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A Nomogram Model for Predicting Prognosis of Patients with Medulloblastoma

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ABSTRACT

AIM: To identify the prognostic factors associated with cancer-specific survival in medulloblastoma (MB), and to use them for establishing a nomogram model to predict cancer-specific survival.

MATERIAL and METHODS: In total, 268 patients with MB were included; they were rigorously respectively screened from the Surveillance, Epidemiology, and End Results database from 1988 to 2015 and statistically analyzed in R language. This study focused on cancer-specific death and used the cox regression analysis for variable filtering. The model was calibrated using C-index, area under the curve (AUC), and calibration curve.

RESULTS: As per our findings, it was determined that extension (localized: hazard ratio [HR]=0.5899, p=0.00963; further extension: indicator) and treatment modality (radiation after surgery chemotherapy sequence unknown: HR=0.3646, p=0.00192; no surgery: indicator) were statistically significant in the prognosis of MB and were finally utilized to construct a nomogram model for predicting the condition. The AUC values were 0.649, 0.629, and 0.64 at 2, 3, and 5 years, respectively.

CONCLUSION: Tumor extension and treatment modality were independent prognostic factors for MB.

KEYWORDS: medulloblastoma, nomogram, prognostic factors, concordance index (C-index), time-dependent receiver operating characteristic (ROC)

ABBREVIATIONS: SEER: Surveillance, Epidemiology, and End Results database, **MB:** Medulloblastoma, **WHO:** World Health Organization, **C-index:** Concordance index, **ROC:** Time-dependent receiver operating characteristic, **HR:** Hazard ratio, **AUC:** Area under the curve, **CSRT:** Craniospinal radiotherapy, **CNS:** Central nervous system

INTRODUCTION

The name "medulloblastoma (MB)" was coined by Harvey Cushing and Percival Bailey in 1925. Earlier, Drs. Cushing and Bailey had used the term "cerebral spongiform cell tumor" to describe a posterior fossa tumor in preadolescents. They later changed this name to MB (10), which is now known as one of the most reported malignant tumors in the skull of children that accounts for approximately 20% of all intracranial tumors in children (8,11). MB has a high degree of malignancy, is accompanied by low survival rates, and is prone to recurrence as well as metastasis. A vast majority of these tumors generally occur in children, although a relatively low incidence has been reported in adults. The standard treatment for MB includes postoperative adjuvant radiotherapy and chemotherapy (14). The mortality rate of patients is high due to the high degree of tumor malignancy. Therefore, the prognosis is especially crucial for patients with MB.

Many studies on MB have been conducted; however, there are currently very few studies as regards the cancer-specific survival of MB. Nomograms can visualize the prognosis and help clinicians discover treatment options.

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Therefore, in this present study, we aimed to identify the prognostic factors associated with cancer-specific survival in MB and use them to establish a nomogram model for predicting cancer-specific survival. At last, tumor extension and treatment modality were independent prognostic factors for the prognosis of MB.

MATERIAL and METHODS

Data Sources and Selection Criteria

Information for patients diagnosed with MB was obtained from the Surveillance, Epidemiology, and End Results (SEER)*Sat version 8.3.8 (https://seer.cancer.gov/) and subjected to statistical analysis using packages implemented in R software (version4.0.5; http://www.r-project.org/).

Forest plot, Kaplan–Meier curve, nomogram, receiver operating characteristic (ROC) curve, and calibration curve were presented with R language (version4.0.5; http://www.r-project.org/) related program packages.

Inclusion and Exclusion Criteria

Patients that met the following inclusion criteria were recruited in this study: (a) those who were diagnosed with MB after histological examination from 1988 to 2015; (b) those who had detailed treatment information, including radiotherapy and chemotherapy; (c) those with malignant behavior recode; (d) those with an active follow-up. Meanwhile, those who met the following exclusion criteria were eliminated from the study: (a) intraoperative rad with another rad before/after surgery (beam radiation) and unknown chemotherapy sequence and (b) unknown survival time (Figure 1).

Patient Characteristics

We analyzed each patient's characteristics, including age, sex, race, year of diagnosis, location, tumor extension, and treatment, such as surgery chemotherapy sequence unknown, surgery, radiation after surgery, radiation after surgery chemotherapy sequence unknown, and no surgery, including radiotherapy only, chemotherapy only, and radiotherapy plus chemotherapy. All patients had an active follow-up.

