Systematic Review and Meta-Analysis

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An evidence-based approach to evaluate the accuracy of amide proton transfer-weighted MRI in characterization of gliomas

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Abstract

Backgroud: To perform a meta-analysis to evaluate the diagnostic accuracy of the amide proton transfer (APT) technique in differentiating high-grade gliomas (HGGs) from low grade gliomas (LGGs).

Methods: Medical literature databases were searched for studies that evaluated the diagnostic accuracy of APT in patients suspected of brain tumor who underwent APT MRI and surgery. Only English language studies and published before September 2018 were considered to be included in this project. Homogeneity was assessed by the inconsistency index. Mean difference (MD) at 95% confidence interval (CI) of all parameters derived from APT was calculated. Publication bias was explored by Egger's funnel plot.

Results: Six eligible studies were included in the meta-analysis, comprising 144 HGGs and 122 LGGs. The APT-related parameter signal intensity (SI) was significantly higher in the HGG than the LGG (WMD = 0.86 (0.61–1.1), $P < .0001$); A significant difference was also found between grade II and grade III (WMD = 0.6 (0.4–0.8), $P < .0001$), and between grade II and grade IV (WMD = 1.07 (0.65–1.49), $P < .0001$).

Conclusions: APT imaging may be a useful imaging biomarker for discriminating between LGGs and HGGs. However, large randomized control trials (RCT) were necessary to evaluate its clinical value.

Abbreviations: APT = amide proton transfer, CEST = chemical exchange-dependent saturation transfer, CI = confidence interval, DWI = diffusion-weighted magnetic resonance imaging, HGG = high-grade gliomas, IVIM = intravoxel incoherent motion imaging, LGG = low-grade gliomas, MD = mean difference, MRS = magnetic resonance spectroscopy, PWI = perfusion magnetic resonance imaging, RCT = randomized control trials, SI = signal intensity.

Keywords: amide proton transfer, glioma grading, meta-analysis, signal intensity

1. Introduction

Early discriminated between high-grade gliomas (HGGs) and low-grade gliomas (LGGs) has been a hot issue of extensive research and be contributed to individualize treatment in patients.[1,2] Conventional contrasted magnetic resonance imaging (MRI) has been accepted as a standard clinical approach for the characterization of gliomas.[3] In particular, the degree of contrast medium enhancement was used as a biomarker of brain tumor grading, while the accuracy of this method was limited.[4] Considering the potential side effects of gadolinium on patients with renal disease, noninvasive functional imaging techniques were still highly desirable.

In recent decades, MRI technology has been developed rapidly, different functional imaging techniques have been widely applied in the differential diagnosis of HGGs and LGGs, such as diffusion weighted imaging (DWI),[5] perfusion weighted imaging (PWI),[6] Magnetic Resonance Spectroscopy (MRS),[7] and Amide proton transfer (APT).[8–18] Among these, APT imaging has been developed as a specific type of chemical exchange-dependent saturation transfer (CEST) imaging technique, providing messages of chemical metabolites present in vivo tissues.[19] Because of APT imaging method was first reported in 2003. This new technique has been most widely studied as an imaging biomarker in several diseases in the brain, including brain tumor grading.[20]

Recent years APT-MRI has been drawn that has the potential to differentiate between HGGs and LGGs accurately by measuring the signal intensity.[14,17] Not long ago, Zou et al[8] found SI was the best quantitative parameter in discriminating WHO II from WHO III gliomas followed by SI. However, Bai et al[16] reported that SI had no significant difference in glioma grading between WHO II vs WHO III gliomas, which contradicted with the results draw from Togao et al.[11,18] The variations in different articles may be due to various types of MRI scanners, imaging parameters, and post-processing technology. Nevertheless, still no relevant reviews have been carried out to assess the accuracy of APT-MRI in differentiating HGGs from LGGs. Therefore, the purpose of this present systematic review and meta-analysis was to evaluate the diagnostic values of APT-MRI in differentiating HGGs from LGGs.

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Table 1

Study and patient characteristics of included studies.

