Magnetic resonance (MR)-based radiomics signature for identification of invisible basal cisterns changes in tuberculous meningitis: a preliminary multicenter study

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Abstract

Objective To develop and evaluate a radiomics signature based on magnetic resonance imaging (MRI) from multicenter datasets for identification of invisible basal cisterns changes in tuberculous meningitis (TBM) patients.

Methods Our retrospective study enrolled 184 TBM patients and 187 non-TBM controls from 3 Chinese hospitals (training dataset, 158 TBM patients and 159 non-TBM controls; testing dataset, 26 TBM patients and 28 non-TBM controls). nnU-Net was used to segment basal cisterns in fluid-attenuated inversion recovery (FLAIR) images. Subsequently, radiomics features were extracted from segmented basal cisterns in FLAIR and T2-weighted (T2W) images. Feature selection was carried out in three steps. Support vector machine (SVM) and logistic regression (LR) classifiers were applied to construct the radiomics signature to directly identify basal cisterns changes in TBM patients. Finally, the diagnostic performance was evaluated by the receiver operating characteristic (ROC) curve analysis, calibration curve, and decision curve analysis (DCA).

Results The segmentation model achieved the mean Dice coefficients of 0.920 and 0.727 in the training and testing datasets, respectively. The SVM model with 7 T2WI-based radiomics features achieved best discrimination capability for basal cisterns changes with an AUC of 0.796 (95% CI, 0.744–0.847) in the training dataset, and an AUC of 0.751 (95% CI, 0.617–0.886) with good calibration in the testing dataset. DCA confirmed its clinical usefulness.

Conclusion The T2WI-based radiomics signature combined with deep learning segmentation could provide a fully automatic, non-invasive tool to identify invisible changes of basal cisterns, which has the potential to assist in the diagnosis of TBM.

Key Points

• The T2WI-based radiomics signature was useful for identifying invisible basal cistern changes in TBM.
• The nnU-Net model achieved acceptable results for the auto-segmentation of basal cisterns.
• Combining radiomics and deep learning segmentation provided an automatic, non-invasive approach to assist in the diagnosis of TBM.

Keywords Magnetic resonance imaging · Tuberculous meningitis · Deep learning · Radiomics
Introduction

Tuberculosis (TB) is still one of the top ten causes of death globally, and before the coronavirus (COVID-19) pandemic, it was the leading cause of death from a single infectious agent [1]. Tuberculous meningitis (TBM) is the most serious form of TB, accounting for about 5–10% of extrapulmonary TB [2]. In the early stage, non-specific prodromal symptoms are typically of insidious onset, and then slowly progress to meningitis, causing enormous difficulty in the early diagnosis and subsequently the treatment of the disease [3]. Even after receiving anti-TB drug treatment, the mortality rate of TBM is still as high as 10.0–36.5% [4]. The clinical outcome mainly depends on the initial stage of treatment. Therefore, early diagnosis and treatment are of great significance for improving the prognosis of TBM patients.

Magnetic resonance imaging (MRI) is the most useful and widely available imaging method for the diagnosis and management of TBM and the affiliated complications [5]. Basal meningeal enhancement is the most consistent neuroradiological findings in TBM [6]. It shows a distinctive tendency to involve the basal cisterns in TBM, especially the suprasellar, prepontine, crural, and ambient cisterns [7]. However, the imaging finding can hardly be detected by conventional radiological examinations before advanced stages [8]. In a previous study, basal cisterns were used as region of interest (ROI) to quantitatively measure the destruction of blood-brain barriers in TBM through dynamic contrast-enhanced MR perfusion. However, in cases with low levels of blood-brain barrier disruption and minor inflammatory changes that occur in early stages, the role of dynamic contrast-enhanced MR perfusion was limited [9]. Therefore, it is still difficult to detect intracranial lesions timely, especially the invisible pathological changes of basal cisterns, which are closely associated with poor outcomes.

