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Research Article

Risk Analysis of Distal Metastasis in Chondrosarcoma and the Development and Validation of a Novel Clinical Prediction Model: A Clinical Study Based on the SEER Database

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Purpose. Distal metastasis in chondrosarcoma is associated with a poor prognosis. The aim of this study was to develop and validate columnar maps to predict the risk of distal metastasis in patients with chondrosarcoma, thereby contributing to clinical diagnosis and treatment. *Methods*. Data from chondrosarcoma patients obtained from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2016 were then screened by univariate and multifactorial logistic regressions to construct a predictive distal metastasis risk. The model discrimination of nomogram was assessed by calibration plots, while the predictive accuracy and clinical values were measured by decision curve analysis (DCA). In addition, predictive column line plots were validated in an in-house test set. *Results*. A total of 1,290 patients were included and randomized in a 7 to 3 ratio into a training group ($n = 906$) and a test group ($n = 384$). After logistic regression analysis, the significant variables were gender, tumor pathological grade, laterality, primary tumor stage, regional lymph node metastasis, surgical treatment, and chemotherapy. Calibration curves showed agreement between column line graph predictions and actual observations, while DCA showed the clinical utility of the nomogram. In addition, ROC showed good discrimination and calibration in the training (AUC = 0.937, 95% CI 0.919–0.952) and validation groups (AUC = 0.91, 95% CI 0.877–0.937). *Conclusions*. The nomogram for distal metastasis risk in patients with chondrosarcoma can effectively predict the individualized risk of distal metastasis and provide clinicians with enlightening information to optimize treatment options.

1. Introduction

Chondrosarcomas (CSs) are a group of heterogeneous bone malignancy with diverse histopathological and clinical features characterized by the production of a cartilaginous stroma [1], which are the second most frequent type of bone malignancy after osteosarcoma, accounting for approximately 20% of all types of bone malignancy. They are commonly found in male adults within flat bones; the pelvis and femur are two common sites of involvement, although any bone may be affected. Most chondrosarcomas exhibit indolent, with approximately 90% below intermediate grade, and stably behave and rarely metastasize [1]. Approximately 8% of the patients with chondrosarcoma developed distant metastasis [2]. Recently, there are no common therapies such as radiotherapy or chemotherapy regimens, and targeted drugs are still under basic research and clinical trials [3]. Fortunately, CS is insensitive to chemotherapy and radiotherapy, after complete surgical resection at present. The prognosis of combined pre- and postsurgical

radiotherapy and chemotherapy is significantly better than that of surgical treatment alone [3]. Some studies have shown that distant metastases occur in 8–38% of patients with chondrosarcoma, which can greatly affect the execution of surgery and make complete resection of the tumor extremely difficult [4]. Pulmonary metastases with local recurrence are the most common reason for death in CS. Prospective research treatment of chondrosarcoma is, therefore, necessary [5], and clinicians treating patients with chondrosarcoma must determine the likelihood of metastasis [6], and it is necessary to identify risk factors for distal metastases, requiring an expansion of treatment options and approaches to improve clinical outcomes. For the current studies, predicting survival in individual patients remains difficult [7].

Since chondrosarcomas with lower incidence are relatively rare, studies assessing prognostic factors are difficult to carry out while requiring a large sample size. The National Cancer Institute's SEER program is a comprehensive source of population-based cancer incidence and survival information from the United States, collecting 18 population-based cancer registries representing approximately 27.8% of the total U.S. population [8]. This study is based on the SEER database, which does not require patient authorization, to investigate risk factors for distal metastasis of chondrosarcoma at the time of initial diagnosis, considering that this database has been providing site-specific data on metastatic tumors since 2010, by collecting information on the demographic and clinical characteristics of chondrosarcoma.

Nomogram is commonly used to generate the likelihood of clinical events through complex computational formulas [4, 9]. With nomograms, clinicians can assess the risk of clinical events, personalize individual treatment alternatives, and optimize treatment strategy. Considering the important role of distal metastasis in the chondrosarcoma prognosis, this research study aimed to assess patients at high risk of distal metastasis from chondrosarcoma through the use of a nomogram.

2. Methods

2.1. Data Sources and Inclusion Criteria. This study was based on the clinical data of patients with chondrosarcoma from the SEER database. Patients with a pathological diagnosis of chondrosarcoma in the SEER database were retrieved through the SEER ∗ Stat software, along with the third edition of the International Classification of Oncology (ICDO-3), morphology code (9220) used to identify chondrosarcoma. The data in this study included patients diagnosed with chondrosarcoma from 2010 to 2016. Exclusion criteria were as follows: (1) patients with no positive pathology; (2) patients with unknown survival; (3) tumors that were not the first occurrence; (4) more than one primary tumor; (5) distal metastasis information unknown; and (6) regional lymphatic fluid information was incomplete for lymph node metastases.

Data were extracted from the SEER database including age, sex, race, primary site, survival duration, laterality, tumor pathology grade, primary tumor stage, surgical treatment, radiotherapy, chemotherapy, and lymph node metastasis. These data were derived from the variable "CS site-specific factor 6." In addition, less than 20 tumor sites were categorized as "other."

