Systematic Review/Meta-Analysis

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Evaluating the effectiveness of nicardipine prolonged-release implants in patients with subarachnoid hemorrhage: a meta-analysis and meta-regression analysis

Ibrahim Khalil, MBBS[a,*], Imran Hossain, MBBS[b], Arindam Das Joy, MBBS[a], M Rafiqul Islam, MBBS[c]

Introduction and importance: Subarachnoid hemorrhage (SAH) is a critical condition with high morbidity and mortality, often complicated by cerebral vasospasm and delayed cerebral ischemia (DCI). Nicardipine, a calcium channel blocker, has shown promise in mitigating these risks. This meta-analysis evaluates the effectiveness and safety of nicardipine prolonged-release implants in reducing SAH complications.

Methods: A comprehensive literature search was conducted in PubMed, Cochrane Library, Embase, and ClinicalTrials.gov, identifying seven eligible studies involving 775 patients with SAH. Randomized controlled trials (RCTs) and observational studies were included. The primary outcome was the incidence of cerebral vasospasm, while secondary outcomes included DCI and delayed ischemic neurologic deficit (DIND). Risk ratios (RR) with 95% confidence intervals (CI) were calculated using random-effects meta-analysis.

Results: Nicardipine implants significantly reduced the risk of cerebral vasospasm (RR = 0.38, 95% CI [0.23, 0.61], $P < 0.0001$) and DCI (RR = 0.33, 95% CI [0.18, 0.58], $P = 0.0002$). However, no significant effect was observed on DIND (RR = 0.68, 95% CI [0.33, 1.39], $P = 0.29$) or functional outcomes (modified Rankin scale; RR = 2.03, 95% CI [0.85, 4.87], $P = 0.11$).

Conclusion: Nicardipine prolonged-release implants are effective in reducing the incidence of cerebral vasospasm and DCI in SAH patients, with potential benefits in preventing these complications. However, they do not significantly impact functional outcomes, indicating the need for complementary rehabilitation strategies. Further large-scale studies are needed to confirm these findings.

Keywords: cerebral vasospasm, delayed cerebral ischemia, meta-analysis, nicardipine implants, subarachnoid hemorrhage

Introduction

Subarachnoid hemorrhage (SAH) is a catastrophic neurological event characterized by bleeding into the subarachnoid space, most commonly resulting from the rupture of an intracranial aneurysm. Although SAH accounts for only 5–10% of all stroke cases, it disproportionately contributes to stroke-related morbidity and mortality, frequently leading to severe long-term disability among survivors. Despite significant advancements in diagnostic imaging, surgical interventions, and intensive care management, the prognosis for SAH patients remains dismal, primarily due to secondary complications such as cerebral vasospasm and delayed cerebral ischemia (DCI)[1-3].

Cerebral vasospasm, affecting approximately 50–70% of SAH patients, is a major contributor to delayed brain injury. It typically manifests between days 3 and 14 post-hemorrhage, characterized by prolonged constriction of cerebral arteries, which leads to ischemia and exacerbates neurological deficits. DCI, a multifactorial phenomenon involving altered cerebral perfusion, microvascular dysfunction, and cortical spreading depolarization, further complicates the clinical course and

HIGHLIGHTS

- Nicardipine prolonged-release implants significantly reduce cerebral vasospasm.
- Implants lower the risk of delayed cerebral ischemia (DCI).
- No significant impact was noted on functional outcomes and modified Rankin scale.
- Impact on delayed ischemic neurologic deficit (DIND) was also non-significant.
- Meta-regression analysis suggests the need for large-scale randomized studies.

[a]Dhaka Medical College and Hospital, Dhaka, Bangladesh, [b]Faculty of Medicine, University of Dhaka, Dhaka, Bangladesh and [c]Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh

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*Corresponding author. Address: Dhaka Medical College and Hospital, Secretariat Road, Shahbagh, Dhaka 1000, Bangladesh. E-mail: ibrahim124904@gmail.com (I. Khalil).

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impairs recovery. Together, vasospasm and DCI are critical determinants of poor neurological outcomes, including functional impairment and increased mortality rates[3-5].

In recent years, calcium channel blockers (CCBs) have become integral to the medical management of cerebral vasospasm. Nicardipine, a dihydropyridine CCB, has shown promise due to its potent vasodilatory effects mediated by the inhibition of calcium influx into vascular smooth muscle cells. While intravenous nicardipine has demonstrated efficacy in managing acute vasospasm, its systemic administration presents limitations, including the risk of hypotension, variable drug concentrations at the target site, and the absence of sustained therapeutic effects. These challenges have spurred the development of novel drug delivery systems aimed at optimizing the efficacy and safety of nicardipine treatment[2,6,7].

Nicardipine prolonged-release implants represent a novel pharmacologic intervention designed to overcome these limitations. These implants provide localized and sustained drug release directly at the site of the ruptured artery, thereby minimizing systemic side effects and ensuring a more consistent therapeutic effect in the vicinity of vascular injury. Early clinical trials and observational studies have yielded promising results, suggesting that nicardipine implants may effectively reduce the incidence of vasospasm and improve cerebral blood flow dynamics. However, the impact of these implants on broader clinical outcomes, including DCI, delayed ischemic neurologic deficits (DIND), and functional recovery, remains uncertain[7-10].

Despite initial encouraging findings, the existing body of evidence is fragmented, with studies often reporting inconsistent results. Some trials demonstrate substantial reductions in vasospasm and DCI, whereas others fail to show meaningful improvements in long-term functional outcomes, as assessed by tools such as the modified Rankin scale (mRS). These discrepancies underscore the need for a comprehensive evaluation of the efficacy and safety of nicardipine prolonged-release implants in SAH patients. Given the heterogeneity of the available data and the necessity for more definitive conclusions, this meta-analysis aims to synthesize the existing evidence and critically assess the role of nicardipine implants in the management of SAH. Specifically, we will evaluate the impact of these implants on the incidence of cerebral vasospasm, DCI, DIND, and functional recovery, and explore the potential of this treatment to enhance clinical outcomes in this critically ill patient population.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency. The study protocol was prospectively registered in the PROSPERO database to outline the objectives, eligibility criteria, and methodological approaches prior to initiating the review process[11,12]. The work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

Eligibility criteria

To ensure the inclusion of relevant and high-quality studies, the following eligibility criteria were established:

1. Population: Studies involving adult patients (≥18 years) with a confirmed diagnosis of SAH, regardless of the underlying etiology, were included.
2. Intervention: Only studies evaluating the use of nicardipine prolonged-release implants as part of the therapeutic strategy for managing SAH were considered.
3. Comparison: Studies must have included a comparison group receiving standard care or alternative therapeutic interventions without the use of nicardipine implants.
4. Outcomes: Studies were required to report at least one of the following outcomes:
5. Primary outcome: incidence of cerebral vasospasm.
6. Secondary outcome: incidence of DCI, DIND, and functional outcomes (e.g., mRS).

