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Imaging prediction of isocitrate dehydrogenase (IDH) mutation in patients with glioma: a systemic review and meta-analysis

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Abstract

Objectives To evaluate the imaging features of isocitrate dehydrogenase (IDH) mutant glioma and to assess the diagnostic performance of magnetic resonance imaging (MRI) for prediction of IDH mutation in patients with glioma.

Methods A systematic search of Ovid-MEDLINE and EMBASE up to 10 October 2017 was conducted to find relevant studies. The search terms combined synonyms for 'glioma', 'IDH mutation' and 'MRI'. Studies evaluating the imaging features of IDH mutant glioma and the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma were selected. The pooled summary estimates of sensitivity and specificity and their 95% confidence intervals (CIs) were calculated using a bivariate random-effects model. The results of multiple subgroup analyses are reported.

Results Twenty-eight original articles in a total of 2,146 patients with glioma were included. IDH mutant glioma showed frontal lobe predominance, less contrast enhancement, well-defined border, high apparent diffusion coefficient (ADC) value and low relative cerebral blood volume (rCBV) value. For the meta-analysis that included 18 original articles, the summary sensitivity was 86% (95% CI, 79%–91%) and the summary specificity was 87% (95% CI, 78–92%). In a subgroup analysis, the summary sensitivity of 2-hydroxyglutarate magnetic resonance spectroscopy (MRS) [96% (95% CI, 91–100%)] was higher than the summary sensitivities of other imaging modalities.

Conclusions IDH mutant glioma consistently demonstrated less aggressive imaging features than IDH wild-type glioma. Despite the variety of different MRI techniques used, MRI showed the potential to non-invasively predict IDH mutation in patients with glioma. 2-Hydroxyglutarate MRS shows higher pooled sensitivity than other imaging modalities.

Key Points

- *IDH mutant glioma showed frontal lobe predominance, less contrast enhancement, well-defined border, high ADC value, and low rCBV value.*
- *The diagnostic performance of MRI for prediction of IDH mutation in patients with glioma is within a clinically acceptable range, the summary sensitivity was 86% (95% CI, 79–91%) and the summary specificity was 87% (95% CI, 78–92%).*
- *In a subgroup analysis, the summary sensitivity of 2-hydroxyglutarate MRS [96% (95% CI, 91–100%)] was higher than the summary sensitivities of other imaging modalities.*

Keywords Glioma · Magnetic resonance imaging · Diffusion · Perfusion · Magnetic resonance spectroscopy

Abbreviation

ADC	Apparent diffusion coefficient
APTw	Amide proton transfer-weighted
DWI	Diffusion-weighted imaging
HSROC	Hierarchical summary receiver operating characteristic
IDH	Isocitrate dehydrogenase
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

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PWI Perfusion-weighted imaging
QUADAS-2 Quality assessment of diagnostic accuracy studies-2
rCBV Relative cerebral blood volume
WHO World Health Organization

Introduction

In the 2016 World Health Organization (WHO) classification [1], grades II, III and IV gliomas are divided into isocitrate dehydrogenase (IDH) mutant glioma and IDH wild-type glioma. IDH mutation occurs in most WHO grade II and III gliomas, and also in secondary glioblastoma [2]. The IDH gene plays important roles in metabolism, cellularity and angiogenesis [3]. Recent studies revealed that IDH mutant glioma demonstrates significant positive effects on survival and chemosensitivity compared with IDH wild-type glioma [4–6].

Immunohistochemistry and genomic sequence analysis are regarded as "gold standard" methods for detecting IDH mutations in patients with glioma [3]. However, these methods are invasive because they require histopathological specimens; furthermore, a biopsy may also lead to an incorrect result due to intratumoural heterogeneity. In addition, minor changes after biopsy may change the staging. Intratumoural genetic heterogeneity reduces the value of invasive biopsy-based genomic analysis but provides opportunities for medical imaging procedures that can depict the entire tumour in a non-invasive and repeatable way. Therefore, a non-invasive and accurate method to predict IDH mutation may have great potential in routine clinical practice and could help with the implementation of appropriate management procedures in patients with glioma.

Magnetic resonance imaging (MRI) has served as an important non-invasive modality of choice for examining gliomas. Recently, multiple studies reported on the imaging features and/or the high diagnostic performance of MRI for prediction of IDH mutation in patients with glioma [7–34]. Various MRI modalities have been used, including conventional MRI as well as advanced techniques such as diffusion-weighted imaging (DWI) or perfusion-weighted imaging (PWI). In addition, 2-hydroxyglutarate magnetic resonance spectroscopy (MRS) has been introduced to detect the oncometabolite 2-hydroxyglutarate, which is a direct consequence of an IDH mutation [35]. Moreover, radiomics approaches using high-throughput quantitative imaging features have been successfully used in IDH mutation detection [36]. Therefore, imaging prediction of IDH mutation would be a valuable adjunct in and informative to clinical decision-making, and will become valuable as IDH mutant inhibitors become clinically available, and might be used as neoadjuvant therapy [37].

However, the imaging prediction of IDH mutation has not yet been systematically evaluated. Moreover, factors affecting the diagnostic performance should be found if heterogeneity exists. Therefore, the purpose of our study was to evaluate the imaging features of IDH mutant glioma and to assess the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma.

Materials and methods

This systematic review and meta-analysis were performed and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [38].

Literature search

A systematic search of Ovid-MEDLINE and EMBASE up to 10 October 2017 was conducted to find studies evaluating the imaging features of IDH mutant glioma and the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma. The search terms combined synonyms for 'glioma', 'IDH mutation' and 'MRI' as follows: [(glioma*) OR (glioblastoma*) OR (astrocytoma*) OR (astroglioma*) OR (oligodendroglial)] AND [("isocitrate dehydrogenase") OR (IDH) OR (IDH1) OR (IDH1/2)] AND [(magnetic resonance imaging) OR (MR imaging) OR (MRI)]. The bibliographies of identified studies were screened to expand the extent of the search. The systematic search was limited to English language publications.

Inclusion criteria

Studies (or subsets of studies) were included if they satisfied all of the following criteria: (1) patients with grade II, III and IV gliomas histopathologically confirmed according to the 2007 or 2016 WHO classification criteria [1, 39]; (2) conventional MRI, advanced MRI or radiomics approach performed before treatment; (3) a reference standard based on immunohistochemistry analysis for IDH1 mutation (R132H) and/or genomic sequencing analysis for the IDH1 and IDH2 genes; (4) sufficient detail for acquisition of the imaging features of IDH mutant glioma or reconstruction of 2 × 2 tables for determination of the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma.

Exclusion criteria

Studies were excluded if any of following criteria were met: (1) case reports or case series involving less than ten patients; (2) conference abstracts, letters, editorials, comments and reviews; (3) a study population comprised of patients with recurrent glioma; (4) studies focusing on topics other than the

use of MRI to diagnose IDH mutation; (5) studies with a partially overlapping patient population. For studies with an overlapping study population or study period, the study with the largest and latest population was included. Authors of the studies were contacted for provision of further information when 2 × 2 tables could not be obtained.

Data extraction and quality assessment

A standardised form was used to extract the following data from the included studies: (1) study characteristics: authors, publication year, affiliation, duration of patient recruitment, study design (prospective vs retrospective design), study enrolment (consecutive vs non-consecutive enrolment), the reference standard, interval between MRI and the reference standard, and blinding to the reference standard; (2) demographic and clinical characteristics: sample size, number of patients with IDH mutation, mean age (range), male and female ratio, and underlying disease; (3) technical characteristics of MRI: magnetic field strength, scanner manufacturer and model, head coil channels, types of MRI techniques or sequences, the specific technical parameters, and cut-off values for diagnosing IDH mutation; (4) MRI interpretation: number of readers, experience, and blinding to the reference standard; (5) imaging features of IDH mutant glioma and the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma.

The methodological quality assessment was evaluated using tailored questionnaires and the criteria of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [40]. Literature selection, data extraction, and quality assessment were performed independently by two reviewers (C.H.S. and H.S.K.). If disagreement was present, a third reviewer (S.J.K.) was consulted to reach a consensus.

