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'EVALUATION OF EFFICACY OF PERFUSION MRI IN DIFFERENTIATING HIGH GRADE GLIOMAS FROM OTHER CNS LYMPHOMAS AND SOLITARY BRAIN METASTASIS: A SYSTEMATIC REVIEW''

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ABSTRACT:

Background: Treatment evaluation of patients with tumor is crucial for clinical decision-making. Conventional contrast MRI struggles to distinguish between tumor progression and treatment effects. High-grade gliomas (HGGs), primary central nervous system lymphomas (PCNSLs), and solitary brain metastasis (SBMs) often exhibit similar enhancement patterns on MR imaging and complicating diagnosis. Perfusion MRI, which provides insights into tumor vascularity and microcirculation, may improve diagnostic accuracy. This systematic review aim to assess the effectiveness of perfusion MRI in differentiating HGGs from PCNSLs and SBMs.

Method: We performed this study based on the preferred reporting items for systematic review. The literature search was conducted using an electronic database for related articles published in English from PubMed, Scopus, the Web of Science, and Cochrane with periods from 2014 to 2023. Literature screening, data extraction, and risk of bias assessment were independently performed.

Results: A total of 765 articles were found, with 13 studies meeting the eligibility criteria. These studies included a total of 368 HGG patients, 131 SBM patients, and 102 PCNSL patients. Most of the studies included were retrospective studies. The mean age of the enrolled patients was 61.2 years. The majority of articles demonstrated low risk (62.82%), signifying reliability, while 19.23% of the studies were classified as 'unclear,' indicating some ambiguity without invalidating the results. Studies classified as 'high risk' (17.95%) indicated substantial bias and potential errors. For analysis, relative cerebral blood volume (rCBV) was a useful parameter for differentiating HGG from PCNSL and SBM, demonstrating significantly higher rCBV values for HGG.

Conclusion: Perfusion MRI is a promising non-invasive imaging method with good accuracy in diagnosing different types of brain tumors. The relative cerebral blood volume (rCBV) can facilitate

the differentiation between HGG from PCNSLs and SBMs. Specifically, dynamic susceptibility contrast MRI (DSC-MRI) shows high diagnostic performance in stratifying gliomas.

Keywords: *HGG, SBM, Perfusion MRI, DSC-MRI*

INTRODUCTION:

The most common primary brain tumors are glioblastoma (GBM), which accounts for approximately 49%, and primary central nervous system lymphoma (PCNSL), which constitutes 2–7% of cases. [1] Additionally, solitary brain metastasis represents 25–30% of brain metastases. [2] Pretreatment characterization and differentiation of malignant brain tumors using MR imaging remains a challenging problem in daily practice. Proper initial diagnosis and appropriate treatment significantly influence patient outcomes, but the management strategies can vary greatly depending on the type of lesion. [3] The distinction between PCNSLs, high-grade gliomas, and brain metastases is difficult, if not impossible, using conventional MR imaging due to their similar appearances. [4] However, accuracy and differentiation are crucial, as the prognosis and treatment differ substantially among PCNSLs, high-grade gliomas, and brain metastases. [5] .

Among intra-axial brain tumors, gliomas are the most common. [6] It exhibits varying levels of necrosis, mitotic activity, vascular growth, as well as cellular and nuclear pleomorphism. [7] High-grade gliomas (WHO grades III and IV) are particularly invasive and highly vascular. [8] Due to their intrinsic tendency to undergo progressive genetic alterations and malignant transformation, patients with high-grade gliomas typically have a poor survival period.

Perfusion imaging has proven invaluable in accurately predicting the histological grade of cerebral neoplasms, offering reliable insights into tumor physiology, including microvascularity, angiogenesis, necrosis, and cellularity.[9] Perfusion MRI can visualize neovascularization and provide information on tissue blood volume, flow, and oxygenation by detecting signal changes in arteries and veins with contrast agents. Parameters such as relative cerebral blood volume (rCBV), mean transit time (MTT), and relative cerebral blood flow (rCBF) help to grade gliomas [10,11]
Perfusion MRI typically consists dynamic contrast-enhanced MRI (DCE-MRI) or arterial spin labeling (ASL) techniques. [12] Techniques like dynamic susceptibility contrast (DSC)-MRI, DCE-MRI, intra-voxel incoherent motion (IVIM)-MRI, and ASL-MRI provide information about the microvascular physiology of tumors. Among these techniques, DSC-MRI is the most widely used. [13].
Various studies with different methodologies and outcomes have been published on the grading of gliomas. However, a comprehensive review of the accuracy of perfusion-based MRI to predict the molecular characteristics of glioma from PCNSLs and SBM is still lacking. Therefore, this systematic review aims to evaluate the efficacy of perfusion MRI in differentiating high-grade gliomas from other primary central nervous system (CNS) lymphomas and solitary metastases.

