Identification of a clinical web-based nomogram to predict overall survival in elderly retroperitoneal sarcoma patients
A population-based study

Honghong Zheng, MD[a] iD, Junqiang Wei, MD[b],*

Abstract

The purpose of this study was to develop a web-based nomogram and risk stratification system to predict overall survival (OS) in elderly patients with retroperitoneal sarcoma (RPS). Elderly patients diagnosed with RPS between 2004 and 2015 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. We used univariate and multivariate Cox analysis to identify independent prognostic factors. We plotted the nomogram for predicting the OS of elderly RPS patients at 1, 3, and 5 years by integrating independent prognostic factors. The nomograms were subsequently validated by receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA). By calculating the Nomogram score for each patient, we build a risk stratification model to evaluate the survival benefit of elderly RPS patients. A total of 722 elderly RPS patients were included in our study. The nomogram includes 5 clinicopathological variables as independent prognostic factors: age, histological subtype, grade, metastasis status, and surgery. Through the validation, we found that the nomogram has excellent prediction performance. Then web-based nomograms were established. We performed a web-based nomogram and a risk stratification model to assess the prognosis of elderly RPS patients, which are essential for prognostic clustering and decision-making about treatment.

Abbreviations: CI = confidence interval, DCA = decision curve analysis, HR = hazard ratio, OS = overall survival, ROC = receiver operating characteristic, RPS = recursive sarcoma, SEER = surveillance, epidemiology, and end results, STS = soft tissue sarcomas.

Keywords: elderly, nomogram, overall survival, prognosis, retroperitoneal sarcoma, risk stratification model

1. Introduction

Primary retroperitoneal sarcoma (RPS) is a rare type of malignant tumor of mesenchymal tissue originating in the retroperitoneal space, accounting for 10% to 15% of all soft tissue sarcomas (STS).[1,2] Consistent with other sites of STS, surgical treatment is the recommended approach for RPS.[3] Patients with RPS who underwent surgery had an improved prognosis, with a 5-year overall survival (OS) rate of approximately 40% to 70%.[4–6] However, due to the late onset of clinical symptoms and the deep anatomical location of RPS, the prognosis of patients remains unsatisfactory.[7] Therefore, survival and prognostic assessment of RPS patients is essential in STS research.

It is well known that older people (age ≧ 65 years) are a particular group. STS in elderly patients accounts for nearly 50% of the total sarcoma patients.[8,9] Elderly RPS patients tend to have the following characteristics: decreased physiological function, high tumor occultation, relatively mild clinical symptoms, and limited acceptable treatment modalities.[10,11] These characteristics lead to the specificity and complexity of the disease in elderly RPS patients. Previous studies have also confirmed that age is an independent prognostic factor for RPS, and the older the age, the worse the prognosis of RPS patients.[8,9] However, as far as we know, few studies have focused on the elderly RPS patient population. Due to the specificity and complexity of the disease in elderly RPS patients, a single clinicopathological feature cannot comprehensively and effectively assess the prognosis of patients.[12] Nomograms are a convenient statistical tool that combines multiple prognostic factors to predict the prognosis of individual cancer patients.[13] In addition, web-based nomograms have more robust capabilities to accurately predict the prognosis of patients over a range

of time through intuitive data and graphics.[12,14] Therefore, to acquire a keener understanding of elderly RPS patients, this study was designed to identify prognostic factors for elderly RPS patients by analyzing clinicopathological characteristics and developing a web-based nomogram and risk stratification model to predict OS.

2. Methods

2.1. Patients

The clinicopathological characteristics of patients were collected from the Surveillance, Epidemiology, and End Results (SEER) database, covering approximately 28% of the U.S. population.[15] We have obtained permission to access the SEER database (15708-Nov2020). Patients were included based on the following criteria: have a histological diagnosis of STS in retroperitoneum; have been diagnosed by "year of diagnosis" from 2004 to 2015; be more than 65 years[16]; and have complete follow-up data. Exclusion criteria: RPS was not the first primary tumor, and the clinicopathological information of elderly RPS patients was incomplete.

2.2. Data element

Data about the following variables were extracted: age (65–69, 70–74, 74–79, and ≧80 years), race (White, Black, and Other [American Indian/Alaskan Native, Asian/Pacific Islander]), sex (female and male), grade (grade I, grade II, grade III, and grade IV), Histological subtype (undifferentiated sarcoma, fibrosarcoma, liposarcoma, leiomyosarcoma, and other sarcomas), tumor size (tumor ≦ 5 cm, tumor > 5 cm and ≦ 10 cm, tumor > 10 cm and ≦ 15 cm, and tumor > 15 cm), lymph node metastasis status (no or yes), distant metastasis status (no or yes), surgery (no or yes), radiotherapy (no or yes), and chemotherapy (no or yes). OS was defined as the time from diagnosis to death due to any cause.

2.3. Nomogram construction and validation

We divided elderly RPS patients diagnosed from 2004 to 2013 into the training and validation I sets in a 7:3 ratio, and we included patients diagnosed from 2014 to 2015 as the validation II set. Univariate and multivariate Cox regression analyses were performed to identify the independent prognostic factors.

Table 1

Demographic and clinical characteristics of elderly retroperitoneal sarcoma patients.

