

An evidence-based approach to assess the accuracy of diffusion kurtosis imaging in characterization of gliomas

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Abstract

Objective: Accurate and noninvasive pathologic grading of glioma patients before surgery was crucial to guiding clinicians to select appropriate treatment and improve patient prognosis. This study was performed to investigate the potential diagnostic value of diffusion kurtosis imaging (DKI) to distinguish high-grade gliomas (HGGs) from low-grade gliomas (LGGs) based on an evidence-based approach.

Methods: Relevant articles that used DKI to distinguish HGG from LGG in Embase, PubMed, China Knowledge Resource Integrated database (CNKI), Web of Knowledge, and Cochrane Libraries databases were electronically searched to April 31, 2018 by 2 reviewers. All analysis was performed by using Meta-disc1.4 and Stata. Influence factors on the diagnostic accuracy were evaluated using meta-regression analysis.

Results: Five eligible studies were included in this meta-analysis. The pooled sensitivity (SEN) and specificity (SPE) was 91% (confidence interval [CI]: 0.78–0.96; $P = .02$) and 91% (CI: 0.80–0.97; $P = .01$). The pooled data showed that diagnostic odds ratio (DOR) of DKI was 79.75 (CI: 31.57–201.45). The area under the curve (AUC) of summary receiver operating characteristic curve was 0.96. There is no evidence that our research has a threshold effect (Spearman correlation coefficient: 0.300, $P = .624$) and publication bias. Meta regression analysis identified that country, language, field strength, and parameter of magnetic resonance imaging had no significant effect on diagnostic performance.

Conclusion: The present meta-analysis shows that the mean kurtosis values derived from DKI may be useful in characterization of gliomas with high sensitivity and specificity. Taken into consideration the small sample of this study, we need to be cautious when interpreting the results of this study.

Abbreviations: AUC = area under the curve, CI = confidence interval, CNKI = China Knowledge Resource Integrated database, DKI = diffusion kurtosis imaging, DOR = diagnostic odds ratio, DWI = diffusion-weighted imaging, FN = false negative, FP = false positive, LR = likelihood ratio, MK = mean kurtosis, SEN = sensitivity, SPE = specificity, SROC curve = Summary Receiver Operating Characteristic curve, TN = true negative, TP = true positive, WHO = World Health Organization.

Keywords: diffusion kurtosis, gliomas, grading, magnetic resonance imaging

1. Introduction

Gliomas are the most common primary intraaxial brain tumors, which were classified into different grades on the basis of the World Health Organization (WHO) neuropathologic guidelines.^[1] Gliomas are characterized of high incidence rate, high recurrence rate, and high mortality rate.^[2] Low-grade glioma

(LGG) contained WHO grades I and II, WHO grades III and IV pertained to high-grade glioma (HGG). The prognosis and clinical management of patients depend on the accurate classification of gliomas.^[3] Histologic pathologic examination has always been the gold standard for diagnosis, but this was not noninvasive examination.^[4] Noninvasive methods urgently warranted for preoperative glioma grading.

Diffusion kurtosis imaging (DKI) was an extension of diffusion-weighted imaging (DWI) technology; however, DWI can only reflect the change in the diffusion capacity of water molecules, which cannot determine its anisotropy.^[5] DWI assumed that diffusion of water molecule following with a Gaussian distribution. This hypothesis has been experimentally proven to be not suitable when using high b -values.^[6] DKI was a new functional magnetic resonance technique that depicted the non-Gaussian distribution of water molecules in tissues.^[7] As a non-Gaussian imaging technique, DKI reflected more complexity of the microstructural environment (such as or ganelles, cell membranes, and water compartments) than DWI. Although DKI has been widely used in the central nervous system, there are also small studies focusing on other extracerebral structures, including prostate, breast, and kidney.^[8–10] In recent years, classification of gliomas has been widely concerned by more researchers.^[11,12] Mean kurtosis (MK) was the most representa-

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tive parameter of DKI, which represented the average value of kurtosis along all directions.^[13] Although previous studies suggested that the derived DKI parameter (MK) had high diagnostic accuracy of gliomas grading, there were controversial results between these studies.^[14–18] Therefore, we designed the present meta-analysis to evaluate the accuracy of DKI for differential diagnosis between HGG and LGG.

