Risk Analysis for Pulmonary Metastasis of Chondrosarcoma and Establishment and Validation of Novel Clinical Prediction Models: a Clinical Study Based on the SEER Database

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Abstract

Objective: Lung metastasis of chondrosarcoma is associated with poor prognosis. The purpose of this study was to develop and validate the nomogram to predict the risk of lung metastasis in patients with chondrosarcoma, thus contributing to clinical diagnosis and treatment.

Methods: Data on chondrosarcoma patients from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2016 were then screened by univariate and multivariate Logistic regression to construct a Nomogram predicting lung metastasis risk. Nomogram model discrimination was assessed by calibration charts, while prediction accuracy and clinical values were measured by decision curve analysis (DCA) and clinical impact charts. In addition, the predicted Nomogram were validated in the internal test set.

Results: A total of 944 patients were enrolled and randomly divided into the training group (n=664) and the validation group (n=280) in a ratio of 7 to 3. After logistics regression analysis, significant variables were gender, age, marital status, tumor volume and lymphatic metastasis. Calibration curves show consistency between Nomogram predictions and actual observations, while DCA and clinical impact diagrams show the clinical utility of Nomogram. In addition, ROC also showed good discrimination and calibration in the training group (AUC = 0.789, 95%CI 0.789 – 0.808) and the validation group (AUC = 0.796, 95%CI 0.744 – 0.841).

Conclusions: Nomogram for lung metastases in chondrosarcoma can effectively predict the individual risk of lung metastases and provide clinicians with enlightening information to optimize treatment.

1. Introduce

Chondrosarcoma is the third most common primary malignant bone tumor after myeloma and osteosarcoma^[1]. At present, surgical resection is the main treatment method for chondrosarcoma. Radiotherapy is only suitable for unresectable lesions or extensive marginal resection is not possible. Chemotherapy is only recommended for young patients with good tolerance, but its therapeutic effect is minimal according to the current research^[2,3]. According to previous studies, 8 to 38% of patients with chondrosarcoma develop distant metastases, and most distant metastases occur in the lungs^[4-7]. The occurrence of lung metastasis is a poor predictor of prognosis in chondrosarcoma patients^[8]. The overall survival rate of patients with lung metastasis at 10 years was 17% and metastasis rate was 9.6%, according to the analysis of the relevant studies^[9]. In addition, up to 13% of recurrent chondrosarcomas were more poorly differentiated than the primary tumor^[1, 10]. The appearance of tumor metastasis will greatly affect the performance of surgery, and complete resection of the tumor becomes extremely difficult. Therefore, clinicians treating patients with chondrosarcoma must determine the possibility of metastasis, and it is necessary to determine risk factors for lung metastasis in patients with chondrosarcoma^[11]

Chondrosarcoma is a rare tumor, accounting for 20% of primary osseous malignancies, with an estimated incidence of 1:200,000^[4, 12]. The low and sporadic incidence of chondrosarcoma makes the clinical study of chondrosarcoma very difficult. The SEER program from the National Cancer Institute is a comprehensive source of population-based cancer incidence and survival information from 18 population-based cancer regions in the United States, representing about 27.8% of the U.S. population^[13]. Using the advantages of the SEER database without patient authorization, this study considered that the database has provided data on specific sites of metastatic tumor since 2010 and collected demographic and clinical characteristics of chondrosarcoma to investigate risk factors for pulmonary metastasis (PM) of chondrosarcoma at initial diagnosis^[14].

Nomogram is used worldwide to generate the possibility of clinical events through complex computational formulas^[15]. With Nomogram, clinicians can assess the risk of clinical events, personalize individual treatment plans, optimize treatment regimens, and more active follow-up. Given the important role of PM in the prognosis of patients with chondrosarcoma, this study aimed to evaluate patients with high risk of lung metastasis with Nomogram.

2. Method

2.1 Data source and inclusion criteria

Use SEER * Stat version 8.3.6. The International Taxonomy of Tumors, 3rd edition (ICDO-3), Morphological code (9220) for the identification of chondrosarcoma. Patients pathologically diagnosed as chondrosarcoma from 2010 to 2016 were included. Exclusion criteria were as follows: (1) no positive pathology; (2) Unknown survival time; (3) It is not the first case; (4) There is more than one primary tumor; (5) There is unknown lung metastasis information. (6) Regional lymph node metastasis information is incomplete.

Data from the SEER database included age, race, sex, race, marriage, major sites, single or multiple tumors, tumor size, and lymph node metastasis. These data are determined by the variable "CS Site-specific factor 6". Patients were classified as married, unmarried (including single, divorced, separated and widowed). Fewer than 20 tumor sites were classified as "other."

