Comparing the Characteristics and Predicting the Survival of Head and Neck Melanoma versus Body Melanoma: A Population-based Study

Yuxin Ding

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Runyi Jiang

Spinal Tumor Center, Department of Orthopaedic Oncology, Changzheng Hospital, Second Military Medical University, Shanghai, 200003

Yuhong Chen

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Jing Jing

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Xiaoshuang Yang

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Xianjie Wu

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Xiaoyang Zhang

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Jiali Xu

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Piaopiao Xu

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

ShuChen LiuHuang

China Academy of Art, Hangzhou, 310000

Zhongfa Lu (✉ lzf@skin.zju.edu.cn)

Department of Dermatology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China, No. 88, Jiefang Road, Hangzhou 310009

Research Article

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Abstract

Background: Previous studies have reported poorer survival in head and neck melanoma (HNM) than in body melanoma (BM). Individualized tools to predict the prognosis for patients with HNM or BM remain insufficient. We aim to compare the characteristics of HNM and BM, and establish and validate the nomograms for predicting the 3-, 5- and 10-year survival of patients with HNM or BM.

Methods: We studied patients with HNM or BM from 2004 to 2015 in the Surveillance, Epidemiology, and End Results (SEER) database. The HNM group and BM group were randomly divided into training and validation cohorts. We performed the Kaplan-Meier method for survival analysis, and used multivariate Cox proportional hazards models to identify independent prognostic factors. Nomograms for HNM patients or BM patients were developed via the rms package, and were measured by the concordance index (C-index), the area under the receiver operator characteristic (ROC) curve (AUC) and calibration plots.

Results: Of 70605 patients acquired, 21% (n=15071) had HNM and 79% (n=55534) had BM. The HNM group contained more older patients, male patients, and lentigo maligna melanoma, and more frequently had thicker tumors and metastases than the BM group. The 5-year CSS and OS rates were $88.1 \pm 0.3\%$ and $74.4 \pm 0.4\%$ in the HNM group and $92.5 \pm 0.1\%$ and $85.8 \pm 0.2\%$ in the BM group, respectively. Eight independent prognostic factors (age, sex, histology, thickness, ulceration, stage, metastases, and surgery) were identified to construct nomograms for HNM patients or BM patients. The performance of the nomograms were excellent: the C-index of the CSS prediction for HNM patients and BM patients in the training cohort were 0.839 and 0.895, respectively; in the validation cohort, they were 0.848 and 0.888, respectively; the AUCs for the 3-, 5- and 10-year CSS rates of HNM were 0.871, 0.865 and 0.854 (training), and 0.881, 0.879 and 0.861 (validation), respectively; of BM, the AUCs were 0.924, 0.918 and 0.901 (training) and 0.916, 0.908 and 0.893 (validation), respectively; and the calibration plots showed great consistency.

Conclusions: The characteristics of HNM and BM are heterogeneous, and we constructed and validated specific nomograms as practical prognostic tools for patients with HNM or BM.

1 Background

Worldwide, cutaneous melanoma is an important public health problem and accounts for 1.7% of all newly diagnosed primary malignant tumors annually[1]. In the United States, the incidence of cutaneous melanoma continues to rise, and the 5-year relative survival rate is 92% (2009–2015)[2]. Many studies have reported that anatomic location is an important prognostic factor for primary cutaneous melanoma[3–5], and head and neck melanoma (HNM) should be treated differently from melanoma in other regions (body melanoma, BM) [6–9]. The head and neck areas are more likely to be exposed to chronic and continued sun exposure, while other body areas usually receive intermittent UV radiation[10, 11]. When considering the cancer density, cutaneous melanoma occurs more frequently in the head and neck regions than in the trunk and extremity regions[7–9]. In addition, many studies have reported poorer survival in HNM[12–14]. Therefore, a further understanding of the characteristics and prognostic factors of HNM and BM is necessary to help clinical management.

To date, limited studies have compared the clinical features of HNM and BM patients based on a large population[9, 14, 15], and few have compared the prognostic factors of the two subsites[16]. Although several studies estimated that some variables, such as age, sex, histology and thickness, were independent prognostic factors for HNM[15, 17, 18], no integrated tool that utilizes all available information to comprehensively predict the survival rate of HNM patients has been developed. A nomogram is a widely used graphical depiction of a predictive tool that can provide the overall probability of a specific outcome for any patient[19, 20]. Nomograms can integrate all sorts of factors to estimate tumor prognosis and have been confirmed to be a reliable instrument in numerous survival analysis studies[21, 22]. Consequently, we performed a population-based study to compare the clinicopathological characteristics and treatments of HNM and BM and to identify independent prognostic factors of the two subgroups. We aimed to establish and validate the nomograms for predicting the 3-, 5- and 10-year survival of patients with HNM or BM.

2 Methods

2.1 Patient selection

The information of eligible patients from 2004 to 2015 was obtained using SEER*Stat (version 8.3.8) from the Surveillance, Epidemiology, and End Results (SEER) database. In general, extracting SEER data does not require informed patient consent, and the SEER database does not provide case-identifying information. As a consequence, approval from the institutional review board is not required.

