Development and validation of a prognostic nomogram for predicting the overall survival of myxofibrosarcoma patients: a large population-based study

Shuai Cao[1][#][^], Jie Li[1][#][^], Jun Zhang[2][^], Haopeng Li[1][^]

[1]Department of Orthopedics, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [2]School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, China

Contributions: (I) Conception and design: S Cao; (II) Administrative support: H Li; (III) Provision of study materials: J Zhang; (IV) Collection and assembly of data: J Li; (V) Data analysis and interpretation: S Cao, J Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Haopeng Li, MD. Department of Orthopedics, The Second Affiliated Hospital of Xi'an Jiaotong University, 157th West Fifth Road, Xi'an, China. Email: lihaopeng3993@163.com.

Background: Although some studies have explored prognostic factors of myxofibrosarcoma (MFS), the sample sizes were small, generally fewer than 100 patients. There is still no effective prognostic model for MFS patients based on a large population and comprehensive factors. The present study was designed to establish and validate a large population-based, clinically relevant prognostic nomogram for predicting 3- and 5-year overall survival (OS) in patients with MFS.

Methods: We identified patients with MFS (ICD-O-3 code: 8811/3) who were diagnosed between 2004 and 2015 from the Surveillance, Epidemiology, and End Results database and separated them into training and validation cohorts (7:3 ratio). Survival was described using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were used to identify prognostic factors of survival. An individual nomogram was established to predict OS at 3 and 5 years in MFS patients. The discriminative ability and predictive accuracy of the nomogram were compared to those of the traditional American Joint Committee on Cancer (AJCC) staging system in the training and validation cohorts. Finally, MFS patients were divided into two subgroups based on the prognostic index (PI) score of the nomogram, and the survival outcomes of the subgroups were compared.

Results: A total of 1,270 patients were included. Age at diagnosis, total number of in situ or malignant tumors, tumor size, tumor site, tumor extension, AJCC stage, surgical status, chemotherapy, and radiotherapy were the independent predictors of survival and were included in the nomogram. The nomogram had C-indexes of 0.806 in the training cohort and 0.783 in the validation cohort, which were greater than those of the sixth edition of the AJCC staging system (training cohort, 0.669 and validation cohort, 0.674). Decision curve analysis (DCA) revealed that the nomogram was useful with high clinical net benefits. Survival outcomes were significantly different between the different risk subgroups (P<0.001).

Conclusions: A novel nomogram based on a large population was constructed to evaluate survival outcomes for MFS. Its predictive efficacy was markedly superior than that of the traditional sixth edition of the AJCC staging system.

Keywords: Myxofibrosarcoma (MFS); outcomes; SEER database; receiver operating characteristic curve; decision curve analysis (DCA)

Introduction

Myxofibrosarcoma (MFS) represents 5% of soft tissue sarcomas (1-3), and soft tissue sarcomas account for less than 1% of all malignancies (4-5). MFS was first described in 1977, and it was originally considered myxoid degeneration of malignant fibrous tissue cell tumors (6-9). It is usually found in elderly individuals, with a median age at diagnosis of 64–75 years, and mainly occurs in the extremities, especially the lower extremities (1-4). MFS has a higher local recurrence (LR) rate and relatively better outcomes than other soft tissue sarcomas; the 5-year overall survival (OS) rate is 60–80%, and the LR rate exceeds 25% (1,4,6,10). However, the optimal therapeutic strategy for MFS remains unclear (11). Surgery followed by adjuvant radiotherapy is considered the standard therapeutic strategy in clinical practice (1,3,4,12). However, the sensitivity of sarcomas to radiotherapy and the effect of radiotherapy on local incision remains controversial (1,4,6,7,10). Moreover, anthracyclines and ifosfamide-based chemotherapy, as well as novel targeted therapies, are rarely administered, so their roles in the treatment of MFS are uncertain (1,2,4,13-15).

Clinicians should consider comprehensive factors when treating an individual patient, which is crucial to each patient's outcome. However, prognostic predictions and clinical decisions depend mainly on the American Joint Committee on Cancer (AJCC) staging system, which has been considered an effective method for evaluating the risk of malignant tumors for 40 years (16). However, this system has some limitations, such as not taking into account the anatomical site, pathological type, or patient characteristics (8). Although some studies have explored prognostic factors of MFS, such as molecular markers, tumor size, tumor grade, surgical margin, and LR (6,11,17-21), the sample sizes were small, generally fewer than 100 patients (1-3). Therefore, the findings were not consistent among the different studies. For example, Sanfilippo *et al.* confirmed that tumor size, tumor grade, and resection margins were statistically significant predictors of survival in MFS patients (1). However, Mühlhofer *et al.* found that tumor grade and metastasis were significant prognostic factors of survival, whereas negative surgical margins were not a significant prognostic factor (6).

The nomogram, a prognostic tool that is tailored to an individual patient, is a novel effective tool for clinicians to estimate patient outcomes. Demographic data, clinical data, and histopathological data are integrated to construct a model to specifically predict more individualized and accurate outcomes. Relevant studies have validated the utility of nomograms in predicting prognosis in cancer patients (22-24). Nomograms can be used to solve some of the problems in the AJCC staging system or other prognostic methods. However, to our knowledge, there is still no effective prognostic nomogram model for MFS patients based on a large population and comprehensive factors. This study aimed to develop and validate a large population-based, clinically relevant nomogram to estimate the survival of MFS patients as a useful clinical tool. We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2588).

Methods

Data source

The Surveillance, Epidemiology, and End Results (SEER) database is a population-based cancer reporting system of the National Cancer Institute that is publicly available for researchers. The SEER data, covering approximately 28% of the total population of the United States, have become increasingly utilized in the study of cancer epidemiology and outcomes over the past three decades (25-27). We downloaded SEER Datasets and Software (RRID:SCR_003293) version #8.3.6 (http://seer.cancer.gov/seerstat/) and acquired the data from Identity-SEER 18Regs Custom Data (with additional treatment fields), Nov 2017 Sub (1973-2015 varying). To construct and validate the novel nomogram, all patients were randomly allocated to the training or validation cohorts (seed =15). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval was not required in the current study because the SEER research data are publicly available. Moreover, we registered

and received access to the SEER database (accession No. 16375-Nov2018).