Ethics Approval and Consent to Participate

The article data was selected from a public SEER database and did not involve ethical issues.

Statistical Analysis

Firstly, factors with *p*-values of <0.05 were selected as potential risk factors in univariate analysis using the cox regression analysis. Thereafter, we constructed a prediction model with all the risk factors (p<0.05) and gradually selected the best prediction model based on the Akaike information criterion results (6). Then, the model was visualized on a nomogram. The concordance index (C-index) and time-dependent ROC curve (5,16) accessed the precision and discrimination of the model. The calibration curve visualized the comparison between the actual probability and the predicted outcomes of the model (3). The median was used to calculate the cutoff value of continuous variables to evaluate the calibration curve and discrimination by 100 re-sampling methods.

All statistical analyses were performed using the R software (version4.0.5; http://www.r-project.org/).

We used multiple imputation methods to impute the data due to missing data in the extension. The best cutoff values were obtained by X-tile software (v3.6.1).

RESULTS

Clinicopathological Characteristics of Patients

In total, 268 patients with MB were recruited for this study. A summary of their basic information is outlined in Table I.

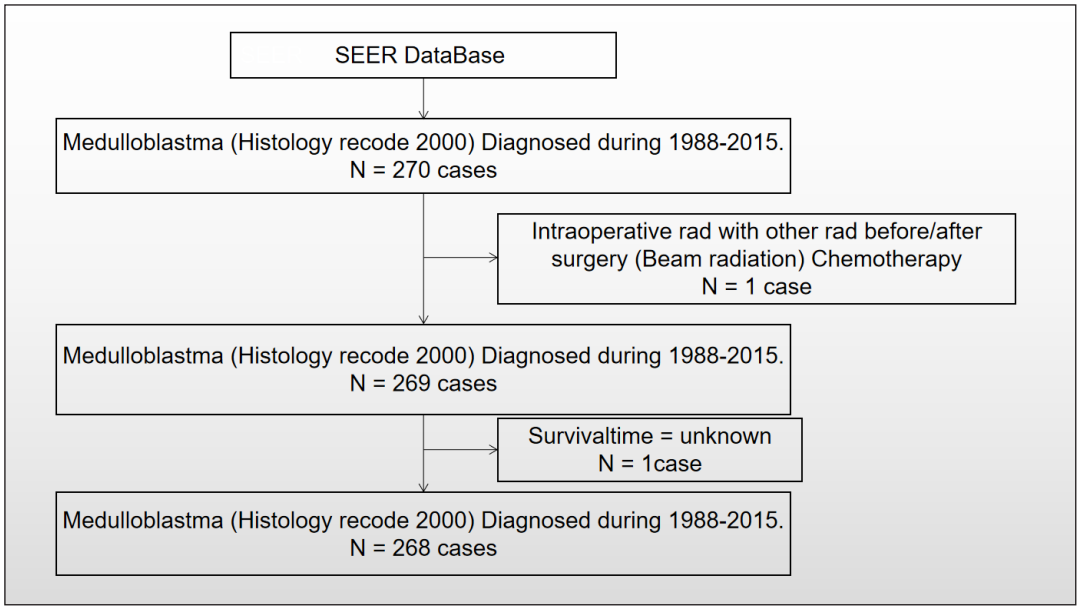

Figure 1: Flow chart of patient selection.

Table I: Baseline Clinicopathological Features and Treatments

Variables	Number of patients
Age	**268**
<10	137
>=10	131
Race	**268**
White	210
Other	58
The year of diagnosis	**268**
<2000	138
>=2000	130
Location	**268**
Other	250
Overlap lesion	18
Sex	**268**
Female	102
Male	166
Extension (After interpolation)	**268**
Further extension	71
Localized	197
Treatment	**268**
Radiation after surgery	51
Radiation after surgery Chemotherapy	94
Surgery Chemotherapy sequence unknown	53
Surgery	48
No surgery	22

To summarize, the male-to-female ratio in this study was 1.63:1. Caucasians (n = 210 cases, 80.2%) comprised a vast majority of the people in this cohort. The ratio of ≥10 years old to <10 years old was approximately 1:1. The ratio of MB before and after the year 2000 was approximately 1:1. All patients had positive histology.

Univariate Analysis

Cox univariate analysis showed statistical significance in extension and treatment. The univariate analysis results are shown in Figure 2.