Data synthesis and analysis

Identification of the imaging features of IDH mutant glioma and the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma were the primary outcome for the meta-analysis. The results of multiple subgroup analyses of different imaging modalities, WHO grade and histology are reported.

For the included studies, 2 × 2 tables were reconstructed to identify their sensitivity and specificity. If the diagnostic performances of multiple MRI sequences were separately assessed, we chose the results with higher performance. If multiple results from training and testing (validating) sets were given in studies developing a model, the results from the test set were selected.

Heterogeneity was determined using the following: (1) Cochran's Q-test with $p < 0.05$ indicating the presence of heterogeneity; (2) Higgins inconsistency index (I^2) test with the following criteria for interpretation of the degree of heterogeneity: I^2 = 0–40%, heterogeneity might not be important; 30–60%, moderate heterogeneity may be present; 50–90%, substantial heterogeneity may be present; 75–100%, considerable heterogeneity [41]; (3) visual assessment of the coupled forest plot to evaluate the presence of a threshold effect, i.e. a positive correlation between sensitivity and false positive rate among the included studies; (4) a Spearman correlation coefficient >0.6 indicating a considerable threshold effect [42].

The pooled summary estimates of sensitivity and specificity and their 95% CIs were calculated using a bivariate random-effects model [43–47]. For graphical presentation of the study results, a hierarchical summary receiver operating characteristic (HSROC) curve with 95% confidence and prediction regions was plotted. Publication bias was assessed using Deeks' funnel plot, and statistical significance was determined using Deeks' asymmetry test [48].

We performed multiple subgroup analyses according to different imaging modalities, WHO grades and histology: (1) conventional MRI; (2) diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI); (3) magnetic resonance spectroscopy (MRS); (4) 2-hydroxyglutarate MRS; (5) radiomics; (6) lower-grade glioma (grade II and III); (7) glioblastoma (grade IV gliomas) only; (8) oligodendroglioma (grade II, III); (9) grade II, III and IV gliomas. In addition, we also performed meta-regression analysis to explain the effects of heterogeneity. The following covariates were considered for the bivariate model: (1) mean age [< 49 years (median value of the included studies) vs ≥ 49 years]; (2) study enrolment (consecutive vs non-consecutive enrolment); (3) analysis of the type of IDH mutation (IDH1 only vs IDH1/2); (4) number of MRI readers; (5) blinding to the reference standard (MRI readers); (6) magnetic field strength of MRI (3 T only vs 1.5 or 3 T); (7) number of imaging modalities (single vs combination).

All statistical analyses were performed using the "metandi" and "midas" modules in Stata 10.0 (StataCorp, College Station, TX, USA) and the "mada" package in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). A value of $p < 0.05$ was taken to indicate statistical significance.

Results

Literature search

Our detailed study selection process is described in Fig. 1 and Electronic Supplementary Material (ESM). Finally, 28 original articles evaluating the imaging features of IDH mutant glioma in a total of 2,146 patients with glioma were included in our study [7–34].

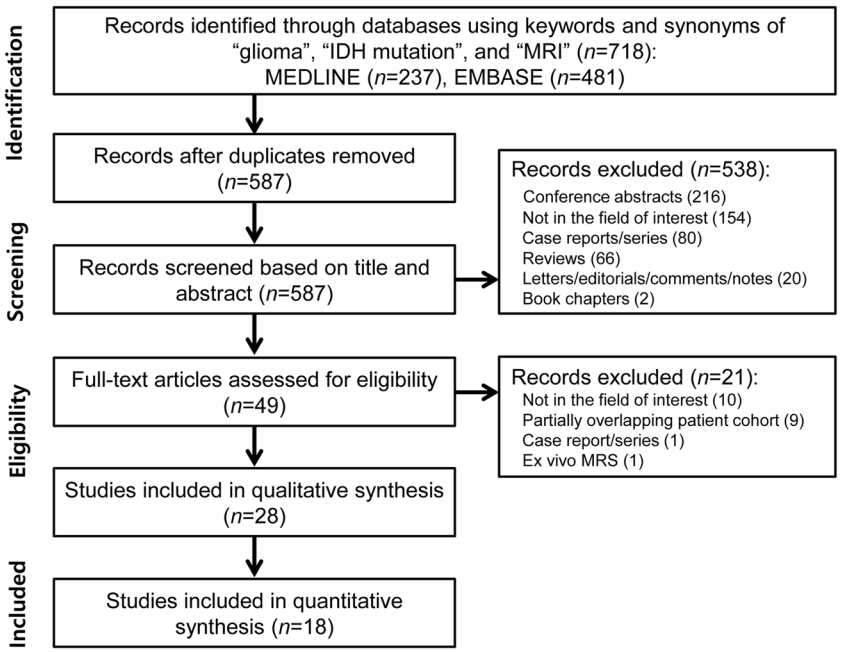

Fig. 1 Flow diagram of the study selection process for this systematic review and meta-analysis

Characteristics of the included studies

The detailed patient and study characteristics are shown in Table 1. Seven studies only included patients with glioblastoma, with the percentage of patients with IDH mutation ranging from 3.3 to 20.9% [12, 14, 18, 20, 24, 26, 34]. The other studies included patients with grade II, III, or IV glioma, with IDH mutation rates ranging from 30.8 to 88.3%.

All included studies used immunohistochemistry and/or genomic sequence analysis as a reference standard. Nine studies used only genomic sequence analysis as a reference standard and three studies used only immunohistochemistry for IDH1 as a reference standard. Immunohistochemistry was performed for mutated IDH1 (R132H) protein expression, and genomic sequence analysis was performed for mutations in IDH1 or IDH2 genes [14].

MRI characteristics of the included studies

The detailed MRI characteristics are shown in Table 2. Thirteen studies used only 3-T scanners [9–14, 19, 21, 24–27, 31], eight studies used 1.5- or 3-T scanners [16–18, 23, 29, 30, 32, 34], two studies used 7 T [22, 28] and five studies did not state the scanner strength [7, 8, 15, 20, 33]. A variety of different MRI techniques were used to predict IDH mutation: conventional MRI in nine studies [7, 15, 18, 23, 26, 30, 32–34], DWI/PWI in eight studies [10, 12, 14, 17, 24, 25, 29, 31], MRS in three studies [11, 16, 27], 2-hydroxyglutarate MRS in two of the three studies [11, 27], radiomics in three studies [8, 9, 20], sodium MRI in one study [28], susceptibility weighted imaging in one study [22] and diffusion kurtosis imaging in one study [21]. For 16 studies using advanced MRI techniques except MRS, whole tumour analysis was used by means of region-of-interest (ROI)-based analysis in nine studies [10, 12, 17, 21, 22, 24, 25, 28, 29], texture analysis in three studies [8, 9, 20] and histogram analysis in two studies [19, 31]. MRI was interpreted by one to four neuroradiologists, neurosurgeons or neurologists, with the readers' level of experience ranging from 5 to 30 years.

The results of the quality assessment according to QUADAS-2 are illustrated in Fig. 2 and ESM. The quality of the studies was considered moderate, with 20 of the 28 studies satisfying at least four of the seven QUADAS-2 domains.

Imaging features of IDH mutant glioma: a systematic review

Studies using conventional MRI demonstrated a variety of imaging features of IDH mutant glioma. IDH mutant glioma was commonly located in the frontal lobe [16, 18, 23, 29, 30, 32–34]. IDH mutant glioma was less likely have contrast enhancement than IDH wild-type glioma [16, 18, 26, 33, 34] and IDH mutant glioma showed well-defined borders [23, 33]. One study reported that all 'T2–FLAIR mismatch' cases were positive for IDH mutant glioma [15]. The representative case studied by conventional MRI is shown in Fig. 3.

