Clinical-MRI Radiomics Enables the Prediction of Preoperative Cerebral Spinal Fluid Dissemination in Children With Medulloblastoma

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Research

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Abstract

**Background:** Medulloblastoma (MB) is the most common pediatric embryonal tumor. Accurate identification of cerebral spinal fluid (CSF) dissemination is important in prognosis prediction. Both MRI of the central nervous system (CNS) and CSF cytology will appear false positive and negative. Our objective was to investigate the added value of enhanced T1 weighted images-based radiomics features to clinical characteristics in predicting preoperative CSF dissemination for children with MB.

**Materials and Methods:** This retrospective study included 84 children with histopathologically confirmed MB (60 children in the training cohort and 24 children in the validation cohort). The children with normal head and spine magnetic resonance images (MRI) and no subsequent dissemination in one year were diagnosed as non-CSF dissemination. The CSF dissemination was manifested as intra-cranial or -spinal nodular enhanced lesions. Clinical features and conventional MRI features were collected and evaluated. A total of 385 radiomics features were extracted from enhanced T1 weighted images. Minimum redundancy, maximum correlation and least absolute shrinkage and selection operator were performed to select the features with the best performance in predicting preoperative CSF dissemination. A combined clinical-MRI radiomics prediction model was developed using multivariable logistic regression. Receiver operating curve analysis was used to validate the predictive performance. Nomogram and decision curve analysis (DCA) were developed to evaluate the clinical utility of combined model.

**Results:** Thirty-one children were confirmed to have preoperative CSF dissemination. One clinical and nine radiomics features were selected for predicting preoperative CSF dissemination. The combined model incorporating clinical and radiomics features had best predictive performance both in the training and validation cohorts. In the validation cohort, a threshold of 0.311 yielded an area under the curve of 0.87, a sensitivity of 77.8%, a specificity of 86.7%, and an accuracy of 83.3%. The clinical utility of the model was confirmed by a clinical-MRI radiomics nomogram and DCA.

**Conclusions:** The combined model incorporating clinical, conventional MRI and radiomics features could be applied to predict preoperative CSF dissemination for children with MB as a noninvasive biomarker, which could aid in risk evaluation.

**Background**

Medulloblastoma (MB) is the most common embryonal tumor located in the posterior cranial fossa. It usually affects young children before the age of 9 years [1]. Approximately 30% of children with newly diagnosed MB have cerebral spinal fluid (CSF) dissemination with either magnetic resonance imaging (MRI) suggestive of disseminative nodules or CSF cytological demonstrated tumor cells [2].

At present, the standard treatment for MB is maximum resection followed by risk-adapted adjuvant chemoradiotherapy. Depending on the absence or presence of adverse prognostic factors including age younger than 3 years, anaplastic histopathologic subtype, CSF dissemination and residual tumor greater than 1.5 cm in diameter, the child with MB will be stratified into an average or high risk group [3]. The 2016 World Health Organization classification of tumors of the central nervous system (CNS) grades MB by its molecular profiling, which has a more reliable performance in stratifying the risk of MB and guiding clinical treatment strategies [4].
Although the advances regarding the molecular characteristics of MB could aid risk stratification, accurate identification of CSF dissemination remains important in prognosis prediction.

Both MRI of the CNS and CSF cytology will appear false positive and negative. On one hand, MRI of the CNS is not able to detect early dissemination, while on the other hand, the equivocal findings such as enhanced meningeal thickening and nerve roots clumping may be misdiagnosed as dissemination [5, 6]. Because of technical or sampling problems, CSF cytology may fail to detect the tumor cells. Multiple CSF sampling may improve the diagnostic accuracy, but at the cost of additional discomfort to children as more lumbar punctures would be required [7]. Therefore, establishing a noninvasive biomarker for predicting CSF dissemination will be of great significance.

MRI is the modality of choice for risk stratification in children with MB. It can provide more information than conventional MRI features evaluated by radiologists, because images are not data mined [8].