Exclusion criteria

Studies were excluded if they met any of the following criteria:

- Case reports, reviews, or animal model studies.
- Studies lacking sufficient data for outcome extraction.
- Non-peer-reviewed articles, abstracts, or conference presentations.

Search strategy

A comprehensive literature search was performed across multiple electronic databases to identify relevant studies. The databases included:

- PubMed
- Embase
- Cochrane Library (Cochrane CENTRAL)
- ClinicalTrials.gov

The search spanned from the inception of each database up to 1 August 2024. Both Medical Subject Headings (MeSH) terms and free-text keywords were utilized to capture relevant studies. The search strategy incorporated terms related to subarachnoid hemorrhage, nicardipine, calcium channel blockers, and prolonged-release implants. An example of the PubMed search query is as follows:

((((“Subarachnoid Hemorrhage”[Mesh] OR “subarachnoid hemorrhage” OR “SAH”)) AND ((“Nicardipine”[Mesh] OR “nicardipine”)) OR (“Prolonged-Release”[Mesh] OR “prolonged-release” OR “implant”)) AND (“Cerebral Vasospasm” [Mesh] OR “cerebral vasospasm” OR “Delayed Cerebral Ischemia”[Mesh] OR “DCI” OR “Delayed Ischemic Neurologic Deficit”[Mesh] OR “DIND”))

Additionally, reference lists of included studies and pertinent review articles were manually screened to identify any additional eligible studies.

Study selection

Two reviewers were independently screened titles and abstracts for eligibility. Discrepancies were resolved through discussion or third-reviewer adjudication.

Data extraction

Data extraction was conducted using a standardized form to ensure consistency and accuracy. The key variables extracted included:

- Study characteristics: Author(s), publication year, study design, sample size, and setting.
- Patient characteristics: Age, sex, etiology of SAH, and baseline clinical status.
- Intervention details: Nicardipine implant dosage, formulation, and duration of treatment.
- Outcome measures: Incidence of cerebral vasospasm, DCI, DIND, and functional outcomes (e.g., mRS).
- Risk of bias metrics: Tools and criteria used to assess the quality of each study.

Data extraction was performed independently by two reviewers, with discrepancies resolved through discussion or consultation with a third reviewer to ensure accuracy and minimize bias.

Data synthesis and statistical analysis

Data synthesis and statistical analyses were performed using a random-effects meta-analysis approach to account for potential heterogeneity among studies. The following steps were undertaken:

- Software: Review Manager (RevMan) Version 5.4 and R Studio were used for data analysis, with R Studio facilitating more advanced statistical modeling where necessary.
- Effect measures: Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes, such as the incidence of vasospasm.
- Heterogeneity assessment: The I^2 statistic was employed to evaluate heterogeneity among studies, categorized as:
  - Low heterogeneity: $I^2 < 25\%$
  - Moderate heterogeneity: $I^2 = 25–50\%$
  - High heterogeneity: $I^2 > 50\%$

In cases of substantial heterogeneity ($I^2 > 50\%$), subgroup analyses were conducted based on study design (RCT vs.

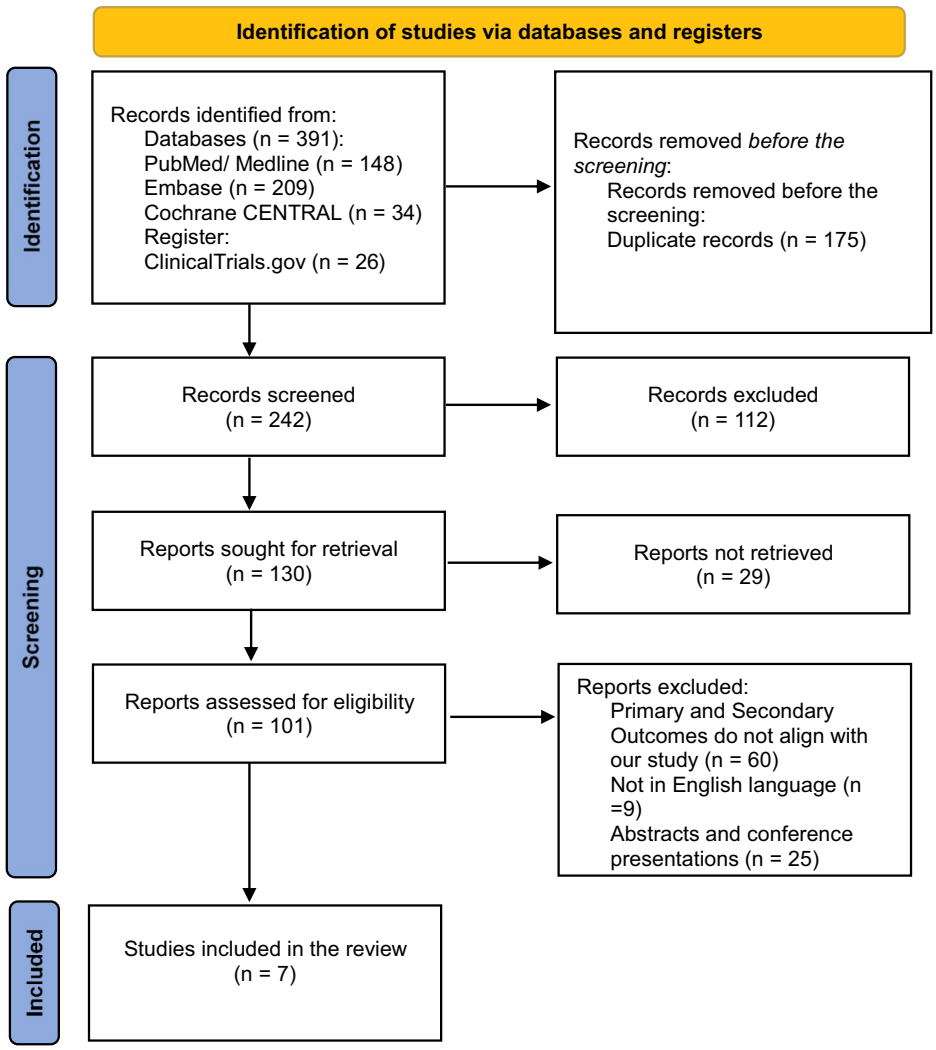

Figure 1. PRISMA 2020 flow diagram for systematic reviews which included searches of databases and registers[11].

