The diagnostic value of quantitative analysis of ASL, DSC-MRI and DKI in the Grading of Cerebral Gliomas: A Meta-Analysis

Luan Jixin

Liaocheng People's Hospital

Mingzhen Wu

Liaocheng People's Hospital

Xiaohui Wang

Liaocheng People's Hospital

Lishan Qiao

Liaocheng University

Guifang Guo

Liaocheng People's Hospital

Chuanchen Zhang (✉ chuanchensci@126.com)

Shandong First Medical University <https://orcid.org/0000-0002-8467-5202>

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Abstract

Objective

To perform quantitative analysis on the efficacy of using relative cerebral blood flow (rCBF) in arterial spin labeling (ASL), relative cerebral blood volume (rCBV) in dynamic magnetic sensitivity contrast-enhanced magnetic resonance imaging (DSC-MRI), and mean kurtosis (MK) in diffusion kurtosis imaging (DKI) to grade cerebral gliomas.

Methods

Literature regarding ASL, DSC-MRI, or DKI in cerebral glioma grading in both English and Chinese were searched from PubMed, Embase, Web of Science, CBM, China National Knowledge Infrastructure (CNKI), and Wanfang Database as of April 2019. A Meta-Analysis was performed to evaluate the efficacy of ASL, DSC-MRI, and DKI in the grading of cerebral glioma.

Result

A total of 54 articles (11 in Chinese and 43 in English) were included. Three quantitative parameters in the grading of cerebral glioma, rCBF in ASL, rCBV in DSC-MRI, and MK in DKI had an overall sensitivity of 0.88[95%CI(0.83,0.92)], 92[95%CI(0.83,0.96)], 0.88[95%CI(0.82,0.92)], and an overall specificity of 0.91[95%CI(0.84,0.94)], 0.81[95%CI(0.73,0.88)], 0.86[95%CI(0.78,0.91)] respectively. The overall area under the ROC curve were 0.95[95%CI(0.93,0.97)], 0.91[95%CI(0.89,0.94)], 0.93[95%CI(0.91,0.95)] respectively.

Conclusion

Quantitative parameters rCBF, rCBV and MK have high diagnostic efficacy for preoperative grading of cerebral gliomas.

Introduction

Gliomas are the most common primary tumors of the central nervous system, accounting for about 45% of all intracranial tumors [1]. According to the World Health Organization (WHO) classification in 2016, (WHO I~II) is a low-grade glioma, (WHO III~IV) is a high-grade glioma [2]. Surgical resection combined with radiotherapy and chemotherapy is still the basic treatment for glioma. Low-grade glioma grows slowly and has a favorable prognosis in general [3]; on the other hand, the 5-year survival rate of high-grade glioblastoma is only 2%[4]. Therefore, accurate assessment of the pathological grade of glioma before surgery is of great clinical significance to determine the surgical resection range and to improve the survival rate of patients.

In the course of glioma progression, the microstructures of tumors (tumor cell density, cell proliferation activity, and microvessel density, etc.) will undergo tremendous changes, reflecting the changes in histopathological characteristics of tumors [5]. Traditional morphological magnetic resonance imaging (MRI) can estimate the extent of histopathological differentiation of tumors based on cytotoxic edema, hemorrhage, necrosis, heterogeneity of signal intensity, degree and range of signal enhancement. However, studies have shown that the enhancement of glioma is not completely consistent with tumor grade [6]. One article reports that the sensitivity of conventional MRI to differentiate high-grade gliomas from low-grade gliomas ranges from 55.1% to 83.3%[7].

With the continuous development of MRI technology, multi-modal fMRI technology has been used to evaluate the biological characteristics of glioma from different perspectives and has potential application value in the grading of glioma. Among them, artery spin labeling (ASL) and dynamic magnetic sensitivity enhanced perfusion imaging (DSC-MRI) are perfusion-weighted imaging techniques, while diffusion kurtosis imaging (DKI) is a diffusion magnetic resonance imaging technique. Quantitative perfusion parameters such as relative cerebral blood flow (rCBF) in ASL, relative cerebral blood volume (rCBV) in DSC and MK in DKI are receiving more attention in the clinical application of preoperative grading of glioma. Compared with low-grade glioma, high-grade glioma has a more abundant blood supply, so hemodynamic perfusion parameters will increase significantly [8]. The cellular pleomorphism and nuclear polymorphism in high-grade gliomas are more marked than those in low-grade gliomas, and the parameters associated with water molecular diffusion are also larger [9].

Most previous research only utilizes perfusion imaging or diffusion imaging to investigate the grading of glioma, focusing on meta-analysis of diagnostic accuracy. The meta-analysis of quantitative parameters of the above imaging methods are lacking. Moreover, previous efforts are only focused on the meta-analysis of diagnostic accuracy and lacking the meta-analysis on quantitative parameters of the above imaging methods. Due to the small sample size and incomplete parameters of individual studies, the reliability and repeatability of the technology are still unclear. Therefore, we propose a large sample-size comprehensive meta-analysis to resolve the conflicting findings in different studies and to evaluate the diagnostic performance of the quantitative perfusion parameters in glioma grading.

