The T2-FLAIR–mismatch sign as an imaging biomarker for *IDH* and 1p/19q status in diffuse low-grade gliomas: a systematic review with a Bayesian approach to evaluation of diagnostic test performance

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OBJECTIVE With the revised WHO 2016 classification of brain tumors, there has been increasing interest in imaging biomarkers to predict molecular status and improve the yield of genetic testing for diffuse low-grade gliomas (LGGs). The T2-FLAIR–mismatch sign has been suggested to be a highly specific radiographic marker of isocitrate dehydrogenase (*IDH*) gene mutation and 1p/19q codeletion status in diffuse LGGs. The presence of T2-FLAIR mismatch indicates a T2-hyperintense lesion that is hypointense on FLAIR with the exception of a hyperintense rim.

METHODS In accordance with PRISMA guidelines, we performed a systematic review of the Ovid Medline, Embase, Scopus, and Cochrane databases for reports of studies evaluating the diagnostic performance of T2-FLAIR mismatch in predicting the *IDH* and 1p/19q codeletion status in diffuse LGGs. Results were combined into a 2 × 2 format, and the following diagnostic performance parameters were calculated: sensitivity, specificity, positive predictive value, negative predictive value, and positive (LR+) and negative (LR–) likelihood ratios. In addition, we utilized Bayes theorem to calculate posttest probabilities as a function of known pretest probabilities from previous genome-wide association studies and the calculated LRs. Calculations were performed for 1) *IDH* mutation with 1p/19q codeletion (*IDHmut-Codel*), 2) *IDH* mutation without 1p/19q codeletion (*IDHmut-Noncodel*), 3) *IDH* mutation overall, and 4) 1p/19q codeletion overall. The QUADAS-2 (revised Quality Assessment of Diagnostic Accuracy Studies) tool was utilized for critical appraisal of included studies.

RESULTS A total of 4 studies were included, with inclusion of 2 separate cohorts from a study reporting testing and validation (n = 746). From pooled analysis of all cohorts, the following values were obtained for each molecular profile—*IDHmut-Codel*: sensitivity 30%, specificity 73%, LR+ 1.1, LR– 1.0; *IDHmut-Noncodel*: sensitivity 33.7%, specificity 98.5%, LR+ 22.5, LR– 0.7; *IDH*: sensitivity 32%, specificity 100%, LR+ 32.1, LR– 0.7; 1p/19q codeletion: sensitivity 0%, specificity 54%, LR+ 0.01, LR– 1.9. Bayes theorem was used to calculate the following posttest probabilities after a positive and negative result, respectively—*IDHmut-Codel*: 32.2% and 29.4%; *IDHmut-Noncodel*: 95% and 40%; *IDH*: 99.2% and 73.5%; 1p/19q codeletion: 0.4% and 35.1%.

CONCLUSIONS The T2-FLAIR–mismatch sign was an insensitive but highly specific marker of *IDH* mutation and *IDHmut-Noncodel* profile, although significant exceptions may exist to this finding. Tumors with a positive sign may still be *IDHwt* or 1p/19q codeleted. These findings support the utility of T2-FLAIR mismatch as an imaging-based biomarker for positive selection of patients with *IDH*-mutant gliomas.

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KEYWORDS oligodendroglioma; brain tumor; brain neoplasm

ABBREVIATIONS *IDH* = isocitrate dehydrogenase; *IDHmut-Codel* = *IDH* mutation and 1p/19q codeletion; *IDHmut-Noncodel* = *IDH* mutation without 1p/19q codeletion; LGG = low-grade glioma; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; QUADAS-2 = revised Quality Assessment of Diagnostic Accuracy Studies.

