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Original article

Risk prediction of cerebrovascular events with carotid plaque magnetic resonance analysis: A meta-analysis

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ABSTRACT

Background and purpose. – It is not conclusive that magnetic resonance (MR)-based carotid atherosclerotic plaque assessment identifies high-risk features associated with cerebrovascular events. We aimed to systematically summarize the association of MR imaging (MRI)-determined intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), and thinning/rupture of the fibrous cap (TRFC) with subsequent ischemic events.

Materials and methods. – We performed a comprehensive literature search evaluating the association of MRI-based carotid plaque composition with ischemic outcomes. We included cohort studies examining IPH, LRNC, or TRFC with mean follow-up of ≥ 6 months and an outcome measure of ipsilateral ischemic events. A meta-analysis was done according to the Cochrane guideline.

Results. – We identified 13 studies including 1.150 patients and 1.208 analyzed carotid arteries, with mean follow-up of 21.1 months. The hazard ratios (HR) for IPH, LRNC, and TRFC as predictors of subsequent ischemic events were 4.41 (95% CI: 2.87, 6.79), 3.00 (95% CI: 1.51, 5.95), and 5.94 (95% CI: 2.66, 13.28), respectively. The predictive value of carotid plaque MRI for ischemic events was acceptable, with sensitivity of 0.80 (95% CI: 0.66, 0.90) and specificity of 0.63 (95% CI: 0.57, 0.68). However, it was limited to confirm or exclude future ischemic events in clinical context, with positive likelihood ratio (LR) of 2.2 (95% CI: 1.9, 2.5) and negative LR of 0.31 (95% CI: 0.18, 0.55). No statistically significant heterogeneity or publication bias was observed.

Conclusion. – The presence of IPH, LRNC, and TRFC determined by MRI is associated with increased risk of future ischemic events, but its predictive value is moderate and should not be used for confirmation or exclusion of future ischemic events in clinical context.

Introduction

Atherosclerotic carotid plaque represents a major cause of cerebral ischemia. Plaque composition and specifically vulnerability are increasingly important in identifying patients at risk for cerebrovascular events [1–3]. With the introduction of high-resolution magnetic resonance imaging (MRI), non-invasive identification of plaque compositions in the carotid arteries is feasible with good correlation to histopathology [4,5]. However, it is not conclusive whether there are differences in the risk profiles of specific plaque components such as intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), or thinning/rupture of the fibrous cap (TRFC) because of relatively small studies. Therefore, we undertook a systematic review and meta-analysis of the available published literature to investigate the predictive value of carotid plaque MRI for cerebrovascular events.

Materials and methods

We searched PubMed, EMBASE, and the Cochrane library through May 2017 using medical subject headings “carotid plaque OR carotid artery OR atherosclerotic plaque” and “magnetic resonance imaging OR MRI”. Search results were limited to adults and no language restrictions. References of reviewed articles were also searched for relevant titles.

Abbreviations: IPH, Intraplaque Hemorrhage; LRNC, Lipid-Rich Necrotic Core; TRFC, Thinning/Rupture Of The Fibrous Cap.

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Criteria for including studies

Studies with MRI-based characterization of carotid artery plaque composition and its association with ipsilateral stroke or transient ischemic attack (TIA) or amaurosis fugax were eligible. Specific inclusion criteria were: follow-up for more than 6 months, ≥ 1.5-T MRI scanners, and detailed assessment of IPH or LRNC or TRFC in the carotid arteries at the baseline examination. Studies were excluded if they did not provide risk estimates or crude numbers of prevalence and outcome.

Data extraction and quality assessment

Two independent raters (B.J. and D.H.) abstracted data using a standardized form, and discrepancies were resolved by discussion. We extracted the following data: author, year of publication, design of study (prospective or retrospective), region of population, follow-up duration, sample size, age, percentage of men, presence or absence of symptoms, and field strength of MRI scanner. Clinical outcomes included the raw data or sufficient data for cerebrovascular events (amaurosis fugax or TIA or stroke).

The same two raters evaluated the study quality using the Newcastle-Ottawa Quality assessment scale for cohort studies. This instrument is recommended for use by the Cochrane Collaborative Group for the assessment of quality of non-randomized studies. Assessment of quality is graded by the description of patient selection (4 criteria), study-control group comparability (1 criterion), and outcome assessment (3 criteria). Based on previous recommendations, studies meeting ≥ 5 criteria were considered to be of high quality. Publication bias was assessed using the Deeks' test.

