep	35	NA	6
Noiphithak 2023[22]	188	Thailand	Single	CC/ES	51[a]	130 (69)	Lobar and Deep	50	<12	6
Lv 2023[23]	128	China	Single	CC/ES	56	85 (66)	Deep	30	<24	6
Pradilla 2024[13]	150	Multinational	Multi	MIPS/CMT	63	150 (50)	Lobar and Deep	55[b]	<24	6
Beck 2024[14]	201	Multinational	Multi	DC/CMT	61[a]	134 (68)	Deep	57[b]	<72	12
Xu 2024[25]	721	China	Multi	CC/MIPS/ES	57	497 (69)	Lobar and Deep	49	<36	6

ICH, intracerebral hemorrhage; hrs, hours; mons, months; ES, endoscopic surgery; CC, conventional craniotomy; MIPS, minimally invasive puncture surgery; DC, decompressive craniectomy; CMT, conservative medical treatment; NA, not available. [a]Median age. [b]Median ICH volume.

Table 1: **Characteristics of included studies.**

(eFig. 2). Among the 20 RCTs reporting other secondary outcomes, one study (5.0%) had a high risk of bias due to randomization process,[44] and six studies[10–14,25] (30.0%) had a low risk of bias (eFig. 3).

Moderate certainty evidence from 12 RCTs (2876 patients)[9–14,22–24,37–39,41–43,45–52,54–56] showed that compared to CMT, surgery improved the proportion of ICH patients who achieved good functional outcome at 6 months (RR 1.31, 95% CI 1.13–1.52; RD 9.1%, 95% CI 3.1–15.3; I^2 = 36%; Fig. 2 and Table 2). We found no evidence of publication bias (Egger's test P = 0.54; eFig. 4). MIS including ES and MIPS increased the chance of a good functional outcome at 3 months, 6 months, and 12 months (Fig. 3).

Our NMA found moderate certainty evidence that compared to CMT, both ES (RR 1.51, 95% CI 1.18–1.93; RD 9.4%, 95% CI 3.3–17.1) and MIPS (RR 1.48, 95% CI 1.24–1.76; RD 15.7%, 95% CI 7.9–24.9) were more effective in improving good functional outcome whereas no significant difference was found for CC (RR 1.09, 95% CI 0.87–1.35; RD 3.5%, 95% CI −5.0 to 13.5) or DC (RR 0.86, 95% CI 0.34–2.18; RD −0.4%, 95% CI −2.1 to 3.7) at 6 months. Besides, there is no significant different between ES and MIPS (RR 1.03, 95% CI 0.80–1.32; RD 1.0%, 95% CI −6.5 to 10.5) at 6 months (Fig. 2 and eTables 4 and 5).

Moderate certainty evidence from 13 RCTs (3399 patients)[9–14,24,38–41,45,50] suggested that compared with CMT, surgical treatment reduced the risk of death at 6 months (RR 0.82, 95% CI 0.71–0.95; RD −5.1%, 95% CI −8.2 to −1.4; I^2 = 14%; Fig. 4 and Table 2). We found no evidence of publication bias (Egger's test P = 0.26; eFig. 12). The pooled results of mortality assessed at 7 days, 1 month, 3 months, 6 months, and 12 months showed similar results (Fig. 3).

