Individualized Prediction of Overall Survival for Metastatic Ewing sarcoma of Bone

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Research Article

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Abstract

Background: Few models have been used to estimate the survival rate of patients metastatic Ewing sarcoma of bone are scarce. We aimed to develop nomograms for predicting 3-, 5-year survival for these patients.

Methods: We extracted 686 cases of metastatic Ewing's sarcoma diagnosed between 1973 and 2016 from the Surveillance, Epidemiological and End Results (SEER) database. Univariate and multivariate Cox analysis were used to determine independent prognostic factors. The nomograms are based on the results of multivariate Cox analysis. We also evaluate the performance of these prediction models through the analysis of time-dependent receiver operating characteristic curve, concordance index, calibration curve and decision curve.

Results: Age, surgery, tumor size, treatment method and chemotherapy were considered to be important predictors of overall survival of bone metastatic Ewing's sarcoma. Based on these factors, the nomogram models were established and verified internally. These models have good identification and calibration characteristics. A risk classification system based on nomogram has also been constructed to promote risk stratification of metastatic Ewing's sarcoma and to optimize clinical management.

Conclusions: We developed the first nomograms and corresponding risk classification system to predict the survival of patients with bone metastatic Ewing's sarcoma. These easy-to-use tools can help oncologists and surgeons make accurate survival assessments.

Introduction

Ewing's sarcoma(ES) is a rare malignant bone tumor, which has the highest incidence in children and adolescents, second only to osteogenic sarcoma[1–4]. Primary bone ES patients with metastasis usually have a poor prognosis, with a 5-year event-free survival rate of 20–30%[4, 5]. With the development of local excision and systemic chemotherapies, the survival rate of ES has been greatly improved in recent years. However, despite the progress in treatment, the prognosis of metastatic ES is still poor compared with the primary site of ES. In addition, no accurate prediction model was designed for individual survival assessment of patients with ES.

Several previous studies have reported on the prediction of metastatic Ewing's sarcoma(MES) models-ROC[6]. But now, nomograms were the graphical description of predictive statistical model, which has been widely used to accurately predict the survival of cancer patients, such as bladder cancer, colon and breast cancer[7–11]. To the best of our knowledge, nomogram have not been used in patients with metastatic ES.

The Surveillance, Epidemiology and End Results (SEER) are provided free of charge and contain epidemiological information from 18 cancer registries in the United States. Therefore, in this study, we tried to make a comprehensive prognosis assessment of metastatic ES and develop a nomogram to reliably estimate the 3-5-year survival rate in large sample data.

Methods

Patient population

The information on patients of study were gathered from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, which contains prospectively collected data on demographics, lesion, the first course of treatment, and survival of all cancer patients from state cancer registries across the United States. The selection criteria are as follows: (a) according to the International Classification of Oncological Diseases third Edition (ICDO-3) tissue code 9620, confirmed bone Ewing's sarcoma (ES) with metastasis; (b) 1973 to 2016 diagnosis of; (c) primary tumor marker bone and joint; (d) ES is the only malignant tumor; (e) patient has a complete follow-up. The clinical information of patients was excluded, including unknown marital status, race, tumor location, type of surgery, tumor size, chemotherapy and radiotherapy.

variables and endpoints

The SEER database assembled from the following variables includes age at diagnosis of ES, ethnicity (white, black vs other), gender (male vs female), tumor location (appendage, axial rib, srernum and clavicle or others), tumor size, surgery (yes vs no), treatment (surgery vs radiotherapy and surgery), radiotherapy(yes vs no), chemotherapy (yes vs no), and marital status (married vs single). According to the average value, the age was grouped into: < 20-years and > = 20-years. The tumor size was grouped according to the average value of the cohort(8.8cm). The endpoint was defined as overall survival.

Nomogram establishment and statistical analysis

Independent prognostic factors importantly related to OS in ES patients were performed by Univariate and multivariate Cox proportional hazard regression analysis, when P was < 0.05. Based on the results of multivariate Cox analysis, a nomogram was established to estimate the 3-5-year OS rate of ES patients. Next, the nomogram model was verified internally. The discriminant capacity of the nomogram was assessed based on concordance index (C-index), time-dependent receiver operating characteristic curve (ROC) and the area under the curve (AUC). The consistency between the predicted OS of nomogram and the actual results was gained with the calibration curve. These analyses were operated by bootstrap resampling (1000 resamples). Moreover, the clinical application value of nomogram model was evaluated by decision curve analysis of (DCA).

Foremost, we calculated the score of each patient in the nomogram score model. Next, the risk classification systems were established according to the total score of each patient, and the patients are divided into three groups (high-risk, intermediate-risk and low-risk) according to the best cut-off value. The OS of MES patients in different risk groups were compared and exhibited through the Kaplan-Meier curve and log-rank test method.

The best cut- off point was carried out by The X-tile program (version 3.6.1)[12]. The survival curve was drawn by Kaplan-Meier method. The data came from The SEER*Stat software (version 8.3.5; NCI,

Bethesda), all data of study was analyzed with SPSS software (version 24.0; IBM Corporation) and R software (version 3.13). When the P value was < 0.05, it was regarded as statistically significant.