2.2. Nomogram Construction, Validation, and Clinical Application. Patients with chondrosarcoma who met the inclusion criteria were randomly divided into training and validation groups in a ratio of 7 to 3. Subsequently, the following variables were selected for the study: age, race, gender, laterality, survival time, tumor pathological grade, primary tumor metastasis, primary site, surgical treatment, radiotherapy, chemotherapy, and lymph node metastasis. Univariate and multivariate binary logistic regressions were applied to identify independent risk factors with a forward stepwise regression method. Nomogram was constructed based on the results of logistic regression analysis. Calibration plot chart of clinical prediction model (calibration plot) and ROC curve were plotted, and ROC was used to estimate the predictive performance of column line plot. The larger area under the ROC curve (AUC) means the better the discriminatory ability or prognostic accuracy of the variable. In addition, decision curve analysis (DCA) plots the net benefit (NB) under a range of reasonable risk thresholds that were consistent with clinical practice and were used to assess the clinical utility of column line plots in decision-making.

2.3. Statistical Methods and Software. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as proportions. Continuous and categorical variables were compared by *t*-test and chi-square test of SPSS, respectively. IBM SPSS Statistics version 26.0 (SPSS Inc., Chicago, IL, USA) and R software version 4.0.5 (http://www.r-project.org) performed the above statistical methods, and several R packages (including regplot, rms, rmda, and pROC) were applied to plot graphs, such as nomogram, calibration plot, DCA plot, and ROC curve. KM curves were plotted by GraphPad Prim 8.0. All P values were bivariate, values of $P < 0.05$ were considered statistically significant, and confidence intervals (CIs) were expressed at the 95% confidence level.

3. Results

3.1. Results of Single-Factor and Multifactor Logistic Regression. A total of 1,290 patients were included in the statistics, and by the univariate and multifactorial logistic regressions, the extracted variables were first subjected to univariate logistic regression analysis, which showed that age, survival time, tumor pathology grading classification, gender, laterality, primary tumor stage, surgical treatment, and chemotherapy were prognostic factors affecting distal metastasis ($P < 0.05$). Further multifactorial logistic risk was performed, resulting in seven factors as independent prognostic factors for distal metastasis (Table 1), such as gender (female: dominance ratio (OR) 0.368, 95% CI (0.150–0.901), $P < 0.05$), tumor pathological grade (GIII:

Table 1: Univariate and multifactorial logistic regression analysis of risk factors for metastases in patients with chondrosarcoma.

Variables	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age (years)	1.018 (1.002–1.035)	<0.05	1.005 (0.983–1.027)	0.656
Survival time (month)	0.959 (0.944–0.975)	<0.001	0.985 (0.965–1.005)	0.146
Race				
White	Ref	Ref	Ref	Ref
Black	1.337 (0.512–3.491)	0.553	—	—
Other	0.583 (0.138–2.467)	0.464	—	—
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.275 (1.36–0.554)	<0.001	0.368 (0.150–0.901)	<0.05
Primary site				
Limb bones	Ref	Ref	Ref	Ref
Axis of a bone	1.569 (0.858–2.872)	0.144	—	—
Other	1.794 (0.580–5.554)	0.311	—	—
Grade				
Well differentiated; grade I	Ref	Ref	Ref	Ref
Moderately differentiated; grade II	4.897 (1.413–16.972)	<0.05	3.047 (0.689–13.474)	0.142
Poorly differentiated; grade III	15.267 (4.253–54.803)	<0.001	6.921 (1.410–33.983)	<0.05
Undifferentiated; anaplastic; grade IV	21.957 (4.935–97.697)	<0.001	3.006 (0.439–20.588)	0.262
Unknown	14.559 (4.162–50.923)	<0.001	6.216 (1.385–27.891)	<0.05
Laterality				
Left	Ref	Ref	Ref	Ref
Right	3.186 (1.533–6.622)	<0.01	2.674 (1.029–6.945)	<0.05
Other	2.384 (1.026–5.542)	<0.05	1.890 (0.584–6.115)	0.288
T				
T1	Ref	Ref	Ref	Ref
T2	8.456 (3.652–19.578)	<0.001	4.698 (1.732–12.738)	<0.01
T3	42.515 (8.463–213.564)	<0.001	59.117 (8.152–428.709)	<0.001
TX	9.101 (3.588–23.082)	<0.001	4.074 (1.221–13.594)	<0.05
N				
N0	Ref	Ref	Ref	Ref
N1	25.901 (6.699–100.184)	<0.001	9.168 (1.572–53.669)	<0.05
NX	8.290 (3.441)	<0.001	6.743 (1.874–24.269)	<0.01
Surgery				
No	Ref	Ref	Ref	Ref
Yes	0.102 (0.057–0.183)	<0.001	0.237 (0.101–0.555)	<0.01
Radiation				
No	Ref	Ref	Ref	Ref
Yes	0.841 (0.327–2.165)	0.720	—	—
Chemotherapy				
No	Ref	Ref	Ref	Ref
Yes	23.505 (11.957–46.205)	<0.001	19.188 (7.554–48.740)	<0.001