Author	Year	Country	MRI type	Study design	No. of patients	No. of LGG	No. of HGG	M/F	Percentage of HGG
Zou	2018	China	Philips	Prospective	30	11	19	9/21	63.3%
Su	2017	China	GE	Prospective	42	28	14	28/14	33.3%
Choi	2017	Korea	Philips	Prospective	46	24	28	25/21	60.8%
Bai	2017	China	GE	Prospective	44	18	26	23/21	59.1%
Togao	2016	Japan	Philips	Retrospective	34	20	14	22/12	41.1%
Sakata	2018	Australia	Siemens	Prospective	49	15	34	32/17	69.4%

HGG = high-grade gliomas, LGG = low-grade gliomas, M/F = Male/Female.

2. Methods

2.1. Data sources

We searched 4 electronic databases, including PubMed, Web of Science, Embase, and EBSCO, to obtain related studies estimating the relationship between APT and glioma grading, published from inception to September, 2018. The search terms were used: ("Amide proton transfer" or "APT") and ("glioma" or "brain tumour" or "brain neoplasm") and ("grade" or "grading"), without any limitation applied. Both eligible studies were approved by local ethics committees.

Studies were included if they matched the following criteria: evaluated the diagnostic accuracy of APT for differentiating between HGG and LGG, providing histologic results by biopsy or surgery. The parameter (SI) values between low-grade (WHO grade II) and high-grade (WHO grade III or IV) gliomas were calculated. Articles were excluded if they met the following criteria: they comprised <10 HGG patients or LGG patients; Patients had no surgery, radiotherapy, or chemotherapy before APT MRI.

2.2. Quality assessment and data extraction

The quality of the eligible studies was evaluated by 2 independent authors using the Quality Assessment of Diagnostic Studies.[21] Besides, the following characteristics of included studies were extracted from each study: first author, year of publication, study design, number of patients, examination results, and MRI

