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ORIGINAL ARTICLE

Development and validation of a nomogram containing the prognostic determinants of chondrosarcoma based on the Surveillance, Epidemiology, and End Results database

Jun Zhang[1,2,3] · Zhenyu Pan[1,2,4] · Fanfan Zhao[1,2] · Xiaojie Feng[1,2] · Yuanchi Huang[3] · Chuanyu Hu[5] · Yuanjie Li[6] · Jun Lyu[1,2,7]

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Abstract

Background We aimed to develop and validate a reliable nomogram for predicting the disease-specific survival (DSS) of chondrosarcoma patients.

Methods The Surveillance, Epidemiology, and End Results (SEER) database was queried from 2004 to 2015 to identify cases of histologically confirmed chondrosarcoma. Multivariate Cox regression analysis was performed to identify independent prognostic factors and construct a nomogram for predicting the 3- and 5-year DSS rates. Predictive values were compared between the new model and the American Joint Committee on Cancer (AJCC) staging system using concordance indexes (C-indexes), calibration plots, integrated discrimination improvement (IDI), net reclassification improvement (NRI), and decision curve analysis (DCA).

Results Multivariate Cox regression identified 1180 patients, who were used to establish a nomogram based on a new model containing the predictive variables of age, socioeconomic status, tumor size, surgery status, chemotherapy status, and AJCC staging. In the nomogram, age at diagnosis is the factor with the highest risk, followed by AJCC stage IV and tumor size > 100 mm. Both the C-index and the calibration plots demonstrated the good performance of the nomogram. Moreover, both NRI and IDI were improved compared to the AJCC staging system, and also DCA demonstrated that the nomogram is clinically useful.

Conclusion We have developed a reliable nomogram for determining the prognosis and treatment outcomes of chondrosarcoma patients that is superior to the traditional AJCC staging system.

Keywords Nomogram · Chondrosarcoma · Survival · SEER

Jun Zhang and Zhenyu Pan contributed equally to this work.

✉ Yuanjie Li
liyj2010@xjtu.edu.cn

✉ Jun Lyu
lujun2006@xjtu.edu.cn

[1] Clinical Research Center, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

[2] School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi, China

[3] Department of Orthopaedics, Baoji Municipal Central Hospital, Baoji, Shaanxi, China

[4] Department of Pharmacy, The Affiliated Children Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

[5] Center of Stomatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

[6] Department of Human Anatomy, Histology and Embryology, School of Basic Medical Sciences, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi, China

[7] Institute of Evidence-Based Medicine and Knowledge Translation, Henan University, Kaifeng, China

Introduction

Chondrosarcoma is a heterogeneous group of malignant bone neoplasms involving hyaline cartilage differentiation, which is characterized by the production of cartilage matrix [1, 2]. Chondrosarcoma is the second most common malignancy of bone in adults, with a 5-year DSS rate of 70% [3, 4]. However, high-grade chondrosarcoma is prone to local recurrence or metastasis, and sometimes it results in a poor outcome [5]. This means that there is an urgent need to develop a program system that is technically feasible and easy to apply to stratify the prognosis of patients with chondrosarcoma. A useful anatomic staging system should classify patients into groups of increasing risk based on the local (T), regional (N), and distant (M) extent of disease, basing decisions regarding treatment options, and stratifying patients into risk categories for clinical trials [6]. The AJCC staging system has played an important role in prognostic evaluations of malignancies for a long time [6, 7]. This staging system can be used to divide patients into different risk categories so as to facilitate clinical risk assessments and clinical treatment decisions. Nevertheless, increasing numbers of researchers are realizing that the AJCC staging system also has some limitations, since it only takes tumor size and histological metastasis into account [8, 9]. Some studies have demonstrated that several clinicopathological characteristics are independent prognostic factors for malignancies [7, 10], and there are also reports that the age at diagnosis, race, sex, marital status, SES, and surgery status significantly affect the survival of certain patients [11-14].

Nomogram is a reliable and convenient tool for identifying positive and negative prognostic factors, and they are widely used for determining tumor prognoses [15, 16]. To the best of our knowledge, no previous report has compared the prognostic value of a nomogram for chondrosarcoma with that of the sixth edition of the AJCC staging system. To improve the predictive accuracy for this disease, the present study established and validated a nomogram for chondrosarcoma utilizing demographic and survival information obtained from the SEER database.