METHODOLOGY:

The protocol for this study was formulated in accordance with the Preferred Reporting Guidelines for Systematic Reviews and PRISMA-P declaration with all modifications was recorded. The conduct of the review was guided by the Cochrane Handbook and reporting adhered to the PRISMA statements. Although the review was not registered.

SEARCH STRATEGY

A comprehensive literature search encompassed the following electronic databases: MEDLINE via PubMed, Embase, Google Scholar, the Cochrane Library, Web of Science, Wiley Online Library, Scopus, and other relevant databases.

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and selected keywords in various combinations, such as Glioma OR Glioblastoma, High-grade Glioma (HGG), Primary Central Nervous System Lymphoma (PCNSL) OR Lymphoma, Metastatic Brain Tumors, Solitary Brain Metastasis, MRI Perfusion, and MR PW. The search was restricted to publications in the English language.

Inclusion criteria:

- Patients aged 18 years or older.
- Patients with histopathologically confirmed Primary Central Nervous System Lymphoma (PCNSL) or glioblastoma (WHO classification grade IV).
- Patients with histopathologically confirmed glioblastoma or Solitary Brain Metastasis (SBM) (WHO classification grade III or IV).
- Studies evaluating the diagnostic accuracy of perfusion MRI for differentiating between Grade HGGs form lymphoma or metastasis.
- Both (male and female) were included.
- Articles written in the English language.

EXCLUSION CRITERIA:

- Case reports and case series.
- Conference articles.
- Incomplete texts or articles lacking essential data.
- Duplicate articles that are excluded from the study.
- Articles published before 2013.
- Studies utilizing only conventional MRI without perfusion imaging.

Data Analysis:

Following the extraction of articles from various databases, the articles were organized in an excel sheet, where duplicate were systematically removed. Then each articles abstract was independently assessed and paper was conducted according to the established protocol. The complete texts of the chosen papers were then thoroughly reviewed, resulting in the final selection of relevant research. Two reviewers independently performed full-text screening for any difference of opinion that emerged during data extraction, consensus was reached between the two reviewers by discussion or consultation with a third reviewer.

QUALITY ASSESSMENT OF INDIVIDUAL STUDIES:

Utilizing the RevMan software, we conducted a comprehensive evaluation of the risk of bias for randomized controlled trials employing the Cochrane-associated tool. The risk assessment domains were categorized as having either a high, indeterminate, or low risk based on criteria such as selection bias (random sequence generation), performance bias (blinding of patients and personnel), attrition bias (incomplete outcome data), selective reporting (reporting bias), and other potential biases.

STATISTIC ALANALYSIS: In this review, 13 studies were included. Microsoft Office Excel 2013 (Microsoft Corporation, USA) was used for the piloting data extraction, and RevMan software version 5.4 was utilized. The risk of bias was evaluated separately by two review authors. The Risk of Bias Tool for Randomized Controlled Trials was employed to evaluate the included trials, categorizing them as high risk (+), unclear risk (?), or low risk (-). Various domains were evaluated.

RESULTS:

