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Diagnostic accuracy of dynamic contrast-enhanced magnetic resonance imaging for distinguishing pseudoprogression from glioma recurrence: a meta-analysis

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Abstract

Background: It is crucial to differentiate accurately glioma recurrence and pseudoprogression which have entirely different prognosis and require different treatment strategies. This study aimed to assess the diagnostic accuracy of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) as a tool for distinguishing glioma recurrence and pseudoprogression.

Methods: According to particular criteria of inclusion and exclusion, related studies up to May 1, 2019, were thoroughly searched from several databases including PubMed, Embase, Cochrane Library, and Chinese biomedical databases. The quality assessment of diagnostic accuracy studies was applied to evaluate the quality of the included studies. By using the "mada" package in R, the heterogeneity, overall sensitivity, specificity, and diagnostic odds ratio were calculated. Moreover, funnel plots were used to visualize and estimate the publication bias in this study. The area under the summary receiver operating characteristic (SROC) curve was computed to display the diagnostic efficiency of DCE-MRI.

Results: In the present meta-analysis, a total of 11 studies covering 616 patients were included. The results showed that the pooled sensitivity, specificity, and diagnostic odds ratio were 0.792 (95% confidence interval [CI] 0.707–0.857), 0.779 (95% CI 0.715–0.832), and 16.219 (97.5% CI 9.123–28.833), respectively. The value of the area under the SROC curve was 0.846. In addition, the SROC curve showed high sensitivities (>0.6) and low false positive rates (<0.5) from most of the included studies, which suggest that the results of our study were reliable. Furthermore, the funnel plot suggested the existence of publication bias.

Conclusions: While the DCE-MRI is not the perfect diagnostic tool for distinguishing glioma recurrence and pseudoprogression, it was capable of improving diagnostic accuracy. Hence, further investigations combining DCE-MRI with other imaging modalities are required to establish an efficient diagnostic method for glioma patients.

Keywords: Meta-analysis; Dynamic contrast-enhanced magnetic resonance imaging; Pseudoprogression; Diagnostic accuracy; Glioma

Introduction

As the most common primary brain tumors, gliomas account for about 80% of all malignant brain tumors as well as 30% of all central nervous system tumors.[1] To date, present standard therapy includes surgical approaches, such as gross total or subtotal excision, followed by concomitant chemo-radiotherapy and temozolomide adjuvant chemotherapy.[2] However, such treatment may cause radiation-induced damage to brain tissue of glioma patients and increase the risk of recurrence. Pseudoprogression is a sub-acute clinical entity, which is characterized by the expansion of existing lesions or the appearance of new lesions within 12 weeks after radiation therapy. In contrast to true tumor progression, the lesions induced by pseudoprogression subsequently stabilize or shrink without further treatment.[3] In several previous reports on glioma patients, the occurrence rate of pseudoprogression is in the range of 15% to 60%.[4-6] In many cases, lesions of pseudoprogression exhibit contrast enhancement on contrast-enhanced magnetic resonance imaging (MRI) or computed tomography, which is similar with those of tumor

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progression.[7,8] Because therapeutic protocols between recurrences and pseudoprogression are totally different, it is important to explore a method for distinguishing them correctly in the treatment of glioma.

As one of the modern imaging tools, the dynamic contrast-enhanced (DCE)-MRI technique has been extensively applied to tumor diagnosis.[9,10] Based on the DCE-MRI, the physician can detect the microcirculation in the tissue of patients by analyzing the changes of some pharmacokinetic parameters, which include the extravascular extracellular space per unit volume of tissue (V_e), the rate transfer constant (K_{ep}), the blood plasma volume per unit volume of tissue (V_p), and the volume transfer constant (K_{trans}). Some previous research studies have suggested that the parameters provided by DCE-MRI, such as V_e and K_{trans}, in pseudoprogression were obviously different from those in true progression.[11,12] Besides, an earlier study conducted by Bisdas *et al*[13] and Haider *et al*[14] demonstrated that the parameters provided by DCE-MRI are capable of diagnosing recurrent and radiation injury. Nevertheless, these studies present a major limitation, that is the small sample size.

The purpose of this meta-analysis was to explore the value of DCE-MRI-derived pharmacokinetic parameters in distinguishing glioma recurrence from pseudoprogression for glioma patients.