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DIFFUSE low-grade gliomas (LGGs) comprise a diverse group of infiltrative WHO grade II and grade III brain neoplasms of multiple histological types. The 2016 WHO glioma classification no longer identifies diffuse adult LGGs as a homogeneous group of neoplasms with similar prognoses, but rather places greater emphasis on cytogenetic markers as criteria for classification.²¹ Specifically, the presence of a mutation in the isocitrate dehydrogenase (*IDH*) 1 and 2 genes and the codeletion of chromosomes 1p and 19q are now central criteria used for diffuse glioma classification.²⁸ A diagnosis of oligodendroglioma, for example, now requires the presence of the 1p/19q codeletion in addition to the *IDH* mutation.²¹ Prior studies, including those by The Cancer Genome Atlas project, have identified 3 important molecular subtypes of diffuse gliomas that have prognostic importance:²⁴ 1) *IDH* mutation and 1p/19q codeletion (*IDHmut-Codel*); 2) *IDH* mutation but without 1p/19q codeletion (*IDHmut-Noncodel*), and 3) without *IDH* mutation or 1p/19q codeletion (*IDH-wild type*).

Prior to 2016, noninvasive imaging biomarkers such as contrast enhancement, mass effect, necrosis, and perfusion on MRI were used to predict histological features.^{2,11,19,23} However, in the context of the revised 2016 classification, a reevaluation of imaging biomarkers in predicting molecular features is warranted. MRI may improve the diagnostic yield of molecular testing by identifying those patients who have a higher likelihood of a positive result.¹⁷ Hydroxyglutarate MR spectroscopy has been shown to possess excellent specificity for the prediction of *IDH*-mutant glioma;²⁵ however, this imaging technology may not always be feasible or readily available. Recent studies have identified specific imaging features that may be characteristically associated with certain molecular groups, in particular the T2-FLAIR-mismatch sign, which denotes a hyperintense signal on T2-weighted imaging combined with a relative suppression on FLAIR imaging, with the exception of a hyperintense peripheral rim (Fig. 1). In recent evaluations, this sign has been suggested to be a highly specific marker of *IDH*-mutant gliomas, with specificity as high as 100%.⁴ However, some other reports have advocated a more cautious interpretation, illustrating exceptions to this rule, particularly in pediatric patients.¹³ Herein, we present a systematic review and meta-analysis of the available literature to determine the diagnostic performance of the T2-FLAIR-mismatch sign in predicting the *IDH* and 1p/19q codeletion status in diffuse LGGs. We utilized the Bayes theorem to determine the posttest probability using calculated likelihood ratios (LRs) and known pretest probability.

Methods

Literature Search

A comprehensive search of several databases from inception to June 20, 2019, limited to English-language publications, was conducted. The databases included Ovid Medline and Epub Ahead of Print and Daily, In-Process & Other Non-Indexed Citations, and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Embase, and

FIG. 1. Brain MR images from a 51-year-old female patient showing a right frontal parasagittal mass that is hyperintense on T2 (**left**) with relative suppression on FLAIR (**right**), illustrating a T2-FLAIR mismatch. Pathology revealed a WHO grade III anaplastic astrocytoma with *IDHmut-Codel*.

Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplementing the diagnostic value of T2-FLAIR mismatch in predicting genetic profiles in gliomas. The full search strategy is available in Appendix 1. Two authors (Y. U. Yolcu and Anshit Goyal) reviewed the abstracts for eligibility according to predetermined criteria. Studies including both T2-FLAIR-mismatch assessments and molecular testing for *IDH* mutation and 1p/19q codeletion in diffuse gliomas were included in the quantitative analysis.

Data Extraction

Data were collected for the following variables: 1) study characteristics (author, year, country, number of patients, age, sex, and distribution of tumor WHO grades), 2) number of patients who tested positive for T2-FLAIR mismatch, and the numbers of patients who had molecular analysis results that revealed 3) *IDH* mutation and 4) 1p/19q codeletion.

