How to Predict Cancer-Specific Death of Patients with Chondrosarcoma: A Prognostic Model Based on Competing Risk

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Research Article

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Abstract

Background. As chondrosarcoma is the second highest primary malignant tumor of bone, it is necessary to find a way to predict the prognosis of chondrosarcoma. But the current model rarely involves the study of competing risk. This is a retrospective study with the aim of establishing a prognostic model and a nomogram based on competing risk to predict the probability of cancer-specific death (CSD) at 3 and 5 years. The Fine and Gray regression is a targeted statistical method, which makes the results more authentic and reliable.

Methods. A total of 1674 chondrosarcoma patients were identified from the SEER database, and they were divided into training cohort and validation cohort by year of diagnosis. These two cohorts were used to develop and validate the prognostic model to predict the 3-year and 5-year probabilities of CSD, with non-CSD as the competing risk. Model accuracy made use of some verification functions, such as C-index, receiver operating characteristic curve (ROC), calibration plot, area under curve (AUC) and Brier score.

Results. According to the outcomes of the model: older age (subdistribution hazards ratio(95%CI): 1.02 (1.01-1.03); $P<0.001$), dedifferentiated CHS (SHR(95%CI): 2.16 (1.30-3.59); $P=0.003$), high grade (SHR(95%CI): 2.60 (1.83-3.68); $P<0.001$), Regional involvement (SHR(95%CI): 3.15 (2.01-4.93); $P<0.001$), Distant metastasis (SHR(95%CI): 11.56 (6.82-19.59); $P<0.001$), tumor excision (SHR(95%CI): 0.47 (0.25-0.87); $P=0.02$) and Radical resection (SHR(95%CI): 0.54 (0.32-0.90); $P=0.02$) were significantly. They obviously promoted the increase of CSD.

Conclusion. This prognostic model considered the competing risks of chondrosarcoma, and the nomogram can effectively predict the probability of CSD in patients with chondrosarcoma, which is suitable for clinical application.

Background

Chondrosarcoma is the second largest primary malignant tumor of bone, and its basic feature is the production of cartilage matrix. Unlike osteosarcoma and Ewing's sarcoma, chondrosarcoma often occurs in adults, and the overall prognosis is relatively better (the 5-year survival rate of osteosarcoma is 53.9%, Ewing's sarcoma is 50.6%, and chondrosarcoma is 75.2%)[1]. However, it is necessary to establish a model to better help clinicians evaluate the prognosis of patients. The nomogram transforms the complex regression equation into a visual graph, making the results of the prediction model more readable, and facilitating the prediction of the overall survival rate and cancer-specific survival rate of patients[2-4].

Literature studies show that by comparing the overall survival rate and disease-specific survival rate, it can be concluded that patients who have survived for ten years are more likely to die from events unrelated to chondrosarcoma[5]. In many prediction models, Kaplan–Meier and Cox regression models

are often used, which do not pay attention to cancer-specific death (CSD) and non-cancer-specific death (NCSD)[2, 4, 6, 7]. This often leads to biased results and cannot effectively play their role[8].

Competitive risk analysis is a special type of survival analysis, which is a supplement to Kaplan–Meier and Cox regression model. The purpose is to correctly estimate the marginal probability of an event in the presence of competing events. When patients are exposed to many risk factors, it will overestimate the cumulative incidence of exposure factors if the data that died from other events are also recorded as censored data. At this time, using the Fine and Gray Regression Model is the best choice[9, 10].

Chondrosarcoma is a disease process which is very suitable for long-term database evaluation, because the treatment mode remains basically unchanged during the study period. Chondrosarcoma has been considered as a surgical disease for decades. During the whole data collection period, the ten-year survival rate of chondrosarcoma patients has not changed significantly, and surgery is still the main treatment⁵. Therefore, we developed a chondrosarcoma outcome prediction model based on competitive risk, evaluated the performance of the model through various methods, and evaluated its clinical application.