2.2 Construction, validation and clinical utility of nomogram

Patients with chondrosarcoma meeting the inclusion criteria were randomly divided into the training group and the verification group in a ratio of 7 to 3. The following variables were then selected for study: age, race, sex, race, marriage, major site, single or multiple tumors, tumor size, and lymph node metastasis. Then, univariate and multivariate binary logistics regression was used to identify independent risk factors by means of forward stepwise selection method. Nomogram was constructed according to logistic analysis regression analysis results. A clinical Calibration plot and ROC curve were also drawn, and ROC was used to estimate the predictive performance of the line graph. The higher the area under the ROC curve (AUC), the better the variable discrimination ability or prognostic accuracy. In

addition, decision curve analysis (DCA) charts net gain (NB) at a range of reasonable risk thresholds consistent with clinical practice to assess the clinical utility of a nomogram in decision making. Based on DCA, a clinical impact map was developed to visually display the estimated number of high-risk patients for each risk threshold.

2.3 Statistical methodologies and software

Continuous variables are expressed as mean $\pm$ standard deviation (SD), and categorical variables as proportions. Continuous variables and categorical variables were compared by SPSS t test and Chi-square test. IBM SPSS Statistics version 26.0 (SPSS Inc., Chicago, Ill., USA) and R software version 3.6.2 (<http://www.r-project.org>) perform the above statistical methods and apply r-packages (including Regogram, RMS, RMDA, and pROC) to plot graphs, such as Nomogram, Calibration plot, DCA graph, and ROC curve. The KM curve was drawn by GraphPAD Prim8.0. All P values are bidirectional, $P < 0.05$ is considered statistically significant, and the confidence interval (CIs) is expressed as a 95% confidence level.

3. Result

3.1 Univariate and multivariate logistic regression results

A total of 944 patients were included in the statistics. In univariate and multivariate logistic regression analysis, the extracted variables were firstly analyzed using univariate logistic regression analysis, which showed that age, gender, marital status, tumor size and lymph node metastasis were prognostic factors affecting LM ($P < 0.05$). Further multi-factor logistics risks, the results showed that there were four LM independent prognostic factors (Table 1), namely gender (female: advantage ratio (OR) 0.435, 95%CI 0.212–0.891, $P < 0.05$), age (OR = 1.026, 95%CI 1.005–1.048, $P < 0.05$), tumor size (OR = 1.003, 95%CI 1.005–1.048, $P < 0.05$), lymphatic metastasis (positive: OR = 27.164, 95%CI 6.267–117.741, $P < 0.0001$; Unknown: OR = 8.027, 95%CI 2.643–24.379, $P < 0.0001$). Specific results are shown in Table 1.

3.2 Demographic baseline characteristics

A total of 944 patients were randomly divided into the training group ($n = 664$) and the test group in a ratio of 7, and then summarized in Table 2. There were no statistically significant differences between the training and validation groups ($P < 0.05$).

3.3 Construction and validation of Nomogram for pulmonary metastasis of chondrosarcoma

The results of univariate and multivariate logistic regression were used to construct THE Nomogram of LM (Fig. 1A). As shown in the figure, lymphatic metastasis was the best predictor, followed by tumor size, marital status, age and sex. The Nomogram calibration graph (Fig. 2B, c) shows that there is good consistency in the apparent curve between the training and test groups. In the training and verification groups, the AUC values of Nomogram were 0.789 (95%CI 0.762–0.851) and 0.796 (95%CI 0.744–0.841), respectively (Fig. 2A, B). According to the ROC curve of the training set, Nomogram values were more

important than other variables, including age (AUC = 0.674, 95%CI 0.644 to 0.704), lymphatic metastasis (0.610, 0.578 to 0.641), marital status (AUC = 0.600, 95%CI 0.568 to 0.632), gender (AUC = 0.588, 95%CI 0.568 to 0.632), and tumor size (0.710, 95%CI 0.680 to 0.739). Similarly, the value of Nomogram in the test set was higher than that of single factor, as shown in Table 3.

3.4 Clinical utility of LM nomogram

Kaplan-meier survival curves for total survival (OS) were plotted for 944 patients enrolled in the study (Fig. 3A), and there were significant differences between the two groups ($P < 0.001$), suggesting that patients with chondrosarcoma expecting LM would have a significant survival disadvantage. After that, as shown in the DCA curve (Fig. 3B), the threshold value of about 0.1–0.8 is the maximum benefit of LM. In addition, the clinical impact diagram of the training set (Fig. 3C) showed that, within the most favorable threshold probability range, there were always more patients expected to be at high risk than those who actually had LM, with an acceptable cost-benefit ratio.

