Systematic Review and Meta-Analysis

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Accuracy of ADC derived from DWI for differentiating high-grade from low-grade gliomas

Systematic review and meta-analysis

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Abstract

Objective: Quantitative apparent diffusion coefficient (ADC) values of diffusion weighted imaging (DWI) could be applied to grade gliomas. This meta-analysis was conducted to assess the accuracy of ADC analysis in differentiating high-grade (HGGs) from low-grade gliomas (LGGs).

Methods: PubMed, Cochrane library, Science Direct, and Embase were searched to identify suitable studies up to September 1, 2018. The quality of studies was evaluated by the quality assessment of diagnostic accuracy studies (QUADAS 2). We estimated the pooled sensitivity, specificity, positive and negative likelihood ratios (LR), diagnostic accuracy ratio (DOR) with 95% confidence intervals (CI), and determined the accuracy of the data by using the summary receiver operating characteristic (SROC) and calculating the area under the curve (AUC) to identity the accuracy of ADC analysis in grading gliomas.

Results: Eighteen studies including 1172 patients were included and analyzed. The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC with 95% CIs of DWI with *b* values of 1000 s/mm^2 for separating HGGs from LGGs were 0.81 (95% CI 0.75–0.86), 0.87 (95% CI 0.81–0.91), 6.1 (95% CI 4.2–8.9), 0.22 (95% CI 0.17–0.29), 28 (95% CI 17–45), and 0.91 (95% CI 0.88–0.93), respectively. DWI with *b* values of 3000 s/mm^2 showed slightly higher accuracy than that of 1000 (sensitivity 0.80, specificity 0.90 and AUC 0.92). Meta-regression analyses showed that field strengths and *b* values had significant impacts on diagnostic efficacy. Deeks testing confirmed no significant publication bias in all studies.

Conclusions: This meta-analysis suggested that ADC analysis of DWI have high accuracy in differentiating HGGs from LGGs. Standardized methodology is warranted to guide the use of this technique for clinical decision-making.

Abbreviations: ADC = apparent diffusion coefficient, AUC = area under the curve, CI = confidence intervals, DOR = diagnostic accuracy ratio, DTI = diffusion tensor imaging, DWI = diffusion weighted imaging, FN = false negative, FP = false-positive, HGG = high-grade glioma, LGG = low-grade glioma, LR = likelihood ratios, MRI = magnetic resonance imaging, PWI = perfusion-weighted imaging, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, SROC = summary receiver operating characteristic, TN = true-negative, TP = true positive.

Keywords: apparent diffusion coefficient, diffusion weighted imaging, glioma, meta-analysis

1. Introduction

Gliomas are the most common vtype of primary malignant brain tumor. According to the 2007 World Health Organization (WHO) tumor classification, gliomas are categorized into grades I–IV, where III–IV are high-grade gliomas (HGGs), and I–II are low-grade gliomas (LGGs).[1] HGG is highly aggressive tumor, which exhibit great aggression and proliferative activity and has a dismal prognosis despite various therapeutic managements. While LGG is low malignant tumor associated with a longer life expectancy.[2–4] Surgical resection is the preferred treatment for most gliomas. After surgery, HGG normally requires adjuvant therapy, such as radiotherapy and chemotherapy to prevent rapid recurrence, while LGG is usually followed by close observation.[5] Due to the high malignancy of HGG, complete surgical resection of tumor is critical for individualizing therapeutic strategies. Hence, identification of tumor level prior to surgery is of important significance for intraoperative decision-making.

Magnetic resonance imaging (MRI) is the imaging method of first choice for depicting gliomas. Most assessments used to differentiate gliomas were based on contrast enhancement of the

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tumor.[6] With the development of technology, several physiological MRI techniques including MR spectroscopy, diffusion-weighted imaging (DWI), and perfusion-weighted imaging (PWI), have also been applied to grading gliomas.[7,8] The ADC derived from DWI is negatively correlated with cell proliferation indices, which has shown increasing potential as a noninvasive imaging biomarker for preoperative tumor grading.[9,10] Various studies have investigated the role of DWI with quantitative ADC in the differentiation between HGGs from LGGs.[11,12] However, these studies were inconclusive because of insufficient sample and different diagnostic algorithms. The aim of this meta-analysis was to systematically evaluate the accuracy of DWI- derived ADC for discriminating HGGs from LGGs.

2. Methods

2.1. Search strategy

As this is a meta-analysis, ethical approval was not necessary. This systematic review and the meta-analysis was performed following the guidelines for the diagnostic studies.[13]

PubMed, Cochrane library, Science Direct, and Embase were searched on September 1, 2018, and no start date limit was applied. The search key words were "diffusion weighted imaging," "DWI," "apparent diffusion coefficient," "glioma," "brain neoplasm," and "brain tumor." No language restriction was exposed. Reference lists of relevant articles were also manually searched. Two reviewers independently reviewed the articles. Disagreements were resolved by consensus.

2.2. Study selection criteria

The studies were selected on the basis of the following criteria:

1. Clinical trials assessing the diagnostic accuracy of DWI for differentiating HGGs from LGGs;
2. using histopathology as criterion standard;
3. Sufficient information to calculate true positive (TP), false-positive (FP), true-negative (TN), and false negative (FN).

