Differentiation Between Primary Central Nervous System Lymphoma and Atypical Glioblastoma Based on MRI Morphological Feature and Signal Intensity Ratio: A Retrospective Multicenter Study

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Objectives: To investigate the value of morphological feature and signal intensity ratio (SIR) derived from conventional magnetic resonance imaging (MRI) in distinguishing primary central nervous system lymphoma (PCNSL) from atypical glioblastoma (aGBM).

Methods: Pathology-confirmed PCNSLs (n = 93) or aGBMs (n = 48) from three institutions were retrospectively enrolled and divided into training cohort (n = 98) and test cohort (n = 43). Morphological features and SIRs were compared between PCNSL and aGBM. Using linear discriminant analysis, multiple models were constructed with SIRs and morphological features alone or jointly, and the diagnostic performances were evaluated via receiver operating characteristic (ROC) analysis. Areas under the curves (AUCs) and accuracies (ACCs) of the models were compared with the radiologists’ assessment.

Results: Incision sign, T2 pseudonecrosis sign, reef sign and peritumoral leukomalacia sign were associated with PCNSL (training and overall cohorts, \( P < 0.05 \)). Increased \( T_1 \) ratio, decreased \( T_2 \) ratio and \( T_2/T_1 \) ratio were predictive of PCNSL (all \( P < 0.05 \)). ROC analysis showed that combination of morphological features and SIRs achieved the best diagnostic performance for differentiation of PCNSL and aGBM with AUC/ACC of 0.899/0.929 for the training cohort, AUC/ACC of 0.794/0.837 for the test cohort and AUC/ACC of 0.869/0.901 for the overall cohort, respectively. Based on the overall cohort, two
radiologists could distinguish PCNSL from aGBM with AUC/ACC of 0.732/0.724 for radiologist A and AUC/ACC of 0.811/0.829 for radiologist B.

**Conclusion:** MRI morphological features can help differentiate PCNSL from aGBM. When combined with SIRs, the diagnostic performance was better than that of radiologists’ assessment.

**Keywords:** primary central nervous system lymphoma, glioblastoma, magnetic resonance imaging, signal intensity ratio, morphological feature

**INTRODUCTION**

Preoperative distinguishing primary central nervous system lymphoma (PCNSL) from glioblastoma (GBM) is of highly clinical relevance because treatment strategies for the two diseases vary substantially. In patients with GBM, surgical resection followed by concurrent chemoradiation is the first-line treatment, whereas patients with PCNSL usually undergo stereotactic biopsy followed by high-dose methotrexate (1, 2). Moreover, preoperative application of steroids may affect the histopathologic diagnosis of PCNSL (2). Therefore, reliable preoperative differentiation of both entities is important.

Conventional magnetic resonance (MR) imaging features allow distinguishing PCNSL from typical GBM for most patients because PCNSL in an immunocompetent patient usually manifests as a homogeneously enhanced mass lesion on contrast-enhanced T1-weighted (T1CE) images. And typical GBM usually exhibits an irregular rim-like enhancement with necrosis (3, 4). However, this enhancement pattern is not reliable in cases of atypical glioblastoma (aGBM) with no visible necrosis, which complicates the discrimination between aGBM and PCNSL (5, 6).

Both conventional and advanced MR techniques have been reported to be helpful in differentiating PCNSL from GBM (7–12). However, most of these studies enrolled all GBM patients, which can be differentiated from PCNSL based on findings of conventional MRI in most cases. A few studies on differentiating PCNSL from aGBM involve advanced imaging sequences or radiomics strategy (5, 6, 13, 14). Despite great advances, these techniques are associated with increased costs and postprocessing time and may not be routinely adopted by every patient in clinical practice. In contrast, T2-weighted imaging (T2WI), T1-weighted imaging (T1WI), and T1CE imaging are almost always available. Systematic evaluation of MRI morphological features of PCNSL and aGBM is, however, lacking. As an important supplement to subjective analysis, easily obtained quantitative parameters can further provide diagnostic information. Considering the pathophysiological difference between PCNSL and aGBM may be reflected in the form of signal intensity ratio (SIR), whether SIR analysis is effective in distinguishing aGBM from PCNSL remains largely unknown.

Here, we endeavored to compare morphological features and analyze SIR based on conventional MR sequences (T1WI, T2WI, and T1CE) to develop a quick and easy tool for differentiation of PCNSL and aGBM.

**MATERIALS AND METHODS**

Ethics review board approvals from three institutions were obtained, and written informed consent was waived for this retrospective study.

