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Prognostic model for predicting overall and cancer-specific survival among patients with superficial spreading melanoma

A SEER based study

Qiang Ji, MD[a], Jun Tang, MD[b], Shulian Li, MS[c], Junjie Chen, PD[b,*]

Abstract

Skin malignant melanoma is one of the most aggressive skin tumors. Superficial spreading melanoma (SSM) is the most common histological type, which can originate from different body skin sites, and some patients can still accumulate regional lymph nodes and even have distant metastasis in some cases. This study used the relevant data from the monitoring, epidemiology and results database of the National Cancer Institute database to study the overall survival (OS) and cancer-specific survival (CSS) of SSM patients and established an SSM nomogram to evaluate the prognosis of patients. A total of 13,922 patients were collected from the monitoring, epidemiology and results database of the National Cancer Institute and randomly divided into a training cohort (8353 cases) and a validation cohort (5569 cases). Univariate and multivariate Cox regression analysis were used to determine prognostic factors, and these factors were used to construct OS and CSS nomograms for patients with SSM. Finally, the discrimination and consistency of the nomogram model were evaluated by the consistency index (C-index), area under the curve (AUC) and calibration curve. Multivariate Cox regression analysis suggested that age, sex, tumor site, the American joint committee on cancer T stage and the first primary melanoma were independent predictors of OS and CSS in patients with SSM and that the American joint committee on cancer N stage was also an independent predictor of CSS in patients with SSM. Based on the above prognostic factors, this study constructed a predictive model. The *C*-index of the model OS and CSS for this training cohort was 0.805 [95% CI: 0.793–0.817] and 0.896 [95% CI: 0.878–0.913], respectively. The AUC values for 1-, 3-, and 5-year OS were 0.822, 0.820, and 0.821, respectively, and the AUC values for CSS were 0.914, 0.922, and 0.893, respectively. The data indicated that both nomograms showed better predictive accuracy. The calibration curves of the training cohort and the validation cohort were in good agreement. The nomogram has superior predictive performance in predicting 1-, 3-, and 5-year OS and CSS prognosis in patients with SSM and can provide a reference for individualized treatment and clinical counseling of SSM.

Abbreviations: AUC = area under the curve, AJCC = the American joint committee on cancer, CSS = cancer-specific survival, NM = nodular melanoma, OS = overall survival, SEER = surveillance, epidemiology and end results, SSM = superficial spreading melanoma.

Keywords: cancer-specific survival, nomogram, overall survival, prognosis, superficial spreading melanoma

1. Introduction

Skin malignant melanoma is a skin tumor associated with overexposure to ultraviolet light and, although a small proportion of all skin malignancies, is the leading cause of death among skin malignancies.[1–3] The incidence of malignant melanoma in the United States continues to increase at an annual rate of approximately 3%.[4,5] Superficial spreading melanoma (SSM) and nodular melanoma (NM) are the most common subtypes of melanoma, occur in white people, and account for more than 80% of all malignant melanomas.[6] Greenwald et al, after summarizing the previous literature, pointed out that the two are distinct biological entities with unique molecular characterizations and clinical differences.[7] When superficial extended melanoma is diagnosed at an early stage, it is only in the radial growth phase, and the lesion is limited to the skin, but it has long-term development to invade the subdermal cell population, that is, in the vertical growth phase. Survival has important negative effects.[8,9]

The American joint committee on cancer (AJCC) staging system has been an important reference for cancer treatment.[10]

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The datasets generated during and/or analyzed during the current study are publicly available.

We acknowledge the SEER database for providing their platforms and contributors for uploading their meaningful datasets. SEER belongs to public databases. The patients involved in the database obtained ethical approval.

[a] Department of Burn and Plastic Surgery, West China Hospital, Sichuan University, Guoxue Alley, Wuhou District, Chengdu, China, [b] Department of Thyroid Surgery, West China Hospital, Sichuan University, Guoxue Alley, Wuhou District, Chengdu, China, [c] Department of Thyroid Surgery, West China Hospital, Sichuan University, Guoxue Alley, Wuhou District, Chengdu, China.

