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# Development and validation of a nomogram and risk stratification system to predict overall survival after surgical repair for pediatric patients with medulloblastoma based on easily accessible variables

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**Abstract. – OBJECTIVE: This study aimed to develop and validate a nomogram and risk stratification system for the overall survival of pediatric patients with medulloblastoma after surgical repair.**

**PATIENTS AND METHODS: In this multicenter, retrospective study, consecutive patients who underwent surgery for medulloblastoma at Shanghai Children's Medical Center and the First Affiliated Hospital of Fujian Medical University from 2010 to 2022 formed the training and external validation datasets, respectively. Univariable and multivariable Cox regression analyses were performed to identify variables associated with mortality in the training dataset. A nomogram prediction model was developed based on independent variables in the multivariable Cox regression analysis to predict the 1-, 3-, and 5-year overall survival. The area under receiver operating characteristic curve (AUC) and calibration curve were used to evaluate the discrimination and calibration of the nomogram. A risk stratification system based on the median risk score was also established to divide patients into two risk groups.**

**RESULTS: In the training dataset, Cox regression analyses identified tumor size, brainstem involvement and chemotherapy as independent predictors for overall survival. The AUC of the nomogram was 0.75 at 1 year, 0. 75 at 3 years, 0.77 at 5 years in the training dataset, 0.74 at 1 year, 0.70 at 3 years, and 0.70 at 5 years in the validation dataset. The calibration curve for the probability of 1-, 3-, and 5-year survival showed good agreement between the nomogram prediction and actual observation in the training and validation datasets. The risk stratification system could perfectly classify patients into two risk groups, and the overall survival in the two groups had a good division.**

**CONCLUSIONS: This low-cost, convenient, and noninvasive nomogram can be translated into clinical practice as a tool for risk stratification and individualized prognosis prediction for children with medulloblastoma.**

*Key Words:*
Medulloblastoma, Pediatric surgery, Central nervous system, Nomogram, Overall survival, Training dataset, Validation dataset.

## Introduction

Medulloblastoma is the most common pediatric malignant tumor in the central nervous system (CNS), originating in the cerebellum and spreading throughout the CNS, which accounts for nearly 20% of all pediatric brain tumors[1,2]. Although advances in surgical techniques,

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perioperative management, radiotherapy and chemotherapy regimens have improved survival in this population, the prognosis remains relatively poor[3]. The 10-year overall survival was about 60%[4]. In addition, many survivors suffer from serious adverse effects of radiotherapy and chemotherapy, including hearing impairment, second cancers, diabetes, hypertension, endocrine deficiencies, and neuro-cognitive impairments[5]. Some patients are over-treated because of the imprecision of current treatments and risk stratification systems. In contrast, others may miss the opportunity of an appropriate therapy, which will affect the overall prognosis[6]. The current consensus is that treatments for medulloblastoma need to be based on risk stratification. Individual responses vary widely, and current therapies fail to recognize patient tumor heterogeneity. Severe side effects of inaccurate treatment indicate the need for a refined therapeutic approach. The most popular classification systems for medulloblastomas are histological and molecular classification schemes. According to the 2016 World Health Organization (WHO)[7] classification of CNS tumors, medulloblastomas are histologically divided into subtypes based on their morphology: classic, medulloblastoma with extensive nodularity, desmoplastic/nodular, and large cell/anaplastic. The clinical risk classification system is based on age and metastasis status at diagnosis, extent of residual disease, and histology[7]. However, studies[7] have found that histopathological classification does not better predict the prognosis, risk stratification and clinical treatment guidance. With the advancement of clinical molecular diagnostic techniques, risk stratification and individualized therapy based on molecular subtypes have emerged. According to the 2016 WHO classification, medulloblastomas are classified into molecular subtypes: two groups attributed to pathogenic mutations in the wingless (WNT) or sonic hedgehog (SHH) pathways, respectively (the WNT and SHH groups), and two groups with undefined molecular characteristics termed as Group 3 and Group 4. SHH group is then classified into TP53-mutant and TP53-wildtype subtypes according to the mutation status of TP53[7]. The molecular risk classification system is based on molecular, clinical, and histopathological characteristics[7]. Some molecular subtypes are associated with pathogenic mechanisms, clinical features, and prognoses. However, the application of molecular classification systems in daily clinical practice is limited because of equipment and personnel requirements. In addition, molecular detection is costly and will increase the financial burden on patients. The lack of medical insurance and the inaccessibility of advanced adjuvant examination impairs the ability to perform molecular stratification systems. Therefore, it is necessary to develop a reliable, simple and cost-effective stratification system that is easy to implement in clinical practice.

A nomogram is a graphical, mathematical presentation of a clinical predictive model through a comprehensive evaluation of outcome-related risk factors to generate a precise individualized prediction for different patients[8]. The nomogram has been widely used as a prognosis-predictive tool in oncology in recent years[9]. However, the current nomograms used to predict the prognosis of patients with medulloblastoma are flawed. Previous predictive models incorporated protein or gene profiles or imaging data that were expensive or not readily available in the clinical setting. We sought to build and validate a nomogram incorporating clinical data that are easily acquired to predict the individual risk of patients with medulloblastoma.