2. Materials and methods

2.1. Search strategy

Relevant articles that used DKI to distinguish HGG from LGG in Embase, PubMed, China Knowledge Resource Integrated database (CNKI), Web of Knowledge, and Cochrane Libraries databases were electronically searched to April 31, 2018 by 2 reviewers. The search strategy was based on the following Medical Subject Headings and key words: “kurtosis” or “diffusion kurtosis imaging” or “DKI”; “brain tumor” or “glioma” or “astrocytoma” or “neoplasms”; “sensitivity” or “specificity” or “false-negative” or “false-positive” or “diagnosis” or “accuracy”; “grading” or “grade”.

2.2. Study selection

The included criteria for literature selection were as follows: Papers on the human application of DKI to differentiate HGG from LGG. Studies that used histopathology examination as the gold standard; only publications in English and Chinese. (4) True positive (TP), true negative (TN), false negative (FN), and false positive (FP) values calculated from the raw data. There were no other further restrictions. Unpublished data, reviews, case reports, conference abstracts, letters, comments, and editorials were excluded.

2.3. Data extraction

Data collection mainly included the following content: author, publication year, number of patients, mean age, magnetic resonance imaging (MRI) field strength, and MRI technique parameters. The overall TP, TN, FP, and FN values were extracted. The included study quality was performed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, which involved 14 assessment items.^[19]

The SEN, SPE, positive and negative likelihood ratio (LR) and DOR with their 95% confidence intervals were calculated and analyzed. We also calculated the area under the curve of Summary Receiver Operating Characteristic (SROC) curve. The Spearman correlation coefficient was applied to evaluate the threshold effect. We also used inconsistency (I^2) to test heterogeneity between studies. If $I^2 > 50\%$, which indicates the presence of heterogeneity.^[20] Sensitivity analysis was performed to assess the impact of single study on the overall estimate. Deek funnel plots test Deek test was recommended to evaluate the publication bias.^[21] All analysis was performed by using Meta-disc1.4 and Stata.

3. Results

Based on the above search strategy, 77 potentially initial papers were selected. About 21 nonhuman studies and 16 reviews excluded based on their titles and abstracts, the remaining 12 articles were screened for full-text evaluation. Finally, the remaining 5 eligible literature sources were included in this meta-analysis that met the inclusion criteria.^[14–18] The results of the selection process are presented in Figure 1. A total of 116 LGG patients and 154 HGG patients were enrolled into the included studies ($n=5$). The data acquisition of DKI was acquired with 3-T equipment in all of studies, and 3 studies

