Systematic Review and Meta-Analysis

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Based on arterial spin labeling helps to differentiate high-grade gliomas from brain solitary metastasis

A systematic review and meta-analysis

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Abstract

Background: We first introduced this meta-analysis was to assess the accuracy of arterial spin labeling (ASL) in the differentiating high-grade gliomas (HGG) from brain solitary metastases (BSM).

Methods: The PubMed, Web of Knowledge, and Cochrane Libraries and China National Knowledge Infrastructure databases were searched up to August 31, 2018. The pooled weighted sensitivity and specificity, summary receiver operating characteristic curve (SROC), sensitivity analysis, and threshold effect analysis were performed on Stata version 12.0 and Meta-Disc version 1.4. Deeks' funnel plot asymmetry test was performed to assess publication bias.

Results: Of 5 eligible articles, of the 346 lesions from 346 patients, 274 were HGG, and 72 were BSM. The forest pooled sensitivity of 0.88 (95% confidence interval [CI]: 0.65, 0.96) and specificity of 0.85 (95% CI: 0.74, 0.92) of ASL were reported in this meta-analysis. The pooled area under the curve of SROC was 0.92 (95% CI: 0.89, 0.94). Sensitivity analysis demonstrated that the pooled estimates were reliable. No evident publication bias was obtained ($P = .38$).

Conclusion: The parameters derived from ASL with high accuracy in differentiating HGG from BSM. However, results must be interpreted with caution due to the small sample size considered. Large sample prospective studies were necessary to assess and confirm its clinical value.

Abbreviations: ASL = arterial spin labeling, AUC = area under the curve, BSM = brain solitary metastases, CNKI = China Knowledge Resource Integrated database, CI = confidence interval, DOR = diagnostic odds ratio, FN = false-negative, FP = false-positive, HGG = high-grade gliomas, rCBF = related cerebral blood flow, SEN = sensitivity, SPE = specificity, SROC = summary receiver operating characteristic curve, TP = True-positive, TN = true-negative.

Keywords: ASL, gliomas, meta-analysis, metastasis, MRI

1. Introduction

High-grade gliomas (HGG) and metastases are the most common malignant tumors in the brain. Preoperative distinction between HGG and metastases was of vital importance as the clinical course, treatment and prognosis of HGG and metastatic tumor are totally different.[1] The precise diagnosis and subsequently proper treatment significantly affected patient's survival. The main problem was that differentiation between HGG and metastases on conventional MR sequences, which may show as solitary strongly enhancing brain tumors surrounded by a T2-hyperintense edema.[2] Different biological behaviors and pathological characteristics were helpful to differentiating HGG from solitary metastases.[3] The growth of HGG is invasive, HGG infiltrated the surrounding tissues through the nerve fiber bundles, and therefore the peritumoral area was accompanied by a large number of tumor cells.[4] Yet, metastases were transformed through the bloodstream to the brain parenchyma by extracerebral tumors.[5] Compression of the venous veins was attributed to peritumoral edema. Therefore, the peritumoral of the brain metastatic was presented as vasogenic edema and absence of tumor cells.[6]

An advanced magnetic resonance imaging (MRI) technique such as arterial spin labeling (ASL) perfusion MRI)provides physiologic and hemodynamic information related to tumoral vascularity.[7] ASL was a promising non-contrast-enhanced imaging technique for evaluating brain tumors, which was now well established in clinical. ASL was widely used in brain tumors diagnosis and grading.[8–10] Several studies have reported

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the tumor blood flow derived from ASL was significantly higher in HGG than in LGG potential higher sensitivity relative to conventional imaging techniques.[10,11] It provided high-resolution morphological information regarding the lesions. ASL had also demonstrated diagnostic value in differentiating HGG from brain solitary metastases.[12]

Several studies have reported that related cerebral blood flow (rCBF) in HGG was significantly higher than in metastasis ($P < .05$),[13–15] While previous reports demonstrated that rCBF values may not be sufficient for discriminating metastatic tumors from HGG.[16,17] Meta-analysis has been recognized as an effective method to answer a wide variety of clinical questions by summarizing and reviewing previously published quantitative research.[18] So far, the contribution of ASL on the discrimination of HGG from brain solitary metastases based on meta-analysis has been unpublished. We first introduced this meta-analysis was to assess the accuracy of ASL in the differentiating HGG from brain solitary metastases.

