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Risk factors for and predictive nomogram of overall survival in adult patients with craniopharyngiomas

A SEER population-based study

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Abstract

Studies with relatively large sample size as well as long-term follow-up focusing on adult craniopharyngioma (CP) patients are still lacking. We attempted to identify independent prognostic factors and establish a nomogram model to estimate survival rates for adult CP patients.

The Surveillance, Epidemiology, and End Results database was used to obtain data on patients with CP. Univariable and multivariable Cox analyses were utilized to identify the prognostic factors of adult CP patients. A survival prediction model was constructed and its predictive performance was also assessed.

A total of 991 patients (695 in training group and 296 in validation group) were eligible for final inclusion. Multivariate Cox analysis presented that age at diagnosis, marital status, race, tumor size, and surgery type were statistically significant prognostic factors for overall survival (all $P < .05$). A graphical predicting nomogram model was developed to calculate the predicted patients' survival probabilities at 1, 2, 5, and 10 years. The concordance indexes were 0.708 ± 0.019 and 0.750 ± 0.025 for the training and validation samples, respectively, demonstrating favorable discrimination abilities. Similarly, the time-dependent area under curve also showed overall satisfactory discrimination ability. Favorable consistencies between the predicted and actual survival were presented according to the calibration curves.

An easy-to-use nomogram, being proven to be with reliable discrimination ability and accuracy, was established to help predict overall survival for adult patients with CP using the identified significant prognostic factors.

Abbreviations: AUC = area under curve, C = craniopharyngioma, CI = confidence interval, GTR = gross total resection, HR = hazard ratio, OS = overall survival, RT = radiotherapy, SEER = Surveillance, Epidemiology, and End Results, STR = subtotal resection.

Keywords: craniopharyngioma, nomogram, overall survival, SEER database

1. Introduction

Craniopharyngioma (CP) is a type of rare benign epithelial tumor, thought to rise from remnants of Rathke pouch, accounting for 2% to 5% of all primary intracranial tumors.[1–4] This type of tumor occurs across all ages with a bimodal peak age distribution at 5 to 14 years old and 65 to 74 years old.[5,6] These tumors frequently originate along the hypophyseal–pharyngeal duct (craniopharyngeal duct), and their special primary tumor location abutting the optic nerves/chiasm, pituitary gland, and hypothalamus usually causes significant patient disability and mortality, posing a severe challenge for the clinical management.[7,8] Currently, surgery remains the first choice for tumor treatment. Some studies have reported that subtotal resection (STR) followed by adjuvant radiotherapy (RT) achieved similar outcomes as gross total resection (GTR) in pediatric population.[2,9,10] However, extent of tumor resection remains controversial, especially for adult CP patients.

As has been reported, CPs in adults were related to worse prognosis, suggesting that survival probability estimation is needed for this disease for promotion of neurosurgeon–patient communication and optimization of individual treatment, as well as follow-up management strategies. In addition, as a reliable graphical calculating model, nomogram has been used in many kinds of tumors for prognostic prediction.[11,12]

This study was mainly based on the SEER database and was conducted in compliance with the Helsinki Declaration. We obtained permission to access the SEER program research data files. The need for informed patient consent was waived because of the retrospective nature of the study.

The authors have no funding and conflicts of interest to disclose.

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

This study was approved by the ethics committee of Huangshi Central Hospital Hospital.

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Nevertheless, to our knowledge, there is no nomogram model having been established for adult CP patients. Moreover, due to the rarity of this disease, studies with relatively large sample size as well as long-term follow-ups focusing on adult population are still lacking.

Thus, to address these issues, we retrieved the Surveillance, Epidemiology, and End Results (SEER) database to obtain a representative study cohort of adult CP patients for our comprehensive analysis. Furthermore, a nomogram model for predicting 1-, 3-, 5-, and 10-year OS was also successfully developed and internally validated.

2. Materials and methods

2.1. Cohort selection

Data on patients diagnosed with CP were extracted from SEER database. Data screening was referred to the following inclusion criteria: diagnosed with CP according to the International Classification of Diseases for Oncology Third Edition histology code: 9350/0, 9350/1, 9350/3, 9351/0, 9351/1, 9351/3, 9352/1; primary tumor site was craniopharyngeal duct (site code: C-75.2); patients aged ≥20 years; diagnosed from 2004 to 2016; availability of the survival information and follow-up data. Patients with unknown information on race, surgery type, and RT were excluded.

2.2. Covariates

Demographic and clinicopathological variables involved in our study included age at diagnosis, race, gender, year of diagnosis, patient marital status, tumor histology, and tumor size. Treatment information including surgery types and RT were also obtained for our analysis. Continuous variables including age at diagnosis and tumor size were stratified based on the running log-rank test.[13,14] Primary outcome of the analysis was the overall survival (OS), which was defined by patient survival months and vital status.

2.3. Nomogram development and statistical analysis

First, CP patients were randomly divided into training and testing sets with a ratio of 7:3. Training group was used for model development, and testing group was for model validation. Univariable and multivariable Cox proportional hazards regression analyses were employed to identify independent prognostic factors. On the basis of these results, the nomogram model for OS prediction was developed and validated for 1-, 2-, 5-, and 10-year survival probability estimation. Discrimination ability of the model was quantified using the concordance index and time-dependent area under the curve (AUC) value. Calibration curves were generated to depict the consistency between model-predicted OS and actual survival.

Comparisons between random groups employed chi-square tests or Student *t* tests as appropriate. Kaplan-Meier survival analysis with log-rank test was also conducted. Data extraction and statistical analyses were performed using SEER*Stat software (version 8.3.8) and R software (version 4.0.2). A *P* value of < .05 was considered statistically significant.

2.4. Ethics and dissemination

This study was approved by the ethics committee of Huangshi Central Hospital Hospital.