**Patients**

Potentially eligible patients from Tangdu Hospital (from January 2012 to June 2021), XD Group Hospital (from January 2015 to May 2021), and West China Hospital (from January 2016 to June 2021) were identified with pathologically proven PCNSL or GBM.

Inclusion criteria were as follows: 1) no prior treatment history before MR examination, including biopsy, surgery, radiotherapy, chemotherapy, or corticosteroid treatment; 2) pretreatment MRI with conventional sequences available, including axial T1WI, T2WI, and T1CE imaging; 3) no hemorrhage inside the tumor based on T1WI and T2WI; 4) all PCNSL patients were immunocompetent. The exclusion criteria were as follows: 1) typical GBM with visible necrosis; 2) poor image quality with motion artifacts or susceptibility; 3) intracranial metastasis from systemic lymphoma. Atypical GBM was defined as solid enhancement with no visible necrosis based on axial T2WI and T1CE imaging, which were evaluated by two independent raters (YY and GX, with 5 and 10 years of experience in neuro-oncology imaging, respectively). When discrepancy exists, consensus was reached through discussion with a senior radiologist (G-BC, with 27 years of experience in brain tumor diagnosis).

According to the inclusion and exclusion criteria, 98 patients (center 1, n = 72; center 2, n = 26) with pathologically proven PCNSL (n = 66) or aGBM (n = 32) were consecutively enrolled and comprised the training cohort. Another cohort of 43 patients from center 3 with a diagnosis of PCNSL (n = 27) or aGBM (n = 16) comprised the external test cohort. The flow diagram for patient selection is shown in Figure 1.

**MR Image Acquisition**

MRI scans were performed at three institutions with different protocols and various scanners. The routine sequences included axial T1WI, T2WI, and T1CE imaging. The detailed MRI parameters are provided in Table S1 in the Supplementary Material. All patient names were de-identified prior to analysis.

**Image Analysis**

Qualitative morphological features, which were characterized based on the criteria outlined in Table 1, were analyzed.
independently by two neuroradiologists (YY and GX), who were
blinded to the final results. The inconsistency between them was
resolved by discussion with a third senior neuroradiologist (G-
BC). Notably, reef sign, peritumoral leukomalacia sign, and T2 pseudonecrosis sign were defined in our study for the first time
(representative cases, see Supplementary Material Figure S1).

ITK-SNAP software (version 3.8.0; http://itksnap.org) was
used for SIR analysis (15). The abovementioned two
neuroradiologists independently placed region of interest
(ROI) for further consistency testing. The details of ROI
placement strategy are shown in Figure S2 and Table S2 in
Supplementary Material. Finally, four quantitative parameters,
including T2 ratio (rT2), T1 ratio (rT1), T1CE ratio (rT1CE), and
rT2/rT1 ratio (T2/T1), were obtained for each patient. The
calculation formula is as follows:

\[
\begin{align*}
    rT_2 &= \frac{\text{mean signal intensity of the lesion (SI}_{\text{lesion}})\text{ on T}_2\text{WI}}{\text{mean signal intensity of contralateral normal white matter (SI}_{\text{control}})} \\
    rT_1 &= \frac{\text{SI}_{\text{lesion}}\text{ on T}_1\text{WI}}{\text{SI}_{\text{control}}} \\
    rT_1\text{CE} &= \frac{\text{SI}_{\text{lesion}}\text{ on T}_1\text{CE}}{\text{SI}_{\text{control}}} \\
    T2/T1 &= \frac{rT_2}{rT_1}
\end{align*}
\]

**Radiologist’s Assessment**

Two neuroradiologists (LZ and L-FY, with 10 and 17 years’
experience in radiology, respectively) independently reviewed
the images. All radiologists had no prior knowledge of exact
number of each entity and the final results. They can only have
access to conventional MR images (T1WI, T2WI, and T1CE).
Diagnosis was based on subjective analysis according to their
clinical experience. The final diagnosis was recorded using a 4-
point scale (1 = definite GBM; 2 = likely GBM; 3 = likely PCNSL;
and 4 = definite PCNSL). To assess intra-observer agreement,
radiologists reevaluated images after a 2-month washout period.

