Countway Systematic Review Protocol

Hematoma Location as an Effect Modifier of Surgical Evacuation in Spontaneous Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Introduction

Title of Your Review

Hematoma Location as an Effect Modifier of Surgical Evacuation in Spontaneous Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Authors & Roles

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- Mohsen Mazen Alqawasma, Hebron University, Faculty of Medicine — mhusenmazen@gmail.com — second independent reviewer for study screening, data extraction, and risk-of-bias assessment, contributing to the resolution of disagreements and manuscript development.

Support

This review received no external funding, and no funder or sponsor had any role in the design, conduct, or reporting of this study.

Background

Review Rationale

Spontaneous intracerebral hemorrhage (ICH) is the deadliest subtype of stroke, with 30-day mortality approaching 40% and the majority of survivors left with significant disability (Sheth, 2022). Surgical evacuation of the hematoma has long been proposed as a means of reducing mass effect and secondary brain injury, yet the two largest randomized trials of conventional craniotomy — STICH and STICH-2 — failed to demonstrate a clear overall functional benefit over medical management (Mendelow et al., 2005; Mendelow et al., 2013). A post-hoc subgroup analysis of STICH suggested that patients with superficial, lobar hematomas might benefit from surgery, while deep hematomas showed no such signal; this observation directly motivated the design of STICH-2, which restricted enrollment to lobar ICH.

The subsequent generation of minimally invasive surgery (MIS) trials has revived this question without resolving it. MISTIE III found no overall functional benefit of catheter-based evacuation with thrombolysis, though greater hematoma clearance correlated with better outcomes (Hanley et al., 2019). ENRICH demonstrated an overall functional benefit of early MIS evacuation, but this benefit was concentrated in lobar hemorrhages, with a Bayesian adaptive design stopping enrollment for futility in the deep-hemorrhage stratum after only 48 patients (Pradilla et al., 2024). The MIND trial, published in 2025, found no significant overall benefit of endoscopic evacuation over medical management (Arthur et al., 2025). Across this literature, hematoma location — deep versus lobar — recurs as a plausible effect modifier, consistent with the distinct underlying pathophysiology of the two subtypes: deep ICH is predominantly attributable to hypertensive small-vessel arteriopathy, while lobar ICH is frequently associated with cerebral amyloid angiopathy (CAA), a pathology with different vessel fragility and recurrence risk (Charidimou et al., 2022).

A 2025 systematic review and meta-analysis (Al-Salihi et al., 2025, Medicina) pooled 13 studies of MIS versus medical management and reported a pre-specified subgroup analysis by location: pooled mixed-location studies showed a significant functional benefit of MIS, while deep-only studies did not, though no formal statistical test for subgroup interaction was reported. This analysis, while the most contemporary of its kind, excluded conventional craniotomy trials — including STICH-2, the only randomized trial to enroll a purely lobar population — and therefore could not fully characterize the deep-versus-lobar contrast. Notably, this general approach has precedent dating to the original STICH-2 protocol (Gregson et al., 2011), which included an exploratory pooled analysis of lobar hematoma outcomes across the surgical trials available at the time; that analysis has not been updated to incorporate the modern generation of randomized surgical trials published since 2013, including trials of minimally invasive evacuation such as MISTIE III, ENRICH, and MIND, as well as other contemporary studies relevant to the broader surgical evidence base.

To our knowledge, no contemporary systematic review and meta-analysis has comprehensively incorporated both conventional craniotomy and minimally invasive surgical evacuation trials to formally evaluate hematoma location as an effect modifier of the surgery-versus-medical-management effect across the modern randomized evidence base. Existing evidence has largely relied on separate location-specific analyses or subgroup comparisons, which do not necessarily establish a statistically significant difference in treatment effects between locations. An updated synthesis is therefore needed to distinguish within-trial evidence of treatment-by-location interaction from more indirect between-trial comparisons. This review will address this gap by systematically synthesizing randomized evidence and formally evaluating whether the effect of surgical evacuation, compared with medical management, differs between deep and lobar intracerebral hemorrhage. A systematic review and meta-analysis method was chosen because a body of randomized trials with quantifiable functional and mortality outcomes is available; however, the strength of evidence for effect modification will be interpreted according to whether location-specific treatment effects are derived within the same trial or indirectly across different trials.