4. Discussion

To our knowledge, this is the first study to establish Nomogram based on the SEER database to analyze the high risk of lung metastases in chondrosarcoma. According to a large population-based study, about 8% of patients with chondrosarcoma develop distant metastases^[16]. Because the prognosis of patients with chondrosarcoma associated with PM is poor^[17], it is necessary to identify some factors to identify the risk factors for patients with high risk of PM.^[9, 18] The results of this study showed that PM was more likely in patients with larger tumor size, lymphatic metastasis, married, malignant, male, and older age.

The present study found that larger tumors had a higher risk of PM. In univariate and multivariate logistic regression analysis, tumor volume was associated with PM risk, and THE OR value was 1.003, indicating that the risk of PM was 1.003 times higher for each 1 mm increase in tumor volume. The possible reason for this is that larger tumors indicate that the tumor is likely to grow for longer, increasing the likelihood of metastasis^[19]. Relevant studies have shown that larger chondrosarcoma may represent a poorer survival expectation^[18, 20, 21], and tumor size over 10 cm is an omen of poor prognosis^[22], which is also consistent with the conclusion of this study. With regard to age at diagnosis, the study concluded that the older the person is at the time of diagnosis, the greater the risk of metastasis. The results of Logistics analysis in Table 2 show that the risk of transfer is 1.026 times higher for each year of age. Previous studies have shown that age is an independent risk factor for poor prognosis in patients with chondrosarcoma^[23]. A 2018 retrospective analysis identified age over 60 as an independent risk factor for PM, with older patients more likely to develop metastatic disease, and the study explained the poor prognosis in older patients^[21]. This is also consistent with the conclusion of this study. But it does not explain exactly why advanced age becomes chondrosarcoma and LM is replaced. Therefore, further research is needed on the cause of age leading to a higher risk of LM.

In addition, it is worth noting that this study found the influence of marital status on LM. This study found that married people had a higher LM detection rate than unmarried people, with a statistical difference. Some studies have proved that marital status is a protective factor for survival, and married cancer patients have a significant survival advantage compared with unmarried patients [24, 25]. This may be due to the fact that married patients may have better financial conditions, or better medical and stable follow-up with the support of their spouse, and thus may be able to detect lung metastases earlier. Unfortunately, the SEER database does not have more detailed data on patients' financial status to further study the effect of financial status on PM. This study showed that male patients with chondrosarcoma had a higher risk of DEVELOPING LM than female patients, and the difference was statistically significant. OR value showed that the risk of LM in female patients was only 0.4 times that in male patients. Some studies have suggested that men are an independent risk factor for survival of patients with chondrosarcoma [19, 26, 27]. Considering that men have a higher LM risk, it may affect survival expectations.

According to the results of Table 2 Logistics regression analysis, the LM risk of patients with lymph node metastasis is about 27 times higher than that of patients without lymph node metastasis (OR = 27.164), and the LM risk of patients with unknown lymph node metastasis is about 8 times higher than that of patients without lymph node metastasis (OR = 8.027). Lymphatic metastasis is rare in bone tumors and may be due to the absence of lymphatic vessels in bone tissue [28]. Studies have suggested that lymphatic vessels are absent in normal bone, benign and malignant intrarenal bone, and this study suggests that lymphatic vessels may be present in the connective tissue covering the periosteum, and that lymphatic vessel diffusion occurs only when the tumor extends through the periosteum to adjacent connective tissue [29]. Thus, the presence of lymphatic metastases may indicate that the patient's tumor is more aggressive. Even though bone tumors have a low percentage of lymphatic metastasis, they are associated with a very high risk of LM, and it is necessary to examine the lymphatic status. Similarly, some studies believe that it is essential to always examine the evidence of regional lymph node metastasis [30], which is consistent with the conclusion of this study. LM - related factors of lymphatic metastasis still need to be further studied.

Nomogram is a quantitative tool for assessing risks and benefits that has been widely used in the medical field for clinical decision-making in a variety of diseases [31, 32]. In previous studies, several Nomogram have been developed and validated to predict specific survival and overall survival for chondrosarcoma [33–35]. However, Nomogram has not been reported for predicting LM. In this study, 944 cases of chondrosarcoma were obtained from the SEER database, and a Nomogram was established to predict LM based on five prognostic factors in logistics regression analysis (i.e., gender, age, tumor size, marital status, and lymphatic metastasis). Moreover, compared with other single variables, LM Nomogram showed better diagnostic efficiency and proved to have better predictive ability after calibration diagram and ROC curve test (Fig. 1.2 and Table 3). DCA curve (Fig. 3B) shows that LM has the maximum benefit when the threshold is about 0.1–0.8. In addition, the clinical impact diagram (Fig. 3C) shows that within the threshold range, there is an acceptable cost-benefit ratio. This demonstrates the

value of Nomogram in this study, which can be further applied and improved in clinical practice, enabling clinicians to use Nomogram to select better medical examinations and optimize treatment regimens.