**Statistical Analysis**

All statistical analyses were performed with SPSS 20.0 software
(IBM Corp., Chicago, IL, USA) and R software version 3.6.1
(http://www.R-project.org). The normal distribution of data was
investigated with Kolmogorov–Smirnov test. Numerical
variables with normal distribution were denoted as mean and
standard deviation. Continuous and categorical variables were
compared using two-sample t-test and Fisher’s exact test,
respectively. The intraclass correlation coefficient (ICC) was
**TABLE 1 | MRI morphological feature definition.**

| Variable                        | Classification criteria                                                                 |
|---------------------------------|----------------------------------------------------------------------------------------|
| **Localization**                |                                                                                        |
| Only supratentorial              | The location of the tumor is supratentorial                                            |
| Only infratentorial              | The location of the tumor is infratentorial                                             |
| Supra- and infratentorial        | The location of the tumor is both supratentorial and infratentorial                     |
| **Lesion type**                 |                                                                                        |
| Solitary demarcated             | Solitary tumor with demarcated boundary                                                 |
| Multiple demarcated             | Multiple tumor with demarcated boundary                                                 |
| Solitary infiltrative           | Solitary tumor with infiltrative boundary                                               |
| Multiple infiltrative           | Multiple tumor with infiltrative boundary                                               |
| **Streak-like edema**           | The shape of peritumoral edema is streak-like                                           |
| Incision sign                   | Single or multiple reef-like foci present as hypointensity on T1WI, hyperintensity on T2WI, and brighter signal within contrast-enhanced area of the lesion |
| Butterfly sign                  | Lesion involving the corpus callosum can infiltrate transcallosally, appearing as a symmetric “butterfly” appearance on T1CE imaging |
| Angular sign                    | The irregular enhancement lesions protrude to a certain direction, showing a sharp angle appearance |
| Peritumoral leukomalacia sign    | The area adjacent to the tumor shows hypointensity on T1WI, hyperintensity on T2WI, and no contrast enhancement on T1CE imaging |
| T2 pseudonecrosis sign          | On T2WI, the edge of the tumor is isointense to slightly hyperintense (gray matter as reference), accompanied by hyperintensity within the tumor. After the injection of contrast agent, the entire tumor shows significant and uniform enhancement |
| **Involvement of structures**   |                                                                                        |
| Central structures              | Involvement of basal ganglia, thalamus, or brainstem                                    |
| Cortex                          | Involvement of cortex                                                                   |
| Subventricular zone             | Involvement of subventricular zone                                                      |
| Corpus callosum                 | Involvement of corpus callosum                                                         |

used to test the consistency of SIRs between the two radiologists. Intra-observer agreements of radiologist’s assessment were evaluated with Cohen’s kappa coefficient. Linear discrimination analysis (LDA) models for distinguishing aGBM from PCNSL were constructed with SIRs and morphological features alone or jointly. Receiver operating characteristic (ROC) analysis was performed to determine the performance of radiologists’ assessment and different models in the training, test, and overall cohorts, and accuracy (ACC) and area under the curve (AUC) were obtained. \( P < 0.05 \) indicated a significant difference.

**RESULTS**

**Demographic Characteristics**

Patient demographic characteristics are summarized in Table 2. In this study, 93 PCNSLs (47 men, 46 women; mean age, 58.49 ± 12.56 years) and 48 aGBMs (29 men, 19 women; mean age, 55.12 ± 10.9 years) were enrolled. There were no significant differences in age and gender distribution between the two diseases (all \( P > 0.05 \)). The vast majority of patients (83 out of 93 PCNSLs and 47 of 48 aGBMs) received surgical resection. Patients in the PCNSL group were pathologically confirmed as diffuse large B-cell lymphoma. Despite the diversity of clinical symptoms, headache, dizziness, or nausea was the most common initial symptom for patients with aGBM (44.1%, 41 out of 93) or PCNSL (41.7%, 20 out of 48).

**Comparison of MRI Morphological Features Between Primary Central Nervous System Lymphoma and Atypical Glioblastoma**

MRI morphological features for both groups are shown in Table 3. Incision sign, reef sign, T2 pseudonecrosis sign, and peritumoral leukomalacia sign were detected in the PCNSL group but none in the aGBM group. Among them, reef sign and peritumoral leukomalacia sign were statistically different in both training (all \( P < 0.001 \)) and test cohorts (reef sign, \( P = 0.003 \); peritumoral leukomalacia sign, \( P = 0.018 \)). Similarly, significant statistical differences between the two groups were observed in incision sign and T2 pseudonecrosis sign based on the training cohort (all \( P < 0.001 \)), whereas the differences in the test cohort were not statistically significant. Accounting for the small sample size of the test cohort, in order to increase the statistical power, we combined the training and test cohorts and performed statistical analysis on the overall cohort again. The results showed that incision sign and T2 pseudonecrosis sign were significantly different between the two groups (all \( P < 0.001 \)). In addition, PCNSL was more likely to involve both supratentorial and infratentorial compartment than aGBM based on the overall cohort (\( P = 0.036 \)). There were no significant differences in lesion type, streak-like edema, butterfly sign, angular sign, and involvement of structures between the PCNSL and aGBM groups (all \( P > 0.05 \)).

