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An evidence-based approach to assess the accuracy of intravoxel incoherent motion imaging for the grading of brain tumors

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Abstract

Background: Differentiation of high-grade gliomas (HGGs) and low-grade gliomas (LGGs) is an important clinical problem because treatment strategies vary greatly. This study was performed to investigate the potential diagnostic value of incoherent intravoxel motion imaging (IVIM) to distinguish HGG from LGG by meta-analysis.

Methods: A computerized search of the literature was performed using the free-access PubMed database, Web of Science, and Chinese biomedical database, and relevant articles until September 18, 2018 that used IVIM to distinguish HGG from LGG were included. All analyses were performed using Review Manager 5.3 and Stata. Mean difference (MD) at 95% confidence interval (CI) of the apparent diffusion coefficient (ADC), diffusion coefficient value (D), perfusion fraction value (f), and perfusion coefficient value (D*) were summarized.

Results: Nine studies were used for general data pooling. In the tumor parenchyma (TP) regions, subgroup analysis revealed D* in HGG is higher than in LGG (MD = 1.19, P = .002), and D in HGG is lower than in LGG (MD = −1.06, P = .001). However, no significant difference in f (MD = 0.89, P = .056) was detected between HGG and LGG. In the white matter regions, HGG had higher D* (MD = 0.76, P = .04) compared with LGG, while no marked differences between the D value (P = .07) and f (P = .09) values.

Conclusion: The present meta-analysis shows that the ADC, D, and D* values derived from IVIM may be useful in differentiating HGG from LGG. Considering the small sample of this study, we need to be cautious when interpreting the results of this study. Other prospective and large-sample randomized controlled trials were needed to establish the value of IVIM in differentiating HGG from LGG.

Abbreviations: ADC = apparent diffusion coefficient, CI = confidence interval, D = diffusion coefficient value, D* = perfusion coefficient value, DWI = diffusion-weighted magnetic resonance imaging, f = perfusion fraction value, HGG = high-grade glioma, IVIM = incoherent intravoxel motion imaging, LGG = low-grade gliomas, MD = mean difference, MVD = microvessel density, NM = not mentioned, PWI = perfusion magnetic resonance imaging, TP = tumor parenchyma, WHO = World Health Organization, WM = white matter.

Keywords: glioma, grading, intravoxel incoherent motion imaging, meta-analysis, magnetic resonance imaging

1. Introduction

Glioma is one of the most common malignant tumors of the primary intracranial tumors in adults, with a tendency to be aggressive from low to high grades.[1] It is of great clinical significance to accurately determine the grading of gliomas due to the difference in clinical treatment and prognosis[2,3]; however, conventional magnetic resonance imaging (MRI) and contrasted MRI cannot effectively distinguish high-grade glioma (HGG) from low-grade glioma (LGG).

Increasing functional magnetic resonance imaging techniques have been applied to the classification of gliomas, especially diffusion-weighted imaging (DWI)[4] and perfusion magnetic resonance imaging (PWI).[5] Currently, DWI is the only way to measure diffusion of water molecular in vivo, which can reflect the pathologic changes of tumor cell density. In general, decreased cellularity, increased extracellular space, and low nuclear-to-cytoplasmic ratio are believed to be the features of low-grade tumors[6] and therefore can be used to evaluate the grading of a brain tumor.[7] In addition, the evaluation of tumor vascularity is valuable in determining the histologic grade of gliomas; compared with LGG, HGGs have a greater change in angiogenesis. Compare with DWI, PWI can provide the perfusion information for the grading of gliomas.[8,9] Both DWI and PWI are helpful for preoperative grading of a brain tumor. At present, the new technology of magnetic resonance imaging, intravoxel incoherent motion imaging (IVIM), can be used to obtain the

diffusion and perfusion of tissue without using a contrast agent.[10]