2. Methods

2.1. Search strategy

The PubMed, Web of Knowledge, and Cochrane Libraries and China National Knowledge Infrastructure (CNKI) databases were searched using the following terms: "arterial spin labeling or ASL" and (brain metastasis) OR (brain metastases) OR (metastatic brain tumor*) OR (cerebral metastasis) OR (cerebral metastases) OR solitary metasta*)) AND (glioma) OR (glioblastoma). English and Chinese language publications were limited to our search. This study was also limited to human studies. In addition, we reviewed references of relevant guidelines, reviews, and meta-analyses identified in PubMed.

2.2. Eligibility criteria and data extraction

Studies were required to meet the following inclusion criteria:

(1) population: patients had enhancing brain lesion;
(2) ASL was applied to differentiate HGG from brain metastasis;
(3) reference standard: histopathological diagnosis and clinical follow-up were considered as reference standard;
(4) the eligible studies must have sufficient data to reconstruct 2×2 tables for sensitivity and specificity.

Conference abstracts, reviews, letters, case reports, animal studies, editorials, and short surveys that did not provide sufficient information for reconstruction of 2×2 tables were excluded.

2.3. Quality assessment and data extraction

Study quality was assessed based on the 14 items of quality assessment of diagnostic accuracy studies by 2 reviewers independently.[19] Two authors independently worked on