2.5. Patient and public involvement

This study was mainly based on the SEER database and was conducted in compliance with the Helsinki Declaration. We obtained permission to access the SEER program research data files. The need for informed patient consent was waived because of the retrospective nature of the study.

3. Results

3.1. Patients' baseline characteristics

Table 1 shows the baseline characteristics of the patients included in this study. A total of 991 patients (695 in training group and 296 in validation group) were eligible for final inclusion according to the inclusion and exclusion criteria. Among these patients, the percentages of male patients were 49.4% (n = 343) and 53.0% (n = 157) in the training and validation samples, respectively. The mean age were 50.67 ± 16.08 and 51.85 ± 15.93 years in the training and validation samples at the time of diagnosis. Three different categories of surgery extents were conducted for this analysis, including nonsurgical treatment in 402 patients (290 in training group and 112 in validation group), STR in 175 patients (116 in training group and 59 in validation group), and GTR in 414 patients (289 in training group and 125 in validation group). Following the index therapies, adjuvant RT was applied to 76.2% (n = 755, 526 in training group and 229 in validation group) of the patients. The tumor size was available in 493 and 201 patients in the 2 groups, with an average tumor size of 35.57 ± 12.25 and 35.23 ± 18.93 mm, respectively.

The Kaplan-Meier survival curves for the patients' OS of training and validation groups are shown in Figure 1. The overall patients' survival at 1, 2, 5, and 10 years were 89.0%, 84.5%, 73.3%, and 60.7%, and 87.5%, 82.0%, 73.6%, and 57.3% in training and validation groups, respectively.

3.2. Results of univariate and multivariate Cox analyses

Figure 2 shows the results of running log-rank test for the continuous predictors, presenting the optimal cutoff points to split these factors into dichotomous variables. The optimal cutoff points detected for the 3 variables (year of diagnosis, age at diagnosis, and tumor size) were year of 2014, 52 years, and 25 mm, respectively.

The results of univariate Cox analysis are shown in Table 2. As a result, the Black race encountered an increased overall risk of mortality when comparing to the White race (HR = 1.883, 95% CI: 1.364–2.599, *P* < .001). The therapeutic modality of biopsy/STR was associated with an increased OS when comparing to the nonsurgical group (HR = 0.674, 95% CI: 0.454–1.000, *P* = .050). However, GTR did not seem to achieve a better survival than STR. Application of adjuvant RT (HR = 0.670, 95% CI: 0.460–0.970, *P* = .033), married patients (HR = 0.733, 95% CI: 0.544–0.987, *P* = .041), and age of <52 at diagnosis (HR = 3.500, 95% CI: 2.600–4.900, *P* < .001) were demonstrated to be significantly associated with increased OS.

All of the variables related to significantly (*P* < .05) or marginally (*P* < .15) different OS were further enrolled into the multivariate Cox analysis. The forest plot in Figure 3 shows the effect sizes of multivariate Cox analysis, presenting that age at diagnosis (≥52 vs <52, HR 3.62, 95% CI: 2.60–5.05, *P* < .001), marital status (married vs single, HR = 0.72, 95% CI: 0.53–0.99, *P* = .041), race (Black vs White, HR = 1.74, 95% CI: 1.24–2.43, *P* = .001), tumor size (≥25 mm vs <25 mm, HR = 1.78, 95% CI: 1.22–2.59, *P* = .003), and surgery type (biopsy/STR vs no surgery, HR = 0.65, 95% CI: 0.43–0.97, *P* = .033) remained to be statistically significant prognostic factors for OS.

3.3. Establishing and validation of nomogram model

Based on the significant prognostic factors screened by a multivariate Cox model, a graphical predicting nomogram model

Table 1

Baseline characteristics of patients in training and validation groups.

	Overall (N = 991)	Training set (N = 695)	Validation set (N = 296)	*P* value*
Race				
White	707 (71.3%)	500 (71.9%)	207 (69.9%)	.796
Black	189 (19.1%)	129 (18.6%)	60 (20.3%)	
Others	95 (9.6%)	66 (9.5%)	29 (9.8%)	
Gender				
Male	500 (50.5%)	343 (49.4%)	157 (53.0%)	.321
Female	491 (49.5%)	352 (50.6%)	139 (47.0%)	
Year of diagnosis				
<2014	751 (75.8%)	533 (76.7%)	218 (73.6%)	.346
≥2014	240 (24.2%)	162 (23.3%)	78 (26.4%)	
Histology				
Papillary	129 (13.0%)	84 (12.1%)	45 (15.2%)	.408
Adamantinomatous	334 (33.7%)	236 (34.0%)	98 (33.1%)	
Craniopharyngioma, NOS	528 (53.3%)	375 (54.0%)	153 (51.7%)	
Surgery type				
No surgery	175 (17.7%)	116 (16.7%)	59 (19.9%)	.362
Biopsy/STR	414 (41.8%)	289 (41.6%)	125 (42.2%)	
GTR	402 (40.6%)	290 (41.7%)	112 (37.8%)	
Radiotherapy				
No	755 (76.2%)	526 (75.7%)	229 (77.4%)	.626
Yes	236 (23.8%)	169 (24.3%)	67 (22.6%)	
Tumor size, mm				
<25	296 (29.9%)	207 (29.8%)	89 (30.1%)	.717
≥25	399 (40.3%)	285 (41.0%)	114 (38.5%)	
Unknown	296 (29.9%)	203 (29.2%)	93 (31.4%)	
Age at diagnosis, yr				
<52	498 (50.3%)	358 (51.5%)	140 (47.3%)	.252
≥52	493 (49.7%)	337 (48.5%)	156 (52.7%)	
Marital status				
Single	403 (40.7%)	283 (40.7%)	120 (40.5%)	.879
Married	515 (52.0%)	359 (51.7%)	156 (52.7%)	
Unknown	73 (7.4%)	53 (7.6%)	20 (6.8%)	

GTR = gross total resection, NOS = not other specific, STR = subtotal resection.