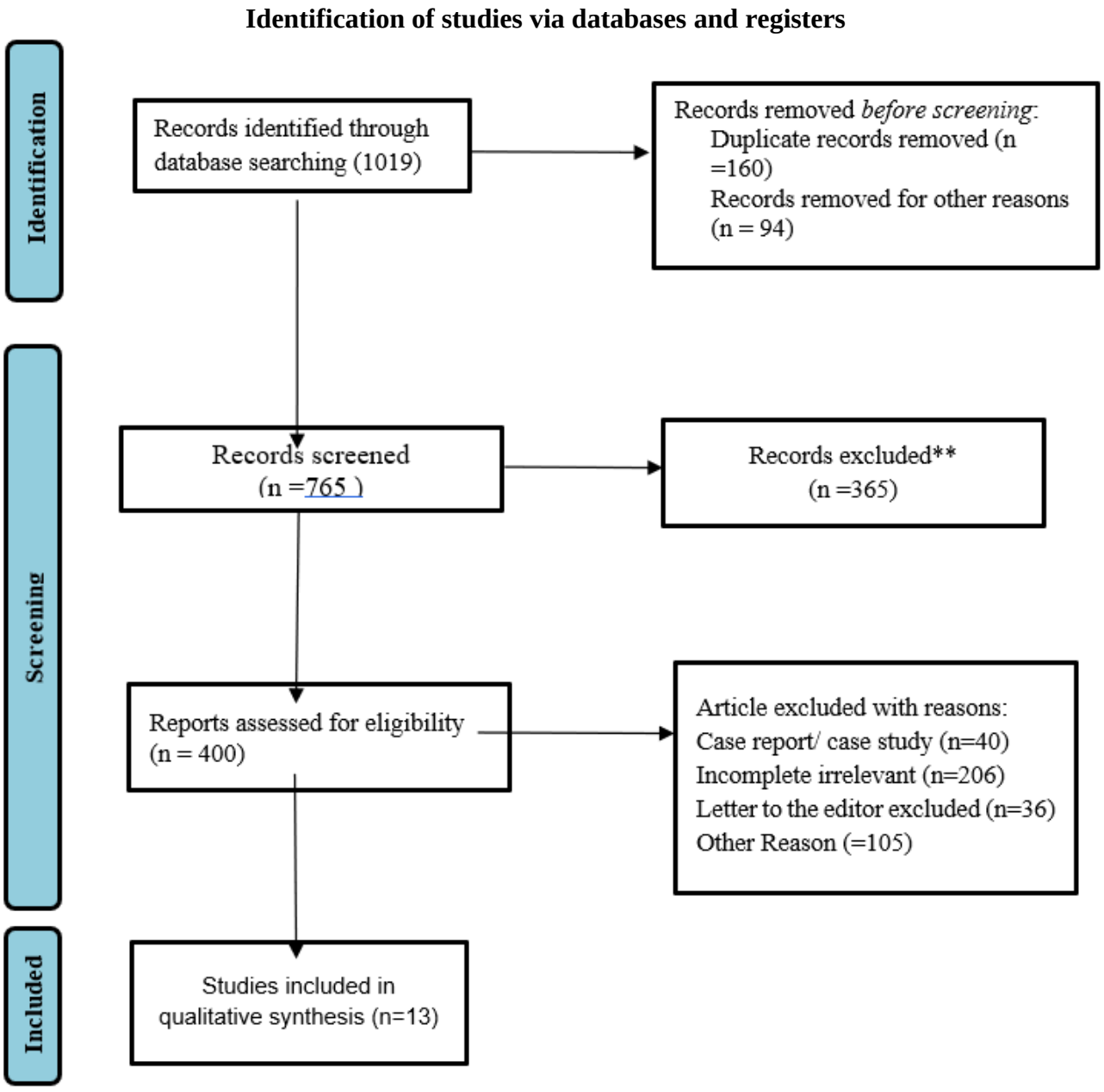

Figure 1. Illustrates the PRISMA flow diagram as well as the article's specified relevant database.

STUDY SELECTION:

A total of 1019 articles were identified through our electronic database search. After removing duplicate articles (160) and 94 due to irrelevant data and being out of scope, the remaining 765 articles underwent further screening. Upon detailed screening, 365 articles were found to be irrelevant to the present review, and an additional 36 letter to the editor articles were removed. Following the predefined inclusion criteria, full-text articles underwent evaluation for the review. Incomplete, irrelevant data, as well as case reports and case studies, were excluded. After thorough screening and data analysis, a total of 13 articles met the criteria for inclusion in the systematic review. These articles spanned from 2014 to 2023. (From **Figure 1.)**

TABLE 1: Perfusion MRI Parameters in distinguish High Grade glioma, Primary central nervous system lymphoma and Solitary brain metastasis