Data analysis

Raw data for dichotomous event outcomes were converted to annualized event rates. We used standard statistics to summarize the individual risk estimates, and to pool the natural logarithms of the hazard ratios (HR) using a random effects model. A meta-regression analysis was performed to identify sources of the detected high degree of heterogeneity of the risk estimates, including the following pre-specified variables: design of study (prospective or retrospective), region of population, follow-up duration, sample size, age, percentage of men, presence or absence of symptomatic, strength field of MRI scanner, and MRI technology (multisequence or single sequence).

We calculated summary sensitivity, specificity, likelihood ratios (LRs), diagnostic odds ratio (DOR), summary receiver-operating characteristic (ROC) curves with their 95% confidence intervals (CI) using a bivariate mixed-effects binomial regression model. This model was used due to frequent zero cells that occurred because most patients with negative MRI findings do not have cerebrovascular events, and the events were not common even among patients with positive scans. The clinical utility of carotid plaque MRI was evaluated using the likelihood ratios to calculate post-test probability based on Bayes' theorem and the likelihood ratio matrix, respectively.

The Cochran-Q test and measured inconsistency (I^2) were used to assess the heterogeneity. Statistical analysis was performed with the Stata software version 14.0 (Stata, College Station, Texas). Two-tailed *P* value of less than 0.05 was considered to be significant.

Results

We identified 13 studies [6–18] that met the inclusion and exclusion criteria (Fig. 1). The majority of studies were conducted in North America and Europe (69%), whereas only four (31%) studies were performed in Asia. Two (15%) studies were retrospective in design, majority of studies (85%) were of a prospective nature. Twelve studies were performed with MRI scanner of 1.5-T, and one with 3.0-T. All included studies were rated good quality (Table 1). There were 1.150 patients with 1.208 analyzed carotid arteries included by mean follow-up of 21.1 months. The mean age was 71.8 years ± 2.6, and the patients were 78.4% ± 11.2 male. There

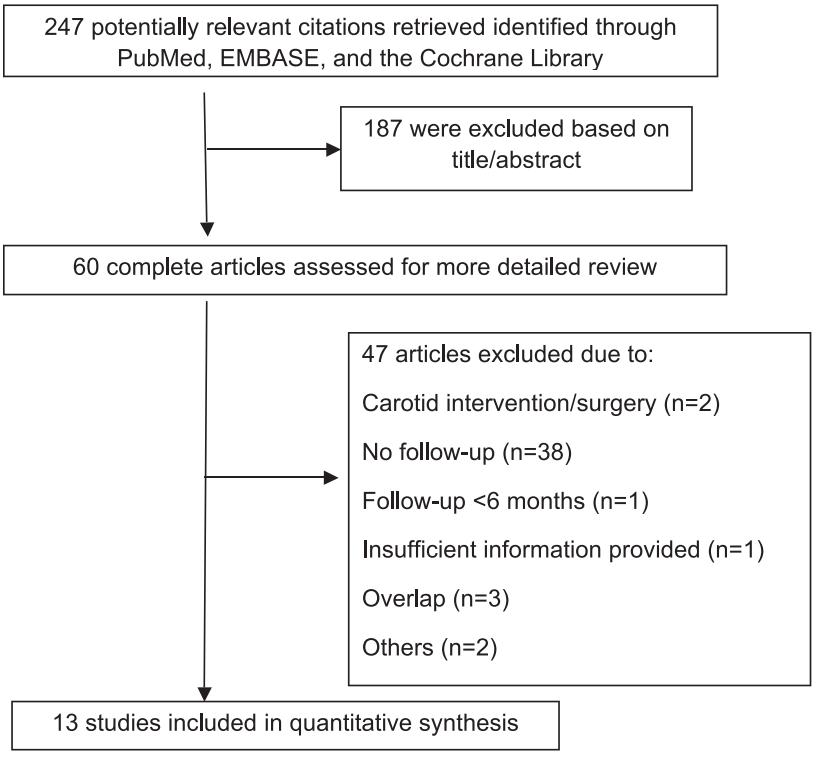

Fig. 1. Flow diagram of the reviewing process.

Table 1
Characteristics of included studies.