Materials and methods

Data source and inclusion criteria

Information about patients was acquired from the SEER database for chondrosarcoma from 2004 to 2015, which covers approximately 30% of the population of the USA and includes cases from 18 population-based registries [15]. Utilizing data from the SEER database does not require informed patient consent, including since no case-identifying information is provided in that database.

We searched for chondrosarcoma patients using the following ICD-O-3 (third edition of the International Classification of Diseases for Oncology) histological subtype codes: "chondrosarcoma, NOS" (9220/3), "juxtacortical chondrosarcoma" (9221/3), "chondroblastoma, malignant" (9230/3). The demographic variables of interest for the patients included age at diagnosis, sex, race, and marital status. The composite SES variable of the percentage of persons in the county living below the national poverty threshold in Census 2000 [17] was divided into three levels using previously reported cutoff points [17, 18]: $< 10\%$ (low poverty), 10–19.99% (moderate poverty), and $\geq 20\%$ (high poverty). In addition, the primary site of chondrosarcoma was categorized into extremity, axial skeleton, and other. Tumor size was categorized into ≤ 50 mm (small), > 50 mm and ≤ 100 mm (intermediate), > 100 mm (large), and unknown [19]. Surgery, radiotherapy, and chemotherapy were categorized into "yes" and "no/unknown" statuses. Patients with missing or unknown information on survival duration or AJCC stage were excluded.

Statistical analysis and nomogram construction

Continuous variables that conformed to a normal distribution are expressed as mean ± SD values. The age at diagnosis is expressed as the median with 25th and 75th percentiles. Categorical variables are expressed as percentages. Survival plots were generated using the Kaplan–Meier method. Multivariate Cox proportional-hazards regression models were constructed based on the results of the univariate analysis to determine the factors that are associated with survival. Based on the predictive model with the identified prognostic factors, a nomogram was constructed for predicting the 3- and 5-year disease-specific survival (DSS) rates.

Validation of the nomogram

The nomogram was validated by measuring discrimination and calibration curves both internally (with a training cohort) and externally (with a validation cohort). Receiver-operating characteristic (ROC) curves were generated to evaluate the performance of the nomogram for the concordance indexes (C-indexes) based on the areas under the ROC curves (AUCs). The agreement between the predicted probability and the actual outcome was evaluated by calibration plotting. Both discrimination and calibration were evaluated using bootstrapping with 1000 resamples to calculate a corrected C-index. Further, improvements in the predictive

accuracy of the new model were estimated by calculating the relative integrated discrimination improvement (IDI) and the net reclassification improvement (NRI), as described by Pencina et al. [20]. Finally, we compared the clinical usefulness and net benefit of the new predictive model and the AJCC staging system using decision curve analysis (DCA) in training cohort, as described by Vickers and Elkin [21].

Statistical analyses were conducted using SPSS (version 24.0, SPSS, Chicago, IL, USA) and R software (version 3.0.1; https://www.r-project.org). Probability values of $p < 0.05$ were considered statistically significant, and all statistical tests were two-sided.

Results

Baseline patient characteristics

The search applying the inclusion criteria identified 2500 chondrosarcoma patients in the SEER database. Information on the survival duration was missing or unknown for two patients, and that on the AJCC stage was missing or unknown for 811 patients. These exclusions resulted in a final total of 1687 chondrosarcoma patients being randomly assigned to either the training cohort ($n = 1180$, for construction and internal validation of the nomogram) or the validation cohort ($n = 507$, for external validation of the nomogram).

The included patients ranged in age from 4 to 98 years, and the median ages at the time of diagnosis were 52.2 both in the training and validation cohorts. The main demographic informations of the patients showed that being male (55.7% and 57.4% in the training and validation cohorts, respectively), white (87.2% and 86.6%), married (56.4% and 59.0%), had a moderate poverty status (52.6% and 50.9%), had the primary site in the extremity (45.3% and 45.6%), were at AJCC stage I (78.6% and 76.9%), had received surgery (89.2% and 88.9%), had not received radiotherapy (86.7% and 85.6%), and had a no/unknown chemotherapy status (95.2% and 93.9%). The clinicopathological characteristics of all the patients are listed in Table 1.

