

Nomograms predicting overall survival and cancer-specific survival in osteosarcoma patients (STROBE)

Wenhao Chen, MD^{a,*}, Yuxiang Lin, MM^b

Abstract

The aim of this study was to develop nomograms to predict long-term overall survival and cancer-specific survival of patients with osteosarcoma.

We carried out univariate and multivariate analyses and set up nomograms predicting survival outcome using osteosarcoma patient data collected from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (2004–2011, n = 1426). The patients were divided into a training cohort (2004–2008, n = 863) and a validation cohort (2009–2011, n = 563), and the mean follow-up was 55 months.

In the training cohort, 304 patients (35.2%) died from osteosarcoma and 91 (10.5%) died from other causes. In the validation cohort, 155 patients (27.5%) died from osteosarcoma and (12.3%) died from other causes. Nomograms predicting overall survival (OS) and cancer-specific survival (CSS) were developed according to 6 clinicopathologic factors (age, tumor site, historic grade, surgery, AJCC T/N, and M), with concordance indexes (C-index) of 0.725 (OS) and 0.718 (CSS), respectively. The validation C-indexes were 0.775 and 0.742 for OS and CSS, respectively.

Our results suggest that we have successfully developed highly accurate nomograms for predicting 5-year OS and CSS for osteosarcoma patients. These nomograms will help surgeons customize treatment and monitoring strategies for osteosarcoma patients.

Abbreviations: AJCC = American Joint Committee on Cancer, CIF = cumulative incidence function, CSS = cancer-specific survival, NOS = not otherwise specified, OS = overall survival, SEER = Surveillance, Epidemiology and End Results, SES = socioeconomic status.

Keywords: database, nomogram, osteosarcoma, prediction, survival

1. Introduction

Osteosarcoma is the most common primary sarcoma of bone and affects patients of every age.^[1] Due to clinicopathologic heterogeneity, 5-year overall survival (OS) of osteosarcoma patients varies from 28% to 70%.^[2,3] Therefore, accurate estimates of osteosarcoma patient prognoses based on clinical characteristics would help clinicians provide appropriate individual treatment.

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Availability of data and materials: Osteosarcoma patient data in this study were collected from the SEER program of the National Cancer Institute. Final selection criteria were described in the patient data collection paragraph of the section Materials and Methods. All data are accessible from the SEER database or the authors.

The authors have no funding and conflicts of interest to disclose.

^a Affiliated Union Hospital, Fujian Medical University, Department of Orthopedics, ^b Affiliated Union Hospital, Fujian Medical University, Department of Breast Surgery, Fuzhou, China.

* Correspondence: Wenhao Chen, Fujian Medical University Union Hospital, 350001 Fuzhou, China (e-mail: 15606075620@163.com).

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Because osteosarcoma is a rare tumor, with an estimated incidence of 1.7 to 4.4 per million per year depending on age,^[1,4,5] obtaining a meaningful number of patients to study is challenging. We used the Surveillance, Epidemiology and End Results (SEER) program database, which is a common tool used for the analysis of rare cancers. The SEER program collects and publishes cancer incidence and survival data from 19 population-based cancer registries covering approximately 28% of the US population. To our knowledge, no such studies on osteosarcoma have been conducted using data from a national database.

Nomograms, which are useful scoring and visualization predictive tools, can estimate individual patient survival with higher accuracy than the widely used American Joint Committee on Cancer (AJCC) TNM staging system. Nomograms have been extensively applied for a variety of cancers,^[6–12] and are based on a series of factors that are considered together. The purpose of the investigation was to develop osteosarcoma nomograms that predict long-term OS and cancer-specific survival (CSS) based on multiple clinical characteristics, for the first time with this large number of cases from the SEER database, to improve individual patient treatment and follow-up strategy.

2. Materials and methods

2.1. Patient data collection

Osteosarcoma patient data were collected from the SEER program of the National Cancer Institute. Ethical approval was waived because we got the registered account the approval of

using patients' data for research purposes, from SEER database. The study conforms to the provisions of the Declaration of Helsinki. Informed patient consent was not required for data released by the SEER database.

For data collected from the SEER program, the initial selection criteria were as follows: the osteosarcoma primary tumor site was bones and joints, malignant behavior, and diagnosed between 2004 and 2011. Final selection criteria were as follows: active follow-up; clinical and pathological information including age, race, sex, tumor site, tumor grade, and AJCC/TNM stage were complete and definite; morphology diagnosis was osteosarcoma that was confirmed microscopically. The patients were divided into a training cohort and validation cohort.

2.2. Data elements

For analyses, clinical characteristics were transformed into categorical variables on the basis of recognized cutoff values. Patients were categorized into 3 distinct age groups (0–24 years; 25–59 years; ≥ 60 years), as has been previously reported.^[1,13] Race classifications included white, black, and others. Primary tumor sites included axial skeleton and extremities. Histologic subtypes included osteosarcoma, not otherwise specified (NOS), and others (chondroblastic osteosarcoma, fibroblastic osteosarcoma, telangiectatic osteosarcoma, osteosarcoma in Paget disease, small cell osteosarcoma, central osteosarcoma, intraosseous well-differentiated osteosarcoma, parosteal osteosarcoma, periosteal osteosarcoma, and high grade surface osteosarcoma). Grade was categorized into 4 groups (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated). Laterality included left, right, not a paired site (axial), and bilateral. All patient TNM classifications were staged according to the 6th edition AJCC Staging Manual.^[14] The SEER historic stage included localized, regional, distant, and unstaged. Tumor-directed surgery included surgery performed and surgery not performed due to all reasons. Marital status included married and others (divorced, separated, single, unknown, and widowed). We compiled socioeconomic status (SES) data for all patients with osteosarcoma and categorized the resulting income, poverty, and education data for the country of residence into quartiles, as has been done in previous investigations.^[1,13] We then assigned each quartile a number from 1 to 4, with a higher number reflecting higher income, less poverty, or more education. For median family income, the quartiles were $< \$46,450$, $\$46,450$ to $\$51,400$, $\$51,400$ to $\$63,550$, and $> \$63,550$. For the percentage of individuals below the poverty line, the quartiles were $> 17.90\%$, 12.44% to 17.90% , 8.41% to 12.43% , and $< 8.41\%$. For the percentage of individuals at least 25 years old with < 12 years of education, the quartiles were $> 28.77\%$, 18.82% to 28.77% , 15.16% to 18.81% , and $< 15.16\%$.