1. Materials And Methods

1.1

Literature Retrieval

A thorough search for literature from 2005–2019 relating to ASL, DSC-MRI or DKI in the grading of cerebral gliomas was performed, using sources from PubMed, Embase, Web of Science, CBM, China National Knowledge Infrastructure (CNKI), Wanfang Database English search keywords: (astrocytoma or

glioblastoma or glial tumor or astrocytic tumor or glioma or oligodendroglioma or oligodendroglial tumor) and(DKI or Diffusional Kurtosis or Imaging Kurtosis Imaging or kurtosis or DSC-MRI or Dynamic susceptibility contrast-enhanced MRI or Dynamic Susceptibility Contrast or DSC or rCBV or rCBF or ASL or arterial spin-labeling or perfusion or Continuous ASL perfusion or PASL or 3DpCASL or three-dimensional pseudo-continuous arterial spin labeling) Chinese search keywords: "arterial spin-labeling","Diffusion kurtosis imaging","Dynamic Contrast-enhanced Perfusion MR Imaging","grading","brain glioma","glioma". Only studies written in English or Chinese were selected. In order to avoid missing documents, the combination of Electronic Search and manual Search were performed.

1.2

Literature Inclusion and Exclusion Criteria

1.2.1

Inclusion Criteria:

(1) ASL, DSC-MRI or DKI were used to differentiate gliomas of different grades; (2) At least one quantitative parameter of rCBF, rCBV and MK could be extracted or calculated from the study; (3) Only pathological diagnoses were included; (4) All subtypes of gliomas were included; (5) Fourfold table values of diagnostic tests can be obtained directly or indirectly, i.e. true-positive, true-negative, false-positive, and false-negative; (6) The quality evaluation scores of the included studies were at least 9 since high-quality studies are the basis for reliable meta-analysis.

1.2.2 Exclusion criteria:

(1) animal experiments, such as animal experiments of rats; (2) any unpublished conference abstracts, comments, duplication of literature or research; (3) similar studies written by the same author; (4) lack of key data; (5) use of other imaging methods (such as CT, PET, etc.).

1.3

Data Extraction from literature

The basic information includes first author's name, country, the time of publication, patient age, tumor grade, number of cases, instrument type and field strength, journal of publication, methods, sequence and so on. Diagnostic information includes sensitivity, specificity, Fourfold table and the ROC curve with the corresponding AUC value. If the information could not be obtained directly, the statistics were performed with the number of HGG and LGG cases and the sensitivity and specificity provided by the literature using RevMan 5.3 Software [10]. For articles providing sample size, median, extremum or quartile, methods of Luo et al. [11] and Wan et al. [12] were applied to estimate the mean and standard deviation of samples respectively [13] and - the mean and standard deviation [14] from data of grade 3 and 4 gliomas subgroup were calculated. The basic information of the literature included is shown in Table 1.

1.4

Quality Evaluation

The quality assessment of diagnostic accuracy studies (QUADAS) -2 recommended by Cochrane Collaboration was adopted as the evaluation criterion [15]. QUADAS-2 consists of the following key aspects: patient selection, index test, gold standard, flow and timing. Each of them is assessed in terms of risk of bias and signaling questions (yes/no/unclear) are included to assist in judgements. When the criterion is yes, the score increases by 1 point. The scores of literature quality evaluation are shown in Table 1.

Database search was performed using methods described above. Retrieved hits were previewed at the title and abstract level was conducted by two researchers independently. For those literature that potentially comply to the inclusion criteria, full text was read to decide whether or not to include. If there were any disagreements especially on quality assessment, it was resolved by discussion with a third senior clinician. All selected studies were previously published, so there was no need for ethical review and approval or patients consent.

1.5 Data Analysis

1.5.1 Heterogeneity Test

Heterogeneity caused by different type of research design, age and gender of patients, pathological subtypes and other variables is a critical factor influencing the accuracy of results. The existence Non-threshold effect was tested by Q-test and I^2 value using RevMan 5.3 Software. $I^2 \leq 50\%$ indicates insignificant heterogeneity, and a Fixed-effect model was applied to merge statistics. $I^2 \geq 50\%$ indicates substantial heterogeneity, and a random-effect model was used to merge statistics. Q-test level was $p < 0.05$.

1.5.2 Meta-Analysis

RevMan 5.3 Software (Cochrane Collaboration, Oxford, UK) was used to calculate the effect size and 95% CI. The overall sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic ratio, AUC and its 95% CI were calculated by Stata 13.1, and SROC curves were constructed.

