Int J Clin Exp Med 2019;12(2):1584-1599
www.ijcem.com /ISSN:1940-5901/IJCEM0072416

Original Article

Clinicopathological nomograms model to predict long-term overall survival and cancer-specific survival in skin cutaneous melanoma: a population-based study

Zhuhui Duan[1*], Jukun Song[2*], Yadong Wang[2*], Chen Zhu[3], Juxiang Peng[3], Xinhai Yin[2], Jianguo Liu[4], Hui Chen[1], Lingkai Su[1]

[1]Affiliated Hospital of Stomatology, Medical College, Zhejiang University, Hangzhou, P. R. China; [2]Department of Oral and Maxillofacial Surgery, Guizhou Provincial People's Hospital, Guizhou, China; [3]Guiyang Hospital of Stomatology, Medical College, Guiyang, P. R. China; [4]Special Key Laboratory of Oral Diseases Research, Stomatological Hospital Affiliated to Zunyi Medical College, Zunyi, Guizhou Province, China. [*]Equal contributors.

Received January 9, 2018; Accepted October 8, 2018; Epub February 15, 2019; Published February 28, 2019

Abstract: Skin cutaneous melanoma (SCM) is one of the most aggressive skin cancers with a high mortality rate and incidence rate. The aim of this study was to develop clinical nomograms that can be used to predict long-term overall survival and cancer-specific survival (CSS) in patients with SCM. The patients diagnosed between 2004 and 2013 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. The patients were randomly divided into two cohorts: the Training (70%, n = 22,101) and Validation (30%, n = 9,479). The probability of cancer-specific survival (CSS) and death from other causes was calculated by competing risk regression model. Of the 31,580 patients, 4,865 died from SCM and 2,215 died from other causes. The 3- and 5-year probabilities of overall death were 0.671 and 0.865 in the training cohorts, respectively. The 3- and 5-year probabilities of specific death were 0.410 and 0.506 in the training cohorts, respectively. The univariate and multivariate analysis was used to choose the independent prognosis variable for OS and CSS. A nomogram model predicting the overall survival and cancer-specific survival was established according to 14 clinicopathologic characteristics (age at the time of diagnosis, race, sex, tumor location, tumor histology, TNM stage, Breslow thickness, Clark level, tumor ulceration, tumor size, radiotherapy, and surgery of primary site), with higher concordance indexes in both internal validation (0.860 for OS and 0.901 for CSS) and external validation (0.859 for OS and 0.904 for CSS). The nomogram model had high accuracy in estimating the probabilities of OS and CSS for patients with SCM. The established nomograms can help clinicians to screen patients with higher risk of SCM, and facilitate individualized treatment.

Keywords: Nomogram, skin cutaneous melanoma

Introduction

Skin cutaneous melanoma (SCM) is an aggressive form of skin cancer with a high mortality rate and incidence rate among all malignancies [1, 2]. In 2017, an estimated 87,110 new cases of SCM were diagnosed and an estimated 9,730 deaths were reported in the USA alone, making SCM the sixth and seventh leading cause of cancer-related deaths in men and women, respectively. It was estimated that 74,640 cases of melanoma in situ predicted for 2017 [3]. Owing to its clinicopathological heterogeneity , the incidence rates for SCM range from 25% to 61% among men and 11% to 43% among women in the United States, while the mortality rates range from 10% to 26%, and the 5-year survival rate of SCM is 78% for men and 86% for women [4, 5]. Therefore, accurate estimates for prognosis of SCM patients based on clinicopathological characteristics would help physicians to provide effective individualized treatment. SCM patients are also at high risk of death from other factors such as distant metastasis, secondary cancers, and chemo- radio therapeutic toxicity. As a result, overall survival rate might not accurately describe the survival rate of SCM patients, but estimated specific-death may be more accurate in describing the survival of SCM patients. Therefore, it is impor-

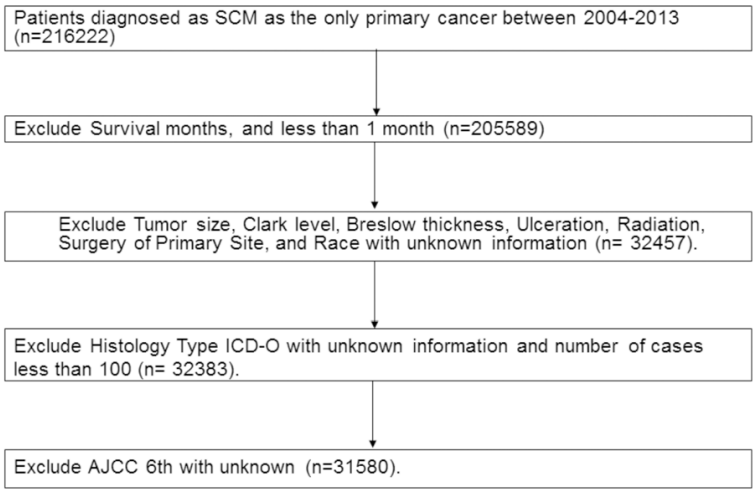

Figure 1. Flow chart for the SEER data selection.

tance to eliminate competing causes of death when evaluating SCM cancer-specific survival.

Our objective was to use a large retrospective population-based database to evaluate and estimate the probability of cancer-specific death and competing causes risk analysis, and to develop SCM nomograms that predict long-term OS and CSS probabilities based on multiple clinicopathological risk factors to improve individualized treatments and prognosis.

Materials and methods

Ethics statement

The study was approved by the Ethical Committee of GuiZhou People's Hospital. Informed patient consent was not required because data was extracted from the SEER database.

Data source and patient selection criteria

We used the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (http://seer.cancer.gov/) to screen all patients with SCM diagnosed between 2004 and 2013, which included cancer data from 17 population-based registries among 14 states across the United States, and comprise approximately 28% of the United States population [6, 7]. The specific inclusion criteria used to identify eligible patients were as follows: 1) The years of diagnosis ranged from 2004 to 2013; 2) CS Schema v0204+ was skin cutaneous melanoma; 3) Histological type ICD-O-3 was limited to 8720/3 (malignant melanoma, NOS), 8721/3 (nodular melanoma), 8742/3 (lentigo malignant, melanoma), 8743/3 (superficial spreading melanoma), 8744/3 (acral lentiginous melanoma, malignant), 8745/3 (desmoplastic melanoma, malignant), and 8772/3 (spindle cell melanoma, NOS), 4) SCM primary tumor site was the head and neck (skin of lip, scalp, and neck, external ear, other/unspecific parts of face and eyelid), trunk (skin of trunk), limbs (skin of lower limb and hip, upper limb and shoulder), and genitals (skin of labium minus, labium majus, clitoris, vulva, overlapping lesion of vulva, penis, glans penis, prepuce and body of penis). The exclusion criteria were as follows: 1) Multiple primary cancers were excluded; 2) Patients with a survival of less than one month and unknown; 3) Lack information of tumor size, Clark level, Breslow thickness, ulceration, radiation, primary surgery site, and race (for the detailed inclusion and exclusion criteria, see **Figure 1**).