2.3. Nomograms

The training cohort was used to establish the OS and CSS nomograms. The OS was defined as the time from diagnosis to death or censoring (if a patient was alive at the last follow-up). The Kaplan–Meier method and log-rank test were used to conduct the univariate prognostic analysis. Variables that were possible prognostic factors ($P < .05$) on univariate analyses were included in the multivariate Cox proportional hazards analysis to reveal independent OS factors ($P < .05$). Then, the independent factors in the multivariate analysis were used to build nomograms

Table 1

Clinical characteristics and outcomes of the training and validating cohorts.

Variables	Stratification	Training (n=863)		Validating (n=563)	
		No.	%	No.	%
Age	0–24	509	58.98	319	56.66
	25–59	250	28.97	163	28.95
	>60	104	12.05	81	14.39
Race	White	659	76.36	425	75.49
	Black	131	15.18	91	16.16
	Other	73	8.46	47	8.35
Sex	Male	473	54.81	310	55.06
	Female	390	45.19	253	44.94
Site	Axial	201	23.29	155	27.53
	Extremity	662	76.71	408	72.47
Grade	Well	43	4.98	27	4.80
	Moderately	76	8.81	38	6.75
	Poorly	244	28.27	184	32.68
	Un	500	57.94	314	55.77
Laterality	Left	355	41.14	233	41.39
	Right	374	43.34	247	43.87
	Not a paired	131	15.18	83	14.75
Histology	Bilateral	3	0.35	0	0.00
	Others	307	35.57	205	36.41
	Osteosarcoma	556	64.43	358	63.59
T	T1	340	39.40	204	36.23
	T2	355	41.14	272	48.31
	T3	28	3.24	13	2.31
	TX	140	16.22	74	13.14
N	N0	789	91.43	526	93.43
	N1	18	2.09	17	3.02
	NX	56	6.49	20	3.55
M	M0	687	79.61	453	80.46
	M1a	79	9.15	49	8.70
	M1b	79	9.15	48	8.53
	M1NOS	0	0.00	7	1.24
SEER historic stage	MX	18	2.09	6	1.07
	Localized	269	31.17	180	31.97
	Regional	395	45.77	251	44.58
	Distant	186	21.55	121	21.49
Surgery	Unstaged	13	1.51	11	1.95
	Yes	752	87.14	477	84.72
Status	No	111	12.86	86	15.28
	Alive	468	54.23	339	60.21
Insurance	Death	395	45.77	224	39.79
	Yes	324	37.54	545	96.80
Marital	No	12	1.39	13	2.31
	Unknown	527	61.07	5	0.89
	Others	643	74.51	423	75.13
Education	Married	220	25.49	140	24.87
	$\geq 28.77\%$	33	3.82	23	4.09
	18.82%–28.77%	265	30.71	166	29.48
	15.16%–18.81%	120	13.90	76	13.50
Income	$< 15.16\%$	445	51.56	298	52.93
	$< 46,450$	37	4.29	33	5.86
	$< 51,400$	39	4.52	21	3.73
	$< 63,550$	302	34.99	210	37.30
	$\geq 63,550$	485	56.20	299	53.11
Poverty	$\geq 17.90\%$	147	17.03	110	19.54
	12.44%–17.90%	368	42.64	235	41.74
	8.41%–12.44%	253	29.32	156	27.71
	$< 8.41\%$	95	11.01	62	11.01

for 3-year and 5-year OS for patients with osteosarcoma by employing a stepwise-selection method in the R software. The CSS was defined as the time from diagnosis to death attributed to

Table 2
Univariate analysis of OS in the nomogram cohort.

Variables	P	HR	95% CI
Age, y			
0–24	Ref.		
25–59	.005	1.393	1.108–1.751
>60	<.001	4.097	3.163–5.307
Race			
White	Ref.		
Black	.636	0.934	0.705–1.238
Other	.965	1.008	0.710–1.430
Sex			
Female	Ref.		
Male	.604	0.949	0.778–1.157
Site			
Extremity	Ref.		
Axial	<.001	0.519	0.420–0.643
Grade			
Well	Ref.		
Moderately	.289	0.689	0.345–1.373
Poorly	.028	1.858	1.071–3.225
Unstaged	.147	1.490	0.869–2.556
Laterality			
Left	Ref.		
Right	.607	1.060	0.850–1.322
Not a paired site	<.001	1.806	1.373–2.375
Bilateral	.320	2.031	0.503–8.199
Histologic subtypes			
Osteosarcoma, NOS	Ref.		
Others	.009	1.311	1.074–1.649
T			
T1	Ref.		
T2	.065	1.243	0.987–1.565
T3	<.001	2.649	1.653–4.244
TX	<.001	1.947	1.479–2.564
N			
N0	Ref.		
N1	<.001	3.687	2.194–6.196
NXs	<.001	2.783	2.024–3.826
M			
M0	Ref.		
M1a	<.001	2.483	1.855–3.322
M1b	<.001	5.081	3.867–6.677
MX	.001	2.709	1.518–4.832
SEER historic stage			
Localized	Ref.		
Regional	.003	1.491	1.145–1.941
Distant	<.001	4.246	3.231–5.580
Unstaged	.005	3.033	1.402–6.561
Surgery			
Not performed	Ref.		
Yes	<.001	3.369	2.631–4.314
Insurance			
Yes	Ref.		
No	.705	1.171	0.518–2.648
Unknown	.291	0.895	0.729–1.099
Marital status			
Married	Ref.		
Others	<.001	1.717	1.392–2.119
Education			
≥28.77%	Ref.		
18.82%–28.77%	.382	1.291	0.729–2.286
15.16%–18.81%	.544	1.207	0.658–2.213
≤15.16%	.427	1.255	0.716–2.198

(continued)

Table 2
(continued).