Excluded criteria: combination with other methods, animal studies, case reports, abstracts, without sufficient calculable data, duplicated reports, or studies based on the same study.

One author (Wang QP) conducted the initial searching according to the inclusion and exclusion criteria. Then, two investigators (Lei DQ and Yuan Y) independently examined all potentially relevant articles. Disagreements were resolved by consensus.

2.3. Date extraction and quality assessment

Two investigators (Wang QP and Lei DQ) independently assessed the quality and potential bias and extracted the data of included studies. We extracted the following data: first author, year of publication, country, study design (retrospective or prospective), sample size, patient age, MRI field strengths, *b* values, mean ADC, cut-off values, TP, FP, TN, FN, sensitivity, and specificity values in regards to tumor grading. If the TP, FP, TN, and FN were not reported, we calculated backwards using indexes including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

The quality of each study was assessed based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) guidelines, which is an established, evidence-based tool for systematic reviews of diagnostic studies designed.

2.4. Statistical analysis

Meta-analyses were performed using the software Stata 11.0. The pooled sensitivity, specificity, positive and negative likelihood ratios (LRs), and diagnostic odds ratio (DOR) were calculated using the extracted data of TP, TN, FP, and FN. The accuracy of the data was determined using a summary receiver operating characteristic plot (SROC) and summarizing that curve by calculating the area under the curve (AUC). In general, a diagnostic tool is regarded failed when AUC values were between 0.5 and 0.6, poor when AUC values were between 0.6 and 0.7, fair when AUC values were between 0.7 and 0.8, good when AUC values were between 0.8 and 0.9, and excellent when AUC values were between 0.9 and 1.[14]

2.5. Meta-regression and subgroup analyses

We performed meta-regression and subgroup analyses to observe the effects caused by substantial heterogeneity of the different diagnostic algorithms. Studies were grouped based on MRI performed at different field strengths (3.0 or 1.5 T), study design (retrospective or prospective) and *b* values (3000 or 1000 s/mm^2).

2.6. Publication bias

The publication bias was assessed using Deeks funnel plot asymmetry test, where $P < .05$ suggests a potential publication bias.

3. Results

3.1. Literature research

A total of 181 studies were initially identified using the above mentioned search strategy, which were then screened in title and abstract. Of these, 75 articles were further evaluated in full text. According to the inclusion criteria, 18 studies[7,11,12,15–29] were retrieved. Five articles were excluded because relevant data could not be extracted. Three studies which could not provide enough data to construct the 2×2 table were also excluded. The study selection process is shown in Figure 1.

3.2. Study characteristics

Ultimately, 18 studies with 1172 participants were enrolled in this meta-analysis. The detailed characteristics of included studies were given in Table 1. Three studies were prospective and others were retrospective cohort studies. The MR examinations were performed on a 1.5 T scanner in eight studies, 3.0 T in nine studies and one study not mentioned. ADC maps were generated from DWI in the *b*-value of 1000 s/mm^2 in 13 studies and 3000 s/mm^2 in 1 study. Four studies evaluated the diagnostic performance of ADC maps at these two *b* values. The mean ADC values of HGGs and LGGs ranged from 0.647–1.274 and 0.863–1.534, respectively. Eight studies took minimum ADC as differentiation criterion with cut-off values ranging from 0.216 to 1.60. Three studies used ADC ratio (ADCR) as differentiation criterion and the cut-off values ranged from 0.86 to 1.50. Mean ADC values