** Correspondence: Junjie Chen, Department of Burn and Plastic Surgery, West China Hospital, Sichuan University, Guoxue Alley, Wuhou District, Chengdu 610041, China (e-mail: cenying_0141@163.com).*

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The TNM classification is mainly applied to data on the SSM and NM subtypes in skin malignant melanoma. However, due to the lack of demographic and pathological characteristics, the pure AJCC staging system has some limitations when applied to the prognostic analysis of skin malignant melanoma. A recent study by Blair et al indicated that the inclusion of melanoma subtypes in the AJCC guidelines may affect treatment, staging, and monitoring.[11] Therefore, to provide comprehensive guidance to clinicians, it is necessary to establish a predictive model for skin malignant melanoma subtypes separately.

The nomogram model can show higher prediction accuracy, good calibration quality and promising decision analysis.[12] At present, various nomograms related to melanoma have been published in the literature, such as gastrointestinal melanoma, vulvar melanoma, skin nodular melanoma, etc., but no nomograms specifically designed for SSM have been reported.[13–15] Therefore, we used relevant data from the surveillance, epidemiology and end results (SEER) database to build an SSM nomogram to assess patient prognosis.

2. Materials and Methods

2.1. Collection of baseline information

We performed a population-based cross-sectional analysis according to the National Cancer Institute SEER. We identified all cases with SSM by selecting the year of diagnosis from 2000 to 2018, the International Classification of Diseases in Oncology, Third Edition (ICD-0-3) histology and site code 8743. Patients with unknown or unspecified TNM stage, survival time, survival status, and surgical status were excluded from this study. Follow-up information showed age at diagnosis (<60 years old, ≥60 years old), race, sex, primary site (C44.2-External ear, C44.3-Skin other/unspec parts of face, C44.4-Skin of scalp and neck, C44.5-Skin of trunk, C44.6-Skin of upper limb and shoulder, C44.7-Skin of lower limb and hip), AJCC TNM stage (*T*1–*T*4, excluding TX; N0 and *N*1- *N*3, excluding NX), SEER stage (local, regional, and distant), whether melanoma was one primary and the first of 2 or more primaries, survival status, and survival time.

2.2. Statistical analysis

In univariate analysis, if the measurement data did not obey a normal distribution, the mean value fell between *Q*1 and *Q*3, which was expressed by the quartile method; the measurement data with a normal distribution were expressed as the mean ± standard deviation, and the unpaired method was used. Data t test. With patient death as the dependent variable, variables with $P < .05$ were included in Cox regression analysis to determine the relative influencing factors on overall survival (OS)

Table 1

Baseline demographic and clinical characteristics in patients with SSM.

	Overall (N = 13,922)	Training cohort (N = 8353)	Validation cohort (N = 5569)	*P*-value
Age				.727
<60	6972 (50.1%)	4173 (50.0%)	2799 (50.3%)	
≥60	6950 (49.9%)	4180 (50.0%)	2770 (49.7%)	
Sex				.660
Female	6528 (46.9%)	3904 (46.7%)	2624 (47.1%)	
Male	7394 (53.1%)	4449 (53.3%)	2945 (52.9%)	
Race				.223
Black	16 (0.1%)	10 (0.1%)	6 (0.1%)	
Other	131 (0.9%)	69 (0.8%)	62 (1.1%)	
White	13,775 (98.9%)	8274 (99.1%)	5501 (98.8%)	
Primary site				.876
Trunk	5359 (38.5%)	3213 (38.5%)	2146 (38.5%)	
Head face and neck	1890 (13.6%)	1148 (13.7%)	742 (13.3%)	
Lower limbs	2835 (20.4%)	1688 (20.2%)	1147 (20.6%)	
Upper limbs	3838 (27.6%)	2304 (27.6%)	1534 (27.5%)	
T stage				.840
T1a	7815 (56.1%)	4680 (56.0%)	3135 (56.3%)	
T1b	2994 (21.5%)	1797 (21.5%)	1197 (21.5%)	
T2a	1791 (12.9%)	1079 (12.9%)	712 (12.8%)	
T2b	362 (2.6%)	210 (2.5%)	152 (2.7%)	
T3a	387 (2.8%)	241 (2.9%)	146 (2.6%)	
T3b	316 (2.3%)	183 (2.2%)	133 (2.4%)	
T4a	88 (0.6%)	57 (0.7%)	31 (0.6%)	
T4b	169 (1.2%)	106 (1.3%)	63 (1.1%)	
N stage				.490
N0	13,241 (95.1%)	7925 (94.9%)	5316 (95.5%)	
N1a	375 (2.7%)	241 (2.9%)	134 (2.4%)	
N1b	42 (0.3%)	27 (0.3%)	15 (0.3%)	
N2a	123 (0.9%)	72 (0.9%)	51 (0.9%)	
N2b	17 (0.1%)	13 (0.2%)	4 (0.1%)	
N2c	41 (0.3%)	24 (0.3%)	17 (0.3%)	
N3	83 (0.6%)	51 (0.6%)	32 (0.6%)	
Summary stage				.191
Localized	13,190 (94.7%)	7893 (94.5%)	5297 (95.1%)	
Regional	650 (4.7%)	412 (4.9%)	238 (4.3%)	
Distant	82 (0.6%)	48 (0.6%)	34 (0.6%)	
First malignant primary indicator				.286
No	2751 (19.8%)	1626 (19.5%)	1125 (20.2%)	
Yes	11,171 (80.2%)	6727 (80.5%)	4444 (79.8%)	