Variables	P	HR	95% CI
Income			
≤46,450	Ref.		
46,450–51,400	.359	0.745	0.397–1.398
51,400–63,550	.078	0.660	0.416–1.047
≥63,550	.200	0.746	0.477–1.167
Poverty			
≥17.90%	Ref.		
12.44%–17.90%	.758	0.957	0.722–1.267
8.41%–12.44%	.781	0.959	0.712–1.291
≤841	.786	0.949	0.652–1.382

osteosarcoma or censoring (if a patient was alive at the last follow-up or death from other causes). The cumulative incidence function (CIF) was used to assess the probability of death. Variables whose *P* values were <.05 for the CIF values were considered significant independent CSS factors. Similarly, we developed nomograms with those significant independent factors, to predict 3-year and 5-year CSS in patients with osteosarcoma.

2.4. Nomograms validations

The validation cohort was employed to estimate the predictive accuracy of the model by performing internal validation; by C-index, performed using bootstrapping with 1000 resamples, and by calibration plots using 10-fold cross validation. The C-indexes

Table 3
Multivariate analysis of OS in the nomogram cohort.

Variables	P	HR	95% CI
Age			
0–24	Ref.		
25–59	<.001	1.760	1.367–2.266
>60	<.001	3.620	2.709–4.839
Site			
Extremity	Ref.		
Axial	<.001	0.565	0.440–0.726
T			
T1	Ref.		
T2	.320	1.137	0.883–1.464
T3	.083	1.756	0.930–3.316
TX	.002	1.622	1.192–2.206
M			
M0	Ref.		
M1a	.064	1.865	0.094–3.606
M1b	<.001	4.010	2.082–7.724
MX	.001	2.096	1.027–4.276
SEER historic stage			
Localized	Ref.		
Regional	.003	1.504	1.147–1.974
Distant	.125	1.694	0.865–3.317
Unstaged	.518	0.728	0.277–1.909
Surgery			
Not performed	Ref.		
Yes	<.001	1.819	1.360–2.433