Variables	Total set		Training set		Validation I set		Validation II set		χ^2	P Value
	n	%	n	%	n	%	n	%		
Sex									1.083	.582
Female	373	51.66	214	52.97	81	48.21	78	52		
Male	349	48.34	190	47.03	87	51.79	72	48		
Age (yr)									15.745	.015
65–69	237	32.83	117	28.96	61	36.31	59	39.33		
70–74	190	26.32	114	28.22	31	18.45	45	30		
74–79	149	20.64	88	21.78	41	24.4	20	13.33		
≧80	146	20.22	85	21.04	35	20.83	26	17.33		
Race									1.912	.752
White	594	82.27	334	82.67	135	80.36	125	83.33		
Black	61	8.45	35	8.66	13	7.74	13	8.67		
Other	67	9.28	35	8.66	20	11.9	12	8		
Grade									9.848	.131
Grade I	233	32.27	138	34.16	51	30.36	44	29.33		
Grade II	87	12.05	59	14.6	15	8.93	13	8.67		
Grade III	187	25.9	93	23.02	48	28.57	46	30.67		
Grade IV	215	29.78	114	28.22	54	32.14	47	31.33		
Histological subtype									7.398	.494
Undifferentiated sarcoma	67	9.28	36	8.91	20	11.9	11	7.33		
Fibrosarcoma	22	3.05	13	3.22	7	4.17	2	1.33		
Liposarcoma	430	59.56	237	58.66	96	57.14	97	64.67		
Leiomyosarcoma	193	26.73	113	27.97	41	24.4	39	26		
Other sarcoma	10	1.39	5	1.24	4	2.38	1	0.67		
Tumor size									8.49	.204
Tumor ≦ 5 cm	47	6.51	27	6.68	9	5.36	11	7.33		
Tumor > 5 cm and ≦ 10 cm	154	21.33	88	21.78	41	24.4	25	16.67		
Tumor > 10 cm and ≦ 15 cm	157	21.75	88	21.78	43	25.6	26	17.33		
Tumor > 15 cm	364	50.42	201	49.75	75	44.64	88	58.67		
Lymph node metastasis status									2.215	.33
No	703	97.37	396	98.02	161	95.83	146	97.33		
Yes	19	2.63	8	1.98	7	4.17	4	2.67		
Distant metastasis status									3.5	.174
No	643	89.06	365	90.35	143	85.12	135	90		
Yes	79	10.94	39	9.65	25	14.88	15	10		
Surgery									0.071	.965
No	101	13.99	57	14.11	24	14.29	20	13.33		
Yes	621	86.01	347	85.89	144	85.71	130	86.67		
Radiotherapy									2.711	.258
No	527	72.99	286	70.79	130	77.38	111	74		
Yes	195	27.01	118	29.21	38	22.62	39	26		
Chemotherapy									2.027	.363
No	629	87.12	353	87.38	150	89.29	126	84		
Yes	93	12.88	51	12.62	18	10.71	24	16		

A nomogram was performed to predict patients' survival at 1, 3, and 5 years based on the independent prognostic factors. The discriminatory ability of the nomogram was determined using the area under curve values from the receiver operating characteristic (ROC) curves. The accuracy of the nomogram was verified using calibration curves and decision curve analysis (DCA) curves. We created a web-based nomogram based on the excellent efficacy of the validation. By calculating the Nomogram score for each patient, we build a risk stratification model to evaluate the survival benefit of elderly RPS patients.

2.4. Statistical analyses

We identified independent prognostic factors for OS in elderly RPS patients by univariate and multivariate Cox regression analysis. ROC curves, calibration curves, and DCA were used to assess the efficacy of the nomogram. Kaplan–Meier curves were used to estimate OS in different risk groups and evaluate the significance of differences in OS using the log-rank test. Categorical variables were analyzed using the chi-square test. All statistical analyses were performed in R software (version 4.1.1), and statistical significance was assumed for P values <.05.

3. Results

3.1. Clinicopathological characteristics of elderly RPS patients

Overall, 722 elderly RPS patients who met the criteria from the SEER database were included. We assigned 404, 168, and 150 elderly RPS patients to training, validation I, and validation II sets. The clinicopathological characteristics of the patients in the training and validation sets are shown in Table 1. The chi-square test results indicated no significant differences in the distribution of clinicopathological features between the training set, validation I set, and validation II set. Generally, most elderly RPS patients were female (n = 373, 51.66%), aged 65 to 69 years (n = 237; 32.83%), and white (n = 594, 82.27%). Moreover, the tumor characteristics of most RPS patients were

