REVIEW

MRA versus DSA for the follow-up imaging of intracranial aneurysms treated using endovascular techniques: a meta-analysis

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/neurintsurg-2019-014936).

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Received 26 March 2019
Revised 10 April 2019
Accepted 15 April 2019
Published Online First 2 May 2019

To cite: Ahmed SU, Mocco J, Zhang X, *et al*. *J NeuroIntervent Surg* 2019;**11**:1009–1014.

ABSTRACT

Background Treated aneurysms must be followed over time to ensure durable occlusion, as more than 20% of endovascularly treated aneurysms recur. While digital subtraction angiography (DSA) remains the gold standard, magnetic resonance angiography (MRA) is attractive as a non-invasive follow-up technique. Two different MRA techniques have traditionally been used: time-of-flight (TOF) and contrast-enhanced (CE) MRA. We analysed data from studies comparing MRA techniques with DSA for the follow-up of aneurysms undergoing endovascular treatment. Subgroup analysis of stent-assisted coiling (SAC) and flow diversion (FD) techniques was completed.

Methods Comprehensive searches using the Embase, PubMed, and Cochrane databases were performed and updated to November 2018. Pooled sensitivity and specificity were calculated using aneurysm occlusion status as defined by the Raymond–Roy occlusion grading scale.

Results The literature search yielded 1579 unique titles. Forty-three studies were included. For TOF-MRA, sensitivity and specificity of all aneurysms undergoing endovascular therapy were 88% and 94%, respectively. For CE-MRA, the sensitivity and specificity were 88% and 96%, respectively. For SAC and FD techniques, sensitivity and specificity of TOF-MRA were 86% and 95%, respectively. CE-MRA had sensitivity and specificity of 90% and 92%.

Conclusion MRA is a reliable modality for the follow-up of aneurysms treated using endovascular techniques. While the data are limited, MRA techniques can also be used to reliably follow patients undergoing FD and SAC. However, clinical factors must be used to optimize follow-up regimens for individual patients.

INTRODUCTION

Intracranial aneurysms have a global prevalence of approximately 3%.[1] Aneurysm-related morbidity and mortality primarily arises from their rupture (or re-rupture), and treatment strategies aim to secure aneurysms to eliminate this risk. Endovascular treatment of intracranial aneurysms has evolved significantly over the last decade and now includes coil occlusion, with or without stent assistance, as well as parent vessel reconstruction using flow-diverting stents. Treated aneurysms must be followed over time to ensure durable occlusion as more than 20% of endovascularly treated aneurysms recur, with 9% requiring retreatment.[2]

While digital subtraction angiography (DSA) remains the gold standard test for diagnosis of aneurysm recurrence, it is an invasive imaging technique with several associated risks. These include the risks of ionizing radiation exposure, nephrotoxicity from iodine-based contrast agents, cerebral thromboembolism, as well as iatrogenic arterial damage. Reported rates of neurological complications are 0.34–1.3%.[3 4] Since durability of the aneurysm treatment must be confirmed over time, requiring multiple diagnostic studies, the risks associated with DSA follow-up are amplified. Higher costs associated with DSA are also relevant in this context, and must be accounted for in devising follow-up regimens.[5]

Magnetic resonance angiography (MRA) has been used in the follow-up of endovascularly treated cerebral aneurysms as it is a non-invasive technique and reduces some of the risks associated with serial DSA examinations. Two different MRA techniques have traditionally been used: time-of-flight (TOF) and contrast-enhanced (CE) MRA. Of these, TOF-MRA has the advantage of not requiring intravenous contrast agent administration.

While meta-analyses have previously assessed the diagnostic performance of MRA techniques compared with DSA, these have been limited by the quality of the data.[6] Furthermore, no studies have previously assessed the diagnostic quality of MRA in cases of stent-assisted coiling or flow diversion. The most recent of these have been the meta-analyses by van Amerongen *et al*[7] and Menke *et al*.[8] Both authors conclude that MRA has moderate-to-high diagnostic performance when compared with DSA. However, the body of evidence has since increased. Furthermore, studies assessing stent-assisted coiling and flow diversion have also been performed.

Our meta-analysis aims to include newer studies, with a significant increase in the available cases analyzed, and include available evidence on stent-assisted coiling and flow diversion cases as these techniques become increasingly used by neurointerventionalists.