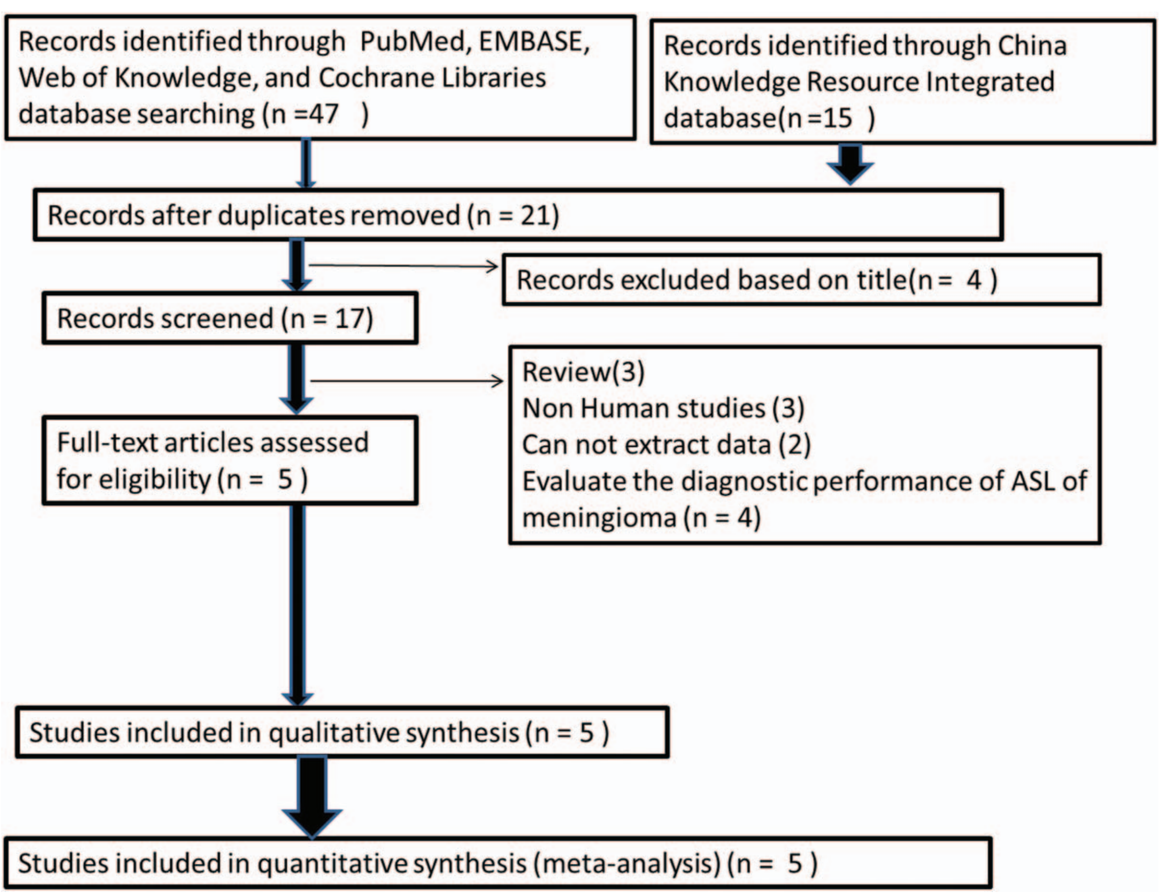

Figure 1. Flow chart of studies selection in this meta-analysis.

Table 1

Characteristics of studies included in the meta-analysis.

Author	Year	Country	Field strength	MRI type	Study design	No. of patients	No. of HGG	No. of Metastatic	Mean of age	Cutoff	Percentage of HGG
Ding	2014	China	3 T	GE	retrospective	86	48	38	50	0.895	55.8%
Sunwoo	2016	Korea	3 T	Siemens	retrospective	128	89	38	57.3	0.4	69.5%
Lin	2016	China	3 T	GE	retrospective	52	24	28	53.1	1.14	46.1%
Ganbold	2017	Japan	3 T	GE	prospective	38	25	13	65.3	NM	65.7%
Weber	2006	Germany	1.5 T	Siemens	prospective	42	35	7	NM	0.5	83.3%

HGG = high-grade gliomas, MRI = magnetic resonance imaging, NM = not mentioned.

extracting the following data: baseline characteristics of study (first author, year of publication, study design, number, and age of patients); MRI parameters (ASL technical, field strength, diagnostic threshold for differentiating HGG from brain metastasis). Additionally, reference standard (histopathology, follow-up) data were also collected. Finally, the values of true-positive (TP), false positive (FP), true negative (TN), and false negative (FN) were calculated. Any controversy existed in this study; a third reviewer assessed all involved problems. Consensus on all disagreements was a prerequisite for data analysis.

2.4. Statistical analysis

The pooled weighted sensitivity and specificity, summary receiver operating characteristic curve, sensitivity analysis, and threshold effect analysis were performed on Stata version 12.0 (College Station, TX) and Meta-Disc version 1.4 (Unit of Clinical Biostatistics, Madrid, Spain). The inconsistency index (*I*-squared, I^2) was done to evaluate the possibility of heterogeneity among individual studies. If $I^2 > 50\%$, it indicated that heterogeneity exists in this study.[20] Publication bias analysis was assessed by using the Deeks' funnel plot test. $P < .05$ was recognized as statistical significance.

3. Results

The search process was summarized in Figure 1. Based on the results of computer search and manual cross-checking of reference lists, 47 citations (32 English and 15 Chinese) were retrieved. A total of 21 articles remained by using Endnote citation manager to remove duplicate articles. After the initial evaluation, we found 21 eligible articles (15 English and 6 Chinese). After reading the full texts and abstracts, we excluded 12 of the 17 relevant articles for the following reasons: the aim of

