



Web-based nomograms for predicting the prognosis of adolescent and young adult skin melanoma, a large population-based real-world analysis

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Background: Invasive cutaneous melanoma is one of the most common malignant diseases among adolescents and young adults (aged 15–40 years) in the United States. We aimed to develop web-based nomograms to precisely predict overall survival and cancer-specific survival in this group of patients with cutaneous melanoma.

Methods: We analyzed the overall and cancer-specific death events in 19,887 patients who underwent surgical resection of cutaneous melanoma from Surveillance, Epidemiology and End Results database and developed web-based clinic-pathologic prediction models for overall survival and cancer specific survival based on Cox regression. C-statistics of Harrell and time-dependent Receiver Operating Characteristic Curve (ROC) were used to evaluate the prognostic accuracy of nomograms.

Results: Multivariate Cox regression model analysis suggested that age, sex, race, tumor location, Clark level, ulceration, thickness, and N stage were independently associated with both overall survival and cancer-specific survival in adolescent and young adult patients with cutaneous melanoma. The nomograms performed excellently in predicting overall survival and cancer-specific survival with C-index being 0.875 (95% CI: 0.847–0.903) and 0.901 (95% CI: 0.876–0.925), respectively. Time-dependent ROC verified that the prognostic accuracy of nomograms was better than that of American Joint Committee on Cancer staging system and other prognostic factors.

Conclusions: These user-friendly nomograms can precisely predict overall survival and cancer-specific survival in cutaneous melanoma patients treated with surgical resection, which may help to make individualized postoperative follow-up and therapeutic schemes.

Keywords: Surveillance epidemiology and end results; melanoma; web-based nomogram

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Introduction

Cutaneous melanoma (CM) is one of the most common and lethal skin malignant disease among adolescents and young adults in the United States (1). The past decades have witnessed a constant increase of its incidence of in adolescents and young adults (2,3). Compared with elder patients, these patients usually present different distribution patterns and possible distinct biological behaviors (4-7).

Though melanoma is characterized by the uncontrolled growth of pigment-producing cells, primary surgical resection offers the best opportunity of cure for patients with early-stage CM. However, even for CM patients treated with curative resection, long-term survival still varies significantly for patients with the same American Joint Committee on Cancer (AJCC) stage which is currently the most accepted prognosis predicting system and therapeutic decision making guideline (8). Therefore, many studies have been conducted to explore the potential prognostic factors associated with survival of CM to improve survival prediction (9-15). Nevertheless, limited previous studies focused on adolescent and young adult patients (16,17) and no effective prognosis predicting model has been built to estimate long-term survival for these patients.

Therefore, the Surveillance Epidemiology and End Results (SEER) database was used to comprehensively evaluate the survival factors in adolescent and young adult CM patients treated with surgical resection. User-friendly web-based prediction nomograms were developed to estimate overall survival (OS) and cancer-specific survival (CSS) for adolescent and young adult CM patients to help to guide individualized therapeutic schemes and postoperative follow-up.

We have presented this article in accordance with the TRIPOD reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-1295>).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

Data from the Surveillance Epidemiology and End Results (SEER) Program of the United States National Cancer Institute (released in 2016) were extracted and analyzed in this study. SEER database, collecting cancer incidence and

survival data from 18 regional population registries, is a large population-based cancer registry. The SEER data are publicly available for studies of cancer-based epidemiology and clinical-pathological features of multiple kinds of cancers.

Inclusion criteria were as follows: (I) patients were aged 15–40 years old; (II) patients were pathologically confirmed as CM; (III) patients were diagnosed between year 2004 and 2014; (IV) all patients received surgical resection; (V) CM was the only primary tumor. Patients who met the following criteria were excluded in this study: (I) patients with distant metastatic site; (II) patients with unknown information of thickness or lymph node metastasis; (III) all patients were staged according to the AJCC Tumor-Nodal-Metastasis (TNM) Staging Classification for melanoma (Seventh Edition, 2010). Finally, a total of 19,887 patients were identified in our study.

Statistical analysis

The OS was defined as the time from treatment to death from any cause, and the CSS was defined as the time from treatment to the death from skin melanoma. Univariate analysis was used to examine the association between various prognostic predictors and OS, CSS. Significant prognostic predictors associated with OS and CSS were included to perform multivariate analyses by using the Cox proportional hazards model. $P < 0.05$ was considered statistically significant. As several clinicopathological variables except for T and N stage in the SEER database had missing data, and simply excluding patients with missing data is inefficient and would increase the risk of selection bias, we used multiple imputation method to re-input the missing data before analysis.

Web based nomograms were developed using R and JavaScript, and the model performance for prognostic accuracy was evaluated by time-dependent receiver operating characteristic curve (ROC) and Harrell's concordance index (c-index). All statistical evaluation was conducted with R 2.15.0 software (Institute for Statistics and Mathematics, Vienna, Austria).