On DWI, several studies consistently demonstrated that IDH mutant glioma showed higher mean apparent diffusion coefficient (ADC) values than IDH wild-type glioma [10, 17, 25, 29, 31]. In addition, IDH mutant glioma had a minimally invasive diffusion tensor imaging (DTI) phenotype [14] and fractional anisotrophy value was significantly lower in IDH mutant glioma than IDH wild-type glioma [25]. On PWI, several studies consistently demonstrated that IDH mutant

Table 1 Study and patient characteristics of the included studies

Author (year of publication)	No. of patients (*n*)	IDH mutation (*n*)	IDH mutation (%)	Histology (WHO grade)	Mean age (years)	Range
Zhou et al [7] (2017)	84	63	75.0	Astrocytoma, oligodendroglioma (grade II)	NA	NA
Zhang et al [8] (2017)	120	54	45.0	Glioma (grade II, III)	51.7	30-85
Yu et al [9] (2017)	30	25	83.3	Astrocytoma, oligodendroglioma (grade II)	NA	NA
Xing et al [10] (2017)	42	17	40.5	Astrocytoma (grade II, III)	41.8	8-72
Tietze et al [11] (2017)	35	19	40.5	Astrocytoma, oligodendroglioma (grade II, III, IV)	NA	18-65
Tan et al [12] (2017)	36	6	16.7	Astrocytoma (grade II, III, IV)	49.8	NA
Stadlbauer et al [13] (2017)	69	25	36.2	Astrocytoma, oligodendroglioma (grade II, III, IV)	NA	NA
Price et al [14] (2017)	70	9	12.9	Glioblastoma (grade IV)	59.3	22-73
Patel et al [15] (2017)	60	53	88.3	Astrocytoma, oligodendroglioma (grade II, III,)	NA	NA
Nakae et al [16] (2017)	58	22	37.9	Astrocytoma, oligodendroglioma (grade II, III, IV)	NA	NA
Leu et al [17] (2017)	65	43	66.2	Astrocytoma, oligodendroglioma (grade II, III)	46.5	21-85
Lasocki et al [18] (2017)	153	5	3.3	Glioblastoma (grade IV)	64.4	NA
Jiang et al [19] (2017)	27	20	74.1	Astrocytoma, oligodendroglioma (grade II)	39.6	NA
Hsieh et al [20] (2017)	39	7	17.9	Glioblastoma (grade IV)	57.9	NA
Hempel et al [21] (2017)	49	33	67.3	Glioma (grade II, III, IV)	44	21-65
Grabner et al [22] (2017)	30	15	50.0	Glioma (grade II, III, IV)	51 (median)	21-78
Delfanti et al [23] (2017)	40	27	67.5	Glioma (grade II, III)	NA	NA
Yamashita et al [24] (2016)	43	9	20.9	Glioblastoma (grade IV)	NA	NA
Xiong et al [25] (2016)	84	67	79.8	Oligodendroglioma (grade II, III)	41.5	24-60
Wang et al [26] (2016)	280	45	16.1	Glioblastoma (grade IV)	NA	NA
Choi et al [27] (2016)	42	34	81.0	Astrocytoma, oligodendroglioma (grade II, III, IV)	NA	NA
Biller et al [28] (2016)	34	15	44.1	Glioma (grade I, II, III, IV)	51.3	NA
Wasserman et al [29] (2015)	37	18	48.6	Astrocytoma (grade III)	48	20-81
Sonoda et al [30] (2015)	122	44	36.1	anaplastic astrocytoma, anaplastic oligodendroglioma (grade III)	NA	NA
Lee et al [31] (2015)	52	16	30.8	Anaplastic astrocytoma, glioblastoma (grade III, IV)	50	22-72
Reyes-Botero et al [32] (2014)	50	43	86.0	Anaplastic oligodendroglioma	48	24-78
Qi et al [33] (2014)	193	117	60.6	Anaplastic astrocytomas, diffuse astrocytomas	36.5 (median)	18-72
Carrillo et al [34] (2012)	202	14	6.9	Glioblastoma (grade IV)	56.2	23-79

Author (year of publication)	Male:female	Duration of patient recruitment	Institution	Study design	Consecutive enrolment	IDH mutation	Reference standard
Zhou et al [7] (2017)	NA	NA	The Second Xiangya Hospital, Central South University, China	NA	NA	IDH1	NA
Zhang et al [8] (2017)	52:68	NA	Dana-Farber/Brigham and Women's Cancer Center	retrospective	NA	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Yu et al [9] (2017)	15:15	2016	Fudan University, Huashan Hospital, China	retrospective	NA	IDH1	Genomic sequencing analysis
Xing et al [10] (2017)	26:16	2014.7-2016.6	First Affiliated Hospital of Fujian Medical University, China	retrospective	NA	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Tietze et al [11] (2017)	21:14	NA	Aarhus University Hospital, USA	NA	NA	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Tan et al [12] (2017)	24:12	2011.1-2013.8	Shuguang Hospital Affiliated with Shanghai University of Traditional Chinese Medicine, China	retrospective	NA	IDH1	Immunohistochemistry + genomic sequencing analysis
Stadlbauer et al [13] (2017)	NA	2015.7-2016.4	University of Erlangen and the University Clinic of St Pölten, Austria	retrospective	yes	IDH1	NA
Price et al [14] (2017)	55:15	2011.8-2014.10	University of Cambridge, England	prospective	NA	IDH1	Immunohistochemistry + genomic sequencing analysis
Patel et al [15] (2017)	NA	2011-2014	NYU Langone Medical Center, USA	retrospective	NA	IDH1	Immunohistochemistry + genomic sequencing analysis
Nakae et al [16] (2017)	NA	2005-2015	Fujita Health University, Japan	retrospective	NA	IDH1/2	Genomic sequencing analysis
Leu et al [17] (2017)	38:27	2010-2016	David Geffen School of Medicine, University of California, USA	retrospective	NA	IDH1	Genomic sequencing analysis
	89:64	2007.9-2011.3	Peter MacCallum Cancer Centre, Australia	NA	NA	IDH1	Immunohistochemistry

Table 1 (continued)

Author (year of publication)	Male:female	Duration of patient recruitment	Institution	Study design	Consecutive enrolment	IDH mutation	Reference standard
Lasocki et al [18] (2017)							
Jiang et al [19] (2017)	15:12	NA	Johns Hopkins University, USA	retrospective	NA	IDH1	Immunohistochemistry + genomic sequencing analysis
Hsieh et al [20] (2017)	28:11	NA	4 institutions[a], USA	NA	yes	IDH1	NA
Hempel et al [21] (2017)	27:13	2012.10-2016.3	Eberhard Karls University, Germany	retrospective	yes	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Grabner et al [22] (2017)	12:18	2009-2015	Medical University of Vienna, Austria	prospective	NA	IDH1	Immunohistochemistry
Delfanti et al [23] (2017)	NA	2008.4-2015.3	University of California, San Diego, USA	retrospective	NA	IDH1	Immunohistochemistry + genomic sequencing analysis
Yamashita et al [24] (2016)	NA	2007.5-2013.8	Graduate School of Medical Sciences, Kyushu University, Japan	retrospective	yes	IDH1	Genomic sequencing analysis
Xiong et al [25] (2016)	40:44	2012.1-2014.6	Fudan University, Huashan Hospital, China	retrospective	NA	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Wang et al [26] (2016)	159:121	2007.4-2010.5	Beijing Tian Tan Hospital, China	retrospective	NA	IDH1	Genomic sequencing analysis
Choi et al [27] (2016)	NA	2.5-year period	University of Texas Southwestern Medical Center, USA	prospective	NA	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Biller et al [28] (2016)	NA	NA	University of Heidelberg, Germany	NA	NA	NA	Genomic sequencing analysis
Wasserman et al [29] (2015)	16:21	2010.1-2013.5	Ottawa Hospital, Canada	retrospective	NA	IDH1	Immunohistochemistry
Sonoda et al [30] (2015)	NA	NA	Tohoku University Hospital, Japan	retrospective	NA	IDH1/2	Genomic sequencing analysis
Lee et al [31] (2015)	32:20	2005.5-2012.12	Seoul National University College of Medicine, South Korea	retrospective	NA	IDH1/2	NA
Reyes-Botero et al [32] (2014)	31:19	NA	Prise en charge des OLigodendrogliomes Anaplasiques (POLA) network	retrospective	NA	IDH1/2	Genomic sequencing analysis
Qi et al [33] (2014)	109:84	2003.1-2007.12	Nanfang Hospital, Southern Medical University, China	retrospective	NA	IDH1/2	Immunohistochemistry + genomic sequencing analysis
Carrillo et al [34] (2012)	114:88	1999-2009	David Geffen School of Medicine, University of California, USA	retrospective	NA	IDH1	Genomic sequencing analysis