Data selection

This was a retrospective study. We included data from patients with MFS (ICD-O-3 code: 8811/3) according to the 2013 World Health Organization Classification of Soft Tissue Tumors (Fourth Edition) who were diagnosed between 2004 and 2015 from 18 registry centers in the SEER database. MFS diagnoses were confirmed by histology or cytology examinations, and data from 2,234 patients were obtained. Patients with missing crucial information, such as unknown survival status, unknown survival time, or unknown treatment, and age at diagnosis <18 were excluded. Finally, data from 1,270 patients were included after filtration (inclusion and exclusion criteria are shown in *Figure 1*). The variables of interest were identified, including age at diagnosis, sex, race, marital status, socioeconomic status (SES), tumor site, tumor size, tumor extension, AJCC stage, grade, total number of *in situ* or malignant tumors, surgical status, radiotherapy, and chemotherapy. The outcomes assessed in this study included the 3- and 5-year OS rates. OS was calculated from the date of first diagnosis of MFS to death or loss to follow-up. The data of patients who were lost to follow-up or who were still alive at the last follow-up were censored. The SES variable was divided into three levels using previously reported cutoff points: <10% (low), ≥10% and <20% (moderate), and ≥20% (high) (23). A tumor was considered to be in the soft tissues of the extremities if it was in the soft tissue of the upper limbs, shoulders, lower limbs, or hips and in the soft tissues of other sites if it was in soft tissues of the head, face, neck, thorax, abdomen, pelvis, trunk, etc. All other tumors at different sites, including the bones, peritoneum, retroperitoneum, heart, and nerves, were classified into one group. Tumor size was categorized as ≤50 or >50 mm (recorded as the largest dimension or diameter of the tumor). Tumors were labeled as confined, localized, or metastatic (extension to adjacent connective tissue or distant organ) according to the tumor extension. Tumor grade was categorized into grade I (well-differentiated), grade II (moderately differentiated), grade III (poorly differentiated), and grade IV (undifferentiated). Patient data were randomly divided into a training cohort and a validation cohort at a ratio of 7:3, with the training cohort having 889 patients

and the validation cohort having 381 patients.

Statistical analysis

The univariate analysis was performed using the Kaplan-Meier method and univariate Cox regression analysis. Survival curves were compared using the log-rank test. Variables identified as significant on univariate analysis were entered into the multivariate Cox proportional hazards regression models to identify the independent prognostic factors of MFS. Cox regression model was used to handle missing data and build a nomogram with the variables identified in the multivariate analysis. The variance inflation factor (VIF) was used to assess multicollinearity among the covariates. Variables with VIF >5 were considered to have multicollinearity and were not included in the final model. A nomogram was constructed to predict the 3- and 5-year OS, and its efficacy was compared with that of the AJCC staging system, 6th edition. The discriminative ability and predictive accuracy of the nomogram were evaluated by receiver operating characteristic (ROC) curve analysis, the concordance index (C-index), integrated discrimination improvement (IDI), and net reclassification improvement (NRI). Calibration curves described the agreement between the predicted probabilities of the nomogram and the observed outcomes. The clinical net benefits of the nomogram were determined by decision curve analysis (DCA). Further, a prognostic index (PI) score was calculated using the nomogram for each patient in the training and validation cohorts, and the patients were divided into a high-risk group and low-risk group based on the PI score. Finally, survival analysis was used to estimate the ability of the nomogram to distinguish patients from different risk groups.

The nomogram was constructed using R software version 3.1.0 (https://www.r-project.org). Survival curves were drawn using GraphPad Prism 8 software (GraphPad Software, Inc., La Jolla, CA, USA). All statistical analyses were performed using SPSS, version 26 (IBM, Armonk, NY, USA), and a two-tailed P<0.05 was considered statistically significant.

Results

Demographic data

Data from 1,270 patients were included, including 889 in
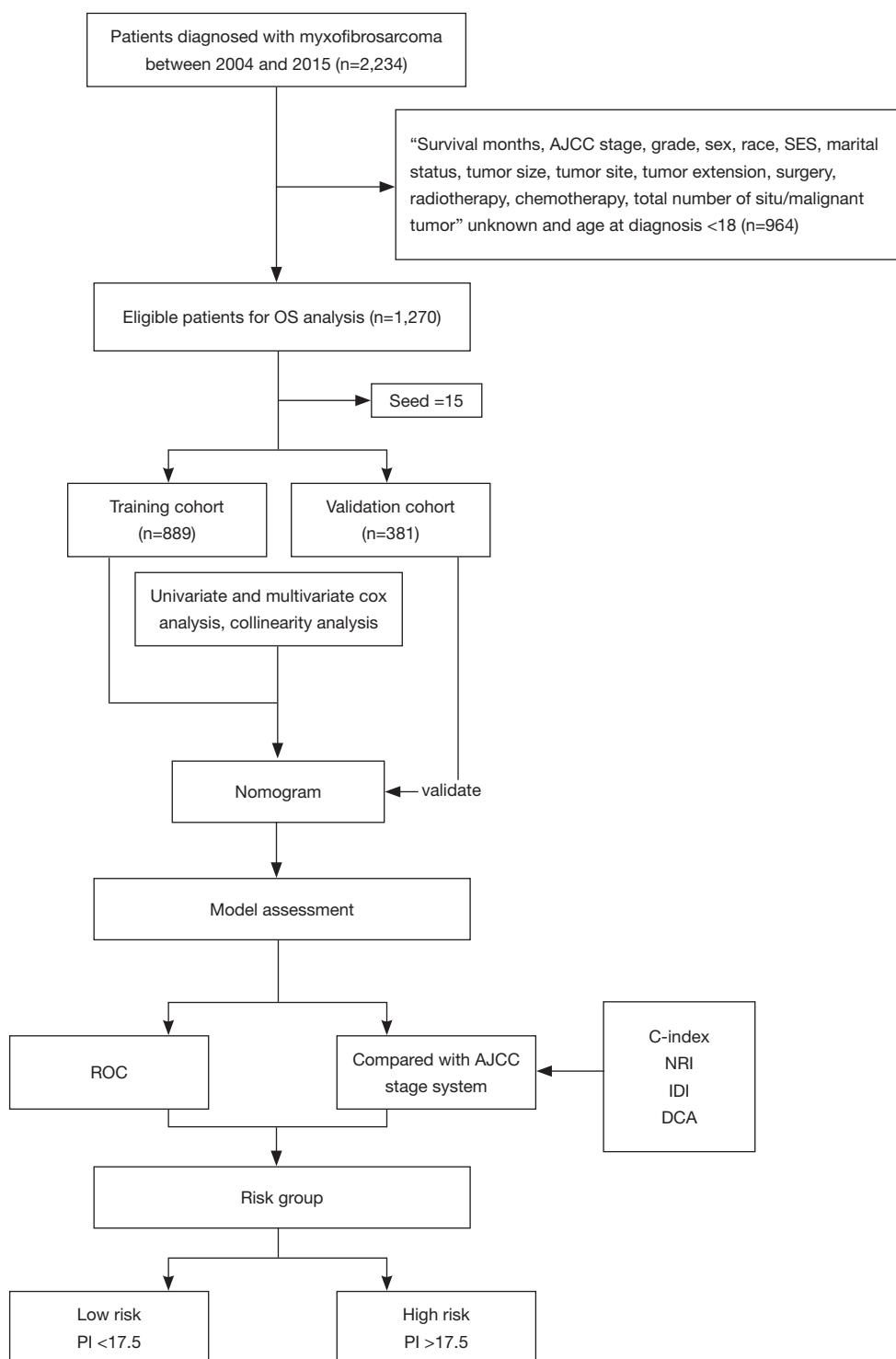
Figure 1 Schematic representation of the research design and flowchart. OS, overall survival; PI, prognostic index; SES, socioeconomic status; DCA, decision curve analysis; NRI, net reclassification improvement; IDI, integrated discrimination improvement; ROC, receiver operating characteristic curve; AJCC, American Joint Committee on Cancer.