Results

Population features

Due to known a lot of differences characteristics of ES patients, 686 patients were consistent with all analyses(Fig. 1). In generally, over half (63.3%) of the MES patients were under 20 years old, and with the vast majority of whites (88.0%). Male was majority (59.6%). The primary site were the appendix and axis (43.0% vs 35.9%). The patients close to radiotherapy and chemotherapy were 49.5% and 95.5%, respectively. Tumor size is based on 8.8cm (45.0% vs 34.5%). These patients were more likely to be unmarried (86.9%) and surgery (49.4%). Simple surgical treatment of tumor accounted for 79.0%, radiotherapy and surgical treatment accounted for 21.0% respectively. In addition, detailed baseline features were shown in Table 1.

Table 1
Patient characteristics in the study.

Variable	Category	All
Total		686(100)
Age	< 20	434(63.3)
	>=20	252(36.7)
Sex	Female	277(40.4)
	Male	409(59.6)
Race	White	604(88.0)
	Black	27(3.9)
	Other	55(8.1)
Lacation	Appendicular	295(43.0)
	Axial	246(35.9)
	Rib,srernum and clavicle	80(11.7)
	Other	65(9.4)
Surgery	Yes	385(56.1)
	No	301(43.9)
Radiation	Yes	339(49.4)
	No	347(50.6)
Chemotherapy	Yes	655(95.5)
	No	31(4.5)
Tumor_size(cm)	< 8.8	309(45.0)
	>=8.8	237(34.5)
	Unknow	140(20.5)
Marital status	Unmarried	596(86.9)
	Married	90(13.1)
Treatment	Surgery only	542(79.0)
	RT and surgery	144(21.0)

RT, radiotherapy.

Independent prognostic predictors for patients

Age, race, tumor location, surgery, tumor size, marital status, treatment method and chemotherapy were vital associated with overall survival of patients by univariate regression analysis ($P < .05$, Fig. 2). However, age, surgery, tumor size, treatment method and chemotherapy were considered as independent risk factors of OS for patients of metastatic Ewing's sarcoma of bone by multiple regression analysis (Fig. 2).

Establishment and validation

In order to individually predict the 3-, 5-year overall probability for patients of MES (metastatic Ewing's sarcoma), nomogram was established according to the results by multiple regression analysis. And the nomograms were internally validated (Fig. 3). The distinctiveness of nomograms displayed perfectly in our study (C-index was 0.72). In terms of calibration, the tracking effect of nomogram prediction results and observation results is also very good (Fig. 4A). The accuracy of the nomogram predictive model with different conventional clinical features could be compared further. Comparing the AUCs of ROC curve, we can see that nomogram has the strongest discriminative ability (Fig. 4B, C). Underlying time-dependent C-index, nomogram models revealed better than all other clinical variables at any times after diagnosis (Fig. 4D). Eventually, DCA showed that nomogram models demonstrated the best net benefit for 3-, 5-year OS, indicating the favorable clinical effectiveness of these predictive models (Fig. 4E, F). Overall, these findings suggested that the nomograms had better nature in predicting 3- or 5-year OS in metastatic Ewing sarcoma patients than individual clinical risk factors.

Risk classification system

Beyond that nomogram, risk classification systems were constructed based on the total score of patients, which was used to group into a high-risk, intermediate-risk or low-risk, according to the score of patients generated by the nomograms (Table 2). According to the best cutoff values of total score gaited by X-tile program, the patients were divided into the low-risk (score 80–112), intermediate-risk (score 113–133), and high-risk groups (score $\geq$ 134). The prognosis of different risk groups showed accurately distinguished by the risk classification systems by the Kaplan-Meier mothed (Fig. 5).

Table 2
Score assignment and risk stratification

Variable	Category	Score
Age	< 20	0
	>=20	18
Surgery	Yes	0
	No	24
Chemotherapy	Yes	0
	No	27
Tumor size	< 8.8	86
	>=8.8	94
	Unknow	100
Treatment	Surgery only	0
	RT and surgery	13
Risk classification	Low-risk	< 113
	Intermediate-risk	113–133
	High-risk	>=134

RT, radiotherapy.

Discussion

Individualized medical treatment is playing a more and more important role in cancer treatment. By establishing a prognostic model, treatment stratification can be improved to avoid overtreatment or undertreatment, while risks and responses adapt to treatment. As a statistical tool widely used in all areas of oncology, the nomogram can be used to calculate all the cumulative effects of integrated key variables in a simple and easy-to-use way to estimate the survival rate.

To the best of our knowledge, this study is the first to develop nomograms to evaluate metastatic ES 3-,5-year OS, emphasizing the relative contribution of readily available clinicopathological variables to outcome prediction. In addition, our nomogram model also shows superiority in clinical application through DCA,. In addition, the newly proposed risk classification system based on nomogram can also help surgeons classify risks more objectively. We also found that age, surgery, treatment, chemotherapy and tumor size were independent predictors of OS in this study.