The eligible patients were randomly divided into: a training cohort (70%) and a validation cohort (30%) to establish and validate a competing risk-nomogram model. Continuous variables, such as age, tumor size, and Breslow thickness were transformed into categorical variable based on recognized cutoff values. Age was classified into six groups: ≤ 29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, and ≥ 70 years. Breckness thickness was divided into five groups: < 1 mm, 1-2 mm, 2-3 mm, 3-4 mm, and > 4 mm. Tumor sizes were classified into six groups: < 1 cm, 1-2 cm, 2-3 cm, 3-4 cm, 4-5 cm and > 5 cm. Clark level was classified into four groups: I/II, III, IV, and V. All patients were regrouped according to the 6th American Joint Committee on Cancer (AJCC) TNM staging system. Race was divided into white, black, and other (including American Indian/AK Native, Asian/Pacific Islander).

Prognostic analyzes

We defined OS as failure at the time of patient death, or censoring if a patient was alive at the

Table 1. Patient's demographic and clinical characteristics

Variable	Training cohort (N = 22101)		Validation cohort (N = 9479)	
	Frequency	Percent (%)	Frequency	Percent (%)
Sex				
Female	9848	44.56	4192	44.22
Male	12253	55.44	5287	55.78
Age				
≤ 29	1126	5.10	458	4.83
30-39	1958	8.86	857	9.04
40-49	3617	16.37	1583	16.70
50-59	5035	22.79	2041	21.53
60-69	4727	21.39	1969	20.77
≥ 70	5638	25.51	2571	27.12
Race				
White	21721	98.28	9347	98.61
Black	132	0.60	45	0.47
Other (American Indian/AK Native, Asian/Pacific Islander)	248	1.13	87	0.92
TNM stage (AJCC 6th)				
T stage				
T1	14246	64.46	6087	64.22
T2	3547	16.05	1528	16.12
T3	2237	10.12	980	10.34
T4	2071	9.37	884	9.33
N stage				
N0	19437	87.95	8389	88.50
N1	1129	5.11	448	4.73
N2	637	2.88	255	2.69
N3	401	1.81	169	1.78
NX	497	2.55	218	2.30
M stage				
M0	21413	96.89	9203	97.09
M1	310	1.40	111	1.17
MX	378	1.71	165	1.74
Tumor location				
Skin of head and neck	4281	19.37	1836	19.37
Skin of trunk	7615	34.62	3224	37.01
Skin of limbs	10104	45.72	4374	46.14
Skin of genitals	101	0.46	45	0.47
Histologic sbutype				
Malignant melanoma, NOS	9471	42.85	4089	43.14
Nodular melanoma	2412	10.91	991	10.45
Lentigo maligna melanoma	1182	5.35	537	5.67
Superficial spreading melanoma	8157	36.91	3475	36.66
Acral lentiginous melanoma, malignant	328	1.48	153	1.61
Desmoplastic melanoma, malignant	255	1.15	117	1.23
Spindle cell melanoma, NOS	296	1.34	117	1.23
Breslow thickness				
< 1 mm	734	3.32	338	3.57
1-2 mm	1070	4.84	525	5.54
2-3 mm	2315	10.47	945	9.97
3-4 mm	2341	10.59	1007	10.62
> 4 mm	15641	70.77	6664	70.30

Clark level				
I	0	0	0	0
II	7834	35.45	3366	35.51
III	5574	25.22	2378	25.09
IV	7241	32.76	3129	33.01
V	1452	6.57	606	6.39
Tumor ulcertion				
Yes	3701	16.75	1604	16.92
No	18400	83.25	7875	83.08
Tumor size				
≤ 1 cm	11967	54.15	5048	53.25
1-2 cm	6125	27.71	2610	27.53
2-3 cm	1710	7.74	762	8.04
3-4 cm	670	3.03	319	3.37
4-5 cm	401	1.81	162	1.71
≥ 5 cm	1228	5.56	578	6.10
Radiotion				
Yes	387	1.75	152	1.60
No	21714	98.25	3927	98.40
Surgery of primary site				
Yes	21845	98.84	9368	98.83
No	256	1.16	111	1.17
Survival months				
Median(IQR)				

last follow-up. The CSS was defined as failure if a patient died of SCM, or censoring if a patient was alive at the last follow-up or death due to other reasons. The OS were conducted using the Kaplan-Meier and Cox proportional hazards models. Variables with a *P* value of less than 0.05 were considered as independent prognostic OS factors, and the included prognostic factors were used to build nomograms model for OS. The SPSS 19.0 software (IBM Corp., Armonk, USA) was used to identify independent prognostic factors.

Competing risk analyzes

Death from melanoma and from other causes were two types of events in the competing risk analysis. Death from other causes was considered to be a competing risk [8-10]. We performed a competing risk analysis to produce the cumulative incidence function (CIF) for different groups. The 3- and 5-years were recognized as the cutoff of time. The R "cmpprsk" packages were used to build the model of competing risk analysis.

Construction of nomograms model

Nomogram model was established based on the results of the Cox proportional hazard model in the training cohort. To decrease overfit bias, the nomogram model was subjected to bootstrapping with 1000 resamples as quantified by the concordance index (C-index) for internal validation in the training cohort and external validation in the validation cohort. The value of C-index ranged from 0.5 to 1.0, with 0.5 suggesting no discrimination and 1.0 indicating a perfect discrimination. Construction, validation, and calibration of the nomograms were developed using the R version 3.1.2 software (Institute of Statistics and Mathematics, Vienna, Austria; www.r-project.org). The R "rms" packages were used to build the nomogram models. The score of nomogram models was estimated and visualized by the "nomogramEx" package. All *P* values were two-sided, and those less than 0.01 were considered statistically significant for many patients.