1.5.3 Publication bias

Publication bias was evaluated with Deek's funnel plot by Stata 13.1 software. $P > 0.1$ indicated that there was no publication bias.

1.5.4 Sensitivity Analysis

After selection of the literature, the remaining studies were included in meta-analysis, and their stability were evaluated.

Table.1. Basic information of included studies

First author	Region	Average or median age	n	Gliomas grade(n)	Instrument Type and Field Strength	Technique	Diagnostic parameters	QUADAS-2 score
Arisawa 2018[16]	Japan	50(19–74)	34	I + II(15),III + IV(19)	GE 3.0T	ASL,DSC	rCBF,rCBV	12
Cebeci 2014[17]	Turkey	47 ± 14	33	I + II(13),III + IV(20)	Philips 3.0T	ASL	rCBF	13
Fudaba 2014[18]	Japan	59.8 ± 16.8	32	II(9),III(8),IV(15)	Siemens 3.0T	ASL	rCBF	13
Furtner 2014[19]	Australia	54 ± 17	33	II(7),III(7),IV(19)	Siemens 3.0T	ASL	rCBF	12
Jiang J 2014[20]	China	42.7 ± 15.3	23	I + II(10),III + IV(13)	GE 3.0T	ASL	rCBF	12
Kim 2008[21]	South Korea	43(19–74)	61	I + II(26),III + IV(35)	GE 1.5T	ASL	rCBF	11
Liao H 2016[22]	China	40.5	41	I + II(20),III + IV(21)	GE 3.0T	ASL	rCBF	11
Liu 2014[23]	China	8–75	38	I(5),II(17),III(7),IV(9)	GE 3.0T	ASL	rCBF	12
Ma 2017[24]	China	46 ± 18	50	I + II(27),III + IV(23)	GE 3.0T	ASL,DSC	rCBF,rCBV	11
Qiao F 2015[25]	China	50(26–72)	28	I + II(11),III + IV(17)	GE 3.0T	ASL	rCBF	10
Roy 2013[7]	India	43	64	I(3),II(23),III(9),IV(29)	GE 3.0T	ASL	rCBF	11
Shen 2016[26]	China	42	52	I + II(25),III + IV(27)	GE 3.0T	ASL	rCBF	9
Tian Q 2015[27]	China	47(19–76)	45	I + II(19),III + IV(26)	GE 3.0T	ASL	rCBF	12
Wang N 2019[28]	China	48(23–81)	53	I(1),II(15),III(13),IV(24)	GE 3.0T	ASL	rCBF	10
Morana 2018[29]	Italy	9(2–17)	37	I(8),II(14),III(6),IV(9)	Philips 1.5T	ASL,DSC	rCBF,rCBV	10
Wolf 2005[30]	USA	50 ± 12	26	I + II(7),III + IV(19)	Siemens 3.0T	ASL	rCBF	10
Xiao 2015[31]	China	43.3(6–74)	43	I + II(19),III + IV(24)	GE 3.0T	ASL	rCBF	11
Yang 2016[32]	China	51 ± 15.34	43	II(15),III(15),IV(13)	Siemens 3.0T	ASL	rCBF	12
Zeng 2017[33]	China	50 ± 13	58	II(13),III(17),IV(28)	GE 3.0T	ASL	rCBF	11
Zhao J 2016[34]	China	42(15–64)	18	I + II(8),III + IV(10)	GE 3.0T	ASL	rCBF	9
Van Cauter 2014[35]	Belgium	55	31/35	I + II(12),III + IV(19)-DSC I + II(13),III + IV(22)-DKI	Philips 3.0T	DSC,DKI	rCBV,MK	9
Awasthi 2012[36]	India	16–65	76	I + II(21),III + IV(55)	GE 1.5T	DSC	rCBV	12
Boxerman 2016[37]	USA	52(19–80)	43	II(11),III(9),IV(23)	GE 1.5T	DSC	rCBV	12
Brendle 2018[38]	Germany	23–79	41	I + II(24),III + IV(17)	Siemens 3.0T	DSC	rCBV	14
Catalaa 2006[39]	USA	23–78	17	II(8),III(9)	GE 1.5T	DSC	rCBV	11
Cuccarini 2016[40]	Italy	39.6 ± 12.6	68	I + II(42),III + IV(26)	Siemens 1.5T	DSC	rCBV	12
Dallery 2017[41]	France	9.4(2.1–17.9)	30	I(7),II(4),III(7),IV(12)	GE 3.0T	DSC	rCBV	11
Falk 2014[42]	Sweden	22–79	25	II(18),III(7)	Philips 3.0T	DSC	rCBV	10
Fatima 2014[43]	Brazil	36.23 ± 16.95	38	I + II(16),III + IV(22)	GE 1.5T	DSC	rCBV	13
Hilario 2012[44]	Spain	23–79	162	II(32),III(29),IV(101)	GE 3.0T	DSC	rCBV	10
Huang 2015[45]	China	45(17–72)	35	I(2),II(12),III(9),IV(12)	Siemens 3.0T	DSC	rCBV	9
Kim 2013[46]	South Korea	35	63	II(9),III(16),IV(38)	Siemens 3.0T	DSC	rCBV	9
Law 2006[47]	USA	42(4–85)	73	II(31),III(16),IV(26)	Siemens 3.0T	DSC	rCBV	11