Table 2

Univariate and multivariate Cox proportional hazards regression analyses for overall survival.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex						
Female	Reference					
Make	1.012	0.802–1.276	.923			
Age (yr)						
65–69	Reference			Reference		
70–74	1.202	0.869–1.662	.266	1.419	1.012–1.989	.042
74–79	1.431	1.018–2.011	.039	1.527	1.077–2.163	.017
≧80	2.174	1.564–3.021	<.001	2.416	1.685–3.465	<.001
Race						
White	Reference					
Black	0.963	0.622–1.492	.867			
Other	1.127	0.757–1.680	.555			
Grade						
Grade I	Reference			Reference		
Grade II	1.625	1.113–2.373	.012	1.32	0.879–1.983	.181
Grade III	2.172	1.579–2.988	<.001	1.933	1.370–2.727	<.001
Grade IV	2.145	1.586–2.901	<.001	2.306	1.639–3.245	<.001
Histological subtype						
Undifferentiated sarcoma	Reference			Reference		
Fibrosarcoma	0.673	0.338–1.341	.261	0.612	0.303–1.237	.172
Liposarcoma	0.409	0.278–0.603	<.001	0.591	0.388–0.899	.014
Leiomyosarcoma	0.662	0.438–0.998	.049	0.621	0.409–0.944	.026
Other sarcoma	0.281	0.067–1.177	.082	0.428	0.101–1.808	.248
Tumor size						
Tumor ≦ 5 cm	Reference		.268			
Tumor > 5 cm and ≦ 10 cm	1.381	0.793–2.405	.254			
Tumor > 10 cm and ≦ 15 cm	1.61	0.931–2.787	.089			
Tumor > 15 cm	1.601	0.956–2.682	.074			
Lymph node metastasis status						
No	Reference					
Yes	1.087	0.513–2.304	.827			
Distant metastasis status						
No	Reference			Reference		
Yes	2.958	2.087–4.191	<.001	1.979	1.312–2.985	.001
Surgery						
No	Reference			Reference		
Yes	0.233	0.171–0.317	<.001	0.303	0.216–0.426	<.001
Radiotherapy						
No	Reference					
Yes	0.831	0.641–1.077	.161			
Chemotherapy						
No	Reference			Reference		
Yes	2.147	1.567–2.944	<.001	1.321	0.905–1.929	.149

CI = confidence interval, HR = hazard ratio.<

grade I (n = 373, 51.66%), liposarcoma (n = 430, 59.56%), tumor > 15 cm in greatest dimension (n = 364, 50.42%), no lymph node metastasis (n = 703, 97.37%), and no distant metastasis (n = 643, 89.06%). In terms of treatment options, 621 patients (86.01%) performed surgery, and 195 patients (27.01%) performed chemotherapy, 93 cases (12.88%) performed radiotherapy.

3.2. Identification of independent prognostic factors

Through univariate analysis and subsequent multivariate Cox analysis, age (70–74 years: hazard ratio [HR] = 1.419, 95% confidence interval [CI] = 1.012–1.989, P value = .042; 75–79 years: HR = 1.527, 95% CI = 1.077–2.163, P value = .017; ≧80 years: HR = 2.416, 95%CI = 1.685–3.465, P value < .001; 65–69 years as a reference), grade (grade II: HR = 1.320, 95% CI = 0.879–1.983, P value = .181; grade III: HR = 1.933, 95% CI = 1.370–2.727, P value < .001; grade IV: HR = 2.306, 95%CI = 1.639–3.245; grade I as a reference), Histological subtype (fibrosarcoma: HR = 0.612, 95% CI = 0.303–1.237, P value = .172; liposarcoma: HR = 0.591, 95%CI = 0.388–0.899, P value = .014; leiomyosarcoma: HR = 0.621, 95% CI = 0.409–0.944, P value = .026; other sarcoma: HR = 0.428, 95% CI = 0.101–1.808, P value = .248; undifferentiated sarcoma as a reference), distant metastasis (Yes: HR = 1.979, 95%CI = 1.312–2.985, P value = .001; No as a reference), surgery (performed: HR = 0.233, 95%CI = 0.171–0.317; not performed as a reference) were found to be statistically significant factors for OS, as shown in Table 2.

3.3. Nomogram construction and validation

The nomogram included 5 independent prognostic factors in the multivariate regression analysis (see Fig. 1). ROC curves showed that the area under curve of the nomogram model for the 1-, 3-, and 5-year OS reached 0.736, 0.774, and 0.785 in the training set (see Fig. 2A–C); 0.788, 0.761, and 0.722 in the validation I set (see Fig. 2D–F); and 0.750, 783, and 0.801 in the validation II set (see Fig. 2G–I). Moreover, we compared the predictive accuracy of the nomogram with a single independent prognostic factor, and the results showed that the nomogram showed higher predictive accuracy in the training and validation I and II sets. The time dependence curves of OS also performed well (see Fig. 2J–L). In addition, the calibration curves demonstrated the robust calibration capability of the nomogram (see Fig. 3). DCA showed that the nomogram was an excellent tool for predicting survival in elderly RPS patients (see Fig. 4).

