Surgical outcomes from haematoma evacuation for intracerebral haemorrhage in the INTERACT3 study

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Summary

Background There is ongoing controversy as to whether surgical intervention to haematoma evacuation benefits patients with acute intracerebral haemorrhage (ICH). This study aimed to evaluate the association of surgical intervention to evacuate the haematoma and 6-month functional outcome in participants of the third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3).

Methods This was a secondary analysis of INTERACT3, which enrolled adults (age ≥18 years) spontaneous ICH patients within 6 h after onset. INTERACT3 was an international, multicentre, prospective, stepped-wedge, cluster randomised, blinded outcome assessed, clinical trial undertaken at 121 hospitals in 10 countries between December 12, 2017 and December 31, 2021. To limit heterogeneity in the results, we restricted analyses to participants in China. The primary outcome was poor functional outcome, defined by a score of 5–6 on the modified Rankin scale (mRS), at 6 months. Secondary outcomes include a mRS score of 4–6 and mortality at 6 months. Sensitivity analysis included propensity score matched analysis and the imputation of missing outcome variables. The effect of timing on surgical outcome was also evaluated. The INTERACT3 trial was registered at ClinicalTrials.gov (NCT03209258) and CHiCTR.org.cn (ChiCTR-IOC-17011787).

Findings Of 5772 participants (mean age 62.0 ± 12.5 years) at 82 sites in China, 1411 (24.4%) received surgery in which craniotomy (72.6%) was the most common approach. After adjustment for confounding variables, surgery to evacuate the haematoma was associated with lower odds of a poor functional outcome (odds ratio 0.71, 95% CI 0.55–0.92; p = 0.010)

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and mortality (odds ratio 0.55, 95% CI 0.40–0.75; p = 0.0001) at 6 months. The association was consistent in propensity score matching analysis and sensitivity analysis by imputation. We did not detect significant differences in outcome between those who received surgery on the same day of hospital arrival compared to those who received surgery on the second or later days. In analysis limited to participants with supratentorial ICH and with a haematoma volume 30 mL or more, evacuation of the haematoma was associated with lower odds of poor functional outcome (n = 1234, odds ratio 0.68, 95% CI 0.46–0.99; p = 0.042) and mortality (n = 1291, OR 0.45, 95% CI 0.29–0.69; p = 0.0003).

Interpretation This secondary analysis of the INTERACT3 indicates that evacuation of the haematoma is associated with better chances of surviving free of severe disability after acute ICH. With the evolution of instrument and techniques, further trial should address the role of haematoma evacuation in deep ICH patients, the time window and difference between mini-invasive techniques.

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Keywords: Intracerebral haemorrhage; Haematoma evacuation; Secondary analysis; INTERACT3

Research in context

Evidence before this study

We searched PubMed (from January 1, 1970, to April 20, 2025) and Embase (from January 1, 1947, to April 20, 2025), with a restriction to English-language publications using the following terms: "intracerebral haemorrhage OR haemorrhagic stroke" AND "surgery OR surgical treatment OR craniotomy OR endoscopy OR aspiration OR minimally invasive surgery" AND "multicentre OR multisite". We identified several high-quality trials on haematoma evacuation for spontaneous intracerebral haemorrhage (ICH), while only the Early Minimally Invasive Removal of Intracerebral Hemorrhage (ENRICH) trial reported a positive effect of early haematoma evacuation in 300 ICH patients, which is appeared to be attributable to lobar but not deep ICH. The Swiss Trial of Decompressive Craniectomy vs. Best Medical Treatment of Spontaneous Supratentorial Intracerebral Haemorrhage (SWITCH) provides weak evidence that decompressive craniectomy without haematoma evacuation might have lower odds of poor outcome (modified Rankin scale [mRS] scores 5–6) in severe deep ICH. INTERACT3 was an international, multicentre, prospective, stepped-wedge, cluster randomised, blinded outcome assessed, clinical trial to estimate whether implementing a goal-directed care bundle including early intensive blood pressure lowering could improve outcomes in spontaneous ICH patients. The pragmatic design with systematic assessment of clinical outcomes of INTERACT3 allowed further analysis on the effect of haematoma evacuation on functional outcome in ICH.

Added value of this study

In this secondary analysis of INTERACT3 trial, we included 5722 patients with parenchymal ICH from 82 sites in China, with 1411 received surgical treatment for haematoma evacuation and 4776 (82.8%) patients were deep ICH. After adjustment for confounders, haematoma evacuation was significantly associated with a lower odds of mRS 5–6 and mortality at 6 months. Propensity score matched analysis and sensitivity analysis by imputation were consistent with the primary results. Furthermore, when focusing on those participants with a supratentorial haematoma volume ≥30 mL, which is a common indication for surgical intervention as well as an inclusion criteria for clinical trials, we also found the benefits of surgery from haematoma evacuation with an decreased odds of mRS 5–6 at 6 months.

Implications of all the available evidence

Findings from this study support the active treatment that haematoma evacuation could be considered in clinical practice for patients with spontaneous ICH. The effect of minimally invasive surgery including endoscopy and aspiration on the functional outcome in ICH patients, especially in deep ICH, should be tested in future trials. Furthermore, the time window as well as the difference between different techniques need to be estimated as well.