First author	Region	Average or median age	n	Gliomas grade(n)	Instrument Type and Field Strength	Technique	Diagnostic parameters	QUADAS-2 score
Wang M 2011[48]	China	42.9 ± 14.7	23	I(1),II(5),III(8),IV(9)	Siemens 3.0T	ASL,DSC	rCBF,rCBV	9
Nguyen 2016[49]	Canada	54	43	I + II(10),III + IV(33)	Siemens 3.0T	DSC	rCBV	12
Santarosa 2016[8]	Italy	55.4(22–79)	26	II(9),III(4),IV(13)	Philips 3.0T	DSC	rCBV	9
Server 2011[50]	Norway	57.73 ± 12.95	79	II(18),III(14),IV(47)	GE 3.0T	DSC	rCBV	10
Togao 2017[51]	Japan	14–75	34	I + II(20),III + IV(14)	Philips 3.0T	DSC	rCBV	12
Wang X 2016[52]	China	41 ± 15	37	I + II(14),III + IV(23)	GE 3.0T	ASL,DKI	rCBF,MK	10
Falk Delgado 2017[53]	Sweden	48 ± 15	35	II(23),III(12)	Philips 3.0T	DKI	MK	10
Gao A 2017[54]	China	48.66 ± 13.42	34	II(21),III(13)	Siemens 3.0T	DKI	MK	10
Hempel 2017[55]	USA	50 ± 14	50	II(25),III(15),IV(10)	Siemens 3.0T	DKI	MK	11
Jiang 2015[56]	China	41 ± 14	74	I(3),II(31),III(19),IV(21)	GE 3.0T	DKI	MK	10
Li 2016[57]	China	47	37	I + II(16),III + IV(21)	Siemens 3.0T	DKI	MK	9
Lin 2018[58]	China	42–75	96	I + II(84),III + IV(12)	GE 3.0T	DKI	MK	10
Maximov 2017[59]	Germany	18–59	24	II(8),III(8),IV(8)	GE 3.0T	DKI	MK	11
Qi 2018[60]	China	11–67	39	I + II(13),III + IV(26)	Siemens 3.0T	DKI	MK	9
Raab 2010[61]	Germany	56	18	II(5),III(13)	Siemens 3.0T	DKI	MK	11
Raja 2016[62]	Germany	35	18	II(9),III(9)	Philips 3.0T	DKI	MK	12
Tan 2016[63]	China	50	60	I + II(25),III + IV(35)	GE 3.0T	DKI	MK	11
Tietze 2015[64]	Denmark	42	34	II(12),III(7),IV(15)	Siemens 3.0T	DKI	MK	10
Zheng G 2014[65]	China	40.3 ± 19.5	21	I(2),II(3),III(7),IV(9)	GE 3.0T	ASL,DSC	rCBF,rCBV	10
Wang Y 2017[66]	China	47.5(25–75)	32	I + II(14),III + IV(18)	Siemens 3.0T	DKI	MK	10
Zhao 2019[67]	China	25–75	52	II(24),III(8),IV(20)	Siemens 3.0T	DKI	MK	12

2. Results

2.1

Literature Retrieval Results

Fifty-four studies were selected for inclusion after reading the full text, of which 43 were in English and 11 were in Chinese. Patients include both adults and children. The studies were conducted in the following countries: China (n = 24), India (n = 2), Italy (n = 3), Spain (n = 1), Turkey (n = 1), Sweden (n = 2), Japan (n = 3), Norway (n = 1), the United States (n = 5), Canada (n = 1), Korea (n = 2), France (n = 1), Germany (n = 4), Denmark (n = 1), Belgium (n = 1), Brazil (n = 1), Australia (n = 1). Seven studies reported two methods. Of those studies including quantitative data and Continuous Variable Forest Map, 20 was in ASL, 22 in DSC, 15 in DKI of the studies. Of those studies including fourfold table data for meta-analysis of diagnostic tests, 19 was in ASL, 19 in DSC, 16 in DKI. The retrieval process is shown in Fig. 1.

2.2 Analysis

2.2.1 rCBF in ASL

Twenty studies assessing the difference of rCBF between HGG and LGG were included. Heterogeneity test showed that $\chi^2 = 66.79$, $I^2 = 72\%$, $P < 0.001$, indicating substantial heterogeneity. Therefore, the random effect model was applied to estimate the overall rCBF. The overall rCBF was 1.45 (1.12, 1.77), $P < 0.001$ (Fig. 2).