Table 1 Patient characteristics in the study

Variable	Training cohort ($n = 1180$)	Validation cohort ($n = 507$)
Age at diagnosis, median (25–75th percentile)	52.2(40–65)	52.2(40–66)
Sex *n* (%)		
Male	657 (55.7)	291 (57.4)
Female	523 (44.3)	216 (42.6)
Race *n* (%)		
White	1029 (87.2)	439 (86.6)
Black	78 (6.6)	32(6.3)
Other	73 (6.2)	36 (7.1)
Marital status *n* (%)		
Married	665 (56.4)	299 (59.0)
Single/domestic partner	285 (24.1)	122 (24.1)
DSW	230 (19.5)	86 (17.0)
SES *n* (%)		
Low poverty	478 (40.5)	212 (41.8)
Medium poverty	621 (52.6)	258 (50.9)
High poverty	81 (6.9)	37 (7.3)
Site *n* (%)		
Extremity	535 (45.3)	231 (45.6)
Axial skeleton	491 (41.6)	211 (41.6)
Other	154 (13.1)	65 (12.8)
Tumor size *n* (%)		
≤ 50 mm	444 (37.6)	183 (36.1)
> 50–100 mm	416 (35.2)	172 (33.9)
> 100 mm	291 (24.7)	136 (26.8)
Unknown	29 (2.5)	16 (3.2)
AJCC *n* (%)		
I	928 (78.6)	390 (76.9)
II	146 (12.4)	65 (12.8)
III	16 (1.4)	10 (2.2)
IV	90 (7.6)	42 (8.3)
Surgery *n* (%)		
Yes	1053 (89.2)	451 (88.9)
No/unknown	127 (10.8)	56 (11.1)
Radiotherapy *n* (%)		
Yes	157 (13.3)	73 (14.4)
No	1023 (86.7)	434 (85.6)
Chemotherapy *n* (%)		
Yes	57 (4.8)	31 (6.1)
No/unknown	1123 (95.2)	476 (93.9)

DSW divorced, separated and widowed, *SES* socioeconomic status

Kaplan–Meier survival analysis and multivariate Cox regression analysis results

Descriptive epidemiological and survival statistics were calculated for all variables. Kaplan–Meier method was used to calculate the specific survival curve of chondrosarcoma. The Kaplan–Meier results are shown in Fig. 1. Several multivariate models were developed to identify independent prognostic variables. Sex, race, marital status, site, and radiotherapy status were found to not be associated with significant differences in DSS, and so the age at diagnosis, SES, tumor size, AJCC stage, surgery status, and chemotherapy status were entered into the multivariate Cox regression analysis. The multivariate analysis demonstrated that age at diagnosis [hazard ratio (HR) 1.025; 95% confidence