Methods

Literature search

Based on the PubMed, Embase, Cochrane Library, and Chinese biomedical databases, relevant articles published before May 1, 2019, were searched comprehensively and systematically. In this study, the search strategy was ("glioma" OR "glioblastoma" OR "brain tumour" OR "brain tumor" OR "astrocytoma" OR "neuroectodermal tumor" OR "neuroectodermal tumour" OR "brain neoplasm" OR "neuroglioma" OR "glial tumor" OR "glial tumour" OR "oligodendroglioma" OR "oligodendrocytoma") AND ("Dynamic contrast enhanced T1 MRI" OR "K_{trans}" OR "DCE") AND ("MRI" OR "magnetic resonance" OR "MR") AND ("pseudoprogression" OR "recurrence" OR "recurrent" OR "tumor progression" OR "postradiation" OR "radiation necrosis" OR "radiation injury"). Only articles published in English were accepted. At the same time, the relevant references listed in the retrieved articles were also widely scanned to seek other articles of possible eligibility.

Study selection

The included studies were in line with the following criteria:

(1) Design of the study: retrospective (R)/prospective (P) study.
(2) Patients: expansion of existing lesions or appearance of new lesions in the radiotherapy target area of glioma patients.
(3) Diagnostic tool: DCE-MRI.
(4) Data: adequate data for calculating true positives (TPs), false positives (FPs), false negatives (FNs), and true negatives (TNs).

The studies with the following characteristics were excluded:

(1) Review articles, abstracts, comments, proceedings, meetings, case reports, and letters.
(2) Studies highly correlated with glioma but without related data for our analysis.

When contradictory results appeared, full discussions were performed to resolve disagreements.

Data extraction and quality assessment

According to the criteria of study selection, we extracted several types of characteristics from the articles, which included study characteristics (name of the first author, source of publication, year of publication, and study design), patient characteristics (age, sex, and numbers of the population), tumor treatment (radiation therapy dose and chemotherapy drug), and parameters of DCE-MRI. The values of TP, FP, FN, and TN were also calculated. The quality of included studies was evaluated by using the quality assessment of diagnostic accuracy studies (QUADAS-2).[15] The included studies were determined based on the consensus of all authors and analyzed by the Review Manager (version 5.3, Cochrane Collaboration, Oxford, UK).

Statistical analysis

In this meta-analysis, data from each included study were analyzed using the bivariate approach of Reitsma *et al*[16] in the R package "mada."[17] Statistical heterogeneity between studies was determined by using Cochran Q-statistic and I^2 statistic. If significant heterogeneity was detected (presence of P value < 0.05 for the Cochran Q test and $I^2 > 50\%$), the DerSimonian and Laird random-effects model was used; in other cases, the Mantel-Haenszel fixed-effects model was applied. Pooled sensitivity, specificity, and their 95% CIs were calculated and shown as forest plots.[18-20] Besides, the summary receiver operating characteristic (SROC) curve area was also calculated. When the values of area under the curve (AUC) was >0.8, the studied parameters were considered to be of great potential for actual clinical application. In addition, publication bias was explored by constructing a funnel plot to visualize the available data and a regression test for the funnel plot to statistically test any asymmetry in the funnel plot with the "meta" R package.[21] Moreover, Deek funnel plot asymmetry test was also applied to assess the publication bias by using the Stata software (version 12.0).[22]

Results

Study selection and summary of included studies

After a comprehensive and systematic search of multiple databases, a total of 509 records were returned. Initially, a

total of 35 publications were identified as duplicate studies and excluded. Afterward, 463 studies were excluded for diverse reasons (not original researches, not relevant studies, or insufficient data) based on their title, abstract, and full text. Finally, the remaining 11 records were included in this meta-analysis.[7,11,12,23-30] More details of the study selection are depicted in Figure 1.

The main characteristics of studies, patients, tumor treatment, and parameters of DCE-MRI in each included study are presented in Table 1. The included studies consisted of two prospective studies and nine retrospective studies, which were published between 2011 and 2019. Moreover, a total of 616 patients with glioma were included in the studies. The gender ratio among studies was comparable. The clinical or history pathology of patients was used as a reference standard for the included studies. Besides, the TP, TN, FP, and FN of each study are also shown in Table 1.

Quality evaluation

We applied QUADAS-2 to assess the quality of the included studies. The result for evaluation of quality is shown in Figure 2. As we can see, there was only one study with a high-risk bias in the reference standard. For applicability concerns, we found that only one study regarding the selection of patient was treated as a high concern for the reference standard. In addition, the overall attributes of the included studies with high, low, or unclear risk of bias are as shown in a graph [Figure 2]. In general, the quality of the included studies was relatively high with a low-risk bias and applicability concerns and met the requirements of this meta-analysis.

