Apparent diffusion coefficient for genetic characterisation of untreated adult gliomas: a meta-analysis stratified by methods

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Abstract

Background:

Isocitrate dehydrogenase (IDH) mutation and chromosome 1p19q genotyping have become fundamental to the prognostic grouping of adult diffuse gliomas. Apparent diffusion coefficient (ADC) values may enable non-invasive prediction of glioma molecular status. The purpose of this systematic review and meta-analysis was to investigate the diagnostic accuracy of ADC for IDH and 1p19q genotyping, considering measurement techniques and tumour grade.

Methods:

A systematic search of PubMed and Cochrane Library databases was performed in December 2024. Studies were grouped according to the ADC parameter measured and the measurement techniques used. A meta-analysis was performed, supplemented by Egger's regression testing. The quality of studies was assessed with the QUADAS-2 tool.

Results:

Thirty-three studies including a total of 4297 patients fulfilled the inclusion criteria. IDH mutation and 1p19q deletion status were assessed by 30 and 14 studies respectively. Pooled area under the curve (AUC) values for the prediction of an IDH mutation and 1p19q codeletion ranged from 0.743 (0.680-0.805) to 0.804 (0.689-0.919), and 0.678 (0.614-0.741) to 0.692 (0.600-0.783). No significant differences were identified between regional and volumetric measurements, between ADCmean and ADCmin values, or comparing normalised and raw ADC data.

Conclusion:

This meta-analysis supports ADC as an imaging biomarker in untreated gliomas, specifically to predict IDH status. ROI measurement, particularly by a single ADC_{mean}, is rapid, reproducible and appears statistically equivalent

to volumetric read outs. We found no evidence for superior diagnostic accuracy by ADC normalisation. Published ADC thresholds have been summarised for consideration of prospective testing across institutions.

Keywords

Glioma, glioblastoma, isocitrate dehydrogenase (IDH), apparent diffusion coefficient, diffusion-weighted imaging

Key points

- Apparent diffusion coefficient (ADC) values support the prediction of glioma IDH status.
- Regional and volumetric ADC performance was equivalent in meta-analysis.
- ADC thresholds are proposed for sensitive identification of glioblastoma genetics.

Importance of the study

Predicting brain tumour genotypes has become an important objective in radiological diagnosis. This is particularly the case for identifying molecular glioblastoma, which may otherwise be at risk of inequitable low grade triage. Multiple studies have proposed apparent diffusion coefficient values as a biomarker of diffuse glioma IDH and 1p19 status. This systematic review and meta-analysis examined the entire available literature on the subject, including a variety of different measurement methods. Thresholds for prospective research and clinical trial application are proposed.

Introduction

Gliomas represent the most common primary malignancy of the central nervous system (CNS) in adults and are frequently incurable (1–3). Molecular markers of prognostic relevance have become fundamental in the diagnosis of gliomas as defined in the World Health Organization (WHO) 2021 Classification of CNS Tumors (4). Diffuse gliomas are divided into three genetic groups based on the presence of an isocitrate dehydrogenate gene mutation (IDH-mutant, IDH^{mut}), with or without chromosome 1p19q codeletion ($1p19q^{codel}$) (4). Glioblastoma (GBM) is the most lethal type of glioma, characterised by absence of an IDH mutation (IDH-wildtype, IDH^{wt}) and malignant histology (WHO grade 4) (4). In contrast, most IDH-mutant tumours are low-grade gliomas (WHO grades 2-3), divided into $IDH^{mut}/1p19q^{retained}$ astrocytomas and $IDH^{mut}/1p19q^{codel}$ oligodendrogliomas (2,4,5).

Glioma genotyping is essential for risk stratification and to guide clinical management. GBM is treated by resection followed by radiotherapy and temozolomide chemotherapy (6–9). Maximising tumor resection prolongs the survival of GBM, which creates an argument for prompt identification (5,8,10). A proportion of IDH^{wt} tumours display histological low-grade features but belong to the molecular class of GBM, requiring radical treatment with a risk of comparably poor outcomes (1,2,4). On the contrary, the survival in IDH^{mut} WHO grade 4 tumours tends to be longer than in GBM (1). In IDH^{mut} astrocytomas, postoperative tumor volume is independently associated with survival, whereas $1p19q^{codel}$ oligodendrogliomas preferentially respond to chemotherapy (11). A preoperative prediction of IDH status could help better utilise sequencing resources in situations where IDH sequencing is not routine for all gliomas and/or where geographical inequities contribute to diagnostic delays (12,13).

Diffusion-weighted imaging (DWI) performed with b-values of 0 s/mm^2 and 1000 s/mm^2 (sometimes with an additional b-value of 500 s/mm^2) is widely integrated into clinical glioma MRI protocols (14,15). From this, apparent diffusion coefficient (ADC) maps are calculated to estimate the magnitude of diffusion in each image voxel (14). ADC values have been negatively correlated with glioma cellularity in most studies but other factors, including matrix composition, influence ADC (16,17). Several studies reported higher ADC values in IDH^{mut} gliomas compared to IDH^{wt} tumours, which may enable non-invasive prediction of glioma genotype (18–20). However, it is unknown whether measurement methods influence the accuracy of ADC results for glioma molecular diagnosis. Much of the

published literature on the diagnostic accuracy of ADC values for characterising gliomas predates the WHO 2021 Classification of CNS Tumors (4). Specifically, older studies highlighted differences in ADC parameters between high-grade and low-grade gliomas, without reporting on genetic status (21). This raises the possibility of a WHO grade influence on ADC diagnostic accuracy.

The purpose of this systematic review and meta-analysis was to investigate the diagnostic accuracy of ADC for glioma IDH and 1p19 status prediction by measurement techniques and considering the possible influence of glioma WHO grade.

Methods

A literature review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22). The meta-analysis component of the research was prospectively registered on 23rd July 2024 with the University of Nottingham Repository (http://doi.org/10.17639/nott.7439)(23).

Information sources and search strategy

A systematic search of Pubmed and Cochrane databases was commenced on 1st September 2023 and last updated on 21st December 2024 to identify studies reporting the diagnostic accuracy of ADC for glioma IDH and 1p19q status prediction. To capture the genotyping era, a filter was applied to only include studies published since 2013 (10 years prior to the commencement of the analysis). Full details of the search terms are provided in the Supplementary Material.

Eligibility criteria

Inclusion criteria were: original research in diffuse glioma (WHO grades 2-4), DWI/ADC or mean diffusivity/ADC calculated from diffusion tensor imaging (DTI) performed on glioma patients pre-treatment, assessment of the diagnostic or prognostic value of one or more diffusion parameters for the purpose of glioma grouping (e.g. WHO grade, genotype), quantitative measurements described without or alongside histogram

parameters or advanced computation, and studies no more than 10 years retrospect to capture the genotyping era (24).

Exclusion criteria were: no diffusion-weighted (DWI/ADC or diffusion-tensor imaging [DTI]) sequence interpretation, animal/laboratory measurements, studies confined to paediatric gliomas (defined as <5 adult cases), review articles, case reports of <5 cases, conference abstracts, no English full text, any previous treatment (surgery, radiotherapy, chemotherapy) and tumour types other than diffuse glioma.

Study selection and data collection process

The titles and abstracts of all studies identified by the search were uploaded into the Rayyan online systematic review platform (25). Each abstract was independently screened by two reviewers (F.B. and J.S.). Following unblinding of each reviewer's screening results, conflicts were resolved through consensus. Candidate full texts were independently reviewed by the same reviewers against the inclusion and exclusion criteria with conflicts resolved after unblinding. Each reviewer (F.B. and J.S.) extracted data from all included studies into Microsoft Excel (Microsoft Excel for Mac, Version 16.88, Microsoft Corporation). The complete data extraction was compared, and discrepancies were resolved in consensus discussion with two senior authors (S.T. and N.S.).

Data items

Items extracted consisted of author details and publication year, study design, research purpose, patient number, age, sex, microscopic WHO grade(s) and histopathological diagnoses, immunohistochemistry methods, IDH and 1p19q status, DWI acquisition details, diffusion parameter(s) measured, measurement methods (e.g. region of interest [ROI] defined as a single slice measurement(s) or volume of interest [VOI] defined as a measurement(s) obtained from multiple image slices) and interobserver testing, where published. The WHO numerical grade is Arabic throughout the manuscript in keeping with the latest WHO 2021 convention. The original grading nomenclature has been retained where older Roman grades were used in research publications. The key outcome measure was the

receiver operating characteristic [ROC] area under the curve [AUC] value of the diffusion parameter(s) used for IDH or 1p19q genotyping of gliomas.

Study risk of bias assessment

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (26). The QUADAS-2 questions were defined through a planning consultation between the authors and are listed in the Supplementary Material. Studies which did not report consecutive or random enrolments, were assigned high risk of bias in the patient selection domain. If more than one reference standard was used, a high risk of bias was assigned in the reference standard domain. For the flow and timing domain, any interval between the index and reference tests greater than two weeks was labelled as high risk of bias. If the interval between the index and reference tests was not specified, this was labelled as unclear risk of bias. Each study was independently assessed by two reviewers (F.B and J.S.) with disagreements resolved through consensus with one senior author present (N.S.).

Statistical analysis and synthesis methods

A meta-analysis was performed to estimate the diagnostic performance of ADC measurements. For studies with 95% confidence intervals (CIs) but not standard error (SE) values, the 95% CIs were used to calculate the SE values by dividing the CI range by 3.92 as specified in the Cochrane Handbook for Systematic Reviews of Interventions (27). For studies in which AUC values were reported without an SE value or CI, the corresponding authors were emailed three times to supply the missing data. If SE and/or CI values remained unconfirmed, an estimate of the SE value was calculated using Equation II described by Cortes and colleagues (28).

Studies were grouped according to the ADC parameter measured (e.g. minimum ADC (ADCmin) or mean ADC (ADCmean)), and the method of measurement (ROI or VOI). Studies which marked ROIs in the visually perceived lowest regions of the ADC map were coded as ADCmin. Studies which described placing a ROI across the largest axial tumour cross section were classified as ADCmean. Studies taking an average ADC measurement from multiple ROIs placed within a tumour, but not targeting the lowest regions of the ADC map, were also classified as ADCmean. Studies, which targeted the visually perceived lowest ADC regions were classed as ADCmin, even where these lowest ADC values were averaged. This grouping served the purpose of meta-analysis to align methods as closely as possible, irrespective of individual publication nomenclature. The data were further grouped based on whether absolute or normalised (e.g. to contralateral normal-appearing white matter [CNAWM]) ADC measurements were recorded.