**Comparison of Signal Intensity Ratios Between Primary Central Nervous System Lymphoma and Atypical Glioblastoma**

The \( rT2, rT1, T2/T1, \) and \( rT1 CE \) values calculated for PCNSLs and aGBMs are summarized in Table 4. \( T2/T1 \) and \( rT2 \) values in aGBMs were significantly higher than those in PCNSLs in both the training and test cohorts (all \( P < 0.001 \)). The \( rT1 \) value in aGBMs was significantly lower than that in PCNSLs (training cohort, \( P < 0.001 \); test cohort, \( P = 0.048 \)). The \( rT1 CE \) value of PCNSLs was slightly higher than that of aGBMs, but the difference was not statistically significant (all \( P > 0.05 \)). The representative cases are shown in Figures 2, 3.
Efficacy Analysis of Diagnostic Models and Radiologists’ Assessment in Differentiating Primary Central Nervous System Lymphoma From Atypical Glioblastoma

Table 5 exhibits the diagnostic performance of different models and radiologists’ assessment. For univariate quantitative parameters analyses, compared to models 4 (rT2) and 6 (rT1), model 5 (rT2/rT1) achieved higher efficacy, with an AUC of 0.805 [95% confidence interval (CI), 0.718–0.893] for the training cohort, 0.719 (95% CI, 0.593–0.844) for the test cohort, and 0.822 (95% CI, 0.752–0.892) for the overall cohort, for distinguishing PCNSL from aGBM. For multiple variable combination analysis, models 2 and 3 were constructed with quantitative (rT2 + T2/T1 + rT1) and qualitative parameters (localization + incision sign + reef sign + peritumoral leukomalacia sign + T2 pseudonecrosis sign), respectively. The diagnostic performance of model 2 is better than that of model 3, with an AUC of 0.826 (95% CI, 0.709–0.885) for the training cohort, 0.778 (95% CI, 0.624–0.877) for the test cohort, and 0.833 (95% CI, 0.754–0.892) for the overall cohort, for distinguishing PCNSL from aGBM. When all the quantitative and qualitative parameters were combined, model 1 achieved the highest diagnostic efficiency, with an AUC of 0.889 (95% CI, 0.828–0.969) for the training cohort, 0.794 (95% CI, 0.666–0.922) for the test cohort, and 0.869 (95% CI, 0.807–0.932) for overall cohort.

For radiologist’s assessment, the diagnostic performance of radiologist B with more experience (AUC = 0.811, ACC = 0.829, sensitivity = 0.857, and specificity = 0.831) was better than that of radiologist A (AUC = 0.732, ACC = 0.724, sensitivity = 0.736, and specificity = 0.710).

Reproducibility of Signal Intensity Ratio Measurement and Radiologist’s Assessment

Table 6 shows that both inter-reader agreement for SIR measurement and intra-reader agreement for radiologist’s assessment achieved good performance, with ICC/Kappa value ranging from 0.796 to 0.913. For SIR measurements, inter-reader agreement was highest for the measurement of rT2 (ICC = 0.913). Regarding reproducibility of radiologist’s assessment, experienced radiologist B (Kappa = 0.903) showed higher intra-reader agreement than that of radiologist A (Kappa = 0.796).

**DISCUSSION**

Differentiating PCNSL from aGBM (with no visible necrosis) is challenging. In the present study, we found that T2 pseudonecrosis sign, incision sign, reef sign, and peritumoral leukomalacia sign were closely related to PCNSL. Compared to radiologist’s assessment, model 1, which combined the SIRs and MRI morphological features, achieved the best diagnostic performance in distinguishing PCNSL from aGBM.

During the past decades, various MR modalities and different analysis strategies were explored to differentiate PCNSL from GBM (7–10, 13, 14, 16, 17), whereas the present study focused on SIR analysis of conventional MR sequences mainly based on the following four considerations. First, in clinical practice, T1WI, T2WI, and T1CE imaging are routinely obtained for patients with PCNSL and GBM. Despite promising results, a recent systematic review suggested that conclusions derived from radiomics should not be generalized to clinical practice without further validation. Second, radiomics approach can be used for differential diagnosis of PCNSL and GBM. Despite promising results, a recent systematic review suggested that conclusions derived from radiomics should not be generalized to clinical practice without further validation.