Age has been shown to be an independent prognostic factor[13, 14], consistent with previous studies, suggesting that aging is associated with poor outcomes in EWS. Metastatic disease at the diagnosis were more likely in age > 40 years old in Ewing patients[15]. For example, in head and neck EWS[16], it is reported that age over 15 years old significantly reduces survival. Zhan et al[17] found that age > 40 years old was associated with more severe OS.

As we all know, surgical resection is the main way of local treatment for patients with ES[18]. Surgery have considered to be a predictor of survival in patients with malignant tumors[13]. This is consistent with our data. In addition, for patients with metastatic tumors, resection of primary tumors can reduce pain, improve quality of life and prolong survival.

The standard of care for patients with Ewing's sarcoma is neoadjuvant chemotherapy, followed by locally controlled radiotherapy or extensive resection of the remaining tumor within a reasonable and safe range, or combined therapy[15, 16, 19]. Similarly, this was also an independent predictor of OS in this study. This is consistent with the results of our study, which indicates that radiotherapy and surgery are effective methods for local control of Ewing's sarcoma in most patients with OS results[20].

Chemotherapy and appropriate local control play an important role in the treatment of Ewing's sarcoma[13]. Local control can be achieved by surgery, radiotherapy or a combination of both, depending on the expected incidence and functional outcome[21]. In our study, chemotherapy was also an independent predictor of OS in patients with MES. This is similar to other studies. Before advanced modern chemotherapy, less than 10 per cent of ES patients survived for more than five years after diagnosis[22].

Several ES studies have demonstrated the correlation between tumor size and survival[13, 23, 24]. The larger the tumor size (> 8.8cm), the worse the prognosis and the lower the survival rate of ES patients[14]. Our data show a similar trend. The larger the tumor, the more aggressive it is and the more nutrients it needs, while metastatic Ewing's sarcoma is more common in the elderly, and they are generally associated with other bases, such as diabetes, hypertension, heart disease and so on.

ES is a kind of radiosensitive tumor[18]. Radiotherapy can effectively control the local area and reduce the local recurrence[25]. However, the role of adjuvant radiotherapy is still controversial. Previous studies have found that radiotherapy alone in ES patients is associated with a shorter 5-year survival, but for most ES patients, radiotherapy is no worse than surgery alone[20]. Our study shows that about half of the patients (49.4%) received radiotherapy, but the treatment had nothing to do with survival. The effect of radiotherapy on MES patient needs to be clarified in the future. Other study found had no effects in elderly patients with radiotherapy[26].

Several limitations should be acknowledged in our research. First of all, because of its retrospective study, potential selection bias was unavoidable. Secondly, study population with missing data of gathered variables are eliminated, which may generate selection shift. Other creatures and processing data are

also not available. Ultimately, on account of our model only considers independent predictors, when the survival rate of patients with metastatic Ewing sacral tumor is low, the nomogram prognostic model will underestimate the survival rate of patients with metastatic Ewing sacral tumor. In addition, although the model is built using a large number of queues, external validation is still necessary.

Conclusions

In our study, we found that the age, surgery, treatment, chemotherapy and tumor size were significantly associated with OS of patients with Ewing sarcoma of bone, metastasis at diagnosis. Moreover we established the first nomograms of Ewing sarcoma. And 3-, 5-year OS in ES were internally verified at the individual case level. The novel risk classification systems were developed according to score by nomograms. It can be also put into use to facilitate risk stratification in Ewing sarcoma of bone for metastasis for optimization of clinical management.

References

1. Ye C, Dai M, Zhang B. Risk Factors for Metastasis at Initial Diagnosis With Ewing Sarcoma. Front Oncol. 2019;9:1043. https://doi.org/10.3389/fonc.2019.01043.
2. Karski EE, McIlvaine E, Segal MR, et al. Identification of Discrete Prognostic Groups in Ewing Sarcoma. Pediatr Blood Cancer. 2016;63(1):47–53. https://doi.org/10.1002/pbc.25709.
3. Sultan I, Rihani R, Hazin R, Rodriguez-Galindo C. Second malignancies in patients with Ewing Sarcoma Family of Tumors: A population-based study. Acta Oncol. 2010;49(2):237–44. https://doi.org/10.3109/02841860903253538.
4. DuBois S, Krailo M, Gebhardt M, et al. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. Cancer. 2015;121(3):467–75. https://doi.org/10.1002/cncr.29065.
5. Womer R, West D, Krailo M, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012;30(33):4148–54. https://doi.org/10.1200/jco.2011.41.5703.
6. Cheung MR. Optimization of predictors of Ewing sarcoma cause-specific survival: a population study. Asian Pac J Cancer Prev. 2014;15(10):4143–5. https://doi.org/10.7314/apjcp.2014.15.10.4143.
7. Wang Z, Cheng Y, Chen S, et al. Novel prognostic nomograms for female patients with breast cancer and bone metastasis at presentation. Ann Transl Med. 2020;8(5):197. https://doi.org/10.21037/atm.2020.01.37.
8. Takakura Y, Okajima M, Kanemitsu Y, et al. External validation of two nomograms for predicting patient survival after hepatic resection for metastatic colorectal cancer. World journal of surgery. 2011;35(10):2275–82. https://doi.org/10.1007/s00268-011-1194-4.

9. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008;26(8):1364–70. https://doi.org/10.1200/JCO.2007.12.9791.
10. Fang W, Yang ZY, Chen TY, Shen XF, Zhang C. Ethnicity and survival in bladder cancer: a population-based study based on the SEER database. J Transl Med. 2020;18(1):145. https://doi.org/10.1186/s12967-020-02308-w.
11. Xu J, Ma T, Ye Y, et al. Surgery on primary tumor shows survival benefit in selected stage IV colon cancer patients: A real-world study based on SEER database. J Cancer. 2020;11(12):3567–79. https://doi.org/10.7150/jca.43518.
12. RL C, M D-F DLR. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clinical cancer research: an official journal of the American Association for Cancer Research. 2004;10(21):7252–9. https://doi.org/10.1158/1078-0432.Ccr-04-0713.
13. Shi J, Yang J, Ma X, Wang X. Risk factors for metastasis and poor prognosis of Ewing sarcoma: a population based study. J Orthop Surg Res. 2020;15(1):88. https://doi.org/10.1186/s13018-020-01607-8.
14. Lee J, Hoang B, Ziogas A, Zell J. Analysis of prognostic factors in Ewing sarcoma using a population-based cancer registry. Cancer. 2010;116(8):1964–73. https://doi.org/10.1002/cncr.24937.
15. Wang Z, Li S, Li Y, et al. Prognostic factors for survival among patients with primary bone sarcomas of small bones. Cancer management research. 2018;10:1191–9. https://doi.org/10.2147/cmar.S163229.
16. Pisconti S, Della Vittoria Scarpati G, Buonerba C, et al. Management of Ewing Sarcoma Family of Tumors: A Short Description of a Rare Primitive Uterine pPNET and Literature Review. OncoTargets therapy. 2020;13:1179–84. https://doi.org/10.2147/ott.S213233.
17. Karski EE, Matthay KK, Neuhaus JM, Goldsby RE, Dubois SG. Characteristics and outcomes of patients with Ewing sarcoma over 40 years of age at diagnosis. Cancer Epidemiol. 2013;37(1):29–33. https://doi.org/10.1016/j.canep.2012.08.006.
18. Arshi A, Sharim J, Park DY, et al. Prognostic determinants and treatment outcomes analysis of osteosarcoma and Ewing sarcoma of the spine. Spine J. 2017;17(5):645–55. https://doi.org/10.1016/j.spinee.2016.11.002.
19. Reed D, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. Cancer. 2017;123(12):2206–18. https://doi.org/10.1002/cncr.30589.
20. Ning M, Perkins S, Borinstein S, Holt G, Stavas M, Shinohara E. Role of radiation in the treatment of non-metastatic osseous Ewing sarcoma. Journal of medical imaging radiation oncology. 2016;60(1):119–28. https://doi.org/10.1111/1754-9485.12389.
21. Kaçmaz İ, Keçeci B, Basa C, Sabah D. Treatment of pelvic Ewing's sarcoma: Pros and cons of chemotherapy plus definitive radiotherapy versus surgery. Acta orthopaedica et traumatologica turcica. 2020;54(1):42–8. https://doi.org/10.5152/j.aott.2020.01.601.

22. Hustu H, Holton C, James D, Pinkel D. Treatment of Ewing's sarcoma with concurrent radiotherapy and chemotherapy. The Journal of pediatrics. 1968;73(2):249–51. https://doi.org/10.1016/s0022-3476(68)80078-2.
23. Wan Z, Huang Z, Chen L. Survival outcome among patients with Ewing's sarcoma of bones and joints: a population-based cohort study. Sao Paulo medical journal = Revista paulista de medicina. 2018;136(2):116–22. https://doi.org/10.1590/1516-3180.2017.0236230917.
24. Miller B, Gao Y, Duchman K. Does surgery or radiation provide the best overall survival in Ewing's sarcoma? A review of the National Cancer Data Base. Journal of surgical oncology. 2017;116(3):384–90. https://doi.org/10.1002/jso.24652.
25. Albergo J, Gaston C, Parry M, et al. Risk analysis factors for local recurrence in Ewing's sarcoma: when should adjuvant radiotherapy be administered? *The bone & joint journal.* 2018(2): 247–255. https://doi.org/10.1302/0301-620x.100b2.Bjj-2017-0222.R1.
26. Liu H, Wang J, Zhang D, Lan S, Chen Q. Clinical Features and Prognostic Factors in Elderly Ewing Sarcoma Patients. Medical science monitor: international medical journal of experimental clinical research. 2018;24:9370–5. https://doi.org/10.12659/msm.911882.

