INPLASY

Early microsurgical clipping as an alternative to delayed endovascular coiling for ruptured intracranial aneurysms in resource-limited settings where timely intervention is not feasible: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202640077

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 April 2026 and was last updated on 23 April 2026.

INTRODUCTION

Review question / Objective Primary objective:
To compare 6-month functional outcomes (modified Rankin Scale [mRS] 0-2) between early clipping (<24 or <48 hours) and delayed coiling (≥24 or ≥48 hours) for patients with ruptured intracranial aneurysms.
Secondary objectives:
1. To compare mortality rates (in-hospital, 30-day, 6-month, 1-year)
2. To compare rebleeding rates after initial treatment
3. To compare complete aneurysm occlusion rates (Raymond-Roy Class 1)
4. To compare procedure-related complications (cerebral infarction, symptomatic vasospasm, intraoperative rupture, hydrocephalus requiring shunt, seizure, retreatment)
5. To explore subgroup effects by aneurysm location, clinical severity, and presence of intracerebral hematoma.

Rationale Ruptured intracranial aneurysms (aSAH) account for approximately 5% of all strokes but carry a mortality rate of 40-50%, with rebleeding occurring in 4-14% of patients within the first 24 hours after symptom onset and associated with mortality exceeding 50-80%. Current international guidelines unanimously recommend prompt treatment of the ruptured aneurysm, ideally within 24 to 72 hours.

Two principal treatment modalities exist: microsurgical clipping and endovascular coiling. Landmark trials (ISAT, BRAT) established that coiling offers better functional outcomes at 1 year, though clipping provides higher complete obliteration and lower retreatment rates. However, these trials predominantly enrolled good-grade patients and excluded those with large intracerebral hematomas or poor clinical grades, limiting generalizability to real-world practice.

Beyond modality choice, treatment timing critically affects outcomes. Multiple studies demonstrate

that early treatment (within 24 hours) reduces rebleeding risk and may improve functional outcomes compared with delayed treatment. However, existing evidence primarily compares early versus delayed treatment within the same modality—early clipping vs. late clipping or early coiling vs. late coiling.

A critical evidence gap remains: In many healthcare institutions, particularly those without 24/7 access to neurointerventional suites, endovascular coiling cannot be performed within the recommended 24-hour window and is often unavoidably delayed beyond 24-48 hours. In such resource-limited settings, clinicians face a genuine dilemma: wait for delayed coiling (accepting ongoing rebleeding risks) or proceed with early clipping (accepting greater invasiveness of open surgery).

To date, no high-quality systematic review or meta-analysis has directly compared early clipping versus delayed coiling in this specific context. This knowledge gap prevents the development of evidence-based treatment algorithms for the substantial proportion of aSAH patients treated in institutions where timely endovascular services are not available. This systematic review and meta-analysis aims to address this gap and provide evidence-based guidance for clinicians facing this common clinical dilemma.

Condition being studied Aneurysmal subarachnoid hemorrhage (aSAH) is the condition being studied. aSAH occurs when an intracranial aneurysm ruptures, leading to bleeding into the subarachnoid space surrounding the brain. It accounts for approximately 5% of all strokes but carries a disproportionately high burden of mortality (40-50%) and long-term disability. The most critical modifiable risk factor for poor outcome is rebleeding, which occurs in 4-14% of patients within the first 24 hours after the initial hemorrhage and is associated with mortality rates exceeding 50-80%.

This systematic review focuses specifically on patients with acute aSAH caused by a ruptured saccular (berry) aneurysm, requiring urgent treatment to secure the aneurysm and prevent rebleeding. The study compares two treatment strategies: early microsurgical clipping versus delayed endovascular coiling.

Excluded conditions include unruptured intracranial aneurysms, traumatic aneurysms, mycotic (infectious) aneurysms, and dissecting aneurysms, as these have different pathophysiologies and treatment considerations.