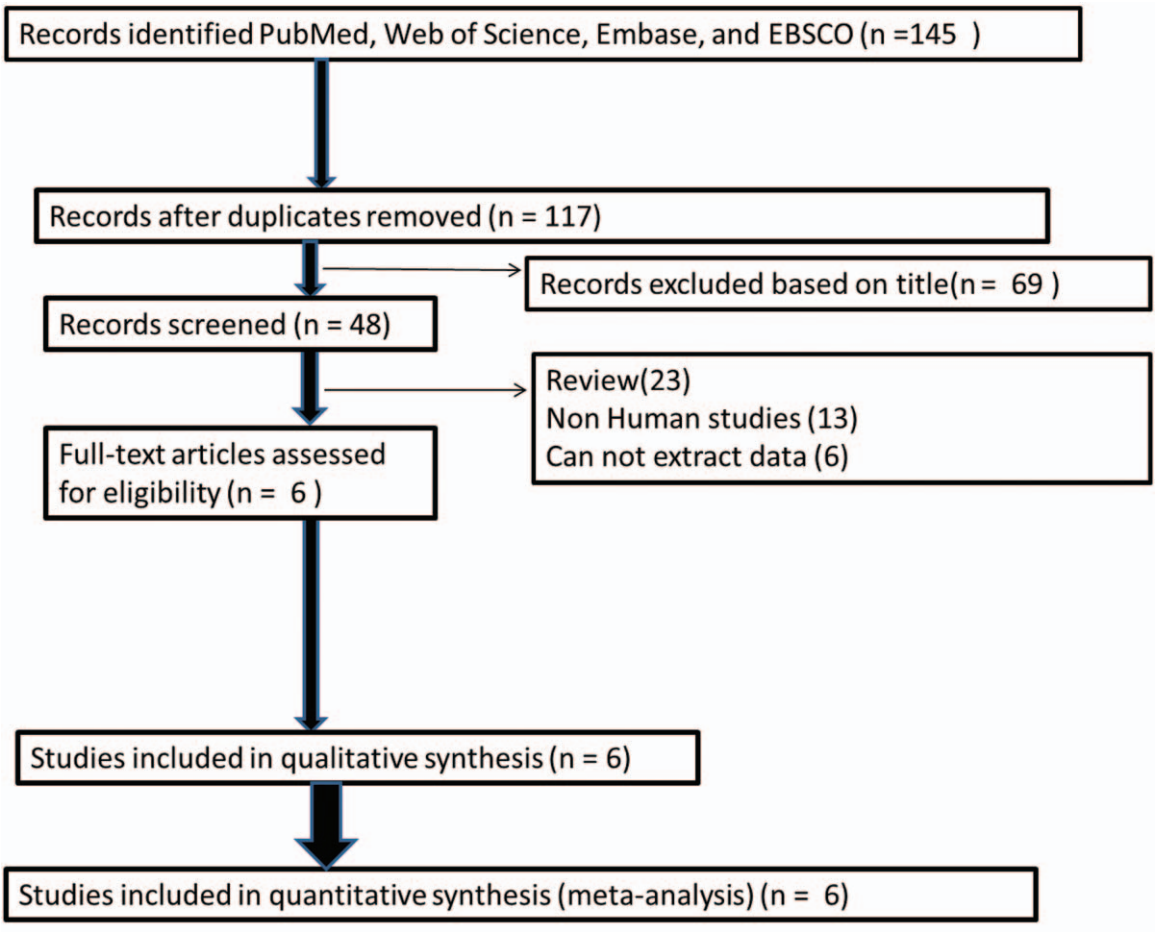

Figure 1. Flowchart of search process.

parameters. For each study, the mean difference (MD) and a standard deviation value derived from APT between HGG and LGG were extracted. The overall effect size was described as the mean and 95% confidence interval (CI).

2.3. Statistical analysis

Exploring heterogeneity was vital to understand the possible elements that potentially influence accuracy from different studies. The STATA software version 12 was applied to estimate the heterogeneity among eligible studies by the Chi-square value test. $P < .05$ or $I^2 > 50\%$ revealed heterogeneity existed in the study. Random effects coefficient model was used if heterogeneity was observed; otherwise a fixed-effects coefficient model was used. The presence of publication bias was detected by Egger's funnel plot and asymmetry test by using STATA12.0.

3. Results

The search initially produced 145 potential literature references (Fig. 1). A total of 117 articles remained by using Endnote citation manager to remove duplicate articles. Review of the titles from the remaining 117 articles led to 69 studies being excluded; these studies were focused on animal, patients with tumors recurrence, and MRI evaluation of chemotherapy response. After reading the abstracts of the remaining 38 articles, 32 were excluded based on the lack of sufficient data, and duplicated population. Finally, 6 published English studies met our inclusion and exclusion criteria. Individual study characteristics of these eligible studies were presented in Table 1.

Table 1 listed detailed information from 6 included articles published from 2003 to 2018 with sample sizes ranging from 20 to 151. All of the studies were conducted in Asia (3 in China, 1 in Japan, 1 in Korea), and 1 in Australia. Three of the MRI scanners used in the studies were from Philips, 2 from General Electrics, the rest of Siemens. The magnetic field strength of the MRI scanners among included studies was 3.0 T. Values of SI were recorded in 5 studies (Fig. 2), data of SI between WHO II and WHO III were recorded in 3 studies (Fig. 3), data of SI between WHO II and WHO IV were also observed in 3 studies (Fig. 4). The APT-related parameter signal intensity (SI) was significantly higher in the HGG than the LGG (WMD = 0.86 (0.61–1.1), $P < .0001$); A significant difference was also found between grade II and grade III (WMD = 0.6 (0.4–0.8), $P < .0001$), and between grade II and grade IV (WMD = 1.07 (0.65–1.49), $P < .0001$). A homogeneity test of SI between HGGs and LGGs with $I^2 = 78.9\%$ (P = .001).

3.1. Sensitivity analysis and publication bias

Sensitivity analysis refers to the reanalysis of data after excluding a single study.[22] We evaluated the effect of a single study on the pooled results by excluding each study. The pooled weighted mean deviation did not alter when a single study was excluded. The presence of publication bias was visually evaluated by Egger's funnel plot. Results of Egger's funnel plot test ($P = .703$) did not yield strong evidence for publication bias (Fig. 5). Actually, the actual pooled effect size was almost equal to the theoretical pooled effect size.