OR = 6.921, 1.410–33.983, $P < 0.05$; unclear tumor grading: OR = 6.216, 1.385–27.891, $P < 0.05$), laterality (right: OR = 2.674, 1.029–6.945, $P < 0.05$), primary tumor stage (T2 : OR = 4.698, 1.732–12.738, $P < 0.01$; T3 : OR = 59.117, 8.152–428.709, $P < 0.001$; TX : OR = 4.074, 1.221–13.594, $P < 0.05$), regional lymph node metastasis (positive: OR = 9.168, 1.572–53.669, $P < 0.05$; unknown: 6.743, 1.874–24.269, $P < 0.01$), surgical treatment (OR = 0.237, 0.101–0.555, $P < 0.01$), and chemotherapy (OR = 19.188, 7.554–48.740, $P < 0.001$). The specific results are shown in Table 1 as single- and multifactor logistic regression analysis.

3.2. Baseline Characteristics of Patients with Nonmetastatic and Metastatic Chondrosarcoma. The 1,290 patients were grouped by M0 and M1 and are then summarized in Table 2. Age, tumor pathological grade, laterality, primary tumor stage, regional lymph node metastasis, surgical treatment, chemotherapy, and survival time were shown to be prognostic factors affecting distal metastasis ($P < 0.05$).

3.3. Population Baseline Characteristics. The 1,290 patients were randomized into a training group ($n = 906$, 7 to 3 ratio) and a validation group ($n = 384$), which are then summarized in Table 3. There were no statistically significant differences between the training and validation groups ($P > 0.05$).

3.4. Construction and Validation of Nomogram for Distal Metastasis of Chondrosarcoma. The results of univariate and multivariate logistic regressions were used to construct the nomogram of distal metastasis (Figure 1(a)). The primary tumor stage was the best predictor, followed by chemotherapy, tumor pathological grade, lymph node metastasis,

Table 2: Baseline of chondrosarcoma patients without and with metastases.

Variable	Level	Overall ($N = 1290$)	M0 ($N = 1215$)	M1 ($N = 75$)	P
Race (%)	Black	96 (7.4)	90 (7.4)	6 (8.0)	0.752
	Other	77 (6.0)	74 (6.1)	3 (4.0)	
	White	1117 (86.6)	1051 (86.5)	66 (88.0)	
Age (mean (SD))	NA	53.44 (18.12)	52.96 (18.06)	61.16 (17.43)	<0.001
Sex (%)	Female	571 (44.3)	550 (45.3)	21 (28.0)	0.005
	Male	719 (55.7)	665 (54.7)	54 (72.0)	
Primary site (%)	Axis bone	677 (52.5)	629 (51.8)	48 (64.0)	0.068
	Bone of limb	544 (42.2)	522 (43.0)	22 (29.3)	
	Other	69 (5.3)	64 (5.3)	5 (6.7)	
Laterality (%)	Left	496 (38.4)	482 (39.7)	14 (18.7)	0.001
	Not a paired site	293 (22.7)	268 (22.1)	25 (33.3)	
	Right	501 (38.8)	465 (38.3)	36 (48.0)	
Grade (%)	Moderately differentiated; grade II	518 (40.2)	492 (40.5)	26 (34.7)	<0.001
	Poorly differentiated; grade III	129 (10.0)	115 (9.5)	14 (18.7)	
	Undifferentiated; anaplastic; grade IV	39 (3.0)	32 (2.6)	7 (9.3)	
	Unknown	169 (13.1)	146 (12.0)	23 (30.7)	
	Well differentiated; grade I	435 (33.7)	430 (35.4)	5 (6.7)	
T (%)	T1	716 (55.5)	704 (57.9)	12 (16.0)	<0.001
	T2	389 (30.2)	351 (28.9)	38 (50.7)	
	T3	13 (1.0)	9 (0.7)	4 (5.3)	
	TX	172 (13.3)	151 (12.4)	21 (28.0)	
N (%)	N0	1237 (95.9)	1178 (97.0)	59 (78.7)	<0.001
	N1	11 (0.9)	5 (0.4)	6 (8.0)	
	NX	42 (3.3)	32 (2.6)	10 (13.3)	
Surgery (%)	No	177 (13.7)	133 (10.9)	44 (58.7)	<0.001
	Yes	1113 (86.3)	1082 (89.1)	31 (41.3)	
Lymph node dissection (%)	No	1213 (94.0)	1142 (94.0)	71 (94.7)	1
	Yes	77 (6.0)	73 (6.0)	4 (5.3)	
Radiation (%)	No	1149 (89.1)	1081 (89.0)	68 (90.7)	0.79
	Yes	141 (10.9)	134 (11.0)	7 (9.3)	
Chemotherapy (%)	No/unknown	1231 (95.4)	1181 (97.2)	50 (66.7)	<0.001
	Yes	59 (4.6)	34 (2.8)	25 (33.3)	
Survival months (mean (SD))	NA	34.19 (24.16)	35.38 (24.00)	14.99 (18.03)	<0.001