## Patients and Methods

### Patients

This multicenter, retrospective study was approved by the Ethics Committee of Shanghai Children's Medical Center (SCMCIRB-K2022159-1) and the First Affiliated Hospital, Fujian Medical University (IEC-FOM-013-2.0). An individual informed consent was obtained from the patients or their parents. From 2010 to 2022, all pediatric patients with a histological diagnosis of medulloblastoma underdoing primary surgical repair were identified through the hospital databases. The histology of all patients was reviewed by a specialized institutional neuropathologist to confirm the diagnosis. Inclusion criteria were as follows: (1) patients younger than 18 years old; (2) pathological diagnosis of medulloblastoma; (3) undergoing primary surgical repair; (4) no prior anticancer therapy; and (5) complete clinical characteristic and follow-up data. The training dataset consisted of patients from Shanghai Children's Medical Center, while the external validation dataset consisted of patients from the First Affiliated Hospital, Fujian Medical University. The training dataset was used to construct the

prediction model, and the validation dataset was used to assess the predictive performance of the model built on the training dataset.

### Data Collection

Perioperative data, including patient demographics, clinical examination results, and surgical details, were obtained from electronic medical records. Follow-up data were acquired from outpatient clinic records. Clinical data collected included age, sex, tumor size and location, the extent of surgical resection, pathologic type, chemotherapy and radiotherapy use, relapse, and survival status. The overall mortality was used as the primary endpoint for this study. All surgical patients discharged alive from the hospital were required to return for regular outpatient follow-up visits. If patients missed a scheduled follow-up visit, our follow-up staff would contact them *via* telephone, social media, or e-mail. Some patients who lived far away were required to visit local hospitals, and external medical records were obtained.

### Surgery Procedure

The third ventricle cisternostomy reduces intracranial hypertension and assists with the direct surgical removal of the tumor. Under general anesthesia with tracheal intubation, an antibiotic is given intravenously at least 15 minutes before the skin incision. The patient is slowly put in the prone position, and the head is fixed in a three-nail head brace (Headrest System, DORO) in a neutral position with great attention to protect the skin to avoid contact complications and to leave the eye without any compression. The head is inclined forward, and the chin is aligned in a way that allows for the insertion of one finger between the sternum and the chin. Hair was shaved, and the localization was performed using the neuronavigation system (StealthStation® S7® System, Medtronic, Inc., Minneapolis, MN, USA). After careful disinfection with an iodine solution, a straight midline skin incision was made from 1 cm above the occipital tuberosity to the C2 or C3 level. Muscles were dissected to expose the occipital bone and the posterior arch of C1. The bone flap is opened using a milling cutter with four burr holes. The upper edge of the bone window reaches the level of the transverse sinus, and the lower edge is at the level of the foramen magnum. The posterior arch of C1 is removed, if necessary, to improve exposure and prevent postoperative edema and bleeding. Bone wax is applied on the bone edge to stop bleeding. The dura is suspended and opened in a Y-shaped form to acquire adequate exposure. When the incision is complete, the inferior occipital sinus is sutured to avoid bleeding. Some cerebrospinal fluid is slowly released from the cisterna magna for improved exposure. Cottonoids are placed between the cerebellar tonsils and medulla oblongata to prevent tumor dissemination into the subarachnoid space. The pursuit of the operation is complete resection. However, if the tumor is closely attached to important structures such as the fourth ventricle, brainstem, and spinal cord, it is better to leave a small residue. A vermis split is carefully performed, and the incision should not extend over the medullary velum. The goals of this surgical approach are to expose the upper pole of the tumor on the midline and to observe the floor of the fourth ventricle. Before tumor resection, a sample is sent for pathological examination. The texture of medulloblastomas is usually heterogeneous, and the soft part can be removed with an aspirator, while the hard part can be removed in blocks with a bipolar. Cotton balls and the bipolar are used to stop the bleeding. The reduction of tumor volume contributes to the exposure of the boundaries between the tumors and the cerebellum. The tumor at the opening of the aqueduct should be removed as much as possible to promote cerebrospinal fluid circulation. The tumor usually attaches to the floor of the fourth ventricle. The reduction of tumor volume helps elevate the tumor's lower pole for inspecting the lower part of the floor. If there is no infiltration in the lower region of the floor, a cotton ball is placed between the tumor and the floor, and the tumor is gradually separated along the boundary. When the floor is emptied, further exploration of the lateral recesses is needed to prevent the omission of the tumor. In case of infiltration in the floor, it is difficult to remove the tumor completely, and a residual tumor is left. Nerve damage in the brainstem or the floor of the fourth ventricle should be avoided. The posterior inferior cerebellar artery, whose branches supply blood for the medulloblastoma, must be protected. After tumor resection, active bleeding is checked carefully, and hemostatic gauze is placed in the cavity. The dura is tightly closed and covered with a patch. The skull flap is fixed with titanium bars and nails. Subcutaneous drainage is used, and the muscle and scalp layers are closed.

### Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR), and the difference was analyzed using Student's *t*-test or Mann-Whitney U test, as appropriate. Categorical variables were presented as absolute numbers or percentages, and the difference was analyzed using Pearson $\chi^2$ or Fisher's exact test. Univariable and multivariable Cox regression models were used to identify factors associated with mortality in the training dataset. Variables with $p < 0.05$ in the univariable model were entered into the multivariable model. The results were expressed as hazard ratio (HR) with a corresponding 95% confidence interval (CI). For binary outcome measures, a minimum of 5 events per variable is required to ensure precision. In the training dataset, the sample size was satisfied (29 events for 5 variables in the multivariable Cox regression model and three variables in the nomogram)[10]. Then, a nomogram based on independent variables in the multivariable Cox regression model was constructed to predict 1-, 3-, and 5-year survival. Based on the contribution of each variable to the outcome, the nomogram could indicate the relationship between variables in the model by drawing a line segment with a certain proportion, which converted the complex regression equation into intuitional graphic visualization. The area under the receiver operating characteristic curve (AUC) was used to assess the discrimination ability of the nomogram. The calibration of the nomogram was determined using the calibration plots by comparing the predicted survival rate with the actual survival rate. A risk stratification system based on the median risk score calculated from the nomogram in the training dataset was also established to separate patients into two risk groups: the low-risk and high-risk groups. This approach to establishing risk stratification systems has been used in many studies[11] of predictive model development. The overall survival in the two-risk group was compared using the Kaplan-Meier curves and the log-rank test in the training and validation datasets. R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. The survival package was used for the Cox regression model and Kaplan-Meier curve analysis. The rms package was used for nomograms and calibration curves. The timeROC package was used for receiver operating characteristic curve analysis. The program code for statistical analysis could be obtained from the corresponding author upon reasonable request. A two-sided $p < 0.05$ was considered statistically significant.

## Results

### Patient Characteristics

A total of 151 patients were considered for inclusion in the study (96 males and 55 females). The median age at surgery was 6.9 (IQR, 3.5-9.4) years. Most patients (128, 84.8%) underwent total resection, and the remaining underwent subtotal resection (23, 15.2%). The brainstem was involved in 37 patients, and lateral location was found in 43 patients. The median tumor size was (IQR, 4.1-5.5) cm. Histopathology was categorized as follows: classic medulloblastoma, 70 patients (46.4%); desmoplastic medulloblastoma, 44 patients (29.1%); large cell anaplastic medulloblastoma, 18 patients (11.9%); medulloblastoma with extensive nodularity, 9 patients (6.0%); unknown, 10 patients (6.6%). After surgical repair, 105 patients (69.5%) received chemotherapy and 91 (60.3%) received radiotherapy. Follow-up ranged from 11 days to 12.2 years, averaging 2.1 years. During the follow-up, 63 relapsed patients were identified. The overall 1-, 3- and 5-year survivals were 79.1%, 62.1% and 52.2%, respectively. A total of 76 patients from Shanghai Children's Medical Center were classified as a training dataset, while the remaining 75 patients from the First Affiliated Hospital, Fujian Medical University, were classified as the validation dataset. The clinical characteristics of the two datasets are presented in Table I.

### Univariate and Multivariate Analyses

The results of univariate and multivariate Cox regression analysis are shown in Table II. In the training dataset, univariate Cox regression analysis demonstrated that tumor size ($p = 0.021$), lateral location ($p = 0.016$), brainstem involvement ($p = 0.006$), radiotherapy ($p = 0.006$), and chemotherapy ($p = 0.004$) were associated with mortality. Multivariate Cox regression analysis identified tumor size ($p = 0.048$), brainstem involvement ($p = 0.013$), and chemotherapy ($p = 0.020$) as independent factors associated with mortality.

### Construction and Validation of Survival-Related Nomogram

Based on independent variables in the multivariable Cox regression model, a nomogram

**Table I.** Clinical characteristics of patients in the training and validation datasets.

| Attribute | Training dataset (n = 76) | Validation dataset (n = 75) |
|---|---|---|
| Sex | | |
| Female | 28 | 27 |
| Male | 48 | 48 |
| Age (years) | 5.81 (2.67-8.43) | 7.56 (4.39-11.43) |
| Histology | | |
| Classic | 30 | 40 |
| Desmoplastic | 31 | 13 |
| LCA (Large Cell Anaplastic) | 13 | 5 |
| MBEN (Medulloblastoma with | 0 | 9 |
| Extensive Nodularity) | | |
| Unknown | 2 | 8 |
| Brainstem Involvement | | |
| Yes | 15 | 22 |
| No | 61 | 53 |
| Location | | |
| Midline | 47 | 61 |
| Lateral | 29 | 14 |
| Radiotherapy | | |
| Yes | 52 | 39 |
| No | 24 | 36 |
| Chemotherapy | | |
| Yes | 61 | 44 |
| No | 15 | 31 |
| Size (cm) | 5.0 (4.0-5.3) | 5.0 ± 1.4 |
| Surgery | | |
| Total Resection | 59 | 69 |
| Subtotal Resection | 17 | 6 |
| Relapse | | |
| No | 45 | 43 |
| Yes | 31 | 32 |
| Status | | |
| Alive | 47 | 45 |
| Deceased | 29 | 30 |

