SUPPLEMENTAL MATERIAL

INTRACRANIAL ANEURYSM WALL ENHANCEMENT AS AN INDICATOR OF INSTABILITY: SYSTEMATIC REVIEW AND META-ANALYSIS

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TABLE S1. SEARCH STRATEGY

PubMed search strategy
("Intracranial Aneurysm"[Mesh] OR (aneurysm*[tiab] AND (intracranial[tiab] OR cerebral[tiab] OR berry[tiab] OR brain[tiab] OR cranial[tiab] OR intracerebral[tiab]))) AND (Magnetic resonance imaging [Mesh] OR magnetic resonance [tiab] OR MR [tiab] OR MRI [tiab] OR MRA [tiab]) AND (image enhancement [Mesh:noExp] OR enhanc* [tiab] OR gadolinium [tiab] OR vessel wall* [tiab] OR contrast [tiab]) AND ("Subarachnoid Hemorrhage"[Mesh] OR "Aneurysm, Ruptured"[Mesh] OR "Disease Progression"[Mesh] OR rupture*[tiab] OR hemorrhage[tiab] OR haemorrhage[tiab] OR sah[tiab] OR grow*[tiab] OR increase*[tiab] OR enlarge*[tiab] OR develop*[tiab] OR progress*[tiab] OR unstable [tiab] OR stability [tiab])
Embase search strategy
('Intracranial Aneurysm'/exp OR (aneurysm* AND (intracranial OR cerebral OR berry OR brain OR cranial OR intracerebral)):ab,ti) AND ('nuclear magnetic resonance imaging'/de OR (‘magnetic resonance’ OR MR OR MRI OR MRA):ab,ti) AND (‘contrast enhancement’/de OR 'image enhancement'/exp OR (enhanc* OR gadolinium OR ‘vessel wall*’ OR contrast):ab,ti) AND ('subarachnoid hemorrhage'/exp OR 'aneurysm rupture'/exp OR 'disease exacerbation'/exp OR (rupture* OR hemorrhage OR haemorrhage OR sah OR grow* OR increase* OR enlarge* OR develop* OR progress* OR stability OR unstable):ab,ti) NOT ('conference abstract'/it)

TABLE S2. THE DIFFERENT DEFINITIONS OF GROWING AND SYMPTOMATIC ANEURYSMS

Study	Definition of growth	Definition of symptomatic
Edjlali (2018)	"In case of morphologic change (emergence of a bleb, irregularities of the pouch) or noted growth in aneurysm size"	"When aneurysmal cranial nerve compression was manifest or when patients presented with thunderclap headaches but no subarachnoid haemorrhage after exclusion of differential diagnosis"
Matsushige (2019)	"Aneurysmal growth was defined as enlargement by >1 mm or obvious morphological change. The pattern of morphological change was classified as follows: stable (defined as no morphological changes), whole sac expansion (defined as enlargement of the whole aneurysm sac), and daughter sac formation (defined as development of a bleb or another aneurysmal component)."	N/A
Fu (2021)	N/A	"(i) with sentinel headache (development of a sudden and severe headache on the ipsilateral side of the aneurysms within 2 weeks of admission without prior history of headache within the previous 5 years)2,17 or (ii) with oculomotor nerve palsy (a sudden headache with one or several symptoms of pupillary light reflex disappearing, ptosis, or extraocular myoparalysis on the ipsilateral side of the aneurysm within 1 month before admission)"
Wang (2019)	N/A	"patients with neurologic symptoms (e.g., sudden headache or blepharoptosis) related to the location of the aneurysm"
Zhu (2020)	N/A	"(1) cranial nerve deficits associated with UIA (e.g., abrupt unilateral visual loss, diplopia, retrobulbar pain, pupillary light reflex disappearing, ptosis, extraocular myoparalysis, or trigeminal pain); (2) acute headache: sudden, intense headache at onset with resolution in the following 72 h; (3) chronic headache: chronic and recurrent headache with a marked improvement after surgical intervention of the aneurysm."
Zhong (2020)	N/A	"An aneurysm was considered symptomatic when aneurysmal cranial nerve deficits were present or when patients presented with emerging headaches, but no subarachnoid hemorrhage, after exclusion of differential diagnoses."
Omodaka (2019)	"1) maximum aneurysm diameter increase by 2 mm or more, 2) appearance of bleb, or 3) de novo aneurysm formation."	"Symptomatic (neurological deficit) at the time MR vessel wall imaging was acquired. General headache was not considered as a symptom."
Vergouwen (2019)	"growth of ≥1 mm in at least 1 direction."	N/A
Gariel (2020)	"a measurable increase in size ≥1 mm of maximal aneurysm diameter or by appearance of irregularity on the aneurysmal pouch, on coregistered maximal intensity projections."	N/A