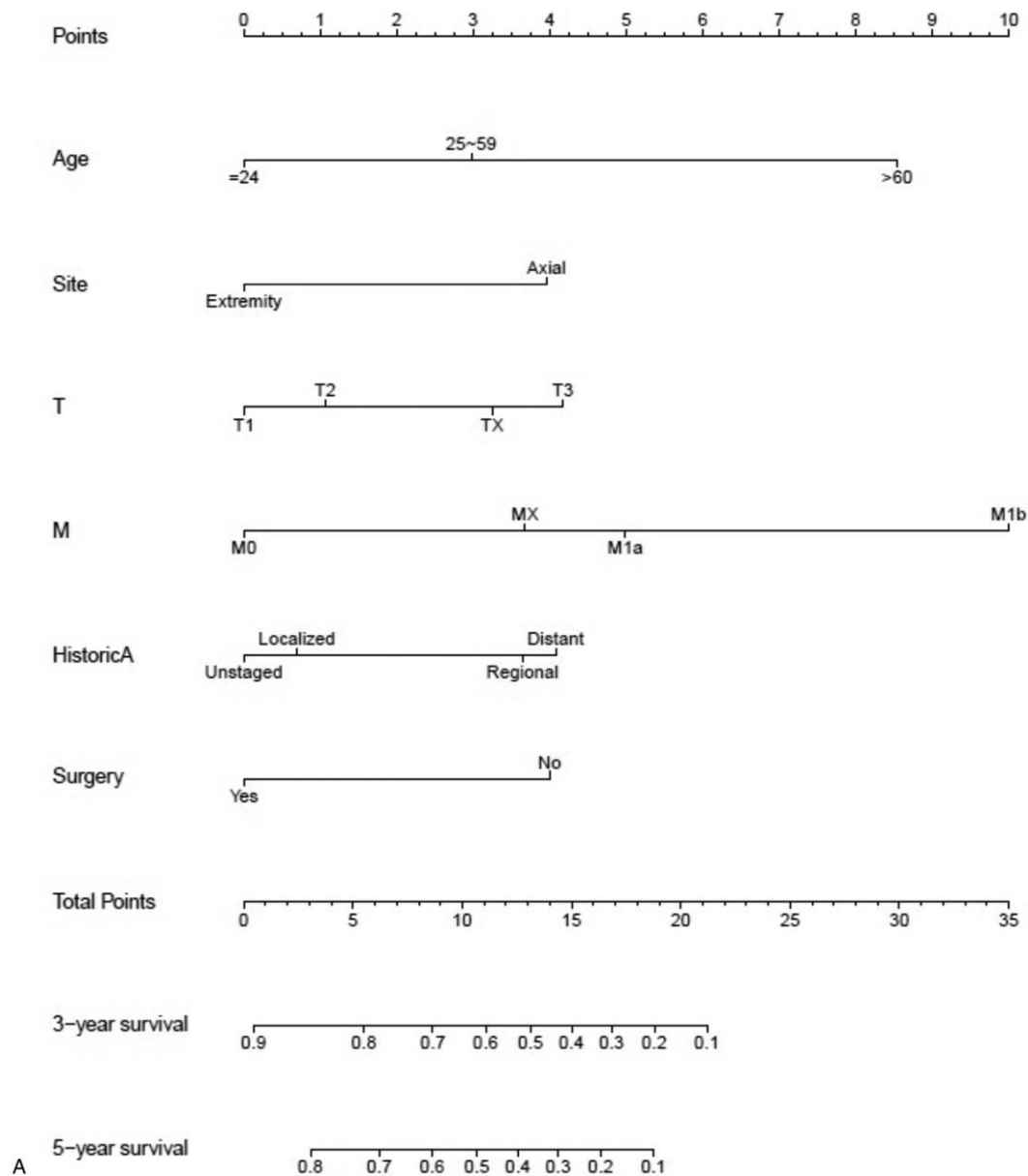


Figure 1. Nomograms predicting 3- and 5-year OS (A) and CSS (B).

quantified the discrimination between predicted and actual situations, with values ranging from 0.5 to 1.0, representing no discrimination to perfect discrimination. In addition, a marginal estimate versus model was used to plot a calibration curve that presented the correlation between nomogram-predicted and actual survival. The C-indexes (both OS and CSS) of our nomogram were compared with those of the classical model of survival prediction, the AJCC staging system, and a significant difference was defined by $P < .001$.

2.5. Statistical management

All statistical analysis was conducted using the SPSS software version 22.0 (SPSS Inc., Chicago, IL) and the R software version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) with the R packages rms and cmprsk.

3. Results

3.1. Clinical characteristics of patients

After applying the collecting criteria, a total of 1426 primary osteosarcoma patients from the SEER database of the National Cancer Institute, diagnosed between 2004 and 2011, were included in this study. The patients were divided into a training cohort (2004–2008, $n=863$) and a validation cohort (2009–2011, $n=563$). The mean follow-up period was 54.8 ± 37.5 months. Clinical characteristics and outcomes are listed in Table 1.

3.2. Nomograms construction

After univariate analyses, age, tumor site, laterality, histologic subtypes, T (AJCC, tumor size), N (AJCC, lymph nodes), M

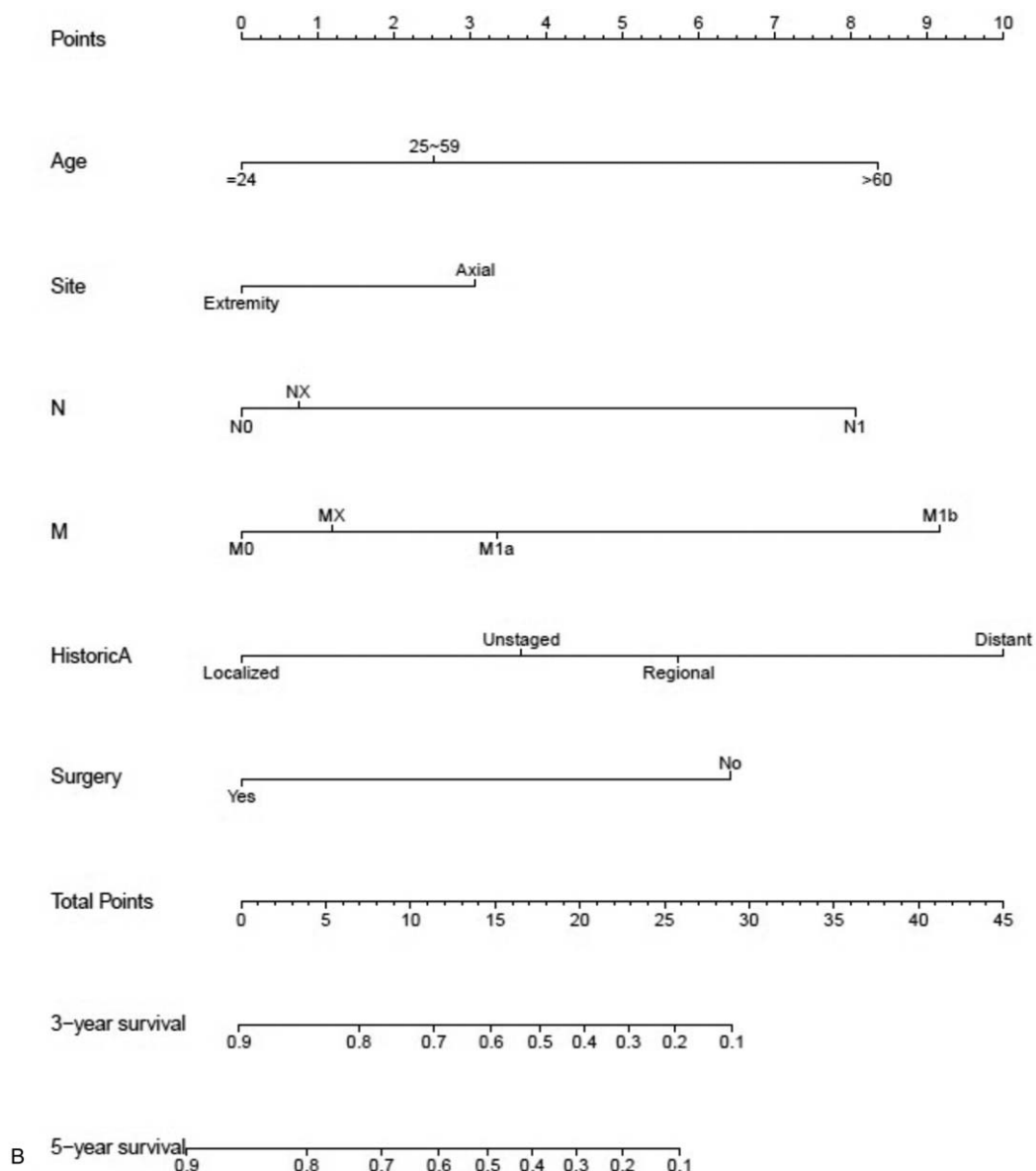


Figure 1. (continued).