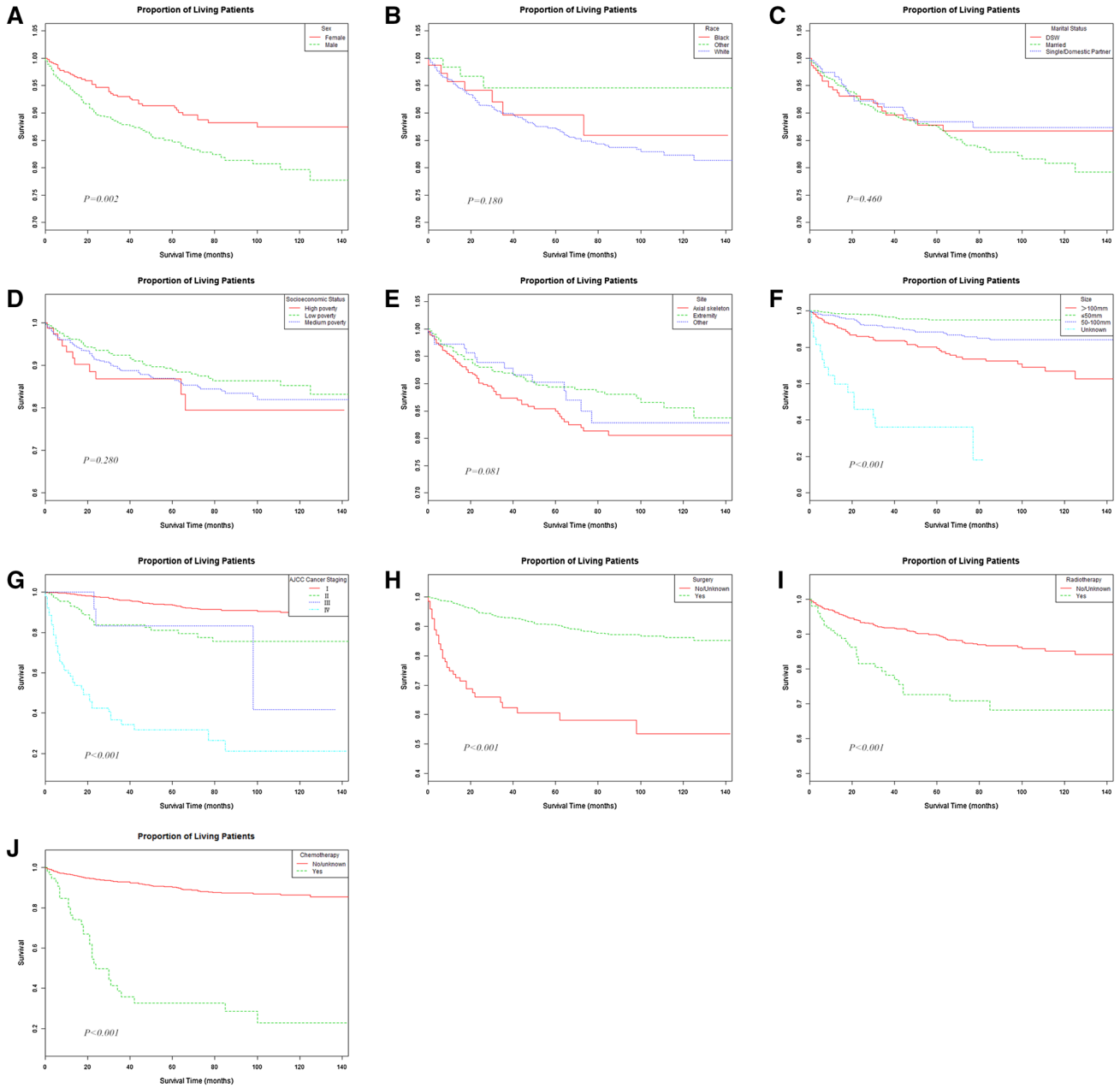

Fig. 1 Kaplan–Meier estimated specific survival in patients with chondrosarcoma stratified by sex (**a**), race (**b**), marital status (**c**), socioeconomic status (**d**), site (**e**), size (**f**), AJCC staging (**g**), surgery (**h**), radiotherapy (**i**), and chemotherapy (**j**)

interval (CI) 1.013–1.036; $p < 0.001$], medium poverty (HR 1.474; 95% CI 1.013–2.145; $p < 0.05$), tumor size > 50–100 mm (HR 2.562; 95% CI 1.439–4.560; $p < 0.01$), size > 100 mm (HR 4.000; 95% CI 2.251–7.107; $p < 0.001$), unknown size (HR 4.418; 95% CI 1.968–9.915; $p < 0.001$), AJCC stage II (HR 2.722; 95% CI 1.669–4.440; $p < 0.001$), AJCC stage IV (HR 6.973; 95% CI 3.969–12.251; $p < 0.01$), and nonsurgical treatment (HR 1.913; 95% CI 1.212–3.019; $p < 0.001$) were independent negative predictors of DSS, whereas a no/unknown chemotherapy status (HR 0.398; 95% CI 0.238–0.664; $p < 0.001$) were weak positive predictors of DSS. Table 2 indicates that other high poverty SES and AJCC stage III were not significant risk factors ($p = 0.052$ and 0.194, respectively).

Table 2 Selected variables in the SEER database by multivariate Cox regression analysis (training cohort)

Variable	Multivariate analysis		
	Hazard ratio	95% CI	*p* value
Age at diagnosis	1.025	1.013–1.036	0.000***
SES			
Low poverty	Reference		
Medium poverty	1.474	1.013–2.145	0.043*
High poverty	1.947	0.994–3.815	0.052
Tumor size			
≤ 50 mm	Reference		
> 50–100 mm	2.562	1.439–4.560	0.001**
> 100 mm	4.000	2.251–7.107	0.000***
Unknown	4.418	1.968–9.915	0.000***
AJCC			
I	Reference		
II	2.722	1.669–4.440	0.000***
III	2.182	0.673–7.077	0.194
IV	6.973	3.969–12.251	0.000***
Surgery			
Yes	Reference		
No/unknown	1.913	1.212–3.019	0.005**
Chemotherapy			
Yes	Reference		
No/unknown	0.398	0.238–0.664	0.000***

SEER Surveillance, Epidemiology, and End Results, *HR* hazard ratio, *SES* socioeconomic status, *AJCC* American Joint Committee on cancer