SSM = superficial spreading melanoma.

or cancer-specific survival (CSS) in SSM patients. Based on the independent risk factors for death in SSM patients, a nomogram prediction model was constructed. The *C*-index was calculated to obtain the predictive value of the model, and the receiver operating characteristic curve was used to evaluate the predictability of the nomogram. To verify the applicability of the model, we performed in-house validation in the validation cohort and plotted a calibration curve. All statistical data analyses were performed using SPSS for Windows (version 22) and *R* statistical software (version 3.6.1), and statistical significance was estimated at $P < .05$.

3. Results

3.1. Study cohorts and patient characteristics

A total of 13,922 SSM patients with information available for AJCC melanoma staging data were collected from the National Cancer Institute's Surveillance, Epidemiology, Outcomes database SEER. In terms of demographics, the number of patients was predominantly male (7394 cases, 53.1%), elderly patients (6950, 49.9%), and white (13,775, 98.9%). In terms of tumor characteristics, the most important anatomical sites were the limbs (including the upper and lower limbs, 48.0%), followed by the trunk (38.5%), and the head, face and neck (13.6%). All patients were randomly divided into a training group (8353 cases) and a validation group (5569 cases) at a ratio of 6:4. The demographic and clinicopathological characteristics are shown in Table 1.

3.2. Univariate and multivariate analyses and identification of predictive factors

Table 2 lists the single variable analysis results in the training queue. Determining age, sex, distant transfer, AJCC stage T and N period and whether the first primary malignant SSM is considered to be related to prognostic factors of the patient OS and CSS rate.

To further clarify the risk factors for SSM, we constructed a multivariable model of OS and CSS (see Table 3). Age is an important factor affecting the survival, OS and CSS, and the prognosis of patients ≥60 years is poorer than that of young patients. Sex had a significant effect on SSM patient survival, and the OS and CSS of women were better than those of men. AJCC T stage, which represents the thickness of the tumor and whether it is accompanied by ulceration, has a significant correlation with the prognosis of patients with SSM. OS and CSS were significantly decreased in patients with distant metastases and undiagnosed first primary melanoma SSM. Regional lymph node metastasis is also a risk factor for CSS in patients with SSM.

3.3. Construction of the nomogram and predictive model verification

Based on the above prognostic factors, this study constructed nomogram models for predicting OS and CSS in patients with SSM (see Fig. 1). The *C*-index for OS and CSS for this model was 0.805 [95% CI: 0.793–0.817] and 0.896 [95% CI: 0.878–0.913],

Table 2

Univariate analysis of OS and CSS rates in training cohort in patients with SSM.