Introduction

Despite a considerable amount of research effort, there is ongoing controversy as to the role of surgery in the management of patients with acute spontaneous intracerebral haemorrhage (ICH).[1,2] A meta-analysis of 21 randomised controlled trials showed that both open

craniotomy and minimally-invasive surgery (MIS) can improve functional outcome and reduce mortality in patients with supratentorial ICH, but there was significant heterogeneity in the treatment effect across the individual trials.[3] Differences in the design, intervention, and populations are likely explanations for the findings.[2] Most recently, the Early Minimally Invasive Removal of Intracerebral Haemorrhage (ENRICH) trial reported a positive effect of a novel MIS approach in 300 ICH patients (69.3% with lobar ICH) using a Bayesian analytical approach.[4] The effect of haematoma evacuation appeared to be attributable to lobar ICH, while it was not apparent for patients with anterior basal ganglia haemorrhage.[4] For deep ICH, the Swiss Trial of Decompressive Craniectomy vs. Best Medical Treatment of Spontaneous Supratentorial Intracerebral Haemorrhage (SWITCH) showed a trend towards avoiding a very poor outcome (modified Rankin scale [mRS] scores 5–6) from decompressive craniectomy in 201 participants with a severe deep supratentorial ICH.[5] The inspiring results from these clinical trials encourage further exploration of the surgical outcomes from haematoma evacuation for ICH.

The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3) showed clear benefits from the implementation of a care bundle with time- and target-based protocols that incorporated early intensive blood pressure (BP) lowering as a system of care in a broad range of patients with ICH.[6] As the pragmatic stepped-wedge cluster randomised design allowed a large number of patients to be recruited with a broad range of characteristics, a high level of selection bias that arises from conventional individual patient randomised trials was avoided. Herein, we present results of secondary analysis that aimed to determine the relation of haematoma evacuation and functional outcome in patients with ICH.

Methods

Study design, participants, and setting

INTERACT3 was an international, multicentre, prospective, stepped-wedge, cluster randomised, blinded outcome assessed, clinical trial undertaken at 121 hospitals located in nine low- and middle-income countries (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Vietnam), and one high-income country (Chile), as outlined elsewhere.[6] Participating hospitals either had no or inconsistent protocols for managing abnormal physiological variables in patients with acute ICH and were willing to implement the required interventional care bundle as part of routine care. Adult (age ≥18 years) patients with CT confirmed primary ICH who presented within 6 h after symptom onset were considered for enrolment. Details of the inclusion and exclusion criteria are described elsewhere.[7] The trial is registered at ClinicalTrials.gov (NCT03209258) and the Chinese Clinical Trial Registry (ChiCTR-IOC-17011787). In this secondary analysis of INTERACT3, we included the patients with parenchymal ICH from China as: 1) there were approximately 90% of the participants were recruited in China in INTERACT3 study; 2) most of the surgery for haematoma evacuation were performed in China; 3) less variations in the surgical procedures and system of care in the same region. The surgical types for haematoma evacuation included craniotomy, endoscopy and catheter aspiration with or without thrombolysis, whereas patients who received external ventricular drainage or craniectomy were excluded.

Procedures

Demographic and clinical data, including the level of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS, range 0–42, with higher scores indicating greater severity), were collected at the time participants were admitted to hospital. Clinical status and details of hospital management including surgery, were collected from baseline to Day 7 (or before discharge if earlier). Study outcomes were recorded centrally through telephone follow-up of participants at 6 months by independent staff blinded to randomised treatment allocation. The primary outcome was poor functional outcome, defined as a mRS score 5–6, at 6 months. The mRS is a standard 7-categorical global measure of functional outcome with scores ranging from 0 to 6, in which scores of 0–1 indicate a favourable outcome without or with symptoms but no disability; scores of 2–5 indicate increasing amounts of disability (and dependency); and a score of 6 indicates death. Secondary outcomes included mRS 4–6 and mortality at 6 months.

Statistical analysis

All analyses were undertaken at the patient level using logistic regression with adjustment as a random effect for cluster (hospital), a fixed categorical effect of time (4 randomised interventional time periods), and a fixed effect of the group assignment of each cluster at each period, as undertaken for the main results.[8] Since the period lengths were not equal and the times of enrolment of the different clusters varied widely, a 6-month calendar period was used to adjust for the effect of time. Baseline characteristics and hospital management with a p-value of <0.1 shown in univariate comparisons were included as covariates in the multivariable analysis of the association of surgery and clinical outcome. A propensity score matching analysis was conducted as a sensitivity analysis to reduce baseline imbalances between the groups using a nearest neighbour matching with a caliper width of 0.20. Propensity scores were calculated for all the baseline covariates, with unbalanced covariates (standardised differences >0.1) further

adjusted in the multivariable models to determine associations of surgery and outcomes. Subgroup analysis included age, sex, region, baseline neurological severity, history of hypertension, prior antithrombotic treatment, baseline haematoma volume, admission to an intensive care unit (ICU), randomised treatment and haematoma location. As outcome data were missing in >10% of participants, multiple imputation was conducted as a further sensitivity analysis with all covariates (including the outcome variable) in the mixed model (method outlined in Appendix 1 of Supplementary Material). A worse-case scenarios imputation, which assumes that all the missing primary outcomes had the worse outcomes was conducted as another sensitivity analysis. We further explored the impact of surgery by time to intervention using date (same day of hospital arrival vs. second day vs. later days) and type of surgery on the primary outcome. Further exploratory analysis was undertaken in patients with supratentorial ICH with a haematoma volume ≥30 mL, as this is popular criteria for surgery in routine practice. Data are reported with odds ratios (OR) and 95% confidence intervals (CI). All analyses were undertaken with SAS Enterprise Guide (version 8.2).

