Untersuchung der Wirksamkeit und Sicherheit ausgewählter therapeutischer Verfahren in der Neurologie anhand von Meta-Analysen

Inauguraldissertation
zur Erlangung des Grades eines Doktors der Medizin
des Fachbereichs Medizin
der Justus-Liebig-Universität Gießen

vorgelegt von Hammed, Ali
aus Tartus

Gießen 2025

Aus dem Fachbereich Medizin der Justus-Liebig-Universität Gießen

Betreuer/in: Prof. Dr. Tanislav, Christian

Gutachter/in: Prof. Dr. Uhl, Eberhard

Tag der Disputation:

12.02.2026

Inhalt

1. Einleitung 7

1.1. Hintergrund zum ersten Manuskript 10

1.2. Hintergrund zum zweiten Manuskript 13

1.3. Hintergrund zum dritten Manuskript 17

2. Übersicht zu den Manuskripten 21

2.1. Erstes Manuskript 22

2.2. Zweites Manuskripts 23

2.3. Drittes Manuskript 24

3. Manuskripte in der Originalversion 25

3.1. Erstes Manuskript 25

3.2. Zweites Manuskript 41

3.3. Drittes Manuskript 55

4. Abschlussdiskussion 81

4.1. Erstes Manuskript 81

4.2. Zweites Manuskript 86

4.3. Drittes Manuskript 93

5. Zusammenfassung 99

6. Literaturverzeichnis 103

7. Ehrenwörtliche Erklärung 105

8. Danksagung 107

9. Tabellarischer Lebenslauf 109

10. Anhang 111

1. Einleitung

In der modernen medizinischen Forschung hat sich die Meta-Analyse als unverzichtbares Instrument etabliert, um die Evidenzlage zu klären und die Grundlage für fundierte klinische Entscheidungen zu schaffen. Diese systematische Methode ist entwickelt worden, um Ergebnisse zahlreicher einzelner Studien zu einer spezifischen Frage hinsichtlich Wirksamkeit und Sicherheit medizinischer Maßnahmen zu aggregieren und zu analysieren. Diese Methode ist insbesondere in der klinischen Forschung wichtig, um Erkenntnisse aus unterschiedlichen Untersuchungen zusammenzufassen und eine verbindliche Empfehlung für den klinischen Alltag zu entwickeln [1-2].

Stellenwert von Meta-Analysen in der evidenzbasierten Medizin

Die Evidenzbasierte Medizin zielt darauf ab, klinische Entscheidungen basierend auf der besten verfügbaren wissenschaftlichen Evidenz zu treffen. Durch die systematische Zusammenführung und Auswertung von Daten aus verschiedenen Studien tragen Meta-Analysen dazu bei, die Relevanz wissenschaftlicher Erkenntnisse zu unterstreichen. Einzelstudien können unterschiedliche oder widersprüchliche Ergebnisse liefern, doch der Zweck einer umfassenden Meta-Analyse besteht darin, diese Unterschiede auszugleichen und zu minimieren und ein einheitliches Gesamtbild zu schaffen. Ein Merkmal von Meta-Analysen ist die Bewertung der Varianz einzelner Studienergebnisse und deren Gewichtung, um dadurch mathematisch verlässliche Schätzungen zu erhalten [2,4].

Ein weiterer Vorteil von Meta-Analysen besteht in der Möglichkeit, Subgruppenanalysen durchzuführen. Diese erlauben es, spezifische Untergruppen von Patienten mit individuellen Eigenschaften zu identifizieren, die stärker oder schwächer von einer bestimmten Intervention profitieren könnten. Besonders in der Neurologie ist dies von großer Bedeutung, da sich Patientenpopulationen in ihren demografischen Merkmalen, genetischen Prädispositionen und Krankheitsverläufen stark unterscheiden können. Subgruppenanalysen bieten die Grundlage für die Entwicklung spezifischer Behandlungsstrategien, wodurch sich die Qualität und Effizienz der Behandlung

erheblich verbessern lassen [2,3]. Ein Beispiel hierfür ist eine Meta-Analyse randomisierter kontrollierter Studien zur Behandlung von ischämischen Schlaganfällen, die Aufschluss über die Wirksamkeit von Therapien in verschiedenen Altersgruppen, Geschlechtern oder definierten Patientensubgruppen mit unterschiedlichen Vorerkrankungen geben kann [4].

Methodische Herausforderungen und Vorteile von Meta-Analysen

Obwohl Meta-Analysen eine wertvolle Ergänzung zur wissenschaftlichen Forschung darstellen, sind diese nicht ohne methodische Herausforderungen. Die Qualität und Verlässlichkeit einer Meta-Analyse hängt entscheidend von der Qualität der eingeschlossenen Studien ab. Studien mit methodischen Mängeln, wie z. B. einem kleinen Stichprobenumfang, fehlender Randomisierung oder Verblindung, können Verzerrungen verursachen und die Ergebnisse der Meta-Analyse verfälschen. Daher ist es wichtig, dass nur Studien eingeschlossen werden, die strenge methodische Kriterien erfüllen; dadurch werden Verzerrungen minimiert und die Zuverlässigkeit der Ergebnisse erhöht [4].

Ein weiteres häufiges Problem bei Meta-Analysen ist die Heterogenität der Studienergebnisse. Diese Heterogenität kann durch Unterschiede in den Studiendesigns, den untersuchten Populationen, den verwendeten Interventionen und den herangezogenen Endpunkten entstehen. Eine hohe Heterogenität kann die Vergleichbarkeit der Studien beeinträchtigen und die Validität der Ergebnisse infrage stellen [4]. Zur Bewältigung dieser Herausforderung werden statistische Verfahren wie das „random-effects“-Modell verwendet, um Unterschiede zwischen den Studien auszugleichen und realistischere Schätzungen der Effektgrößen so präzise wie möglich herauszuarbeiten [3-4]. Zusätzlich tragen Sensitivitätsanalysen dazu bei, die Robustheit der Ergebnisse zu überprüfen und sicherzustellen, dass einzelne Studien nicht zu sehr ins Gewicht fallen und die Gesamtanalyse verfälschen [2-4].

Ein weiterer wichtiger Aspekt, der bei der Durchführung von Meta-Analysen berücksichtigt werden sollte, ist der Publikationsbias. Studien mit positiven oder signifikanten Ergebnissen werden oft bevorzugt veröffentlicht, während solche mit negativen oder nicht signifikanten Resultaten seltener erscheinen. Dieser Bias kann dazu

führen, dass die Ergebnisse einer Meta-Analyse verzerrt werden und ein unrealistisch positives Bild der untersuchten Intervention entsteht [2-4]. Techniken wie die Funnel-Plot-Analyse können helfen, das Ausmaß des Publikationsbias zu bewerten und seine potenziellen Auswirkungen auf die Ergebnisse zu minimieren [1-4]. Der Einschluss von unveröffentlichten Studien, wie beispielsweise die sogenannte „graue Literatur“, kann ebenfalls dazu beitragen, ein vollständigeres Bild der Evidenz zu erhalten und den Publikationsbias zu reduzieren [2,3].

Praktische Bedeutung von Meta-Analysen in der klinischen Neurologie

Meta-Analysen haben einen direkten und bedeutenden Einfluss auf die klinische Praxis, da sie häufig die Grundlage für die Entwicklung von Behandlungsleitlinien und Therapieempfehlungen bilden. Sie bieten Ärzten und anderen Gesundheitsdienstleistern eine fundierte Basis, auf der sie Entscheidungen treffen können, die den besten wissenschaftlichen Erkenntnissen entsprechen. In der Neurologie, wo Krankheitsbilder oft komplex sind und von vielen Faktoren beeinflusst werden können, bieten Meta-Analysen wertvolle Erkenntnisse, um die beste Behandlungsstrategie für verschiedene Erkrankungen zu identifizieren. Dies gilt insbesondere für Erkrankungen wie Schlaganfälle, Multiple Sklerose und degenerative Erkrankungen des zentralen und peripheren Nervensystems [5].

Ein anschauliches Beispiel für die Bedeutung von Meta-Analysen ist die Forschung zur Behandlung der Multiplen Sklerose (MS). Diese chronische, fortschreitende Erkrankung des zentralen Nervensystems verursacht eine Vielzahl neurologischer Symptome und stellt eine große Herausforderung für die medizinische Versorgung dar. Durch Meta-Analysen konnte die Wirksamkeit verschiedener Immunmodulatoren und krankheitsmodifizierender Therapien systematisch untersucht werden. Sie helfen nicht nur dabei, die effektivsten Behandlungsoptionen zu identifizieren, sondern auch wichtige Fragen zur langfristigen Sicherheit und zu den spezifischen Wirkungen in unterschiedlichen Patientensubgruppen aufzuzeigen. Solche Erkenntnisse sind entscheidend, um die Versorgung von MS-Patienten kontinuierlich zu verbessern [6]. Ein weiteres Beispiel für den praktischen Nutzen von Meta-Analysen ist die Untersuchung von Nutzen der Therapie der Thrombolyse- oder Thrombektomie beim akuten

ischämischen Schlaganfall. Dabei wird gezielt erforscht, welche Patienten am meisten von dem einem oder anderem Verfahren profitieren können. Solche Analysen helfen, die Behandlung besser auf individuelle Bedürfnisse abzustimmen und die Erfolgschancen zu erhöhen [7].

1.1. Hintergrund zum ersten Manuskript

Die erste Publikation widmet sich der wichtigen Frage, ob die Kombination aus intravenöser Thrombolyse (IVT) und mechanischer Thrombektomie (MT) im Vergleich zur alleinigen MT bei Patienten mit akutem ischämischen Schlaganfall, der durch einen Verschluss einer hirnversorgenden Arterie verursacht wurde, Vorteile bietet. Diese Fragestellung ist besonders relevant, da die Behandlung des akuten ischämischen Schlaganfalls in den letzten Jahren erhebliche Fortschritte erfahren hat. Angesichts der Tatsache, dass der Schlaganfall weltweit eine der Hauptursachen für Behinderung ist und für viele Patienten tödlich enden kann, sind schnelle und wirksame Behandlungsoptionen essenziell, um Schäden zu begrenzen und die Überlebenschancen der Patienten zu erhöhen [1,2]. Dabei spielen zeitkritische Behandlungsentscheidungen eine entscheidende Rolle, um die Durchblutung des Gehirns so schnell wie möglich wiederherzustellen und das Fortschreiten des Infarkts einzudämmen. Jede Minute zählt, da ein verzögerter Eingriff zu irreversiblen neurologischen Schäden führen kann.

Die intravenöse Thrombolyse (IVT) ist eine etablierte Behandlungsmethode, die in den aktuellen Leitlinien empfohlen wird, wenn sie innerhalb des Zeitfensters von 4,5 Stunden nach Beginn des Schlaganfalls angewendet wird. Das Ziel der intravenösen Thrombolyse (IVT) besteht darin, das Blutgerinnsel, das die Durchblutung des Gehirns blockiert, medikamentös aufzulösen. Durch diesen Ansatz kann die Durchblutung des betroffenen Hirnareals wiederhergestellt werden, wodurch sich neurologische Schäden begrenzen lassen. Parallel dazu hat sich die mechanische Thrombektomie (MT) als eine besonders wirksame Methode zur Wiederherstellung der zerebralen Durchblutung bewährt, insbesondere bei Patienten mit Arterienverschlüssen, die durch große Thromben hervorgerufen werden. Dabei wird der Thrombus mechanisch aus der betroffenen Arterie entfernt. Die MT kommt vor allem bei Patienten zum Einsatz, sich

im entsprechenden Zeitfenster befinden und technisch die mechanische Entfernung eines Thrombus interventionell möglich ist. Beide Methoden sind in der Behandlung des akuten Schlaganfalls zugelassen und schließen sich nicht gegenseitig aus, werden in Kombination oder alleine in Abhängigkeit von Kontraindikationen/ anderen limitierenden Faktoren (unzugänglicher Gefäßverschluss) in der klinischen Routine angewendet [1, 4]. Die Frage, ob die alleinige mechanische Thrombektomie (MT) mit der Kombination aus intravenöser Thrombolyse (IVT) und MT – der sogenannten Bridging-Therapie (BT) – vergleichbar ist, hat daher eine hohe klinische Relevanz. Sie beeinflusst nicht nur die Optimierung von Behandlungsstrategien, sondern auch die effiziente Nutzung der Ressourcen im Gesundheitswesen. Die Bridging-Therapie bietet den Vorteil, dass durch die initiale IVT ein Blutgerinnsel teilweise aufgelöst wird, wodurch möglicherweise die Voraussetzungen für eine nachgeschaltete MT verbessert werden können. Allerdings birgt die Anwendung von IVT auch Risiken, insbesondere die Gefahr von Blutungen, die bei einer verspäteten Anwendung das Blutungsrisiko erhöht.

Studien und Meta-Analysen zur Wirksamkeit und Sicherheit der Bridging-Therapie im Vergleich zur alleinigen mechanischen Thrombektomie (MT) haben bisher zu unterschiedlichen Ergebnissen geführt. Einige Untersuchungen legen nahe, dass die alleinige MT in Bezug auf die Selbstständigkeit des Patienten bei der Verrichtung seiner alltäglichen Aktivitäten nach 90 Tagen, die Gesamtmortalität und die erfolgreiche Wiederherstellung der Durchblutung nicht wesentlich schlechter abschneidet als die Kombinationstherapie. Diese Erkenntnisse werfen wichtige Fragen über den zusätzlichen Nutzen der intravenösen Thrombolyse bei Patienten auf, die sich einer mechanischen Thrombektomie unterziehen, und können potenziell Einfluss auf künftige Behandlungsstrategien haben [8]. In bestimmten Situationen, insbesondere wenn die Zeit vom Auftreten der Symptome bis zur Verabreichung der IVT weniger als 2 Stunden und 20 Minuten beträgt, könnte die alleinige MT sogar von Vorteil sein [7,8]. Hierbei spielt die sogenannte „**Door-to-Needle-Zeit**“ eine kritische Rolle, da eine Verzögerung bedingt durch eine vorhergehende IVT den Behandlungserfolg einer kombinierten IVT zusammen mit einer Thrombektomie negativ beeinflussen kann.

Eine Meta-Analyse, die die direkte endovaskuläre Thrombektomie (DEVT) mit der Bridging-Therapie verglich, fand heraus, dass die DEVT hinsichtlich der Selbstständigkeit des Patienten bei der Verrichtung seiner alltäglichen Aktivitäten nach 90 Tagen, der Mortalität und der erfolgreichen Reperfusion nicht unterlegen war [8]. Dies deutet darauf hin, dass die alleinige mechanische Thrombektomie (MT) eine praktikable und möglicherweise ebenso effektive Behandlungsoption sein könnte, insbesondere bei Patienten, bei denen Kontraindikationen für die intravenöse Thrombolyse (IVT) bestehen oder bei denen eine schnelle endovaskuläre Intervention im Vordergrund steht. Interessanterweise zeigte dieselbe Meta-Analyse, dass die Rate symptomatischer intrakranieller Blutungen (sICH) in der Gruppe, die eine Bridging-Therapie erhielt, höher war. Diese Ergebnisse unterstreichen die Notwendigkeit einer sorgfältigen Risikoabwägung der Kombinationstherapie, insbesondere bei Patienten mit erhöhtem Blutungsrisiko [7,8]. Allerdings stellten andere Studien fest, dass es nach Risikofaktor-Adjustierung keinen signifikanten Unterschied für das Risiko einer sICH zwischen BT und MT allein gibt [7,8].

Ein weiterer in der Fachliteratur diskutierter Aspekt ist die potenzielle Rolle der Bridging-Therapie bei der Verbesserung der Mikrozirkulation und der Verhinderung von mikroembolischen Ereignissen während der mechanischen Thrombektomie (MT). Theoretisch könnte die Vorbehandlung mit intravenöser Thrombolyse (IVT) kleinere Thrombusfragmente auflösen, die sich bei der mechanischen Entfernung des Hauptthrombus lösen und in periphere Gefäße gelangen könnten. Dies würde dazu beitragen, das Risiko sekundärer Infarkte zu reduzieren und die Gesamteffizienz der Behandlung verbessern [5]. Diese Hypothese ist jedoch noch nicht abschließend bewiesen und bedarf weiterer Forschung, um die genaue Wechselwirkung zwischen IVT und MT zu klären. Die Wahl der optimalen Behandlungsstrategie sollte nicht allein auf der allgemeinen Wirksamkeit der Methoden basieren, sondern auch patientenspezifische Faktoren berücksichtigen. Dazu zählen das Alter des Patienten, die Größe und Lage des Thrombus, die Zeit seit Beginn der Symptome sowie der allgemeine Gesundheitszustand. So könnten Patienten mit einem erhöhten Blutungsrisiko oder Kontraindikationen für eine intravenöse Thrombolyse (IVT) von einer direkten mechanischen Thrombektomie (MT) profitieren. Im Gegensatz dazu könnte bei

Patienten, die frühzeitig nach Auftreten der Symptome behandelt werden und keine Kontraindikationen aufweisen, die Kombinationstherapie Vorteile bieten, da sie potenziell eine schnellere und umfassendere Wiederherstellung der Durchblutung ermöglicht.

Die aktuellen Ergebnisse der Meta-Analyse und der damit verbundenen Studien legen nahe, dass eine individualisierte Herangehensweise erforderlich ist, um die besten Behandlungsergebnisse zu erzielen. Die Einführung von patientenspezifischen Behandlungsprotokollen, die eine rasche Identifizierung der optimalen Therapieoption ermöglichen, könnte die Behandlungsergebnisse und die Effizienz des Schlaganfallmanagements insgesamt verbessern.
Auch wenn die von uns durchgeführte Metaanalyse wichtige Erkenntnisse hervorgebracht hat, die Debatte über die optimale Anwendung von intravenöser Thrombolyse (IVT) und mechanischer Thrombektomie (MT) – sei es in Kombination oder als alleinige Intervention – im Kontext des ischämischen Schlaganfalls ist noch nicht abschließend geklärt. Um die offenen Fragen zu beantworten, sind weitere randomisierte kontrollierte Studien notwendig, die ein tieferes Verständnis der besten Behandlungsansätze ermöglichen. Die Ergebnisse der vorliegenden Publikation leisten einen wichtigen Beitrag zu dieser Diskussion, indem sie wertvolle Erkenntnisse über die potenziellen Vorteile und Risiken der verschiedenen Strategien liefern. Sie bilden eine solide Basis für die Entwicklung evidenzbasierter Leitlinien, die darauf abzielen, die Akuttherapie von Schlaganfällen weiter zu verbessern und patientenorientiert zu optimieren.

1.2. Hintergrund zum zweiten Manuskript

Die zweite Publikation befasst sich mit einer der häufigsten und komplexesten Erkrankungen des Bewegungsapparates, der sogenannten Ischialgie, die hauptsächlich durch lumbale Bandscheibenvorfälle (LDH) verursacht wird. Die Ischialgie ist ein Zustand, der durch Schmerzen entlang des Nervus ischiadicus gekennzeichnet ist, die vom unteren Rücken über das Gesäß und die Beine bis in die Füße ausstrahlen kann. Diese Erkrankung kann entweder akut oder chronisch verlaufen, wobei die chronische

Ischialgie oft eine langwierige und belastende Symptomatik darstellt. Die Ischialgie ist weit verbreitet und betrifft weltweit eine erhebliche Zahl an Menschen. Die Lebenszeitprävalenz wird auf etwa 13% bis 40% geschätzt, wobei etwa 90% der Fälle auf lumbale Bandscheibenvorfälle zurückzuführen sind [2]. Bei den restlichen 10% können auch andere Ursachen wie Muskelverspannungen im unteren Rücken, das Piriformis-Syndrom, foraminale Stenosen, spinale Stenosen oder Spondylolisthesen eine Rolle spielen [9].

Die aktuelle Meta-Analyse konzentriert sich darauf, die Wirksamkeit chirurgischer Eingriffe im Vergleich zu konservativen Therapieansätzen bei Patienten mit chronischer Ischialgie infolge eines lumbalen Bandscheibenvorfalls zu untersuchen. Die Symptome einer Ischialgie können stark variieren, umfassen jedoch häufig intensive, brennende oder stechende Schmerzen entlang des Nervus ischiadicus. In schwereren Fällen treten zusätzlich neurologische Symptome auf, wie ein Taubheitsgefühl oder Paresen der betroffenen Muskulatur, die die Lebensqualität der Betroffenen erheblich beeinträchtigen können.

Ziel der hier präsentierten Meta-Analyse ist es, Erkenntnisse darüber zu gewinnen, welche Behandlungsmethode die besten Ergebnisse für diese Erkrankung liefert. Für Patienten mit chronischer Ischialgie stehen verschiedene therapeutische Ansätze zur Verfügung, die auf den spezifischen Symptomen und dem Schweregrad der Erkrankung basieren. Diese reichen von konservativen Maßnahmen, wie Physiotherapie und medikamentöser Behandlung, bis hin zu invasiveren chirurgischen Eingriffen, wie der Diskektomie oder andere Dekompressionsverfahren.

Konservative Behandlungsansätze sind häufig die erste Wahl bei der Behandlung der Ischialgie infolge eines Bandscheibenvorfalles. Sie zielen darauf ab, die Schmerzen zu lindern, die Funktionalität zu erhalten und das Fortschreiten der Erkrankung zu verhindern, ohne dass unmittelbar auf invasive Eingriffe zurückgegriffen werden muss. Zu den konservativen Maßnahmen gehören unter anderem physiotherapeutische Maßnahmen, Dehnübungen und manuelle Therapie. Sie zielen darauf ab, die Beweglichkeit der Wirbelsäule zu verbessern, die Muskulatur zu stärken und die

Belastung des Nervus ischiadicus zu verringern. Insbesondere bei weniger schweren Fällen hat sich die Physiotherapie als sehr effektiv erwiesen [9]. Bei schweren Fällen, die mit neurologischen Symptome einhergehen sind und/oder bei bildmorphologisch ausgeprägten Befunden mit drohender Aggravation wird dann das operative Therapieverfahren bevorzugt [9,10].

Schmerzmittel und entzündungshemmende Medikamente wie nichtsteroidale Antirheumatika (NSAR) oder Kortikosteroide können verwendet werden, um akute Schmerzen zu lindern und Entzündungsreaktionen zu reduzieren. Bei stärkeren Schmerzen können auch opioidhaltige Präparate oder Antidepressiva zur Schmerzmodulation in Erwägung gezogen werden. In einigen Fällen werden auch Injektionen von Kortikosteroiden in den Bereich des betroffenen Bandscheibenvorfalls angewendet, um die Entzündungsreaktion zu lindern. Eine Änderung des Lebensstils, wie z.B. die Verbesserung der Körperhaltung, das Vermeiden von langem Sitzen oder das Erlernen von ergonomischen Techniken bei alltäglichen Aktivitäten, kann ebenfalls eine Linderung der Beschwerden bringen.

Die konservativen Methoden bieten einen hohen Grad an Wirksamkeit und können bei bis zu 90% der Patienten zu einer Verbesserung der Symptome führen [10]. Ein wesentlicher Vorteil dieser Methoden ist, dass sie nicht invasiv sind und kein Komplikationsrisiko besteht.
Sie sind in der Regel kostengünstiger und erfordern kürzere Krankenhausaufenthalte oder gar keine stationäre Behandlung. Bei chronischer Ischialgie, die trotz konservativer Behandlung weiterhin besteht oder sich verschlechtert, können chirurgische Eingriffe notwendig werden. Die gängigsten chirurgischen Verfahren sind die Diskektomie und die Dekompression, bei denen der betroffene Bandscheibenvorfall entweder entfernt oder entlastet wird, um den Druck auf den Nervus ischiadicus zu verringern.

Die Diskektomie ist ein chirurgischer Eingriff, bei dem der Teil der Bandscheibe entfernt wird, der Druck auf den Nervus ischiadicus ausübt. Diese Methode wird besonders dann empfohlen, wenn konservative Behandlungen nicht ausreichend wirken und Schmerzen weiterhin bestehen. In der Regel erfolgt die Diskektomie minimalinvasiv über einen

kleinen Schnitt und hat sich bei vielen Patienten mit Bandscheibenvorfällen als sehr effektiv erwiesen.

Dekompressionsverfahren kommen hingegen zum Einsatz, wenn neben einem Bandscheibenvorfall weitere Ursachen wie Spinalkanalstenosen oder Knochenwucherungen (Osteophyten) den Nerv zusätzlich komprimieren. Ziel ist es, den Druck auf den betroffenen Nerv durch gezielte Entlastung zu verringern, um Schmerzen und andere neurologische Symptome zu reduzieren. Chirurgische Eingriffe bieten den Vorteil einer schnelleren Schmerzlinderung im Vergleich zu konservativen Behandlungen, insbesondere bei schwerwiegenden Fällen der Ischialgie. Viele Patienten erleben bereits unmittelbar nach der Operation eine deutliche Besserung der Symptome. Chirurgische Eingriffe sind jedoch nicht ohne Risiken; Infektionen, Nervenschäden oder das Wiederauftreten der Symptome müssen in diesem Zusammenhang erwähnt werden [11].

Eine zentrale Fragestellung der hier präsentierten Meta-Analyse ist der Vergleich der Wirksamkeit chirurgischer Eingriffe gegenüber konservativen Therapieansätzen bei Patienten mit chronischer Ischialgie infolge eines lumbalen Bandscheibenvorfalls. Die bisher vorliegenden Daten deuten darauf hin, dass chirurgische Interventionen meist zu einer schnelleren Linderung der Rückenschmerzen führen. Im Gegensatz dazu scheinen konservative Behandlungsansätze langfristig eine bessere Wirkung auf die Reduktion der Beinschmerzen sowie auf die allgemeine Lebensqualität der Patienten zu haben. Die Erkenntnisse unterstreichen die Bedeutung einer individuellen Therapieentscheidung, die sowohl die kurzfristigen als auch die langfristigen Ziele der Behandlung berücksichtigt [10,11].

Ein bedeutender Vorteil der konservativen Behandlung liegt darin, dass sie nicht invasiv ist und in der Regel mit keinem Risiko für Komplikationen einhergeht. Sie eignet sich besonders für Patienten, bei denen die Symptome mild sind oder das Risiko einer Operation als zu hoch eingeschätzt wird. Auf der anderen Seite können chirurgische Eingriffe eine entscheidende Option für Patienten darstellen, die unter anhaltenden oder schwerwiegenden Beschwerden leiden und bei denen konservative

Maßnahmen keine ausreichende Linderung gebracht haben. Diese duale Herangehensweise betont die Notwendigkeit einer individuellen Behandlungsstrategie, die sowohl die Schwere der Symptome als auch die spezifischen Bedürfnisse und Risiken des Patienten berücksichtigt.

Die systematische Analyse der vorliegenden Daten zeigt, dass sowohl chirurgische als auch konservative Behandlungsansätze ihre eigenen Vorteile aber auch Nachteile haben. Chirurgische Eingriffe bieten eine schnelle und signifikante Schmerzlinderung, was besonders bei schweren Fällen der Ischialgie von Bedeutung ist. Auf der anderen Seite bieten konservative Methoden eine nicht-invasive und oft sicherere Option für Patienten mit weniger ausgeprägten Beschwerden. Der Schlüssel zum Erfolg liegt in der richtigen Auswahl der Behandlung basierend auf der Schwere der Symptome, dem allgemeinen Gesundheitszustand des Patienten und den individuellen Risikofaktoren. Für die klinische Praxis bedeutet dies, dass eine personalisierte Therapie notwendig ist, die sowohl die medikamentöse und physiotherapeutische Unterstützung als auch chirurgische Optionen berücksichtigt, um die bestmöglichen Ergebnisse für den Patienten zu erzielen. Eine frühzeitige Diagnose und die richtige Wahl der Behandlungsmethoden können den Verlauf der Erkrankung positiv beeinflussen und langfristige Gesundheitsprobleme verhindern.

Diese Analyse verdeutlicht, wie wichtig es ist, den richtigen Behandlungsansatz für die chronische Ischialgie auszuwählen. Während chirurgische Eingriffe bei vielen Patienten eine schnelle Linderung der Symptome bieten, zeigen konservative Methoden eine nachhaltige Wirkung auf die Lebensqualität. Die Wahl der optimalen Therapie sollte stets auf den individuellen Bedürfnissen der Patienten basieren und sowohl die Vor- als auch die Nachteile jeder Methode abwägen. Zukünftige Studien könnten helfen, genauere Richtlinien für die Auswahl der Behandlungsmethoden für Patienten mit chronischer Ischialgie weiter zu entwickeln und zu optimieren.

1.3. Hintergrund zum dritten Manuskript

Die dritte Publikation widmet sich der Behandlung unrupturierter intrakranieller Aneurysmen (UIAs), die aufgrund ihres Rupturrisikos und die daraus resultierende

subarachnoidale Blutung (SAH) eine bedeutende klinische Herausforderung darstellen. Zerebrale Aneurysmen sind ein Risiko für intrakranielle Blutungen, ihre Behandlung hat einen großen Einfluss auf die Mortalität und Morbidität von Betroffenen [12]. Unrupturierte intrakranielle Aneurysmen haben eine Prävalenz von etwa 2-5%; diese Zahl zeigt, dass ein beträchtlicher Teil von Betroffenen mit einem Aneurysma der intrakraniellen Arterien leben, ohne dass dieses zu einem akuten klinischen Vorfall führt [13].

Eine zentrale Frage bei der Behandlung von unrupturierten intrakraniellen Aneurysmen (UIAs) ist, ob diese prophylaktisch/präventiv behandelt werden sollten, um das Risiko einer Ruptur zu verringern. Patienten ohne Symptome oder erkennbare Risikofaktoren für eine Ruptur werden konservativ behandelt und im Verlauf beobachtet [13]. Diese "watchful waiting"-Strategie beinhaltet regelmäßige Kontrolluntersuchungen, ohne sofortige Intervention [12,13]. Sie wird häufig bei kleineren, asymptomatischen Aneurysmen angewendet, bei denen die Rupturgefahr als gering eingeschätzt wird [13].

Bei Patienten mit einem höheren angenommen Rupturrisiko hingegen ist die Wahl der geeigneten Behandlungsstrategie von entscheidender Bedeutung. Ziel ist es, das Risiko einer akuten Blutung zu minimieren und durch den Eingriff keine Schäden zu verursachen. Für die Entscheidung für eine der Therapieoptionen spielen unterschiedliche Faktoren eine Rolle; die Lokalisation des Aneurysmas, die Zugangsmöglichkeiten zum Aneurysma für das eine oder andere Verfahren, die Größe des Aneurysmas und die morphologische Konfiguration bestimmen die Auswahl des Verfahrens [12-14].

Die Technik des chirurgischen Clippings beinhaltet die invasive Maßnahme einer Kraniotomie, bei der ein Clip direkt am Aneurysma platziert wird, um dieses auszuschalten. Während das chirurgische Clipping effektiv darin ist, Aneurysmen zu verschließen, ist es mit einer Reihe von Herausforderungen und Risiken verbunden, wie beispielsweise der Notwendigkeit einer invasiven Operation, die mit einer längeren Erholungszeit und potenziellen Komplikationen wie einer Infektion oder direkten Hirnverletzung einhergehen kann [14].

In den letzten Jahren hat sich das endovaskuläre Coiling als eine weniger invasive Alternative zum chirurgischen Clipping etabliert. Das endovaskuläre Coiling ist eine minimalinvasive Technik, bei der ein Katheter durch die Arterie zum Aneurysma geführt wird. Dort wird ein draht- oder spiralförmiges Material (Coil) in das Aneurysma eingeführt, um es von innen zu verschließen und so eine Ruptur zu verhindern. Diese Technik hat den Vorteil, dass sie ohne Kraniotomie auskommt, was das Risiko für postchirurgische Komplikationen verringert und die Erholungszeit erheblich verkürzt [14]. Ein weiterer Vorteil des endovaskulären Coiling besteht darin, dass diese Methode bei Patienten angewendet werden kann, die möglicherweise nicht für eine offene Operation in Frage kommen, sei es aufgrund von Alter, Komorbiditäten oder anderen limitierenden Faktoren.

Die Diskussion darüber, welche Behandlungsstrategie für Patienten mit unrupturierten intrakraniellen Aneurysmen (UIAs) am besten geeignet ist, bleibt weiterhin kontrovers. In der klinischen Praxis besteht nach wie vor erhebliche Unsicherheit darüber, wann, bei wem und ob das chirurgische Clipping oder das endovaskuläre Coiling gewählt werden sollte [12,13]. Beide Ansätze haben ihre eigenen Vor- und Nachteile. Während das Clipping durch seine langfristige Effektivität besticht, ist es invasiver und birgt höhere perioperative Risiken. Das Coiling hingegen ist weniger invasiv und bietet eine kürzere Erholungszeit, erfordert jedoch in bestimmten Fällen ein Wiederholen der Maßnahme [12]. Diese Unsicherheiten erfordern eine sorgfältige interdisziplinäre Abwägung um die bestmögliche Therapieoption für das einzelne Individuum auszusuchen; systematische Auswertungen von vorhandenen Daten die dazu Auskunft geben können sind hier von großem Nutzen [13].

Die vorliegende Meta-Analyse zielt darauf ab, die Frage zu beantworten in welcher Situation das chirurgische Clipping oder das endovaskuläres Coiling als Behandlungsoption der UIAs die beste Wahl darstellt, um dem Patienten effektiv zu helfen und Risiken zu minimieren. Unsere Meta-Analyse zeigt, dass das endovaskuläre Coiling als eine weniger invasive Methode mit einer geringeren Mortalität und Morbidität assoziiert ist, die weniger Komplikationen verursacht und eine schnellere Erholung des Patienten nach dem Eingriff ermöglicht. Auf der anderen Seite zeigt das

chirurgische Clipping zu einem höheren Prozentsatz einen kompletten Verschluss des Aneurysmas, ohne dass weitere Eingriffe in der Folge erforderlich sind. Beide Verfahren sind jedoch hochwirksam, um das Risiko einer Ruptur zu minimieren und das Überleben der Patienten zu sichern.

Die Relevanz dieser Analyse für die klinische Praxis ist erheblich, da sie den Ärzten eine evidenzbasierte Grundlage bietet, um fundierte Entscheidungen über die Behandlung von UIAs zu treffen. Durch die Berücksichtigung der spezifischen Merkmale des Aneurysmas sowie der demografischen und gesundheitlichen Faktoren der Patienten kann die richtige Wahl getroffen werden, um das bestmögliche Ergebnis für den Patienten zu erzielen. Zudem zeigt diese Analyse, wie wichtig es ist, neue Techniken wie das endovaskuläre Coiling in die klinische Praxis zu integrieren, um im interdisziplinären Diskurs dem Patienten die sicherste und effektivste Behandlung anzubieten.

2. Übersicht zu den Manuskripten

Die drei hier präsentierten Publikationen basieren auf einer umfassende Analyse der aktuell verfügbaren Daten und untersuchen welche Behandlungsstrategie in der jeweiligen Situation Vorteile bieten. Aus dem Bereich des klinischen Faches der Neurologie wurden dabei bei drei Krankheitsentitäten unterschiedliche Therapieoptionen auf Wirksamkeit und Sicherheit untersucht. Dafür werden nach ganz bestimmten Kriterien veröffentlichte klinische Studien analysiert und jeweils zur einer Meta-Analyse aggregiert. Alle drei Meta-Analysen wurden im SCI (Science Citation Index (SCI) bzw. PubMed) verzeichneten Zeitschriften veröffentlicht.

Die erste Arbeit widmet sich der Akuttherapie von Schlaganfällen und untersucht welchen Nutzen die Kombinationstherapie bestehend aus mechanischer Thrombektomie und intravenöser Thrombolyse gegenüber der Thrombektomie alleine bietet.

Die zweite Publikation richtet den Fokus auf die Behandlung der chronischen Ischialgie infolge eines lumbalen Bandscheibenvorfalles und vergleicht den chirurgischen mit dem konservativen Ansatz zur Behandlung der Störung.

Die dritte Arbeit untersucht die präventive Behandlung eines unrupturierten intrakraniellen Aneurysmas durch das Verfahren des operativen Clippings versus der endovaskulären Methode des Aneurysma-Coilings, um das Risiko einer Ruptur des Aneurysmas zu reduzieren und damit der damit verbundenen lebensbedrohlichen Subarachnoidalblutung.

Gemeinsam tragen diese Meta-Analysen dazu bei, die klinische Entscheidungsfindung zu verbessern und Behandlungsstrategien zu fördern, die auf individuelle Bedürfnisse der Patienten zugeschnitten sind.

2.1. Erstes Manuskript

Comparative Effectiveness of Intravenous Thrombolysis plus Mechanical Thrombectomy versus Mechanical Thrombectomy Alone in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

Autor(en): Ali Hammed, Almonzer Al-Qiami, Ahmad Alzawahreh, Josef Rosenbauer, Eman Ayman Nada, Zina Otmani, Nada G. Hamam, Asmaa Zakria Alnajjari, Elsayed Mohamed Hammad, Rawan Hamamreh, Karel Kostevi, Gregor Richter, Christian Tanislav

Veröffentlicht in: *Cerebrovascular Diseases*, DOI: 10.1159/000541033, veröffentlicht am 24. August 2024

In dieser Meta-Analyse wurde die kombinierte Anwendung von intravenöser Thrombolyse (IVT) und mechanischer Thrombektomie (MT) mit der alleinigen MT bei der Behandlung von akuten ischämischen Schlaganfällen verglichen. Ziel war es, die Wirksamkeit und Sicherheit der Kombinationstherapie gegenüber der alleinigen MT zu bewerten.