It is known that IVIM has been applied not only to the classification of central nervous system tumors[11] but also to other tumors, such as liver cancer,[12] renal tumors,[13] prostate cancer,[14] and breast lesions.[15] IVIM can be used to evaluate the pure molecular diffusivity (performed by the parameters apparent diffusion coefficient [ADC] and diffusion coefficient value [D]) and perfusion-related diffusivity (performed by parameters perfusion coefficient value [D*] and perfusion fraction value [f]).[16] The D* value was influenced by microvessel density (MVD) of the brain tumor, which was associated with the b velocity of blood flow and average length of capillaries. As is known, the HGG often have increased neoangiogenesis, the velocity of capillary blood flow was usually higher in HGG than LGG, which lead to increase the D* value.[12] Valerio et al suggested that parameter f was dependent on the abundance of capillaries, which measured translational motions related to the microcirculation of blood flow.[14] High vascularity was an important factor in the histopathologic grading of brain tumor, because of the HGG was characterized with higer neoangio-genesis and nuclear cytoplasmic ratio than LGG, which was supported by the increased f value.[14] Previous studies have indicated the important role of these 4 parameters in tumor grading, but the controversy remains in the literature. We performed a quantitative meta-analysis to assess the role of the parameters derived from IVIM in the preoperative grading of gliomas.

2. Materials and methods

2.1. Search strategy

A computerized search was performed by using the free-access PubMed database, Web of Science, and Chinese biomedical database, including relevant articles until September 18, 2018. The following Medical Subject Headings and search algorithms were used: ("intravoxel incoherent motion MR imaging" or "IVIM") AND ("glioma" or "brain tumor" or "brain neo-plasm") AND ("grade" or "grading"). English and Chinese language restrictions were applied.

2.2. Eligibility criteria for study selection

The inclusion criteria were the following: IVIM was performed to distinguish HGGs (WHO grades III and IV) from LGGs (WHO grades I and II). Histopathology had been used as the gold standard. ADC, D, D*, and f values were reported for effective calculations. The study included at least 10 patients. In addition, if an overlap between studies was identified, the more recent report was chosen to avoid data redundancy. Patients had no surgery, radiotherapy, or chemotherapy before IVIM. Animal studies, case reports, reviews, letters, editorials, and comments were excluded.

2.3. Data collection

For each included study, relevant data were extracted including article characteristics (1st author, year of publication), basic demographics (mean age of patients, number of patients), and technical characteristics (imaging field strength, parameters of IVIM techniques). Two authors independently collected the information of the all included publications. The ADC, D, D*,

and f values of the tumor parenchyma (TP) region and contralateral white matter (WM) region were tabulated as the mean values and standardized differences values. Two reviewers investigated the quality of each study using the Quality Assessment of Diagnosis Accuracy Studies score tool (QUA-DAS-2) independently.[17]

2.4. Statistical analysis

The mean difference (MD) of all parameters between HGG and LGG were calculated. At the same time, the MD between the TP region and WM region were also calculated. The overall effect size was presented as the mean and 95% confidence interval (CI). We also used inconsistency (I^2) to test heterogeneity attributable to study variation. If $I^2 > 50\%$, which indicates the presence of heterogeneity, subgroup analyses were performed to observe weight of the different variables on the diagnostic results.[18] The main analysis was performed using the standard meta-analytic methods for combining data for diagnostic accuracy tests. All analysis was performed by using Review Manager 5.3 and Stata.

3. Results

3.1. Search results

Initially, a total of 176 potential articles were selected, and 48 articles remained after the removal of duplicates. After screening titles and abstracts, 29 articles were identified to be fit for full-text evaluation. After completion of the full-text search, an additional 10 review articles and 7 nonhuman articles were excluded. Three additional articles were omitted because they did not provide sufficient data to calculate the diagnostic test parameters. Finally, only 9 eligible articles contained sufficient information to meet the inclusion criteria of this analysis.[19–27] A flowchart of the selection process is shown in Figure 1.

3.2. Study characteristics

Characteristics of the 9 selected studies are shown in Table 1. A total of 318 patients were included in the 9 studies. In these 9 studies, a total of 185 patients with HGG and 133 patients with LGG were included. In all of the eligible studies, data were acquired with 3T magnets except 2 studies examined IVIM at 1.5 T. Mean age was heterogeneously reported (Table 1). The number of b values and TR/TE also differed among studies. The result of quality assessment is illustrated in Table 2. Because pathologic examination was chosen as the reference standard, other factors were judged to be at a "low risk of bias."