N/A = Not applicable

TABLE S3. MINORS QUALITY ASSESSMENT

Item	Matsushige (2019)	Edjlali (2018)	Omodaka (2016)	Wang (2018)	Nagahata (2016)	Gariel (2020)	Vergouwen (2019)	Omodaka (2019)	Fu (2021)	Wang (2019)	Zhu (2020)	Zhong (2020)
A clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2	2	2
Prospective collection of data	1	2	0	1	1	2	2	1	2	1	1	2
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study endpoint	1	2	2	1	2	1	2	1	2	2	2	1
Follow-up period appropriate to the aim of the study	N/A	N/A	N/A	N/A	N/A	2	1	N/A	N/A	N/A	N/A	N/A
Loss to follow-up less than 5%	N/A	N/A	N/A	N/A	N/A	0	2	N/A	N/A	N/A	N/A	N/A
Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0
An adequate control group	2	2	2	2	2	N/A	N/A	2	2	2	2	2
Contemporary groups	2	2	2	2	2	N/A	N/A	2	2	2	2	2
Baseline equivalence of groups	2	2	2	2	2	N/A	N/A	2	2	2	2	0
Adequate statistical analysis	0	2	2	2	1	2	2	2	2	2	2	2
Total points	14	18	16	16	16	13	15	16	18	17	17	15

We scored items from 0 to 2. A score of 0 reflects an unreported item. A score of 1 reflects an item that is reported but inadequate. A score of 2 reflects an item that is reported and adequate. The maximum obtainable score is 20 for cross-sectional studies and 18 for longitudinal studies, taking 'N/A'-items into account. N/A = not applicable.

TABLE S4. SUBGROUP META-ANALYSIS OF CROSS-SECTIONAL STUDIES WITH GROWTH OR SYMPTOMATIC PRESENTATION AS OUTCOME

Variable	Subgroup	No. of studies	PR (95% CI)	I^2	P-value heterogeneity
AWE Assessment	Qualitative	6	4.40 (2.60-7.45)	67%	0.01
	Quantitative	1	7.20 (2.32-22.37)	n/a	n/a
Aneurysm size	< 7mm	5	3.85 (2.46-6.02)	56%	0.06
	≥ 7mm	2	9.88 (4.39-22.26)	0%	0.48
Geographic region	Japan	2	3.65 (0.92-14.38)	80%	0.03
	Other	5	5.17 (3.50-7.65)	23%	0.27
Outcome	Growth	2	3.65 (0.92-14.38)	80%	0.03
	Symptomatic	4	5.76 (3.74-8.86)	20%	0.29
	Growth and symptomatic	1	3.42 (1.63-7.18)	n/a	n/a

n/a = not applicable.

TABLE S5. PERFORMANCE OF DIFFERENT QUALITATIVE AND QUANTITATIVE AWE DEFINITIONS

Study	Outcome	AWE definition	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Reproducibility	
								Inter-rater	Intra-rater
Edjlali (2018)	Growth + Symptomatic	CAWE, grade 2 and grade 3*	0.677	64.5 (47.6-81.3)	68.1 (62.6-73.6)	18.5	94.4	Grade 2: 0.87 (0.80-0.92)	NR
		Grade 3	0.762	61.3 (44.1-78.4)	84.4 (80.1-88.7)	28.3	94.3	0.88 (0.81-0.92)	NR
Omodaka (2016)	Rupture	WEI (cutoff value of 0.53)	0.75	96	47	NR	NR	0.92 (0.81-0.97)	0.94 (0.86-0.98)
Wang (2018)	Rupture	Enhancement Ratio (threshold of 61.5%)	0.798 (0.703-0.893)	89.5	63.2	NR	NR	NR	NR
Nagahata (2016)	Rupture	Faint enhancement†	NR	98.4	81.9	NR	NR	NR	NR
		Strong enhancement†	NR	73.8	95.2	NR	NR	NR	NR
Fu (2021)	Symptomatic	AWE pattern (0, no; 1, focal; 2, circumferential)	0.79	NR	NR	NR	NR	0.87 (0.83-0.92)	NR
		WEI (cutoff value of 0.56)	0.78	NR	NR	NR	NR	ICC=0.98 (0.97-0.98)	NR
		AWE pattern + WEI	0.91	95.7	73.4	NR	NR	N/A	N/A
Wang (2019)	Symptomatic	Enhancement Ratio (threshold of 60.5%)	0.903 (0.836-0.970)	90.3	87.9	NR	NR	NR	NR
Zhu (2020)	Symptomatic	AWE area (0, none; 1, focal less than 50%; 2, incomplete between 50-99%; 3, complete enhancement)	0.888	72.2	92.0	NR	NR	0.88	NR
Edjlali (2020)	Growth	Increased AWE during follow-up	NR	67	100	96	100	0.87 (0.72-1.0)	NR

*This table includes the performance of other AWE definitions than the qualitative definition of 'presence' vs 'absence' of AWE. Data between parentheses are 95% CIs. *grade 2 is thin circumferential enhancement and grade 3 is thick (>1mm) circumferential enhancement. †'strong' is definite enhancement equal to choroid plexus or venous plexus and 'faint' is increased wall signal intensity compared to precontrast scan. CAWE = circumferential arterial wall enhancement. PPV = positive predictive value. NPV = negative predictive value. NR = not reported. WEI = Wall Enhancement Index. AUC = Area under the curve. ICC = intraclass correlation coefficient. N/A = Not applicable.*