Results

Clinical and pathological characteristics

A total of 31,580 eligible patients were included in the study, including 22,101 patients in the training cohort and 9,479 patients in the validation cohort. The clinical and pathological characteristics of the cohort study are shown in

Table 2. Five- and Ten-years cumulative incidences of death among patients in the training cohort

Variable	Cumulative Incidence of Death Resulting From Skin Melanoma			Cumulative Incidence of Death Resulting From Other Causes		
	3-y	5-y	P	3-y	5-y	P
All Patients	0.410	0.506		0.261	0.359	
Sex			< 0.001			0.016
Female	0.383	0.472		0.279	0.379	
Male	0.424	0.525		0.251	0.349	
Age at diagnosis, years			< 0.001			< 0.001
≤ 29	0.310	0.366		0.000	0.050	
30-39	0.496	0.665		0.059	0.095	
40-49	0.538	0.665		0.077	0.102	
50-59	0.595	0.759		0.148	0.208	
60-69	0.600	0.800		0.173	0.242	
≥ 70	0.655	0.845		0.358	0.489	
Race			< 0.001			0.673
White	0.403	0.499		0.264	0.364	
Black	0.667	0.756		0.156	0.200	
Other (American Indian/AK Native, Asian/Pacific Islander)	0.603	0.724		0.138	0.489	
TNM stage (AJCC 6th)						
T stage			< 0.001			< 0.001
T0	NA	NA		NA	NA	
T1	0.214	0.272		0.335	0.518	
T2	0.366	0.518		0.238	0.323	
T3	0.493	0.614		0.230	0.287	
T4	0.599	0.691		0.210	0.248	
N stage			< 0.001			< 0.001
N0	0.290	0.385		0.317	0.445	
N1	0.646	0.793		0.111	0.142	
N2	0.712	0.794		0.121	0.146	
N3	0.809	0.874		0.084	0.092	
NX	0.327	0.364		0.430	0.561	
M stage			< 0.001			0.008
M0	0.376	0.478		0.271	0.376	
M1	0.855	0.906		0.077	0.081	
MX	0.288	0.437		0.388	0. 485	
Tumor location			< 0.001			< 0.001
Skin of head and neck	0.371	0.461		0.308	0.408	
Skin of trunk	0.464	0.573		0.197	0.301	
Skin of limbs	0.393	0.484		0.277	0.373	
Skin of genitals	0.4790	0.592		0.265	0.286	
Histologic sbutype			< 0.001			< 0.001
Malignant melanoma, NOS	0.37	0.492		0.253	0.358	
Nodular melanoma	0.577	0.667		0.230	0.266	
Lentigo maligna melanoma	0.106	0.129		0.424	0.659	
Superficial spreading melanoma	0.266	0.389		0.289	0.436	
Acral lentiginous melanoma, malignant	0.594	0.729		0.135	0.188	
Desmoplastic melanoma, malignant	0.406	0.493		0.232	0.333	
Spindle cell melanoma, NOS	0.520	0.570		0.300	0.320	
Breslow thickness			< 0.001			< 0.001
< 1 mm	0.348	0.455		0.277	0.366	
1-2 mm	0.214	0.232		0.321	0.509	
2-3 mm	0.127	0.180		0.327	0.567	

3-4 mm	0.170	0.190		0.395	0.592	
> 4 mm	0.447	0.552		0.247	0.330	
Clark level			< 0.001			< 0.001
I	NA	NA		NA	NA	
II	0.103	0.141		0.376	0.604	
III	0.264	0.360		0.298	0.436	
IV	0.460	0.582		0.237	0.311	
V	0.630	0.712		0.202	0.234	
Tumor ulcertion			< 0.001			< 0.001
Yes	0.584	0.681		0.211	0.256	
No	0.272	0.369		0.300	0.441	
Tumor size			< 0.001			< 0.001
≤ 1 cm	0.323	0.416		0.271	0.400	
1-2 cm	0.396	0.517		0.259	0.357	
2-3 cm	0.437	0.506		0.308	0.383	
3-4 cm	0.502	0.576		0.261	0.318	
4-5 cm	0.545	0.626		0.228	0.293	
≥ 5 cm	0.560	0.674		0.188	0.269	
Radiotion			< 0.001			0.006
No	0.382	0.479		0.273	0.378	
Yes	0.796	0.874		0.100	0.109	
Surgery of primary site			0.818			0.156
No	0.475	0.500		0.388	0.438	
Yes	0.409	0.507		0.258	0.357	

Table 1. In the whole cohort, 5.02% of patients were less than 29 years old, 8.91% were 30-39 years old, 16.47% were 40-49 years old, 22.41% were 50-59 years old, 21.20% were 60-69 years old, and 25.99% were above 70 years old. The median age at the time of diagnosis was 58.0 years in the whole cohort. The median follow-up length was 46.0 months (range, 2-119 months). By the end of last follow-up, 7515 (23.07%) patients of the entire population had died, including 4,865 from SCM and 2,650 from other causes.

Of the 22,101 patients in the training cohort, 21,721 (98.28%) were white and 12,253 (55.44%) were male. T3-T4 tumors accounted for 19.49% of all tumors, while positive lymph nodes and distant metastases accounted for 12.05% and 1.40%, respectively. Most tumors were predominantly noted on the limbs (45.72%) and trunk (34.62%), with less than 20% arising from genitals, head, and neck. The three most prevalent histologic subtypes were melanoma NOS (42.85%), superficial spreading melanoma (36.91%), and nodular melanomas (10.91%). The majority of melanomas were > 4-mm thick, with 3.3% patients having less than 1 mm thick. The majority of melanomas were Clark level II and III, with 6.57% tumors being of Clark level V. 3701 (16.75%) tumors had ulceration. The size of tumors in the majority of melanomas was ≤ 1 cm, with 1.8% of tumors having sizes between 4-5 cm. 387 (1.75%) and 21845 (98.84) patients received radiotherapy and surgery, respectively.

Prognostic analyzes of OS

The univariate analysis of sex, age at diagnosis, TNM stage, tumor location, histologic subtype, Breslow thickness, Clark level, tumor size, radiation, and surgery of primary site revealed that they were significantly associated with OS (**Table 2**). Based on multivariate analysis, age was the most significant prognostic factor for OS of patient ≥ 70 years old. Consistent with previous studies, men had poorer prognosis of OS than women [4]. Tumor size, TNM stage, and Clark level were significant independent predictors for OS. Other factors that were associated with poor OS are skin of genitals, tumor ulceration, and radiation. Compared to melanoma NOS histology, other histologic subtypes except for nodular melanoma were not associated with prognosis OS. Surgery was associated with improved OS.