model integrating tumor size, chemotherapy, and brainstem involvement for predicting the 1-, 3-, and 5-year survival rates after surgical repair of medulloblastoma is constructed and presented in Figure 1. Tumor size was the most important factor for survival, whereas brainstem involvement had the least effect. The score for the individual variable is obtained by dropping a perpendicular line from that variable onto the horizontal score line. Scores of all individual variables are summed to provide the total score. The total score is then used to obtain the predicted survival probability. The AUCs of the nomogram were 0.75 at 1 year, 0. 75 at 3 years, and 0.77 at 5 years in the training dataset (Figure 2A), and 0.74 at 1 year, 0.70 at 3 years, and 0.70 at 5 years in the validation dataset (Figure 2B), suggesting a sustained level of accuracy. The calibration of the nomogram was determined using the calibration plots by comparing the predicted survival rate with the actual survival rate. The calibration curve for the probability of 1-, 3-, and 5-year survival showed good agreement between the nomogram prediction and actual observation both in the training and validation datasets, suggesting good fitness (Figure 3). We also developed a risk stratification system according to the total scores of each patient obtained from the nomogram (Figure 4). All patients were grouped into either the low-risk or high-risk group. Both in the training and validation datasets, Kaplan-Meier analysis revealed statistically significant differences in the overall survival ($\chi^2 = 8.8$, $p = 0.003$; $\chi^2 = 5.4$, $p = 0.020$).

## Discussion

This study identified tumor size, brainstem involvement and chemotherapy as independent predictors for overall survival after surgical repair in pediatric patients with medulloblastoma. A prognostic nomogram model was developed

**Table II.** Univariate and multivariate Cox regression analyses on variables to predict overall survival in the training dataset.

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) |
| Sex | | | | |
| Female | - | Reference | | |
| Male | 0.973 | 0.987 (0.459-2.124) | | |
| Age | 0.841 | 1.011 (0.916-1.122) | | |
| Surgery | | | | |
| Total Resection | - | Reference | | |
| Subtotal Resection | 0.074 | 2.012 (0.935-4.333) | | |
| Tumor Size | 0.021 | 1.537 (1.068-2.211) | 0.048 | 1.556 (1.005-2.410) |
| Location | | | | |
| Midline | - | Reference | - | Reference |
| Lateral | 0.016 | 2.459 (1.180-5.122) | 0.052 | 2.243 (0.994-5.066) |
| Brainstem Involvement | | | | |
| No | - | Reference | - | Reference |
| Yes | 0.006 | 2.768 (1.332-5.750) | 0.013 | 2.713 (1.232-5.973) |
| Radiotherapy | | | | |
| Yes | - | Reference | - | Reference |
| No | 0.006 | 2.768 (1.332-5.750) | 0.770 | 1.166 (0.415-3.278) |
| Chemotherapy | | | | |
| Yes | - | Reference | - | Reference |
| No | 0.004 | 3.139 (1.452-6.789) | 0.020 | 3.256 (1.202-8.826) |

and externally validated based on these independent predictors to predict the overall survival of pediatric patients with medulloblastoma. The present study is the first to integrate these three clinical parameters simultaneously to build a nomogram to predict overall survival after surgical repair for pediatric patients with medulloblastoma. This nomogram showed good discrimination and calibration in the training and validating datasets. This low-cost, convenient,