Identification of Independent Prognostic Factors in the Cohort

Multivariate analysis results in our study cohort were shown in Figure 3. In summary, two independent factors were identified and incorporated into the multivariate analysis. These included extension (localized: hazard ratio [HR]=0.5899, p=0.00963) and treatment (surgery chemotherapy sequence unknown: HR=0.6216, p=0.17937; radiation after surgery chemotherapy sequence unknown: HR=0.3646, p=0.00192; radiation after surgery: HR=0.5810, p=0.12582; surgery: HR=0.6218, p=0.16575). Additionally, we have generated the Kaplan–Meier curve to evaluate the impact of all dependent prognostic factors on patient's survival (Figure 4).

Establishment of a Nomogram Model to Predict the Prognosis of Patients

The nomogram showed the independent prognostic factors

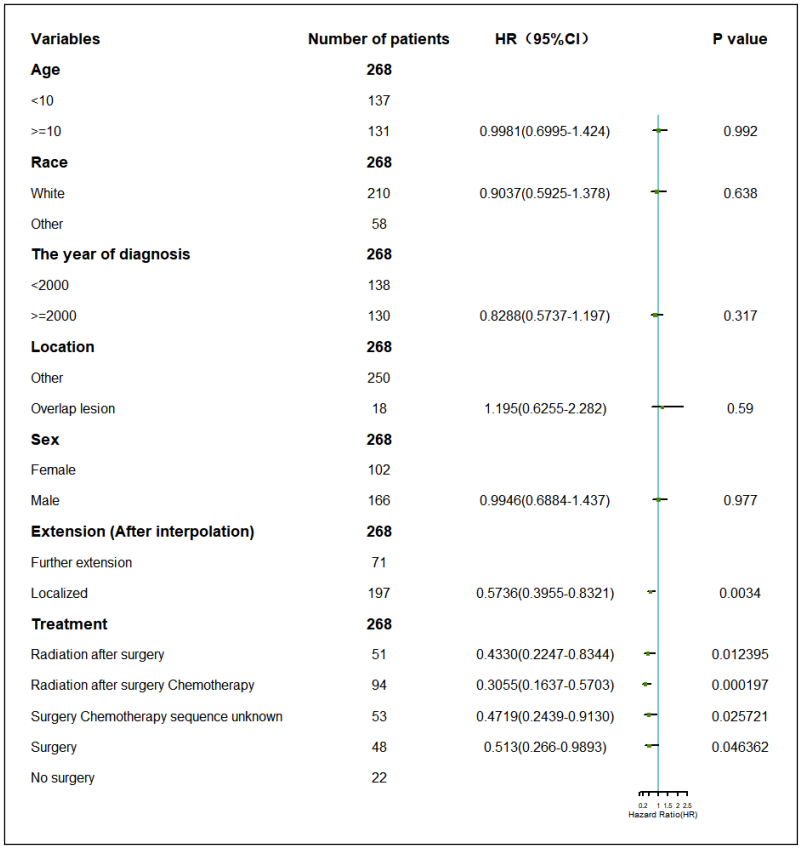

Figure 2: Clinicopathological features of the patients and results of the univariate COX proportional hazards analysis (HR, 95%confidence interval).

Variables	Number of patients	HR（95%CI）	p-value
Extension (After interpolation)	**268**		
Further extension	71		
Localized	197	0.5899(0.3956-0.8797)	**0.00963**
Treatment	**268**		
Radiation after surgery	51	0.5810(0.2898-1.1645)	0.12582
Radiation after surgery Chemotherapy	94	0.3646(0.1928-0.6898)	**0.00192**
Surgery Chemotherapy sequence unknown	53	0.6216(0.3105-1.2443)	0.17937
Surgery	48	0.6218(0.3176-1.2174)	0.16575
No surgery	22		

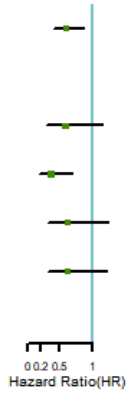

Figure 3: Results of the multivariate analysis of various factors (HR, 95% confidence interval).