This study still has limitations. First of all, this study is a retrospective analysis, with data bias and certainty, and lack of systematic and prospective data. At the same time, as a single-center study, even if divided into training group and verification group, there is still a lack of external validation by other institutions, which may lead to overfitting of Nomogram to predict LM.

5. Conclusion

In this study, a large population cohort from the SEER data set was screened, and by statistical analysis, gender, age, marital status, tumor size, and lymphatic metastasis were identified as prognostic factors for LM. Men, older age, larger tumor volume, and lymphatic metastasis are independent risk factors for LM. Nomogram was further constructed based on statistical analysis to predict LM in chondrosarcoma patients. Based on the results of internal validation, DCA curves and clinical impact diagrams, Nomogram in this study can effectively predict the individualized risk of LM.

Declarations

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Authors' Contributions

LWL and WHS conceived and designed the study. WHS, NLJ and ZWS acquired and analyzed the data. HZH interpreted the data and drafted the manuscript. All authors contributed to and revised the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declared no competing interests

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Tables

Table 1
Univariate and multivariate logistic regression analysis

	Univariate		Multivariate	
Variables	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	1.038 (1.019–1.057)	< 0.0001	1.026(1.005–1.048)	< 0.05
Race				
White	Ref	Ref	/	/
Black	1.237 (0.429–3.567)	0.694	/	/
Other	0.696 (0.164–2.953)	0.623	/	/
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.454 (0.232–0.887)	< 0.05	0.435(0.212–0.891)	< 0.05
Marital				
No	Ref	Ref	Ref	Ref
Yes	2.840(1.309–6.160)	< 0.01	2.151(0.212–5.207)	0.89
Primary site				
Limb bones	Ref	Ref	/	/
Aix of bones	0.539(0.278–1.044)	0.067	/	/
Other	0.820 (0.189–3.3558)	0.791	/	/
Sequence number				
Only	Ref	Ref	/	/
More	0.840(0.385–1.831)	0.661	/	/
Tumor size(mm)	1.004(1.001–1.007)	< 0.01	1.003(1.000-1.006)	< 0.05
Lymph				
No	Ref	Ref	Ref	Ref
Yes	31.429(8.087-122.415)	< 0.0001	27.164 (6.267-117.741)	< 0.0001

	Univariate		Multivariate	
Unknow	10.776 (3.908–29.712)	< 0.0001	8.027(2.643–24.379)	< 0.0001

Table 2
Baseline characteristics of training group and validation group

	Training group(n = 664)	Validation group(n = 280)	P value
Age (years)	54.6 ± 18.2	56.23 ± 17.6	0.206
Sex			0.388
Male	373(56.2%)	166(59.3%)	
Female	291(59.3%)	114(40.7%)	
Marital			0.336
No	249(37.5%)	95(33.9)	
Yes	415(62.5%)	185(66.1%)	
Tumor size(mm)	79.9 ± 72.6	77.4 ± 48.7	0.598
Lymph			
No	646(97.3%)	269(96.1%)	0.536
Yes	5(0.8%)	4(1.4%)	
unknow	13(2.0%)	7(2.5%)	

Table 3
AUC values for the training and verification groups

	Training group(n = 664)		Validation group(n = 280)	
Variable	AUC	95%CI	AUC	95%CI
age	0.674	0.644 to 0.704	0.640	0.581 to 0.697
lymph	0.610	0.578 to 0.641	0.612	0.553 to 0.670
marital	0.600	0.568 to 0.632	0.614	0.554 to 0.671
sex	0.588	0.556 to 0.620	0.516	0.456 to 0.576
Tumor size	0.710	0.680 to 0.739	0.730	0.674 to 0.781
Nomogram	0.789	0.762 to 0.815	0.796	0.744 to 0.841

Figures

Figure 1

Nomogram and correction curves predict the risk of liver metastases in patients with chondrosarcoma. Nomogram (a) contains five features that describe the patient by mapping their values to the covariate scale. A Calibration plot of the predicted training group (B) and test group (C) is shown on the right.

Figure 2

Nomogram's ROC curve analysis, used to indicate Nomogram ability to discriminate. In the Nomogram of training (A) and testing (B) groups, the AUC was 0.789 (95%CI 0.762-0.851) and 0.796 (95%CI 0.744-0.841), respectively, proving that the Nomogram had good predictive ability.

A. Kaplan-Meier

B.DCA

C.临床影响图

Figure 3

a. Kaplan-Meier survival curve, B. Decision curve analysis (DCA), C. Clinical impact chart of chondrosarcoma patients: The red curve (Number high risk) represents the Number of persons Nomogram classified as positive (high risk) at each threshold probability. The blue curve (Number high risk with outcome) is the Number of true positive persons under each threshold probability.