Radiomics is an approach that is able to extract high-throughput quantitative features from medical images [9]. In theory, radiomics features are able to reflect biological characteristics of the tumor, and could aide in differential diagnosis, and prognosis and distant metastasis prediction, among others [10-12]. In this present study, we investigated the added value of enhanced T1 weighted images-based radiomics to clinical characteristics in predicting preoperative CSF dissemination for children with MB.

**Materials And Methods**

**Patients**

This retrospective study was approved by the Institutional Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (ethics approval number: XHEC-D-2020-136), and therefore, informed consent was waived. Children (139 in total) with pathologically confirmed MB were reviewed between November 2006 and November 2018.

The inclusion criteria included: (i) availability of preoperative head MRI with diagnostic-quality; (ii) availability of spine MRI with diagnostic-quality performed pre- or postoperative but before adjuvant therapy; (iii) children without CSF dissemination confirmed by head and spine MRI required follow-up results for one-year; and (iv) without any previous treatment. The exclusion criteria included: (i) insufficient head and spine MRI quality; (ii) without one-year follow-up results for children without CSF dissemination; (iii) previous treatment; and (iv) equivocal findings on spine MRI such as enhanced meningeal thickening and nerve roots clumping.

Clinical features, including age, gender and histopathologic subtype (classic, desmoplastic-nodular, MB with extensive nodularity and large cell/anaplastic) of all children with MB were collected via medical records.

The workflow of this retrospective study is displayed in Fig. 1.

**Imaging acquisition**

All of the children underwent preoperative contrast-enhanced head MRI using a 3.0-T MRI scanner (Signal HDxt, GE Healthcare, Boston, MA, USA) with an 8-channel head coil. The contrast-enhanced T1 weighted images were obtained with a slice thickness of 4 mm and a matrix of 512 × 512. Children also underwent contrast-enhanced
spine MRI, which was given either preoperative or postoperative but before adjuvant therapy. Axial and sagittal enhanced T1 weighted images were obtained with a thickness of 3 mm and gap of 0 mm. The detailed parameters for head and spine MRI are provided in Appendix E1 and E2.

The contrast material was administrated with a dose of 0.1 mmol/kg (Gadopentetate Dimeglumine, Beilu, Beijing, China). Children that were unable to remain motionless during the MRI examination were sedated with chloral hydrate (0.5 mg/kg).

**Qualitative image evaluation**

All of the head and spine MR images were reviewed by two pediatric radiologists (H.Z and J.N.L, with 9 and 12 years of experience, respectively, in pediatric neuroradiology). Discrepancies were resolved by consulting with a third pediatric neuroradiologist (Y.H.L) with 30 years of experience. A set of conventional MRI features were evaluated, including the location of the tumor, contrast enhancement pattern, intratumoral necrosis, hemorrhage, calcification, peritumoral edema and the minimal apparent diffusion coefficient (minADC) value. A description for these features is provided in Appendix E3.

The enhanced head and spine MR images were used for CSF dissemination assessment. Children with normal head and spine MR images and no subsequent dissemination at the one year follow-up were regarded as the non-CSF dissemination group. CSF dissemination was manifested as intra-cranial or -spinal nodular lesions and leptomeningeal enhancement. Children with equivocal findings on head and spine MR images were excluded.

**Image segmentation and Radiomics feature extraction**

The delineation of MB and radiomics extraction is shown in Fig. 2. One radiologist (H.Z with 9 years of experience in pediatric neuroradiology) determined the volume of interest (VOI) of the tumor on contrast enhanced T1 weighted images using software package ITK-SNAP ([www.itksnap.org](http://www.itksnap.org)). The peritumoral edema and surrounding vessels was carefully avoided. The segmentations were examined by another pediatric neuroradiologist (M.L with 20 years of experience). Both were blinded to the CSF dissemination status.