METHODS

Study acquisition

We carried out comprehensive database searches using the Embase, PubMed, and Cochrane databases. The search was updated to November 29, 2018.

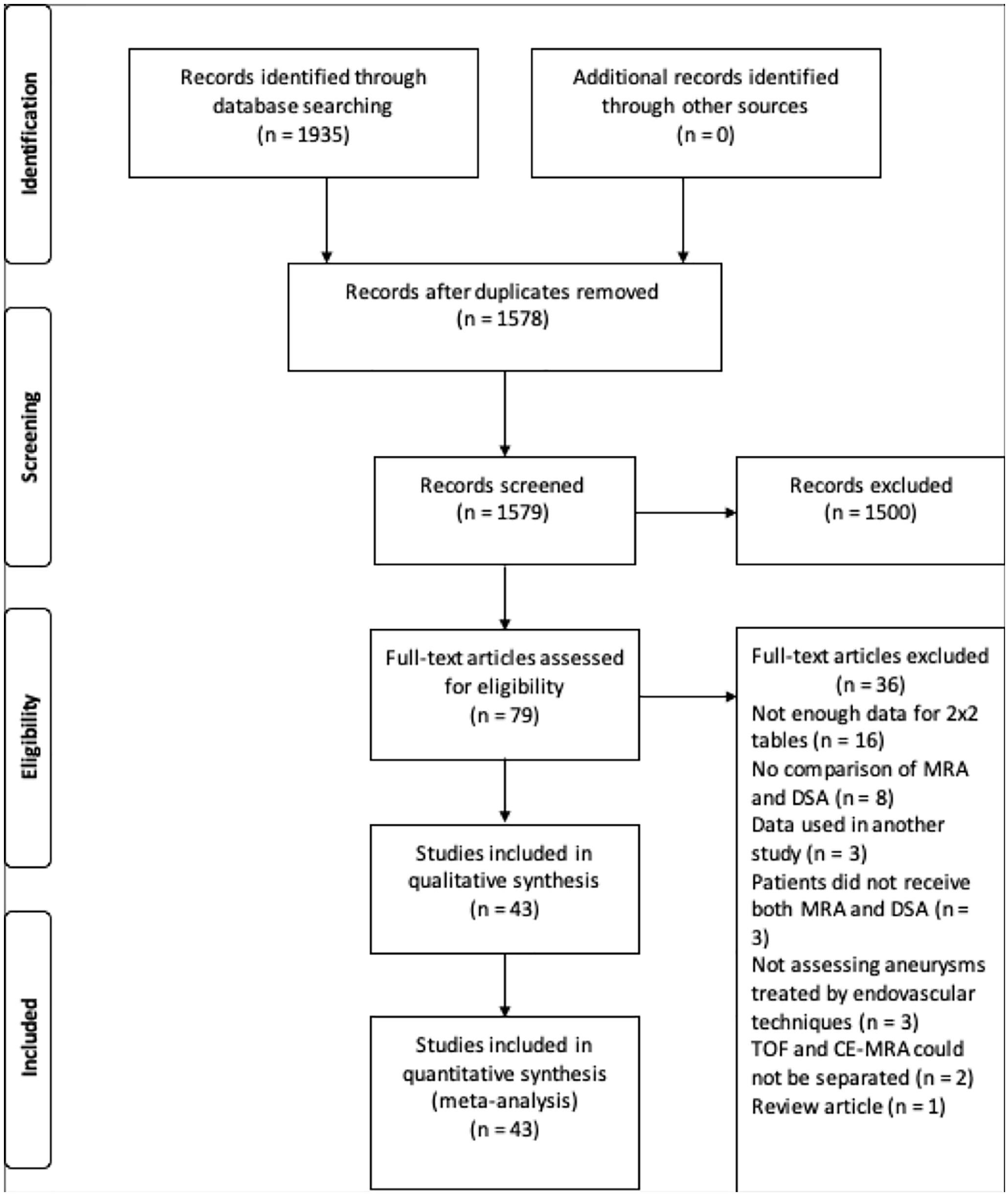

Figure 1 Study inclusion flow diagram.