Ethics approval

This study is a secondary analysis of data originally collected under INTERACT3 study. The Biomedical Ethics Committee of West China Hospital approved the study before the commencement of any patient recruitment (Ethics Reference No. 22017 Review [217]). According to funding request from Medical Research Council, additional approval (Ethic Reference: 26596-tgr2r-ls: cardiovascular sciences, deptof) had been obtained from Research Ethics Committee of the University of Leicester, United Kingdom. Ethics approval was obtained at each site before site activation. All participants provided informed consent at the time of the original study. The secondary analysis of de-identified data was determined to be exempt from additional ethical review.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis and interpretation, or writing of the report.

Results

Of the 7036 INTERACT3 participants with acute ICH recruited between December 12, 2017, and December 31, 2021, 6356 (90.3%) patients were from China. After further screening, a total of 5772 patients from 82 sites in China with parenchymal ICH and surgical data available for these analyses in whom 1411 (24.4%) received surgical intervention for haematoma evacuation and 4361 (75.6%) received medical treatment alone (Fig. 1). Table 1 shows that in comparison to participants who did not receive surgery, those who had surgery were younger (mean age 58.8 vs. 63.1 years), had higher systolic BP (175.6 mmHg vs. 172.9 mmHg), higher median NIHSS scores (22 vs. 11), lower median GCS scores (9 vs. 13), larger haematoma mean volumes (39 vs. 10 mL) and greater intraventricular extension (33.2% vs. 21.8%).

There were 977 (69.3%) participants who received surgery on the same day of admission to hospital and 336 (23.9%) who had surgery on the following day (Table 2). More than half of the surgical patients received a craniotomy (72.6%); the other interventions included catheter aspiration with or without thrombolysis (22.5%) and endoscopy (4.8%). Compared to participants without surgery, those who received surgery were more likely to receive more intravenous BP lowering (86.5% vs. 75.5%), antipyrexia treatment (17.2% vs. 4.7%), mechanical ventilation (64.6% vs. 5.9%), and assisted feeding (78.2% vs. 42.7%) (Table 2).

Table 3 shows in univariate analysis, there were higher likelihood of mRS 5–6 in the surgery group compared to medical group (36.7% vs. 19.2%) at 6 months. However, after adjustment for baseline characteristics and hospital management variables, surgery for haematoma evacuation was associated with lower odds of mRS 5–6 (OR 0.71, 95% CI 0.55–0.92; p = 0.010), and mortality (OR 0.55, 95% CI 0.40–0.75; p = 0.0001) at 6 months, while there was no difference with regard mRS 4–6 (OR 1.04, 95% CI 0.82–1.33, p = 0.732). Similar results were found in propensity score matched analysis (matching characteristics have shown in Supplemental Table S1), with haematoma evacuation being associated with reduced odds of mRS 5–6 (OR 0.74, 95% CI 0.56–0.98; p = 0.034) and mortality (OR 0.52, 95% CI 0.37–0.72; p = 0.0001) (Table 3). The results were consistent in the sensitivity analysis by imputation (Supplemental Table S2). There were significant interactions between surgery and the pre-specified subgroups of sex, neurological severity, baseline haematoma volume, ICU admission, and randomised treatment (Fig. 2).

There was no significant difference in the primary outcome according to the day of surgery (Supplemental Table S3). Compared with craniotomy, MIS including endoscopy and catheter aspiration with or without thrombolysis, was not associated with mRS 5–6 at 6 months after ICH (Supplemental Table S4). Among participants with supratentorial ICH and a haematoma volume ≥30 mL, haematoma evacuation was associated with lower odds of mRS 5–6 (n = 1234, OR 0.68, 95% CI 0.46–0.99; p = 0.042) and mortality (n = 1291, OR 0.45, 95% CI 0.29–0.69; p = 0.0003) (Supplemental Table S5). No significant differences were found on the date of surgery undertake in this group of patients (Supplemental Table S6).