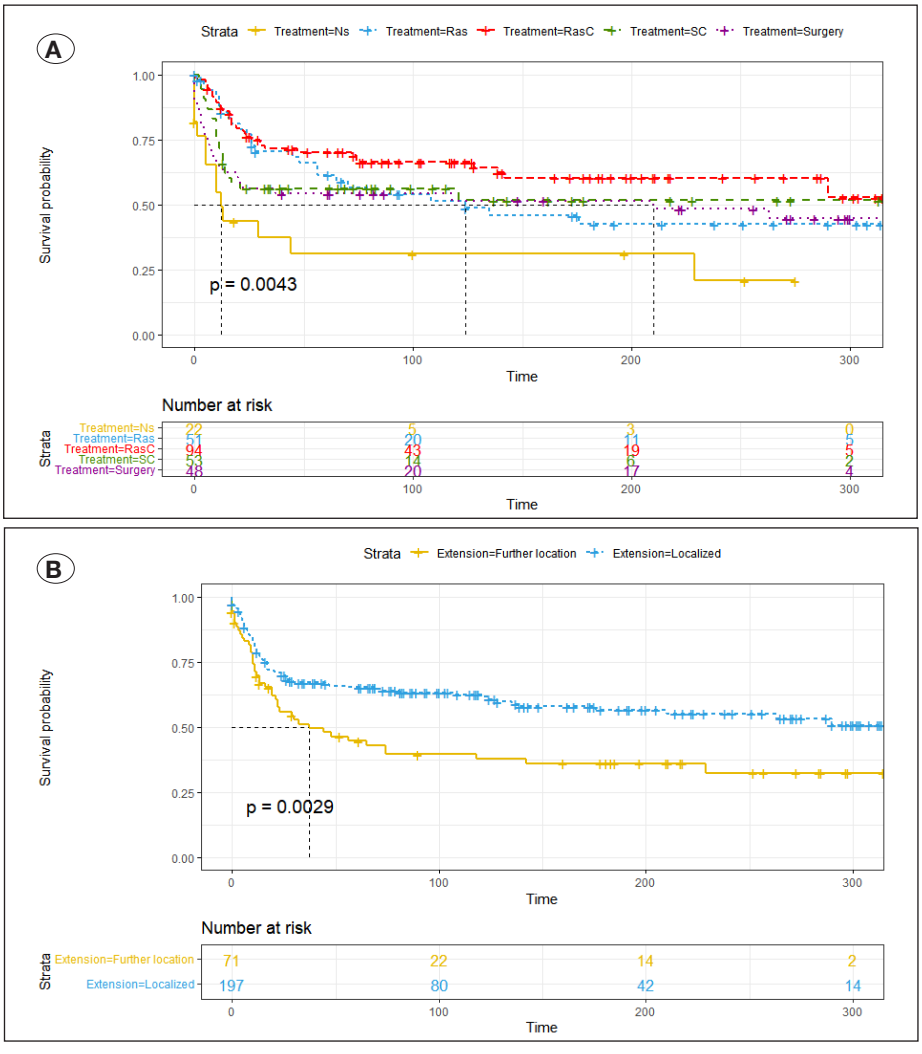

Figure 4: Kaplan-Meier curve for patients with medulloblastoma. Treatment **(A)**, Extension **(B)**. Ras= Radiation after surgery, Ras C= radiation after surgery chemotherapy sequence unknown, SC= surgery chemotherapy sequence unknown Ns= No surgery. The time unit is month.

in the cohort (Figure 5). In the nomogram, each variable was matched to a score on the scale, and the total score was obtained by the sum of the scores of each variable. Finally, the survival rate was obtained based on the total score corresponding to the score scale. The proportions of extension and treatment could be seen in the nomogram.

Validation of the Nomogram

The C-index for predicting model (including extension and treatment) discrimination was 0.622 in the nomogram. The model's discriminatory ability was accessed by the time-dependent ROC curve (Figure 6). The area under the curve (AUC) value was 0.649, 0.629, and 0.64 at 2, 3, and 5 years, respectively. These showed that the model had a good discriminatory ability (Figure 7). The calibration curves were able to visualize the comparison between the actual probability and the predicted outcomes of the model.

DISCUSSION

Discovering the factors that influence the prognosis of rare diseases, such as MB, is imperative to accurately design effective treatment approaches. This present study screened a total of 268 patients with MB from the SEER database from 1988 to 2015, identified possible risk factors associated with the occurrence of MB, and revealed that tumor extension and treatment were significant risk factors. These were later used to establish a nomogram model to predict the disease prognosis.

