A nomogram to predict the progression-free survival of clival chordoma

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OBJECTIVE Chordoma shows poor patient prognosis because of its high recurrence rate. Even though many clinical factors and biomarkers are reported to be associated with prognosis, no prediction model has been applied clinically. Thus, the authors aim to derive and validate a prognostic nomogram to predict progression-free survival (PFS) of chordoma.

METHODS A total of 201 patients were randomly divided into a derivation group (151 cases) and a validation group (50 cases). The expression levels of biomarkers were quantified using tissue microarray analysis. A nomogram was established via univariate and multivariate Cox regression analysis in the derivation group. The predictive performance of the nomogram was then tested in the validation group.

RESULTS The mean follow-up interval was 57 months (range 26–107 months). One clinical factor and 3 biomarkers were confirmed to be associated with PFS, including degree of resection, E-cadherin, Ki-67, and VEGFA. The nomogram with these prognostic factors had areas under the receiver operating characteristic curve of 0.87 and 0.95 in the derivation group at 3 years and 5 years, respectively, compared with 0.87 and 0.84 in the validation group. Calibration and score-stratified survival curve were good in the derivation group and validation group, respectively.

CONCLUSIONS The established nomogram performs well for predicting the PFS of chordoma and for risk stratification, which could facilitate prognostic evaluation and follow-up.

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KEYWORDS chordoma; progression-free survival; nomogram; oncology

CHORDOMA is a rare bone tumor with the characteristics of aggressive growth and poor prognosis, and is considered to arise from notochordal remnants.¹⁷ The annual incidence of the tumor is close to one case per million people, which accounts for 1%–4% of all malignant bone tumors.¹³ The tumor mainly locates in the axial skeleton: almost 50% are found in the sacrococcygeal region, followed by the clival region (35%) and mobile spine (15%).²⁰ It is pathologically classified into three types: conventional, chondroid, and dedifferentiated.⁶

Chordoma is not sensitive to chemotherapy and radiotherapy.¹⁵ Targeted drugs do not show satisfactory effect either. Thus, gross-total resection (GTR) is still the first

choice of neurosurgeons. However, the tendency of chordomas to adhere to and infiltrate into important structures make it difficult to achieve GTR, resulting in high recurrence rates.¹⁶ So far, there has been no study reporting a method for predicting the prognosis of clival chordoma. A nomogram is a clinically practical prediction model that has been used in many tumors, such as prostate and gastric cancers.⁹ Use of a nomogram could help doctors make clinical decisions and effectively follow-up patients, which would improve the prognosis.¹⁰ Therefore, establishing a nomogram to predict the prognosis of clival chordoma could be very useful, and predicting the prognosis is critical to both neurosurgeons and patients for treatment deci-

ABBREVIATIONS AUC = area under the ROC curve; GTR = gross-total resection; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; PI = prognostic index; PR = partial resection; ROC = receiver operating characteristic; STR = subtotal resection; TMA = tissue microarray.

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sion-making. The aim of our study is to create and validate a nomogram to predict progression-free survival (PFS) of clival chordoma.

Methods

Study Population

A total of 201 patients who underwent an operation using an endonasal endoscopic approach or craniotomy approach between January 2008 and December 2014 at Beijing Tiantan Hospital were included in the study. The inclusion criteria were as follows: 1) the lesions were located in the clival region, 2) the histopathological diagnosis was chordoma, 3) medical records were complete, and 4) the follow-up interval was at least 24 months. Exclusion criteria were as follows: 1) tumor specimen was insufficient for building the tissue microarray (TMA), 2) medical records were incomplete, 3) and patients were lost to follow-up. The medical ethics committee of Beijing Tiantan Hospital approved the study.

The degree of resection was determined by comparing postoperative with preoperative imaging, and divided into three categories: gross-total resection (GTR; no residual tumor in the postoperative imaging), subtotal resection (STR; < 5% residual tumor), and partial resection (PR; > 5% residual tumor).⁴ Tumor volume was estimated by using the Coniglobus formula³ (length × width × height/2).