	OS univariate analysis		CSS univariate analysis	
	HR 95% CI	*P*-value	HR 95% CI	*P*-value
Age (<60 vs ≥60)	6.063 (5.128–7.168)	<.001	2.092 (1.647–2.658)	<.001
Sex (female vs male)	2.008 (1.752–2.301)	<.001	2.139 (1.671–2.739)	<.001
Race		.789		.104
White	Reference	Reference	Reference	Reference
Black	0.600 (0.110–3.286)	.553	0.999 (0.998–1.000)	.579
Others	0.585 (0.124–2.759)	.493	2.359 (1.015–5.483)	.040
Primary site		<.001		<.001
Trunk	Reference	Reference	Reference	Reference
Head face and neck	2.354 (1.977–2.804)	<.001	1.986 (1.502–2.627)	<.001
Lower limbs	0.732 (0.598–0.895)	.002	0.617 (0.436–0.874)	.006
Upper limbs	1.091 (0.925–1.287)	.299	0.560 (0.404–776)	<.001
T stage		<.001		<.001
T1a	Reference	<.001	Reference	Reference
T1b	1.349 (1.123–1.622)	<.001	3.289 (2.103–5.144)	<.001
T2a	2.391 (1.977–2.891)	<.001	6.877 (4.463–10.595)	<.001
T2b	4.809 (3.511–6.588)	<.001	22.847 (13.838–37.721)	<.001
T3a	5.493 (4.112–7.340)	<.001	27.194 (16.997–43.510)	<.001
T3b	8.154 (5.966–11.144)	<.001	46.563 (29.235–74.160)	<.001
T4a	6.595 (4.061–10.710)	<.001	43.005 (21.598–85.628)	<.001
T4b	23.288 (15.327–35.384)	<.001	95.275 (57.169–157.780)	<.001
N stage		<.001		<.001
N0	Reference	Reference	Reference	Reference
N1a	3.208 (2.411–4.267)	<.001	10.354 (7.288–14.708)	<.001
N1b	5.280 (2.443–11.412)	<.001	17.819 (7.655–41.482)	<.001
N2a	3.840 (2.341–6.299)	<.001	19.654 (11.928–32.383)	<.001
N2b	3.413 (1.049–11.106)	.030	34.366 (11.442–103.213)	<.001
N2c	12.800 (5.586–29.334)	<.001	28.956 (13.989–59.939)	<.001
N3	10.124 (5.792–17.696)	<.001	32.383 (17.906–58.566)	<.001
Summary stage		<.001		<.001
Localized	Reference	Reference	Reference	Reference
Regional	5.164 (4.187–6.369)	<.001	17.275 (13.290–22.453)	<.001
Distant	8.662 (4.896–15.327)	<.001	22.753 (12.801–40.444)	<.001
First malignant primary indicator (Yes vs No)	0.356 (0.310–0.410)	<.001	0.499 (0.391–0.637)	<.001

CSS = cancer-specific survival, OS = overall survival, SSM = superficial spreading melanoma.

Table 3

Multivariate analysis of OS and CSS rates in training cohort in patients with SSM.

	OS multivariate analysis		CSS multivariate analysis	
	HR 95%*CI*	*P*-value	HR 95%*CI*	*P*-value
Age (<60 vs ≥ 60)	0.237 (0.200–0.280)	<.001	0.587 (0.455–0.758)	<.0001
Sex (female vs male)	0.785 (0.683–0.901)	.001	0.723 (0.555–0.940)	.015
Primary site		<.001		.009
Trunk	Reference	Reference	Reference	Reference
Scalp face and neck	1.380 (1.159–1.643)	<.001	1.545 (1.077–2.217)	.018
Lower limbs	0.835 (0.681–1.025)	.084	0.959 (0.636–1.447)	.842
Upper limbs	0.950 (0.811–1.112)	.520	1.513 (0.089–2.102)	.014
T stage		<.001		<.0001
T1a	Reference	<.001	Reference	Reference
T1b	0.152 (0.113–0.205)	<.001	0.034 (0.021–0.057)	<.0001
T2a	0.191 (0.140–0.261)	<.001	0.105 (0.065–0.170)	<.0001
T2b	0.275 (0.203–0.374)	<.001	0.172 (0.110–0.269)	<.0001
T3a	0.496 (0.345–0.715)	<0.001	0.566 (0.345–0.928)	.024
T3b	0.488 (0.349–0.684)	<.001	0.515 (0.330–0.804)	.004
T4a	0.648 (0.462–0.910)	.012	0.702 (0.458–1.075)	.104
T4b	0.680 (0.440–1.052)	.083	0.612 (0.332–1.131)	.117
N stage		.065		.042
N0	Reference	Reference	Reference	Reference
N1a	0.507 (0.311–0.827)	.007	0.366 (0.189–0.708)	.003
N1b	0.541 (0.345–0.849)	.008	0.534 (0.312–0.914)	.022
N2a	0.489 (0.243–0.987)	.046	0.567 (0.245–1.316)	.187
N2b	0.577 (0.331–1.005)	.052	0.697 (0.386–1.260)	.232
N2c	0.550 (0.190–1.587)	.269	1.158 (0.457–2.935)	.757
N3	0.906 (0.477–1.721)	.764	0.796 (0.389–1.631)	.533
Summary stage		<.001		<.0001
Localized	Reference	Reference	Reference	Reference
Regional	2.090 (1.347–3.241)	.001	2.284 (1.363–3.828)	.002
Distant	0.605 (0.423–0.867)	.006	0.480 (0.280–0.822)	.007
First malignant primary indicator (yes vs no)	1.733 (1.523 –1.973)	<.001	1.690 (1.307–2.185)	<.001