Data analysis

As the heterogeneity between the included studies was significant ($I^2 = 77.5\%$ and Cochran-Q <0.05), the

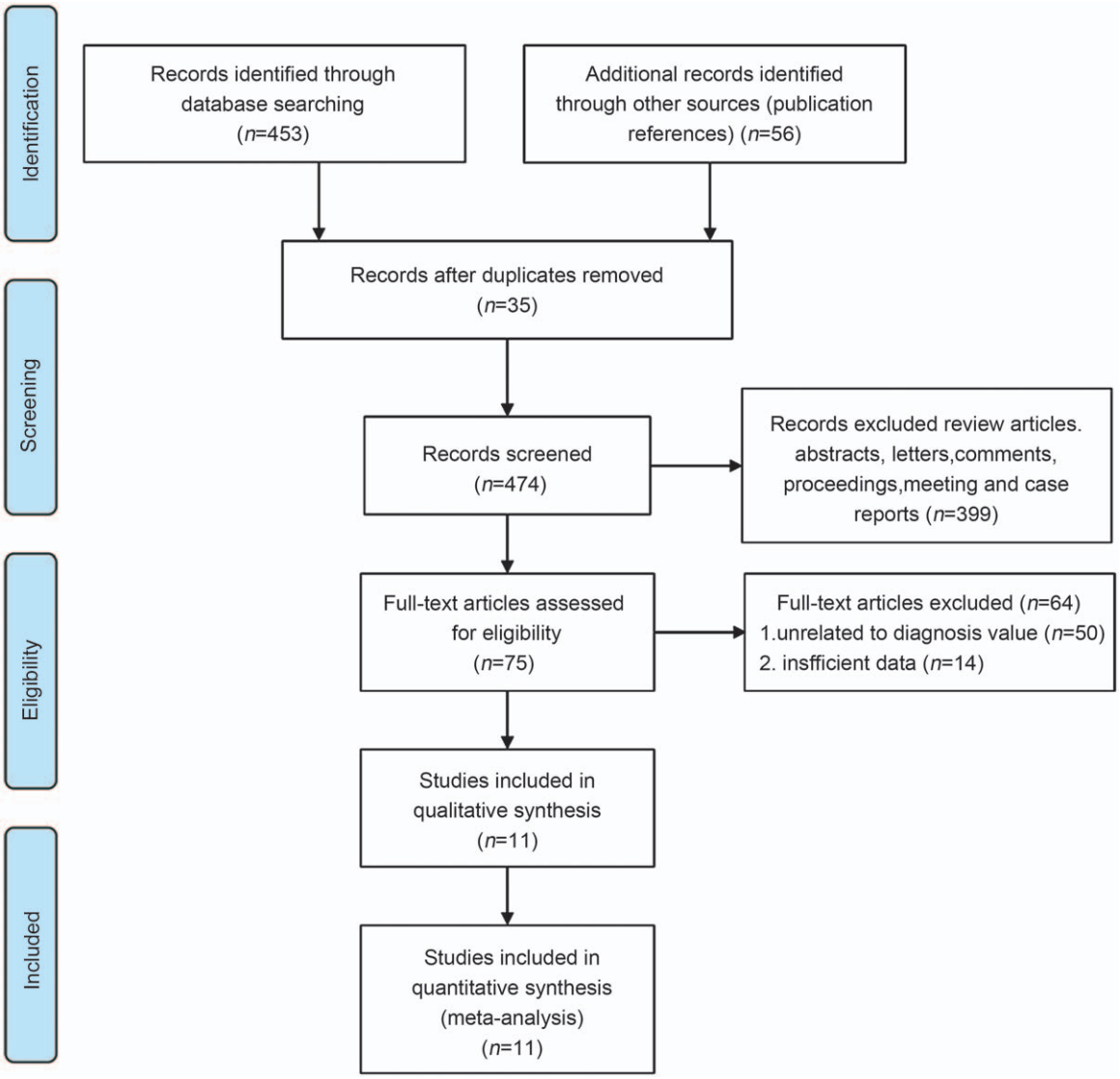

Figure 1: Flow diagram of studies on dynamic contrastenhanced magnetic resonance imaging (DCE-MRI) as a tool for distinguishing glioma recurrence and pseudoprogression identified in meta-analysis.

Table 1: Characteristics of the included studies.

