Nomogram for predicting disease-specific survival in osteosarcoma

Xia Yang¹, Yajie Yang², Xin Weng³, Meng Zhang²

¹Department of Pathology, Sir Run Run Shaw hospital of Zhejiang University, Hangzhou, Zhejiang 310020, China; ²Department of Pathology, Shenzhen Second People’s Hospital, Shenzhen, China.

To the Editor: Osteosarcoma (OS) is the most common malignant primary bone tumor majorly affecting children, adolescents, and young adults. Statistic studies showed that up to 20% of OS patients have clinically detectable metastatic tumor at presentation, and >85% of metastases occurs in the lung. Thus, identifying risk factors that reflect the biological characteristics and survival of OS could lead to better interventions for patients.

Currently, nomogram has been considered as a commonly viable predictive model to provide the prognostic probabilities of independent patients. Compared to the traditional tumor-node metastasis (TNM) staging system, nomogram could integrate more important prognostic factors and provide a more precise evaluation of prognosis. Several nomograms have been established for predicting the risk of recurrence and the benefit of surgery and systemic therapy in OS. However, unavoidable deficiencies have marred these studies. Thus, in the present research, we intended to develop and validate a nomogram and risk model for predicting the disease-specific survival (DSS) and risk stratification of OS patients.

Patients diagnosed of OS from 2004 to 2015 were obtained from the Surveillance, Epidemiology, and End Results Program (SEER) database. The inclusion criteria are as follows: 1) pathological diagnosis of OS was made between 2004 and 2015 and 2) OS as the primary tumor at presentation, and up to 20% of OS patients have clinically detectable metastatic tumor at presentation, and >85% of metastases occurs in the lung. Thus, identifying risk factors that reflect the biological characteristics and survival of OS could lead to better interventions for patients.

In addition, all procedures conducted in this research were in accordance with the Declaration of Helsinki.

A total of 1639 patients were enrolled in this research: 881 patients in the training set, 408 patients in the validation cohort I, and 350 patients in the validation cohort II. In the training set, the following clinicopathologic features were found to be statistically significant factors for DSS: age at diagnosis (≥18 vs. <18: HR 2.07, 95% confidence interval (CI) 1.63–2.63, P < 0.001), histologic grade (grade III vs. grade I: HR 5.09, 95% CI 1.61–16.13, P = 0.006; grade

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IV vs. grade I: HR 4.86, 95% CI 1.55–15.29, \( P = 0.007 \), tumor size (>5 cm vs. <2 cm: HR 2.09, 95% CI 1.29–3.38, \( P = 0.003 \)), distant metastasis (metastasis vs. no metastasis: HR 3.07, 95% CI 2.35–4.01, \( P < 0.001 \)), and surgery of primary tumor (local resection vs. no surgery: HR 0.31, 95% CI 0.22–0.44, \( P < 0.001 \); amputation vs. no surgery: HR 0.49, 95% CI 0.33–0.71, \( P < 0.001 \)) [Table 1]. Thus, we included all these prognostic factors for nomogram construction.

A predictive nomogram for prognosis integrating five independent risk factors was constructed. The total score was generated to predicted 1-year, 2-year, and 3-year DSS for a specific patient by adding all scores based on these clinical variables [Supplementary Figure 1A, http://links.lww.com/CM9/A814]. The C-indexes in the training (0.72, 95% CI 0.68–0.76), the validation I (0.78, 95% CI 0.76–0.82), and the validation II (0.80, 95% CI 0.77–0.83) cohorts suggested excellent accuracy in predicting the DSS. In the training cohort, the area under curve (AUC) values of the nomogram to predict 1-year, 2-year, and 3-year DSS was 0.75, 0.69, and 0.67, respectively. The prediction accuracy of the nomogram for DSS probability in the validation cohort I was 0.71, 0.76, and 0.74, respectively, and the AUC values of the nomogram to predict 1-year, 2-year, and 3-year DSS in the validation cohort II was 0.82, 0.76, and 0.76, respectively. The calibration curves in the training set and the validation set suggested that the nomogram-based predictive outcome had good consistency with the actual prognosis results [Supplementary Figure 1A-M, http://links.lww.com/CM9/A814].

According to the cut-off values provided by X-tile, a risk stratification model was generated on the basis of each patient’s total score from the nomogram. All the patients were stratified into two groups: low-risk group (979/1639, 45.6%; total score <59) and high-risk group (660/1639, 39.8%; total score 59–106). For the demographic and clinicopathologic features, patients from the high-risk group prone to be younger, with higher histopathologic grade, large tumor burden, and distant disease compared to their counterparts. In terms of treatment, patients from the high-risk group tend to not have received CT and RT compared to their counterparts. The median DSS