Study	Number of patients	Number of carotid arteries	Index	Positive MRI		Negative MRI	
				n	Events	*n*	Events
Lin 2006 [4]	53	53	All	22	6	31	1
Takaya 2006 [5]	154	154	IPH	43	8	68	3
			TRFC	–	10	–	1
			LRNC	111	11	43	1
Yamada 2007 [6]	35	50	IPH	22	4	28	0
Altaf 2008 [7]	64	64	IPH	39	13	25	1
Singh 2009 [8]	75	98	IPH	36	6	62	0
Sadat 2010 [9]	61	61	IPH	31	–	30	–
			TRFC	27	–	34	–
			LRNC	19	–	42	–
Kume 2010 [10]	165	165	IPH	78	22	87	7
Kurosaki 2011 [11]	62	62	IPH	32	6	30	1
Mono 2012 [12]	62	65	IPH	16	0	49	5
			TRFC	42	4	23	1
			LRNC	16	3	49	2
Kwee 2013 [13]	126	126	IPH	40	7	86	6
			TRFC	55	11	71	2
			LRNC	63	10	63	3
Hosseini 2013 [14]	179	179	IPH	114	57	65	5
Lorena 2013 [15]	77	77	All	36	9	41	0
			IPH	21	5	40	0
Simpson 2015 [16]	37	54	IPH	28	9	26	4
SUM	1150	1208	IPH	500	148	639	33
			TRFC	97	15	94	3
			LRNC	190	24	155	6
			All	58	15	72	1
Annual event rate (%)			IPH	18.6	3.3		
			TRFC	14.0	2.8		
			LRNC	8.1	3.0		
			All	25.2	2.8		

IPH: intraplaque hemorrhage; TRFC: thinned/ruptured fibrous cap; LRNC: lipid-rich necrotic core.

Table 2
Adverse cerebrovascular events by study and MRI result.

Study	Region	Study design	Field strength	Sample size (*n*)	Follow-up (months)	Age (years)	Male (%)	Stenosis of carotid Artery	Presentation	Quality		
										Selection	Comparison	Outcome
Lin, 2006 [4]	China	Prospective	1.5 T	53	6	69.2	83	–	Symptomatic	4	1	2
Takaya, 2006 [5]	America	Prospective	1.5 T	154	38.2	71.1	82	50–79%	Asymptomatic	4	1	3
Yamada, 2007 [6]	Japan	Retrospective	1.5 T	35	12	70	83.2	Mean 45%	Mix	4	1	2
Altaf, 2008 [7]	UK	Prospective	1.5 T	64	28	72.7	80	30–69%	Symptomatic	4	1	3
Singh, 2009 [8]	Canada	Prospective	1.5 T	75	24.9	74.8	100	50–70%	Asymptomatic	4	1	3
Sadat, 2010 [9]	UK	Prospective	1.5 T	61	16.9	74	–	45–58%	Symptomatic	4	1	3
Kume, 2010 [10]	Japan	Prospective	1.5 T	165	26	70.9	81.2	Mean 75%	Mix	4	1	3
Kurosaki, 2011 [11]	Japan	Retrospective	1.5 T	62	9.1	77.8	81	>70%	Symptomatic	4	1	3
Mono, 2012 [12]	Switzerland	Prospective	3.0 T	62	18.9	68.7	74	>50%	Asymptomatic	4	1	3
Kwee, 2013 [13]	Netherlands	Prospective	1.5 T	126	12	69	62.7	30–69%	Symptomatic	4	1	3
Hosseini, 2013 [14]	UK	Prospective	1.5 T	179	17.5	71.7	70.9	>50%	Symptomatic	4	1	3
Lorena, 2013 [15]	Germany	Prospective	1.5 T	77	41.1	72.8	54.5	50–99%	Asymptomatic	4	1	3
Simpson, 2015 [16]	UK	Prospective	1.5 T	37	24	70.5	87	30–99%	Symptomatic	4	1	3

Note: both symptomatic and asymptomatic.

were 12 studies referring to IPH, but only four to TRFC and LRNC, respectively (Table 2).

Annualized event rates

The weighted average annualized cerebrovascular events rate for positive versus negative MRI was 18.6 versus 3.3% for IPH ($P = 0.003$), 14.0 versus 2.8% ($P = 0.121$) for TRFC, and 8.1 versus 3.0% ($P = 0.275$) for LRNC.