the training cohort and 381 in the validation cohort. In the entire cohort, the median age at diagnosis was 63 years, and the age range was 18–98 years. The median follow-up period was 41 months (range, 1–143 months), the 3- and 5-year OS rates were 80.7% and 74.3%, respectively, and the 3- and 5-year disease-specific survival rates were 90.2% and 87.3%, respectively.

In the entire cohort, the median tumor size was 59 mm (range, 2–996 mm). Men (54.3% in the training cohort and 53.8% in the validation cohort), whites (83.7% and 83.5%, respectively), married patients (60.0% and 57.5%, respectively), and patients with moderate SES (53.7% and 53.8%, respectively) were most common in both cohorts. In terms of tumor characteristics, tumors in the soft tissue of the extremities (71.3% in the training cohort and 74.8% in the validation cohort), tumors >50 mm (56.2% and 53.3%, respectively), confined tumors (52.1% and 53.0%, respectively), grade II tumors (36.1% and 40.4%, respectively), and AJCC stage I tumors (51.2% and 52.2%) were predominant in both cohorts. In terms of treatment, surgery (97.9% in the training cohort and 96.1% in the validation cohort) was the most common treatment, whereas few patients underwent chemotherapy (8.8% and 9.8%, respectively). In the entire cohort, approximately the same proportions of patients did (53.9%) and did not (46.1%) receive radiotherapy (*Table 1*).

Kaplan-Meier survival analysis

The OS curve was calculated using the Kaplan-Meier method in the training cohort. Most of the variables were significantly correlated with OS (P<0.05), except sex, race, radiotherapy, and SES (P>0.05) (*Figure 2*).

Univariate Cox regression analysis

In the univariate regression analysis, ten variables (age at diagnosis, marital status, tumor size, tumor site, tumor extension, tumor grade, AJCC stage, surgery status, chemotherapy, and total number of *in situ* or malignant tumors) were significantly associated with OS (P<0.05), whereas sex, race, SES, and radiotherapy were not significantly associated with OS (P>0.05) (*Table 2*).

Multivariate Cox regression analysis

Based on the results obtained from the Kaplan-Meier survival analysis, univariate Cox regression analysis and clinical reasoning, we included eleven variables in the multivariate analysis: age at diagnosis, AJCC stage, marital status, tumor grade, tumor size, tumor extension, tumor site, surgery, chemotherapy, radiotherapy, and the total number of *in situ* or malignant tumors. Multivariate analysis revealed that age at diagnosis, AJCC stage, tumor size, tumor extension, tumor site, surgery, chemotherapy, radiotherapy, and the total number of *in situ* or malignant tumors were the independent prognostic factors for MFS. Collinearity analysis showed that the VIFs among all the variables were <5 (Table S1).

Nomogram construction and validation

Multivariate Cox proportional hazards regression model indicated the risk of death was significantly increased for patients with older age, AJCC stage II–IV, chemotherapy, tumor size >50 mm, >3 *in situ* or malignant tumors, localized tumors, metastasized tumors, and primary tumors located in the bones, peritoneum, retroperitoneum, heart, and nerves (P<0.05). In contrast, the risk of death for patients who underwent surgery and radiotherapy was decreased significantly (P<0.05) (*Figure 3*, Table S2).

Finally, a novel nomogram was constructed to predict the 3- and 5-year OS using age, AJCC stage, chemotherapy, surgical status, radiotherapy, tumor size, total number of *in situ* or malignant tumors, tumor site, and tumor extension (*Figure 4*). Age at diagnosis, which had the highest effect, was converted into 100 points, and then the points assigned to the remaining variables were calculated to measure their effect size. The points were then added, and that sum corresponded to the predicted probability of 3- and 5-year OS. The predicted probability ranged from 0.1 to 0.9.

ROC curve analysis was performed to test the accuracy of the nomogram (*Figure 5*). The areas under the curve (AUCs) for 3- and 5-year OS in the training cohort were 0.769 and 0.759, respectively. Likewise, the validation cohort had relatively high AUCs of 0.793 and 0.752 for 3- and 5-year OS, respectively. The C-indexes of the nomogram were greater than those of the sixth edition of the AJCC staging system (*Table 3*). The calibration curves had an acceptable level of agreement between the predicted survival probabilities of the nomogram and the observed survivals (*Figure 6*).

The NRI values for 3- and 5-year OS are shown in *Table 4*. The IDI values for 3- and 5-year OS were 0.157 (P<0.001) and 0.180 (P<0.001) in the training cohort, respectively, and 0.111 (P<0.001) and 0.134 (P<0.001) in the validation

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Table 1 Characteristics of patients with myxofibrosarcoma

Variable	Total (n=1,270)	Training (n=889)	Validation (n=381)
Age at diagnosis, median [range]	63 [18–98]	63 [18–98]	62 [18–97]
Sex, n (%)			
Male	688 (54.2)	483 (54.3)	205 (53.8)
Female	582 (45.8)	406 (45.7)	176 (46.2)
Race, n (%)			
White	1062 (83.6)	744 (83.7)	318 (83.5)
Black	98 (7.7)	62 (6.9)	36 (9.4)
A/PI	103 (8.1)	78 (8.7)	25 (6.6)
AI/AN	7 (0.6)	5 (0.7)	2 (0.5)
Site, n (%)			
STE	919 (72.4)	634 (71.3)	285 (74.8)
STOS	319 (25.1)	237 (26.7)	82 (21.5)
Other	32 (2.5)	18 (2.0)	14 (3.7)
Grade, n (%)			
I	199 (15.7)	145 (16.3)	54 (14.2)
II	475 (37.4)	321 (36.1)	154 (40.4)
III	213 (16.8)	142 (16.0)	71 (18.6)
IV	383 (30.1)	281 (31.6)	102 (26.8)
AJCC stage, n (%)			
I	654 (51.5)	455 (51.2)	199 (52.2)
II	319 (25.1)	221 (24.9)	98 (25.7)
III	246 (19.4)	180 (20.2)	66 (17.4)
IV	51 (4.0)	33 (3.7)	18 (4.7)
Surgery, n (%)			
No	34 (2.7)	19 (2.1)	15 (3.9)
Yes	1,236 (97.3)	870 (97.9)	366 (96.1)
Radiotherapy, n (%)			
No/unknown	585 (46.1)	401 (45.1)	184 (48.3)
Yes	685 (53.9)	488 (54.9)	197 (51.7)
Chemotherapy, n (%)			
No/unknown	1,157 (91.1)	811 (91.2)	346 (90.8)
Yes	113 (8.9)	78 (8.8)	35 (9.2)