3.3. Quantitative analysis

All included studies reported values of D* and f in TP areas. The pooled data revealed that D* is significantly higher in HGG compared with LGG (MD = 1.19, 95% CI 0.45 – 1.94, P = .002), with heterogeneity ($I^2 = 87.7\%$). Seven studies reported values of ADC in TP regions. The pooled data showed that ADC was significantly lower in HGG than LGG (MD = −1.14, 95% CI −1.69 to −0.59, P < .001), with a high level of heterogeneity ($I^2 = 74.8\%$). Eight studies reported values of D in TP regions. The pooled data also showed that D was significantly lower in HGG than LGG (MD = −1.06, 95% CI −1.68 to −0.44, P = .001). However, no significant difference in f values (MD = 0.89; 95% CI −0.02 to 1.8; P = .056) was detected between HGG and LGG. The above results are shown in Figure 2.
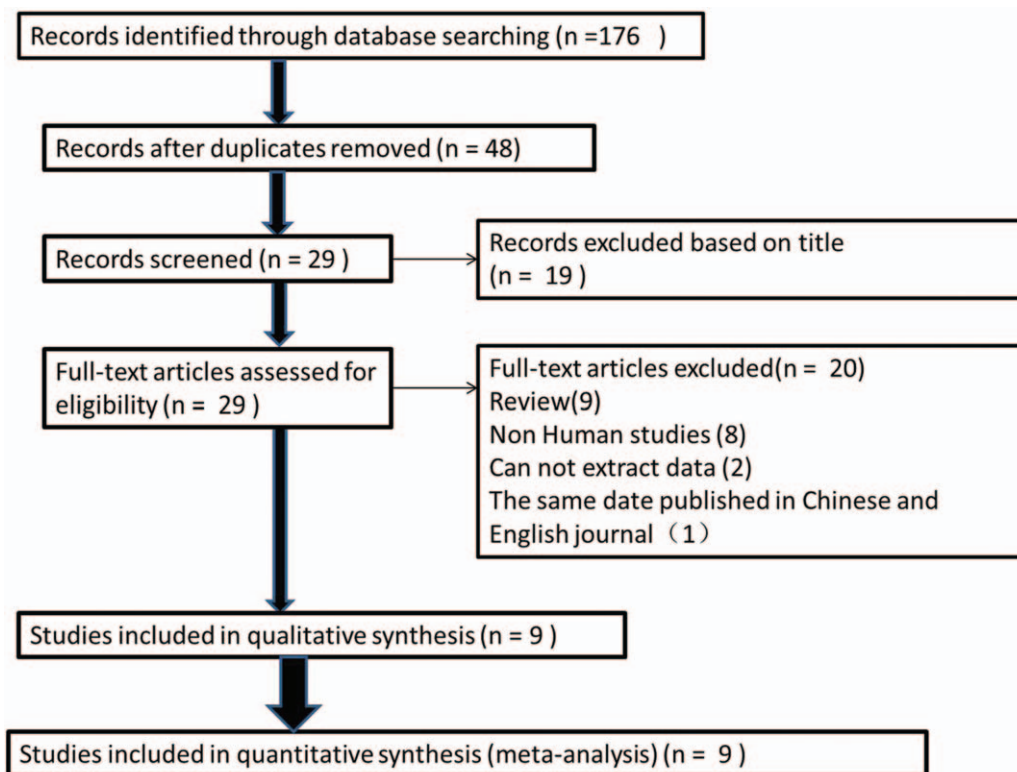
Figure 1. Flowchart of search process.

Table 1

Characteristics of studies included in the meta-analysis.