As a quantitative analysis approach, radiomics can convert image data of ROI into high-resolution, discoverable feature space data using automated data characterization algorithms, and finally achieves deeper analysis and application of information [10]. It has been widely used in oncologic imaging, including differential diagnosis, tumor staging, genotyping, treatment response, and patient survival prediction [11–13]. It is worth mentioning that due to the qualitative and quantitative problems in the conventional imaging diagnosis of non-neoplastic lesions, radiomics researches of non-neoplastic diseases also have important clinical value. For instance, Kassner et al demonstrated that texture analysis may identify acute ischemic stroke patients who are most likely to undergo hemorrhagic transformation with a greater accuracy than visual inspection of gadolinium enhancement [14]. Using the venous sinuses and basal cisterns as ROIs, Arnold et al achieved a high diagnostic accuracy in separating spontaneous intracranial hypotension patients and healthy controls with a fully automatic algorithm. And least axis length and volume were the best discriminating radiomics features in the suprasellar cistern [15].

To extract features from images, ROIs should be delineated first. Convolutional neural networks have been extensively applied in the medical image segmentation [16, 17]. nnU-Net is a newly proposed model for medical segmentation tasks [18], and its core design idea is to obtain more reliable segmentation results for various datasets through adaptive preprocessing and model training strategies, rather than manual parameter tuning [18, 19]. Owing to its unique advantages, it has been broadly utilized in medical image segmentation, such as coronavirus disease 2019 segmentation [20], kidney and kidney tumor segmentation [21], and breast and fibroglandular tissue segmentation [22]. Until now, no relevant research has been conducted to apply nnU-Net for the segmentation of basal cisterns.

Therefore, the present study first aimed to assess the application of nnU-Net for automatic segmentation of basal cisterns. Then, radiomics features were extracted from nnU-Net segment-ed ROIs and a radiomics signature was constructed to explore changes of basal cisterns in TBM patients, which might be undetectable by the naked eye on conventional MR images.

Materials and methods

Patients and MR acquisition

The retrospective study was approved by the institutional review board in all participating centers, and the requirement for written informed consent was waived. Patients with TBM were...
enrolled from 3 Chinese hospitals, which consisted of the Shanghai Public Health Clinical Center (SPHCC; Shanghai, China), Guangxi Zhuang Autonomous Region Chest Hospital (GZAR-CH; Liuzhou, China), and Liuzhou People’s Hospital (LPH; Liuzhou, China) from January 2015 to December 2020. The inclusion criteria were as follows: (1) patients who were diagnosed with definite or probable TBM according to Marais et al.’s criteria [5] and (2) patients with no definite lesions in conventional cranial MR images on admission. The exclusion criteria were as follows: (1) patients who were co-infected with other pathogens in the central nervous system; (2) patients with poor-quality MR images; and (3) patients who underwent cranial surgery or chemo-radiotherapy. The control group consisted of patients admitted in the same period with normal cranial MRI and no final clinical diagnosis involving TB infection. A total of 184 TBM patients and 187 age- and gender-matched non-TBM controls were included. The dataset was divided into training dataset (n = 317 [SPHCC (61 TBM patients + 69 non-TBM controls); GZAR-CH (97 TBM patients + 90 non-TBM controls)]) and testing dataset (n = 54 [LPH (26 TBM patients + 28 non-TBM controls)]). The study flowchart is shown in Fig. 1.

All patients received conventional cranial MRI via different 1.5-T scanners. We only retrieved T2-weighted (T2W)
and FLAIR images from the picture archiving and communication system. The detailed parameters of three scanners and the MRI protocols are summarized in Table 1.

### Basal cisterns segmentation

The basal cisterns were defined as ROI, including the suprasellar cistern, crural cisterns, ambient cisterns, quadrigeminal corpus cisterns, prepontine cisterns, and sylvian cisterns (Fig. 2). Manual segmentation was performed by a radiologist with 2 years of experience in neuroradiology, and the results were confirmed by another radiologist with 28 years of experience in neuroradiology using an open-source ITK-SNAP software version 3.6.0 (www.itksnap.org). The ROIs were delineated on each slice of the FLAIR images containing basal cisterns, using the corresponding T2W images as visual guidance.