Immunohistochemical Staining and Analysis

Formalin-fixed, paraffin-embedded chordoma specimens were used to build a TMA. Sections (4 μm thick) were cut from each TMA. The automated immunohistochemical staining system (Leica BOND III) was used to perform immunohistochemical staining. The stained TMA slides were scanned by a Leica Aperio AT2 scanner at a magnification of 400×. The digital images were analyzed by Leica Aperio ImageScope software (version 12.3). The H-score was calculated to quantify staining intensity. The H-score = 1 × (percentage of weakly positive) + 2 × (percentage of moderately positive) + 3 × (percentage of strongly positive).¹¹ Thus, the H-score ranges from 0 to 300.

Statistical Analysis and Nomogram Construction

All patients were randomly divided into two groups (ratio of patients in the derivation group to those in the validation group = 3 to 1). The chi-square test or t-test was used to evaluate differences between the two groups. Cox regression analysis (univariate and multivariate) was used to identify the risk factors. First we performed univariate Cox regression analysis using all the clinical and biomarker variables. Then, multivariate Cox regression analysis was performed using variables with p values < 0.05 in the univariate analysis. The backward model¹⁴ was used to select the independent factors, which was used to establish the nomogram.

A nomogram was formulated based on the results of multivariate Cox regression analysis in the derivation group. To evaluate the nomogram performance, the area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the sensitivity and specificity of the nomogram,⁷ and a calibration curve was drawn as

an indicator of internal calibration.⁵ Regarding the AUC, a value > 0.7 indicates a good discrimination. The nomogram performance was then further evaluated in the validation group by ROC and calibration curve. Lastly, according to the nomogram, we calculated the risk score for every patient. Patients were divided into two groups (high-risk vs low-risk) by the mean score. The PFS was compared between the high-risk and low-risk groups using the Kaplan-Meier method. The biomarker expression levels were also compared between the two groups.

Statistical analyses were performed using the R statistical program (version 3.5.1). The following packages were used during analysis: “survival” (Terry M. Therneau), “plyr” (Hadley Wickham), “rms” (Frank E. Harrell), and “survminer” (Alboukadel Kassambara). A p value < 0.05 was defined as statistically significant.

Results

Patient Summary

A total of 201 patients (111 men and 90 women) were included in the study. These patients harbored 149 primary and 52 recurrent chordomas. The mean patient age was 41.02 years (range 3–78 years). The mean duration of medical history was 19.24 months (range 0.5–120 months). Tumor volume ranged from 1.44 cm³ to 210 cm³ (mean 33.36 cm³). According to the Al-Mefty classification,¹ there were 28, 97, and 76 cases of type I, type II, and type III chordomas, respectively. TR was achieved in 64 cases (31.8%), STR in 66 cases (32.8%), and PR in 71 cases (35.4%). There are 89 patients (44.3%) receiving postoperative radiotherapy. The mean follow-up interval was 57 months (range 26–107 months).

The patients were randomly divided into two groups (derivation group, n = 151 cases; validation group, n = 50 cases). Patient characteristics are shown in Table 1, which were similar overall between the derivation and validation groups.

Univariate and Multivariate Analysis

Based on literature reviews and previous results from our research team, we focused on 8 clinical factors and 50 biomarkers that could be prognostic factors. Then, Cox regression analysis was performed in the derivation group to determine the potential prognostic factors. The median PFS was 24 months. The PFS rates at 3 and 5 years were 41.8% and 27.9%, respectively.

Univariate Cox regression analysis was used to explore the association between prognosis and each clinical factor and biomarker. Among 8 clinical factors, 3 factors (GTR, Al-Mefty type I, and primary chordoma) were significantly favorable clinical factors. Among 50 biomarkers, 8 (Ki-67, E-cadherin, Ras, NF-KB, BRCA2, Caspase-8, VEGFA, and SFRP4) were significant prognostic biomarkers (Fig. 1).