Eigenanteil der Autoren:

Konzeption und Design: Ali Hammed MD, Almonzer Al-Qiami, Christian Tanislav MD
Datenanalyse: Ali Hammed, Almonzer Al-Qiami, Christian Tanislav MD
Verfassen des Manuskripts: Ali Hammed, Almonzer Al-Qiami, Christian Tanislav MD
Mitwirkung bei der Erstellung und Bearbeitung des Manuskripts: Josef Rosenbauer MD, Asmaa Zakria Alnajjar, Rawan Hamamreh
Datenextraktion und Bewertung des Risikos für Verzerrungen: Elsayed Mohamed Hammad, Zina Otmani, Ahmad Alzawahreh, Nada G. Hamam, Eman Ayman Nada
Kritische Rückmeldung und Manuskriptüberprüfung: Karel Kostev, DMSc, PhD, Gregor Richter MD
Supervision: Ali Hammed, Christian Tanislav

2.2. Zweites Manuskripts

Surgical versus Conservative Management of Chronic Sciatica (>3 Months) due to Lumbar Disc Herniation: Systematic Review and Meta-Analysis

Autor(en): Ali Hammed, Almonzer Al-Qiami, Hamza Alsalhi, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh, Abdelrahman Hamouda, Christian Tanislav

Veröffentlicht in: Cureus Journal, DOI: 10.7759/cureus.59617. eCollection, veröffentlicht am 5. April 2024

Diese Meta-Analyse untersucht die Wirksamkeit und Sicherheit von chirurgischen Eingriffen im Vergleich zu konservativen Therapien bei Patienten mit chronischer Ischialgie infolge eines lumbalen Bandscheibenvorfalls. Die Autoren analysierten in der hier präsentierten Arbeit, welcher Behandlungsansatz bei dieser Patientengruppe am effektivsten ist.

Eigenanteil der Autoren:

Konzeption und Design: Abdelrahman Hamouda, Ali Hammed, Hamza Alsalhi, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh
Datenakquise, Analyse und Interpretation: Abdelrahman Hamouda, Hamza Alsalhi, Christian Tanislav, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh
Verfassen des Manuskripts: Abdelrahman Hamouda, Ali Hammed, Hamza Alsalhi, Christian Tanislav, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh
Kritische Überprüfung des Manuskripts: Ali Hammed, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud
Supervision: Ali Hammed, Christian Tanislav

2.3. Drittes Manuskript

Preventive clipping versus coiling in unruptured intracranial aneurysms: A comprehensive meta-analysis and systematic review to explore safety and efficacy

Autor(en): Ali Hammed, Almonzer Al-Qiami, Omar Alomari, Zina Otmani, Salah Hammed, Khaled Sarhan, Mohamed Derhab, Abdelrahman Hamouda, Josef Rosenbauer, Karel Kostev, Gregor Richter, Veit Braun, Christian Tanislav

Veröffentlicht in: Neurological Sciences Journal, DOI: 10.1007/s10072-024-07963-1, veröffentlicht am 30. Januar 2025

Diese umfassende Meta-Analyse untersucht die Wirksamkeit und Sicherheit der Behandlung von unrupturierten intrakraniellen Aneurysmen (UIAs) mit chirurgischem Clipping im Vergleich zu endovaskulärem Coiling. Ziel der Studie war es, die Prävention von Aneurysma-Rupturen zu optimieren und die sicherste und effektivste Therapie für diese Patienten zu bestimmen. Das Ergebnis unterstützt die Entscheidungsfindung in der klinischen Praxis und trägt dazu bei, evidenzbasierte Richtlinien für die Behandlung von UIAs zu entwickeln.

Eigenanteil der Autoren:

Konzeption und Design: Ali Hammed, Omar Alomari, Almonzer Al-Qiami, Salah Hammed, Khaled Sarhan, Mohamed Derhab, Abdelrahman Hamouda
Datenakquise, Analyse und Interpretation: Almonzer Al-Qiami, Omar Alomari, Zina Otmani, Salah Hammed, Ali Hammed, Abdelrahman Hamouda
Verfassen des Manuskripts: Ali Hammed, Almonzer Al-Qiami, Josef Rosenbauer, Omar Alomari, Karel Kostev, Abdelrahman Hamouda
Kritische Überprüfung des Manuskripts: Salah Hammed, Almonzer Al-Qiami, Mohamed Derhab, Gregor Richter. Veit Braun
Supervision: Christian Tanislav, Ali Hammed

3. Manuskripte in der Originalversion

3.1. Erstes Manuskript

Comparative Effectiveness of Intravenous Thrombolysis plus Mechanical Thrombectomy versus Mechanical Thrombectomy Alone in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis.

Hammed A, Al-Qiami A, Alzawahreh A, Rosenbauer J, Nada EA, Otmani Z, Hamam NG, Alnajjar AZ, Mohamed Hammad E, Hamamreh R, Kostev K, Richter G, Tanislav C.; Cerebrovasc Dis. 2024 Aug 24:1-14. doi: 10.1159/000541033. Epub ahead of print. PMID: 39182478.

Cerebrovascular Diseases

Cerebrovasc Dis
DOI: 10.1159/000541033

Received: June 7, 2024
Accepted: August 13, 2024
Published online: August 24, 2024

Comparative Effectiveness of Intravenous Thrombolysis plus Mechanical Thrombectomy versus Mechanical Thrombectomy Alone in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

Ali Hammed[a] Almonzer Al-Qiami[b] Ahmad Alzawahreh[c] Josef Rosenbauer[a] Eman Ayman Nada[d] Zina Otmani[e] Nada G. Hamam[f] Asmaa Zakria Alnajjar[g] Elsayed Mohamed Hammad[h] Rawan Hamamreh[c] Karel Kostev[i] Gregor Richter[j] Christian Tanislav[a]

[a]Department of Neurology and Geriatrics, Diakonie Hospital Jung Stilling Siegen, Siegen, Germany; [b]Faculty of Medicine and Health Sciences, Kassala University, Kassala, Sudan; [c]Faculty of Medicine, The Hashemite University, Zarqaa, Jordan; [d]Faculty of Pharmacy, Tanta University, Gharbia, Egypt; [e]Faculty of Medicine, Mouloud Mammeri University, Tizi-Ouzou, Algeria; [f]Faculty of Medicine, Cairo University, Cairo, Egypt; [g]Negida Academy, Medical Research Group of Egypt, Arlington, TX, USA; [h]Faculty of Medicine, Alexandria University, Alexandria, Egypt; [i]University Hospital, Phillips University Marburg, Marburg, Germany; [j]Department of Neuroradiology, Diakonie Hospital Jung Stilling Siegen, Siegen, Germany

Keywords
Acute ischemic stroke · Bridging therapy · Mechanical thrombectomy · Thrombolysis · Meta-analysis

Abstract
Introduction: The treatment of acute ischemic stroke due to large artery vessel occlusion experienced a dramatic development within the last decade. This meta-analysis investigates the effectiveness of bridging therapy (BT) versus mechanical thrombectomy (MT) alone in treating acute ischemic stroke. ***Methods:*** Two independent reviewers assessed two-arm clinical trials from Scopus, PubMed, Web of Science, and the Cochrane Library up to January 2024. Data extraction and quality were evaluated using the ROBINS-2 tool. Our primary outcomes were improvement in NIHSS scores and 90-day modified Rankin Scale (mRS) score. ***Results:*** This meta-analysis, which included 2,638 participants from 8 randomized controlled trials, found that BT resulted in a greater improvement in NIHSS scores from baseline compared to endovascular treatment alone (mean difference [MD] 0.96, 95% confidence interval [CI]: [0.73–1.20], $p < 0.00001$). Additionally, BT group achieved successful recanalization more frequently before and after thrombectomy. Thrombectomy alone hat a shorter time from stroke onset to groin puncture compared to BT (MD 9.91, 95% CI: [4.31–15.52], $p = 0.005$). Functional outcomes, mortality rates, symptomatic intracerebral hemorrhage rates, and long-term recovery metrics, such as Barthel index and modified Rankin Scale scores, were comparable between both treatment approaches. ***Conclusion:*** BT is superior to

karger@karger.com
www.karger.com/ced

Correspondence to:
Almonzer Al-Qiami, almonzer.m.o.ahmed@kassalauni.edu.sd

endovascular treatment alone based on NIHSS score improvement and successful reperfusion rates before and after thrombectomy. Despite MT alone demonstrating a shorter time from stroke onset to groin puncture (MD of 9.91 min), it did not contribute to greater NIHSS improvement at 24 h and 7 days. Further trials with larger sample sizes are warranted to enhance precision in clinical guidance.

Introduction

The treatment of acute ischemic stroke due to large artery vessel occlusion has experienced dramatic development within the last decade, with a variety of therapeutic approaches emerging that are increasingly well adapted to individual patient circumstances [1, 2]. The current guidelines recommend that patients with acute ischemic stroke from a large arterial occlusion undergo intravenous thrombolysis (IVT) within 4.5 h of stroke onset [3]. Furthermore, in addition to IVT, standards also recommend mechanical thrombectomy (MT) in the case of a treatable large arterial occlusion. This approach is based on the premise that IVT can initiate recanalization and potentially improve microvascular flow, thereby enhancing the efficacy of subsequent MT [1]. Depending on stroke patterns, both procedures can each be performed alone or together [1, 4].

While IVT itself is an effective therapy, MT alone is also effective in treating acute ischemic stroke, improving outcomes among patients ineligible for IV alteplase [2] in particular. The question is whether MT alone is as effective as MT plus systemic lysis (also called bridging therapy or BT), especially for patients eligible for IVT. Some studies suggest that MT alone may be non-inferior to bridging therapy (BT) in terms of efficacy and safety, and may be associated with a significant benefit if the time between symptom onset and expected administration of IVT is no more than 2 h and 20 min [5].

A meta-analysis comparing direct endovascular thrombectomy (DEVT) alone and BT found statistically significant non-inferiority of DEVT compared to BT with regard to 90-day functional independence, mortality, and successful reperfusion. Interestingly, the symptomatic intracranial hemorrhage (sICH) rate was superior in the DEVT group [2]. Another study found no significant difference in the risk of sICH between the BT and MT alone groups after adjusting for confounders [4].

The choice between BT and MT alone should consider individual patient factors including the timing of stroke onset, the size and location of the occlusion, and the patient's overall health status. While BT remains the standard of care for eligible patients, MT alone is a viable option, particularly when IVT is contraindicated or when rapid reperfusion is necessary.

The aim of our study was to refine treatment protocols and identify which patient subgroups with ischemic stroke due to large vessel occlusion benefit most from intravenous alteplase plus endovascular treatment compared to endovascular treatment alone. We compare both methods regarding successful recanalization (TICI 2b-3), NIHSS scores, functional outcomes (mRS, Barthel Index), mortality rates, symptomatic intracerebral hemorrhage rates, and median final lesion volume on follow-up imaging. Our goal was to determine which treatment is more effective in practice, guiding future stroke management guidelines.

Methods

This systematic review was conducted in accordance with the guidelines outlined in the Cochrane Handbook of Systematic Reviews of Interventions [6] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [7]. The prespecified protocol for this review is registered with PROSPERO (CRD42024498238). We conducted the analysis using Review Manager (RevMan) Version (7.5.0) [8].

Eligibility Criteria

Inclusion criteria:

Population: studies about patients with large cerebral artery occlusion or tandem lesions.

- Intervention: studies in which the experimental group received bridging therapy (intravenous alteplase and MT).
- Comparator: studies in which the control group received MT only.
- Study design: only randomized clinical trials were included.

Exclusion criteria:

Studies that met the following criteria were excluded: (1) case reports, case series, or observational studies; (2) review articles or meta-analyses; (3) animal studies; (4) conference abstracts and letters; (5) descriptive studies or studies that did not report our predefined outcomes.

This review included studies involving patients with large cerebral artery occlusion or tandem lesions who underwent BT, comprising intravenous alteplase administration followed by MT. Studies in which the

control group received MT alone were also included. Eligible studies were required to report clear efficacy and safety outcome measures. Only randomized clinical trials were considered for inclusion. Conversely, studies meeting the following exclusion criteria were excluded: (1) case reports, case series, or observational studies; (2) review articles or meta-analyses; (3) animal studies; (4) conference abstracts and letters; (5) descriptive studies or those failing to report predefined outcomes.

Search Strategy and Screening

We conducted a comprehensive search across multiple databases including PubMed, Scopus, Embase, and Web of Science (WOS) with no restrictions on language or publication date. This systematic search was carried out for all studies published up until January 2024, utilizing a combination of search terms related to MT, endovascular therapy, and large cerebral artery occlusion. The search strategy included terms such as "mechanical thrombectomy," "endovascular thrombectomy," "bridging therapy," "intravenous thrombolysis," and specific descriptors for large vessel ischemic stroke. Articles identified during the search were imported into the Covidence website [9] for deduplication and initial screening based on title and abstract. Three review authors independently assessed the relevance of the search results, with potential studies undergoing further eligibility screening by two additional reviewers. Any discrepancies were resolved through discussion with the first author.

Data Collection

Three review authors independently extracted relevant data from the included studies using predefined data extraction forms available online. The extracted data encompassed two main aspects: (1) baseline characteristics of study participants, including age, sex, weight, occlusion site, time from stroke onset to randomization, time from randomization to start of alteplase, median ASPECTS (IQR) score, history of stroke, hypertension, atrial fibrillation, CTP admission, mismatch (%), eTICI score of more than 2c, angiographic improvement, TMAX >6 volume, infarct expansion rate, LKW to reperfusion, Barthel Index of 95–100 at 90 days, improved angiographic eTICI score, and study location; and (2) examined outcomes such as mRS at 90 days, vasospasm, mortality, successful reperfusion, NIHSS mean difference (MD), serious adverse events within 90 days, Barthel Index score of 95–100 at 90 days, improvement in the modified Rankin scale at 90 days, median final lesion volume on follow-up imaging (mL), time from stroke onset to groin puncture, infarction in new territory at 5–7 days, large or malignant MCA infarction, and need for embolization of new territory. Data extraction was conducted separately for the intervention group and the comparative group.

Categorical data were expressed as event count and number of participants, while continuous outcomes were expressed as median, interquartile range, and number of participants. A fourth review author meticulously checked the extracted data and addressed any missing data to ensure data integrity and accuracy before proceeding with the analysis. Any disagreements arising were resolved through discussion among the review authors.

Quality Assessment

To assess the risk of bias (RoB) in each study included, two review authors utilized the Cochrane RoB tool for randomized trials version 2 (ROB2) [10]. This tool evaluates seven domains: (1) sequence generation (selection bias), (2) allocation sequence concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective outcome reporting (reporting bias), and (7) other potential sources of bias. For each domain, we categorized the risk as "low risk," "some concerns," or "high risk" based on predetermined criteria and followed the algorithms suggested by ROB 2.0 to make final judgments. This rigorous assessment allowed us to evaluate the quality and reliability of the studies included and ensure the validity of our findings.

Measures of Treatment Effect

Primary outcome measures:

- Improvement in NIHSS score.
- 90-day modified Rankin Scale (mRS) score.

Secondary outcome measures:

- Successful recanalization before thrombectomy.
- Successful recanalization (TICI 2b-3) after thrombectomy.
- Symptomatic intracerebral hemorrhage.
- Mortality.
- Barthel Index score of 95–100 at 90 days.
- Improvement in modified Rankin scale at 90 days.
- Median final lesion volume on follow-up imaging (mL).
- Time from stroke onset to groin puncture.

Synthesis Methods

For outcomes that constitute dichotomous data, the risk ratio (RR), along with its confidence interval (CI), was pooled in the Mantel-Haenszel random-effect model. For outcomes that constitute continuous data, the MD between the two groups from the baseline to the endpoint, with its CI, was pooled in the random-effect model.

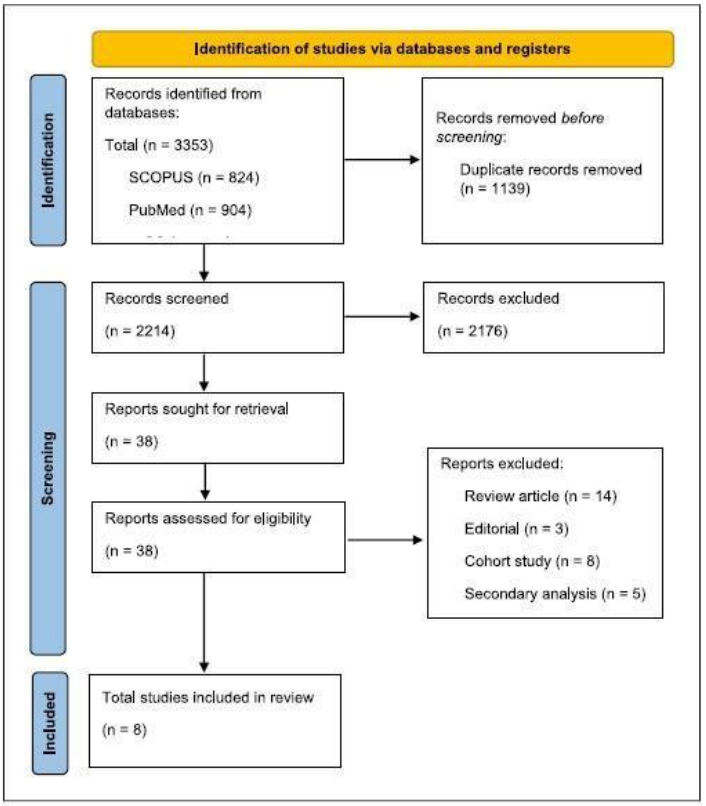


Fig. 1. PRISMA flow diagram of studies' screening and selection.

Results

Study Selection and Characteristics

As shown in Figure 1, 3,353 studies were identified in the initial search. After removing duplicates, 2,214 studies remained. Following the screening of titles and abstracts, 2,176 studies were excluded, leaving 38 articles for full-text screening. Of these, eight articles [4, 11–18] met the eligibility criteria and were included in our study.

Study and Treatment Characteristics

Study and treatment characteristics are summarized in Table 1. The analysis included 2,638 participants. The most common artery occlusion across the studies was M1, the first segment of the middle cerebral artery. The intervention used in all studies was BT, with thrombectomy alone as the comparator. Additional details are provided in Table 1 for a more comprehensive examination of study and treatment characteristics.

Risk of Bias

The RoB assessment is illustrated in Figure 2. Seven RCTs were classified as having low RoB, while one RCT was deemed to have moderate RoB.

Meta-Analysis

Efficacy Outcomes

Improvement in NIHSS Score

Five studies reported NIHSS score improvements after 24 h, and three studies reported improvements after 7 days. The meta-analysis using a fixed-effects model indicated that improvement in the NIHSS score from baseline favored the BT group (MD 0.96, 95% CI: [0.73–1.20], $p < 0.00001$). Subgroup analysis showed that the BT group had better improvement after 24 h (MD 0.94, 95% CI: [0.56–1.32], $p < 0.00001$) and after 7 days (MD 0.98, 95% CI: [0.67–1.29], $p < 0.00001$), as shown in Figure 3.

Favorable Outcome (mRS 0–2)

Eight studies (n = 2,638 patients) reported the frequency of patients with a favorable outcome based on the mRS score (ranging from zero to 2). The pooled RR for a favorable outcome (mRS 0–2) did not favor either technique (RR 1.05, 95% CI: [0.97–1.13]), as shown in Figure 4.

Successful Reperfusion before Thrombectomy

Five studies (n = 2,085 patients) reported the frequency of successful recanalization achieved with IVT before MT. The pooled RR for successful recanalization favored the BT group (RR 2.42, 95% CI: [1.43–4.10], p = 0.001), shown in Figure 5.

Successful Recanalization (TICI 2b-3) after Thrombectomy

Eight studies (n = 2,523 patients) reported the frequency of successful recanalization (TICI 2b–3) for both techniques. The pooled RR for successful recanalization (TICI 2b–3) favored the BT group (RR 1.05, 95% CI: [1.01–1.09], p = 0.009), as shown in Figure 6.

Barthel Index Score of 95–100 at 90 Days

Four studies (n = 1,294 patients) reported the Barthel Index. The pooled relative risk (RR) of a Barthel Index score of 95–100 at 90 days did not favor either technique (RR 1.13, 95% CI: [0.93–1.37], p = 0.22), as shown in Figure 7.

Improvement in Modified Rankin Scale at 90 Days

Six studies (n = 1,308 patients) reported improvement in the modified Rankin Scale at 90 days. The overall MD in improvement in mRS from baseline did not favor either technique (MD -0.04, 95% CI: [−0.22–0.13], p = 0.63), as shown in Figure 8.

Safety Outcomes

Symptomatic Intracerebral Hemorrhage

Eight studies (n = 4,731 patients) reported the frequency of symptomatic intracerebral hemorrhage (ICH). The pooled RR for ICH did not favor either technique (RR 1.23, 95% CI: [0.88–1.74], p = 0.23), as shown in Figure 9.

Mortality

Seven studies (n = 2,420 patients) reported 90-day mortality. The pooled RR for mortality did not favor either technique (RR 0.91, 95% CI: [0.75–1.10], p = 0.34), as shown in Figure 10.

Table 1. Studies selected for inclusion in the present meta-analysis

Study ID	Age, median (IQR), years		Sex, female, *n* (%)		Predominant occlusion location		Time from stroke onset to therapy start (hours), median (IQR)		ASPECTS (score), median (IQR)	
	MT + IVT	MT alone	MT + IVT	MT alone	MT + IVT	MT alone	MT + IVT	MT alone	MT + IVT	MT alone
LeCouffe et al. [12] (2021)	69 (61–77)	72 (62–80)	122 (45.9)	112 (41)	M1	M1	135 (106–185)	130 (103–180)	9 (8–10)	9 (8–10)
Mitchell et al. [13] (2022)	70 (61–78)	69 (60–79)	68 (47)	59 (40)	M1	M1	–	–	10 (9–10)	10 (9–10)
Zi et al. [14] (2021)	70 (60–78)	70 (60–77)	52 (44.1)	50 (43.1)	M1	M1	210 (179–55)	200 (155–247)	8 (7–9)	8 (7–9)
Pang W et al. [15] (2022)	64 (59–69)	63 (59–68)	14 (35)	16 (40)	M1	M1	–	–	–	–
Renú et al. [16] (2022)	73 (71–76)	73 (69–67)	28 (46)	24 (46)	M2	M2	–	–	9 (9–10)	10 (8–10)
Suzuki et al. [4] (2021)	76 (67–80)	74 (67–80)	31 (30)	45 (45)	M1	M1	–	–	–	–
Fischer et al. [17] (2022)	72 (65–81)	73 (64–81)	104 (50)	105 (52)	M1	M1	107 (99–102)	198 (91–155)	8 (7–9)	8 (7–9)
Yang et al. [18] (2020)	69 (61–76)	69 (61–76)	148 (45)	138 (42.2)	M1	M1	213 (126–215)	167 (125–206)	9 (7–10)	10 (7–10)

IQR, interquartile range; MT, mechanical thrombectomy; IVT, intravenous thrombolysis; ASPECTS, Alberta Stroke Program Early CT Score; M1, proximal part of the middle cerebral artery; M2, distal part/branch of the middle cerebral artery.

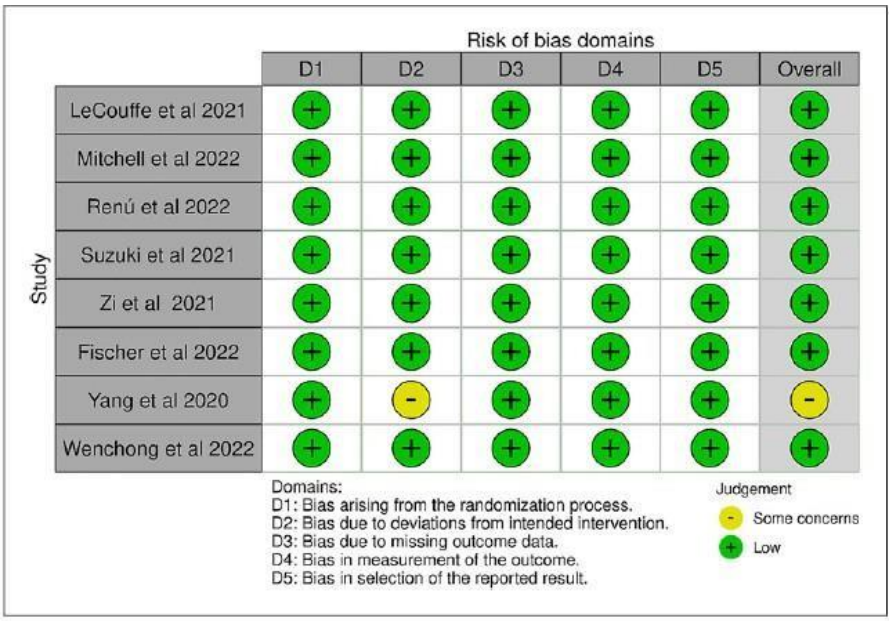


Fig. 2. Risk of bias assessment for the studies selected for inclusion in the analysis.

Median Final Lesion Volume on Follow-Up Imaging

Three studies (n = 1,308 patients) reported the median final lesion volume. The overall MD in the median final lesion volume did not favor either technique (MD −4.16, 95% CI: [−9.41–1.09], p = 0.12), as shown in Figure 11.

Time from Stroke to Groin Puncture

Five studies (n = 3,985 patients) reported the time from stroke onset to groin puncture. The analysis using a fixed-effects model showed that the MT alone group had a shorter time from onset of stroke to puncture (MD 9.91, 95% CI: [4.31–15.52], p = 0.005), as shown in Figure 12.

Discussion

The main results of our meta-analysis comparing BT (combination of IVT and MT) to thrombectomy alone in stroke patients with a large artery occlusion revealed that both treatment strategies are safe and effective measures. Functional outcomes, mortality rates, and rates for symptomatic intracerebral hemorrhages and long-term recovery parameters such as Barthel Index scores and mRs scores were comparable for patients treated using both modalities. However, our analysis showed some advantages for the BT group. Patients treated with BT were more likely to achieve successful recanalization before and after the thrombectomy procedure. This increased success in restoring blood flow is likely why these patients showed more significant improvements in their neurological status (as measured by the NIHSS) both at 24 h and at 7 days after treatment compared to those who received thrombectomy alone.

We compared our findings to those of previous meta-analyses within the same domain. Cuadra-Campos et al. [19], in their meta-analysis of six randomized open-label clinical trials, found no significant difference in functional independence between the two groups (48.8 vs. 50.7%), although the BT group had slightly better outcomes (OR = 0.93, 95% CI: 0.79–1.09, p = 0.37; I^2 = 0%). They also found that successful reperfusion was higher in the BT group (OR = 0.75, 95% CI: 0.60–0.94, p = 0.01; I^2 = 0%). Similarly, Wang et al.'s review, comprising 29 observational studies and one RCT, yielded results favoring BT in terms of functional independence, mortality, and recanalization rates, with ORs of 0.67, 1.23, and 1.07, respectively [2]. Conversely, the non-inferiority meta-analysis by Charles B. Majoie et al. [20] highlighted

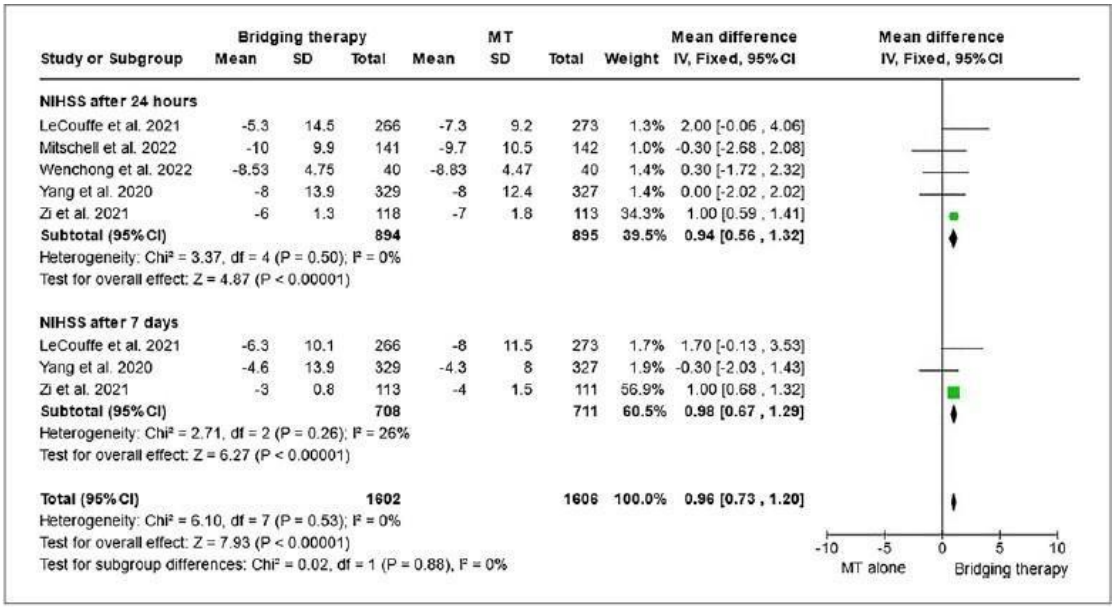


Fig. 3. Forest plot of mean differences in improvement in NIHSS score. Std, standard mean difference; SD, standard deviation; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

that combining IVT with endovascular treatment was not inferior to endovascular treatment alone based on the mRS score at 90 days. While we are presenting these newer significant clinical findings, it is important to note that our meta-analysis included a larger number of patients across eight clinical trials. Additionally, our statistical approach provides a more accurate depiction of effect size estimates, making our results more reliable, and enhances the evidence base for guiding treatment decisions.

Evaluation of Successful Recanalization before and after Recanalization

We found that BT was more effective in achieving successful recanalization both before and after thrombectomy compared to thrombectomy alone. Patients who received BT were significantly more likely to have their blood flow restored before the thrombectomy procedure, likely due to the clot-dissolving effects of IVT. This preliminary restoration of blood flow helps make the subsequent mechanical removal of the clot more effective.

Furthermore, even after the thrombectomy procedure, patients in the BT group continued to show better outcomes. The combined approach of IVT and MT seems to facilitate a more thorough and efficient restoration of blood flow, leading to higher rates of successful recanalization (TICI 2b–3). These findings align with previous studies [19, 21] and suggest that the initial use of IVT can enhance the effectiveness of the subsequent mechanical intervention.

By starting the reperfusion process earlier with IVT, BT not only aids in breaking down the clot but also primes the affected vessels for more effective mechanical clot removal. This dual approach appears to offer a synergistic benefit, resulting in better overall recanalization rates compared to MT alone. However, it is important to consider that BT might also increase the risk of hemorrhagic transformation, which can complicate the recanalization process.

Assessment of Stroke Severity and Prediction of Prognosis

Patients treated with BT had a greater improvement in NIHSS score from baseline compared to those treated with thrombectomy alone. This finding is supported by our fixed-effect model analysis, which

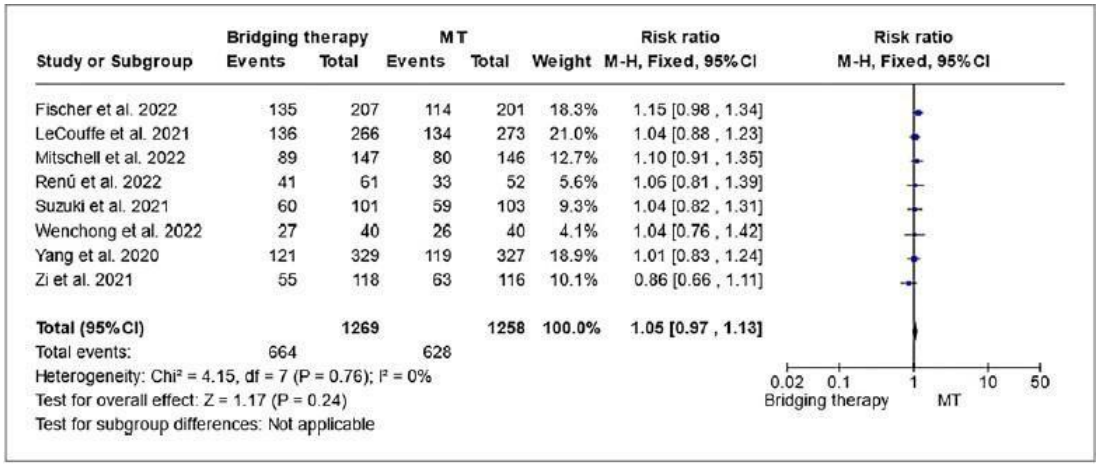


Fig. 4. Forest plot summarizing the pooled RR of the dichotomous study outcome (mRS 0–2) between the bridging therapy group and the MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

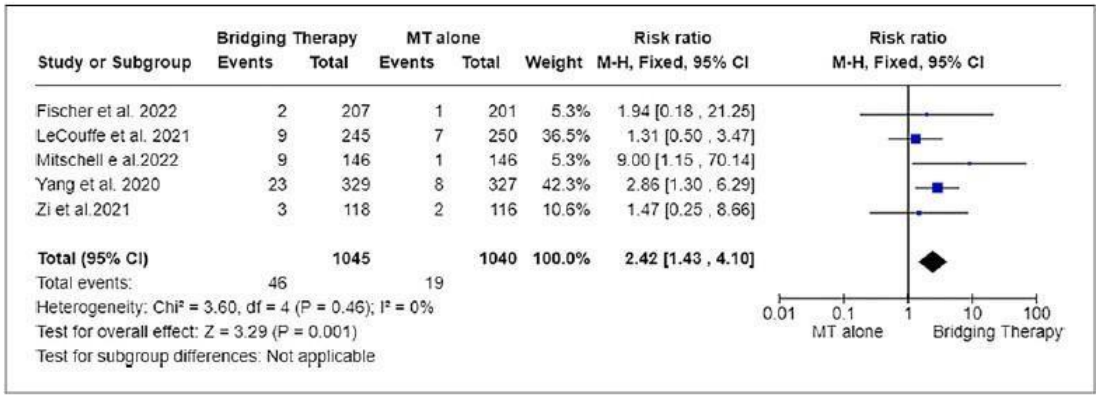


Fig. 5. Forest plot summarizing the pooled RR of the dichotomous study outcome (Successful recanalization before Thrombectomy) between the bridging therapy group and the MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; overall effect; P, *p* value for significance of overall effect.

showed that the improvement in NIHSS from baseline significantly favored the BT group. Additionally, subgroup analysis indicated that this improvement was consistent both after 24 h and after 7 days. This significant improvement highlights the potential benefits of combination therapy. The initial administration of IVT may help in reducing clot burden and facilitating better mechanical removal of the clot, leading to early

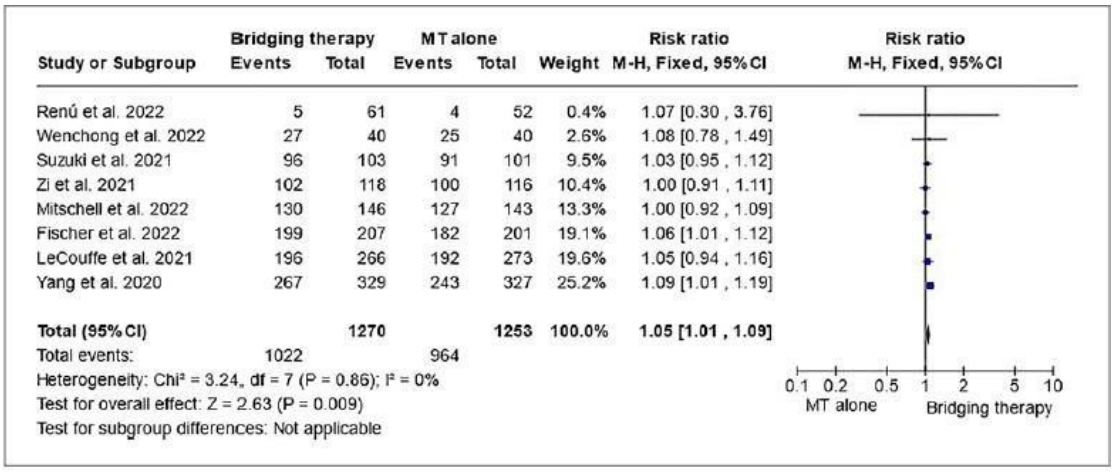


Fig. 6. Forest plot summarizing the pooled RR of the dichotomous study outcome (Successful recanalization (TICI 2b–3) after Thrombectomy) between the bridging therapy group and the MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

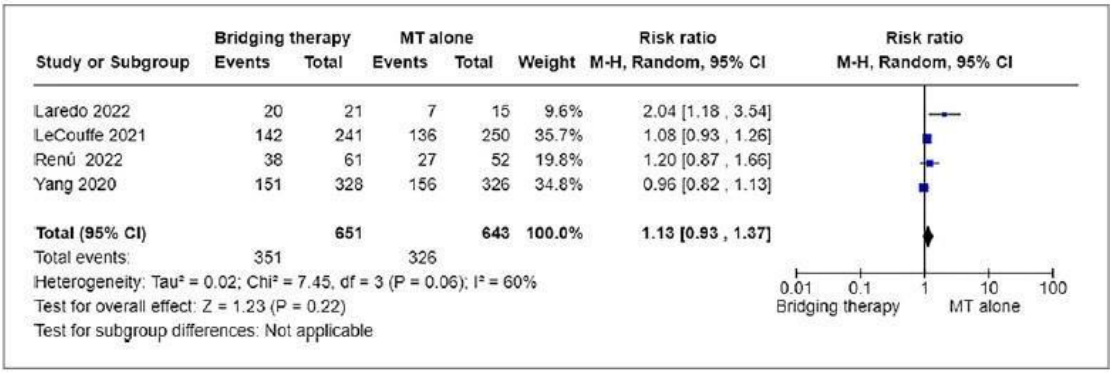


Fig. 7. Forest plot summarizing the pooled RR of the dichotomous study outcome (Barthel Index score) between the bridging therapy group and the MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

and effective reperfusion. This early reperfusion likely results in reduced infarct size and improved neurological function, which is reflected in the NIHSS scores.