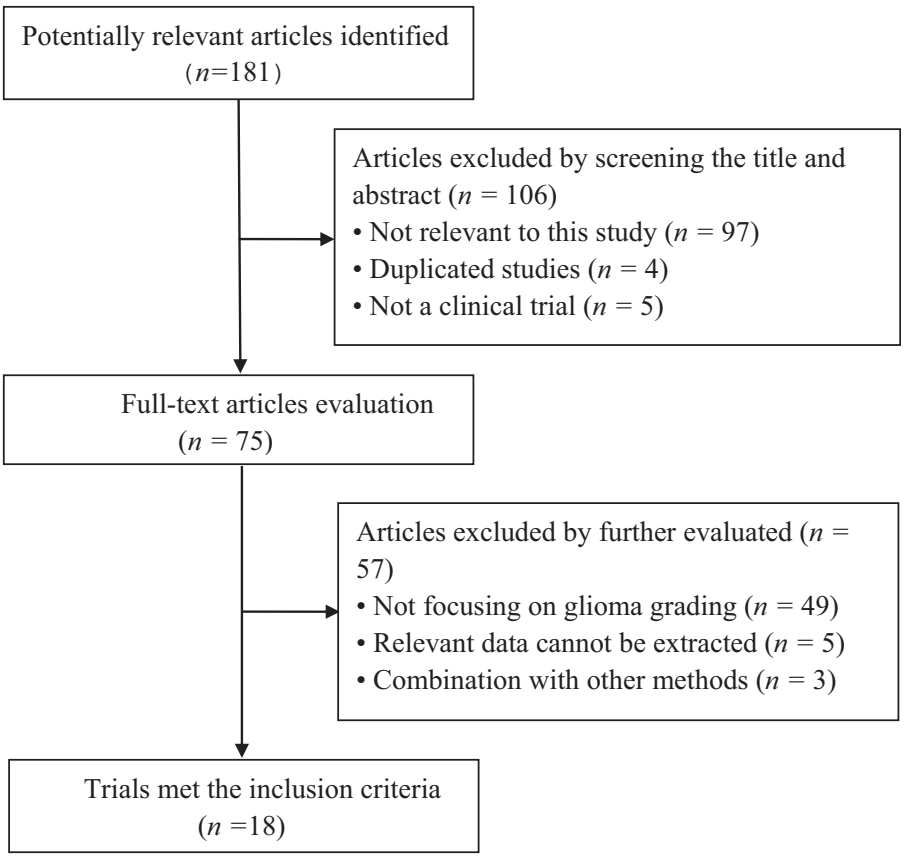

Figure 1. Results of literature search.

Table 1

Baseline characteristics of included studies.

First author	Year	Country	Study design	No. of patients	No. of HGGs	No. of LGGs	Field strengths	Mean age (SD or range)	*b* values (s/mm^2)	Mean ADC of HGGs	Mean ADC of LGGs	Cut-off value
Lee EJ	2008	Canada	re	118	107	11	1.5 T	42	1000	1.035 (0.9–1.240)	1.19 (1.03–1.725)	min ADC 1.06
Chen ZY	2009	China	re	110	48	62	3.0 T	40.4	1000	0.773 ± 0.175	1.057 ± 0.299	min ADC 0.9
Murakami R	2009	Japan	re	50	34	16	1.5 T	53	1000	NA	NA	min ADC 1.16
Andres server	2011	Norway	re	74	59	15	1.5 T	HGG:60.6 ± 14.27 LGG:49.0 ± 15.00	1000	0.986 ± 0.274	1.179 ± 0.206	min ADC 1.07
Kang Y	2011	Korea	re	27	21	6	1.5 T	NA	1000	1.274 ± 0.259	1.094 ± 0.161	min ADC 0.702
									3000	0.829 ± 0.115	0.863 ± 0.116	min ADC 0.440
Chih-Chun WU	2012	China	re	135	94	41	1.5 T	1–80	1000	1.06–1.28	1.74–2.00	ADCR 1.5
Ryu YJ	2014	Korea	re	40	32	8	1.5 T	NA	1000	0.836 ± 0.235	1.030 ± 0.185	ADCR 0.86
M. de fatima va	2014	Brazil	re	38	22	16	1.5 T	36.23 ± 16.95	1000	1.193 ± 0.279	1.534 ± 0.382	min ADC 1.60
Xiao HF	2015	China	pro	43	24	19	3.0 T	43.3 (6–74)	1000	1.204 ± 0.188	1.418 ± 0.375	mean ADC 0.76
Arevalo-Perez J	2015	USA	re	63	43	20	1.5 T	54.3	1000	0.804 ± 0.254	1.356 ± 0.386	min ADC 1.08
Bai Y	2015	China	re	62	34	28	3.0 T	46 (25–68)	3000	NA	NA	mean ADC 0.70
Han H	2017	China	re	39	13	26	3.0 T	NA	1000	0.868 ± 0.172	1.423 ± 0.519	mean ADC 1.161
									3000	0.647 ± 0.136	1.046 ± 0.286	mean ADC 0.814
Hu YC	2017	China	re	109	81	28	NA	46.9 ± 17.2	1000	0.895 ± 0.192	1.364 ± 0.334	mean ADC 1.115
									3000	0.982 ± 0.230	0.647 ± 0.148	mean ADC 0.763
Zeng Q	2017	China	pro	63	45	18	3.0 T	47 (26–76)	1000	1.106 ± 0.263	1.437 ± 0.269	mean ADC 1.128
									3000	0.745 ± 0.165	1.008 ± 0.149	mean ADC 0.875
Wang S	2018	China	re	30	18	12	3.0 T	47.6 ± 15.1	1000	1.25 ± 0.38	1.38 ± 0.21	min ADC 0.216
Cao M	2018	China	pro	50	31	19	3.0 T	53.2 ± 16.4	1000	1.03	1.26	mean ADC 1.252
Chen X	2018	China	re	72	38	34	3.0 T	45.5 (11–70)	1000	0.869 ± 0.207	1.433 ± 0.433	mean ADC 1.065
Xu J	2018	China	re	49	29	20	3.0 T	45 (13–71)	1000	0.98 ± 0.23	1.35 ± 0.23	ADCR 1.497

ADC = apparent diffusion coefficient, ADCR = ADC ratio, HGG = high grade gliomas, LGG = low grade gliomas, min = minimum, NA = not mentioned, pro = prospective, re = retrospective, SD = standard deviation, T = Tesla.

Table 2

Results of the QUADAS-2 quality assessment of included studies.