NA not available, *IDH* isocitrate dehydrogenase

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Table 2 MRI characteristics of the included studies

Author (year of publication)	Magnet strength (T)	Vendor	Scanner	Head coil	MRI techniques	Slice thickness	Contrast agents	Cut-off	Number of readers	Reader experience	Blinding to the reference standard
Zhou et al [7] (2017)	NA	NA	NA	NA	conventional MRI	Visually Accessible Rembrandt Images (VASARI)			2 neuroradiologists	20, 7	yes
Zhang et al [8] (2017)	NA	NA	NA	NA	radiomics				1 radiologist	NA	NA
Yu et al [9] (2017)	3	Siemens	Magnetom Trio 3 T	NA	radiomics		support vector machine (SVM)		NA	NA	NA
Xing et al [10] (2017)	3	Siemens	Magnetom Verio TIM	8	conventional MRI/DWI/DSC	spin-echo echo-planar sequence, gradient-recalled T2*-weighted echo-planar imaging sequence	ADC_{min}, rADC, $rCBV_{max}$		2 neuroradiologists	NA	yes
Tietze et al [11] (2017)	3	Philips	Achieva	8	MRS	optimised PRESS sequence	2HG concentration	2 mM	1 neuroradiologist	8	NA
Tan et al [12] (2017)	3	Siemens	Viero	8	DSC	gradient-echo echo-planar technique	normalised rCBV	5.63	2 neuroradiologists	11, 7	yes
Stadlbauer et al [13] (2017)	3	Siemens	TIM Trio	12	quantitative blood oxygenation level-dependent imaging/vascular architectural mapping	multi-echo gradient-echo sequence, dynamic susceptibility contrast-enhanced perfusion MR imaging data obtained with spin-echo and gradient-echo echo-planar imaging sequences	microvessel type indicator (MTI)		2 neuroradiologists, 2 neurosurgeons	25, 22 / 30, 25	NA
Price et al [14] (2017)	3	Siemens	Magnetom Trio	12	DTI	single-shot spin-echo echo-planar imaging sequence	minimal invasive phenotype, if the p abnormality was similar to the q abnormality		1 neurosurgeon	15	yes
Patel et al [15] (2017)	NA	NA	NA	NA	conventional MR				2 neuroradiologists	NA	yes
Nakae et al [16] (2017)	1.5, 3	Philips	Achieva	standard head coil	MRS	point-resolved spectroscopy (PRESS) method	mIns/tCho		1 neuroradiologist	NA	NA
Leu et al [17] (2017)	1.5, 3	NA	NA	NA	DWI/DSC	NA	ADC, normalised rCBV	multivariate model	NA	NA	NA
Lasocki et al [18] (2017)	1.5, 3	Siemens, GE	Magnetom TIM Trio, SIGNA HDx, SIGNA LX	NA	conventional MRI	Visually Accessible Rembrandt Images (VASARI)	frontal lobe location or all tumours with >33% nCET		1 neuroradiologist	NA	NA
Jiang et al [19] (2017)	3	Philips	Achieva	NA	amide proton transfer-weighted (APTw) MRI	fat suppressed, single-shot, fast spin-echo pulse sequence	whole tumour histogram-based (50th percentile) APTw parameter	1.45	2 neuroradiologists	10, 7	NA
Hsieh et al [20] (2017)	NA	NA	NA	NA	radiomics	computer-aided diagnosis system based on radiomic features	texture features (grey-level co-occurrence matrix)		1 neuroradiologist	13	yes
Hempel et al [21] (2017)	3	Siemens	Biograph mMR	NA	diffusion kurtosis imaging	spin-echo echo-planar imaging DW imaging sequence	normalised mean kurtosis (MK_n),		NA	NA	NA

Table 2 (continued)

Author (year of publication)	Magnet strength (T)	Vendor	Scanner	Head coil	MRI techniques	Slice thickness	Contrast agents	Cut-off	Number of readers	Reader experience	Blinding to the reference standard
							mean diffusivity (MD_n)				
Grabner et al [22] (2017)	7	Siemens	Magnetom 7 T	24 or 32	susceptibility-weighted imaging (SWI)				NA	NA	NA
Delfanti et al [23] (2017)	1.5, 3	NA	NA	NA	conventional MR				2 neuroradiologists	10, 6	yes
Yamashita et al [24] (2016)	3	Philips	Achieva 3 T TX	8	DWI/ASL	pulsed ASL technique	relative tumour blood flow	1.55	2 neuroradiologists	NA	yes
Xiong et al[25] (2016)	3	Siemens	Verio	8	conventional MRI/DTI	single-shot echo-planar imaging diffusion tensor sequence	DTI (rmADC + rmFA) and conventional MRI		2 neuroradiologists	12, 5	yes
Wang et al [26] (2016)	3	Siemens	Trio	NA	conventional MR				2 neuroradiologists	experienced	yes
Choi et al [27] (2016)	3	Philips	NA	8	MRS	2HG-optimised point-resolved spectroscopy (PRESS) method	2HG concentration	1 mM	NA	NA	NA
Biller et al [28] (2016)	7	Siemens	Magnetom 7 T	N	sodium MR	3D attenuation adapted projection reconstruction technique	NaR:NaT		NA	NA	NA
Wasserman et al [29] (2015)	1.5, 3	NA	NA	NA	conventional MRI/DWI	NA	minimum ADC	0.950×10^{-3} mm^2/s	1 neuroradiologist	NA	yes
Sonoda et al [30] (2015)	1.5, 3	NA	NA	NA	conventional MR				NA	NA	NA
Lee et al [31] (2015)	3	GE, Siemens	Signa Excite, Verio	8, 32	DWI/DSC	single-shot spin-echo echo-planar imaging sequence, single-shot gradient-echo echo-planar imaging sequence	normalised rCBV slope [(C90-C10)/0.8]	1.99	1 neuroradiologist	9	NA
Reyes-Botero et al [32] (2014)	1.5, 3	NA	NA	NA	conventional MR				2 neuroradiologists and 2 neurologists	NA	yes
Qi et al [33] (2014)	NA	NA	NA	NA	conventional MR				2 neuroradiologists and 1 neurosurgeon	NA	yes
Carrillo et al [34] (2012)	1.5, 3	NA	NA	NA	conventional MRI		logistic regression analysis (higher of % of nCET, larger size of tumour, presence of cysts, presence of satellites)		1 neuroradiologist	NA	yes

MRI magnetic resonance imaging, *MRS* magnetic resonance spectroscopy, *DWI* diffusion-weighted imaging, *DSC* dynamic susceptibility-weighted contrast-enhanced imaging, *DTI* diffusion tensor imaging, *ASL* arterial spin labelling, *2HG* 2-hydroxyglutarate, *nCET* non-contrast enhancing tumour, *rCBV* relative cerebral blood volume, *ADC* apparent diffusion coefficient, *FA* fractional anisotropy