Table 1 (continued)

Table 1 (continued)

Variable	Total (n=1,270)	Training (n=889)	Validation (n=381)
Tumor size, n (%)			
≤50 mm	567 (44.6)	389 (43.8)	178 (46.7)
>50 mm	703 (55.4)	500 (56.2)	203 (53.3)
Extension, n (%)			
Confined	665 (52.4)	463 (52.1)	202 (53.0)
Localized	336 (26.4)	236 (26.5)	100 (26.2)
Metastasis	269 (21.2)	190 (21.4)	79 (20.8)
Total number of in situ/malignant tumors, n (%)			
≤3	1,249 (98.3)	875 (98.4)	374 (98.2)
>3	21 (1.7)	14 (1.6)	7 (1.8)
Marital status, n (%)			
Single	216 (17.0)	148 (16.6)	68 (17.8)
Married	752 (59.2)	533 (60.0)	219 (57.5)
Other	302 (23.8)	208 (23.4)	94 (24.7)
SES, n (%)			
Low	505 (39.8)	360 (40.5)	145 (38.1)
Moderate	682 (53.7)	477 (53.7)	205 (53.8)
High	83 (6.5)	52 (5.8)	31 (8.1)

SES, socioeconomic status; A/PI, Asian or Pacific Islander; STE, soft tissue of extremities; STOS, soft tissue of other sites; AI/AN, American Indian/Alaska Native; AJCC stage, American Joint Committee on Cancer stage.

cohort, respectively. The efficacy of the new model was superior to that of the AJCC staging system.

The DCA graphs showed a significant net benefit of the nomogram for almost all threshold probabilities in both the training and validation cohorts compared to the AJCC staging system (*Figure 7*).

Kaplan-Meier curves showed that there were significant differences in survival between the high-risk group (PI >17.5) and the low-risk group (PI <17.5) (P<0.001) (*Figure 8*).

Discussion

Traditionally, treatment selection and outcome assessment
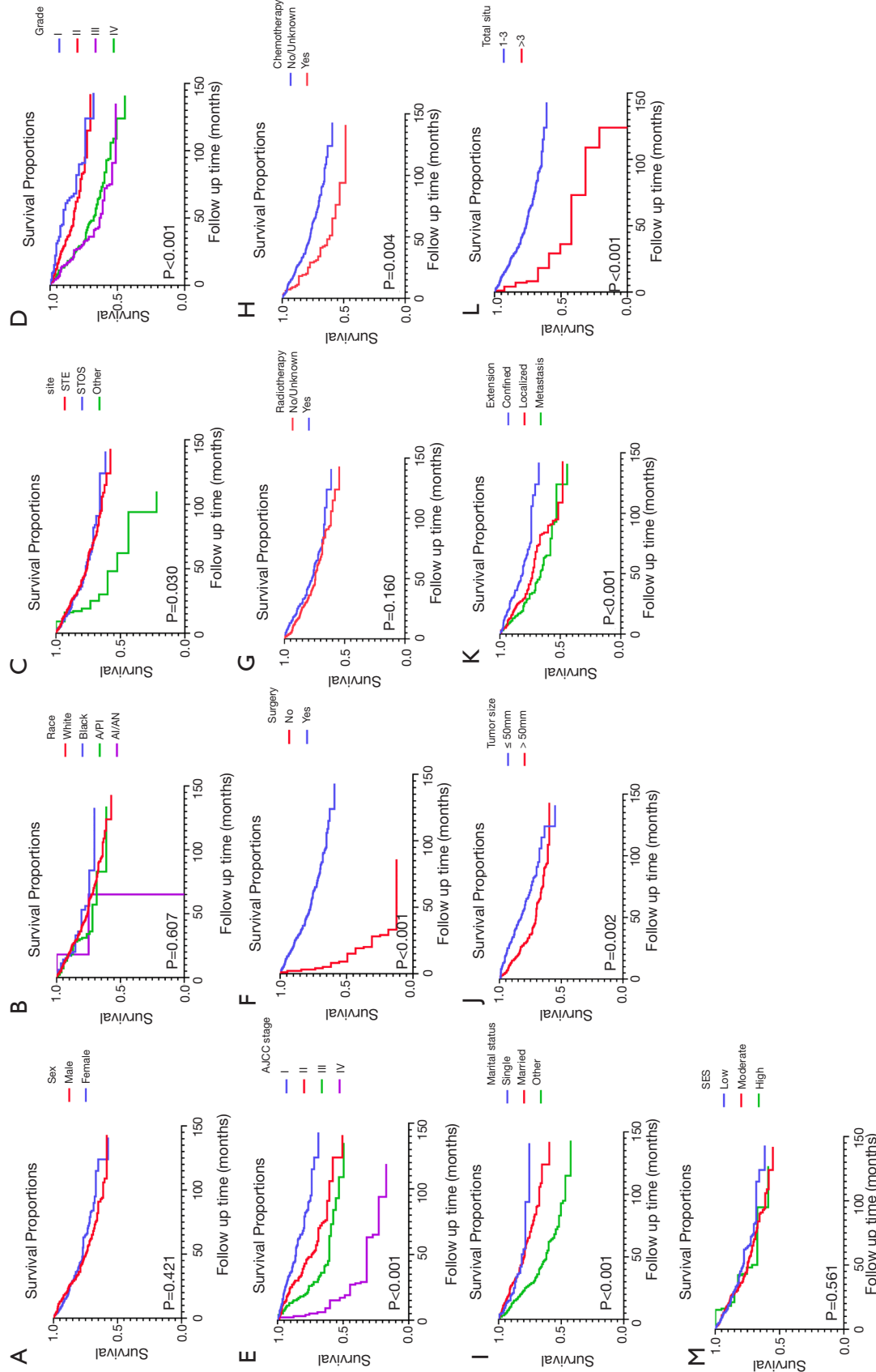
Figure 2 Survival curve of OS stratified by sex (A), race (B), site (C), grade (D), AJCC stage (E), surgery (F), radiotherapy (G), chemotherapy (H), marital status (I), tumor size (J), extension (K), total number of malignant/situ tumors (L) and socioeconomic status (M). OS, overall survival; A/PI, Asian or Pacific Islander; STE, soft tissue of extremities; STOS, soft tissue of other sites; AI/AN, American Indian/Alaska Native; Total situ, total number of in situ/malignant tumors; AJCC stage, American Joint Committee on Cancer stage.