**TABLE 2 | Baseline demographics of patients.**

| Variable | Training cohort (n = 98) | Test cohort (n = 43) | Overall cohort (n = 141) |
|----------|-------------------------|---------------------|-------------------------|
|          | PCNSL (n = 66) | aGBM (n = 32) | PCNSL (n = 27) | aGBM (n = 16) | PCNSL (n = 93) | aGBM (n = 48) | P |
| Age (mean ± SD) | 60.3 ± 11.5 | 57.4 ± 9.84 | 55.16 ± 8.21 | 53.16 ± 8.21 | 58.49 ± 12.56 | 55.12 ± 10.9 | 0.0236 |
| Gender (N/%) | 1.000 | | 0.528 | | 0.289 |
| Male | 54.5% (36/66) | 56.3% (18/32) | 40.7% (11/27) | 43.8% (11/26) | 50.5% (47/93) | 60.4% (29/48) | 0.732 |
| Female | 45.5% (30/66) | 43.7% (14/32) | 59.3% (16/27) | 56.2% (5/16) | 49.5% (46/93) | 39.6% (19/48) | 0.116 |
| Symptoms (N/%) | | | | | | | |
| Headache/dizziness/nausea | NA | 33.3% (9/27) | 56.2% (9/16) | 41.7% (20/48) | 44.1% (41/93) | 41.7% (20/48) | 0.0004 |
| Visual disturbances | 4.5% (3/66) | 3.1% (1/32) | 0 | 6.3% (1/16) | 3.2% (3/93) | 4.2% (2/48) | 0.289 |
| Seizure | 12.1% (8/68) | 18.8% (6/32) | 11.1% (3/27) | 18.7% (5/26) | 11.8% (11/93) | 18.7% (9/48) | 0.141 |
| Dysesthesia or hypesthesia | 10.6% (7/66) | 12.5% (4/32) | 29.7% (8/27) | 12.5% (2/16) | 16.1% (15/93) | 12.5% (6/48) | 0.861 |
| Paresis | 6.1% (4/66) | 21.8% (7/32) | 14.8% (4/27) | 0 | 8.6% (8/93) | 14.6% (7/48) | 0.329 |
| Articulation disorder | 9.1% (6/66) | 0 | 0 | 0 | 6.5% (6/93) | 0 | 0.0005 |
| Psychiatric symptoms | 9.1% (6/66) | 9.4% (3/32) | 11.1% (3/27) | 6.3% (1/16) | 9.7% (9/93) | 8.3% (4/48) | 0.418 |
| Biopsy | 87.9% (58/66) | 96.9% (31/32) | 92.6% (25/27) | 100% (16/16) | 89.2% (83/93) | 97.9% (47/48) | 0.148 |
| Resection | 12.1% (8/66) | 3.1% (1/32) | 7.4% (2/27) | 0 | 10.8% (10/93) | 2.1% (1/48) | 0.0005 |

PCNSL, primary central nervous system lymphoma; aGBM, atypical glioblastoma. NA, not available.
TABLE 3 | MRI morphological features in PCNSL and aGBM.