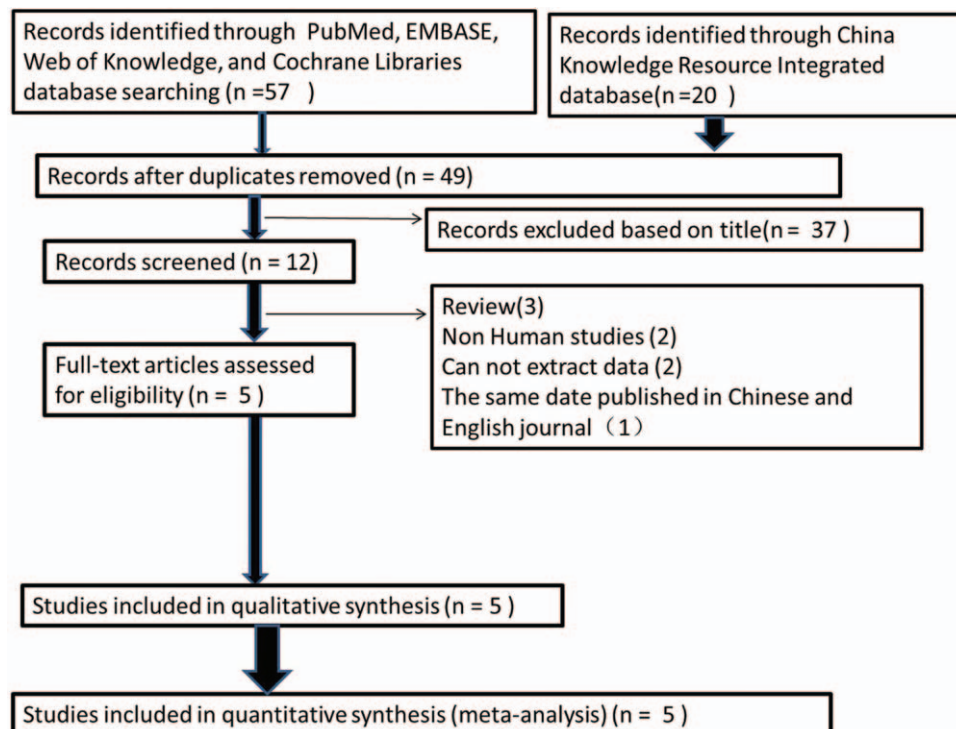


Figure 1. Flowchart of the selection and identification process.

Table 1
Characteristics of studies included in the meta-analysis.

Author	Year	Country	Field strength	MRI type	Patients	LGG/HGG	Mean age	TR/TE, ms	Mix <i>b</i> value, s/mm ²	No. of <i>b</i>	QUADAS
Tan	2014	China	3 T	GE	60	25/35	NM	6500/115	2000	3	10
Van	2014	Belgium	3 T	Philips	35	16/19	55	3200/90	2800	3	12
Jiang	2015	China	3 T	GE	72	34/40	42	6500/85	2500	2	13
Bai	2016	China	3 T	GE	69	28/34	46	7000/80	2500	6	12
Qi	2017	China	3 T	Siemens	39	13/26	54.35 ± 11.31	6000/98	2000	3	13

HGG=high-grade glioma, LGG=low-grade glioma, MRI=magnetic resonance imaging, NM=not mentioned.

examined by GE MRI; 5 studies were presented in English Journal and four authors were Chinese. The range of the maximum *b* value was 2000 to 2800 s/mm². The age distribution was reported heterogeneously. The mean age was shown in 4 studies. These above data are displayed in Table 1.

Pooled sensitivity of MK derived from DKI was 91% (confidence interval [CI]: 0.78–0.96), moderate heterogeneity (*I*²=66.7%, *P*=.02) is shown in Figure 2. Five studies assessed the specificity of MK derived from DKI, the pooled specificity was 91% (CI: 0.80–0.97). As shown in Figure 2, there was evidence of