Risk stratification and predictive value

The pooled HR was 4.41 (95% CI: 2.87, 6.79) for positive MRI versus negative MRI in predicting cerebrovascular events of patients with IPH ($P < 0.001$), 5.94 (95% CI: 2.66, 13.28) for TRFC ($P < 0.001$), 3.00 (95% CI: 1.51, 5.95) for LRNC ($P = 0.002$), and the overall HR was 12.94 (95% CI: 2.26, 74.20) ($P = 0.004$). No significant heterogeneity was observed (Fig. 2), as well as no significant difference in the risk estimate according to the pre-specified variables by regression meta-analysis.

Due to more information obtained for IPH, our pooled analysis was focused on IPH. The test parameters for carotid plaque MRI to predict future cerebrovascular events among patients with IPH versus those without IPH were obtained using SROC curves (Fig. 3), with area under curve (AUC) of 0.72 (95% CI: 0.68, 0.75), sensitivity of 0.80 (95% CI: 0.66, 0.90), specificity of 0.63 (95% CI: 0.57, 0.68), positive LR of 2.2 (95% CI: 1.9, 2.5), negative LR of 0.31 (95% CI: 0.18, 0.55), and DOR of 7.0 (95% CI: 4.0, 13.0).

No publication bias was observed ($P = 0.66$) (Fig. 4).