By using an in-house software Analysis Kit (GE healthcare), a total of 385 radiomics features were extracted automatically from the VOI including histogram parameters, volume and shape parameters, Haralick features, gray-level co-occurrence parameters and gray-level run-length matrix parameters.

**Features selection, prediction model building and validation**

Eighty-four children were randomly distributed to the training and validation cohorts according to a 7:3 ratio. Differences in clinical and conventional MR imaging characteristics between the children with and without CSF dissemination in the training and validation cohorts were assessed. A clinical prediction model was built using the features with significant differences.

In the training cohort, minimum redundancy and maximum correlation (mRMR) and least absolute shrinkage and selection operator (LASSO) were performed to reduce dimension and select the radiomics features with the strongest CSF dissemination related correlation. The radiomics score (rad-score) of each child with MB was calculated by adding all of the products of the selected features and their corresponding coefficients, after which a radiomics prediction model was built. A combined clinical-radiomics prediction model was developed using
multivariable logistic regression, which incorporated selected clinical- and rad-scores. A clinical-radiomics nomogram was then constructed in the training cohort.

The receiver operating characteristic (ROC) curves were used to evaluate the predictive performance of the clinical, radiomics and combined models in both the training and validation cohorts. The area under the curves (AUC), sensitivities, specificities, negative predictive values (NPV), positive predictive values (PPV) and accuracy were calculated. After, the Hosmer-Lemeshow test was performed to assess the goodness-of-fit of the combined model. Decision curve analysis (DCA) was implemented to determine the clinical usefulness of the prediction models in the training and validation cohorts at different threshold probability.

Statistical analysis

The differences of clinical and conventional MRI characteristics between the training and validation cohorts, as well as between children with and without CSF dissemination in their respective cohorts were evaluated using independent t tests or Chi-squared tests according to the type of the data. The optimal values of the ROCs were determined using Youden's index. Delong’s test was used to assess the differences in the AUC values between the clinical and clinical-radiomics combined models.

All statistical analyses were performed using the R software package (version 3.4.2, http://www.Rproject.org). The ROC curves were performed using the “pROC” package. Multivariate logistic regression was plotted with the “rms” package. The Hosmer-Lemeshow test was conducted using the “Resource Selection” package. DCA was developed with the function of “dca.R”. \(P < 0.05\) was set as statistical significance.

Results

Clinical features of the children

According to the inclusion criteria, a total of 84 children with MB were recruited in this study. None of the children experience extra-CNS metastases. Thirty-one children (36.9%) were confirmed to have CSF dissemination by head and spine MRI evaluation. Four children had only intracranial dissemination while 27 children had both intracranial and intraspinal dissemination. Fifty-three children without CSF dissemination were identified by MRI evaluation and follow up information.

The clinical features of the children in the training and validation cohorts are displayed in Table 1. There were no significant differences between the two cohorts in terms of clinical features except for histopathological subtype. In the training cohort, children were significantly younger \((P=0.028)\) in the CSF dissemination group than in the non-CSF dissemination group.

Feature selection, prediction model building and validation

In the training cohort, nine radiomics features with the strongest CSF dissemination features were selected using mRMR and LASSO (Fig. 3). The rad-score was calculated using the following formula:

\[
\text{Rad-score} = -0.557 \times \text{Kurtosis} \\
-0.502 \times \text{ShortRunHighGreyLevelEmphasis_AllDirection_offset7_SD}
\]
\[-0.538 \times \text{ClusterShade\_AllDirection\_offset7\_SD}\]
\[-0.444 \times \text{RunLengthNonuniformity\_angle0\_offset1}\]
\[-0.909 \times \text{Inertia\_angle45\_offset1}\]
\[-0.248 \times \text{Inertia\_angle0\_offset4}\]
\[-0.026 \times \text{RunLengthNonuniformity\_AllDirection\_offset1}\]
\[-0.204 \times \text{GLCMEntropy\_angle135\_offset7}\]
\[-0.17 \times \text{Intensity/Variability} – 0.735\]

The combined clinical-radiomics prediction model was developed using multivariate logistic regression analysis. The nomogram was built with age and Rad-score in the training cohort (Fig.4). The AUC of the value of the combined model was 0.89. When the threshold valued 0.311, the sensitivity, specificity, NPV, PPV and accuracy were 90.9% (20/22), 76.3% (29/38), 93.5% (29/31), 69.0% (20/29) and 81.7% (49/60), respectively. The AUC of the clinical model was much lower (0.67), which indicated that radiomics features could improve performance.