While previous studies, such as those by Campbell et al. [22], suggested that MT alone might lead to better neurological outcomes, our findings indicate that the combination approach of BT actually provides greater improvement in neurological status, emphasizing the importance of achieving early and effective reperfusion, which is more readily accomplished with the dual approach of BT.

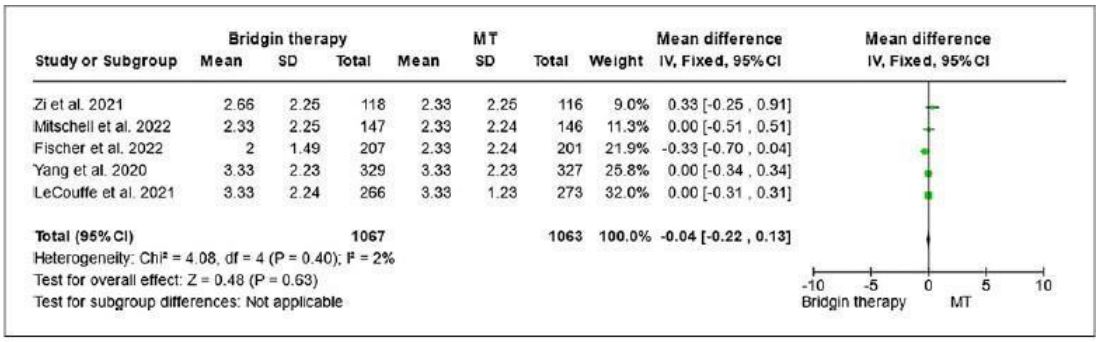


Fig. 8. Forest plot summarizing the pooled RR of the dichotomous study outcome (Improvement in modified Rankin scale at 90 days) between the bridging therapy group and the MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

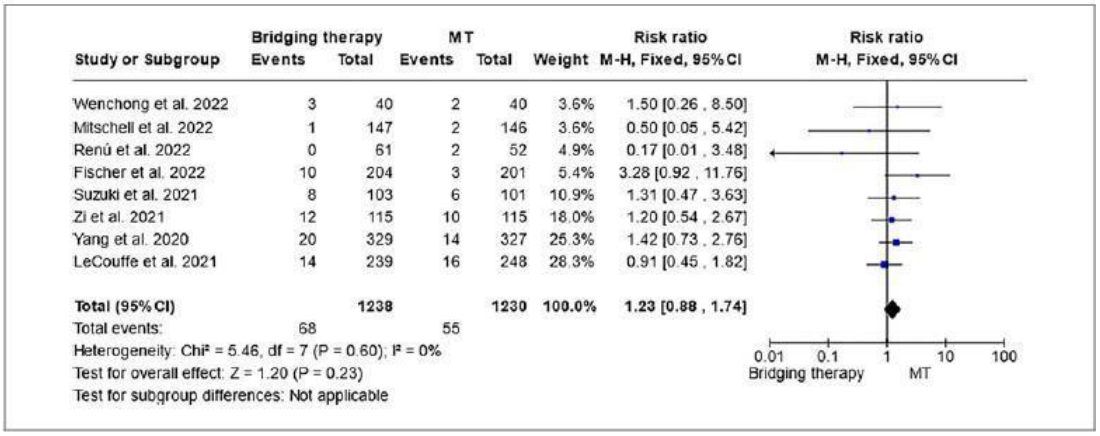


Fig. 9. Forest plot summarizing the pooled RR of the dichotomous study outcome (Symptomatic intracerebral haemorrhage) between the bridging therapy group and the MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

However, it is important to note that while NIHSS scores reflect immediate neurological improvement, they may not always translate into better long-term functional independence or quality of life, as measured by metrics like mRS scores. Therefore, while BT shows significant short-term neurological benefits, further studies are needed to evaluate its impact on long-term outcomes and overall quality of life for stroke patients.

Emphasizing the Importance of Time from Onset to Puncture

The importance of the time from stroke to puncture cannot be overstated in the treatment of acute ischemic stroke. Studies have shown that faster treatment leads to better outcomes for patients, with each minute delay resulting in a loss of 1.9 million neurons and a decrease of 3–4% in the likelihood of a good outcome [23]. In

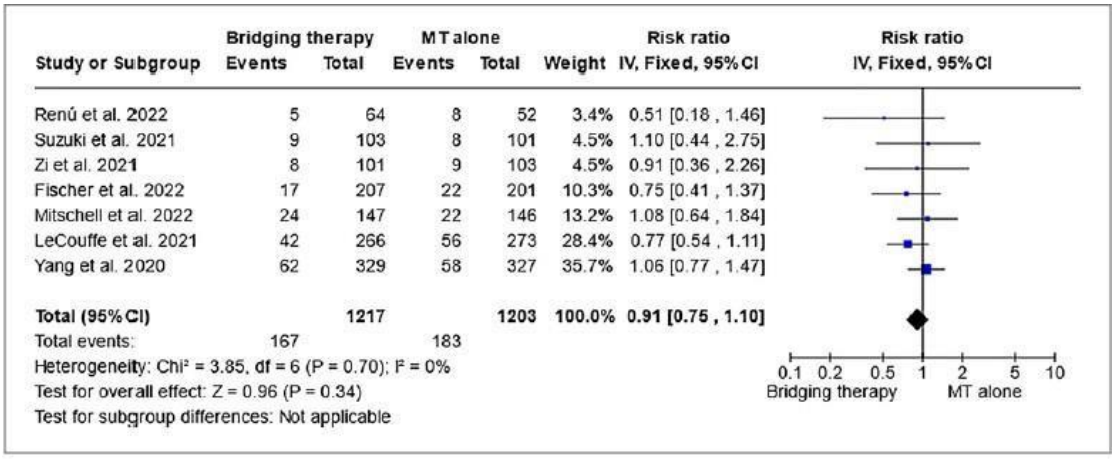


Fig. 10. Forest plot summarizing the pooled RR of the dichotomous study outcome (Mortality) between the bridging therapy group and MT alone group. RR, risk ratio; P, *p* value; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

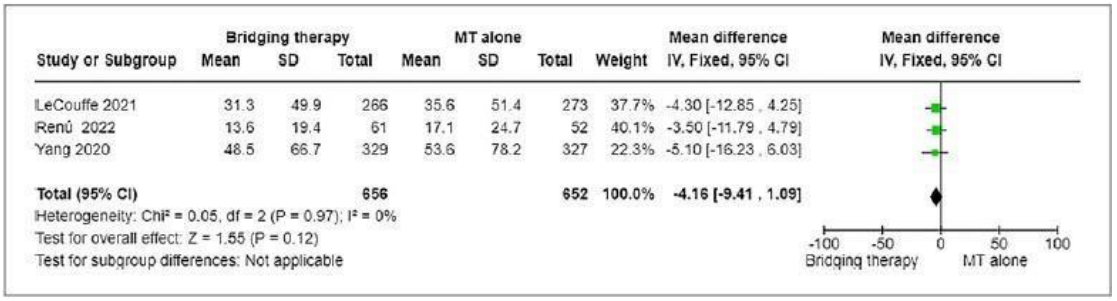


Fig. 11. Forest plot of mean differences in median final lesion volume. Std, standard mean difference; SD, standard deviationl; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

2015, the Society of Neurointerventional Surgery set benchmarks for quality assurance, recommending a door-to-puncture time of <60 min and a door-to-reperfusion time of <90 min [24]. However, despite these efforts, delays in prehospital care, specifically from symptom onset to hospital door arrival (onset-to-door time) persist in some cases, potentially undermining the benefits achieved during in-hospital treatment [25]. Our analysis revealed that the time from stroke onset to groin puncture was shorter in the thrombectomy alone group than in the BT group. This is consistent with the existing literature, which has shown that MT alone is associated with faster treatment times than BT [23]. While there was a statistically significant difference of just 10 min between the times from stroke onset to puncture for the MT alone compared to the BT group, it is uncertain whether this small difference would significantly affect patient outcomes.

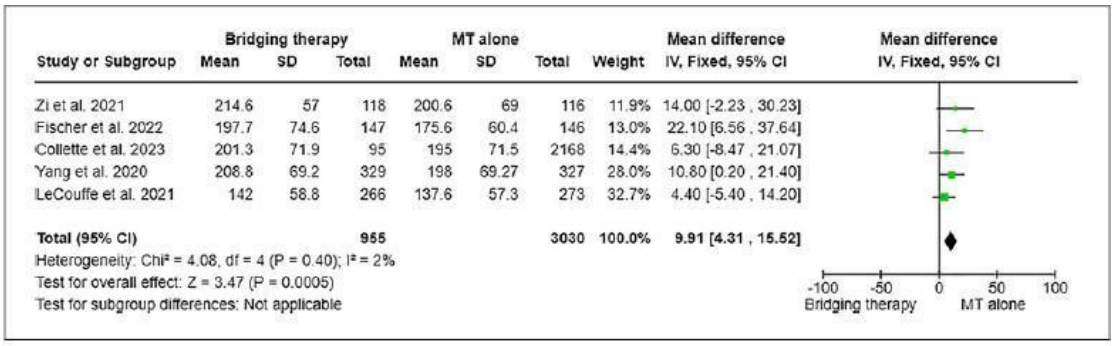


Fig. 12. Forest plot of mean differences in time from stroke to groin puncture. Std, standard mean difference; SD, standard deviationl; CI, confidence interval; df, degrees of freedom; Chi^2, statistical test for heterogeneity; P, *p* value of Chi^2 (evidence of heterogeneity of intervention effects); I^2, degree of heterogeneity between trials; Z, test for overall effect; P, *p* value for significance of overall effect.

Symptomatic Intracranial Hemorrhage

While our analysis of sICH found no significant difference in the risk of sICH between the MT and BT groups (RR, 1.18; 95% CI: [0.86–1.62]; $p = 0.32$), our findings are consistent with some studies in the literature but diverge from others. Kolahchi et al. reported significantly higher rates of sICH in the BT group compared to MT (OR = 0.73 [95% CI, 0.56–0.96], $I^2 = 0\%$, $p = 0.02$), particularly in the non-RCT subgroup and the combined group of patients with occlusion of the anterior and/or posterior circulation [26]. However, the absence of significant differences in the anterior group analysis and subgroup analysis of RCT and non-RCT studies complicates the interpretation of their results. This discrepancy might be attributed to variations in study designs or other unaccounted factors across studies. Similarly, Cuadra-Campos et al. found no statistically significant differences in the risk of sICH between the MT and BT groups [19]. These findings align with our meta-analysis results and suggest that, overall, both treatment strategies are associated with comparable rates of sICH.

Nevertheless, it is important to recognize the potential for publication bias and the inherent limitations of the studies included in our analysis. Variability in patient populations and methodologies could introduce biases and confounders that could influence the observed outcomes. Additionally, the definition and assessment of sICH vary between studies, potentially affecting the comparability of results.

Evidence Update and Meaning of Study

To our knowledge, this is the only study to provide a pooled effect for a large number of dependent variables. Although the previous meta-analysis [19] provided a comparable number of included studies, they predominantly utilized OR for risk analysis, we employed RR for several reasons. First, the outcomes assessed in our study, including sICH, mortality, recanalization, and functional outcome measured by an mRS score of 0–2, were binary events, making RR more suitable. RR allows for a direct comparison of event risks between patients with AIS receiving different treatment strategies, facilitating a clear understanding of relative risk associations. RR is easier to interpret in clinical settings compared to OR, which can be challenging to grasp intuitively. It also allowed us to quantify risk differences between treatment groups more directly, especially given the predominance of RCTs in our analysis. Moreover, RR provides a clearer measure of the impact of intervention on adverse events and functional outcomes, aiding clinicians in making informed decisions and assessing risks more accurately in clinical practice. Thus, in addition to adding a substantial amount of new data, our statistical approach provides a more accurate depiction of effect size estimates, thereby enhancing the evidence base for guiding treatment decisions and optimizing patient care.

To further contextualize our findings, we considered the guidelines provided by Powers et al. [11]. The guidelines issued by the American Heart Association/American Stroke Association offer evidence-based recommendations for healthcare professionals involved in the care of patients with stroke. They affirmed the critical role of reperfusion therapies, such as IVT and endovascular thrombectomy, in optimizing patient outcomes. Our findings align with these recommendations, particularly

regarding the importance of timely intervention and need for individualized treatment approaches based on patient characteristics and stroke severity.

Although our meta-analysis provides valuable insights into treatment outcomes, it is essential to interpret our findings in the broader stroke care landscape outlined in the guidelines by Powers et al. [11]. Clinical decision making should consider factors such as patient eligibility, treatment accessibility, and institutional resources to ensure the most effective and appropriate treatment for each patient.

Limitations

Our meta-analysis is also subject to a number of limitations, which should be acknowledged at this point. In a field with a relatively new established therapeutic measure (MT), it can be expected that there will only be a limited amount of investigations available for analysis. Therefore, a major limitation of this study is the small number of studies included in the analysis. Furthermore, no data were available on parameters related to vascular status, which might have influenced the selection of patients for inclusion in one of the studies concerned, and we were therefore unable to determine the reasons such parameters were used to exclude potentially eligible patients. However, we also need to underline the comprehensive character of our analysis: we considered all available studies of relevance on the topic, an aspect that makes our meta-analysis highly relevant with regard to recommendations for clinical practice.

Conclusion

BT, combining IVT and MT, is more effective than MT alone, showing greater improvements in NIHSS scores and higher rates of successful reperfusion before and after thrombectomy. Although MT alone had a shorter time from stroke onset to groin puncture by 9.91 min, this did not result in better NIHSS improvements at 24 h or 7 days. While NIHSS scores indicate immediate neurological improvement, they may not predict long-term functional independence. Thus, further studies are needed to assess its impact on long-term outcomes and quality of life.

Statement of Ethics

The prespecified protocol for this review is registered with PROSPERO (CRD42024498238). An ethics statement was not required for this study type since no human or animal subjects or materials were used.

Conflict of Interest Statement

The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

Funding Sources

The authors have received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

Ali Hammed MD, Almonzer Al-Qiami, Christian Tanislav, MD: conceptualized and designed the study and performed data analysis. Ali Hammed, Almonzer Al-Qiami and Christian Tanislav, MD: wrote the manuscript. Josef Rosenbauer MD, Asmaa Zakria Alnajjar, and Rawan Hamamreh: contributed to writing and editing the manuscript. Elsayed Mohamed Hammad, Zina Otmani, Ahmad Alzawahreh, Nada G.Hamam, and Eman Ayman Nada: performed data extraction and assessed the RoB. Karel Kostev, DMSc, PhD, and Gregor Richter MD: reviewed and provided critical feedback on the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Fischer U, Kaesmacher J, Mendes Pereira V, Chapot R, Siddiqui AH, Froehler MT, et al. Direct mechanical thrombectomy versus combined intravenous and mechanical thrombectomy in large-artery anterior circulation stroke: a topical review. Stroke. 2017;48(10):2912–8. https://doi.org/10.1161/STROKEAHA.117.017208

2 Wang Y, Wu X, Zhu C, Mossa-Basha M, Malhotra A. Bridging thrombolysis achieved better outcomes than direct thrombectomy after large vessel occlusion: an updated meta-analysis. Stroke. 2021;52(1):356–65. https://doi.org/10.1161/STROKEAHA.120.031477

3 IV thrombolysis + thrombectomy vs. Thrombectomy alone for acute ischaemic stroke: American college of cardiology. American college of cardiology. 2024. Available from: https://www.acc.org/latest-in-cardiology/journal-scans/2024/02/15/17/58/time-to-treatment-with

4 Suzuki K, Matsumaru Y, Takeuchi M, Morimoto M, Kanazawa R, Takayama Y, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. JAMA. 2021;325(3):244–53. https://doi.org/10.1001/jama.2020.23522
5 Rodriguez-Calienes A, Galecio-Castillo M, Farooqui M, Hassan AE, Jumaa MA, Divani AA, et al. Safety outcomes of mechanical thrombectomy versus combined thrombectomy and intravenous thrombolysis in tandem lesions. Stroke. 2023;54(10):2522–33. https://doi.org/10.1161/STROKEAHA.123.042966
6 Higgins JPT, Thomas J, Chandler J. Cochrane Handbook for systematic Reviews of interventions version 6.4. Cochrane; 2023. (updated August 2023) Available from: www.training.cochrane.org/handbook
7 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
8 Review Manager (RevMan) Version (7.5.0) The Cochrane Collaboration; 2024. Available from: revman.cochrane.org.
9 Covidence systematic review software. Veritas Health Innovation. Melbourne, Australia. Available from: www.covidence.org
10 Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. https://doi.org/10.1136/bmj.d5928
11 Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(9):2032–60.
12 LeCouffe NE, Kappelhof M, Treurniet KM, Rinkel LA, Bruggeman AE, Berkhemer OA, et al. A randomized trial of intravenous alteplase before endovascular treatment for stroke. N Engl J Med. 2021;385(20):1833–44. https://doi.org/10.1056/NEJMoa2107727
13 Mitchell PJ, Yan B, Churilov L, Dowling RJ, Bush SJ, Bivard A, et al. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. Lancet. 2022;400(10346):116–25. https://doi.org/10.1016/S0140-6736(22)00564-5
14 Zi W, Qiu Z, Li F, Sang H, Wu D, Luo W, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. JAMA. 2021;325(3):234–43. https://doi.org/10.1001/jama.2020.23523
15 Pang W, Chen Z, Zhang Z, et al. Observation on the efficacy and safety of direct thrombectomy and bridging therapy in treating patients with acute large vessel occlusive ischaemic stroke within 4.5 h after onset. Journal of Qiqihar Medical University, 2022, Vol. 43, No.1.
16 Renú A, Millán M, San Román L, Blasco J, Martí-Fàbregas J, Terceño M, et al. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. JAMA. 2022;327(9):826–35. https://doi.org/10.1001/jama.2022.1645
17 Fischer U, Kaesmacher J, Strbian D, Eker O, Cognard C, Plattner PS, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet. 2022;400(10346):104–15. https://doi.org/10.1016/S0140-6736(22)00537-2
18 Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. N Engl J Med. 2020;382(21):1981–93. https://doi.org/10.1056/NEJMoa2001123
19 Cuadra-Campos MDC, Vásquez-Tirado GA, Bravo-Sotero MDC. Direct mechanical thrombectomy versus bridging therapy in acute ischemic stroke: a systematic review and meta-analysis of randomized clinical trials. World Neurosurg X. 2024;21(21):100250. https://doi.org/10.1016/j.wnsx.2023.100250
20 Majoie CB, Cavalcante F, Gralla J, Yang P, Kaesmacher J, Treurniet KM, et al. Value of intravenous thrombolysis in endovascular treatment for large-vessel anterior circulation stroke: individual participant data meta-analysis of six randomised trials. Lancet. 2023;402(10406):965–74. https://doi.org/10.1016/S0140-6736(23)01142-X
21 Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–31. https://doi.org/10.1016/S0140-6736(16)00163-X
22 Albers GW, Lansberg MG, Kemp S, Tsai JP, Lavori P, Christensen S, et al. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). Int J Stroke. 2017;12(8):896–905. https://doi.org/10.1177/1747493017701147
23 Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95. https://doi.org/10.1056/NEJMoa1415061
24 McTaggart RA, Ansari SA, Goyal M, Abruzzo TA, Albani B, Arthur AJ, et al. Initial hospital management of patients with emergent large vessel occlusion (ELVO): report of the standards and guidelines committee of the Society of Neuro-Interventional Surgery. J Neurointerv Surg. 2017;9(3):316–23. https://doi.org/10.1136/neurintsurg-2015-011984
25 Pulvers JN, Watson JDG. If time is brain where is the improvement in prehospital time after stroke? Front Neurol. 2017;8:617. https://doi.org/10.3389/fneur.2017.00617
26 Kolahchi Z, Rahimian N, Momtazmanesh S, Hamidianjahromi A, Shahjouei S, Mowla A. Direct mechanical thrombectomy versus prior bridging intravenous thrombolysis in acute ischemic stroke: a systematic review and meta-analysis. Life Basel Switz. 2023;13(1):185. https://doi.org/10.3390/life13010185

3.2. Zweites Manuskript

Surgical versus Conservative Management of Chronic Sciatica (>3 Months) Due to Lumbar Disc Herniation: Systematic Review and Meta-Analysis.

Hammed A, Al-Qiami A, Alsalhi H, Almansi A, Massoud M, Alzawahreh A, Hamouda A, Tanislav C. Cureus. 2024 May 4;16(5):e59617. doi: 10.7759/cureus.59617. PMID: 38832179; PMCID: PMC11145364.

Cureus
Part of SPRINGER NATURE

Open Access Review Article

Published via Negida Research Academy

Surgical vs. Conservative Management of Chronic Sciatica (>3 Months) Due to Lumbar Disc Herniation: Systematic Review and Meta-Analysis

Received 02/03/2024
Review began 04/12/2024
Review ended 04/18/2024
Published 05/04/2024

DOI: 10.7759/cureus.59617

Ali Hammed [1], Almonzer Al-Qiami [2], Hamza Alsalhi [3, 4], Amjad Almansi [5], Mahmoud Massoud [6], Ahmad Alzawahreh [7], Abdelrahman Hamouda [8], Christian Tanislav [1]

1. Department of Geriatrics and Neurology, Diakonie Hospital Jung Stilling, Siegen, DEU 2. Neurological Surgery, Faculty of Medicine, Kassala University, Kassala, SDN 3. Negida Academy, Medical Research Group of Egypt, Arlington, USA 4. Faculty of Medicine, Hashemite University, Amman, JOR 5. Neurology, Prince Hamza Hospital, Amman, JOR 6. Neurology, Faculty of Medicine, Al-Azhar University, Damietta, EGY 7. Neurology, Faculty of Medicine, The Hashemite University, Zarqaa, JOR 8. Department of Neurologic Surgery, Mayo Clinic, Rochester, USA

Corresponding author: Abdelrahman Hamouda, hamouda.abdelrahman@mayo.edu

Abstract

Sciatica, characterized by leg or back symptoms along the sciatic nerve pathway, often manifests as a chronic condition lasting over 12 weeks. Decision-making between nonoperative treatment and immediate microdiscectomy for chronic sciatica remains challenging, due to the complex relationship between symptom duration, severity, and lumbar discectomy outcomes. In this systematic review, we conducted a comprehensive search across Scopus, PubMed, Web of Science, and the Cochrane Library, identifying relevant two-arm clinical trials up to September 2023. Rigorous screening and data extraction were performed by two independent reviewers, with study quality evaluated using the risk of bias 2 (RoB) tool. This meta-analysis incorporated four studies comprising 352 participants. Our analysis revealed that conservative treatment was associated with a significant reduction in leg pain and improvement in, SF mental, and physical scores compared to surgical intervention. However surgical treatment demonstrated significant improvement in back pain. In conclusion, our findings suggest that surgical intervention may be more effective than non-surgical treatment for chronic sciatica-related back pain. Conservative treatment significantly reduces leg pain while improving mental and physical health outcomes. Ultimately, our findings support conservative as the initial approach unless surgery is warranted, particularly in cases with neurological deficits or cauda equina syndrome.

Categories: Neurology, Neurosurgery
Keywords: conservative management, surgical management, leg vas score, back vas score, lumbar disc herniation, chronic sciatica

Introduction And Background

Sciatica encompasses a wide range of leg and back symptoms, commonly characterized by a sharp or burning pain along the sciatic nerve path extending from the buttock to the leg, and possibly reaching the foot or ankle. [1] Sciatica is a global problem, with lifetime incidence ranging from 13% to 40%. Approximately 90% of instances of sciatica are attributed to lumbar disc herniations (LDH) [2], additionally, it can result from lower back muscle spasms, pyriform syndrome, neural foraminal stenosis, spinal stenosis, and spondylolisthesis [1]. Complete recovery is rare in sciatica caused by LDH, often resulting it prolonged durations of discomfort, and drastically impacting the patients' quality of life [3]. Albeit rare, if left untreated, it can result in muscle weakness, absence of tendon reflexes or sensory deficits, and bladder dysfunction in some cases.

LDH sciatica treatment options are conservative measures such as physical therapy and pharmacotherapy, or surgical interventions, including discectomy and decompression procedure [4]. Conservative treatment of LDH sciatica can lead to up to a 90% improvement in patients [5], while surgical treatment offers comparable results but is recommended only if symptoms persist following a trial of conservative treatment [6]. However, previous literature failed to show long-term superiority of one approach over the other, even though surgical intervention may offer short-term advantages [7]. Thus, choosing between nonoperative treatment and immediate microdiscectomy, especially for chronic sciatica associated with LDH (>12 weeks) remains a hassle for surgeons and patients [4].

Limited trials comparing surgical to non-surgical treatments for chronic sciatica have hindered the establishment of clear guidelines. Therefore, this systematic review aims to assess the efficacy of surgical intervention versus non-surgical alternatives for individuals with chronic sciatica associated with LDH.

Review

Methods

Our study followed the widely accepted PRISMA guidelines for systematic reviews and meta-analyses, ensuring the utmost accuracy and reliability of our findings [8]. The meta-analysis was registered on

How to cite this article
Hammed A, Al-Qiami A, Alsalhi H, et al. (May 04, 2024) Surgical vs. Conservative Management of Chronic Sciatica (>3 Months) Due to Lumbar Disc Herniation: Systematic Review and Meta-Analysis. Cureus 16(5): e59617. DOI 10.7759/cureus.59617

PROSPERO under ID CRD42023469621.

Search strategy and selection criteria

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2011), PubMed, SCOPUS, and Web of Science from inception to November 2023 for relevant randomized clinical trials using the following search strategy: (Sciatica OR Sciatic Neuralgia OR Neuralgias, Sciatic) AND (Conservative Treatments OR Treatment, Conservative OR Conservative Management OR Conservative Managements OR Conservative Therapy OR Conservative Therapies OR Epidural Injections OR Steroid Injections OR Nerve Blocks OR Nerve Root Blocks OR Heat Therapy OR Cold Therapy OR Physiotherapy OR Exercise Therapy OR Infrared Therapy) AND (Surgical Interventions OR Operative Procedures OR Operative Procedure OR Surgical Procedures OR Procedure, Surgical OR Surgical Management OR Surgical Managements OR Lumbar Discectomy OR Microdiscectomy OR Laminectomy OR Laminotomy OR Lumbar Decompression).

This study includes only parallel double-arm randomized clinical trials conducted on adult patients (above 18 years) diagnosed with chronic sciatica for more than 3 months due to LDH at the levels of L3-L4, L4-L5, and L5-S1 (Table *1*). The comparison was made between patients treated with surgical microdiscectomy and patients with the same diagnosis treated with non-surgical methods such as spinal manipulation, epidural steroid injection, functional education, physiotherapy, or oral analgesics.

Included Criteria for the Study	Excluded Criteria
Parallel double-arm randomized clinical trials, adult patients aged 18 years and above, patients diagnosed with chronic sciatica lasting more than 3 months, patients diagnosed with lumbar disc herniation at the levels of L3-L4, L4-L5, and L5-S1, comparison between patients treated with surgical microdiscectomy and patients treated with non-surgical methods. Non-surgical methods include spinal manipulation, epidural steroidal injection, functional education, physiotherapy, or oral analgesics.	Studies that are not parallel double-arm randomized clinical trials, patients with acute sciatica (duration less than or equal to 3 months), patients with other causes for lumbar pain such as deformity, scoliosis, or any other underlying spinal pathology not related to lumbar disc herniation.

TABLE 1: The inclusion and exclusion criteria

To screen the articles we obtained, we utilized the Rayyan website [9]. Our team of reviewers carefully evaluated the titles and abstracts of the retrieved citations. The article screening process was conducted independently. The eligibility screening process was conducted in two stages: initially, by screening abstracts and subsequently by retrieving and screening full-text articles to ascertain their eligibility for meta-analysis. In the event of any conflicts arising during the screening process, our team resolved them through consensus. Ultimately, we identified four randomized controlled trials (RCTs) that were eligible for data extraction.

The primary outcomes we assessed included the visual analog scale (VAS) for leg pain intensity and back pain intensity. Secondary outcomes included safety outcomes such as adverse events following surgical or non-surgical treatment, and the Short Form-36 (SF-36) mental and physical components were also assessed. For each outcome, data were obtained at 6 weeks (1.5 months), 3 months, and 6 months follow-up durations.

Data extraction and management

Two authors extracted data independently using specially developed data extraction forms. Baseline data were collected on participants, including age, sex, number of participants, number of smokers, level of LDH, duration of pain complaints, and physical status. Primary outcomes (leg pain intensity and back pain intensity), in addition to secondary outcomes (SF-36 mental and physical), were recorded.

Risk of bias assessment

Two authors reviewed the included studies to assess their potential risk of bias (RoB). Rob 2 tool was used. They evaluated each study based on specific criteria such as random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other sources of bias. The authors used the recommended methods by The Cochrane Collaboration to assign a judgment of low risk, high risk, or unclear (due to lack of information or uncertainty over the potential for bias) [10]. Any disagreements between the authors were resolved through consensus, and a third author was consulted if necessary to resolve any remaining disagreements.

Data analysis

We analyzed the study results that are both clinically and statistically homogeneous using the Review Manager software [11]. In this meta-analysis, the Mantel-Haenszel test was used for dichotomous outcomes, and the inverse variance method was used for continuous outcomes in a random-effects model. In cases

where there is not enough data for meta-analysis, or if the included studies have diverse outcomes, we presented a narrative synthesis.

Two authors evaluated the study participants, interventions, and outcomes to ensure clinical homogeneity. Meta-analysis was conducted if both authors agreed that the criteria were met. We used the I statistic to measure statistical heterogeneity. When heterogeneity was found, a sensitivity test or meta-regression analysis was warranted.

Results

Study Selection

As demonstrated in Figure *1*, 1598 studies were identified in the initial search, with 1279 remaining after removing duplicates. After screening titles and abstracts, 1155 studies were excluded, resulting in 124 articles for full-text screening. Of these articles, four were included, while 107 were excluded with reasons.

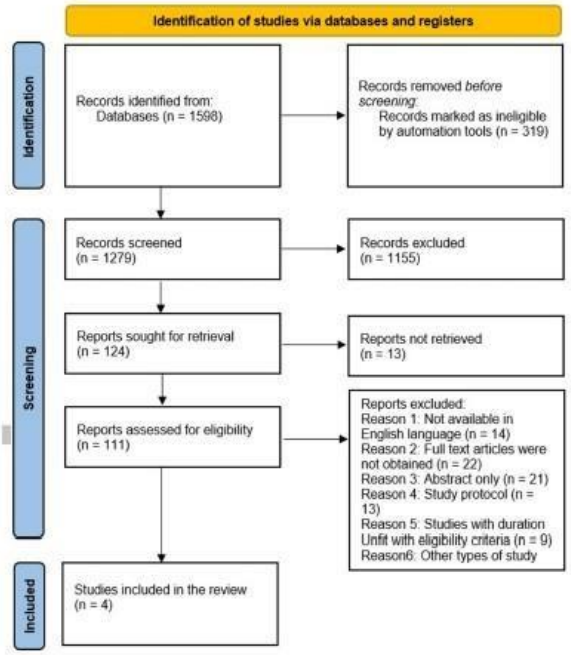


FIGURE 1: PRISMA flow diagram of the study selection process

Study and Treatment Characteristics

Study and treatment characteristics are summarized in Table *2*. A total of 352 participants (average age 40.4 ± 4.30 years, 202 (57.4) were male) were included in the analysis. The duration of complaints ranged from 3 to 12 months and L5-S1 was the most reported affected spine level. The intervention used across the studies was microdiscectomy, while the comparator involved conservative treatments such as day-to-day functioning education, physiotherapy, oral analgesics, and steroid injections. Additional details are available in Table *2* for a more in-depth examination of the study and treatment characteristics.

Study ID	Type of Intervention & Comparator		Age (Years) (Mean±SD)		Level of LDH		Gender (Male) N. (%)		Number of Smokers		Medications at Intake		Work Status		Duration of Complaint (Months)	
	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Compar
McMorland et al. 2010 [12]	Surgical microdiscectomy	Epidural steroid/local anesthetic injection	41.9	41.8	L3-L4 (1), L4-L5 (8), L5–S1 (11)	L3-L4 (0), L4- L5 (11), L5–S1 (9)	13 (65%)	11 (55%)	22	23	None (3), Over-the-counter (2), Prescription Nonnarcotic (12), Narcotics (3)	None (3), over-the-counter (1), Prescription Nonnarcotic (13), Narcotics (3)	Employed (8), Medical leave (9)	Employed (8), medical leave (11), unemployed (1)	95±34	55±61
Abd-Elaal et al. 2022 [13]	Microdiscectomy	Day-to-day functioning education, physiotherapy, and oral analgesics, and steroid injections	38.0±8.3	37.1 ± 11.9	L4-L5 (17), L5-S1 (47)	L4-L5 (20), L5-S1 (44)	37 (58%)	39 (61%)	-	-	NSAID: 27, COX-2 Inhibitors: 8	NSAID: 35, COX-2 Inhibitors: 4	Unemployed (related to the disease): 8, unemployed (Unrelated to the disease): 5, employed: 44, disability: 5, student: 1	Unemployed (related to the disease): 8, unemployed (unrelated to the disease): 8, employed: 48, disability: 1, student: 1	7.7 ± 2.9	7.7 ± 2.1
Bailey et al. 2021 [14]	Microdiscectomy	Day-to-day functioning education, physiotherapy, and oral analgesics, and steroid injections	38.0±8.3	37.1±11.9	L4-L5 (17), L5-S1 (47)	L4-L5 (20), L5-S1 (44)	37 (58%)	39 (61%)	-	-	-	-	-	-	7.7 ± 2.9	7.7 ± 2.1
Aronsohn et al. 2010 [15]	Percutaneous microdiscectomy	Epidural steroid/local anesthetic injection	41.4±10.3	51.2 ± 12.4	-	-	18 (63.8%)	10 (44.8%)	8	8	-	-	-	-	3-6 months (3), 6-12 months (5), >12 months (12)	3-6 mon (6), 6-12 months (>12 mo (8)

TABLE 2: The characteristics of the included studies' populations

Risk of Bias

The RoB assessment is demonstrated in Figure 2. The three RCTs [12-14] were of low RoB. One RCT was of moderate RoB [15].

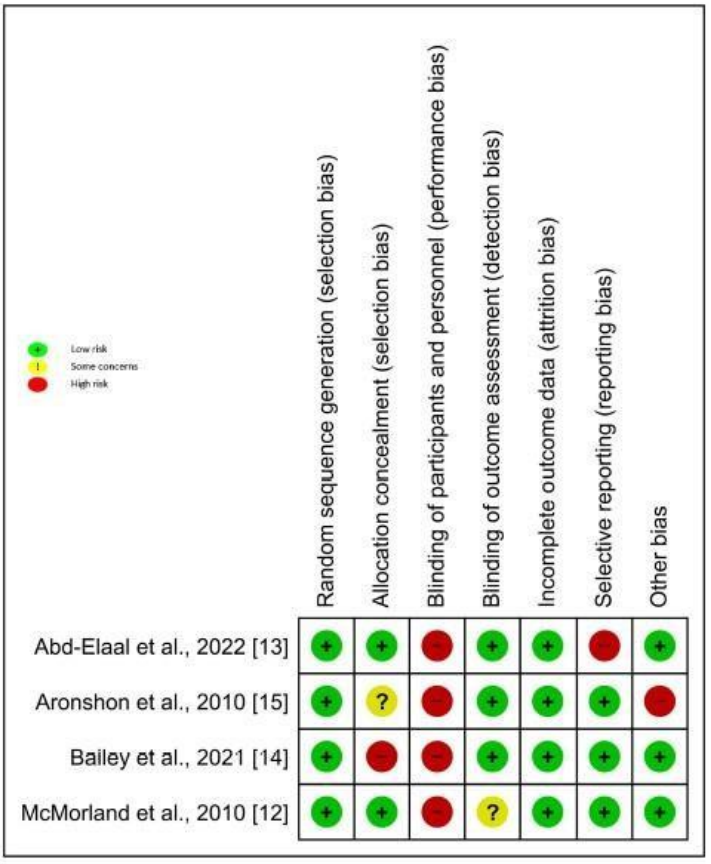


FIGURE 2: RoB-2 (Quality assessment)

RoB: risk of bias

RoB summary: Review authors' judgments about each risk of bias item for each included study.