laterality, surgical treatment, and gender. The calibration plots of the nomogram (Figures 1(b) and 1(c)) showed that the apparent curves, in both training and validation groups, showed good consistency. The AUC values of nomogram were 0.937 (95% CI 0.919–0.952) and 0.91 (95% CI 0.877–0.937) in the training and validation groups, respectively (Figures 2(a) and 2(b)). According to the ROC curves in the training set, the values of nomogram were more important than other variables, including tumor pathological grade (AUC = 0.733, 95% CI 0.703 to 0.762), laterality (0.591, 0.558 to 0.623), primary tumor stage (AUC = 0.608, 95% CI 0.575 to 0.640), gender (AUC = 0.635, 95% CI 0.603 to 0.666), and surgical treatment (0.718, 95% CI 0.688 to 0.748). Similarly, nomogram values were higher in the test set than in the univariate, as shown in Table 4.

3.5. Clinical Usefulness of the Distal Metastasis Nomogram. Kaplan-Meier survival curves for overall survival (OS) were plotted for the 1,290 patients enrolled in the study (Figure 3(a)), and there was a significant difference between the Kaplan-Meier survival curves for the two groups ($P < 0.001$), suggesting that patients with chondrosarcoma who are expected to develop distal metastases would have a significant survival disadvantage. Subsequently, the DCA curve shown (Figure 3(b)) with a threshold of approximately 0–0.7 was the maximum gain for distal metastasis.

4. Discussion

This study is a study to analyze the risk of distal metastasis in chondrosarcoma based on the SEER database. According to the study, approximately 8% of patients with chondrosarcoma develop distal metastases [10]. Since patients with chondrosarcoma combined with distal metastases have a poor prognosis, it is necessary to identify relevant factors to identify patients with chondrosarcoma at high risk for distal metastases [11]. The results of this study showed that patients with tumor pathological grade 3, i.e., hypofractionated tumor and tumor with an unclear grade, laterality to the right, higher stage of primary tumor, lymph node metastasis, male, nonsurgical treatment, and chemotherapy alone were at higher risk of distal metastasis.

This study found that tumors with grade 3 pathology versus unclear grade had a higher risk of distal metastasis. In both univariate and multifactorial logistic regression analyses, tumor pathology grade 3 and unclear grade were associated with the risk of distal metastasis, with OR values of 6.921 and 6.216, respectively, representing a 6.921- and 6.216-fold higher risks of distal metastasis in

Table 3: Baseline data table of the training group and the validation group.

Variable	Level	Overall ($N = 1290$)	Training group ($N = 906$)	Validation group ($N = 384$)	P
Race (%)	Black	96 (7.44)	65 (7.17)	31 (8.07)	0.6624
	Other	77 (5.97)	57 (6.29)	20 (5.21)	
	White	1117 (86.59)	784 (86.53)	333 (86.72)	
Age (median (IQR))	NA	54.000 [41.000, 67.000]	54.000 [41.000, 67.000]	55.000 [41.000, 67.000]	0.6463
Sex (%)	Female	571 (44.26)	401 (44.26)	170 (44.27)	1
	Male	719 (55.74)	505 (55.74)	214 (55.73)	
Primary site (%)	Axis bone	677 (52.48)	471 (51.99)	206 (53.65)	0.6012
	Bone of limb	544 (42.17)	383 (42.27)	161 (41.93)	
	Other	69 (5.35)	52 (5.74)	17 (4.43)	
Laterality (%)	Left	496 (38.45)	353 (38.96)	143 (37.24)	0.6818
	Not a paired site	293 (22.71)	200 (22.08)	93 (24.22)	
	Right	501 (38.84)	353 (38.96)	148 (38.54)	
Grade (%)	Moderately differentiated; grade II	518 (40.16)	346 (38.19)	172 (44.79)	0.1098
	Poorly differentiated; grade III	129 (10.00)	99 (10.93)	30 (7.81)	
	Undifferentiated; anaplastic; grade IV	39 (3.02)	28 (3.09)	11 (2.86)	
	Unknown	169 (13.10)	127 (14.02)	42 (10.94)	
	Well differentiated; grade I	435 (33.72)	306 (33.77)	129 (33.59)	
T (%)	T1	716 (55.50)	503 (55.52)	213 (55.47)	0.8912
	T2	389 (30.16)	272 (30.02)	117 (30.47)	
	T3	13 (1.01)	8 (0.88)	5 (1.30)	
	TX	172 (13.33)	123 (13.58)	49 (12.76)	
N (%)	N0	1237 (95.89)	869 (95.92)	368 (95.83)	0.6182
	N1	11 (0.85)	9 (0.99)	2 (0.52)	
	NX	42 (3.26)	28 (3.09)	14 (3.65)	
M (%)	M0	1215 (94.19)	853 (94.15)	362 (94.27)	1
	M1	75 (5.81)	53 (5.85)	22 (5.73)	
Surgery (%)	No	177 (13.72)	124 (13.69)	53 (13.80)	1
	Yes	1113 (86.28)	782 (86.31)	331 (86.20)	
Lymph node dissection (%)	No	1213 (94.03)	854 (94.26)	359 (93.49)	0.6848
	Yes	77 (5.97)	52 (5.74)	25 (6.51)	
Radiation (%)	No	1149 (89.07)	807 (89.07)	342 (89.06)	1
	Yes	141 (10.93)	99 (10.93)	42 (10.94)	
Chemotherapy (%)	No/unknown	1231 (95.43)	859 (94.81)	372 (96.88)	0.14
	Yes	59 (4.57)	47 (5.19)	12 (3.12)	
Survival months (median (IQR))	NA	31.000 [13.000, 53.000]	31.000 [13.000, 54.000]	30.500 [13.000, 51.000]	0.2844