| Variable                                      | Training cohort (n = 98) | Test cohort (n = 43) | Overall cohort (n=141) |
|------------------------------------------------|--------------------------|---------------------|------------------------|
|                                                | PCNSL (n = 66)           | aGBM (n = 32)       | PCNSL (n = 27)         | aGBM (n = 16)         | PCNSL (n = 93)       | aGBM (n = 48)       | P         |
| Localization (N/%)                             |                          |                     |                        |                        | 0.090                | 0.716                | 0.036     |
| Only supratentorial                             | 94% (62/66)              | 90.6% (29/32)       | 92.6% (25/27)          | 87.5% (14/16)          | 93.5% (87/93)        | 89.6% (43/48)       | 0.974     |
| Only infratentorial                             | 1.5% (1/66)              | 9.4% (3/32)         | 3.7% (1/27)            | 12.5% (2/16)           | 2.2% (2/93)          | 10.4% (5/48)        | 0         |
| Supra- and infratentorial                       | 4.5% (3/66)              | 0                   | 3.7% (1/27)            | 0                      | 4.3% (4/93)          | 0                    | 0         |
| Lesion type (N/%)                              |                          | 0.180               |                        |                        |                      | 0.111                | 0.008     |
| Solitary demarcated                            | 30.3% (20/66)            | 46.9% (15/32)       | 66.7% (18/27)          | 37.5% (8/16)           | 40.9% (38/93)        | 43.8% (21/48)       | 0.974     |
| Multiple demarcated                            | 0                       | 0                   | 0                      | 0                      | 0                    | 0                    | 0         |
| Solitary infiltrative                          | 37.9% (25/66)            | 21.9% (7/32)        | 33.3% (9/27)           | 62.5% (10/16)          | 36.6% (34/93)        | 35.4% (17/48)       | 0         |
| Multiple infiltrative                          | 31.8% (21/66)            | 31.2% (10/32)       | 0                      | 0                      | 22.5% (21/93)        | 20.8% (10/48)       | 0         |
| Streak-like edema (N/%)                        |                          | 0.391               |                        |                        | 1.000                |                      | 0.470     |
| Yes                                           | 43.9% (29/66)            | 34.4% (11/32)       | 29.6% (8/27)           | 31.2% (5/16)           | 39.8% (37/93)        | 33.3% (16/48)       | 0.004     |
| No                                            | 56.1% (37/66)            | 65.4% (21/32)       | 70.4% (19/27)          | 68.8% (11/16)          | 60.2% (56/93)        | 66.7% (32/48)       | 0.003     |
| Incision sign (N/%)                            |                          | 0.008               |                        |                        | 0.069                |                      | <0.001    |
| Yes                                           | 19.7% (13/66)            | 0                   | 22.2% (6/27)           | 0                      | 20.4% (19/93)        | 0                    | 0         |
| No                                            | 80.3% (53/66)            | 100% (32/32)        | 77.8% (21/27)          | 100% (16/16)           | 79.6% (74/93)        | 100% (48/48)        | 0.001     |
| Reef sign (N/%)                                |                          | <0.001              |                        |                        | 0.003                |                      | 0.001     |
| Yes                                           | 42.4% (28/66)            | 0                   | 40.7% (11/27)          | 0                      | 41.9% (39/93)        | 0                    | 0         |
| No                                            | 57.6% (38/66)            | 100% (32/32)        | 59.3% (16/27)          | 100% (16/16)           | 58.1% (54/93)        | 100% (48/48)        | 1.000     |
| Butterfly sign (N/%)                           |                          | 0.353               |                        |                        | 0.520                |                      | 0.004     |
| Yes                                           | 10.6% (7/66)             | 15.6% (5/32)        | 14.8% (4/27)           | 6.3% (1/16)            | 11.8% (11/93)        | 12.5% (6/48)        | 0.001     |
| No                                            | 89.4% (59/66)            | 84.4% (27/32)       | 85.2% (23/27)          | 93.7% (15/16)          | 88.2% (82/93)        | 87.5% (42/48)       | 0.001     |
| Angular sign (N/%)                             |                          | 0.556               |                        |                        | 0.386                |                      | 0.001     |
| Yes                                           | 13.6% (9/66)             | 18.7% (6/32)        | 18.5% (5/27)           | 6.3% (1/16)            | 15.1% (14/93)        | 14.6% (7/48)        | 0.001     |
| No                                            | 86.4% (57/66)            | 81.3% (25/32)       | 81.5% (22/27)          | 93.7% (15/16)          | 84.9% (73/93)        | 85.4% (41/48)       | 0.001     |
| Peritumoral leukomalacia sign (N/%)             |                          | <0.001              |                        |                        | 0.018                |                      | <0.001    |
| Yes                                           | 30.3% (20/66)            | 0                   | 29.6% (8/27)           | 0                      | 30.1% (28/93)        | 0                    | 0         |
| No                                            | 69.7% (46/66)            | 100% (32/32)        | 70.4% (19/27)          | 100% (16/16)           | 68.9% (65/93)        | 100% (48/48)        | 0.121     |
| T2 pseudonecrosis sign (N/%)                   |                          | 0.004               |                        |                        | 0.279                |                      | < 0.001   |
| Yes                                           | 21.2% (14/66)            | 0                   | 14.8% (4/27)           | 0                      | 19.4% (18/93)        | 0                    | 0         |
| No                                            | 78.8% (52/66)            | 100% (32/32)        | 85.2% (23/27)          | 100% (16/16)           | 80.6% (75/93)        | 100% (48/48)        | 0.047     |
| Involvement of structures (N/%)                |                          | 0.072               |                        |                        | 0.704                |                      | 0.047     |
| Central structures                             | 27.3% (18/66)            | 9.4% (3/32)         | 29.6% (8/27)           | 31.3% (5/16)           | 27.9% (26/93)        | 16.7% (8/48)        | 0.121     |
| Cortex                                        | 10.6% (7/66)             | 15.6% (5/32)        | 14.8% (4/27)           | 31.3% (5/16)           | 11.8% (11/93)        | 20.8% (10/48)       | 0.008     |
| Subventricular zone                            | 9.1% (8/66)              | 18.8% (6/32)        | 11.1% (3/27)           | 6.25% (1/16)           | 9.7% (9/93)          | 14.6% (7/48)        | 0.001     |
| Corpus callosum                               | 22.7% (15/66)            | 9.4% (3/32)         | 25.9% (7/27)           | 18.8% (3/16)           | 23.7% (22/93)        | 12.5% (6/48)        | 0.001     |

The bold P value suggests a significant difference between the variables in the two cohorts.