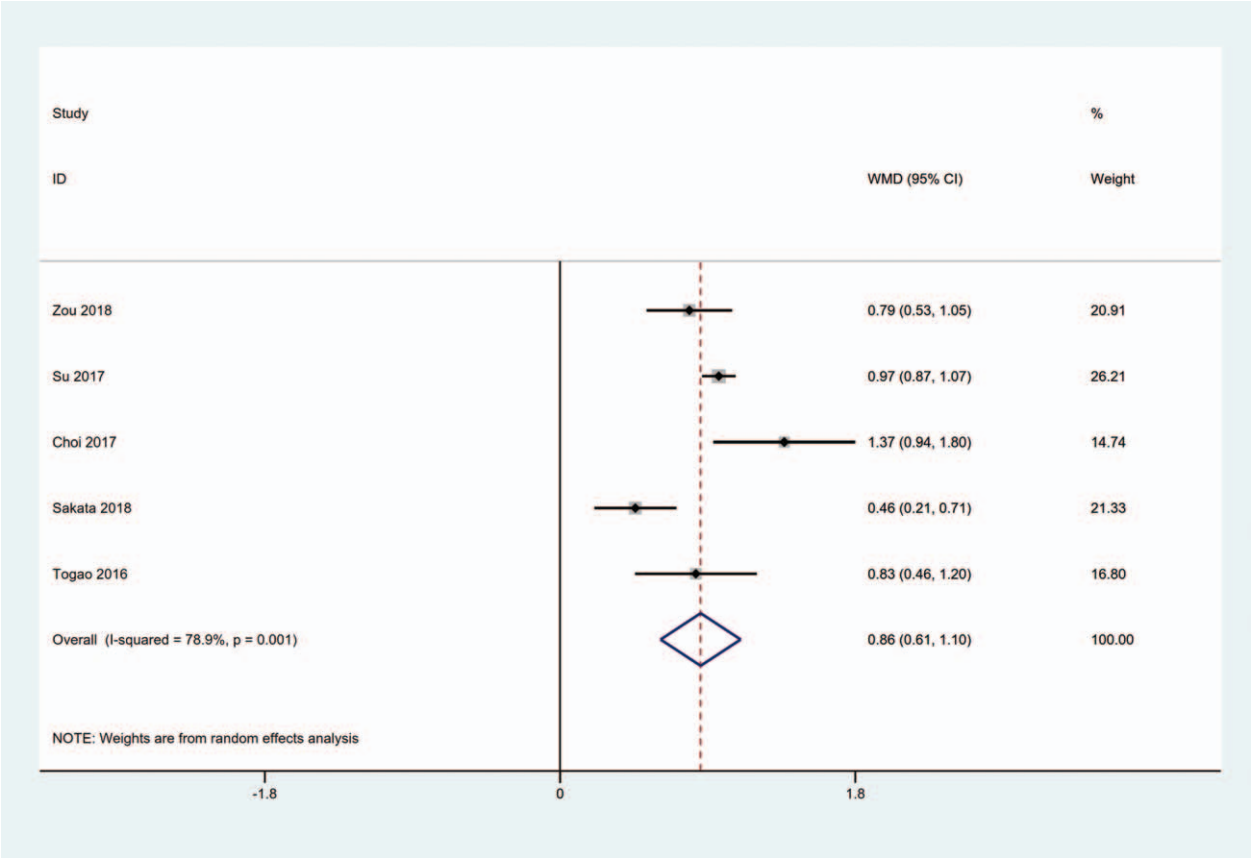

Figure 2. Forest plot of the value of SI between HGGs and LGGs. HGG = high-grade gliomas, LGG = low-grade gliomas, SI = signal intensity.