Specifically, many previous studies have showed that younger children had lower survival rates. However, this study revealed no statistical significance with age. Additionally, the location was identified to be a significant risk factor. However, these findings require further explorations due to the effects of other factors, such as selection bias, a small amount of data, and inaccurate recordings.

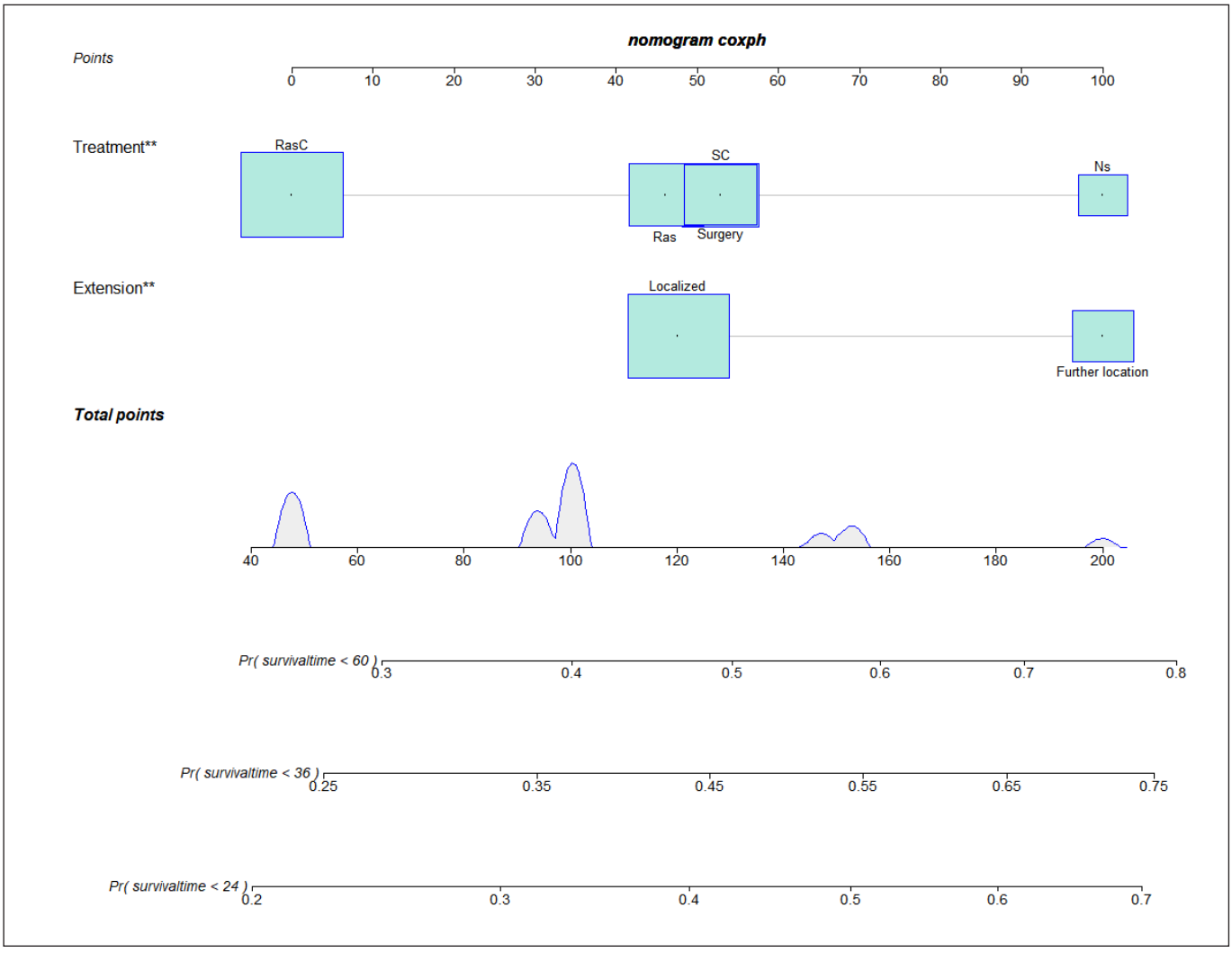

Figure 5: Nomogram predicting cancer-specific death at 24, 36, 60 months in medulloblastoma patients. Prognostic factors included extension and treatment. Each variable on the nomogram could match the scores on the scale and overall scores could be obtained by summing the scores for each variable. Ras = radiation after surgery Ras C = radiation after surgery chemotherapy sequence unknown SC = surgery chemotherapy sequence unknown Ns = No surgery. The time unit is month.