		Risk of bias			Applicability concerns			
First author	Year	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Lee EJ	2008	+	+	−	+	+	?	+
Chen ZY	2009	+	−	+	?	+	+	+
Murakami R	2009	+		?	+	−	+	+
Andres server	2011	+	−	+	+	+	?	+
Kang Y	2011	−	+	+	?	+	+	+
Chih-Chun WU	2012	+	?	+	+	+	+	−
Ryu YJ	2014	+	+	?	+	+	?	+
M. de fatima va	2014	+	+	−	+	?	+	+
Xiao HF	2015	+	+	?	+	−	+	+
Arevalo-Perez J	2015	+	+	+	?	+	+	+
Bai Y	2015	+	?	+	?	+	+	+
Han H	2017	+	+	?	+	?	+	+
Hu YC	2017	+	+	−	+	+	?	+
Zeng Q	2017	+	+	?	+	+	+	+
Wang S	2018	?	+	+	+	+	−	−
Cao M	2018	+	+	?	+	?	+	+
Chen X	2018	+	+	+	−	+	+	+
Xu J	2018	+	?	+	+	+	+	+

+ = low risk, − = high risk, ? = unclear risk.

were taken as differentiation criterion in 7 studies and the cut-off values ranged from 0.70 to 1.252.

3.3. Quality of included studies

The quality assessment of included studies is presented in Table 2 using QUADAS checklist. Overall, the study quality was satisfactory.

3.4. Pooled results of ADC_{3000}

Five studies evaluated the diagnostic performance of ADC maps at *b* values of 3000 s/mm^2. The pooled sensitivity and specificity of DWI for separating HGGs from LGGs were 0.80 (95% CI 0.74–0.85) and 0.90 (95% CI 0.82–0.94), respectively. The forest plots were shown in Figure 2. The pooled PLR and NLR were 7.7 (95% CI 4.4–13.6) and 0.22 (95% CI 0.16–0.29),

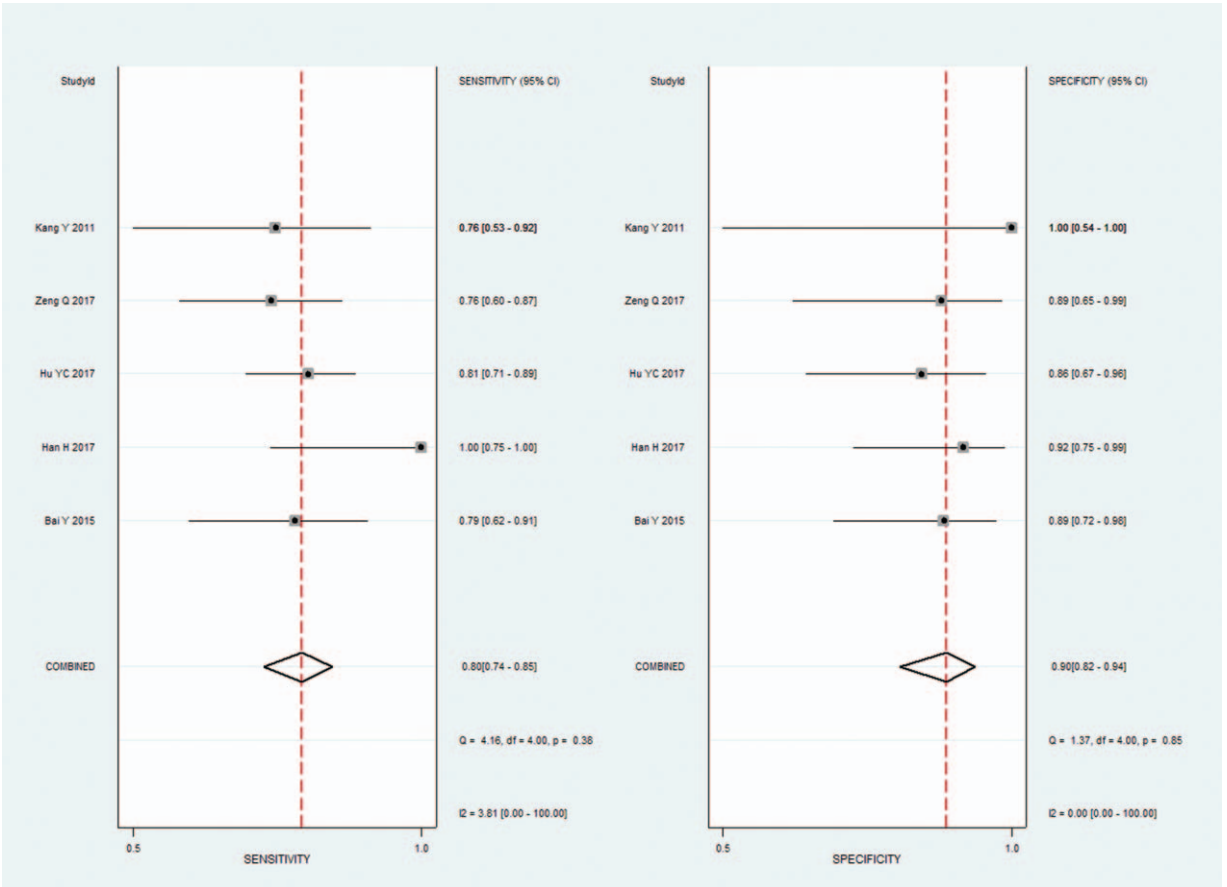

Figure 2. Pooled estimates of diagnostic performance of ADC values derived from DWI at *b* values of 3000 s/mm^2 to differentiate high-grade from low-grade gliomas.