Study inclusion

Acquired studies were screened for appropriateness for inclusion in the meta-analysis. The titles and abstracts were used to exclude studies that did not compare MRA and DSA in the evaluation of endovascularly treated aneurysms. Review articles, meta-analyses, conference abstracts, comments, and editorials were also excluded. For the remaining articles, full-text versions were obtained and analysed for inclusion. Inclusion criteria were: (1) studies comparing at least one MRA technique and DSA for the evaluation of aneurysms treated using an endovascular approach; (2) studies that used a Raymond–Roy or comparable grading scale to assess aneurysm occlusion; and (3) studies that provided suitable data to construct 2×2 contingency tables.

Data acquisition

Included studies were searched for occlusion status data for the meta-analysis. Further data for qualitative and subgroup analysis were also acquired, including number of patients, aneurysms, and studies included, patient age, time to follow-up, time between follow-up modalities, and modality specifics (MRI magnetic field strength, 2D vs 3D DSA).

Study quality

Methodological quality of the included studies was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method.[9–18] Specific care was taken to apply the GRADE criteria to studies of diagnostic test accuracy.[18] The assessment was done by consensus between the researchers.

Data analysis

Studies were included if they provided data regarding accuracy of MRA for detecting residual aneurysmal flow, as defined using the Raymond-Roy or a comparable scale. These data were used to construct 2×2 contingency tables. Meta-DiSc software (http://www.hrc.es/investigacion/metadisc_en.htm) was used for statistical analysis. Pooled sensitivity and specificity with 95% confidence intervals were calculated and subgroup analyses were

Ahmed SU, *et al*. *J NeuroIntervent Surg* 2019;**11**:1009–1014. doi:10.1136/neurintsurg-2019-014936

Table 1 Sensitivity and specificity for time-of-flight magnetic resonance angiography (TOF-MRA) and contrast-enhanced (CE)-MRA versus digital subtraction angiography (DSA)

	TOF-MRA				CE-MRA			
	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Recanalization	0.88 (0.86 to 0.90)	0.94 (0.93 to 0.95)	10.61 (6.53 to 17.23)	0.16 (0.11 to 0.24)	0.88 (0.85 to 0.91)	0.96 (0.94 to 0.97)	11.12 (5.30 to 23.36)	0.16 (0.08 to 0.30)
Residual neck	0.80 (0.74 to 0.86)	0.95 (0.93 to 0.97)	9.14 (4.88 to 17.14)	0.27 (0.16 to 0.46)	0.80 (0.66 to 0.89)	0.95 (0.89 to 0.98)	6.97 (3.71 to 13.09)	0.23 (0.07 to 0.74)
Residual dome	0.94 (0.89 to 0.97)	0.99 (0.98 to 1.00)	20.16 (10.44 to 38.96)	0.17 (0.11 to 0.26)	0.80 (0.70 to 0.88)	0.99 (0.95 to 1.00)	13.23 (4.32 to 40.52)	0.24 (0.09 to 0.66)

carried out. Forest plots and summary receiver operating characteristic curves were used to present the data.

RESULTS

Study inclusion

The search method yielded 865, 25, and 1045 records in the Pubmed, Cochrane, and Embase databases, respectively. After removal of duplicates, 1579 records were screened using titles and abstracts. Seventy-nine records were then used to obtain full-text articles, which were reviewed using the inclusion and exclusion criteria.[19–98] After full-text review, 38 studies were excluded (figure 1). One study was a review article and was excluded.[87] Three studies were excluded as they did not assess follow-up of patients treated with endovascular techniques,[69 71 74] and a further three were excluded as all patients did not receive MRA and DSA at follow-up.[64 70 73] Eight studies were excluded as there was no comparison of MRA and DSA,[62 65–67 75 82 83 95] and two because TOF and CE-MRA data could not be separated.[61 80] Sixteen studies were excluded as they did not contain enough information for 2×2 contingency tables,[53–56 58 59 68 72 76 78 79 81 84–86 97] and three were excluded because the data were used in another study.[60 63 77] Hence, 43 studies remained and were included in the analysis (figure 1): 37 studies assessed coiling,[19–52 57 89 98] of which 10 studies included cases of stent assistance (4–33% of cases)[20 28 30 37 39 45 48 89 98]; five studies assessed stent-assisted coiling[90–93]; and two studies assessed flow diversion.[88 89] Of the studies assessing intracranial stent use, five addressed the status of the parent vessel.[88 90 92 93 96]