Table 3. Five- and Ten-years cumulative incidences of death among patients in the training cohort

Variable	Cumulative Incidence of Death Resulting From Skin Melanoma			Cumulative Incidence of Death Resulting From Other Causes		
	3-y	5-y	P	3-y	5-y	P
All Patients	0.410	0.506		0.261	0.359	
Sex			< 0.001			0.016
Female	0.383	0.472		0.279	0.379	
Male	0.424	0.525		0.251	0.349	
Age at diagnosis, years			< 0.001			< 0.001
≤ 29	0.310	0.366		0.000	0.050	
30-39	0.496	0.665		0.059	0.095	
40-49	0.538	0.665		0.077	0.102	
50-59	0.595	0.759		0.148	0.208	
60-69	0.600	0.800		0.173	0.242	
≥ 70	0.655	0.845		0.358	0.489	
Race			< 0.001			0.673
White	0.403	0.499		0.264	0.364	
Black	0.667	0.756		0.156	0.200	
Other (American Indian/AK Native, Asian/Pacific Islander)	0.603	0.724		0.138	0.489	
TNM stage (AJCC 6th)						
T stage			< 0.001			< 0.001
T0	NA	NA		NA	NA	
T1	0.214	0.272		0.335	0.518	
T2	0.366	0.518		0.238	0.323	
T3	0.493	0.614		0.230	0.287	
T4	0.599	0.691		0.210	0.248	
N stage			< 0.001			< 0.001
N0	0.290	0.385		0.317	0.445	
N1	0.646	0.793		0.111	0.142	
N2	0.712	0.794		0.121	0.146	
N3	0.809	0.874		0.084	0.092	
NX	0.327	0.364		0.430	0.561	
M stage			< 0.001			0.008
M0	0.376	0.478		0.271	0.376	
M1	0.855	0.906		0.077	0.081	
MX	0.288	0.437		0.388	0. 485	
Tumor location			< 0.001			< 0.001
Skin of head and neck	0.371	0.461		0.308	0.408	
Skin of trunk	0.464	0.573		0.197	0.301	
Skin of limbs	0.393	0.484		0.277	0.373	
Skin of genitals	0.4790	0.592		0.265	0.286	
Histologic sbutype			< 0.001			< 0.001
Malignant melanoma, NOS	0.37	0.492		0.253	0.358	
Nodular melanoma	0.577	0.667		0.230	0.266	
Lentigo maligna melanoma	0.106	0.129		0.424	0.659	
Superficial spreading melanoma	0.266	0.389		0.289	0.436	
Acral lentiginous melanoma, malignant	0.594	0.729		0.135	0.188	
Desmoplastic melanoma, malignant	0.406	0.493		0.232	0.333	
Spindle cell melanoma, NOS	0.520	0.570		0.300	0.320	

Breslow thickness			< 0.001			< 0.001
< 1 mm	0.348	0.455		0.277	0.366	
1-2 mm	0.214	0.232		0.321	0.509	
2-3 mm	0.127	0.180		0.327	0.567	
3-4 mm	0.170	0.190		0.395	0.592	
> 4 mm	0.447	0.552		0.247	0.330	
Clark level			< 0.001			< 0.001
I	NA	NA		NA	NA	
II	0.103	0.141		0.376	0.604	
III	0.264	0.360		0.298	0.436	
IV	0.460	0.582		0.237	0.311	
V	0.630	0.712		0.202	0.234	
Tumor ulcertion			< 0.001			< 0.001
Yes	0.584	0.681		0.211	0.256	
No	0.272	0.369		0.300	0.441	
Tumor size			< 0.001			< 0.001
≤ 1 cm	0.323	0.416		0.271	0.400	
1-2 cm	0.396	0.517		0.259	0.357	
2-3 cm	0.437	0.506		0.308	0.383	
3-4 cm	0.502	0.576		0.261	0.318	
4-5 cm	0.545	0.626		0.228	0.293	
≥ 5 cm	0.560	0.674		0.188	0.269	
Radiotion			< 0.001			0.006
No	0.382	0.479		0.273	0.378	
Yes	0.796	0.874		0.100	0.109	
Surgery of primary site			0.818			0.156
No	0.475	0.500		0.388	0.438	
Yes	0.409	0.507		0.258	0.357	

SCM and competing risk analysis

According to the competing risk model, all factors, excluding surgery of primary site, were independent for SCM CSS ($P < 0.05$) (**Table 3**). At 3- and 5-years after diagnosis, the cumulative incidence of death resulting from skin melanoma in the training cohort were 0.410 and 0.506, respectively. The cumulative incidence of death from other causes at 3- and 5-years were 0.261, and 0.359, respectively. Estimates of death resulting from SCM and other causes of clinicopathological variables are shown in **Table 3**. Patients older than 70 years at the time of diagnosis had the highest cumulative incidence of death resulting from SCM (0.655/0.845 for 3/5 years). Male patients had the highest cumulative incidence of death resulting from skin melanoma (0.092/0.124 for 3/5 years). Black patients had highest cumulative incidence of death resulting from SCM, while White and "Other" (American Indian/AK Native, Asian/Pacific Islander) patients had lower cumulative incidence of death resulting from skin melanoma. The TNM stage also had a significant influence on the prognostic factors. Additionally, patients with skin of genitals and Acral lentiginous melanoma had higher cumulative incidence of death resulting from SCM ($P < 0.001$). Similarly, increasing Clark level and tumor size had higher cumulative incidence of death resulting from SCM. The CIF in different Breslow thickness groups showed a U-shaped trend, with thinness and thickness having poor prognosis, while the median Breslow thickness had the highest survival. Treatment with radiation decreased the cumulative incidence of death resulting from skin melanoma from 0.796/0.874 for 3/5 years to 0.382/0.479 for 3/5 years. There was no significant difference in the subgroup of surgery of primate site. All variables, excluding surgery of primate site,

