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Quantitative Consistency of Amide Proton Transfer-weighted MRI for Brain Tumor Differentiation: meta-analysis of clinical evidence

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ADMINISTRATIVE INFORMATION

Support - The study was supported in part by 2R01NS083654, I3 Medical Technology Research Award from Emory School of Medicine, Georgia Clinical and Translational Award, National Center for Ad-vancing Translational Sciences (NCATS, UL1–TR002378), Georgia Tech/Emory Biolocity program support, and P51OD011132 to Emory National Primate Research Center.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - Dr. Sun has contributed as an inventor to a patent for the quasi-steady-state (QUASS) CEST MRI algorithm for standardization of CEST data. Emory University owns and manages the patent.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 April 2026 and was last updated on 21 April 2026.

INTRODUCTION

Review question / Objective In this meta-analysis, we evaluated heterogeneity in both the diagnostic accuracy of APT imaging and the mean difference in contrast values between high-grade and low-grade gliomas. We observed the impact of incomplete parameter reporting and attempted to use principal component analysis to interpret decision-making behavior for parameter setting across parameters with respect to their role in APTw imaging. Additionally, we explored whether the observed heterogeneity could be explained by variations in CEST imaging parameters, using meta-regression . In addition, we quantify the results of our investigation by exploring two additional questions: 1. Using the first principal component of each set of parameters as a surrogate for similarity across parameters, does the aver-age choice of parameters (or closest to the mean of the principal component) represent more optimized diagnostic accuracy or larger mean difference versus outliers (or S.D. outside of the mean)? 2. Using metrics such as leave-one-out meta-analysis (LOOMA), are there outliers for our meta-analysis of diagnostic accuracy (AUC) and quantitative consistency (M.D.), even with recent efforts to push for standardization of parameters and quantification.

Rationale Accurate grading of brain gliomas is important, and amide proton transfer-weighted (APTw) MRI shows promise for non-invasive tumor differentiation. This study aimed to perform a

comprehensive review and meta-analyses to demonstrate heterogeneity in both diagnostic accuracy and quantitative consistency of APTw MRI in distinguishing high-grade gliomas (HGGs) from low-grade gliomas (LGGs), highlight issues with reporting standards and identify sources of heterogeneity through meta-regression.

Condition being studied Magnetic Resonance (MR) imaging plays an increasingly vital role in the diagnosis, characterization, and monitoring of brain tumors, with over 80,000 new cases being discovered every year. A key driver for the continued expansion of MR imaging applications is its distinct tissue contrast that differentiates tumors from surrounding tissue. The World Health Organization has established a glioma grading system based on histopathological and molecular features, categorizing tumors from low-grade (I/II) to high-grade (III/IV) . Accurate tumor grading plays a critical role in prognosis estimation and treatment planning, directly impacting patient out-comes and quality of life.

METHODS

Search strategy This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive computerized search of the PubMed, Medline, and Embase databases was performed to identify relevant studies published between January 1, 2013, and January 18, 2026. The search aimed to assess the diagnostic performance and consistency of APTw MRI in glioma grading. Search terms were structured to capture the following three domains: (1) APT imaging, (2) brain tumor patients, and (3) glioma grading. These concepts were combined with Boolean operators and synonyms. The study was conducted in strict accordance with a pre-defined internal protocol. To ensure transparency and reproducibility, the research follows the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Me-ta-Analyses) guidelines. All methods, inclusion criteria, and analysis plans were established prior to the data extraction phase to minimize bias.

Participant or population Adult patients with histopathologically confirmed gliomas will be included.

Intervention The studied diagnostic was pretreatment APT imaging as the index test for glioma grading.

Comparator The diagnostic was compared against histopathologically confirmation of gliomas, where biopsy served as the reference standard for tumor grading.

Study designs to be included Both randomized and nonrandomized study types will be included.

Eligibility criteria Eligible studies met the following criteria: Published in English in a peer-reviewed journal, included patients with histopathologically confirmed gliomas, where biopsy served as the reference standard for tumor grading, employed pretreatment APT imaging as the index test for glioma grading, and reported or provided sufficient data to derive ROC metrics, specifically sensitivity, specificity, and AUC. The exclusion criteria included: Animal or laboratory studies, Reviews, meta-analyses, case reports, conference abstracts or presentations, and Studies lacking either histopathological confirmation or usable APT grading data.

Information sources A comprehensive computerized search of the PubMed, Medline, and Embase databases was performed to identify relevant studies published between January 1, 2013, and January 18, 2026.

Main outcome(s) Meta-analyses of AUC and mean difference demonstrated significant heterogeneity across studies (I^2=73.9% & 78.2%, p<.001). The mean difference was moderated by one SD within the mean of the readout PC (p=.034) and the total PC (p=.02). The heterogeneity for AUC and group mean difference was not substantially reduced by moderating nor LOOMA. Results of meta-regression using all data were similar to those using only data with no missing parameters.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using: QUADAS-2. Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Strategy of data synthesis Data were extracted and organized using Microsoft Excel. Extracted variables included: Study identifiers (author, year, sample size), Group-specific APTw mean differences, standard deviations, and sample sizes, Reported AUC values, including detailed CEST sequence parameters: magnetic field strength (B_0), RF saturation amplitude (B_1) and duration (T_{sat}), repetition time (TR), image readout (e.g., spin-echo vs. gradient-echo, 2D vs. 3D), cutoff thresholds for classification, as well as three principal component

(PC) scores derived from exchange rate, readout, and steady-state.

Subgroup analysis To address the heterogeneity introduced by changes in glioma classification over time, an indicator of publication time was included. The indicator had three categories, 2007-2016, 2017-2021, and 2022-present. The meta regression analyses were fitted with one CEST parameter each time for feature screening. The p-values from the omnibus test for moderators, I^2 and τ^2 statistics were reported to quantify the statistical significance of certain CEST parameters on the variability of the AUC values and mean differences across studies.

Sensitivity analysis Since data imputation is usually performed on the subject level within each study conditional on observed covariates of other subjects, it is not applicable to our case as missing parameters are study-specific. To address the issue with varying levels of missing study parameters, we performed a sensitivity check on meta-analysis and me-ta-regression using a more restrictive complete-case only analysis in addition to the liberal case which maximizes sample size by including studies that may have missing parameters providing those parameters do not preclude the analysis itself. For the restrictive case, we excluded any studies with incomplete parameters of interest. In this case, the number of articles was consistent with all moderator analyses.

Language restriction English.

Country(ies) involved United States.

Keywords Brain Tumor Grading; Amide proton transfer; Chemical Exchange Saturation Transfer.

Contributions of each author

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