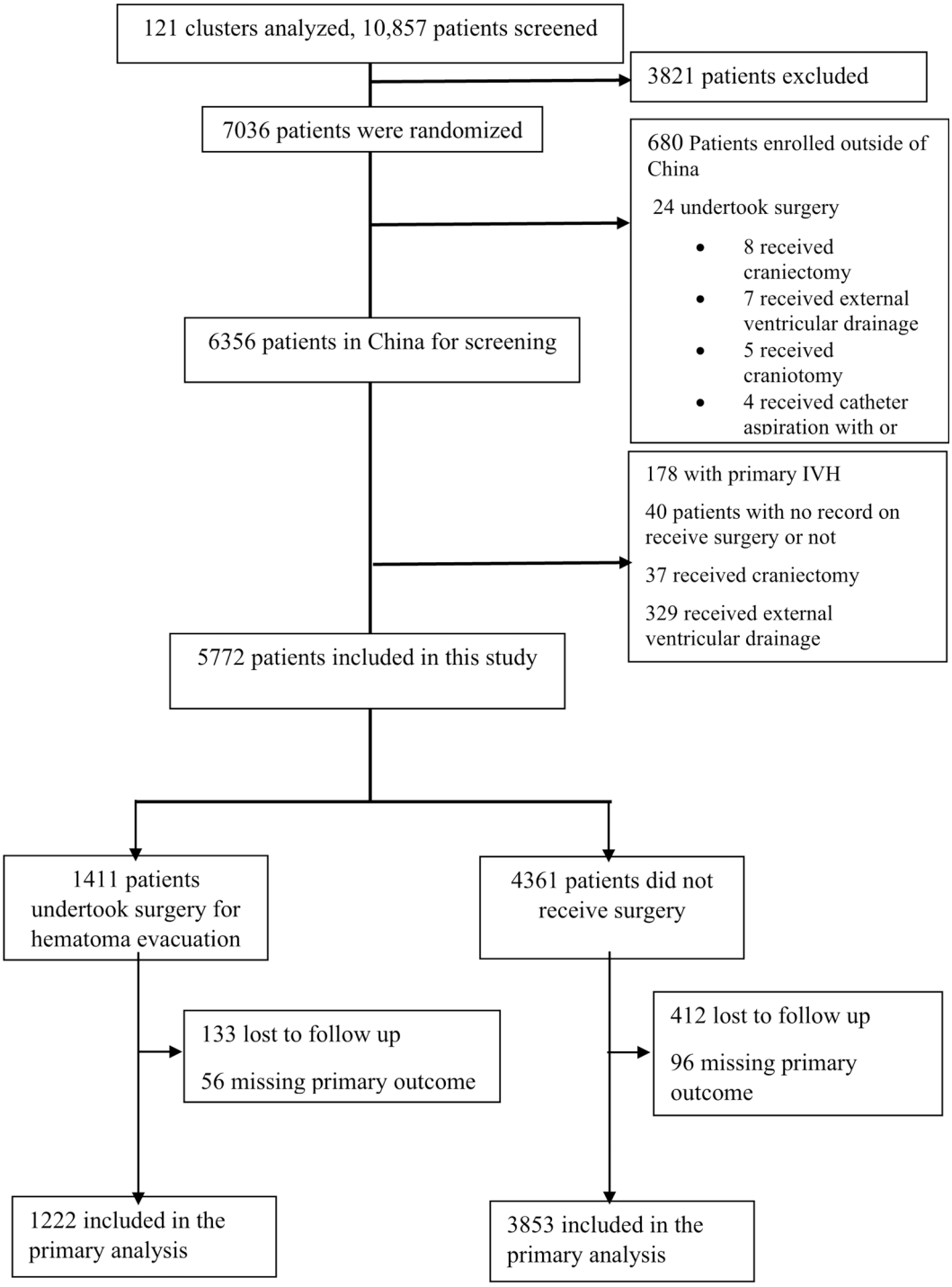

Fig. 1: **Patient flow**.

Discussion

Haematoma evacuation has long been a theoretically promising strategy for ICH, considering the decrease of mass effect as well as the cascade of secondary injury induced by clot-derived factors. This study aimed to define associations of surgery from haematoma evacuation and clinical outcomes in a broad range of patients with acute ICH who participated in the INTERACT3

Baseline characteristics	Overall N = 5772	Surgery N = 1411	No surgery N = 4361	p-value
Age (years)	62.0 (12.5)	58.8 (11.9)	63.1 (12.6)	<0.0001
Sex				
Male	3685 (63.8%)	936 (66.3%)	2749 (63.0%)	0.0249
Female	2087 (36.2%)	475 (33.7%)	1612 (37.0%)	
Medical history				
Hypertension	3984 (69.0%)	961 (68.1%)	3023 (69.3%)	0.3924
Previous stroke	883 (15.3%)	167 (11.8%)	716 (16.4%)	<0.0001
Coronary artery disease	157 (2.7%)	43 (3.0%)	114 (2.6%)	0.3843
Other heart disease	197 (3.4%)	41 (2.9%)	156 (3.6%)	0.2273
Atrial fibrillation	64 (1.1%)	11 (0.8%)	53 (1.2%)	0.1743
Diabetes mellitus	535 (9.3%)	131 (9.3%)	404 (9.3%)	0.9818
Hypercholesterolaemia	118 (2.0%)	26 (1.8%)	92 (2.1%)	0.5373
Current smoker	1169 (20.3%)	319 (22.6%)	850 (19.5%)	0.0113
Current alcohol consumption	1161 (20.1%)	316 (22.4%)	845 (19.4%)	0.0139
Modified Rankin scale score of 0 before onset	4434 (76.8%)	1127 (79.9%)	3307 (75.8%)	<0.0001
Medication at arrival				
Antihypertensive medication	2472 (42.8%)	563 (39.9%)	1909 (43.8%)	0.0106
Blood glucose lowering agents	371 (6.4%)	92 (6.5%)	279 (6.4%)	0.8704
Statin or other lipid lowering agent	119 (2.1%)	26 (1.8%)	93 (2.1%)	0.5054
Aspirin or other antiplatelet agent	277 (4.8%)	82 (5.8%)	195 (4.5%)	0.0407
Anticoagulation agent	43 (0.7%)	6 (0.4%)	37 (0.8%)	0.1081
Systolic Blood Pressure (mmHg)	173.5 (27.4)	175.6 (29.2)	172.9 (26.7)	0.0269
Diastolic Blood Pressure (mmHg)	98.8 (17.3)	99.6 (18.0)	98.5 (17.1)	0.3415
NIHSS at admission	13.0 (6.0, 22.0)	22.0 (14.0, 32.0)	11.0 (5.0, 18.0)	<0.0001
GCS score	12.0 (9.0, 14.0)	9.0 (6.0, 12.0)	13.0 (11.0, 15.0)	<0.0001
Randomised group, n (%)				
Intervention	2598 (45.0%)	631 (44.7%)	1967 (45.1%)	0.8009
Control	3174 (55.0%)	780 (55.3%)	2394 (54.9%)	
Brain imaging features				
Volume of haematoma at baseline	15.0 (8.0, 30.0)	39.0 (25.0, 50.0)	10.0 (5.7, 20.0)	<0.0001
Location of haematoma				
Deep, n (%)	4776 (82.8%)	1168 (82.9%)	3608 (82.8%)	0.9404
Cortical, n (%)	494 (8.6%)	180 (12.8%)	314 (7.2%)	<0.0001
Cerebellum, n (%)	302 (5.2%)	91 (6.5%)	211 (4.8%)	0.0180
Brainstem, n (%)	289 (5.0%)	17 (1.2%)	272 (6.2%)	<0.0001
Intraventricular haematoma, n (%)	1420 (24.6%)	468 (33.2%)	952 (21.8%)	<0.0001