Materials And Methods

Research Subjects

Researchers' data were obtained from SEER. A total of 6,070 chondrosarcoma patients were enrolled. The criteria for inclusion were: diagnosis time was from 2004 to 2015, confirmed by histopathology, survival time and event outcome (including cancer-specific deaths and non-cancer-specific deaths). After excluding unqualified patient information, 1,674 patients were included in the final analysis (Fig. 1). The SEERStat version 8.3.9 software was used to download patient data.

Variables and Outcomes

Patient characteristics included age, race, sex, tumor size, tumor grade and tumor range. The patient's age and tumor size were converted into categorical variables (52 years old, 8.37 cm) based on the mean. Tumor grade was shown as four grades in the SEER database: well differentiated, moderately differentiated, poorly differentiated and undifferentiated. We combined the first two as low-level, and the latter as high-level. The tumor range was classified into Localized, Regional, and Distant according to SEER historic stage A (1973–2015). The treatment method is surgical treatment, which is divided into four categories according to the code: no surgery, tumor excision, radical resection, amputation. The outcome of interest in this study was CSD, and NCSD was regarded as the competing risk of CSD.

Construction and Validation of the Prognostic Model for CSD

In order to establish a predictive model, we first divided the data into training cohort (n = 795) and validation cohort (n = 879) by year of diagnosis (2004–2009, 2010–2015). In the training cohort, we confirmed the important role of NCSD in data analysis, then obtained the factors with significant

differences through multivariate Fine and Gray analysis, and established the predictive model with them. Finally, we visualized it with nomogram. The two cohorts were used to calibrate the model, and the calibration methods were ROC, calibration chart, C-index, AUC and Brier score. The statistically significant definition is P value less than 0.05.

Competing Risk and the Fine and Gray Regression Model

In the competing risk-based prognostic model, patients had three status: alive, dead of this cancer (CSD), and dead of other cause (NCSD). NCSD, as a competitive event, will influence the occurrence of CSD. So, we decided to use the Fine and Gray regression model. As early as 1999, Fine and Gray put forward a semi-parametric proportional risk model with partial distribution, and the commonly used endpoint index is cumulative incidence function (CIF). This is a statistical method specifically used to deal with these problems.

Results

Characteristics of Patients with Chondrosarcoma

Table 1 integrated the information of all patients, including the training cohort (47.5%) and validation cohort (52.5%). In the entire cohort, there were 1674 cases, of which 320 patients belonged to CSD, accounting for 19.1%, while NCSD was 5.6%. NCSD accounted for 22.7% of the total deaths, indicating that NCSD was bound to have a huge impact on the research of chondrosarcoma. The average age at diagnosis was 52 years old, and the gender distribution showed slight male superiority (56%). White people make up the majority of the race.

Overall Cumulative Incidence and Single Argument Analysis

To show the overall trend, we draw Kaplan–Meier analysis curve (censoring NCSD) and Fine and Gray analysis curve (Fig. 2). It can be seen that there were obvious differences between the red curve (representing Kaplan-Meier analysis) and the blue curve (representing Fine and Gray analysis). The cumulative incidence of Kaplan-Meier analysis was higher, and the difference between them increased with the extension of survival time.

After that, we plotted single argument cumulative incidence function of CSD and competing risk (Fig. 3). Older age (≥ 52 years), high tumor grade, larger size (≥ 8.4 cm), distant metastasis, dedifferentiated CHS and non-surgical treatment suggested that the increase in the incidence of CSD (Gray's test, all P values were less than 0.001). However, only older age, large tumor size and non-surgical treatment were related to higher incidence of NCSD (Gray test, $P < 0.05$).

Multivariate Analysis for Factors Associated with CSD by the Cox and Fine and Gray Regression Analysis

In the multivariate analysis, we chose and compared Cox regression analysis and Fine and Gray regression analysis to determine the factors related to outcome (Table 2). In multivariate Cox analysis, older age, high tumor grade, tumor stage (regional involvement and distant metastasis), subtype

(dedifferentiated CHS) and surgery (radical resection) were significantly correlated with the prognosis of tumor patients. In multivariate Fine and Gray analysis, the results were similar, but the corresponding P value was smaller. And there was one more related factor: tumor excision ($P = 0.02$).