hypofractionated tumors and tumors with unclear grade than in highly differentiated tumors. It has also been shown that the main prognostic factor for patients with chondrosarcoma is the grade of the tumor, with increased pathological grade suggesting a poor prognosis [12]. Approximately 85% of these tumors are low grade, and overall survival is favorable [13], due to the fact that low-grade chondrosarcomas have abundant cartilage stroma, low cell density, are easily locally confined, and have a good prognosis after surgical resection, whereas high-grade tumors have little cartilage stroma, high cell density, and are prone to metastasis, leading to a poor prognosis [1]. Therefore, high-grade tumors have been considered as an independent risk factor for metastasis and death [14], which is also consistent with the findings of this study. Regarding laterality at diagnosis, this study concluded that the more right-sided tendency at diagnosis, the greater the risk of developing metastasis. The results of logistics analysis in Table 1 show that with right-sided tendency, the risk of developing metastasis is 2.674 times greater than with left-sided tendency. Chondrosarcoma is often a lateral growth, and there are fewer related studies. This study found that right-sided laterality has a higher risk of developing distal metastasis, and the reasons for this need further study. It was found that the higher the primary tumor stage, the higher the risk of distal metastasis. In the univariate and multifactorial logistic regression analyses, T2, T3, and TX were associated with the risk of distal metastasis, with OR values of 4.698, 59.117, and 4.074, respectively, representing that the risk of developing distal metastasis will be higher when the primary tumor is limited to the bone cortex, exceeds the bone cortex, or cannot be determined 4.698, 59.117, and 4.074 times, with the highest risk of distal metastasis at T3 stage. Possible reasons for this phenomenon are that as the tumor volume increases, the depth of infiltration and the extent of collateral tissue involvement increase, and the tumor becomes more