References	Country	Year	Type of study	Case No.	Age (years), mean (range)	Gender (M/F)	Radiotherapy dose (Gy)	Chemotherapy drug	Parameter	TP	FP	TN	FN
Hamilton *et al*[23]	USA	2015	R	24	51	20/4	N/A	TMZ	K_{trans}, K_{ep}, and V_p	12	2	3	7
Yun *et al*[11]	Korea	2015	P	33	54.6 (28–82)	22/11	55.3	TMZ	K_{trans}, V_p	10	1	7	15
Kim *et al*[24]	Korea	2014	R	169	52.2 (25–69)	79/90	59.7	TMZ	AUC (read1)	79	11	8	71
									AUC (read2)	80	13	7	69
Suh *et al*[25]	Korea	2013	R	79	51.2 (25–69)	36/43	59.7	N/A	AUCR50	38	6	4	31
									mAUCRH	37	6	5	31
Narang *et al*[26]	USA	2011	R	29	51.9 (18–70)	16/13	N/A	N/A	nSDEP, MSIVP, and nMSIVP	19	2	1	7
Thomas *et al*[12]	USA	2015	R	37	63 (37–87)	25/12	N/A	TMZ	V_p	19	5	2	11
									K_{trans}	17	7	3	10
Zakhari *et al*[27]	Canada	2019	P	66	54.1	43/23	60	TMZ	K_{trans}	19	9	18	19
									V_p	11	0	16	28
									AUC	32	15	5	13
Nam *et al*[28]	Korea	2017	R	37	57	26/11	N/A	TMZ	K_{trans}	8	3	7	19
									K_{ep}	12	8	3	14
Nael *et al*[29]	USA	2017	R	46	56.8 (32–78)	28/18	59.4–60	TMZ	K_{trans}	23	2	11	10
Chung *et al*[7]	Korea	2013	R	57	50.9 (25-69)	30/27	59.3/59.5	TMZ	mAUCRH	30	3	2	22
									AUCR90	29	3	3	22
Seeger *et al*[30]	Germany	2013	R	40	53.8	24/16	N/A	N/A	K_{trans}	14	3	9	14

AUCR50/90 is one of the cumulative histogram parameters. AUC: Area under the curve; FN: False negative; FP: False positive; K_{ep}: The rate transfer constant; K_{trans}: The volume transfer constant; mAUCRH: Mean area under the time signal-intensity curves ratio at a higher curve; MSIVP: Maximum slope of enhancement in initial vascular phase; nMSIVP: Normalized maximum slope of enhancement in initial vascular phase; nSDEP: Normalized slope of delayed equilibrium phase; P: Prospective study; R: Retrospective study; TMZ: Temozolomide; TN: True negative; TP: True positive; V_p: The extravascular extracellular space per unit volume of tissue.

random-effects model was used in the current analysis. As shown in Figure 3, the overall sensitivity and specificity for differentiating recurrent glioma from pseudoprogression by DCE-MRI were 0.792 (95% CI 0.707–0.857) and 0.779 (95% CI 0.715–0.832), respectively. The analysis of the variability by visual evaluation of the paired forest plots indicated low variability for sensitivity and moderate variability for specificity.

A diagnostic odds ratio of 16.219 (97.5% CI 9.123–28.833) was recorded; this value indicates that the likelihood of the distinction of recurrent glioma from pseudoprogression was approximately 16 times higher using DCE-MRI. The large CI observed was the result of the small study size.

In addition, the SROC curve obtained by the bivariate model is as depicted in Figure 4. The AUC value of the SROC curve was 0.846. Overall, the SROC curve indicated high sensitivities (>0.6) and low FPRs (FPRs = 1–specificity) (<0.5) from most of the included studies.

The slope of the curve was substantially parabolic indicating that sensitivity was dependent on specificity. The sensitivity was very similar across studies while the specificity varied markedly. These results indicate the accuracy of DCE-MRI in the differential diagnostic of recurrent glioma from pseudoprogression.

Evaluation of study heterogeneity

We performed a crosshair plot to show the sensitivity and FPR of each included study. To acquire a view of the scatter of the study results, each study was plotted as a single sensitivity–FPR point along with 95% CIs. As shown in Figure 5, the crosshair of studies from Suh *et al*,[25] Kim *et al*,[24] and Chung *et al*[7] were very close to each other, showing similar sensitivity and specificity; and the specificity of the CIs reported by Suh *et al*[25] was wider than those reported by the other two studies. Meanwhile, we also found that the crosshairs of Seeger *et al*[30] conferred similar sensitivity and specificity with that of Nael *et al*,[29] and the study of Seeger *et al*[29] had a wider specificity for the CIs than Nael *et al*.[29] Besides, there were no significant differences between the specificity values of the 11 included studies in our analysis, while the sensitivity values were significantly different from the specificity values. However, the heterogeneity of the included studies was significant ($I^2 = 77.5\%$).

Publication bias

As shown in Figure 6, the publication bias of this meta-analysis was assessed by constructing funnel plots. The result for the bias test from the "meta" R package showed that the included studies' outcomes exhibited publication bias ($t = 3.21$; $P = 0.005$). Meanwhile, Deek test showed a similar result ($P = 0.01$) [Figure 7], suggesting publication bias in the outcomes of the included studies.