The meta-analysis was performed using the 'Meta-analysis' function on JASP software (JASP Team 2024, version 0.18.3 [Apple Silicon]). The fixed effects model was initially used with Cochran's Q statistic to test for residual heterogeneity, whereby a threshold of $p<0.05$ indicated significant residual heterogeneity. In the case of significant residual heterogeneity, the maximum likelihood model was applied instead. Results are displayed in forest plots with summary estimates presented. Funnel plots were produced and 'Egger's regression test' was performed to assess for plot asymmetry if at least 5 studies were available for analysis. To analyse the influence of WHO grade on AUC values, a linear regression was performed using the quoted AUC values and proportion of WHO grade 4 tumours in each cohort where at least 5 studies reported a specific ADC parameter. Linear regression was performed using GraphPad Prizm Cloud (GraphPad Software, Boston, Massachusetts USA, www.graphpad.com).

Results

Study selection and overview

The database searches yielded 808 unique studies, of which 33 were eligible for inclusion in this review. A PRISMA flow diagram summarising the study selection process is provided in Figure 1.

Thirty-three studies including a total of 4297 patients were included in the final analysis with a mean of 130 patients per study and range of 11 to 475. All 33 studies were retrospective. Across the 33 studies, 30 studies assessed prediction of IDH mutation status (29–58), and 14 studies assessed prediction of 1p19q codeletion status (47–57,59–61). Tables 1-3 summarise the data extracted from each of the 33 included studies grouped according to whether they assessed IDH mutation, both IDH mutation and 1p19q codeletion, or 1p19q codeletion alone.

Cohort composition

The analysed WHO grades varied across the included studies. The most common cohort mixes were WHO grade 2, 3 gliomas (n=11) (30–33,47–51,59,61), and WHO grade 2, 3, 4 gliomas (n=10) (38–41,53–58). A breakdown of studied WHO grades is provided in the Supplementary Material.

MRI field strength

Three studies reported using 1.5T MRI (37,44,61), 20 studies used 3.0T MRI (29,32,35,36,38,39,41–43,46,47,50,51,53–57,59,60), and 9 studies used a combination of 1.5T and 3.0T MRI from multiple vendors (30,31,33,34,40,45,48,52,58). The MRI field strength was not reported in one study (49).

ADC measurement

Eighteen studies used ROI-based measurements (32–34,36,38–42,44–47,50,55,58–60), 13 studies used VOI-based measurements (29,35,37,48–54,56,57,61), and two studies used both ROI and VOI methods (30,31). Of the studies using VOI methods, four studies used automated tumour segmentation techniques (48,49,53,56), whilst the remaining 11 studies described manual whole tumour segmentation (29–31,35,37,50–52,54,57,61). For tumour segmentation, four studies used T2-weighted (T2w) sequences (30,31,50,51), one study used T2-FLAIR (FLAIR) (54),

one study used T2w and FLAIR (52), one study used T1-weighted (T1w) or T2w (37), and one used T1w alone (35). Three studies did not state what sequences were used for tumour segmentation (29,57,61). Studies were broadly consistent in excluding calcified, cystic, haemorrhagic, or necrotic regions of tumours from measurements. Of the 20 studies using ROI methods of ADC measurement, 14 studies assessed minimum ADC values (ADCmin) (30,32–34,36,41,42,44–47,55,59,60) and 12 studies assessed mean ADC values (ADCmean) (31,33,36,38–40,44,45,49,50,58,60). Nine studies did not describe exact ROI definitions for ADC measurements (31,34,37,43,48–50,52,53).

Fifteen studies described measuring normalised ADC values using a comparative ROI (29–33,36,38,39,44,46,47,55,57,59,60). CNAWM with location not further specified (NFS) was used as a comparison in nine studies (29,33,36,38,39,46,55,59,60), whilst contralateral normal-appearing centrum semiovale and contralateral normal-appearing posterior limb of internal capsule were listed in four (30,31,44,57) and two (32,47) studies respectively.

Eleven studies described methods of two observers working in consensus to mark ROIs or VOIs (35,36,38,39,41,44,56,57,59–61). Thirteen studies provided data on intraclass correlation coefficient (ICC) values of ADC measurements (29–31,33,42,45,46,50–53,55,58). The ICC values of ADC measurements were greater than 0.80 in 12 of the 13 studies (29–31,33,42,46,50–53,55,58). One study reported ICC values of 0.532 and 0.598 for ROI-based ADCmean and ADCmin measurements respectively in a cohort of WHO 4 gliomas (45). In two studies ADC measurements were performed by one observer (34,50).

Meta-analysis

Studies were grouped for meta-analysis based on the ADC parameter which they assessed. The primary groups were ADCmean (n=19) (30,31,33,36,38–40,44,45,49–54,56,58,60,61), ADCmin (n=14) (29,30,32–34,36,38,41,42,44,45,47,51,55), rADCmean (n=6) (30,31,33,36,39,60), and rADCmin (n=9)

(30,32,33,36,44,46,47,55,59). Studies which provided AUC values for other ADC metrics, but not one of the 4 previously listed ADC parameters, are described separately (n=4) (35,37,48,50). The groupings of studies by ADC parameters is provided in the Supplementary Material.

IDH

ADCmean

Eight studies used ROI methods, and seven studies used VOI methods to measure ADCmean values to classify glioma IDH mutation status. The cohorts of the eight studies using ROI methods comprised of WHO 1-4 (n=1)(36), WHO 2-3 (n=2)(30,33), WHO 2-4 (n=3)(39,40,58), and WHO 4 gliomas (n=2)(44,45). The seven studies using VOI methods involved cohorts of WHO 2-3 (n=2)(30,39), WHO 2-4 (n=4)(31,53,54,56), and WHO 3 gliomas (n=1)(52).

Two studies by Maynard et al. (33) and Thust et al. (31) were excluded from meta-analysis to avoid pseudoreplication as these reported data on the same cohort of gliomas as another study in the meta-analysis (30). A study by Cheng and colleagues was also excluded from the meta-analysis despite specifying ADCmean values (56), because of retrospective fusion ROI measurements to biopsy sites, which differs from the ROI and VOI methods used in all other studies (56). Cheng et al. reported an AUC value of 0.500 in their cohort of 10 WHO 2-4 gliomas (56).

The pooled AUC values for ROI and VOI methods were 0.760 (0.701-0.818) (I^2=72.623) and 0.799 (0.719-0.879) (I^2=76.737) as shown in Figure 2 (Panel A and B respectively).

rADCmean

Five studies used ROI methods, and two studies used VOI methods to measure rADCmean values to classify glioma IDH mutation status. The cohorts of the five studies using ROI methods comprised of WHO 1-4 (n=1)(36), WHO 2-3 (n=3) (30,31,33), and WHO 2-4 gliomas (n=1) (39). Both studies using VOI methods analysed cohorts of WHO 2-3 gliomas (30,31).

Two studies were again excluded to avoid pseudoreplication (31,33). Due to this, three studies contributed to the meta-analysis of ROI methods, and no meta-analysis was possible for rADCmean studies using VOI methods. The pooled AUC value for studies using ROI methods was 0.778 (0.687-0.870) (I^2=79.330) as shown in Figure 2 (Panel C). Using VOI methods, Thust et al. 2021 reported an rADCmean AUC value of 0.82 (0.76-0.88) in a cohort of 283 WHO 2 and 3 gliomas (30).

ADCmin

Eleven studies used ROI methods, and three studies used VOI methods to measure ADCmin values to classify IDH mutation status. In three of the eleven ROI studies, the generation of ADCmin measurements involved 3 or more individual ROI placements with ADC averaging (36,44,55). The cohorts of the studies using ROI methods comprised of WHO 1-4 (n=1) (36), WHO 2-3 (n=4) (30,32,33,47), WHO 3 (n=1) (34), WHO 2-4 (n=2) (41,55), WHO 3-4 (n=1) (42), and WHO 4 gliomas (n=2) (44,45). Of the two studies using VOI methods, Thust et al. assessed a cohort of WHO 2-3 gliomas, whilst Villanueva-Meyer at al. assessed a cohort of WHO 2 gliomas (29,30).

The studies by Maynard et al. (33), and Xiong et al. (47) were excluded from the ROI meta-analysis to avoid pseudoreplication, because their cohorts overlapped with those of other studies in the analysis (30,32). Studies using ROI methods gave a pooled AUC of 0.743 (0.680-0.805) (I^2=76.055) (Figure 2, Panel D), whilst studies using VOI methods gave a pooled AUC of 0.804 (0.689-0.919) (I^2=89.969) (Figure 2, Panel E).

rADCmin

Eight studies used ROI methods (30,32,33,36,44,46,47,55), and one study used VOI methods (30) to measure rADCmin values to classify glioma IDH mutation status. In 3 studies, ADCmin measurements involved 3 or more individual ROI placements for averaging (36,44,47,55). The eight studies using ROI methods, analysed cohorts of WHO 1-4 (n=1) (36), WHO 2-3 (n=5) (30,32,33,46,47), WHO 2-4 (n=1) (55), and WHO 4 gliomas (n=1) (44). Thust et al. was the only study to use VOI rADCmin methods with a reported AUC of 0.72 (0.66-0.79) (30).

One study by Maynard et al. was again excluded to avoid pseudoreplication (33) with another study in the meta-analysis (30). The study by Xiong and colleagues (47) was also excluded to avoid pseudoreplication, as the study cohort (n=84) appeared to overlap with the cohort of another study (n=90) included in the meta-analysis (51). The pooled AUC values for the remaining six studies which used ROI methods was 0.802 (0.72-0.877) (I^2=83.523) as shown in Figure 2 (Panel F).

1p19q

ADCmean

Six studies assessed ADCmean values as a classifier of glioma 1p19q codeletion status, of which five used VOI methods (51,53,54,56,61) and one used ROI methods (60).