Construction and Validation of a Predictive Model for Incidence of CSD in the Training Cohort

According to the data of multi-factor Fine and Gray regression analysis in Table 2, we constructed a prognostic model of CSD incidence and named it AG3S (a: age, g: grade, s: subtype, stage, surgery). Then we used a nomogram to visualize it (Fig. 4). By counting and evaluating five indicators, a total score can be calculated, and the corresponding 3-year and 5-year probability of CSD can be found in the figure. The β -coefficients of each predictor in the model were marked in Table 2.

Next, we began to verify the clinical reliability of the model. On the basis of training cohort and validation cohort, we plotted time-dependent receiver-operating characteristic (ROC) and calibration plot respectively to demonstrate the performance of the model (Fig. 5). In the ROC chart, the curve was full and closed to the upper left of the chart, indicating that the model had a good phase and performed well in the two cohorts. In the calibration chart, the 3-years and 5-years curves were both close to 45 degrees, which shows that the predicted probability of CSD occurrence was in good agreement with the actual probability. C-index, AUC and Brier score were all in Table 3, and the data perform well. Finally, we calculated the AUC in the 10-fold cross-validation, and the result was 0.84[3].

Discussion

In this study, we focused on the NCSD in the context of survival analysis. Using data from the SEER database, we successfully established the prognostic nomogram predicting the outcome of patients with chondrosarcoma based on the Fine and Gray's competing risk regression model. The model showed good discrimination and calibration, with high value for clinical application.

To use the competing-risk based nomogram, clinical surgeons only need to collect the information of age, grade, stage, surgery and chondrosarcoma subtype, to calculate the CSD probability of the patient. Here we exemplified the use of the nomogram with an assumed patient of 40 years old (-0.245 points), with myxoid CHS (0.311 points), high tumor grade (1.054 points), regional involvement (1.208 points), and was treated with radical resection (-0.778 points). He totally scored 1.55 according to the nomogram, so the 3-year and 5-year CSD probabilities were predicted to be 0.234 and 0.31. It's notable that the prediction here is only the probability of CSD, and patients still have the possibilities of NCSD.

In the multivariate Fine and Gray regression analysis, significant variables were age, grade, stage, surgery and subtype. The incidence of CSD in the elderly is higher, which is in line with the actual situation. Old patients tend to refuse surgery, probably due to low tolerance to surgical treatment [6]. Similarly, the physical condition of old people are less healthy than the young and may suffer from a variety of chronic diseases, such as diabetes and hypertension, which increases the risk of unfavorable events after aggressive treatment.

Compared with women, men have a worse but insignificant prognosis[11]. Some literatures believe that this is related to early osteoarthritis[12]. One of the possible reasons is that men tend to do more serious physical labor and more intense sports, which promotes osteoarthritis, and then leads to a high incidence of chondrosarcoma and a higher CSD.

Tumor grade is an undisputed important influencing factor on the outcome of patients, and the 5-year survival rate between low grade and high grade even reaches 5 times[7, 13]. High-grade chondrosarcoma tends to metastasize in the early stage. The higher the pathological grade of tumor, the greater the possibility of recurrence will be, thus increasing the risk of CSD[4].

CHS has a long overall survival time and a good prognosis, but there are significant differences among its subtypes[6, 11]. The 5-year survival rate was 11% for dedifferentiated CHS, and 49% for myxoid CHS[7]. Subtypes with poor survival rate are known to be associated with high grade[5]. Chondrosarcoma subtypes and grade affect the survival and prognosis of patients by tumor metastasis. Therefore, identifying the subtype of chondrosarcoma is important for the outcome evaluation in diagnosed patients.