Discussion

The misdiagnosis of pseudoprogression or true progression might lead to wrong clinical treatment decisions and unnecessary surgery; thus, it is urgent to explore an accurate method to distinguish pseudoprogression from tumor recurrence in glioma treatment. As known, changes in the contrast-enhancement area on MRI are commonly used as an indicator for the therapy response or tumor relapse in patients, but conventional MRI cannot correctly differentiate tumor recurrence from pseudoprogression.

As with the development of MRI technology, several advanced MRI modalities appeared in recent years, such as

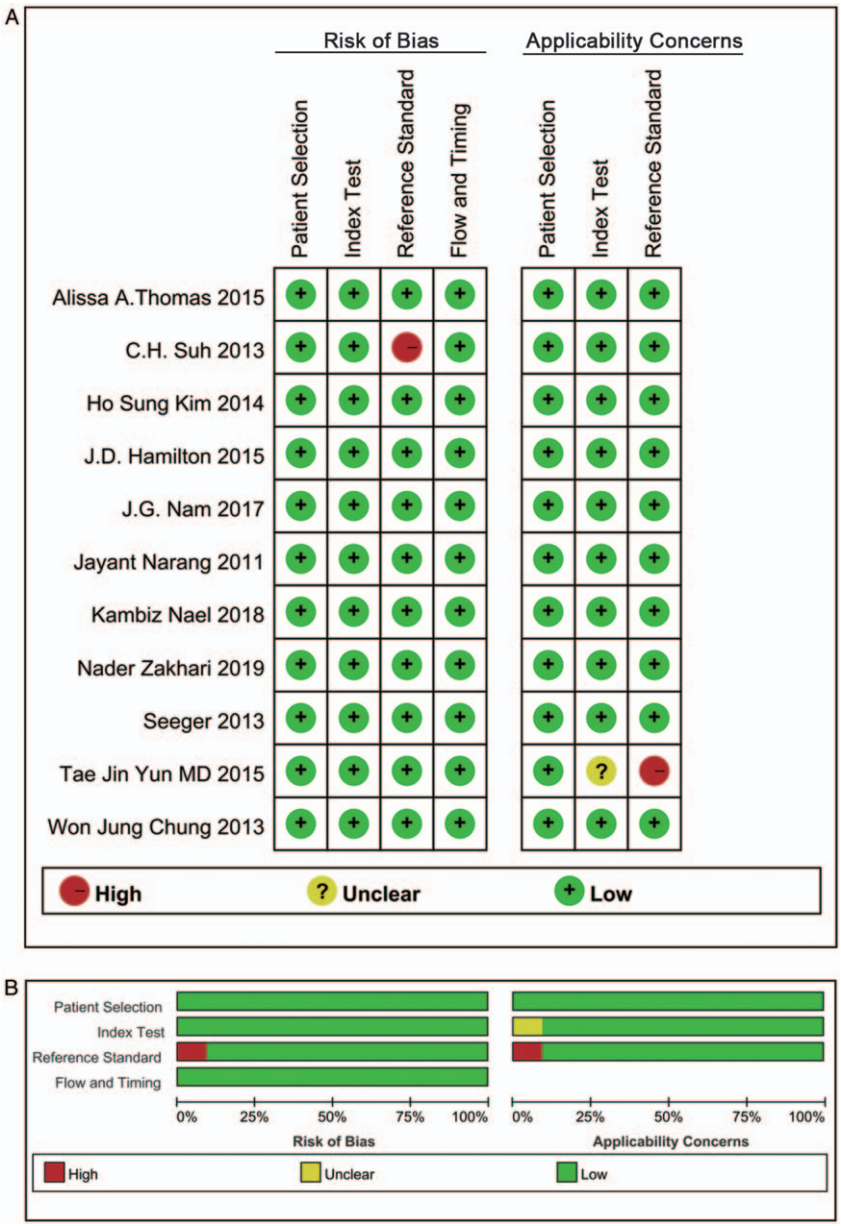

Figure 2: The methodological quality (A) summary and (B) graph of the included studies using the QUADAS-2 tool. Green, red, and yellow circles represent good, low, and unclear (left) risk of bias or (right) applicability concerns, respectively. QUADAS-2: Quality assessment of diagnostic accuracy studies.

the DCE-MRI and dynamic susceptibility contrast (DSC)-MRI. Compared with the DSC-MRI, the DCE-MRI has distinct advantages with greater spatial resolution, better estimations of vascular leakiness, and less artifact from sources of susceptibility.[31] Some clinical studies indicated that DCE-MRI might provide useful information for the prognosis of glioma models or patients.[32,33] A research of Hou *et al*[34] revealed that DCE-MRI could be used to evaluate the hypoxia status of the glioma model. Meanwhile, a previous study conducted by Thomas *et al*[12] revealed that the lower mean and 90th percentile values for both V_p and K_{trans} showed a correlation with pseudoprogression. Besides, the study also suggested that the parameters of DCE-MRI, V_p ratio, and K_{trans} ratio could be used as predictors for the determination of lesion etiology.