3.4. Web-based nomogram and risk stratification model

We created a web-based nomogram on shinyapps.io (https://zhehongli.shinyapps.io/retsts/). The specific operation of the web-based nomogram would be described by way of example: On the left side of the page are optional patient clinicopathological characteristics and follow-up times, for example, we assume a 70 years old RPS patient A is leiomyosarcoma, is grade I, has distant metastases, undergone primary site surgery. At the same time, we set the predicted survival timeline to 36 months (see Fig. 5A). Click "Predict" and the "Survival plot" on the right side plots the survival curve of patients with the same pathological characteristics as patient A (see Fig. 5B). The "Predicted Survival" on the right side plots the 3-year survival probability and 95% CI of patient A (see Fig. 5C). The "Numerical Summary" on the right calculates the 3-year survival probability and 95% CI of patient A (see Fig. 5D). In addition, by calculating the Nomogram score for each patient, we build a risk stratification model to evaluate the survival benefit of elderly RPS patients. We used X-tile to classify all patients into 3 groups: low-risk group (total score ≦ 98), medium-risk group (total score between 99 and 151), and high-risk group (total score > 152). Kaplan–Meier curves were performed on the training set, the validation I set, and the validation II set. The
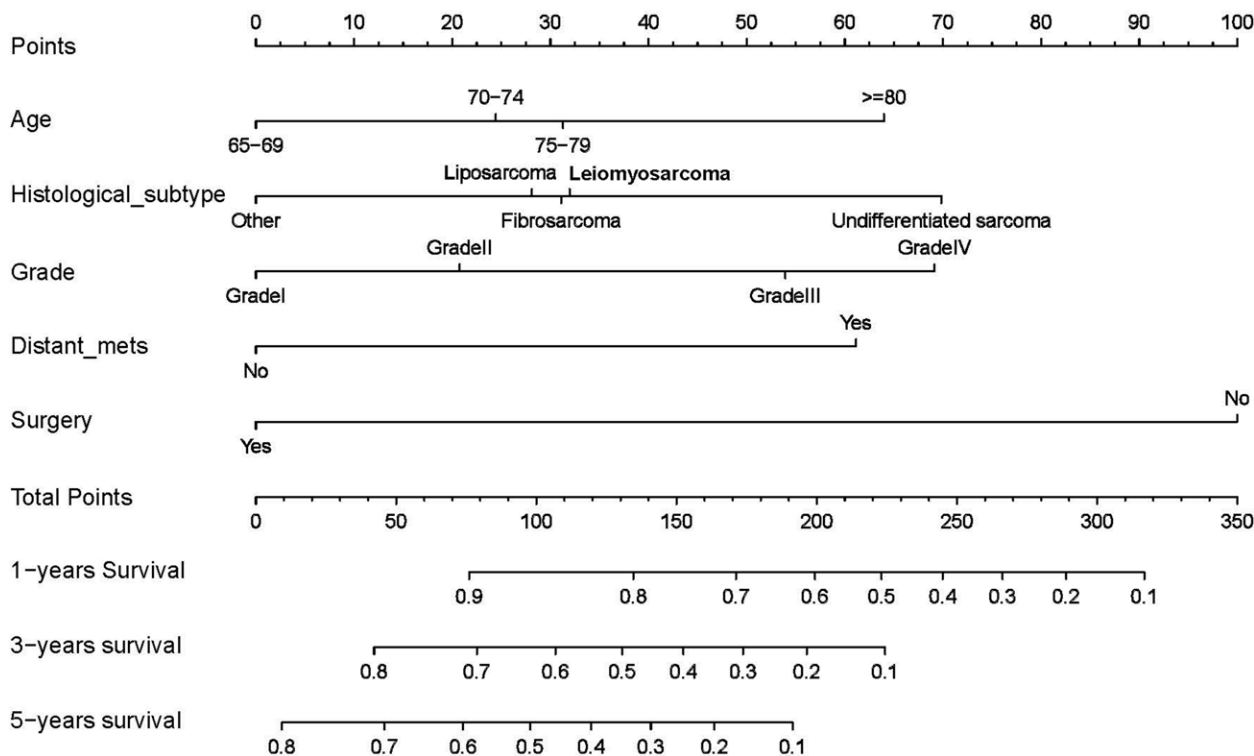
Figure 1. Nomogram. Nomogram for predicting 1-, 3-, and 5-year overall survival in elderly patients with retroperitoneal sarcoma.
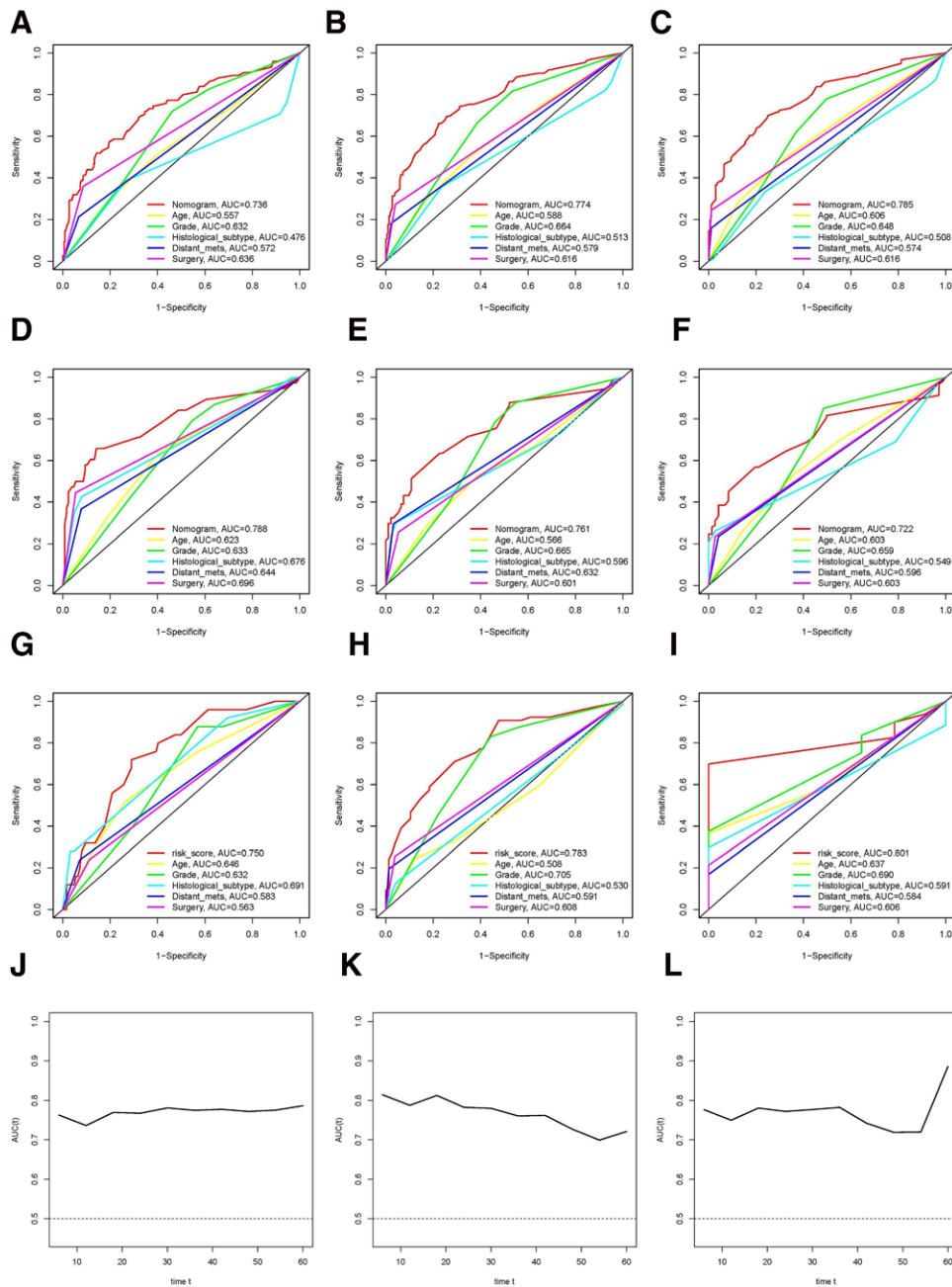
Figure 2. ROC curves. ROC curves for predicting 1-year (A), 3-year (B), and 5-year (C) overall survival in the training set; ROC curves for predicting 1-year (D), 3-year (E), and 5-year (F) overall survival in the validation I set; ROC curves for predicting 1-year (G), 3-year (H), and 5-year (I) overall survival in the validation II set; The time-dependent ROC curves of the nomograms for the training set (J), the validation I set (K) and the validation II set (L). ROC, receiver operating characteristic.