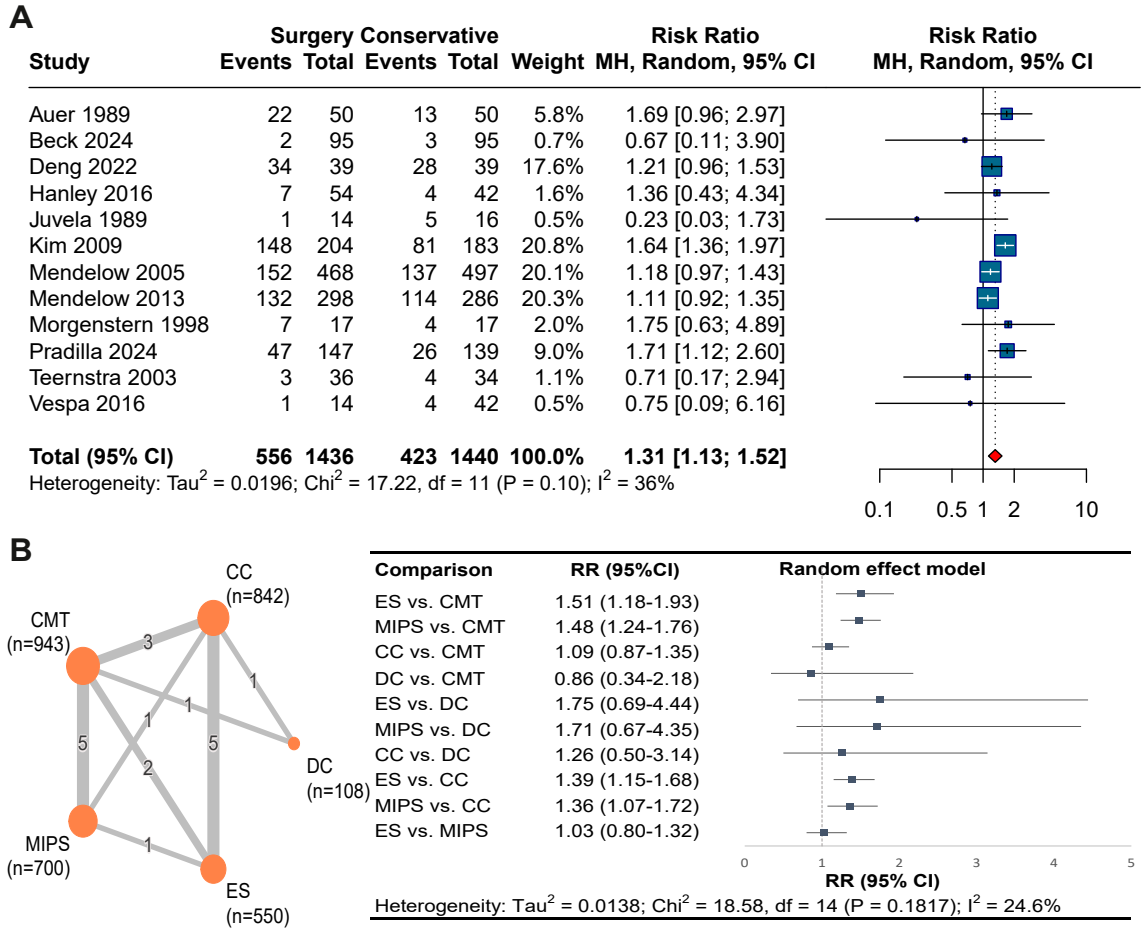


Fig. 2: Forest plot of good functional outcome at 6 months, (A) all type of surgeries vs. conservative medical treatment, (B) network meta-analysis of different types of surgeries. ES, endoscopic surgery; CC, conventional craniotomy; MIPS, minimally invasive puncture surgery; DC, decompressive craniectomy; CMT, conservative medical treatment.

The NMA found moderate certainty evidence that compared to CMT, ES (RR 0.66, 95% CI 0.52–0.85; RD –17.0%, 95% CI –24.0 to –7.5) and CC (RR 0.75, 95% CI 0.60–0.94; RD –6.3%, 95% CI –10.1 to –1.5) reduced the risk of mortality at 6 months. Low certainty evidence suggested that MIPS (RR 0.83, 95% CI 0.69–1.01; RD –3.3%, 95% CI –5.9 to 0.2) and DC (RR 0.63, 95% CI 0.38–1.03; RD –10.5%, 95% CI –17.6 to 0.9) may show no significant difference in mortality compared with CMT (Fig. 4 and eTables 6 and 7).

Studies that compared the rebleeding rate after surgery were eligible for this analysis. Low certainty evidence from eight RCTs (1798 patients)[22,25,36,47–49,53,55] suggested insignificant difference in the rebleeding rate between MIS and CC (7.8% vs. 11.6%; RR 0.75, 95% CI 0.49–1.16; RD –2.9%, 95% CI –5.9 to 1.9; I^2 = 36%; eFig. 17 and Table 2).