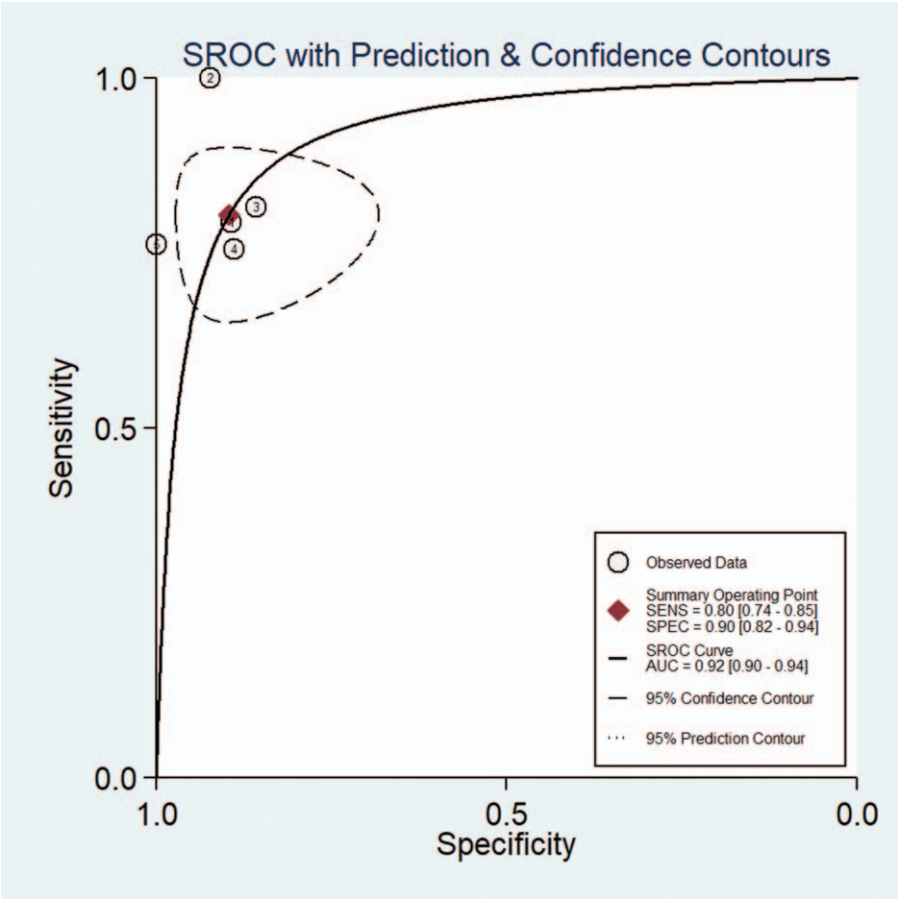

Figure 3. Summary receiver operating characteristics (SROC) curve of ADC values derived from DWI at *b* values of 3000 s/mm^2 to differentiate high-grade from low-grade gliomas.

respectively. The DOR was 35 (95% CI 17–73). The AUC was 0.92 (95% CI 0.90–0.94). The SROC curve was shown in Figure 3. The results demonstrating excellent diagnostic performance of ADC derived from DWI with *b* values of 3000 s/mm^2 in discrimination of HGGs from LGGs.

3.5. Pooled results of ADC_{1000}

Seventeen studies evaluated the diagnostic performance of ADC maps at *b* values of 1000 s/mm^2. The pooled sensitivity, specificity, PLR, NLR, and DOR with 95% CIs of DWI with *b* values of 1000 s/mm^2 for separating HGGs from LGGs were 0.81 (95% CI 0.75–0.86), 0.87 (95% CI 0.81–0.91), 6.1 (95% CI 4.2–8.9), 0.22 (95% CI 0.17–0.29), and 28 (95% CI 17–45), respectively. The forest plots were shown in Figure 4. The SROC curve analysis was used to summarize overall diagnostic accuracy. The AUC was 0.91 (95% CI 0.88–0.93). The SROC curve was shown in Figure 5. ADC_{1000} showed high diagnostic performance, but slightly lower than that of ADC_{3000} in discrimination of HGGs from LGGs.

3.6. Meta-regression and subgroup analyses

The results of the meta-regression and subgroup analyses were presented in Figure 6. The study design type (prospective or retrospective) had no impact on diagnostic accuracy. Two other factors field strengths and *b* values had significant impact on both sensitivity and specificity. The results indicated that higher field strengths and *b* values might improve the diagnostic performance of ADC derived from DWI in grading gliomas.

3.7. Publication bias

Publication bias was examined using Deeks plot asymmetry test, and the funnel plot based on ADC_{1000} did not reveal significant publication bias ($P = .48$). The funnel plots were shown in Figure 7.

4. Discussion

We assessed the accuracy of ADC derived from DWI in differentiating HGGs from LGGs. The pooled meta-analysis showed the AUC of *b* values of 3000 and 1000 s/mm^2 were 0.92 and 0.91, respectively. The results demonstrated that ADC derived from DWI had high diagnostic performance in discrimination of HGGs from LGGs.