Selected references:

Sheth, K. N. (2022). Spontaneous intracerebral hemorrhage. New England Journal of Medicine, 387, 1589–1596. https://doi.org/10.1056/NEJMra2201449

Mendelow, A. D., Gregson, B. A., Fernandes, H. M., et al. (2005). Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas (STICH): A randomised trial. Lancet, 365, 387–397. https://doi.org/10.1016/S0140-6736(05)70233-6

Mendelow, A. D., Gregson, B. A., Rowan, E. N., et al. (2013). Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): A randomised trial. Lancet, 382, 397–408. https://doi.org/10.1016/S0140-6736(13)60986-1

Hanley, D. F., Thompson, R. E., Rosenblum, M., et al. (2019). Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): A randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet, 393, 1021–1032. https://doi.org/10.1016/S0140-6736(19)30195-3

Pradilla, G., Ratcliff, J. J., Hall, A. J., et al. (2024). Trial of early minimally invasive removal of intracerebral hemorrhage. New England Journal of Medicine, 390, 1277–1289. https://doi.org/10.1056/NEJMoa2308440

Arthur, A. S., Jahromi, B. S., Saphier, P. S., et al. (2025). Minimally invasive surgery vs medical management alone for intracerebral hemorrhage: The MIND randomized clinical trial. JAMA Neurology, 82, 1113–1121. https://doi.org/10.1001/jamaneurol.2025.3151

Al-Salihi, M. M., Al-Jebur, M. S., Saha, R., et al. (2025). Minimally invasive surgery versus medical management for spontaneous supratentorial intracerebral hemorrhage: An updated systematic review and meta-analysis of randomized and propensity score–matched studies. Medicina, 61, 2216. https://doi.org/10.3390/medicina61122216

Gregson, B. A., Rowan, E. N., Mitchell, P., et al. (2011). Surgical trial in lobar intracerebral haemorrhage (STICH II) protocol. Trials, 12, 124. https://doi.org/10.1186/1745-6215-12-124

Charidimou, A., Boulouis, G., Frosch, M. P., et al. (2022). The Boston criteria version 2.0 for cerebral amyloid angiopathy: A multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurology, 21, 714–725. https://doi.org/10.1016/S1474-4422(22)00208-3

Review Objectives

Primary research question (PICO with effect modifier): Among adults with spontaneous supratentorial intracerebral hemorrhage [P], does hematoma location — deep versus lobar [effect modifier] — modify the effect of surgical hematoma evacuation [I], compared with best medical or conservative management [C], on functional outcome and mortality [O]?

A PICO framework augmented with an explicit effect-modifier term is used because the central objective of this review is not solely to estimate the overall effect of surgery, but to evaluate whether the magnitude of the treatment effect differs according to hematoma location. The primary assessment of effect modification will prioritize within-trial location-specific treatment comparisons where available. Comparisons of pooled treatment effects derived from separate location-specific trials will be considered indirect evidence and interpreted with appropriate caution (see Methods for Synthesis).

Methods

This review will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019) and reported according to PRISMA 2020 (Page et al., 2021) and, for meta-analyses of effect modification, guidance on subgroup and interaction analysis in Deeks, Higgins & Altman (Cochrane Handbook, Chapter 10). Any deviations from the methods proposed here will be documented and the protocol updated accordingly, with the date and nature of the amendment recorded.