In this study, the inclusion criteria were as follows: 1) patients had a confirmed diagnosis of malignant cutaneous melanoma with ICD-O-3/WHO 2008 morphology codes 8721–8723, 8726–8728, 8730, 8740–8746, 8760–8761, 8770–8774, 8780 and 8790; 2) the codes of the primary site were C440–C447; 3) patients acquired a diagnosis with a living status; and 4) patients had active follow-up. The exclusion criteria were as follows: 1) clinical diagnosis without pathological reports; 2) acquired diagnosis from autopsy or death certificate only; and 3) unknown survival months. Fifteen variables were extracted from the SEER program, including age, sex, race, histology, anatomic site, thickness, ulceration, stage, metastases, primary site surgery, radiation, chemotherapy, survival time, overall survival (OS) status and cancer-specific survival (CSS) status. We excluded patients who did not have complete information on all the above variables. The stage in the SEER program referred to the stage of lymph nodes, including localized, regional and distant lymph nodes.

CSS was defined as the duration from the first day of follow-up to the day of death due to malignant cutaneous melanoma or the day of the last follow-up, while OS was defined as the time from the first day of follow-up to death from any cause or the end of the follow-up. Patients whose OS was recorded as dead but had 0 survival months in SEER were assigned a survival time of 0.5 months for analysis, while patients alive at follow-up with 0 survival months were excluded. Patients with anatomic site codes C440- Skin of lip, C441- Eyelid, C442- External ear, C443- Skin other/unspecific parts of face, or C444- Skin of scalp and neck were assigned to the HNM group, while those whose site was coded as C445- Skin of trunk, C446- Skin of upper limb and shoulder, or C447- Skin of lower limb and hip were assigned to the BM group.

Ultimately, a total of 70605 malignant cutaneous melanoma patients (15071 HNM patients and 55534 BM patients) were acquired for further analysis. The patient selection workflow is shown in Fig. 1.

2.2 Statistical analysis

Qualitative data are described as numbers and percentages, and quantitative data are described as means with standard deviations (SDs) and ranges. X-tile software (Yale University, New Haven, CT, USA) was employed to define the optimal cutoff values of continuous variables. X-tile software divided age into three subgroups for all possible divisions and selected the optimal cutoff value based on the highest chi-square value calculated by Kaplan-Meier survival analysis and the log-rank test. According to CSS, the optimal cutoff values for age were subdivided into ≤ 58 , 59–78 and ≥ 79 years, while based on OS, the optimal cutoff points were ≤ 63 , 64–79, and ≥ 80 years (Fig. 1). Melanoma thickness was classified into five subsets based on the American Joint Committee on Cancer (AJCC) staging system and the thin melanoma study (< 0.6 mm, 0.6–1.0 mm, 1.01–2.0 mm, 2.01–4.0 mm, and > 4.0 mm)[23].

For nomogram construction and validation, the HNM group and BM group were randomly divided into training and validation cohorts (split ratio: 7:3). Chi-square analysis or Fisher's exact test was performed to compare the baseline characteristics between the HNM group and BM group and to calculate the associations between the training cohort and the validation cohort. $P < 0.05$ was considered significant.

In the univariate analysis, the Kaplan-Meier method and the log-rank test were conducted to determine significant prognostic factors in the training cohort for CSS or OS by SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Variables with $p < 0.1$ were included in the multivariate Cox proportional hazards model to determine the independent prognostic factors ($p < 0.05$). Furthermore, corresponding hazard ratios were calculated. GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA) was used to create survival analysis curves for the independent prognostic factors. Notably, as specific information for radiotherapy and chemotherapy was not provided in the SEER database, we did not conduct survival analysis for the two factors.

2.3 Nomogram construction and validation

In the HNM group and BM group, nomograms based on the results of the Cox regression model were developed for the 3-year, 5-year and 10-year CSS rates via the rms package in R (version 4.0.1). Predictive prognostic nomograms for OS were also constructed for the two groups. The performance and predictive value of the nomograms were measured by the concordance index (C-index) and the area under the receiver operator characteristic (ROC) curve (AUC). In addition, calibration plots were used to assess the prediction accuracy of the nomograms by comparing the predicted values with the actual outcomes.

3 Results

3.1 Comparing the characteristics of head and neck melanoma versus body melanoma

A total of 70605 eligible patients diagnosed with malignant cutaneous melanoma from 2004 to 2015 were evaluated in this study, and the total population was divided into an HNM group and a BM group according to the anatomic site of the tumor.

The comparison of the two groups are summarized in table 1. The HNM cohort contained 15071 (21%) patients, and the BM cohort contained 55534 (79%) patients. Compared with the BM group, the HNM group contained more older patients (mean age 64.6 vs. 57.2 years) and male patients (72.4% vs. 52.3%). Superficial spreading melanoma (SSM) was the most common histological type in both groups, but lentigo maligna melanoma (LMM) was much more frequent in the HNM group than in the BM group (31.8% vs. 6.6%). HNM patients were diagnosed at a thicker stage, more frequently had metastases and were more often treated with radiation than BM patients. The mean survival time was 60.59 months in the HNM group and 67.76 months in the BM group. The 5-year CSS and OS rates were $88.1 \pm 0.3\%$ and $74.4 \pm 0.4\%$ in the HNM group and $92.5 \pm 0.1\%$ and $85.8 \pm 0.2\%$ in the BM group, respectively. In addition, the Kaplan-Meier curves showed that the prognosis of patients with BM was better than that of patients with HNM (Fig. 2).

HNM = head and neck melanoma; BM = body melanoma.

All HNM patients were randomly divided into training ($n = 10551$) and validation ($n = 4520$) cohorts. Using the same method, 38876 BM patients were assigned to the training cohort, and 16658 BM patients were assigned to the validation cohort. Tables 2 shows that there were no significant differences between the training and validation cohorts.