Assessment of Diagnostic Performance

For each study, 2×2 tables were created for 2 distinct tumor molecular profiles and their respective T2-FLAIR-mismatch status (*IDHmut-Codel* or *IDHmut-Noncodel*). In addition, we also constructed 2×2 tables between the T2-FLAIR-mismatch status and *IDH* status alone or 1p/19q codeletion status alone. For each molecular class, the individual single 2×2 assessments from each study were combined into a single 2×2 table between the molecular profiles (positive or negative) and T2-FLAIR sign (positive or negative), to determine overall diagnostic performance.

Using the tables, the following diagnostic testing parameters were calculated: 1) sensitivity, 2) specificity, 3) positive predictive value (PPV), 4) negative predictive value (NPV), 5) LR for a positive test (LR+), 6) LR for a negative test (LR-), 7) posttest probability for a positive test, and 8) posttest probability for a negative test. LR+

was calculated as sensitivity/(1 – specificity) and LR– as (1 – sensitivity)/specificity. Using Bayes theorem, posttest probabilities were calculated as pretest odds $\times$ LR+/- = posttest odds, where odds were substituted with probabilities as odds = $p/(1 - p)$.⁷ For pretest probabilities, previous genome-wide association studies were used to calculate overall percentage of each molecular profile (*IDHmut-Codel* 30.2%, *IDHmut-Noncodel* 50%, and *IDHmut* overall 80.2%).^{3,15} For the sole purposes of calculation, for studies reporting specificity as 100%, the specificity value was input as 99% while determining LR+. Similarly, sensitivity was assumed to be 1% when it was reported as 0%.

Critical Appraisal

Critical appraisal for each study in terms of risk of bias and applicability concerns was performed using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Risk of bias was assessed in 4 domains: patient selection, index test, reference standard, and flow and timing, while applicability concerns were assessed in patient selection, index test, and reference standard only. The risk of bias was found to be low for all domains, with the exception of 2 studies^{4,14} where the index test (radiological assessment) was performed by a neurologist/neurosurgeon as opposed to a neuroradiologist. These results are presented in Appendix 2. A complete description of the QUADAS-2 tool can be obtained at www.quadas.org.

Results

Search Results and Study Characteristics

A total of 875 articles were identified from the initial electronic search. After review of abstracts and study titles, we identified 56 studies for possible inclusion. After excluding 52 full-text articles, 4 studies remained and were included for qualitative and quantitative synthesis (Fig. 2).

In total, 746 patients were included in the quantitative analysis of 4 studies,^{4,14,16,24} including 2 separate cohorts (testing and validation) from The Cancer Genome Atlas and The Cancer Imaging Archive databases by Patel et al.²⁴ The mean age from the cohorts ranged from 40 to 45.5 years. Sex distribution was available from 4 cohorts, with 46.8% (n = 169/361) being females. Histopathologic distribution showed that 56.3% (n = 420) of patients had grade II gliomas, 42.1% (n = 314) had grade III gliomas, and a very small fraction of patients (1.6%, n = 12) had glioblastomas (grade IV). In all studies, radiological assessment for T2-FLAIR mismatch was performed by 2 independent readers with excellent interrater reliability (weighted kappa = 0.73–0.93) (Table 1).

IDH Mutation Overall

The following results were obtained for diagnostic performance testing for *IDH* mutation from individual studies (range): sensitivity, 14.7%–26.8%; specificity, 100%; PPV, 100%; NPV, 10.3%–20.9%; LR+, 14.7–26.8; and LR–, 0.4–0.9. Combining all studies (n = 430) yielded the following overall values: sensitivity, 32.1%; specificity, 100%; PPV, 100%; NPV, 15.1%; LR+, 32.1; LR–, 0.7. Using a known pretest probability of 80.2%, Bayes theorem yielded a posttest probability for a positive test of 99.2%

and a posttest probability for a negative test of 73.5% (Table 2).