GRADE assessment

The methodological quality of the included studies was assessed using the GRADE criteria, as applied to studies of diagnostic test accuracy. Since the included studies were comparing the diagnostic accuracy of MRA to DSA using a cohort, all were initially granted the maximal starting score of 4. One study included separate cohorts of patients treated with flow diversion and coiling, and both were assessed separately.[89] Six studies were rated down for indirectness[36 57 88 89 92 98] and two for inconsistency.[41 96] Seventeen studies had deductions made due to quality issues such as using non-consecutive patients or non-blinded assessment of tests.[19 23–25 29 34 37 40 45 50 52 89 90 92 96 98] Overall, 22 studies (50%) were given a score of 4, 16 (36%) were scored 3, 5 (11%) studies scored 2, while 1 (2%) study scored 1.

Data analysis

Overall sensitivity and specificity of TOF-MRA and CE-MRA are presented in table 1 and summarized in figure 2. For TOF-MRA, sensitivity for any recanalization was 88% (95% CI 86% to 90%) and specificity was 94% (95% CI 93% to 95%). CE-MRA had similar sensitivity and slightly higher specificity at 88% (95% CI 85% to 91%) and 96% (95% CI 94% to 97%), respectively.

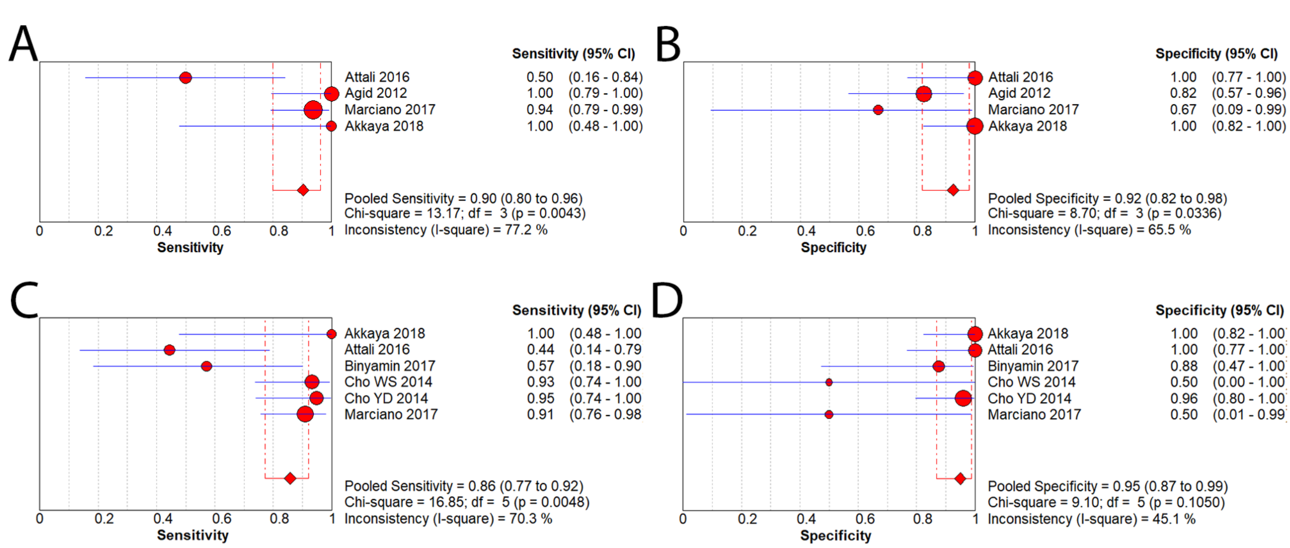

Figure 2 Pooled sensitivity and specificity for aneurysm recanalization. (A) Contrast-enhanced magnetic resonance angiography (CE-MRA) sensitivity. (B) CE-MRA specificity. (C) Time-of-flight (TOF)-MRA sensitivity. (D) TOF-MRA specificity.