(AJCC, metastasis), SEER historic stage, surgery performed, and marital status were found to be statistically associated with OS ($P < .05$), whereas sex, race, grade, income, poverty, education, and insurance status were not (Table 2). Multivariate analyses revealed that 6 variables were independent prognostic factors for OS in patients with osteosarcoma ($P < .05$); age, tumor site, T, M, SEER historic stage, and surgery performed (Table 3). These variables were used to develop the nomogram for predicting 3-year and 5-year OS (Fig. 1A). Similarly, after univariate and multivariate analyses (Tables 4 and 5), 6 variables were independent prognostic factors for CSS in patients with osteosarcoma: age, tumor site, N, M, SEER historic stage, and surgery performed. From this data another nomogram was created using these variables for predicting 3-year and 5-year CSS (Fig. 1B). The survival curves for OS and CSS are shown in Figures 2 and 3.

3.3. Nomograms validation

In the training cohort, 304 patients (35.2%) died from osteosarcoma and 91 (10.5%) died from other causes. In the validation cohort, 155 patients (27.5%) died from osteosarcoma and (12.3%) died from other causes. The C-indexes for OS and CSS in the training cohort were 0.725 (95% confidence interval [CI], 0.700–0.750) and 0.718 (95% CI, 0.688–0.748), respectively. We performed internal validation of the nomograms with the validation cohort from the SEER database. Models showed good accuracy with a C-index of 0.775 (95% CI, 0.744–0.806) and 0.742 (95% CI, 0.712–0.772) for OS and CSS, respectively. The calibration curves approached the 45-degree ideal match straight line, indicating that the nomograms for OS and CSS in osteosarcoma were generally well calibrated (Fig. 4).

Table 4
Univariate analysis of CSS in the nomogram cohort.

Variables	P	HR	95% CI
Age			
0–24	Ref.		
25–59	.267	1.158	0.894–1.500
>60	<.001	2.667	1.931–3.684
Race			
White	Ref.		
Black	.680	0.934	0.677–1.290
Other	.398	1.175	0.808–1.710
Sex			
Female	Ref.		
Male	.680	0.954	0.760–1.196
Site			
Extremity	Ref.		
Axial	0.003	0.674	0.522–0.872
Grade			
Well	Ref.		
Moderately	.183	0.592	0.274–1.280
Poorly	.143	1.568	0.860–2.859
Unstaged	0.283	1.377	0.768–2.470
Laterality			
Left	Ref.		
Right	.445	1.101	0.861–1.408
Not a paired site	.046	1.407	1.006–1.968
Bilateral	.797	1.294	0.181–9.269
Histologic subtypes			
Osteosarcoma, NOS	Ref.		
Others	.065	1.256	0.986–1.600
T			
T1	Ref.		
T2	.005	1.462	1.124–1.901
T3	<.001	3.327	2.008–5.514
TX	<.001	1.831	1.315–2.550
N			
N0	Ref.		
N1	<.001	4.422	2.578–7.586
NX	<.001	2.157	1.441–3.231
M			
M0	Ref.		
M1a	<.001	2.823	2.059–3.870
M1b	<.001	5.006	3.651–6.863
MX	.167	1.772	0.787–3.992
SEER historic stage			
Localized	Ref.		
Regional	<.001	1.817	1.327–2.487
Distant	<.001	5.166	3.734–7.145
Unstaged	.062	2.627	0.952–7.252
Surgery			
Not performed	Ref.		
Yes	<.001	3.032	2.264–4.060
Insurance			
Yes	Ref.		
No	.547	1.317	0.537–3.226
Unknown	.291	0.965	0.763–1.221
Marital status			
Married	Ref.		
Others	.007	1.409	1.098–1.807
Education			
≥28.77%	Ref.		
18.82%–28.77%	.432	1.299	0.677–2.492
15.16%–18.82%	.535	1.244	0.624–2.480
≤15.16%	.501	1.246	0.657–2.361

(continued)

Table 4
(continued).

Variables	P	HR	95% CI
Income			
≤46,450	Ref.		
46,450–51,400	.961	0.983	0.491–1.968
51,400–63,550	.185	0.692	0.402–1.193
≥63,550	.420	0.805	0.475–1.364
Poverty			
≥17.90%	Ref.		
12.44%–17.90%	.560	0.910	0.663–1.250
8.41%–12.44%	.833	0.965	0.691–1.346
≤8.41%	.379	0.821	0.528–1.275

3.4. Nomograms compared with AJCC

The C-indexes (0.725 for OS and 0.718 for CSS) of our nomogram were compared with those of the classical model of survival prediction, the AJCC staging system, whose C-indexes were 0.663 (95% CI, 0.636–0.690) and 0.664 (95% CI, 0.633–0.695) for OS and CSS, respectively. There was a significant difference between the 2 models ($P < .001$). Our nomograms have better power for predicting the prognosis of patients with osteosarcoma.

4. Discussion

Osteosarcoma is a highly malignant bone tumor with a low incidence. Due to all kinds of clinical factors, such as histological diversity, metastasis, tumor size, location, and invasion, the 5-year overall survival rate of osteosarcoma patients varies widely, ranging from 28% to 70%.^[2,3] Therefore, there are still some challenges when making treatment-related decisions and

Table 5
Multivariate analysis of CSS in the nomogram cohort.