In this study, our findings suggest that DCE-MRI could aid in distinguishing recurrence from pseudoprogression in glioma patients. The DCE-MRI showed high sensitivity (0.792) and specificity (0.779). These data indicate that the DCE-MRI could be used as a diagnostic tool for differentiating recurrent and pseudoprogression in patients with glioma.

There are several strengths in this meta-analysis. First, to reduce the risk of selection bias, the study selection, data extraction as well as evaluation of the risk of bias were conducted by the three authors respectively and independently. Besides, all the included studies were highly correlated with the diagnostic value of DCE-MRI for recurrence, radiation injury, or/and pseudoprogression in glioma patients. In addition, this meta-analysis assessed the

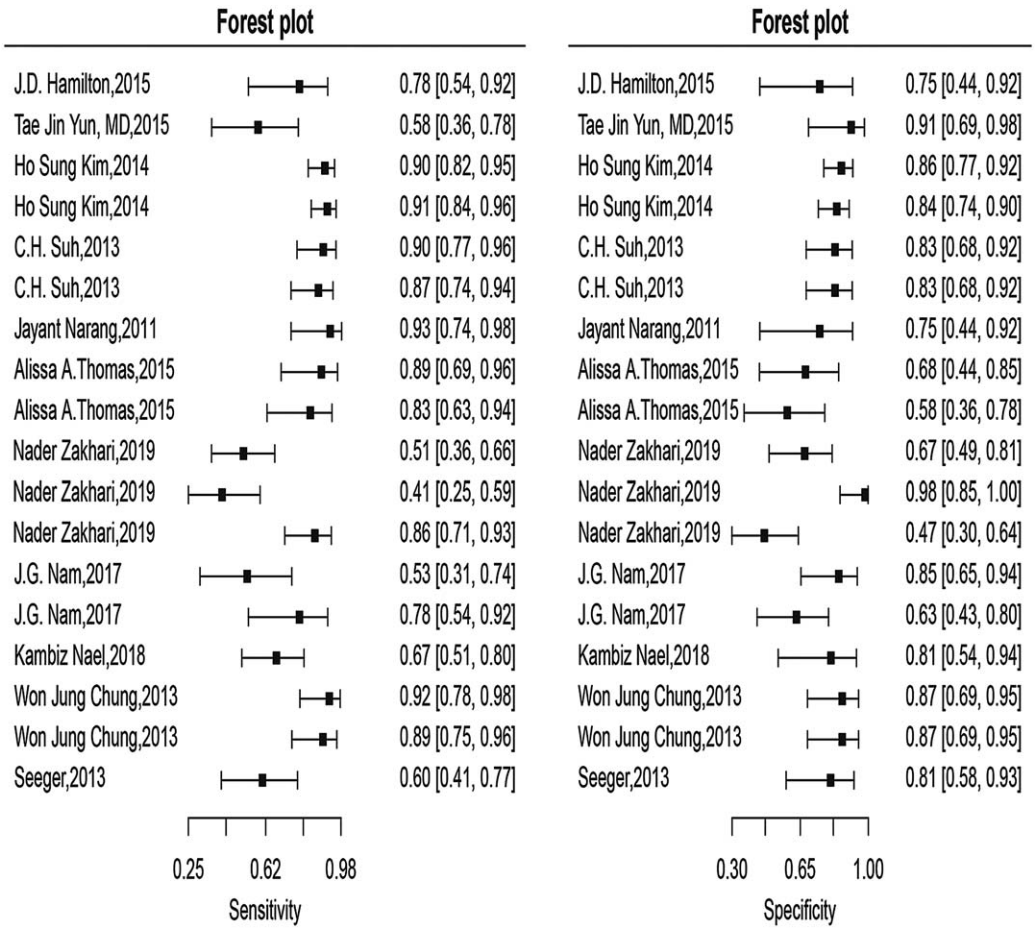

Figure 3: Paired forest plots indicating the sensitivity and the specificity of the DCE for differentiating recurrent glioma from pseudoprogression. DCE: Dynamic contrast-enhanced.