CSS = cancer-specific survival, OS = overall survival, SSM = superficial spreading melanoma.

respectively. The 1-, 3-, and 5-year area under the curve (AUC)'s for OS in patients with SSM were 0.822, 0.820, and 0.821, respectively. The corresponding values of AUC for predicting CSS rate were higher, 0.914, 0.922, and 0.893, respectively, which indicated that both had higher predictive ability, and the latter had higher predictive accuracy (see Fig. 2). Figure 3 shows the 1-, 3-, and 5-year OS and CSS prediction calibration plots for the training and validation cohorts, and the results showed good consistency between the prediction and observation probability.

4. Discussion

This study established OS and CSS prognostic nomograms for SSM patients from the SEER database with good discriminative, calibrated, and comparable predictive power. After multivariate analysis and statistics, age, sex, lesion location, distant metastasis, AJCC stage, T stage, N stage and whether the first primary malignant SSM was diagnosed early were determined, and the prognosis of SSM patients was related to the OS rate and CSS rate. Assessment of patient-related and tumor-related factors by nomogram quantitatively predicts 1-, 3-, and 5-year OS and CSS rates in patients, informs patient prognosis, and enables individualized decisions about monitoring and treatment.

Age is a highly significant and powerful predictor of outcome in patients with skin melanoma; although there is no significant predictor of lymph node involvement, recurrence, or metastasis, age ≥ 60 years may be associated with more aggressive histology in patients with skin melanoma characteristics and poorer outcomes.[16] Our study was based on the median age of previous studies of melanoma, with an age cutoff of 60 years, and demonstrated that ≥ 60 years was a negative predictor of OS and CSS prognosis in patients with SSM, and the results were consistent with the study of Michael et al[17] Men have a higher incidence of melanoma than women, and women have a higher relative survival rate than men.[18,19] This study also demonstrated lower OS and CSS rates in male patients with SSM, which is consistent with previous studies. Compared with patients of other races, the incidence of SSM in whites was significantly higher than that in other people of color, but the data in this study showed that the number of cases in people of color was very small, and race was not an independent factor in our study. Population epidemiological statistics also found that the SSM subtype is more common in the trunk and limbs, which are intermittently exposed to sunlight, which is consistent with previous reports.[20] Multivariate regression analysis also suggested that patients with SSM in the head, face and neck had lower OS and CSS, which were independent predictors of SSM.

In 2009, the US Cancer Joint Committee AJCC incorporated tumor thickness, ulcers, mitosis rate and lymph nodular state in the recurrence of susceptible melanoma patients.[21] Among them, T (tumor) staging includes mitosis (*T*1) in the presence of the overall tumor thickness, the presence of ulcers and a thickness of < 1 mm.[22] A number of studies have confirmed that thin- and medium-thickness tumors (BRESLOW thickness ≤ 4.0 mm) are favorable prognostic factors for survival in patients with SSM.[23] Our research also explains that with the increase in SSM tumor T staging, the SSM patients significantly declined. The AJCC description of the eight editions pointed out that the number of lymphatic junctions in the area of skin melanoma violations still follows the old version, and the microstrian stove, satellite stove or shift transfer stove is categorized into N1C, N2C and N3C. It is generally believed that the region lymph node is disturbed, the number of transfers is increased and the transitional transfer stove, the shorter