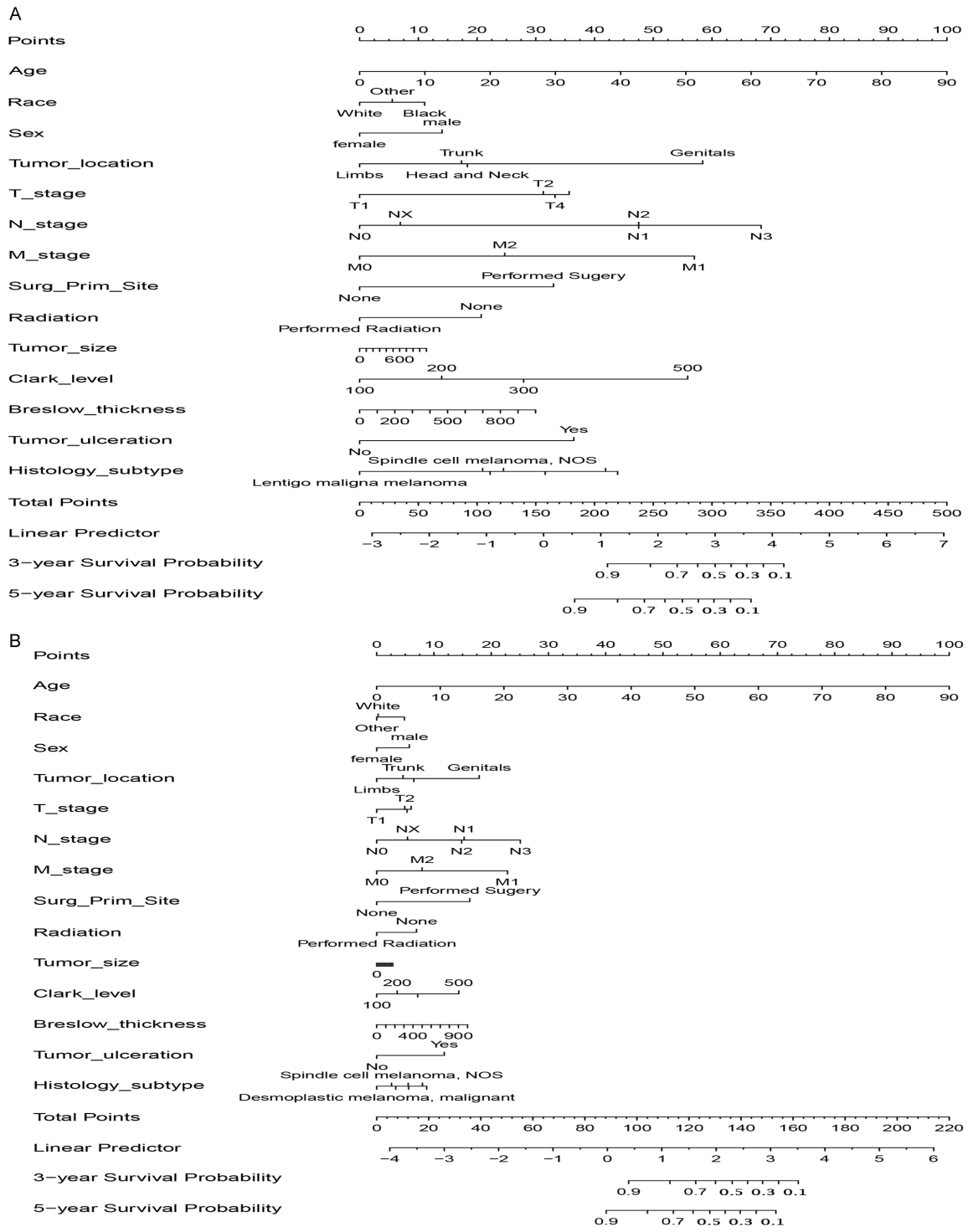

Figure 2. Nomograms for estimating 3- and 5-year survival. A. Overall survival (OS) and B. Cancer-specific survival (CSS) in patients with SCM.

were significantly correlated with cumulative incidence of death resulting from skin melanoma, and they were used to build the nomograms to predict the 3- and 5-year CSS. All variables that were significantly correlated with SCM were used to construct the nomograms to predict the 3- and 5-year probability of CSS and OS in SCM.

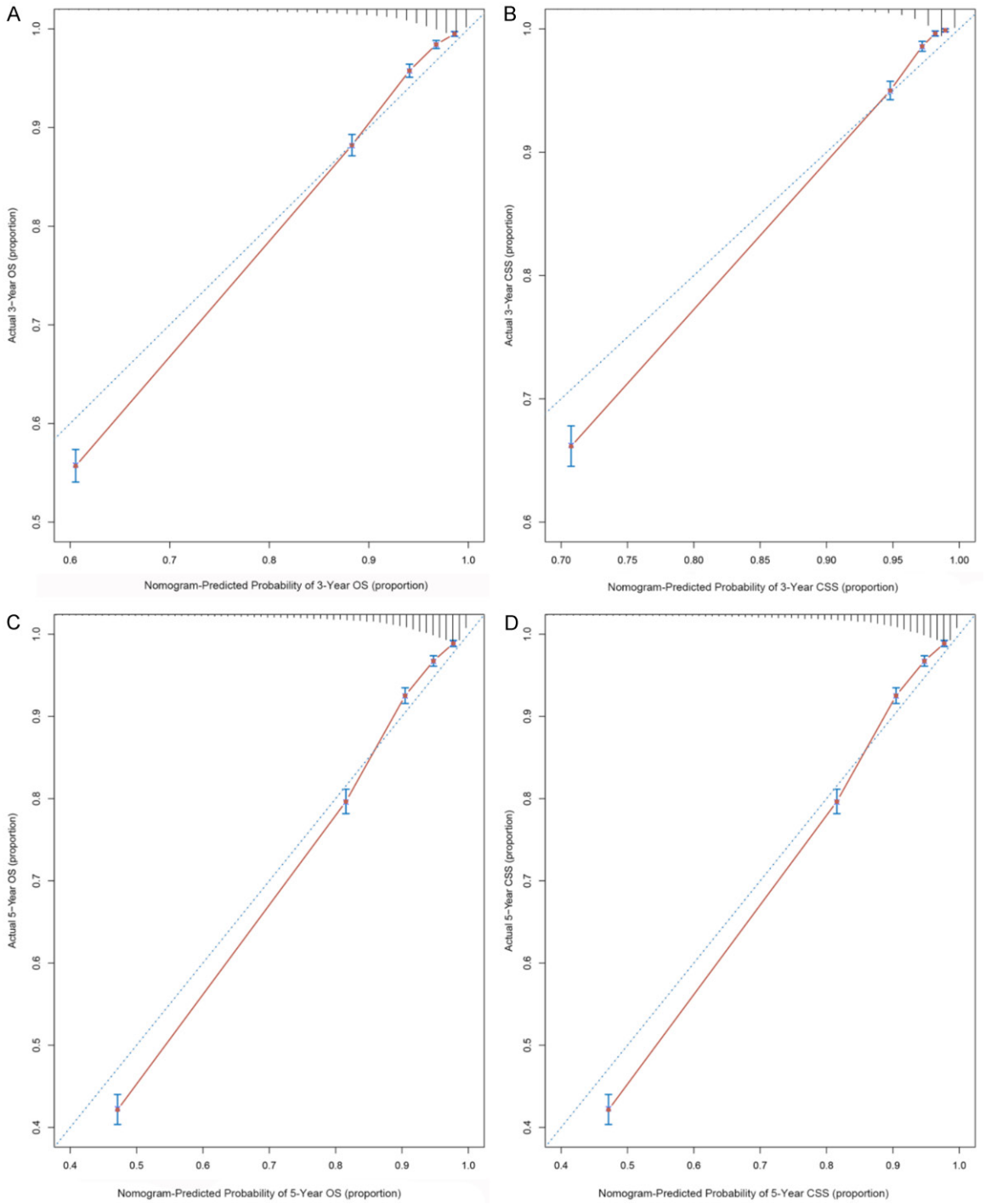

Figure 3. Internal calibration of the nomograms. (A) 3- and (C) 5-year overall survival (OS) calibration curves; (B) 3- and (D) 5-year cancer-specific survival (CSS) calibration curves.