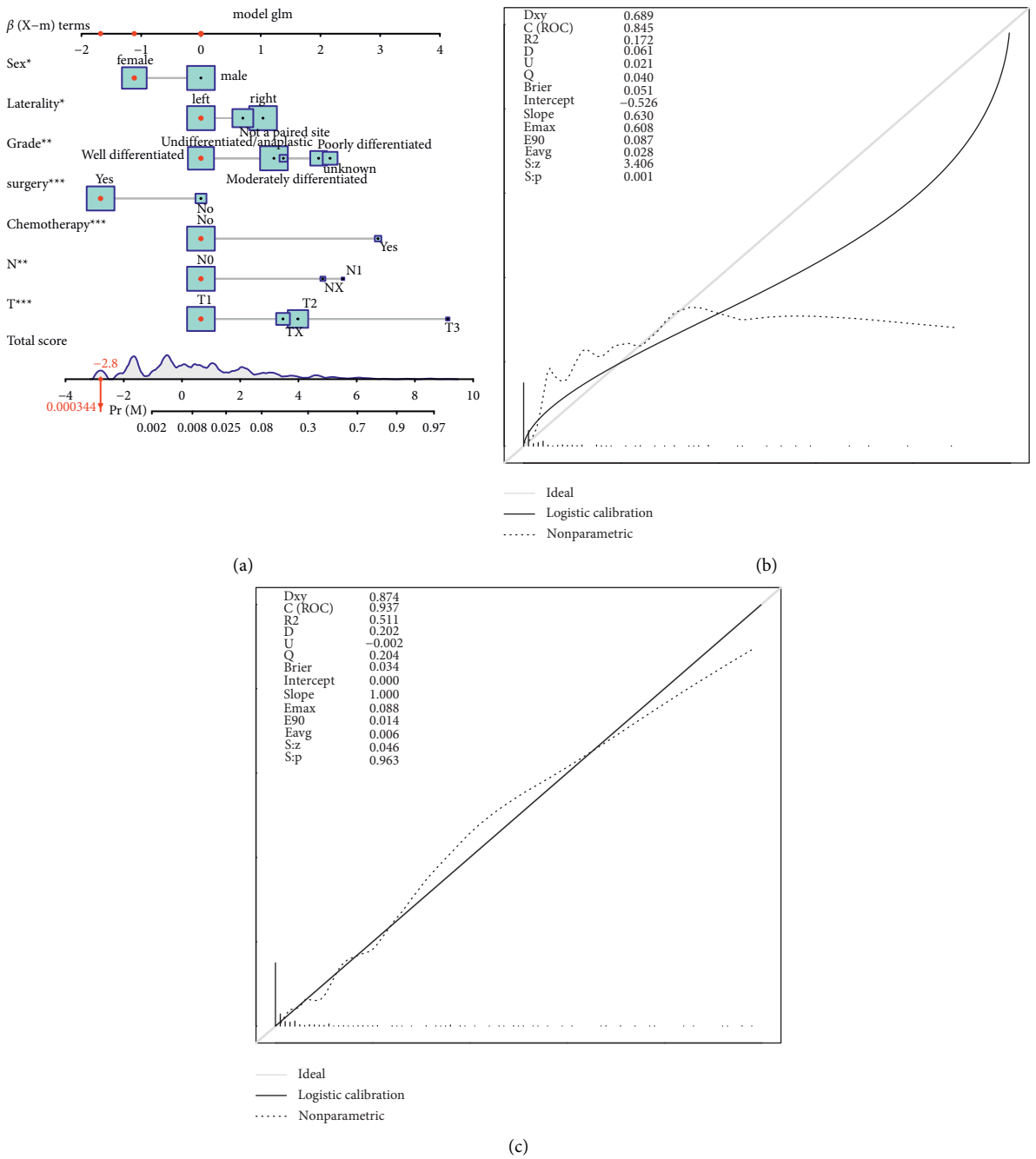

Figure 1: Line plots and calibration curves to predict the risk of distal metastasis in patients with chondrosarcoma. Seven features are included in the nomogram (a) and illustrated by mapping their values to covariate scales for patients. The calibration plot that predicts the training group (b) and the test group (c) is shown on the right.

aggressive and also predicts a higher degree of malignancy, thus increasing the likelihood of metastasis [15]. It has been suggested that larger chondrosarcomas may be a predictor of poor survival expectations [16], which is also consistent with the findings of this study.

It is also noteworthy that this study found studies showing that inability to undergo surgical resection and chemotherapy alone has a higher risk of metastasis, with an OR of 19.188 in univariate and multifactorial logistic regression analyses, representing an inability to resect and a 19.188-fold higher risk of distal metastasis after chemotherapy alone. A related study found chemotherapy to be an important risk factor, and the results indicated that patients receiving chemotherapy were more likely to have higher tumor grade, larger tumor size, and greater tumor extent [17], consistent with the findings of this study. This may be related to the ineffective delivery of chemotherapeutic agents, with some studies showing that tumors poorly respond to chemotherapy, and no significant improvement in disease-free survival or overall survival was seen compared

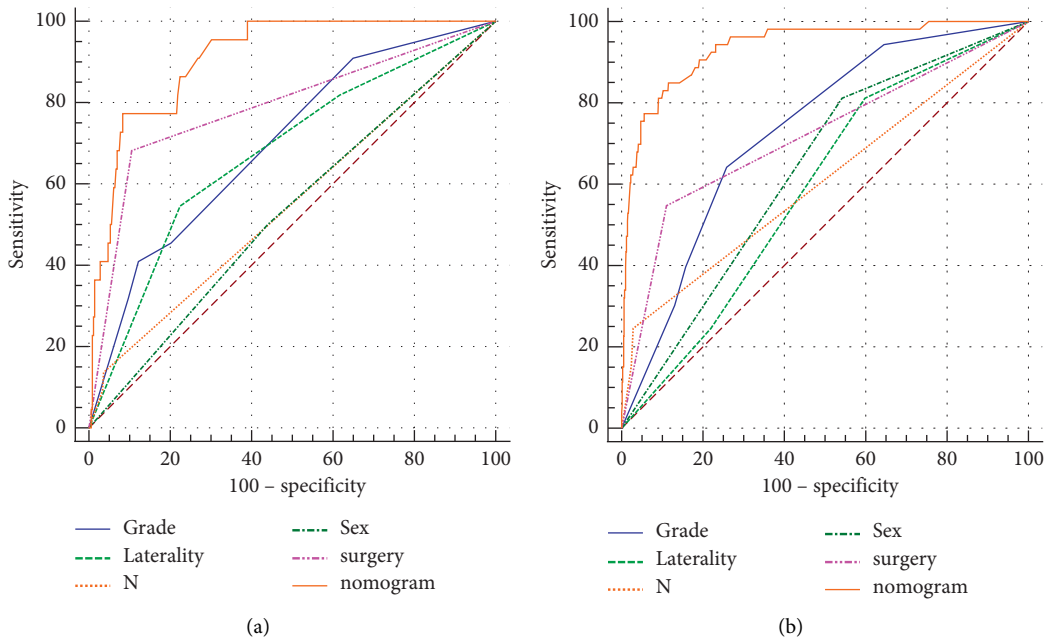

Figure 2: ROC curve analysis of nomogram for indicating the discriminative ability of nomogram. In the nomogram of training (a) and testing (b) groups, the AUC was 0.937 (95% CI 0.919–0.952) and 0.91 (95% CI 0.877–0.937), respectively, which proved that the nomogram had a good predictive ability.

Table 4: AUC of the training group and validation group.