| Variables                  | Univariable analysis | Multivariable analysis |
|----------------------------|----------------------|------------------------|
| Age at diagnosis           |                      |                        |
| <18 years                  | 1.00 (reference)     | 1.000                  |
| ≥18 years                  | 1.69 (1.35–2.12)     | <0.001                 |
| Race                       |                      |                        |
| Caucasian                  | 1.00 (reference)     | 1.000                  |
| African                    | 0.95 (0.70–1.29)     | 0.753                  |
| Other                      | 1.20 (0.83–1.75)     | 0.330                  |
| Sex                        |                      |                        |
| Male                       | 1.00 (reference)     | 1.000                  |
| Female                     | 0.95 (0.76–1.18)     | 0.631                  |
| Histologic grade           |                      |                        |
| Well differentiated, grade 1| 1.00 (reference)     | 1.000                  |
| Moderately differentiated, grade 2| 1.82 (0.52–6.39) | 0.350                |
| Poorly differentiated, grade 3  | 5.48 (1.74–17.25) | 0.004                  |
| Undifferentiated, grade 4   | 4.91 (1.57–15.36)   | 0.006                  |
| Tumor size                 |                      |                        |
| <2 cm                      | 1.00 (reference)     | 1.000                  |
| 2–3 cm                     | 1.27 (1.01–1.59)     | 0.043                  |
| >5 cm                      | 3.66 (2.30–5.82)     | <0.001                 |
| Node metastasis            |                      |                        |
| No                         | 1.00 (reference)     | 1.000                  |
| Yes                        | 4.16 (2.55–6.79)     | <0.001                 |
| Distant metastasis         |                      |                        |
| No                         | 1.00 (reference)     | 1.000                  |
| Yes                        | 3.35 (2.63–4.27)     | <0.001                 |
| Surgery                    |                      |                        |
| No                         | 1.00 (reference)     | 1.000                  |
| Yes                        | 0.24 (0.17–0.34)     | <0.001                 |
| Radiation                  |                      |                        |
| No                         | 1.00 (reference)     | 1.000                  |
| Yes                        | 1.22 (1.33–2.76)     | 0.003                  |

CI: Confidence interval; DSS: Disease-specific survival; OS: Osteosarcoma.
in the low- and high-risk groups was 61.6 months (95% CI 55.6–72.4) and 47.4 months (95% CI 40.5–56.8), respectively. The Kaplan-Meier curves indicated that the risk stratification model could well differentiate DSS in all subgroups [Supplementary Figure 1N, http://links.lww.com/CM9/A814].

In the present study, we identified five demographic and clinicopathologic characteristics to serve as independent prognostic factors in patients with OS, including age at diagnosis, histologic grade, tumor stage, distant metastasis, and surgery of primary tumor. Then, we established a risk classifier based on these features to stratify different prognosis status of OS patients. The large number of samples in this cohort and the broad eligibility criteria of patients, which include those with local and metastatic disease, low-grade and high-grade tumor, extremity and non-extremity site, extend the application of our findings to clinical practice.

In detail, we found that those aged >18 years had poorer outcomes after diagnosis of OS when compared with younger patients. Besides, a statistically significant association was found between presences of metastases with DSS. Furthermore, patients with higher grade tumor had a lower survival rate, and tumor size was a statistically significant prognostic factor for DSS in OS patients; these results were consistent with the previous publications. For the prognostic value of treatment, undergoing surgery (both local resection and amputation) but not systemic therapy was associated with better outcome in OS patients. Many retrospective analyses of large cohort have proven a better outcome of primary surgery in OS patients, especially those with high-grade tumor. However, the survival benefit of CT and RT for management of OS remains controversial. Numerous trials have been conducted to investigate the survival benefit of CT or RT in OS patients. Worse outcome has been found in those with a poor histologic response after CT in the European and American Osteosarcoma Study 1 (EURAMOS-1) trial. However, Meyers et al. found that intensification of neoadjuvant chemotherapy (NAC) increased the number of good responders but did not alter the overall survival on the basis of histologic response. Besides, several previous studies and clinical trials showed that the application of RT significantly decreased local recurrence. However, CT did not decrease the risk of systemic recurrence, and neither CT nor RT nor both were associated with improved survival in patients with localized OS. In this analysis, we were unable to demonstrate any positive effect of systemic CT or RT on survival; neither CT nor RT was an independent prognosis factor for DSS, which means the survival value of adjuvant CT and RT in OS needs further investigation.

In our study, a nomogram was conducted for predicting DSS on the basis of these significant prognostic factors and showed a favorable accuracy and accordance in predicting the survival rate of individual patients. Moreover, a risk stratification model was established to further classify patients of distinct risk subgroups, which provided critical information for indicating prognosis in the classified risk groups. In comparison with some nomograms and risk models constructed in the previous studies, the eligibility criteria of our study are distinct and explicit, avoiding the selective bias in some previous studies. Meanwhile, we enrolled a great number of OS samples from the SEER database, and the focus of our research is not confined to specific site or high-grade disease, which broadens the relevance of findings implied to clinical practice.

There are some limitations in the present research. First is the retrospective nature of this study. Second, information about some potential prognostic factors, including surgical margins, complications, detailed treatments, and treatment sequence, was not provided in the SEER database. Third, the nomogram and risk stratification model we constructed lacks validation in external cohorts. Thus, future prospective and translational studies should be performed to validate our findings.

In conclusion, this research identified potential prognostic factors for predicting DSS in OS patients. The conducted nomogram and risk stratification model provided a quantitative method to predict DSS of individuals and well-classified patients of different risk subgroups. Future large scale, multi-center, and prospective studies are needed to validate our findings.

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Conflicts of interest
None.

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