Meta-analysis

Back Pain Analysis

Three trials reported findings for back pain (Figure 3). Back pain was measured using the VAS score. To assess the effect of the intervention on back pain, a random-mode meta-analysis was conducted using the standardized mean difference (SMD).

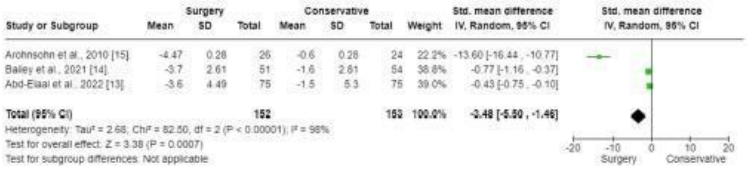


FIGURE 3: Back pain: Surgery vs. conservative

Forest plot of standardized mean differences in back pain symptom VAS score.

Std: standard mean difference; SD: standard deviation, CI: confidence interval; df: degrees of freedom; Chi^2: statistical test for heterogeneity; P: p-value of Chi^2 (evidence of heterogeneity of intervention effects); I^2: amount of heterogeneity between trials; Z: test for overall effect; Overall effect P: p-value for significance of overall effect; VAS: visual analog scale.

The results of the meta-analysis indicated that surgery had a significant effect and decrease in back pain in patients with chronic sciatica (SMD:-3.82; CI (-5.99 to -1.66); p = 0.0005). To fix heterogeneity, sensitivity tests were conducted, and the Aronsohn study was excluded. The results showed that surgery had a significant effect (SMD: -0.57; CI (-0.92 to -0.22); p = 0.001) (Figure 4). The heterogeneity p-value was 0.17.

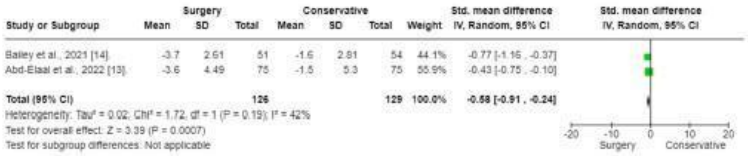


FIGURE 4: Back pain (Sensitivity test)

Forest plot of standardized mean differences in back pain symptom VAS score.

Std: standard mean difference, SD: standard deviation, CI: confidence interval; df: degrees of freedom; Chi^2: statistical test for heterogeneity; P: p-value of Chi^2 (evidence of heterogeneity of intervention effects); I^2: the amount of heterogeneity between trials; Z: test for overall effect; Overall effect P: p-value for significance of overall effect; VAS: visual analog scale.

Leg Pain Analysis

Leg pain was measured using the VAS score (Figure 5). To assess the effect of the intervention on leg pain, a random-mode meta-analysis was conducted using the SMD. The results of the meta-analysis demonstrated a significant positive impact of conservative treatment on patients experiencing leg pain with chronic sciatica (SMD 2.60; CI (0.02 to 5.18); p = 0.05). In an attempt to resolve heterogeneity, sensitivity tests were conducted, and the Aronsohn study was excluded (Figure 6). The results showed that surgery had a significant effect on leg pain (SMD difference: -1.61; CI (-1.92 to -1.31); p = 0.00001). The heterogeneity p-value was 0.3.

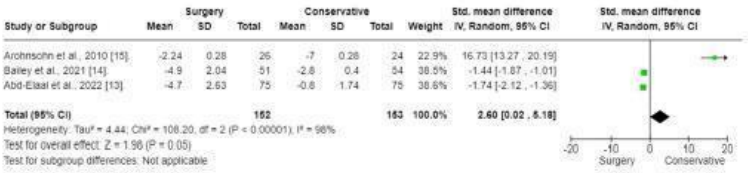


FIGURE 5: Leg pain: Surgery vs. conservative

Forest plot of standardized mean differences in leg pain symptom VAS score.

Std: standard mean difference; SD: standard deviation; CI: confidence interval; df: degrees of freedom; Chi^2: statistical test for heterogeneity; P: p-value of Chi^2 (evidence of heterogeneity of intervention effects); I^2: amount of heterogeneity between trials; Z: test for overall effect; overall effect P: p-value for significance of overall effect; VAS: visual analog scale.

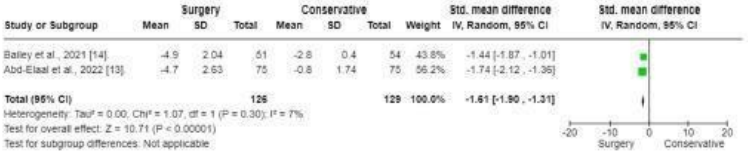


FIGURE 6: Leg pain (Sensitivity test)

Forest plot of standardized mean differences in leg pain symptom VAS score.

Std: standard mean difference; SD: standard deviation; CI: confidence interval; df: degrees of freedom; Chi^2: statistical test for heterogeneity; P: p-value of Chi^2 (evidence of heterogeneity of intervention effects); I^2: amount of heterogeneity between trials; Z: test for overall effect; Overall effect P: p-value for significance of overall effect; VAS: visual analog scale.

Short Form (SF)-36 Score Mental Analysis

To assess the effect of the intervention on SF-36 scores in mental analysis, a fixed-mode meta-analysis was conducted using the SMD (Figure 7). The results of the meta-analysis highlighted a significant positive impact of conservative treatment on SF-36 mental score in patients with chronic sciatica (SMD= 5.7; CI (1.02:10.37); p = 0.02).

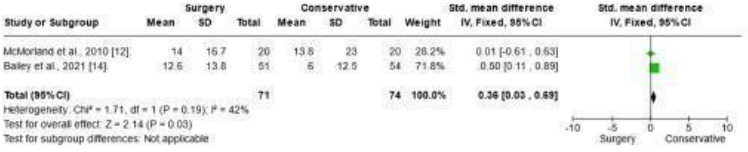


FIGURE 7: SF-36 mental analysis

Forest plot of standardized mean differences in SF-36 mental analysis.

Std: standard mean difference; SD: standard deviation; CI: confidence interval; df: degrees of freedom; Chi^2: statistical test for heterogeneity; P: p-value of Chi^2 (evidence of heterogeneity of intervention effects); I^2: amount of heterogeneity between trials; Z: test for overall effect; Overall effect P: p-value for significance of overall effect; SF: short form.

SF-36 Score Physical Analysis

To assess the effect of the intervention on SF-36 scores in physical analysis, a fixed-mode meta-analysis was conducted using the SMD. The results of the meta-analysis revealed a significant improvement in the conservative treatment of SF-36 mental analysis in patients with chronic sciatica (SMD 0.96; CI (0.61:1.30); p = 0.0001).

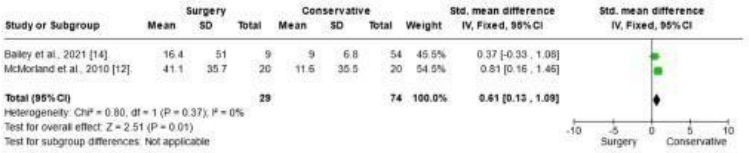


FIGURE 8: SF-36 score physical analysis

Forest plot of standardized mean differences in SF-36 physical analysis.

Std: standard mean difference; SD: standard deviation; CI: confidence interval; df: degrees of freedom; Chi^2: statistical test for heterogeneity; P: p-value of Chi^2 (evidence of heterogeneity of intervention effects); I^2: amount of heterogeneity between trials; Z: test for overall effect; Overall effect P: p-value for significance of overall effect; SF: short-form.

Meta-Regression Analysis

To determine the impact of various variables on low back pain including age, BMI, and sex, meta-regression was performed. Analysis showed no association between age (OR (95% CI) = -0.164 (CI (-0.577-0.249), P =0.443), BMI (OR (95% CI) =-9.646 (CI (-0.117-0.08), P=0.322) and sex (OR (95% CI)=-0.214 (CI (-0.544-0.217) P=0.09) and the effect size.

Discussion

Overall Effect of Surgical vs. Non-Surgical Treatment

In the meta-analysis of our included studies [12-15] involving patients with persistent sciatica caused by lumbar disk herniation, conservative treatment may be more effective than surgical intervention in reduction of the leg pain, with a marginal statistical significance (p = 0.05). Back pain analysis suggests that conservative treatment is associated with a remarkable improvement in back pain. Additionally, conservative treatment has a more substantial impact on the SF-36 mental score (SMD = 5.70) and SF-36 physical score, suggesting that it offers long-term benefits for both physical and mental health when compared to surgical intervention. These results underscore the potential advantages of prioritizing conservative approaches over surgery in the management of chronic sciatica stemming from lumbar disk herniation.

Update on Evidence and Significance of the Study

Microdiscectomy-related randomized trials are effective in the management of both leg and back pain. However, this finding is not consistent with our results for leg pain. This discrepancy can potentially be explained by the fact that patients included in our study were required to have symptoms for a minimum of three months [16,17].

Comparing our results with earlier studies, we found that a recently published systematic review revealed that discectomy was initially beneficial, but the effect declined over time compared with either non-surgical care or epidural steroid injections. Generally, discectomy resulted in faster relief of pain and disability, but it was inconsistent over time as it lasted only for 12 months. However, it's important to note that they included in their analysis a wide range of pain-compliant durations, with a majority of studies having durations of less than 3 months, which was the minimum eligible duration for inclusion in our study [18].

The evaluation of the quality-of-life outcomes post-intervention is of utmost importance in guiding therapeutic decisions. Our study has revealed surprising and meaningful results, indicating that conservative therapy is associated with superior improvement regarding quality of life compared to surgical modalities. This finding emphasizes the importance of considering not only clinical outcomes but also the impact on patients' overall well-being. The observed benefits in quality of life after conservative therapy suggest that it may be a preferable and patient-centered approach in certain cases. These results highlight the need for a comprehensive assessment that goes beyond traditional clinical measures, recognizing the holistic impact of interventions on individuals' lives.

Surgical treatment for sciatica typically involves the removal of disc herniation or part of the disc, as well as addressing any stenosis causing nerve compromise. The primary goal of surgery is to address alarming symptoms including severe leg pain and muscle weakness. It is widely agreed that immediate surgery is necessary for cauda equina syndrome, while elective surgery is recommended for unilateral sciatica. A relatively old randomized trial indicates that surgical intervention may yield better outcomes after one year, but there are no significant differences in results after four and 10 years of follow-up [19, 20]. Moreover, previous literature demonstrated that patients who waited 12 weeks or more to undergo surgery reported worse pain 6 months post-surgery compared to those with a shorter waiting period [21]. A randomized controlled trial by Peul et al. was conducted to compare the outcomes of patients who received early lumbar

disc surgery within 2 weeks versus those who underwent prolonged conservative treatment with later surgery if necessary [16]. The study found that although the overall outcomes were similar at 1 year, patients in the early surgery group experienced faster pain relief and global perceived recovery. Notably, the early treatment group had lower leg pain intensity during the first 6 months of follow-up. Additionally, a cost-utility analysis by van den Peul et al. from the same study revealed that while lumbar disc surgery was initially more expensive than non-surgical care, the benefits of faster recovery and reduced absenteeism from work ultimately offset the difference in costs [22].

A retrospective analysis of the SPORT data revealed that patients with a symptom duration of 6 months or longer experienced deleterious outcomes compared to those with a shorter duration, regardless of whether they received surgical or non-surgical treatment [21]. Specifically, patients who received early intervention (either surgery or conservative) within the first 6-12 weeks of symptom onset experienced greater pain relief, improved function, and higher satisfaction compared to those who underwent delayed treatment.

On the other hand, there are contraindications for surgery in chronic sciatica, including poor overall health, active infection, severe neurological deficits, coagulopathy, or bleeding disorders [21,22].

The main objective of non-surgical sciatica treatment is pain reduction, achieved either through the use of pain relievers or by reducing inflammation, which, in turn, alleviates pressure on the nerve root [15,22]. A systematic review study concluded that conservative treatments do not significantly alter the typical progression of sciatica in the majority of patients or alleviate symptoms [23]. Other treatment options for acute and chronic sciatica are intravenous and subcutaneous anti-TNF-α, which show very promising results in such patients [22]. Additionally, epidural steroid was recommended as a beneficial intervention for the disease due to its superior ability to reduce ODI [24]. It is important to note that non-surgical treatments are not always effective in treating the underlying cause of sciatica such as disc herniation or stenosis but rather focus on relieving symptoms such as pain, which is why they are defined as conservative treatment [25].

Sciatica can be influenced by various factors like nerve injury, inflammation, and disturbances in microglia [23]. After nerve injury, Schwann cells undergo important changes that help in fixing injured peripheral nerves [25]. Central sensitization is another potential factor as it amplifies neural signaling in the central nervous system, making people more sensitive to non-painful stimuli, and causing heightened pain responses. Symptoms linked to central sensitization, including widespread pain and sensitivity in nerves, can negatively impact a person's quality of life [26,27].

The severity of central sensitization, measured by the Central Sensitization Inventory (CSI), is significantly connected to symptoms before surgery and the quality of life in people having lumbar spine surgery [28]. Understanding these processes is vital for creating targeted therapies that adjust the inflammatory response. Since sciatic pain can last a long time and may involve more than just the initial cause, it's important to approach treatment in a careful and nuanced way. Considering this, it may be beneficial to assess risk factors before deciding between surgical and non-surgical options. For example, individuals with a history of mental stress may benefit more from conservative treatment, while those with occupational risk factors may benefit from a combination of conservative treatment and occupational advice before considering surgical options if symptoms persist.

The Optimal Timing for Surgical Intervention

A review conducted by Cochrane indicated that the long-term effects of surgical intervention for chronic sciatica are uncertain, and there is a lack of evidence regarding the best timing for surgery [29]. Several factors must be considered when determining the best timing for surgery in patients with chronic sciatica. These factors include the severity and longevity of symptoms, the underlying cause of the condition, the patient's overall health and functional status, and the potential risks and benefits of surgical intervention.

Additionally, recent studies have suggested that early surgical intervention may lead to better long-term outcomes for certain patients with chronic sciatica. The researchers concluded that early surgery may be more effective in relieving symptoms and preventing long-term disability in patients with severe and persistent sciatica [24].

On the other hand, some experts argue that a period of conservative management should be attempted before considering surgery for chronic sciatica. They suggest that many patients may experience spontaneous improvement in their symptoms with time and that surgical intervention should be reserved for those who fail to respond to noninvasive treatments. Additionally, delaying surgery allows for the identification and treatment of any reversible contributing factors, such as muscle imbalances or poor posture, which may alleviate symptoms without the need for invasive procedures.

However, some patients may prefer conservative over surgical treatment, especially if they think that conservative would be beneficial or if they have any concerns about the risk of surgery. For instance, although 40% of patients referred to spinal manipulative therapy for LDH-induced sciatica may fail to achieve satisfactory relief, the evident risk and cost profile associated with operative care argue for careful consideration by physicians and patients of spinal manipulative therapy before opting for surgical intervention [30].

Ultimately, the decision regarding the timing of surgery for chronic sciatica should be individualized based on each patient's unique circumstances. Healthcare providers should carefully assess the severity and duration of symptoms, the underlying cause of the condition, and the patient's overall health and functional status when determining the most appropriate course of treatment.

The Lack of Significant Effects of Age, Sex, and BMI on the Treatment Outcomes

Meta-regression analysis was conducted to explore the potential influence of age, sex, and BMI on the treatment effects. However, none of these variables were found to significantly affect the results. This suggests that the observed treatment effects are not influenced by these demographic or clinical characteristics. However, there may be other confounding factors that were not reported by our included studies [13, 14, 15, 16] that may influence the results, such as occupation.

Implications of the Findings for Clinical Practice and Decision-Making

International guidelines generally recommend surgical treatment for sciatica secondary to LDH if patients have not responded to comprehensive non-surgical treatment because surgery can provide more immediate and effective relief from symptoms [16]. Non-surgical treatments such as physical therapy, medication, and injections may not always provide sufficient relief for patients with severe or persistent symptoms. Surgery can directly address the underlying cause of the sciatica-nerve root compression-thereby reducing pain and improving function. Additionally, surgery may be recommended if there are signs of neurological deficits or if the patient's quality of life is significantly impacted by their symptoms. These recommendations are because many people with acute sciatica will have improvements in their condition over time [31]. But when it comes to chronic sciatica, the pain is already persisting for a long time, that's why surgical intervention should be considered if that's the case.

The Impact of the Study on the Existing Literature

To the best of our knowledge, this is the first systematic review and meta-analysis study that compares surgery versus non-surgical treatment while accounting for the clinical and prognostic differences in patients with chronic sciatica. Additional advantages include the standardized care that the non-surgical group's patients received, which included standardized chiropractic spine manipulation, analgesics, physiotherapy, and epidural steroid injections. In the Abd-Elaal et al. study [13], it was demonstrated that the crossover effect was reduced due to the extended wait time for a surgical appointment. Bailey et al. [14], in their secondary analysis, provided a relatively extended follow-up period to conduct an intention-to-treat analysis at the 2-year follow-up. Additionally, the nonoperative cohort received standardized treatment, and patients were excluded if the radiculopathy they presented with had been treated with the nonoperative modalities used in their trial, to avoid bias against nonoperative care. A further advantage of this trial is that patients randomized to nonoperative care received treatment from a separate study physician while on the surgeon's waitlist. Surgery, if needed, happened after the usual 6-month wait, delaying crossover effects in our study compared to contemporary RCTs.

Limitations and potential sources of bias

One limitation of our study was the small number of included studies. Although we used a comprehensive search strategy, our search retrieved only three RCTs that included a small number of patients, thereby affecting the significance of our results. Another possible limitation of our study is the high heterogeneity observed in our results, despite our efforts to adjust for possible confounding factors and include only studies with similar designs (RCTs). Piriformis syndrome, on the other hand, can mimic chronic sciatica and cannot be determined based on lumbar MRI findings alone. It is necessary to mention the possibility that piriformis syndrome may be involved, and we must proceed with caution

The significant heterogeneity observed can be attributed to confounding factors such as work status and type of occupation. Unfortunately, we were unable to investigate their effects using meta-regression due to a lack of available data. Even when we were able to conduct meta-regression for age, sex, and pain duration variables, we found that they did not significantly affect our results.

Recommendations for future research

There is a need for multicenter global prospective RCTs, including patients with more than 4 months of symptoms, to compare the effectiveness of surgical and non-surgical approaches for persistent sciatica and to mitigate bias from genetic and physical factors among collaborators. These trials are crucial for addressing clinical uncertainties and optimizing patient care in real-time situations. Additionally, it is important to investigate the long-term outcomes of both surgical and conservative treatments for patients with persistent sciatica.

Conclusions

Our findings suggest that surgical intervention may be more effective than non-surgical treatment for chronic sciatica-related back pain. Conservative treatment has been found to significantly reduce leg back pain and improve mental and physical health outcomes. However, its effects on leg pain reduction are less conclusive. It is essential to emphasize that conservative treatment should always be the initial approach

unless surgery is warranted, such as in cases involving neurological deficits or cauda equina syndrome, as outlined in international guidelines. Therefore, for cases of chronic sciatica without neurological deficits, conservative treatment may be more appropriate for long-standing conditions. However, this result must be interpreted carefully, considering the significant heterogeneity observed, which in turn can be attributed to confounding factors that we could not adjust for.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Abdelrahman Hamouda, Ali Hammed, Hamza Alsalhi, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh

Acquisition, analysis, or interpretation of data: Abdelrahman Hamouda, Hamza Alsalhi, Christian Tanislav, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh

Drafting of the manuscript: Abdelrahman Hamouda, Ali Hammed, Hamza Alsalhi, Christian Tanislav, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud, Ahmad Alzawahreh

Critical review of the manuscript for important intellectual content: Abdelrahman Hamouda, Almonzer Al-Qiami, Amjad Almansi, Mahmoud Massoud

Supervision: Ali Hammed, Christian Tanislav

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We thank Dr. Ahmed Negida for his support and comments.

References

1. Stafford MA, Peng P, Hill DA: Sciatica: A review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. Br J Anaesth. 2007, 99:461-73. 10.1093/bja/aem238
2. Koes BW, van Tulder MW, Peul WC: Diagnosis and treatment of sciatica. BMJ. 2007, 334:1313-7. 10.1136/bmj.39223.428495.BE
3. Rainville J, Hartigan C, Jouve C, Martinez E: The influence of intense exercise-based physical therapy program on back pain anticipated before and induced by physical activities. Spine J. 2004, 4:176-83. 10.1016/j.spinee.2003.08.031
4. Awad JN, Moskovich R: Lumbar disc herniations: Surgical versus nonsurgical treatment. Clin Orthop Relat Res. 2006, 443:183-97. 10.1097/01.blo.0000198724.54891.3a
5. McCulloch JA: Focus issue on lumbar disc herniation: Macro- and microdiscectomy. Spine. 1996, 21:45S-56S. 10.1097/00007632-199612151-00005
6. Pacaud A, Darloy J, Flipo RM, Paccou J, Assaker R, Cortet B: Frequency and determinants of surgical treatment in patients with uncomplicated disc-related sciatica hospitalized in the Rheumatology Department of Lille University Hospital. J Spine Surg. 2022, 8:453-61. 10.21037/jss-22-43
7. Jacobs WC, van Tulder M, Arts M, et al.: Surgery versus conservative management of sciatica due to a lumbar herniated disc: A systematic review. Eur Spine J. 2011, 20:513-22. 10.1007/s00586-010-1603-7
8. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021, 372:n71. 10.1136/bmj.n71
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A: Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016, 5:210. 10.1186/s13643-016-0384-4
10. Sterne JA, Savović J, Page MJ, et al.: RoB 2: A revised tool for assessing risk of bias in randomised trials . BMJ. 2019, 366:l4898. 10.1136/bmj.l4898
11. The Cochrane Collaboration: : Review Manager (RevMan). Version 5.4. Nordic Cochrane Centre, Copenhagen; 2020.
12. McMorland G, Suter E, Casha S, du Plessis SJ, Hurlbert RJ: Manipulation or microdiskectomy for sciatica? A prospective randomized clinical study. J Manipulative Physiol Ther. 2010, 33:576-84. 10.1016/j.jmpt.2010.08.013
13. Abd-Elaal AA, Hegazy MA-E-B, Massoud ME: Surgery versus conservative care for persistent sciatica lasting 3 to 6 months. Egypt J Hosp Med. 2022, 88:3681-3. 10.21608/ejhm.2022.250655
14. Bailey CS, Glennie A, Rasoulinejad P, et al.: Discectomy compared with standardized nonoperative care for chronic sciatica due to a lumbar disc herniation: A secondary analysis of a randomized controlled trial with 2-year follow-up. J Bone Joint Surg Am. 2021, 103:2161-9. 10.2106/JBJS.21.00448

15. Aronsohn J, Chapman K, Soliman M, Shah T, Costandi S, Michael R, Abadir AR: Percutaneous microdiscectomy versus epidural injection for management of chronic spinal pain. Proc West Pharmacol Soc. 2010, 53:16-9.
16. Peul WC, van Houwelingen HC, van den Hout WB, et al.: Surgery versus prolonged conservative treatment for sciatica. N Engl J Med. 2007, 356:2245-56. 10.1056/NEJMoa064039
17. Buttermann GR: Treatment of lumbar disc herniation: Epidural steroid injection compared with discectomy: A prospective, randomized study. J Bone Joint Surg. 2004, 86:670-9.
18. Weinstein JN, Lurie JD, Tosteson TD, et al.: Surgical vs nonoperative treatment for lumbar disk herniation: The Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA. 2006, 296:2451-9. 10.1001/jama.296.20.2451
19. Liu C, Ferreira GE, Abdel Shaheed C, et al.: Surgical versus non-surgical treatment for sciatica: Systematic review and meta-analysis of randomised controlled trials. BMJ. 2023, 381:e070730. 10.1136/bmj-2022-070730
20. WEBER H : Lumbar disc herniation: A controlled, prospective study with ten years of observation . Spine. 1983, 8:131-40.
21. Rihn JA, Hilibrand AS, Radcliff K, et al.: Duration of symptoms resulting from lumbar disc herniation: effect on treatment outcomes: Analysis of the Spine Patient Outcomes Research Trial (SPORT). J Bone Joint Surg Am. 2011, 93:1906-14. 10.2106/JBJS.J.00878
22. Peul WC, van den Hout WB, Brand R, Thomeer RT, Koes BW: Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: Two year results of a randomised controlled trial. BMJ. 2008, 336:1355-8. 10.1136/bmj.a143
23. Guo JR, Jin XJ, Shen HC, Wang H, Zhou X, Liu XQ, Zhu NN: A comparison of the efficacy and tolerability of the treatments for sciatica: A network meta-analysis. Ann Pharmacother. 2017, 51:1041-52. 10.1177/1060028017722008
24. Gibson JN, Waddell G: Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev. 2007, CD001350. 10.1002/14651858.CD001350.pub3
25. Wei J, Su W, Zhao Y, et al.: Maresin 1 promotes nerve regeneration and alleviates neuropathic pain after nerve injury. J Neuroinflammation. 2022, 19:32. 10.1186/s12974-022-02405-1
26. Clark AK, Gentry C, Bradbury EJ, McMahon SB, Malcangio M: Role of spinal microglia in rat models of peripheral nerve injury and inflammation. Eur J Pain. 2007, 11:223-30. 10.1016/j.ejpain.2006.02.003
27. Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ: Establishing clinically relevant severity levels for the central sensitization inventory. Pain Pract. 2017, 17:166-75. 10.1111/papr.12440
28. Yunus MB: Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes . Semin Arthritis Rheum. 2007, 36:339-56. 10.1016/j.semarthrit.2006.12.009
29. Akeda K, Yamada J, Takegami N, et al.: Evaluation of central sensitization inventory in patients undergoing elective spine surgery in a multicenter study. Global Spine J. 2023, 13:1716-27. 10.1177/21925682211047473
30. Raymond J, Chan VK, Darsaut TE: Understanding how the research question impacts trial design: Examples from discectomy trials. Neurochirurgie. 2023, 69:101460. 10.1016/j.neuchi.2023.101460
31. Stochkendahl MJ, Kjaer P, Hartvigsen J, et al.: National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. Eur Spine J. 2018, 27:60-75. 10.1007/s00586-017-5099-2

3.3. Drittes Manuskript

Preventive clipping versus coiling in unruptured intracranial aneurysms: A comprehensive meta-analysis and systematic review to explore safety and efficacy.

Hammed A, Al-Qiami A, Alomari O, Otmani Z, Hammed S, Sarhan K, Derhab M, Hamouda A, Rosenbauer J, Kostev K, Richter G, Braun V, Tanislav C.; Neurol Sci. 2025 Jan 30. doi: 10.1007/s10072-024-07963-1. Epub ahead of print. PMID: 39883353.

Neurological Sciences
https://doi.org/10.1007/s10072-024-07963-1

REVIEW ARTICLE

Preventive clipping versus coiling in unruptured intracranial aneurysms: A comprehensive meta-analysis and systematic review to explore safety and efficacy

Ali Hammed[1] · Almonzer Al-Qiami[2] · Omar Alomari[3] · Zina Otmani[4] · Salah Hammed[5] · Khalid Sarhan[6] · Mohamed Derhab[7] · Abdelrahman Hamouda[8] · Josef Rosenbauer[1] · Karel Kostev[9] · Gregor Richter[10] · Veit Braun[11] · Christian Tanislav[1]

Received: 10 September 2024 / Accepted: 14 December 2024

Abstract

Background Surgical clipping and endovascular coiling are both effective in preventing aneurysmal subarachnoid hemorrhage, but the choice between these interventions remains controversial, leading to treatment disparities across medical centers.

Methods A systematic review and meta-analysis were conducted, including relevant two-arm clinical trials up to September 2023, sourced from Scopus, PubMed, Web of Science, and the Cochrane Library. Our primary outcomes were complete occlusion rates during mid-term and long-term follow-ups. Standard mean differences and risk ratios were used to analyze variations in outcomes. Python meta-analysis with sensitivity testing and regional subgroup analysis was used to resolve heterogeneity.

Results The analysis included 139,485 participants. Clipping demonstrated significantly higher complete occlusion rates in midterm follow-up (RR = 0.83, 95% CI [0.75, 0.91], p = 0.0001) but was associated with a higher risk of procedural complications such as bleeding and ischemic stroke. Coiling showed a higher risk of retreatment (RR = 3.46, 95% CI [1.21, 9.86], p = 0.02), yet it had lower procedural complications (RR = 0.54, 95% CI [0.38, 0.78], p < 0.0009), shorter hospital stays (MD 4.36, 95% CI [2.96, 5.77], p = 0.0001), and better post-procedural outcomes as indicated by lower modified Rankin Scale scores (RR = 0.73, 95% CI [0.55, 0.97], p = 0.03). Long-term occlusion rates were comparable between the two methods.

Conclusion While clipping achieves higher mid-term occlusion rates, coiling is associated with fewer complication rates, shorter hospital stays, and potentially better long-term outcomes. Treatment decisions should be individualized, considering patient-specific characteristics and procedural feasibility.

Keywords Intracranial arterial aneurysm · Subarachnoid hemorrhage · Coiling · Clipping

✉ Ali Hammed
Ali.Hammed@diakonie-sw.de

[1] Department of Geriatrics and Neurology, Diakonie Hospital Jung Stilling, Siegen, Germany

[2] Neurological Surgery, Faculty of Medicine, Kassala University, Kassala, Sudan

[3] Hamidiye International School of Medicine, University of Health Sciences, Istanbul, Turkey

[4] Faculty of Medicine, Mouloud Mammeri University, Tizi-Ouzou, Algeria

[5] Faculty of Medicine, Aleppo University, Aleppo, Syria

[6] Faculty of Medicine, Mansoura University, Mansoura, Egypt

[7] Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

[8] Neurological Surgery, Mayo Clinic, Rochester, Minnesota, USA

[9] University Hospital, Phillips University Marburg, Marburg, Germany

[10] Department of Neuroradiology, Diakonie Hospital Jung Stilling, Siegen, Germany

[11] Department of Neurosurgery, Diakonie Hospital Jung Stilling, Siegen, Germany

Introduction

Cerebral aneurysms significantly contribute to intracranial hemorrhage, stroke, and mortality [1, 2]. Unruptured intracranial aneurysms (UIAs), which have a prevalence of 2–5%, necessitate timely treatment due to the risks of direct compression or rupture leading to subarachnoid hemorrhage (SAH) [3–5]. The primary goal for treating ruptured aneurysms are survival with minimal morbidity during the acute SAH phase and the prevention of recurrent bleeding. In contrast, the treatment of UIAs aims to avert rupture and its complications, such as SAH and neurological deficits [5].

For patients without symptoms or risk factors for rupture, UIAs can be managed conservatively with continuous observation. However, selecting the appropriate treatment for high-risk individuals is critical. Although surgical treatments offer high cure rates, the associated risks of death and complications, particularly in high-risk populations, must be considered [6]. Traditionally, aneurysms were treated with open surgical clipping, but endovascular and microsurgical techniques have become preferred due to their less invasive nature [3, 5, 7]. Surgical clipping involves a craniotomy to place a clip on the aneurysm, while endovascular coiling is a minimally invasive procedure that occludes the aneurysm from within the vessel [1, 2].

There is considerable debate among clinicians regarding the optimal treatment strategy for UIAs. The choice often depends on physician preference, aneurysm characteristics, and patient demographics [8]. In the United States and Western Europe, there is a growing trend towards endovascular coiling [9, 10]. Conversely, in Japan, microsurgical clipping remains the preferred method [11]. While surgical clipping is associated with higher closure rates and lower recurrence, endovascular coiling has shown lower overall mortality and morbidity [12].

Given these varying practices and opinions, this meta-analysis consolidates evidence from studies comparing surgical clipping and endovascular coiling of UIAs to inform treatment decisions.

Materials and Methods

This systematic review and meta-analysis adhered to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA statement 2020) [23]. The prespecified protocol for this review is registered with PROSPERO

Eligibility criteria

We included studies with comparative designs, incorporating both randomized controlled trials (RCTs) and observational studies that directly compared the outcomes of coiling versus clipping. Studies excluded from our analysis were those not conducted in English and those focusing exclusively on either coiling or clipping without a direct comparison between the two techniques.

PICO criteria

Population: Studies involving patients with unruptured aneurysms who underwent either coiling or clipping.

Intervention: Studies where the treatment group received coiling.

Comparator: Studies where the control group underwent clipping.

Outcome: Studies that reported on outcomes such as short-term or long-term complete occlusion, retreatment rate, ischemia, death, procedural bleeding, length of hospital stay, modified Rankin score (mRS >2), and complications related to the procedure.

Study design

Information sources

We conducted an in-depth investigation into the comparative efficacy and safety of clipping versus coiling for unruptured intracranial aneurysms by thoroughly searching four major electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. The objective of this comprehensive meta-analysis was to synthesize the available evidence up to September 2023, providing insights into the relative effectiveness and safety profiles of these two interventions for unruptured intracranial aneurysms.

Search strategy

((unruptured intracranial aneurysms OR unruptured cerebral aneurysm or UIAs) AND (coil* OR coiling OR coil embolization for endovascular treatment) AND (clipping OR clip*))

Selection process

Records identified through the literature search underwent a two-stage screening process. Initially, articles were evaluated for eligibility based on their titles and abstracts. Subsequently, full-text articles corresponding to eligible abstracts were retrieved and subjected to further screening for eligibility.

Data collection process and data items

Data were extracted into a standardized data extraction sheet, encompassing [1] study characteristics, [2] population demographics, [3] risk of bias assessment, and [4] outcome measures.

Study risk of bias assessment

Two independent reviewers evaluated the risk of bias in the included studies. For the 28 non-randomized studies, we utilized the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [14]. This tool assesses potential bias across seven domains: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and reported results. Each domain was categorized as having no information, low, moderate, serious, or critical risk of bias. Disagreements between reviewers were resolved through discussion and, if needed, adjudication by a third reviewer.

For the single randomized controlled trial (RCT) included in our analysis, we applied the Cochrane risk-of-bias tool Version 2 (ROB 2) [15]. ROB 2 evaluates bias across five domains: randomization process, adherence to interventions, missing outcome data, outcome measurement, and selective reporting. Bias in each domain was classified as low risk, some concerns, or high risk. Disagreements among reviewers regarding ROB 2 assessments were resolved in a similar manner as for ROBINS-I assessments.

Measures of treatment effect

Primary outcome measures Complete occlusion rates in mid-term and long-term follow-up.

Secondary outcome measures Mortality
Procedural bleeding
Retreatment
Procedural complications
Cerebral ischemia,
Modified Rankin score (mRS > 2)
Length of hospital stay
Synthesis methods

For dichotomous outcomes, we pooled the Risk Ratio (RR) and its confidence interval (CI) using the Mantel-Haenszel random-effects model.

For continuous outcomes, we calculated the standard mean difference (MD) with its confidence interval (CI) between the baseline and endpoint for each group using the random-effects model.

Heterogeneity between studies was tested using the I2 statistic and was considered statistically significant if the I2 value was >50%. Funnel plots were used to visually estimate publication bias. We used the fixed effects model if there was no heterogeneity and the random effects model if there was heterogeneity. $P<0.05$ was considered statistically significant. In addition, we performed sensitivity analysis to assess the robustness of the synthesis of results in the meta-analysis

The quality of evidence was assessed using GRADEpro GDT [58], ensuring a thorough evaluation process.

Subgroup analysis

We conducted subgroup analyses for observational studies in accordance with the study design (prospective vs. retrospective).

Meta-regression analysis

We conducted a meta-regression analysis based on age, sex, location of the aneurysm, width of the aneurysm neck, and diameter of the aneurysm.

Assessing the heterogeneity

Heterogeneity among the included studies and subgroups was assessed visually using forest plots, with additional statistical evaluation via the Cochrane Q test and the I^2 statistic, performed in RevMan Web for Windows. Significant heterogeneity was predefined as a P-value less than 0.1 and an I^2 value exceeding 50%, indicating notable inconsistency among study outcomes. To address this heterogeneity, the PythonMeta tool was applied, alongside sensitivity analyses and subgroup analyses to identify and manage sources of variability.

Results

Study selection

As depicted in Figure 1, a total of 1,414 studies were initially identified through the search process, and 902 remained after removing duplicates. Following the screening of titles and abstracts, 850 studies were excluded, leaving 52 articles for full-text screening. Ultimately, 31 articles met the inclusion criteria and were included in our study, while 21 articles were excluded for various reasons.