risk stratification model was shown to accurately distinguish between the survival rates of the 3 groups (Fig. 6).

4. Discussion

This study was conducted in 4 steps. First, a retrospective analysis of elderly RPS patients in the SEER database was performed to obtain independent prognostic factors. Second, we developed 1 prognostic nomogram to assess the prognosis of elderly RPS patients. Third, ROC curves, calibration curves, and DCA were used to evaluate the effectiveness of the nomogram in the training set and validation set. Finally, a web-based nomogram was created to promote and apply the research results.

Aging is associated with an increase in the prevalence of cancer; more than 50% of sarcoma patients are elderly.[8,17] The symptoms of elderly RPS patients are often atypical, and lacking regularity often masks the signs of the tumor, leading to a poor prognosis.[18,19] A consensus has been reached in many studies that the prognosis of elderly RPS patients is worse than that of young and middle-aged.[20–22] However, to our knowledge, studies focusing on the prognosis of elderly RPS patients are lacking. Therefore, a retrospective analysis of the SEER database to model the prognosis of elderly RPS patients with a nomogram could help clinicians guide treatment.

Previous studies have shown that age is an independent prognostic factor in RPS patients.[20,21] Our study builds on this by arguing that the prognosis is worse in older than younger
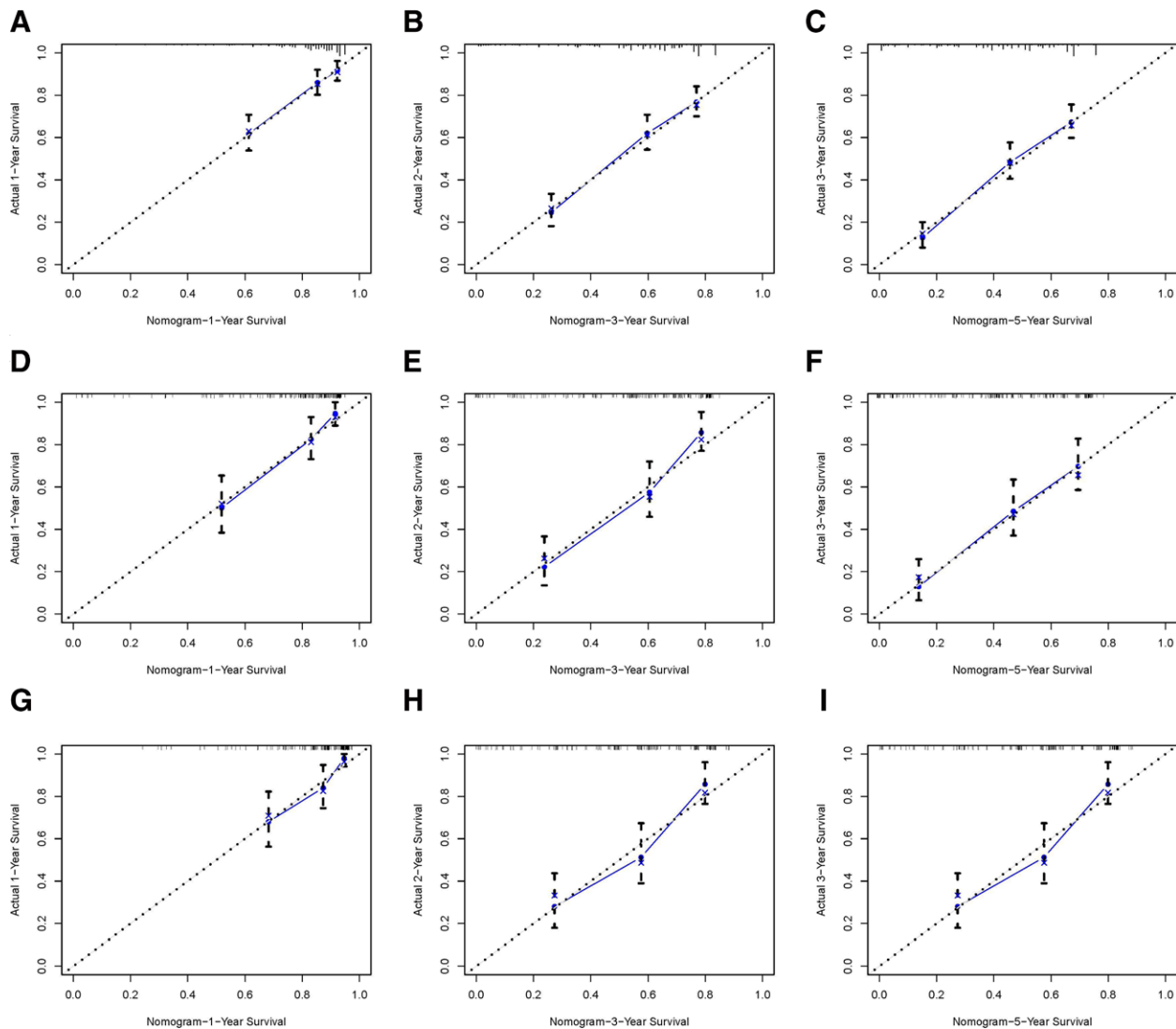
Figure 3. Calibration curves. Calibration curves of the nomogram for the 1-year (A), 3- year (B), and 5-year (C) overall survival prediction of the training set; 1-year (D), 3- year (E), and 5-year (F) overall survival prediction of the validation I set; 1-year (G), 3- year (H), and 5-year (I) overall survival prediction of the validation II set.