Data are n (%), mean (SD), or median (IQR). BP, denoted blood pressure; GCS, Glasgow coma scale; NIHSS, National Institutes of Health stroke scale.

Table 1: **Baseline characteristics.**

study. The key finding of our study was that the surgery from haematoma evacuation of ICH was superior to the medical treatment in relation to the lower likelihood of death or major disability (mRS 5–6). This result was confirmed in propensity score matched and sensitivity analyses. Furthermore, we failed to detect the difference in outcomes by the timing of surgery or the approach for haematoma evacuation.

Neurosurgeons as well as patients or their caregivers were very active in ICH management in China, where haematoma evacuation were frequently chosen as a treatment strategy when needed. Only nine patients outside of China received haematoma evacuation in INTERACT3. Although including only patients from China in these analysis raises issues of selection bias, the large-scale, pragmatic, stepped-wedge, cluster randomised controlled design of INTERACT3 allowed data to be obtained that closely matches those of routine systems of care.

The large sample size with systematic assessment of clinical outcomes in INTERACT3 allow us to explore the controversial topic of the effects of surgery from haematoma evacuation in patients with spontaneous ICH. The first large-scale international multi-center, Surgical Trials in Intracerebral Haemorrhage (STICH) failed to show a benefit of early surgery in 1033 patients with supratentorial ICH, but a considerable number of them crossed over from medical treatment to surgery due to clinical deterioration.[9] On the basis of a small but clinically relevant survival advantage in the subgroup of patients with lobar ICH, the follow-up STICH II trial did not show a clear result to influence practice.[10] While

Hospital management	Overall N = 5772	Surgery N = 1411	No surgery N = 4361	p-value
Surgical procedure time from hospital arrival				
Same day		977 (69.3%)		
2nd day		336 (23.9%)		
More than 2 days		96 (6.8%)		
Surgical procedure type				
Craniotomy		1025 (72.6%)		
Endoscopy		68 (4.8%)		
Catheter aspiration with or without thrombolysis		318 (22.5%)		
Admission department to hospital, n (%)				
Neurosurgery	4707 (81.5%)	1086 (77.0%)	3621 (83.0%)	<0.0001
Neurology	324 (5.6%)	18 (1.3%)	306 (7.0%)	<0.0001
Intensive care	628 (10.9%)	279 (19.8%)	349 (8.0%)	<0.0001
Emergency department	23 (0.4%)	8 (0.6%)	15 (0.3%)	<0.0001
Others	90 (1.6%)	20 (1.4%)	70 (1.6%)	<0.0001
Treatment during the first 24 h				
BP lowering treatment, n (%)	4515 (78.2%)	1221 (86.5%)	3294 (75.5%)	<0.0001
Intensive treatment for glucose control, n (%)	371 (6.4%)	92 (6.5%)	279 (6.4%)	0.8704
Oral agents for glycaemic control, n (%)	302 (81.4%)	75 (81.5%)	227 (81.4%)	0.9728
Insulin treatment for glycaemic control, n (%)	89 (24.0%)	20 (21.7%)	69 (24.7%)	0.5600
Antipyrexia treatment, n (%)	448 (7.8%)	242 (17.2%)	206 (4.7%)	<0.0001
Management during 2–7 days				
Intravenous BP lowering, n (%)	3979 (68.9%)	1168 (82.8%)	2811 (64.5%)	<0.0001
Oral BP lowering, n (%)	3926 (68.0%)	807 (57.2%)	3119 (71.5%)	<0.0001
Insulin, n (%)	701 (12.1%)	264 (18.7%)	437 (10.0%)	<0.0001
Pyrexia treatment, n (%)	1160 (20.1%)	612 (43.4%)	548 (12.6%)	<0.0001
PCC administrated, n (%)	548 (9.5%)	219 (15.5%)	329 (7.5%)	<0.0001
Fresh frozen plasma, n (%)	143 (2.5%)	112 (7.9%)	31 (0.7%)	<0.0001
Vitamin K administrated, n (%)	234 (4.1%)	105 (7.4%)	129 (3.0%)	<0.0001
Mechanical ventilation, n (%)	1170 (20.3%)	911 (64.6%)	259 (5.9%)	<0.0001
Intensive care admission, n (%)	2099 (36.4%)	1051 (74.5%)	1048 (24.0%)	<0.0001
Assisted feeding, n (%)	2965 (51.4%)	1103 (78.2%)	1862 (42.7%)	<0.0001
Decision to withdraw active care, n (%)	30 (0.5%)	8 (0.6%)	22 (0.5%)	0.7766

Data are n (%), mean (SD), or median (IQR). BP, denotes blood pressure; FFP, fresh frozen plasma; ICU, intensive care unit; PCC, prothrombin complex concentrate.