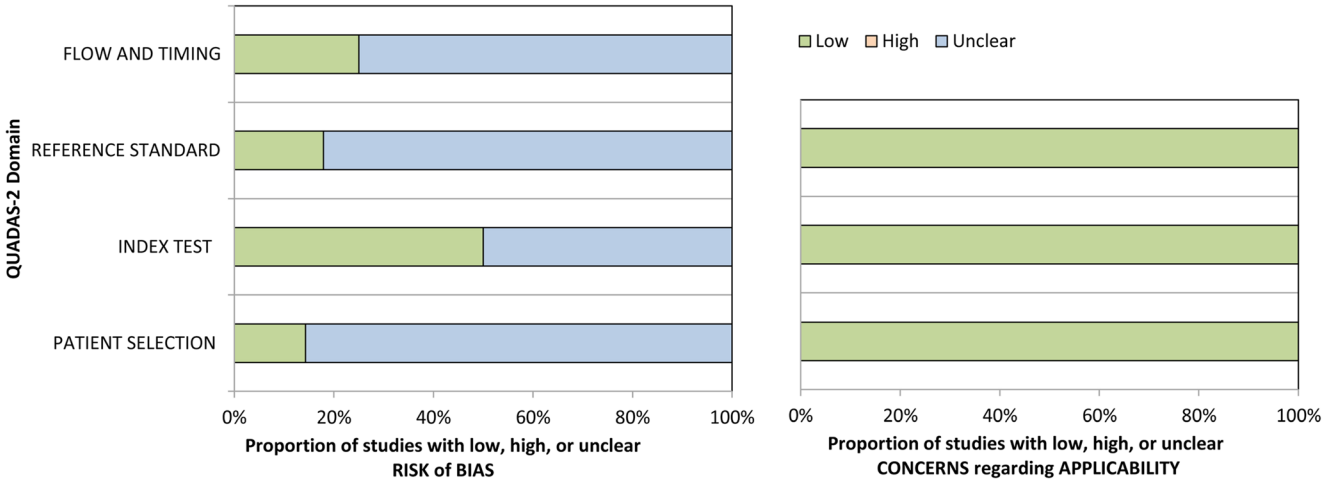

Fig. 2 Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria for the 28 included studies

glioma showed lower relative cerebral blood volume (rCBV) values than IDH wild-type glioma [10, 12, 17]. In addition, IDH mutant glioma also showed lower tumour blood flow than IDH wild-type glioma [24].

Multiple other advanced MRI techniques including sodium MRI [28], susceptibility weighted imaging [22], diffusion kurtosis imaging [21], amide proton transfer-weighted (APTw) MRI [19], quantitative blood oxygenation level–dependent imaging/vascular architectural mapping [13] were used to identify imaging features of IDH mutant glioma.

Diagnostic performance of MRI for prediction of IDH mutation: a meta-analysis

Eighteen original articles evaluated the diagnostic performance of MRI for prediction of IDH mutation in a total of

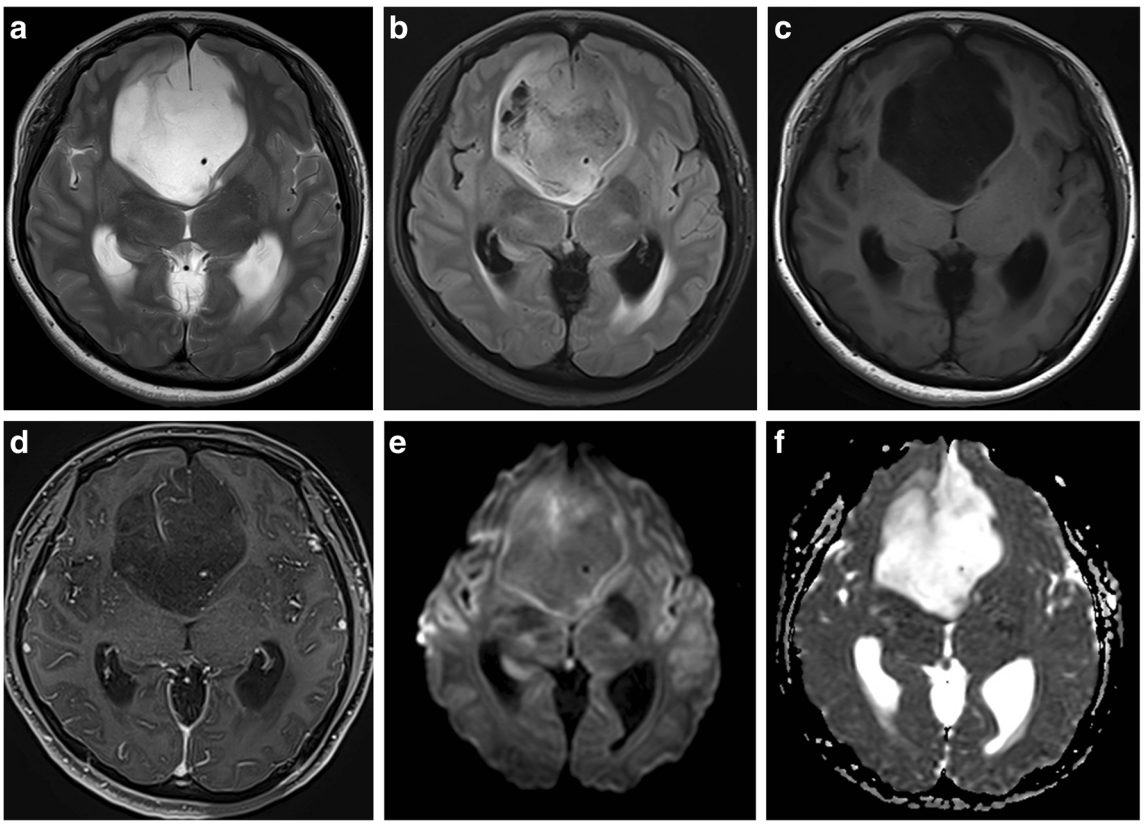

Fig. 3 Images obtained in a 44-year-old woman with histologically proven IDH mutant glioma. **a** T2-weighted image shows a well-defined high signal intensity mass in both frontal lobe. **b** FLAIR image shows relatively hypointense signal. **c** T1-weighted and **d** contrast-enhanced T1-weighted images show no enhancement. **e** DWI and **f** corresponding ADC map reveal high ADC

1,168 patients with glioma for a meta-analysis [7, 9–14, 16–20, 24, 25, 27, 29, 31, 34]. The sensitivities and specificities of the individual studies were 56–100% and 51–100% respectively. The Q-test demonstrated that heterogeneity was present across the studies (Q = 23.846, p < 0.01). The Higgins I^2 statistic demonstrated moderate heterogeneity in the sensitivity (I^2 = 63.9%) and substantial heterogeneity in the specificity (I^2 = 91.9%). A coupled forest plot of the sensitivity and specificity revealed no evidence of a threshold effect (Fig. 4). The Spearman correlation coefficient between the sensitivity and false-positive rate was 0.288 (95% CI, -0.207 to 0.665), also indicating no threshold effect.

For all 18 studies combined, the summary sensitivity was 86% (95% CI, 79–91%) and the summary specificity was 87% (95% CI, 78–92%; Fig. 4). In the HSROC curve, there was a large difference between the 95% confidence region and the 95% prediction region, indicating the possibility of heterogeneity across the studies (Fig. 5). The area under the HSROC curve was 0.93 (95% CI, 0.90–0.95). The Deeks' funnel plot showed that the likelihood of publication bias was low, with a p value of 0.88 for the slope coefficient (ESM Fig. 1).

Subgroup analyses

We performed multiple subgroup analyses to assess various clinical settings (Table 3). In terms of the various imaging modalities, studies using 2-hydroxyglutarate MRS demonstrated a summary sensitivity of 96% (95% CI, 91–100%) and a specificity of 85% (95% CI, 62–100%). The summary sensitivity of 2-hydroxyglutarate MRS was higher than in the other imaging modalities.

In terms of WHO grade and histology, the summary sensitivity was 85% (95% CI, 72–93%) and the specificity 82% (95% CI, 70–89%) in studies that only included lower-grade glioma (grade II and III). In studies that only included glioblastoma, the summary sensitivity was 90% (95% CI, 80–100%) and the specificity 91% (95% CI, 82–99%). In studies including oligodendroglioma, the summary sensitivity was 87% (95% CI, 80–94%) and the specificity was 83% (95% CI, 71–94%).