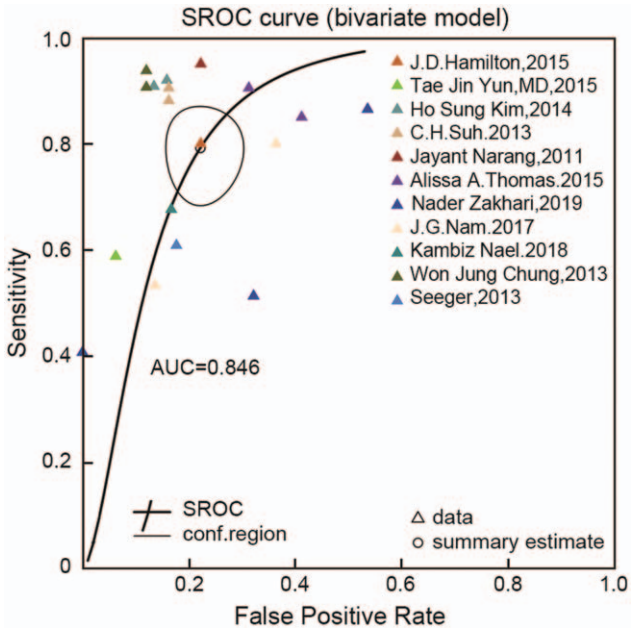

Figure 4: SROC curve with individual study outcomes. SROC: Summary receiver operating characteristic.

diagnostic value of DCE-MRI for distinguishing glioma recurrence from pseudoprogression in patients. Furthermore, this meta-analysis is rigorously in compliance with the preferred reporting items for systematic reviews and meta-analyses protocols.[35,36]

However, our meta-analysis still presents some limitations. There is obvious heterogeneity across the included studies in the current meta-analysis; thus, the results from the analysis should be explained more cautiously. First, the number of studies that meet the inclusion criteria of this meta-analysis is limited, and the small number of cases may slightly reduce the reliability of the results. Second, most of the included studies were retrospective researches, except for two that were prospective researches. Third, the various clinical characteristics of the study cases, such as age, radiotherapy dose, and chemotherapy, could be significant sources of heterogeneity because treatment methods and age are correlated with recurrence and pseudoprogression in glioma. Finally, this meta-analysis only included English language literature, which might lead to missing some other articles and hence result in the publication bias in this meta-analysis. Nevertheless, we believe the results of this study are valuable as the exclusion of non-English publications from systematic reviews had a minimal effect on overall conclusions.[37]

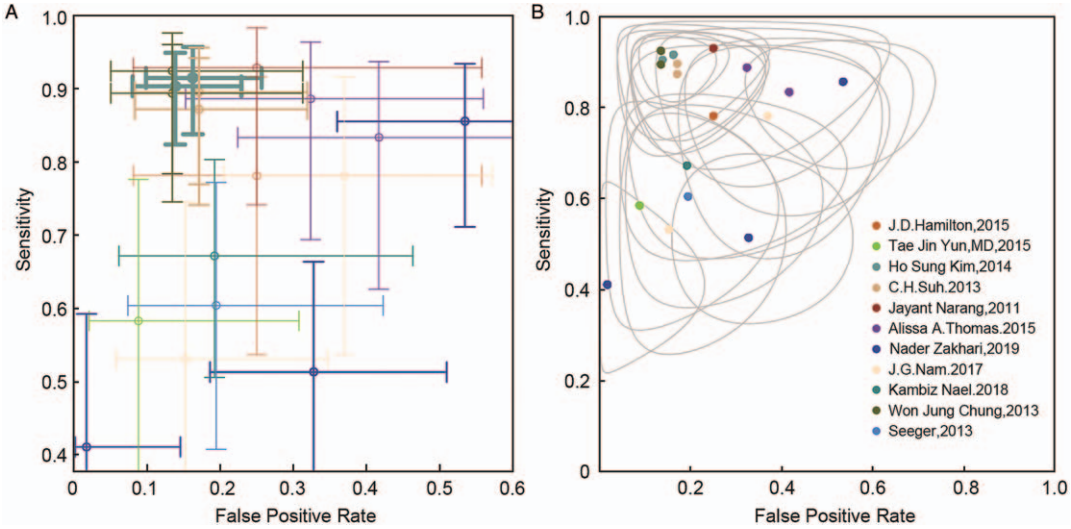

Figure 5: Crosshair plot of individual study outcomes representing the sensitivity and FPR (FPR = 1–specificity) (A) and a plot with confidence regions (B) for each study. FPR: False positive rate.