Table 2 Subgroup analysis of different treatment techniques comparing sensitivity and specificity of time-of-flight magnetic resonance angiography (TOF-MRA) and contrast-enhanced (CE)-MRA

	TOF-MRA				CE-MRA			
Treatment	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Coiling	0.86 (0.83 to 0.89)	0.90 (0.87 to 0.92)	7.92 (4.91 to 12.79)	0.17 (0.11 to 0.27)	0.87 (0.81 to 0.92)	0.92 (0.88 to 0.95)	8.76 (4.48 to 17.15)	0.19 (0.12 to 0.31)
Stent-assisted coiling + flow diversion	0.86 (0.77 to 0.92)	0.95 (0.87 to 0.99)	6.10 (1.93 to 19.23)	0.24 (0.09 to 0.64)	0.90 (0.80 to 0.96)	0.92 (0.82 to 0.98)	5.60 (2.54 to 12.35)	0.14 (0.03 to 0.72)

Neck residuals were more difficult to detect using either technique, with sensitivity of 80% (95% CI 74% to 86%) using TOF-MRA and 80% (95% CI 66% to 89%) using CE-MRA.

Table 2 summarizes the subgroup analysis for coiled aneurysms compared with stent-assisted coiling and flow diversion techniques. For these techniques, sensitivity and specificity of TOF-MRA was 86% (95% CI 83% to 89%) and 90% (95% CI 87% to 92%), while CE-MRA showed sensitivity and specificity of 87% (95% CI 81% to 92%) and 92% (95% CI 88% to 95%), respectively (figures 3 and 4). Studies that included stent-assisted coiling in their coiling cohort were excluded from this subgroup analysis.