elderly RPS patients. Our results suggested that grade, histological subtype, and distant metastasis significantly predicted OS in the nomogram. Meanwhile, surgery is still the most beneficial treatment for elderly RPS patients, and resection of the primary site improves their prognosis. Our retrospective analysis showed that 491 (85.84%) elderly patients with RPS underwent surgical treatment and the remaining patients did not. Chemotherapy and radiotherapy are necessary treatment modalities for RPS.[3,23] Our results showed that chemotherapy was a prognostic factor for elderly RPS patients in a univariate Cox regression analysis (*P* value < .001), but neither chemotherapy nor chemotherapy was an independent prognostic factor for elderly RPS patients, which may be related to age-related treatment toxicity.[24] Similar to other malignancies, the grade is an independent predictor of RPS in the elderly.[25] Our findings demonstrated that in the nomogram, higher scores of patients with high-grade RPS correspond to a worse prognosis. In clinical practice, metastasis often indicates a poor prognosis. The 5-year survival rate for non-metastatic STS is 60%–80%, while the 5-year survival for metastatic STS is only 10% to 20%.[26,27] Our study proposes a specific score

for metastases in the nomogram and the use of metastases in combination to assess the prognosis of patients. Although other studies have described the prognostic value of different clinicopathological features (age, histological subtype, grade, metastasis status, and surgery),[20,28,29] our study is a quantitative study that makes full use of the value of each variable and scores them to evaluate the prognosis, which is more objective compared to the traditional evaluation. Moreover, we combined these independent prognostic factors and created a web-based nomogram, which is the first prognostic line graph model for the field of elderly RPS. We are confident that our study will have higher predictive efficacy and clinical utility.