Higgins, J. P. T., Thomas, J., Chandler, J., et al. (Eds.). (2019). Cochrane Handbook for Systematic Reviews of Interventions (1st ed.). Wiley.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71

Eligibility Criteria — Study Types and Characteristics

Study types: Randomized controlled trials (RCTs) comparing surgical hematoma evacuation with best medical or conservative management will be included. Non-randomized studies, including retrospective and prospective observational studies and propensity-score–matched analyses, will be excluded. Trials comparing two or more active surgical techniques without a medical-management-only arm (e.g., MISICH, MISTICH) will be excluded from the primary surgery-versus-medical-management analysis; such trials may be considered separately in exploratory procedure-type analyses, provided the relevant randomized comparisons and location-specific outcome data are available. Systematic reviews and meta-analyses will not be included in the primary synthesis, but their reference lists will be screened for potentially eligible primary trials.

No date restriction will be applied. Only studies published in English will be included due to resource constraints of the research team; this is a methodological limitation, as it may exclude relevant non-English trials, and will be stated explicitly in the final review's limitations section.

Eligible Population(s)

Adults (≥18 years) with spontaneous, non-traumatic supratentorial intracerebral hemorrhage will be eligible. Hemorrhage secondary to trauma, aneurysm rupture, arteriovenous malformation, tumor, or hemorrhagic transformation of ischemic stroke will be excluded where these populations can be distinguished. Infratentorial hemorrhage, including cerebellar and brainstem hemorrhage, will be excluded because its surgical indications and clinical management differ substantially from those of supratentorial ICH and are not the subject of the deep-versus-lobar location question addressed here.

Studies will be eligible regardless of baseline hematoma volume, neurological severity, presence of intraventricular hemorrhage, or premorbid functional status, provided that they otherwise meet the prespecified intervention and comparator criteria. Trials including mixed populations will be included

only when data for eligible participants can be separated, or when the ineligible population constitutes a negligible component of the randomized cohort and does not materially affect interpretation.

Independent Variable (Intervention) and Effect Modifier

Intervention: Surgical hematoma evacuation, including conventional open craniotomy; minimally invasive catheter-based evacuation with or without adjunctive thrombolytic agents; stereotactic aspiration; endoscopic evacuation; and other image-guided or robot-assisted techniques designed primarily to remove the hematoma. Decompressive craniectomy performed without attempted hematoma evacuation will be excluded, because its principal therapeutic target is intracranial pressure and mass effect rather than clot removal. Trials involving combined procedures will be eligible only when hematoma evacuation represents the principal randomized intervention.

Effect modifier of interest: hematoma location, categorized as deep or lobar.

- Deep ICH: hemorrhages located in the basal ganglia, putamen, globus pallidus, thalamus, or other deep supratentorial structures, as classified by the original trial.
- Lobar ICH: hemorrhages centered within the cerebral lobes (frontal, temporal, parietal, or occipital), as classified by the original trial.

Because anatomical terminology varies across trials, each trial's original classification will be recorded verbatim and mapped to the prespecified deep or lobar category where anatomically appropriate; the mapping decision will be recorded per trial. The terms “superficial” and “lobar” will not automatically be treated as synonymous — “superficial” (as used in STICH, defined as ≤ 1 cm from the cortical surface) is not anatomically identical to lobar ICH, since a superficial hemorrhage could in principle extend from a deep structure. STICH location-specific findings will therefore not automatically be mapped to the lobar category; the primary analysis will use only classifications that can be mapped reliably to the prespecified deep and lobar definitions. Where alternative reasonable mappings are possible (e.g., treating STICH's superficial subgroup as lobar), sensitivity analyses will explore their influence on the pooled estimates, without assuming that superficial hemorrhage is equivalent to lobar hemorrhage. Where a trial's classification cannot be reliably mapped to deep or lobar under any reasonable interpretation, those data will not be forced into either category and will be addressed separately.

Within-trial versus between-trial evidence: Trials enrolling only one location category (lobar-only or deep-only) may contribute to location-specific pooled estimates, but do not provide direct within-trial evidence of treatment-by-location interaction. The primary assessment of effect modification will therefore prioritize trials that include both deep and lobar ICH and report location-specific treatment effects; location-specific estimates obtained by comparing separate single-location trials are considered indirect, between-study evidence and will be interpreted cautiously, since observed differences may reflect trial-level characteristics in addition to hematoma location (see Methods for Synthesis).