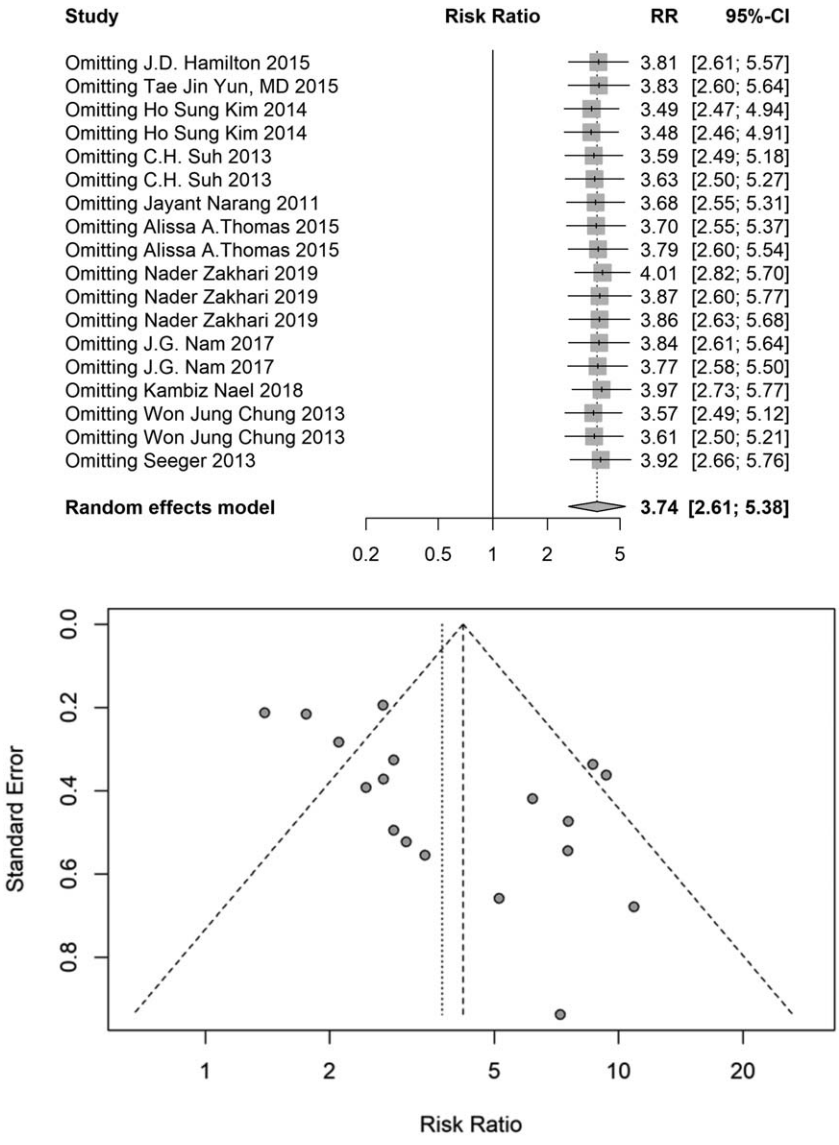

Figure 6: Funnel plot.

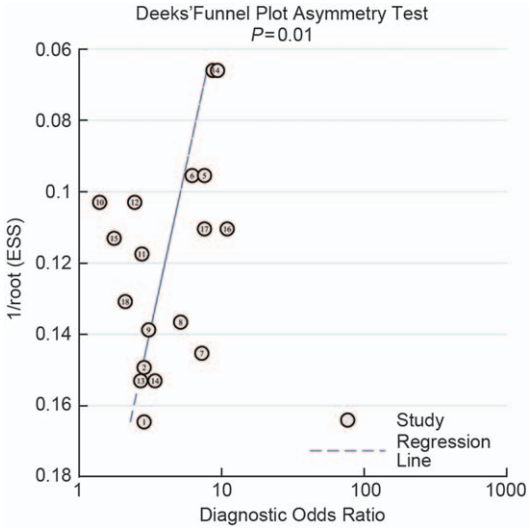

Figure 7: Deek funnel plot.

Furthermore, as the sample size of the included studies is relatively small, we did not perform subgroup analysis.

In summary, DCE-MRI showed the potential for improvement of the diagnostic accuracy in distinguishing glioma recurrence from pseudoprogression. However, owing to the drawbacks of our study as listed earlier, additional studies with larger sample sizes would be required to obtain a more credible result. Moreover, further investigations on diagnosis efficiency of combining the DCE-MRI with other imaging modalities might aid in establishing an efficient diagnostic method for distinguishing glioma recurrence from pseudoprogression in glioma patients.

Conflicts of interest

None.

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