METHODS

Search strategy Databases:

PubMed/MEDLINE

Embase

Cochrane Central Register of Controlled Trials (CENTRAL)

Web of Science

ClinicalTrials.gov (grey literature)

Search period: From database inception to December 31, 2025

PubMed search strategy:
(("intracranial aneurysm"[MeSH] OR "cerebral aneurysm"[tiab] OR "brain aneurysm"[tiab] OR "subarachnoid hemorrhage"[MeSH] OR "SAH"[tiab])
AND
("clipping"[tiab] OR "microsurgical clipping"[tiab] OR "open surgery"[tiab] OR "surgical clipping"[tiab])
AND
("coiling"[tiab] OR "endovascular coiling"[tiab] OR "endovascular treatment"[tiab] OR "endovascular therapy"[tiab])
AND
("early"[tiab] OR "ultra-early"[tiab] OR "time-to-treatment"[tiab] OR "timing"[tiab] OR "delayed"[tiab] OR "late"[tiab])).

Participant or population Population: Patients with radiologically confirmed ruptured intracranial aneurysms.

Inclusion criteria:

1. Confirmed diagnosis of ruptured intracranial aneurysm by digital subtraction angiography (DSA), computed tomography angiography (CTA), or magnetic resonance angiography (MRA)

2. Acute aneurysmal subarachnoid hemorrhage (aSAH) requiring urgent treatment

3. Age ≥18 years (no upper age limit)

4. All aneurysm locations: anterior circulation (including middle cerebral artery [MCA], anterior cerebral artery [ACA], anterior communicating

artery [ACom], posterior communicating artery [PCom]), posterior circulation (including basilar artery, vertebral artery, posterior inferior cerebellar artery [PICA])

5. All clinical severity grades: Hunt-Hess grade I-V and World Federation of Neurosurgical Societies (WFNS) grade I-V

6. All Fisher grades (amount and distribution of subarachnoid blood)

7. Both sexes

Exclusion criteria:

1. Unruptured intracranial aneurysms

2. Traumatic aneurysms

3. Mycotic (infectious) aneurysms

4. Dissecting aneurysms

5. Fusiform aneurysms

6. Pediatric population (age <18 years)

7. Pregnant patients (if specifically excluded by original studies, but no a-priori exclusion)

No restrictions will be applied based on race, ethnicity, socioeconomic status, or geographic location.

Intervention Intervention: Early microsurgical clipping for ruptured intracranial aneurysms.

Definition of "early":
- Primary definition: Treatment performed <24 hours after symptom onset (ictus)
- Secondary definition (if primary definition data are insufficient): Treatment performed <48 hours after symptom onset
- The specific definition used by each original study will be recorded and subgroup analysis will be performed based on the definition (<24h vs. 48 hours after ictus (unless clearly defined as "early" by the original study with a different threshold)
3. Hybrid procedures (e.g., clipping + coiling, clipping + bypass, clipping + stent)
4. Clipping performed after failed endovascular treatment (salvage clipping)

Rationale for this intervention:
- Early clipping provides immediate and definitive protection against rebleeding
- Allows simultaneous evacuation of intracerebral hematoma if present
- Particularly suitable for middle cerebral artery (MCA) aneurysms and aneurysms with complex morphology
- Does not require antiplatelet agents (unlike stent-assisted coiling)
- Definitive treatment with low retreatment rates

Variations that will be accepted:
- Different surgical approaches (pterional, lateral supraorbital, mini-pterional, keyhole)
- Different clip types (titanium, cobalt alloy, permanent, temporary)
- Use of intraoperative adjuncts (indocyanine green videoangiography, intraoperative angiography, neurophysiological monitoring)
- Different levels of surgeon experience (as long as procedure is performed by a qualified neurosurgeon)

Variations that will NOT be accepted:
- Clipping combined with other endovascular treatments in the same session
- Clipping for aneurysms that have been previously coiled (salvage clipping - different clinical context)
- Clipping without clear documentation of treatment time.

Comparator Included: RCTs, prospective/retrospective cohorts, case-control studies. Excluded: case reports/series (n<10), reviews, meta-analyses, conference abstracts, animal/in vitro, cross-sectional, single-arm, mixed ruptured/unruptured (if inseparable). Few/no RCTs expected (ethical concerns). Language: English. Time: inception-Dec 31, 2025. Min sample: ≥10/arm for observational studies.