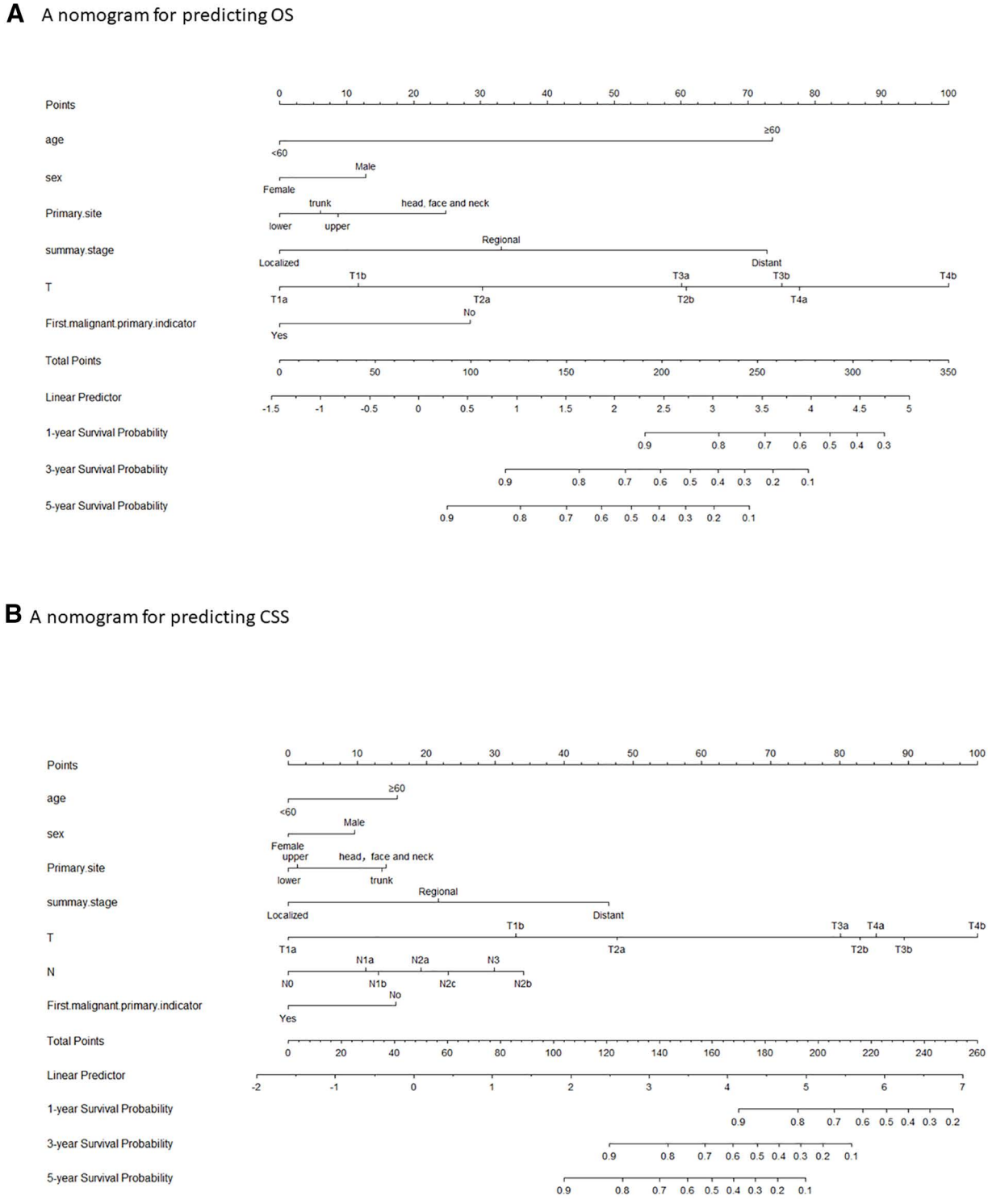

Figure 1. Establishment of a nomogram to predict 1-, 3-, and 5-year OS and CSS rates in patients with SSM. (A) Nomograms associated with predicting OS at 1, 3, and 5 years in patients with SSM. (B) Nomograms predicting 1-, 3-, and 5-year CSS-related nomograms in patients with SSM. CSS = cancer-specific survival, OS = overall survival, SSM = superficial spreading melanoma.

the survival time of the patient, and our study found that the relationship between the region lymph node metastasis was closely related to the CSS of the SSM patient. Tuminoma can be transferred to any part of the whole body, including skin, muscle, distant lymphatic, liver, brain or internal organ.[24,25] The prognosis of patients with melanoma at a distance occurred, and the median survival period in particular untreated patients was only 6 to 9 months.[26] Although there is less transfer risk in SSM than other melanoma subtypes, only 82 patients in this study have a distant transfer, but the Cox multifactor analysis shows that the transfer of tumors is still determined to affect SSM patient CSS.