The NMA found low certainty evidence that there was no significant difference between ES and MIPS (RR 0.71, 95% CI 0.33–1.53; RD –1.6%, 95% CI –3.7 to 2.9; eFig. 18 and eTables 8 and 9).

Low certainty evidence from four RCTs (1026 patients)[23,25,49,54] suggested that there was no significant difference between MIS and CC in brain infection (4.8% vs. 5.8%; RR 0.80, 95% CI 0.43–1.51; RD –1.2%, 95% CI –3.3 to 2.9; I^2 = 0%; eFig. 19 and Table 2).

Low certainty evidence from five RCTs (1250 patients)[10,11,13,14,24] suggested that compared with CMT, surgery failed to reduce pulmonary infection (10.2% vs. 14.2%; RR 0.69, 95% CI 0.43–1.11; RD –4.4%, 95% CI –8.1 to 1.6; I^2 = 33%; eFig. 20 and Table 2).

The NMA found moderate certainty evidence that both ES (RR 0.39, 95% CI 0.23–0.69) and MIPS (RR 0.35, 95% CI 0.20–0.60; RD –5.3%, 95% CI –6.6 to –3.3) were reduced risk of pulmonary infection compared to CMT, while CC (RR 0.74, 95% CI 0.46–1.18; RD –3.6%, 95% CI –7.4 to 2.5) and DC (RR 0.93, 95% CI 0.55–1.58; RD –2.2%, 95% CI –14.0 to 18.0) did not show a

Certainty assessment	Summary of findings									Certainty of evidence
No of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Study event rates		Relative effect (RR (95% CI))	Absolute effects estimates	
						Arm 1	Arm 2		Arm 1	Arm 2
Good functional outcome at 6 months; surgery vs. CMT										
2916 (12)	Serious limitations[a]	No serious limitations	No serious limitations[a]	No serious limitations	Undetected	556/1476 (37.7%)	423/1440 (29.4%)	**RR** 1.31 (1.13–1.52)	514/1000 Difference: 91 more per 1000 (from 38 more to 153 more)	423/1000	⊕⊕⊕O **Moderate**
Mortality at 6 months; surgery vs. CMT										
3399 (13)	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	395/1702 (23.2%)	477/1697 (28.1%)	**RR** 0.82 (0.71–0.95)	230/1000 Difference: 51 fewer per 1000 (from 82 fewer to 14 fewer)	281/1000	⊕⊕⊕O **Moderate**
Pulmonary infection; surgery vs. CMT										
1250 (5)	Serious limitations[a]	No serious limitations	No serious limitations	Serious limitations[c]	Undetected	65/638 (10.2%)	87/612 (14.2%)	**RR** 0.69 (0.43–1.11)	98/1000 Difference: 44 fewer per 1000 (from 81 fewer to 16 more)	142/1000	⊕⊕OO **Low**
Rebleeding; MIS vs. CC										
1798 (8)	No serious limitations	No serious limitations	No serious limitations	very serious limitations[d]	Undetected	82/1046 (7.8%)	87/752 (11.6%)	**RR** 0.75 (0.49–1.16)	87/1000 Difference: 29 fewer per 1000 (from 59 fewer to 19 more)	116/1000	⊕⊕OO **Low**
Brain infection; MIS vs. CC										
1026 (4)	No serious limitations	No serious limitations	No serious limitations	very serious limitations[e]	Undetected	30/627 (4.8%)	23/399 (5.8%)	**RR** 0.80 (0.43–1.51)	46/1000 Difference: 12 fewer per 1000 (from 33 fewer to 29 more)	58/1000	⊕⊕OO **Low**
Evacuation rate; ES vs. CC										
797 (6)	Serious limitations[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	No application	No application	**MD** 7.03 (3.42–10.65)	No application Difference: 7.03 mL more (from 3.42 more to 10.65 more)	No application	⊕⊕⊕O **Moderate**
Evacuation rate; MIPS vs. CC										
797 (6)	Serious limitations[a]	Serious limitations[b]	No serious limitations	very serious limitations[f]	Undetected	No application	No application	**MD** −13.13 (−38.81 to 12.54)	No application Difference: 13.13 mL fewer (from 38.81 fewer to 12.54 more)	No application	⊕OOO **Very low**