Variables	P	HR	95% CI
Age			
0–24	Ref.		
25–59	.062	1.303	0.987–1.722
>60	<.001	2.393	1.690–3.387
Site			
Extremity	Ref.		
Axial	.028	0.724	0.544–0.965
N			
N0	Ref.		
N1	.003	2.326	1.333–4.058
NX	.745	1.081	0.676–1.728
M			
M0	Ref.		
M1a	.256	1.419	0.776–2.597
M1b	.002	2.587	1.406–4.759
MX	.793	1.143	0.420–3.112
SEER historic stage			
Localized	Ref.		
Regional	<.001	1.833	1.337–2.513
Distant	<.001	2.886	1.606–5.187
Unstaged	.520	1.480	0.448–4.889
Surgery			
Not performed	Ref.		
Yes	<.001	1.950	1.405–2.708

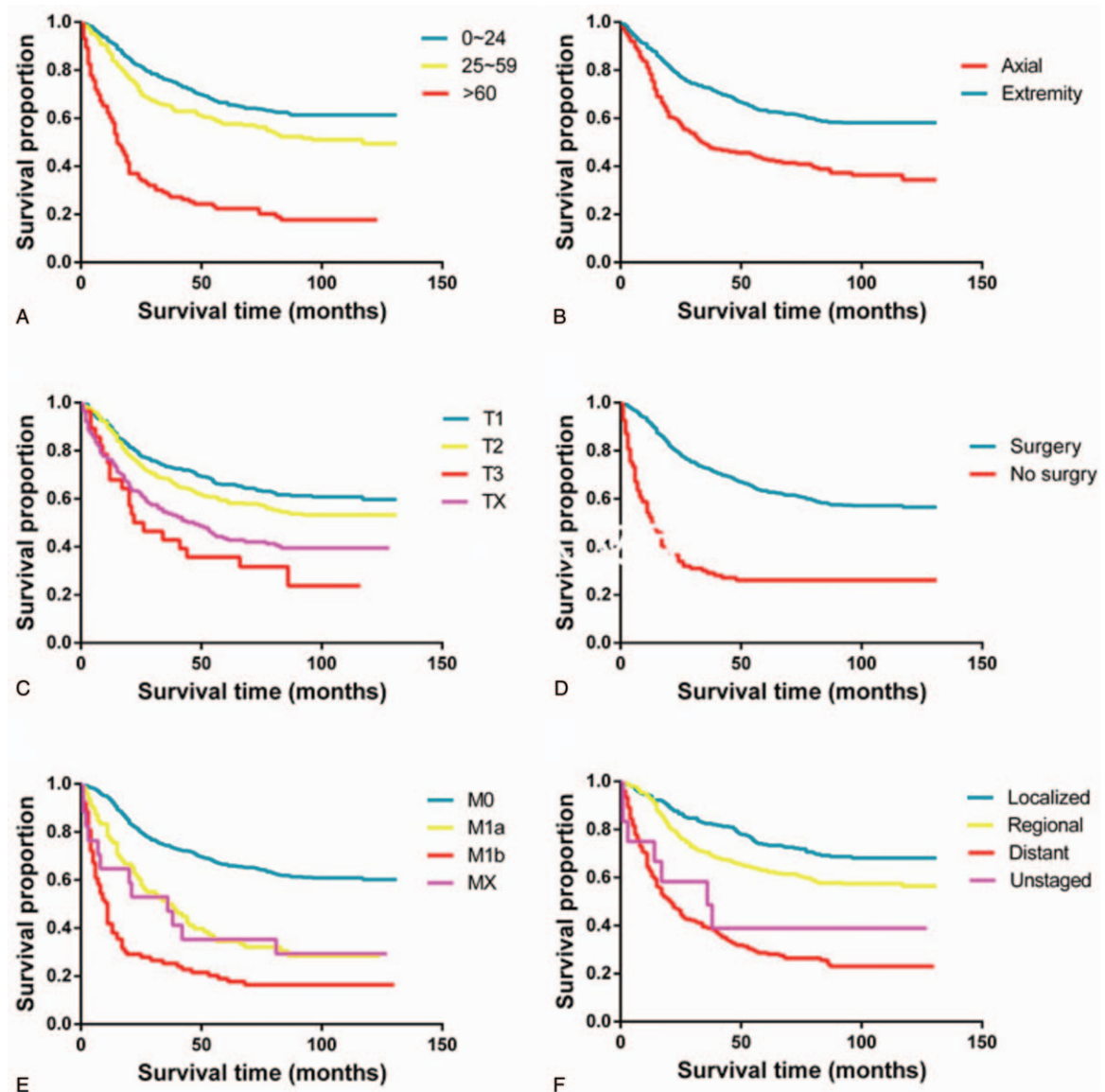


Figure 2. Kaplan–Meier curves for significant factors derived from multivariate analyses in OS: (A) age, (B) primary tumor site (axial or extremity), (C) T stage, (D) surgery, (E) M stage, and (F) the SEER historic stage (tumor invasion).

establishing follow-up strategies. A nomogram is a powerful statistical tool that can help in the decision making process. To our limited knowledge, there is no well-design nomogram for osteosarcoma based on a nation-wide population. Using the data selected from the SEER database with a mean follow-up of 55 months, we developed nomograms for predicting 3- and 5-year OS and CSS in patients with osteosarcoma.

For the predictive accuracy of nomograms, we used the Kaplan–Meier method and the Cox’s proportional hazards regression model to select factors to develop the OS nomogram. A competing risk model was used to select factors for the development of the CSS nomogram. In addition, C-indexes and calibration plots were applied to estimate the predictive accuracy of the models by performing internal validation. All nomogram C-indexes were >0.7 and there was excellent agreement between calibration curves and 45-degree perfect match straight lines.