Results

Patients' baseline characteristics

Among the 19,887 adolescent and young adult patients, 7,378 (37.1%) are men and 12,509 (62.9%) are women;

8,384 cases are with superficial spreading melanoma, 1,036 with nodular melanoma, and 954 with other uncommon melanomas. As for the tumor Clark level, 8,171 (40.70%) are level II; 5,600 (27.80%) are level III, 6,116 (30.00%) are level IV and 294 (1.50%) are level V. In terms of the AJCC TNM stage, stage I, stage IIA, stage IIB, stage IIC, and stage III have 16,991 (85.44%), 837 (4.21%) were, 433 (2.18%), 123 (0.62%) and 1,503 (7.56%) patients respectively at the time of diagnosis. The detailed demographic and characteristics and imputation percentage are presented in *Table 1*.

Prognostic factors for OS and CSS

To evaluate the association between baseline characteristics and prognosis, univariate Cox regression analysis were performed. In univariate analysis, age, sex, race, tumor location, histologic subtype, Clark level, ulceration, thickness, and N stage were significantly associated with OS and CSS ($P < 0.05$). Multivariate Cox regression model was further conducted to evaluate the independence of the above significant prognostic factors. In both models of OS and CSS, age, sex, race, tumor location, Clark level, ulceration, thickness, and N stage were verified to be independent prognostic factors in patients with CM (*Tables 2, 3*, $P < 0.05$). Histologic subtype lost its independence in predicting OS and CSS.

Development and performance evaluation of prediction models

To predict OS and CSS of skin melanoma patients, two nomograms were established by multivariate Cox regression model according to all significantly independent factors for OS and CSS (*Figure 1A,B*). Nomograms can be interpreted by summing up the points assigned to each variable, which is indicated at the top scale. The total points can be converted to predicted 5-year probability of death and recurrence or metastasis for a patient in the lowest scale. The Harrell's c-indexes for OS and CSS prediction were 0.875 (95% CI: 0.847–0.903) and 0.901 (95% CI: 0.876–0.925), respectively. Calibration curves for two nomograms (*Figure 1C,D*) revealed no deviations from the reference line and there is no need for recalibration.

Time dependent ROC analysis suggested that the nomograms we developed are more accurate in predicting OS and CSS than the AJCC stage and other prognostic factors (*Figure 2*). A histogram of nomogram-predicted

probabilities within each of the AJCC stage is shown in *Figure 3* and depicts the variation in predicted outcome within each of the AJCC version 3 subgroups.

To create user-friendly accessibility, the underlying statistical formulas were implemented in web-based nomograms. Patients or medical workers can estimate individual OS and CSS by entering the basic clinicopathological information, time of prediction. *Figure 4* shows a screenshot of the web-based nomograms which are available on <http://youthcm.site/>.

Discussion

Although many studies have identified clinical and molecular predictors for long term survival after resection of CM, limited researches focused on improving the evaluation of prognosis for adolescent and young adult patients and no practical and user-friendly predictive models have been developed. To our knowledge, we for the first time analyzed OS and CSS predicting factors comprehensively and built user-friendly web-based nomograms to precisely predict long term survival for adolescent and young adult patients based on SEER database. The web-based nomograms we constructed perform excellently in predicting OS and CSS with C-index being 0.875 (95% CI: 0.847–0.903) and 0.900 (95% CI: 0.876–0.925), respectively.

In this study, we found that age, sex, race, tumor location, Clark level, ulceration, thickness, and N stage are independently associated with OS and CSS. These variables have been reported in previous studies conducted in the overall CM patients (18–20). Consistent with published studies, older age, male, non-white, high Clark level, present ulceration, nodular melanoma, head and neck melanoma, and advanced tumor stage are related to elevated probability of melanoma mortality. Notably, univariate analysis suggested histological subtype is a prognostic factor and the nodular CM have worse prognosis than patients with superficial spreading melanoma. However, after adjusting other factors, histological subtype is not an independent OS and CSS predictor. Previous studies covering all age groups have confirmed that nodular melanoma is characterized with aggressive biological behavior and is an independent prognostic factor for poor survival (21,22). The possible reason accounting for this discrepant result in our study can be firstly inferred that significant confounding bias caused by other prognostic factors exists among different histological subtype groups. Actually, further underlying reasons could attribute to the great heterogeneity among

Table 1 Clinicopathological features of adolescent and young adult melanoma patients

Features	No. of patients	%	% imputed
Age, years			0%
15–25	3,382	17.01	
26–40	16,505	82.99	
Sex			0%
Male	7,378	37.10	
Female	12,509	62.90	
Race			6%
White	19,589	98.50	
Black	87	0.44	
Other	211	1.06	
Tumor location			5.10%
Face	484	2.43	
Low limb	5,375	27.03	
Neck	1,352	6.80	
Trunk	8,256	41.51	
Up limb	4,404	22.15	
Overlapping	16	0.08	
Histologic subtype			0%
Superficial spreading melanoma	8,384	42.16	
Nodular melanoma	1,036	5.21	
Other uncommon melanomas	954	4.80	
Unspecific	9,513	47.84	
Clark level			12%
II	8,171	40.70	
III	5,600	27.80	
IV	6,116	30.00	
V	294	1.50	
Ulceration			3%
No	18,299	92.01	
Yes	1,588	7.99	
Thickness			0%
≤1	15,232	76.59	
1.01–2.0	2,783	13.99	