PCNSL, primary central nervous system lymphoma; aGBM, atypical glioblastoma.
be interpreted with caution due to the suboptimal quality of the studies (17). In contrast, the traditional analysis method is time-saving and easy for clinical implementation and interpretation.

Third, clinical experience of radiologists suggests that PCNSL has slightly higher T1WI and lower T2WI signal intensity than GBM. However, visual judgment is subjective, and precise quantitative assessment is needed, especially for those that cannot be differentiated by the naked eye. Although T1 and T2 mapping can accurately quantify T1 and T2 values of tissue, they are not performed as routine sequences due to long scanning time and complex postprocessing. In contrast, signal intensity of the lesion is easily obtained from T1WI and T2WI but is susceptible to many factors, including the characteristics of the tissue itself (T1 value, T2 value, and proton density) and MRI equipment and scanning parameters (field strength, repetition time, and echo time). Therefore, in this study, the SIR was used as a quantitative parameter to eliminate the influence of different MRI scanners and imaging parameters on the results. Similar to our study design, the SIR also showed potential for differential diagnosis in other scenarios (12, 24–26). However, different from previous studies, we used an external test cohort to further clarify the actual diagnostic performance of the SIR. Fourth, our study

### Table 4: Quantitative MR signal intensity ratio comparisons between PCNSL and aGBM.

| Variable | Training cohort (n = 98) | Test cohort (n = 43) | Overall cohort (n = 141) |
|----------|--------------------------|---------------------|-------------------------|
|          | PCNSL (n = 66) | aGBM (n = 32) | P   | PCNSL (n = 27) | aGBM (n = 16) | P   | PCNSL (n = 93) | aGBM (n = 48) | P   |
| rT2     | 1.259 ± 0.113           | 1.690 ± 0.364       | <0.001       | 1.297 ± 0.139           | 1.845 ± 0.239           | <0.001       | 1.269 ± 0.121           | 1.675 ± 0.326           | <0.001       |
| rT1     | 0.629 ± 0.176           | 0.464 ± 0.118       | <0.001       | 0.658 ± 0.131           | 0.570 ± 0.138           | 0.048        | 0.638 ± 0.164           | 0.499 ± 0.134           | <0.001       |
| T2/T1   | 2.159 ± 0.625           | 3.839 ± 1.163       | <0.001       | 2.028 ± 0.384           | 3.049 ± 0.851           | <0.001       | 2.121 ± 0.567           | 3.576 ± 1.125           | <0.001       |
| rT1CE   | 2.431 ± 0.564           | 2.198 ± 0.475       | 0.532        | 2.296 ± 0.489           | 2.065 ± 0.724           | 0.269        | 2.418 ± 0.741           | 2.298 ± 0.569           | 0.473        |

The bold P value suggests a significant difference between the variables in the two cohorts.

PCNSL, primary central nervous system lymphoma; aGBM, atypical glioblastoma.

**Figure 2**

(A–C) A 68-year-old woman with primary central nervous system lymphoma (PCNSL) presented with left hemiparesis for 1 month. MRI showed a left frontal lobe lesion with iso- to slight hyperintensity on T2WI (A), slight hypointensity on T1WI (B), and marked homogeneous enhancement on T1CE imaging (C) (take gray matter for reference). The quantitative parameters showed that rT1, rT2, T2/T1, and rT1CE were 0.65, 1.20, 1.82, and 1.87, respectively. The case was correctly diagnosed as PCNSL by models 1, 2, 4, and 5 and radiologist B while wrongly classified as glioblastoma (GBM) by radiologist A.

(D–F) A 43-year-old woman with GBM presented with seizure. MRI showed a left frontal lobe lesion with isointensity on T2WI (D), slight hypointensity on T1WI (E), and marked homogeneous enhancement on T1CE imaging (F) (take gray matter for reference). The quantitative parameters showed that rT1, rT2, T2/T1, and rT1CE were 0.66, 1.46, 2.25, and 2.11, respectively. The case was correctly diagnosed as GBM by models 1, 2, 4, 5, and 6 and radiologist B while wrongly classified as PCNSL by radiologist A.
did not involve complex image preprocessing, including image registration, brain extraction, and standardization. ITK-SNAP software used in our study can realize simultaneously quantitative measurement of T1WI and T2WI signal intensity in the same ROI without image registration. The entire analysis was limited to the time required to identify lesions and electronically locate ROIs. From the clinical point of view, this approach may be a highly cost-effective quantitative analysis tool.