Of the 5 studies using VOI methods, Nuessle et al.(54), Liu et al. (51), and Su et al. (53) only assessed the prediction of 1p19q codeletion amongst IDH^{mut} gliomas whilst Latysheva et al., used a cohort comprising 71 WHO 2-3 gliomas of which 33 were oligodendrogliomas and 38 were astrocytomas (note molecular status was not reported for all) (61). Cheng et al. used a cohort of WHO 2-4 gliomas which included 6 IDH^{wt}, 5 $IDH^{mut}/1p19q^{retained}$, and 2 $IDH^{mut}/1p19q^{codel}$ gliomas, however due to their methods of retrospectively identifying ROIs from surgical biopsy

sites by fusing intraoperative MRI with pre-operative imaging, this study was not included in the meta-analysis (56). Cheng et al. reported an AUC of 0.916 using this method (56). The pooled AUC of the remaining 4 studies using VOI methods was 0.692 (0.600-0.783) (I^2=44.948) (forest plot provided in Supplementary Material).

Cui et al. were the only to use ROI methods in a cohort of 35 WHO 2 gliomas, of which 33 were IDH-mut, reporting an AUC of 0.820 for the prediction of 1p19q codeletion status (60).

rADCmean

One study provided an AUC value for rADCmean as a predictor of 1p19q codeletion status. Cui et al. used ROI methods to measure rADCmean values in a cohort of 35 WHO 2 gliomas, of which 3 were IDH^{wt} and 32 were IDH^{mut}, reporting an AUC value of 0.81 (0.67-0.95)(60).

ADCmin

One study assessed ADCmin values as a classifier of 1p19q codeletion status. Ma et al. reported an AUC value of 0.68 (0.57-0.80) when using the average ADC value of three ROIs placed on the visually perceived lowest regions of the ADC map to identify 1p19q codeletion amongst IDH^{mut} gliomas (55).

rADCmin

Three studies measured rADCmin values using ROI methods to predict 1p19q codeletion status giving a pooled AUC value of 0.678 (0.614-0.741) (I^2=0) (forest plot provided in Supplementary Material) (47,55,59). Ma et al. and Yang et al. assessed this amongst IDH-mut gliomas only whilst Xiong et al. used a cohort of 84 oligodendroglial tumours (47,55,59).

Summary of studies not included in the prior groupings

Two studies reported ADC entropy as the best performing ADC parameter for the classification of IDH mutation status. Su et al. used VOI methods to measure ADC entropy values in a cohort of 52 WHO 3 gliomas, obtaining an AUC of 0.724 (0.572-0.845) (35). Gihr et al. similarly used VOI methods in a cohort of 87 WHO 1-4 gliomas and reported an AUC value of 0.804 (0.6849-0.9231) (37).

Aliotta et al. reported AUC values for 75th percentile and 50th percentile ADC values in the classification of IDH mutation and 1p19q codeletion status, respectively (48). Using automated tumour volume segmentation, in a cohort of 41 WHO 2-3 gliomas, 75th percentile ADC achieved an AUC of 0.81 (0.78-0.84) for the classification of IDH mutation status and 50th percentile ADC achieved and AUC of 0.83 (0.80-0.86) for the classification of 1p19q codeletion (48).

Cho et al. measured median tumour rADC values using VOI methods in a cohort of non-enhancing WHO 2-3 gliomas (57). They reported AUC values of 0.848 for distinguishing IDH^{mut} astrocytomas from all other gliomas, 0.805 for distinguishing between IDH^{mut} astrocytomas and IDH^{mut} oligodendrogliomas, and 0.883 for distinguishing IDH^{mut} astrocytomas from IDH^{wt} gliomas (57).

Lee. et al assessed whether ADC values could be used to distinguish IDH^{mut},1p19q^{retained} gliomas from IDH^{wt} gliomas in a cohort of 110 WHO 2 and 3 gliomas. They reported 10th percentile ADC values, measured using ROI methods, provided an AUC of 0.751 (0.617-0.886) (50).

Aliotta et al. assessed whether IDH^{mut}/1p19^{retained} gliomas could be distinguished from all other gliomas using ADC histogram parameters derived from automatically segmented tumour volumes (49). In a validation set of

93 WHO 2 and 3 gliomas from The Cancer Imaging Archive (TCIA) database, both ADCmean and volume of ADC >1.5 provided an AUCs of 0.81 (CIs not provided) (49).

Influence of WHO grade on ADC performance for IDH genotyping

The linear regression analysis of reported AUC values for each ADC parameter (with at least 5 observations) and the proportion of WHO 4 gliomas in the study cohorts showed no significant association between AUC and WHO grade ($p>0.05$ for all ADC parameters). Full results are provided in the Supplementary Material.

ADC thresholds

ADC threshold values for IDH genotyping were proposed by multiple studies included in the meta-analyses, with values below the threshold denoting IDH^{wt} status in each cohort. There were 34 instances of threshold recommendations reported across the included publications, for which descriptive statistics are listed in Table 4. The maximum (Max) value specifies the threshold at which sensitivity for IDH^{wt} status would be maximised across the included studies.

Risk of bias in studies

Egger's regression analysis for funnel plot asymmetry

Funnel plots were created, and Egger's regression analysis was performed for the ADCmean (ROI), ADCmean (VOI), ADCmin (ROI), and rADCmin (ROI) predictions of IDH mutation status as these groups contained at least 5 studies. Funnel plots can be found in the Supplementary Material. Egger's regression analysis revealed no significant funnel plot asymmetry for each of the ADC parameters (ADCmean (ROI) $z = -1.897$ ($p=0.058$), ADCmean (VOI) $z = -1.502$ ($p=0.133$), ADCmin (ROI) $z = -1.449$ ($p=0.147$), rADCmin (ROI) $z = -1.850$ ($p=0.064$)).

QUADAS-2

The results of the QUADAS-2 tool risk of bias and applicability assessments, as well as information on individual studies are provided in the Supplementary Material. All studies were retrospective. Five studies reported enrolling a consecutive or random sample of patients, whilst the remaining 28 studies were unclear regarding patient selection methods. Two studies reported using one observer to obtain ADC measurements with no consensus or comparison with a second observer. In one study, one observer obtained all ADC values with a smaller subset of cases being reviewed by a second observer. Seven studies did not specify methods of testing for IDH mutation or 1p19q deletion. Twenty-seven studies did not specify the time between the index and reference tests. Nine studies were deemed to be at high risk of bias in the flow and timing domain due to either not all patients receiving the same reference standard (e.g. in some studies 1p19q co-deletion was assessed with either fluorescent immunocytochemistry or chromosomal analysis), or not all patients being included in the final analysis (e.g. due to missing data on IDH mutation status). In two studies, the interval between the reference and index test was reported as less than 1 year, which was also allocated high risk of bias.

Discussion

Defining molecular status has become central to the prognostic grouping of diffuse gliomas (4). MRI genotyping has the potential to impact the timing and extent of tumour resection (62), including to accelerate radical therapy for non-contrast-enhancing glioblastoma stages (8), which may otherwise receive a low-grade working diagnosis (63). Based on numerous studies, which proposed ADC as an imaging biomarker in glioma, we investigated the performance of ADC parameters for IDH and 1p19q genotyping.

This systematic review highlights that the published literature is spread across several methods of ADC measurement. Firstly, methods varied between ROI and VOI approaches. The meta-analysis indicates only minor differences between the diagnostic performance of regional and volumetric values measurements (AUC ROI 0.760

vs VOI 0.799 for ADC_{mean} and ROI 0.743 vs VOI 0.804 for ADC_{min}). The similarity between the diagnostic accuracy of ROI and VOI ADC for the classification of IDH mutation status has been documented previously (64,65). Volumetric measurements appear optimal through capture of all representative tissue, but we found no statistical evidence for their superiority. Regional measurements are much easier to obtain and require no software beyond standard MRI viewing equipment. Thus, ROI ADC values may serve as the fastest approach with the advantage of being widely available.

For the meta-analysis, studies were grouped by measurement extent (ROI vs. VOI), by ADC parameter (mean vs. min) and according to whether ADC values were absolute or normalised, whereby each item could influence quantitative results. Surprisingly, the diagnostic performance of ADC for IDH genotyping is similar across all of these method differences. Comparing the 95% CIs of the pooled AUC values revealed no statistically significant differences between ROI and VOI measurements of ADC_{mean}, $rADC_{mean}$, ADC_{min}, or $rADC_{min}$. Drawing one ADCmean ROI across the largest glioma cross-section may be perceived as easier than deciding on the visually lowest ADC parts of a tumour. Furthermore, in several (3 of 11) studies using ROI ADC_{min} measurements, these involved outlining 3 or more regions for averaging.

Applying the maximum threshold proposed by studies for a chosen ADC method would represent the most sensitive strategy for identifying IDH^{wt} status (at the expense of specificity over using the median). For ROI ADCmean, this would correspond to 1.3 x 10^{-3} mm^2/s (n=7 studies), or alternatively an rADCmean threshold of 1.75 could be memorable for its similarity to perfusion thresholding, although this is based on fewer (n=3) studies (66). ROI ADCmin values < 1.1 x 10^{-3} mm^2/s or ROI rADCmin values <1.4 should prompt suspicion for IDH^{wt} genetics.

Encouragingly, the ICC calculations exceeded 0.80 in 12 of 13 studies which reported these, confirming high interobserver agreement for ADC (29–31,33,42,45,46,50–53,55,58). The only study reporting lower ICC values (0.53 for ROI ADCmean and 0.60 for ROI ADCmin) was conducted in WHO grade 4 gliomas, potentially reflecting a

complexity in marking ROIs within necrotic tumours (45). Twenty-four of 33 studies excluded necrotic, cystic, haemorrhagic, or calcified glioma components, where present. This seems justified based on their potential to confound tumour measurements; however little data exists on the performance of ADC according to such exclusions. In one study by Lewis et al. using ADC texture analysis, the performance for IDH typing was slightly improved by excluding necrotic gliomas (67).

The pooled AUC estimates were lower for 1p19q genotyping than IDH genotyping, with estimates of 0.692 (0.600-0.783) for volumetric ADC mean measurements, and 0.678 (0.614-0.741 for regional rADCmin measurements. Moreover, in 8 of 9 studies, either only IDH^{mut} gliomas were examined, or study cohorts including mostly IDH^{mut} gliomas were examined. This markedly limits the generalisability of 1p19q results for clinical practice. Glioma IDH genotyping is essential due to the strong association with survival, whereas prognosis differences are often less pronounced for IDH^{mut} subgroups, although 1p19q status may influence systemic therapy (6).