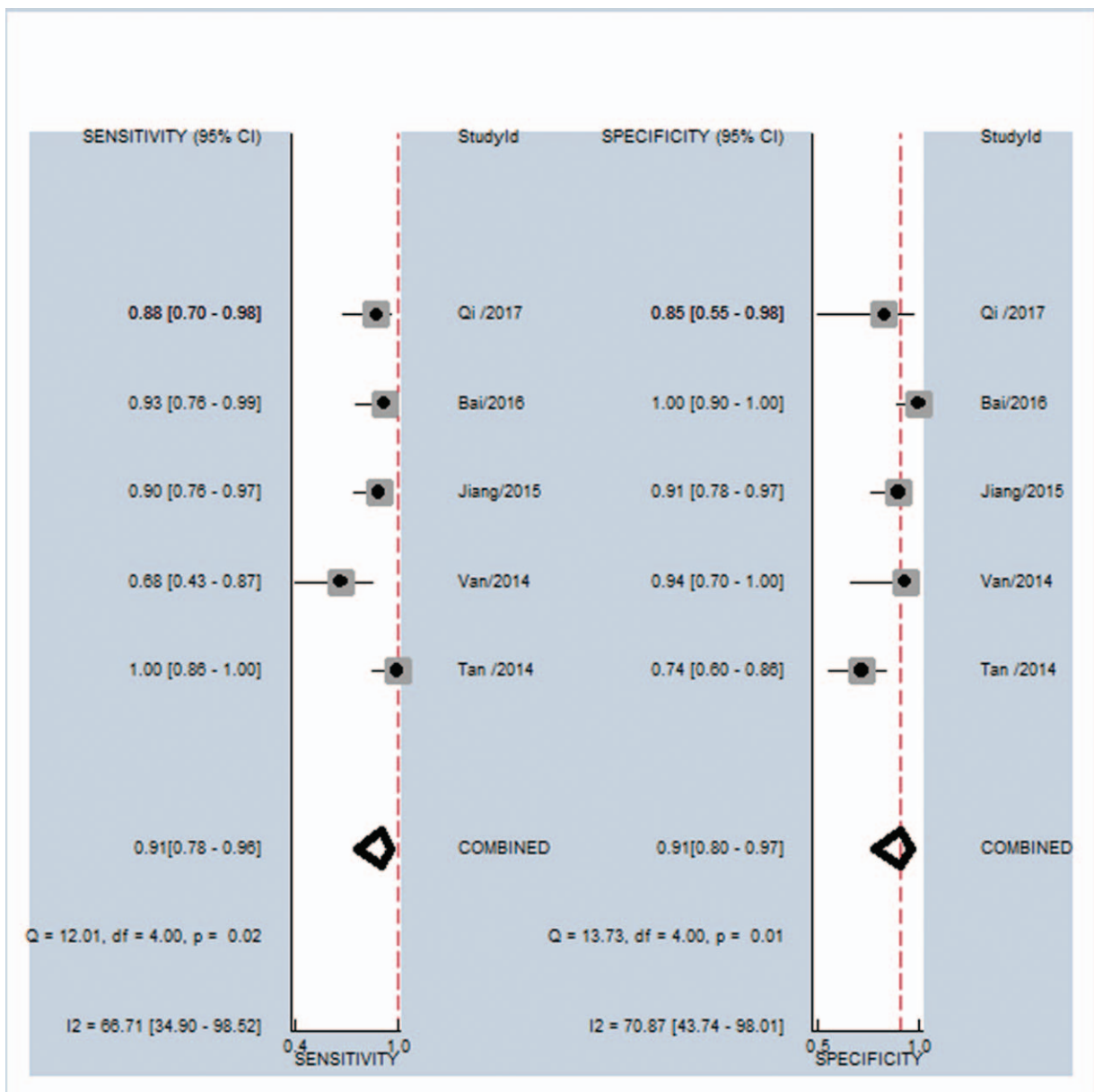


Figure 2. Forest map of sensitivity and specificity of diffusion kurtosis imaging.