Table 2
The characteristics of patients between the training cohort and the validation cohort

The characteristics of patients between the training cohort and the validation cohort						
the HNM group			the BM group			
	Training cohort (%)	Validation cohort (%)	P value	Training cohort (%)	Validation cohort (%)	P value
Total	10551(70.0)	4520(30.0)		38876(70.0)	16658(30.0)	
Age			0.21			0.748
<=58	3349 (31.7)	1467 (32.5)		20275 (52.2)	8666 (52.0)	
59–78	4885 (46.3)	2023 (44.8)		14790 (38.0)	6324 (38.0)	
>=79	2317 (22.0)	1030 (22.8)		3811 (9.8)	1668 (10.0)	
Sex			0.62			0.836
Male	7653 (72.5)	3260 (72.1)		20359 (52.4)	8707 (52.3)	
Female	2898 (27.5)	1260 (27.9)		18517 (47.6)	7951 (47.7)	
Race			0.911			0.31
White	10452 (99.1)	4476 (99.0)		38267 (98.4)	16417 (98.6)	
^a Others	99 (0.9)	44 (1.0)		609 (1.6)	241 (1.4)	
Histology			0.31			0.067
NM	1680 (15.9)	672 (14.9)		5448 (14.0)	2457 (14.7)	
LMM	3328 (31.5)	1470 (32.5)		2589 (6.7)	1049 (6.3)	
SMM	4306 (40.8)	1862 (41.2)		27177 (69.9)	11571 (69.5)	
^b Other Melanoma	1237 (11.7)	516 (11.4)		3662 (9.4)	1581 (9.5)	
Thickness			0.38			0.013
< 0.6mm	4691 (44.5)	2026 (44.8)		17866 (46.0)	7435 (44.6)	
0.6-1.0mm	1814 (17.2)	787 (17.4)		8410 (21.6)	3588 (21.5)	
1.01-2.0mm	1666 (15.8)	728 (16.1)		6073 (15.6)	2673 (16.0)	
2.01-4.0mm	1268 (12.0)	491 (10.9)		3666 (9.4)	1671 (10.0)	
> 4.0mm	1112 (10.5)	488 (10.8)		2861 (7.4)	1291 (7.8)	
Ulceration			0.459			0.43
No	8841 (83.8)	3810 (84.3)		33040 (85.0)	14113 (84.7)	
Yes	1710 (16.2)	710 (15.7)		5836 (15.0)	2545 (15.3)	

the HNM group			the BM group	
Stage		0.795		0.159
Localized	9051 (85.8)	3893 (86.1)	34591 (89.0)	14729 (88.4)
Regional	1320 (12.5)	548 (12.1)	3731 (9.6)	1677 (10.1)
Distant	180 (1.7)	79 (1.7)	554 (1.4)	252 (1.5)
Metastases		0.937		0.251
No	10405 (98.6)	4456 (98.6)	38501 (99.0)	16479 (98.9)
Yes	146 (1.4)	64 (1.4)	375 (1.0)	179 (1.1)
Surgery		0.545		0.591
No	245 (2.3)	97 (2.1)	773 (2.0)	319 (1.9)
Yes	10306 (97.7)	4423 (97.9)	38103 (98.0)	16339 (98.1)

3.2 Identification of prognostic factors

The univariate analysis revealed that nine variables (age, sex, race, histology, thickness, ulceration, stage, metastases, and surgery) were potential clinical determinants of CSS in the HNM group. In addition, the same nine significant factors were identified in the BM group. Table 3 shows the 5-year CSS and OS rates for the subgroups. The factors above were further identified by multivariate Cox proportional hazards models, in which the results revealed that eight variables (age, sex, histology, thickness, ulceration, stage, metastases, and surgery) were independent prognostic factors in the HNM training cohort, and the same eight independent prognostic factors were identified in the BM training cohort (Table 4). The survival analysis curves for the identified independent factors of CSS for the HNM group and the BM group are illustrated in Fig. 3. The survival analysis curves for OS in the two groups are shown in Fig. S1.

Table 3
Univariate analysis of factors affecting cancer-specific and overall survival

Factors	5-year Cancer-Specific Survival rate				5-year Overall Survival rate			
	(% , mean $\pm$ SD)				(% , mean $\pm$ SD)			
	HNM	P value	BM	P value	HNM	P value	BM	P value
Age (CSS/OS)		0.001		0.001		0.001		0.001
<=58 / <=63	91.5 $\pm$ 0.5		94.8 $\pm$ 0.2		88.5 $\pm$ 0.5		92.7 $\pm$ 0.2	
59–78 / 64–79	88.3 $\pm$ 0.5		91.6 $\pm$ 0.3		75.7 $\pm$ 0.8		81.7 $\pm$ 0.4	
>=79 / >=80	80.2 $\pm$ 1.1		82.6 $\pm$ 0.7		41.0 $\pm$ 1.2		48.8 $\pm$ 1.0	
Sex		0.001		0.001		0.001		0.001
Male	86.9 $\pm$ 0.4		90.5 $\pm$ 0.2		73.3 $\pm$ 0.6		82.7 $\pm$ 0.3	
Female	90.6 $\pm$ 0.6		94.8 $\pm$ 0.2		77.2 $\pm$ 0.9		89.7 $\pm$ 0.2	
Race		0.011		0.001		0.366		0.001
White	87.9 $\pm$ 0.4		92.8 $\pm$ 0.1		77.4 $\pm$ 0.5		86.2 $\pm$ 0.2	
^a Others	82.3 $\pm$ 4.7		80.2 $\pm$ 1.8		71.5 $\pm$ 5.4		73.5 $\pm$ 2.0	
Histology		0.001		0.001		0.001		0.001
NM	67.7 $\pm$ 1.4		72.4 $\pm$ 0.7		53.7 $\pm$ 1.4		62.1 $\pm$ 0.7	
LMM	96.1 $\pm$ 0.4		97.7 $\pm$ 0.3		80.2 $\pm$ 0.8		86.2 $\pm$ 0.8	
SMM	91.0 $\pm$ 0.5		96.8 $\pm$ 0.1		79.9 $\pm$ 0.7		91.9 $\pm$ 0.2	

HNM, head and neck melanoma; BM, body melanoma.