Absolute risk difference was estimated based on the calculated risk ratio and the overall event rate across the control groups for each outcome. ES, endoscopic surgery; CC, conventional craniotomy; MIPS, minimally invasive puncture surgery; CMT, conservative medical treatment; MIS, minimally invasive surgery. [a]Rated down 1 level due to risk of bias. [b]Rated down 1 level due to moderate heterogeneity. [c]The 95% CI includes both important benefit (−8.1%) and important harm (1.6%). [d]The 95% CI includes both important benefit (−5.9%) and important harm (1.9%). [e]The 95% CI includes both important benefit (−3.3%) and important harm (2.9%). [f]The 95% CI includes both important benefit (12.54 mL) and important harm (38.81 mL).

Table 2: **GRADE evidence profile of surgical interventions for spontaneous supratentorial intracerebral haemorrhage.**

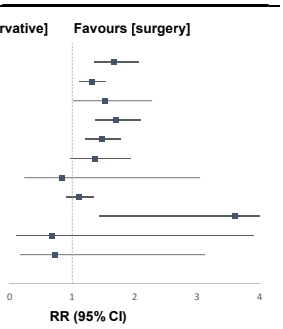
significant difference. Moderate certainty evidence showed that compared to CC, both ES (RR 0.54, 95% CI 0.39–0.74; RD −12.6%, 95% CI −16.7 to −7.1) and MIPS (RR 0.48, 95% CI 0.33–0.68; RD −14.1%, 95% CI −18.1 to −8.7) decreased the risk of pulmonary infection (eFig. 21 and eTables 10 and 11).

Moderate certainty evidence from seven RCTs (1242 patients)[22,23,25,36,49,51,54] suggested that the evacuation rate of ES was found to be higher than that of CC (MD 7.03, 95% CI 3.42–10.65; I^2 = 94%; eFig. 22 and Table 2). Very low certainty evidence from two RCTs (542 patients)[25,36] suggested that no difference between MIPS and CC (MD −13.13, 95% CI −38.81 to 12.54; I^2 = 99%; eFig. 22 and Table 2).

Concerning the surgical timing, patients undergoing surgery within 24 h have a higher likelihood of a good functional outcome, when compared to those undergoing surgery within 72 h after ICH onset (test of interaction P = 0.03; within 24 h RR 1.70, 95% CI 1.35–2.14; within 72 h RR 1.23, 95% CI 1.04–1.45; Fig. 5). Applying ICEMAN criteria, we judged the credibility as moderate bordering on high (eTable 3). A large number of trials for between-trial comparisons, a priori specified direction of the effect, the implausibility of chance as an

A

Good functional outcome Surgery type	Follow-up	No. studies	Surgery Events	Surgery Total	Conservative Events	Conservative Total	RR (95% CI)	I^2(%)
All types of surgery	3 months	6	148	400	93	416	1.67(1.36-2.05)	0
	6 months	12	556	1436	423	1440	1.31(1.13-1.52)	36
	12 months	6	136	555	96	566	1.52(1.02-2.27)	39
Minimally invasive surgery	3 months	5	144	361	87	378	1.70(1.38-2.09)	0
	6 months	7	262	544	160	529	1.47(1.22-1.77)	2
	12 months	4	115	408	87	423	1.37(0.98-1.92)	11
Conventional craniotomy	3 months	2	4	39	6	38	0.84(0.24-3.04)	0
	6 months	3	140	329	123	319	1.11(0.92-1.34)	35
	12 months	1	18	54	5	54	3.6(1.44-9.00)	/
Decompressive craniectomy	6 months	1	2	95	3	95	0.67(0.11-3.90)	/
	12 months	1	3	93	4	89	0.72(0.17-3.12)	/