Figures

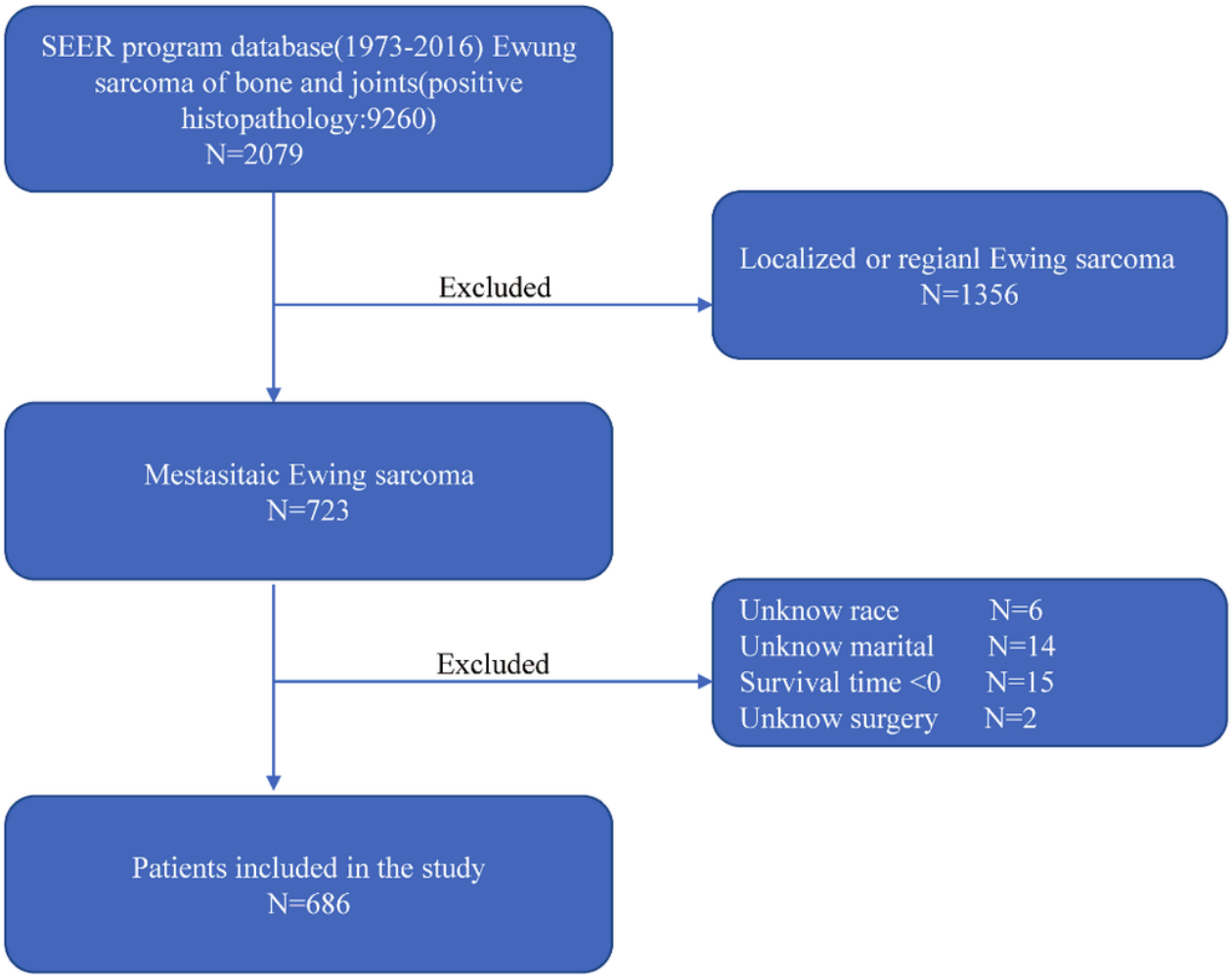

Figure 1

The diagram showed the enrolling process. Based on this criteria, finally 686 patients from SEER database were included in this study. SEER, Surveillance, Epidemiology, and End Results.