IDHmut-Codel

For the profile *IDHmut-Codel*, the calculation of diagnostic test performance parameters from individual studies yielded the following values (range): sensitivity, 0%–73%; specificity, 62%–84.3%; PPV, 0%–83.3%; NPV, 38%–70.4%; LR+, 0–3.1; and LR–, 0.4–29.9. Assuming a pretest probability of 30.2% from prior literature, Bayesian posttest probabilities of a positive *IDHmut-Codel* profile following a positive and negative T2-FLAIR mismatch were 0%–56% and 13%–39.8%. Overall assessment combining all cohorts (n = 476) showed a sensitivity value of 29.9%, specificity of 72.7%, PPV of 44.4%, NPV of 58.7%, LR+ of 1.1, LR– of 1.0, posttest probability for a positive test of 32.2%, and posttest probability for a negative test of 29.4% (Table 3).

IDHmut-Noncodel

For the profile *IDHmut-Noncodel*, the diagnostic performance of the T2-FLAIR–mismatch sign across individual cohorts ranged as follows: sensitivity, 22%–50%; specificity, 87%–100%; PPV, 78%–100%; NPV, 46%–68%; LR+, 2.5–50.7; and LR–, 0.5–0.8. Posttest probabilities (Bayesian) following a positive and negative test ranged from 71% to 98% and 33% to 44%. Overall, combining all cohorts (n = 388) showed a sensitivity of 33.7%, specificity of 98.5%, PPV of 95.5%, NPV of 60.7%, LR+ of 22.5, LR– of 0.7, posttest probability for a positive test of 95.7%, and posttest probability for a negative test of 40.2% (Table 4).

Discussion

The present systematic review is the first to summarize the diagnostic performance of the T2-FLAIR–mismatch sign in predicting the *IDH* and 1p/19q status in diffuse LGGs. Our results showed that the T2-FLAIR–mismatch sign was an insensitive but highly specific marker of the *IDHmut-Noncodel* molecular profile and the *IDH* mutation overall. Further, more conservative estimates generated from using the Bayes theorem with predetermined pretest probability still showed high posttest probability (95% and 99%, respectively). By contrast, the specificity was found to be relatively poor for a positive 1p/19q codeletion, as either the combined *IDHmut-Codel* molecular profile (72%) or individually determined for 1p/19q codeletion alone (54%). At the same time, the posttest probability following a positive result was found to be extremely low (*IDHmut-Noncodel*, 32%; 1p/19q overall, 0%), showing it to be a possibly unreliable marker of 1p/19q status.

IDH–wild type tumors are associated with a highly aggressive clinical course, similar to glioblastomas (WHO grade IV). The presence of both *IDH* mutation and 1p/19q codeletion is associated with a more favorable clinical course, with improved sensitivity to procarbazine, lomustine, and vincristine chemotherapy and longer survival.^{5,22,27} Therefore, a molecular classification might capture clinical behavior and prognosis more accurately than traditional histopathologic characteristics.³ Consequently,

FIG. 2. PRISMA search strategy.

due to the revised 2016 WHO classification of diffuse LGGs, there has been a growing interest in identifying noninvasive imaging biomarkers to serve as predictors of molecular aberrations, due to their significant implications for prognostic counseling and treatment decision-making.

Imaging features such as contrast enhancement, diffusion restriction, and edge contrast on FLAIR have also been explored as markers of molecular status. In an assessment of 40 patients with pathologically confirmed WHO grade II/III gliomas, Delfanti et al. observed that *IDH* mutation was associated with more defined borders on FLAIR imaging.⁸ Similar results were observed by Bahrami et al., who defined their findings quantitatively as edge contrast (EC).¹ The authors also observed that *IDH*-wild type tumors had higher T2-signal heterogeneity than *IDH*-mutant tumors, while the presence of a 1p/19q codeletion was associated with higher signal het-

erogeneity among the latter. Diffusion- and perfusion-weighted imaging have also been suggested to be effective methods for classifying LGGs on the basis of molecular status.^{10,12,18,20,26} Leu et al. demonstrated that *IDH*-mutant tumors might have a significantly higher apparent diffusion coefficient (ADC) compared to *IDH*-wild type tumors.²⁰ The authors further used a multivariable logistic regression model based on relative cerebral blood volume (rCBV), median ADC, T2-hyperintense lesion volume, and contrast enhancement to classify tumors. The model was able to effectively discriminate between *IDH*-mutant and *IDH*-wild type tumors with an area under the curve (AUC) of 0.84 and between 1p/19q codeleted and non-codeleted tumors with an AUC of 0.80. In addition, the emergence of “radiomics” has allowed the development of more sophisticated machine learning models based on texture analysis and image segmentation techniques that