Study name	Year	Field strength	No. of patients	Mean age	TR/TE, ms	Thickness, mm	No. of *b* values	QUADAS
	2013	1.5T	22	65	3300/83	3	14	11
Federau	2014	3T	21	52.3	4000/99	4	16	10
Hu	2014	3T	42	47	3000/min	5	13	12
Lin	2015	3T	24	42	3000/87.5	5	20	10
Shen	2016	3T	52	NM	5200/70.8	5	16	13
Togao	2010	3T	45	50.9	2500/70	5	13	11
Zhang Lei	2016	1.5T	28	46.9	6000/61–64	6	14	9
Zhang Jin	2017	3T	40	45	2500/59	NM	16	9
Xu	2018	3T	55	53.3	2700/90	5	7	10

NM = not mentioned, QUADAS = Quality Assessment of Diagnosis Accuracy Studies score tool.

Table 2

Assessment of study quality (Quality Assessment of Diagnosis Accuracy Studies score tool).

		Risk of bias				Application concerns		
Study ID	Year	Patient selection	Index test	Reference test	Flow and timing	Patient selection	Index test	Reference standard
Bisdas	2013	−	−	−	−	+	−	−
Federau	2014	−	−	−	−	?	−	−
Hu	2014	?	−	−	−	−	−	+
Lin	2015	−	−	−	−	−	−	+
Shen	2016	−	−	−	−	−	−	−
Togao	2010	−	−	−	−	−	−	−
Zhang Lei	2016	+	−	−	−	?	−	−
Zhang Jin	2017	?	−	−	−	+	−	+
Xu	2018	+	−	−	−	+	−	−

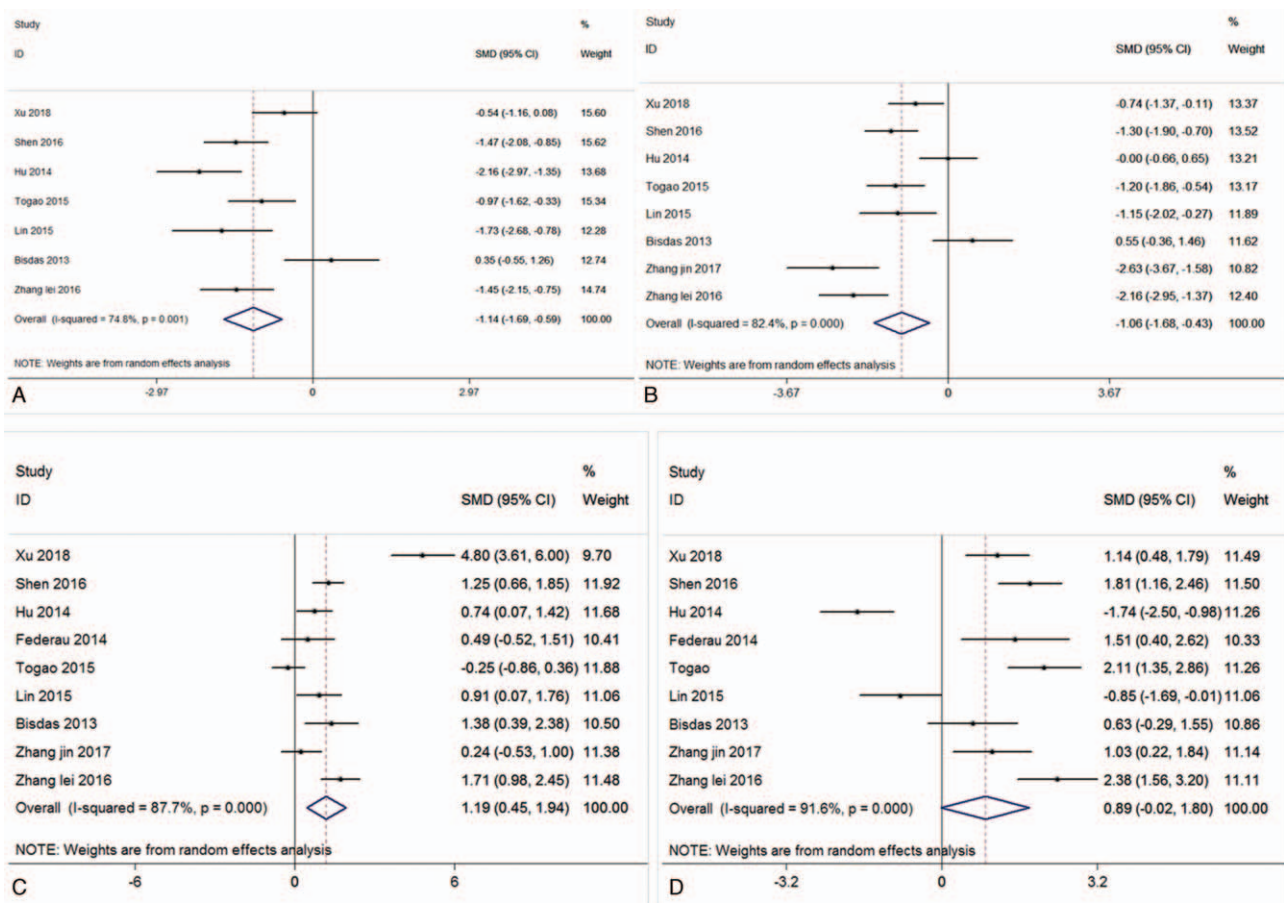? = unclear risk, − = low risk, + = high risk.