Most previous studies enrolled all PCNSL and GBM cases, regardless of sign of intratumoral necrosis as a powerful indicator to distinguish the two entities, and their inclusion criteria could partially explain the higher ACC (7, 8, 10, 27). Therefore, we reasoned that confining our study to PCNSL and aGBM cases is closer to the clinical diagnostic dilemma in order to seek more powerful imaging signs to identify the two entities. In our study, four morphological features were closely associated with PCNSL, including incision sign, T2 pseudonecrosis sign, reef sign, and peritumoral leukomalacia sign. Among them, the diagnostic value of incision sign has been confirmed in a previous study (28). T2 pseudonecrosis sign, reef sign, and peritumoral leukomalacia sign, defined by the present study for the first time, were observed only in PCNSL and not in aGBM. For T2 pseudonecrosis sign, the mismatch between heterogeneous T2WI signals and homogeneous enhancement is the diagnostic core, which may be related to the degree of tumor infiltration along the white matter fiber bundles. The reef sign was defined as single or multiple foci that presented as hypointensity on T1WI, hyperintensity on T2WI, and brighter signal within contrast-enhanced area of the lesion. Although the corresponding pathological mechanism of this sign is still unclear, it may be related to the leakage of contrast medium in the tumor area (29). Peritumoral leukomalacia sign was defined as an area manifested as hypointensity on T1WI and hyperintensity on T2WI in the region adjacent to the tumor. The possible explanation is that the PCNSL cells are closely arranged and cluster along vascular channels, which destroy the blood supply of the adjacent brain parenchyma, resulting in encephalomalacia (30). The above four imaging signs were
TABLE 5 | Diagnostic efficacy of different models and radiologists’ assessment in differentiating PCNSL from aGBM.

| Cohort | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 |
|--------|---------|---------|---------|---------|---------|---------|
| AUC (95% CI) | 0.899 (0.828–0.969) | 0.826 (0.709–0.885) | 0.797 (0.768–0.82) | 0.833 (0.754–0.892) | 0.823 (0.785–0.882) | 0.751 (0.661–0.841) |
| ACC (95% CI) | 0.929 (0.858–0.971) | 0.857 (0.772–0.919) | 0.872 (0.806–0.923) | 0.823 (0.703–0.846) | 0.868 (0.802–0.928) | 0.832 (0.703–0.846) |
| Sensitivity | 0.813 | 0.625 | 0.687 | 0.671 | 1.000 | 0.531 |
| Specificity | 0.985 | 0.963 | 0.979 | 0.941 | 0.556 | 0.969 |
| PPV | 0.963 | 0.909 | 0.941 | 0.851 |
| NPV | 0.916 | 0.842 | 0.872 | 0.872 |
| P | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

TABLE 6 | Reproducibility of signal intensity ratio measurements and radiologists’ assessment.

| Variable | ICC/Kappa | 95% CI |
|----------|-----------|--------|
| rT2 | 0.913 | 0.811–0.952 |
| rT1 | 0.892 | 0.833–0.945 |
| rT1/CE | 0.876 | 0.796–0.967 |
| Radiologist A | 0.796 | 0.654–0.869 |
| Radiologist B | 0.903 | 0.832–0.988 |

CONCLUSION

T2 pseudonecrosis sign, reef sign, and peritumoral leukomalacia sign are closely related to PCNSL, which are never reported before. Compared to radiologists’ assessment, the combination model of morphological features and SIRs can provide better diagnostic performance in distinguishing PCNSL from aGBM.

DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions: The raw data are not publicly available due to them containing information that could compromise research.
participant privacy/consent. Requests to access these datasets should be directed to hanyu0920@163.com.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the institutional review board from Tangdu Hospital, XD Group Hospital, and West China Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

**AUTHOR CONTRIBUTIONS**

G-BC and L-FY conceived the study. YH, Z-JW, and W-HL participated in the study design. YH, Z-JW, W-HL, YY, JZ, X-BY, LZ, GX, S-ZW, and L-FY performed the data acquisition. All authors participated in the data interpretation. YH drafted the first version of the report. All authors contributed to the article and approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.811197/full#supplementary-material

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