Study and treatment characteristics

Study and treatment characteristics are outlined in Table 1. The analysis included a total of 139,485 participants. The predominant aneurysm type across all studies was located

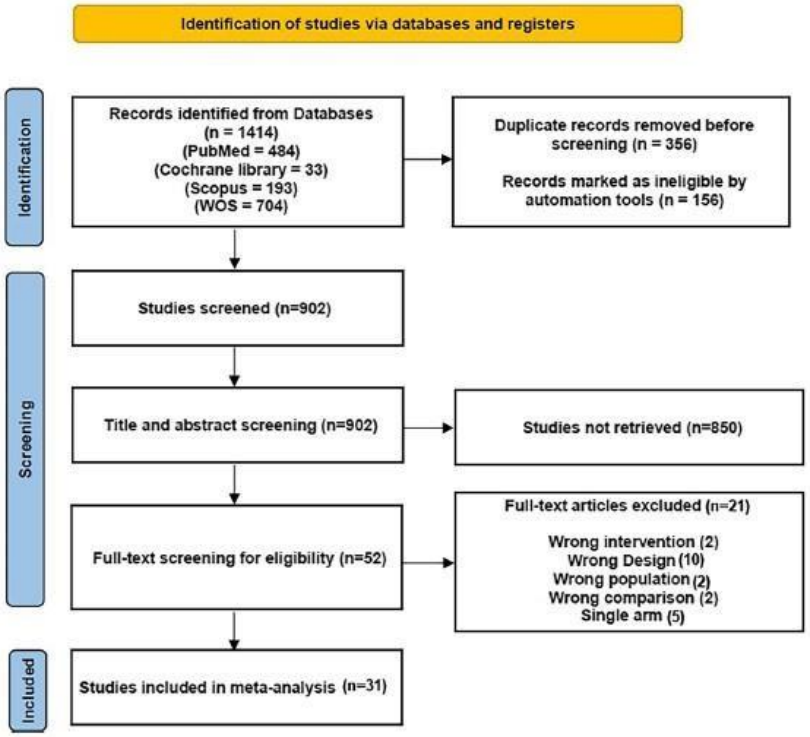


Fig. 1 Description of the study selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines

in the MCA (first segment of the middle cerebral artery). Coiling was uniformly applied as the intervention in the studies, with clipping serving as the comparator. For more comprehensive insights into the study and treatment specifics, refer to Table 1.

Risk of bias assessment results

When employing the ROBINS-I tool to assess non-randomized studies, we identified a low risk of bias in 17 studies, a moderate risk in 10 studies, a serious risk in 3 study (details are outlined in Figure 2). The ROB 2 assessment of the randomized controlled trial (RCT) indicated some concerns regarding potential bias (details are provided in Figure 3).

Short-term complete occlusion

Short-term complete occlusion is defined as the assessment of occlusion within 6 months. 11 of the studies (n = 1,039 patients) included data on short-term complete occlusion, and the overall complete occlusion rate favored the clipping technique (RR = 0.83, 95% CI [0.75, 0.91], p = 0.0001). Pooled data were heterogeneous under a random effect model (p = 0.05, I2 = 45%); [Figure 4]. Subgroup analysis based on study design showed echoed the same results in the prospective (RR 0.83, 95% CI [0.75 to 0.92], p = 0.0005) and retrospective studies (RR 0.82, 95% CI [0.71 to 0.95], p = 0.003).

To address heterogeneity, a sensitivity test was performed using Python meta-analysis: After excluding **Diaz et al.**, the meta-analysis of the remaining 10 studies with 971 patients found that clipping was significantly more effective than coiling in achieving complete occlusion within six months (RR = 0.83, 95% CI [0.75–0.91], p = 0.0001), increasing the likelihood of occlusion by 17%. [Figure 5].

Subgroup Analysis by Study Design

- **Prospective Studies**: RR = 0.83 (95% CI [0.75–0.92], p = 0.0005), favoring clipping.

Table 1 Selected studies included in the meta-analysis

Study ID	Age (mean + SD)		Sex (F/M)		Location of aneurysm	Country	Study type	Aneurysm diameter or dome width (mm)		Neck width (mm)	
	Coiling	Clipping	Coiling	Clipping				Coiling	Clipping	Coiling	Clipping
Brinjikji et al. 2011 [9]	56.1 (29.4)	53.2 (25.7)	25,600/8,449	22,315/7,571	mixture	USA	retrospective	-	-	-	-
McDonald et al. 2013 [10]	58 (50–67)	55 (47–63)	2,776/775	1,019/369	mixture	France	prospective	-	-	-	-
Kim et al. 2018 [21]	-	-	-	-	anterior circulation	USA	prospective	-	-	-	-
Bekelis et al. 2016 [22]	72.7	70.5	4,490/1,630	1,960/625	mixture	USA	prospective	6.8	9.2	-	-
Mohammad et al. 2020 [23]	60.8 (12.5)	64 (9.5)	39/14	96/51	anterior ICA	Japan	retrospective	6.13 (3.1)	5.1 (2.3)	3.6 (1.5)	3.6 (1.7)
Brilstra et al. 2003 [31]	51	50	15/4	23/9	middle cerebral artery	Netherlands	prospective	-	-	-	-
Dammann et al. 2014 [38]	54	53.7	10/6	65/22	middle cerebral artery	Germany	retrospective	7.2	6	-	-
Diaz et al. 2014 [39]	-	-	-	-	middle cerebral artery	USA	retrospective	-	-	-	-
Erdem et al. 2011 [40]	-	-	-	-	middle cerebral artery	Germany	prospective	7.3 ± 3.8	6.1 ± 2.3		
Jang et al. 2015 [41]	-	-	-	-	middle cerebral artery	Korea	retrospective	-	-	-	-
Duan et al. 2014 [42]	57.6	52.2	38/11	49/16	posterior circulation	USA	retrospective	7.57	8.22	-	-
Frontera et al. 2012 [43]	55	54	27/6	29/7	anterior circulation	USA	retrospective	6.8	7.7	-	-
Yang et al. 2019 [44]	74.09 (3.88)	73.28 (2.81)	44/20	10/4	anterior circulation	USA	retrospective	-	-	-	-
Suzuki et al. 2015 [45]	61.9	59.6	61/19	106/35	internal carotid artery	Norway	retrospective	54.2 (12.1)	-	-	-
Solheim et al. 2006 [46]	-	-	22/9	30/14	middle cerebral artery	USA	retrospective	9.5	8.3	-	-
Lad et al. 2013 [47]	54	53	3,343/1,064	2,751/845	mixture	Korea	prospective	-	-	-	-
Jalbert et al. 2015 [48]	72.47	70.77	6,260/1,682	3,326/1,031	mixture	Japan	retrospective	-	-	-	-
Iwanuro et al. 2007 [49]	-	-	-	-	anterior circulation	China	retrospective	-	-	-	-
Huang et al. 2019 [50]	52.7 (9.6)	49.8 (11.2)	23/14	30/15	mixture	Germany	retrospective	-	-	-	-
Gerlach et al. 2007 [51]	48.2	47.6	27/10	59/22	middle cerebral artery	Canada	retrospective	9.18	-	-	-
Darsaut et al. 2023 [52]	56.1(10)	56.9 (10)	98/45	105/43	anterior circulation	Korea	retrospective	7.7 (3–20)	7.9 (3–24)	-	-
Cho et al. 2020 [53]	76.95 (2.04)	76.37 (2.15)	34/10	7/11	anterior ACOMA	USA	prospective	9.4 (4.55)	6.60 (2.33)	-	-
Mascitelli et al. 2022 [54]	62 (11.8)	60.3 (11.3)	110/30	59/25	anterior MCA	USA	prospective	6.6 (3.4)	5.7 (3.2)	4.6 (1.8)	4.3 (1.7)
Haeren et al. 2022 [55]	58 (12.59)	58.33 (11.85)	21/26	40/41	anterior ACOMA	Finland	retrospective	5.66 (1.35)	5 (2.96)	3 (1.48)	3 (1.48)
Pflaeging et al. 2021 [56]	59.3(10)	54.1 (10.8)	34/6	90/30	middle cerebral artery	Germany	retrospective	6.6 (3.3)	7 (3.6)	3.8 ±1.3	4 (1.6)
Luo et al. 2022 [57]	48.93 (8.91)	48.89 (8.45)	46/19	46/19	middle cerebral artery	China	prospective	-	-	-	-
Wiebers et al. 2003 [64]	53·7 (13·1)	51·5 (11·4)	351/100	1456/461	Internal carotid artery	USA	prospective	-	-	-	-
Song 2015 et al. [65]	56.4 (11.1)	56.0 (9.0)	444/122	379/179	ICA	South Korea	retrospective	-	-	-	-
Kunz et al .2012 [66]	52.4 (10.7)	52.3 (10.4)	127/73	210/96	Mixture	Germany	Retrospective	17.2	13.7	-	-
Alshekhlee et al. 2010 [67]	52.56 (15.7)	53.41 (11.2)	2441/1056	2815/923	ICA	USA	Retrospective	-	-	-	-

Lai et al. [68]: Age (mean + SD): N/A ,Sex (F/M): N/A, Location of aneurysm: N/A Country: Australia, Study type: Retrospective cohort study Aneurysm diameter or dome width (mm): N/A Neck width (mm): N/A

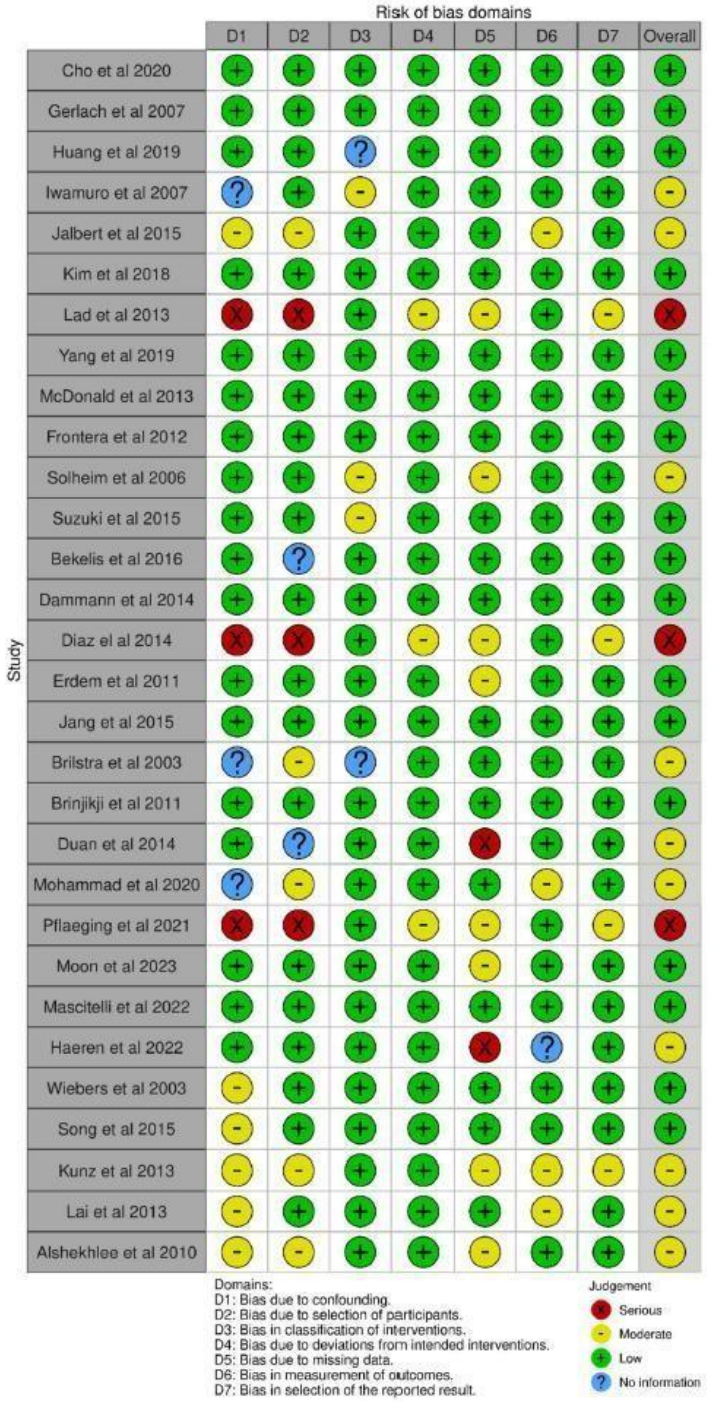


Fig. 2 Risk of bias assessment for the studies selected for inclusion in the meta-analysis: ROBINS 1

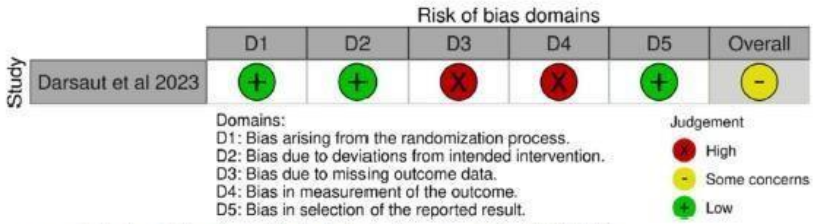


Fig. 3 Risk of bias assessment for the studies selected for inclusion in the metaanalysis: ROBINS 2

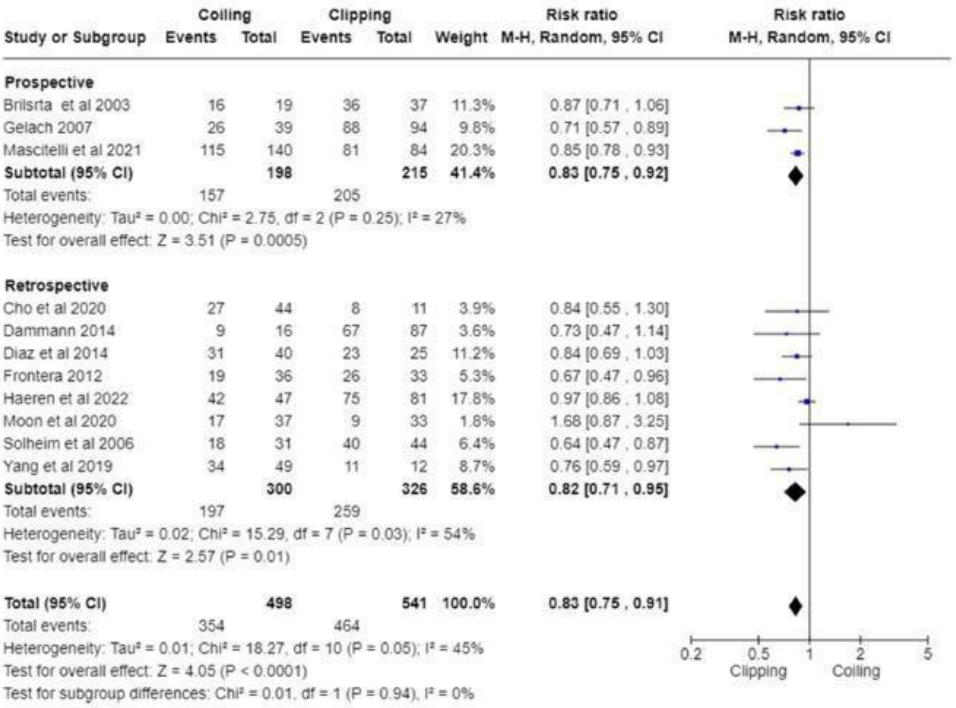


Fig. 4 Forest plot illustrating the combined risk ratio (RR) for the dichotomous outcome (Short-term complete occlusion) between the Coiling and Clipping groups. The plot includes RR (risk ratio), P (*p*-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P (*p*-value indicating evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), overall effect, and P (*p*-value for significance of overall effect)

- **Retrospective Studies**: RR = 0.82 (95% CI [0.71–0.95], $p = 0.003$), also favoring clipping.

These findings remained consistent across both prospective and retrospective study designs, with no heterogeneity ($I^2 = 0\%$), reinforcing the reliability of the results.

Quality of the evidence: ⊕⊕⊕⊕ High

Long term complete occlusion

Long-term complete occlusion is defined as the assessment of occlusion more than 12 months after treatment. Of the

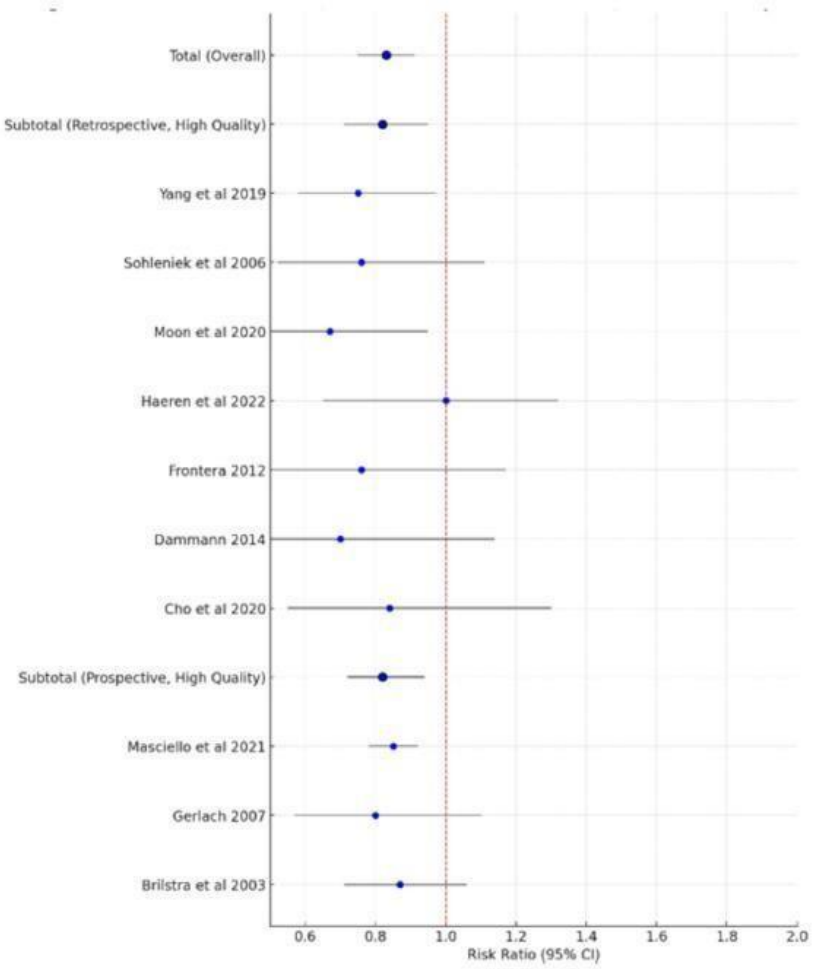


Fig. 5 Forest Plot after Sensitivity Analysis for Short-term Complete Occlusion

Study or Subgroup	Coiling Events	Coiling Total	Clipping Events	Clipping Total	Weight	Risk ratio M-H, Random, 95% CI
Dammann et al 2014	9	16	71	87	20.5%	0.69 [0.44 , 1.07]
Frontera et al 2012	21	36	27	33	24.0%	0.71 [0.52 , 0.98]
Huang et al 2019	33	41	48	51	27.8%	0.86 [0.72 , 1.01]
Darsaut 2023	114	142	84	148	27.8%	1.41 [1.20 , 1.66]
Total (95% CI)		**235**		**319**	**100.0%**	**0.90 [0.63 , 1.30]**
Total events:	177		230			

Heterogeneity: Tau² = 0.12; Chi² = 28.45, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable

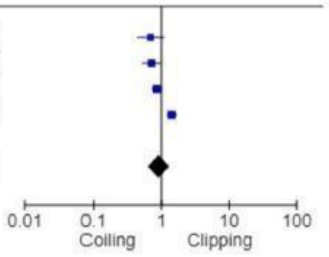


Fig. 6 Forest plot depicting the pooled risk ratio (RR) of the dichotomous study outcome (Long-term complete occlusion) comparing the Coiling group versus the Clipping group. Key indicators include RR (risk ratio), P (*p*-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P (*p*-value indicating evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), overall effect, and P (*p*-value for significance of overall effect)

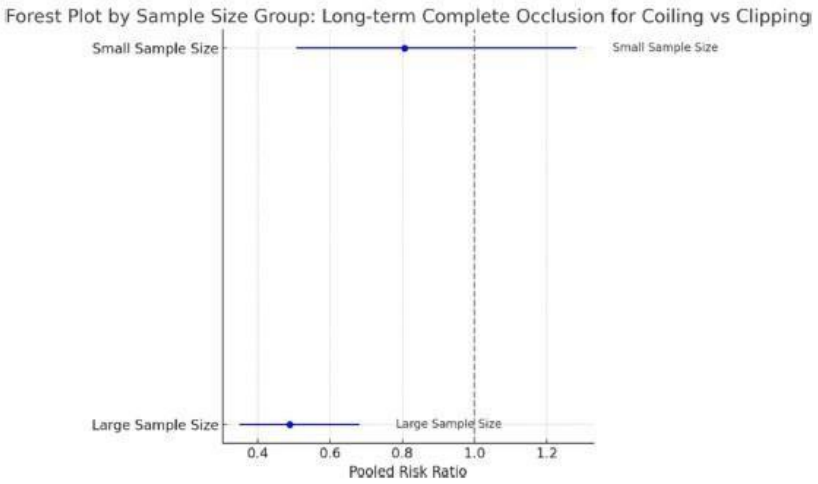


Fig. 7 Forest Plot by Sample Size Group: (Long-term complete occlusion)

publications included in our analysis, 4 studies (n = 554 patients) assessed long term complete occlusion, indicating similar rates for the two intervention types (RR = 0.9, 95% CI [0.63, 1.30], p = 0.57). [Figure 6].

To address heterogeneity, a subgroup analysis was performed using Python meta-analysis: The subgroup analysis by sample size revealed no heterogeneity in either group (I^2 = 0%). In the large sample studies, coiling was associated with a significant reduction in occlusion risk (pooled RR = 0.49, 95% CI [0.35, 0.68]), whereas smaller sample studies showed no significant difference between coiling and clipping (pooled RR = 0.81, 95% CI [0.51, 1.28]). [Figure 7]. These findings suggest that larger studies consistently favor coiling, while smaller studies show more variability.

Quality of the evidence: ⊕⊕⊕◯ Moderate

Mortality

Some 7 studies (n = 81136 patients) reported risk of death within 30 days. Coiling intervention is associated with a lower risk of 30-day mortality (RR 0.56, 95% CI [0.48 to 0.66], p = 0.00001). [Figure 8]. Pooled data were heterogeneous under a random effect model (p = 0.63, I2 = %); Subgroup analysis revealed similar results in retrospective studies (RR 0.55, 95% CI [0.47 to 0.65], p = 0.00001), despite the absence of significant differences in the prospective studies (RR 0,72, 95% CI [0.32 to 1,62], p = 0.9).

Quality of the evidence: ⊕⊕⊕⊕ High

Procedural bleeding

Of the publications included in our analysis, 12 studies (n = 21,249 patients) noted the rate of procedural bleeding. The Clipping technique was associated with higher rates of bleeding (RR = 0.52, 95% CI [0.35, 0.78], p = 0.002) than Coiling group. [Figure 9]. Pooled data were heterogeneous under a random effect model (p = 0.002, I2 = 63%). Subgroup analysis of the risk of procedural bleeding based on study design demonstrated the same result in prospective (RR 0.57, 95% CI [0.32 to 1.01]) and retrospective studies (RR 0.5, 95% CI [0.27 to 0.91]).

To address heterogeneity, a regional subgroup analysis was performed using Python meta-analysis:

- **USA**: Pooled RR = 0.17 (95% CI [0.13, 0.21]), favoring coiling with reduced bleeding risk. Moderate to high heterogeneity (Q = 7.48, p = 0.024, I^2 = 73.2%) suggests study variability.
- **Europe**: Pooled RR = 0.33 (95% CI [0.15, 0.76]), favoring coiling with no heterogeneity (Q = 1.64, p = 0.65, I^2 = 0%), indicating consistent findings.
- **Asia**: Pooled RR = 0.70 (95% CI [0.38, 1.29]), showing no significant difference. No heterogeneity (Q = 0.58, p = 0.97, I^2 = 0%). [Figure 10].

The findings suggest that coiling significantly reduces bleeding risk in the USA and Europe, with higher variability in the USA. No significant benefit is observed in Asia,

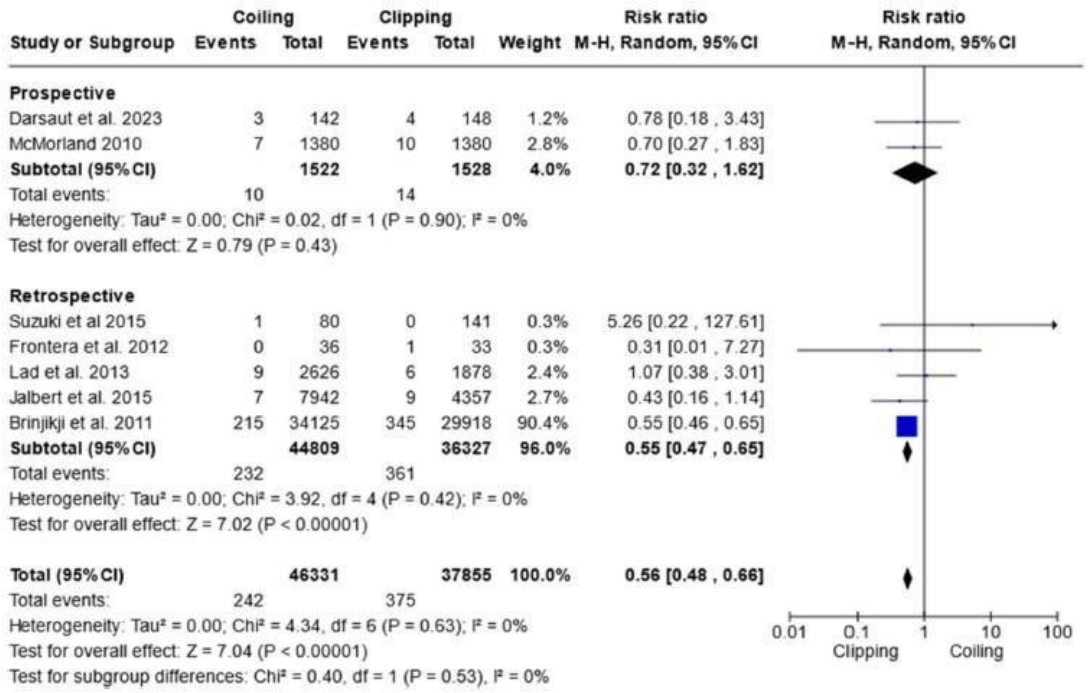


Fig. 8 Forest plot presenting the pooled risk ratio (RR) for the dichotomous study outcome (Risk of death within 30 days) comparing the Coiling group and the Clipping group. The plot includes RR (risk ratio), P (*p*-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P (*p*-value indicating evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), overall effect, and P (*p*-value for significance of overall effect)

highlighting potential regional differences in outcomes that may relate to clinical practices or patient populations.

Quality of the evidence: ⊕⊕⊕◯ Moderate

Retreatment

Overall, 9 studies (n = 17,752 patients) reported the frequency of retreatment following either intervention. The coiling technique was associated with higher rates of retreatment (RR = 3.46, 95% CI [1.21, 9.86], p = 0.02) than surgical clipping. Pooled data were heterogeneous under a random effect model (p = 0.0001, I2 = 89%); [Figure 11]. Subgroup analysis based on study design led to the same conclusion in prospective studies (RR 13.2 95% CI [1.73 to 100.92], p = 0.01), despite the absence of significant differences in the retrospective studies (RR 2.7, 95% CI [0.86 to 9.86], p = 0.09).

To address heterogeneity, a regional subgroup analysis was performed using Python meta-analysis:

- **USA**: Pooled RR = 0.09 (95% CI [0.03, 0.25]), indicating a significant reduction in retreatment rates with coiling. High heterogeneity (Q = 23.83, p < 0.0001, I^2 = 91.6%) suggests variability across studies.
- **Europe**: Pooled RR = 0.16 (95% CI [0.14, 0.18]), showing a substantial reduction in retreatment rates with coiling. Very high heterogeneity (Q = 33.08, p < 0.0001, I^2 = 93.95%).
- **Asia**: Pooled RR = 0.75 (95% CI [0.23, 2.40]), with no significant difference between coiling and clipping. No heterogeneity (Q = 0.06, p = 0.80, I^2 = 0%). [Figure 12].

The USA and Europe show significant heterogeneity, indicating variability in outcomes likely due to differences in clinical practices or patient populations. In contrast, Asia has no heterogeneity but a wide confidence interval, suggesting either limited data or consistent outcomes. These regional variations underscore the influence of local practices on retreatment rates.

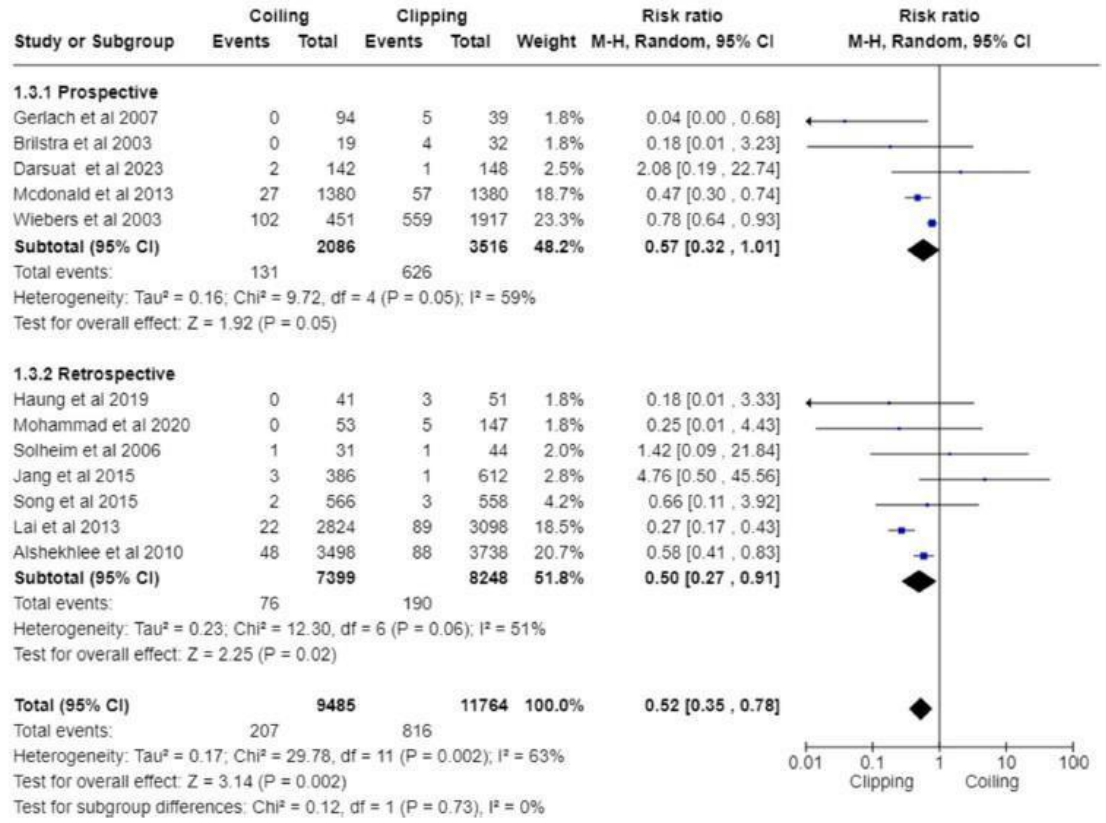


Fig. 9 Forest plot illustrating the combined risk ratio (RR) for the dichotomous study outcome (Procedural bleeding) comparing the Coiling group to the Clipping group. The forest plot includes RR values with associated P-values, confidence intervals (CI), degrees of freedom (df), Chi^2 statistics for heterogeneity testing, corresponding P-values for Chi^2, I^2 values indicating heterogeneity between studies, Z-test for overall effect, overall effect estimates, and P-values for significance of the overall effect

Quality of the evidence: ⊕⊕⊕◯ Moderate

Procedural complications

Procedural complications are defined as approach-related issues such as wound healing, myocardial infarction, groin hematoma, pneumonia, vessel injury, seizures, etc.

Only 8 studies (n = 8975 patients) reported the frequency of procedure-related complications for both interventions, finding that coiling was associated with lower rates of such complications (RR = 0.54, 95% CI [0.38, 0.78], p = <0.0009). Pooled data were heterogeneous under a random effect model (p = 0.02, I2 = 59%); [Figure 6]. Subgroup analysis revealed similar results in prospective (RR 0.33, 95% CI [0.24 to 0.45], p = <0.00001) and retrospective studies (RR 0.67, 95% CI [0.57 to 0.77] p = <0.00001). [Figure 13].

Quality of the evidence:⊕⊕⊕⊕ High

To address heterogeneity, a regional subgroup analysis was performed using Python meta-analysis:

- **USA**: Pooled RR = 0.25 (95% CI [0.19, 0.31]), indicating a strong reduction in procedural complications with coiling. Low heterogeneity (Q = 2.14, p = 0.34, I^2 = 6.6%) suggests consistency across studies.
- **Europe**: Pooled RR = 0.07 (95% CI [0.06, 0.08]), showing a substantial reduction in complications. Heterogeneity is not assessable due to only one study.
- **Asia**: Pooled RR = 0.70 (95% CI [0.39, 1.28]), with no significant difference between coiling and clipping. No heterogeneity (Q = 1.36, p = 0.72, I^2 = 0%). [Figure 14].

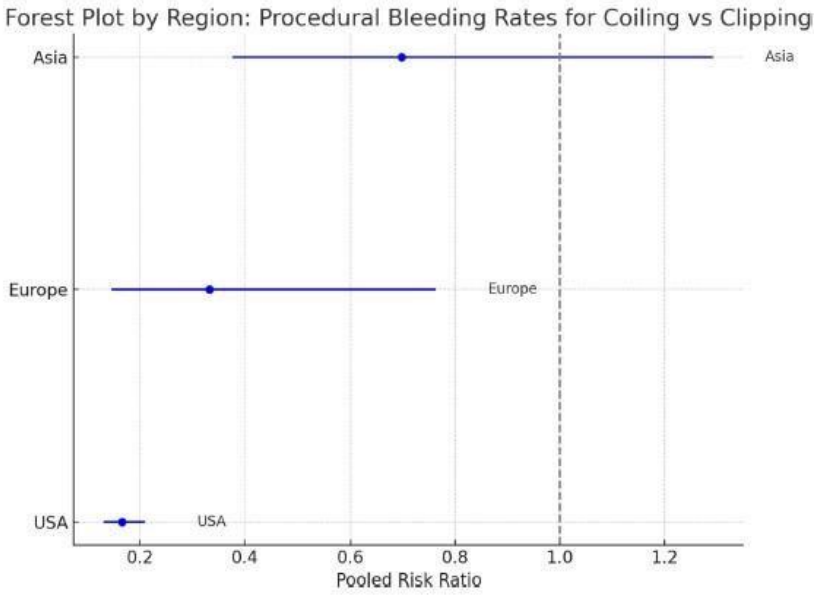


Fig. 10 Forest Plot by Region: Procedural Bleeding Rates for Coiling Vs Clipping

This analysis shows consistent benefits of coiling in reducing complications in the USA and Europe, with low or no heterogeneity. Asia's results are less definitive, with a wider confidence interval and no heterogeneity. These findings suggest that regional factors, such as clinical practices, may affect outcome consistency, with the USA showing particularly high reliability in results.

Cerebral Ischemia

In 16 studies (n = 14,140 patients), The Clipping technique was associated with higher rates of ischemic stroke (RR = 0. 73, 95% CI [0.53, 0.99], p = 0.05) than the Coiling technique. Subgroup analysis demonstrated lower rates of ischemic stroke in the coiling arm in prospective studies (RR 0.39, 95% CI [0.29 to 0.53], p = 0.00001), but no significant difference in retrospective studies (RR 0.88, 95% CI [0.58 to 1.32], p = 0.53). [Figure 15].

To address heterogeneity, a regional subgroup analysis was performed using Python meta-analysis:

- **Asia**: Pooled RR = 1.14 (95% CI [0.61–2.15]), indicating no significant difference between coiling and clipping for ischemic stroke risk. No heterogeneity (Q = 1.77, p = 0.88, I^2 = 0%).
- **Europe**: Pooled RR = 0.84 (95% CI [0.56–1.27]), slightly favoring coiling but not statistically significant. Low to moderate heterogeneity (Q = 7.87, p = 0.25, I^2 = 23.7%) suggests minor variability due to study or population differences.
- **USA**: Pooled RR = 0.45 (95% CI [0.37–0.54]), showing a clear benefit for coiling with no heterogeneity (Q = 0.22, p = 0.64, I^2 = 0%). [Figure 16].

This analysis shows consistent findings with minimal heterogeneity in Asia and the USA, where coiling is particularly favorable in the USA. Europe shows a slight trend toward coiling with low to moderate heterogeneity, likely due to regional variations in study design or patient characteristics. These findings highlight potential regional influences on treatment outcomes between coiling and clipping.

Quality of the evidence: ⊕⊕⊕⊕ High

Modified rankin score (mRS >2)

An analysis of 13 studies (n = 5,441 patients) revealed that the clipping group had a worse Rankin Score and higher morbidity compared to the coiling group in post-procedural mRS > 2 (RR 0.73, 95% CI [0.55 to 0.97], p = 0.03). Subgroup analysis demonstrated the same result in the clipping arm in retrospective studies (RR 0.72, 95% CI [0.53 to 0.96], p = 0.03), but no significant difference was found in prospective studies. [Figure 17].