Figure 2. Forest plots of parameters in TP regions. (A) Forest plot of apparent diffusion coefficient (ADC) value. (B) Forest plot of D value. (C) Forest plot of $D*$ value. (D) Forest plot of f value.

Three studies demonstrated that $D*$ in HGG significantly higher compared with LGG in WM areas (MD = 0.76, 95% CI 0.04–1.48, P = .04) with high heterogeneity (I^2 = 70%, P = .04; Fig. 3), while no marked differences between the D (P = .07) and f (P = .09) values were observed between HGG and LGG.

3.4. Subgroup analysis

Of the 8 included studies, 6 studies used 3T MRI. The pooled data revealed that $D*$ is significantly lower in LGG compared with HGG (MD = 0.63, 95% CI 0.34–0.92, P < .0001), with a low level of heterogeneity (I^2 = 39%, P = .14). Of the 8 included studies, 6 studies were published in an English journal. This study also shows that $D*$ is significantly higher in HGG compared with LGG (MD = 0.75, 95% CI 0.35–1.15, P = .0002); however, heterogeneity decreased from 57% to 40%.

3.5. Assessment of publication bias

No significant bias was observed by Begg test in diffusion parameters (D and ADC), interestingly, there was no evidence that significant publication bias in perfusion parameters ($D*$ and f), details of the information are summarized in Figure 4.

4. Discussion

The HGG cannot be reliably differentiated from LGG using conventional MR techniques, such as T2-weighted and
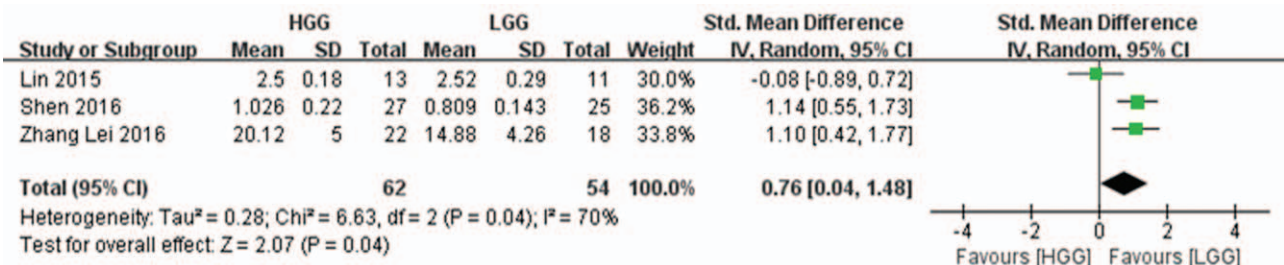