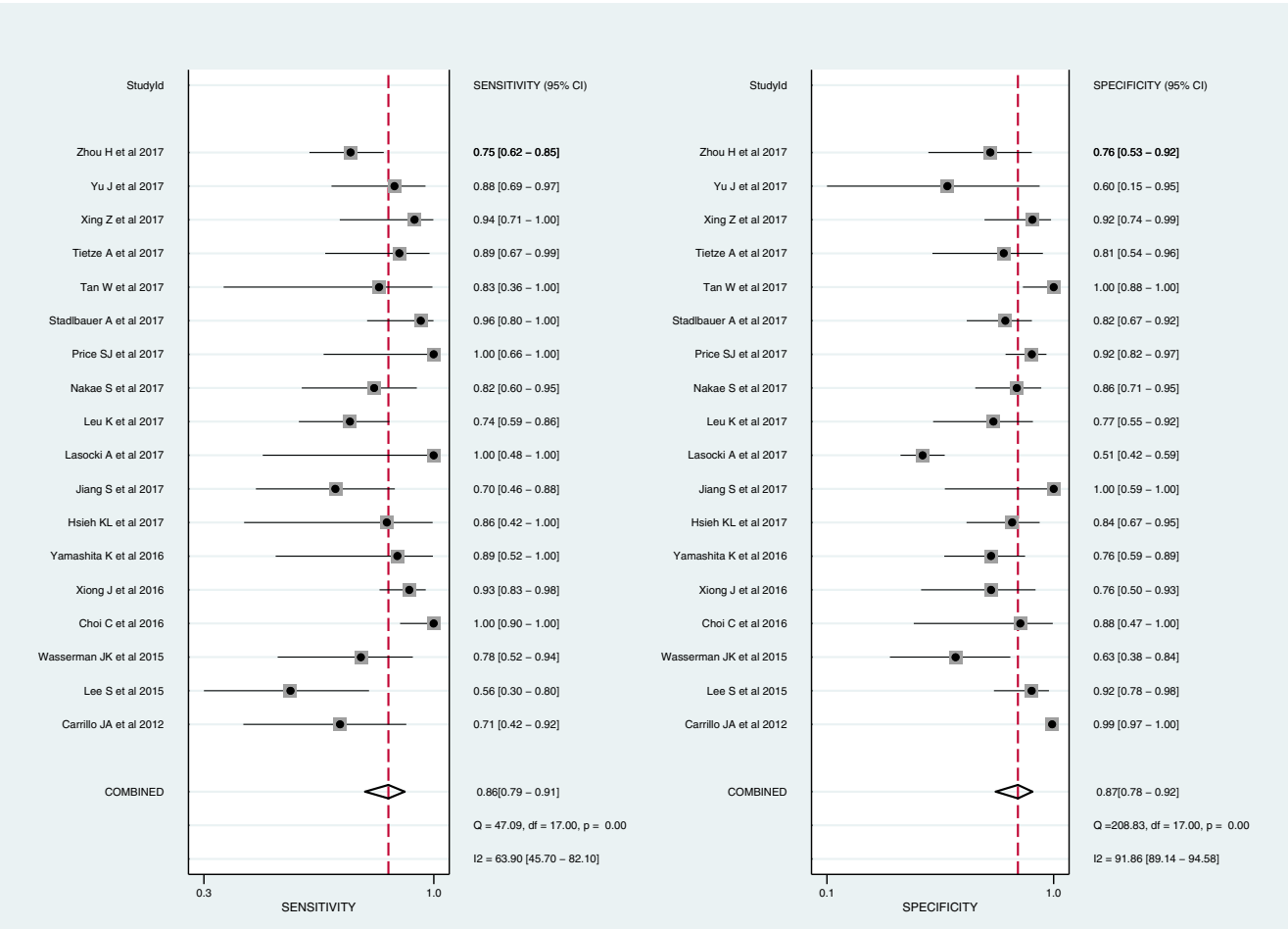

Fig. 4 Coupled forest plots of the pooled sensitivity and specificity for the diagnostic performance of MRI for prediction of IDH mutation. Numbers are pooled estimates with 95% confidence intervals (CI) *in parentheses*; *horizontal lines* indicate 95% CIs

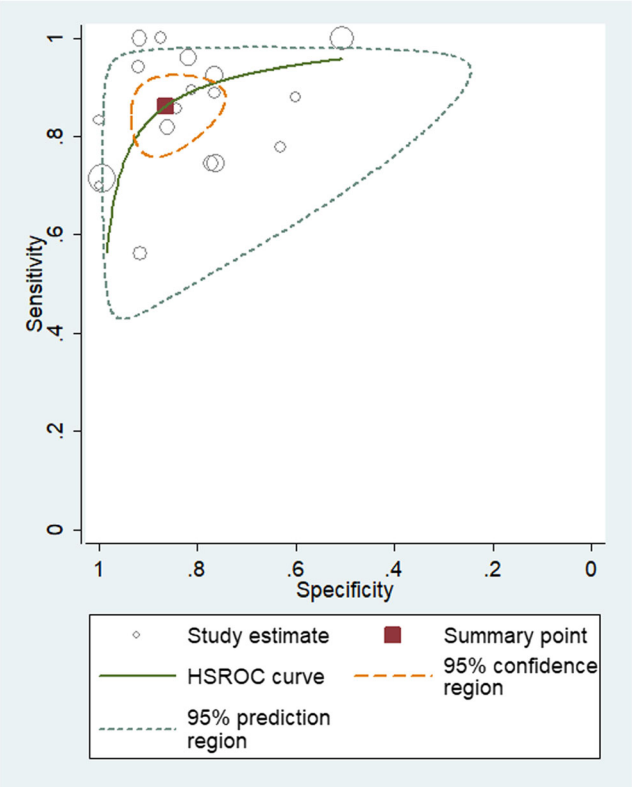

Fig. 5 Hierarchical summary receiver operating characteristic (HSROC) curve of the diagnostic performance of MRI for imaging prediction of IDH mutation in patients with glioma. The summary sensitivity was 86% (95% CI, 79–91%), the summary specificity was 87% (95% CI, 78–92%), and the area under the HSROC curve was 0.93 (95% CI, 0.90–0.95). In the HSROC curve, there was a large difference between the 95% confidence region and the 95% prediction region, indicating the possibility of the presence of heterogeneity between the studies

Meta-regression

Meta-regression was performed to explain the effects of heterogeneity (Table 4). Among the various potential covariates, analysis of the type of IDH mutation (IDH1 only vs IDH1/2) and the number of MRI readers were associated with study heterogeneity. Studies analysing IDH1/2 [89% (95% CI, 82–96%)] showed higher sensitivities than studies analysing IDH1 only [84% (95% CI, 76–92%); $p = 0.01$]. The use of two or more MRI readers [86% (95% CI, 78–94%)] resulted in higher sensitivity than was obtained with a single reader [83% (95% CI, 73–92%); $p = 0.03$]. Otherwise, mean age, study enrolment, blinding to the reference standard, magnetic field strength of the scanner, and number of imaging modalities (single vs combination) were not significant factors affecting the heterogeneity.

Discussion

Our study demonstrates that IDH mutant glioma showed frontal lobe predominance, less contrast enhancement, well-defined border, high ADC value, and low rCBV value. In addition, the diagnostic performance of MRI for prediction of IDH mutation in patients with glioma is within a clinically acceptable range, even though a variety of MRI techniques were used across the examined studies. The summary sensitivity was 86% (95% CI, 79–91%), the summary specificity was 87% (95% CI, 78–92%), and the area under the HSROC curve was 0.93 (95% CI, 0.90–0.95). In the subgroup analyses, the summary sensitivity of 2-hydroxyglutarate MRS [96% (95% CI, 91–100%)] was higher than the sensitivities of the other imaging modalities. Heterogeneity was present across the studies, with analysis of the type of IDH mutation (IDH1 only vs IDH1/2) and the number of MRI readers being associated with this study heterogeneity. Despite the variety of different MRI techniques used in the examined studies, our analysis indicates that MRI has the potential to non-invasively predict IDH mutation in patients with glioma.