Normalisation of ADC values is aimed at reducing MRI scanner and acquisition-related variations in ADC measurements. If normalisation is performed, the centrum semiovale represents a preferable target (68). No significant differences were observed between the pooled AUCs of normalised ADC measurements and raw ADC measurements. Several studies provided AUCs for both absolute and normalised ADC values. Du et al., Thust et al. (2018 and 2021), and Liu S et al. all reported similar AUCs when using regional measurements of ADCmean and rADCmean (30,31,36,39). Likewise, no significant AUC differences were identified in the 6 studies which assessed absolute and normalised regional ADCmin measurements (30,32,36,44,47,55).

The possible effect of WHO grade distribution in the different study cohorts was explored based on the hypothesis that developing necrosis may confound ADC measurements in WHO grade 4 glioblastoma, possibly more so than in solid IDH^{wt} early disease stages (69). However, many studies that analysed cohorts of different WHO grades did not report diagnostic accuracy separately for each WHO grade (38–41,53–56,58). The small number of studies

within each meta-analysis together with limited cohort details, precluded a further subgroup analysis. It is however noteworthy that one research group stratified WHO grade 2-3 gliomas by enhancement pattern (non-enhancing, solid-patchy enhancing and rim-enhancing with necrosis) with an observation that ROI ADC values appeared strongly associated with IDH genotype in non-enhancing and solid-patchy enhancing tumours, but not in necrotic tumours (30).

Limitations

Our research was limited by several factors. Heterogeneity exists within the meta-analyses with I^2 values ranging from 0% to 89.969%. All evidence included in this review originates from retrospective research. ADC maps from 1.5T and 3T ADC MRI scanners of different vendors contributed to the analysis with potential to impact quantification of absolute ADC values. Several studies omitted reporting on the blinding of observers to histopathological data, and some studies did not state the CIs of the AUC values. Studies in which the ADC values were combined with other imaging parameters (e.g. visual parameters on anatomical MRI) had to be excluded, if the AUC values for ADC were not provided separately.

To facilitate meta-analysis, studies were grouped according to the final consensus of 4 reviewers (F.B., J.S., NS., S.T), however this may not reflect the entirety of methodological differences. Funnel plots could only be produced for analyses including five or more studies, and in a few instances SE values were deducted by a mathematical formula (28). We did not explore the potential impact of manual (30) versus automated (48,49,53,56) glioma segmentation on ADC results, and this may represent a topic for further study where the availability of automated volumetric ADC extraction will likely grow. The future use of ADC values for glioma molecular diagnosis will most likely benefit from integration with other parameters such as visual features, physiological MRI metrics and age (18,33). Furthermore, the presence of necrosis has been associated with IDHwt status and may predict this

irrespective of ADC (70). In the future, automated segmentation may facilitate the integration of volumetric ADC measurements into clinical workflows (71). Furthermore, prospective research is required to validate proposed ADC thresholds.

Practical guidance

Whilst considering limitations of the presented data, and meta-analysis generally, it appears possible to arrive at preliminary guidance on how to perform and use ADC measurements in clinical practice. Firstly, obtaining a measurement is preferable to qualitative inspection, which is an unreliable predictor of IDH status with poor interobserver agreement (72). The placement of a circular ROI to measure ADCmean in the largest solid tumour cross-section (or in the largest solid tumour focus, where this is not an entire cross-section due to necrosis) is deemed suitable with a view to workflow integration. If preferred, normalised values, or alternatively ADCmin measurements, can be justified where their use is already established in local practice. We refer to Figure 1 in Maynard et al. 2020 for an example of glioma and normal white matter ROI placements, with the note that these should be interpreted as draft guidance (33). In support of the identification of high-risk disease, it is suggested to align measurements of ADC towards sensitive IDHwt identification, particularly for lesions of perceived 'low grade' morphology. Radiological assessments should consider further factors, including age and differentials of diffuse glioma.

Conclusion

This meta-analysis supports ADC as an imaging biomarker in untreated gliomas, specifically to predict IDH status. Published ADC thresholds have been summarised and should be considered for prospective testing. ROI measurement, particularly a single ADCmean, is rapid, reproducible and appears statistically equivalent to volumetric read outs. We found no evidence for altered diagnostic accuracy through ADC normalisation. Future research should aim to formulate numerical thresholds across multiple institutions.

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Conflict of interest

The authors declare no conflict of interest for the work presented.

Contributions

ST and NS conceptualised the review topic and created the initial draft protocol. ST, NS, FB and JS were involved in reviewing and refining the research protocol. FB and JS performed the screening, data extraction and QADAS-2 assessments. ST and NS led the consensus reviews. CT defined the statistical methods. All authors contributed to the results analysis, interpretation and manuscript.

S.T. and F.B. are the guarantors of the research.

Data availability

A summary of the data extracted from all included studies is provided in the Supplementary Material together with the QUADAS-2 assessment, funnel plots and linear regression. Further information can be made available upon reasonable request. No original study data were generated in this research.

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Figure legends:

Figure 1: PRISMA flow diagram

Figure 2: Forest plots showing pooled estimate of AUC values from studies using each ADC parameter as a predictor of IDH mutation status

A = ADCmean (ROI methods), B= ADCmean (VOI methods), C = rADCmean (ROI methods), D = ADCmin (ROI methods), E = ADCmin (VOI methods), F = rADCmin (ROI methods). Asterix (*) denotes studies where standard error was not provided and therefore estimated using a formula. Circumflex (^) denotes studies where 3 or more ROI measurements were averaged to determine ADC_{min} values.

Tables

Table 1: Summary of studies assessing IDH mutation only.

Summary of study author, year of publication, main research purpose, composition of study cohort (WHO grade, IDH status, 1p19q status, sex), methods of ADC measurements, and key results for studies assessing IDH mutation only. Studies are listed from low to higher WHO grade(s).

Abbreviations: ADC: Apparent Diffusion Coefficient, AUC: Area under the curve, cMRI: Conventional MRI, CNAWM: Contralateral normal appearing white matter, CNS: Central nervous system, Codel: Codeletion, DG: Diffuse gliomas, DTI: Diffusion tensor imaging, DWI: Diffusion weighted imaging, F: Female, GBM: Glioblastoma multiforme, HGGs: High grade gliomas, IDH: Isocitrate dehydrogenase, IQR: Interquartile range, LGGs: Low grade gliomas, M: Male MRI: Magnetic Resonance Imaging, Mut: Mutant, NAWM: Normal appearing white matter, NS: Not stated, ROI: Region of interest, Sens: Sensitivity, Spec: Specificity, T1w: T1-weighted imaging. T2w: T2-weighted imaging, VOI: Volume of interest, Wt: Wild-type.

Table 2: Summary of studies assessing IDH mutation and 1p19q codeletion

Summary of study author, year of publication, main research purpose, composition of study cohort (WHO grade, IDH status, 1p19q status, sex), methods of ADC measurements, and key results for studies assessing both IDH mutation and 1p19 codeletion.

Abbreviations: ADC: Apparent Diffusion Coefficient, AUC: Area under the curve, cMRI: Conventional MRI, CNAWM: Contralateral normal appearing white matter, CNS: Central nervous system, Codel: Codeletion, DG: Diffuse gliomas, DTI: Diffusion tensor imaging, DWI: Diffusion weighted imaging, F: Female, GBM: Glioblastoma multiforme, HGGs: High grade gliomas, IDH: Isocitrate dehydrogenase, IQR: Interquartile range, LGGs: Low grade gliomas, M: Male,

MRI: Magnetic Resonance Imaging, Mut: Mutant, NAWM: Normal appearing white matter, NS: Not stated, ROI: Region of interest, Sens: Sensitivity, Spec: Specificity

T1w: T1 weighted imaging. T2w: T2-weighted imaging, VOI: Volume of interest, Wt: Wild-type.

Table 3: Summary of studies assessing 1p19q codeletion alone

Summary of study author, year of publication, main research purpose, composition of study cohort (WHO grade, IDH status, 1p19q status, sex), methods of ADC measurements, and key results for studies assessing 1p19 codeletion only.

Abbreviations: ADC: Apparent Diffusion Coefficient, AUC: Area under the curve, CodeI: Codeletion, DG: Diffuse gliomas, DTI: Diffusion tensor imaging, DWI: Diffusion weighted imaging, F: Female, IDH: Isocitrate dehydrogenase, M: Male, MRI: Magnetic Resonance Imaging, Mut: Mutant, ROI: Region of interest, Sens: Sensitivity, Spec: Specificity, VOI: Volume of interest, Wt: Wild-type.

Table 4: Proposed ADC thresholds for IDH genotyping according to studies included in the meta-analyses.

*N: number, SD=standard deviation, Min=minimum, Max=maximum. ADC values in units of *10^{-3} mm^2/s. rADC values have no unit.*

Table 1: Summary of studies assessing IDH mutation only.

Summary of study author, year of publication, main research purpose, composition of study cohort (WHO grade, IDH status, 1p19q status, sex), methods of ADC measurements, and key results for studies assessing IDH mutation only. Studies are listed from low to higher WHO grade(s).

Abbreviations: ADC: Apparent Diffusion Coefficient, AUC: Area under the curve, cMRI: Conventional MRI, CNAWM: Contralateral normal appearing white matter, CNS: Central nervous system, Codel: Codeletion, DG: Diffuse gliomas, DTI: Diffusion tensor imaging, DWI: Diffusion weighted imaging, F: Female, GBM: Glioblastoma multiforme, HGGs: High grade gliomas, IDH: Isocitrate dehydrogenase, IQR: Interquartile range, LGGs: Low grade gliomas, M: Male MRI: Magnetic Resonance Imaging, Mut: Mutant, NAWM: Normal appearing white matter, NS: Not stated, ROI: Region of interest, Sens: Sensitivity, Spec: Specificity

T1w: T1-weighted imaging. T2w: T2-weighted imaging, VOI: Volume of interest, Wt: Wild-type.