Trials enrolling mixed populations but reporting only aggregate outcomes without location-specific treatment effects may contribute to the overall surgery-versus-medical-management analysis but will not contribute directly to the primary effect-modification analysis. No outcome-by-location data will be imputed solely from baseline location proportions. Study authors may be contacted for clarification or unavailable subgroup data where feasible.

Comparator

Best medical or conservative management without planned surgical hematoma evacuation. Medical management will be defined according to the care protocol of each individual trial and may include blood pressure management, reversal of anticoagulation or coagulopathy where appropriate, management of intracranial pressure, and standard neurocritical care. Trials in which the comparator consists exclusively of another surgical technique, without a medical-management-only arm, will not be eligible for the primary analysis.

Outcomes and Priorities

PRIMARY OUTCOME 1 — Functional outcome.

The proportion of participants achieving the trial-defined favorable functional outcome at the follow-up time point closest to 180 days will be the primary functional outcome. Where a 180-day assessment is unavailable, the nearest assessment between 90 and 180 days will be prioritized. The functional scale and dichotomization threshold used by each trial will be recorded. The primary meta-analysis will pool trial-defined favorable functional outcomes; because dichotomization thresholds may differ across trials (e.g., mRS 0–2 versus mRS 0–3), the exact definition used by each trial will be reported alongside the pooled estimate. Sensitivity analyses will then be conducted separately for mRS 0–2, mRS 0–3, and other outcome definitions, wherever at least two trials using a given definition are available. Where sufficient data are available, an analysis using a harmonized functional outcome definition will also be performed.

PRIMARY OUTCOME 2 — Long-term all-cause mortality.

All-cause mortality at the follow-up time point closest to 180 days.

SECONDARY OUTCOMES

- Early all-cause mortality at 30 days or the nearest reported early time point
- Rebleeding or hematoma re-expansion requiring reintervention
- Serious adverse events, as defined by the original trials; because definitions differ substantially across studies, adverse events will not be combined into a new composite outcome unless the component definitions are sufficiently comparable
- Intensive care unit length of stay
- Quality of life and activities-of-daily-living measures, including the Barthel Index or equivalent validated measures, where reported

All reported follow-up time points will be extracted to permit sensitivity analyses according to follow-up duration.

Methods

Information Sources

PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL),Scopus, and Web of Science will be searched from database inception to the search date, with no date restriction. Trial registries (ClinicalTrials.gov, WHO ICTRP) will be searched for completed-but-unpublished trials, and the reference lists of all included trials and topically relevant prior systematic reviews will be hand-searched.

Search Strategy

https://doi.org/10.5281/zenodo.22287144

Deliberately excluded from the search: location terms (e.g., “lobar,” “deep,” “basal ganglia”) will not be used as search or filter terms. Older trials frequently do not mention hematoma location in the title, abstract, or database indexing, so filtering on location at the search stage would risk excluding otherwise-eligible trials. Location eligibility will instead be determined during full-text screening and data extraction, once each trial's location breakdown can be assessed directly from the full text.

Data Management & Extractions

Zotero will be used for reference management and de-duplication. Rayyan (Ouzzani et al., 2016) will be used to support title and abstract screening and full-text screening. AI-assisted features, where available, may be used for workflow support or prioritization; however, all final screening decisions and eligibility determinations will be made independently by two human reviewers. Data extraction and risk-of-bias assessments will also be performed and verified by human reviewers. Search results will be screened by title and abstract, followed by full-text evaluation against the pre-specified eligibility criteria. Disagreements between reviewers will be resolved through discussion and consensus. If consensus cannot be reached, the disagreement will be documented and an independent methodological or clinical expert will be consulted where feasible.