To implement a fully automatic radiomics pipeline, nnUNet was used to train a segmentation model. We utilized the two-dimensional nnUNet [18], which is based on U-Net architecture [23], and provided as part of nnUNet for the automated design of medical segmentation models. The input image size was set to 320 × 320 with a batch size of 32. A total of 6 down-sampling operations were performed. Leaky rectified linear unit was used as activation function, and instance normalization was employed for feature map normalization. The loss function was the sum of Dice loss and cross-entropy loss. Stochastic gradient descent with an initial learning rate of 0.01 was used for training. Five-fold cross-validation was utilized to avoid overfitting. T2W images were resampled with FLAIR images as a reference, and the resample method was sitkBSpline. Finally, automatically segmented ROIs were employed to extract radiomics features.

### Feature extraction

Radiomics features were extracted from segmented ROIs in FLAIR images and T2W images which aligned to FLAIR images (normalized to the range of [0, 100]). The pixel-voxel resampling method was sitkBSpline. For Laplacian of Gaussian (LoG) filters, $\lambda = 5.0$ was used. For texture feature extraction, a fixed bin width 5 was used. In our study, the

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**Table 1** Cranial MRI protocols of different scanners in three hospitals

| Hospital   | MRI model       | Sequence | TR/TE (ms) | FOV (mm) | Matrix (mm) | Slice thickness (mm) |
|------------|-----------------|----------|------------|----------|-------------|----------------------|
| GZAR-CH    | Siemens Avanto 1.5 T | T2W      | 4000/89    | 240      | 384*241     | 5                    |
|            |                  | FLAIR    | 6000/92    | 240      | 384*224     | 5                    |
| SPHCC      | Philips Achieva 1.5 T | T2W      | 4000/110   | 240      | 256*256     | 5                    |
|            |                  | FLAIR    | 6000/120   | 240      | 256*256     | 5                    |
| LPH        | GE HD 1.5 T      | T2W      | 3000/105   | 240      | 320*224     | 6                    |
|            |                  | FLAIR    | 8400/145   | 240      | 320*192     | 6                    |

*FLAIR* fluid attenuated inversion recovery, *FOV* field of view, GZAR-CH Guangxi Zhuang Autonomous Region Chest Hospital, LPH Liuzhou People’s Hospital, SPHCC Shanghai Public Health Clinical Center, *TE* echo time, *TR* repetition time, *T2W* T2-weighted

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![Fig. 2](image-url) Placement of the basal cisterns as ROIs on axial FLAIR images. Red color denotes the prepontine cistern (a). Orange, yellow, blue, green, and purple colors denote the suprasellar cistern, crural cisterns, ambient cisterns, quadrigeminal cistern, and sylvian cisterns, respectively (b). ROI, region of interest; FLAIR, fluid-attenuated inversion recovery
following features were extracted: (1) shape-based features; (2) first-order features; (3) texture features: gray-level co-occurrence matrix (GLCM), gray-level dependence matrix (GLDM), gray-level run length matrix (GLRLM), gray-level size zone matrix (GLSZM), and neighboring gray tone difference matrix (NGTDM). We used the up-sampling to balance positive and negative samples in the training dataset. All features were normalized to the range of $[-0.5, 0.5]$ before further use.

**Feature selection and radiomics signature development**

To reduce overfitting or bias in the radiomics features, three steps were considered for feature selection. Firstly, the independent-sample $t$ test was used for preliminary feature screening, and the features without significant difference between the TBM and non-TBM groups in the training dataset were removed. Secondly, the Pearson correction coefficient (PCC) analysis was employed to eliminate redundancy and to maintain independency among the features. One of the features with a high correlation (PCC > 0.90) was removed. The final step for feature selection was bound with the model building, as described below.

Support vector machine (SVM) and logistic regression (LR) were used to construct the radiomics signature, and their combinations with two feature selection algorithms, namely recursive feature elimination (RFE) and relief, were explored. For each combination, we built the model using five-fold cross-validation on the training dataset. To determine the number of features retained in the final model, the number of features was iterated from 1 to 30 using either RFE or relief, and the averaged cross-validation AUC values were plotted against the number of features. Then, the 1-SE rule was used to find the best number of features in the model; that is, the model with the smallest number of features and a cross-validation AUC within one standard error from the highest AUC was chosen as the best model.