Study	**Research purpose**	**WHO Grades**	**Cohort size and composition**	**Age (years), Sex**	**ROI or VOI methods**	**Results**
Villanueva-Meyer JE et al. 2018	To identify MRI markers predictive of IDH mutational status in grade II diffuse gliomas (DGs) and evaluate the complementary	2	100 WHO 2. (IDH-wt = 22, IDH-mut = 65)	IDH-wt Median 58. IDH-mut Median 41. Sex NS	VOI Tumour delineated on all axial slices to calculate min, mean and max ADC of tumour. Necrosis, cysts,	- ADCmin: AUC 0.905 (0.830–0.954), Cut off <0.9x10^{-3}, Sens 91%, Spec 76%, p<0.001.

	roles of MRI features and IDH mutational status to better predict outcomes for these patients.				haemorrhage, vessels avoided	
Thust SC et al. 2021	To compare volumetric and regional ADC measurement techniques for glioma genotyping with a focus on IDH status prediction.	2,3	283 (WHO 2 and 3) (IDH-wt = 79, IDH-mut 1p19q-retained = 104, IDH-mut 1p19q-codel = 100)	Median 30, IQR 33-53. 164M, 119F	ROI and VOI Regional ADC measurements: 3, small, 30-40mm^2 ROIs placed in visually perceived lowest ADC portions of glioma, remaining in solid component. ADCmean: 1 large ROI placed on largest axial tumour cross section. Calcium, cysts, haemorrhage, vessels avoided from ROIs. VOI: whole	- VOI ADCmin: Cut off 0.81 x10^{-3}mm^2/s, Sens 68.4%, Spec 60.3%, AUC 0.68 (0.61-0.75). - VOI rADCmin (5th percentile): Cut off 1.08, Sens 68.4%, Spec 61.3%, AUC 0.72 (0.66-0.79). - VOI ADCmean: Cut off 1.19 x10^{-3}mm^2/s, Sens 77.2%, Spec 64.2%, AUC 0.78 (0.72-0.84). - VOI rADCmean: Cut off 1.60, Sens 86.8%, Spec 60.8%, AUC 0.82 (0.76-0.88). - ROI ADCmin: Cut off 1.07 x10^{-3}mm^2/s, Sens 82.3%, Spec 61.3%, AUC 0.79 (0.73-0.85). - ROI rADCmin: Cut off 1.40, Sens 85.5%, Spec 62.3%, AUC 0.81 (0.76-0.86). - ROI ADCmean: Cut off 1.34 x10^{-3}mm^2/s, Sens 84.8%, Spec 60.3%, AUC 0.81 (0.75-0.86). - ROI rADCmean: Cut off 1.75, Sens 86.8%, Spec 62.3%, AUC 0.83 (0.77-0.88). p<0.001 for all.

					tumour segmentation incorporating entire T2-weighted signal abnormality.	
Thust SC et al. 2018	To investigate if quantitative ADC measurements can predict genetic subtypes of non-gadolinium-enhancing gliomas, comparing whole tumour against single slice analysis.	2,3	44 (WHO 2 = 26, WHO 3 = 18) (IDH-wt = 14, IDH-mut 1p19q-retained = 16, IDH-mut 1p19q-codel = 14)	IDH-wt Mean 53+/-14. IDH-mut 1p19-retained Mean 33.9+/-8.6. IDH-mut 1p19q-codel Mean 38.9+/-8.3. 22M, 22F	ROI and VOI ROI placed on largest tumour cross section, sparing the tumour margin. VOI: whole tumour segmentation incorporating entire T2-weighted signal abnormality.	- ADCmean (VOI): Cut off 1201(x10^{-6}mm^2/s), sens 0.83, spec 0.86, AUC 0.85. - rADCmean (VOI): Cut off 1.65, sens 0.80, spec 0.92, AUC 0.86. - ADCmean (ROI) 1st observer: Cut off 1.83, sens 0.86, spec 1.00, AUC 0.93. - ADCmean (ROI) 2nd observer: Cut off 1.76, sens 0.86, spec 0.91, AUC 0.88.
Xiong J et al. 2016	To assess whether DTI metrics could aid the noninvasive detection of IDH mutations and their correlations with tumor proliferation and	2,3	90 (WHO 2 = 54, WHO 3 = 36). (IDH-mut = 67, IDH-wt = 23) (Oligodendroglioma = 29, Anaplastic oligodendroglioma = 24,	WHO II Mean 40+/-10. WHO III Mean 46+/-11 42M, 38F	ROI 4-6 ROIs placed in solid tumour. The lowest ADC from the ROIs drawn by two observers was averaged and	- ADCmin: Cut off 0.81, Sens 78.7%, Spec 79.2%, AUC 0.77. - rADCmin: Cut off 1.19, Sens 80.9%, Spec 76.9%, AUC 0.80.

	microvascular density (MVD) in oligodendroglial tumours.		Oligoastrocytoma = 25)		used as the as the minimum ADC value. ROIs also placed in peritumoural region to calculate peritumoural ADC. Calcification, cysts, haemorrhage, necrosis avoided.	
Maynard J et al. 2020	To evaluate clinically available MRI parameters for predicting IDH status in patients with glioma.	2,3	339 (Study sample = 290, test sample = 49) (WHO 2 and 3) (Study sample: IDH-wt = 82, IDH-mut 1p19q-retained = 107, IDH-mut 1p19q-codel = 101) (Test sample: IDH-wt = 9, IDH-mut 1p19q-retained = 21, IDH-mut 1p19q-codel = 19)	Study sample: Median 10, IQR 33-52, Range 17-77. 169M,121F. Test sample age and sex NS.	ROI 1) 3 ROIs (30-40mm^2) placed in visually perceived lowest ADC portions of each tumour; lowest ROI mean ADC measurement designated as ADCmin. 2) One large ROI placed to cover the largest axial	- rADCmean: AUC 0.83. - ADCmin: AUC 0.78. - rADCmin: AUC 0.8. - ADCmean: AUC 0.81.

					tumour cross section; used as ADCmean. Tumour margins, necrosis, haemorrhage, calcification avoided.	
Wasserman JK et al. 2015	To determine whether pathological and/or radiological variables exist that can reliably distinguish IDH1-R132H-positive from IDH1-R132H-negative tumours and to identify variables associated with early mortality.	3	37 WHO 3. (Anaplastic astrocytoma = 28: IDH R132H-mut = 12, IDH-wt = 16. Anaplastic oligoastrocytoma = 9: IDH R132H-mut =6, IDH-wt =3)	Mean 68, Range 20-81. 16M, 21F	ROI Small ROI (25mm^2) placed in region of lowest apparent ADC, by visual inspection, to determine ADCmin values.	- ADCmin: Cut off 0.950 x10^{-3}mm^2/s, Sens 76.9%, Spec 65.2%, AUC 0.711 (0.534-0.887), p=0.033.
Su CQ et al. 2019	To examine whether texture analysis of DWI combined with conventional MRI could non-invasively predict IDH1 mutational	3	52 WHO 3. (IDH-mut n=21: 11 anaplastic astrocytoma, 10 anaplastic oligodendroglioma. IDH-wt n=25 (13 anaplastic	Mean = 47.8+/-12, Range 18-72 25M, 21F	VOI Tumour manually outlined on contrast-enhanced T1WI as areas of abnormal	- ADCentropy, AUC 0.724 (0.572-0.845), Cut off >5.763, Sens 71.4%, Spec 76%.

	status in anaplastic gliomas.		astrocytoma, 12 anaplastic oligodendroglioma)		enhancement and non-enhancing tumour. Vessels, necrosis, oedema avoided.	
Du N et al. 2022	To explore the correlation between MRI morphological characteristics, ADC parameters and pathological grade and IDH gene phenotypes of gliomas.	1,2,3,4	166 (WHO 1= 12, WHO 2 = 31, WHO 3 = 18, WHO 4 = 105) (IDH-wt = 112, IDH-mut = 48) *No IDH status for 6 patients.	Mean 51.1+/- 15.9, Range 14-85. 92M, 74F	ROI 1) ADCmin: 3 different 20-30mm^2 ROIs placed on visually determined lowest ADC; mean taken as ADCmin. 2) ADCmean: ROI plotted as large as possible on largest transverse cross-section of tumour. Cysts, calcification, necrosis, vessels avoided.	- ADCmin: AUC 0.653 (0.561-0.745), Cut off 0.98, Sens 45.83, Spec 83.04. - ADCmean: AUC 0.643 (0.555-0.731), Cut off 1.05, Sens 75.00, Spec 58.04. - rADCmin: AUC 0.656 (0.566-0.746), Cut off 1.14, Sens 62.50, Spec 66.96. - rADCmean: AUC 0.652 (0.562-0.742), Cut off 1.40, Sens 70.83, Spec 59.82.

Gihr G et al. 2022	To investigate (I) the potential of ADC histogram analysis for distinguishing LGGs and HGGs and (II) whether those parameters are associated with Ki-67 immunolabelling, the IDH1 mutation profile and the MGMT promoter methylation profile.	1,2,3,4	82 (WHO 1 = 7, WHO 2 = 19, WHO 3 = 11, WHO 4 = 45) (IDH-wt = 58, IDH-mut = 19) *No IDH status for 5 patients.	WHO I+II Mean 34. WHO III+IV Mean 62. 34M, 48F	VOI Tumour volumes manually drawn in T1W or T2W images along the border of visible signal alteration (contrast enhancing region or T2W hyperintense region) in every slice of detectable tumour. Volume used for histogram analysis.	- ADC Entropy, AUC 0.8040 (0.6849–0.9231), p<0.0001. Cut off <5.488, Sens 0.73. Spec 0.97. - ADCmax, AUC 0.7314 (0.6054–0.8573), p=0.0026. - Skewness, AUC 0.7486 (0.6235–0.8737), p=0.0012.
Springer E et al. 2022	To use MR Fingerprinting-derived T1 and T2 relaxation maps to differentiate diffuse gliomas according to IDH mutation.	2,3,4	24 (WHO 2= 10, WHO 3 = 5, WHO 4 = 9) (WHO2Diffuse Astrocytoma = 7: IDH-mut = 6, IDH-wt = 1. WHO 2Oligodendroglioma IDH-mut 1p19q-codel = 3. WHO III Anaplastic	Mean 58.6, Range 23-77. 15M, 9F	ROI ROIs marked on 1) solid part of tumour with and without contrast enhancement (mean number of ROIs per case = 2.7), 2) perilesional	- ADCmean: AUC 0.875, p<0.001.