*The *P* values were calculated based on Student *t* test and chi-square test for the continuous and categorical variables, respectively.

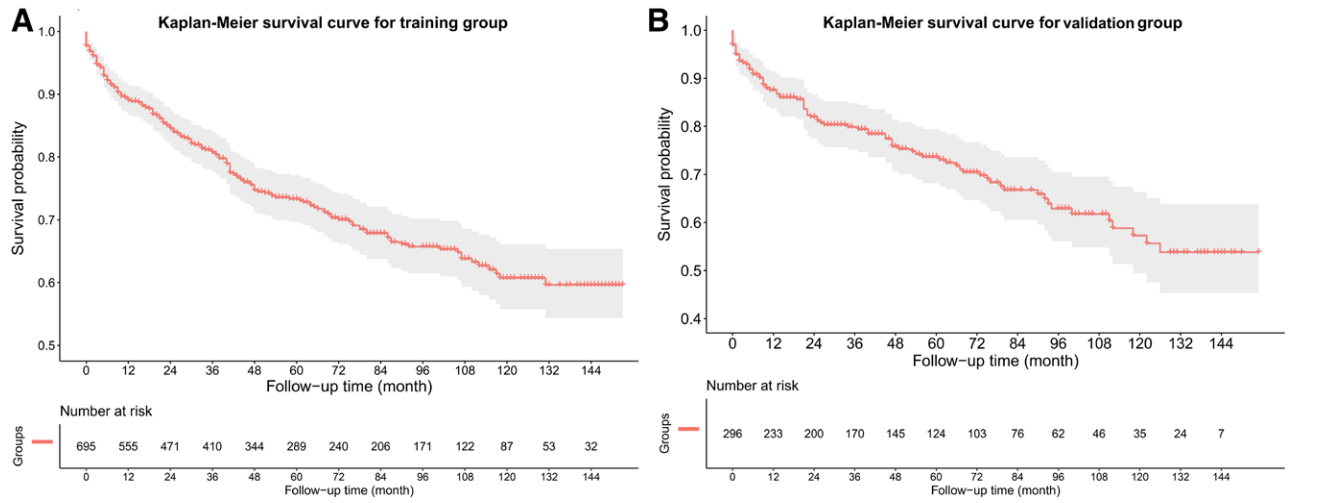

Figure 1. Kaplan-Meier survival curve of overall survival for training (A) and validation (B) samples.

was developed to calculate the predicted patients' OS probabilities at 1, 2, 5, and 10 years (see Fig. 4). Exclusively, the application of adjuvant RT, being only marginally related to OS, was also enrolled as an item in our novel nomogram model for the wide acceptance of the significant prognostic effect. As a result, in total, 6 prognostic factors were finally displayed in the nomogram. Kaplan-Meier survival curves of these 6 predictors are presented in Figure 5, giving the survival curve and risk table for each individual group.

The concordance indexes were 0.708 ± 0.019 and 0.750 ± 0.025 for the training and validation samples, respectively, demonstrating that the newly established nomogram possesses both favorable discrimination abilities. Similarly, the time-dependent AUC plot in Figure 6 shows an overall satisfactory distribution of AUC value at a continuous time period between 0 and 10 years, both for model evaluation in training and validation samples. The calibration curves at 1, 2, 5, and 10 years for the training and validation samples are displayed

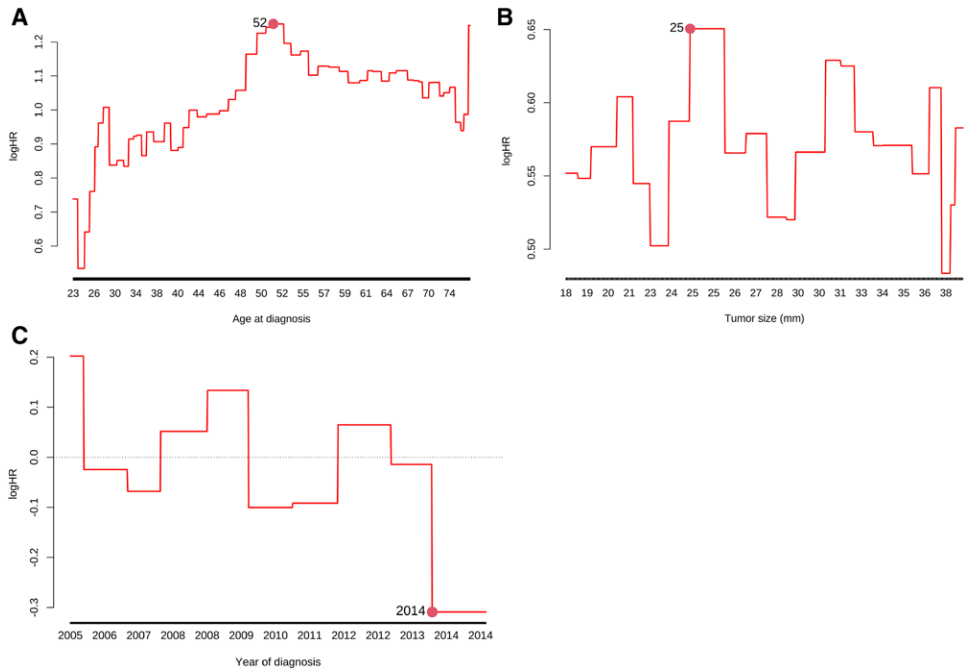

Figure 2. Results of running log-rank tests for detecting the optimal cutoff points of continuous variables including age at diagnosis (A), tumor size (B), and year of diagnosis (C). The optimal cutoff points for the 3 variables were 52, 25, and 2014, respectively.