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Table 2 Univariate Cox regression analysis was used to determine the independent factors affecting overall survival for myxofibrosarcoma

Variables	Univariate analysis		
	HR	95% CI	P
Age at diagnosis	1.053	1.043–1.063	<0.001
Sex			
Male	Reference		
Female	0.895	0.682–1.174	0.422
Race			
White	Reference		
Black	0.835	0.476–1.467	0.531
A/PI	1.172	0.730–1.882	0.512
AI/AN	1.983	0.492–7.999	0.336
Site			
STE	Reference		
STOS	0.975	0.717–1.324	0.869
Other	2.376	1.212–4.659	0.012
Grade			
I	Reference		
II	1.294	0.784–2.137	0.314
III	2.861	1.718–4.765	<0.001
IV	2.618	1.623–4.223	<0.001
AJCC stage			
I	Reference		
II	1.811	1.276–2.569	<0.001
III	2.783	1.976–3.919	<0.001
IV	8.849	5.513–14.204	<0.001
Surgery			
No	Reference		
Yes	0.106	0.063–0.181	<0.001
Radiotherapy			
No/unknown	Reference		
Yes	0.825	0.630–1.080	0.162
Chemotherapy			
No/unknown	Reference		
Yes	1.760	1.189–2.604	<0.01

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis		
	HR	95% CI	P
Tumor size (mm)			
≤50	Reference		
>50	1.561	1.177–2.071	<0.01
Extension			
Confined	Reference		
Localized	1.738	1.253–2.412	<0.001
Metastasis	2.097	1.516–2.900	<0.001
Total situ			
≤3	Reference		
>3	3.748	1.985-7.079	<0.001
Marital status			
Single	Reference		
Married	1.207	0.777–1.876	0.403
Other	2.480	1.567–3.926	<0.001
SES			
Low	Reference		
Moderate	1.168	0.879–1.552	0.285
High	1.135	0.618–2.085	0.683

SES, socioeconomic status; A/PI, Asian or Pacific Islander; STE, soft tissue of extremities; STOS, soft tissue of other sites; AI/AN, American Indian/Alaska Native; Total situ, total number of in situ/malignant tumors; AJCC stage, American Joint Committee on Cancer stage.

for patients with malignant soft tissue sarcomas has relied on the TNM staging system to a great extent. Indeed, the TNM staging system has been widely used to stage malignant tumors for over 40 years. This is an anatomic staging method, which has the advantages of simple parameters, easy operation, and high universality. However, a clear disadvantage of this method is that it ignores some critical factors, such as age, tumor location, histological subtype, and treatment. Even though the latest edition of the AJCC staging system improved the tumor staging method and added new parameters to predict patient prognosis, the inherent defects of the staging system still exist (22). A nomogram is a novel effective tool for

Characteristics	Subtype	HR[95%CI]	Forest plot	*p*
Age		1.053[1.043-1.063]		***
Site	STE	Reference		
	STOS	1.017[0.736-1.405]		N
	Other	2.641[1.282-5.443]		**
Surgery	No	Reference		
	Yes	0.227[0.120-0.431]		***
RT	No/Unk	Reference		
	Yes	0.496[0.366-0.674]		***
Chemotherapy	No/Unk	Reference		
	Yes	1.618[1.034-2.533]		*
TumorSize	≤50mm	Reference		
	>50mm	1.541[1.087-2.186]		*
TotalSitu	≤3	Reference		
	>3	5.463[2.821-10.579]		***
Extension	Confined	Reference		
	Localized	1.487[1.061-2.085]		*
	Metastasis	1.566[1.906-2.237]		*
AJCC	I	Reference		
	II	1.877[1.271-2.773]		**
	III	2.044[1.364-3.064]		***
	IV	5.185[2.879-9.339]		***

Figure 3 Multivariable Cox proportional hazards regression models and forest plot for the myxofibrosarcoma. *, P<0.05; **, P<0.01; ***, P<0.001. HR values for forest plot were shown in Table S2. CI, influence interval; RT, radiotherapy; SES, socioeconomic status; STE, soft tissue of extremities; STOS, soft tissue of other sites; Total situ, total number of *in situ*/malignant tumors; AJCC stage, American Joint Committee on Cancer stage.

clinicians to estimate patient outcomes. In this study, we constructed a specific nomogram for MFS patients using the SEER database. Our nomogram included AJCC stage and other factors to predict the survival outcome. The C-indexes of the nomogram were superior to those of the AJCC staging system, 6th edition in both the training and validation cohorts. Furthermore, the DCA graph showed a significant net benefit of the nomogram. Finally, there were significant differences in survival among different risk groups (P<0.001), which proved that the nomogram could identify patients in different risk groups.

There are few relevant studies on prognosis prediction

in MFS patients, and in the available studies, the sample size is usually limited to dozens to hundreds (28,29). The SEER database is a large database that collects information on cancer patients from 18 centers that cover 28% of the population of the United States, which could improve the generalizability of our training cohort and validation cohort to some extent. However, concerns still exist. In the current study, we conducted a large population-based study using the SEER database (n=1,270). The median age at diagnosis was 63 years, which was slightly lower than the previously reported range of 64–72 years (1,30,31). The median follow-up period was 41 months, which was lower than what has been observed in previous studies (51–53 months) (1,4). The 3- and 5-year OS rates were 80.7% and 74.3%, respectively, and the 3- and 5-year disease-specific survival rates were 90.2% and 87.3%, respectively, which suggested relatively good outcomes. In terms of tumor characteristics, the median size was 59 mm, which is smaller than the previously reported 60–95 mm (1,4,10). Tumors were most common in the extremities, especially in the lower extremities, which is consistent with the results of previous studies (1,6,10).