Table 1

Baseline population charcteristics of included studies

Study	Sample Size	Age	Sex (Female/Male)	Study Design (RCT/ Observational)	WFNS Grade	Fisher Group	Aneurysms Location	NPRI Usage
Wessels et al. (2024) [13]	41 (Implant= 21, Control= 20)	Mean ± SD: 54.2 ± 10.5 years	31F/10M (76% Female)	RCT (Randomized, Double-Blind)	Grade 3: 17 (41%), Grade 4: 24 (59%)	Modified Fisher Scale 1-2: 4 (10%) Scale 3: 21 (53%), Scale 4: 15 (38%)	MCA: 11 (27%) ICA: 11 (27%) ACA: 17 (41%) Other: 2 (5%)	10 Implants: 21 (51%)
Kuroi et al. 2020 [14]	291	Mean: 63.3 years (26–92)	194F/97M (67% Female)	Observational	Grade 1–3: 138 (47%)	Group 3: 218 (75%)	Anterior Circulation: 243 (84%)	130 (45%)
Schneider et al. 2011 [15]	81	Mean: 52.3 years	52% Female	Observational (Case-control)	Not reported	Group 3: 27 (100%)	Not reported	6–10 NPRIs
Kasuya et al. 2011 [16]	136	Mean: 51.7 years <59 (55), <69 (43), ≥70 (38)	87F/49M (64% Female)	Observational (multi-center study)	Grade 1: 42 (31%) Grade 2–3: 60 (44%) Grade 4–5: 34 (25%)	Group 2–4: 46 (34%) Group 3: 90 (66%)	Anterior Circulation: 133 (98%) Posterior: 3 (2%)	2–5 pellets: 81 (60%) 6–9 pellets: 49 (36%) 10-12 pellets: 6 (4%)
Krischek et al. 2007 [17]	100	Mean: 52.71 years ≤59 years: 43 (43%) 60–69 years: 26 (26%) ≥70 years: 31 (31%)	66F/34M (66% Female)	Observational	Grade 1: 38 (38%) Grade 2-3: 32 (32%) Grade 4-5: 30 (30%)	Group 3: 86 (86%) Group 2, 4: 14 (14%)	ACA: 42 (42%) MCA: 30 (30%) ICA: 25 (25%) Posterior: 3 (3%)	2–5 pellets: 54 (54%) 6-9: 38 (38%) 10-12 pellets: 8 (8%)
Barth et al. (2006) [18]	29 (Intervention= 14, Control= 15)	Mean ± SD: 52.5 ± 7 years	Control: 75% Female, NPRI: 63% Female	RCT (Randomized)	Not reported	Group 3: 100%	Anterior circulation in NPRI: 88% Anterior circulation in Control: 81%	10 Implants: 14 (48%)
Kasuya et al. 2004 [19]	97 (Intervention: 69, Control: 28)	Mean: 55years ≤49: 22 (22%) 50–59: 28 (29%) 60–69: 24 (25%) ≥70: 23 (24%)	66F/31M (68% Female)	Observational (consecutive cohort)	Grade 1: 43 (44%) Grade 2–3: 22 (23%) Grade 4: 19 (20%) Grade 5: 9 (9%)	Group 1: 29 (30%) Group 2: 25 (25%) Group 3: 37 (38%) Group 4: 7 (7%)	ACA: 36 (37%) MCA: 21 (22%) ICA: 29 (30%) Posterior: 11 (11%)	69 (71%)

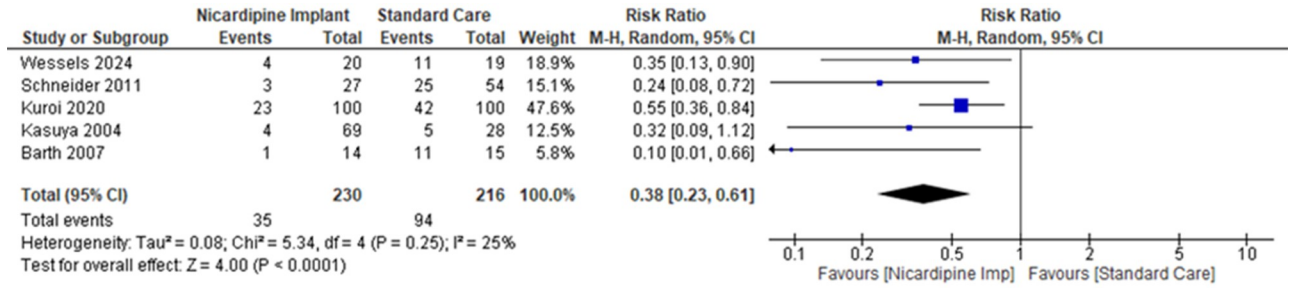

Figure 2. Forest plot showing incidence of cerebral vasospasm.

observational), patient characteristics, and treatment protocols to explore potential sources of variability.

- Sensitivity analyses: Sensitivity analyses were performed by excluding studies with a high risk of bias to assess the robustness and reliability of the meta-analysis findings.

Publication bias

To evaluate the presence of publication bias, funnel plots were generated for outcomes reported in five or more studies. Additionally, Egger's regression test was applied to quantify funnel plot asymmetry and detect potential small-study effects. These analyses help in identifying any systematic bias that could affect the overall conclusions of the meta-analysis.

Results

Study selection and characteristics

A comprehensive search strategy identified a total of 417 records across the selected databases. After importing these records into Rayyan and removing duplicates, 391 unique studies remained for initial screening based on titles and abstracts. Two independent reviewers assessed the relevance of each study, resulting in the exclusion of 261 studies. Consequently, 130 full-text articles were retrieved for detailed evaluation. Of these, 29 studies were excluded due to the unavailability of full texts or access restrictions, leaving 101 reports for eligibility assessment. Ultimately, seven studies met all inclusion criteria and were included in both qualitative and quantitative analyses (Fig. 1).

The included studies encompassed a total of 775 patients, with mean ages ranging from 52.3 to 63.3 years. The majority of participants were female (64–76%). Study designs consisted of five observational studies and two RCTs. Most patients presented with World Federation of Neurosurgical Societies (WFNS) Grades 1–3 and were classified under Fisher Group 3. Anterior circulation aneurysms were predominant, accounting for up to 98% of cases, with involvement of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and internal carotid artery (ICA) reported. The utilization rate of nicardipine prolonged-release implants (NPRI) varied between 45% and 71% in observational studies and was 51% in RCTs. Reporting of cerebral vasospasm and delayed ischemia was inconsistent across studies. Functional outcomes, measured by mRS, were reported in one study with 35% of patients achieving mRS scores of 0–2 at discharge. The use of rescue therapies and aneurysm treatment modalities was variably documented (Table 1).