The above-mentioned processes were undertaken using an open-source free software, Feature Explorer version 0.5.0 [24], which used PyRadiomics version 3.0 [25] and scikit-learn version 0.22.2 in the back for feature extraction and subsequent signature developing.

**Validation of the radiomics signature**

To evaluate the discrimination competence of the radiomics signatures, the receiver operating characteristic (ROC) curve was plotted to obtain the values of AUC in the training and testing datasets. The specificity, sensitivity, and accuracy were also calculated using a threshold value maximizing Youden index on the training and testing datasets. DeLong’s test was used to compare different AUCs of radiomics signatures. Subsequently, the calibration curve was plotted to evaluate the calibration ability. Decision curve analysis (DCA) was employed to estimate the clinical usefulness of the radiomics signatures.

**Statistical analysis**

The statistical analyses were performed with the SPSS 22.0 software, R software version 3.6.3, and SciPy version 1.7.0 or scikit-learn version 0.24.2 on Python version 3.7.1. Features were compared by the independent-sample $t$ test or the Mann-Whitney $U$ test. In statistical tests of characteristics of patients, the Mann-Whitney $U$ test was used for numerical variables, and the chi-square test or Fisher’s exact test was used for categorical variables. $p < 0.05$ indicated a statistical significance.

**Results**

**Patient characteristics**

In this study, there were 184 patients in the TBM group (male (129) vs. female (55); mean age, 39.57 ± 16.26 years old) and 187 individuals in the non-TBM group (male (121) vs. female (66); mean age, 39.75 ± 13.97 years old). The clinical characteristics of the patients are given in Table 2.

**nnU-Net-based segmentation performance**

The mean Dice coefficient and the 95-percentile of the average symmetric Hausdorff distance were used to evaluate the segmentation model. The mean Dice coefficient was 0.920 in the training dataset and 0.727 in the testing dataset. The Hausdorff distance values of the segmentation were 0.216 and 1.449 in the training and testing datasets, respectively. The results of manual and automatic segmentation are shown in Fig. 3.

**Radiomics feature selection and radiomics signature developing**

A total of 200 features were extracted from the automatically segmented basal cisterns in T2W and FLAIR images, respectively. We initially used the independent-sample $t$ test to remove features whose distributions in the TBM and non-TBM groups exhibited no significant difference. The remaining features were used in further signature developing, where PCC analysis was employed for dimensionality reduction and RFE or relief for feature selection. In total, 7 T2W features were retained in the SVM model (linear kernel with C-parameter = 1.0), and 13 FLAIR features were retained in the LR model (Table 3).
Performance and validation of the radiomics signature

The results of the two radiomics signatures are shown in Fig. 4 and Table 4. Using 7 selected optimal features, the T2WI–based radiomics signature derived from the SVM classifier achieved an AUC of 0.796 (95% CI, 0.744–0.847) in the training dataset, and was then confirmed in the testing dataset with an AUC of 0.751 (95% CI, 0.617–0.886), the result of which showed a better performance compared with that of the FLAIR–based radiomics signature in the testing dataset (AUC = 0.676; 95% CI, 0.529–0.823). However, DeLong’s test showed no significant difference between the above two radiomics signatures (p = 0.152).

In the training datasets, the calibration curves of the two radiomics signatures demonstrated good agreement between prediction and observation (Fig. 5a, c). In the testing datasets, the calibration curve of the T2WI–based radiomics signature exhibited better consistency than that of the FLAIR–based radiomics signature, with a mean absolute error of 0.033 and 0.047, respectively (Fig. 5b, d). The DCA is depicted in Fig. 6. The curve analysis showed that T2WI–based and FLAIR–based radiomics signature offered certain high overall net benefits, while the performance of T2WI–based was better.