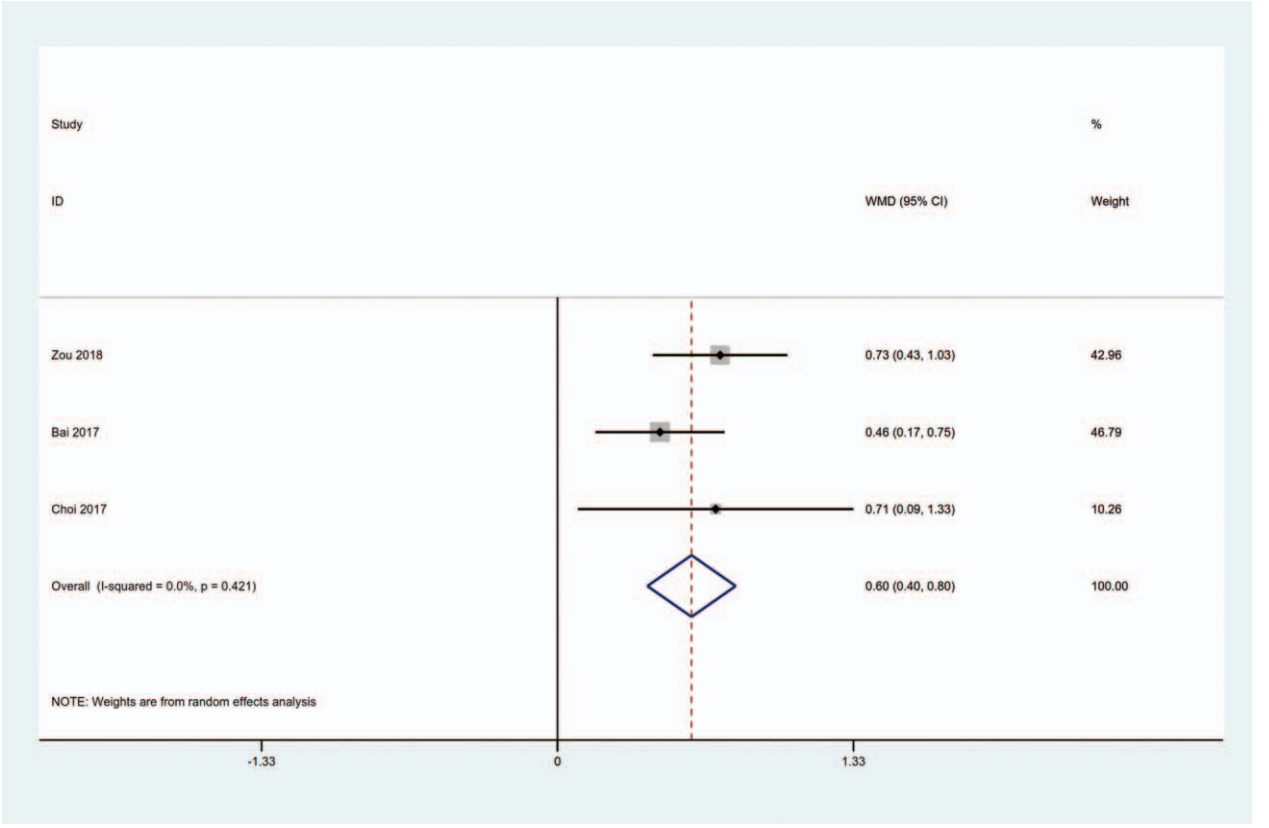

Figure 3. Forest plot of the value of SI between WHO II gliomas and WHO III gliomas. SI = signal intensity.