B

Mortality Surgery type	Follow-up	No. studies	Surgery Events	Surgery Total	Conservative Events	Conservative Total	RR (95% CI)	I^2(%)
All types of surgery	7 days	6	22	629	45	614	0.50(0.30-0.97)	26
	1month	8	67	813	105	808	0.66(0.50-0.88)	0
	3 months	5	62	387	80	374	0.73(0.58-0.93)	0
	6 months	13	395	1702	477	1697	0.82(0.71-0.95)	14
	12 months	7	129	581	175	592	0.79(0.65-0.95)	16
Minimally invasive surgery	7 days	4	11	507	32	487	0.37(0.18-0.78)	16
	1month	5	49	674	74	664	0.66(0.46-0.93)	0
	3 months	4	39	348	54	336	0.71(0.49-1.04)	0
	6 months	8	137	799	178	776	0.76(0.63-0.92)	0
	12 months	4	69	408	104	423	0.73(0.56-0.96)	21
Conventional craniotomy	7 days	1	8	26	8	26	1.00(0.44-2.26)	/
	1month	2	11	43	14	43	0.72(0.23-2.29)	35
	3 months	2	23	39	26	38	0.75(0.55-1.01)	0
	6 months	3	137	340	83	329	0.84(0.60-1.18)	0
	12 months	2	39	80	41	80	0.97(0.65-1.45)	30
Decompressive craniectomy	7 days	1	3	96	5	101	0.63(0.16-2.57)	/
	1month	1	7	96	17	101	0.43(0.19-1.00)	/
	6 months	1	16	95	27	95	0.59(0.34-1.03)	/
	12months	1	21	93	30	89	0.67(0.42-1.08)	/

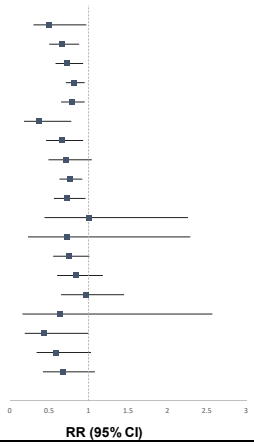


Fig. 3: Forest plot of surgery vs. conservative medical treatment at different follow-up times, (A) good functional outcome, (B) mortality.

explanation, testing only a small number of effect modifiers, and the use of an appropriate random effect model in the analysis all support the credibility of the subgroup effect. The lack of the within-trial comparison decreases the credibility. The subgroup analyses provided no support for subgroup effects for good functional outcome based on haematoma volume (test of interaction $P = 0.86$), for mortality based on surgical time window (test of interaction $P = 0.94$), and for mortality based on haematoma volume (test of interaction $P = 0.79$).

Sensitivity analyses showed that alterations in the definition of good functional outcome, the use of OR, the exclusion of studies with a high risk of bias, the exclusion of studies published more than two decades ago, and the exclusion of studies with fewer than 50 participants did not result in statistically significant alterations to the pooled effects for good functional outcomes (eFigs. 5–11) and mortality (eFigs. 13–16).

Discussion

Our systematic review and meta-analysis supports for the hypothesis that surgical intervention for evacuation of spontaneous supratentorial ICH is associated with improved functional outcomes and a reduced risk of death. The advantages of surgical haematoma removal are particularly pronounced when MIS including ES and MIPS are used and when the procedure is initiated within 24 h after symptom onset. We did not find subgroup effect of average baseline haemorrhage. In addition, MIS appears to mitigate the risk of pulmonary infections and does not elevate the likelihood of rebleeding. In particular, ES is associated with superior hematoma evacuation rates. Sensitivity analyses support the robustness of our results.

ICH is a neurological emergency, and 70% of patients are at risk of early neurological deterioration within the first 24 h.[57] Surgery can prevent brain herniation, reduce intracranial pressure, and minimize the toxic effects of hematomas on surrounding brain tissue.[8] Prompt hematoma evacuation prevents expansions and mitigates secondary brain injury, crucial for the patient's prognosis.[15] ES is a minimally invasive procedure that facilitates hematoma aspiration under direct visual guidance, thereby minimizing disruption to surrounding brain tissue. Compared to other techniques, ES proves more effective in hematoma evacuation.[8] A post hoc exploratory analysis of the MISTIE III trial