Incidence of cerebral vasospasm

The meta-analysis included five studies comprising 446 participants (230 in the nicardipine group and 216 in the standard care group) to evaluate the incidence of cerebral vasospasm (Fig. 2). The pooled analysis revealed a significant reduction in the risk of cerebral vasospasm associated with nicardipine implants compared to standard care (RR = 0.38, 95% CI [0.23, 0.61], $P < 0.0001$). Heterogeneity was low ($I^2 = 25\%$), indicating consistent results across the included studies.

Incidence of delayed cerebral ischemia (DCI)

Four studies with a total of 297 participants (155 in the nicardipine group and 142 in the standard care group) assessed the incidence of DCI (Fig. 3). The pooled risk ratio demonstrated a significant reduction in DCI risk with nicardipine implants (RR = 0.33, 95%

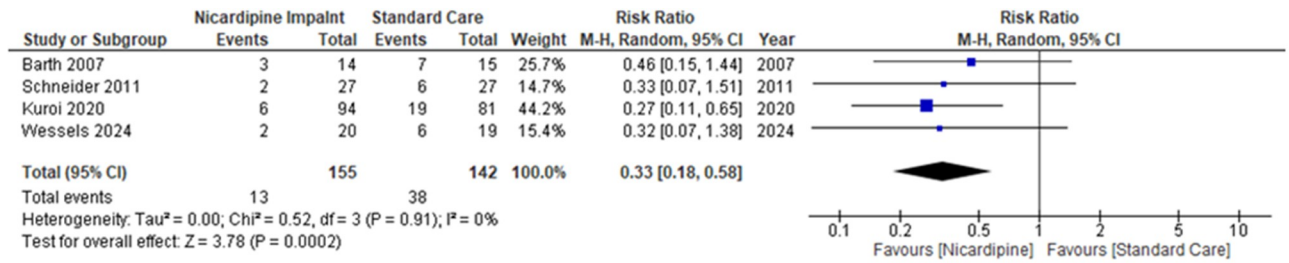

Figure 3. Forest plot of delayed cerebral ischemia (DCI).

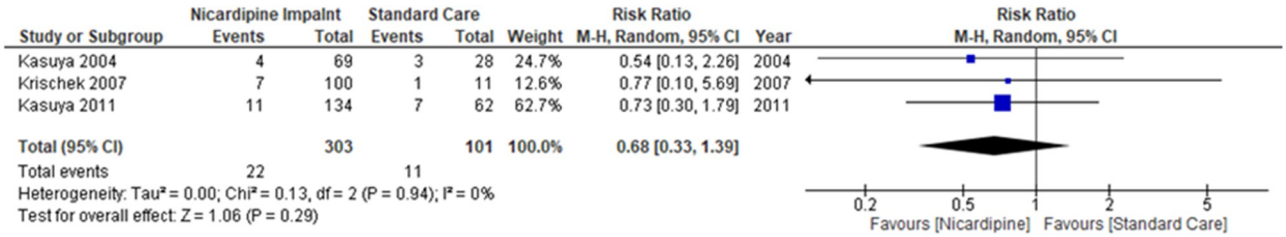

Figure 4. Forest plot of delayed ischemic neurologic deficit (DIND).

CI [0.18, 0.58], P = 0.0002). Heterogeneity was negligible (I^2 = 0%), suggesting uniform findings across studies.

Incidence of delayed ischemic neurologic deficit (DIND)

The analysis of DIND included three studies with 404 participants (303 in the nicardipine group and 101 in the standard care group) (Fig. 4). The pooled risk ratio was 0.68 (95% CI [0.33, 1.39], P = 0.29), indicating no statistically significant difference between the nicardipine and standard care groups. Heterogeneity remained negligible (I^2 = 0%), reflecting consistent results across the studies.

Impact on functional outcomes: modified Rankin scale

Functional outcomes, as measured by mRS, were evaluated in two studies (Barth 2011; Wessels 2024) (Fig. 5). The individual risk ratios were 2.67 (95% CI: 0.55–12.88) and 1.80 (95% CI: 0.63–5.14), respectively. The pooled risk ratio was 2.03 (95% CI: 0.85–4.87, P = 0.11), suggesting a trend toward improved functional outcomes with nicardipine implants, although this did not reach statistical significance. Heterogeneity was low (I^2 = 0%). The wide confidence intervals indicate limited precision, underscoring the need for further studies to conclusively determine the impact of nicardipine on functional recovery.

Publication bias

Assessment of publication bias was conducted using funnel plots for outcomes reported in five or more studies. Visual inspection did not reveal significant asymmetry, and Egger's regression test corroborated the absence of substantial publication bias (P > 0.05) for all primary and secondary outcomes (Fig. 7). Table 2 shows risk of bias of included studies.

Meta-regression analysis

A meta-regression was performed to assess the impact of mean age, percentage of female participants, study design (RCT vs. observational), and sample size on the effect sizes across the included studies. As presented in Table 3, none of the predictors demonstrated a statistically significant association with the effect size. Specifically, mean age had an estimated coefficient of 6.38 (P = 0.290), suggesting a non-significant positive relationship. The percentage of female participants showed a negative estimate of –0.81 (P = 0.328), indicating no significant effect. Study design (RCT) was associated with a decrease in effect size by 4.27 units (P = 0.157), while sample size exhibited a slight negative association with an estimate of –0.28 (P = 0.293). All 95% confidence intervals for these predictors included zero, further supporting the lack of significant findings. These results imply that, within the scope of the current analysis, mean age, gender distribution, study design, and sample size (Figure 8, 9, and 10) do not significantly explain the variability in effect sizes observed across the studies. The absence of significant moderators may be attributed to the limited number of studies included, potentially reducing the statistical power of the meta-regression. Future research with a larger dataset and additional relevant covariates is recommended to further explore potential sources of heterogeneity.

Sensitivity analysis

The leave-one-out sensitivity analysis was conducted to assess the influence of individual studies on the overall effect size of nicardipine prolonged-release implants in SAH patients. As shown in Fig. 11, the results remained robust after the removal of any single study. The effect size (OR) for cerebral vasospasm and DCI consistently favored the nicardipine treatment, with narrow confidence intervals across all iterations. This suggests that no single study significantly altered the pooled effect, indicating the stability and reliability of the findings. However, the statistical significance was retained for all comparisons, demonstrating that the removal of individual studies did not introduce any major changes in the conclusions.