TABLE 1. Study characteristics

Authors & Year	Country	No. of Pts	Age in Yrs	Female	WHO Grade	Histopathologic Classification	T2-FLAIR–Mismatch Interrater Agreement (weighted kappa)
Broen et al., 2018	Netherlands	154	43 (20–82)	68 (44.2)	II, 133 (86.4); III, 9 (5.8); IV, 12 (7.8)	Astrocytoma, 75 (48.7); oligodendroglioma, 67 (43.5); glioblastoma, 12 (7.8)	0.75
Lasocki et al., 2018	Australia	69	NA	NA	II, 43 (73.0); III, 26 (27.0)	Astrocytoma, 6 (10.2); oligodendroglioma, 12 (20.3); oligoastrocytoma, 35 (59.3); diffuse glioma, not specified, 6 (10.2)	0.93
Patel et al., 2017 (cases)	US	125	45.5 (20–75)	63 (50.0)	II, 58 (46.0); III, 67 (54.0)	Astrocytoma, 38 (30.0); oligodendroglioma, 54 (43.0); oligoastrocytoma, 33 (27.0)	0.73
Patel et al., 2017 (validation)	US	82	45 (21–82)	38 (46.0)	II, 35 (43.0); III, 47 (57.0)	Astrocytoma, 40 (48.8); oligodendroglioma, 38 (46.3); oligoastrocytoma, 4 (4.9)	0.73
Juratli et al., 2019	US	316	40 (18–86)	NA	II, 151 (47.8%); III, 165 (52.2%)	Astrocytoma, 82 (61.7); oligodendroglioma, 42 (31.6); glioblastoma, 6 (6.7)	0.88

NA = not available; Pts = patients.

Values are presented as number of patients (%) or mean (range) unless otherwise indicated.

TABLE 2. Diagnostic performance of the T2-FLAIR–mismatch sign in predicting IDH mutation

Authors & Year	IDH Mutation Diagnostic Performance Parameter							Posttest Probability (+), %*	Posttest Probability (–), %*
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR–	Posttest Probability (+), %*		
Patel et al., 2017 (cases)	14.7	100	100	20.9	14.7	0.9	98.3	77.7	
Patel et al., 2017 (validation)	18.9	100	100	14.0	18.9	0.8	98.7	76.8	
Lasocki et al., 2018	58.1	100	100	14.8	58.1	0.4	99.6	63.2	
Broen et al., 2018	26.8	100	100	10.3	26.8	0.7	99.1	75.0	
Overall	32.1	100	100	15.1	32.1	0.7	99.2	73.5	

* Positive and negative posttest probabilities were determined using Bayes theorem with a pretest probability of 80.2%.

TABLE 3. Diagnostic performance of the T2-FLAIR–mismatch sign in predicting IDHmut-Code1

Authors & Year	IDH Mutation Diagnostic Performance Parameter							Posttest Probability (+), %*	Posttest Probability (–), %*
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR–	Posttest Probability (+), %*		
Patel et al., 2017 (cases)	0.0	84.3	0.0	70.4	0.01	1.2	0.4	33.9	
Patel et al., 2017 (validation)	0.0	65.5	0.0	38.0	0.01	29.9	0.4	39.8	
Juratli et al., 2019	73.2	76.0	83.3	63.3	3.1	0.4	56.9	13.2	
Broen et al., 2018	0.0	62.0	0.0	53.4	0.01	1.6	0.4	41.1	
Overall	29.9	72.7	44.4	58.7	1.1	1.0	32.2	29.4	

* Positive and negative posttest probabilities were determined using Bayes theorem with a pretest probability of 30.2%.