Construction and validation of a prognostic nomogarm model

Many risk factors recognized by the Cox model were used to construct nomograms to predict the probability of OS and CSS in SCM in the training cohort (**Figure 2**). The age, race, sex, tumor site, tumor histology, TNM stage, Breslow thickness, Clark level, tumor ulceration, tumor size, radiotherapy, and surgery of primary site were included in the nomograms. The nomograms suggested that TNM stage, age at the

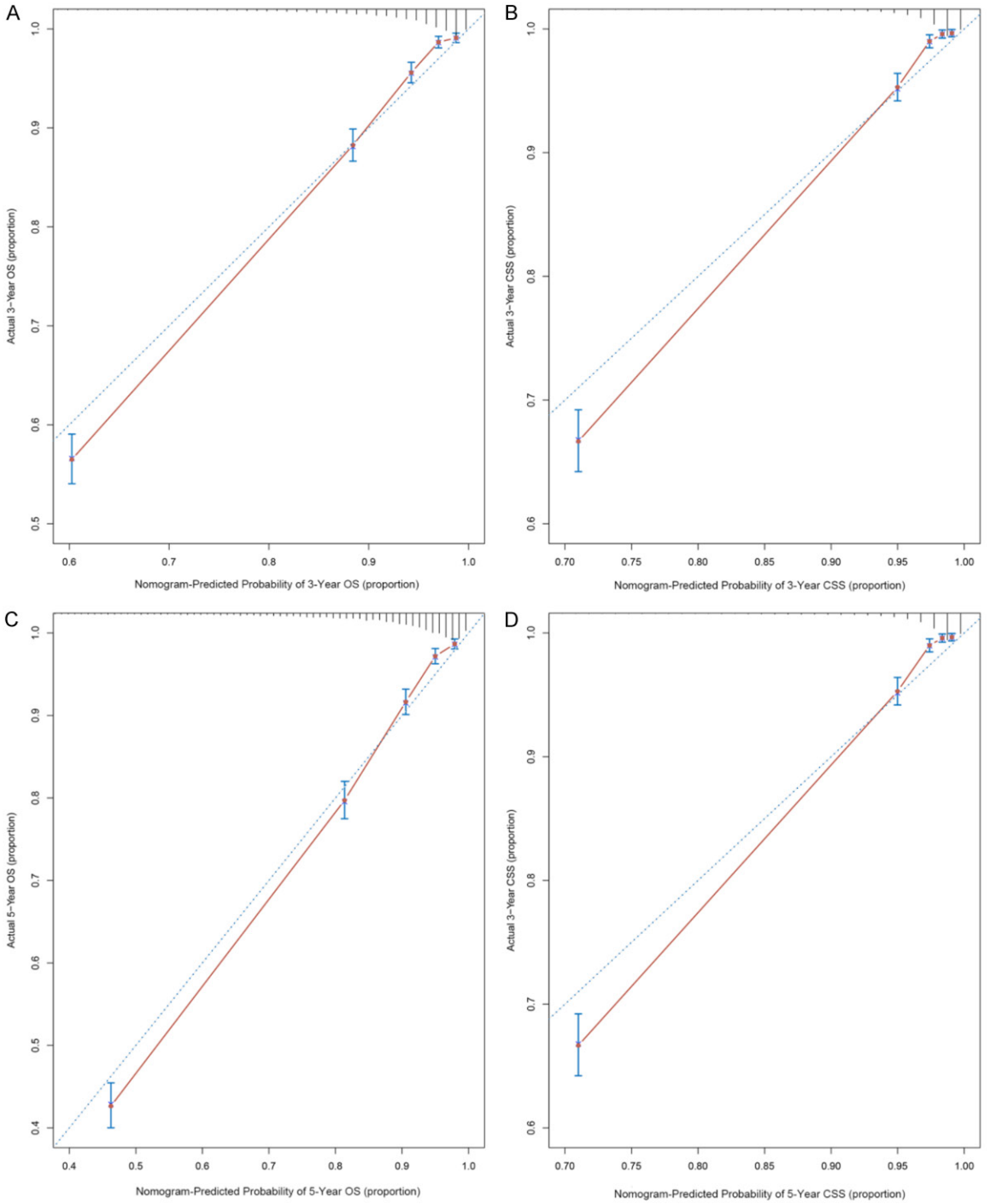

Figure 4. External calibration of the nomograms. (A) 3- and (C) 5-year overall survival (OS) calibration curves; (B) 3- and (D) 5-year cancer-specific survival (CSS) calibration curves.

time of diagnosis, and tumor location were the main influencing factors of prognosis, while tumor size had a low influence.

We performed both internal and external validation of nomograms using the bootstrap method. Internal validation in the training cohort showed that the nomograms were able to accurately predict the CSS with a C-index of 0.901 (95% CI = 0.895-0.907) and OS with a C-index of 0.860 (95% CI = 0.854-0.866). The calibration plots demonstrated an excellent agree-