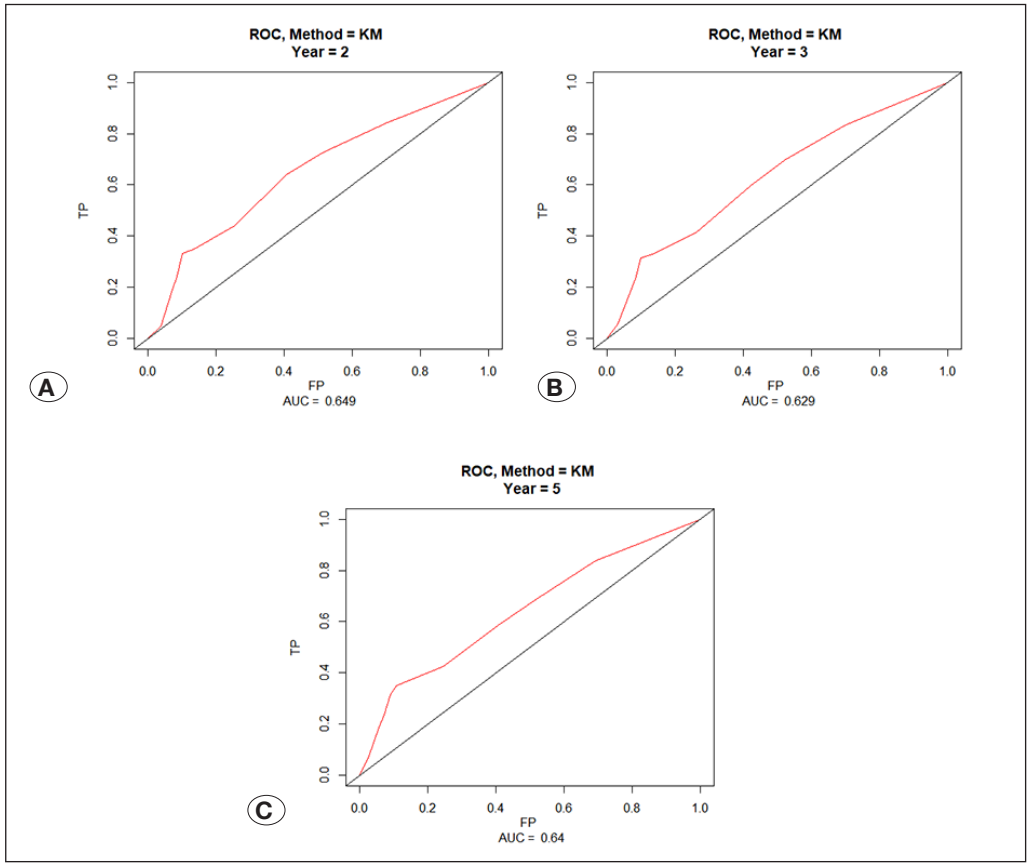

Figure 6: Calibration of nomogram.