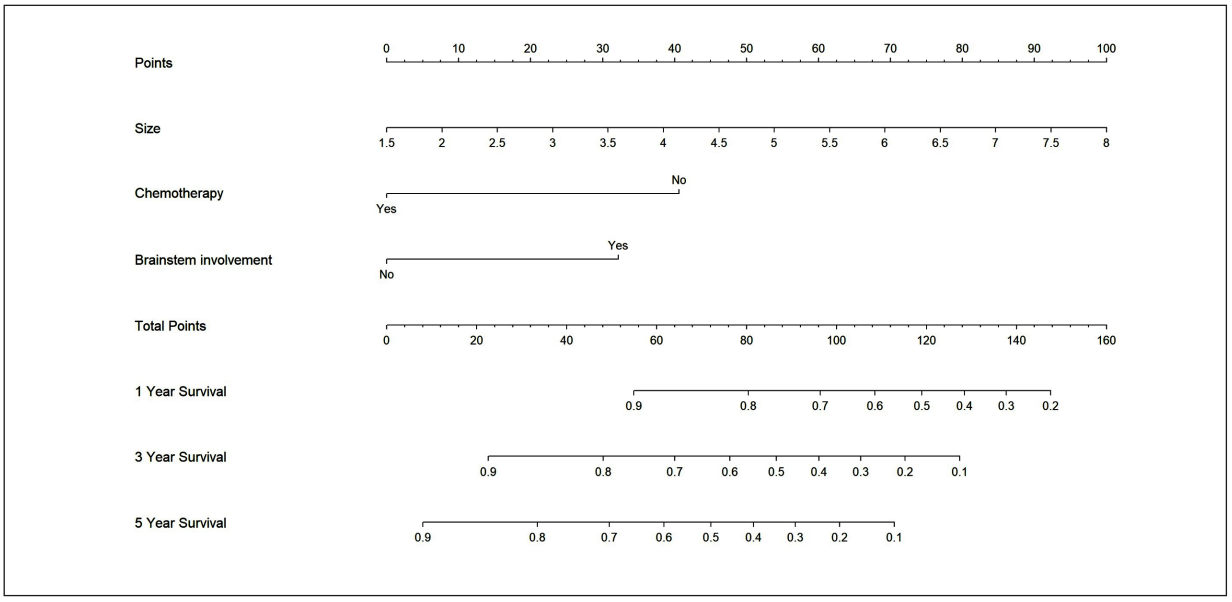


**Figure 1.** Nomograms to predict survival in pediatric patients after surgical repair of medulloblastoma. Three variables were included in the nomogram prediction model, namely: tumor size, chemotherapy, and brainstem involvement. The score for the individual variable is obtained by dropping a perpendicular line from that variable onto the horizontal score line. Scores of all individual variables are summed to provide the total score. The total score is then used to obtain the predicted survival probability.

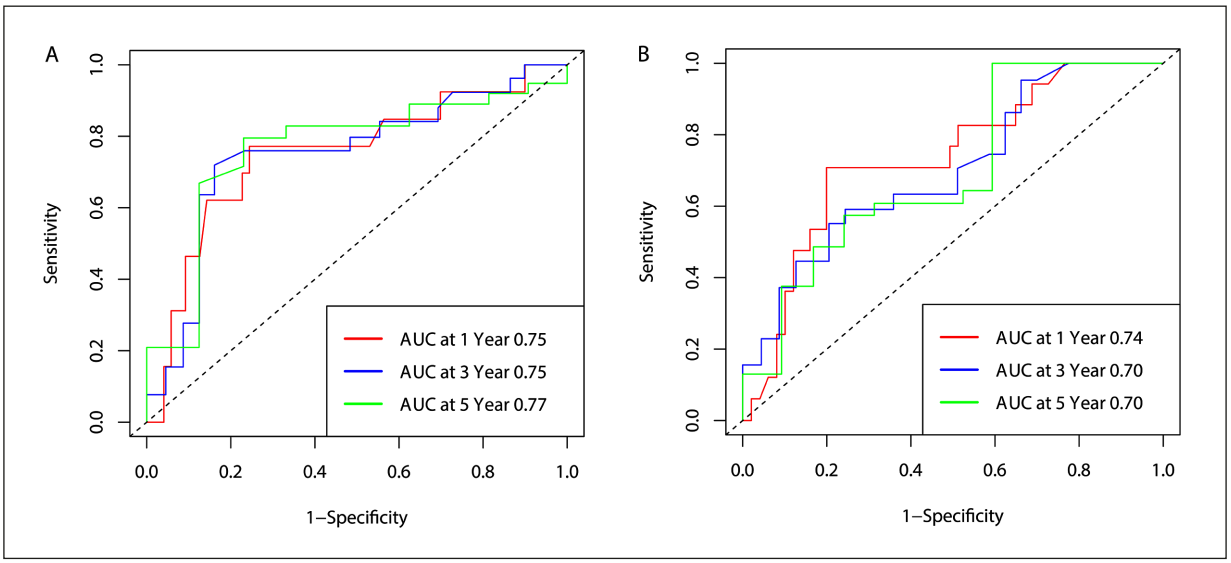


**Figure 2.** **A**, Receiver operating characteristic (ROC) plots and area under the ROC curve (AUC) of the nomogram in the training dataset (76 patients). **B**, ROC plots and AUC of the nomogram in the validation dataset (75 patients). The AUCs of the nomogram were 0.75 at 1 year, 0. 75 at 3 years, and 0.77 at 5 years in the training dataset (76 patients) (**A**), and 0.74 at 1 year, 0.70 at 3 years, and 0.70 at 5 years in the validation dataset (75 patients) (**B**), suggesting a sustained level of accuracy.

and noninvasive nomogram can be translated into clinical practice as a tool for risk stratification and individualized prognosis prediction for children with medulloblastoma.