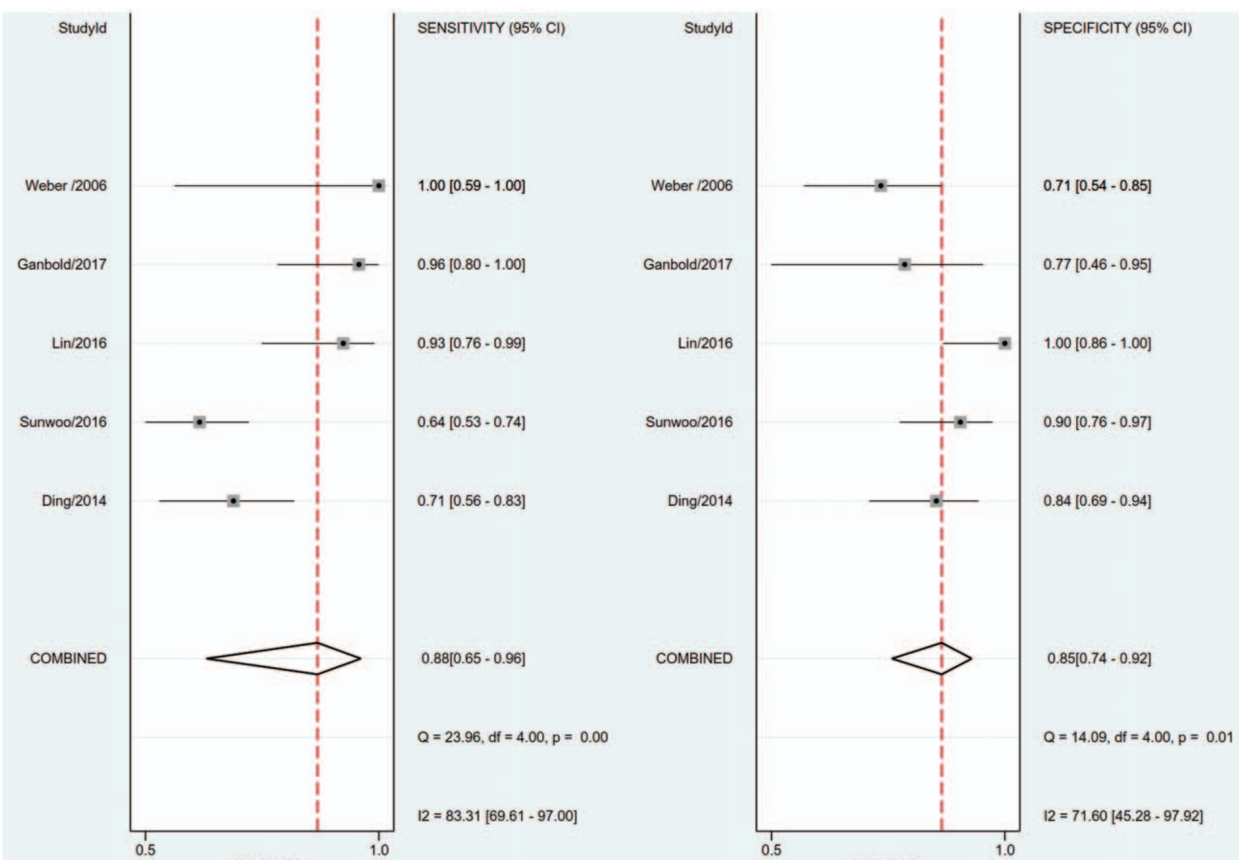

Figure 2. Forest map of sensitivity and specificity of ASL. ASL = arterial spin labeling.