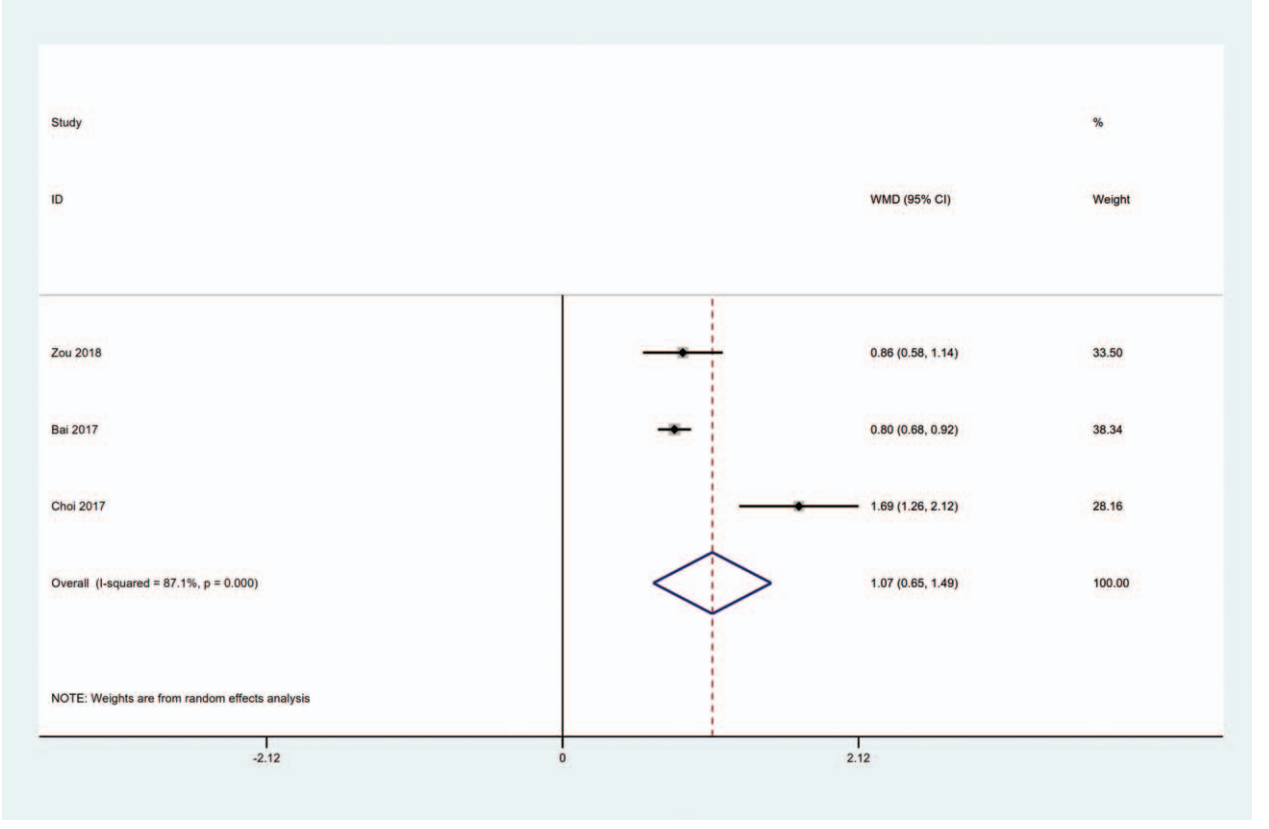

Figure 4. Forest plot of the value of SI between WHO II gliomas and WHO IV gliomas. SI = signal intensity.

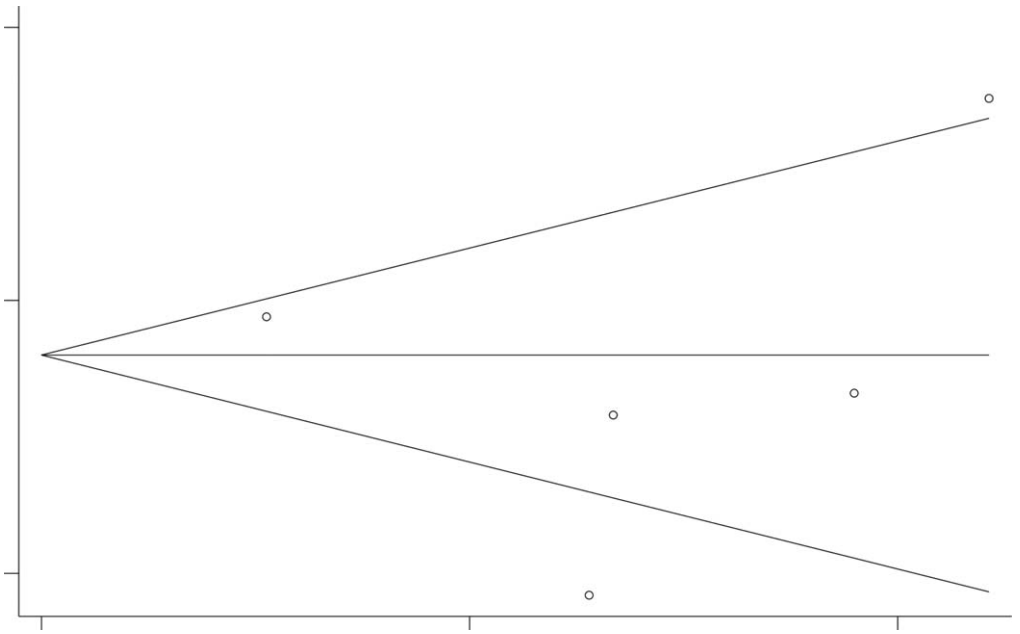

Figure 5. Funnel plot of publication bias.