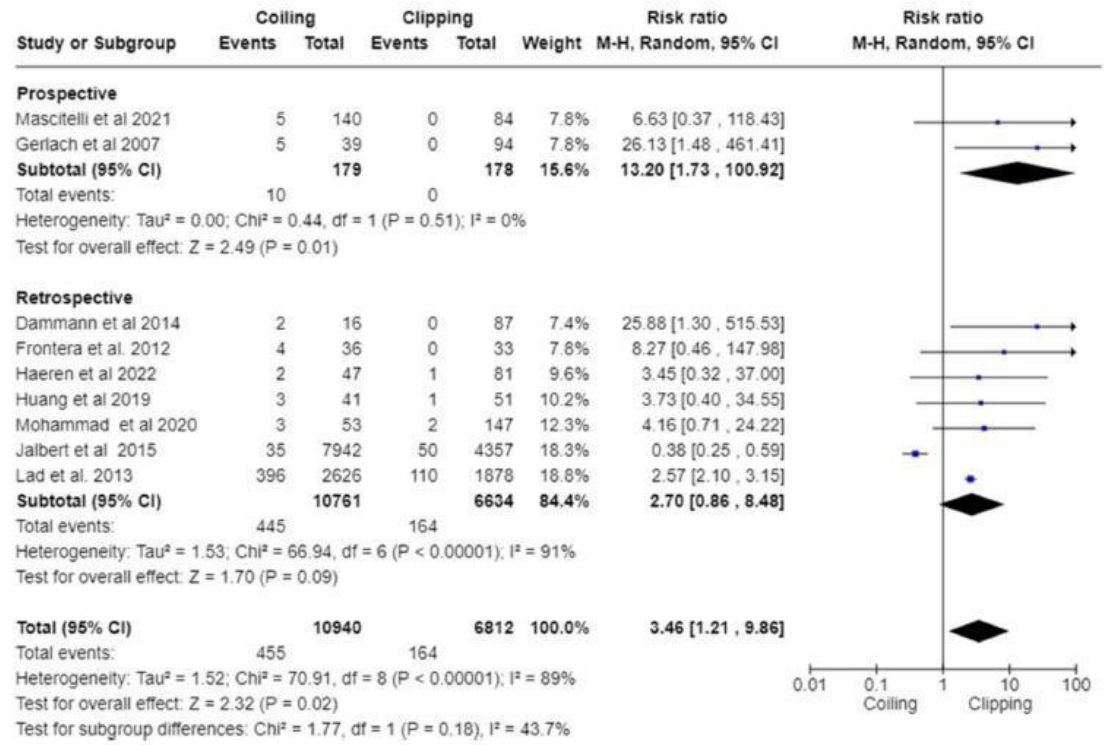


Fig. 11 Forest plot illustrating the combined risk ratio (RR) for the dichotomous study outcome (Retreatment) comparing the Coiling group to the Clipping group. The plot includes RR values alongside their associated P-values, confidence intervals (CI), degrees of freedom (df), Chi^2 statistics used for testing heterogeneity, corresponding P-values for Chi^2 indicating evidence of intervention effect heterogeneity, I^2 values indicating degree of heterogeneity between studies, Z-test for overall effect, overall effect estimates, and P-values indicating significance of the overall effect

Quality of the evidence: ⊕⊕⊕⊕ High

Length of hospital stay

Among 10 studies (n = 47,277patients), surgical clipping was associated with a longer length of hospital stay (MD 4.36, 95% CI [2.96, 5.77], p = 0000.1). Subgroup analysis, revealed similar results in prospective (MD 4.95, 95% CI [3.2 to 6.71], p = <0.000001) and retrospective studies (MD 4.01, 95% CI [2.23 to 5.8] p = <0.0001).[Figure 18].

To address heterogeneity, a regional subgroup analysis was performed using Python meta-analysis:

- **USA**: Pooled MD = 3.19 (95% CI [3.06, 3.32]), indicating that clipping is associated with a longer hospital stay. High heterogeneity (Q = 17.99, p = 0.0004, I^2 = 83.3%) suggests variability across studies.
- **Europe**: Pooled MD = 7.85 (95% CI [5.64, 10.06]), showing a stronger association for longer hospital stays with clipping. No heterogeneity (Q = 0.94, p = 0.33, I^2 = 0%) indicates consistency across studies.
- **Asia**: Pooled MD = 3.20 (95% CI [2.61, 3.79]), also favoring clipping for longer hospital stays. Substantial heterogeneity (Q = 15.49, p = 0.0038, I^2 = 74.2%) suggests variability among studies. [Figure 19].

The results show consistent findings in Europe, where clipping is associated with longer hospital stays and no heterogeneity. In contrast, the USA and Asia show high heterogeneity, likely due to differences in patient demographics, clinical practices, or study methodologies, highlighting the influence of regional factors on hospitalization outcomes associated with clipping.

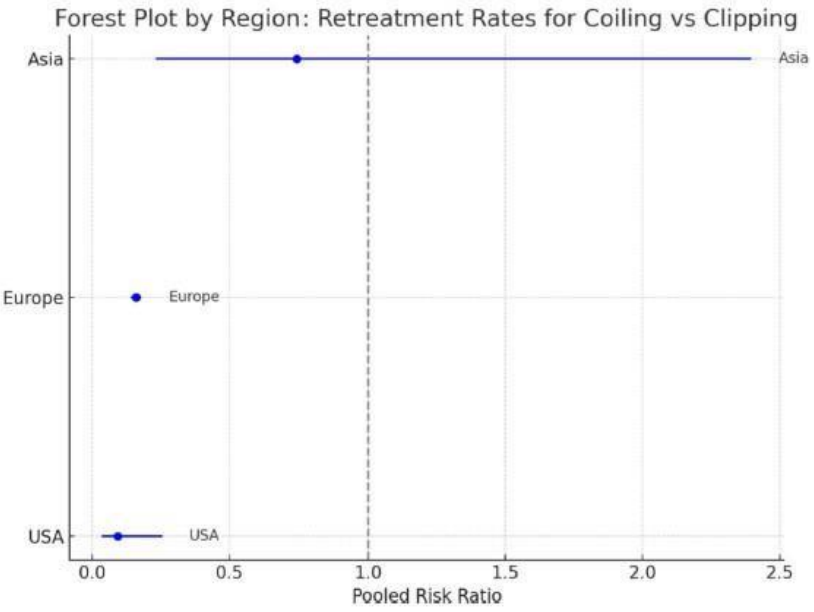


Fig. 12 Forest Plot by Region: Retreatment Rates for Coiling Vs Clipping

Study or Subgroup	Coiling Events	Coiling Total	Clipping Events	Clipping Total	Weight	Risk ratio M-H, Random, 95% CI
Prospective						
Mascitelli et al 2021	15	140	24	84	16.5%	0.38 [0.21 , 0.67]
McMorland 2010	33	1380	106	1380	22.0%	0.31 [0.21 , 0.46]
Subtotal (95% CI)		**1520**		**1464**	**38.5%**	**0.33 [0.24 , 0.45]**
Total events:	48		130			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 6.79 (P < 0.00001)						
Retrospective						
Moon et al 2020	2	37	1	33	2.2%	1.78 [0.17 , 18.78]
Huang et al. 2019	2	41	3	51	3.7%	0.83 [0.15 , 4.73]
Mohammad et al 2020	3	53	10	147	6.5%	0.83 [0.24 , 2.91]
Duan et al. 2014	6	56	13	69	10.4%	0.57 [0.23 , 1.40]
Jang et al. 2015	8	386	14	612	11.0%	0.91 [0.38 , 2.14]
Lad et al. 2013	261	2626	285	1878	27.7%	0.65 [0.56 , 0.77]
Subtotal (95% CI)		**3199**		**2790**	**61.5%**	**0.67 [0.57 , 0.77]**
Total events:	282		326			
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 5 (P = 0.91); I² = 0%						
Test for overall effect: Z = 5.32 (P < 0.00001)						
Total (95% CI)		**4719**		**4254**	**100.0%**	**0.54 [0.38 , 0.78]**
Total events:	330		456			
Heterogeneity: Tau² = 0.12; Chi² = 17.00, df = 7 (P = 0.02); I² = 59%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
Test for subgroup differences: Chi² = 15.13, df = 1 (P = 0.0001), I² = 93.4%						

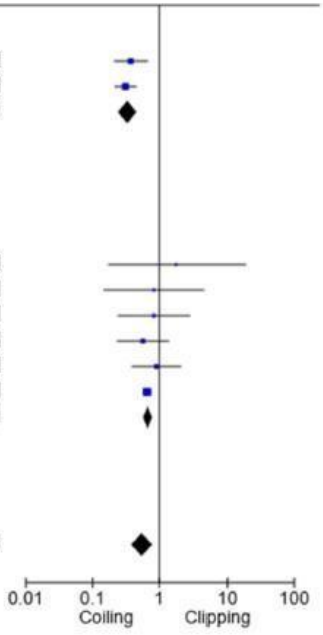


Fig. 13 Forest plot summarizing the pooled risk ratio (RR) for procedural complications, comparing the Coiling group to the Clipping group. Key metrics include: RR (risk ratio), P (*p*-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P of Chi^2 (evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), and P for significance of overall effect

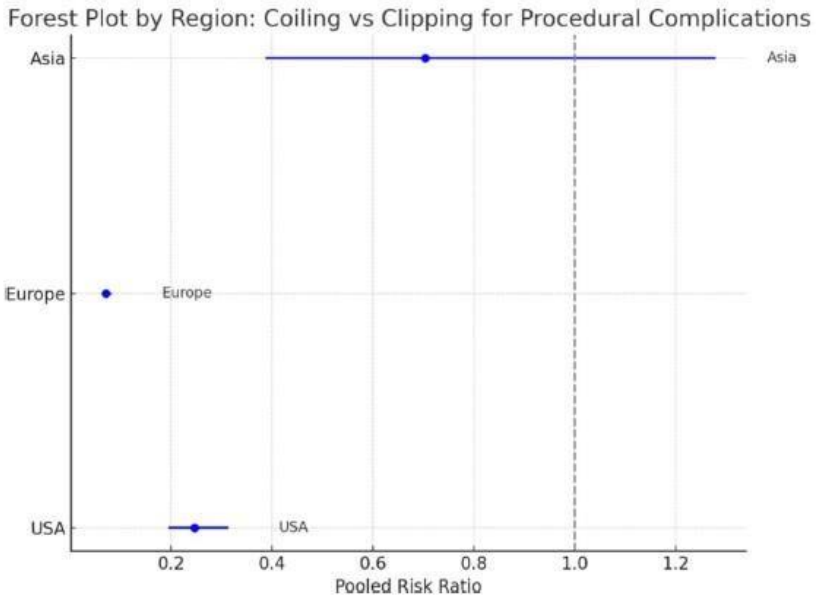


Fig. 14 Forest Plot by Region: Coiling vs Clipping for Procedural Complications

Quality of the evidence: ⊕⊕⊕◯ Moderate

Meta-regression analysis

We performed a meta-regression analysis, considering age, sex, aneurysm location, aneurysm neck width, and aneurysm diameter as variables. However, the analysis did not uncover any significant associations between these factors and outcomes such as occlusion rate, death, ischemia, or procedural bleeding.

Discussion

In this systematic review and meta-analysis, we compared the outcomes of coiling and clipping in the management of unruptured intracranial aneurysms. Our findings demonstrate significant advantages of coiling over clipping in most study outcomes, including short-term and long-term complications, retreatment rates, cerebral ischemia, length of hospital stay, and mortality. However, coiling did not show superior results in functional outcomes measured by the mRS or in procedural complications. Additionally, clipping is associated with longer averaging estimated by five days more than coiling. Mortality rates for both procedures remain low (<1%), but when combining data from both study types -pro and retrospective- coiling appears to offer a slight advantage. Importantly, both treatment modalities are associated with a high likelihood of favorable functional outcomes, with 94% of patients achieving a modified Rankin Scale score of ≤2. However, there is a significant statistical difference showing that coiling is associated with better morbidity outcomes.

Our analysis benefits from addressing heterogeneity through sensitivity and regional subgroup analyses, ensuring that findings are robust and applicable across different clinical practices. This approach confirms that coiling consistently reduces procedural risks, including ischemia, mortality, bleeding, and other complications, while facilitating shorter hospital stays. Conversely, the higher midterm occlusion rates observed with clipping are associated with higher procedural risks.

Hwang et al. reported that coiling is associated with lower risks of disability and complications, though long-term mortality rates are comparable between coiling and clipping [61]. A 2024 meta-analysis published in *Turkish Neurosurgery* supports these findings, noting that while clipping offers better midterm occlusion and lower retreatment rates, it is also associated with higher procedural risks, including increased ischemic events and longer hospital stays [62]. Similarly, a meta-analysis by Kang et al. found that coiling results in fewer immediate complications but is associated with higher recurrence rates [63].

Overall, our study, which utilizes the largest dataset to date, confirms that while clipping provides superior midterm occlusion rates, coiling is preferred due to its lower risks of ischemia, mortality, complications, procedural bleeding, and shorter hospital stays. Coiling may also be associated with lower morbidity rates.

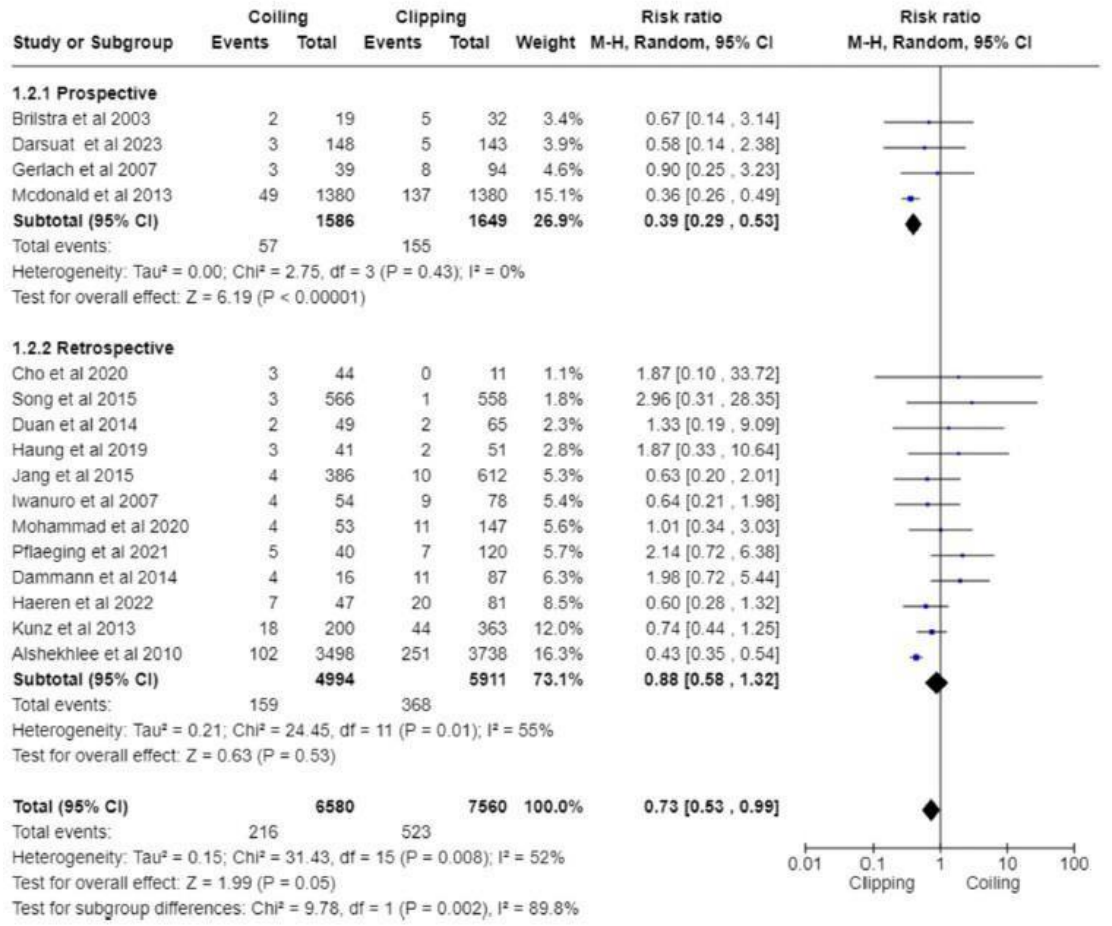


Fig. 15 Forest plot summarizing the pooled risk ratio (RR) of the dichotomous study outcome (cerebral ischemia) between the Coiling group and the Clipping group. Key metrics include: RR (risk ratio), P (*p*-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P of Chi^2 (evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), and P (*p*-value for significance of overall effect)

Occlusion rates

At six months, clipping demonstrates higher occlusion rates; however, this benefit is offset by the one-year mark, as coiling achieves comparable occlusion rates but with a higher need for retreatment. The superiority of the coiling technique observed in both prospective and retrospective studies, which aligns with the previous literature [17]. However, the pooled RR of long-term complete occlusion did not favor either technique. These findings suggest a consistent trend favoring clipping for achieving short-term complete occlusion of unruptured intracranial aneurysms (UIAs). Similarly, Sturiale et al. [20] reported that clipping provides superior short-term occlusion rates while achieving comparable long-term outcomes to coiling for UIAs. In our analysis, the overall complete occlusion rate also favored the clipping technique for short-term complications, suggesting that clipping may be more effective in achieving immediate occlusion compared to coiling. This can be attributed to the mechanical stability provided by clipping, which allows for a more secure and definitive closure of the aneurysm immediately post-procedure. In contrast, long-term outcomes revealed no significant differences between the two techniques across all studies, with only larger studies indicating a noteworthy advantage for coiling. This discrepancy may arise from the inherent limitations of smaller studies, which often have reduced statistical power and increased variability in outcomes. Larger studies, benefiting from a more

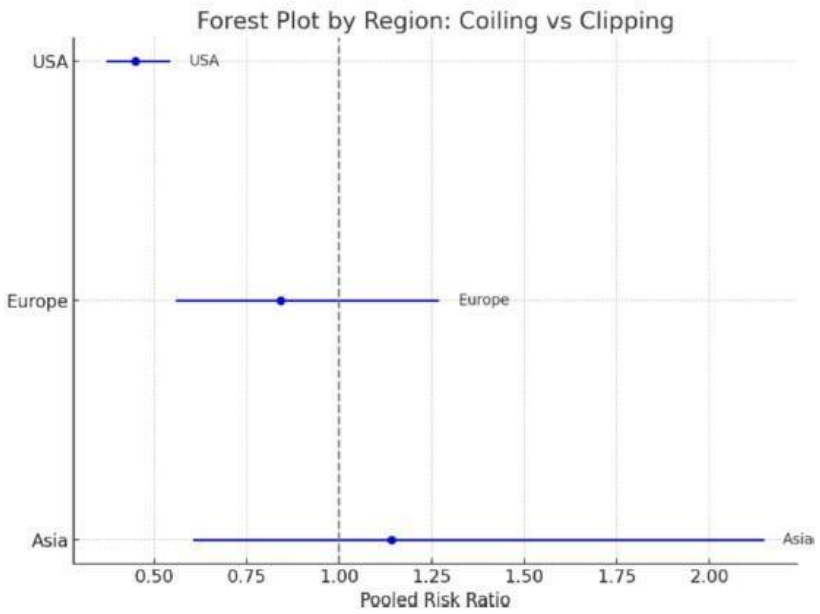


Fig. 16 Forest Plot by Region: cerebral ischemia

extensive patient base and diverse clinical scenarios, can provide a clearer picture of the long-term effectiveness and risks associated with each intervention. The results suggest that while clipping may be superior for achieving short-term occlusion, the effectiveness of coiling may become more pronounced over time, emphasizing the need for careful consideration of both immediate and long-term outcomes when selecting a treatment strategy for patients.

Mortality and complications

The analysis of mortality risk within 30 days across seven studies (n = 81,136 patients) indicates that the coiling intervention is associated with a significantly lower risk of 30-day mortality compared to clipping, with a risk ratio (RR) of 0.56 (95% CI [0.48 to 0.66], p = 0.00001). This finding highlights the potential safety advantage of coiling, suggesting that patients undergoing this procedure may experience a reduced likelihood of death shortly after treatment. However, the pooled data exhibited heterogeneity, indicating variability in the study results that cannot be attributed solely to chance. While some retrospective studies, report no significant differences in mortality rates between the two techniques [21, 22]. Our analysis shows that coiling demonstrates an overall advantage when combining both retrospective and prospective data. The subgroup analysis reveals a more nuanced picture. The retrospective studies consistently show a significantly lower mortality risk associated with coiling (RR 0.55, 95% CI [0.47 to 0.65], p = 0.00001), reinforcing the notion that coiling might be safer in a broader, real-world context where the complexities of individual patient cases are considered. In contrast, the prospective studies do not demonstrate significant differences in mortality risk between the two techniques (RR 0.72, 95% CI [0.32 to 1.62], p = 0.9). This lack of significance in prospective studies may be due to more rigorous patient selection criteria and controlled conditions, which can limit variability and may not capture the same risk factors present in the larger, more diverse cohorts analyzed in retrospective studies.

Ischemic stroke and retreatment

Our analysis of cerebral ischemia rates indicates that clipping is associated with higher ischemic stroke rates compared to coiling, suggesting that coiling may offer a protective effect, particularly in the short term. Subgroup analysis indicates that coiling is associated with significantly lower ischemic stroke rates in prospective studies (RR 0.39, 95% CI [0.29 to 0.53], p = 0.00001). In contrast, retrospective studies showed no significant difference (RR 0.88, 95% CI [0.58 to 1.32], p = 0.53). Conversly, the findings from Mohamed et al. (2020) reveal a more nuanced outcome regarding ischemic events in their retrospective study. They reported a significantly higher incidence of asymptomatic ischemic events in the coiling group (24.5%) compared to the clipping group (2%). However, they noted that the rates of symptomatic

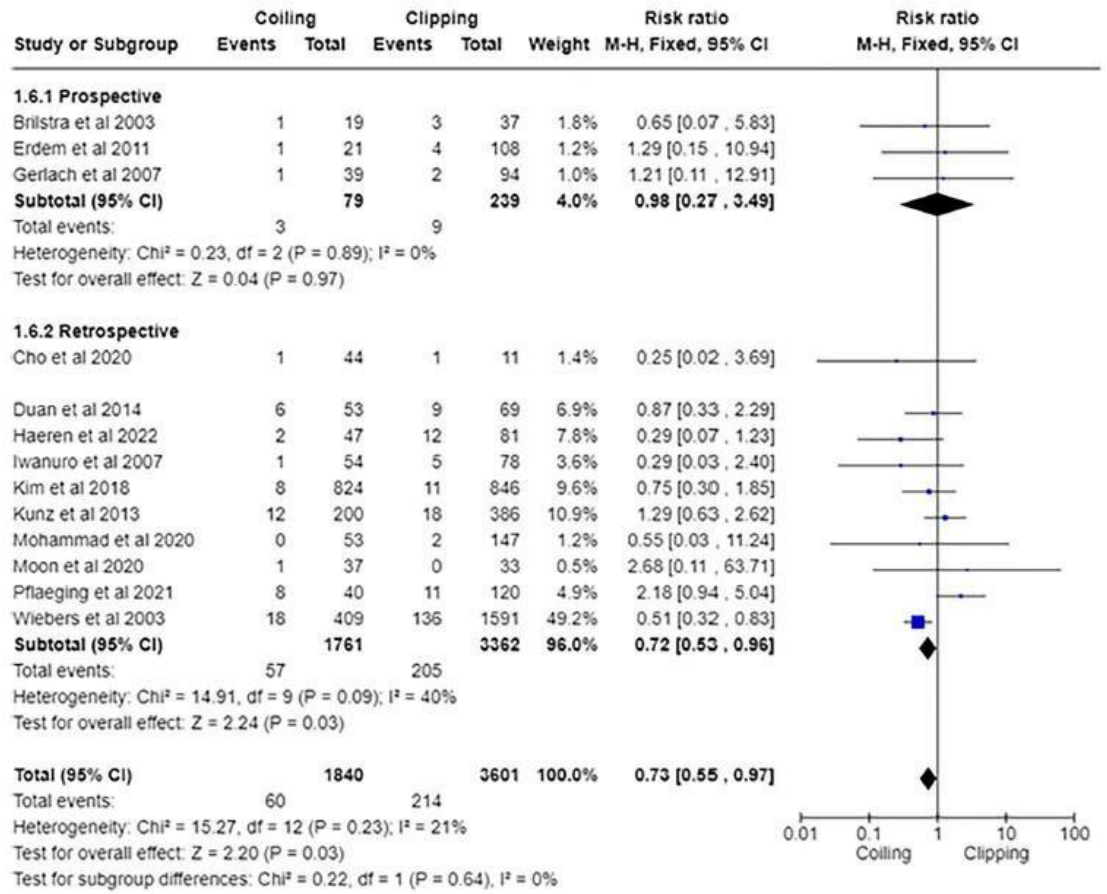


Fig. 17 Forest plot summarizing the pooled risk ratio (RR) of the dichotomous study outcome (Modified Rankin Score (mRS >2)) between the Coiling group and the Clipping group. Key metrics include: RR (risk ratio), P (*p*-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P of Chi^2 (evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), and P (*p*-value for significance of overall effect)

ischemic complications were equal in both groups (7.5%) [23]. While our analysis did not find significant differences in overall ischemic stroke rates, Mohamed et al.'s results suggest that coiling may be associated with a higher likelihood of asymptomatic ischemic events. This highlights the importance of considering both symptomatic and asymptomatic ischemic complications when evaluating the safety and efficacy of treatment techniques.

Regional analysis reveals significant differences in ischemic stroke risk between clipping and coiling techniques. In Asia, the findings indicate that there is no meaningful distinction in ischemic stroke risk between the two approaches, suggesting that regional factors may play a role in influencing outcomes. In Europe, while coiling shows a slight advantage over clipping, the difference is not substantial enough to be considered statistically significant. Conversely, in the USA, the results strongly favor coiling, suggesting that it is associated with significantly lower rates of ischemic stroke compared to clipping.

When examining retreatment rates, we found that coiling is associated with higher frequencies of retreatment compared to surgical clipping, aligning with existing literature [16, 19, 23, 24]. The significant increase in retreatment rates is consistent across prospective studies, whereas retrospective studies did not demonstrate a substantial difference. Notably, regional analysis reveals further discrepancies: in the USA and Europe, coiling is linked to significantly lower

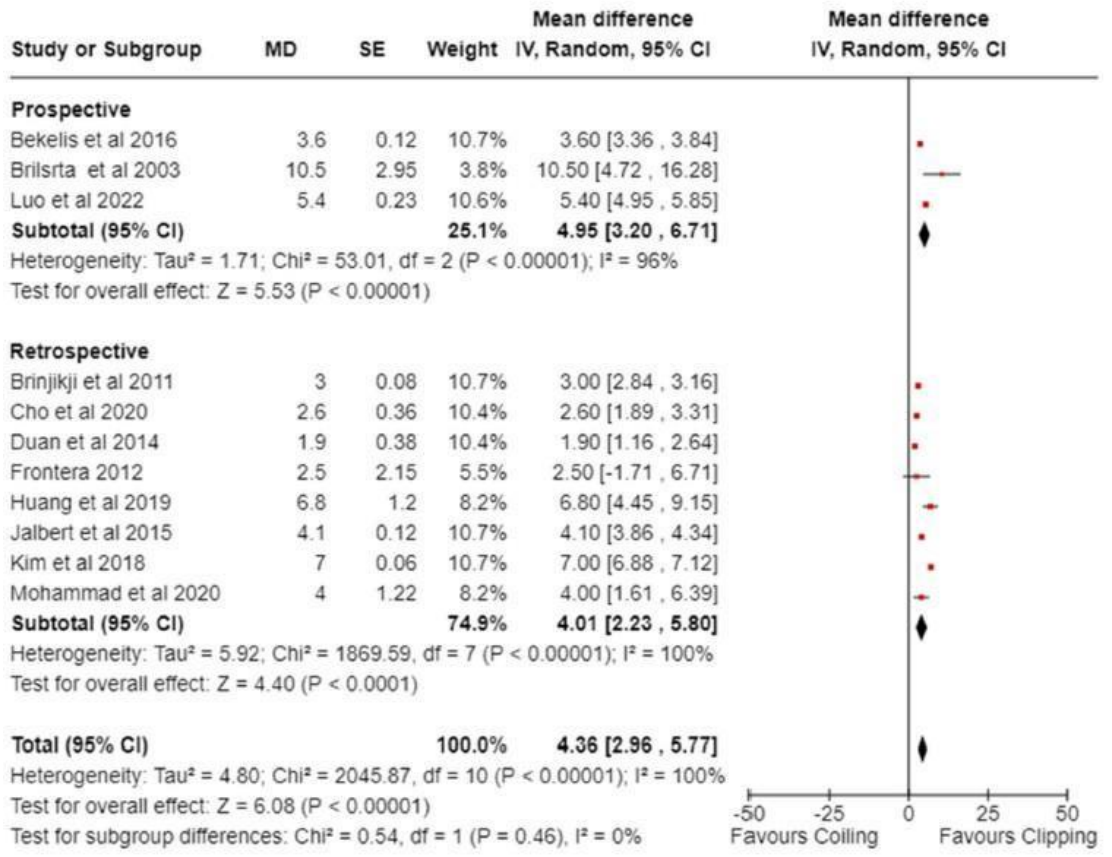


Fig. 18 Forest plot summarizing the mean difference (MD) of the continuous study outcome (length of hospital stay) between the Coiling group and the Clipping group. Key metrics include: MD (mean difference), SE (standard error), P (p-value), CI (confidence interval), df (degrees of freedom), Chi^2 (statistical test for heterogeneity), P of Chi^2 (evidence of heterogeneity of intervention effects), I^2 (degree of heterogeneity between studies), Z (test for overall effect), and P (p-value for significance of overall effect)

retreatment rates, while in Asia, there is no significant difference between the two techniques, despite the lack of variability in outcomes.

These regional variations underscore the influence of local practices on both ischemic stroke and retreatment rates. Factors such as surgical techniques, operator experience, patient selection criteria, and healthcare systems likely contribute to the observed disparities. Additionally, demographic factors like age, comorbidities, and genetic predispositions may affect the risk profiles of patients in different regions, potentially leading to differences in the efficacy of each treatment approach.

Hospital stay and patient outcomes

Our collective analysis shows that patients treated with endovascular coiling tend to have shorter hospital stays compared to those undergoing surgical clipping, aligning with previous findings in the literature [24, 25]. In our study, the percentage of patients with mRS >2 was 1.3% among clipping patients and 0% among coiling patients, suggesting a trend towards better patient outcomes in the coiling group, although this difference did not reach statistical significance. Similarly, the literature indicates favorable outcomes in the coiling group compared to the clipping group, although statistical significance was not explicitly stated [16, 25]. Overall, these consistent trends enhance the reliability and applicability of our study's findings.

The regional subgroup analysis highlights significant variations in the association between surgical clipping and length of hospital stay. In the USA, clipping is linked to longer hospital stays, but high heterogeneity indicates variability in outcomes. Conversely, European studies show a stronger and more consistent association between clipping

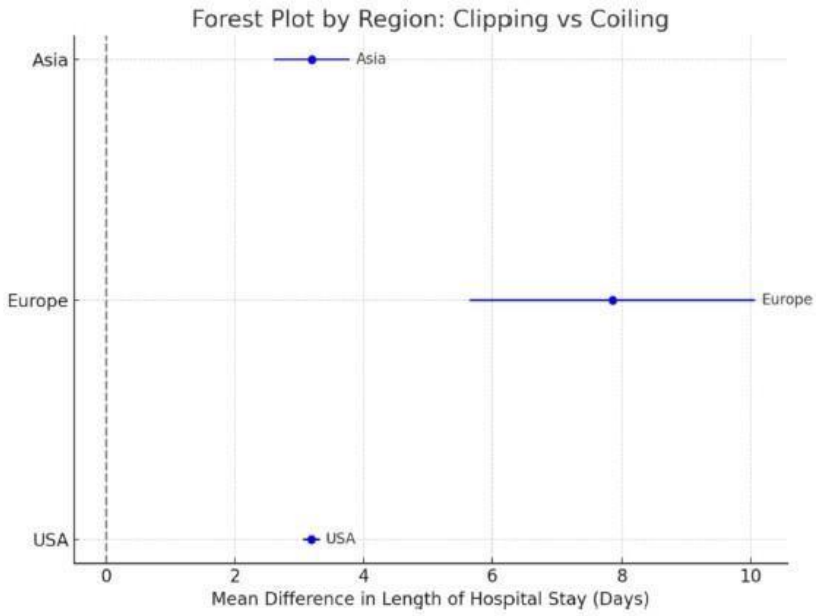


Fig. 19 Forest Plot by Region: length of hospital stay

and increased length of stay, suggesting more standardized clinical practices within that region. In Asia, while clipping also correlates with longer hospital stays, substantial heterogeneity points to differing outcomes across studies, potentially reflecting diverse clinical practices and patient characteristics.

Procedural complications

Our results indicate that coiling is associated with significantly lower rates of complications compared to surgical clipping. Coiling provides a robust protective effect against approach-related issues such as wound healing problems, myocardial infarction, groin hematomas, pneumonia, vessel injury, and seizures. In contrast, clipping necessitates skull opening and complete visualization of the aneurysm, leading to a higher incidence of intraoperative challenges and complications, including inadequate exposure, brain tissue injury, vessel damage resulting in hemorrhage, and vessel occlusion causing ischemia [9, 68]. This advantage is particularly relevant for the predominantly elderly and frail population with UIAs. A retrospective analysis by Taha et al. reported a notable periprocedural technical complication rate of 19.35% for surgical clipping from 2001 to 2004 [26].

In the United States, coiling significantly reduces procedural complications, with consistent findings across studies. European data further support this, demonstrating an even greater reduction, although based on a single study. Conversely, Asian results show no significant difference in complication rates between coiling and clipping, suggesting that the advantages of coiling may be less pronounced in this region. The wider confidence interval in Asia reflects variability in clinical practices, patient characteristics, or study designs.

Choosing between clipping and coiling

Choosing between endovascular coiling and open surgical clipping for treating intracranial aneurysms involves assessing the benefits and risks associated with each option. Both methods aim to permanently exclude the aneurysm from cerebral circulation while preserving critical arteries. Traditionally, open surgery has been considered the standard approach, but studies such as the International Subarachnoid Aneurysm Trial (ISAT) and the International Study of Unruptured Intracranial Aneurysms (ISUIA) have challenged this paradigm [27–29]. Understanding these studies requires consideration of patient demographics, available clinical expertise, and measured outcomes. For instance, ISAT excluded patients with life-threatening hematomas, specific anatomical features, or prior unsuccessful endovascular treatments. ISAT results indicated that endovascular coiling yielded better outcomes for survival without disability at one year compared to surgical clipping for ruptured intracranial aneurysms. However, these findings may not universally apply, as the ISAT cohort predominantly

comprised European patients with small anterior circulation aneurysms. Although mortality rates were similar between the two methods, coiling was associated with higher rates of rebleeding and retreatment [28].

Concerns regarding the long-term durability of endovascular treatment have arisen, with studies reporting symptomatic re-hemorrhaging in patients with partially treated aneurysms years after the initial procedure. Long-term follow-up is crucial, as underscored by the Dutch Aneurysm Screening after Surgical Treatment for Ruptured Aneurysms (ASTRA) Study, which identified a significant incidence of new aneurysm formation 15 years post-surgical clipping [30].

Advancements in endovascular techniques have introduced nuanced management approaches, such as "greater than 95% occlusion" and "near-complete occlusion." However, the implications of treating partially occluded aneurysms over the long term remain uncertain [31]. Surgical clipping, while offering more durable and complete obliteration, carries higher risks related to neurobehavioral outcomes compared to endovascular methods [32–35].

Therefore, the selection between clipping and coiling should consider factors like aneurysm complexity, size, geometry, and accessibility. The presence of both clipping and coiling capabilities in specialized centers with high case volumes significantly influences outcomes, with high-volume centers demonstrating lower mortality rates and improved patient outcomes compared to low-volume centers [36, 37].

Quality of evidence assessment

The quality of evidence in previous systematic reviews has frequently been uncertain. Recent meta-analyses (61–63), for instance, have provided evidence that is often unclear. In contrast, our study delivers high-quality evidence for outcomes such as the Modified Rankin Score, cerebral ischemia, procedural complications, and short-term complete occlusion, although the quality of evidence related to mortality remains lower.

This study distinguishes itself as the first to present a pooled effect covering a wide range of dependent variables. Although prior meta-analyses (61–63) included numerous studies, their methodology often lacked transparency regarding the quality of evidence and primarily used odds ratios (OR) for risk analysis. We chose to employ risk ratios (RR) for several compelling reasons. RR is particularly suited for the binary outcomes in our analysis—such as complete occlusion rates in midterm and long-term follow-up, Mortality, Procedural bleeding, Retreatment, Procedural complications, Cerebral ischemia and Modified Rankin score (mRS >2) as it enables a more direct comparison of event risks between treatment groups. Unlike OR, which can be complex and less intuitive for clinical interpretation, RR provides clearer and more practical insights that enhance clinical decision-making. By using RR, we more accurately quantified risk differences between treatment groups, allowing for a clearer assessment of intervention impacts on adverse events and functional outcomes, thereby supporting clinicians in making well-informed decisions.

To ensure the robustness and applicability of our findings across various clinical practices, we applied Python-based meta-analysis techniques, following guidelines similar to those in Masoumi's tutorial on Python meta-analysis [69]. These methods included conducting sensitivity analyses by sequentially excluding individual studies to evaluate their influence on the overall outcomes, as well as performing regional subgroup analyses to capture variations across different clinical settings. By implementing these strategies, we effectively identified and addressed heterogeneity, resulting in a refined and reliable analysis that strengthens the evidence base for guiding clinical practice.