Independent risk factors of local recurrence include insufficient surgical margin and tumor size greater than 10 cm[14]. Some previous pointed out that local recurrence and overall survival rate have no effect on multivariate analysis[15, 16]. However, many literatures argued that local recurrence of secondary chondrosarcoma is associated with worse disease-specific survival[17–20]. Although our results did not include the size of the tumor, the difference between surgical methods was shown in the nomogram. The difference between several surgeries lies in the range of the margins and in whether the tumor is completely removed[21, 22]. A wide surgical margin provides the highest long-term disease-free survival rate[23]. Because SEER database doesn't collect recurrence data, we could not judge the correlation between recurrence and CSD. Nevertheless, through practical results and research reports, surgery is the main and preferred method for the treatment and control of chondrosarcoma[21, 24]. Unlike osteosarcoma and Ewing sarcoma, Chondrosarcoma is usually resistant to chemotherapy. The resistance may be due to slow proliferation, overexpression of multidrug resistance protein 1 (MDR1), limited vascular links and dense hyaline extracellular matrix[12, 25]. As a result, we did not analyze the effect of chemotherapy on the outcome of patients with chondrosarcoma.

This study also has its limitations. First, there are inherent biases in retrospective research. Secondly, The SEER database did not collect specific details about the type, dose and duration of chemotherapy and radiotherapy, and the use of other oral drugs[4, 26]. The explanation of the operation method is only coded, and there was no more detailed explanation[7]. Third, the collected data cannot distinguish whether the purpose of treatment is curative or palliative, so the survival outcomes could not be fully assessed[5]. To truly understand the predicting ability of the nomograms, it is necessary to carry out forward-looking verification, or at least to use another database to verify[2]. Because the development and verification of the nomogram was based on the SEER database, future research should investigate whether it is can be validated by samples from other registries.

Conclusion

In summary, we have successfully established a prognostic model based on competitive risk to predict the incidence of CSD in 3- and 5-years. This model has good performance and can be applied to clinic.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: SEERStat 8.3.9

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: Binxiang Zhu and Yimin Dong wrote major manuscripts and texts. Hongyu Zhu helped collect and organize information. Zijian Dong helped validate the model. All authors reviewed the manuscript.

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Tables

Due to technical limitations, Tables are only available as a download in the Supplemental Files section.

Figures

Figure 1

A flowchart showing the inclusion and exclusion process of this study. A total of 8799 patients were identified from SEER database, and 1,674 eligible patients were included in the final analysis.

Figure 2

Cumulative incidence of CSD analyzed by the Kaplan-Meier and Fine & Gray competing risk method. CSD indicates cancer-specific death. The competing risk is equal to non-CSD.

Figure 3

Cumulative incidence function of CSD and competing risk for patients with chondrosarcoma. The cumulative incidence of CSD and competing risk were presented by age (A), size (B), tumor grade (C), tumor range (D), subtype (E) and surgery treatment (F). In each panel, competing risk (dotted line) is equal to NCSD, in contrary to CSD (solid line). In figure 3C, low-grade CHS indicates well differentiated and moderately differentiated CHS, whereas high-grade CHS represents poorly differentiated and undifferentiated CHS. $P = 0$ in each CIF plot indicates a P value < 0.0001 . CHS indicates chondrosarcoma; CIF, cumulative incidence function; CSD, cancer-specific death; NCSD, non-cancer-specific death.

Figure 4

A nomogram for predicting the probability of CSD in chondrosarcoma in 3 and 5 years. Use a hypothetical patient as an example to illustrate the usage of nomogram. The red vertical line indicates the characteristics of the patient. The patient was 40 years old (-0.245 points), with myxoid CHS (0.311 points), high tumor grade (1.054 points), regional involvement (1.208 points), and was treated with radical resection (-0.778 points). He totally scored 1.55 according to the nomogram, so the 3-year and 5-year CSD probabilities were predicted to be 0.234 and 0.31.

Figure 5

The performance of Nomogram is evaluated by time-dependent receiver operating characteristics (ROC) and calibration chart. (A) and (B) represent ROC of 3-year (blue line) and 5-year (green line) CSD prediction in training and validation cohort, while (C) and (D) represent calibration charts of nomogram when predicting 3-year (yellow line) and 5-year (red line) CSD.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.Characteristicof1674PatientsWithCHS.xlsx](#)
- [Table2CoxandFineGrayRegression.xlsx](#)
- [Table3.CindexAUCandBrierScoretoAssessthePerformanceoftheModel.xlsx](#)