Table 2

Results of univariate Cox analysis.

Variables	Number of patients, n (%)	HR	95% CI for HR	*P* value
Race				
White	500 (71.9%)	Reference		.349
Black	129 (18.6%)	1.883	1.364–2.599	<.001***
Other	66 (9.5%)	0.667	0.360–1.235	.197
Gender				
Male	343 (49.4%)	Reference		
Female	352 (50.6%)	0.890	0.670–1.200	.450
Year of diagnosis				
≥2014	162 (23.3%)	Reference		
<2014	533 (76.7%)	1.014	0.611–1.684	.956
Histology				
Papillary	84 (12.1%)	reference		.060
Adamantinomatous	236 (34.0%)	1.460	0.830–2.569	.189
Craniopharyngioma, NOS	375 (54.0%)	1.671	0.975–2.864	.062
Surgery types				
No surgery	116 (16.7%)	Reference		.014*
Biopsy/STR	289 (41.6%)	0.694	0.474–1.016	.061
GTR	290 (41.7%)	0.674	0.454–1.000	.050*
Radiotherapy				
No	526 (75.7%)	Reference		
Yes	169 (24.3%)	0.670	0.460–0.970	.033*
Tumor size, mm				
<25	207 (29.8%)	Reference		.003**
≥25	285 (41.0%)	1.890	1.300–2.747	<.001***
Unknown	203 (29.2%)	1.834	1.231–2.732	.003**
Age at diagnosis, yr				
<52	358 (51.5%)	Reference		
≥52	337 (48.5%)	3.500	2.600–4.900	<.001***
Marital status				
Single	283 (40.7%)	Reference		.224
Married	359 (51.7%)	0.733	0.544–0.987	.041*
Unknown	53 (7.6%)	0.999	0.586–1.705	.998

The bold *P* values indicate significant ($P < .05$) or marginally significant ($P < .15$) differences, and the corresponding variables were further analyzed using multivariate Cox model.

CI = confidence interval, GTR = gross total resection, HR= hazard ratio, NOS = not other specific, STR = subtotal resection.

*$P < .05$

**$P < .01$

***$P < .001$.

in Figures 7 and 8, respectively. Generally, favorable consistencies between the predicted and actual survival were presented, indicating satisfactory accuracy of the novel predicting model.

4. Discussion

Nowadays, the optimal management of patients living with CPs remains controversial, and scoring systems for predicting the patients' OS have seldom been established till now. As one of the most crucially evaluated outcomes following treatment of CPs, the predicted OS plays a great role in consideration of the treatment choice. In our current study, based on a large number of records from the SEER database, 6 variables were identified as prognostic factors to be associated with patients' OS, using which a validated nomogram was generated to provide survival probabilities at 12, 24, 60, and 120 months for each individual patient.

Research about CPs have been predominately focused on the children population.[15–17] In these previous studies, a number of patients' characteristics have been evaluated on the prognostic effect on the OS. In the study of Liu et al,[15] they performed a 20-year population-based study with the aim of evaluating the outcome of children with CPs, showing that none of the factors including period of diagnosis, sex, age at diagnosis, greatest tumor dimension, extent of resection, and RT use was significantly associated with the OS and progress-free survival. Exclusively, patients who received surgery and adjuvant RT had marginally better progress-free survival and OS. Hill et al[16] evaluated the outcomes of pediatric CPs treated with different patterns of care and identified the factors associated with OS, presenting equivalent OS among groups of patients treated with STR + RT, GTR, and definitive RT. In addition, tumor size, sex, and age were also shown to be nonsignificantly associated with OS. However, a study by Chen et al[17] investigated the relationship between the operative approaches, clinical pathological factors, and curative effect of the surgical treatment in the children patients with CPs. As a result, the degree of tumor calcification, histological types of tumor (adamantinous CPs vs squamous papillary CPs), and postoperative adjuvant RT were significantly associated with OS, whereas the operative approach and