4. Discussion

To date, an evidence-based approach to evaluate the accuracy of APT-weighted MRI in characterization of gliomas has been unreported. This result could provide us with clues to investigate the diagnostic value of preclinical tumor grading via APT measurements. It has been demonstrated that APT was capable of effectively differentiating primary central nervous system lymphomas and high-grade gliomas,[23] benign and atypical meningioma;[24] but also malignant gliomas from benign tumor.[25] However, studies on the efficacy of APT-based grading of brain tumor have challenged. Choi et al[15] reported that SI for grades II and IV was significantly different ($P = .002$), while the SI for grades II and III showed no significant difference ($P = .059$). In contrast, compared with grade II gliomas, Zou et al[8] reported that SI derived from APT of grade III and IV gliomas with larger SI ($P < .05$), whereas there was no statistically significant differences for all measured parameters within WHO grade III and IV gliomas ($P > .05$). It was possible that inhomogeneous of the results among included studies, may influence by study design and parameters examined. Thus, in order to address the variations from studies, meta-analysis can improve accuracy of APT by increasing sample size.

This meta-analysis has 3 major findings. First, we demonstrated that the pooled weighted value of SI was significantly higher in the HGG than the LGG (WMD = 0.86 (0.61–1.1), $P < .0001$). Second, our results also revealed that a significant difference was also found between grade II and grade III (WMD = 0.6 (0.4–0.8), $P < .0001$). Third, our meta-analysis indicated that SI in WHO grade IV was higher than grade II (WMD = 1.07 (0.65–1.49), $P < .0001$). Previous studies showed that SI was positively correlated with the glioma grading and Ki-67. Park et al[25] considered that APT was a promising noninvasive imaging method for assessing the cellular proliferation of gliomas. The lower APT signal intensity in the LGGs may be attributed to the loosen cellularity in these tumors comparison with the HGGs.[9] Our results were consistent with previous articles indicating higher SI for HGGs than for LGGs, which were attributed to the higher cell density, along with increased peptide concentrations and mobile protein. In our present study, the results presented that the signal intensity was significantly different between the WHO II, III and IV gliomas, which were also consistent with the results of previous studies.[10,12]

According to the forest map, there is a possibility that significant heterogeneity in this meta-analysis could have arisen from differences in MRI scanners, data acquisition, patients examined among the 6 chosen studies. Since the technology was first introduced in 2003, only 6 studies have been included in this project, which was uncontrollable. While publication bias did not exist in this meta-analysis, we cannot rule out that some biases possible source of unreported papers.

Although our findings indicate that APT was useful for predicting the grading of brain gliomas, some inherent limitations existed in our study and should be considered when interpreting our results. First, all included studies in our meta-analysis originate from Asia (Japan, Korea, and China), which may represent one source of heterogeneity. Second, since the pathological results of the included studies were based on the 2007 WHO standard, the updated 2017 WHO standard believes that genes provide more valuable information. Third, there was a notable heterogeneity in our meta-analyses. Subgroup analysis was not implemented, since 6 papers have been included in this meta-analysis, which was uncontrollable. The sensitivity and specificity of the measure could not be evaluated currently. Future high-quality and large-scale randomized studies were warranted.

5. Conclusion

To date, we have not found any articles using the APT technique as a preclinical diagnostic marker for distinguishing HGGs from LGGs. Although the limitations of our meta-analysis, all currently evidence indicated that APT was an accurate and noninvasive imaging technique for distinguishing HGGs from LGGs. In the future, large-scale randomized trials were necessary

to evaluate the clinical value of APT and to establish standards of scanning parameters.

Author contributions

Conceptualization: Jiaying Zhao.
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Formal analysis: Huan Xie.
Software: Wenfei Li.
Writing – original draft: Songtao Huang, Wenfei Li.
Writing – review & editing: Wenfei Li.