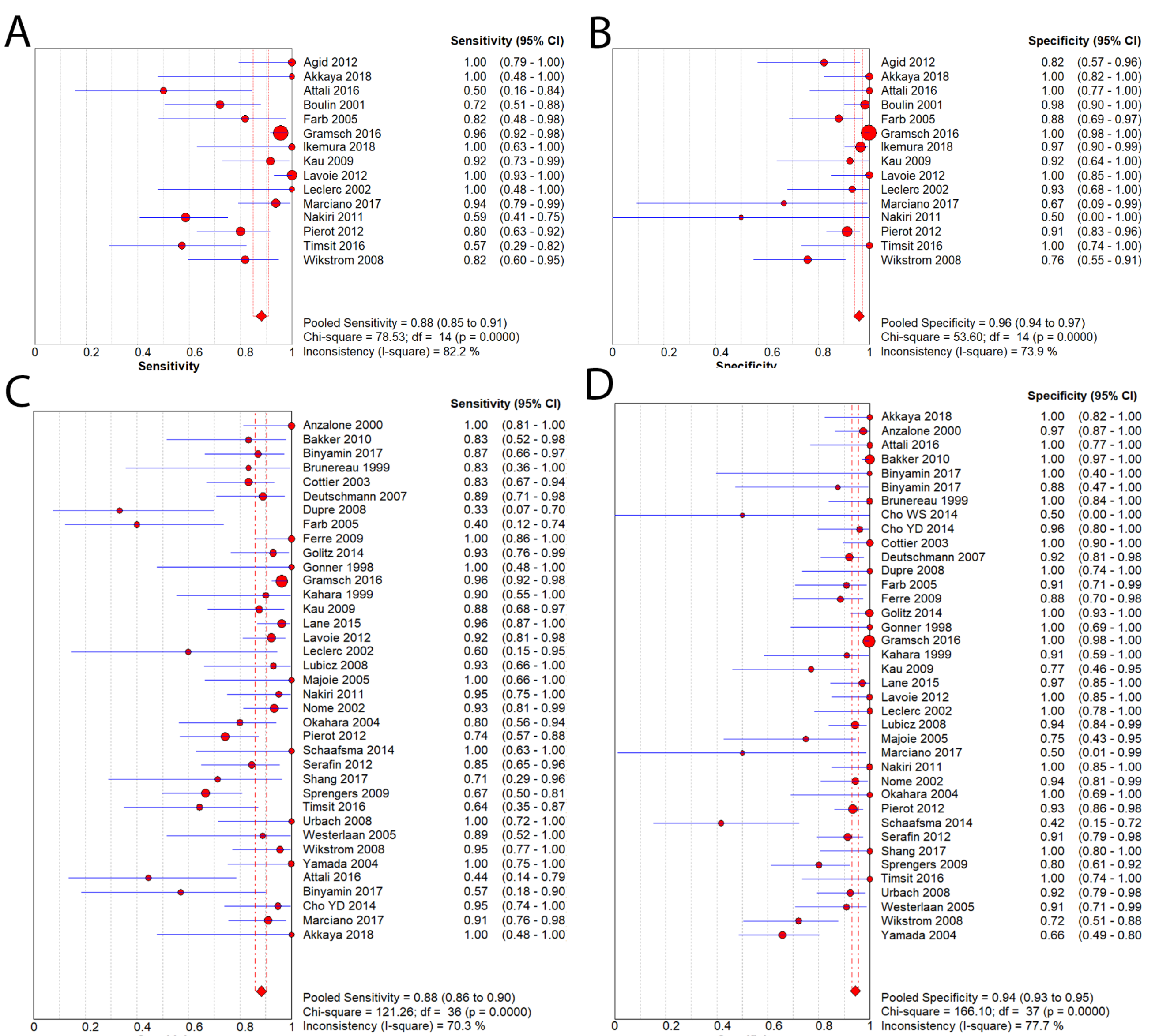

Figure 3 Pooled sensitivity and specificity for aneurysm recanalization for cases of flow diversion and stent-assisted coiling. (A) Contrast-enhanced magnetic resonance angiography (CE-MRA) sensitivity. (B) CE-MRA specificity. (C) Time-of-flight (TOF)-MRA sensitivity. (D) TOF-MRA specificity.

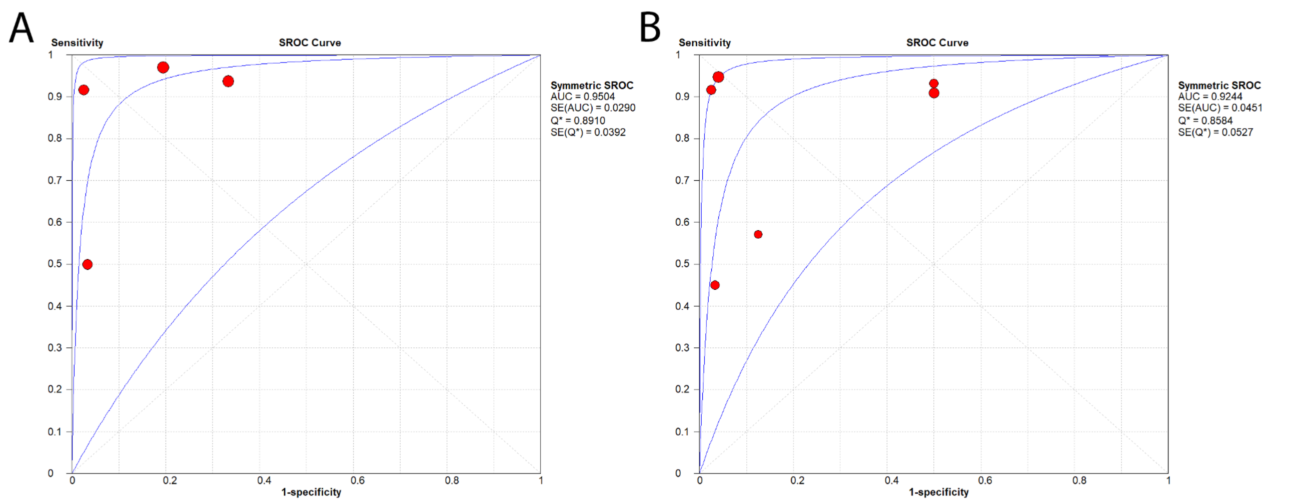

Figure 4 Summary receiver operating characteristic for flow diversion and stent-assisted coiling cases. (A) Contrast-enhanced magnetic resonance angiography (CE-MRA). (B) Time-of-flight (TOF)-MRA.

Further subgroup analyses were performed by distinguishing different study characteristics: DSA technique (2D vs 3D), MRI field strength (1.5T vs 3T), strength of evidence, and study design (prospective vs retrospective). These results are summarized in table 3.

DISCUSSION

The results of this study show that MRI techniques remain reliable in the detection of residual aneurysms after endovascular treatment. Furthermore, subgroup analysis shows high sensitivity and specificity for stent-assisted coiling and flow diversion techniques. While both sensitivity and specificity are integral to the assessment of a diagnostic test, the clinical context of the study will help determine which characteristic is of greater value. Aneurysm follow-up using MRA alone will have to provide a high degree of sensitivity in order to capture all recanalizations.