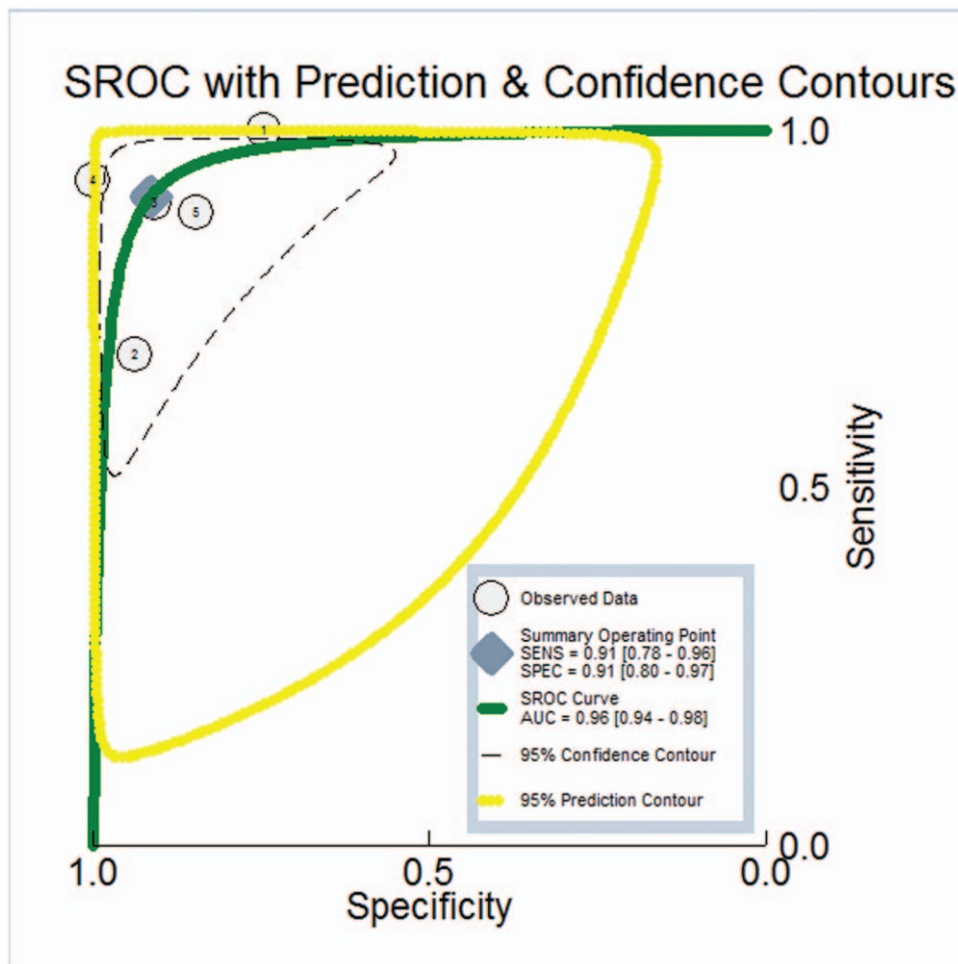


Figure 3. Summary Receiver Operating Characteristic of diffusion kurtosis imaging in characterization of gliomas.

a considerable heterogeneity ($I^2=70.8\%$, $P=.01$). Overall, the AUC of SROC plot (Fig. 3) was 0.96 (CI: 0.96–0.98), indicating higher diagnostic accuracy for DKI. Besides, DOR (Fig. 4) of DKI also provides strong evidence to illustrate the diagnostic performance. There is no evidence that our research has a threshold effect (Spearman correlation coefficient: 0.300, $P=.624$).

Sensitivity analysis was carried out and results showed that the statistical difference was not significant in any study excluded. Deek tests for the overall analysis reported publication bias exist in Figure 5 ($P=.4$).

Factors influencing the diagnostic performance of DKI were performed by Meta-disc1.4. Meta regression analysis showed that country, language and parameter of MRI did not affect the

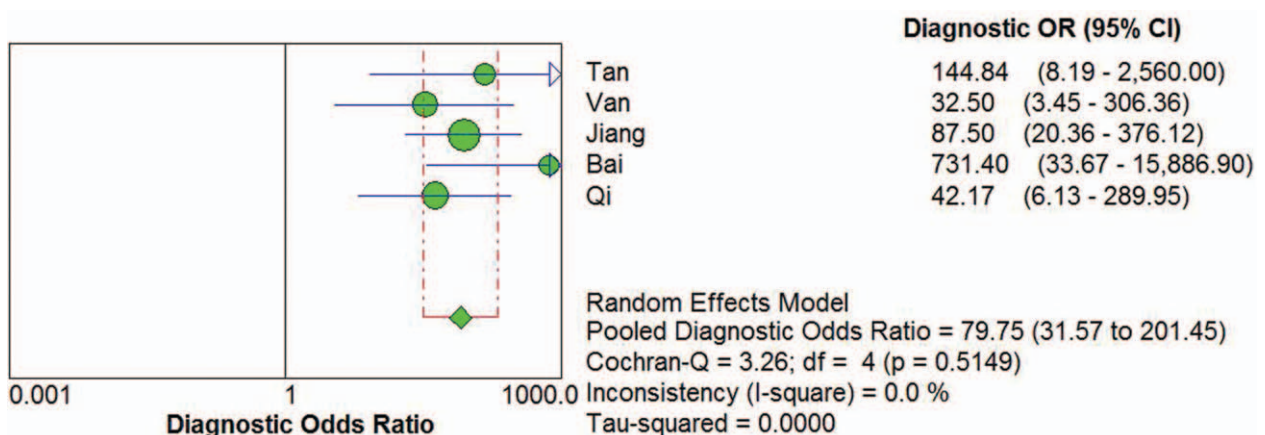


Figure 4. Forest map of diagnostic odds ratio of diffusion kurtosis imaging.