SD, standard deviation; CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.

^a Others = black, Asian or pacific islander, American indian/Alaska native.

^b Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722–8723, 8730, 8740–8741, 8744–8746, 8761, 8770–8774, 8780.

Factors	5-year Cancer-Specific Survival rate				5-year Overall Survival rate			
	(%, mean $\pm$ SD)				(%, mean $\pm$ SD)			
	HNM	P value	BM	P value	HNM	P value	BM	P value
^b Other Melanoma	81.9 $\pm$ 1.3		86.7 $\pm$ 0.6		68.3 $\pm$ 1.5		78.6 $\pm$ 0.7	
Thickness		0.001		0.001		0.001		0.001
< 0.6mm	96.8 $\pm$ 0.3		98.6 $\pm$ 0.1		84.1 $\pm$ 0.6		93.3 $\pm$ 0.2	
0.6-1.0mm	93.2 $\pm$ 0.7		97.4 $\pm$ 0.2		79.6 $\pm$ 1.1		92.2 $\pm$ 0.3	
1.01-2.0mm	85.9 $\pm$ 1.0		91.6 $\pm$ 0.4		72.8 $\pm$ 1.2		85.6 $\pm$ 0.5	
2.01-4.0mm	73.2 $\pm$ 1.5		78.5 $\pm$ 0.8		58.8 $\pm$ 1.6		68.2 $\pm$ 0.9	
> 4.0mm	58.6 $\pm$ 1.8		57.5 $\pm$ 1.1		45.1 $\pm$ 1.7		46.0 $\pm$ 1.1	
Ulceration		0.001		0.001		0.001		0.001
No	92.2 $\pm$ 0.3		96.5 $\pm$ 0.1		79.1 $\pm$ 0.5		90.9 $\pm$ 0.2	
Yes	64.3 $\pm$ 1.4		69.1 $\pm$ 0.7		50.3 $\pm$ 1.4		58.5 $\pm$ 0.7	
Stage		0.001		0.001		0.001		0.001
Localized	92.7 $\pm$ 0.3		96.4 $\pm$ 0.1		78.7 $\pm$ 0.5		90.0 $\pm$ 0.2	
Regional	61.7 $\pm$ 1.6		65.5 $\pm$ 0.9		51.0 $\pm$ 1.6		58.2 $\pm$ 0.9	
Distant	36.6 $\pm$ 4.2		30.5 $\pm$ 2.4		28.4 $\pm$ 3.8		26.0 $\pm$ 2.3	
Metastases		0.001		0.001		0.001		0.001

HNM, head and neck melanoma; BM, body melanoma.

SD, standard deviation; CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.

^a Others = black, Asian or pacific islander, American indian/Alaska native.

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Factors	5-year Cancer-Specific Survival rate				5-year Overall Survival rate			
	(%, mean $\pm$ SD)				(%, mean $\pm$ SD)			
	HNM	P value	BM	P value	HNM	P value	BM	P value
No	88.7 $\pm$ 0.4		93.2 $\pm$ 0.1		75.1 $\pm$ 0.5		86.7 $\pm$ 0.2	
Yes	30.1 $\pm$ 4.5		20.3 $\pm$ 2.4		23.8 $\pm$ 4.2		17.6 $\pm$ 2.2	
Surgery		0.002		0.061		0.001		0.001
No	82.0 $\pm$ 3.0		91.6 $\pm$ 1.2		60.8 $\pm$ 3.8		80.7 $\pm$ 1.7	
Yes	88.0 $\pm$ 0.4		92.6 $\pm$ 0.2		74.7 $\pm$ 0.5		86.1 $\pm$ 0.2	
HNM, head and neck melanoma; BM, body melanoma.								
SD, standard deviation; CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.								
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Table 4
Multivariate analysis of factors affecting cancer-specific and overall survival

Factors	Cancer specific survival				Overall survival			
	HR (95% CI)				HR (95% CI)			
	HNM	p value	BM	p value	HNM	p value	BM	p value
Age (CSS/OS)								
<=58 / <=63	Reference		Reference		Reference		Reference	
59–78 / 64–79	1.4 (1.213–1.615)	< 0.001	1.402 (1.290–1.523)	< 0.001	2.571 (2.319–2.850)	< 0.001	2.743 (2.583–2.913)	< 0.001
>=79 / >=80	2.219 (1.892–2.602)	< 0.001	2.487 (2.237–2.765)	< 0.001	7.668 (6.918–8.498)	< 0.001	8.028 (7.516–8.575)	< 0.001
Sex								
Male	Reference		Reference		Reference		Reference	
Female	0.789 (0.686–0.908)	0.001	0.694 (0.642–0.750)	< 0.001	0.854 (0.784–0.930)	< 0.001	0.663 (0.629–0.698)	< 0.001
Histology								
NM	Reference		Reference		Reference		Reference	
LMM	0.534 (0.429–0.665)	< 0.001	0.557 (0.421–0.737)	< 0.001	0.794 (0.700–0.901)	< 0.001	0.984 (0.876–1.106)	0.787
SMM	0.834 (0.712–0.978)	0.025	0.611 (0.552–0.675)	< 0.001	0.851 (0.760–0.953)	0.005	0.723 (0.672–0.777)	< 0.001
^a Other Melanoma	0.606 (0.512–0.718)	< 0.001	0.812 (0.731–0.902)	< 0.001	0.655 (0.579–0.739)	< 0.001	0.811 (0.748–0.878)	< 0.001
Thickness								
< 0.6mm	Reference		Reference		Reference		Reference	
HNM, head and neck melanoma; BM, body melanoma.								
CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.								
^a Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722–8723, 8730, 8740–8741, 8744–8746, 8761, 8770–8774, 8780.								