Multivariate Cox regression analysis was performed among clinical factors and candidate biomarkers, respectively. We found that among the 3 significant clinical factors in univariate Cox regression, degree of resection was the only statistically significant independent prognostic factor. Among the 8 candidate biomarkers, 3 biomarkers

TABLE 1. Patient characteristics

Characteristic	Derivation Group	Validation Group	p Value
No. of patients (%)	151 (75.1)	50 (24.9)	
Sex, n (%)			0.97
Male	84 (55.6)	27 (54.0)	
Female	67 (44.4)	23 (46.0)	
Mean age (range), yrs	41.89 (8–78)	38.38 (3–69)	0.17
Mean duration of history (range), mos	20.62 (1–120)	15.09 (0.5–96)	0.23
Mean volume (range), cm ³	32.54 (1.74–180.31)	35.82 (1.44–210)	0.59
AI-Mefty classification, n (%)			0.12
Type I	25 (16.6)	3 (6.0)	
Type II	73 (48.3)	24 (48.0)	
Type III	53 (35.1)	23 (46.0)	
Primary tumor, n (%)	110 (72.8)	39 (78.0)	0.59
Recurrent tumor, n (%)	41 (27.2)	11 (22.0)	
Degree of resection, n (%)			0.15
GTR	49 (32.5)	15 (30.0)	
STR	54 (35.8)	12 (24.0)	
PR	48 (31.7)	23 (46.0)	
Postop radiotherapy, n (%)			>0.99
Yes	67 (44.4)	22 (44.0)	
No	84 (55.6)	28 (56.0)	
Complications, n (%)			>0.99
Yes	67 (44.4)	22 (44.0)	
No	84 (55.6)	28 (56.0)	

(Ki-67, E-cadherin, and VEGFA) were independent prognostic factors. Table 2 presents the results of univariate and multivariate Cox regression analysis among clinical factors and candidate biomarkers in the derivation group.

Based on the clinical factors and biomarkers, we established a PFS prediction model in the derivation group. The prognostic index (PI) was calculated by the following equation: $PI = 0.8904 \times \text{degree of resection} + 0.0291 \times \text{E-cadherin score} + 0.0447 \times \text{Ki-67 score} + 0.0035 \times \text{VEGFA score}$. The higher the PI was, the worse the prognosis would be.

Nomogram Derivation and Validation

A nomogram (Fig. 2) representing the prognostic model was derived to make it easier to use clinically. The estimated 3- and 5-year PFS rates were obtained according to the sum of each variable score. The ROC curve was used to evaluate the sensitivity and specificity of the nomogram. The model showed a good sensitivity and specificity with AUCs of 0.87 and 0.95 for PFS prediction at 3 and 5 years, respectively (Fig. 3A). The calibration graph was drawn with the predicted 3-year PFS rate and corresponding observed PFS rate. It showed a good calibration of the nomogram (Fig. 3C).

According to the established nomogram, the score of each patient in the derivation group was calculated. Furthermore, the derivation group was divided into two groups by the mean score (cutoff value 105): a low-risk

group (lower than the mean score of the group) and a high-risk group (higher than the mean score of the group). The median PFS of the low-risk group was 48 months, which was significantly higher than that of the high-risk group (12 months, $p < 0.0001$; Fig. 4A). The mean Ki-67 positive rate of the low-risk group in the derivation dataset was 9.79%, which was significantly lower than that of high-risk group (19.60%, $p < 0.0001$; Table 3).

To validate the nomogram's stability, we conducted a validation study using a validation group. The AUCs of the nomogram in the validation group were 0.87 and 0.84 for PFS prediction at 3 years and 5 years, respectively, demonstrating a good prediction (Fig. 3B). The calibration graph of the validation group showed a moderate calibration (Fig. 3D). The validation group was also divided into two groups (low-risk and high-risk groups) by the same cutoff value of the derivation group (cutoff value = 105). The median PFS values of the low-risk and high-risk groups were 42 and 12 months ($p = 0.0002$), respectively. The score-stratified survival curve showed satisfactory stratification (Fig. 4B). The mean Ki-67 positive rate of the low-risk group in the validation dataset was 8.74%, which was significantly lower than that of the high-risk group (18.42%, $p = 0.0002$; Table 3).