The CSF dissemination predictive performance of combined prediction model was also robust when applied to the validation cohort. The AUC was 0.87 and the sensitivity, specificity, NPV, PPV, and accuracy were 77.8% (7/9), 86.7% (13/15), 86.7% (13/15), 77.8% (7/9) and 83.3% (20/24), respectively. The ROCs are shown in Fig. 5. The Hosmer-Lemeshow test demonstrated that the goodness-of-fit of the combined model was high in both the training and validation cohorts (Fig. 6A and 6B). DCA revealed that at every threshold probability, it was more beneficial using the combined model than the clinical model alone (Fig. 6C).

**Discussion**

In the present study, we developed and validated a clinical-radiomics combined model for preoperative prediction of CSF dissemination in children with MB. The nomogram combined the age of the children and an enhanced T1-weighted images based radiomics signature. The results demonstrated that compared with the prediction model built using clinical features alone, the radiomics signature could improve the predictive performance of CSF dissemination. The AUC was increased from 0.67 to 0.89 in the training group. The sensitivity, specificity, NPV and PPV were relatively higher both in the training and validation cohorts. The higher sensitivity indicated that the combined model could identify children with CSF dissemination accurately. These children should undergo examinations with higher specificity, such as CNS MRI and CSF cytology to evaluate the dissemination staging.

Children with CNS dissemination should be given aggressive therapy, as prognosis is usually poor, no matter the molecular subtype. It is, therefore, paramount to establish a method to accurately diagnose CNS dissemination. Traditionally, diagnosis of CSF dissemination encompassed comprehensively analyzing the combined results of CNS MRI and CSF cytology [13, 14], both of which may over- or underestimate the CSF dissemination. On one hand, overestimation leads to higher risk stratification and unnecessarily high radiotherapy doses, which could affect the quality of life of children with MB. On the other hand, underestimation leads to lower risk stratification and lower radiotherapy doses, which could increase the possibility of tumor recurrence and decrease survival. Identification of tumor cells by CSF cytology is an important element of the diagnosis of CSF dissemination.
However, a negative result must be viewed with caution due to high rates of technique and sampling errors [15]. Multiple lumbar punctures may improve tumor cells detection, but causes increased pain to children and also delays corresponding adjuvant treatment.

In this retrospective study, CSF cytology results of several children were not obtained. Therefore, the diagnosis of CSF dissemination depended on head and spine MRI. Children without CSF dissemination were identified by negative head and spine MRI and outcome at the one-year follow up. This diagnosis strategy is consistent with the literature determining the status of CSF dissemination by using overall survival [6]. The equivocal findings in spine MRI such as linear enhancement, clumping and enhancement of nerve roots can be misdiagnosed as CSF dissemination, all of which can be identified in preoperative MRI. Therefore, extreme care is needed and close follow-up is required to confirm any initial diagnosis.

Radiomics can evaluate the intratumoral heterogeneity and predict prognosis by extracting high throughput quantified features using medical images. A previous study, indicated that when the prediction accuracy of the radiomics signature was constructed by using 24 radiomics features from preoperative computerized tomography images for lymph nodes metastasis in patients with colorectal cancer, the concordance index was 0.773 [16]. In another study, when the radiomics signature was constructed using T2-weighted images the prediction accuracy was improved compared with a model built only using clinical features for synchronous distant metastasis in patients with rectal cancer, where the (AUC) for the combined model and clinical model was 0.827 and 0.779, respectively [12].