In this study, we combined three clinical characteristics to construct a nomogram for predicting the overall survival after surgical repair of medulloblastoma. The calibration curve showed good agreement between the actual and predicted overall survival, indicating good predictive performance of the nomogram. The receiver operating characteristic curve analyses showed good discrimination ability of this nomogram. Stratification analysis showed that the nomogram could divide pediatric medulloblastoma patients into high- and low-risk groups. The nomograms achieve reliable and stable risk stratification and individualized prediction of overall survival in both the training and the validation cohorts, indicating good clinical applicability. This nomogram could be a promising tool for facilitating patient counseling, individualized treatment decision-making, and follow-up schedules for children with medulloblastoma. The risk stratification system established in this study is essential concerning different therapeutic modalities and may benefit two groups of patients with medulloblastoma. The low-risk group with a high chance of survival may receive fewer adjuvant therapies to reduce the long-term morbidity and adverse effects of adjuvant therapies. The high-risk group with a poor prognosis is given intensive treatment, novel therapeutic approaches, and close follow-up to improve outcomes. For patients, knowing their predicted risk improves their awareness of their disease, helps them communicate their risk levels with doctors and others, and encourages their compliance with therapy and follow-up. This model has the following advantages: (i) simple and non-invasive, (ii) requires no additional testing cost, and (iii) could be used for regular follow-up and monitoring. The nomogram in our study is easily accessible to clinicians, even in developing, poorly equipped countries.

Although several nomograms have been developed previously, the flaws of these models might limit the clinical application. Guo et al[11] built a nomogram to predict the overall survival of patients with medulloblastoma based on the Surveillance, Epidemiology, and End Results (SEER) database. However, the SEER database failed to provide complete information on critical clinical and pathological parameters such as tumor size, location and histopathology. In addition, patients in their study spanned nearly half a century, which might not reflect the contemporary diagnosis and treatment of medulloblastoma. Liu et al[12] and Zheng et al[13] extracted imaging features from MRI to predict the prognosis for pediatric medulloblastoma. However, differences in MRI