In this study, we constructed a nomogram to predict the survival time of elderly RPS patients. A total of 5 independent prognostic factors were used to construct the nomogram, including age, grade, histological subtype, distant metastasis, and surgery. Based on the excellent efficacy of the nomogram (verified by ROC curves, calibration curves, and DAC in 2 validation sets), we built a web-based nomogram. Compared with the static nomogram, the dynamic nomogram (web-based nomogram) can accurately predict the prognosis of patients in
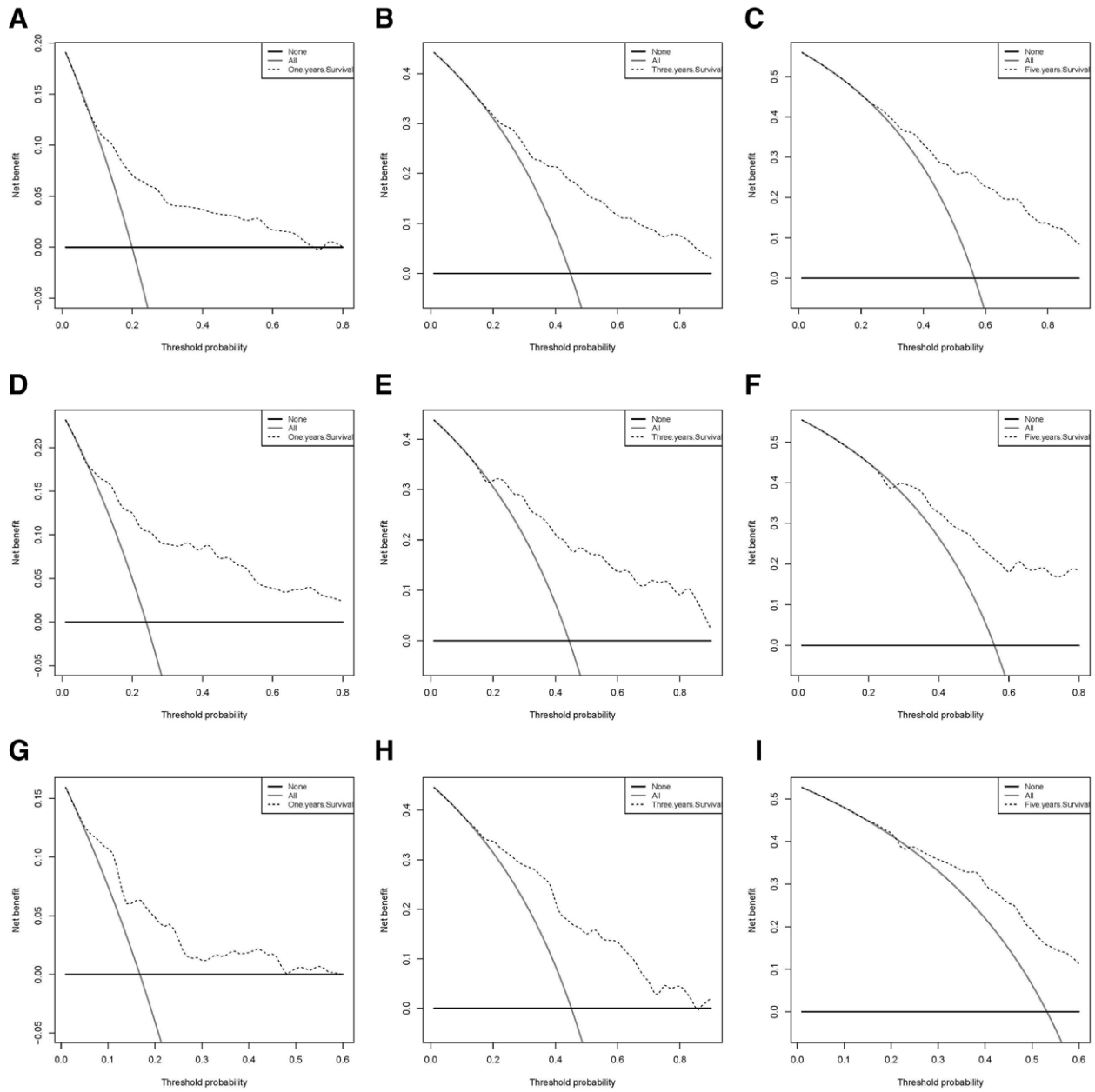
Figure 4. Decision curve analysis (DCA). DCA of the nomogram for predicting the 1-year (A), 3-year (B), and 5-year (C) overall survival in the training set; the 1-year (D), 3-year (E), and 5-year (F) overall survival in the validation I set; and the 1-year (G), 3-year (H), and 5-year (I) overall survival in the validation II set. DCA, decision curve analysis.

the smallest unit of months, and the dynamic nomogram has a more robust generalization and clinical application value.[12] Finally, by calculating the Nomogram score for each patient, we built a risk stratification model to evaluate the survival benefit of elderly RPS patients. To the best of our knowledge, this is the first web-based nomogram study for elderly RPS patients, and we have also developed a risk prediction model for elderly RPS patients. In this study, we built 2 validation sets (validation I and II set) using 2 types of stratification (diagnosis time stratification and random stratification) to validate the nomogram's validity.

However, there is no 100% accurate prediction model, and the same is true for our web-based nomogram, and our research still has some shortcomings. Firstly, our study was retrospective, and statistical bias is inevitable despite developing strict nadir criteria. Secondly, the SEER database covers a limited number of variables, so our study could not fully include independent prognostic factors demonstrated in previous studies, such as the extent of resection.[3,24] Thirdly, although we developed 2 internal validation sets to validate the predictive power of the nomogram for elderly RPS patients, there is still a lack of independent data sets for external validation.