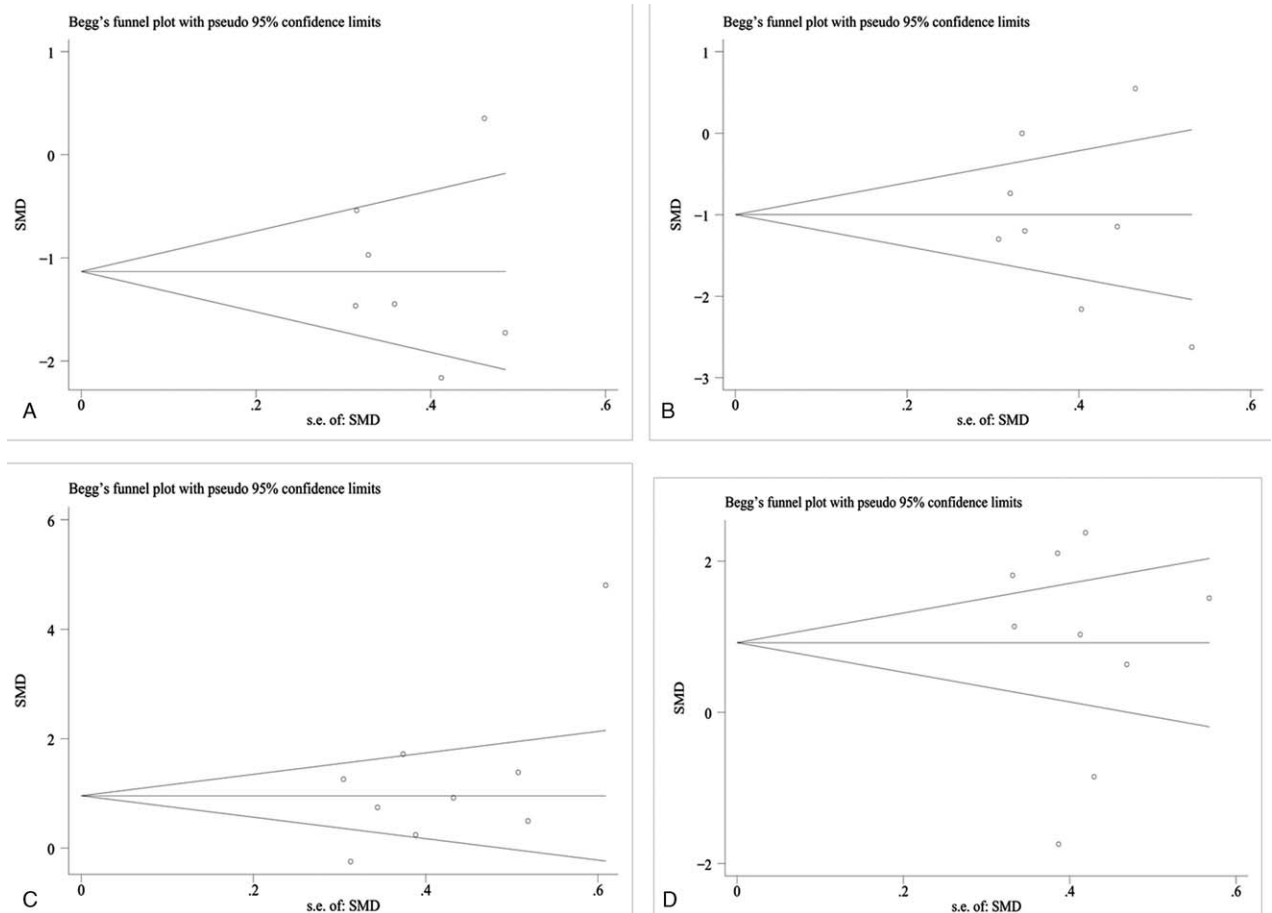**Figure 3.** Forest plots of $D*$ in white matter regions.

Figure 4. Funnel plot of publication bias. (A) Publication bias of apparent diffusion coefficient (ADC) value in TP areas. (B) Publication bias of *D* value in TP areas. (C) Publication bias of *D** value in TP areas. (D) Publication bias of *f* value in TP areas.