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Nomogram construction

A nomogram (Fig. 2) was constructed based on the data for the multivariate Cox regression model in Table 2. Given that age had the largest coefficient absolute value; it was set as reference scale ranging from 0 to 100. Each predictor had its factors with points and marks on its line according to the set scale. The total points of the nomogram would be summed and subsequently converted into the probabilities of 3- and 5-year DSS. There were parallel lines below the figure with linear relationship scales with each other [15, 16]. The nomogram showed that the age at diagnosis and AJCC stage IV made the highest risk contributions to the prognosis, followed by tumor size > 100 mm, AJCC stage II, tumor size 50–100 mm, having received chemotherapy, AJCC stage III, being high poverty and medium poverty SES, and no/unknown surgery status.

Performance of the nomogram

Based on the C-index analysis of the SEER training cohort, the nomogram provided relatively high C-indexes for the 3- and 5-year DSS rates of 0.909 and 0.858, respectively; the corresponding values for the external validation cohort were also high, at 0.848 and 0.811. The nomogram system provided better C-indexes than the sixth edition of the AJCC staging system, indicating that the new model had better discriminative ability (Fig. 3). The calibration curves in Fig. 4 depict the calibration of the new model in terms of the agreement between the predicted probabilities and observed outcomes for 3- and 5-year DSS.

Validation of the nomogram

The NRI value in the training cohort was 0.253 (95% CI 0.149–0.529) for 3 years of follow-up and 0.302 (95% CI 0.184–0.606) for 5 years of follow-up; the corresponding values in the validation cohort were 0.025 (95% CI − 0.286 to 0.435) and 0.183 (95% CI − 0.283 to 0.571), respectively. These results indicate that the new model exhibited markedly superior predictive performance compared to the AJCC model. Similarly, the IDI values for 3 and 5 years of follow-up were 0.042 ($p = 0.002$) and 0.049 ($p < 0.001$), respectively.

Clinical usefulness

DCA graphically showed the ideal net benefits of the new model in the training cohort for 3- and 5-year DSS (Fig. 5), which indicates that the model is clinical useful and would have a positive impact on practical decision making.

Discussion

In 2017, approximately 3260 patients were newly diagnosed with malignant primary bone tumors in the United States of America (USA) [22]. Chondrosarcoma constitutes about 30% of all primary malignant osseous sarcomas, which makes it the second most common histological type [23]. Chondrosarcoma is well known to be a malignant tumor comprising transformed cells that produce a cartilaginous matrix without a tumor osteoid. Chondrosarcoma is considered to be more resistant than other malignant primary bone tumors to radiotherapy and chemotherapy due to its abundant extracellular matrix, fewer dividing cells, and slow growth [24, 25]. Surgical resection remains the primary treatment option for chondrosarcoma, and complete en bloc