In the present study, we first identified the factors affecting the survival of patients with MFS. Age at diagnosis, AJCC stage, tumor size, tumor extension, tumor site, surgery status, chemotherapy, radiotherapy, and the total number of *in situ* or malignant tumors were the nine independent factors affecting survival. We found that age at diagnosis had the greatest effect on survival: the older the patient at diagnosis, the worse the outcome. Previous studies have shown a significant increase in LR in patients older than 65 years (2), which may explain why age affects survival. Similarly, survival outcomes were worse in patients with tumors >5 cm. It has been reported that the prognosis of patients with tumors >7.5 cm is significantly poorer than those with smaller tumors (3). We did not identify tumor grade as an independent prognostic factor for OS in multivariate Cox analysis, which differs from the results of the study by Sambri *et al.* (16,30,31). Considering that there may be collinearity between AJCC stage and tumor grade, which can lead to deviation in the conclusion, we performed collinearity analysis. All of the factors had a VIF <5, suggesting that there was no collinearity between AJCC stage and grade.

Although there is currently no standard treatment for MFS (10), surgery was the most common treatment in this study (97.3%). However, it can be difficult for surgeons to achieve negative margins in some areas, and adjuvant

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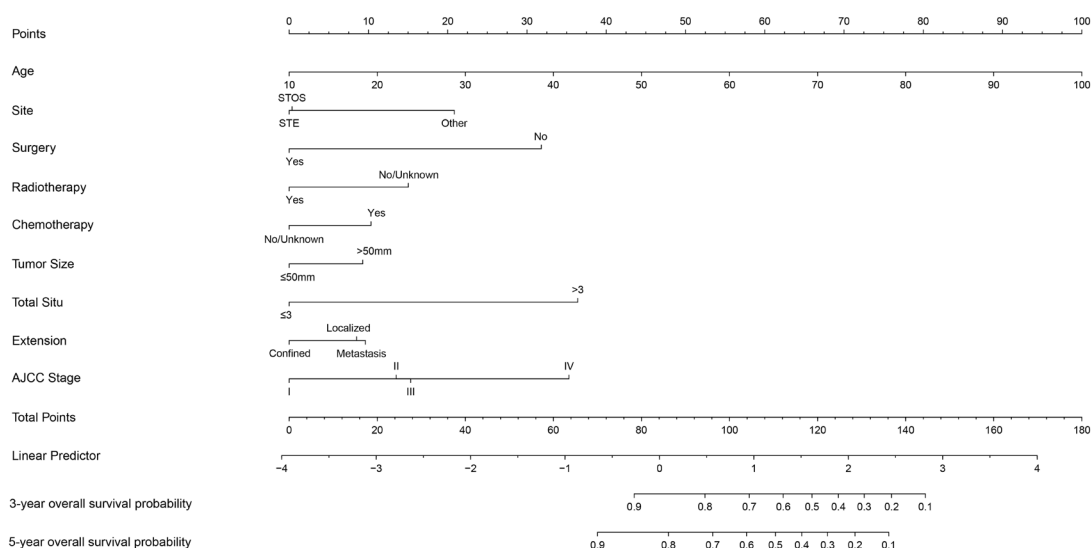
Figure 4 Nomogram for predicting 3- and 5-year overall survival. It showed that the risk of death was significantly increased for patients with older age, AJCC stage II–IV, chemotherapy, tumor size >50 mm, >3 *in situ* or malignant tumors, localized tumors, and metastasized tumors, primary tumors located in the bones, peritoneum, retroperitoneum, heart, and nerves. In contrast, the risk of death for patients who underwent surgery and radiotherapy was decreased significantly. SES, socioeconomic status; STE, soft tissue of extremities; STOS, soft tissue of other sites; Total situ, total number of in situ/malignant tumors; AJCC stage, American Joint Committee on Cancer stage.
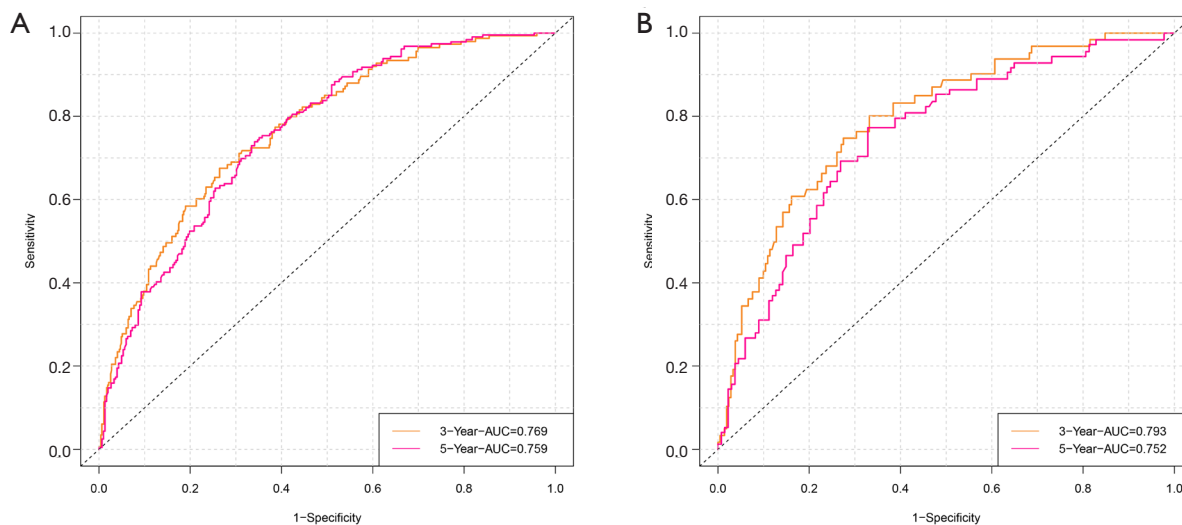
Figure 5 The receiver operating characteristic curve (ROC curves) for the training cohort (A) and validation cohort (B). The discriminative ability of the nomogram was evaluated by the areas under the ROC curves (AUC). The red line represents the ROC of 3-year survival. The blue line represents the ROC of 5-year survival.

radiotherapy is particularly critical (31-34). Boughzala-Bennadji *et al.* confirmed that a combination of R0 resection (absence of tumor within 1 mm from the inked surface) and adjuvant radiation therapy provided the best local

control (4). In our study, univariate Cox regression analysis suggested that radiotherapy was not significantly associated with OS (P=0.162). However, considering the clinical significance and the P value, we decided to include it in the

Table 3 C-index of Nomogram and AJCC staging system

Model	Training cohort		Validation cohort	
	C-index	95% CI	C-index	95% CI
Nomogram	0.806	0.804–0.808	0.783	0.778–0.788
AJCC staging system	0.669	0.666–0.672	0.674	0.668–0.680