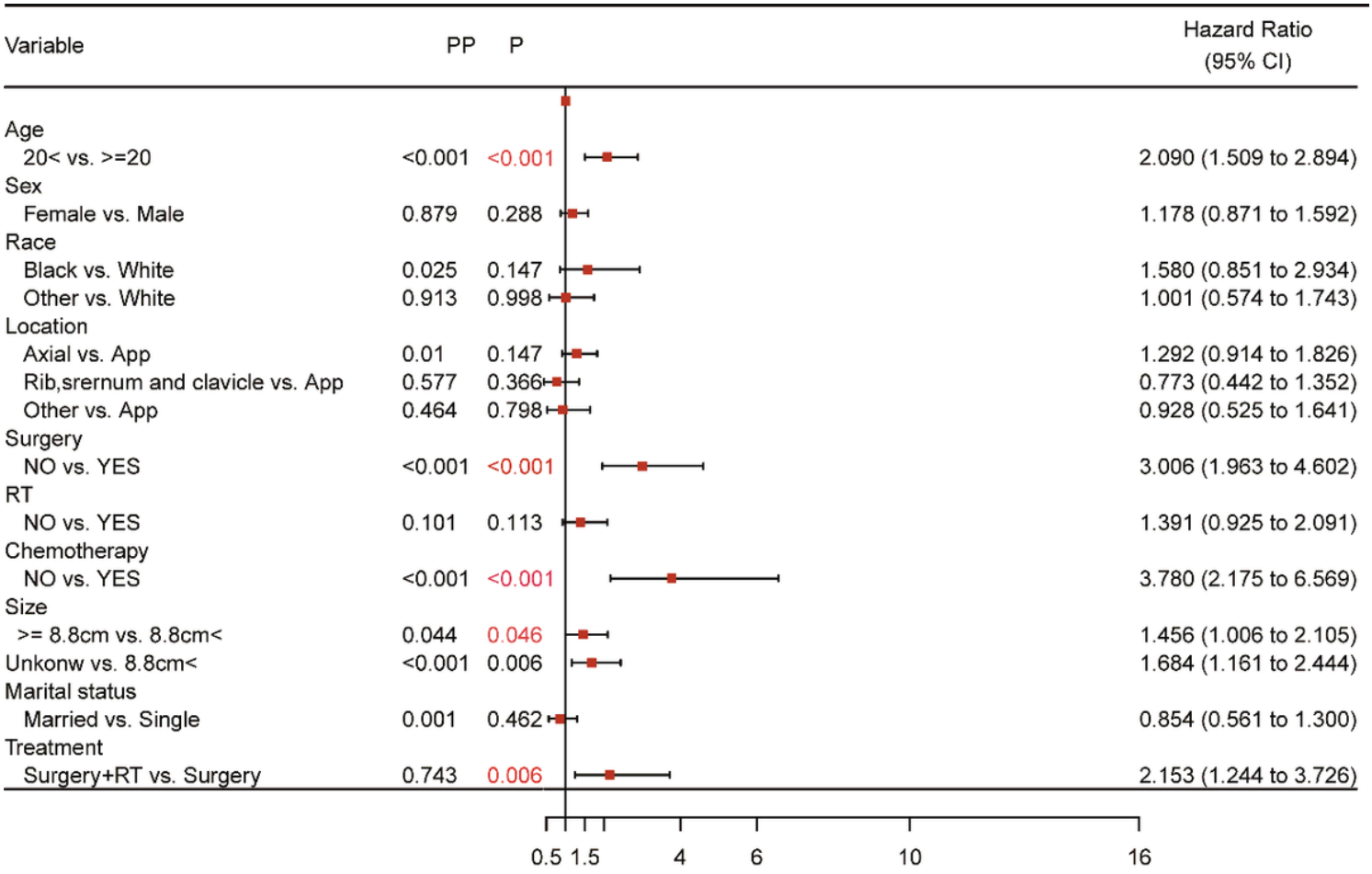

Figure 2

Forest plots showing results of univariate and multivariate Cox analyses in the study. RT, radiotherapy.