Factors	Cancer specific survival				Overall survival			
	HR (95% CI)				HR (95% CI)			
	HNM	p value	BM	p value	HNM	p value	BM	p value
0.6-1.0mm	1.845 (1.446–2.354)	< 0.001	1.802 (1.520–2.137)	< 0.001	1.232 (1.093–1.389)	0.001	1.159 (1.066–1.259)	0.001
1.01-2.0mm	3.285 (2.643–4.082)	< 0.001	3.171 (2.718–3.698)	< 0.001	1.557 (1.383–1.753)	< 0.001	1.443 (1.327–1.569)	< 0.001
2.01-4.0mm	3.942 (3.139–4.951)	< 0.001	4.328 (3.683–5.086)	< 0.001	1.767 (1.551–2.014)	< 0.001	1.951 (1.780–2.140)	< 0.001
> 4.0mm	4.403 (3.428–5.655)	< 0.001	5.535 (4.672–6.558)	< 0.001	2.078 (1.787–2.417)	< 0.001	2.513 (2.270–2.781)	< 0.001
Ulceration								
No	Reference		Reference		Reference		Reference	
Yes	1.843 (1.615–2.103)	< 0.001	2.235 (2.045–2.443)	< 0.001	1.472 (1.340–1.618)	< 0.001	1.778 (1.668–1.895)	< 0.001
Stage								
Localized	Reference		Reference		Reference		Reference	
Regional	2.547 (2.196–2.954)	< 0.001	3.203 (2.923–3.509)	< 0.001	1.677 (1.501–1.873)	< 0.001	2.049 (1.913–2.195)	< 0.001
Distant	3.686 (2.015–6.744)	< 0.001	5.287 (4.097–6.824)	< 0.001	2.434 (1.523–3.891)	< 0.001	3.679 (2.941–4.602)	< 0.001
Metastases								
No	Reference		Reference		Reference		Reference	
Yes	2.323 (1.237–4.363)	0.009	2.540 (1.935–3.335)	< 0.001	2.061 (1.244–3.413)	0.005	2.273 (1.777–2.908)	< 0.001

HNM, head and neck melanoma; BM, body melanoma.

CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.

^a Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722–8723, 8730, 8740–8741, 8744–8746, 8761, 8770–8774, 8780.

Factors	Cancer specific survival				Overall survival			
	HR (95% CI)				HR (95% CI)			
	HNM	p value	BM	p value	HNM	p value	BM	p value
Surgery								
No	Reference		Reference		Reference		Reference	
Yes	0.370 (0.263– 0.520)	< 0.001	0.538 (0.411– 0.705)	< 0.001	0.568 (0.457– 0.707)	< 0.001	0.511 (0.433– 0.604)	< 0.001
HNM, head and neck melanoma; BM, body melanoma.								
CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.								
^a Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722–8723, 8730, 8740–8741, 8744–8746, 8761, 8770–8774, 8780.								

CSS = cancer-specific survival; HNM = head and neck melanoma; BM = body melanoma

3.3 Nomogram development

In this study, eight independent prognostic factors were included to construct nomograms for HNM patients or BM patients to predict 3-, 5-, and 10-year CSS and OS (Fig. 4).

(a,c) predicting CSS and OS for HNM training cohort; (b,d) predicting CSS and OS for BM training cohort.

CSS = cancer-specific survival; OS = overall survival; HNM = head and neck melanoma;

BM = body melanoma.

The nomogram of HNM showed that thickness (> 4.0 mm), which had the largest absolute values, was the strongest contributor to the risk of CSS prognosis, followed by distant stage, no surgery, having metastases and age > 79 years. Notably, thickness (> 4.0 mm) also contributed to the highest CSS risk in the BM nomogram, but distant stage had similar points. Present metastases, age over 79 years and ulceration were strong factors after distant stage in the BM nomogram of CSS.

By adding the scores of each predictor based on individual conditions (Table 5), the HNM nomogram and BM nomogram can be used to predict the probability of 3-, 5- and 10-year CSS and OS rates for HNM patients and BM patients, respectively. For example, Patient A is a 65-year-old male patient who had a head (scalp) tumor thickness of 3.0 mm and was diagnosed with localized SSM without ulceration and metastases and then underwent surgery. A total of 161.38 points were given to this patient, and the estimated 10-year CSS rate was 77%. Patient B, who had all the same clinical features as patient A and underwent surgery but had a

tumor site on the body (shoulder), had a total of 132.03 points. Eventually, this patient's predicted 10-year CSS was 87%, which was 10% higher than the CSS rate of patient A.

Table 5
Detailed scores of predictors in nomograms.