The overall sensitivity and specificity of MRA is higher than that found previously by van Amerongen *et al*[7] and Menke *et al*.[8] In the study by van Amerongen *et al*, sensitivity and specificity of CE-MRA for any residual were 85% and 88%, respectively, compared with 86% and 86% for TOF-MRA. Furthermore, both the sensitivity and specificity of CE-MRA were higher than that for TOF-MRA in our study, unlike the previously reported literature. Contrast timing and a narrow scanning interval were posited as potential reasons for lower rates of CE-MRA sensitivity and specificity in the past, and overall improvements in these scanning characteristics may be the reasons for this improvement.

Rates of detection of aneurysm dome residuals were higher than those for neck residuals using both MRA techniques. This was an expected finding, but was not observed in previously reported meta-analyses. One possible explanation for this was

Table 3 Subgroup analysis of various imaging and study characteristics

	TOF-MRA				CE-MRA			
Study Characteristic	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
2D DSA	0.85 (0.82 to 0.89)	0.92 (0.89 to 0.94)	9.04 (5.24 to 15.59)	0.18 (0.11 to 0.29)	0.86 (0.79 to 0.91)	0.94 (0.91 to 0.96)	11.74 (5.38 to 25.59)	0.22 (0.11 to 0.43)
3D DSA	0.88 (0.84 to 0.92)	0.94 (0.91 to 0.96)	9.51 (4.07 to 22.19)	0.16 (0.09 to 0.30)	0.80 (0.72 to 0.86)	0.88 (0.78 to 0.94)	4.17 (1.74 to 10.00)	0.20 (0.08 to 0.50)
1.5T MRA	0.87 (0.83 to 0.90)	0.93 (0.91 to 0.95)	11.21 (6.27 to 20.06)	0.17 (0.10 to 0.29)	0.91 (0.86 to 0.95)	0.94 (0.90 to 0.96)	10.33 (5.21 to 20.47)	0.14 (0.07 to 0.27)
3T MRA	0.86 (0.82 to 0.90)	0.92 (0.88 to 0.94)	7.16 (3.42 to 14.98)	0.19 (0.11 to 0.32)	0.73 (0.64 to 0.81)	0.92 (0.86 to 0.96)	5.75 (2.43 to 13.58)	0.34 (0.20 to 0.60)
GRADE 1–2	0.95 (0.89 to 0.98)	0.88 (0.80 to 0.93)	13.58 (1.60 to 115.39)	0.09 (0.04 to 0.17)				
GRADE 3–4	0.88 (0.85 to 0.90)	0.95 (0.94 to 0.96)	10.18 (6.06 to 17.10)	0.18 (0.12 to 0.27)	0.88 (0.84 to 0.91)	0.96 (0.94 to 0.97)	9.85 (4.26 to 22.82)	0.17 (0.09 to 0.34)
Prospective	0.84 (0.81 to 0.87)	0.92 (0.9 to 0.94)	7.39 (4.43 to 12.31)	0.21 (0.15 to 0.32)	0.82 (0.76 to 0.87)	0.92 (0.88 to 0.95)	6.81 (3.54 to 13.12)	0.24 (0.14 to 0.41)
Retrospective	0.93 (0.90 to 0.95)	0.97 (0.96 to 0.98)	16.84 (8.22 to 34.49)	0.11 (0.05 to 0.22)	0.94 (0.90 to 0.96)	0.98 (0.97 to 0.99)	23.10 (5.01 to 106.56)	0.09 (0.02 to 0.40)

CE, constrast-enhanced; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; MRA, magnetic resonance angiography; TOF, time-of-flight.

insufficient data specifying the degree of residual aneurysm, as evidenced by wider 95% CIs in previous meta-analyses. The overall sensitivity and specificity of dome residuals has increased significantly, but 95% CIs remain wide for both TOF-MRA and CE-MRA.

The sensitivity and specificity of MRA techniques for detecting aneurysm residuals in patients undergoing stent-assisted coiling and flow diversion was comparable to the coiling-only group in our subgroup analysis. This was an unexpected finding, since stent-associated artifacts are felt to interfere with assessment of residual aneurysm flow. More false negatives are expected with TOF compared with CE-MRA, and this is borne out by the lower TOF sensitivity compared with CE-MRA for aneurysms treated with intracranial stents. However, stent use does not appear to affect TOF sensitivity compared with coiling-only. TOF sensitivity was higher for the stent-assisted/flow diversion group since fewer false positives were identified. This result lends reassurance to the follow-up of these patients using MRA. However, only seven studies were available for the stent-assisted and flow diversion subgroup, and further study is required to confirm this finding. It is also important to note that nine studies with varying incidence of stent deployment were excluded from this subgroup analysis as they did not separately report cases of stent-assisted coiling.