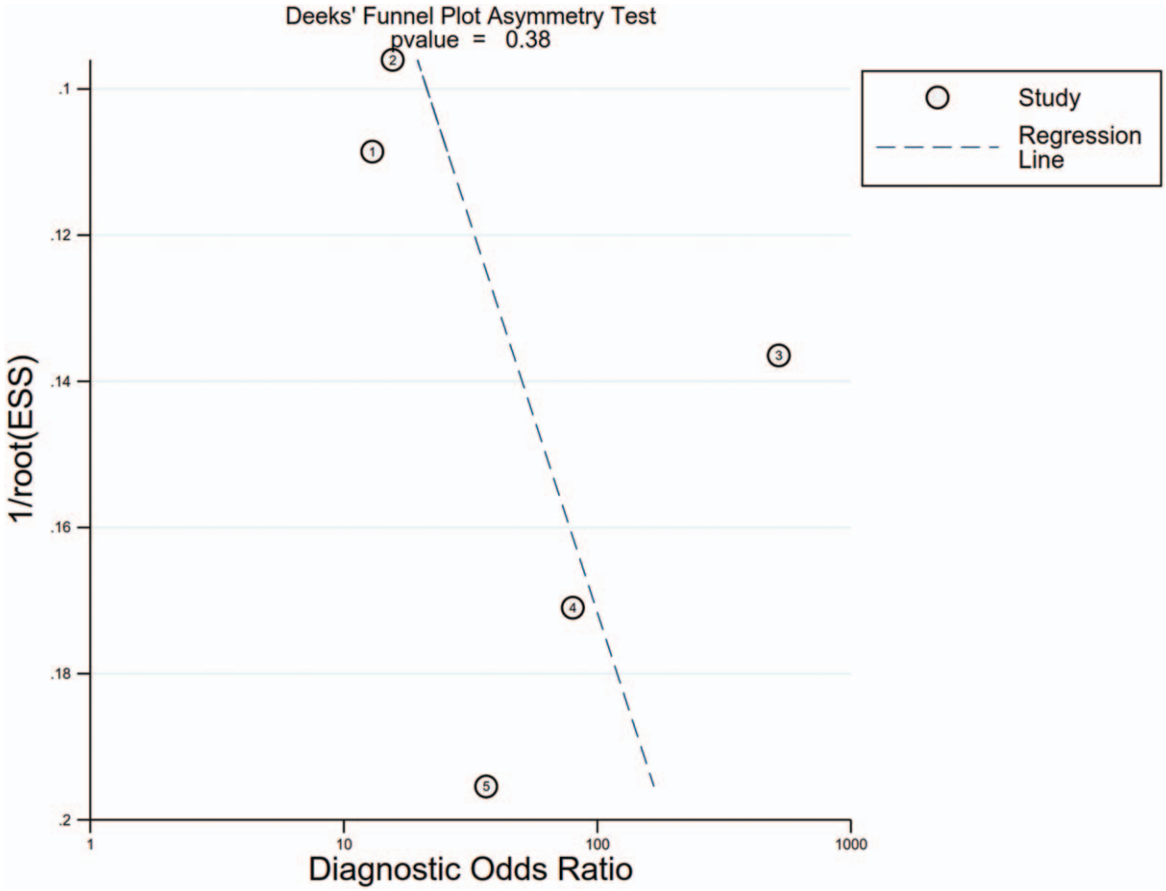

Figure 3. Publication bias analyzed by Deek funnel plot.

studies was to estimate the diagnostic performance of ASL of brain tumor (n=4); Review of clinical application of ASL in the diagnosis of central nervous system diseases (n=3); Among the various parameters, the peritumoral relative cerebral blood volume as the measurement parameter was used in all studies. Articles did not provide adequate data that could be used to calculate TP, FP, TN, and FN values of rCBF (n=5); finally, 5 articles (4 English and 1 Chinese) met all inclusion and selected for data analysis.[13–17]

The basic study characteristics for eligible studies were presented in Table 1. In total, 346 patients were reviewed from the 5 papers. Of the 346 lesions from 346 patients, 274 were HGG, and 72 were brain metastasis tumors. The mean age of the patients was variable ranging from 50 to 63.7 years. In 5 studies, 2 articles were prospective, 3 were retrospective, and the sample size ranged from 38 to 128. Four studies placed the region of interest (ROI) in the surrounding area of the tumor and 1 in the tumoral area. Four studies reported using 3.0-T MRI field strength, while only 1 studies adopted 1.5 T MRI systems. Reference standard was described in all studies with histopathology.