Discussion

Chordoma has a poor prognosis because of a high recurrence rate. It has been reported that the 5-year rates

FIG. 1. Univariate Cox regression analysis of 8 clinical factors (**A**) and 50 biomarkers (**B**). Scatter diagram showed that 3 clinical factors and 8 biomarkers were statistically significant. The red vertical line represents a p value of 0.05. Figure is available in color online only.

TABLE 2. Univariate and multivariate Cox regression analysis

Variable	Univariate Analysis (p Value)	Multivariate Analysis		
		HR	95% CI	p Value
Clinical factors				
Age	0.498			
Sex (female vs male)	0.4223			
Duration of history	0.1294			
Volume	0.1055			
Degree of resection (PR or STR vs GTR)	<0.0001	2.7167	1.9413–3.802	<0.0001
AI-Mefty classification (type II or type III vs type I)	0.0013	NS		
Recurrent vs primary chordoma	0.0018	NS		
With vs without postop radiotherapy	0.3234			
Biomarkers				
Ki-67 expression level	<0.0001	1.0285	1.0107–1.047	0.0016
E-cadherin expression level	0.0036	1.0231	1.0081–1.038	0.0024
Ras expression level	0.0062	NS		
NF-KB expression level	0.0107	NS		
BRCA2 expression level	0.0115	NS		
Caspase-8 expression level	0.0183	NS		
VEGFA expression level	0.0281	1.0079	1.0027–1.013	0.0029
SFRP4 expression level	0.0284	NS		

CI = confidence interval; NS = predictors nonselected with the backward method.

for PFS and overall survival (OS) were 59.2% and 77.3%, respectively.²² Postoperative enhanced MRI is the most widely used evaluation technique in follow-up. There are, as far as we know, many prognostic factors that have been reported, such as degree of resection, radiotherapy,² SNF5, PDGFR- β ,²¹ PARP1, etc. However, few prediction models have been established in the published studies, which is inconvenient for early diagnosis or regrowth monitoring. Therefore, we decided to establish an efficient prediction

model to predict regrowth of clival chordoma using clinical factors and biomarkers.

Many articles have reported clinical factors associated with PFS, but no consensus has been reached in this respect. As has been consistently shown in previous studies,^{12,15} radical resection can significantly improve a patient's prognosis. Among the clinical factors in this study, degree of resection was the only independent prognostic factor, which is the most important prognostic factor (haz-

FIG. 2. Nomogram for 3- and 5-year PFS in patients with clival chordomas.

FIG. 3. A and B: ROC curves of the nomogram in the derivation (A) and validation (B) groups. **C and D:** Calibration of the nomogram in the derivation (C) and validation (D) groups. Figure is available in color online only.

FIG. 4. Kaplan-Meier survival curve of patients in the derivation (**A**, $p < 0.0001$) and validation (**B**, $p < 0.0001$) groups stratified by nomogram-predicted score. In the low-risk group, the score is lower than the mean score of the group; in the high-risk group, the score is higher than the mean score of the group. Figure is available in color online only.

ard ratio [HR] = 2.7167). With the assistance of intraoperative navigation and Doppler ultrasonography, the neurosurgeon can recognize important structures surrounding the tumors, which improves the GTR rate without increasing the complication rate. Thus, GTR with protection of surrounding structures is the first choice of neurosurgeons.

Radiotherapy, especially proton therapy, has been reported to improve local control and PFS of chordoma.² In our study, the multivariate Cox regression analysis showed that radiotherapy has no relation with PFS. This indicates that chordoma is resistant to radiotherapy, and more studies are needed to explore its role in prolonging PFS.