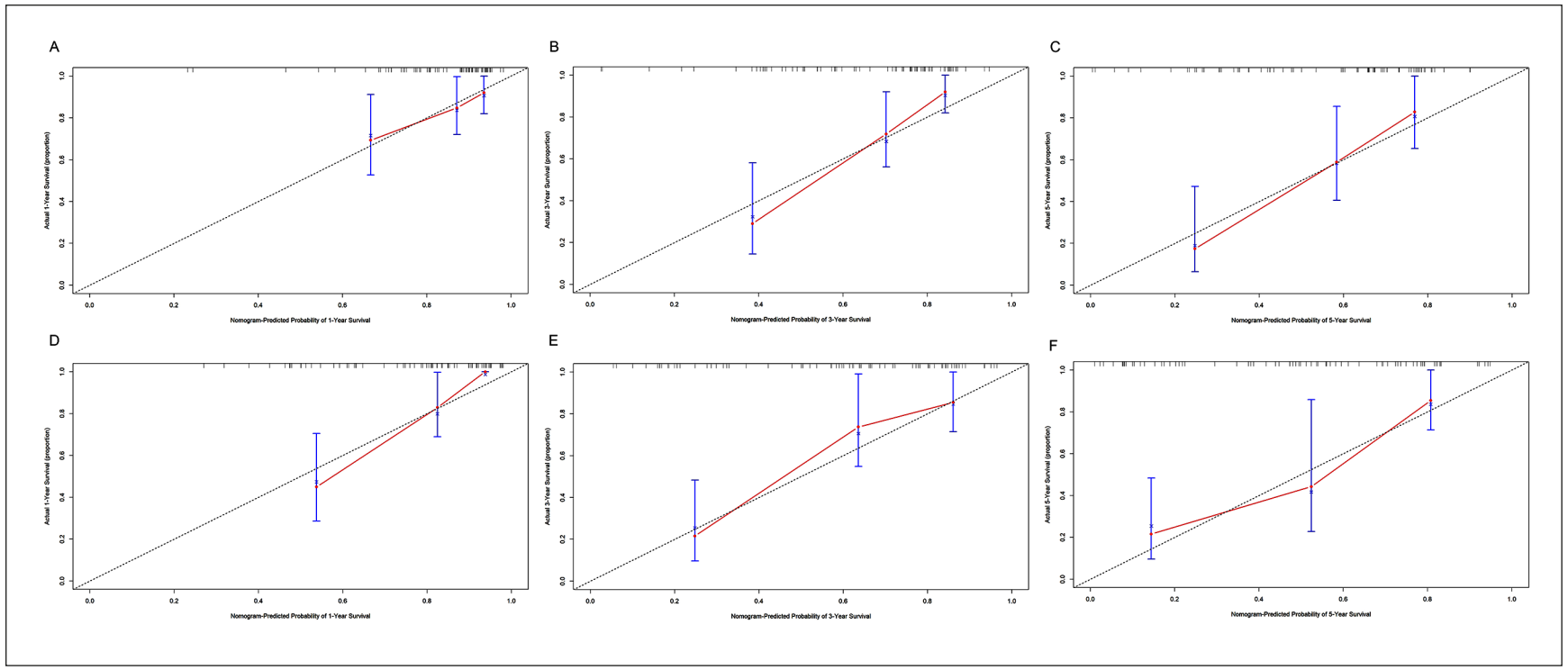


**Figure 3.** The performance of the nomogram in the training dataset (76 patients) (**A-C**) and the validation dataset (75 patients) (**D-F**) was evaluated by calibration curves. **A-C**, respectively, stand for the 1-, 3-, and 5-year survival rate of the training dataset (76 patients), and (**D**), (**E**), and (**F**), respectively, stand for the 1-, 3-, and 5-year survival rate of the validation dataset (75 patients). Calibration curves depict the calibration in terms of the agreement between the predicted and observed outcomes. The y-axis represents the actual survival. The x-axis represents the nomogram-predicted survival. The diagonal dotted line represents a perfect prediction by an ideal model. The red solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction ability. The calibration curve for the probability of 1-, 3-, and 5-year survival showed good agreement between the nomogram prediction and actual observation in the training (76 patients) and validation (75 patients) datasets, suggesting good fitness.

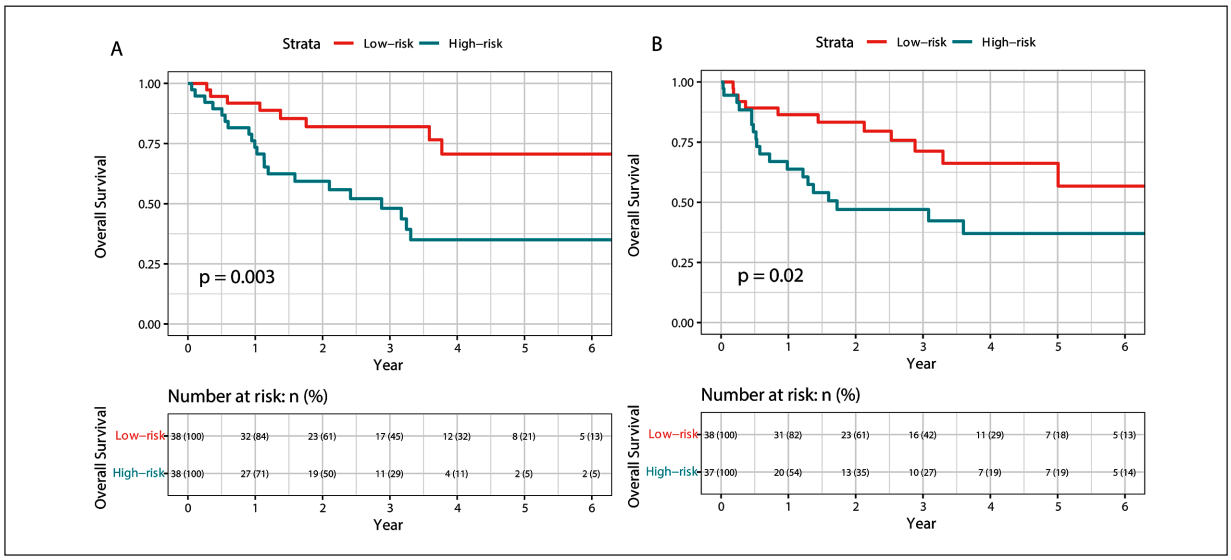


**Figure 4.** Kaplan-Meier curves of overall survival for risk classification based on the median value of the nomogram scores in the training dataset (76 patients) (**A**) and the validation dataset (75 patients) (**B**). Both in the training (76 patients) and validation (75 patients) datasets, Kaplan-Meier analysis revealed statistically significant differences in the overall survival ($\chi^2 = 8.8$, $p = 0.003$; $\chi^2 = 5.4$, $p = 0.020$).

scanners, image acquisition parameters, and image processing techniques across hospitals may influence the reproducibility of quantitative imaging measures. Besides, some imaging parameters were not routinely available, and the biological meaning was unclear. Some researchers[14-18] established prognostic models based on array or sequencing data. In recent years, many advances have been made in the molecular signature analysis of medulloblastoma. Methods integrating clinical characteristics and genomic features have been applied to the prognosis prediction of medulloblastoma. These approaches have better predictive performance than traditional clinical modalities and are expected to improve risk stratification for standard treatment regimens. Molecular targets discovered in proteomics and genomic studies may guide precise and targeted therapy. However, multiple factors keep these models in the research stage and limit their application in clinical practice. It is increasingly recognized that significant heterogeneity exists inside the tumor tissue. The biopsy tissue samples cannot fully capture comprehensive information about tumor tissue. Many molecular markers are not sufficiently reliable, suffer from limited sensitivity and specificity and are inherently unstable, which limits their application in daily clinical practice. The published methods of molecular signature are invasive and time-consuming. The application of molecular signatures in daily clinical practice is limited because of the requirement of equipment and personnel. Molecular detection techniques are costly and will increase the financial burden on patients. Neurosurgical care in most institutions in developing countries has not yet been able to apply molecular signatures to medulloblastoma treatment regimens. The lack of medical insurance and the inaccessibility of advanced adjuvant examination hurts the ability to perform molecular signature analysis. In our study, the variables included in the predictive model are clinically accessible, and the model is easy to implement in clinical practice.