Because the prognosis and the therapeutic approach differ considerably according to the grade of glioma, accurate grading of tumor is of vital importance. The histopathology is the gold standard for diagnosis of glioma, but it is an invasive procedure. To provide more accurate information and avoid unnecessary operations of glioma, the role of MR cannot be neglected. With

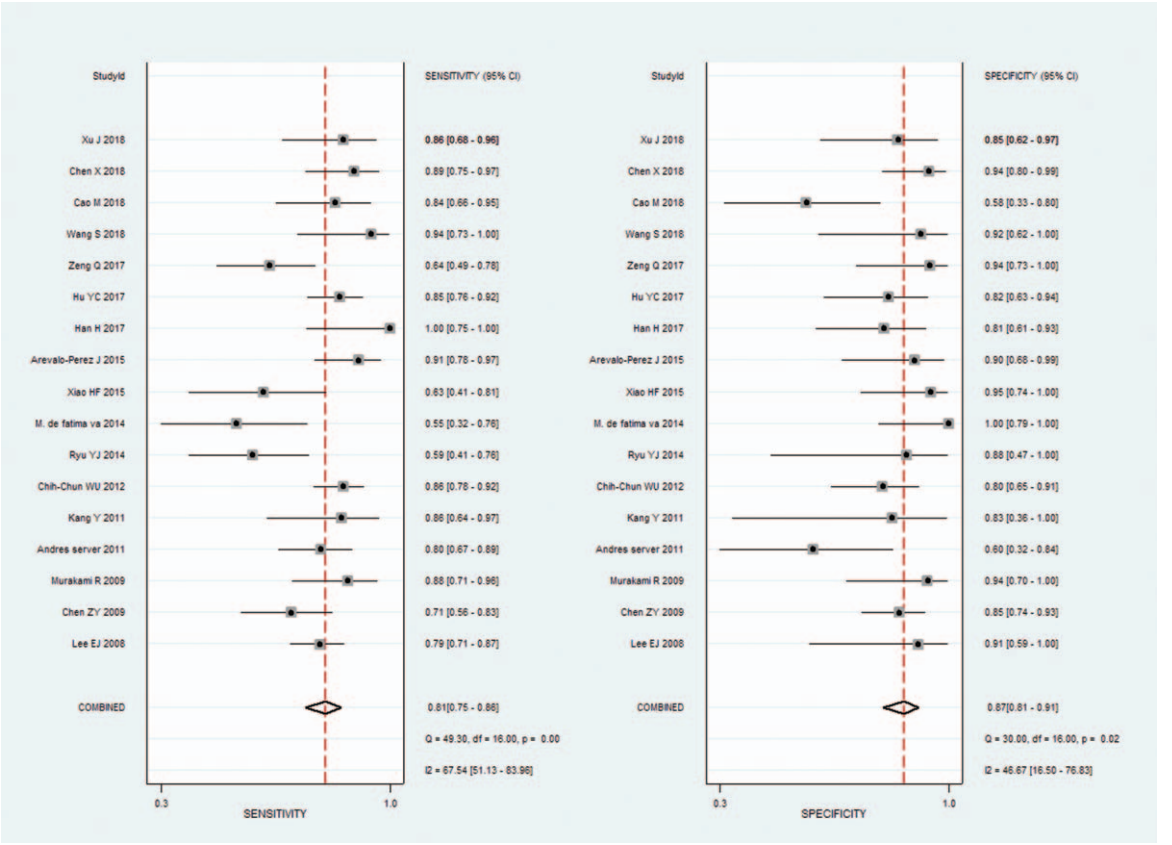

Figure 4. Pooled estimates of diagnostic performance of ADC values derived from DWI at *b* values of 1000 s/mm^2 to differentiate high-grade from low-grade gliomas.