The AI-Mefty classification is an important factor during the preoperative assessment,¹ which reveals the dif-

ficulty of resection. However, it was not an independent prognostic factor in our study. We speculate that this classification affects patients' PFS through affecting the resection rate.

Ki-67 locates in the nucleus, which is positive in proliferating cells, and shows the proliferative activity of cells.¹⁸ In our previous study, the average OS in the low Ki-67 expression group was significantly longer than that in the high Ki-67 expression group.¹⁹ Karamchandani et al.⁸ also found that a chordoma with high Ki-67 expression would recur within 2 months. VEGFA and E-cadherin expressions are prognostic markers in oral squamous cell carcinoma, hepatocellular carcinoma, clear cell renal cell carcinoma, and others. However, few articles have reported the

TABLE 3. Comparisons between the low-risk and high-risk groups

Variable	Derivation Group			Validation Group		
	Low-Risk*	High-Risk*	p Value	Low-Risk*	High-Risk*	p Value
Mean H-score of E-cadherin $\pm$ SD	104.03 $\pm$ 9.26	114.36 $\pm$ 15.72	<0.0001	105.29 $\pm$ 9.14	112.51 $\pm$ 15.27	0.044
Mean Ki-67 index $\pm$ SD	9.79% $\pm$ 8.51%	19.60% $\pm$ 12.29%	<0.0001	8.74% $\pm$ 6.08%	18.42% $\pm$ 10.53%	0.0002
Mean H-score of VEGFA $\pm$ SD	140.64 $\pm$ 39.28	155.30 $\pm$ 46.01	0.037	134.05 $\pm$ 38.43	166.10 $\pm$ 50.36	0.014
Mean score $\pm$ SD†	77.07 $\pm$ 17.97	132.72 $\pm$ 18.43	<0.0001	77.73 $\pm$ 16.72	135.49 $\pm$ 22.86	<0.0001
Median PFS, mos	48	12	<0.0001	42	12	0.0002

* Divided by the same cutoff value (105), which was the mean score of the derivation group.

† Calculated according to the established nomogram.

prediction value of E-cadherin and VEGFA in chordoma. In our study, we are the first to report that they are independent prognostic factors, which provides a new research direction.

Even though many biomarkers are reported to be associated with prognosis, none of them have been adapted for clinical use because of their low sensitivity and inconvenience. To assist the neurosurgeon in clinical decision-making, we developed a nomogram using the clinical factor and biomarkers. The cutoff value derived from the nomogram could obviously divide patients into long and short PFS groups. We consider it a very useful tool to predict the PFS of chordoma, help neurosurgeons make decisions, and stratify patients for follow-up. All of the factors included in the nomogram are objective factors, guaranteeing its stability and wider applicability.

However, our study has some limitations. First, the nomogram needs to be further evaluated by prospective research with larger sample sizes in multiple centers. Second, the role of radiotherapy remains controversial. Some published articles found that radiotherapy, especially proton therapy, could prolong PFS. In contrast, some reported that radiotherapy did not offer a survival benefit. In our study, the Cox regression analysis showed no relationship between radiotherapy and PFS. This may be due to the low proportion of postoperative radiotherapy. Thus, the role of radiotherapy needs to be further studied.

Conclusions

We found that degree of resection as well as E-cadherin, Ki-67, and VEGFA expression levels were independent prognostic factors of PFS in patients with clival chordoma. The established nomogram, consisting of a clinical factor and biomarkers, provides a novel tool to predict prognosis and performs well for risk stratification. The sensitivity and specificity is good in both the derivation and validation groups.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zhang, Bai, Wang, Wei. Acquisition of data: Zhai, Bai, M Li. Analysis and interpretation of data: Zhai, M Li. Drafting the article: Zhai. Critically revising the article: Zhai, Wei. Reviewed submitted version of manuscript: Zhai, Bai, M Li, Wang, C Li, Wei. Statistical analysis: Zhai. Administrative/technical/material support: Zhang, C Li, Wei. Study supervision: Zhang, Wang, C Li, Wei.

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