The status of the parent vessel is another question that arises in cases of intracranial stent placement. Of the seven studies that assessed intracranial stent deployment, five addressed the patency of the parent vessel.[88 90 92 93 96] In another study, TOF-MRA was felt to be incapable of accurately assessing parent vessel patency and only DSA data were reported.[91] Of the five studies that did compare MRA and DSA, one rated the ability of MRA to assess in-stent stenosis as poor in >95% of cases.[92] One study reported significantly higher rates of in-stent stenosis with CE-MRA, with false positives found in 24% of cases.[90] Attali *et al*[88] and Akkaya *et al*[96] both found perfect sensitivity with both TOF-MRA and CE-MRA for in-stent stenosis, but low rates of specificity for both TOF-MRA (32% and 14%) and CE-MRA (64% and 43%), respectively. Van Amerongen *et al* described five possible sources of heterogeneity in their data, including publication bias, enrollment methods, DSA technique used as the reference standard, MRI magnet field strength, and study quality. These reasons also apply to our meta-analysis. Significantly higher sensitivity and specificity were found for GRADE 1–2 studies than for GRADE 3–4 studies. Furthermore, retrospective studies showed higher sensitivity and specificity than prospective studies for both TOF-MRA and CE-MRA.

A further potential source of heterogeneity is the time interval between the reference DSA and the MRA study. The mean intervals were ≤7 days in 29 studies; 7–30 days for two studies; 30–90 days for four studies; and >90 days in one study (102 days). Six studies did not specify this interval. A significant time interval between the studies will artificially raise or lower the sensitivity and specificity if the aneurysm occlusion status changes within this time period. This change will also depend on which test was performed earlier. Two processes in the time course of aneurysm evolution after endovascular treatment are important in this regard: (1) the progressive thrombosis and occlusion of an aneurysm with residual flow at the end of the procedure; and (2) aneurysm recanalization after initial occlusion. Further investigation, especially involving flow diversion, should minimize the interval between comparison studies in order to minimize this source of heterogeneity.

Applicability of the data to clinical practice is a valid concern. Some aneurysms, such as paraclinoid carotid and carotid cave aneurysms, may be more difficult to assess and potentially reduce the diagnostic performance of MRA techniques. Other factors such as aneurysm size are also potential impediments to diagnostic performance. The studies included in the meta-analysis do not specify the aneurysm morphology beyond the vessel location, and thus this information cannot be gleaned from this meta-analysis. However, most of the included studies (30/43, see online supplementary materials) included consecutive patients, thus providing an accurate sampling of aneurysms treated in a clinical setting. Further studies should aim to address these factors when assessing MRA performance.

The inter- and intra-rater reliability was fair-to-high in the studies that addressed this topic. However, there were few observers in all of the included studies. A larger study of inter-rater reliability of angiographic occlusion of coiled aneurysms found fair concordance (kappa=0.35) between a multicenter group of neurosurgeons and neuroradiologists.[99] Further research in this domain may benefit from voxel-based assessment of aneurysm recanalization, which has recently been investigated.[100]

CONCLUSION

This study demonstrates the reliability of MRA techniques in the follow-up of aneurysms treated using endovascular techniques, with excellent rates of sensitivity and specificity for both TOF-MRA and CE-MRA. Sensitivity and specificity were both higher for dome residuals, which are more likely to require retreatment, than for neck residuals. Follow-up of aneurysms treated with intracranial stents, with or without adjunctive use of coils, also showed high rates of sensitivity and specificity for both techniques. Further studies may add to this body of knowledge and may also provide data to assess the parent vessel following intracranial stent placement.

Contributors SUA and RDL: study design, data acquisition and analysis, manuscript preparation, and editing. JM: study design, manuscript preparation, and editing. XZ: data analysis, manuscript preparation, and editing. MK, AD, and KN: study design, and manuscript editing. All authors were involved with manuscript final approval and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Study characteristics and the search strategy are available as supplementary materials. Original 2 x 2 data for the meta-analysis are available from the corresponding author upon request.

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