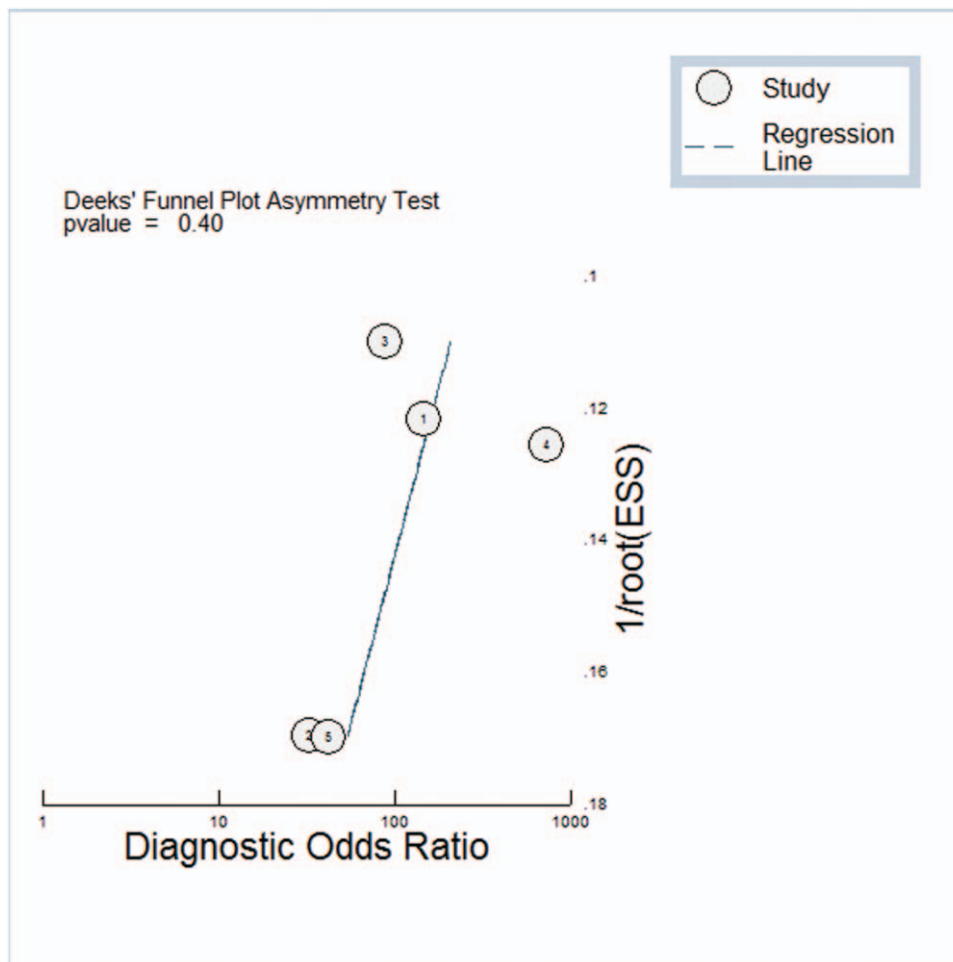


Figure 5. Publication bias analyzed by Deek funnel plot.

diagnosis of DKI significantly. Meta regression analysis also identified that quality of study had no significant effect on diagnostic performance. No correlation between other investigated covariates and diagnostic performance was identified.