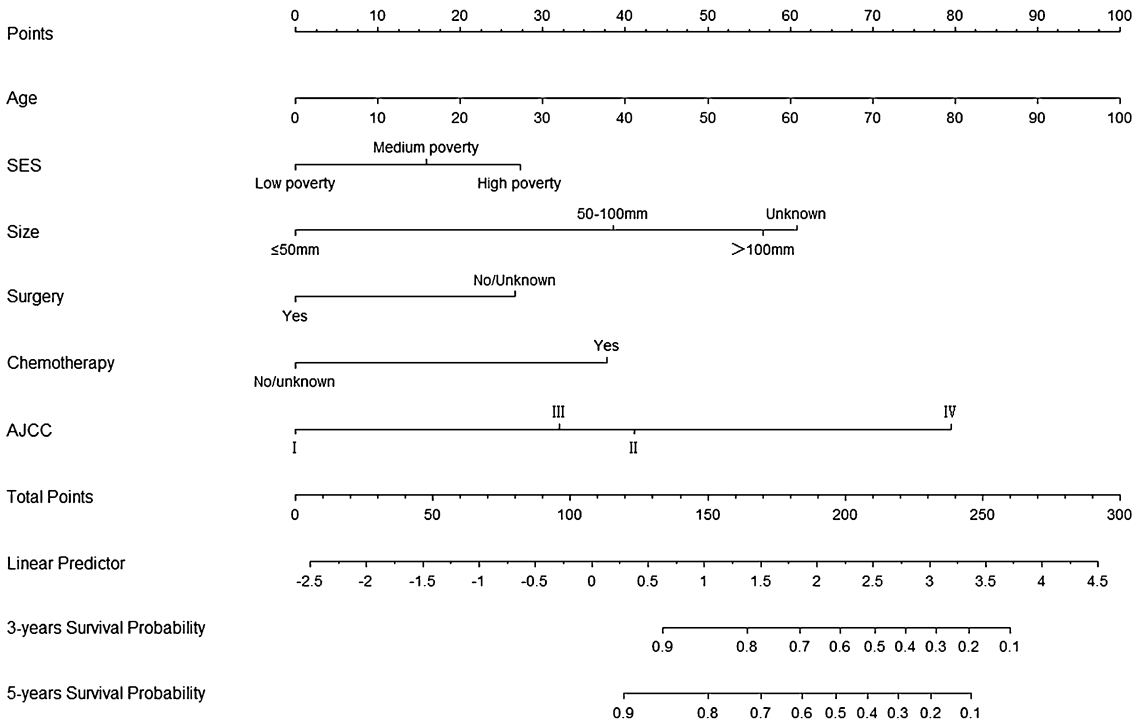

Fig. 2 Nomogram predicting 3-year and 5-year survival. SES, socioeconomic status; AJCC, 6th AJCC tumor stage

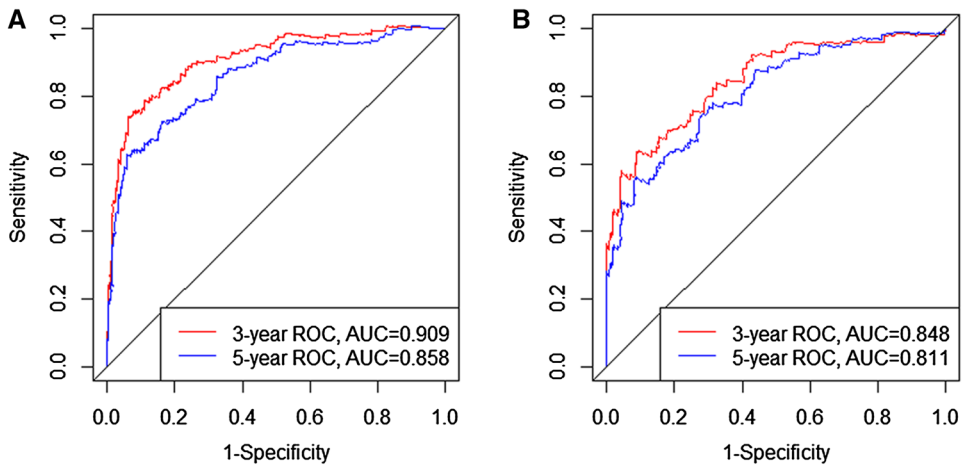

Fig. 3 ROC curves. ROC curve analyses were generated to test the performance evaluating between the new model and the traditional AJCC model, by the AUC. **a** Came from the training set, **b** came from the validation set

excision is an effective therapy for aggressive tumors [26]. Early diagnosis and early surgical treatment are important for improving the prognosis of chondrosarcoma. The prognosis of chondrosarcoma is currently mainly assessed using the American Joint Committee on Cancer (AJCC) staging system [11]. However, clinically we have found that some patients with chondrosarcoma at the same AJCC stage have completely different clinical outcomes, which indicates that there are still limitations judging the prognosis of chondrosarcoma using the AJCC staging system alone [27].

Based on the above-described situation, we constructed a nomogram for the prognosis of chondrosarcoma based on the large-population data queried from the SEER database. The nomogram constructed after Cox regression was based on the following formula: probability of event at time, $t = S_0(t)^{\exp(\beta 1x1+\beta 2x2\ldots)}$ [16], where β are the regression coefficients and x are the reported values of the covariates. $S_0(t)$ is known as the baseline survival function, and the regression coefficient is estimated from the data to construct the variable axis in the nomogram, S_0 is used for the conversion from the total point to the predicted probability (Fig. 1). The