2.2.2 rCBV in DSC-MRI

Twenty-two studies assessing the difference of rCBV between HGG and LGG were included. Heterogeneity test showed that $\chi^2 = 74.23$, $I^2 = 72\%$, $P < 0.001$, indicating substantial heterogeneity. Therefore, the random effect model was applied to estimate the overall rCBV. The overall rCBV was 1.37 (1.08, 1.66), $P < 0.001$ (Fig. 3).

2.2.3 MK in DKI

Fifteen studies assessing the difference of MK between HGG and LGG were included. Heterogeneity test showed that $\chi^2 = 46.39$, $I^2 = 70\%$, $P < 0.001$, indicating substantial heterogeneity. Therefore, the random effect model was applied to estimate the overall MK. The overall MK was 1.57 (1.21, 1.93), $P < 0.001$ (Fig. 4).

2.2.4 Diagnostic Value

Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic ratio and area under curve were summarized according to the studies including fourfold table (Table 2). The results showed that rCBF had the highest diagnostic ratio of 71 (31,163). According to the SROC curve (Fig. 5), the largest AUC was rCBF, followed by MK and rCBV

The incidence of glioma is about 45% of all intracranial tumors [63]. Fagan diagram of diagnostic grading of glioma by rCBF, rCBV and MK is shown in Fig. 6. If the prior probability is 45%, the posterior probability of rCBF, rCBV and MK is 88%, 80% and 83% respectively. The higher the DOR value, the better the discrimination ability. The DOR value of rCBF is 71 (31,163), indicating an overall high accuracy.

(As shown in Figure A, assuming that the patient's prior probability is 45%, the posterior probability is 88%, and the PLR is 9.)

Table 2
The values of rCBF, rCBV and MK

index	n	Sen (95%CI)	Spe (95%CI)	PLR (95%CI)	NLR (95%CI)	DOR (95%CI)	AUC (95%CI)
rCBF	19	0.88 (0.83,0.92)	0.91 (0.84,0.94)	9.3 (5.4,16.0)	0.13 (0.09,0.20)	71 (31,163)	0.95 (0.93,0.97)
rCBV	19	0.92 (0.83,0.96)	0.81 (0.73,0.88)	5.0 (3.3,7.4)	0.10 (0.05,0.22)	50 (20,129)	0.91 (0.89,0.94)
MK	16	0.88 (0.82,0.92)	0.86 (0.78,0.91)	6.2 (4.1,9.3)	0.14 (0.10,0.21)	44 (26,75)	0.93 (0.91,0.95)

2.2.5 Meta-regression

The results of meta-regression are shown in Table 3. The results showed that among the five covariates in ASL study, region, year of study, number of patients and QUADAS-2 score were all important factors contributing to heterogeneity except for field strength. Among the six covariates in DSC-MRI study, region, year of study, number of patients, field strength and QUADAS-2 score, none had significant impact on heterogeneity. Among the five covariates in DKI study, the year of study, age of patients, number of patients and QUADAS-2 score all had no significant impact on heterogeneity except for region.