4. Discussion

The LGG were characterized by low invasiveness, slow growth, low tumor cell and microvessel density, slow cell proliferation, and insignificant cell atypicality. Therefore, surgery performed without radiotherapy and chemotherapy to achieve long-term survival. However, HGG were characterized by high invasiveness, rapid growth, high density of malignant cells and microvessels, higher cell colonization, and remarkable cell atypicality.^[3] Even if patients received adjuvant therapy and chemotherapy after surgery, the prognosis of patients was still poor. Accurate and noninvasive pathologic grading of glioma patients before surgery was crucial to guiding clinicians to select appropriate treatment and improve patient prognosis. In addition, the glioma parenchyma was heterogeneous, and the pathologic and histologic characteristics (tumor cell density, cell perfusion, and microvessel density) of the gliomas would vary from LGG to HGG, which cannot be detected using conventional MR techniques.

In recent years, many studies about diagnostic applications of DKI have been published. The data presented in Li's study showed that MK varied among the different grades of gliomas significantly, MK was significantly lower in the LGG than that in the HGG.^[22] This also explained that HGG cell components were more complex than LGG, and it also indicated that the high diagnostic accuracy of DKI in grading gliomas quantitatively. Recently Qi examined the differences in kurtosis parameters between HGG and LGG and they found that The SEN, and SPE of the MK were 88% and 85%, respectively,^[17] nevertheless, previous work investigated MK in different glioma grades with the SEN (68%) and SPE (94%).^[14] These controversial results were the purpose of our meta-analysis.

We performed a meta-analysis to explore the validity in the utility of DKI for distinguishing HGG from LGG. A pooled analysis demonstrated that the pooled SEN and SPE of MK derived from DKI was 91% ($P < .05$). The pooled positive LR and negative LR of MK was 7.58 (CI: 3.15–18.22) and 0.14 (CI: 0.06–0.31). Besides, DOR of DKI also provided strong evidence to illustrate the diagnostic performance, which was consistent with previous studies.^[16,17,23]

When a certain numerical limit was exceeded, a fundamental change in diagnostic value occurs, which was interpreted as a threshold effect. Our results indicated that there was no

significant relationship between SEN and SPE in the study, revealing no evidence of threshold effect.

Moderate heterogeneity was observed in SEN and SPE, 1 source of heterogeneity was small sample size; however, this was uncontrollable. Sensitivity analysis was used to evaluate the reliability of meta-analysis results by eliminating some low-quality studies or using different statistical methods to explore their effect on the pooled effect.^[24] Sensitivity analysis was carried out and results showed that the statistical difference was not significant in any study excluded. Although Deek tests demonstrated that no publication bias in this study, taken into consideration the small sample of this study, we need to be cautious when interpreting the results of this study. Of the 5 articles we included, 4 authors were Chinese and another is Belgium, which may implicitly suggest that diagnostic value elevated result from geographical factor.

Although this was the first meta-analysis to assess the ability of DKI in characterization of gliomas with high SEN and SPE, a few potential limitations of our study should be mentioned: Firstly, the sample size is small; the present literature found only 5 studies that directly distinguished HGG from LGG. Secondly, English and Chinese language restrictions were applied in this analysis, thus to some degree, there exists an inclusion bias. Thirdly, Deek tests for the overall analysis reported publication bias exist in our study. Lastly, parameter values of DKI may be affected by postprocessing techniques, such as the definition of tumor ROI was different in different studies, Jiang was the first to report semi-automatic method applied in glioma measurement.^[18] Given this, further a large sample studies were needed, optimization of parameters and postprocessing standardization were helpful to differentiate HGG from LGG accurately.

5. Conclusion

In brief, this current meta-analysis provides evidence that DKI had the high diagnostic accuracy to differentiate HGG from LGG; however, taken into consideration the small sample of this study, we need to be cautious when interpreting the results of this study.

Author contributions

Data curation: Ruiyu Huang, Yanni Chen.

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Methodology: Wenfei Li.

Software: Wenfei Li.

Writing – original draft: Ruiyu Huang, Xvfeng Zhang.

Writing – review & editing: Ruiyu Huang, Xvfeng Zhang.

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