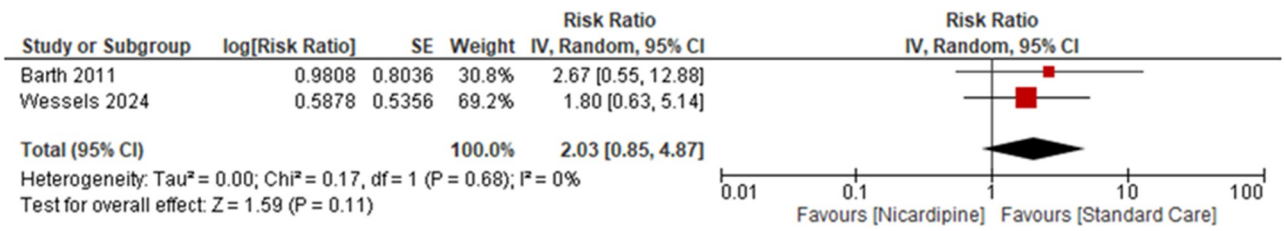

Figure 5. Forest plot of functional outcomes as measured by the modified Rankin scale.

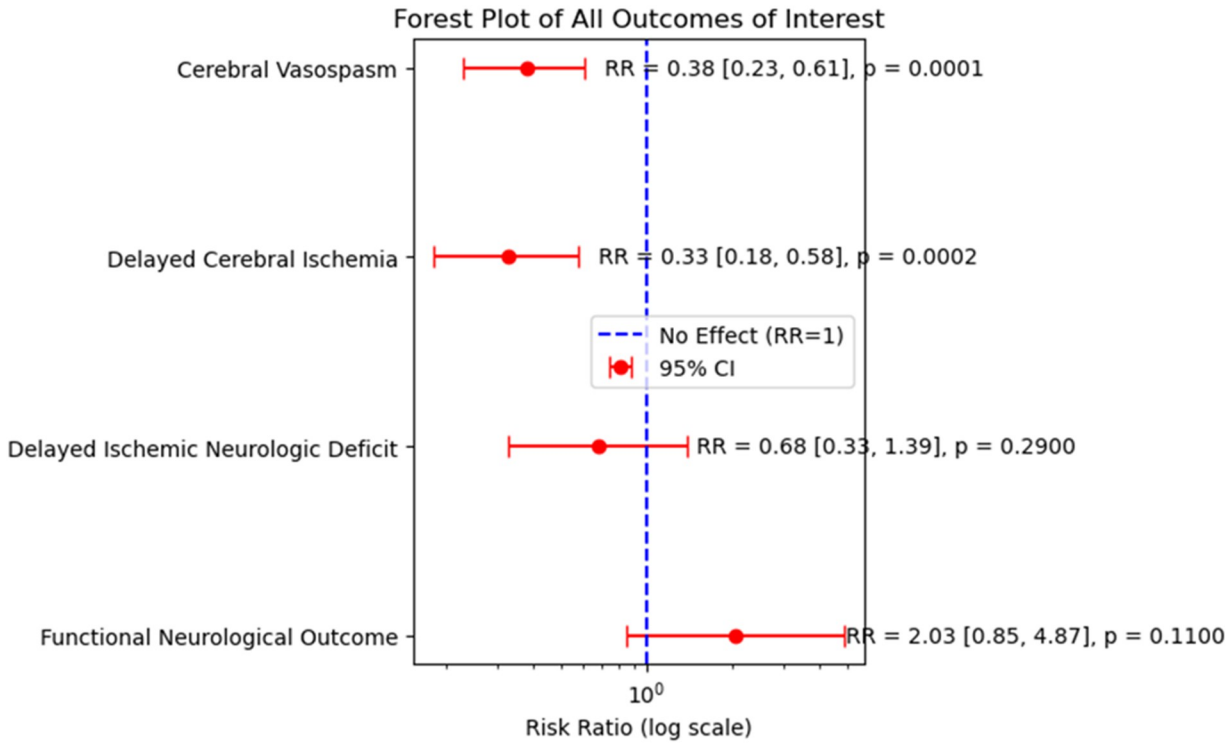

Figure 6. Combined forest plot showing all outcomes of interest.

The influence diagnostics summary (Fig. 12) reveals the impact of each study on various key statistical measures. The plots display values for residuals (rstudent), Cook's distance (cook.d), differences in fits (dffits), and other relevant diagnostics like tau2 and hat statistics. Notably, the diagnostic plots indicate that no single study had an outsized influence on the meta-analysis results, as all metrics remained within reasonable bounds. These diagnostics suggest that the overall conclusions are not unduly affected by any specific study, and the results from the sensitivity analysis are therefore considered robust and reliable.

Discussion

SAH remains a formidable challenge in neurology, with high mortality and morbidity primarily attributed to complications such as cerebral vasospasm and DCI. The findings of this meta-analysis provide compelling evidence supporting the efficacy of nicardipine prolonged-release implants in mitigating these complications, although their effect on long-term functional outcomes remains inconclusive (Fig. 6).

Efficacy in reducing cerebral vasospasm and DCI

Our analysis demonstrated that nicardipine prolonged-release implants significantly reduce the incidence of cerebral vasospasm (RR = 0.38, $P < 0.0001$) and DCI (RR = 0.33, $P = 0.0002$) compared to standard care. These results align with previous studies, such as those by Alexander *et al* (2023) and Iqbal *et al* (2024), which indicate that nicardipine's vasodilatory effects are enhanced when delivered directly to the site of vascular injury."

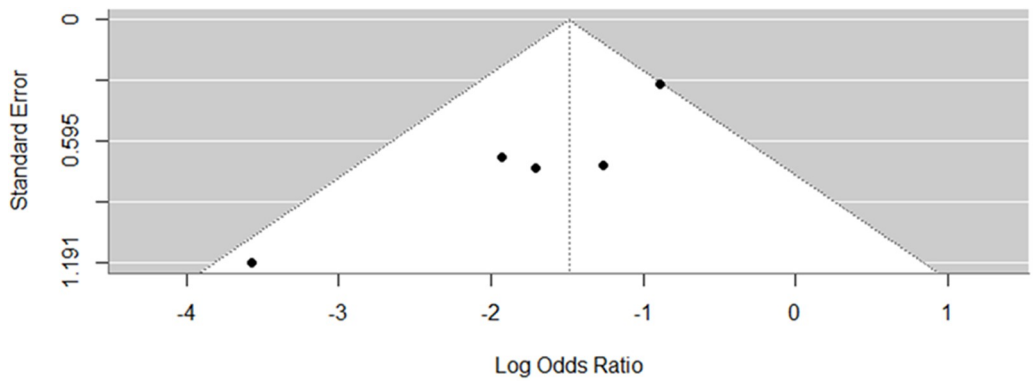

Figure 7. Funnel plot showing the publication bias of included studies.