Sr. No	Author	Study design	Sample Size	Mean age	Lesions	Method	Software	Parameter	HGG	PSNCL/SDM	Cutoff	Specificity	Sensitivity
1.	Hung ND 2023[14]	R	45	59.04 ± 11.12	HGG-27 PCNSL-18	DSC-PWI	-	rCBVt	8.41±2.05	2.34± 1.16	4.15	94%	100%
2.	Cindil E, 2021[15]	R	99	-	HGG-60 ,Metastases-24	DSC-MRI	-	rCBV	4.01±2.51	4.25 ± 3.05	-	-	-
3.	Aparici-Robles F 2021[16]	R	24	63.2	HGG-11 SBM-13	MRI DSC	3T	rKep	-	-	0.96	84.6%	92.3%
4.	**She** Dejun 2019[17]	R	43	-	GB-24 MET-19			**rCBV**	8.32 ±3.62	6.90 ± 2.85	>0.50 threshold	79.17%,	57.69%
5.	Aslan K 2019[18]	-	56	61	HGG-39 SBM-17	MRI		rCBV ADC	3.63 ± 1.40	3.68 ± 1.40	0.61 1.44	87.2% 82%	94.1% 82.4%
6.	Ghodsi S M, 2018[19]	R	35		HGG-20,LGG-15	PWMRI		rCBV rCBF	-	-	>2 >1.4	90%	74%
7.	Makino K 2018[20]	R	87	-	HGG-54 PCNSL-33	PWI,DWI	3.0-T scanner	rCBV ADC	8.42 ± 3.73	2.12 ± 1.05	4.0 1.0	90.7	97.0%
8	Neska-Matuszewska M 2018 [21]	R	74	61	PCNSLs-17, GBM-27, Metastatis-30	Multiparametric T2*DSC	ADW 4.4, GE Medical Systems	rCBV	-	-	0.98	-	-
9	Murayama K, 2018 [22]	R	23	59.8	HGG-15 PCNSL-8	DSC-MRI	OleaSphere V3.0	cCBV c30 ktrans			0.015	87.5	93.33
10	Jiang S, 2016 [23]	R	54	54.6	HGG-29 PCNSL-13	DCE		fMax			12.40	-	-
11.	Bauer AH 2015 [24]	R	23	-	HGG-13 SBM-10	MRI DSC		AUC	3.87 ±1.17	2.55 ± 1.20	0.98	-	-
12.	Satoshi nakajima 2015 [25]	R	34	60.87	HGG-23 PCNSL-11	MRI-DSC	3T	Uncorrect rCBV	4.59 ± 2.76	1.30 ± 0.44	2.09	77.8%	80%
13.	Svolos P, 2013 [26]	R	115	-	HGG-53 solitary metastatic tumors.-18	DSCI	3Tesla MRI	rCBV	7.14 ± 2.33	7.80 ± 2.61	-	92%	81%