In CNS tumors, radiomics is mainly applied to differential diagnosis of tumors, World Health Organization grading, molecular profiling and prognosis prediction in the adult population [17-20]. However, for pediatric MB, research is focused on differential diagnosis of tumors in the posterior cranial fossa and in molecular subtype prediction [21, 22]. Therefore, it is worth exploring an imaging biomarker to detect CSF dissemination based on the MRI radiomics features of pediatric MB.

According to previous reports, the CSF dissemination probability of medulloblastoma has close relationship to molecular subgroups. For example, the prognosis of children with group 3 is very poor and prone to early metastasis [23]. Some MRI features of MB are reliable to predict molecular subgroups, especially their location and degree of enhancement. Group 3 tumors are mainly located in the midline of posterior cranial fossa with strong enhancement, whereas group 4 tumors, although also located at the midline, show minimal enhancement [24]. These imaging features are able to be assessed on enhanced T1 weighted images, and as such, we chose to use this type of enhancement to extract radiomics features.

In the present study, the results demonstrated the added value of radiomics to clinical and conventional MRI characteristics in predicting CSF dissemination for pediatric MB. The higher sensitivity and accuracy of the combined model compared with clinical model alone is encouraging. It is likely that the probability of CSF dissemination could be calculated using the proposed combined model nomogram.

The CSF dissemination prediction model included the clinical variable of age, as group 3 tumors are prone to occur in younger children and infants [25]. Regarding to radiomics features, most of the selected features used to determine the rad-score were texture features. This is consistent with the better performance of texture features compared with first order features in tumor prognosis prediction, as these features may reflect intratumoral heterogeneity [26].
There are several limitations to the current study. First, due to the small sample size of the cohort, useful conventional MRI features for the predictive model could not be used because of selective bias. The association between conventional MRI features and CSF dissemination in children with MB should be further explored in a large-scale study. Second, an external validation from another institution was not performed. A multi-center research with different MRI scanning protocols is needed to evaluate the generalization of our predictive model. Finally, only enhanced T1 weighted images were used in this radiomics research. Multiparametric MRI such as T2 weighted images or fluid-attenuated inversion recovery (FLAIR) sequences, which are important in predicting molecular subgroups of MB should be integrated into the predictive model to improve its robustness.

Conclusions

In summary, our preliminary study demonstrated an enhanced T1 weighted image-based radiomics approach that was shown to improve the prediction accuracy of CSF dissemination in children with MB. A nomogram constructed based on the radiomics signature and selected clinical features may provide useful information for clinical decision making.