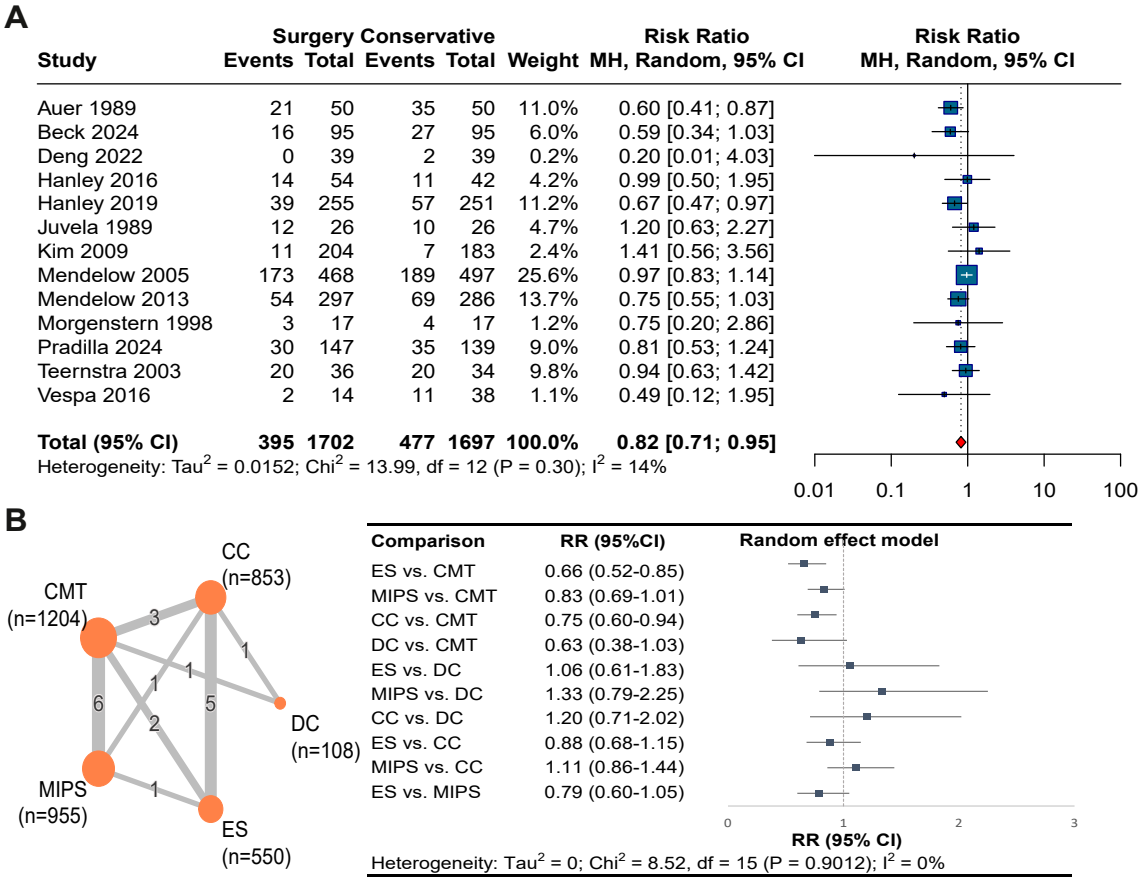


Fig. 4: Forest plot of mortality at 6 months, (A) all type of surgeries vs. conservative medical treatment, (B) network meta-analysis of different types of surgeries. ES, endoscopic surgery; CC, conventional craniotomy; MIPS, minimally invasive puncture surgery; DC, decompressive craniectomy; CMT, conservative medical treatment.

revealed that achieving ≥70% hematoma reduction or reducing hematoma volume to ≤15 mL significantly enhances the likelihood of a favourable outcome.[12] Furthermore, by reducing the incidence of pulmonary infections—which can worsen prognosis, prolong hospital stays, and increase mortality in ICH patients[18]—ES contributes to better overall patient outcomes. Importantly, ES does not elevate the risk of complications such