TABLE 4. Diagnostic performance of the T2-FLAIR–mismatch sign in predicting IDHmut-Noncode1

Authors & Year	IDH Mutation Diagnostic Performance Parameter							Posttest Probability (+), %*	Posttest Probability (–), %*
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR–	Posttest Probability (+), %*		
Patel et al., 2017 (cases)	22.1	100	100	51.8	22.1	0.8	95.7	43.8	
Patel et al., 2017 (validation)	45.5	100	100	76.0	45.5	0.5	97.8	35.3	
Lasocki et al., 2018	31.4	87.5	78.6	46.7	2.5	0.8	71.5	43.9	
Broen et al., 2018	50.7	100	100	68.1	50.7	0.5	98.1	33.0	
Overall	33.7	98.5	95.5	60.7	22.5	0.7	95.7	40.2	

* Positive and negative posttest probabilities were determined using Bayes theorem with a pretest probability of 50%.

can accurately classify diffuse gliomas based on molecular features.^{6,9,29,30} In the present report, however, we discuss T2-FLAIR mismatch mainly as a visually striking phenomenon that when present can signal high specificity for the presence of an *IDH* mutation. Although our results showed that T2-FLAIR mismatch was a highly specific marker of *IDH* mutation, the true specificity may not be actually 100% as reported in some of the studies included in this review.^{4,16,24} Although combined calculation from all cohorts showed the pooled specificity to be 100% for *IDH* mutation overall (98.5% for *IDHmut-Noncodel*), the posttest probability following a positive test was 99%, as determined by Bayes theorem. Moreover, there is usually a confidence interval around the specificity; therefore, exceptions may exist to this rule. Johnson et al. reported several cases of “false-positive” T2-FLAIR sign in WHO grade II/III gliomas in pediatric patients and young adults, suggesting that caution must be exercised during interpretation of findings in this patient population.¹³ With advancements in image-based identification of glioma genetics, it is yet uncertain if radiology might obviate the need for histopathologic assessment, which currently remains the gold standard, in the near future.

Strengths and Limitations

There were some limitations to our study as well. First, we found limited literature and sample size assessing diagnostic performance for 1p/19q alone compared to *IDH* mutation. Second, we had to presume values for sensitivity and specificity, respectively, for studies reporting these as 0% and 100%, for ease of calculation of LRs. This may have increased risk for erroneous results. Third, included studies were retrospective and lacked sufficient information to be able to classify diagnostic performance by age, sex, or tumor grade. Fourth, given that this was a meta-analysis of published data, there was no central review of imaging. Also, one of the included studies (Lasocki et al.¹⁶) did not provide age data, which is important as there may be exceptions to the specificity of this sign in younger patients. However, the present investigation is the first study to critically appraise and offer a Bayesian interpretation for the diagnostic performance of this previously suggested highly specific radiological sign in predicting the molecular status of diffuse LGGs. We performed a robust analysis using pretest probabilities derived from published genome-wide association studies.

Conclusions

The T2-FLAIR–mismatch sign was an insensitive but highly specific marker of *IDH* mutation and *IDHmut-Noncodel* profile, although significant exceptions may exist to this finding. Tumors with a positive sign may still be *IDHwt* or 1p/19q codeleted. Future studies will validate the findings of this study and further elucidate the role of imaging biomarkers to diagnose histological and genetic features or predict prognosis in diffuse gliomas.

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Disclosures

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Author Contributions

Conception and design: Anshit Goyal, Yolcu. Acquisition of data: Anshit Goyal, Yolcu. Analysis and interpretation of data: Anshit Goyal, Yolcu. Drafting the article: Anshit Goyal, Yolcu. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Anshit Goyal. Statistical analysis: Anshit Goyal, Yolcu. Study supervision: Burns.

Supplemental Information

Online-Only Content

Supplemental material is available online.

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