Study designs to be included Included: RCTs, prospective/retrospective cohorts, case-control studies. Excluded: case reports/series (n<10), reviews, meta-analyses, conference abstracts, animal/in vitro, cross-sectional, single-arm, mixed ruptured/unruptured (if inseparable). Few/no RCTs expected (ethical concerns). Language: English. Time: inception-Dec 31, 2025. Min sample: ≥10/arm for observational studies.

Eligibility criteria Inclusion: Ruptured intracranial aneurysms (imaging-confirmed); early clipping (<24/48h); delayed coiling (≥24/48h); outcomes include 6-month mRS; study designs: RCTs, cohorts, case-control.

Exclusion: Unruptured/traumatic/mycotic/dissecting aneurysms; stent-assisted coiling/flow

diversion; unclear timing; no outcome data; case series (n<10); reviews; non-English.

Information sources PubMed, Embase, Cochrane CENTRAL, Web of Science, ClinicalTrials.gov. Search period: database inception to December 31, 2025. Additional sources: reference lists of included studies (hand searching). No restrictions on geographic region.

Main outcome(s) Primary outcome: Favorable functional outcome at 6 months, defined as modified Rankin Scale (mRS) score of 0-2. Where mRS is unavailable, Glasgow Outcome Scale (GOS) score of 4-5 will be used as a proxy.

Secondary outcomes: (1) Mortality (in-hospital, 30-day, 6-month, 1-year); (2) Rebleeding rate; (3) Complete aneurysm occlusion rate (Raymond-Roy Class 1); (4) Complications: cerebral infarction, symptomatic vasospasm, intraoperative rupture, hydrocephalus requiring shunt, seizure, retreatment rate.

Additional outcome(s) No additional outcomes beyond the primary and secondary outcomes specified in the "Main outcome(s)" section. All outcomes of interest have been categorized as either primary (6-month functional outcome) or secondary (mortality, rebleeding, complete occlusion, and complications).

The secondary outcomes listed in the "Main outcome(s)" section represent the complete set of outcomes that will be extracted and analyzed in this systematic review. These include:

1. Mortality (in-hospital, 30-day, 6-month, 1-year)
2. Rebleeding rate
3. Complete aneurysm occlusion rate (Raymond-Roy Class 1)
4. Procedure-related complications (cerebral infarction, symptomatic vasospasm, intraoperative rupture, hydrocephalus requiring shunt, seizure, intracranial infection, retreatment rate)

No other outcomes (e.g., quality of life measures, cognitive function, angiographic recurrence beyond initial occlusion, cost-effectiveness, length of hospital stay) will be systematically extracted or analyzed, as these are either inconsistently reported across studies or fall outside the scope of this review's primary research question.

Data management Data management will follow standard systematic review procedures.

Screening and selection:

All search results will be exported to EndNote X9 for duplicate removal. Two independent reviewers will screen titles and abstracts against eligibility criteria using Rayyan (a web-based systematic review screening tool). Full texts of potentially eligible studies will be retrieved and independently assessed by two reviewers. Disagreements will be resolved through discussion or by consulting a third reviewer. The screening process will be documented in a PRISMA flow diagram.

Data extraction:

Two independent reviewers will extract data using a standardized, pilot-tested Excel extraction form. Extracted variables include study characteristics (author, year, country, design, sample size), patient characteristics (age, sex, aneurysm location, Hunt-Hess grade, Fisher grade, intracerebral hematoma), intervention/comparator details (treatment timing definitions, actual treatment times), and outcome data (mRS, mortality, rebleeding, occlusion, complications).

Data storage:

All extracted data will be stored in password-protected Excel files on a secure institutional server. Data will be backed up weekly to an encrypted external drive. Only the research team will have access.

Data sharing:

Upon publication, the complete data extraction form and analysis code will be made available as supplementary materials or upon reasonable request to the corresponding author.