	Training group			Validation group		
Variable	AUC	SE	95% CI	AUC	SE	95% CI
Grade	0.733	0.03	0.703 to 0.762	0.699	0.0534	0.650 to 0.745
Laterality	0.591	0.0329	0.558 to 0.623	0.678	0.0589	0.628 to 0.724
N	0.608	0.0298	0.575 to 0.640	0.55	0.0374	0.498 to 0.600
Sex	0.635	0.0284	0.603 to 0.666	0.53	0.0561	0.479 to 0.581
Surgery	0.718	0.0349	0.688 to 0.748	0.788	0.0515	0.744 to 0.828
Nomogram	0.937	0.0173	0.919 to 0.952	0.91	0.025	0.877 to 0.937

to cohorts that did not receive chemotherapy [18]. The role of chemotherapy in the treatment of patients with localized and advanced chondrosarcoma is unclear. Although its use in conventional chondrosarcoma has been largely ineffective, recent data suggest that it may play a role in certain chondrosarcoma subtypes, particularly dedifferentiated and mesenchymal variants, and reports suggest that chemotherapy may provide benefit for this particular subtype [19]. Therefore, further research is needed on the role of chemotherapy in the treatment of chondrosarcoma. In this study, we found that the OR of the population treated with surgery compared to the population not treated with surgery showed that the risk of distal metastases was only 0.2 times higher in patients who underwent surgery. Surgical resection is the primary treatment for both primary and metastatic chondrosarcoma [20]. The goal of resection is to remove the primary tumor with clear margins to limit recurrence and metastasis. Currently, 90% to 95% of patients with osteosarcoma of the extremities successfully avoid amputation through limb-preserving surgery [21]. It has also been demonstrated in relevant studies that high-grade chondrosarcoma (grade 2 and above) is best treated with extensive resection [22]. Approximately half of the patients have a good or very good prognosis [23], which is consistent with the findings of this study. This study showed that male patients with chondrosarcoma had a higher and statistically different risk of developing distal metastases compared to female patients. OR values showed that female patients had only 0.4 times the risk of developing LM compared to male patients. A related study found that men were an independent risk factor for survival in patients with chondrosarcoma [24]. Considering that men have a higher risk of distal metastasis, it may, therefore, affect survival expectations.

According to the results of the regression analysis in Table 1 logistics, patients with lymphatic metastases had an approximately 9-fold higher risk of distal metastasis than patients without lymphatic metastases (OR = 9.168), and patients with unknown lymphatic metastases had an approximately 7-fold higher risk of distal metastasis than patients without lymphatic metastases (OR = 6.743). The prevalence of regional lymph node involvement in patients with chondrosarcoma is 1.3% due to the lack of lymphatic vessels in the bone, which rarely metastasize through lymph