The forest plots of sensitivities and specificities among included studies were shown in Figure 2. The combined sensitivity of 0.88 (95% confidence interval [CI]: 0.65, 0.96) and specificity of 0.85 (95% CI: 0.74, 0.92) were reported for the classification of HGG and brain metastasis by ASL in this meta-analysis. The pooled area under the curve (AUC) was 0.92 (95% CI: 0.89, 0.94). Our meta-analysis demonstrated that ASL appears to be a more promising in differentiating HGG from a solitary metastasis. A pooled homogeneity sensitivity of $I^2=83.31\%$ and specificity of $I^2=71.6\%$, respectively. Meta-regression analysis was performed to explore the sources of heterogeneity among the included articles. The covariates included country, field strength, ROI placement, study design, percentage of HGG among eligible studies. However, no significant difference was found statistically ($P>.05$).

3.1. Sensitivity analysis and publication bias

Sensitivity analysis was constructed to determine whether to revise of the inclusion criteria affected the outcomes finally.[21] We evaluated the effect of each study on the pooled results by excluding single study. The pooled data were analyzed again when each study was excluded. The result indicated that there were no significant changes of the pooled weighted sensitivity and specificity, which validated the reliability and rationality of our analysis. Deeks' funnel plot asymmetry test was performed to assess publication bias. Finally, no evident publication bias was obtained through the Figure 3 ($P=.38$).

4. Discussion

In this study, we analyzed the diagnostic value of ASL in the classification of HGG and brain metastasis using a meta-analysis

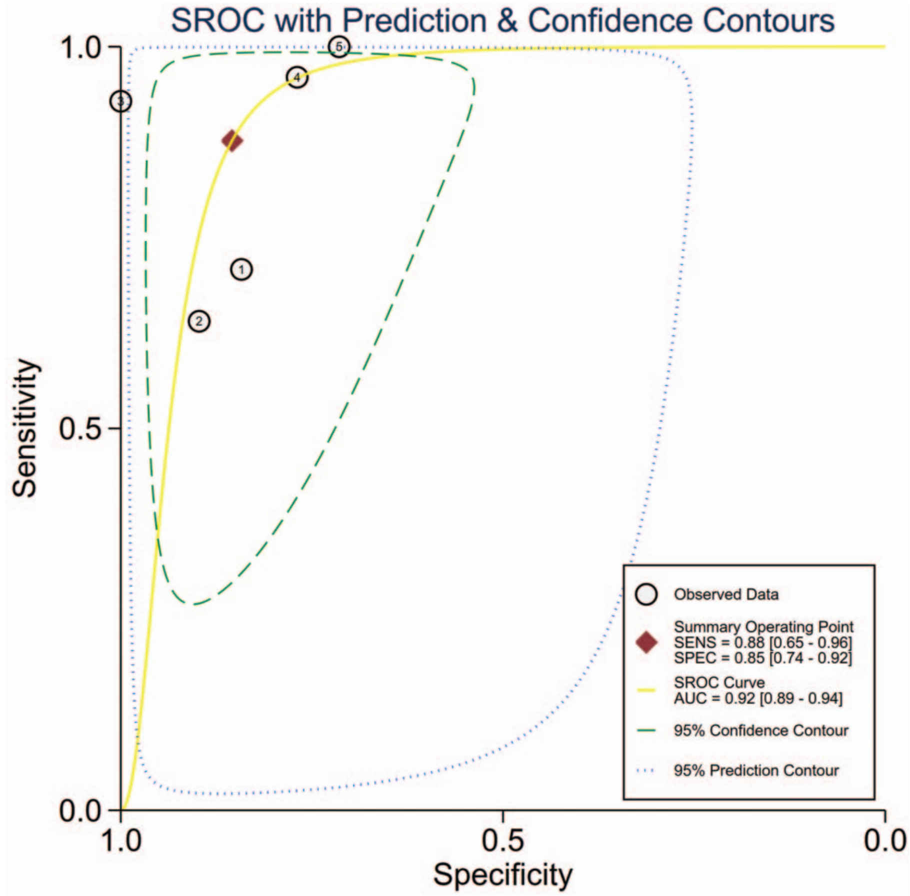

Figure 4. SROC of ASL in characterization of HGG and Solitary Metastatic Brain Tumor. ASL = arterial spin labelling, HGG = high grade gliomas, SROC = summary receiver operating characteristic curve.