Table 3
meta-regression

	Variable	Subgroup	n	Overall estimate of meta-regression			
				Sensitivity(95% CI)	p	Specificity(95% CI)	p
ASL	Region	China	14	0.89(0.84,0.94)	0.01	0.89(0.83,0.95)	0.71
		others	5	0.86(0.77,0.95)		0.94(0.88,1.00)	
	Year	2008–2014	8	0.87(0.80,0.93)	0.00	0.88(0.80,0.96)	0.01
		2015–2019	11	0.89(0.83,0.95)		0.92(0.87,0.98)	
	Number of patients	≤ 40	10	0.90(0.84,0.95)	0.00	0.93(0.87,0.99)	0.01
		≥40	9	0.87(0.81,0.93)		0.88(0.81,0.95)	
	Field strength	1.5T	2	0.90(0.79,1.00)	0.21	0.96(0.90,1.00)	0.13
		3.0T	17	0.88(0.83,0.93)		0.89(0.84,0.94)	
	QUADAS-2 score	≤ 10	7	0.93(0.89,0.98)	0.00	0.94(0.89,1.00)	0.01
		≥10	12	0.84(0.79,0.90)		0.88(0.81,0.94)	
DSC-MRI	Region	China	4	0.94(0.83,1.00)	0.77	0.88(0.74,1.00)	0.14
		others	15	0.91(0.84,0.99)		0.80(0.72,0.88)	
	Year	2006–2014	10	0.95(0.89,1.00)	0.07	0.80(0.69,0.90)	0.20
		2015–2017	9	0.87(0.74,0.99)		0.83(0.73,0.93)	
	Age	≤ 45	9	0.94(0.87,1.00)	0.31	0.85(0.75,0.95)	0.03
		≥45	10	0.90(0.80,1.00)		0.79(0.68,0.89)	
	Number of patients	≤ 40	10	0.95(0.88,1.00)	0.33	0.89(0.82,0.95)	0.56
		≥40	9	0.89(0.79,1.00)		0.72(0.62,0.83)	
	Field strength	1.5T	4	0.98(0.93,1.00)	0.23	0.76(0.60,0.92)	0.00
		3.0T	15	0.90(0.82,0.98)		0.83(0.75,0.91)	
	QUADAS-2 score	≤ 10	10	0.94(0.88,1.00)	0.14	0.86(0.77,0.95)	0.01
		≥10	9	0.88(0.77,0.99)		0.77(0.66,0.88)	
DKI	Region	China	9	0.89(0.83,0.95)	0.01	0.89(0.82,0.95)	0.01
		others	7	0.86(0.77,0.94)		0.81(0.69,0.92)	
	Year	2010–2015	4	0.85(0.75,0.95)	0.14	0.89(0.79,0.99)	0.06
		2016–2019	12	0.89(0.84,0.94)		0.85(0.77,0.96)	
	Age	≤ 48	9	0.85(0.78,0.92)	0.14	0.87(0.79,0.94)	0.02
		≥48	7	0.91(0.85,0.97)		0.84(0.75,0.93)	
	Number of patients	≤ 40	11	0.83(0.77,0.89)	0.32	0.88(0.81,0.94)	0.00
		≥40	5	0.93(0.89,0.98)		0.80(0.70,0.90)	
	QUADAS-2 score	≤ 10	10	0.84(0.78,0.91)	0.18	0.87(0.80,0.94)	0.02
		≥10	6	0.92(0.87,0.97)		0.83(0.72,0.93)	

2.2.6 Subgroup analysis

In ASL, subgroup analysis was carried out based on region and technique; in DSC-MRI, subgroup analysis was carried out based on region and magnetic resonance field strength; in DKI, subgroup analysis was carried out based on region. The results of subgroup analysis are shown in Table 4.

Table.4. Subgroup analysis

	Subgroup	Category	n	p	Sen (95%CI)	Spe (95%CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
ASL	Region	CHINA	14	0.30	0.88 (0.83,0.92)	0.89 (0.81,0.94)	8.4 (4.5,15.4)	0.13 (0.09,0.20)	63 (25,157)	0.94 (0.92,0.96)
		other	5	0.35	0.89 (0.68,0.97)	0.94 (0.84,0.98)	14.0(5.1,38.2)	0.11(0.03,0.40)	123(18,846)	0.96 (0.94,0.98)
	Technique	3DPCASL	10	0.33	0.87 (0.82,0.91)	0.88 (0.81,0.93)	7.6 (4.4,13.1)	0.14 (0.10,0.21)	53 (24,116)	0.92 (0.90,0.94)
		PASL	8	0.46	0.93(0.75,0.98)	0.93(0.80,0.98)	14.2(4.2,48.1)	0.08(0.02,0.31)	183(19,1754)	0.98(0.96,0.99)
DSC-MRI	Region	CHINA	4	0.23	0.91(0.82,0.96)	0.90(0.55,0.99)	9.6(1.5,60.4)	0.10(0.05,0.21)	95 (11,835)	0.89(0.82,0.96)
		other	15	0.00	0.92(0.80,0.97)	0.80(0.70,0.87)	4.6(3.1,6.9)	0.10(0.04,0.26)	46 (15,144)	0.90(0.87,0.92)
	Field strength	3.0 T	15	0.00	0.88(0.79,0.94)	0.82(0.73,0.89)	5.0(3.2,7.7)	0.14(0.08,0.26)	35 (17,73)	0.91(0.88,0.93)
		1.5 T	4	0.01	1.00(0.12,1.00)	0.77(0.57,0.90)	4.4(2.1,9.1)	0.00(0.00,10.67)	2976(0,3125)	0.91(0.89,0.93)
DKI	Region	CHINA	9	0.00	0.90(0.81,0.95)	0.90(0.79,0.95)	8.6(4.3,17.2)	0.11(0.06,0.21)	75 (35,160)	0.95(0.93,0.97)
		other	7	0.46	0.85(0.76,0.91)	0.79(0.69,0.87)	4.1(2.7,6.2)	0.20(0.12,0.32)	21 (10,44)	0.88(0.85,0.91)

2.3 Publication bias

Deek's test was used to evaluate publication bias for studies containing fourfold tables. $P > 0.1$ indicated that there was no publication bias. Among them, 19 studies were included for ASL. Deek's test showed $P = 0.85$ indicating no significant publication bias (Deek's funnel plot Fig. 7a). 19 studies were included for DSC-MRI. Deek's test showed $P = 0.45$ indicating no significant publication bias (Deek's funnel plot Fig. 7b). 16 studies were included for DKI. Deek's test showed $P = 0.12$ indicating no significant publication bias (Deek's funnel plot Fig. 7c).