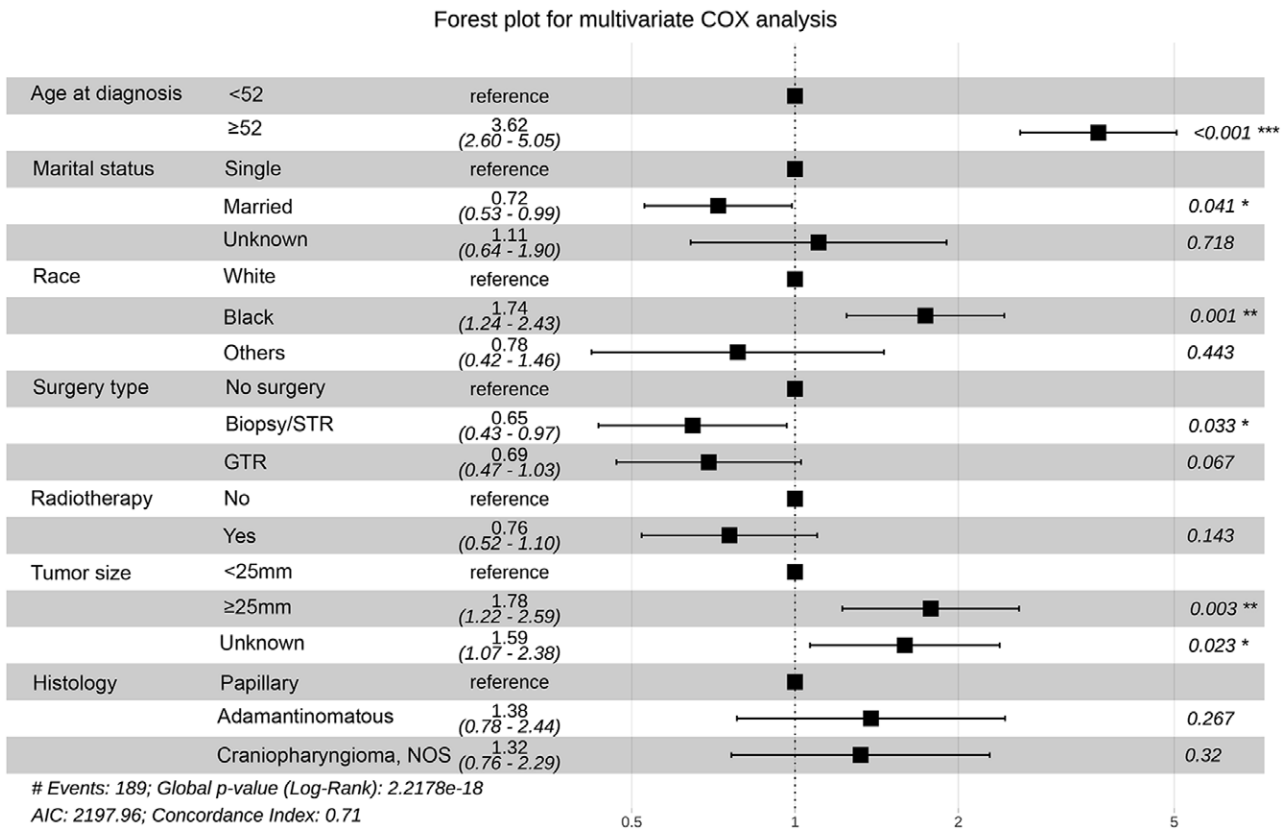

Figure 3. Forest plot for multivariate Cox analysis. *$P < .05$, **$P < .01$, ***$P < .001$.

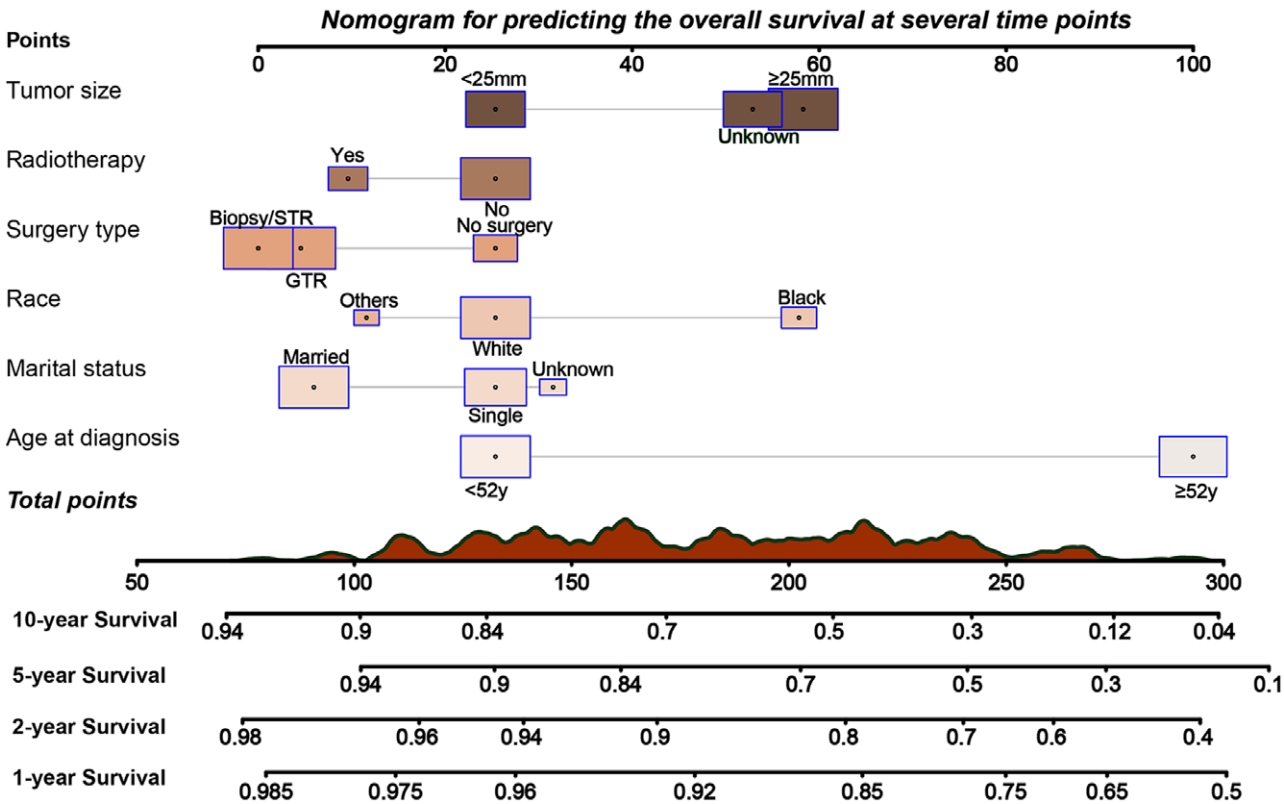

Figure 4. Nomogram for predicting the overall survival at several time points (1, 2, 5, and 10 yr). A total of 6 items, including tumor size, adjuvant radiotherapy, extent of surgery, race, marital status, and age at diagnosis, were listed in the model.