Table 2

Risk of bias of included studies

Study	Study design	Risk of bias method	Selection bias (ROB2/NOS)	Performance bias (ROB2)	Detection bias (ROB2/NOS)	Attrition bias (ROB2)	Reporting bias (ROB2/NOS)	Overall risk of bias (ROB2/NOS)
Wessels *et al* (2024)	RCT	ROB2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kuroi *et al* (2020)	Observational	NOS	High risk	N/A	High risk	N/A	High risk	High risk
Schneider *et al* (2011)	Observational	NOS	High risk	N/A	High risk	N/A	High risk	High risk
Kasuya *et al* (2011)	Observational	NOS	High risk	N/A	High risk	N/A	High risk	High risk
Krischek *et al* (2007)	Observational	NOS	High risk	N/A	High risk	N/A	High risk	High risk
Barth *et al* (2006)	RCT	ROB2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kasuya *et al* (2004)	Observational	NOS	High risk	N/A	High risk	N/A	High risk	High risk

Please update this sentence and put the following one instead. "These results align with previous studies, which indicate that nicardipine's vasodilatory effects are enhanced when delivered directly to the site of vascular injury. The sustained release from implants ensures a consistent therapeutic concentration at the targeted arteries, effectively reversing or preventing vasospasm and improving cerebral blood flow. This localized delivery minimizes systemic side effects like hypotension, which are commonly associated with intravenous administration, thereby offering a superior safety and efficacy profile[20,21].

Furthermore, the reduction in DCI suggests that sustained nicardipine release improves microvascular circulation, thereby reducing the risk of ischemic injury following SAH. These findings are consistent with recent literature on CCBs for vasospasm management. Studies have also noted that sustained delivery systems can target specific vascular sites, optimizing therapeutic outcomes and minimizing systemic side effects. A notable strength of nicardipine implants is their ability to maintain therapeutic drug levels locally, significantly reducing variability and enhancing efficacy compared to intravenous administration[22-24].

No impact on DIND and functional outcomes

However, the impact of nicardipine implants on other critical outcomes, including DIND and long-term functional recovery, was less pronounced. No significant reduction in DIND (RR = 0.68, $P = 0.29$) was observed, and while the trend for improved functional outcomes was positive (RR = 2.03, $P = 0.11$), it did not achieve statistical significance. This finding aligns with earlier studies suggesting that while vasospasm and DCI can be effectively managed with nicardipine implants, broader neuroprotective effects – such as those required for functional recovery – are not guaranteed[6,25,26].

The lack of significant improvement in functional outcomes may be attributable to several factors. Firstly, while the reduction of vasospasm and DCI is pivotal in preventing further neurological injury, functional recovery is influenced by a broader range of factors, including cognitive rehabilitation, neuroplasticity, and the management of other SAH-related complications such as hydrocephalus and seizures. Additionally, mRS may not fully capture subtle cognitive and motor improvements, potentially underestimating the true impact of nicardipine implants on patient recovery. Moreover, the relatively small sample size and variability in the reporting of functional outcomes across the included studies limit the precision of these estimates[27-29].

These findings are consistent with the observed limited effects of vasospasm management on long-term recovery in SAH patients. Similarly, while nicardipine implants can prevent early cerebral ischemia, they may not address other aspects of the recovery process, such as cognitive rehabilitation or brain plasticity, which are essential for improving functional outcomes[29-31].

Implications for clinical practice

The results of this meta-analysis have several important implications for the clinical management of SAH. Nicardipine prolonged-release implants represent a promising advancement in the treatment of cerebral vasospasm and DCI, two major contributors

Table 3

Meta-regression results

Term	Estimate (coefficient)	Std. error	z value	*P* value	95% CI lower bound	95% CI upper bound
Intercept	−270.3633	250.2660	−1.0803	0.2800	−760.8757	220.1491
Mean age	6.3798	6.0298	1.0581	0.2900	−5.4383	18.1979
Sex (% female)	−0.8102	0.8289	−0.9775	0.3283	−2.4348	0.8144
Study design (RCT)	−4.2674	3.0179	−1.4140	0.1574	−10.1825	1.6476
Sample size	−0.2752	0.2615	−1.0525	0.2926	−0.7877	0.2373

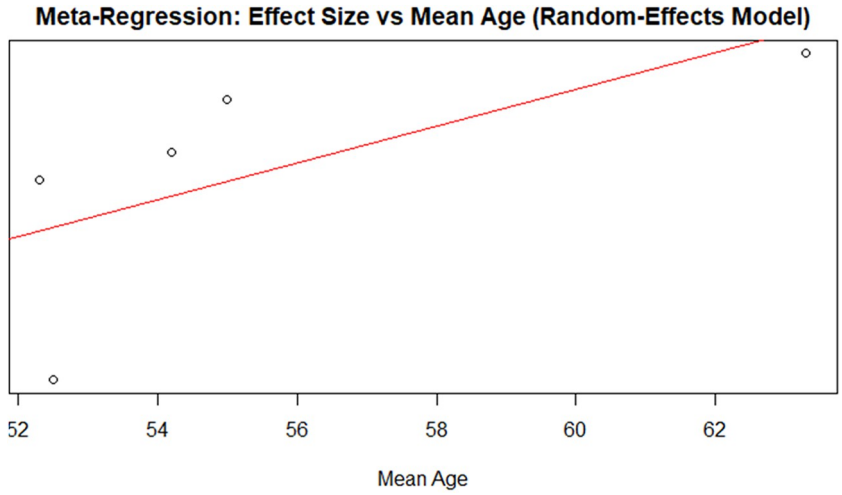

Figure 8. Plot showing meta-regression result of effect size vs mean age.

to adverse outcomes in SAH patients. By targeting vasospasm at its source, nicardipine implants offer a potentially superior approach to standard pharmacologic treatments, particularly in preventing the secondary brain injuries associated with cerebral ischemia[31-33].

However, the absence of significant improvements in long-term functional recovery underscores the need for a multifaceted approach to SAH management. While nicardipine implants may reduce the immediate risk of vasospasm and DCI, additional interventions focused on neurological rehabilitation, cognitive recovery, and secondary prevention will be essential for improving the long-term outcomes of these patients.