			astrocytoma = 4: IDH-mut = 3, IDH-wt = 1. WHO III anaplastic oligodendroglioma IDH-mut 1p19q-codel = 1. WHO IV GBM n = 9: IDH-mut = 1, IDH-wt = 8.)		NAWM (less than or equal to 1cm from tumour or peritumoral oedema), 3) perilesional NAWM less than or equal to 1 cm distant from the tumor or from peritumoral oedema, and 4) contralateral frontal lobe NAWM. Necrosis and haemorrhage avoided.	
Liu S et al. 2022	To explore the feasibility of DWI metrics to predict the histologic subtypes and genetic status of gliomas noninvasively.	2,3,4	111 (WHO 2 = 36, WHO 3 = 32, WHO 4 = 43) (IDH-wt = 65, IDH-mut = 45) *No IDH status for 1 patient.	Mean 44.3+/-12.1. 58M, 53F	ROI 4 ROIs manually placed within solid components of tumours co-registered on T2WI. Cysts, necrosis, haemorrhage,	- - ADCmean: AUC 0.777 (0.688,0.865), cut off 0.0012, sens 88.4, spec 67.7. - rADCmean: AUC 0.836 (0.757,0.914), cut off 1.60, sens 82.2, spec 80.0.

					calcification avoided.	
Kamble AN et al. 2023	Hypothesise that glioma can be stratified into 3 types using a flow chart of 4 yes/no questions, which correlate with the 3 glioma types in the 2021 WHO classification. Propose that radiological stratification would have prognostic implications if correlated with the WHO classification.	2,3,4	475 (Training set = 275, Validation set = 200) (WHO 2, 3, and 4) (Training set: IDH-wt = 124, IDH-mut 1p19q-retained = 54, IDH-mut 1p19q-codel = 21) (Validation set: IDH-wt = 106, IDH-mut 1p19q-retained = 48, IDH-mut 1p19q-codel = 46)	Training set: Type I Mean 47, Type II Mean 45, Type III Mean 55. 152M, 122F. Validation set: Type I Mean 45, Type II Mean 38, Type III Mean 56. 107M, 93F.	ROI ROI placed as homogenously as possible to calculate average tumour ADC after excluding tumour necrosis. Necrosis excluded.	- ADCmean Training dataset: Cut off 1.12, sens 82.1, spec 74.2, AUC 0.841, p <.0.0001. - ADCmean Validation dataset: Cut off 1.20, sens 72.9, spec 64.9, AUC 0.748, p <.0.0001.
Xie Y et al. 2021	To compare the efficacy of parameters from multiple diffusion magnetic resonance imaging for	2,3,4	91 (WHO 2 = 27, WHO 3 = 20, WHO 4 = 43) (IDH-wt = 49, IDH-mut = 41)	IDH-mut Median 53, IQR 46.5-58. IDH-wt Median 41, IQR 34.75-	ROI 3-6 ROIs manually placed in solid part of tumour parenchyma (defined as contrast	WHO II and III tumours: - ADCmin: AUC 0.751, Sens 59.38, Spec 93.33, Cut off 1.084. WHO IV tumours: - No significant difference found between diffusion imaging parameters.

	prediction of IDH1 genotype and assessment of cell proliferation in gliomas.			50.25. 48M, 43F	enhancing areas on T1WI, if no enhancement then the area of abnormal signal on T2FLAIR and T2FSE). The minimum ADC from each ROI was to calculate tumour ADC values. Calcification, cysts, haemorrhage, oedema, necrosis excluded.	
Zhang H et al. 2024	To assess the diagnostic utility of clinical magnetic resonance spectroscopy and diffusion-weighted imaging in distinguishing between	2,3,4	247 (WHO 2 = 76, WHO 3 = 66, WHO 4 = 105) (IDH-wt = 125, IDH-mut = 122)"	Mean 46.96+/-13.92, Range 19-85 141M, 106F	ROI ROI placed on largest axial tumour slice. Mean ADC recorded. Calcification, cysts, haemorrhage, necrosis, and	- ADCmean: Cut off <9.22 x10^{2}mm^2/s, Sens 77.8%, Spec 78.0%, AUC 0.81, p<0.001.

	histological grading and isocitrate dehydrogenase (IDH) classification in adult diffuse gliomas.				vessels avoided.	
Cindil E et al. 2022	Evaluate the diagnostic performance of DWI MRI parameters in the non-invasive prediction of IDH mutation status in HGGs.	3,4	56 (WHO 3 and 4) (GBM IDH-wt = 25, GBM IDH-mut = 10, Anaplastic astrocytoma IDH-wt = 10, Anaplastic astrocytoma IDH-mut = 13))	IDH-mut Mean = 49+/-17. IDH-wt Mean = 58+/-14. 31M, 27F	ROI 1-3 ROIs manually placed on darkest areas on the tumour core that corresponded to enhancing tumour. Lowest ROI ADC value used. Calcium, cysts, haemorrhage, vessels avoided.	- ADCmin: AUC 0.686 (0.795-0.950), Cut off 0.954, Sens 0.74, Spec 0.66, PPV 0.77, NPV 0.58, Accuracy 0.68.
Lee S et al. 2015	To explore the difference between isocitrate dehydrogenase (IDH)-1/2 gene mutation-	3,4	52 (WHO 3 = 15, WHO 4 = 37). (WHO III Anaplastic astrocytoma = 15: IDH-mut = 9, IDH-wt = 6. WHO IV GBM =	Mean 49.81+/-14.5, Range 22-72. 32M, 20F	VOI Tumour borders manually drawn in each section of co-registered	- ADCmean, AUC 0.707 (0.564–0.825), Sens 50, Spec 91.7, cut off>1333.42 (x10^{-6}mm^2/s), p=0.0178. - ADC 10%, AUC 0.707 (0.564–0.825), Sens 50, Spec 97.2, cut off >797 (x10^{-6}mm^2/s), p=0.0250.

	positive and -negative high-grade gliomas (HGGs) using histogram analysis of ADC maps.		37: IDH-mut = 7, IDH-wt = 30)		T2WI. ADC histogram parameters generated.	- ADC 50%, AUC 0.690 (0.547–0.825), Sens 43.7, Spec 91.7, cut off >1,299 (x10^{-6}mm^2/s), p=0.0256.
Halefoglu AM et al. 2023	To investigate whether MRI features can determine IDH mutation in HGG.	4	170 WHO 4. (IDH-wt GBM = 146, IDH-mut astrocytoma = 24).	Mean 57.81+/-12.01. 103M, 67F	ROI 3 ROIs of similar size placed on visually perceived darkest regions of ADC map. Mean of 3 ROIs used as ADCmin. Method of ADCmean is unclear. Cysts, calcification, haemorrhage, necrosis avoided.	- ADCmean: Cut off ≤ 0.879 x10^{-3}mm^2/s, Sens 83.65%, Spec 76.19%, PPV 94.60%, NPV 48.50%, AUC 0.866 (0.770-0.963), p< 0.01. - ADCmin: Cutoff ≤0.765.67 x10^{-3}mm^2/s, Sens 77.88%, Spec 80.95%, PPV 95.30%, NPV 42.50%, AUC 0.860 (0.760-0.960), p< 0.01. - rADCmin: Cut off ≤1.002 x10^{-3}mm^2/s, Sens 91.35%, Spec 85.71%, PPV 96.90%, NPV 66.70%, AUC 0.939 (0.886-0.992), p< 0.01.
Uetani H et al. 2023	To investigate the most useful clinical and MRI parameters for differentiating	4	327 WHO 4. (IDH wt = 306, IDH mut = 21)	Mean 65, Range 24-89 194M, 133F	ROI 4 or more circular ROIs placed within solid tumour, targeting	- ADCmean Reader 1: Cutoff ≥1.014, Sens 55.0%, Spec 70.3%, Acc 69.3%, AUC 0.548 (0.383–0.712). - ADCmean Reader 2: Cutoff ≥0.976, Sens 85.0%, Spec 40.7%,

	IDH mut and wt glioblastomas.				regions with relatively low ADC. Necrosis, haemorrhage, vessels avoided.	Acc 43.5, AUC 0.61 (0.486–0.734). - ADCmin Reader 1: Cutoff ≥1.014, Sens 45.0%, Spec 74.7%, Acc 72.8%, AUC 0.533 (0.364–0.701). - ADCmin Reader 2: Cutoff ≥0.866, Sens 75.0%, Spec 45.9%, Acc 47.7%, AUC 0.539 (0.412–0.665).
Xing Z et al. 2019	To evaluate the contribution of DWI in the enhancing and peri-enhancing region for discriminating IDH genotypes, and the diagnostic values of combining two techniques in the peri-enhancing region compared with those in the enhancing region.	4	75 WHO 4. (IDH-wt = 65, IDH-mut = 10)	IDH-mut Mean = 40.70+/-10.77. IDH-wt Mean = 52.23+/-12.71. 41M, 34F	ROI At least 5 non overlapping ROIs placed in the solid enhancing portion of tumour; mean value of the ROI of the lowest ADC value was used as ADCmin-tumour (ADCmin-t). 5 ROIs placed in the peri-tumoural, non-enhancing region; mean value of the ROI of the lowest ADC value was used as ADCmin-	- rADCmin: AUC 0.703, cut off 0.98, Sens 90%, Spec 55.93%, PPV 25.7%, NPV 97.10%.

					peritumoural region (ADCmin-p). Necrosis, cysts, haemorrhage, vessels avoided.	

*T*able 2: Summary of studies assessing IDH mutation and 1p19q codeletion

Summary of study author, year of publication, main research purpose, composition of study cohort (WHO grade, IDH status, 1p19q status, sex), methods of ADC measurements, and key results for studies assessing both IDH mutation and 1p19 codeletion.