C-CI, influence interval; index, concordance index; AJCC, American Joint Committee on Cancer.
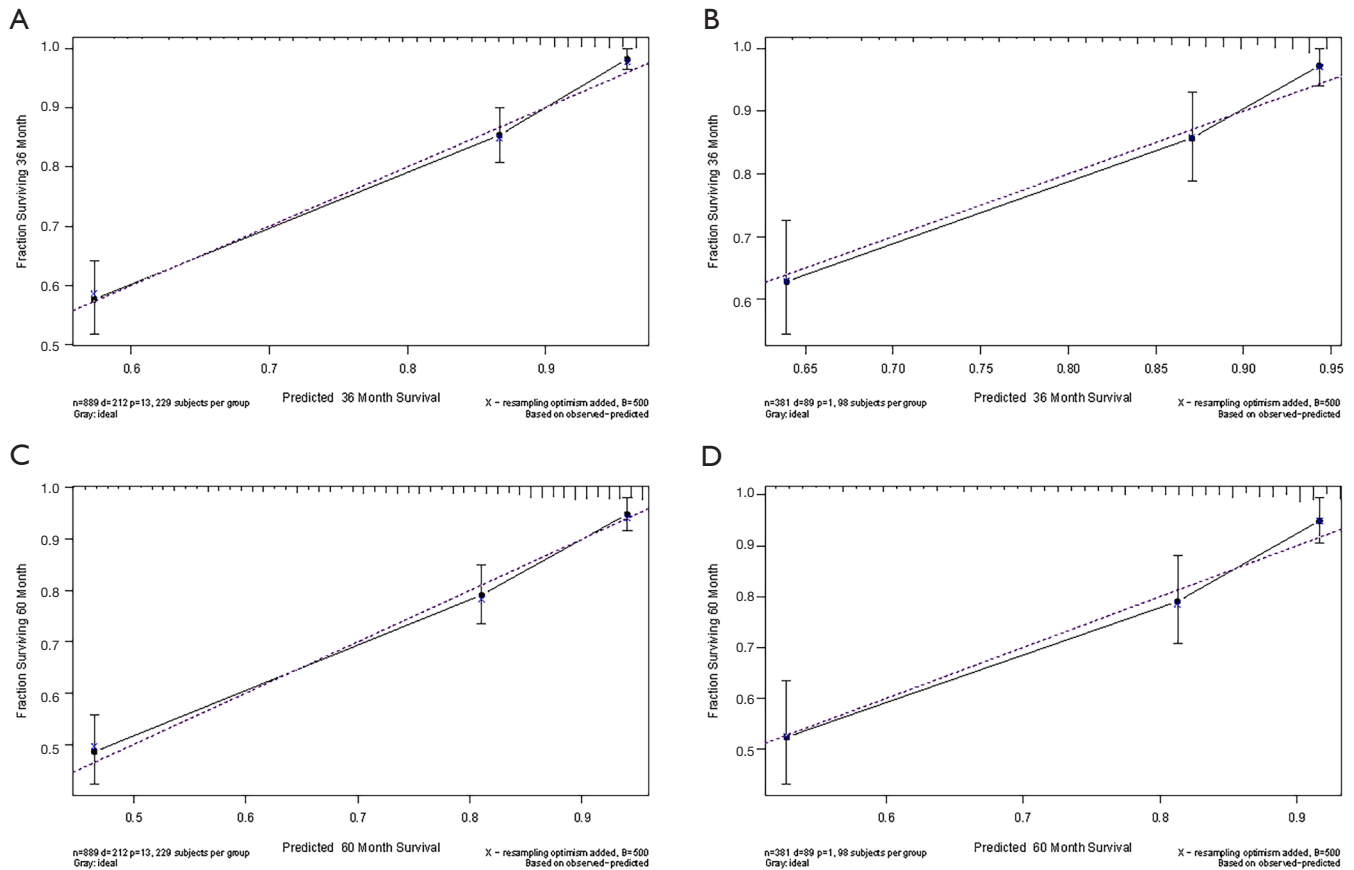
Figure 6 Calibration curves for 3-year (A: training cohort; B: validation cohort) and 5-year survival (C: training cohort; D: validation cohort). The calibration curves had an acceptable level of agreement between the predicted survival probabilities of the nomogram and the observed survivals.

Table 4 The NRI values for 3- and 5-year survival

Cohort	3-year		5-year	
	NRI	95% CI	NRI	95% CI
Training cohort	0.741	0.580–0.923	0.777	0.626–0.958
Validation cohort	0.610	0.278–0.889	0.679	0.314–0.939