In 2016, the WHO classification was updated [1], and many researchers have since made considerable efforts to preoperatively predict IDH mutation in patients with glioma. As an IDH gene mutation may reflect changes in

Table 3 Results of multiple subgroup analyses of MRI for prediction of IDH mutation

Covariates	Subgroup	Meta-analytic summary estimates	
		Sensitivity (95% CI)	Specificity (95% CI)
Imaging modalities	Conventional MRI ($n = 3$)	80% (62–97%)	87% (72–100%)
	DWI/PWI ($n = 8$)	84% (75–94%)	87% (78–97%)
	MRS ($n = 3$)	93% (85–100%)	85% (67–100%)
	2-hydroxyglutarate MRS ($n = 2$)	96% (91–100%)	85% (62–100%)
	Radiomics ($n = 2$)	88% (72–100%)	78% (47–100%)
WHO grade and histology	Lower-grade glioma (grade II and III) ($n = 4$)	85% (72-93%)	82% (70-89%)
	Glioblastoma ($n = 6$)	90% (80–100%)	91% (82–99%)
	Containing oligodendroglioma ($n = 9$)	87% (80–94%)	83% (71–94%)
	Grade II, III and IV gliomas ($n = 11$)	84% (76–92%)	84% (74–94%)

CI confidence intervals, *IDH* isocitrate dehydrogenase, *MRI* magnetic resonance imaging, *MRS* magnetic resonance spectroscopy, *DWI* diffusion-weighted imaging, *PWI* perfusion-weighted imaging

Table 4 Results of the meta-regression of MRI for prediction of IDH mutation

Covariates	Subgroups	Meta-analytic summary estimates			
		Sensitivity (95% CI)	*p* value	Specificity (95% CI)	*p* value
Mean age	<49 years	83% (73–94%)	0.26	85% (67–100%)	0.43
	≥49 years	82% (68–96%)		93% (85–100%)	
Study enrolment	Consecutive enrolment	93% (83–100%)	0.70	82% (63–100%)	0.21
	Non-consecutive enrolment	85% (78–91%)		87% (80–95%)	
IDH mutation	IDH1	84% (76–92%)	0.01	86% (78–94%)	0.21
	IDH1/2	89% (82–96%)		87% (76–98%)	
Number of MRI readers	1	83% (73–92%)	0.03	87% (77–97%)	0.27
	≥2	86% (78–94%)		89% (79–99%)	
Blinding to the reference standard (MRI readers)	Yes	86% (78–94%)	0.06	90% (83–97%)	0.58
	Not explicit	86% (78–94%)		82% (70–94%)	
Magnetic field strength of MRI	3 T	89% (83–95%)	0.55	89% (81–97%)	0.80
	1.5 or 3 T	80% (68–93%)		84% (69–99%)	
Imaging modalities	Single	87% (78–96%)	0.22	91% (84–98%)	0.94
	Combination	86% (76–95%)		82% (69–96%)	

CI confidence intervals, *IDH* isocitrate dehydrogenase, *MRI* magnetic resonance imaging

metabolism, cellularity, or angiogenesis [3], various imaging modalities have been used to predict IDH mutation. In our study, MRI demonstrated clinically acceptable diagnostic performance for imaging prediction of IDH mutation. In the subgroup analyses, imaging modalities including DWI/PWI, MRS and radiomics showed high diagnostic performance. In addition, the summary sensitivity (84–90%) and summary specificity (82–91%) of MRI according to WHO grade and histology were similar. Therefore, MRI in patients with glioma has the potential for not only non-invasive but also highly accurate assessment of underlying IDH mutation.

The current study highlights the fact that since Choi et al. [35] developed and optimised the pulse sequence for 2-hydroxyglutarate MRS, several articles have demonstrated its excellent diagnostic performance in the detection of 2-hyroxyglutarate [11, 27]. In the subgroup analyses, two studies using 2-hydroxyglutarate MRS showed a summary sensitivity of 96% (95% CI, 91–100%) and a summary specificity of 85% (95% CI, 62–100%). The 2-hydroxyglutarate concentration is positively associated with tumour cellularity, and two studies have provided a cut-off value for 2-hydroxyglutarate concentration (1 mM [27] and 2 mM [11]). However, 2-hydroxyglutarate MRS is technically challenging. The quantitative evaluation using 2-hydroxyglutarate MRS requires dedicated software and accurate calibration. One recent study reported that the sensitivity of MRS for detecting 2-hydroxyglutarate is highly dependent on tumour volume [49]. Further technical validation as well as clinical validation should be needed to implement 2-hydroxyglutarate MRS in the clinics. Moreover, further studies analysing other confounders of the correlation or association between MRI and IDH mutation are needed.

There was moderate heterogeneity in the sensitivity (I^2 = 63.9%) and substantial heterogeneity in the specificity (I^2 = 91.9%). The use of a variety of different MRI techniques across all the included studies was regarded as a major cause of heterogeneity in our meta-analysis. In the meta-regression to investigate the cause of heterogeneity, analysis of the type of IDH mutation (IDH1 only vs IDH1/2) and the number of MRI readers were associated with the study heterogeneity. Specifically, studies analysing IDH1/2 (89%) showed significantly higher sensitivity than studies analysing IDH1 only (84%), and the use of at least two readers (86%) showed significantly higher sensitivity than the use of a single reader (83%; p = 0.03). On the basis of these results, we cautiously recommend both analyses for IDH1/2 and the inclusion of at least two MRI readers when predicting IDH mutation in patients with glioma.

Our study is subject to several limitations. First, a variety of different MRI techniques were used to predict IDH mutation, and heterogeneities regarding sensitivity and specificity across the studies were present. To overcome this heterogeneity, we performed meta-regression and multiple subgroup analyses. Second, 12 of 18 studies were retrospective in study design. Third, our study revealed a relatively unclear risk of bias in the quality assessment. However, there were low concerns regarding applicability of all included studies. Fourth, we cannot obtain pooled quantitative cut-off values of DWI and/or PWI parameters to predict IDH mutation. In our study, only 8 of 28 studies used DWI or PWI and the studies did not provide individual patient data. Therefore, methodologically, it is impossible to obtain pooled quantitative cut-off values of DWI and/or PWI parameters to differentiate IDH mutant glioma from IDH wild type glioma. Further studies should be warranted. We utilised robust methodology (hierarchical

logistic regression modelling) [43–45] and reported our study results according to several guidelines: PRISMA [38], the Handbook for Diagnostic Test Accuracy Reviews published by the Cochrane Collaboration [50], and the Agency for Healthcare Research and Quality (AHRQ) [51].

IDH mutant glioma consistently demonstrated less aggressive imaging features than IDH wild-type glioma. Despite the variety of different MRI techniques utilised, MRI has the potential to non-invasively predict IDH mutation in patients with glioma, with 2-hydroxyglutarate MRS showing higher pooled sensitivity than other imaging modalities. Further technical validation as well as clinical validation should be needed to implement 2-hydroxyglutarate MRS in the clinics.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Ho Sung Kim.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors (Chong Hyun Suh) has significant statistical expertise (4 years of experience in a systematic review and meta-analysis).

Ethical approval Institutional Review Board approval was not required because of the nature of our study, which was a systemic review and meta-analysis.

Informed consent Written informed consent was not required for this study because of the nature of our study, which was a systemic review and meta-analysis.

Methodology
• A systemic review and meta-analysis performed at one institution.