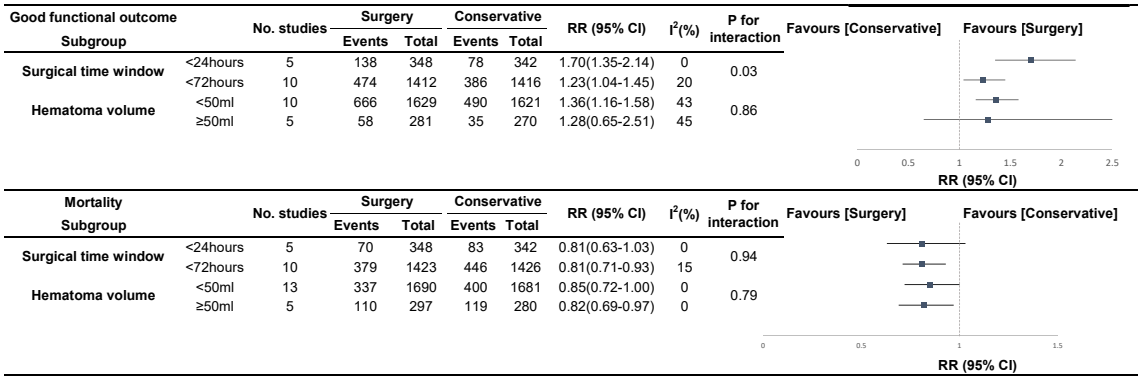


Fig. 5: Forest plot of subgroup analysis.

as rebleeding and intracranial infection compared to other procedures.[8]

Six previous meta-analyses have explored the effect of surgery on patients with ICH.[27,28,58–61] Two previous meta-analyses compared surgery with CMT in ICH patients,[27,58] which found that all types of surgery could improve functional outcomes and reduce mortality at the end of follow-up. Two previous meta-analyses compared MIS with CC and CMT,[59,60] indicating that MIS could reduce the risk of disability and mortality at the end of follow-up. One previous NMA meta-analysis including 20 RCTs (3603 patients) compared CC, ES, MIPS, and CMT with each other,[28] which found that both ES and MIPS could improve functional outcomes and reduce mortality at the end of follow-up. Four meta-analyses performed subgroup analyses to examine the impact of surgical time window on treatment effect with controversial results.[27,59–61] One study found that the sooner the surgery the greater the benefit,[27] while another study suggested that time to randomization of less than 8 h correlated with a decreased probability of a poor outcome.[61] The remaining two studies showed that surgical intervention performed within either 24 or 72 h decreased poor outcomes with no specific subgroup effects.[59,60]

In comparison with the previous studies, our review has added substantial information. Firstly, we identified and incorporated several recently published high-quality RCTs and encompassed DC in addition to hematoma removal surgical procedures such as CC, ES, and MIPS, thereby allowing for a comprehensive assessment of the different surgical procedures. Secondly, following the Cochrane Handbook,[62] we defined multiple outcomes based on different follow-up times and conducted separate analyses accordingly, to avoid selecting the longest follow-up time from each trial, which could mitigate potential heterogeneity between estimates and prevent biased conclusions. Thirdly, our study showed that CC reduced 6-month mortality, while MIPS didn't. This could be due to our larger sample size, which increased the statistical power to identify the effect of CC. Focusing on 6-month follow-up inadvertently reduced the number of studies of relevant studies for MIPS and limited its potential for indirect comparison. Fourthly, our prespecified subgroup analyses have provided additional evidence regarding the optimal surgical timing, highlighting the possibility that patients undergoing surgery within 24 h of ICH onset may benefit more from good functional outcome than those within 72 h. Fifthly, our study classified rebleeding as an outcome attributable to surgical procedures for hematoma removal and demonstrated no meaningful difference in the incidence of rebleeding among patients who underwent CC, ES, or MIPS.

This study has several strengths. Firstly, we have carefully integrated outcomes from various follow-up periods to comprehensively assess the short-term and long-term impacts of surgical intervention in patients with ICH, which allows for a more subtle understanding of how surgical treatments influence both the immediate and extended outcomes for these patients. Secondly, we have conducted preplanned subgroup analyses to explore the most two controversial and critical clinical factors of ICH surgery and assessed the credibility of subgroup effects by using ICEMAN criteria. Thirdly, we conducted a network meta-analysis to evaluate the comparative effectiveness of various surgical procedures. Fourthly, we used GRADE to grade the evidence, providing more information for clinical decision-making.