Table 2: **Management of patients in the first 7 days.**

the ENRICH trial now provides evidence of a benefit of early MIS on functional outcome, this seems most relevant to lobar rather than the more common, deep ICH.[4] The SWITCH trial provided weak evidence that decompressive craniectomy without haematoma evacuation benefits patients with deep ICH,[5] but subgroup analysis of the third Minimally Invasive Surgery Trial in Intracranial Haemorrhage (MISTIE III) showed only a survival advantage rather than benefit to functional outcome from MIS combined with thrombolysis for deep ICH.[11] In our study, the majority of patients had deep ICH and received craniotomy. The high percentage of deep ICH receiving surgery reflected clinical work situation with proactive surgical intervention in China, despite guideline and ENRICH trial showed limited to no functional benefit. This discrepancy is partially driven by the high disease burden as well as the Chinese culture that life-saving is considered more valuable than the impact of residual severe disability. Previous guidelines provided recommendations based on the trials with functional outcome defined as mRS 0–2 or 0–3, which might ignore the potential acceptance of a mRS score of 4 by patients or caregivers. In the ENRICH trial, deep ICH were purposely excluded from further recruitment since they failed to meet a prespecified efficacy threshold in the interim analysis as part of an adaptive clinical trial design. Therefore, the size of the treatment effect in deep ICH, which is clearly less than in cortical ICH, is still worth exploring. Regarding the choice of surgery, it is mainly based on the neurosurgeon's preference and local protocol. The percentage of craniotomy was quite high, mainly because endoscopic haematoma evacuation was not widely adopted in China during the period of INTERACT3, between 2017 and 2021. It was not until the most recent 2022 AHA/ASA guideline recommendation that endoscopic haematoma evacuation was recommended as being useful to reduce mortality compared with medical management alone.[12] The innovation of instrument and mini-invasive techniques

Outcomes	Surgery	No surgery	Unadjusted[a]				Adjusted[b]				PSM[c]			
			N	OR (95% CI)	p-value	ICC	N	aOR (95% CI)	p-value	ICC	N	aOR (95% CI)	p-value	ICC
Primary outcome														
mRS 5–6	449/1222 (36.7%)	738/3853 (19.2%)	5075	2.60 (2.24–3.03)	<0.0001	0.025	4962	0.71 (0.55–0.92)	0.010	0.013	2126	0.74 (0.56–0.98)	0.034	0.027
Secondary outcomes														
mRS 4–6	695/1222 (56.9%)	1150/3853 (29.9%)	5075	3.34 (2.90–3.85)	<0.0001	0.026	4962	1.04 (0.82–1.33)	0.732	0.011	2126	1.06 (0.81–1.37)	0.671	0.030
Death at 6 months	243/1278 (19.0%)	436/3949 (11.0%)	5227	2.08 (1.73–2.50)	<0.0001	0.034	5108	0.55 (0.40–0.75)	0.0001	0.027	2214	0.52 (0.37–0.72)	0.0001	0.044

Note: aOR, denotes adjusted odds ratio; CI, confidence interval; ICC, intraclass correlation coefficient; mRS, modified Rankin Scale; OR, odds ratio. [a]Un-adjusted analysis: logistic regression for death/disability with a random effect for cluster (hospital site), a fixed effect indicating the group assignment of each cluster at each step, and a fixed categorical effect of 6-month interval. [b]Model adjusted baseline characteristics including mRS before stroke, age, sex, baseline NIHSS score, baseline haematoma volume, baseline systolic blood pressure, location of haematoma, intraventricular haemorrhage, previous history of stroke, current smoker and current alcohol user, and hospital management variables during including admission ward, BP lowering treatment (intravenous or oral), insulin treatment, antipyrexia treatment, anticoagulant reversal treatment (administrated PCC, FFP or VitK), Mechanical ventilation, and assist feeding. [c]Model adjusted for unbalanced baseline variables SD > 0.10 include baseline NIHSS score, baseline haematoma volume, presence of intraventricular haemorrhage and further hospital management variables including admission ward, BP lowering treatment (intravenous or oral), insulin treatment, antipyrexia treatment, anticoagulant reversal treatment (administrated PCC, FFP or VitK), Mechanical ventilation, and assist feeding.

Table 3: **Functional outcomes in 6 months follow-up.**

could gradually shift the neurosurgeon's preference and might potentially produce a greater benefit than open craniotomy.

We performed analysis in those participants with a haematoma volume ≥30 mL from a supratentorial ICH as this is a common indication for surgical intervention as well as an inclusion criteria for clinical trials. Our results affirm the potential benefits of surgery from haematoma evacuation through an association with a decreased odds of mRS 5–6 at 6 months. Several ongoing trials are evaluating the effects of surgery to evacuate the haematoma in supratentorial ICH, including the Early Minimally Invasive Image Guided Endoscopic Evacuation of Intracerebral Haemorrhage (EMINENT-ICH, NCT05681988), Ultra-Early, minimally invasive intracerebral haemorrhage evacuation vs. standard treatment (EVACUTATE, NCT04434807), and the Dutch ICH trial (DIST, NCT05460793).