Meta-regression insights

The meta-regression analysis explored the influence of mean age, percentage of female participants, study design (RCT vs. observational), and sample size on effect sizes. As presented in Table 2, none of the predictors demonstrated a statistically significant association with the effect size. Specifically, mean age had an estimated coefficient of 6.38 (P = 0.290), suggesting a non-significant positive relationship. The percentage of female participants showed a negative estimate of −0.81 (P = 0.328), indicating no significant effect. Study design (RCT) was associated with a decrease in effect size by 4.27 units (P = 0.157), while sample size exhibited a slight negative association with an estimate of −0.28 (P = 0.293). All 95% confidence intervals for these predictors included zero, further supporting the lack of significant findings. These results imply that, within the scope of the current analysis, mean age, gender distribution, study design, and sample size do not significantly explain the variability in effect sizes observed across the studies. The absence of significant moderators may be attributed to the limited number of studies included, potentially reducing the statistical power of the meta-regression. Future research with a larger dataset and additional relevant covariates is recommended to further explore potential sources of heterogeneity (Figs. 8, 9, and 10).

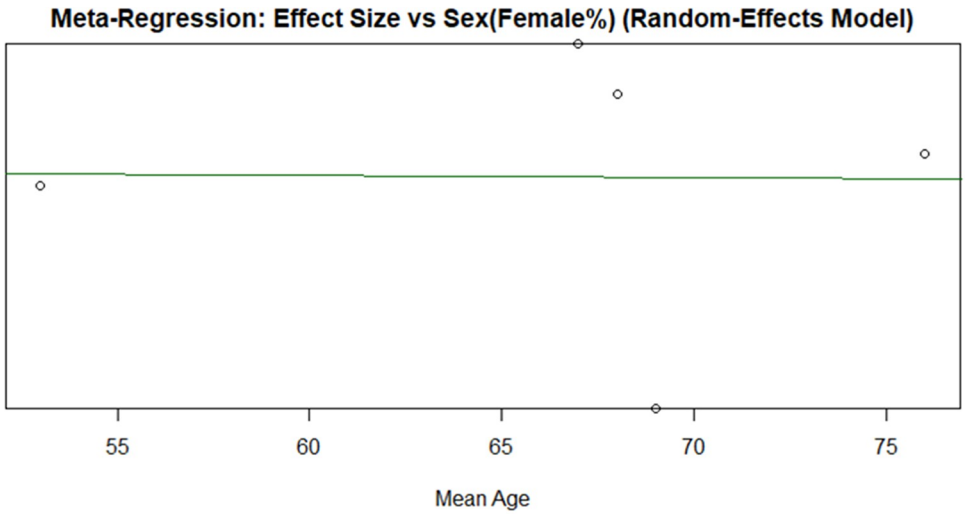

Figure 9. Plot showing meta-regression result of effect size vs age (female %).

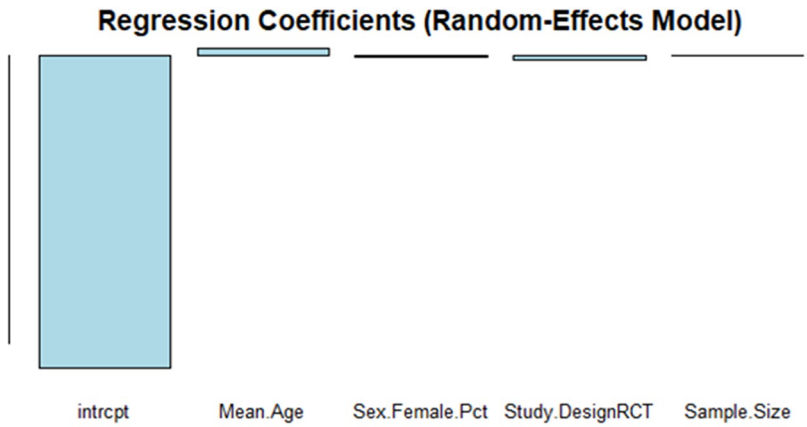

Figure 10. Plot showing multivariate regression coefficients of random effect model.

Limitations and future directions

Despite the promising results, several limitations should be considered. First, the included studies varied in terms of design, patient characteristics, and outcome reporting, which could introduce biases or heterogeneity in the analysis. Additionally, the functional outcomes were sparsely reported, and those that were presented demonstrated wide confidence intervals, indicating limited precision. Larger, more robust randomized controlled trials (RCTs) with consistent outcome measures are needed to clarify the role of nicardipine implants in improving long-term recovery.

Future research should also explore the potential synergistic effects of nicardipine implants when combined with other neuroprotective agents or rehabilitation strategies. Given the complexity of SAH outcomes, personalized treatment approaches that address both immediate ischemia and long-term recovery are likely to yield the best results for patients.

Conclusion

In conclusion, nicardipine prolonged-release implants show promise as a therapeutic strategy for preventing cerebral vasospasm and DCI in patients with SAH. However, their impact on functional recovery remains uncertain, necessitating further studies to fully elucidate their role in comprehensive SAH management.

Ethical approval

Ethical approval was not required for this meta-analysis, as it involved the review of previously published studies. All included studies had already obtained ethical approval from their respective institutional review boards or ethics committees. In accordance with established guidelines, patient consent for the publication of clinical data was either obtained directly from participants or was waived by the ethical review boards of the included studies.