Moreover, the inclusion of significant new data and our robust statistical approach have led to more precise effect size estimations. This strengthens the overall evidence base, improving treatment decision-making and optimizing patient care.

Our findings underscore the need for individualized treatment approaches tailored to patient characteristics and stroke severity, reflecting the emphasis of these guidelines.

Clinical decision-making should also consider factors such as patient eligibility, treatment accessibility, and the resources available at different institutions to ensure each patient receives the most effective and appropriate treatment.

Limitations

Despite the thorough approach used in this study, several limitations should be acknowledged; Firstly, there was significant heterogeneity among the included studies regarding their design, patient demographics, and clinical practices, which could limit the generalizability of our findings. Such variability may result in inconsistencies in outcomes, reducing the applicability of results across different healthcare settings.

Additionally, the extensive time frame considered in the analysis is a limitation, as advancements in medical technology and changes in clinical practices over the years may influence the comparability of the results. The diversity in patient characteristics and types of aneurysms further complicates the analysis, as these factors can affect outcomes in various ways.

The variability in reported outcome measures across studies also poses challenges for effective data synthesis, as not all studies provided comparable primary and secondary outcomes. While we conducted meta-regression and subgroup

analyses to investigate sources of variability, these analyses are observational and do not establish causal relationships; therefore, the findings should be interpreted with caution. Lastly, some included studies may have had short follow-up durations, which could affect the assessment of long-term outcomes.

Conclusion

Our study highlights that clipping achieves higher short-term occlusion rates but is associated with longer hospital stays and higher risks of procedural bleeding and ischemia. By the one-year mark, coiling achieves similar occlusion rates, but has a higher rate of retreatment. Coiling offers advantages including shorter hospital stays, lower procedural risks, a slight mortality benefit, and better morbidity outcomes. Both methods lead to favorable functional outcomes for most patients. Our analysis, strengthened by sensitivity and regional subgroup analyses, ensures that the findings are robust and applicable across various clinical practices.

Acknowledgment We would like to express our gratitude to Mahmoud Masoud, Rawan Hamamerh, Asmaa AlNajjar, and Amjad Almansi for their contributions to this meta-analysis. Although their involvement was limited and some tasks were not fully completed, their early efforts in data collection and preliminary analysis were valuable to the overall project.

Funding The author(s) have received no financial support for the research, authorship, and/or publication of this article.

Data availability Not publicly available.

Declarations

Conflict of interests The author(s) have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

Ethical approval Not applicable.

Informed consent Not applicable.

References

1. Bekelis K, Goodney PR, Dzebisashvili N, Goodman DC, Bronner KK. The Dartmouth Atlas of Health Care. Variation in the Care of Surgical Conditions: Cerebral Aneurysms: A Dartmouth Atlas of Health Care Series. Lebanon (NH): The Dartmouth Institute for Health Policy and Clinical Practice© The Trustees of Dartmouth College.; 2014.
2. Brisman JL, Song JK, Newell DW (2006) Cerebral aneurysms. N Engl J Med. 355(9):928–39. https://doi.org/10.1056/NEJMra052760
3. Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr et al (2015) Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 46(8):2368–400. https://doi.org/10.1161/str.0000000000000070
4. Cianfoni A, Pravatà E, De Blasi R, Tschuor CS, Bonaldi G (2013) Clinical presentation of cerebral aneurysms. Eur J Radiol. 82(10):1618–22. https://doi.org/10.1016/j.ejrad.2012.11.019
5. Tawk RG, Hasan TF, D'Souza CE, Peel JB, Freeman WD (2021) Diagnosis and Treatment of Unruptured Intracranial Aneurysms and Aneurysmal Subarachnoid Hemorrhage. Mayo Clin Proc. 96(7):1970–2000. https://doi.org/10.1016/j.mayocp.2021.01.005
6. Caffes N, Wenger N, Cannarsa G, Oliver J, Onwukwe C, Gandhi D et al (2021) Unruptured cerebral aneurysms in elderly patients: key challenges and management. Ann Med. 53(1):1839–49. https://doi.org/10.1080/07853890.2021.1990393
7. Lai L, Morgan MK (2012) The impact of changing intracranial aneurysm practice on the education of cerebrovascular neurosurgeons. J Clin Neurosci. 19(1):81–4. https://doi.org/10.1016/j.jocn.2011.07.008
8. Darsaut TE, Estrade L, Jamali S, Bojanowski MW, Chagnon M, Raymond J (2014) Uncertainty and agreement in the management of unruptured intracranial aneurysms. J Neurosurg. 120(3):618–23. https://doi.org/10.3171/2013.11.Jns131366
9. Brinjikji W, Rabinstein AA, Nasr DM, Lanzino G, Kallmes DF, Cloft HJ (2011) Better outcomes with treatment by coiling relative to clipping of unruptured intracranial aneurysms in the United States, 2001–2008. AJNR Am J Neuroradiol. 32(6):1071–5. https://doi.org/10.3174/ajnr
10 McDonald JS, McDonald RJ, Fan J, Kallmes DF, Lanzino G, Cloft HJ (2013) Comparative effectiveness of unruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. Stroke. 44(4):988–94. https://doi.org/10.1161/strokeaha.111.000196
11 Alshafai N, Cusimano MD, Falenchuk O (2013) Global differences in the present and future management of cerebral aneurysms. World Neurosurg. 80(6):717–22. https://doi.org/10.1016/j.wneu.2013.01.092
12 Hwang JS, Hyun MK, Lee HJ, Choi JE, Kim JH, Lee NR et al (2012) Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC Neurol. 12:99. https://doi.org/10.1186/1471-2377-12-99
13 Tsianaka E, Al-Shawish A, Potapov A, Fountas K, Spyrou M, Konovalov N (2019) Clipping versus coiling in 5posterior circulation intracranial aneurysms: a meta-analysis. Chin Neurosurg J. 5:16. https://doi.org/10.1186/s41016-019-0163-x
14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP (2016) Robins-i: A tool for assessing risk of bias in non-randomised studies of interventions. Bmj 355:i4919
15. Jonathan ACS, Jelena S, Matthew JP, Roy GE, Natalie SB, Isabelle B, Christopher JC, Hung-Yuan C, Mark SC, Sandra ME, Jonathan RE, Miguel AH, Sally H, Asbjørn H, Daniela RJ, Peter J, Jamie JK, Toby L, Tianjing L, Alexandra M, Barnaby CR, Sasha S, Ian S, Lesley AS, Kate T, Ian RW, Penny FW, Julian PTH (2019) Rob 2: A revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898

16. Sweeney K, Silver N, Javadpour M. Subarachnoid haemorrhage (spontaneous aneurysmal). BMJ Clin Evid. 2016; 2016 .
17 Belavadi R, Gudigopuram SVR, Raguthu CC, Gajjela H, Kela I, Kakarala CL et al (2021) Surgical Clipping Versus Endovascular Coiling in the Management of Intracranial Aneurysms. Cureus. 13(12):e20478. https://doi.org/10.7759/cureus.20478
18 Song J, Kim BS, Shin YS (2015) Treatment outcomes of unruptured intracranial aneurysm; experience of 1,231 consecutive aneurysms. Acta Neurochir (Wien). 157(8):1303–10. https://doi.org/10.1007/s00701-015-2460-2
19. Darsaut TE, Fahed R, Macdonald RL, Arthur AS, Kalani MYS, Arikan F et al (2018) Surgical or endovascular management of ruptured intracranial aneurysms: an agreement study. J Neurosurg. 131(1):25–31. https://doi.org/10.3171/2018.1.Jns172645
20 Sturiale CL, Scerrati A, Ricciardi L, Rustemi O, Auricchio AM, Norri N et al (2022) Clipping versus coiling for treatment of middle cerebral artery aneurysms: a retrospective Italian multicenter experience. Neurosurg Rev. 45(5):3179–91. https://doi.org/10.1007/s10143-022-01822-3
21. Kim YD, Bang JS, Lee SU, Jeong WJ, Kwon OK, Ban SP et al (2018) Long-term outcomes of treatment for unruptured intracranial aneurysms in South Korea: clipping versus coiling. J Neurointerv Surg. 10(12):1218–22. https://doi.org/10.1136/neurintsurg-2018-013757
22. Bekelis K, Missios S, Coy S, Singer RJ, MacKenzie TA. New York State: Comparison of Treatment Outcomes for Unruptured Cerebral Aneurysms Using an Instrumental Variable Analysis. J Am Heart Assoc. 2015;4(7 https://doi.org/10.1161/jaha.115.002190
23 Mohammad F, Horiguchi T, Mizutani K, Yoshida K (2020) Clipping versus coiling in unruptured anterior cerebral circulation aneurysms. Surg Neurol Int. 11:50. https://doi.org/10.25259/sni_1_2020
24 Xin WQ, Xin QQ, Yang XY (2019) Meta-Analysis of Clipping versus Coiling for the Treatment of Unruptured Middle Cerebral Artery Aneurysms: Direct Comparison of Procedure-Related Complications. Neuropsychiatr Dis Treat. 15:3387–95. https://doi.org/10.2147/ndt.S226353
25 Alshekhlee A, Mehta S, Edgell RC, Vora N, Feen E, Mohammadi A et al (2010) Hospital mortality and complications of electively clipped or coiled unruptured intracranial aneurysm. Stroke. 41(7):1471–6. https://doi.org/10.1161/strokeaha.110.580647
26. Taha MM, Nakahara I, Higashi T, Iwamuro Y, Iwaasa M, Watanabe Y et al (2006) Endovascular embolization vs surgical clipping in treatment of cerebral aneurysms: morbidity and mortality with short-term outcome. Surg Neurol. 66(3):277–84. https://doi.org/10.1016/j.surneu.2005.12.031
27. Molyneux A, Kerr R, Stratton I et al (2002) International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 360:1267–74
28. Molyneux AJ, Kerr RS, Yu LM et al (2005) International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 366:809–17
29 Wiebers DO, Whisnant JP, Huston J 3rd et al (2003) Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 362:103–10
30. Wermer MJH, van der Schaaf IC, Velthius BK et al (2005) Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargements of existing aneurysms. Brain 128(Pt10):2421–9
31. Brilstra EH, Rinkel GJ, van der Graaf Y, et al. Quality of life after treatment of unruptured intracranial aneurysms by neurosurgical clipping or by embolisation with coils. A prospective, observational study. Cerebrovasc Dis. 2004;17(1):44-52. https://doi.org/10.1159/000073897
32 Ogden JA, Towgood K, Mee E (2005) Neurological neuropsychological, and functional outcome followingtreatmentforunruptured-intracranialaneurysms. J IntNeuropsycholSoc 11:522–34
33. Bellebaum C, Schafers L, Schoch B et al (2004) Clipping versus coiling: neuropsychological follow up after aneurysmal subarachnoid haemorrhage (SAH). J Clin Exp Neuropsychol 26:1081–92
34. Cross DT 3rd, Tirschwell DL, Clark MA et al (2003) Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. J Neurosurg 99:810–7
35. Johnston SC (2000) Effect of endovascular services and hospital volume on cerebral aneurysm treatment outcomes. Stroke 31:111–7
36. Bardach NS, Zhao S, Gress DR et al (2002) Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. Stroke 33(7):1851–6
37. Solomon RA, Mayer SA, Tarmey JJ (1996) Relationship between the volume of craniotomies for cerebral aneurysm performed at New York state hospitals and in-hospital mortality. Stroke 27:13–7
38. Dammann P, Schoemberg T, Müller O et al (2014) Outcome for unruptured middle cerebral artery aneurysm treatment: surgical and endovascular approach in a single center. Neurosurg Rev. 37(4):643–651. https://doi.org/10.1007/s10143-014-0563-5
39. Diaz OM, Rangel-Castilla L, Barber S, Mayo RC, Klucznik R, Zhang YJ (2014) Middle cerebral artery aneurysms: a single-center series comparing endovascular and surgical treatment. World neurosurgery 81(2):322–329. https://doi.org/10.1016/j.wneu.2012.12.011
40. Güresir E, Vatter H, Schuss P et al (2013) Natural history of small unruptured anterior circulation aneurysms: a prospective cohort study. Stroke. 44(11):3027–3031. https://doi.org/10.1161/STROKEAHA.113.001107
41. Jang EW, Kim YB, Chung J, Suh SH, Hong CK, Joo JY (2015) Clinical Risk Factors Affecting Procedure-Related Major Neurological Complications in Unruptured Intracranial Aneurysms. Yonsei Med J. 56(4):987–992. https://doi.org/10.3349/ymj.2015.56.4.987
42. Duan Y, Blackham K, Nelson J, Selman W, Bambakidis N (2015) Analysis of short-term total hospital costs and current primary cost drivers of coiling versus clipping for unruptured intracranial aneurysms. J Neurointerv Surg. 7(8):614–8. https://doi.org/10.1136/neurintsurg-2014-011249
43. Frontera JA, Moatti J, de los Reyes KM, McCullough S, Moyle H, Bederson JB, Patel A (2014) Safety and cost of stent-assisted coiling of unruptured intracranial aneurysms compared with coiling or clipping. J Neurointerv Surg. 6(1):65–71. https://doi.org/10.1136/neurintsurg-2012-010544
44. Yang H, Jiang H, Ni W et al (2019) Treatment Strategy for Unruptured Intracranial Aneurysm in Elderly Patients: Coiling, Clipping, or Conservative? Cell Transplant. 28(6):767–774. https://doi.org/10.1177/0963689718823517
45. Suzuki M, Yoneda H, Ishihara H et al (2015) Adverse events after unruptured cerebral aneurysm treatment: a single-center experience with clipping/coil embolization combined units. J Stroke Cerebrovasc Dis. 24(1):223–231. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.08.018
46. Solheim O, Eloqayli H, Muller TB, Unsgaard G (2006) Quality of life after treatment for incidental, unruptured intracranial aneurysms. Acta Neurochir (Wien). 148(8):821–830. https://doi.org/10.1007/s00701-006-0804-7

47. Lad SP, Babu R, Rhee MS et al (2013) Long-term economic impact of coiling vs clipping for unruptured intracranial aneurysms. Neurosurgery. 72(6):1000–1013. https://doi.org/10.1227/01.neu.0000429284.91142.56
48. Jalbert JJ, Isaacs AJ, Kamel H, Sedrakyan A (2015) Clipping and Coiling of Unruptured Intracranial Aneurysms Among Medicare Beneficiaries, 2000 to 2010. Stroke. 46(9):2452–2457. https://doi.org/10.1161/STROKEAHA.115.009777
49 Iwamuro Y, Nakahara I, Higashi T et al (2007) Result of neck clipping and coil embolization as a treatment for unruptured aneurysm. Interv Neuroradiol. 13(Suppl 1):151–156. https://doi.org/10.1177/15910199070130S123
50. Huang C, You C (2019) Clipping Versus Coiling in the Management of Unruptured Aneurysms with Multiple Risk Factors. World Neurosurg. 126:e545–e549. https://doi.org/10.1016/j.wneu.2019.02.090
51. Gerlach R, Beck J, Setzer M et al (2007) Treatment related morbidity of unruptured intracranial aneurysms: results of a prospective single centre series with an interdisciplinary approach over a 6 year period (1999–2005). J Neurol Neurosurg Psychiatry. 78(8):864–871. https://doi.org/10.1136/jnnp.2006.106823
52. Darsaut TE, Findlay JM, Bojanowski MW et al (2023) A Pragmatic Randomized Trial Comparing Surgical Clipping and Endovascular Treatment of Unruptured Intracranial Aneurysms. AJNR Am J Neuroradiol. 44(6):634–640. https://doi.org/10.3174/ajnr.A7865
53. Cho WC, Shin YS, Kim BS, Choi JH (2020) Treatment outcome after coiling or clipping for elderly patients with unruptured intracranial aneurysms. J Cerebrovasc Endovasc Neurosurg. 22(2):78–84. https://doi.org/10.7461/jcen.2020.22.2.78
54 Mascitelli JR, Mocco J, Hardigan T et al (2021) Endovascular therapy versus microsurgical clipping of unruptured wide-neck aneurysms: a prospective multicenter study with propensity score analysis. J Neurosurg. 137(2):352–359. https://doi.org/10.3171/2021.10.JNS211942
55. Haeren R, Hafez A, Korja M, Raj R, Niemelä M (2022) Fast Transition from Open Surgery to Endovascular Treatment of Unruptured Anterior Communicating Artery Aneurysms-A Retrospective Analysis of 128 Patients. World Neurosurg. 165:e668–e679. https://doi.org/10.1016/j.wneu.2022.06.122
56. Pflaeging M, Kabbasch C, Schlamann M et al (2021) Microsurgical Clipping versus Advanced Endovascular Treatment of Unruptured Middle Cerebral Artery Bifurcation Aneurysms After a "Coil-First" Policy. World Neurosurg. 149:e336–e344. https://doi.org/10.1016/j.wneu.2021.02.027
57 Luo J, Wang C, Dai Y et al (2022) Efficacy and safety of endovascular therapy versus surgical clipping for patients with unruptured middle cerebral artery bifurcation aneurysms [published correction appears in. J Investig Med. 70(5):1273–1279. https://doi.org/10.1136/jim-2021-002230
58. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2024. Available from gradepro.org.
59. Hwang JS, Hyun MK, Lee HJ, Choi JE, Kim JH, Lee NR, Kwon JW, Lee E (2012) Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC Neurol. 22(12):99. https://doi.org/10.1186/1471-2377-12-99
60. Diana F, Pesce A, Toccaceli G, Muralidharan V, Raz E, Miscusi M, Raco A, Missori P, Peschillo S (2022) Microsurgical clipping versus newer endovascular techniques in treatment of unruptured anterior communicating artery-complex aneurysms: a meta-analysis and systematic review. Neurosurg Rev. 45(2):1089–1100. https://doi.org/10.1007/s10143-021-01647-6
61. Hwang JS, Hyun MK, Lee HJ et al (2012) Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC Neurol. 12:99. https://doi.org/10.1186/1471-2377-12-99
62. Shen Z, Zhao Y, Gu X et al (2024) Systematic Review of Treatment for Unruptured Intracranial Aneurysms: Clipping Versus Coiling. Turk Neurosurg. 34(3):377–387. https://doi.org/10.5137/1019-5149.JTN.23729-18.1
63. Kang XK, Guo SF, Lei Y et al (2020) Endovascular coiling versus surgical clipping for the treatment of unruptured cerebral aneurysms: Direct comparison of procedure-related complications. Medicine (Baltimore). 99(13):e19654. https://doi.org/10.1097/MD.0000000000019654
64. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC (2003) International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms: Natural history, clinical outcome, and risks of surgical and endovaseular treatment. Lancet 362:103–110
65. Song J, Kim BS, Shin YS (2015) Treatment outcomes of unruptured intracranial aneurysm; experience of 1231 consecutive aneurysms. Neurochir (Wien) 157:1303–1310
66. Kunz M, Bakhshai Y, Zausinger S, Fesl G, Janssen H (2013) Brück- mann H, Tonn JC, Schichor C: Interdisciplinary treatment of unruptured intracranial aneurysms: Impact of intraprocedural rupture and ischemia in 563 aneurysms. J Neurol 260:1304–1313
67. Alshekhlee A, Mehta S, Edgell RC, Vora N, Feen E, Mohammadi A, Kale SP, Cruz-Flores S (2010) Hospital mortality and complications of electively clipped or coiled unruptured intracranial aneurysm. Stroke 41:1471–1476
68. Lai LT, ODonnell J, Morgan MK (2013) The risk of seizures during the in-hospital admission for surgical or endovascular treatment ofunruptured intracranial aneurysms. Neurosci 20:1498–1502
69. Masoumi S, Shahraz S (2022) Meta-analysis using Python: a hands-on tutorial. BMC Med Res Methodol. 22(1):193. https://doi.org/10.1186/s12874-022-01673-y

4. Abschlussdiskussion

4.1. Erstes Manuskript

Comparative Effectiveness of Intravenous Thrombolysis plus Mechanical Thrombectomy versus Mechanical Thrombectomy Alone in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis.

Hammed A, Al-Qiami A, Alzawahreh A, Rosenbauer J, Nada EA, Otmani Z, Hamam NG, Alnajjar AZ, Mohamed Hammad E, Hamamreh R, Kostev K, Richter G, Tanislav C.; Cerebrovasc Dis. 2024 Aug 24:1-14. doi: 10.1159/000541033. Epub ahead of print. PMID: 39182478.

In den letzten Jahren hat die Behandlung des akuten ischämischen Schlaganfalls bemerkenswerte Fortschritte gemacht [8]. Besonders die Kombination aus intravenöser Thrombolyse (IVT) und mechanischer Thrombektomie (MT) bei Verschluss einer großen hirnversorgenden Arterie ist mittlerweile etabliert. Trotz ihrer breiten Anwendung bleibt jedoch unklar, ob die Kombination von IVT und MT, die sogenannte Bridging-Therapie, Vorteile gegenüber der alleinigen mechanischen Thrombektomie bietet, sodass diese Frage aktuell Gegenstand wissenschaftlicher Diskussionen ist [8,11]. Ziel der präsentierten Arbeit war es daher, die Bridging-Therapie mit der Durchführung der alleinigen mechanischen Thrombektomie auf Vor- und Nachteile in einer Meta-Analyse zu untersuchen.

Bridging-Therapie versus intravenöse Thrombolyse, Nutzen in der Akutphase.

Die Ergebnisse unserer Analyse zeigen, dass die Bridging-Therapie (IVT + MT) mit einer stärkeren klinischen Verbesserung assoziiert ist; beim Vergleich der NIHSS-Scores (National Institutes of Health Stroke Scale) nach 24 Stunden und nach sieben Tagen zeigen sich diesbezüglich klare Ergebnisse. Der mittlere Unterschied (MD) zwischen den beiden Behandlungsansätzen betrug 0,96 (95% CI [0,73–1,20], $p < 0,00001$). Die frühe IVT mit nachfolgender Thrombektomie scheint insbesondere eine rasche Reperfusion zu fördern und die Zeit zur Rekanalisation zu verkürzen. Diese Beobachtung steht im Einklang mit den abgeleiteten Daten zur Rekanalisation der betroffenen Gefäße. Der

TICI-Score (Thrombectomy in Cerebral Ischemia) ist ein wichtiger Indikator für die erfolgreiche Rekanalisation eines Verschlusses einer hirnversorgenden Arterie. In diesem Zusammenhang konnten wir in unserer Analyse einen hohen Anteil an erfolgreichen Rekanalisationen (TICI 2b–3) in der Bridging-Therapie-Gruppe finden. Unsere Analyse ergänzt die Ergebnisse der Arbeit von Cuadra-Campos und Kollegen, die die oben beschriebenen Vorteile der Bridging-Therapie ebenfalls beobachteten [15].
Unsere Ergebnisse unterstreichen damit die Notwendigkeit eines raschen Handels beim akuten Schlaganfall, die frühzeitige intravenöse Thrombolyse mit nachfolgender Thrombektomie bietet den größten therapeutischen Nutzen für den Patienten.

Klinische Implikationen für die Bridging-Therapie im Zeitverlauf

Obwohl die Bridging-Therapie bei der Verbesserung des NIHSS-Scores unmittelbar nach der Prozedur überlegen war, gab es keine relevanten Unterschiede zwischen den beiden Gruppen in Bezug auf den funktionellen Status nach 90 Tagen. Die gemessenen Werte der modifizierten Rankin-Skala (mRS) zeigten keine nennenswerten Unterschiede (RR 1,05, 95% CI [0,97–1,13], p = 0,23). Dieses Ergebnis ist so zu interpretieren, dass die unmittelbare Verbesserung des neurologischen Status nach der Bridging-Therapie nicht zwangsläufig zu einem besseren funktionellen Satus im Zeitverlauf führt. In diesem Zusammenhang muss hier ein methodisches Bias in der Erhebung der Langzeitscores diskutiert werden. Während die für die akute Evaluation verwendete NIH-Stroke Scale feine klinische Unterschiede diskriminiert, ist die im Langzeitverlauf verwendete modifizierte Rankin-Skala in der Erhebung grob strukturiert und gibt nur global die Funktionalität wieder [16]. Inwiefern feine Unterschiede auch im Langzeitverlauf existieren, bleiben aufgrund dieser methodischen Schwächen unklar. Es ist jedoch anzunehmen, dass, sofern vorhanden, Unterschiede gering ausfallen und keinen nennenswerten Einfluss auf die funktionale Gesundheit insgesamt haben [16,17].

Bridging-Therapie versus intravenöse Thrombolyse, Zeitaspekte.

Ein weiterer relevanter Punkt in unserer Analyse war die Zeit zwischen dem Symptombeginn des akuten Schlaganfalles und der Punktion zur Durchführung der mechanischen Thrombektomie. Diese war in der MT-Gruppe kürzer als in der BT-Gruppe (MD 9,91 Minuten, 95% CI [4,31–15,52], p = 0,005). Diese Beobachtung ist von großer Relevanz, unabhängig von dem Procedere ist eine zügige Durchführung der gewählten Maßnahmen für den Outcome wichtig. Auch wenn der Unterschied in unserer Analyse auf knapp nur 10 Minuten gerechnet wurde, die die Durchführung der alleinigen Thrombektomie bevorteilt, sollte die vorgeschaltete Prozedur der intravenösen Thrombolyse im Grundsatz keine Verzögerung nach sich ziehen. Daher sollten etablierte organisatorische Abläufe in der Akutversorgung des Schlaganfalles der Kliniken kritisch hinterfragt und gegebenenfalls revidiert werden; mögliche Faktoren sollten ausgeschaltet werden, die eine Verzögerung hervorrufen können [17]. Auch eine Verzögerung von 10 Minuten kann beim akuten Schlaganfall im Outcome erhebliche Auswirkungen haben.

Sicherheitsaspekte und symptomatische intrakranielle Blutungen (sICH)

In Bezug auf die Sicherheit fanden wir zwischen den beiden Gruppen keinen relevanten Unterschied bezüglich des Risikos, eine symptomatische intrakranielle Blutung (sICH) (RR 1,23, 95% CI [0,88–1,74], p = 0,23) zu erleiden.Dies ist eine wichtige Erkenntnis, da bei der Verwendung von Thrombolytika und rekanalisierenden Verfahren per se ein erhöhtes Blutungsrisiko angenommen werden muss, das potenziell einen erheblichen Einfluss auf die Therapieentscheidung haben kann. Unsere Ergebnisse stehen im Einklang mit den Ergebnissen vorheriger Analysen, die für beide Prozeduren vergleichbare Risiken bezüglich einer intrakraniellen Blutung herausfanden [16,17].

Aspekte der Mortalität und Langzeitprognose

Die Analyse der Mortalität nach 90 Tagen zeigte keine signifikanten Unterschiede in der Mortalität zwischen den beiden Gruppen (RR 0,91, 95% CI [0,75–1,10], p = 0,34). Diese

Beobachtung zeigt, dass diesbezüglich beide Prozeduren sicher sind und keine wesentlichen Unterschiede in der langfristigen Überlebensrate der Patienten aufweisen. Dies steht im Einklang mit früheren Studien, die ebenfalls keinen relevanten Einfluss auf die Mortalität in Abhängigkeit von der Wahl der Therapiemodalität herausgearbeitet haben [8,17]. In Bezug auf die Langzeitprognose, gemessen anhand des Barthel Index und der mRS, fanden wir keine relevanten Unterschiede zwischen den beiden Gruppen. Diese Ergebnisse deuten darauf hin, dass die Wahl der Behandlungsmethode zum Teil kurzfristige Vorteile bietet, jedoch keinen wesentlichen messbaren Einfluss auf die funktionelle Gesundheit im Langzeitverlauf hat. Auch hier sind unsere Ergebnisse mit denjenigen die von Cuadra-Campos und Kollegen vergleichbar [15], die ebenfalls keine relevanten Unterschiede im Langzeitverlauf feststellten.

Vergleich mit bestehenden Studien und Literatur

Die Ergebnisse dieser Meta-Analyse decken sich weitgehend mit den Erkenntnissen anderer aktueller Studien, wie den Arbeiten von Wang et al. [16] und Cuadra-Campos et al. [17]. Diese Studien betonen ebenfalls die Überlegenheit der Bridging-Therapie (BT) bei der Wiederherstellung der Hirnperfusion. Unterschiede in Bezug auf funktionellen Status und Mortalität, die in einigen früheren Studien zugunsten der alleinigen mechanischen Thrombektomie (MT) festgestellt wurden, könnten durch Variationen in Studiendesigns, Patientenpopulationen oder Behandlungsalgorithmen erklärt werden. Auch methodische Limitationen in der Langzeiterfassung des funktionellen Status könnten hierbei eine Rolle spielen, da die Assessments zur Langzeitevaluation häufig weniger differenziert sind und meist nur den globalen funktionellen Status erfassen.
Ein zentraler Aspekt dieser Analyse ist zweifelsohne der Vorteil bezüglich der Wiederherstellung der Hirnperfusion bei Anwendung der Bridging-Therapie bei gleichzeitig nicht erhöhtem Risikoprofil. Die frühzeitige Wiederherstellung des Blutflusses ist entscheidend, um Hirngewebe zu erhalten und langfristige Schäden zu minimieren. Diese Erkenntnisse stützen die aktuellen Leitlinien der American Heart Association (AHA) und der American Stroke Association (ASA), die Reperfusionstherapien, insbesondere bei großen Arterienverschlüssen, als essenziell hervorheben [18]. Das Ziel bleibt, die Reperfusion so schnell wie möglich zu erreichen,

um den Patienten die besten Chancen auf eine vollständige funktionelle Erholung zu bieten.

Zusammenfassung

Die Bridging-Therapie zeigt bei akuten ischämischen Schlaganfällen infolge eines Verschlusses einer großen hirnversorgenden Arterie klare Vorteile, sowohl bei der Verbesserung des klinisch-neurologischen Befundes als auch hinsichtlich der Wiederherstellung der Hirnperfusion. In Bezug auf die funktionellen Langzeitergebnisse und die Mortalität unterscheiden sich die Bridging-Therapie und die alleinige mechanische Thrombektomie (MT) in unserer Analyse nicht voneinander. Unsere Analyse zeigt, die alleinige mechanische Thrombektomie wird zu einem früheren Zeitpunkt durchgeführt (etwa 10 Minuten), dagegen ist die Punktion zur Durchführung der mechanischen Thrombektomie bei vorausgehender intravenösen Thrombolyse entsprechend verzögert. Diese Beobachtung ist kritisch zu hinterfragen; Kliniker sollten dazu angeregt werden ihre Ablaufprotokolle zu überprüfen und mögliche zeitverzögernde Faktoren auszuschalten. Auch hinsichtlich des Risikos einer intrakraniellen Blutung zeigte unsere Analyse keinen wesentlichen Unterschied zwischen den beiden Prozeduren.

In der Zusammenfassung ist für die klinische Praxis die Bridging-Therapie die bevorzugte Option für die Behandlung von Patienten mit einem akuten Schlaganfall infolge eines Verschlusses einer großen hirnversorgenden Arterie. Beide Prozeduren sind sicher, ein vergleichbares Risiko eine intrakranielle Blutung zu erleiden findet sich bei beiden Prozeduren gleichermaßen. Für Patienten, bei denen eine IVT kontraindiziert ist oder eine schnellere Intervention erforderlich ist, bietet die alleinige MT eine effektive Alternative. Zukünftige Forschung sollte sich darauf konzentrieren, die Langzeitergebnisse und die Auswirkungen auf die Lebensqualität der Patienten weiter zu beleuchten, um evidenzbasierte Empfehlungen für die Behandlung von Schlaganfällen zu optimieren.

4.2. Zweites Manuskript

Surgical vs. Conservative Management of Chronic Sciatica (>3 Months) due to Lumbar Disc Herniation: A Systematic Review and Meta-Analysis

Hammed A, Al-Qiami A, Alsalhi H, Almansi A, Massoud M, Alzawahreh A, Hamouda A, Tanislav C. Cureus. 2024 May 04;16(5):e59617. doi:10.7759/cureus.59617.

In den letzten Jahren hat die Entität der chronischen Ischialgie infolge eines lumbalen Bandscheibenhernie (LDH) an Bedeutung gewonnen. Diese Erkrankung beeinträchtigt sowohl die körperliche als auch psychische Gesundheit der Patienten und beeinflusst nachhaltig die Lebensqualität [11]. Besonders bei persistierenden Beschwerden über einen Zeitraum von mehr als drei Monaten sollten gezielte therapeutische Maßnahmen eingeleitet werden. Diesbezüglich ist eine differenzierte Therapieentscheidung notwendig [19]. Die vorliegende Arbeit untersucht in einer systematischen Übersichtsarbeit und Meta-Analyse, ob die chirurgische Mikrodiskektomie gegenüber einer konservativen Therapie klinische Vorteile in Bezug auf Schmerzreduktion und Lebensqualität bietet.

Konservative Therapie vs. Mikrodiscektomie: Effekte auf Schmerz und Lebensqualität

Unsere Analyse zeigte, dass die konservative Therapie stärker zur Reduktion der in das Bein ausstrahlenden Schmerzen beiträgt (Standardisierte mittlere Differenz (SMD): 2,60; 95%-KI [0,02–5,18]; p = 0,05). Auch auf der psychopathologischen Ebene scheint die konservative Therapie mehr Vorteile zu bieten (SF-36-Mental-Score: SMD:5,7; 95%-KI [1,02–10,37]; p = 0,02). Das gleiche Bild zeigte sich auf der Ebene der funktionalen Gesundheit (physische Score des SF-36: SMD 0,96; 95%-KI [0,61–1,30]; p = 0,0001). Hieraus ergibt sich ein klares Bild: In Bezug auf Lebensqualität und funktionale Gesundheit zur Bewältigung von Alltagsaktivitäten scheint die konservative Therapie der chirurgischen Intervention nicht unterlegen zu sein, sondern stellt insbesondere in den ersten Monaten der Behandlung eine gleichwertige oder sogar überlegene Alternative dar.

Im Gegensatz dazu war die chirurgische Mikrodiskektomie bei Rückenschmerzen wirksamer (SMD: -3,82; 95%-KI [-5,99 bis -1,66]; p = 0,0005). Die Entfernung von

Bandscheibenmaterial und die damit einhergehende Druckentlastung zeigten sich insbesondere bei therapieresistenten Fällen als sehr effektiv. Auch die Sensitivitätsanalyse unter Ausschluss der Aronsohn-Studie bestätigte die überlegene Wirksamkeit der chirurgischen Maßnahme (SMD -0,57; 95%-KI [-0,92 bis -0,22]; p = 0,001). Die Unterschiede im Behandlungserfolg lassen sich unter anderem durch die zugrundeliegende Symptomatik erklären. Radikuläre Beschwerden, die durch Nervenwurzelreizungen entstehen, sprechen häufig gut auf konservative Maßnahmen wie Physiotherapie, Analgetika oder Infiltrationen an[20]. Hier sind insbesondere physiotherapeutische Maßnahmen hervorzuheben, diese tragen hauptsächlich dazu bei Fehlstellungen in der Körperhaltung zu korrigieren, wodurch die Reizung des Spinalnerven durch Verringerung des mechanischen Druckes reduziert wird, was dann zu einer Linderung der Symptomatik führt. Demgegenüber ist axialer Rückenschmerz – also Schmerz, der direkt in der Wirbelsäule entsteht, was durch bereits fixierte pathologische Fehlstellungen hervorgerufen wird – oft therapieresistent gegenüber konservativen Verfahren und erfordert in vielen Fällen eine chirurgische Intervention, etwa zur Dekompression oder Stabilisierung [19, 20]. Diese Differenzierung sollte bei der Therapieentscheidung stets berücksichtigt werden.

Klinische Bedeutung und individuelle Therapieplanung

Unsere Ergebnisse verdeutlichen, dass abhängig vom individuellen Beschwerdebild beide Therapieformen – konservativ und chirurgisch – klinisch relevante Effekte erzielen können. Eine wesentliche Erkenntnis unserer Analyse unterstreicht die Notwendigkeit Therapieentscheidungen individualisiert zu treffen, auf Basis differenzierter klinischer Merkmale. Während konservative Behandlungen bei primär radikulären Schmerzen ohne neurologische Defizite sinnvoll erscheinen, sollte die operative Option insbesondere dann erwogen werden, wenn lokalisierte Rückenschmerzen im Vordergrund stehen.

Diese differenzierte Betrachtung wird auch durch frühere Studien gestützt. So zeigten beispielsweise Peul et al. (2007) [21] in ihrer prospektiv-randomisierten Studie, dass eine frühe mikrochirurgische Diskektomie zu einer rascheren Schmerzreduktion und funktionellen Verbesserung führt, während sich langfristig kein signifikanter Vorteil

gegenüber einer konservativen Therapie nachweisen ließ. Ähnliche Ergebnisse fanden auch Bailey et al. (2016) [11], insbesondere hinsichtlich der Lebensqualität und Arbeitsfähigkeit.