The surgical approach for haematoma evacuation continues to evolve and the approaches of endoscopy, MIS, and catheter evacuation with thrombolysis, were used according to interventional preference but evaluated in several trials.[13,14] In one multicentre randomised controlled trial of 733 participants with supratentorial ICH, endoscopic surgery and stereotactic aspiration were found to be superior to craniotomy with a small bone flap, especially in deep ICH.[13] In the Big data Observatory Platform for Stroke of China, Li et al. analyzed data from 7451 patients who received surgery for ICH between 2019 and 2021 to show that cranial puncture was associated with a lower odds of poor functional outcome compared to craniotomy (OR 0.84, 95% CI 0.70–1.01).[15] In our study, where endoscopy and catheter aspiration with or without thrombolysis were combined as a MIS variable, we did not detect significant between-group difference in functional outcome at 6 months, which might be partially explained by the apparent imbalance of the sample size between both groups. Further trials are needed to explore the difference between approaches, especially those mini-invasive techniques.

There is insufficient data in relation to the time of surgery and outcome in ICH. The median time from the ictus to surgery were 26, 16.75 and 59 h (and 72 h to first dose of alteplase), in the STICH II, ENRICH, and MISTIE III trials, respectively.[4,10,11] Our finding of no significant time relation for surgery was limited by the use of day rather than hour as the dependent variable. A recent systematic review showed 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.[16] One of the concerns that hinders ultra-early evacuation was postoperative rebleeding. Recently, Ali et al. reported that ultra-early evacuation within 5 h of ictus utilizing a refined endoscopic technique is associated with increased intraoperative bleeding but not postoperative