Table 4. Prognostic score for OS and CSS in the Nomograms plot

Variables	OS	CSS
Sex		
Female	0.000	0.000
Male	6.878	22.548
Age at diagnosis,years		
Equation	1.111*Age	1.111*Age
Race		
White	0.000	0.000
Black	1.370	7.617
Other (American Indian/AK Native, Asian/Pacific Islander)	2.741	15.547
T stage		
T1	0.000	0.000
T2	3.514	22.934
T3	7.028	45.869
T4	10.542	68.803
N stage		
N0	0.000	0.000
N1	5.081	18.299
N2	10.163	36.599
N3	15.244	54.899
NX	20.326	73.199
M stage		
M0	0.000	0.000
M1	4.178	18.033
MX	8.356	36.067
Tumor location		
Skin of head and neck	6.468	16.232
Skin of trunk	4.312	10.821
Skin of limbs	2.156	5.411
Skin of genitals	0.000	0.000
Histologic sbutype		
Malignant melanoma, NOS	0.000	0.000
Nodular melanoma	5.345	18.948
Lentigo maligna melanoma	4.276	15.981
Superficial spreading melanoma	3.207	11.370
Acral lentiginous melanoma, malignant	2.318	7.581
Desmoplastic melanoma, malignant	1.069	3.792
Spindle cell melanoma, NOS	0.000	0.000
Breslow thickness		
Equation	0.014*Breslow thickness	0.014*Breslow thickness
Clark level		
II	0.000	0.000
III	4.8130	22.694
IV	9.626	45.388
V	19.252	90.777
Tumor ulcertion		
Yes	0.000	0.000
No	15.181	59.619

Tumor size		
Equation	0.001*tumor size	0.008*tumor size
Radiotion		
No	0.000	0.000
Yes	15.871	52.618
Surgery of primary site		
No	17.720	45.692
Yes	0.000	0.000

ment between the nomograms prediction and actual observation at the 3- and 5-year CSS rate and OS rate (**Figure 3**). External validation in the validation cohort indicated that the C-index was slightly lower: 0.904 (95% CI = 0.886-0.922) for CSS and 0.859 (95% CI = 0.841-0.877) for OS (**Figure 4**). This finding suggested that the established models were reasonably accurate.

The risk score developed from the nomograms model was calculated by the R "nomogramEx" package (**Table 4**). The TNM stage, the age at diagnosis, and tumor location had higher risk scores, while tumor size had a lower score.

Discussion

Skin cutaneous melanoma (SCM) is the most fatal type of cutaneous malignant tumors with great risk to develop into distant and lymph metastases [11, 12]. Its poor prognosis and clinical outcome are due to less effective therapeutic methods currently available. Therefore, a further understanding of the risk factors for SCM development is necessary to identify new early diagnostic factors and therapeutic targets. Prior studies have evaluated the survival difference among different anatomical sites and histological subtypes [13, 14]. Considering that other clinicopathological characteristics like age, race, sex, tumor site, tumor histology, TNM stage, Breslow thickness, Clark level, tumor ulceration, and tumor size are associated with SCM prognosis, they can used to predict the prognosis of SCM. Recently, a non-metastatic SCM study based on SEER database between 2004 to 2007 constructed nomograms, but Breslow thickness, Clark level, tumor ulceration, and tumor size were not included in the study, and the follow-up period was relatively short [15]. Using the SEER database, we screened for SCM patients between 2004 to 2013, and 14 clinicopathological characteristics (age, race, sex, tumor site, tumor histology, TNM stage, Breslow thickness, Clark level, tumor ulceration, tumor size, radiotherapy and surgery of primary site) were considered in this study. The SCM patients had significantly higher 3 and 5-year OS and CSS death probability of 0.410 and 0.506, respectively, and a nomogram was established to predict the 3- and 5-year CSS and OS based on the competing risk analysis.

Several clinicopathological characteristics were proven to be independent prognosis factors for both OS and CSS in the present study, including age, race, sex, tumor site, tumor histology, TNM stage, Breslow thickness, Clark level, tumor ulceration, tumor size, radiotherapy and surgery of primary site. We found that older SCM patients have a greater risk of melanoma-specific mortality and death due to other causes. SCM predominantly occurs in whites, with a slight male predominance. These results are consistent with those of previous studies [3, 16, 17]. With increase in tumor size, TNM stage, and Clark level, the hazard risk resulting from OS was increased, which indicates that these factors are poor independent predictors for OS. Other factors associated with poor OS were skin of genitals and tumor ulceration. Compared to melanoma NOS histology type, other histology subtypes, except for nodular melanoma, were not associated with OS prognosis. Surgery was associated with improved OS. Similar results were reported in a previous study [18]. Most patients did not receive radiotherapy. Interestingly, those that received radiotherapy had a poor prognosis, which indicated that more patients died of other causes of death in the multivariate analysis.

The log-rank test and Cox proportional hazards regression were used to screen for the independent prognosis factors of OS. However, the results obtained cannot be used to identify

prognostic variables of SCM because death from other causes was considered as a competing risk event. Therefore, a competing risk analysis was used to eliminate bias in the results. As reported in this study, the 3 and 5-year cumulative incidence of death resulting from SCM was 0.410 and 0.506, respectively. These findings indicate that more patients died due to SCM during the subsequent two years. These results are consistent with those reported in previous studies [13, 14]. Among these risk factors, age at diagnosis was an important prognostic factor. TNM stage, Breslow thickness, Clark level, and tumor size were also associated with increased CIF resulting from SCM death. Consistent with previous studies, gender-specific disparity in SCM was observed in which men had higher CIF value than women [16, 19]. The causes of gender difference in SCM remain unclear, but they may be attributed to estrogen [20, 21], pregnancy [22, 23], oral contraceptives [24], and hormone replacement therapy [25].

Both 3 and 5-year CSS of SCM patients who received radiotherapy (0.382 and 0.479, respectively) was lower than those who did not receive radiotherapy, while the CIF of death resulting from other causes was increased following radiotherapy. On the contrary, the 3 and 5-year other causes of death of SCM patients who received radiotherapy was higher compared to those who did not receive radiotherapy. Radiotherapy was associated with poor OS probability. This phenomenon indicates that radiotherapy might be associated with increased death from other causes. Interestingly, we found that the 3- and 5-year cause-specific death rates (0.409 and 0.507, respectively) of SCM patients who did not receive surgery of primary site were higher than those of SCM patients who died of other causes. The reason for this is not known.

The prognostic nomograms are based on the model-based prediction tool and incorporates clinical and pathological risk factors known to influence the outcome. To ensure accurate prediction of nomograms, the Cox's proportional hazards regression model was used to select the variables. The nomograms indicated that age at diagnosis, tumor size, and TNM stage have high predictive capability for the prognosis of patients with SCM. In the nomograms plot, the hazard ratios of OS and CSS in different age groups produced a linear association, with older patients having the lowest survival rate. Other clinical and pathological factors including race, sex, tumor site, tumor histology, Breslow thickness, Clark level, tumor ulceration, radiotherapy, and surgery of primary site were also associated with increased SCM mortality.