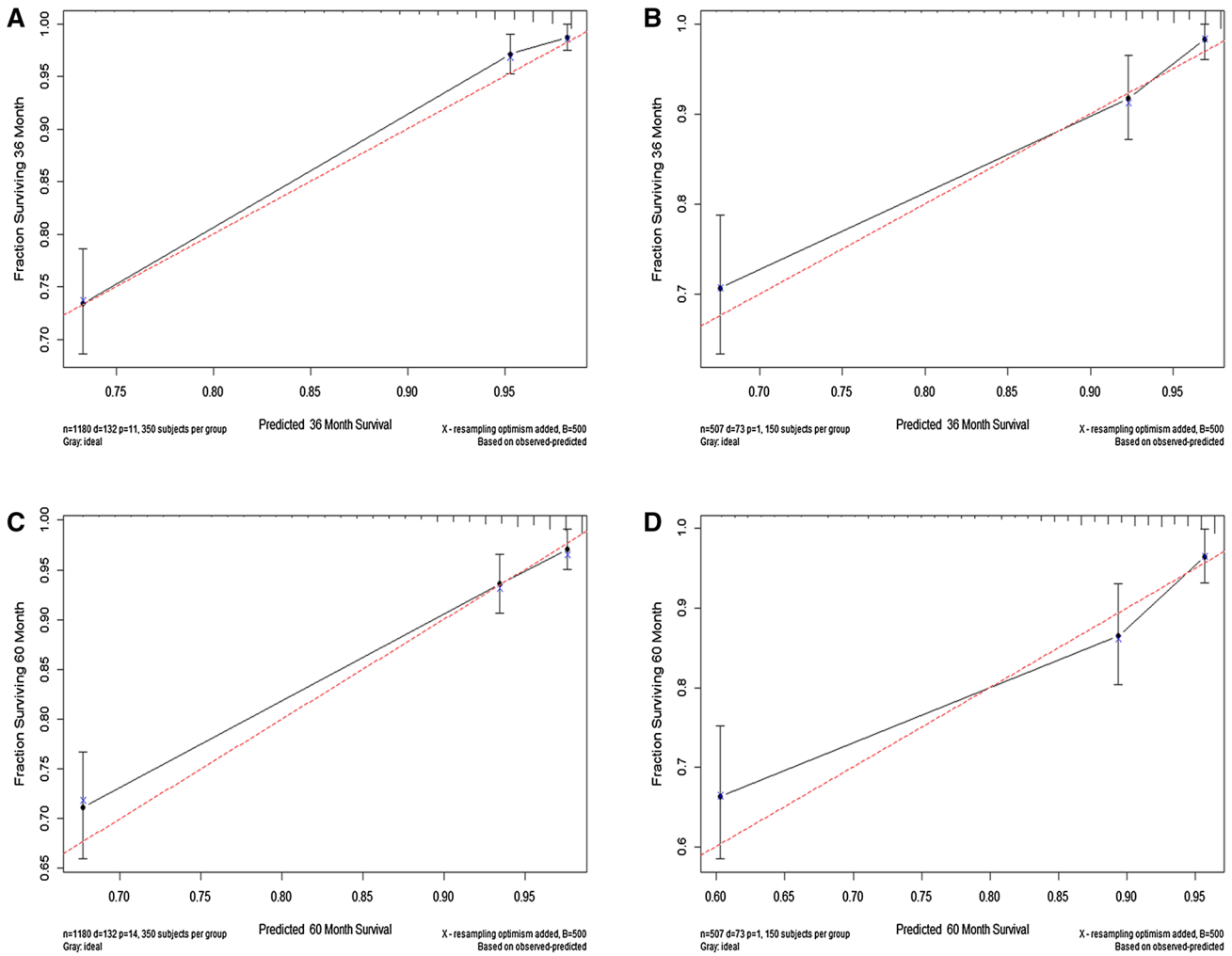

Fig. 4 Calibration curves for 3-year and 5-year survival. Calibration curves depict the calibration of each model in terms of the agreement between the predicted probabilities and observed outcomes of the training set (**a**, **b**) and validation set (**c**, **d**)