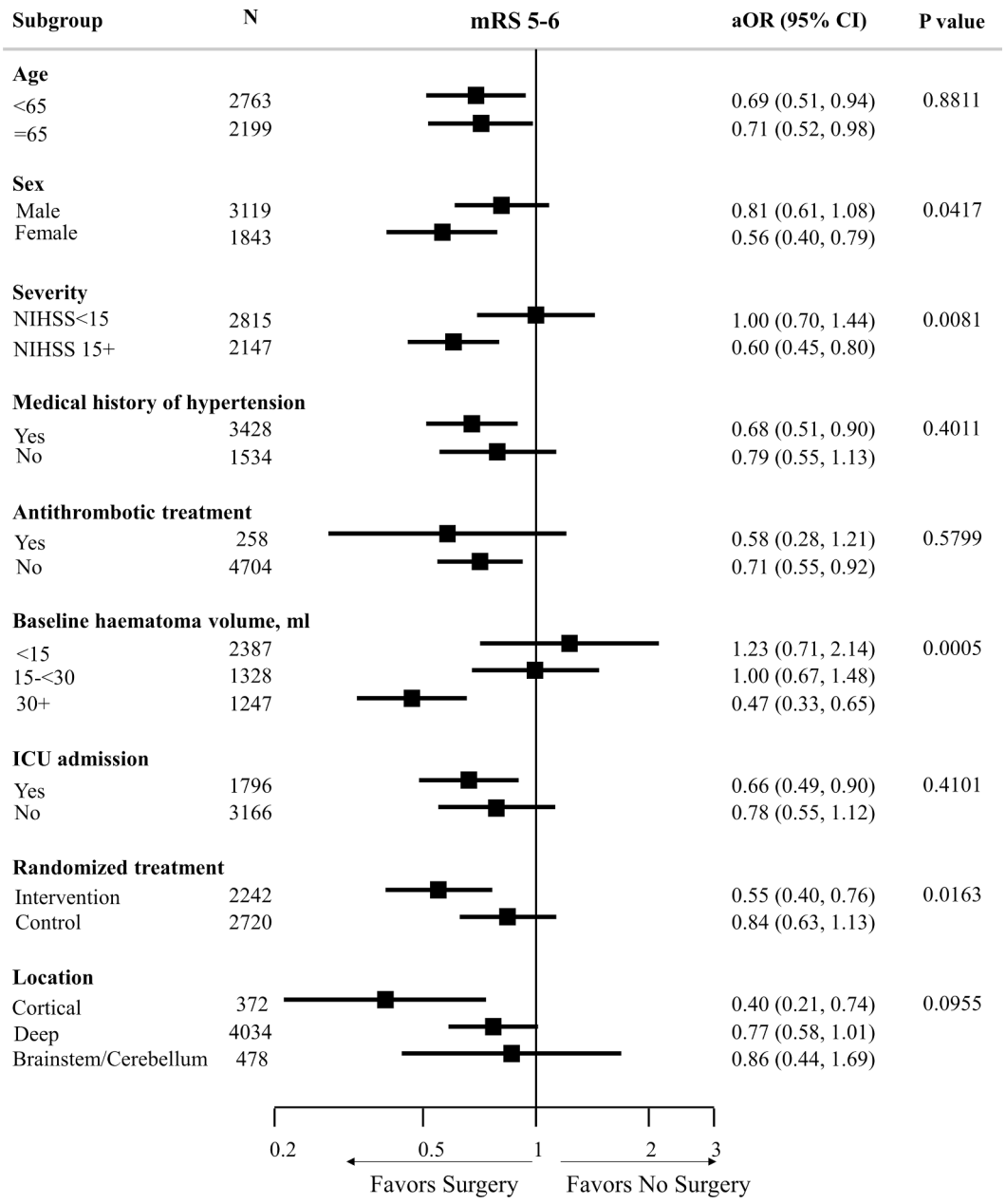

Fig. 2: **Subgroup analysis on primary outcome of mRS 5–6**. Note: Multivariable logistic regression model with a random effect for cluster (hospital site), a fixed effect indicating the group assignment of each cluster at each step, and a fixed categorical effect of 6-month interval, adjusted baseline characteristics variables characteristics: mRS before stroke, age, sex, baseline NIHSS score, baseline haematoma volume, baseline systolic blood pressure, location of haematoma, intraventricular haemorrhage, previous history of stroke, current smoker and current alcohol user, and hospital management variables during including admission ward, BP lowering treatment (intravenous or oral), insulin treatment, antipyrexia treatment, anticoagulant reversal treatment (administrated PCC, FFP or VitK), Mechanical ventilation, and assist feeding.

rebleeding or worse clinical outcomes, which could help to shorten the time window and explore the potential benefit of early surgical treatment for ICH.[17]

In line with the SWITCH trial and a pooled analysis of three clinical trials of decompressive surgery in malignant middle cerebral artery (MCA) infarction,[5,18] we chose to define a very poor functional outcome according to mRS scores 5–6, which differs from the more common use of mRS scores 3–6 or 4–6 in ICH trials. However, this cut point is important in

understanding that the potential benefit of surgery in reducing the chances of an extremely poor outcome, either death or having a bedridden level of disability, is offset by survivors having more severe disability (mRS 3–4). However, an analysis of 28 patients who received hemicraniectomy for malignant MCA infarction showed that surviving such a critical illness with an mRS 4 is acceptable to many patients and their relatives.[19] Moreover, 77% (48/62) of survivors in the SWITCH trial would choose to undergo surgery again in light of their experience.[5] Thus, a comparison of outcomes according to mRS scores 0–4 and 5–6 is reasonable for individualizing decisions over surgery in ICH.

Strengths of this study include the use of a large dataset from a broad range of patients with ICH, and the large proportion of patients with deep haematoma who received different types of surgery. This INTERACT3 cohort included 5722 patients at 82 secondary and tertiary hospitals, which could be representative of the proactive attitude towards surgical treatment for ICH in China, which is quite different from the routine clinical work in Western countries. Secondly, the cluster randomised design and the system of care intervention allowed the collection of routine data and avoided a large degree of selection bias. However, there are several limitations to the interpretation of our results. Firstly, we restricted the analysis in region of China, which might potentially influence the generalisability. However, the results could at least encourage future multicentre trials for haematoma evacuation in ICH treatment, especially for deep haematoma. Secondly, we did not standardise the surgical procedures, including the indications, instrument, trajectory, techniques, as well as length and times of the thrombolysis agent, which could bring potential heterogenicity in surgical performance and limit the adoption in routine clinical work. Future work exploring the effect of surgery in ICH should establish a standardisation of surgical protocols. Moreover, the competency of the neurosurgeon should also be taken into consideration. Thirdly, due to lack of data on an explicit time of surgery from hospital admission, the impact of timing on surgery needs further exploration. Fourthly, there might be potential unmeasured confounding by indication as well as selection bias due to analysis of a trial dataset. Considering this is an observational cohort study with propensity methods conducted in a subgroup of the matched participants, the result on surgery effect might not be generalizable to patients with different characteristics. Lastly, caution is required in the interpretation of subgroup analysis when the reduced sample size reduces the precision of results.

In summary, our study showed that the surgical treatment from haematoma evacuation of ICH is associated with a higher likelihood of survival and avoidance of a bedridden level of disability. Further clinical trials are necessary to allow for a better selection of surgical strategy for ICH, most notably in relation to the time, approach to treatment as well as deep ICH.

Contributors

Concept and design: CY, LS, CSA, JX. Acquisition, analysis or interpretation of data: XH, MO, LM, YL, XL, YJ, XC. Drafting the manuscript: XH, MO, LS, CSA. Critical review of the manuscript for important intellectual content: all authors. Raw data access: QL, MO. Data verification: QL, MO. Statistical analysis: MO. Funding: CY, LS, CSA. Administrative, technical, or material support: XH, MO, LM, YL, XL, YJ, XC. Supervision: CY, LS, CSA, JX. Final decision for submission: CSA.

Data sharing statement

Individual, de-identified participant data used in these analyses can be shared on request from any qualified investigator after the approval of a protocol and signed data access agreement via both the trial steering committee and the research office of The George Institute for Global Health, Sydney, Australia).

Declaration of interests

LS reports funding from the Medical Research Council of the UK, Sichuan Credit Pharmaceutic, and Takeda China; and speaker fees from Takeda China. CSA has received grants from the National Health and Medical Research Council of Australia, the Medical Research Council of the UK, and Takeda China. He is also the chair of the data and safety monitoring boards for several investigator-initiated trials, President-elect of the World Stroke Organisation; and Editor-in-Chief of Cerebrovascular Diseases. CY has received funding from West China Hospital. All other authors declare no competing interests. PMV receives research grants from ANID Fondecyt Regular 1221837, Pfizer and Boehringer Ingelheim.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2025.101669.

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