CI, influence interval; NRI, net reclassification improvement.
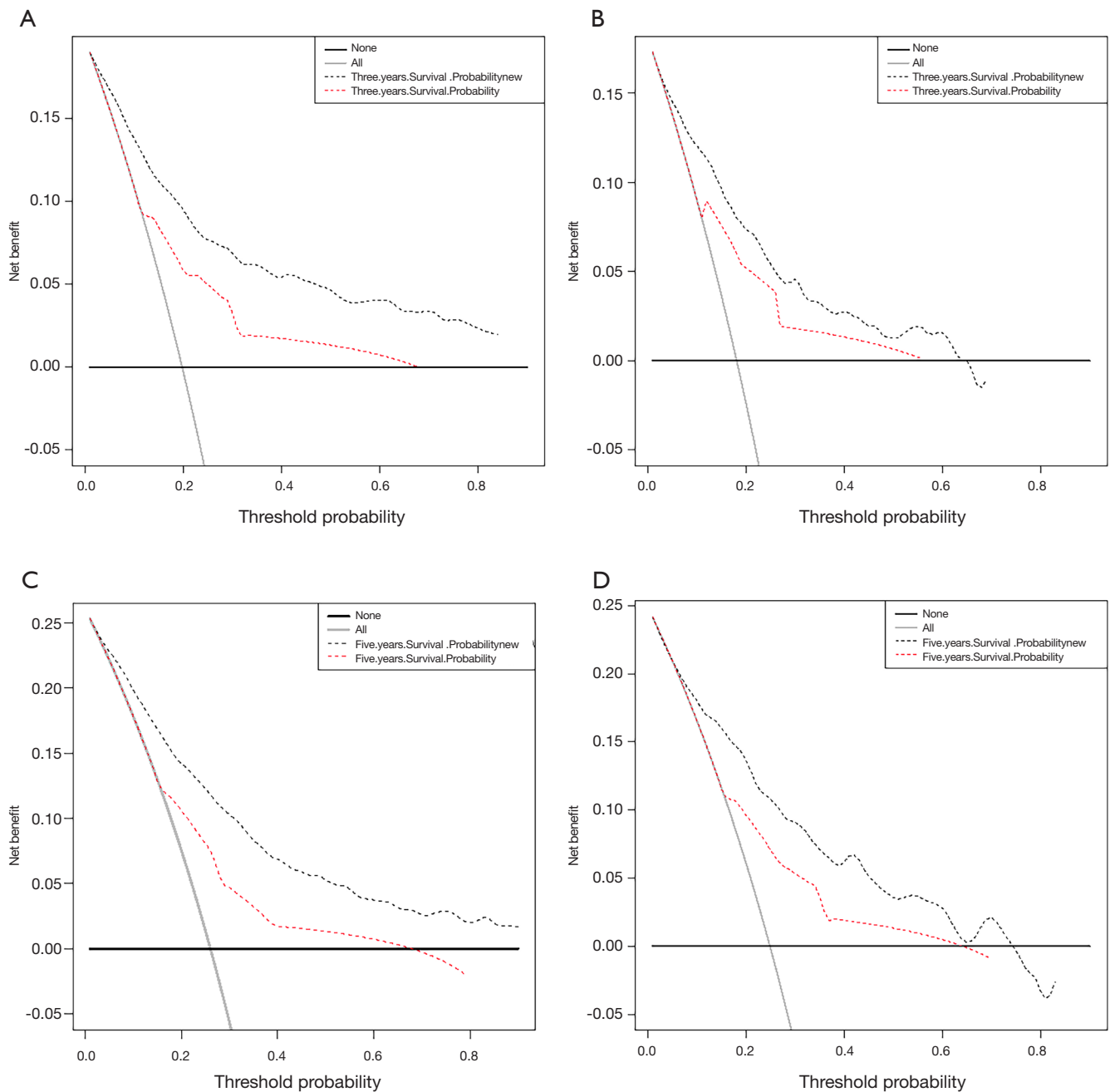
Figure 7 Decision curve analysis (DCA) for 3-year (A: training cohort; B: validation cohort), 5-year (C: training cohort; D: validation cohort) survival. The blue dotted lines represent the DCA of the nomogram; the red dotted lines represent the DCA of AJCC model. "None" means "Assume all patients die", and "All" means "Assume all patients survive". The DCA graphs showed a significant net benefit of the nomogram for almost all threshold probabilities in both the training and validation cohorts compared to the AJCC staging system.
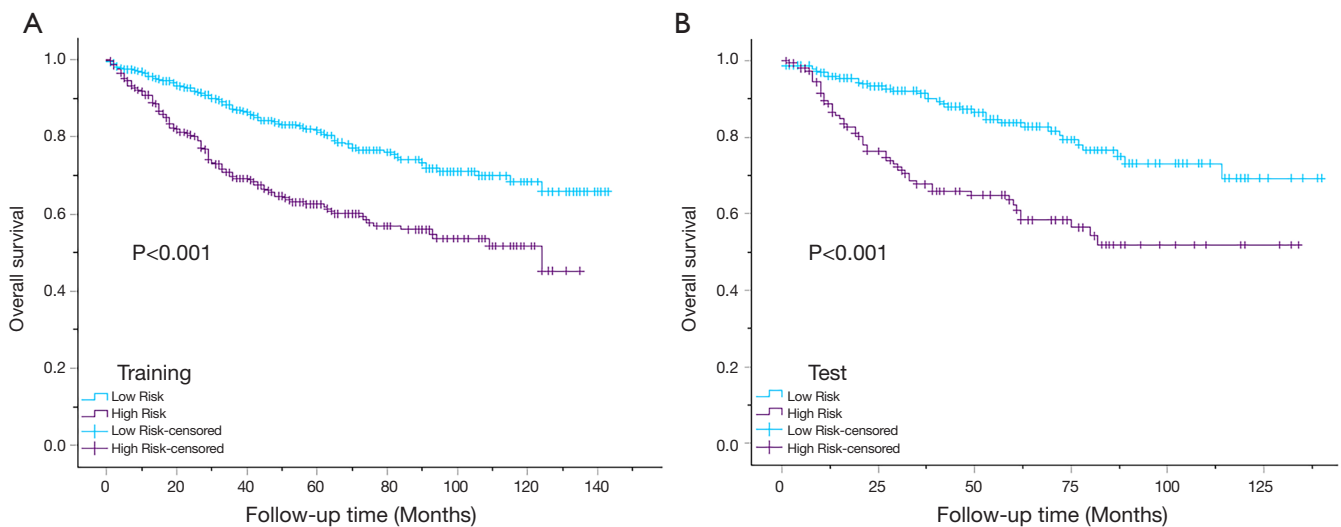
Figure 8 The survival analysis for different risk groups in the training cohort (A) and validation cohort (B). Kaplan-Meier curves showed that there were significant differences in survival between the high-risk group and the low-risk group.

multivariate analysis. The results showed that radiotherapy was indeed an independent factor beneficial to survival (P<0.001, VIF <5). In addition, multivariate Cox regression analysis showed that chemotherapy was an independent poor prognostic factor (hazard ratio =1.618, P<0.035, and VIF <5). However, we cannot arbitrarily assume that chemotherapy increased the risk of death because we cannot state whether patients who received chemotherapy represented a high-risk population. Therefore, further randomized controlled trials or propensity score matching studies should examine this question. Moreover, the SEER database unfortunately does not include the details of radiotherapy and chemotherapy regimens, which leads to the limited applicability of our conclusions.

There were some limitations to our study. First, the information contained in the database is incomplete. In particular, SEER has highly limited data regarding chemotherapy and radiation therapy, such as the dose of radiotherapy and chemotherapeutic drugs, and only includes those used as front-line therapy. In addition to LR, a distinctive feature of MFS is that it has a high rate of LR, and recurrent sarcoma tends to be of higher grade. Therefore, research on recurrence as a risk factor or as an outcome is of great significance (30,35,36). Second, we excluded many patients because of the strict inclusion and exclusion criteria, resulting in a 43% reduction in sample size, which to some extent limits the validity of the

conclusions that can be drawn. Third, there is variability in the predictions when a nomogram is used in the clinic (24). This specific nomogram applies only to patient populations similar to the cohort we studied.

Conclusions

In conclusion, age at diagnosis, tumor size, tumor site, tumor extension, AJCC stage, surgery, chemotherapy, radiotherapy and the total number of *in situ* or malignant tumors were pertinent factors affecting OS in patients with MFS. A novel nomogram that included tumor characteristics and treatment methods was constructed to evaluate survival outcomes for MFS patients. Its predictive efficacy was markedly superior to the traditional AJCC staging system.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the

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TRIPOD reporting checklist Available at http://dx.doi.org/10.21037/tcr-20-2588

Peer Review File: Available at http://dx.doi.org/10.21037/tcr-20-2588

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2588). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval was not required in the current study because the SEER research data is publicly available. Moreover, we registered and got access to the SEER database (accession No. 16375-Nov2018).

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