It is simple and easy to use a nomogram to predict the survival possibility of an osteosarcoma patient. First, a vertical line should be drawn from every factor to the “Point” bar in the nomogram. Thereby, the total points value is obtained. Another vertical line should be drawn from the “Total Points” bar to the survival possibility bar to obtain the corresponding survival. For example, consider a 55 years old male white patient with a T3N0M0 moderate-differentiated localized osteosarcoma (NOS) at the right lower limb, who underwent a surgery. By applying our nomograms, his 5-year OS and CSS predicted is 62% and 86%, respectively.

In this nomogram, increasing patient age is associated with a worse prognosis in patients with osteosarcoma, consistent with previous studies.^[15,16] Older patients may be more likely to present with metastatic disease and worse general health conditions than younger patients. The present study also identified axial tumor location, high SEER historic stage, and large tumor size as independent risk factors for decreased OS and

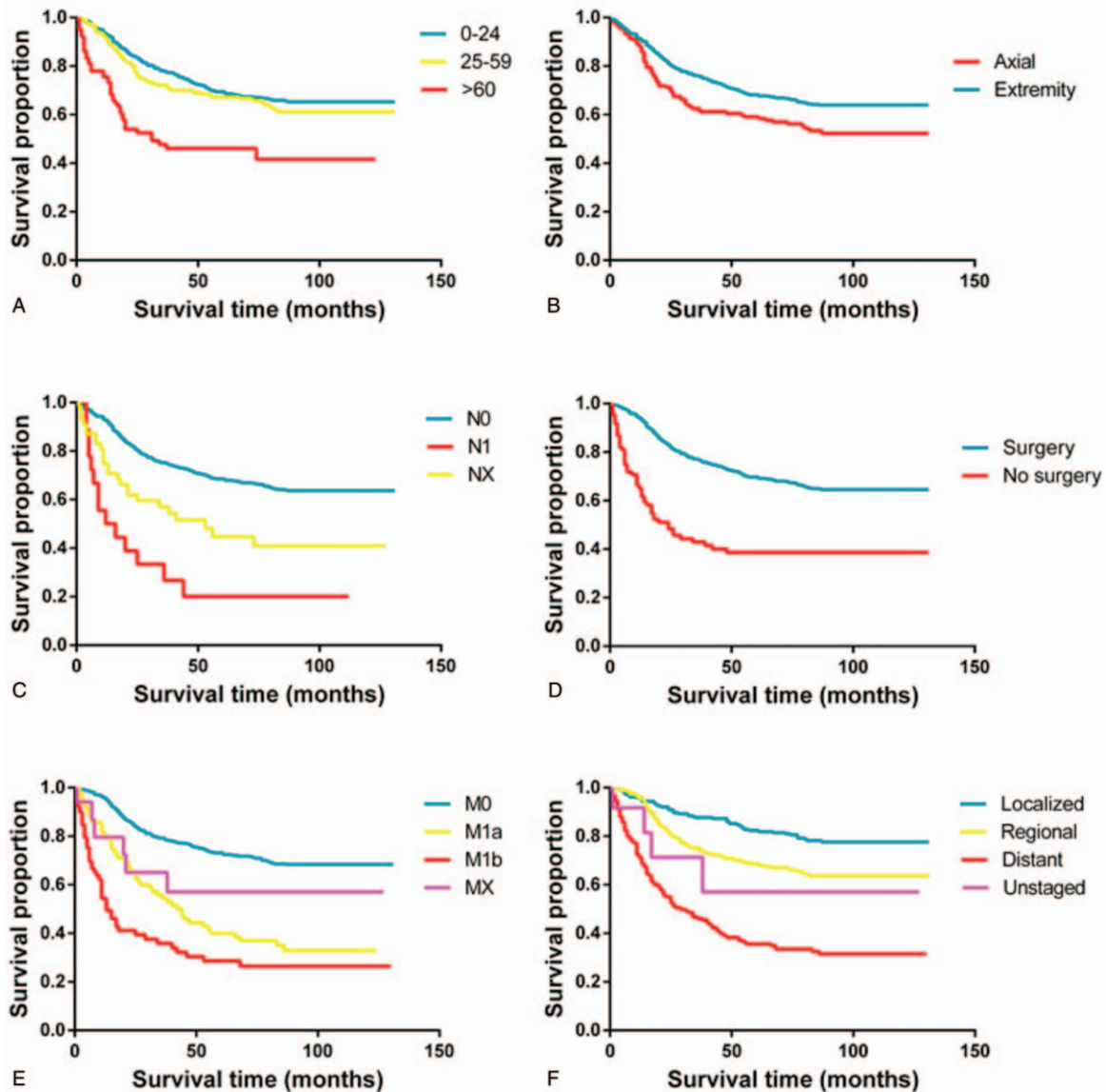


Figure 3. Kaplan–Meier curves for significant factors derived from multivariate analyses in CSS: (A) age, (B) primary tumor site (axial or extremity), (C) T stage, (D) surgery, (E) M stage, and (F) the SEER historic stage (tumor invasion).