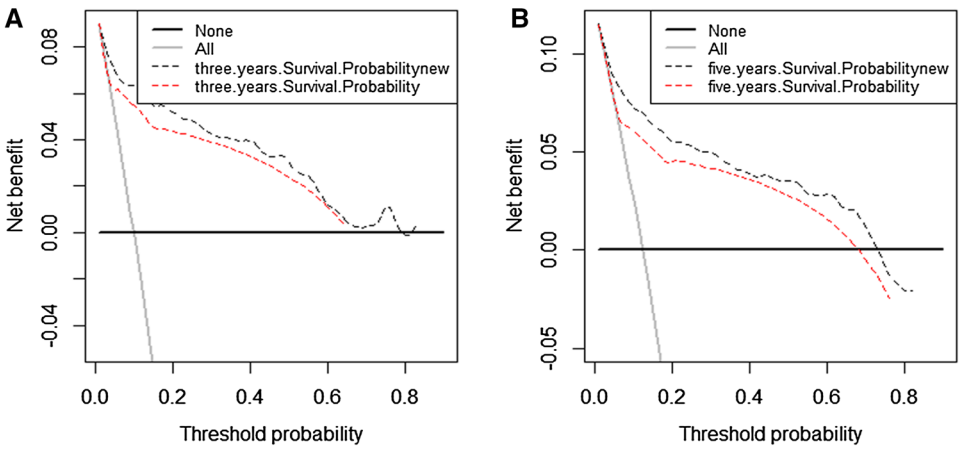

Fig. 5 Decision curve analysis of the training cohort (**a**, **b**) for 3-year and 5-year survival. In the figure, the black dotted line represents the DCA of new model, contrastively, the red dotted line represents the DCA of the traditional AJCC model

new nomogram for chondrosarcoma not only includes the traditional AJCC stage but also covers various clinicopathological characteristics and clinical therapies. After adjusting for other risk factors, the multivariate analysis showed that six variables are independent predictive factors: age at

diagnosis, SES, tumor size, surgery status, chemotherapy status, and AJCC stage.

The nomogram clearly indicates that being older, AJCC stage IV and II, tumor size > 100 mm and 50–100 mm, having received chemotherapy, medium poverty SES, and no/unknown surgery status are the high-risk factors for poor prognosis. This result was similar to Kim et al. reporting that chondrosarcoma patients older than 50 years had worse survival outcomes [28]. We similarly found that increased age was related to a worse survival prognosis for chondrosarcoma patients. These observations indicate that the nomogram is a convenient and exact graphical representation of a mathematical model, indicating very intuitively that various important factors are combined to predict a specific endpoint, and that they are reliable tools for quantifying risk and are widely used for predicting the prognosis of a tumor. A well-designed clinical nomogram can be used to predict the outcome of an individual patient and thereby brings benefits to both clinicians and patients [29].

In this study, we also generated ROC curves to compare the performance between the new model and the traditional AJCC staging system based on AUCs. As seen in Fig. 3, the new model provided relatively higher C-indexes for 3- and 5-year DSS rates in both the training cohort (0.909 and 0.858, respectively) and the internal validation cohort (0.848 and 0.811) compared to the AJCC staging system. These results indicate that our new model provided a good fit to both the randomly assigned training group and the validation group. In addition, we applied calibration curves to depict the calibration of the model in terms of the agreement between the predicted probabilities and observed outcomes. Our new model also showed good performance in both the training and verification sets, as seen in Fig. 4. To determine whether the newly constructed prognostic model provided superior performance and is sufficiently reliable to use in clinical practice, we further applied IDI and NRI to evaluate the performance of our survival model as previously reported [20, 30, 31]. The new model showed better discrimination and calibration than the AJCC staging system, with both IDI and NRI for 3 and 5 years of follow-up producing improved C-indexes, as described in the "Results" section.

Finally, our newly constructed nomogram model contains a wide range of clinical risk factors—including age, SES, tumor size, AJCC stage, surgery status, and chemotherapy status—that are routinely collected and readily available from historical records. In the DCA results shown graphically in Fig. 5, the abscissa is the threshold probability and the ordinate is the net benefit rate [32-35], and this figure illustrates that the new model exhibited ideal net benefits for 3- and 5-year DSS that should justify its clinical use and impact on practical decision making.

Limitations

Similarly to other malignant bone tumors, chondrosarcoma is an exceptionally rare tumor [36, 37], and so our analysis was performed using retrospective data in the SEER database, which inevitably have inherent bias. In addition, a value predicted using the nomogram is suitable as reference information for use by clinicians only, rather than representing an absolutely accurate prognosis. Future studies should focus on developing a well-accepted risk prediction tool for chondrosarcoma [38].

Conclusions

In conclusion, we have established and validated a nomogram for predicting the 3- and 5-year DSS rates in patients with chondrosarcoma based on a large-population-based cohort. The nomogram showed better performance than the traditional AJCC staging system, and so it should be considered a practical tool for prognosis prediction. However, further external validation of the tool is required.

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Compliance with ethical standards

Conflict of interest No financial interests are to be disclosed by the authors.

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