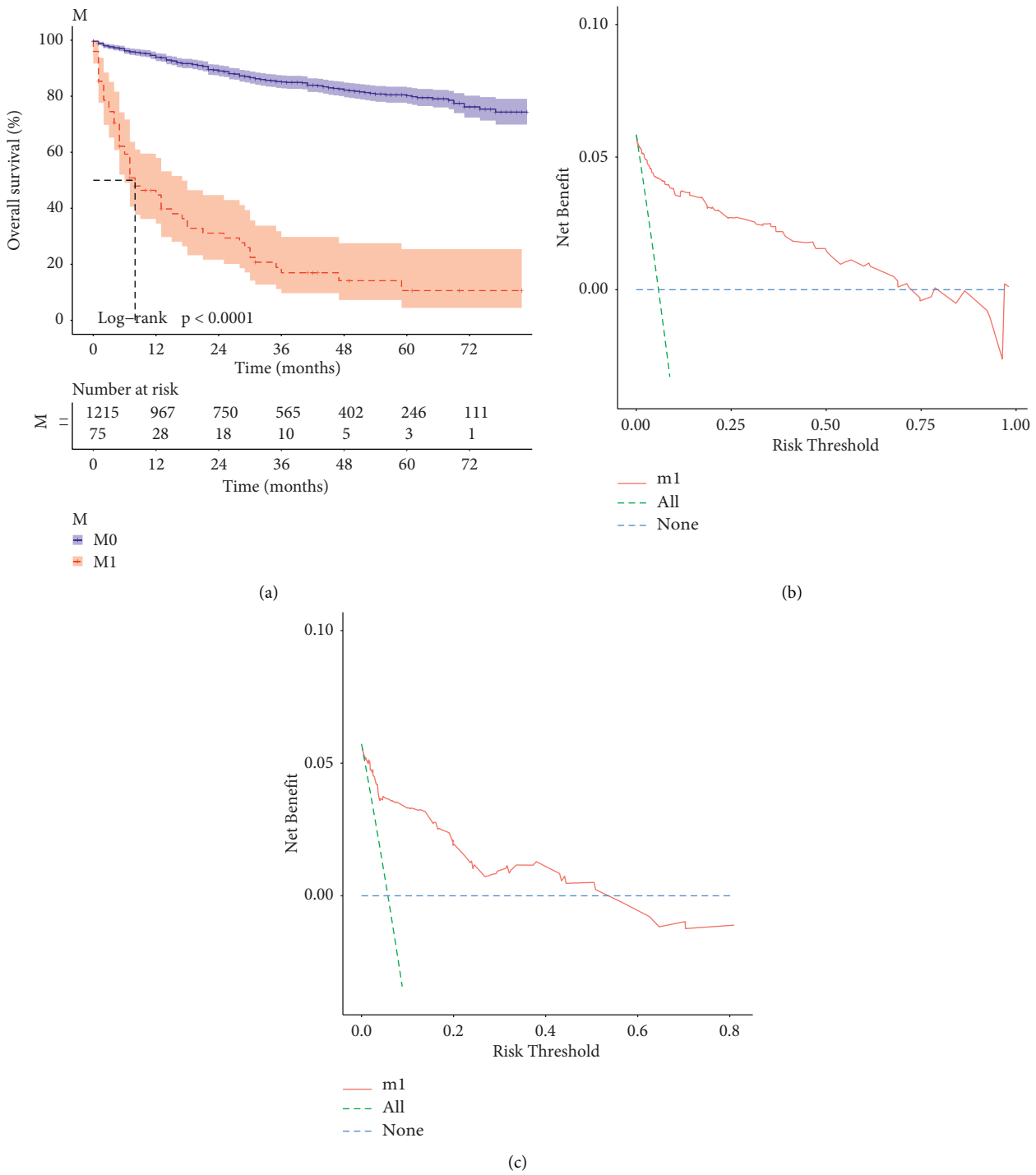

Figure 3: (a) Kaplan-Meier survival curve, (b) decision curve analysis (DCA) internal, and (c) decision curve analysis (DCA) external.

nodes. Therefore, lymph node spread in chondrosarcoma is extremely rare, and lymph node metastasis, although extremely rare in primary osteochondrosarcoma, has been shown to have an overall 5-year survival rate of 28% and 77% in patients with and without regional lymph node metastasis, respectively. Patients with chondrosarcoma with lymph node metastases had a worse prognosis than those who did not report regional lymph node metastases [25, 26], consistent with the findings of this study. This study also found that patients with regional lymph node metastases had different tumor characteristics compared to those without regional lymph node metastases. Most importantly, the finding of regional lymph node involvement independently indicates a lower survival rate in patients with chondrosarcoma; this may be important when planning treatment or advising patients on their condition, so clinicians should more carefully examine patients with chondrosarcoma who have lymph node metastases [27].

Therefore, factors related to lymphatic metastasis and distal metastasis still need to continue to be studied in depth.

Nomogram is a quantitative mathematic tool to assess risk and benefit and has been widely used in the medical field for clinical decision-making in a variety of diseases [28, 29]. In previous studies, several nomograms have been developed and validated to predict specific survival and overall survival in chondrosarcoma [30]. However, a nomogram for predicting distal metastasis has not been reported. In this study, 1,290 chondrosarcoma cases were obtained from the SEER database, and patient prognostic factors (i.e., gender, tumor pathology grading classification, laterality, primary tumor stage, regional lymph node metastasis, surgical treatment, and chemotherapy) based on seven of the logistics regression analyses were used to establish a nomogram for predicting the distal nomogram for distal metastasis that showed better diagnostic efficiency compared to other individual variables as evidenced by calibration plots and ROC curves (Figures 1 and 2, Table 4). This all proves the value of the use of nomograms in this study, which can be further applied and improved in clinical work, and clinicians can choose better medical tests and optimize treatment plans with the help of nomograms.

This study still has limitations. First, this study is a retrospective analysis, and the data are biased and indeed lack systematic and prospective data. Also, as a single-center study, even though it was divided into training and validation groups, it still lacks external validation from other institutions, which may lead to overfitting of the nomogram for predicting distal metastasis.

5. Conclusions

A large population-based cohort from the SEER dataset was screened for this study and statistically analyzed to conclude that age, gender, survival time, tumor pathological grade, laterality, primary tumor stage, and whether or not surgical treatment and chemotherapy were prognostic factors affecting distal metastasis; higher or unclear tumor pathological grade, laterality to the right, higher primary tumor stage, male, lymph node metastasis, chemotherapy, and not the higher tumor pathology grade or rightward, higher primary tumor stage, male, lymph node metastasis, chemotherapy, and no surgical treatment were independent risk factors for distal metastasis. A nomogram was further constructed based on the results of statistical analysis to predict distal metastasis in patients with chondrosarcoma. Based on the results of internal validation, DCA curves and clinical impact maps, the nomogram in this study can effectively predict the individualized risk of distal metastasis.

Data Availability

SEER database within the article is a public dataset.

Ethical Approval

The SEER database is a comprehensive data source developed based on population data and annually updated since its launch in 1973. It is public and identifiably accessible that data analysis is treated as nonhuman subjects by the Office for Human Research Protections. As such, no institutional review board approval and informed consent were required.

Conflicts of Interest

All authors declare that they have no conflicts of interest in this paper.

Authors' Contributions

Wenle Li, Rong Li, and Wanying Li have equally contributed to this work. CLY, RL, QL, and HWP jointly carried out the entire research design. WLL, RL, WYL, CX, and MMM participated in the research and collected and analyzed data. WLL, RL, WYL, and BW drafted the manuscript. CLY and QL provided expert consultation and advice. All authors conceived this research, participated in its design and coordination, and helped polish the language. All authors reviewed the final version of the manuscript.

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