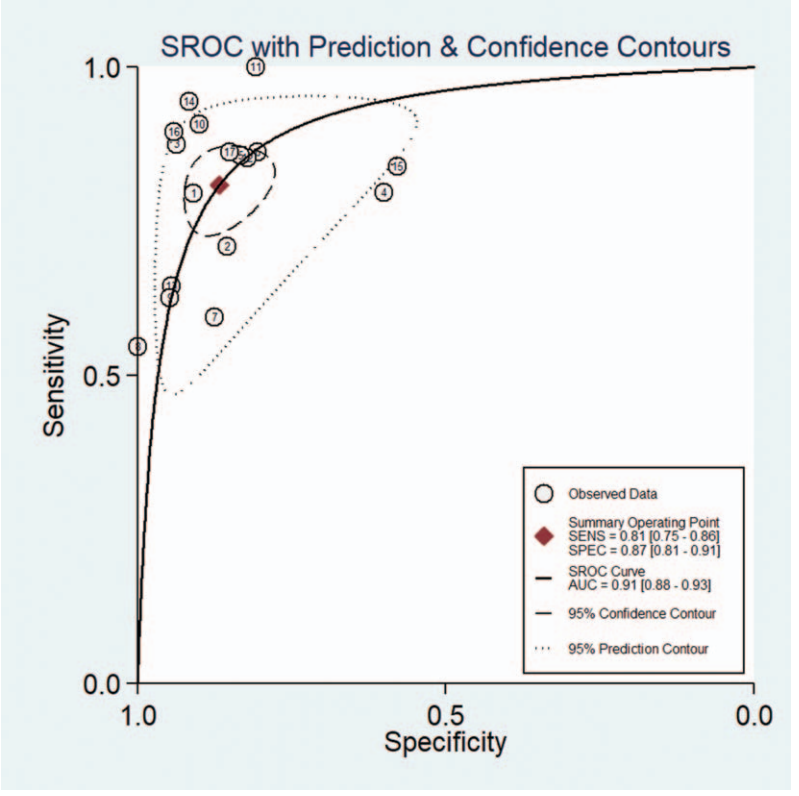

Figure 5. Summary receiver operating characteristics (SROC) curve of ADC values derived from DWI at *b* values of 1000 s/mm^2 to differentiate high-grade from low-grade gliomas.

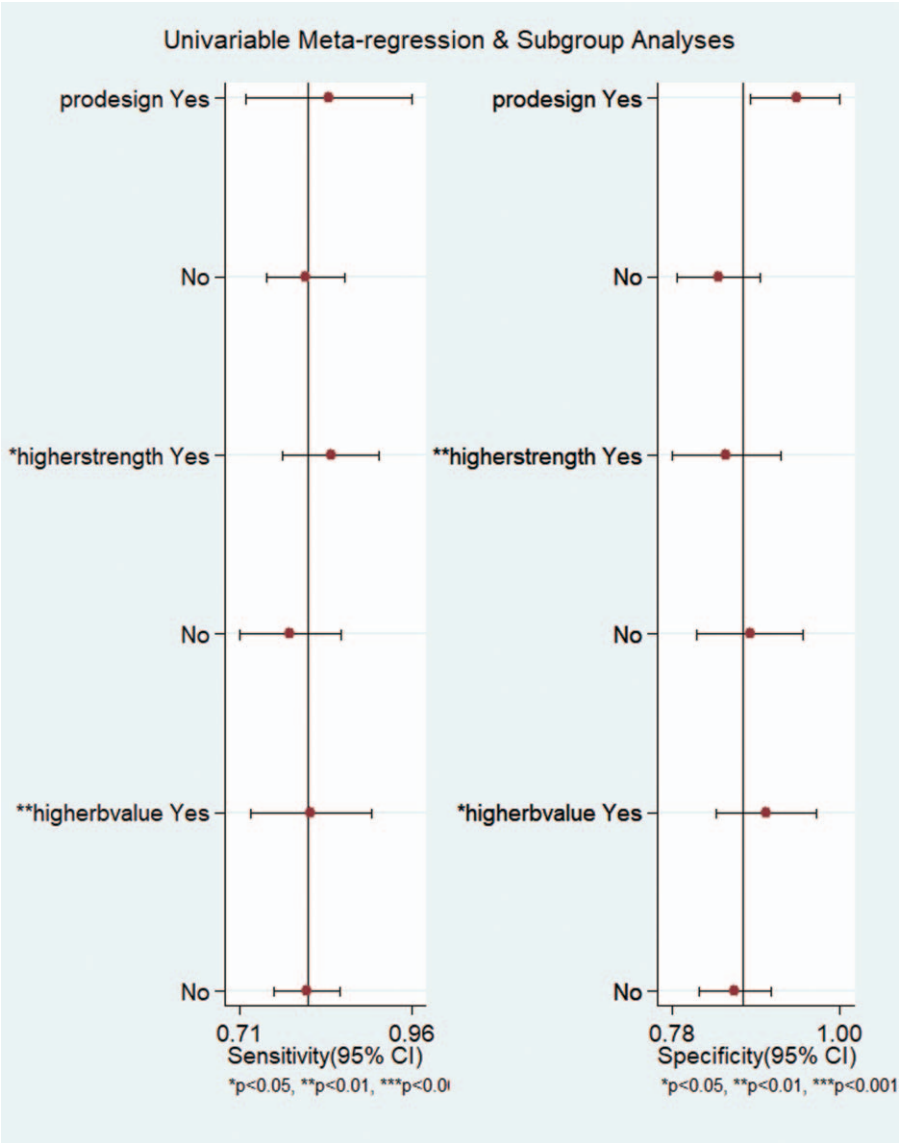

Figure 6. Meta-regression and subgroup analyses of ADC values derived from DWI to differentiate high-grade from low-grade gliomas.

the development of techniques, more and more metabolic and physiologic MR imaging, such as diffusion tensor imaging (DTI), MR spectroscopy, DWI, Dynamic susceptibility contrast (DSC) and Dynamic Contrast-enhanced (DCE) MRI, have been utilized in the assessment of glioma.[30–32] The utilization of DWI has facilitated the observation of microscopic movement of water protons in tissues.[33] Studies have discovered that ADC values derived from DWI are significantly higher in LGG than in HGG patients owing to the decreased cellularity and nuclear cytoplasmic ratio, which make it possible to apply DWI in grading glioma.[34] To date, there have been numerous reports on glioma grading using ADC values derived from DWI.[32,33] However, these studies with insufficient sample and differential diagnostic algorithms could not yield inconclusive results. We conduct this meta-analysis to systematically evaluate the accuracy of DWI for discriminating HGGs from LGGs.