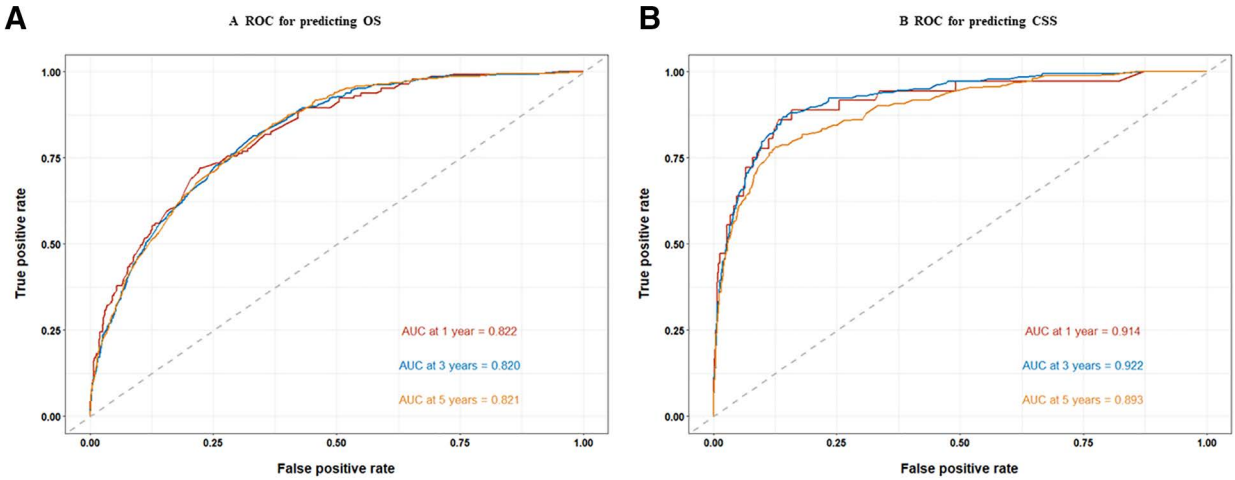

Figure 2. ROC curve analysis for predicting 1-, 3-, and 5-year OS and CSS rates in patients with SSM. (A) OS-related ROC curves of patients with SSM. (B) CSS-related ROC curves of patients with SSM. CSS = cancer-specific survival, OS = overall survival, ROC = receiver operating characteristic, SSM = superficial spreading melanoma.