Quality control:

A third reviewer will randomly check 20% of extracted data for accuracy. Discrepancies will trigger a full review of all extractions by the third reviewer.

Quality assessment / Risk of bias analysis Two independent reviewers will assess the risk of bias for each included study using standardized tools based on study design:

Randomized controlled trials (RCTs):

Cochrane Risk of Bias 2.0 (RoB 2) tool will be used, assessing five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the

outcome, and selection of reported results. Each domain will be rated as "low risk," "some concerns," or "high risk." An overall risk of bias judgment will be assigned to each study.

Non-randomized studies (cohort studies):

ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool will be used, assessing seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Each domain will be rated as "low," "moderate," "serious," or "critical" risk of bias.

Case-control studies:

Newcastle-Ottawa Scale (NOS) will be used, assessing three categories: selection (0-4 points), comparability (0-2 points), and exposure (0-3 points). Studies scoring ≥7 will be considered low risk of bias.

Handling disagreements:

Disagreements between reviewers will be resolved through discussion. If consensus cannot be reached, a third reviewer will make the final decision.

Reporting:

Risk of bias assessment results will be presented in summary tables and figures (using robvis). Studies rated as "critical" (ROBINS-I) or "high" (RoB 2) will be included but will be considered in sensitivity analyses.

Strategy of data synthesis Effect measures:

For binary outcomes (mortality, favorable functional outcome, rebleeding, complete occlusion, complications), pooled odds ratios (ORs) with 95% confidence intervals (CIs) will be calculated. For continuous outcomes (e.g., length of hospital stay, ICU stay), mean differences (MDs) with 95% CIs will be calculated. A two-tailed significance level of $\alpha = 0.05$ will be used for all analyses.

Pooling model:

Due to anticipated clinical and methodological heterogeneity across studies (variations in patient populations, treatment timing definitions, outcome assessment methods), the DerSimonian-Laird random-effects model will be used a priori for all meta-analyses.

Heterogeneity assessment:

Statistical heterogeneity will be quantified using the I^2 statistic, where I^2 75% high heterogeneity. The Cochran's Q test will also be performed, with p 75%), the pooled result will be interpreted with caution, and potential sources of heterogeneity will be explored through subgroup and sensitivity analyses.

Subgroup analyses (data permitting):

1. Aneurysm location: anterior circulation vs. posterior circulation; middle cerebral artery (MCA) vs. other locations
2. Clinical severity: Hunt-Hess grade I-III (good) vs. IV-V (poor)
3. Early definition: <24 hours vs. <48 hours
4. Study design: randomized controlled trials vs. observational studies
5. Intracerebral hematoma: present vs. absent

Subgroup differences will be assessed using meta-regression or interaction tests, with $p < 0.10$ considered significant.

Sensitivity analyses:

1. Leave-one-out analysis: sequential removal of individual studies to assess the influence of each study on the pooled estimate
2. Low-risk bias analysis: restricting analysis to studies with low or moderate overall risk of bias (excluding studies rated as "critical" by ROBINS-I or "high risk" by RoB 2)
3. Fixed-effect model: repeating the analysis using a fixed-effect model to assess the robustness of random-effects results

Publication bias:

If ≥10 studies are included in a meta-analysis, funnel plot asymmetry will be visually inspected. Egger's linear regression test will be performed to statistically assess publication bias ($p < 0.05$ indicates significant asymmetry).

Software:

All statistical analyses will be performed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, Oxford, UK) or R software (meta package, R Foundation for Statistical Computing, Vienna, Austria).

Narrative synthesis:

If meta-analysis is not feasible due to insufficient data or excessive heterogeneity, results will be presented as a narrative synthesis, summarizing findings by study characteristics and outcome categories.

Subgroup analysis The following subgroup analyses will be performed if sufficient data are available (defined as at least 3 studies per subgroup):

1. Aneurysm location:
- Anterior circulation vs. posterior circulation
- Middle cerebral artery (MCA) vs. other locations
Rationale: Anatomical differences may influence treatment outcomes, as MCA aneurysms are often considered more favorable for clipping, while posterior circulation aneurysms may be better suited for coiling.