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews*, 5, 210. https://doi.org/10.1186/s13643-016-0384-4

Data to be Extracted from Included Articles

1. Study identification: Study ID, authors, year of publication, country, trial registration number.

2. Study characteristics: Design, number of centers, enrollment period, sample size (total and per arm), funding source.

3. Participant characteristics: Mean age, sex distribution, baseline GCS, baseline hematoma volume, presence/absence of intraventricular hemorrhage, premorbid mRS.

4. Intervention details: Surgical technique, timing from onset to surgery, use of adjunctive thrombolytic, hematoma clearance rate where reported.

5. Comparator details: Description of medical management protocol.

6. Location data: Number of randomized participants in each treatment arm classified as deep, lobar, or other/unclassified; the anatomical definition used by the original trial; whether both location categories were represented within the same randomized trial; and whether treatment effects were reported separately by location.

7. Outcomes: For each primary and secondary outcome, event counts and total participants for dichotomous outcomes, or means and standard deviations for continuous outcomes, overall and separately by location where available. The exact follow-up time point, outcome definition, and whether the location-specific estimate represents a prespecified subgroup analysis will be recorded.

8. Risk of bias: Domain-level Cochrane RoB 2 judgments (see below).

9. Notes: Free-text field for extraction caveats, e.g., where location data required derivation from a supplementary appendix rather than the main text.

10. Effect-modification data: Availability of within-trial treatment-by-location interaction estimates, subgroup-difference tests, or sufficient data to calculate location-specific treatment effects.

Proposed Additional Analyses

The following pre-specified subgroup and sensitivity analyses are anticipated:

Procedure type and location. Because hematoma location and surgical procedure type may be correlated across the evidence base, procedure type will be examined as an important potential source of heterogeneity and confounding in the interpretation of location-specific effects. Where sufficient data are available, treatment effects will be explored across four categories: deep ICH–MIS, lobar ICH–MIS, deep ICH–conventional craniotomy, and lobar ICH–conventional craniotomy. These analyses will be considered exploratory and interpreted cautiously when individual categories contain few trials.

- Exploratory trial-level meta-regression using the proportion of participants with lobar ICH per trial, to be conducted only where a sufficient number of trials is available; this analysis will not be considered equivalent to direct within-trial evidence of treatment-by-location interaction, given its vulnerability to ecological bias
- Sensitivity analysis restricted to the contemporary trial era (published 2010 or later), given substantial advances in imaging-guided surgical technique over the study period
- Sensitivity analysis excluding trials judged at high overall risk of bias
- Sensitivity analysis by outcome-assessment time window (90 days vs. 180 days vs. longest available follow-up)

Risk of Bias

Risk of bias will be assessed in duplicate by two independent reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (Sterne et al., 2019), evaluating five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Domain-level judgments and supporting quotations

will be documented in full and verified between reviewers, with any disagreements resolved through consensus discussion or third-party arbitration.

Sterne, J. A. C., Savović, J., Page, M. J., et al. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*, 366, l4898. https://doi.org/10.1136/bmj.l4898

Problematic Studies

Before final inclusion and data synthesis, all included studies will be checked for retractions, expressions of concern, major corrections, or substantive post-publication correspondence that may affect trial validity or the interpretation of outcome data (including but not limited to the Retraction Watch Database, where accessible). Any relevant corrigendum or correction will be incorporated into the extracted data where appropriate. Studies with unresolved concerns regarding research integrity will be assessed individually, and their inclusion or exclusion will be justified transparently.

Unit-of-Analysis Issues

For trials with more than two eligible randomized groups, only comparisons relevant to surgical evacuation versus medical or conservative management will be included in the primary analysis. Where two eligible surgical intervention groups are compared with a single shared medical-management group and both surgical groups are included in the same meta-analysis, the shared comparator group will be divided appropriately to avoid double-counting participants, or the surgical groups will be combined where clinically and statistically appropriate. Trials comparing multiple active surgical techniques without a medical-management-only arm (e.g., MISICH) will not contribute to the primary analysis (see Study Types).