Abbreviations

MB: Medulloblastoma; CSF: Cerebral spinal fluid

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

Dengbin Wang and Yuhua Li conceived the idea and designed the work. Chenqing Wu, Ting Gui, Huanhuan Liu, Ming Liu and Yuzhen Zhang obtained the data and segmented the images. Shaofeng Duan analyzed the data. Jinning Li interpreted the data. Hui Zheng wrote the manuscript. Jinning Li critically revised the manuscript. All authors read and approved the final manuscript. All authors are accountable for the contents of this work.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to hospital policy but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by our Institutional Review Board, with reference XHEC-D-2020-136.
Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Clinical and Conventional MRI Characteristics of Children with MB
| Characteristics                        | Training Cohort (n = 60) |       |       | Validation Cohort (n = 24) |       |       |
|---------------------------------------|-------------------------|-------|-------|---------------------------|-------|-------|
|                                       | Non-dissemination (n = 38) | Dissemination (n = 22) | p value | Non-dissemination (n = 15) | Dissemination (n = 9) | p value |
| Age (mean ± SD, years)                | 6.2 ± 3.5                | 4.3 ± 2.5- | 0.028  | 5.1 ±2.9                  | 3.6 ±1.7 | 0.154  |
| Gender (%)                            |                          |       |       |                           |       |       | 1.000  | 0.597  |
| Male                                  | 26 (68.4)                | 15 (68.2) |       | 7 (46.7)                  | 6 (66.7) |       |
| Female                                | 12 (31.6)                | 7 (31.8)      |       | 8 (53.3)                  | 3 (33.3)   |       |
| Histopathologic subtype (%)           |                          |       |       |                           |       |       | 0.632  | 0.444  |
| Classic                               | 33 (86.8)                | 17 (77.3) |       | 10 (66.7)                 | 8 (88.9)   |       |
| Large cell/anaplastic                 | 1 (2.6)                  | 1 (4.5)      |       | 4 (26.7)                  | 1 (11.1)   |       |
| Desmoplastic-nodule                  | 4 (10.5)                 | 4 (18.2)      |       | 1 (6.7)                   | 0 (0.0)    |       |
| Location (%)                          |                          |       |       |                           |       |       | 1.0000 | 0.507  |
| Midline                               | 34 (89.5)                | 20 (90.9) |       | 15 (100.0)                | 9 (100.0)   |       |
| Nonmidline                            | 4 (10.5)                 | 2 (9.1)       |       | 0 (0.0)                   |       |       |
| Enhancement pattern (%)               |                          |       |       |                           |       |       | 0.4032 | 0.052  |
| Diffuse                               | 23 (60.5)                | 17 (77.3) |       | 8 (53.3)                  | 9 (100.0)   |       |
| Incomplete                            | 10 (26.3)                | 3 (13.6)      |       | 4 (26.7)                  | 0 (0.0)    |       |
| Minimal                               | 5 (13.2)                 | 2 (9.1)       |       | 3 (20.0)                  | 0 (0.0)    |       |
| Necrosis or cyst (%)                  |                          |       |       |                           |       |       | 0.8664 | 0.729  |
| None                                  | 5 (13.2)                 | 2 (9.1)       |       | 1 (6.7)                   | 0 (0.0)    |       |
| Small                                 | 22 (57.9)                | 14 (63.6) |       | 8 (53.3)                  | 5 (55.6)   |       |
| Both                                  | 11 (28.9)                | 6 (27.3)      |       | 6 (40.0)                  | 4 (44.4)   |       |
| minADC (mean ± SD) mm²/s              | 0.4 ± 0.1                | 0.4 ± 0.1      |       | 0.5 ± 0.1                 | 0.4 ± 0.1 | 0.0212 |
Figures

Figure 1

Workflow of this study. CSF = cerebral spinal fluid; MRI = magnetic resonance imaging; mRMR = minimum redundancy and maximum correlation; LASSO = least absolute shrinkage and selection operator.
Figure 2

Workflow of image segmentation and radiomics feature extraction. (I) The left panel shows representative tumor slices. The region of interest was delineated manually slice by slice and then a 3D VOI was generated as shown in the image on the right. (II) Radiomics features were extracted from the VOI including histogram parameters, volume and shape parameters and texture features.
Figure 3

The selected radiomics features. The role of selected features contributing to the developed Rad-score are shown. The selected features are plotted on the y-axis, and their regression coefficients in the LASSO analysis are plotted on the x-axis.
Figure 4

The developed clinical–radiomics nomogram for predicting CSF dissemination.

Figure 5

AUC: 0.89 (0.81 - 0.97)
AUC: 0.67 (0.53 - 0.81)
ROC curves of the traditional feature model and nomogram. (A) The AUC was significantly different (0.67 and 0.89, respectively) between the traditional feature model and the nomogram in the training cohort. (B) The AUC of the nomogram was significantly higher than in the traditional feature model. Delong’s test showed that the differences between the ROC curves of the nomogram and clinical model were significantly different in both the training and validation cohorts. ROC = receiver operating characteristic, AUC = area under curve.

Figure 6

Results of the Hosmer-Lemeshow test. The combined model fit well with the real situation both in the training cohort (A) and in the validation cohort (B). Decision curve analysis demonstrated that the combined model had higher net benefit than the traditional model at every threshold probability (C).
Supplementary Files

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