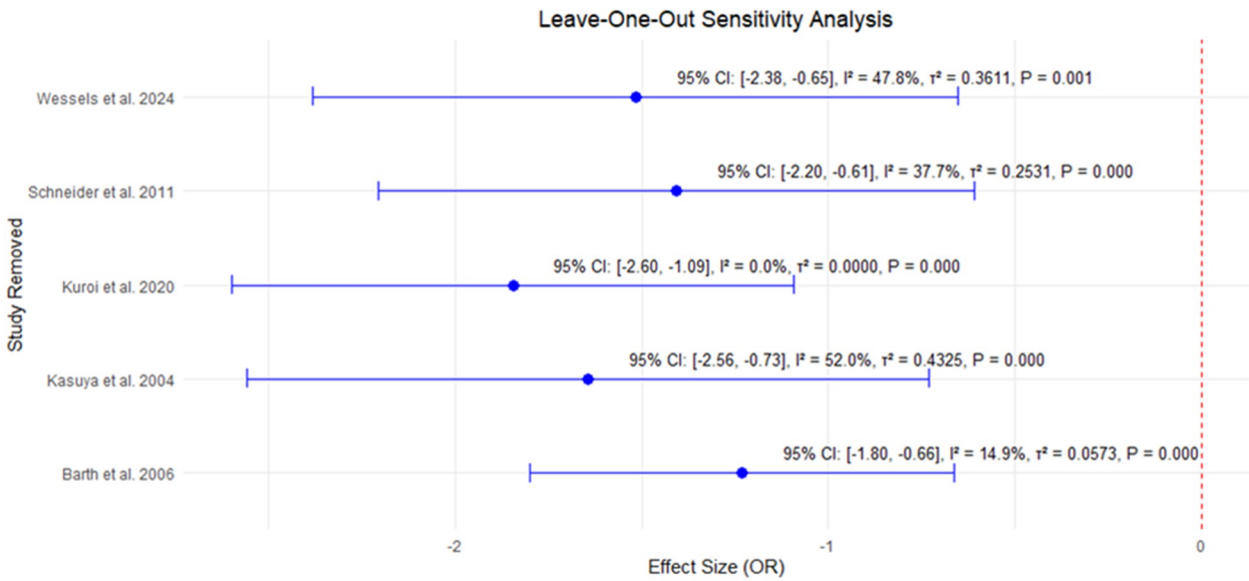

Figure 11. Forest plot showing leave one out sensitivity analysis for primary outcome.

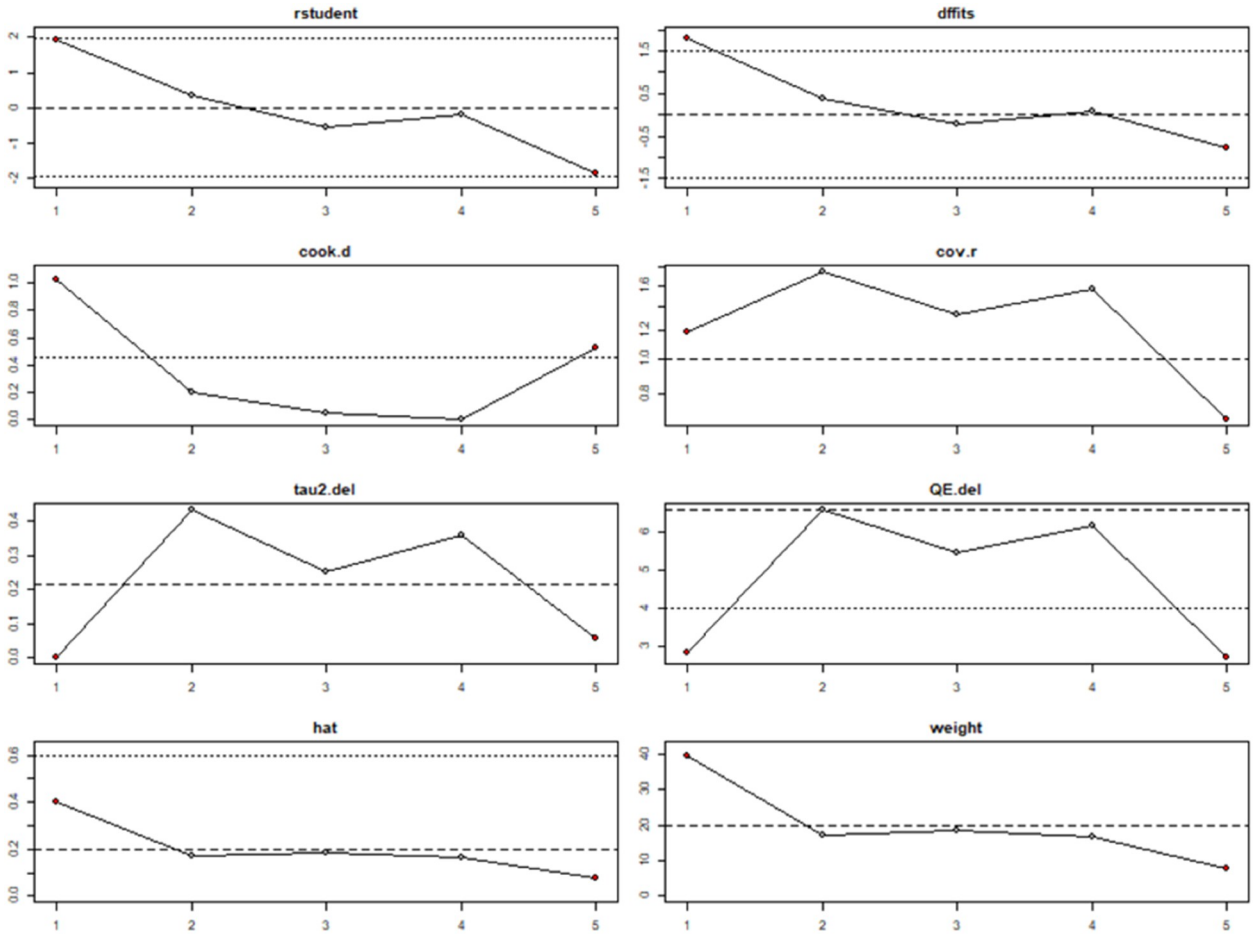

Figure 12. Plot showing influence diagnostics summary.

This meta-analysis adhered to ethical principles regarding the protection of patient privacy and confidentiality, as outlined in the Declaration of Helsinki.

Consent

Written informed consent was already obtained from the patients included in the studies analyzed for this meta-analysis, in accordance with the ethical guidelines of the respective institutions. The patients provided consent for the publication of their clinical data and any associated images used in the included studies. The patients were fully informed about the nature of the studies, the details to be disclosed, and the potential implications of making such information publicly available. Their understanding was confirmed, and they voluntarily agreed to the use of their data for scientific purposes. To ensure privacy and confidentiality, all identifying information, such as names, initials, and hospital numbers, has been omitted. Any images included in this meta-analysis were used with explicit consent from the patients, as they were necessary for the scientific analysis.

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Author's contribution

I.K.: study concept or design, data collection, data analysis or interpretation, writing the paper; I.H.: draft review and edit, screening of the studies; A.D.J.: draft review and edit, screening of the studies; M.R.I.: draft review and edit.

Conflicts of interest disclosure

The authors declare that they have no known financial or personal conflicts of interest that could have influenced the work presented in this manuscript

Guarantor

Ibrahim Khalil.

Research registration unique identifying number (UIN)

The study protocol was registered with PROSPERO (Registration No. CRD42024588089).

Provenance and peer review

None.

Data availability statement

The data supporting the findings of this meta-analysis are derived from previously published studies. These datasets are publicly available through the respective journal repositories, and full citations of the included studies are provided in the reference section. Data from individual studies can be accessed via the respective authors or institutional databases upon reasonable request. Given the nature of this meta-analysis, original datasets generated during the course of the studies included are not available from the authors of this article.

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