Missing Data

For dichotomous outcomes, analyses will use the number of participants randomized to each group as the preferred denominator, consistent with the intention-to-treat principle. The handling of missing outcome data in each trial will be recorded. Where outcome data are missing, no outcome values will be imputed solely to generate location-specific treatment effects. The potential impact of missing data will be considered in the RoB 2 assessment and, where appropriate, sensitivity analyses will explore the influence of assumptions regarding missing outcomes. Study authors may be contacted for clarification or additional published data where feasible.

Methods for Synthesis

For each primary outcome, a pairwise random-effects meta-analysis (restricted maximum likelihood [REML] as the primary model; fixed-effect and an alternative heterogeneity estimator as sensitivity

analyses, given REML's known limitations with a small number of studies) will be conducted separately within the deep-ICH stratum and the lobar-ICH stratum, comparing surgical evacuation with medical management. Risk ratio (RR) with 95% confidence intervals is pre-specified as the primary effect measure for dichotomous outcomes; odds ratios will be used only where RR cannot be calculated from the data reported (e.g., adjusted analyses reporting only OR), and this substitution will be flagged wherever it occurs, to avoid the appearance of having chosen the effect measure after seeing the results.

Effect-modification evidence will be explicitly stratified into two tiers of strength, rather than treated as a single undifferentiated analysis:

Primary within-trial interaction analysis. For each trial that includes both deep and lobar ICH and provides sufficient location-specific outcome data, a treatment-effect estimate will be calculated separately for deep and lobar participants. These location-specific estimates will be entered into a random-effects meta-analysis with hematoma location (deep vs. lobar) specified as a categorical moderator, and a formal subgroup-difference test will be used to assess whether the pooled treatment effect differs significantly between the two location strata. This subgroup-difference test, rather than a trial-level log-effect-difference model with covariance adjustment, is used as the primary assessment of effect modification, consistent with the capabilities of the meta-analysis software used for this review (jamovi MAJOR module / RevMan 5.4). Its result, with the corresponding effect estimates, 95% confidence intervals, and p-value for subgroup difference, will constitute the primary statistical assessment of whether hematoma location modifies the effect of surgical evacuation.

Secondary, between-study comparison. Pooling of lobar-only trials (e.g., STICH-2) against deep-only trials. This is a between-study, indirect comparison, and will be explicitly labeled as carrying a materially greater risk of confounding by trial-level factors — surgical era, procedure type, patient selection, and baseline severity — than the within-trial evidence above. A formal test for subgroup differences between these pooled estimates may also be performed, but will be reported and interpreted as a secondary, hypothesis-supporting analysis, not as equivalent evidence of interaction to the primary within-trial estimate.

Statistical heterogeneity will be quantified using I^2 and Cochran's Q. Analyses will be conducted using jamovi (MAJOR module) and/or RevMan 5.4. The certainty of evidence for the intervention effect within each location stratum will be assessed using standard GRADE (Guyatt et al., 2011). Grading the interaction (effect-modification) evidence itself is methodologically less standardized than grading a main effect; rather than forcing a conventional GRADE table onto the interaction estimate, the credibility of the location-interaction finding will be evaluated using established considerations for subgroup credibility (e.g., whether the interaction was pre-specified, its direction is biologically plausible, it is consistent within-trial rather than only between-study, and it is one of a small number of subgroup hypotheses tested).

Existing Meta-Biases

Potential reporting biases will be assessed by comparing published trial reports with prospectively registered protocols or trial registry records where available; discrepancies between prespecified and reported outcomes will be documented. Where at least 5 studies contribute to a comparable meta-analysis, funnel plots and statistical tests for small-study effects, such as Egger's regression test, may be

used, recognizing their limited power and interpretability when substantial heterogeneity is present. Differences between fixed-effect and random-effects estimates may be explored as part of sensitivity analyses but will not be interpreted independently as evidence of small-study or publication bias.

Registration and Protocol Amendments

This protocol will be registered in PROSPERO prior to completion of study selection, where eligible. Any amendments made after registration will be dated, described, and justified in both the registration record, where permitted, and the final review report.