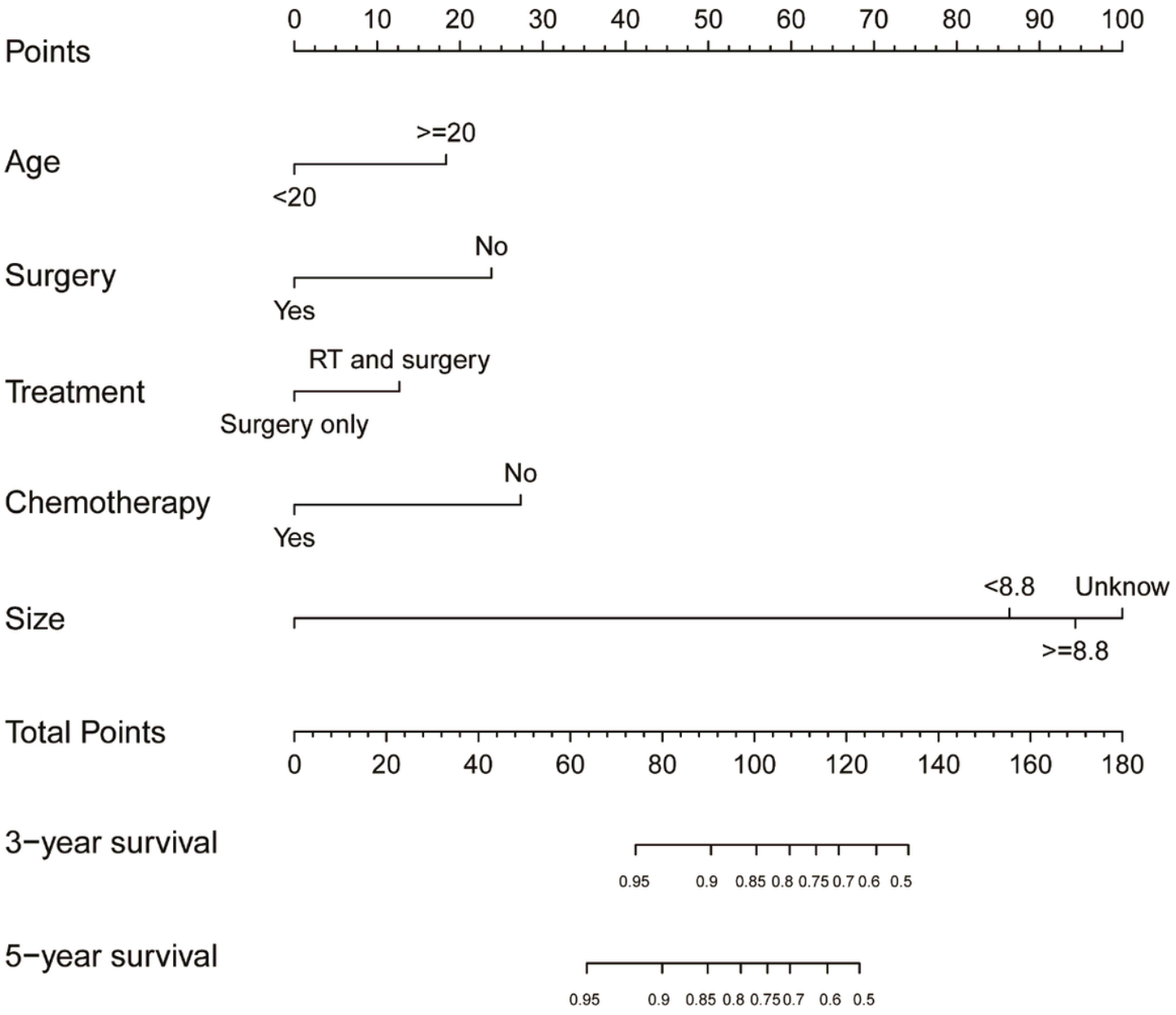

Figure 3

Nomogram predicting 3-, 5-year OS of metastatic Ewing's sarcoma of bone.

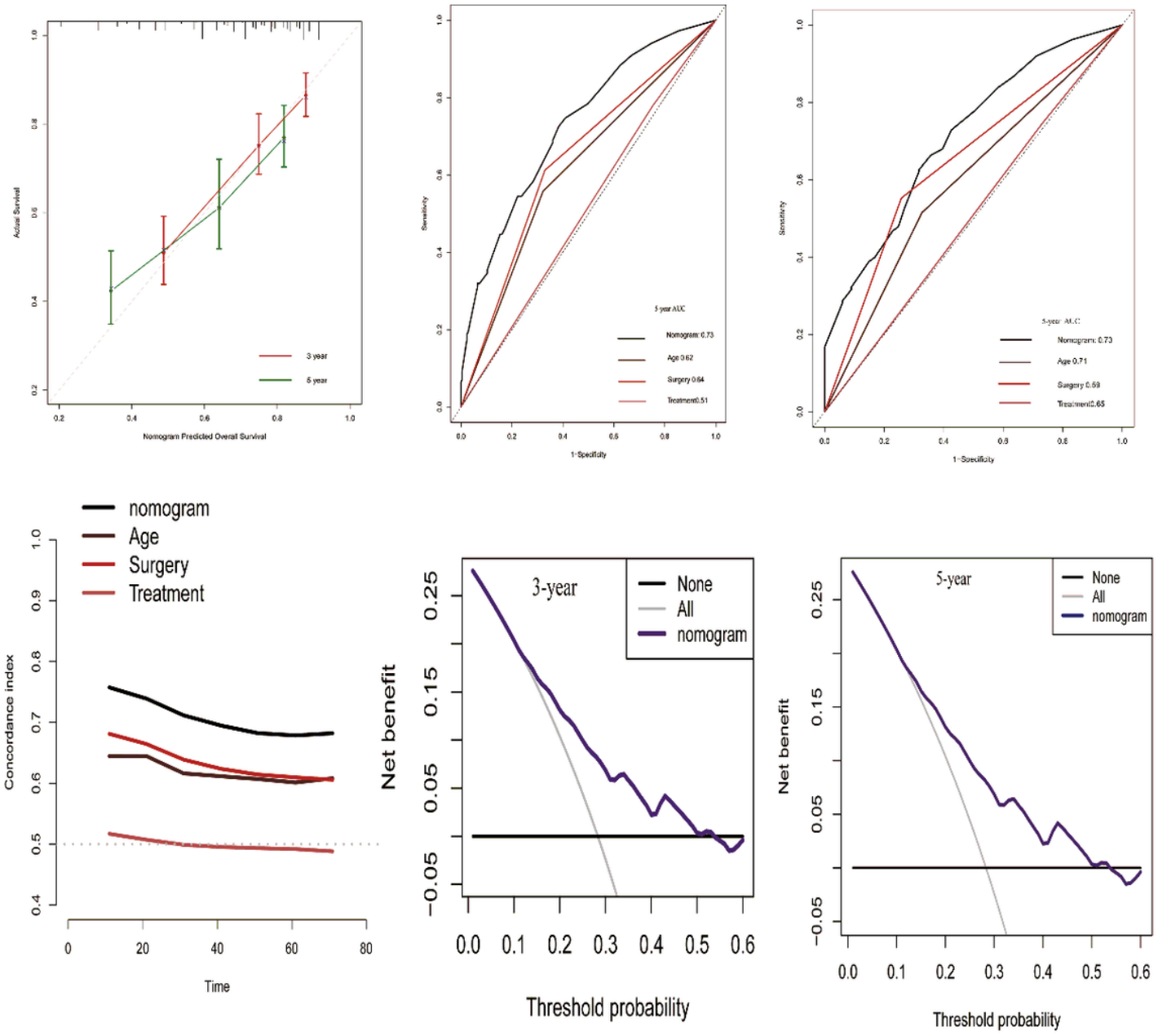

Figure 4

Calibration curves for predicting patient survival at each time point in ES (A). Nomogram predicted survival is plotted on the x-axis, and actual survival is plotted on the y-axis. A plot along the 45-degree line (dashed line) would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. The prognostic performances were compared between nomogram models and different conventional clinical characteristics by ROC curves and time-dependent C-index. Comparison of the ROC curves of the nomogram model and different conventional clinical characteristics for 3- (B), 5- (C) year OS prediction in the training set; The prognostic performance was compared between the nomogram model and different conventional clinical characteristics by calculating the C-index in the training sets(D). Decision curve analysis for the nomogram model and different conventional clinical