	Cancer-specific survival nomogram		Overall survival nomogram	
	HNM	BM	HNM	BM
Total Points	500	450	300	350
Age (CSS/OS)				
<=58 / <=63	0	0	0	0
59–78 / 64–79	22.72	19.7	46.27	48.34
>=79 / >=80	53.84	53.35	100	100
Sex				
Male	16.01	21.38	7.73	19.71
Female	0	0	0	0
Histology				
NM	42.38	34.26	20.88	15.56
LMM	0	0	9.54	14.75
SSM	30.1	5.44	12.91	0
^a Other Melanoma	8.48	22.09	0	5.48
Thickness				
< 0.6mm	0	0	0	0
0.6-1.0mm	41.26	34.39	10.2	7.03
1.01-2.0mm	80.2	67.33	21.67	17.52
2.01-4.0mm	92.55	85.51	27.93	31.99
> 4.0mm	100	100	35.92	44.23
Ulceration				
No	0	0	0	0
Yes	41.37	47.07	19.01	27.64

HNM, head and neck melanoma; BM, body melanoma.

CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.

^a Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722–8723, 8730, 8740–8741, 8744–8746, 8761, 8770–8774, 8780.

Cancer-specific survival nomogram			Overall survival nomogram	
Stage				
Localized	0	0	0	0
Regional	63.22	68.11	25.38	34.43
Distant	88.3	97.55	43.79	62.69
Metastases				
No	0	0	0	0
Yes	57.31	54.93	35.71	39.65
Surgery				
No	67.46	36.21	27.83	32.28
Yes	0	0	0	0
HNM, head and neck melanoma; BM, body melanoma.				
CSS, cancer-specific survival; OS, overall survival; NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.				
^a Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722–8723, 8730, 8740–8741, 8744–8746, 8761, 8770–8774, 8780.				

3.4 Validation and calibration of the nomogram

The C-index and AUC values were used to evaluate the accuracy and discriminative ability of the nomogram. The C-index of the CSS prediction nomogram for HNM patients was 0.839 ± 0.005 in the training cohort and 0.848 ± 0.008 in the validation cohort. The C-index of the CSS nomogram for the BM group were 0.895 ± 0.003 and 0.888 ± 0.004 in the training cohort and the validation cohort, respectively. In addition, the C-index of OS prediction for HNM patients and BM patients in the training cohort were 0.785 ± 0.004 and 0.841 ± 0.002 , respectively; in the validation cohort, they were 0.796 ± 0.006 and 0.840 ± 0.003 , respectively.

The AUCs for the 3-, 5- and 10-year CSS rates in the training cohort of the HNM group were 0.871, 0.865 and 0.854, and those in the validation cohort were 0.881, 0.879 and 0.861, respectively. For predicting the 3-, 5- and 10-year CSS rates in the BM population, the AUCs were 0.924, 0.918 and 0.901 in the training cohort and 0.916, 0.908 and 0.893 in the validation cohort, respectively (Fig. 5). The AUCs for the OS rates in different cohorts are illustrated in Fig. 5.

a-d predicted 3-, 5- and 10-year CSS rates for HNM training and validation cohort, BM training and validation cohort, respectively. e-h predicted 3-, 5- and 10-year OS rates for HNM training and validation cohort, BM training and validation cohort, respectively.

The calibration plots for the probability of 3-, 5- and 10-year CSS showed great consistency between the nomogram-based prediction and the actual observed outcomes (Fig. 6).

The calibration curves predicted CSS of patients with HNM in the training cohort (a-c) and in the validation cohort (d-f). The calibration curves predicted CSS of patients with BM in the training cohort (g-h) and in the validation cohort (j-l).

Similar results were found in the calibration of the OS prediction nomograms (Fig. S2). These results indicated that both the HNM nomogram and the BM nomogram exhibit excellent performance for predicting the survival of malignant cutaneous melanoma patients.

4 Discussion

In this study, we compared the characteristics of HNM patients with those of BM patients based on the data of a large SEER population. Then, we performed survival analysis of the HNM and BM groups to construct nomograms for individualized survival prediction

Hoersch et al[16] compared 844 patients with HNM and 4858 patients with BM and performed univariate and multivariate analyses, but they found no OS differences between patients with HNM and patients with BM, and the identified significant prognostic factors of HNM were inconsistent with those identified in our study. The low number of cases and different populations in that study could have led to the controversial results. Kevin et al[14] performed a comparison of 4561 pediatric patients with HNM or BM, but they did not study prognostic factors. Previous studies have identified significant independent prognostic factors of melanoma, and some nomograms were developed for predicting the OS or CSS of nonmetastatic melanoma patients, melanoma patients with brain metastases or nodular melanoma patients[6, 24–27]. To date, a specific nomogram for HNM or BM has not been developed.

A total of 70605 eligible patients in the United States from 2004 to 2015 were identified in our study. To our knowledge, this was the largest population-based study to perform a comprehensive comparison between HNM and BM, including their characteristics and survival. Furthermore, this is the first time that high-quality nomograms have been constructed for predicting the prognosis of HNM patients and BM patients, respectively.

HNM patients accounted for 21% of all eligible patients in our study, which was consistent with that in previous reports[9, 16]. According to the univariate prognostic factor analysis of all eligible patients, significant differences were seen between patients with HNM and patients with BM. Notably, the 5-year OS rate of HNM patients was over 10% less than that of BM patients. The relatively high frequency and poorer prognosis of HNM suggest that cutaneous melanoma in head and neck areas requires more attention and health management.

Both the mean and median age of patients with HNM were greater than those of BM patients. HNM was found more than twice as frequently as BM in elderly patients (age ≥ 79). The finding that HNM occurred more frequently in elderly individuals was also observed in other population-based studies[7, 28–30]. Elderly individuals usually suffer longer chronic sun exposure than younger individuals in regions of the head and neck, explaining the higher melanoma rate. In addition, based on the subgroup analysis of age, we observed that the 5-year CSS and OS rates were lower for patients with HNM than for those with BM.