This study also has some limitations. Firstly, the review, although comprehensive, is not exempt from the challenges posed by the heterogeneity inherent in the body of research on ICH surgery. Variability in study design, demographics, interventions, and outcomes may impact the consistency and comparability of results, necessitating cautious interpretation of the pooled results, and therefore caution is warranted in concluding our findings. In particular, the definition of "good functional outcome" varied across studies. However, we conducted a sensitivity analysis including only studies reporting mRS 0 to 2, mRS 0 to 3 and 0 to 4 to assess the robustness of the results. Secondly, our study did not include non-English trials, which may inevitably lead to omits of some studies published in other languages, thus leading to language bias. Thirdly, the analysis did not account for the impact of ICH location on surgical outcomes, an important prognostic factor in ICH. Superficial bleeds are more accessible and may yield better surgical results, while deep bleeds are less suitable for surgery and carry a higher risk of tissue damage. Fourthly, according to the inclusion criteria, we did not include combined treatments for different surgical types. However, such studies also provide evidence for the effects of surgical intervention in ICH. For example, the CARICH study showed that clot removal within 72 h without DC reduced the rate of mRS 3–6 and mortality in patients with supratentorial ICH compared with clot removal with DC. The findings showed that DC with hematoma removal may not be beneficial. On the other hand, it also indirectly suggested that surgery to remove the haematoma (under intracranial pressure control) without decompression may improve prognosis.[63]

Our study indicates that for patients with spontaneous supratentorial ICH, surgical interventions, especially ES and MIPS, could be considered in clinical practice. CC may be used as a life-saving measure. While surgical intervention is most beneficial when performed within the first 24 h post-onset, it retains clinical significance even when performed up to 72 h after the onset of symptoms. Nonetheless, these findings still need to be verified by future carefully designed and rigorously conducted RCTs. Additionally, individual

meta-analyses should elucidate the impact of various factors, such as the location of the hematoma, its volume, and the level of patient consciousness, on patient outcomes and the selection of surgical strategies. Current evidence favours surgical intervention within 72 h, with optimal results within the first 24 h, as early surgery may prevent hematoma expansion and mitigate secondary injury.[15] Future research should further confirm the optimal timing of surgical intervention to determine whether earlier intervention results in outcomes, or whether a minimum surgical time window should be proposed to prevent complications such as rebleeding.

In this meta-analysis of RCTs, current moderate certainty evidence suggested that surgery, compared to CMT, increased the likelihood of good functional outcome and reduced mortality at 6 months. A greater functional benefit was found for patients when surgery was performed within 24 h (moderate credibility). ES and MIPS both improved functional outcomes and reduced the risk of pulmonary infection, and ES and CC both reduced mortality at 6 months, ES also had a high haematoma evacuation rate. All these findings suggesting that ES might be an optimal surgical treatment, and well-designed RCTs are still needed to confirm the role of different surgeries in ICH patients.

Contributors

JH and MY contributed equally as co-first authors. JH and MY had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. XS, LL, and XH designed the study. JH and MY drafted the manuscript and conducted the statistical analysis. LL, XS, and XH gave administrative, technical, or material support and supervised the study. JH, MY, YM, FM, YL, XL, JL, HX, KZ, XH, LL, and XS critically revised the article. All authors analysed and interpreted the data. LM, CY and JX provided critical assessment of the neurosurgical procedures of different surgical types and contribute to the revision of the manuscript. JH, MY and LL have verified the underlying data. All authors critically reviewed or revised the manuscript and approved the final version of the manuscript.

Data sharing statement

No additional data available.

Declaration of interests

The authors declare that there is no conflict of interest.

Acknowledgements

This study was funded by the National Natural Science Foundation of China (Grant No. 72204173 and 82274368), National Science Fund for Distinguished Young Scholars (Grant No. 82225049), Fundamental Research Funds for the Central Public Welfare Research Institutes (Grant No. 2020YJSZX-3) and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (Grant No. ZYGD23004).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102999.

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