The impact of tumor size on the prognosis in patients with medulloblastoma remains controversial. Tumor size was included in Chang et al[19]'s staging system. Previous studies[11] and ours indicated that larger tumor size was associated with worse outcomes. We speculated that the results may be ascribed to the following reasons. Severe adhesion often occurs when the tumor is large, and it is difficult to completely separate it from normal tissue, increasing the likelihood of recurrence and metastasis. Therefore, patients with residual disease > 1.5 $cm^2$ or evidence of metastases are defined as high-risk according to North American stratification[20]. Meanwhile, as the extent of resection expands, damage to the inferior vermis, fastigial nucleus, and cerebellar

efferent pathways increases, leading to cerebellar mutism syndrome and cerebellar cognitive affective syndrome[21-24]. However, in most prior studies in the literature, tumor size was not a common risk factor. The development of surgical techniques has led to a shift in focus, where the significance of tumor location and structure appears to outweigh that of size. In our study, poor survival was associated with the invasion of the tumor to the brainstem. Our findings are supported by previous studies[25-27]. Qin et al[25] found that brainstem medulloblastoma had a worse prognosis than cerebellum medulloblastoma. Rutkowski et al[26] and Padovani et al[27] reported a better prognosis for cerebellum medulloblastoma than midline medulloblastoma. The brainstem contains many important structures in a small area to maintain individual vital functions, which will decrease the tolerance to the space-occupying effect when a tumor infiltrates the brainstem. However, Packer et al[28] reported that brainstem involvement was not associated with the survival of newly diagnosed average-risk patients with medulloblastoma, possibly due to the absence of longer-term prognosis data.

The role of chemotherapy in children with medulloblastoma remains to be discussed. The multivariate analysis in our study revealed that receipt of chemotherapy could improve the survival of pediatric patients with medulloblastoma. However, Michiels et al[29] conducted a meta-analysis that included seven randomized controlled trials involving 1,080 children to evaluate the impact of chemotherapy on the prognosis of pediatric medulloblastoma. The authors could not draw a definitive conclusion about the true efficacy of chemotherapy. Yan et al[30] performed a systematic review, which included 18 studies to investigate prognostic survival factors in adolescents and young adults with medulloblastoma. Their study also failed to show a clear effect of chemotherapy. Both studies demonstrated that the role of chemotherapy must be viewed in the context of specific chemotherapy protocols. However, chemotherapy regimens differed in timing, agents, dose, and relationship with radiation, making it impossible to make meaningful comparisons. In addition, the long span between the included studies, with changes in therapeutic regimens over time and a relatively short follow-up, was also a flaw.

### Limitations

This study had several limitations. First, the participating institutions took a leading position in pediatric neurosurgery in China, so our model might not be extrapolated to other hospitals. Second, this study was a retrospective analysis with a small sample size, and the nomogram needed to be further optimized in large-scale and prospective studies. Third, some potential prognostic factors, such as radiotherapy protocols, chemotherapeutic regimens, patient neurological status, and molecular subgroups, were not available in the present study, which might limit the predictive performance of the nomogram. Finally, the duration of follow-up in our datasets was relatively short, which affected the accuracy of the late follow-up information.

## Conclusions

This study identified tumor size, brainstem involvement, and chemotherapy as independent factors associated with overall survival after surgical repair in pediatric patients with medulloblastoma. A prognostic nomogram was developed and validated to predict the overall survival of pediatric patients with medulloblastoma. This nomogram showed good discrimination and calibration in the training and validating datasets. This low-cost, convenient, and noninvasive nomogram can be translated into clinical practice as a tool for risk stratification and individualized prognosis prediction for children with medulloblastoma.

### Conflict of Interest

The authors declare that they have no conflict of interests.

### Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013), and the protocol was reviewed and approved by the Ethics Committee of Shanghai Children's Medical Center (SCMCIRB-K2022159-1) and the First Affiliated Hospital, Fujian Medical University (IEC-FOM-013-2.0).

### Informed Consent

All subjects provided written informed consent for inclusion before they participated in the study.

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### Authors' Contribution

Chenhao Fang and Chen Wen wrote the first draft of the manuscript and performed the statistical analysis. Bo Yang, Yunhai Song, Huiqing Liu, and Lan Tian contributed to the acquisition and interpretation of data. Hong Chen and Nan Bao contributed to the conception and design of the study. All authors contributed to the manuscript revision and read and approved the submitted version.

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### Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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