In accordance with the findings of previous studies[15, 31–33], we found significant sex differences between HNM and BM. Nearly three-quarters of patients with HNM were male, while the percentage of females was close to that of males in the BM population in our study. Usually, women are more active in the prevention of sun exposure on the head and neck, which may reduce the risk of HNM[8]. Females showed a better prognosis than males in both the HNM and BM groups in our study. Interestingly, we observed that the 5-year OS of male patients with BM was better than that of female patients with HNM. This result suggested the important role of head and neck regions.

SSM was the most common histologic subtype of melanoma in both the HNM and BM cohorts, but a higher proportion of SSM was noticed in the latter population. Notably, 31.8% of HNM patients were diagnosed with LMM, while only 6.6% of BM patients had LMM. Other population-based melanoma studies also found that a high percentage of LMM occurred on the head and neck[7, 9]. LMM has a prolonged radial growth phase before entering the vertical phase to invade the dermis[34]. Chronic sun damage to the head and neck may serve as an adverse factor in its evolution. Nodular melanoma is associated with worse prognosis than other histological subtypes[35]. Similarly, our study found that this subtype had the worst prognosis in both the HNM and BM populations. Notably, nodular melanoma on the head and neck showed markedly worse 5-year CSS and OS rates. SSM is thought to be a tumor with a better prognosis[36]. Additionally, SSM on the head and neck had a much poorer prognosis than SSM on other sites.

Previous studies[9, 14, 15, 37] reported that thicker tumors (more than 2.0 mm) were more common on the head and neck, and this result is consistent with the findings of our study. The capillary vessels and lymphatic drainage systems in these areas are rich and complex, and these specialties may facilitate the growth of tumors. In addition, more ulcerations, distant stages and metastases were found in patients with HNM, which may also be related to the complex drainage systems of the head and neck. Thickness has been identified as a prognostic factor of melanoma, and increasing thickness implies worse prognosis[15]; these results were in agreement with those of our study. As thin malignant melanomas account for a high number of melanoma fatalities owing to their large proportion[23], we divided thin melanomas (≤ 1.0 mm) into two subgroups: <0.6 mm and 0.6 – 1.0 mm. We observed that when compared with the <0.6 mm group, the latter subgroup did not show a significant impact on the 5-year survival of patients with BM but decreased the survival rate of HNM patients.

Ulceration, lymph node stage and metastasis have been identified as significant independent factors of cutaneous melanoma in previous studies and were also identified in our study[26, 27]. Notably, when presenting distant metastasis, compared to HNM patients, BM patients had worse 5-year CSS and OS rates.

Furthermore, we compared the treatment differences between patients with HNM and patients with BM. The percentage of HNM patients who underwent surgery was slightly lower, while their radiation rate was higher than that of BM patients. We did not find differences in the proportion of patients who received chemotherapy in these two groups.

Multivariate Cox proportional hazards analysis resulted in a model of HNM with age, sex, histology, thickness, ulceration, lymph node stage, metastases and surgery as independent prognostic variables. The same factors contributed to the model of BM. Furthermore, for convenient utilization of the models in clinical

practice, we developed two nomograms to estimate the individual CSS and OS of patients with HNM, and we constructed another two nomograms for patients with BM.

The nomogram of HNM showed excellent predictive and discriminatory power in predicting CSS, with a C-index of 0.839 (95% confidence interval (CI), 0.834–0.844) in the training cohort and 0.848 (95% CI, 0.840–0.856) in the validation cohort. Similarly, the CSS nomogram for BM had high C-indexes of 0.895 (95% CI, 0.892–0.898) in the training cohort and 0.888 (95% CI, 0.884–0.892) in the validation cohort. The range of AUC values for the CSS nomograms was 0.854–0.924, indicating that our models had great discriminatory ability. In addition, the calibration curves in our study indicated satisfactory consistency between the actual observations and the predicted values. The OS nomograms for HNM and BM also showed good performance for prognosis prediction.

This study has the following limitations that need to be acknowledged. First, we grouped melanoma on the head and neck together as HNM for analysis and did not investigate specific anatomic subsites in this region individually. A similar problem existed in the BM analysis. Previous studies suggested that some precise areas had worse cutaneous melanoma-specific prognoses, such as the scalp and breast[3, 5]. Second, our patients were limited to the SEER program. Although the database covers approximately 28% of the US population from 18 registries, the results of our study might not be generalizable to other regional groups, and future studies are needed to externally validate the proposed nomograms. Third, we could not obtain precise data on radiotherapy and chemotherapy from the SEER database, as patients only had “Yes” or “None/Unknown” labels for these variables; thus, only surgery was included in the survival analysis. Finally, as a retrospective study, it is susceptible to some inherent biases.

5 Conclusion

In summary, we compared the characteristics and survival of HNM and BM, and constructed independent nomograms for HNM and BM patients to facilitate individual health management.

Declarations

Ethics approval and consent to participate: As all the data of this study were derived from the SEER database, institutional review board approval and consent to participate were not demanded.

Consent for publication: Not applicable.

Availability of data and material: The data were collected from the Surveillance, Epidemiology, and End Results (SEER) database (URL: <https://seer.cancer.gov/>, Accession username:12814-Nov2019).

Conflicts of interest: The authors have no conflicts of interest to declare.