References

1. Louis DN, Perry A, Reifenberger G et al (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131:803–820
2. Hartmann C, Meyer J, Balss J et al (2009) Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol 118:469–474
3. Kickingereder P, Sahm F, Radbruch A et al (2015) IDH mutation status is associated with a distinct hypoxia/angiogenesis transcriptome signature which is non-invasively predictable with rCBV imaging in human glioma. Sci Rep 5:16238
4. Brat DJ, Verhaak RG, Aldape KD et al (2015) Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med 372:2481–2498
5. Eckel-Passow JE, Lachance DH, Molinaro AM et al (2015) Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 372:2499–2508
6. Miller JJ, Shih HA, Andronesi OC, Cahill DP (2017) Isocitrate dehydrogenase-mutant glioma: evolving clinical and therapeutic implications. Cancer 123:4535–4546
7. Zhou H, Vallieres M, Bai HX et al (2017) MRI features predict survival and molecular markers in diffuse lower-grade gliomas. Neuro Oncol 19:862–870
8. Zhang B, Chang K, Ramkissoon S et al (2017) Multimodal MRI features predict isocitrate dehydrogenase genotype in high-grade gliomas. Neuro Oncol 19:109–117
9. Yu J, Shi Z, Lian Y et al (2017) Noninvasive IDH1 mutation estimation based on a quantitative radiomics approach for grade II glioma. Eur Radiol 27:3509–3522
10. Xing Z, Yang X, She D, Lin Y, Zhang Y, Cao D (2017) Noninvasive assessment of IDH mutational status in World Health Organization grade II and III astrocytomas using DWI and DSC-PWI combined with conventional MR imaging. AJNR Am J Neuroradiol 38:1134–1144
11. Tietze A, Choi C, Mickey B et al (2018) Noninvasive assessment of isocitrate dehydrogenase mutation status in cerebral gliomas by magnetic resonance spectroscopy in a clinical setting. J Neurosurg 128:391–398
12. Tan W, Xiong J, Huang W, Wu J, Zhan S, Geng D (2017) Noninvasively detecting Isocitrate dehydrogenase 1 gene status in astrocytoma by dynamic susceptibility contrast MRI. J Magn Reson Imaging 45:492–499
13. Stadlbauer A, Zimmermann M, Kitzwogerer M et al (2017) MR Imaging-derived oxygen metabolism and neovascularization characterization for grading and IDH gene mutation detection of gliomas. Radiology 283:799–809
14. Price SJ, Allinson K, Liu H et al (2017) Less invasive phenotype found in isocitrate dehydrogenase-mutated glioblastomas than in isocitrate dehydrogenase wild-type glioblastomas: a diffusion-tensor imaging study. Radiology 283:215–221
15. Patel SH, Poisson LM, Brat DJ et al (2017) T2-FLAIR mismatch, an imaging biomarker for IDH and 1p/19q status in lower-grade gliomas: a TCGA/TCIA project. Clin Cancer Res 23:6078–6085
16. Nakae S, Murayama K, Sasaki H et al (2017) Prediction of genetic subgroups in adult supra tentorial gliomas by pre- and intraoperative parameters. J Neurooncol 131:403–412
17. Leu K, Ott GA, Lai A et al (2017) Perfusion and diffusion MRI signatures in histologic and genetic subtypes of WHO grade II–III diffuse gliomas. J Neurooncol 134:177–188
18. Lasocki A, Tsui A, Gaillard F, Tacey M, Drummond K, Stuckey S (2017) Reliability of noncontrast-enhancing tumor as a biomarker of IDH1 mutation status in glioblastoma. J Clin Neurosci 39:170–175
19. Jiang S, Zou T, Eberhart CG et al (2017) Predicting IDH mutation status in grade II gliomas using amide proton transfer-weighted (APTw) MRI. Magn Reson Med 78:1100–1109
20. Hsieh KL, Chen CY, Lo CM (2017) Radiomic model for predicting mutations in the isocitrate dehydrogenase gene in glioblastomas. J Neurooncol 8:45888–45897
21. Hempel JM, Schittenhelm J, Brendle C et al (2017) Histogram analysis of diffusion kurtosis imaging estimates for in vivo assessment of 2016 WHO glioma grades: a cross-sectional observational study. Eur J Radiol 95:202–211
22. Grabner G, Kiesel B, Wohrer A et al (2017) Local image variance of 7 Tesla SWI is a new technique for preoperative characterization of diffusely infiltrating gliomas: correlation with tumour grade and IDH1 mutational status. Eur Radiol 27:1556–1567
23. Delfanti RL, Piccioni DE, Handwerker J et al (2017) Imaging correlates for the 2016 update on WHO classification of grade II/III gliomas: implications for IDH, 1p/19q and ATRX status. J Neurooncol 135:601–609

24. Yamashita K, Hiwatashi A, Togao O et al (2016) MR imaging-based analysis of glioblastoma multiforme: estimation of IDH1 mutation status. AJNR Am J Neuroradiol 37:58–65
25. Xiong J, Tan W, Wen J et al (2016) Combination of diffusion tensor imaging and conventional MRI correlates with isocitrate dehydrogenase 1/2 mutations but not 1p/19q genotyping in oligodendroglial tumours. Eur Radiol 26:1705–1715
26. Wang K, Wang Y, Fan X et al (2016) Radiological features combined with IDH1 status for predicting the survival outcome of glioblastoma patients. Neuro Oncol 18:589–597
27. Choi C, Raisanen JM, Ganji SK et al (2016) Prospective longitudinal analysis of 2-hydroxyglutarate magnetic resonance spectroscopy identifies broad clinical utility for the management of patients with IDH-mutant glioma. J Clin Oncol 34:4030–4039
28. Biller A, Badde S, Nagel A et al (2016) Improved brain tumor classification by sodium mr imaging: prediction of IDH mutation status and tumor progression. AJNR Am J Neuroradiol 37:66–73
29. Wasserman JK, Nicholas G, Yaworski R et al (2015) Radiological and pathological features associated with IDH1-R132H mutation status and early mortality in newly diagnosed anaplastic astrocytic tumours. PLoS One 10:e0123890
30. Sonoda Y, Shibahara I, Kawaguchi T et al (2015) Association between molecular alterations and tumor location and MRI characteristics in anaplastic gliomas. Brain Tumor Pathol 32:99–104
31. Lee S, Choi SH, Ryoo I et al (2015) Evaluation of the microenvironmental heterogeneity in high-grade gliomas with IDH1/2 gene mutation using histogram analysis of diffusion-weighted imaging and dynamic-susceptibility contrast perfusion imaging. J Neurooncol 121:141–150
32. Reyes-Botero G, Dehais C, Idbaih A et al (2014) Contrast enhancement in 1p/19q-codeleted anaplastic oligodendrogliomas is associated with 9p loss, genomic instability, and angiogenic gene expression. Neuro Oncol 16:662–670
33. Qi S, Yu L, Li H et al (2014) Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms. Oncol Lett 7:1895–1902
34. Carrillo JA, Lai A, Nghiemphu PL et al (2012) Relationship between tumor enhancement, edema, IDH1 mutational status, MGMT promoter methylation, and survival in glioblastoma. AJNR Am J Neuroradiol 33:1349–1355
35. Choi C, Ganji SK, DeBerardinis RJ et al (2012) 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 18:624–629
36. Li Z, Wang Y, Yu J, Guo Y, Cao W (2017) Deep Learning based Radiomics (DLR) and its usage in noninvasive IDH1 prediction for low grade glioma. Sci Rep 7:5467
37. Dang L, Yen K, Attar EC (2016) IDH mutations in cancer and progress toward development of targeted therapeutics. Ann Oncol 27:599–608
38. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:W65–W94
39. Louis DN, Ohgaki H, Wiestler OD et al (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109
40. Whiting PF, Rutjes AW, Westwood ME et al (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155:529–536
41. Higgins J, Green S Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. http://handbook.cochrane.org/chapter_9/9_5_2_ identifying_and_measuring_heterogeneity. htm. Updated March 2011. Accessed 2 October 2017
42. Deville WL, Buntinx F, Bouter LM et al (2002) Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2:9
43. Suh CH, Park SH (2016) Successful publication of systematic review and meta-analysis of studies evaluating diagnostic test accuracy. Korean J Radiol 17:5–6
44. Kim KW, Lee J, Choi SH, Huh J, Park SH (2015) Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers—Part I. General guidance and tips. Korean J Radiol 16:1175–1187
45. Lee J, Kim KW, Choi SH, Huh J, Park SH (2015) Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers—Part II. Statistical methods of meta-analysis. Korean J Radiol 16:1188–1196
46. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH (2005) Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 58:982–990
47. Rutter CM, Gatsonis CA (2001) A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 20:2865–2884
48. Deeks JJ, Macaskill P, Irwig L (2005) The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 58:882–893
49. de la Fuente MI, Young RJ, Rubel J et al (2016) Integration of 2-hydroxyglutarate-proton magnetic resonance spectroscopy into clinical practice for disease monitoring in isocitrate dehydrogenase-mutant glioma. Neuro Oncol 18:283–290
50. Deeks JJ, Bossuyt PM, Gatsonis C (eds) 2013 Cochrane handbook for systematic reviews of diagnostic test accuracy version 1.0.0. The Cochrane Collaboration. http://srdta.cochrane.org/handbook-dta-reviews. Accessed 9 Oct 2017
51. Trikalinos TA, Balion CM, Coleman CI et al (2012) Chapter 8: meta-analysis of test performance when there is a "gold standard". J Gen Intern Med 27(Suppl 1):S56–S66