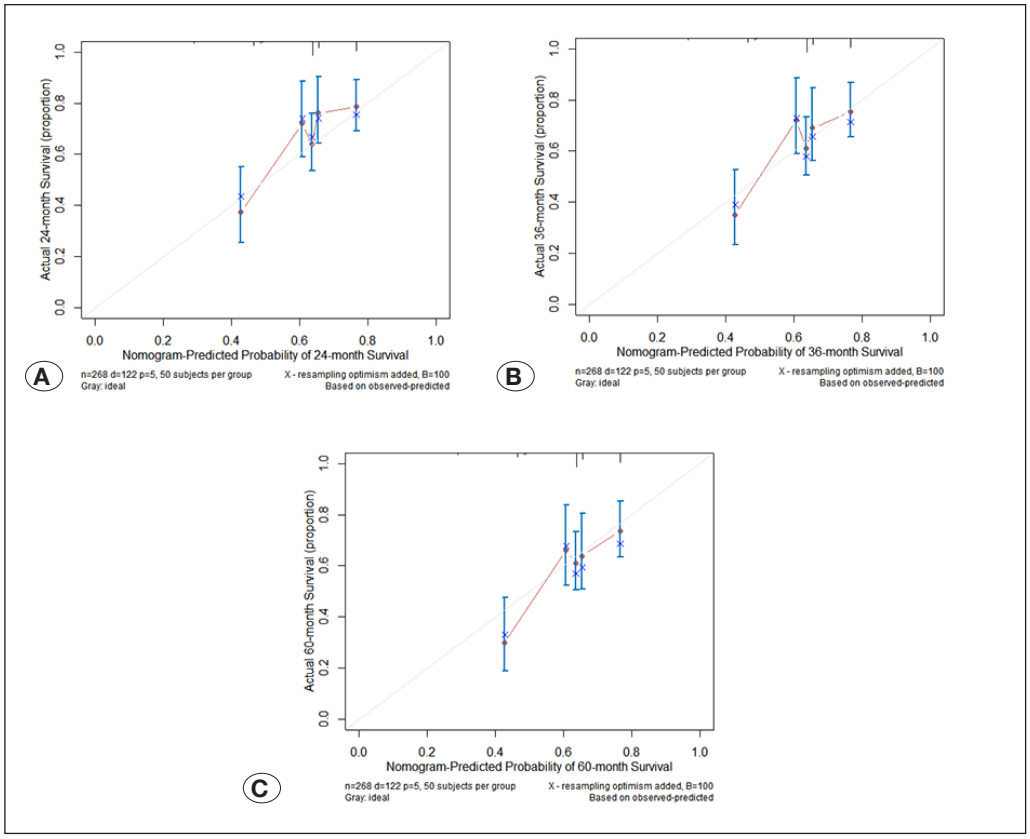

Figure 7: ROC at 2-Year, 3-Year and 5-Year.

This study revealed a statistical significance in the tumor extension. To our knowledge, further extensions have poor prognosis due to greater involvement.

Our results further showed treatment as a significant risk factor for MB occurrence, consistent with the treatment standard for the disease. Generally, MB management in adults is largely inferred from pediatric MB trials due to disease rarity in this population as well as few prospective studies that describe the subject (12). Previous studies have shown that the extent of residual tumor is correlated with the prognosis of children (1,4). Therefore, maximum safe resection is the main goal of surgical resection in adults with MB. Previous studies have also associated higher radiation doses with significant neurocognitive and endocrine sequelae in long-term childhood survivors (13). However, results from a recent retrospective study showed that neurocognitive function was frequently impaired in 70% of adult patients with MB who received radiation (7). Adults tolerated late central nervous system (CNS) toxicity of craniospinal radiotherapy (CSRT) better than children, but this was not the case with acute and subacute radiation toxicity to the bone marrow and other irradiated organs considering their stage of CNS development (2). Additionally, this group of patients was observed to experience cognitive sequelae (7). Chemotherapy plays a crucial role in the treatment of pediatric patients with MB who are younger than 3 years to delay radiotherapy. Hence, this applies to patients with standard-risk diseases who are treated with reduced CSRT as well as those with other high-risk diseases (15). Current conventional treatment for adults with MB comprises maximum safe resection, followed by CSRT with or without adjuvant chemotherapy. This is mainly based on clinical risk stratification, including the extent of resection and the presence of metastatic dissemination within and/or outside the CNS.

The exact drug and optimal timing for pre-chemotherapy with regard to radiotherapy remain controversial despite heavy dependence on adjuvant chemotherapy for MB management in both pediatric and adult populations (9). This controversy in treatment options means that surgery in combination with radiation and chemotherapy remains to be the standard of care.

This study was the first to predict cancer-specific survival in MB and was able to visualize it with a nomogram to help clinicians discover treatment options.

This study also has some shortcomings. First, selection bias was inevitable. Second, data acquisition was incomplete due to missing data records in the SEER database, such as tumor size. Third, the amount of obtained data was limited.

Finally, the current rapid technological advancements, immunotherapy, stem cell transplantation, as well as molecular-targeted and individualized therapies are expected to generate more insights into the underlying mechanisms of action and reveal novel treatment options.

CONCLUSION

Overall, our results indicated that tumor extension and treatment were independent risk factors for cancer-specific survival in MB. These were used to establish a nomogram model to predict the prognosis of patients with MB.

AUTHORSHIP CONTRIBUTION

Study conception and design: HL
Data collection: HL
Analysis and interpretation of results: HL
Draft manuscript preparation: PS
Critical revision of the article: PS
All authors (HL, PS) reviewed the results and approved the final version of the manuscript.

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