The present study has the following strengths: (1) the key strength of this study is that it is a large cohort size based on the high quality SEER database. The conclusions made from the population-based study are more reliable than those of a single study because a large sample size possesses sufficient power. In addition, a large sample size ensures high accuracy in designing prediction models. (2) the Cox's proportional hazards regression model and competing risk analysis were used to screen the variables, all nomograms C- index were more than 0.7 and a consistency between the calibration curve and 45-degree perfect match straight lines was observed, which suggestes that the established model has high accuracy for predicting OS and CSS.

Despite these strengths, some limitations in this study should be considered. First, the study was based on a retrospective design which may have introduced some biases, such as recall bias and selective bias. Therefore, these results need to be further validated in a prospective cohort before they can be applied in clinics. Second, information regarding adjuvant therapy such as chemotherapy, endocrine therapy, and targeted therapy, which are important prognostic risk factors for SCM [26, 27], is not available in the SEER database. Without such information, the nomograms might yield some bias. Finally, external validation of the nomograms was not performed in our study.

In summary, we developed nomograms to estimate the probability of OS and CSS of SCM based on a population-based cohort with long-term follow-up. The constructed nomograms can help clinicians to predict individual prognosis of SCM patients, thus facilitating individualized treatment strategies.

Acknowledgements

The study was supported by the National Science Foundation of China (No. 81700972), Zhejiang Provincial Natural Science Founda-

tion of China (LGF18H140004) and Joint fund project of Guizhou science and Technology Department (No. [2014] 7026).

Disclosure of conflict of interest

None.

Address correspondence to: Lingkai Su and Hui Chen, Affiliated Hospital of Stomatology, Medical College, Zhejiang University, Hangzhou, P. R. China. Tel: +8618627123129; E-mail: 0016730@zju.edu.cn (LKS); Tel: +8613588170380; E-mail: huiczju-66@zju.edu.cn (HC)

References

[1] Purdue MP, Freeman LE, Anderson WF and Tucker MA. Recent trends in incidence of cutaneous melanoma among US Caucasian young adults. J Invest Dermatol 2008; 128: 2905-2908.

[2] Jemal A, Saraiya M, Patel P, Cherala SS, Barnholtz-Sloan J, Kim J, Wiggins CL and Wingo PA. Recent trends in cutaneous melanoma incidence and death rates in the united states, 1992-2006. J Am Acad Dermatol 2011; 65: S17-25, e11-13.

[3] Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[4] Peterson M, Albertini MR and Remington P. Incidence, survival, and mortality of malignant cutaneous melanoma in wisconsin, 1995-2011. WMJ 2015; 114: 196-201.

[5] Insinga RP, Reither EN, Remington PL and Stephenson-Vine L. Trends in malignant melanoma incidence and mortality in wisconsin, 1979-1997. WMJ 2001; 100: 27-31.

[6] Zeng C, Wen W, Morgans AK, Pao W, Shu XO and Zheng W. Disparities by race, age, and sex in the improvement of survival for major cancers: results from the national cancer institute surveillance, epidemiology, and end results (seer) program in the united states, 1990 to 2010. JAMA Oncol 2015; 1: 88-96.

[7] Hankey BF, Ries LA and Edwards BK. The surveillance, epidemiology, and end results program: a national resource. Cancer Epidemiol Biomarkers Prev 1999; 8: 1117-1121.

[8] He P, Eriksson F, Scheike TH and Zhang MJ. A proportional hazards regression model for the sub-distribution with covariates adjusted censoring weight for competing risks data. Scand Stat Theory Appl 2016; 43: 103-122.

[9] Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988; 1141-1154.

[10] Fine JP and Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94: 496-509.

[11] Watson M, Geller AC, Tucker MA, Guy GP Jr and Weinstock MA. Melanoma burden and recent trends among non-Hispanic whites aged 15-49years, United States. Prev Med 2016; 91: 294-298.

[12] White WL and Hitchcock MG. Dying dogma: the pathological diagnosis of epidermotropic metastatic malignant melanoma. Semin Diagn Pathol 1998; 15: 176-188.

[13] Tseng WH and Martinez SR. Tumor location predicts survival in cutaneous head and neck melanoma. J Surg Res 2011; 167: 192-198.

[14] Jethanamest D, Vila PM, Sikora AG and Morris LG. Predictors of survival in mucosal melanoma of the head and neck. Ann Surg Oncol 2011; 18: 2748-2756.

[15] Shen W, Sakamoto N and Yang L. Melanoma-specific mortality and competing mortality in patients with non-metastatic malignant melanoma: a population-based analysis. BMC Cancer 2016; 16: 413.

[16] Roh MR, Eliades P, Gupta S, Grant-Kels JM and Tsao H. Cutaneous melanoma in women. Int J Womens Dermatol 2015; 1: 21-25.

[17] Siegel R, Ma J, Zou Z and Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[18] Raigani S, Cohen S and Boland GM. The role of surgery for melanoma in an era of effective systemic therapy. Curr Oncol Rep 2017; 19: 17.

[19] Tremblay GB, Tremblay A, Copeland NG, Gilbert DJ, Jenkins NA, Labrie F and Giguere V. Cloning, chromosomal localization, and functional analysis of the murine estrogen receptor beta. Mol Endocrinol 1997; 11: 353-365.

[20] Hall G and Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. J Am Acad Dermatol 2005; 53: 555-568; quiz 569-572.

[21] Ohata C, Tadokoro T and Itami S. Expression of estrogen receptor beta in normal skin, melanocytic nevi and malignant melanomas. J Dermatol 2008; 35: 215-221.

[22] Lens M. Melanoma during pregnancy: epidemiology, diagnosis, staging, clinical picture. Recent Results Cancer Res 2008; 178: 165-174.

[23] Daryanani D, Plukker JT, De Hullu JA, Kuiper H, Nap RE and Hoekstra HJ. Pregnancy and early-stage melanoma. Cancer 2003; 97: 2248-2253.

[24] Gefeller O, Hassan K and Wille L. Cutaneous malignant melanoma in women and the role of oral contraceptives. Br J Dermatol 1998; 138: 122-124.

[25] Persson I, Yuen J, Bergkvist L and Schairer C. Cancer incidence and mortality in women re-

ceiving estrogen and estrogen-progestin replacement therapy--long-term follow-up of a Swedish cohort. Int J Cancer 1996; 67: 327-332.

[26] Aguado-Romeo MJ, Benot-Lopez S and Romero-Tabares A. Electrochemotherapy for the treatment of unresectable locoregionally advanced cutaneous melanoma: a systematic review. Actas Dermosifiliogr 2017; 108: 91-97.

[27] Stoica A, Hoffman M, Marta L and Voiculetz N. Estradiol and progesterone receptors in human cutaneous melanoma. Neoplasma 1991; 38: 137-145.