Abbreviations: ADC: Apparent Diffusion Coefficient, AUC: Area under the curve, cMRI: Conventional MRI, CNAWM: Contralateral normal appearing white matter, CNS: Central nervous system, Codel: Codeletion, DG: Diffuse gliomas, DTI: Diffusion tensor imaging, DWI: Diffusion weighted imaging, F: Female, GBM: Glioblastoma multiforme, HGGs: High grade gliomas, IDH: Isocitrate dehydrogenase, IQR: Interquartile range, LGGs: Low grade gliomas, M: Male, MRI: Magnetic Resonance Imaging, Mut: Mutant, NAWM: Normal appearing white matter, NS: Not stated, ROI: Region of interest, Sens: Sensitivity, Spec: Specificity

T1w: T1 weighted imaging. T2w: T2-weighted imaging, VOI: Volume of interest, Wt: Wild-type.

Study	**Research purpose**	**WHO Grades**	**Cohort size and composition**	**Age, Sex**	**ROI or VOI methods**	**Results**
Xiong J et al. 2016	To explore the correlations of cMRI and DTI values with the 1p/19 codeletion and IDH mutations in oligodendroglial tumours.	2,3	84 (WHO 2 = 50, WHO 3 = 34) (IDH-mut = 67, IDH-wt = 17, 1p19q-codel = 60, 1p19q-retained = 24)	Mean 41.5, Range 24-60. 40M, 44F	ROI. 4-6 ROIs placed in solid tumour. The lowest ADC from the ROIs drawn by the two observers was averaged and used as the as the	IDH - ADCmin: cut off 0.85, sens 77.8%, spec 81.2%, PPV 94.2%, NPV 48.0%, AUC 0.82, p=0.001. - rADCmin: cut off 1.19, sens 79.4%, spec 81.2%, PPV 94.3%, NPV 50.0% AUC 0.83, p=0.002. 1p19q

					minimum ADC value. Calcification, cysts, necrosis, haemorrhage avoided.	- ADCmin: cut off 1.13, AUC 0.63, Sens 62.3%, Spec 70.0%, PPV 83.7%, NPV 42.9%, p=0.315.
Aliotta E et al. 2020	To develop an ADC analysis-based approach that can automatically identify IDHmut-noncodel LGG	2,3	227 (WHO 2 and 3, breakdown not provided.) (Internal set = 134: IDH-wt = 31, IDH-mut 1p19q-codel = 54, IDH-mut 1p19q-retained = 49.) (TCIA set = 93: IDH-wt = 18, IDH-mut 1p19q-codel = 26, IDH-mut 1p19q-retained = 49.)	Age NS. Sex NS.	VOI. Fully automated segmentation using 3D-Unet (Internal set) and GLISTRboost (TCIA set) algorithms. Generated ADC histograms.	IDHmut, 1p19q retained vs IDHwt and IDHmut, 1p19q codel. - ADCmin (Internal dataset): Cut off 0.8 x10^{-3}mm^2/s, Sens 0%, Spec 100%, AUC 0.42, p=0.04428. - ADCmin (TCIA dataset): Cut off 0.8 x10^{-3}mm^2/s, Sens 0%, Spec 100%, AUC 0.46, p=0.002. - ADCmean (Internal dataset): Cut off 1.37 x10^{-3}mm^2/s, Sens 53%, Spec 91%, AUC 0.76, p<0.00001. - ADCmean (TCIA dataset): Cut off 1.37 x10^{-3}mm^2/s, Sens 55%, Spec 89%, AUC 0.81, p<0.00001.
Aliotta E et al. 2019	To investigate lower grade glioma grading using a machine learning technique that estimates fractional anisotropy from accelerated diffusion MR imaging scans	2,3	41 (WHO 2 = 26, WHO 3 = 15) (IDH-wt = 15, IDH-mut 1p19q-retained = 14, IDH-mut 1p19q codel = 12)	Mean 45.9, Range 18-76. 24M, 17F.	VOI. Automated segmentation, including enhancing and non-enhancing tumour, with DeepMedic. Regions combined to generate whole tumour	IDH - ADC75%: Sens 84+/-0.06, Spec 0.67+/- 0.05, AUC 0.81+/-0.03, p=0.008. 1p19q - ADC50%: Sens 81+/-0.06, Spec 0.73+/- 0.04, AUC 0.83+/-0.03, p<0.001.

	containing only 3 diffusion-encoding directions.				volumes. ADC histograms generated.	
Lee MK et al. 2020	To assess the diagnostic value of adding the ADC and CBV to the T2/FLAIR mismatch sign for differentiation of the IDH mutation or 1p/19q codeletion.	2,3	110 (WHO 2 = 45, WHO 3 = 65) (IDH-wt = 45, IDH-mut 1p19q-retained = 19, IDH-mut 1p19q codel = 46)	Mean 47.4+/-13.3. 56M, 54F	ROI ROIs drawn to encompass entire hyperintense lesion on FLAIR images and enhancing solid tumour on cases with contrast enhancement. ADC histograms generated.	IDH-mut 1p19q-retained vs IDH-wt - ADC10%, AUC 0.751 (0.617-0.886), Sens 84.2, Spec 63.6, Acc 69.8, p=0.43. No ADC parameters could distinguish IDH-mut and IDH-wt tumours on multivariate analysis.
Liu D et al. 2020	To evaluate the diagnostic performance of ADC histogram parameters for differentiating the genetic subtypes in lower-grade diffuse gliomas and explore which	2,3	56 (WHO 2 = 37, WHO 3 = 19) (IDH-wt = 16, IDH-mut 1p19q-retained = 22, IDH-mut 1p19q codel = 18)	IDH mut: Mean 41.5+/-10.5, Range 23-66. IDH wt: Mean = 51.9+/-	VOI VOI1: Entire tumour included. VOI2: Entire tumour, excluding cystic and necrotic regions. ADC	IDH - ADCmin VOI-1: Cut off 560, Sens 62.5%, Spec 87.5%, AUC 0.749. - ADCmin VOI-2: Cut off 543, Sens 62.5%, Spec 90.0%, AUC 0.831. IDH-mut 1p19q-codel vs IDH-mut 1p191-retained. ADCmean VOI-1: Cut off 1546.32, Sens 95.5%, Spec 55.6%, AUC 0.715.

	segmentation method (ROI-1, the entire tumor ROI; ROI2, the tumor ROI excluding cystic and necrotic portions) performs better.			16.0, Range 21-73. 27M, 29F.	histograms generated.	ADCmean VOI-2: Cut off 1387.97, Sens 81.8%, Spec 72.2%, AUC 0.758.
Hong EK et al. 2021	To evaluate the association of MRI features with the major genomic profiles and prognosis of WHO grade III gliomas compared with those of GBMs.	3	76 (WHO 3 = 76) (IDH-mut = 47, IDH-wt = 29. 1p19q-codel = 19, 1p19q-retained = 57) (Anaplastic astrocytoma = 57, Anaplastic oligodendroglioma = 19)	Mean 47.69, Range 19-68. 47M, 29F	VOI Tumour delineated on axial slices to contain high signal intensity lesions on T2WI and FLAIR, including cystic and necrotic regions. Multiplied by slice thickness and intersection gap to obtain tumour volume per section then summated to	IDH: - ADCmean: Cut off > 1.49, Acc 66.7%, Sens 66.7%, Spec 72.7%, AUC 0.67 (0.56–0.78), p=0.008. 1p19q: - No significant associations between ADC and 1p19q on multivariable regression analysis.

					obtain total tumour volume. ADC histograms generated.	
Su X et al. 2023	To evaluate the value of quantitative MRI biomarkers for the identification of IDH mutation and 1p/19q codeletion in adult patients with diffuse glioma.	2,3,4	216 across test, training and validation set. (WHO 2 ,3, and 4. Breakdown not provided.) (IDH-wt = 127, IDH-mut 1p19q-retained = 33, IDH-mut 1p19q codel = 56)	Mean 45.59. 108M, 65F	VOI Automated segmentation with BraTumIA to include enhancing and nonenhancing tumour and necrosis then core tumours obtained with registration function in FSL. ADC histograms generated.	IDH: - ADCmean (test cohort): Cut off > 1.630, Sens 93.8%, Spec 88.9%, AUC 0.913 (0.827–0.999). - ADC15% (test cohort): Cut off > 1.186, Sens 93.8%, Spec 81.5%, AUC 0.888 (0.782–0.993). 1p19q codeletion amongst IDH mut gliomas: - ADCmean (training cohort): Cut off > 1.397, Sens 100%, Spec 18.8%, AUC 0.409 (0.139–0.624). - ADC15% (training cohort): Cut off > 1.266, Sens 97.500%, Spec 18.8%, AUC 0.440 (0.230–0.651).
Nuessle NC et al. 2021	To investigate the diagnostic performance of in vivo ADC-based stratification of integrated	2,3,4	97 (WHO 2 = 37, WHO 3 = 28, WHO 4 = 32) (IDH-wt astrocytic = 44, IDH-mut astrocytic = 30, 1p19q-codel	Mean 51.6+/-15.3. Sex NS.	VOI VOI manually delineated around entire tumour volume on FLAIR sequences. Necrosis,	IDH: - ADCmean: AUC 0.883. 1p19q codeletion amongst IDH mut gliomas: - ADCmean: AUC 0.699.