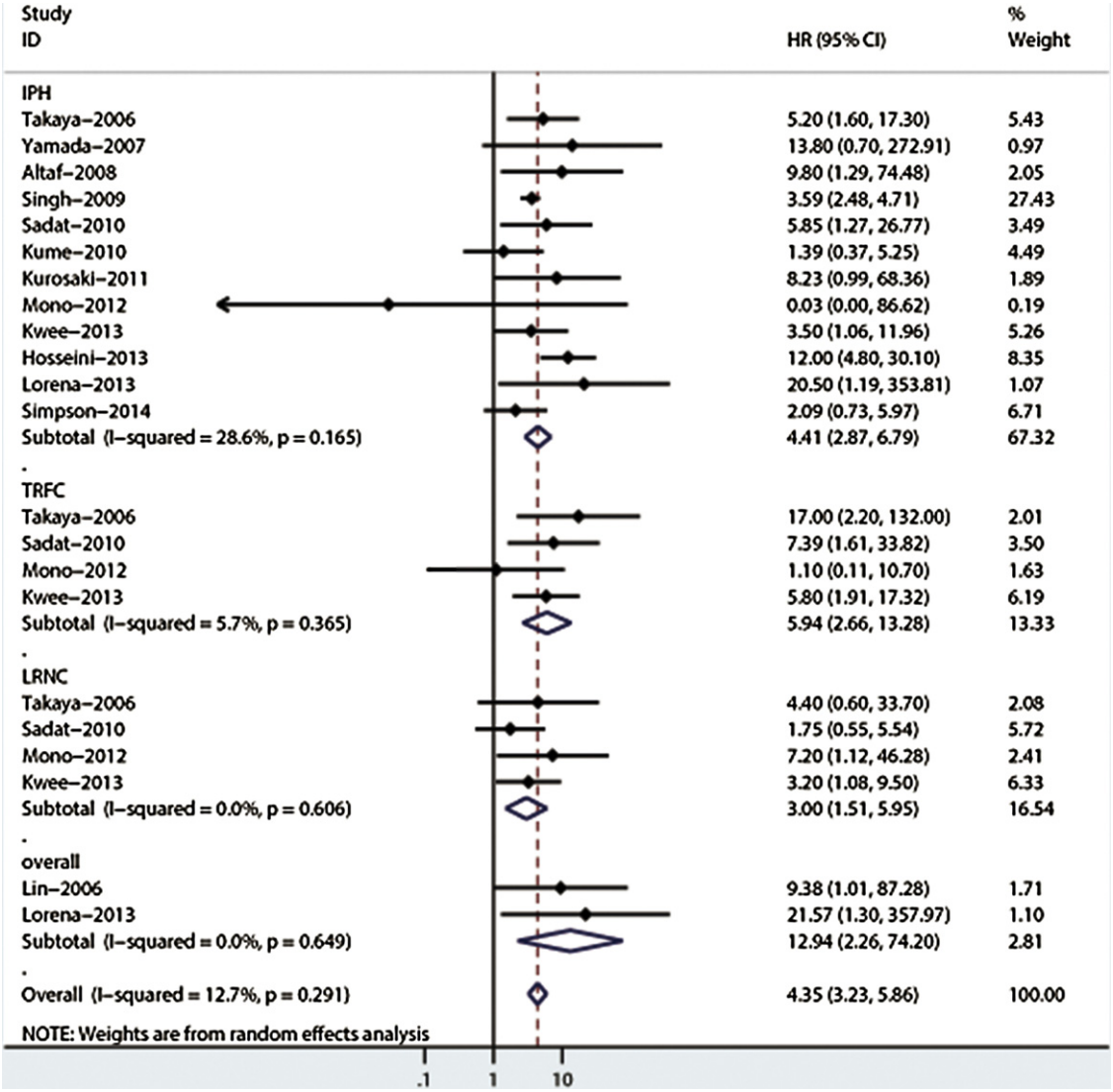

Fig. 2. Forrest plot for the risk associated with the presence of carotid plaque components.

Clinical utility of carotid plaque MRI

The probability modifying plot is a graphical sensitivity analysis of predictive value across a prevalence continuum defining low to high-risk populations (Fig. 5). The positive IPH on MRI could increase the post-test probability to 42 and 87% in patients with a pre-test probability of 25 and 75%, respectively. The negative IPH on MRI could decrease the post-test probability to 48 and 9% in patients with a pre-test probability of 75 and 25%, respectively. The likelihood ratio matrix shows summary point of likelihood ratios obtained as functions of mean sensitivity and specificity in the right lower quadrant suggesting that carotid plaque MRI was limited for confirmation or exclusion of ischemic events (Fig. 6).

Discussion

Plaque composition and specifically vulnerability are increasingly important in identifying patients at risk for cerebrovascular events. Non-invasive imaging might become increasingly important for identifying plaque characteristics in vivo. There has been increasing focus on technical developments in MRI that may allow for the accurate discrimination of tissues found in vulnerable atherosclerotic plaque, such as intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), or thinning/rupture of the fibrous cap (TRFC).

In the current analysis, we systematically evaluated and pooled available evidence on the predictive value of carotid plaque characteristics (specifically IPH) by MRI for the occurrence of cerebrovascular events. Our results indicated that predictive value of carotid plaque MRI is significant for events, with HR of 4.41 for IPH, 5.94 for TRFC and 3.00 for LRNC. Although carotid plaque (IPH) MRI may alter clinical decision making by changing post-probability, it was limited for confirmation or exclusion of cerebrovascular events according to the likelihood ratio matrix.

Despite limited case numbers and wide confidence intervals, the observed predictive values of TRFC/LRNC were promising. A thick fibrous cap appears as a dark band between the bright lumen and grey plaque components, and the absence of this dark band with a bright grey region directly adjacent to the lumen indicates a TRFC. Mitsumori et al. evaluated the accuracy of in vivo multisequence MRI in identifying the TRFC and found good sensitivity (81%) and specificity (90%) [19]. The LRNC appears hyperintense on T1WI and isointense on the TOF scan, with a good correlation between MRI and histology and a high sensitivity and specificity [20].

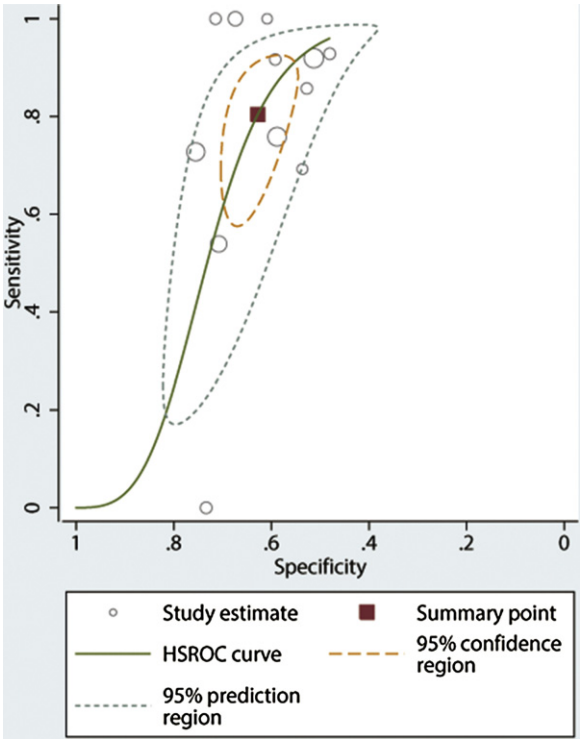

Fig. 3. HSROC curve for prediction of future cerebrovascular events with presence of intraplaque hemorrhage (IPH) on MRI.