to obtain a powerful conclusion. Systematic reviews and meta-analyses aim to collect and analyze individual data related a research question and therefore were considered as a gold standard reach to evidence synthesis. An overall combined sensitivity of 0.88 (95% CI: 0.65, 0.96) and specificity of 0.85 (95% CI: 0.74, 0.92) were calculated in our paper. The pooled AUC was shown in Figure 4 with 0.92 (95% CI: 0.89, 0.94). Our results demonstrated that rCBF values from ASL would be a powerful tool in the classification of HGG and brain metastasis.

These outcomes were well known in the studies have been reported.[22] As expected, patients with HGG showed significantly higher rCBF than those with metastasis in peritumoral areas. Additionally, a recent animal study has reported that the peritumoral edema of glioma not only included tumor cells, but also contained astrocytic swelling and microglial activation; our study demonstrated that rCBF values from ASL with high accuracy in differentiating HGG from brain metastases, which could be explained by the histopathologic findings. Similar finding was also reported in perfusion studies in the classification of GBM and brain metastasis tumors using ASL,[13] of 128 consecutive patients who were diagnosed as glioblastoma (n = 89) and metastasis tumor (n = 39) and underwent operation, the rCBF derived from ASL showed high diagnostic performance with a similar specificity of 84.6%, which was consistent with our findings. Although a lower sensitivity (42.7%) of rCBF was presented, possibly due to small sample size.

Notable heterogeneities were shown in Figure 2. In Figure 4, "shoulder-arm" shape did not seem to be displayed among individual studies, indicating that threshold effect was not a concern. The next step was done to explore the threshold effect in this study. In this meta-analysis, the Spearman correlation coefficient was 0.229 ($P = .208$), indicating that the heterogeneity was unlikely to be attributable to the threshold effect among eligible articles. We performed meta-regression analysis to understand the potential other factors significantly affected heterogeneity among individual studies. However, no significance was found statistically using other covariates, including country, field strength, study design, percentage of HGG ($P > .05$).

These findings seemed to be encouraging, confirming the high diagnostic power of ASL in differentiating gliomas from solitary metastases, several differences and limitations in our meta-analysis should be noted. One limitation of our study was the sample size of included studies; however, articles were uncontrolled and there was no publication bias by Deeks' asymmetry test. Another limitation of was only English and Chinese language publications were searched in PubMed, Web of Knowledge, and Cochrane Libraries, and CNKI databases. Besides, the reliability of a meta-analysis relied on the quality of study heterogeneity; we did not perform subgroup analysis because there were only 5 studies. We performed meta-regression analysis to explore the potential other factors significantly affected heterogeneity among individual studies, yet no evidence was shown to be a significant factor affecting study heterogeneity.

5. Conclusion

To the best of our knowledge, this was the first meta-analysis providing comprehensive insights into the classification of HGG and brain metastasis tumors using ASL. In our study of the rCBF parameters derived from ASL with high accuracy in differentiating HGG from brain metastases. Our study suggested that the ASL was useful for discriminating brain metastatic tumors from HGG. However, results must be interpreted with caution due to the small sample size considered. Large sample prospective studies were necessary to assess and confirm its clinical value.

Author contributions

Conceptualization: Min Fu.
Data curation: Fang Han, Tao Chen, Xiaobo Feng.
Formal analysis: Tao Chen.
Funding acquisition: Min Fu.
Methodology: Changchao Feng, Tao Chen.
Resources: Changchao Feng.
Software: Fang Han, Xiaobo Feng.
Writing – original draft: Min Fu.
Writing – review and editing: Min Fu, Xiaobo Feng.

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