2.4 Sensitivity Analysis

Sensitivity analysis is an important method to deal with heterogeneity and publication bias. There was no significant difference in meta-analysis results of rCBF and rCBV after excluding the literature one by one, suggesting that rCBF and rCBV were more stable to be included in the literature. In DKI, after excluding Falk Delgado's research, χ^2 decreased from 46.39 to 28.11, and I² from 70–54%, suggesting significant heterogeneity brought by this study.

3. Discussion

This meta-analysis revealed higher values of rCBF, rCBV and MK in HGG than that in LGG, indicating statistically significant. The specificity of rCBF is the highest among all parameters, suggesting that the rate of misdiagnosis in rCBF is the lowest. The sensitivity of rCBV is the highest, suggesting that the rate of missed diagnosis in rCBV is the lowest. The results of meta-regression showed that there were many factors contributing to the heterogeneity of ASL studies, while the studies of DSC and DKI were relatively stable. Although three kinds of MRI techniques were included in the whole study, all of them showed high efficacy in diagnostics and could be applied to grade gliomas.

DSC perfusion imaging is performed by intravenous injection of contrast agent, which reaches the tumor tissue through the damaged blood-brain barrier changing the local magnetic field of the tumor and strengthening the solid part of the tumor [8]. Compared to low-grade glioma, High-grade glioma has more abundant blood supply; therefore, the hemodynamic perfusion parameters (rCBV) will increase significantly, which is consistent with the findings of Winkler Frank et al. [68]. Awasthi et al. [36] observed that the MVD (microvessel density) and the positive expression of VEGF(vascular endothelial growth factor) had significant correlation with the pathological grade of glioma and the rCBV value. The MVD and the positive expression of VEGF was significantly higher in high-grade glioma than that in low-grade glioma. rCBV value was also significantly increase in high grade glioma. However, rCBV is not applicable to differentiating glioma from metastasis. Different types of glioma may also lead to different assessments [69].

ASL is a non-invasive perfusion technique in grading HGG and LGG by measuring the ratio of tumor blood flow to contralateral cerebral blood flow (rCBF). In addition, this technique is not affected by the integrity of blood-brain barrier, which help reflect the perfusion status of the tissue more accurately [70]. For children and restless patients, ASL has the advantage of repeated application. The ability to distinguish LGG from HGG by ASL and DSC were about the same when compared in some studies [71]. Luh, W. M. et.al [72] confirmed that the assessments on the effect of blood perfusion of high-grade glioma by ASL and DSC are relatively consistent and closely correlated. According to article [73–75], ASL can replace DSC in assessing blood perfusion of high-grade glioma.

Diffusional kurtosis imaging (DKI), first proposed by Professor Jensen of New York University in 2005, is a technique intending to explore the properties of non-gaussian diffusion of water molecules [76–77]. The most commonly used parameter of DKI is mean kurtosis (MK) which measures the complexity of tissue structure in the region of interest. The cellular pleomorphism and nuclear polymorphism in high-grade gliomas are more significant than those in low grade gliomas. The proliferation of interstitial vessels is also more abundant in HGG and the MK value is higher [9]. Some studies indicated that MK is higher in high-grade gliomas. The area under MK characteristic curve, approximately 0.972, is the largest in terms of detecting the difference between LGG and HGG, Especially for the difference between grade II from grade III gliomas, the area under MK curve can be as high as 0.923[61]. Therefore, MK value can reflect the complexity of glioma microstructures and be used to grade gliomas.

Heterogeneity is common in meta-analysis. After excluding the research of Falk Delgado et al., the heterogeneity of MK decreased from 70–54%. Since there is moderate heterogeneity in this meta-analysis, clinical decisions should be made cautiously based on these results. Heterogeneity may be caused by the following aspects: (1) imbalance in the distribution of HGG and LGG: for instance, grade I gliomas were not studied in some research which resulted bias in case selection; (2) different experimental conditions set by researchers, such as different instrument models, parameter settings, post-processing methods, etc. (3) regional heterogeneity resulted from inclusion of literature from different countries and regions; (4) rCBF can refer to maximum tumor blood flow/normal white matter, maximum tumor blood flow/normal gray matter, or maximum tumor blood flow/normal hemisphere. Strict distinction was not made among the three ratios in some literature, only a general rCBF value was provided,, which may have an impact on the results.

The main limitations of this study are: 1. This study only focused on diagnostic value of ASL,DSC-MRI and DKI in distinguishing LGG from HGG. Each specific pathological grade of glioma was not discussed; 2. Only research in Chinese and English were included, and research in other languages were excluded. 3. The updated WHO classification criteria in 2016 emphasized more on cancer genomics. Therefore, it is necessary to perform meta-analysis of glioma grading based on 2016 WHO classification in the future.