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Authors' contributions: LZF and DYX conceived and designed the study idea. DYX and JRY performed data mining. DYX, CYH and YXS performed data statistical analyses. DYX, JRY and LHSC prepared figures and tables. DYX and JRY drafted the initial manuscript. JJ and WXJ reviewed and edited the initial manuscript. ZXY, XJL and XPP participated in the coordination of the study and reviewed the manuscript. LZF had primary responsibility for the final content. All authors have approved the final version of the manuscript.

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Abbreviations

head and neck melanoma (HNM)

body melanoma (BM)

Surveillance, Epidemiology, and End Results (SEER)

the concordance index (C-index)

the receiver operator characteristic (ROC) curve (AUC)

overall survival (OS)

cancer-specific survival (CSS)

standard deviations (SDs)

American Joint Committee on Cancer (AJCC)

Superficial spreading melanoma (SSM)

lentigo maligna melanoma (LMM)

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Table 1

Table 1 Comparison of head and neck melanoma (HNM) with body melanoma (BM)

	HNM	BM	p value
Total	15071 (21)*	55534 (79)**	
Age, mean/median (y)	64.6/67	57.2/58	
Age (n %)			<0.001
≤58	4816 (32.0)	28941 (52.1)	
59-78	6908 (45.8)	21114 (38.0)	
≥79	3347 (22.2)	5479 (9.9)	
Sex (n %)			<0.001
Male	10913 (72.4)	29066 (52.3)	
Female	4158 (27.6)	26468 (47.7)	
Race (n %)			<0.001
White	14928 (99.1)	54684 (98.5)	
^a Others	143 (0.9)	850 (1.5)	
Histology (n %)			<0.001
NM	2352 (15.6)	7905 (14.2)	
LMM	4798 (31.8)	3638 (6.6)	
SMM	6168 (40.9)	38748 (69.8)	
^b Other Melanoma	1753 (11.6)	5243 (9.4)	
Thickness (n %)			<0.001
<0.6mm	6717 (44.6)	25301 (45.6)	
0.6-1.0mm	2601 (17.3)	11998 (21.6)	
1.01-2.0mm	2394 (15.9)	8746 (15.7)	
2.01-4.0mm	1759 (11.7)	5337 (9.6)	
>4.0mm	1600 (10.6)	4152 (7.5)	
Ulceration (n %)			0.004
No	12651 (83.9)	47153 (84.9)	
Yes	2420 (16.1)	8381 (15.1)	

Stage (n %)			<0.001
Localized	12944 (85.9)	49320 (88.8)	
Regional	1868 (12.4)	5408 (9.7)	
Distant	259 (1.7)	806 (1.5)	
Metastases (n %)			<0.001
No	14861 (98.6)	54980 (99.0)	
Yes	210 (1.4)	554 (1.0)	
Surgery (n %)			0.021
No	342 (2.3)	1092 (2.0)	
Yes	14729 (97.7)	54442 (98.0)	
Radiation (n %)			<0.001
No/Unknown	14519 (96.3)	55055 (99.1)	
Yes	552 (3.7)	479 (0.9)	
Chemotherapy (n %)			0.474
No/Unknown	14869 (98.7)	54833 (98.7)	
Yes	202 (1.3)	701 (1.3)	

NM, nodular melanoma; LMM, Lentigo maligna melanoma; SSM, superficial spreading melanoma.

*HNM constitute 21% of all cutaneous melanomas.

**BM constitute 79% of all cutaneous melanomas.

^a Others=black, Asian or pacific islander, American indian/Alaska native.

^b Other melanoma: International Classification of Diseases for Oncology-O-3, codes 8722-8723, 8730, 8740-8741, 8744-8746, 8761, 8770-8774, 8780.

Figures

Figure 1

(a) Flowchart of patient selection. (b) The optimal cut-off values for age based on cancer-specific survival were ≤ 58 , 59-78, and ≥ 79 years old. (c) The optimal cut-off values for age based on overall survival were ≤ 63 , 64-79, and ≥ 80 years old.

Figure 2

Kaplan-Meier curves of cancer-specific and overall survival based on anatomic site. (a) cancer-specific survival (CSS); (b) overall survival (OS). HNM = head and neck melanoma; BM = body melanoma.

Figure 3

Kaplan-Meier curves of CSS were delineated based on the identified independent prognostic factors, including age, sex, histology, thickness, ulceration, stage, metastases, and surgery (a-d, i-l) for HNM training cohort, (e-h, m-p) for BM training cohort. CSS = cancer-specific survival; HNM = head and neck melanoma; BM = body melanoma

Figure 4

Nomograms predicted the individual 3-, 5- and 10-year survival rates of patients. (a,c) predicting CSS and OS for HNM training cohort; (b,d) predicting CSS and OS for BM training cohort. CSS = cancer-specific survival; OS = overall survival; HNM = head and neck melanoma; BM = body melanoma.

Figure 5

ROC curves evaluated the predictive ability of the nomograms. a-d predicted 3-, 5- and 10-year CSS rates for HNM training and validation cohort, BM training and validation cohort, respectively. e-h predicted 3-, 5- and 10-year OS rates for HNM training and validation cohort, BM training and validation cohort, respectively.

Figure 6

Calibration curves showed the probability of 3-, 5- and 10-year cancer-specific survival (CSS) between the nomogram prediction and the actual observation. Perfect prediction would correspond to the 45-degree line. The calibration curves predicted CSS of patients with HNM in the training cohort (a-c) and in the validation cohort (d-f). The calibration curves predicted CSS of patients with BM in the training cohort (g-h) and in the validation cohort (j-l).

Supplementary Files

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- [SupplementaryMaterial.docx](#)