characteristics in prediction of prognosis at 3-y (E), 5-y (F) point in the training set. The nomograms obtain more net benefits than all other single variables with a wider range of threshold probabilities. ES, Ewing sarcoma; AUC, areas under the ROC curve; C-index, concordance index; ROC, receiver operating characteristic curve

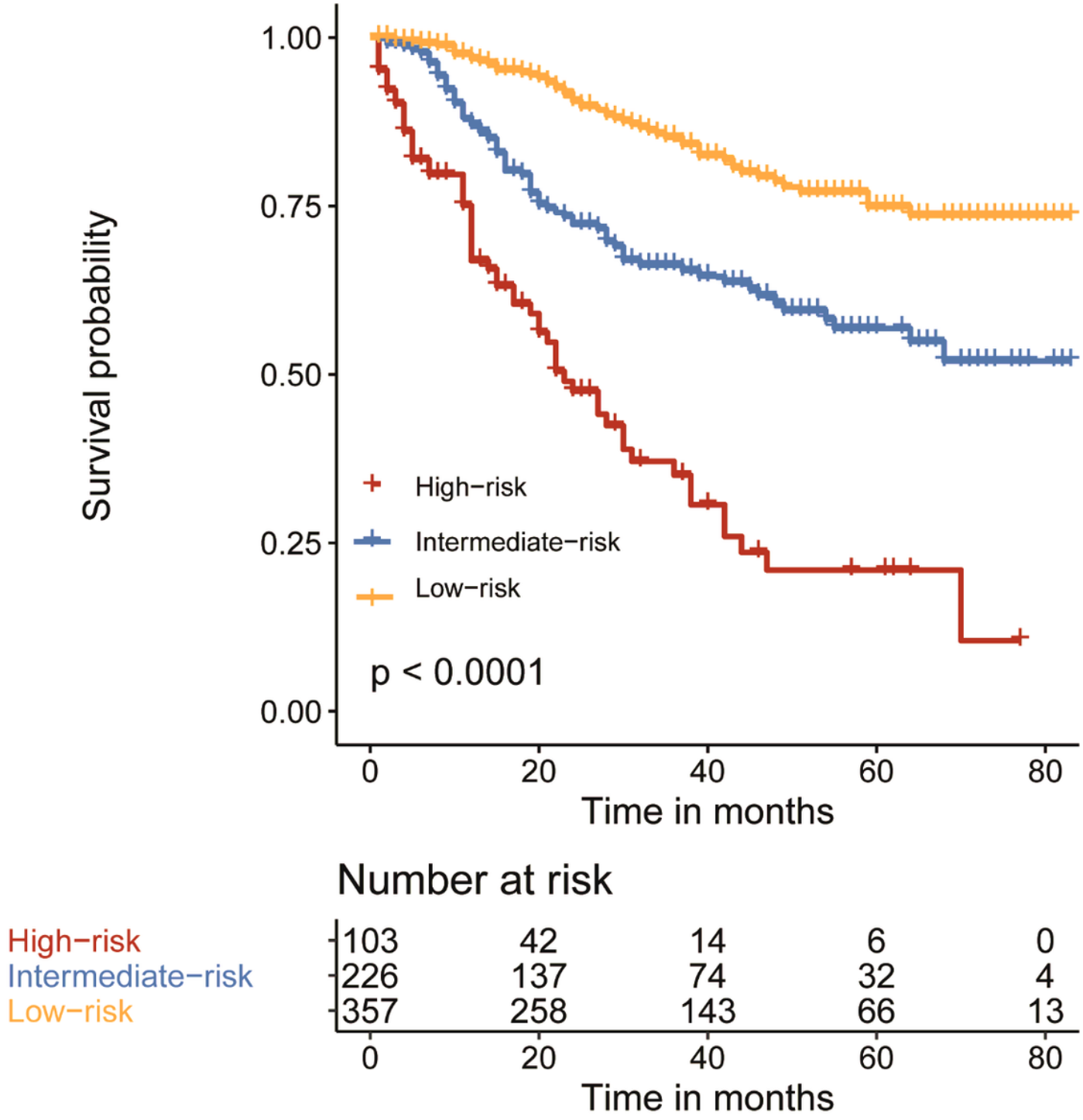

Figure 5

Kaplan-Meier curves of overall survival for the low-, intermediate-, and high-risk patients with metastatic Ewing sarcoma of bone.