This research demonstrated that DWI was useful for discrimination between HGGs and LGGs. In a published meta-analysis based on two kinds of diffusion MRI (DWI and DTI) for glioma grading, the total pooled sensitivity, specificity, and AUC were 85%, 80%, and 0.90%, respectively.[35] However, due to the differential diagnostic algorithms between two sequences, the results might be influenced by a number of heterogeneous factors. In another meta-analysis based on PWI for glioma grading, the pooled sensitivity, specificity and diagnostic odds ratio were 93%, 81%, and 55%, respectively.[36] The results shows that PWI is also a useful tool for discriminating glioma, however, PWI examination requires injection of contrast medium and the results are influenced by many factors, which makes it difficult to widely applicate. According to evidence from a comprehensive meta-analysis, the diagnostic accuracy of DWI in grading glioma is lower than MR spectroscopy, DSC and DCE MRI.[37] However, DWI has specific advantages over other metabolic and physiologic MR imaging that it is easy accessible, nonradioactive and less expensive, thus, this technique is easy to widespread utilize.

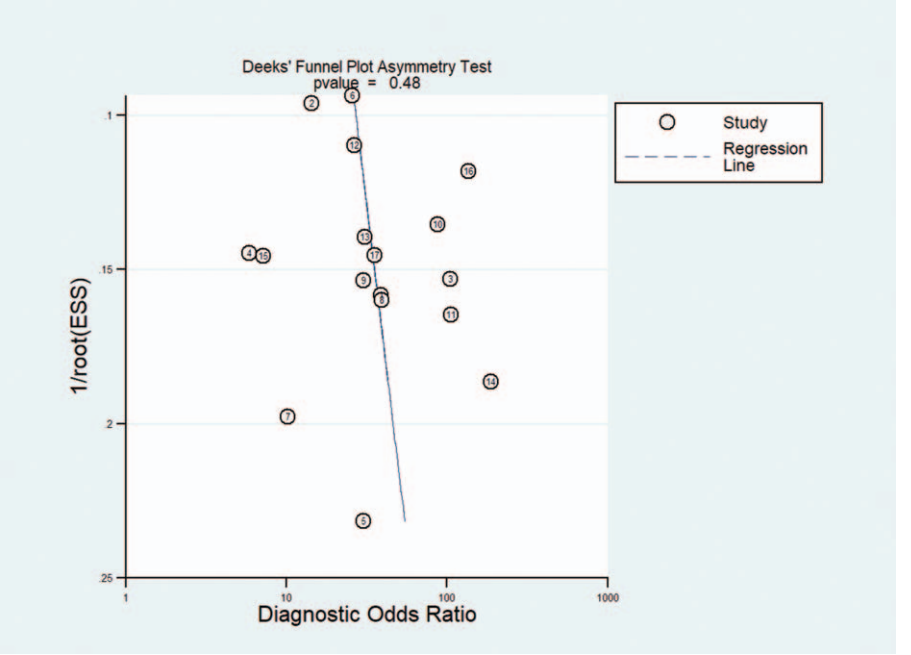

Figure 7. Deeks funnel plots indicating no publication bias ($P = .48$).

Moreover, when combined with other MR sequences, the accuracy could be significantly improved.[29]

However, obvious heterogeneity between studies needs further consideration. Different field strengths (3.0 and 1.5 T), different *b* values used, and different cut-off values could give unexpected substandard results and affect the accuracy of the conclusion. Consistent with previous reports, the present study found that ADC maps obtained from higher *b* value DWI performed at higher field strengths MR systems were more effective than those obtained from lower parameters.[38] The literature reported inconsistent cut-off values. It's hard to draw a conclusion that which is the most appropriate cut-off value for different DWI parameters. We recommend that future studies adopt higher DWI parameters and lay down a standardized technique procedure.

It is worth noting that this study also had several limitations. First, different field strengths, *b* values used, and cut-off values and other heterogeneous factors among studies might influence the consistency of measurements. Second, a number of studies were based on limited participants, which might affect the accuracy of the results. Finally, although no publication bias was detected in this meta-analysis, its potential impact on conclusion could not be neglected. Therefore, well-conducted investigations using a standardized methodology are needed to confirm the discrimination value of ADC derived from DWI on gliomas.

In conclusion, our study suggested that DWI could be an accurate tool for discriminating gliomas. Higher MRI parameters and combination with other techniques might help to improve the diagnostic accuracy. However, more studies are warranted to verify a standardized methodology in the clinical practice.

Author contributions

Conceptualization: Qiang-ping Wang, Nanxiang Xiong.
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Investigation: De-qiang Lei.
Methodology: De-qiang Lei, Ye Yuan, Nanxiang Xiong.
Resources: Ye Yuan.
Software: Ye Yuan.
Supervision: Nanxiang Xiong.
Writing – review & editing: Nanxiang Xiong.

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