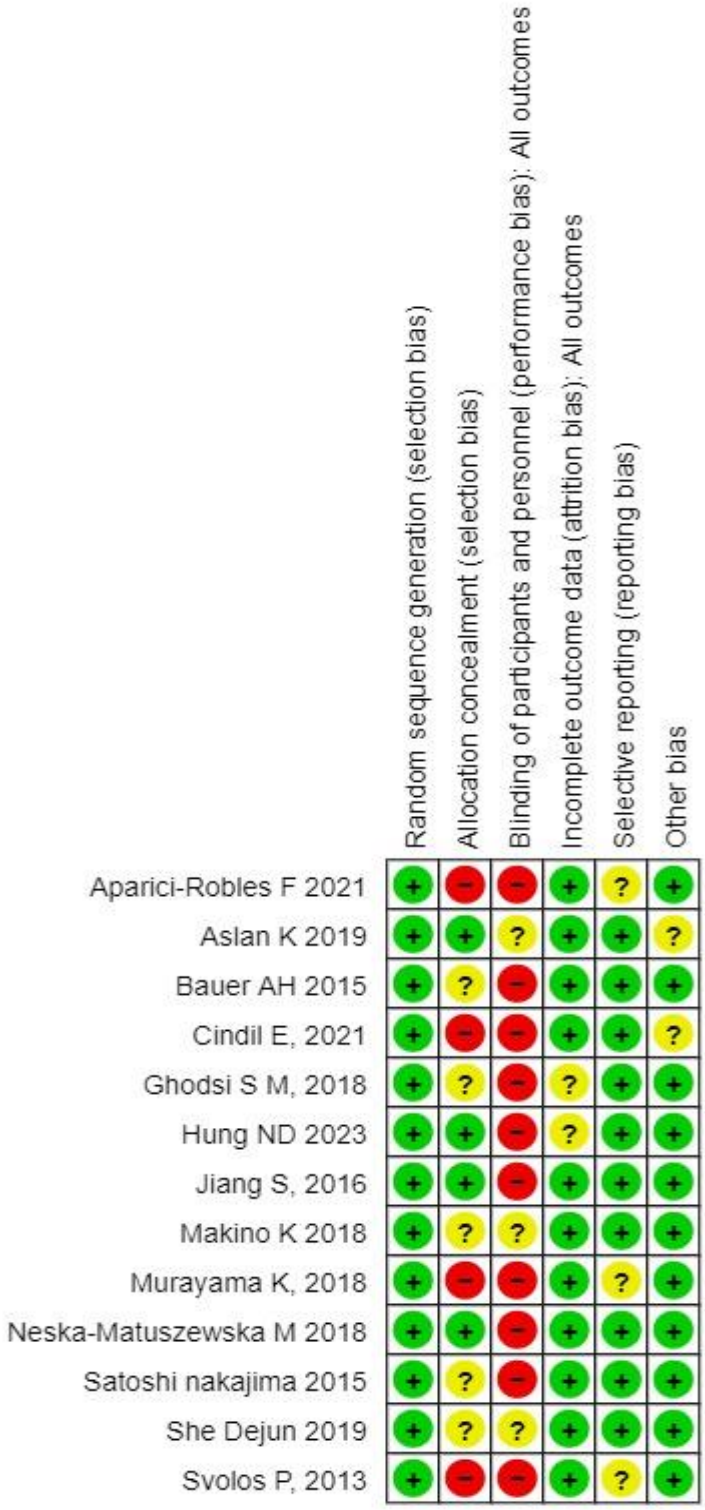

Fig 2: Summary of risk of bias: evaluation of each's study involved item's risk of bias

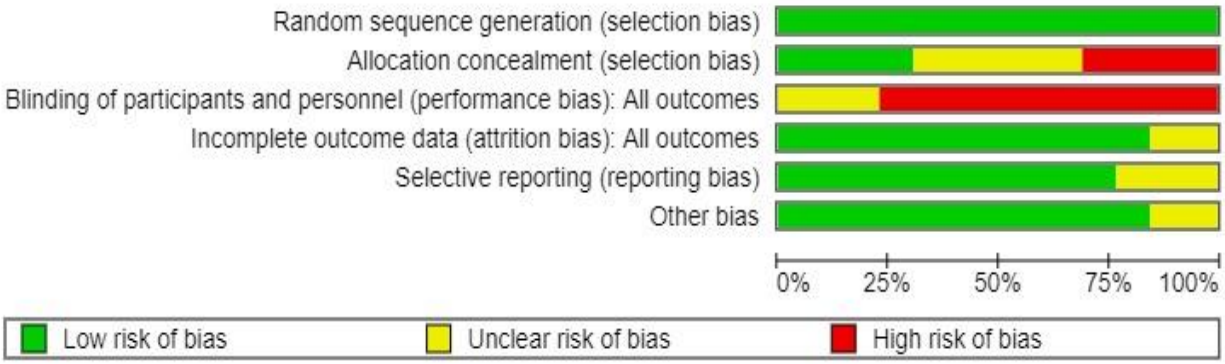

Figure 3: The author's evaluation of each risk of bias item represented as percentages through all involved articles in the risk of bias graph

ELIGIBLE STUDIES CHARACTERISTICS:

In the present systematic review, many studies exhibited high bias in patient's selection and in the conduct or interpretation of the index test due to the retrospective study design. The mean age of patient's enrolled form approximately ranged from 61.

We categorized the 13 eligible studies into two groups assessing the role of perfusion MRI in differentiation: HGGs from PCNSL (n=6) [15,16,18,24, 21, 26] and HGGs from SBM (n=6) - [15,16,18,24, 21, 26] One study was categorized into both the HGGs vs. PCNSLs and HGGs vs. SBM subgroups All features of the included studies are demonstrated in **Table 1.**

This systematic review used the Cochrane "Risk of Bias tool," designed specifically for randomized trials. For randomized controlled trials (RCTs), the Cochrane Collaboration tool was employed to evaluate bias across five domains:

- The method of randomization
- Deviations from intended interventions
- Missing outcome data
- Assessment of risk
- Bias in the selection of the reported result

The majority of articles [14,18,21, 23,24,25] received a low-risk rating (62.82 %) based on the overall bias assessment for each selected work. A "low-risk" study utilized a reliable method to assign patients to different treatment courses, ensuring the reliability of the findings. An "unclear" study (19.23 %) may have had some bias, but it was likely not sufficient to affect the accuracy of the results, possibly due to incomplete data. A "high-risk" study (17.95%) indicated a significant level of bias, potentially leading to erroneous findings, often due to knowledge gaps or reporting inconsistencies. [**Fig:2,3**]

DISCUSSION:

The overall diagnostic performance results indicate that perfusion MRI can be successfully utilized in current neuro-oncological clinical practices. Our work adds to the existing literature and previous systematic reviews and meta-analyses, which have compared the diagnostic value of advanced MRI techniques in brain tumors. However, there is limited research available on the effectiveness of perfusion MRI in distinguishing high-grade gliomas from both primary CNS lymphomas and brain metastases. Therefore, we recognized the need for further investigation into this research topic. The aim of this systematic review was to evaluate the efficacy of perfusion MRI in differentiating high-grade gliomas from both primary CNS lymphomas and brain metastases.