T1-contrasted imaging, because the performance of both imaging techniques is very similar. Nevertheless, from histopathologic aspects, HGG and LGG are markedly different. The grading of brain tumors is determined based on the degree of cellular anaplasia, nuclear atypia, cell density, and microvascular proliferation. IVIM can obtain true diffusion and capillary perfusion by the most commonly used parameters of ADC, *D*, *D**, and *f*. In some sense, the ADC and *D* values are the characterization of cell density and Brownian motion of water molecules within the organization, which is increasingly limited by smaller intercellular gaps. For gliomas, higher-grade tumors have greater cell density and more limited Brownian motion. Therefore, ADC and *D* values may be used to reflect the grade of gliomas.[28,29] Similarly, *D** values can indirectly reflect the microvascular proliferation or angiogenesis of tumors. Federau et al reported that no significant difference was observed for the *D** value,[30] while another previous study showed a significant difference in *D** between LGG and HGG[21]; the same parameter led to inconsistent results. Thus, we performed the present meta-analysis with the hope of resolving the incongruities in multiple studies by increasing the sample size and testing efficiency of each of the three parameters. To the authors' knowledge, this is the first meta-analysis to assess the overall values of IVIM in glioma grading.

We performed a meta-analysis to explore the validity in the utility of IVIM for distinguishing HGG from LGG. In the TP regions, a pooled analysis demonstrated that ADC and *D* values in HGG significantly lower compare with LGG, which was consistent with previous studies.[23,25] Because of HGG tumor cells proliferating rapidly, reducing the outer space, and more obviously limiting the diffusion of water molecules in the extracellular space, HGG had lower ADC and *D* values than LGG. In the present study, *D** value was significantly higher in HGG relative to LGG. It is may be related to the increase of neovascularization, blood supply, and blood flow in HGG.[26] Interestingly, the *f* values showed no significant difference between LGG and HGG, which was inconsistent with the result of recently published studies.[21,23] One possible reason for is the different number of *b* values were applied in included studies, Hu et al[23] suggested that the *b* value might affect the accuracy of the *f* value, the lower *b* values were more vital for receiving perfusion information. Another possible explanation may be that small sample data calculated in our study.

We further analysed the parameters in WM regions to provide additional insight into tumor tissue biology. In the WM regions, our study demonstrated that *D** value in HGG higher than in LGG with a statistical significance of $P = .04$ in the present study. Shen et al[25] revealed that the *D** value was influenced by MVD within the brain tumors, HGG were speculated to have relatively greater *D** value than LGG due to increased microvascular proliferation. The result may suggest that HGG are more infiltrative than LGG in the WM regions.

Moderate or high heterogeneity was observed for some of the IVIM parameters tested. One reason for the observed heterogeneity is that the meta-analysis consisted of a small sample

size, but this was uncontrollable. Based on the results of subgroup analysis of field strength and number of *b* values, heterogeneity decreased greatly. It was predicted that these factors may contribute to the heterogeneity among studies.

A few potential limitations of our study should be mentioned: First, the sample size is small; the present literature found only 8 studies that directly distinguished HGG from LGG. Second, there was heterogeneity among studies in this meta-analysis. Although subgroup analyses were applied, the results cannot explain the heterogeneity fully. Third, English and Chinese language restrictions were applied in this analysis, thus to some degree, there exists an inclusion bias. Furthermore, some inevitable publication bias may exist in our study, although Begg tests for the overall analysis reported no significant publication bias. Lastly, parameter values of IVIM may be affected by postprocessing techniques (the method of select ROI placement),[10] automatic segmentation of tumor area combined with pathologic analysis could overcome this problem.[26] In addition, theoretical and experimental evidence suggest that parameter values of IVIM may be affected by MRI scan parameters.[24] The longer the TE, the lower the *b* value and the higher the *f* value in signal attenuation.[25] The value of $D*$ was different in different brain tissues, and its accuracy was greatly influenced by cerebrospinal fluid.[22] To solve the above problems, it was best to optimize the parameter settings.

5. Conclusion

In conclusion, the present meta-analysis shows that the ADC, *D*, and $D*$ values derived from IVIM may be useful in differentiating HGG from LGG, unfortunately, there was no significant difference in *f* values between LGG and HGG. Considering the small sample of this study, the results of this study should be interpreted with caution because of the small sample size. Prospective, large-sample randomized controlled trials are warranted to establish the value of IVIM in differentiating HGG from LGG.

Author contributions

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Writing – review & editing: Chen Niu, Ming Zhang, Zhanqiu Wang.

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