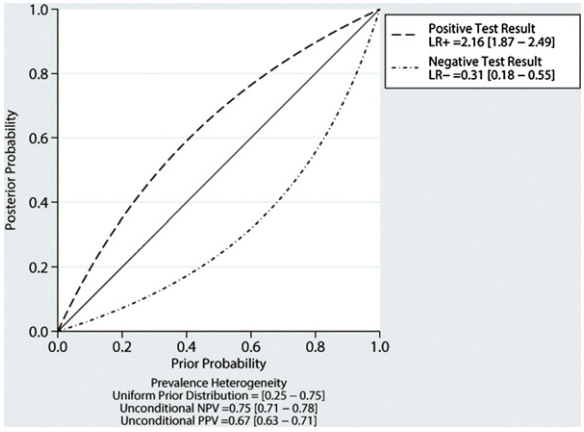

Fig. 5. Relationship between pre-test and post-test probability.

Recent studies suggest that IPH plays a major role in plaque progression and might serve as a measure of risk for the development of future cardiovascular events [21–23]. IPH is defined as the presence of T1W hyperintensity and is often diffuse and located in the LRNC, making it difficult to differentiate. Yuan et al. used a TOF sequence combined with a T1 W sequence to discriminate IPH from LRNC [24]. Although there is still an ongoing controversy over which T1 W sequence is optimal, Saam et al. [23] and our analyses indicate that there is no significant difference in the observed risk between studies with multisequence and that with fat-suppressed T1 W sequence. Although the pre-existing literature shows a controversy regarding the link of IPH with cerebrovascular events, our result indicated a good predictive value of IPH for events with a 4.4-fold higher risk, which is in consistency with Gupta et al. of 4.6. An overlap data was calculated repeatedly (Teng et al. and Sadat et al.) to produce the HR of 5.7 in the study of Saam et al., overestimating the risk of IPH [23]. Additionally, the potential sources of heterogeneity for the pooled risk estimates in the study of Saam et al., such as the proportion of male subjects, symptom status, and sample size, also became not significant after enrolling more studies with 1.150 subjects in our study versus 689 subjects in that study.

We found an absolute annualized event rate of 18.6 versus 3.3% ($P = 0.003$) in subjects with positive versus negative MRI for IPH, which is nearly as same as similar to 17.7 versus 2.4% in the study