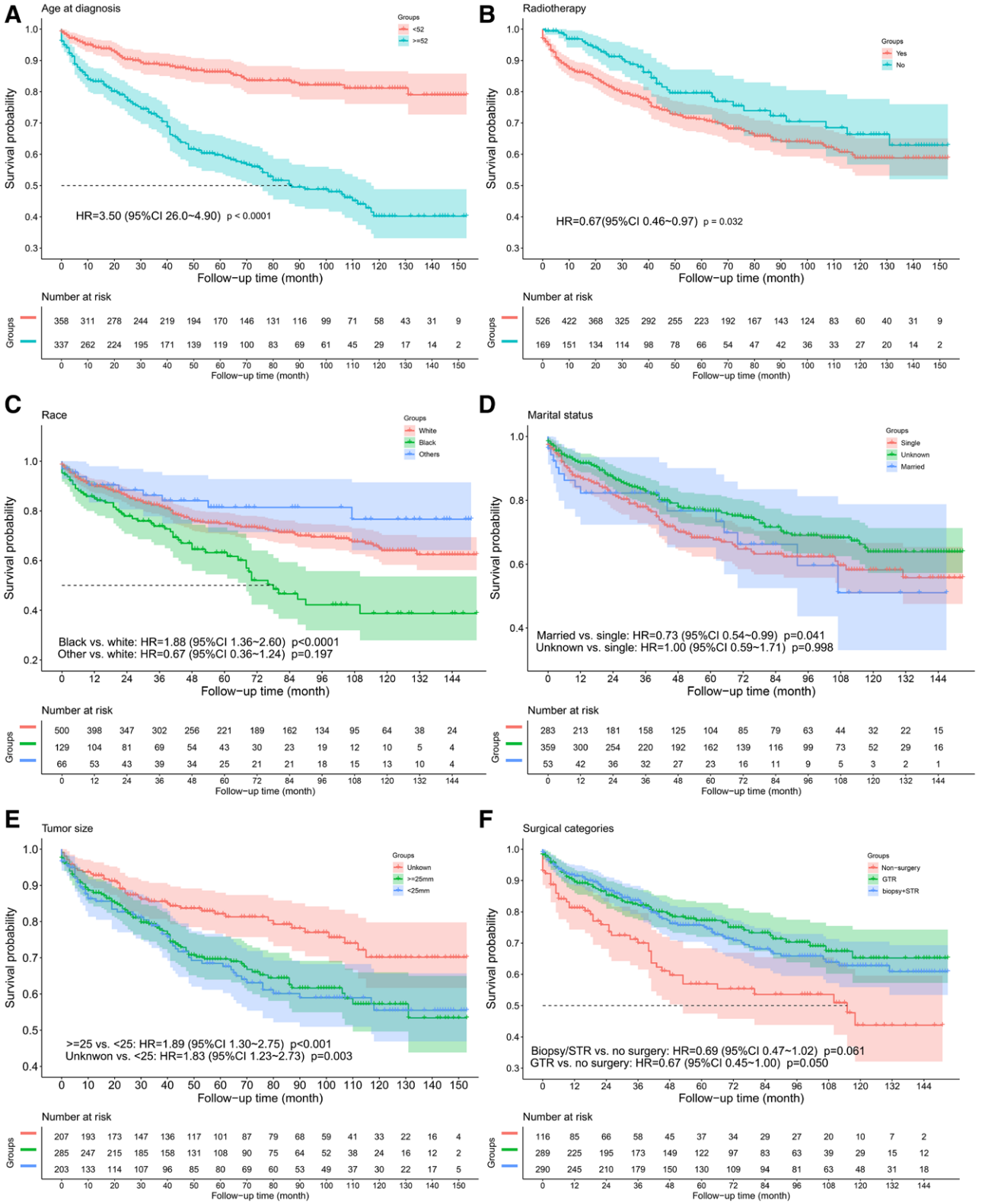

Figure 5. Kaplan-Meier survival curves of the variables included in nomogram, including the age at diagnosis (A), application of adjuvant radiotherapy (B), human race (C), marital status(D), tumor size (E), and extent of surgery (F).

magnetic resonance imaging classification were not significantly related to the OS. The above-mentioned research findings, nevertheless, were derived from children cohort, which might not be suitable for popularization in adults.

This study especially focused on the subgroup of adult patients, presenting convergent results with the formerly published studies.[18–22] Many studies have proven that younger patients have better survival rates.[20,22] Masson-Cote et al[22] reported that in adult CPs patients treated by surgery and RT, age (<53 vs ≥53 years) was identified as the only significant prognostic factor. An optimal cutoff point was detected in the current study, and patients aged >52 years at the tumor

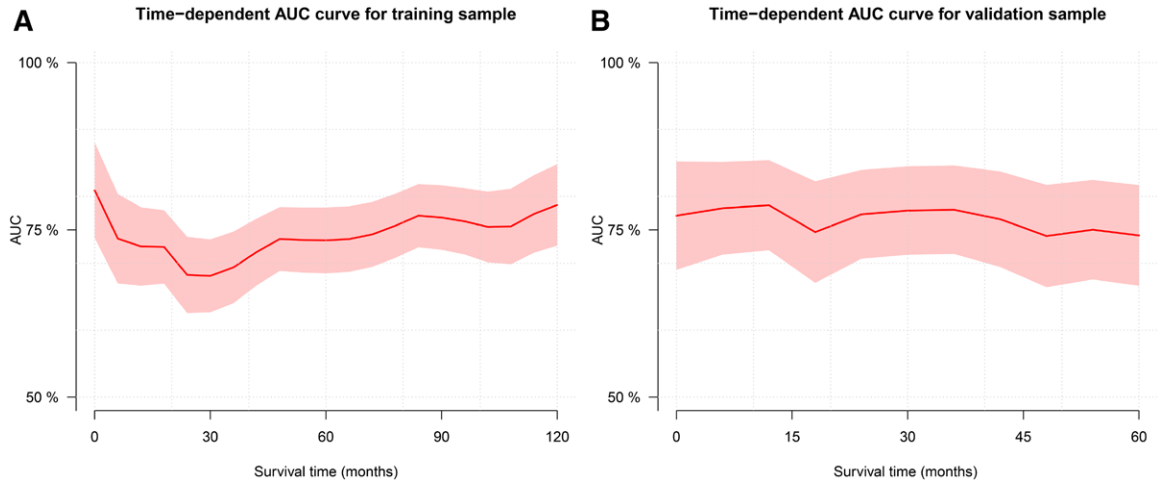

Figure 6. Time-dependent AUC plot for training (A) and validation (B) samples. Both of the training group and validation group showed favorable discrimination ability. AUC = area under curve.