5. Conclusion

We performed a web-based nomogram and a risk stratification model to assess the prognosis of elderly RPS patients, which are essential for prognostic clustering and decision-making about treatment.
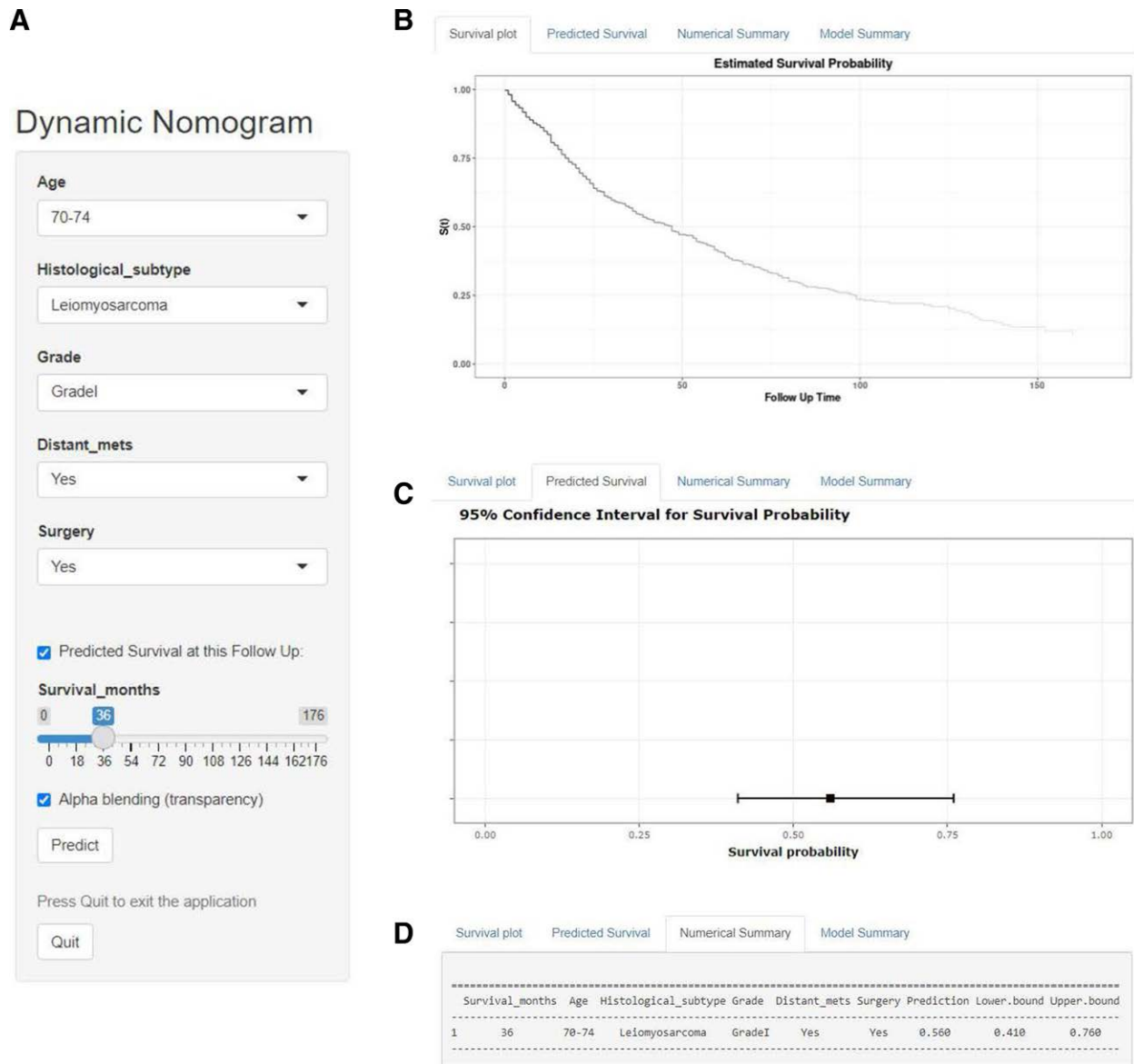
Figure 5. The operation and the output interface of the web-based nomogram. Operation interface (A) included patient's age (65–69, 70–74, 74–79, and ≧80 years), grade (grade I, grade II, grade III, and grade IV), Histological subtype (undifferentiated sarcoma, fibrosarcoma, liposarcoma, leiomyosarcoma, and other sarcomas), distant metastasis status (no or yes), surgery (no or yes), and the predicted survival timeline. According to the input result of the operation interface, click "Predict" to get the survival curve in "Survival plot" (B), overall survival and 95% CIs of the predicted survival time in "Predicted survival" (C), and numerical summary of input information in the operation interface and calculation results in the output interface (D). CI = confidence interval.
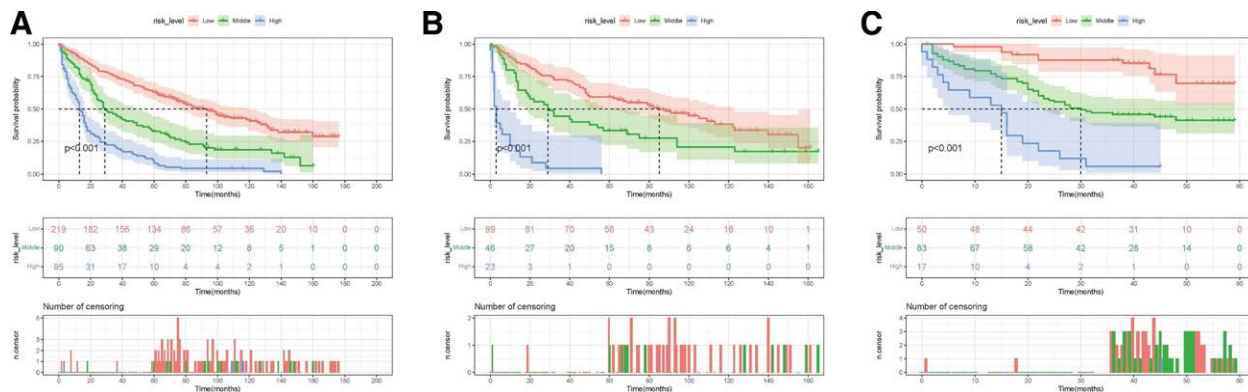
Figure 6. Kaplan–Meier curves. Kaplan–Meier curves of the low-, medium-, and high-risk groups in the training set (A), validation I set (B), and validation II set (C).

Author contributions

Conceptualization: Honghong Zheng, Junqiang Wei.
Data curation: Honghong Zheng.
Funding acquisition: Junqiang Wei.
Investigation: Honghong Zheng.
Methodology: Honghong Zheng.
Software: Honghong Zheng.
Supervision: Junqiang Wei.
Validation: Honghong Zheng, Junqiang Wei.
Visualization: Honghong Zheng.
Writing – original draft: Honghong Zheng, Junqiang Wei.
Writing – review & editing: Junqiang Wei.

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