4. Conclusion

In conclusion, ASL, DSC-MRI and DKI, using rCBF, rCBV and MK as quantitative diagnostic parameters, have high efficacy in distinguishing LGG from HGG, showing bright prospects for clinical application. Among the three methods, ASL has the highest diagnostic value. ASL is safe and noninvasive, able to be applied without a contrast agent. ASL can also be used to examine patients for multiple times and is more acceptable for patients. Therefore, ASL should be encouraged to use more widely in the grading of cerebral glioma.

Abbreviations List

ASL arterial spin labeling

DSC-MRI dynamic magnetic sensitivity contrast-enhanced magnetic resonance imaging

DKI diffusion kurtosis imaging

rCBF cerebral blood flow

rCBV relative cerebral blood volume

MK mean kurtosis

CBM China Biology Medicine disc

CNKI China National Knowledge Infrastructure

3DpCASL three-dimensional pseudo-continuous arterial spin labeling

CT computed tomography

PET positron emission tomography

Declarations

All selected studies were previously published, so there was no need for ethical review and approval or patients consent.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no conflict of interest

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Authors' contributions:

Chuanchen Zhang defined the topic and manuscript outline. Mingzhe Wu finished data collection. Jixin Luan, Xiaohui Wang and Lishan Qiao finished data analysis. Jixin Luan was a major contributor in writing the manuscript. Chuanchen Zhang and Guifang Guo finished manuscript quality control. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of literature screening and identification process

Study or Subgroup	High Grade			Low Grade			Weight	Std. Mean IV, Ra
	Mean	SD	Total	Mean	SD	Total		
Arisawa 2018	2.25	1.01	19	1.47	0.6	15	5.4%	0.8
Cebeci 2014	4.847	1.475	20	1.041	0.574	13	4.1%	3.0
Fudaba 2014	0	0	23	0	0	9		
Furtner 2014	3.09	2.54	26	1.08	0.39	7	4.8%	0.8
Jiang J 2014	3.154	2.907	13	1.291	0.826	10	4.8%	0.7
Kim 2008	0	0	35	0	0	26		
Liao H 2016	2.86	0.9	21	1.25	0.4	20	5.1%	2.2
Liu 2014	0	0	16	0	0	22		
Ma 2017	5.41	3.74	23	2.13	2.26	27	5.9%	1.0
Morana 2018	1.37	0.26	15	0.59	0.27	22	4.5%	2.8
Qiao F 2015	3.42	1.22	17	1.49	0.21	11	4.5%	1.8
Roy 2013	3.34	1.01	38	2.93	0.96	26	6.2%	0.4
Shen 2016	2.021	0.611	27	0.971	0.268	25	5.5%	2.1
Tian Q 2015	2.72	3.22	26	1.02	1.47	19	5.8%	0.6
Wang M 2011	3.34	1.2	17	0.63	0.52	6	3.6%	2.4
Wang N 2019	2.195	0.949	37	1.212	0.504	16	5.7%	1.1
Wang X 2016	1.6	0.42	23	1.16	0.15	14	5.3%	1.2
Wolf 2005	2.84	1.78	19	1.12	0.38	7	4.6%	1.0
Xiao 2015	4.505	2.27	24	1.81	0.979	19	5.5%	1.4
Yang 2016	4.668	3.427	28	2.399	2.397	15	5.7%	0.7
Zeng 2017	2.08	0.63	45	1.03	0.41	13	5.4%	1.7
Zhao J 2016	2.65	0.82	10	1.64	0.63	8	4.2%	1.2
Zheng G 2014	3.44	1.23	16	0.64	0.51	5	3.4%	2.4
Total (95% CI)			538			355	100.0%	1.4
Heterogeneity: Tau ² = 0.38; Chi ² = 66.79, df = 19 (P < 0.00001); I ² = 72%								
Test for overall effect: Z = 8.75 (P < 0.00001)								

Figure 2

Forest plot of mean difference in rCBF between HGG and LGG in ASL. Positive results were observed between HGG and LGG.

Figure 3

Forest plot of mean difference in rCBV between HGG and LGG in DSC-MRI. Positive results were observed between HGG and LGG.

Figure 4

Forest plot of mean difference in MK between HGG and LGG in DKI. Positive results were observed between HGG and LGG.

Figure 5

SROC Curve for Each Parameter in the Grading of Cerebral Glioma A.ASL,B. DSC-MRI,C.DKI

Figure 6

Fagan Map for Each Parameter in the Grading of Cerebral Glioma FIG. 6A.ASL,B. DSC-MRI,C.DKI

Figure 7

Deek's Funnel Plot of Publication Bias A.ASL,B. DSC-MRI,C.DKI