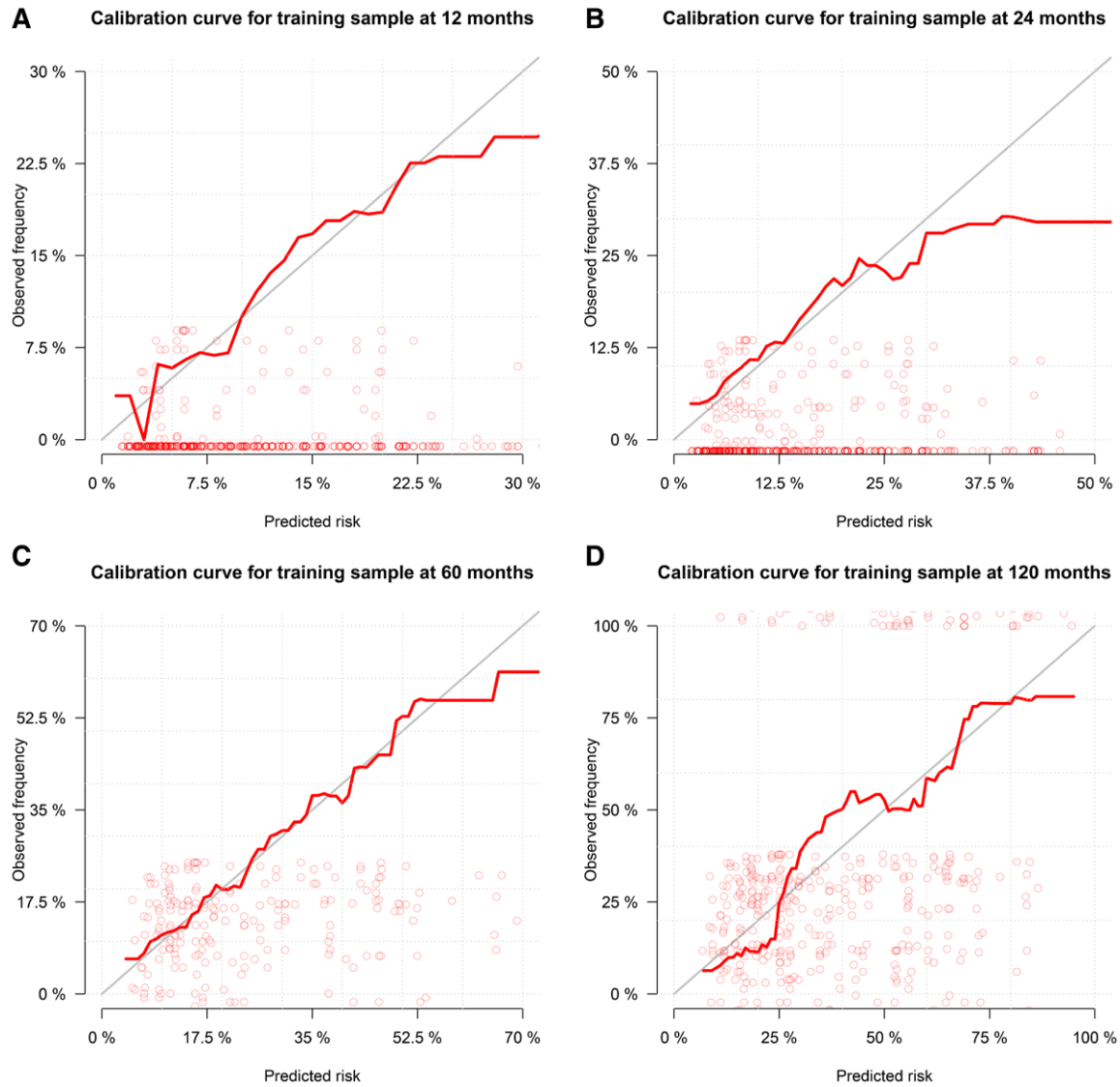

Figure 7. Calibration curves for the training sample at time points of 12 (A), 24 (B), 60 (C), and 120 (D) mo. Satisfactory consistencies between predicted and actual survival probabilities were demonstrated for the 4 different time points.