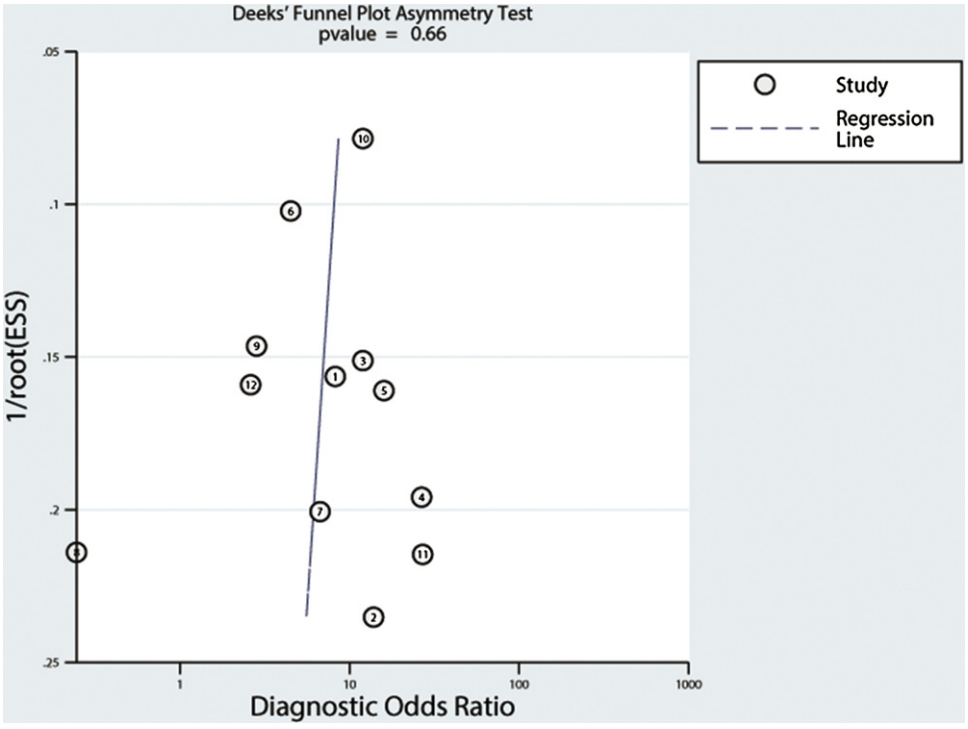

Fig. 4. Funnel plot with superimposed regression line.

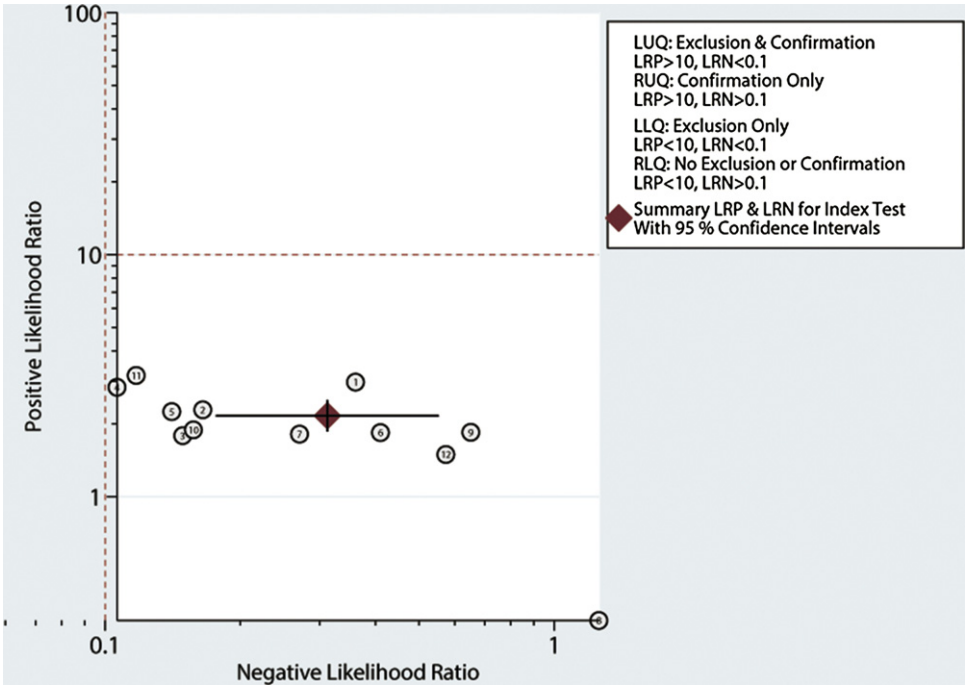

Fig. 6. Likelihood ratio matrix of carotid plaque MRI.

of Saam et al. The event rate in subjects without IPH is relatively low but not zero, indicating risk also dependents of other plaque features, such as TRFC, LRNC, and high-grade stenosis.

In addition to carotid plaque MRI as a routine risk stratification tool, we also highlight potential barriers to the implementation of MRI for confirmation or exclusion of cerebrovascular events.

Our study has limitations. A general limitation of the meta-analysis is that the validity of the results depends on individual original study. First, most studies used a composite measure of stroke/TIA/amaurosis fugax, preventing the accurate calculation of separate HR for stroke, TIA and amaurosis fugax. Second, detailed raw data on test results was not provided, thereby the pooled prevalence of each specific plaque element was not accurately calculated, especially for TRFC and LRNC. Third, our results apply exclusively to patients with > 30% carotid stenosis and cannot be generalized to a population with < 30% stenosis because of as our data is derived from subjects with carotid artery disease of > 30% stenosis. Additionally, MRI protocols were specified in all studies, but slightly different sequences or settings were used.

In summary, we conclude that positive MRI features of carotid plaque including IPH, TRFC, and LRNC are associated with higher risk of cerebrovascular events and may help stratify patients. However, it is limited as a rationale for confirmation or exclusion of future cerebrovascular events in a clinical context.

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