Discussion

In the present study, we first proposed a nnU-Net–based deep learning network for the segmentation of basal cisterns in a multicenter dataset. The mean Dice coefficient in the testing dataset was 0.727, indicating that the segmentation model achieved acceptable results for the basal cistern segmentation. Then, we developed a radiomics signature based on the
segmentation of basal cisterns by nnU-Net using the same dataset. The T2WI–based radiomics signature developed using the SVM classifier showed a certain diagnostic significance for TBM, which might be unnoticeable by the naked eye on conventional MR images. Therefore, automatic segmentation of basal cisterns and the developed radiomics signature might provide supplemental data to assist in the diagnosis of TBM in a fully automatic manner, before the appearance of lesions with visible characteristics.

The pathology of TBM was found to be primarily caused by the host inflammatory response [26]. During the dissemination of Mycobacteria to the brain, some pro- and anti-inflammatory cytokines are induced [27]. Subsequently, granulomatous inflammation occurs in the subarachnoid space,
mainly influencing the basal cisterns [28]. Besides, inflamma-
tory exudates in basal cisterns can block the flow of cerebro-
spinal fluid (CSF), leading to hydrocephalus [28], and can also
cause vasospasm and compression or strangulation of vessels
[29]. Thus, basal meningeal enhancement is the primary ra-
diologic feature of TBM, reflecting microabscess and intense
inflammation of basal meninges. In our study, we used
radiomics analysis to compare the deep image information
of basal cisterns between the TBM and non-TBM groups.
The results showed that there were certain differences between
the two groups that could not be observed by the naked eye,
which were significant to suggest the possibility of TBM.

To reduce the operator-dependent segmentation deviation
and improve the work efficiency, an automatic segmentation
model of basal cisterns was established using nnU-Net in the
present study. It exhibited a high performance in the segmen-
tation of basal cisterns in FLAIR images, as well as an accept-
able capability to generalize by an external testing dataset.
In addition, the automatic segmentation of basal cisterns should
not be limited to the stage without lesions. The segmentation
at different stages of TBM is also valuable for the assessment

Table 3  Coefficients of features in the radiomics signatures

| Features                                      | Coefficients |
|----------------------------------------------|--------------|
| T2W                                          |              |
| Original_firstorder_10Percentile             | 3.252        |
| Shape_MajorAxisLength                        | 2.258        |
| Shape_SurfaceVolumeRatio                     | −1.941       |
| LoG-sigma-5-0-mm-3D_glszm_LowGrayLevelZoneEmphasis | −1.919       |
| LoG-sigma-5-0-mm-3D_firstorder_Skewness      | 1.904        |
| LoG-sigma-5-0-mm-3D_glcmi_ClusterShade       | 0.748        |
| Shape_MinorAxisLength                        | 0.302        |
| Shape_SurfaceVolumeRatio                     | −0.957       |
| FLAIR                                        |              |
| LoG-sigma-5-0-mm-3D_glrIm_GrayLevelNonUniformity | 0.835      |
| Shape_MeshVolume                             | −0.747       |
| LoG-sigma-5-0-mm-3D_glszm_SizeZoneNonUniformityNormalized | 0.589      |
| Original_glszm_SizeZoneNonUniformity         | 0.523        |
| LoG-sigma-5-0-mm-3D_gldm_SmallDependenceEmphasis | 0.450      |
| Original_firstorder_TotalEnergy              | 0.416        |
| LoG-sigma-5-0-mm-3D_gldm_DependenceNonUniformity | 0.383      |
| LoG-sigma-5-0-mm-3D_glszm_GrayLevelNonUniformity | −0.381     |
| Shape_MajorAxisLength                        | 0.369        |
| LoG-sigma-5-0-mm-3D_glszm_SizeZoneNonUniformity | 0.291  |
| LoG-sigma-5-0-mm-3D_firstorder_TotalEnergy   | −0.263       |
| Shape_Maximum2DDiameterColumn                | −0.037       |

FLAIR fluid-attenuated inversion recovery, T2W T2-weighted

Fig. 4 ROC curves for T2WI–based radiomics signature (a) and
FLAIR–based radiomics signature (b) in the training and testing
datasets, respectively. In the testing dataset, the AUC of the
T2WI–based radiomics signature reached 0.751, and the AUC of
the FLAIR–based radiomics signature reached 0.676. AUC, area
under the curve; FLAIR, fluid-attenuated inversion recovery;
ROC, receiver operating characteristic; T2WI, T2–weighted
imaging
Further studies are therefore required to improve the quality of pixel-level segmentation and spatial-level detection.