Aktuelle Leitlinien, wie jene der Deutschen Gesellschaft für Neurochirurgie (DGNC) [22] sowie der North American Spine Society (NASS) [23], empfehlen einen stufenweisen Behandlungsansatz, bei dem zunächst konservative Maßnahmen (wie Schmerztherapie, Physiotherapie und Verhaltensmodifikation) über mindestens sechs Wochen angewendet werden sollen. Eine operative Intervention wird empfohlen, wenn neurologische Defizite auftreten und/oder progredient sind, ein Cauda-equina-Syndrom vorliegt (Notfallindikation), oder wenn trotz konsequenter konservativer Therapie eine signifikante Beeinträchtigung der Lebensqualität oder Arbeitsfähigkeit über mehr als sechs bis zwölf Wochen besteht.
Unsere Ergebnisse stehen im Einklang mit den aktuellen Empfehlungen und bestätigen diese. Insgesamt ergibt sich daraus ein individualisierter Therapieansatz, bei dem die Entscheidung zwischen konservativer und operativer Behandlung unter Berücksichtigung der Symptomatik, Lokalisation der Schmerzen, Lebenssituation, beruflichen Anforderungen und patientenbezogenen Präferenzen getroffen werden sollte.

Sicherheit und Einflussfaktoren

Ein weiterer Aspekt unserer Analyse betrifft die Sicherheit beider Verfahren. In unserer Analyse zeigten sich keine Hinweise auf eine erhöhte Komplikationsrate bei Anwendung beider Verfahren. Auch in der Meta-Regressionsanalyse konnten keine Einflüsse der Faktoren Alter, Geschlecht oder Body-Mass-Index (BMI) auf den Therapieerfolg festgestellt werden [20]. Diese Beobachtung spricht für beide Verfahren, diese sind sicher und bei zweckmäßiger Anwendung bieten diese Vorteile für den Patienten. Demografische Parameter haben offenbar keinen relevanten Einfluss auf die Sicherheit in der Anwendung beider Verfahren. Faktoren wie Berufstätigkeit, psychischer Stress oder weitere Vorerkrankungen sind in der aktuellen Literatur weitgehend unberücksichtigt geblieben, sodass diese Faktoren in unserer Diskussion nur indirekt

adressiert werden können; bei der Planung zukünftiger Studien zu diesem Thema sollten diese Faktoren jedoch eine Rolle spielen [19-22]. Ebenso sollte die Rolle zentraler Prozesse wie Sensibilisierungsmechanismen, wie sie bei chronischen Schmerzsyndromen diskutiert werden, in zukünftigen Studien zu diesem Thema berücksichtigt werden.

Zeitfaktor in der Therapieentscheidung

Ein kritischer Punkt in der Therapieentscheidung ist der Zeitpunkt wann die jeweilige Maßnahme durchgeführt wird. Die Ergebnisse früherer Studien – wie SPORT oder Cochrane-Analysen – zeigen, dass eine frühe chirurgische Intervention unter bestimmten Voraussetzungen Vorteile bringen kann [23,24]. Allerdings weisen diese Studien auch darauf hin, dass nach längeren Beobachtungszeiträumen die Unterschiede zwischen den Therapieoptionen deutlich abnehmen. Unsere Arbeit bestätigt dieses Bild. Während die chirurgische Therapie schneller zur Beschwerdelinderung führt, ist die langfristige Lebensqualität bei konservativ behandelten Patienten vergleichbar gut.
Für die klinische Praxis bedeutet dies, dass die konservative Therapie initial in Betracht gezogen werden sollte, solange keine neurologischen Ausfälle vorliegen. Eine Operation ist insbesondere dann sinnvoll, wenn konservative Maßnahmen innerhalb eines definierten Zeitraums – etwa 6 bis 12 Wochen – nicht zum gewünschten Erfolg führen. Dabei sollte auch die Wartezeit bis zur Operation berücksichtigt werden, da eine zu späte chirurgische Intervention mit einem schlechteren Outcome assoziiert sein kann.

Vergleich mit früheren Studien und methodische Einordnung

Unsere Ergebnisse stehen im Einklang mit mehreren publizierten Studien [20-24]. Hier ist die Arbeit von Weinstein et .al [24]. hervorzuheben; diese fand ebenfalls keinen langfristigen Vorteil der Operation gegenüber des konservativen Vorgehens. Unterschiedliche Ergebnisse früherer Arbeiten lassen sich methodisch erklären, wie beispielsweise durch unterschiedliche Studiendesigns, Patientenkollektive und unterschiedliche Nachbeobachtungszeiträume. Einige ältere Studien haben deutlich

kürzere Beobachtungszeiträume oder ließen darüber hinaus crossover-Bewegungen zu, die insgesamt die Aussagekraft einschränken.

Ein methodischer Vorteil unserer Analyse liegt in der klaren Definition der Zielgruppe: Eingeschlossen wurden ausschließlich Patientinnen und Patienten mit chronischer Ischialgie (> 3 Monate) infolge von lumbalen Bandscheibenvorfalles im Bereich L3-S1. Die ausschließliche Berücksichtigung randomisiert-kontrollierter Studien (RCTs) mit klar definierten Ein- und Ausschlusskriterien gewährleistet eine hohe methodische Qualität der Datenbasis [25]. Dennoch stellt die begrenzte Anzahl verfügbarer Studien eine Einschränkung dar, weshalb die Interpretation der Ergebnisse mit Zurückhaltung erfolgen sollte. Eine direkte Übertragung auf die klinische Praxis ist daher nur unter Berücksichtigung dieser Limitationen möglich.

Praktische Empfehlungen und Ausblick

Basierend auf den vorliegenden Daten kann folgende Empfehlung vorgenommen werden: Die konservative Therapie sollte bei chronischer Ischialgie initial als Behandlungsstandard etabliert bleiben. Sie ist sicher, effektiv und kostengünstig. Erst bei Versagen konservativer Maßnahmen oder Vorliegen neurologischer Ausfälle sollte die chirurgische Mikrodiskektomie als wirksame Zweitlinienoption in Betracht gezogen werden. Die Wahl der Therapie muss stets individuell unter Berücksichtigung von Symptombild, Dauer der Beschwerden, funktionellem Status und Patientenpräferenz getroffen werden.
Ein weiterer wichtiger Punkt betrifft die Aufklärung der Patientinnen und Patienten. Die Erwartungen an chirurgische Eingriffe sind häufig hoch, die Evidenz zeigt jedoch, dass die Unterschiede im Langzeitverlauf geringer ausfallen als angenommen. Hier ist eine realistische Darstellung der zu erwartenden Erfolge beider Therapieformen von zentraler Bedeutung für die gemeinsame Entscheidungsfindung (shared decision making).

Zukünftige Studien sollten sich auf die langfristigen Effekte beider Therapiestrategien konzentrieren und dabei auch patientenzentrierte Outcomes wie Lebensqualität, funktionelle Erholung und Rückkehr in den Beruf berücksichtigen. Multizentrische,

prospektive Studien mit größerer Fallzahl und standardisierter konservativer Therapie könnten dazu beitragen, offene Fragen zur optimalen Versorgungsstrategie bei chronischer Ischialgie besser zu beantworten.

Zusammenfassung

Die vorliegende Meta-Analyse zeigt, dass sowohl konservative als auch chirurgische Behandlungsstrategien bei chronischer Ischialgie infolge einer lumbalen Bandscheibenherniation (LDH) valide, wirksame und sichere Behandlungen darstellen. Die Wahl des geeigneten Vorgehens hängt maßgeblich von der klinischen Symptomatik, der Dauer und Schwere der Beschwerden sowie individuellen Faktoren ab.

Konservative Therapien – insbesondere Physiotherapie, Schmerzmedikation und epidurale Infiltration – führten in der Analyse zu einer Reduktion der in das Bein ausstrahlenden Schmerzen (radikuläre Schmerzen) sowie zu einer messbaren Verbesserung der Lebensqualität. Sie eignen sich vor allem für Patienten ohne neurologische Ausfälle und mit überwiegend radikulärer Symptomatik. Die chirurgische Mikrodiscektomie hingegen erwies sich insbesondere bei therapieresistentem Rückenschmerz als effektiv und bot eine raschere und nachhaltigere Linderung der Beschwerden.

Im Langzeitverlauf zeigten sich hinsichtlich der funktionellen Ergebnisse keine relevanten Unterschiede zwischen den beiden Ansätzen. Dies unterstreicht die Bedeutung einer sorgfältigen Indikationsstellung und der individualisierten Auswahl des Therapieweges. Zudem war keine der untersuchten demografischen Variablen prädiktiv für den Therapieerfolg.

Für die klinische Praxis ergibt sich folgende Empfehlung: Die konservative Behandlung sollte initial bevorzugt werden. Bei fehlendem Ansprechen oder neurologischer Verschlechterung ist eine chirurgische Intervention gerechtfertigt und erfolgversprechend. Entscheidend ist ein interdisziplinärer Behandlungsansatz unter Einbezug des Patienten im Rahmen einer gemeinsamen Entscheidungsfindung.

Zukünftige Forschung sollte patientenzentrierte Parameter wie Lebensqualität, Arbeitsfähigkeit und psychosoziale Belastung stärker in den Fokus rücken, um die Therapieentscheidung weiter zu differenzieren und zu optimieren.

4.3. Drittes Manuskript

Vergleich der präventiven neurochirurgischen Clipping- versus endovaskulären Coiling-Therapie bei unrupturierten intrakraniellen Aneurysmen: Eine systematische Übersichtsarbeit und Meta-Analyse

Hammed A, Al-Qiami A, Alomari O, Otmani Z, Hammed S, Sarhan K, Derhab M, Hamouda A, Rosenbauer J, Kostev K, Richter G, Braun V, Tanislav C.; Neurol Sci. 2025 Jan 30. doi: 10.1007/s10072-024-07963-1. Epub ahead of print. PMID: 39883353.

Einleitung und Zielsetzung

In den letzten Jahren hat sich die Behandlung unrupturierter intrakranieller Aneurysmen (UIAs) stetig weiterentwickelt. Zwei zentrale Verfahren konkurrieren dabei miteinander: das neurochirurgische Clipping und das endovaskuläre Coiling. Beide Therapiestrategien verfolgen das Ziel, Aneurysmen sicher zu verschließen und eine Subarachnoidalblutung (SAB) zu verhindern [27,28]. Aufgrund unterschiedlicher Evidenzlagen und regional variierender Praxisgewohnheiten bleibt jedoch die Frage nach der überlegenen Methode weiterhin Gegenstand der wissenschaftlichen Diskussion. Ziel unserer Meta-Analyse war es daher, das Clipping und Coiling hinsichtlich ihrer Wirksamkeit und Sicherheit systematisch zu vergleichen.

Kurzfristige Aneurysmaokklusion: Clipping zeigt Vorteile

Unsere Analyse zeigt, dass das Clipping im Vergleich zum Coiling häufiger eine vollständige Aneurysmaokklusion innerhalb der ersten sechs Monaten zur Folge hat (RR = 0,83; 95%-KI [0,75–0,91]; p = 0,0001). Dieser Befund wurde sowohl in prospektiven als auch retrospektiven Studien wiederholt beobachtet. Dies korreliert unmittelbar mit einem geringen Risiko eine Blutung in der Folge zu erleiden und bildet damit die Grundlage für einen wichtigen prognostischen Parameter. Im Gegensatz dazu zeigt das Coiling eine geringere Okklusionsrate in der Frühphase. Daraus ergibt sich die Notwendigkeit, dass Patienten, die sich einem Coiling unterziehen in der Nachsorge enger überwacht werden müssen.

Langfristige Aneurysma-Kontrolle: Ähnlicher Effekt beider Verfahren

Obwohl das Clipping kurzfristig im Vorteil ist, nivellieren sich die Unterschiede in der Langzeitbetrachtung. Im Follow-up über 12 Monate hinaus zeigte sich kein relevanter Unterschied in der Okklusionsrate (RR = 0,90; 95%-KI [0,63–1,30]; p = 0,57). Diese Beobachtung bestätigt, dass das Coiling langfristig eine vergleichbare Effektivität erreichen kann, vorausgesetzt, es erfolgt eine engmaschige radiologische Kontrolle und gegebenenfalls eine zeitnahe Nachbehandlung.

Mortalität und funktionelle Ergebnisse: Coiling im Vorteil

Ein entscheidender Vorteil der Coiling-Therapie zeigte sich bei der 30-Tage-Mortalität. Diese war in der Coiling-Gruppe deutlich niedriger (RR = 0,56; 95%-KI [0,48–0,66]; p = 0,00001). Auch hinsichtlich der Erholung funktioneller Fähigkeiten, gemessen am modifizierten Rankin Score (mRS > 2), war das Coiling mit besseren Ergebnissen assoziiert (RR = 0,73; 95%-KI [0,55–0,97]; p = 0,03). Diese Ergebnisse lassen sich mit der geringeren Invasivität des Coiling-Verfahrens und die daraus resultierende kürzere Rekonvaleszenz erklären. Die Ergebnisse dieser Meta-Analyse legen nahe, dass Patienten, die mittels Coiling behandelt werden, eine bessere Aussicht zur schnellerer Rückkehr in den Alltag haben, was dann auch mit einer besseren Lebensqualität einhergeht.

Sicherheitsprofil: Coiling mit geringeren Komplikationsraten

Das Coiling war mit einem geringeren Risiko für prozedurale Komplikationen (RR = 0,54; 95%-KI [0,38–0,78]; p < 0,0009) sowie für zerebrale Ischämien (RR = 0,73; 95%-KI [0,53–0,99]; p = 0,05) assoziiert. Auch das Risiko für intraoperative Blutungen war beim Clipping höher (RR = 0,52; 95%-KI [0,35–0,78]; p = 0,002). Diese Befunde unterstreichen die geringere Belastung durch das Coiling-Verfahren, das insbesondere bei älteren und multimorbiden Patienten eine wichtige Rolle spielt. Die geringere Komplikationsrate ist daher ein bedeutendes Argument für die Wahl des Coilings bei vulnerablen gefährdeten Patientengruppen.

Retreatment-Raten: Clipping langfristig stabiler

Ein Nachteil des Coilings zeigte sich in der erhöhten Rate an Reinterventionen. Die Retreatment-Rate war in der Coiling-Gruppe deutlich erhöht (RR = 3,46; 95%-KI [1,21–9,86]; p = 0,02). Besonders in prospektiven Studien trat dieser Unterschied deutlich hervor. Diese Beobachtung belegt dadurch die Notwendigkeit einer sorgfältigen Patientenselektion und einer strukturierten Nachsorge beim endovaskulären Vorgehen. Für junge Patienten mit einer langen Lebenserwartung könnte Clipping daher trotz höherer initialer Belastung eine langfristig bessere Option darstellen.

Verweildauer im Krankenhaus: Vorteil für Coiling

Die durchschnittliche stationäre Aufenthaltsdauer war beim Clipping deutlich länger (MD = 4,36 Tage; 95%-KI [2,96–5,77]; p = 0,0001). Dieser Unterschied resultiert aus dem invasiven Charakter des neurochirurgischen Eingriffs und dem höheren postoperativen Erholungsbedarf. Das Coiling hingegen ermöglicht eine schnellere Mobilisation und frühere Entlassung aus der Klinik. Dies kann auch aus gesundheitsökonomischer Perspektive von Relevanz sein, insbesondere im Hinblick auf Ressourcenbindung und Behandlungskosten.

Vergleich mit existierender Literatur

Die Ergebnisse unserer Analyse stehen in Übereinstimmung mit den Studien von Hwang et al., Kang et al. und Shen et al., die ebenfalls einen kurzfristigen Vorteil für das Clipping und eine insgesamt bessere Verträglichkeit des Coilings beschrieben haben [27-29]. Unterschiede in der Methodik, Patientenauswahl und regionale Behandlungsalgorithmen können teilweise die Heterogenität der Ergebnisse erklären. Zudem legen aktuelle Studien nahe, dass technologische Fortschritte im Coiling (z. B. Stent-assistiertes Coiling) das Outcome weiter verbessern könnten.

Klinische Implikationen und Therapiewahl

Beide Verfahren – Clipping und Coiling – sind effektive und sichere Strategien zur Behandlung von UIAs. Clipping bietet eine hohe initiale Okklusionsrate, geht jedoch mit höherer prozeduraler Morbidität und verlängerten Krankenhausaufenthalten einher [27-29]. Das Coiling hingegen ermöglicht eine schnellere Erholung, ist mit geringeren Komplikationsraten assoziiert, weist jedoch eine höhere Rate an Reinterventionen auf. Die Wahl der Therapie sollte daher individualisiert erfolgen und Faktoren wie Alter, Komorbiditäten, Lokalisation und Morphologie des Aneurysmas sowie die Expertise des behandelnden Zentrums berücksichtigen. Ein interdisziplinärer Ansatz, unter Einbezug der Neurochirurgie und der interventionellen Neuroradiologie, erscheint essenziell, um patientenzentrierte Entscheidungen zu treffen.

Ausblick und Forschungsperspektiven

Zukünftige Studien sollten prospektiv, multizentrisch und mit längeren Follow-up-Zeiträumen konzipiert werden. Neben klinischen Endpunkten sollten auch patientenrelevante Parameter wie Lebensqualität, neurokognitive Funktionen und gesundheitsökonomische Aspekte untersucht werden. Der Einbezug moderner Bildgebungsverfahren und biometrischer Prädiktoren kann zudem zur Präzisierung der Indikationsstellung beitragen. Darüber hinaus ist die Entwicklung individualisierter Therapiealgorithmen notwendig, um die jeweils optimale Behandlungsoption für unterschiedliche Patientengruppen besser definieren zu können. Auch die Rolle neuer Materialien und Techniken (z. B. Flow-Diverter) sollte in weiteren Analysen betrachtet werden [30,31].

Zusammenfassung

Die vorliegende Meta-Analyse liefert einen umfassenden Überblick über die Vor- und Nachteile der beiden wichtigsten Behandlungsmodalitäten bei unrupturierten intrakraniellen Aneurysmen. Das Clipping überzeugt insbesondere in dem kurzfristigen

Ausschalten des Aneurysmas mit höheren Okklusionsraten und geringerer Notwendigkeit weiterer Eingriffe. Dieser Vorteil wird jedoch durch ein erhöhtes Risiko für prozedurale Komplikationen, zerebrale Ischämien und längere Krankenhausaufenthalte relativiert. Das Coiling hingegen bietet ein günstigeres Sicherheitsprofil, ermöglicht eine schnellere Genesung und zeigt insgesamt bessere funktionelle Ergebnisse, allerdings bei erhöhter Wahrscheinlichkeit einer erneuten Behandlung.

Die Wahl des geeigneten Verfahrens kann nicht pauschal getroffen werden, sondern muss individuell unter Einbeziehung zahlreicher Parameter wie Aneurysmalokalisation, -größe, -morphologie, Patientenalter, Komorbiditäten und Präferenzen erfolgen. Kliniker sollten stets interdisziplinär vorgehen und sowohl die medizinischen als auch psychosozialen Gegebenheiten ihrer Patienten berücksichtigen.

In der klinischen Praxis stellt das Coiling eine bevorzugte Therapieoption bei älteren, multimorbiden oder risikobehafteten Patienten dar, während das Clipping insbesondere bei jungen Patienten mit komplexer Aneurysmamorphologie Berücksichtigung findet.

Insgesamt liefern unsere Ergebnisse eine fundierte Entscheidungsgrundlage für die Wahl des geeigneten Verfahrens bei UIAs und betonen gleichzeitig die Bedeutung einer individualisierten, patientenzentrierten Therapieplanung. Die kontinuierliche Evaluation neuer Techniken und Materialien sowie der Einbezug von Langzeitdaten werden entscheidend sein, um zukünftige Leitlinien evidenzbasiert weiterzuentwickeln.

5. Zusammenfassung

Zusammenfassung (Deutsch)

Diese kumulative Dissertation basiert auf drei systematischen Übersichtsarbeiten und Meta-Analysen, die sich mit der Wirksamkeit, Sicherheit und den klinischen Auswirkungen unterschiedlicher Therapieverfahren zur Behandlung von neurologischen und neurovaskulären Erkrankung befassen. Ziel war es, eine evidenzbasierte Grundlage für die individualisierte Therapieentscheidung in komplexen neuroklinischen Szenarien zu verfeinern.

Im ersten Teil wurde der Nutzen der sogenannten Bridging-Therapie – also die Kombination aus intravenöser Thrombolyse (IVT) und mechanischer Thrombektomie (MT) – im Vergleich zur alleinigen MT bei akutem ischämischem Schlaganfall untersucht. Die Bridging-Therapie führte zu einer signifikant besseren neurologischen Erholung in der Frühphase (gemessen am NIHSS-Score) sowie zu höheren Reperfusionsraten der betroffenen Hirnareale. Diese Vorteile schlugen sich jedoch nicht in einer verbesserten funktionellen Langzeitprognose (mRS nach 90 Tagen) nieder. Das Risiko einer symptomatischen intrakraniellen Blutung war in beiden Gruppen vergleichbar.

Im zweiten Teil wurde die Effektivität konservativer versus chirurgischer Behandlungsmethoden bei der chronischen Ischialgie infolge einer lumbalen Bandscheibenherniation analysiert. Konservative Verfahren wie Physiotherapie und Schmerztherapie verbesserten signifikant die in das Bein ausstrahlende Schmerzen (radikuläre Schmerzen) sowie die Lebensqualität. Die chirurgische Mikrodiskektomie zeigte jedoch insbesondere bei therapieresistenten Rückenschmerzen eine überlegene Wirksamkeit. Beide Ansätze gelten als sicher, wobei die Therapieentscheidung individualisiert auf Grundlage der Symptomkonstellation und Patientenpräferenzen getroffen werden sollte.

Der dritte Teil dieser Dissertation widmet sich dem Vergleich zwischen dem Therapieverfahren des neurochirurgischen Clippings und des endovaskulären Coilings bei unrupturierten intrakraniellen Aneurysmen. Während das Clipping häufiger zu einer vollständigen Aneurysmaokklusion führt, ist es mit einer höheren Rate an prozeduralen Komplikationen und einer längeren Krankenhausverweildauer verbunden. Das Coiling

dagegen bietet den Vorteil geringerer perioperativer Komplikationen und ein günstigerer funktioneller Outcome, jedoch unter Inkaufnahme einer notwendigen Wiederholung der Behandlung.

Insgesamt betonen die Ergebnisse die Notwendigkeit einer patientenzentrierten, differenzierten Therapieplanung. Die Wahl der optimalen Behandlung sollte stets interdisziplinär getroffen werden und individuelle Risikoprofile sowie langfristige Outcome-Ziele berücksichtigen.

Summary (English)

This cumulative dissertation comprises three systematic reviews and meta-analyses that investigate the effectiveness, safety, and clinical implications of neurovascular and spinal treatment strategies. The overarching goal was to establish an evidence-based framework for individualized clinical decision-making in complex neurological care.

The first part examined bridging therapy—defined as the combination of intravenous thrombolysis (IVT) and mechanical thrombectomy (MT)—compared to MT alone in acute ischemic stroke. Bridging therapy resulted in significantly improved early neurological recovery (as measured by the NIHSS score) and higher reperfusion rates. However, these early benefits did not translate into superior long-term functional outcomes, as measured by the modified Rankin Scale (mRS) at 90 days. The risk of symptomatic intracranial hemorrhage was comparable between both treatment groups.

The second part focused on the comparison of conservative versus surgical treatment approaches for chronic sciatica due to lumbar disc herniation. Conservative strategies such as physiotherapy and pain management led to reductions in leg pain and improvements in quality of life. However, surgical microdiscectomy demonstrated superior efficacy, particularly in patients with persistent back pain unresponsive to conservative measures. Both approaches were found to be safe, and treatment should be personalized based on symptom patterns and patient preferences.

The third part assessed neurosurgical clipping versus endovascular coiling for unruptured intracranial aneurysms. While clipping more frequently achieved complete aneurysm occlusion, it was associated with higher rates of procedural complications and longer hospital stays. Coiling, on the other hand, offered better functional outcomes and fewer perioperative risks but carried a higher retreatment rate.

Taken together, the findings underscore the importance of individualized, patient-centered treatment planning. Optimal therapy selection should be guided by interdisciplinary collaboration, anatomical and clinical considerations, and long-term patient outcomes.

6. Literaturverzeichnis

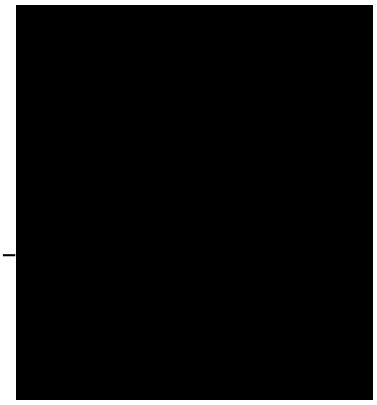
1. Wang XM, Zhang XR, Li ZH, Zhong WF, Yang P, Mao C. A brief introduction of meta-analyses in clinical practice and research. J Gene Med. 2021 May;23(5):e3312. doi: 10.1002/jgm.3312. Epub 2021 Mar 25. PMID: 33450104; PMCID: PMC8243934.
2. Villasís-Keever MÁ, Rendón-Macías ME, García H, Miranda-Novales MG, Escamilla-Núñez A. Systematic review and meta-analysis as a support tools for research and clinical practice. Rev Alerg Mex. 2020 Jan-Mar;67(1):62-72. English. doi: 10.29262/ram.v67i1.733. PMID: 32447868.
3. Kraus, S., Breier, M. & Dasí-Rodríguez, S. The art of crafting a systematic literature review in entrepreneurship research. Int Entrep Manag J 16, 1023–1042 (2020). https://doi.org/10.1007/s11365-020-00635-4
4. Lee YH. An overview of meta-analysis for clinicians. Korean J Intern Med. 2018 Mar;33(2):277-283. doi: 10.3904/kjim.2016.195. Epub 2017 Dec 28. PMID: 29277096; PMCID: PMC5840596.
5. Eickhoff, S.B., Kernbach, J., Bzdok, D. (2020). Meta-Analyses in Basic and Clinical Neuroscience: State of the Art and Perspective. In: Ulmer, S., Jansen, O. (eds) fMRI. Springer, Cham. https://doi.org/10.1007/978-3-030-41874-8_9
6. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol. 2020 Dec;267(12):3489-3498. doi: 10.1007/s00415-019-09395-w. Epub 2019 May 25. PMID: 31129710.
7. Ringleb P., Köhrmann M., Jansen O., et al.: Akuttherapie des ischämischen Schlaganfalls, S2e-Leitlinie, 2022 Version 1.1, in: Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie. Online: www.dgn.org/leitlinien.
8. Kaesmacher J, Cavalcante F, Kappelhof M, et al. Time to Treatment With Intravenous Thrombolysis Before Thrombectomy and Functional Outcomes in Acute Ischemic Stroke: A Meta-Analysis. JAMA. 2024;331(9):764-777. doi:10.1001/jama.2024.0589
9. Oberhofer, E. Bei chronischem "Ischias" nicht zu lange mit der Operation warten . Orthop. Rheuma 23, 22–24 (2020). https://doi.org/10.1007/s15002-020-2845-3
10. van Tulder MW, Koes B, Malmivaara A. Outcome of non-invasive treatment modalities on back pain: an evidence-based review. Eur Spine J. 2006 Jan;15 Suppl 1(Suppl 1):S64-81. doi: 10.1007/s00586-005-1048-6. Epub 2005 Dec 1. PMID: 16320031; PMCID: PMC3454555.
11. Bailey CS, Rasoulinejad P, Taylor D, et al. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. N Engl J Med. 2020;382(12):1093-1102. doi:10.1056/NEJMoa1912658
12. Pontes FGDB, Vasconcelos V, Baptista-Silva JCC, da Silva EMK. Treatments for unruptured intracranial aneurysms. Cochrane Database Syst Rev. 2019;2019(4):CD013312. Published 2019 Apr 16. doi:10.1002/14651858.CD013312
13. Ajiboye N, Chalouhi N, Starke RM, Zanaty M, Bell R. Unruptured Cerebral Aneurysms: Evaluation and Management. ScientificWorldJournal. 2015;2015:954954. doi:10.1155/2015/954954
14. Jiang Z, Chen Y, Zeng C, Feng J, Wan Y, Zhang X. Neurosurgical Clipping versus Endovascular Coiling for Patients with Intracranial Aneurysms: A Systematic Review and Meta-Analysis. World Neurosurg. 2020;138:e191-e222. doi:10.1016/j.wneu.2020.02.091
15. Cuadra-Campos MDC, Vásquez-Tirado GA, Bravo-Sotero MDC. Direct mechanical thrombectomy versus bridging therapy in acute ischemic stroke: A systematic review and meta-analysis of randomized clinical trials. World Neurosurg X. 2023;21:100250. Published 2023 Dec 9. doi:10.1016/j.wnsx.2023.100250
16. Chalos V, van der Ende NAM, Lingsma HF, et al. National Institutes of Health Stroke Scale: An Alternative Primary Outcome Measure for Trials of Acute Treatment for Ischemic Stroke. Stroke. 2020;51(1):282-290. doi:10.1161/STROKEAHA.119.026791
17. Wang Y, Wu X, Zhu C, Mossa-Basha M, Malhotra A. Bridging Thrombolysis Achieved Better Outcomes Than Direct Thrombectomy After Large Vessel Occlusion: An Updated Meta-Analysis. Stroke. 2021;52(1):356-365. doi:10.1161/STROKEAHA.120.031477
18. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2021

Jul;52(7):e483-e484. doi: 10.1161/STR.0000000000000383.]. Stroke. 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375
19. Delitto A, George SZ, Van Dillen L, et al. Low back pain. J Orthop Sports Phys Ther. 2012;42(4):A1-A57. doi:10.2519/jospt.2012.42.4.A1
20. Lequin MB, Verbaan D, Jacobs WC, et al. Surgery versus prolonged conservative treatment for sciatica: 5-year results of a randomised controlled trial. BMJ Open. 2013;3(5):e002534. Published 2013 May 28. doi:10.1136/bmjopen-2012-002534
21. Peul WC, van Houwelingen HC, van den Hout WB, et al. Surgery versus prolonged conservative treatment for sciatica. N Engl J Med. 2007;356(22):2245-2256. doi:10.1056/NEJMoa064039
22. AWMF – Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. (2021). *Konservative, operative und rehabilitative Versorgung bei Bandscheibenvorfall mit radikulärer Symptomatik.* (S2k-Leitlinie, Registernummer 033-048). https://register.awmf.org/assets/guidelines/033-048l_S2k_Konservative-operative_rehabilitative-Versorgung-Bandscheibenvorfall-radikulae_2021-06_01.pdf
23. North American Spine Society. (2020). *Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care: Diagnosis and Treatment of Lumbar Disc Herniation with Radiculopathy.* https://www.spine.org/Portals/0/assets/downloads/researchclinicalcare/guidelines/lumbardischerniation.pdf
24. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA. 2006;296(20):2451-2459. doi:10.1001/jama.296.20.2451
25. Richter, B. Stärken und Limitationen von randomisierten klinischen Untersuchungen (RCT). Diabetologe 2 (Suppl 1), S15–S20 (2006). https://doi.org/10.1007/s11428-006-0086-y
26. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse: updated Cochrane Review. Spine (Phila Pa 1976). 2007;32(16):1735-1747. doi:10.1097/BRS.0b013e3180bc2431
27. Hwang JS, Hyun MK, Lee HJ, et al. Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC Neurol. 2012;12:99. Published 2012 Sep 22. doi:10.1186/1471-2377-12-99
28. Shen Z, Zhao Y, Gu X, et al. Systematic Review of Treatment for Unruptured Intracranial Aneurysms: Clipping Versus Coiling. Turk Neurosurg. 2024;34(3):377-387. doi:10.5137/1019-5149.JTN.23729-18.1
29. Kang XK, Guo SF, Lei Y, et al. Endovascular coiling versus surgical clipping for the treatment of unruptured cerebral aneurysms: Direct comparison of procedure-related complications. Medicine (Baltimore). 2020;99(13):e19654. doi:10.1097/MD.0000000000019654.
30. Williams LN, Brown RD Jr. Management of unruptured intracranial aneurysms [published correction appears in Neurol Clin Pract. 2014 Apr;4(2):98. doi: 10.1212/CPJ.0000000000000019]. Neurol Clin Pract. 2013;3(2):99-108. doi:10.1212/CPJ.0b013e31828d9f6b
31. Fiorella D, Gache L, Frame D, Arthur AS. How safe and effective are flow diverters for the treatment of unruptured small/medium intracranial aneurysms of the internal carotid artery? Meta-analysis for evidence-based performance goals. J Neurointerv Surg. 2020;12(9):869-873. doi:10.1136/neurintsurg-2019-015535

7. Ehrenwörtliche Erklärung

„Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten sowie ethische, datenschutzrechtliche und tierschutzrechtliche Grundsätze befolgt. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt und indirekt an der Entstehung der vorliegenden Arbeit beteiligt waren. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.“

Siegen den 06.06.2025



Ort/Datum

8. Danksagung

Ich möchte mich herzlich bei meinem Betreuer und Mentor, Prof. Dr. med. Christian Tanislav, bedanken. Prof. Tanislav war für mich nicht nur ein akademischer Berater, sondern auch eine väterliche Figur, die mich durch diese anspruchsvolle Reise begleitet hat. Mit seiner umfassenden Unterstützung, seinen wertvollen Ratschlägen und seinem unermüdlichen Einsatz hat er mir nicht nur wissenschaftliche Erkenntnisse vermittelt, sondern mich auch gelehrt, kritisches Denken und wissenschaftliche Integrität in meiner Arbeit zu entwickeln. Seine Fähigkeit, komplexe Sachverhalte verständlich zu erklären und stets ein offenes Ohr für meine Fragen zu haben, war von unschätzbarem Wert. Vielen Dank für die Geduld, die Zeit und die inspirierende Anleitung, die ich erfahren durfte. Ohne seine Förderung wäre diese Arbeit nicht in dieser Form möglich gewesen.

9. Anhang

Ausgewählte Zertifikate:

Abbildung 1: Zertifikat „Systematic Review and Meta-Analysis“ in den USA.

Certificate of Completion

This certificate is awarded to

Ali hammed

For successfully completing the online course:

Course 1: Systematic Review and Meta-Analysis

Offered by The Negida Academy, USA

Date: 2023

Certificate ID: ITQ81UWZ

Abbildung 2: Teilnahmezertifikat ISMISS Summit Forum 2023 in Japan.

CERTIFICATE

of Attendance

Dr. Ali Hammed

This is to certify that

He attended at the Online Meeting of the 5th ISMISS combined with the 15th MISS Summit Forum on 11th Mar.2023 (to 31st Mar. 2023).

Title of His Presentation

Efficacy and safety of bilateral percutaneous Vertebroplasty using titanium intravertebral body implant for traumatic compression vertebral fractures

11th Mar.2023

[redacted]

Fujio Ito, M. D. , ph. D.

The Chairman of the 5th ISMISS combined with the15th MISS Summit Forum

Abbildung 3: Teilnahmezertifikat am Queen Square Neurosurgery Review Course 2022 in Großbritannien.

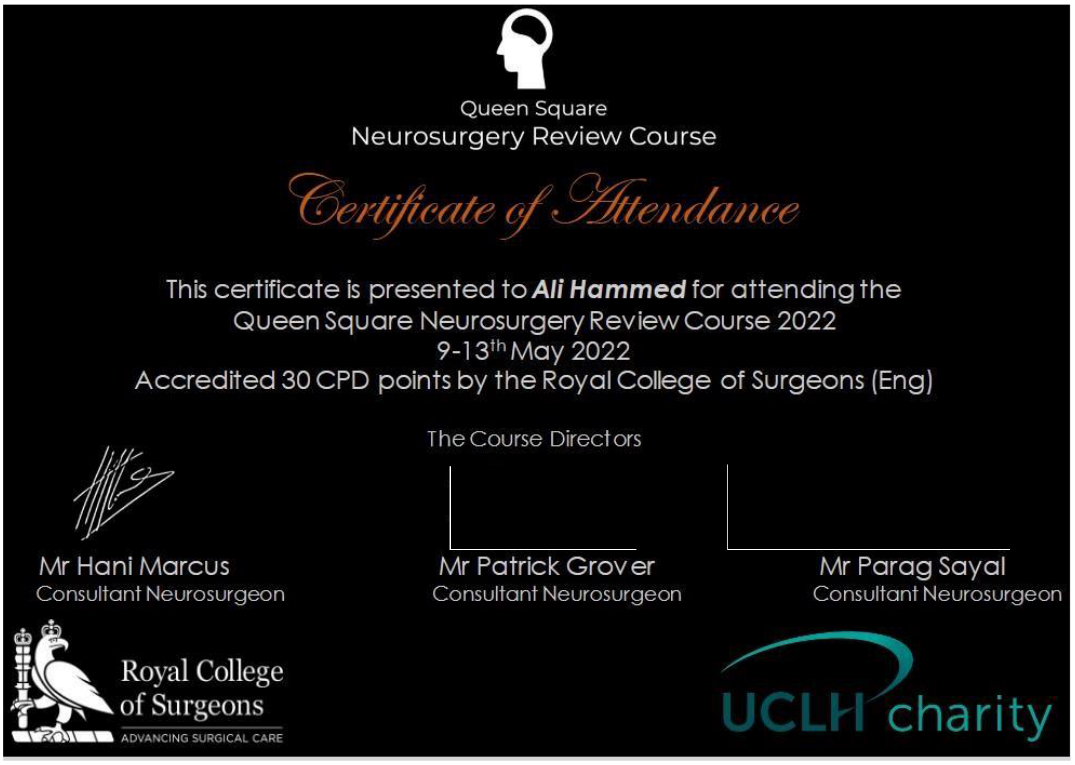


Abbildung 4: Teilnahmezertifikat am SNIS 18th Annual Meeting 2021 mit 25,5 Fortbildungsstunden in den USA