CSS. Axial tumor location, high SEER historic stage, and large tumor size suggest significant challenges for surgeons attempting to obtain adequate margins during surgical resection. In addition, tumors in the axial skeleton are in closer proximity to large vessels, nerves, and important organs, which may increase the likelihood of metastasis.^[1] Furthermore, tumors in the axial skeleton tend to grow undetected, whereas tumors in the extremities tend to show some clinical signs, such as palpable mass and increasing pain, which are evaluated without delay. These reasons partially explain the inferior post surgical results in patients with tumors in the axial skeleton. Finally, it has been demonstrated that metastasis and surgery not performed usually indicate a poor prognosis.^[17–19]

Although our nomograms estimate the prognosis of the patients who suffered from osteosarcoma with a high accuracy, according to C-indexes and calibration plots, our study had certain limitations. First, osteosarcoma TNM stage informa-

tion was not available from the SEER program until 2004. The earliest record included in our study was diagnosed in that year, and we were not able to predict a survival time >5 years. Second, there are likely important independent prognosis factors that have not yet been identified by researchers or recorded by the SEER program, such as chemotherapy^[20–22] and perineural/perivascular invasion. These factors might be associated with the prognosis of osteosarcoma but were not included in our study.

In conclusion, based on a large population based cohort provided by the SEER program, we have developed clinically useful nomograms which can predict 3- and 5-year OS and CSS for patients with osteosarcoma, for the first time with this large number of cases from the SEER database. The performance of these nomograms was accurate and they could help clinicians in making decisions about surgical, adjuvant therapeutic and follow-up strategies to treat osteosarcoma patients more effectively.

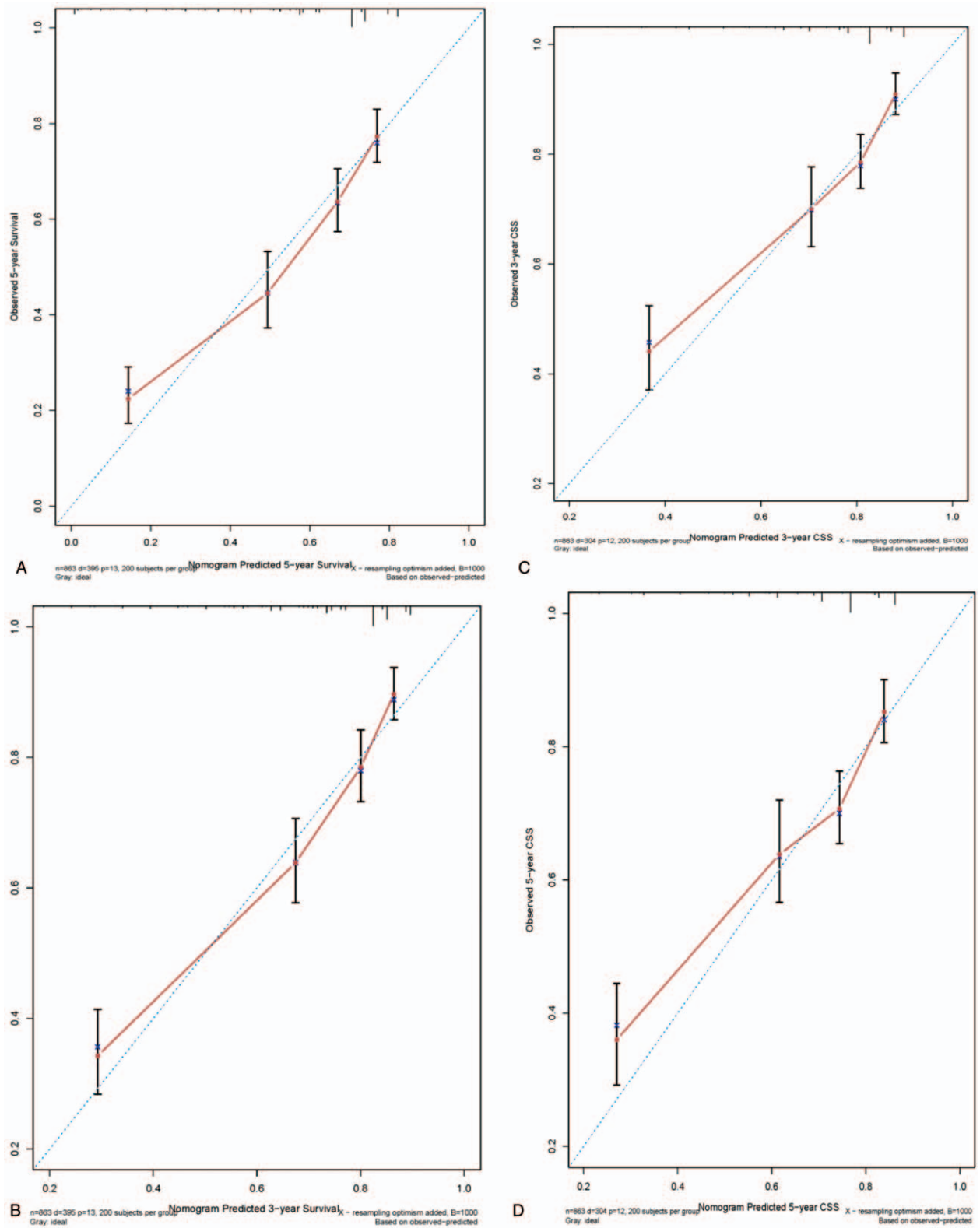


Figure 4. Calibration curves for nomograms predicting 3- and 5-year OS and CSS: (A) 3-year OS, (B) 5-year OS, (C) 3-year CSS, and (D) 5-year CSS.

Author contributions

Study conception and design: WC, YL. Data acquisition and quality control of data: WC, YL. Data analysis and interpretation: WC. Statistical analyses of the data: WC. Manuscript preparation and editing: WC. Final review and approval of manuscript: All authors.

Conceptualization: Wenhao Chen, Yuxiang Lin.

Data curation: Wenhao Chen.

Investigation: Wenhao Chen.

Methodology: Eenhao Chen.

Software: Wenhao Chen.

Supervision: Wenhao Chen.

Validation: Wenhao Chen.

Writing—original draft: Wenhao Chen.

Writing—review and editing: Yuxiang Lin.

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