	molecular glioma grades.		oligodendrogliomas = 23)		oedema, and vessels avoided.	
Ma X et al. 2023	To investigate apparent diffusion coefficient (ADC) as imaging biomarker for preoperatively identifying glioma genotypes based on the 2021 World Health Organization (WHO) classification of CNS tumors.	2,3,4	159 (WHO 2, 3, and 4. Breakdown not provided.) (IDH-wt GBM = 81, IDH-mut 1p19q-retained astrocytoma = 46, IDH-mut 1p19q-codel oligodendroglioma = 32)	Mean 47.6+/-14.4. 93M, 66F	ROI 3 ROIs placed on visually perceived lowest regions of ADC map. Mean of ROI ADC values used as ADCmin. Calcification, cysts, haemorrhage, necrosis avoided.	IDH - rADCmin: AUC 0.86 (0.80-0.92), p<0.0001, Cut off 1.28, Sens 69.2%, Spec 92.6%. - ADCmin: AUC 0.84 (0.78–0.90) , p<0.0001, Cut off 0.93 (x10^{-3}mm^2/s), Sens 65.4%, Spec 91.4%. 1p19q codeletion amongst IDH-mut gliomas - rADCmin: AUC 0.67 (0.56–0.79), p=0.009, Cut off 1.47, Sens 52.5%, Spec 81.2%. - ADCmin: AUC 0.68 (0.57–0.80) , p=0.006, Cut off 1.17 (x10^{-3}mm^2/s), Sens 37.0%, Spec 100%.
Cheng Y et al. 2021	To explore the correlation between the molecular phenotypes of glioma and ADC values.	2,3,4	11 (WHO 2 = 3, WHO 3 = 4, WHO 4 = 4) (IDH-wt = 6, IDH-mut = 5. 1p19q-codel = 2, 1p19q-retained = 9.)	Age NS. Sex NS.	VOI 3D autocontouring segmentation. Vessels excluded.	IDH: - ADCmean: AUC 0.500, p>0.05. 1p19q: - ADCmean: AUC 0.916, p<0.05.
Cho NS et al. 2024	To compare the classification performance of	2,3,4	104 (note 105 lesions) (WHO II = 61, WHO	Mean 42, Range	VOI nADC maps created by	IDH-mut astrocytoma vs IDH-mut oligodendroglioma / IDHwt gliomas

	normalized apparent diffusion coefficient with percentage T2-FLAIR mismatch-volume for differentiating between IDH-mutant astrocytoma and other glioma molecular subtypes.		III = 21, WHO IV = 23) (IDH-wt = 22, IDH-mut = 83)" *Note: only included patients with non-enhancing gliomas.	22-79 59M, 45F	voxel-wise dividision of ADC by the mean ADC value of 3 spherical VOIs in the CNAWM. Tumour segmentations performed manually by one observer and refined by a semi-automated thresholding method using Analysis of Functional NeuroImages software for consistency prior to final review by a second observer. Cysts and CSF excluded.	- Median rADC: AUC 0.848, cut off 1.864, Sens 70.8%, Spec 85.0%, p<0.0001. IDH-mut astrocytoma vs IDH-mut oligodendroglioma IDH-mut astrocytoma vs IDH-mut oligodendroglioma - Median rADC: AUC 0.805, cut off 1.864, Sens 70.8%, Spec 94.4%, p<0.0001. IDH-mut astrocytoma vs IDH-wt glioma - Median rADC: AUC 0.883, cut off 1.849, Sens 70.8%, Spec 95.5%, p<0.0001.

Table 3: Summary of studies assessing 1p19q codeletion alone

Summary of study author, year of publication, main research purpose, composition of study cohort (WHO grade, IDH status, 1p19q status, sex), methods of ADC measurements, and key results for studies assessing 1p19 codeletion only.

Abbreviations: ADC: Apparent Diffusion Coefficient, AUC: Area under the curve, Codel: Codeletion, DG: Diffuse gliomas, DTI: Diffusion tensor imaging, DWI: Diffusion weighted imaging, F: Female, IDH: Isocitrate dehydrogenase, M: Male, MRI: Magnetic Resonance Imaging, Mut: Mutant, ROI: Region of interest, Sens: Sensitivity, Spec: Specificity, VOI: Volume of interest, Wt: Wild-type.

Study	**Research purpose**	**WHO Grades**	**Cohort size and composition**	**Age, Sex**	**ROI or VOI methods**	**Results**
Yang X et al. 2021	To explore whether DWI can predict 1p19q codeletion status of IDH mutant LGGs.	2,3	142 (WHO 2 and 3. Breakdown not provided.) (IDH-mut 1p19q-codel = 73, IDH-mut 1p19q-retained = 69)	IDH-mut 1p19q retained: Mean 38.74+/-10.09. IDH-mut 1p19q-codel: Mean 44.94+/-10.24. 80M, 62F	ROI. At least 5 ROIs placed in solid tumour. ROI with lowest mean ADC used as ADCmin. Avoided cysts, haemorrhage, necrosis.	Identification of 1p19q codeletion in IDH mut gliomas: - nADC: Sens 76.71%, Spec 52.17%, PPV 88.30%, NPV 67.30%, AUC 0.71 (0.60-0.79), p<0.001.

Cui Y et al. 2014	To investigate the correlation between tumour grade and prognostic biomarkers with ADC.	1,2,3,4	82 (WHO 1 =1, WHO 2 = 35, WHO 3 = 22, WHO 4 = 24) (Oligodendroglial = 5, Oligoastrocytic = 29, Astrocytic = 48)	Mean 44.16. 42M, 40F	ROI. 4 ROIs placed in solid tumour. Mean of ROI ADC values used. Avoided CSF, cysts, necrosis, vessels.	Identification of 1p19q codeletion in 35 WHO II gliomas (32 IDHmut, 3 IDHwt): - Mean ADC: Cut off 1,565 $x10^{-6}mm^2/s$, Sens 72%, Spec 88%, AUC 0.82 (0.68-0.97), p=0.003. - Mean nADC: Cut off 2.0, Sens 76.5%, Spec 88%, AUC 0.81 (0.67-0.95), p=0.004.
Latysheva A et al. 2019	To assess the value of DWI to characterize oligodendrogliomas and to distinguish them from astrocytomas.	2,3	71 (WHO 2 = 42, WHO 3 = 29) (Oligodendroglioma = 33, Astrocytoma = 38)	Mean 48+/- 11.2. 35M, 36F	VOI Tumour manually delineated to include enhancing and nonenhancing regions on each axial slice. Whole tumour histogram distributions of ADC generated. Cysts avoided.	Identification of 1p19q codeletion in a cohort of astrocytomas and oligodendrogliomas: - Mean ADC: Cut off 1094 $x10^{-6}mm^2/s$, Sens 63% (54-82), Spec 61% (51-83), PPV 65% (52; 81), NPV 73% (61; 87), AUC 0.76, p=0.009.

Table 4: Proposed ADC thresholds for IDH genotyping according to studies included in the meta-analyses.

	ROI ADCmin	ROI rADCmin	ROI ADCmean	ROI rADCmean	VOI ADCmin	VOI rADCmin	VOI ADCmean	VOI rADCmean
N studies	8	6	7	3	3	1	5	1
Median	**0.95**	**1.17**	**1.05**	**1.6**	**0.81**	**1.08**	**1.38**	**1.6**
SD	0.11	0.16	0.16	0.18	0.19	-	0.19	-
Min	0.77	0.98	0.88	1.4	0.54	-	1.19	-
Max	**1.08**	**1.40**	**1.34**	**1.75**	**0.90**	**1.08**	**1.49**	**1.6**

*N: number, SD=standard deviation, Min=minimum, Max=maximum. ADC values in units of *10^{-3} mm^2/s. rADC values have no unit.*

Figure 1

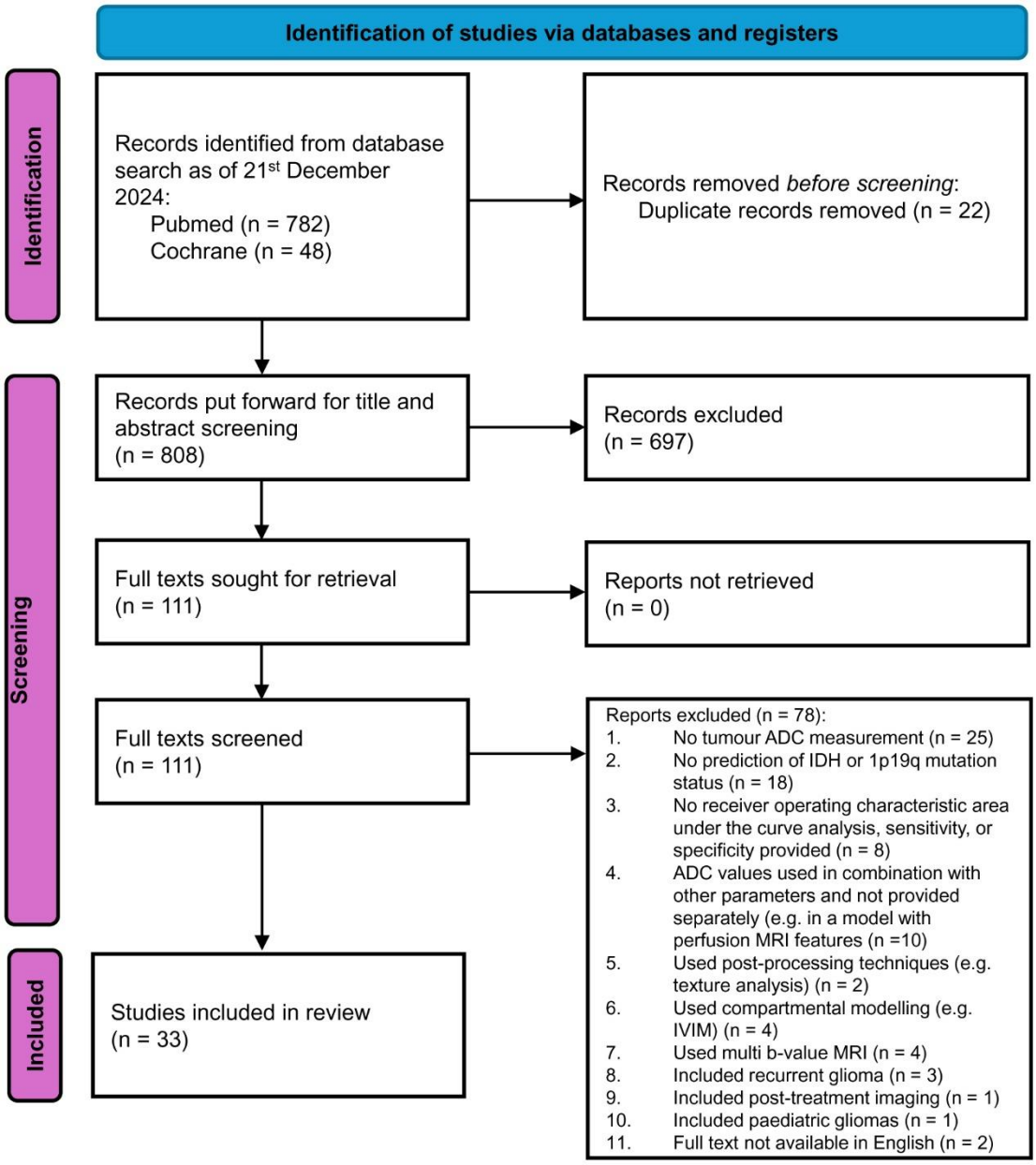

Figure 2