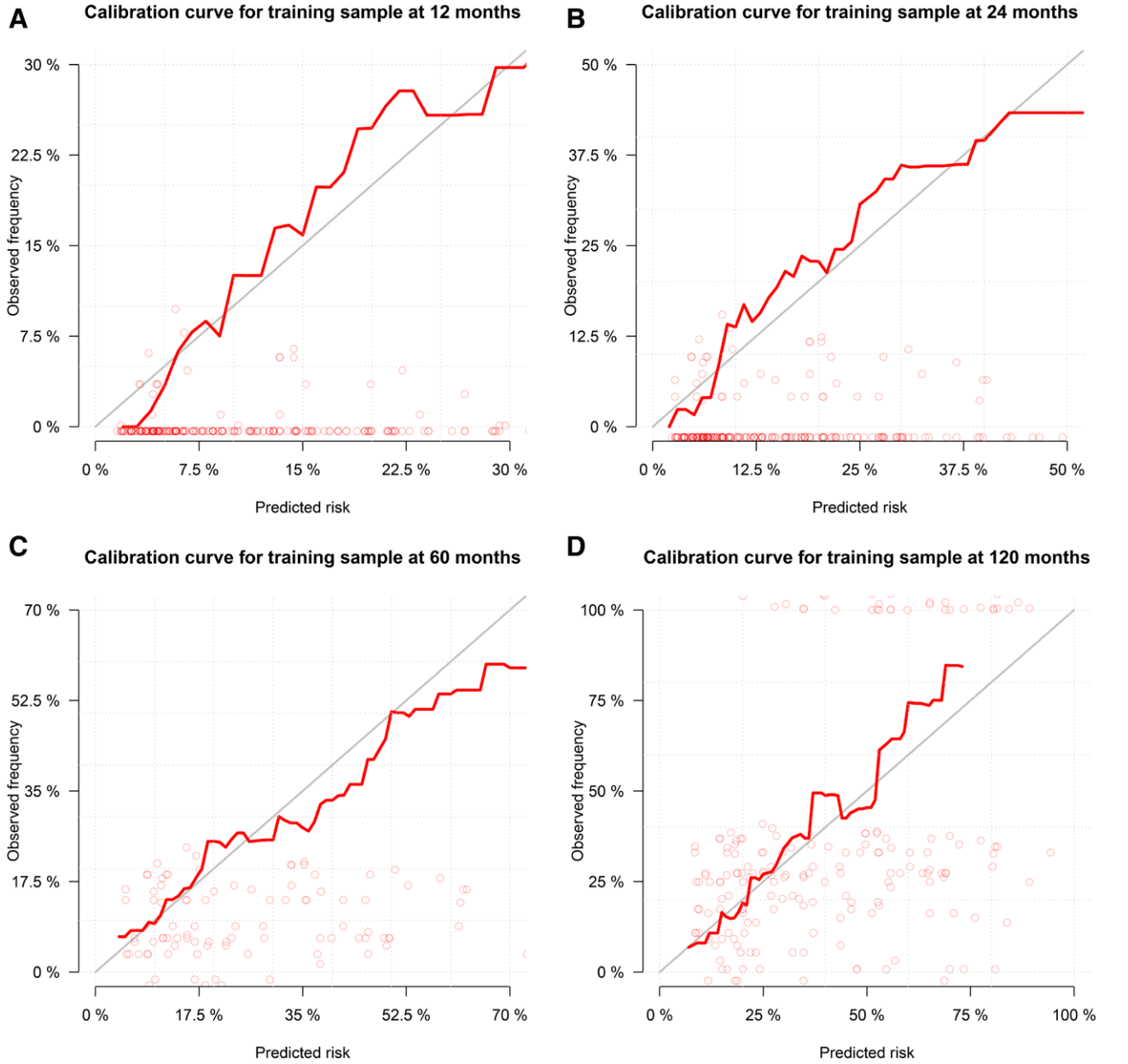

Figure 8. Calibration curves for the validation sample at time points of 12 (A), 24 (B), 60 (C), and 120 (D) mo. Satisfactory consistencies between predicted and actual survival probabilities were demonstrated for the 4 different time points.

diagnosis were proven to have decreased survival rate, which is in accordant with previous results. Zhang et al,[18] observed the 5-year survival of surgically treated patients for CPs and analyzed the potential prognostic factors, showing that the operation type of GTR, adjuvant RT, and neutrophil–lymphocyte ratio were significantly associated with the 5-year survival. The tumor size is likely to be one of the most important prognostic factors, as the diameter of tumor may reflect the progression of lesion and stage of the tumor. Petito et al[19] have shown that a tumor diameter of <3 cm was associated with an increased OS. Our study was in accordant with this previous study; we used another cutoff point and proved that tumor size of <2.5 cm was associated with increased survival. Nowadays, it is elusive whether 1 type of operation management is superior to another one concerning the extent of resection.[10,23–26] Yang et al[10] compared the outcome of patients treated with different extent of resection, including GTR in 256 cases, STR in 101 cases, and STR + adjuvant RT in 85 cases, and no any significance was founded on the differences of progress-free and OS. Similarly, for the comparison between the GTR and STR group, we also failed to identify a significant difference on the OS.

Using these identified factors, we further generated a novel nomogram to help calculate the predicted survival probabilities at several time points, which is so easy to use for clinicians and patients. The SEER database provides a relatively large cohort with long-term follow-ups for the study of adult CP patients, making the developed prediction model more reliable.

This study, nevertheless, has some potential limitations that should be recognized and taken into consideration. First, for its retrospective nature, selection bias could not be avoided. Thus, some future high-quality prospective studies should be designed to further confirm the predictive value of the significant prognostic factors. Second, data on recurrence status, clinical symptoms, performance status, comorbidities, and sequela of treatment were not provided in the SEER database, and detail information on RT was also not available.

Furthermore, potential coding inaccuracy and misclassification of tumor histological type could also raise some concerns. Finally, our newly built prediction model needs to be further validated externally. Some cases from different centers or even different countries/districts should be collected to externally validate the novel model.

5. Conclusions

Based on a large amount of cohort collected from the SEER database, the current study identified that the age at diagnosis, marital status, human race, tumor size, and surgery types were significantly associated with OS of patients living with CPs. A user-friendly nomogram, being proven to be with reliable discrimination ability and accuracy, was then generated utilizing these potential prognostic factors.

Author contributions

Conceptualization: Yong Wu. Data curation: Yong Wu. Formal analysis: Yong Wu. Methodology: Yong Wu and Sheng Hu. Supervision: Bo Xu. Writing – original draft: Yong Wu. Writing – review & editing: Sheng Hu and Bi bo Shao.

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