References

[1] Sahin N, Melhem ER, Wang S, et al. Advanced MR imaging techniques in the evaluation of nonenhancing gliomas: perfusion-weighted imaging compared with proton magnetic resonance spectroscopy and tumor grade. Neuroradiol J 2013;26:531–41.
[2] Zhang S, Zhang C, Song Y, et al. Prognostic role of survivin in patients with glioma. Medicine 2018;97:e0571.
[3] Meng L, Yang S, Hao W, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion mr imaging and proton MR spectroscopic imaging compared with conventional mr imaging. AJNR Am J Neuroradiol 2003;24:1989–98.
[4] Tian Q, Yan LF, Zhang X, et al. Radiomics strategy for glioma grading using texture features from multiparametric MRI. J Magn Res Imaging 2018;48:1518–28.
[5] Wang Q, Zhang J, Xu X, et al. Diagnostic performance of apparent diffusion coefficient parameters for glioma grading. J Neurooncol 2018;139:1–8.
[6] Brendle C, Hempel JM, Schittenhelm J, et al. Glioma grading by dynamic susceptibility contrast perfusion and 11C-methionine positron emission tomography using different regions of interest. Neuroradiology 2018;60:1–9.
[7] Wang J, Liang Y, Fan W, et al. Combination use of ~1H-MRS and DTI in the grading of cerebral gliomas. J Med Imaging 2018;28:362–5.
[8] Zou T, Yu H, Jiang C, et al. Differentiating the histologic grades of gliomas preoperatively using amide proton transfer-weighted (APTW) and intravoxel incoherent motion MRI. NMR Biomed 2018;31:e3850.
[9] Su C, Zhao L, Li S, et al. Amid proton transfer (APT) and magnetization transfer (MT) MRI contrasts provide complimentary assessment of brain tumors similarly to proton magnetic resonance spectroscopy imaging (MRSI). Eur Radiol 2018;29:1203–10.
[10] Sakata A, Okada T, Yamamoto Y, et al. Addition of amide proton transfer imaging to FDG-PET/CT improves diagnostic accuracy in glioma grading: a preliminary study using the continuous net reclassification analysis. AJNR Am J Neuroradiol 2018;39:265–72.
[11] Togao O, Hiwatashi A, Yamashita K, et al. Grading diffuse gliomas without intense contrast enhancement by amide proton transfer MR imaging: comparisons with diffusion- and perfusion-weighted imaging. Eur Radiol 2017;27:578–88.
[12] Su C, Liu C, Zhao L, et al. Amide proton transfer imaging allows detection of glioma grades and tumor proliferation: comparison with Ki-67 expression and proton MR spectroscopy imaging. AJNR Am J Neuroradiol 2017;38:1702–9.
[13] Sakata A, Fushimi Y, Okada T, et al. Diagnostic performance between contrast enhancement, proton MR spectroscopy, and amide proton transfer imaging in patients with brain tumors. J Magn Reson Imaging 2017;46:732–9.
[14] Jeong HK, Han K, Zhou J, et al. Characterizing amide proton transfer imaging in haemorrhage brain lesions using 3T MRI. Eur Radiol 2017;27:1577–84.
[15] Choi YS, Ahn SS, Lee SK, et al. Amide proton transfer imaging to discriminate between low- and high-grade gliomas: added value to apparent diffusion coefficient and relative cerebral blood volume. Eur Radiol 2017;27:3181–9.
[16] Bai Y, Lin Y, Zhang W, et al. Noninvasive amide proton transfer magnetic resonance imaging in evaluating the grading and cellularity of gliomas. Oncotarget 2017;8:5834–42.
[17] Sakata A, Okada T, Yamamoto A, et al. Grading glial tumors with amide proton transfer MR imaging: different analytical approaches. J Neuro-oncol 2015;122:339–48.
[18] Togao O, Yoshiura T, Keupp J, et al. Amide proton transfer imaging of adult diffuse gliomas: correlation with histopathological grades. Neuro-oncology 2014;16:441–8.
[19] Dreher C, Oberhollenzer J, Meissner JE, et al. Chemical exchange saturation transfer (CEST) signal intensity at 7T MRI of WHO IV degrees gliomas is dependent on the anatomic location. J Magn Reson Imaging 2018;49:777–85.
[20] Zhou J, Lal B, Wilson DA, et al. Amide proton transfer (APT) contrast for imaging of brain tumors. Magn Reson Med 2003;50:1120–6.
[21] Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. Chin J Evid Based Med 2007;3:25–125.
[22] Copas JB, Shi JQ. A sensitivity analysis for publication bias in systematic reviews. Stat Methods Med Res 1999;10:251.
[23] Jiang S, Yu H, Wang X, et al. Molecular MRI differentiation between primary central nervous system lymphomas and high-grade gliomas using endogenous protein-based amide proton transfer MR imaging at 3 Tesla. Eur Radiol 2016;26:64–71.
[24] Joo B, Han K, Choi YS, et al. Amide proton transfer imaging for differentiation of benign and atypical meningiomas. Eur Radiol 2018;28:331–9.
[25] Park JE, Kim HS, Park KJ, et al. Histogram analysis of amide proton transfer imaging to identify contrast-enhancing low-grade brain tumor that mimics high-grade tumor: increased accuracy of MR perfusion. Radiology 2015;277:151–61.