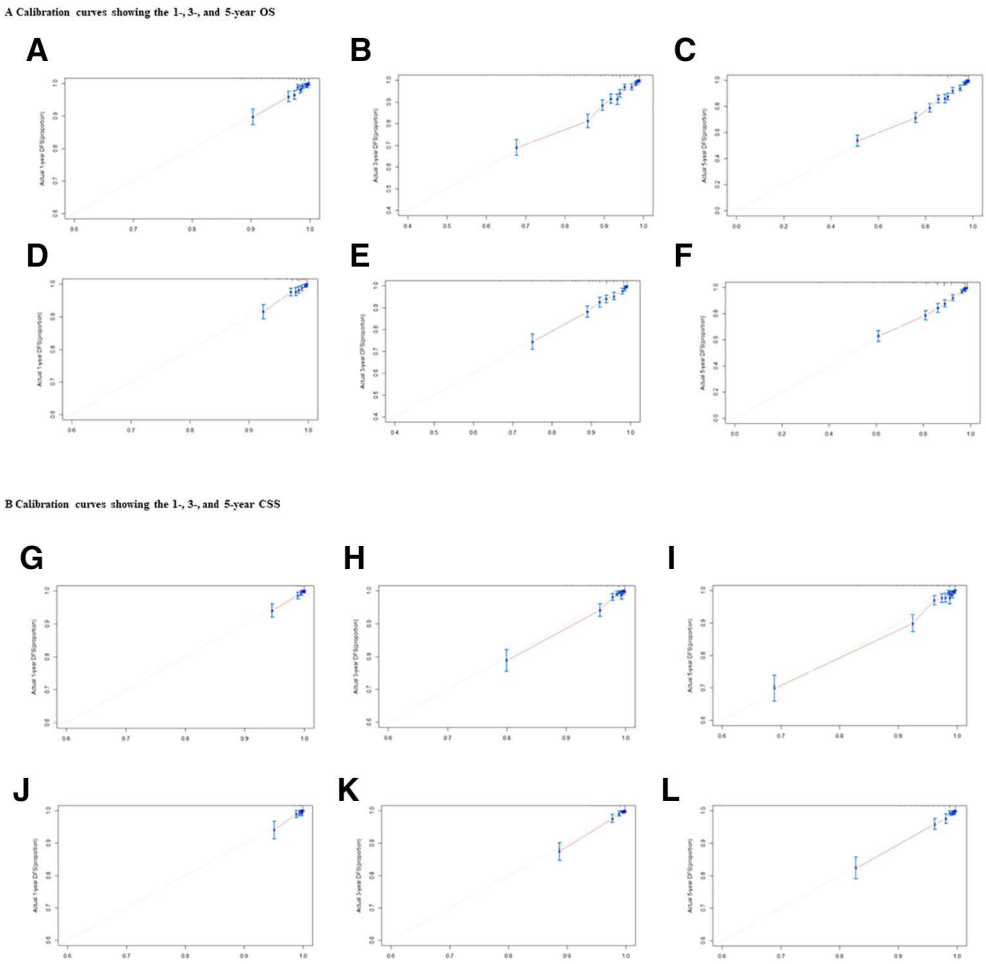

Figure 3. (A–C) Calibration curves showing the 1-, 3-, and 5-year OS probabilities between nomogram predictions and actual probabilities in the training cohort in patients with SSM. (D–F) Calibration curves showing 1-, 3-, and 5-year OS probabilities between nomogram predictions and actual probabilities in the validation cohort for patients with SSM. (G–I) calibration curves showing 1-, 3-, and 5-year CSS probabilities between nomogram predictions and actual probabilities in the training cohort for patients with SSM. (J–L) calibration curves showing 1-, 3-, and 5-year CSS probabilities between nomogram predictions and actual probabilities in the validation cohort for patients with SSM. CSS = cancer-specific survival, OS = overall survival, SSM = superficial spreading melanoma.

In the diagnosis of melanoma, early identification, timely detection and rapid treatment are critical to reduce melanoma incidence and mortality.[27] Compared to other cancers, SSM has the advantage of skin locations, which allows early detection by dermal mirror and biopsy. However, the results in our data show that there are still many patients who do not belong to the first primary melanoma population, and the prediction of OS and CSS in such patients is lower than that in patients with SSM as the first tumor diagnosis.

Nomograms are very useful in predicting the probability of individual clinical events by using individual variables; they are often used as prognostic tools in clinical practice and can be further developed as mobile tool application software.[28] In the nomogram, the age score of ≥ 60 years old, T (AJCC staging) and the absence of distant metastases account for the major parts of the OS scoring system for patients with SSM; in the nomogram of the CSS scoring system of patients, the age score of ≥ 60 years old is significantly lower than that of the OS grading system. According to the total score of the nomograms, clinicians and patients can obtain a risk factor for OS and CSS probability at 1 year, 3 years and 5 years. The CSS column chart has a higher discrimination capability (0.896), higher than the *C* index (0.805) of the OS column chart. Similarly, AUC also indicates good discrimination capabilities. To evaluate the accuracy of the column chart, the OS and CSS verification set calibration curves of the SSM patient were compared, and the results showed that the predictive value had good consistency.

5. Limitations

This study has some limitations that must be addressed. First, treatment factors such as surgery were not considered in this study, as we found that the vast majority of patients had undergone surgery; second, as this was a retrospective review, there may be some selection bias and record entry errors; third, this study did not perform external validation to further evaluate this column name graph.

6. Conclusion

In conclusion, this study determined that age, sex, lesion location, presence of distant metastases, AJCC staging, T stage and diagnosis of first primary malignancy were associated with prognostic factors for the OS rate and CSS rate of patients with SSM. (AJCC staging) N stage is also associated with prognostic factors for the CSS rate. Elderly, male, higher T (AJCC staging) and N (AJCC staging), regional lymph node metastasis, distant metastasis, and SSM patients who are not the first primary malignancy have poorer prognosis. This study confirmed that the nomogram has excellent predictive performance in predicting 1-, 3-, and 5-year OS and CSS rates in SSM patients, which can provide a reference for individualized treatment and clinical counseling of SSM.

Author contributions

Conceptualization: Qiang Ji, Junjie Chen.
Data curation: Qiang Ji, Jun Tang, Shulian Li, Junjie Chen.
Investigation: Shulian Li.
Methodology: Qiang Ji, Jun Tang.
Project administration: Junjie Chen.
Resources: Qiang Ji.
Supervision: Qiang Ji, Jun Tang, Shulian Li, Junjie Chen.
Validation: Jun Tang, Shulian Li.
Visualization: Qiang Ji, Junjie Chen.
Writing – original draft: Qiang Ji, Junjie Chen.

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