The high-throughput extraction of large amounts of features from radiographic images possesses the advantages of objectivity, comprehensiveness, and repeatability, which may be significant for prediction of clinical results [10]. The selection of more features is associated with a higher dimensionality of input data, and the likelihood of overfitting consequently increases, resulting in a lower classification accuracy [30]. Our radiomics signature using the SVM classifier exhibited the best discrimination capability after

| Table 4 Performance of the radiomics signatures |
|------------------------------------------------|
| Metrics (95% CI) | T2WI–based | FLAIR–based |
| Training dataset |          |            |
| AUC              | 0.796 (0.744–0.847) | 0.806 (0.759–0.853) |
| Accuracy         | 0.748 (0.710–0.804) | 0.735 (0.700–0.795) |
| Sensitivity      | 0.829 (0.642–0.881) | 0.797 (0.582–0.925) |
| Specificity      | 0.667 (0.621–0.855) | 0.673 (0.546–0.875) |
| Testing dataset  |          |            |
| AUC              | 0.751 (0.617–0.886) | 0.676 (0.529–0.823) |
| Accuracy         | 0.741 (0.648–0.870) | 0.648 (0.574–0.815) |
| Sensitivity      | 0.731 (0.429–0.960) | 0.808 (0.233–0.950) |
| Specificity      | 0.750 (0.514–1.000) | 0.500 (0.435–1.000) |

AUC area under the curve, CI confidence interval, FLAIR fluid-attenuated inversion recovery, T2WI T2-weighted imaging

Fig. 5 Calibration curves for T2WI–based radiomics signature (a, b) and FLAIR–based radiomics signature (c, d) in the training and testing datasets, respectively. FLAIR, fluid-attenuated inversion recovery; T2WI, T2-weighted imaging
In the current study, we attempted to perform manual and automatic segmentation of basal cisterns on FLAIR images. FLAIR sequences can better display lesions on the brain surface, the semi-oval area, and the brain–CSF junction area by suppressing the signal intensity of CSF. In TBM, sulcal hyperintensity in basal cisterns can be observed on FLAIR images, which could be related to CSF protein concentration and effective echo time [33]. Therefore, FLAIR images assist clinicians to indicate whether there were lesions in the basal cisterns of TBM patients, and to reduce the interference of CSF and vascular signals during segmentation. However, the results showed that the radiomics signature developed based on T2W images had a greater diagnostic performance compared with the signature developed based on FLAIR images. This might be due to the circulatory disturbance of the CSF protein concentration in basal cisterns and the involvement of local cerebrovascular dysfunction during TBM; T2W images, which were sensitive to water in the tissue, were more suitable for radiomics feature extraction and signature construction.

There are some limitations to this study. First, this retrospective study involved only a single infectious agent, and its practical performance in the real clinical scenario needs to be verified by prospective study. In addition, the inclusion of other central nervous system infectious diseases for multi-classification research will help to improve the diagnostic system. Second, owing to the low sensitivity of etiological examination as the gold standard, we used a diagnostic scoring system to enroll TBM patients. Some subjective factors in the scoring system may also cause false-positive results. We could not completely eliminate the influence of such situation on the results. Finally, although we have used automatic segmentation based on nnU-Net to improve the reproducibility of the model, we should compare the influence of different harmonization schemes on the generalization of the model in large-scale multi-institutional studies.

In conclusion, our study proposed a fully automatic deep learning–based radiomics pipeline to identify invisible changes of basal cisterns in TBM. This strategy can warn radiologists about the elevated probability of occurrence of TBM and help improve its diagnosis.

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**Declarations**

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**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.
Statistics and biometry  No complex statistical methods were necessary for this paper.

Informed consent  Written informed consent was waived by the Institutional Review Board.

Ethical approval  Institutional Review Board approval was obtained.

Methodology  
- retrospective
- diagnostic or prognostic study
- multicenter study

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