Based on these study outcomes, it was indicated that patients with high-grade glioma (HGG) generally exhibit higher relative cerebral blood volume (rCBV) values compared to those with primary central nervous system lymphoma (PCNSL) and secondary brain metastases (SBM). However, no significant difference in the intratumoral region between HGG and SBM [15, 16, 18, 24,] was found in the enrolled study.

Most of the studies enrolled in this systematic review found that the CBV and CBF of enhancing tumors were significantly lower in PCNSL compared to glioblastomas. [14,15, 20,25]

According to the research, this is due to the fact that glioblastomas (GBMs) exhibit robust tumor angiogenesis, forming abnormal blood vessel structures like glomeruloid capillaries and immature neocapillaries. These contribute to elevated cerebral blood volumes (CBVs). However, GBM vasculature differs significantly from normal vessels due to poor maturation and pruning, increasing vessel fragility and hemorrhage risk. Chaotic blood flow through these malformed vessels leads to intermittent hypoxia within the tumor. [20, 27,28].

In the present systematic review, we observed that the sensitivity and specificity of the enrolled studies, such as those conducted by **Hung ND et al.** [14], **Aparici Roble et al. [16], Murayama K** et al. [20], and **Satoshi Nakajima et al.** [21], showed values of 94%, 84.6%, 87.5%, and 77.8% for specificity, respectively. Additionally, the sensitivity values were reported as 100%, 92.3%, 93.33%, and 80%, respectively. This is concordant with the previous systematic review conducted by **Okuchi S** et al. [29]. The pooled sensitivity and specificity for differentiating PCNSLs from HGG showed 78% and 81%, respectively.

A recent meta-analysis by **Xu et al.,[**30] assessed 14 studies with 598 participants and concluded that perfusion-weighted imaging was "highly accurate" in differentiating high-grade gliomas from PCNSL.

In the systematic review, a study conducted by **Murayama et al. [22]** revealed that the combination of Ktrans and cCBV could be useful for differentiating between CNSL and HGG. CNSL exhibited a significantly lower C80 cCBV ($P = 0.0025$), significantly higher C30 Ktrans ($P = 0.0025$), and significantly higher C30 Ktrans/C80 cCBV ($P < 0.0001$) than HGG. Similarly, in a study by **Toh CH et al. [31],** the mean CBV ratio and corrected CBV ratio were 1.16 ± 0.66 and 2.28 ± 0.60, respectively, for PCNSLs and 5.00 ± 2.00 and 5.47 ± 2.05, respectively, for glioblastomas, indicating lower CBV in PCNSL. Additionally, the mean K2 values were significantly higher in PCNSLs than in GBMs, demonstrating high significance with a P-value of 0.001.

There are limitations in our systematic review. Firstly, the analysis of studies aiming at grading gliomas revealed publication bias, and the composition of two groups was imbalanced. Most analyses indicated substantial heterogeneity in terms of MR field strength, parameters for efficacy which could affect the outcomes. Additionally, we found some studies compared the diagnostic accuracy of MRI-DCE with MRI-DSC. The study design of the included studies revealed only retrospective analysis, lack of consensus regarding the other study design. We acknowledge that further studies are needed to add credibility.

CONCLUSION:

Our results suggest that maximum relative cerebral blood volume (rCBV) appears to be the most important parameter for differentiating between GBMs, metastases, and PCNSLs. Perfusion MRI emerges as a promising non-invasive imaging method with good accuracy in diagnosing various types of brain tumors. Specifically, dynamic susceptibility contrast MRI (DSC-MRI) demonstrates high diagnostic performance in stratifying gliomas.

Abbreviations:

MRI: Magnetic resonance imaging
HGG: High Grade Glioma
PCNSLs: Primary Central Nervous System Lymphomas
SBM: solitary brain metastasis

rCBV: Relative Cerebral Blood Volume
DSC-MRI: Dynamic susceptibility contrast magnetic resonance imaging
DCE: Dynamic Contrast-Enhanced Magnetic Resonance Imaging

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