2. Clinical severity:
- Good grade (Hunt-Hess I-III) vs. poor grade (Hunt-Hess IV-V)
Rationale: Poor-grade patients have higher mortality and complication rates, and the treatment effect may differ between these populations.

3. Definition of "early" treatment:
- <24 hours vs. <48 hours
Rationale: Different studies use different thresholds for "early" treatment; this analysis will assess whether the treatment effect varies by timing definition.

4. Study design:
- Randomized controlled trials vs. observational studies
Rationale: Observational studies are more susceptible to bias; this analysis will assess the impact of study design on effect estimates.

5. Presence of intracerebral hematoma:
- Present vs. absent
Rationale: Patients with intracerebral hematoma may benefit more from early clipping, which allows simultaneous hematoma evacuation.

Statistical methods for subgroup analysis:

- Subgroup differences will be assessed using meta-regression (for categorical variables) or interaction tests (Borenstein method)
- A p-value < 0.10 will be considered statistically significant for subgroup differences
- Results will be presented in forest plots with subgroups shown separately

Limitations:

Subgroup analyses are exploratory by nature. Results will be interpreted with caution, and the risk of false-positive findings (type I error) due to multiple comparisons will be acknowledged as a limitation in the final report. If data are insufficient for any planned subgroup analysis, it will be omitted and reported as such.

Sensitivity analysis The following sensitivity analyses will be performed to assess the robustness of the pooled results:

1. Leave-one-out analysis:
Sequential removal of each individual study, followed by recalculation of the pooled effect estimate. This will assess whether any single study disproportionately influences the overall result.

2. Low-risk bias analysis:
Restricting the analysis to studies with low or moderate overall risk of bias (excluding studies rated as "critical" by ROBINS-I or "high risk" by Cochrane RoB 2). This will assess the impact of including poor-quality studies on the pooled estimate.

3. Fixed-effect model:
Repeating the analysis using a fixed-effect model (inverse variance method) instead of the primary random-effects model. This will assess whether the choice of pooling model affects the conclusions.

4. Publication status (if feasible):
Comparing results from published studies versus unpublished studies (e.g., from ClinicalTrials.gov) to assess potential publication bias.

Interpretation of sensitivity analyses:

If the direction or statistical significance of the pooled effect estimate remains consistent across all sensitivity analyses, the results will be considered robust. If substantial changes are observed, this will be reported as a limitation, and the findings will be interpreted with caution.

Reporting:

Results of sensitivity analyses will be presented in summary tables or forest plots, as appropriate.

Language restriction English. Only studies published in English will be included due to resource constraints for translation.

Country(ies) involved No restrictions. Studies from any country will be considered for inclusion.

Other relevant information 1. PROSPERO registration: This protocol has been submitted for registration in PROSPERO (submission pending). The registration number will be provided upon acceptance. Due to PROSPERO's current processing delays (over 47,000 annual submissions with limited administrative capacity), INPLASY registration was chosen as an alternative to ensure timely protocol registration.

2. Deviations from protocol: Any significant deviations from this protocol will be documented in the final systematic review report, including the reason for deviation and the stage at which it occurred.

3. Updates: If this protocol is updated (e.g., changes to search strategy, eligibility criteria, or analysis methods), the updated version will be submitted to INPLASY with a new version number and date. Previous versions will remain publicly available.

4. Dissemination: Results will be submitted for publication in a peer-reviewed journal (target: World Neurosurgery) and presented at relevant scientific conferences (e.g., Congress of Neurological Surgeons, Asian Congress of Neurological Surgeons).

5. Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

6. Conflicts of interest: The authors declare no conflicts of interest relevant to this work.

7. Data availability: The complete data extraction form and analysis code will be made available as supplementary materials upon publication or upon reasonable request to the corresponding author.

8. Contact: Questions regarding this protocol should be directed to the corresponding author at [email address].

Keywords Subarachnoid hemorrhage; Intracranial aneurysm; Early clipping; Delayed coiling; Systematic review.

Contributions of each author

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