Table 1 (continued)**Table 1** (continued)

Features	No. of patients	%	% imputed
2.01–4.0	1,241	6.24	
>4.0	631	3.17	
N stage			0%
N0	18,384	92.44	
N1	929	4.67	
N2	404	2.03	
N3	170	0.85	
Stage			0%
I	16,991	85.44	
IIA	837	4.21	
IIB	433	2.18	
IIC	123	0.62	
III	1,503	7.56	
Total	19,887	100.00	

adolescent and young adult and the elderly patients (23). Consequently, the prognostic role of histological subtype should be re-evaluated comprehensively among CM patients at different ages and future well organized prospective studies are warranted to explore the inherent heterogeneity among different histological subtypes in adolescent and young adult patients.

The nomograms are a well-established prediction tool that incorporates significant clinicopathologic factors known to impact survival. It is known as a simple graphical representation of a statistical prediction model that generates a numerical probability of a clinical event. Although the current AJCC TNM staging system is the most influencing prognosis evaluating estimator for CM patients, many valuable prognostic variables, such as age, tumor location and Clark level are not incorporated. As revealed in our study, older age, male, non-white, high Clark level and neck melanoma are independent predictive factors of CM long-term survival. It is easy to imagine that distinct bias in estimating the prognosis cannot be avoided when we considered only TNM stage regardless of other important factors. As illustrated in figure 3 which is a histogram of predicted outcome based on the nomograms for each AJCC stage classification, significant heterogeneity in outcome can be found in each sub-stage, especially in

Table 2 Univariate and multivariate analysis of overall survival (OS) in skin melanoma

Features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, years		0.015		<0.001
15–25	1		1	
26–40	1.30 (1.05–1.61)		1.64 (1.32–2.04)	
Sex		<0.001		0.001
Male	1		1	
Female	0.44 (0.38–0.51)		0.76 (0.65–0.89)	
Race		<0.001		0.002
White	1		1	
Black	2.81 (1.40–5.64)		1.13 (0.55–2.31)	
Other	2.68 (1.68–4.29)		2.19 (1.36–3.53)	
Tumor location		<0.001		<0.001
Face	1		1	
Low limb	0.62 (0.38–1.02)		0.72 (0.44–1.16)	
Neck	1.45 (0.86–2.43)		1.24 (0.74–2.07)	
Trunk	1.029 (0.64–0.65)		1.24 (0.77–1.99)	
Up limb	0.83 (0.51–1.36)		1.09 (0.66–1.78)	
Overlapping	1.88 (0.25–14.11)		4.89 (0.64–37.01)	
Histologic subtype		<0.001		0.194
Superficial spreading melanoma	1		1	
Nodular melanoma	6.45 (5.24–7.94)		0.88 (0.69–1.11)	
Other uncommon melanomas	1.55 (1.11–2.17)		0.78 (0.56–1.11)	
Unspecific	1.21 (1.01–1.45)		0.86 (0.71–1.03)	
Clark level		<0.001		<0.001
II	1		1	
III	2.62 (2.00–3.43)		1.47 (1.11–1.95)	
IV	8.43 (6.68–10.63)		1.81 (1.37–2.39)	
V	41.2 (30.2–57.1)		2.95 (1.99–4.37)	
Ulceration		<0.001		<0.001
No	1		1	
Yes	10.59 (9.12–12.29)		2.55 (2.13–3.06)	
Thickness		<0.001		<0.001
≤1	1		1	
1.01–2.0	5.61 (4.54–6.92)		3.09 (2.43–3.95)	
2.01–4.0	14.24 (11.55–17.54)		4.71 (3.59–6.18)	
>4.0	31.58 (25.58–38.98)		7.50 (5.57–10.10)	
N stage		<0.001		<0.001
N0	1		1	
N1	8.69 (7.18–10.52)		2.23 (1.80–2.76)	
N2	13.98 (11.18–17.49)		3.12 (2.43–4.01)	
N3	32.00 (24.90–41.12)		5.10 (3.83–6.79)	

Table 3 Univariate and multivariate analysis of cancer specific survival (CSS) in skin melanoma

Features	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age, years		0.045		<0.001
15–25	1		1	
26–40	1.26 (1.01–1.60)		1.70 (1.33–2.19)	
Sex		<0.001		0.001
Male	1		1	
Female	0.41 (0.34–0.48)		0.73 (0.62–0.87)	
Race		<0.001		0.013
White	1		1	
Black	3.40 (1.69–6.84)		1.29 (0.63–2.64)	
Other	2.70 (1.61–4.50)		2.14 (1.27–3.60)	
Tumor location		<0.001		<0.001
Face	1		1	
Low limb	0.60 (.35–1.01)		0.66 (0.38–1.12)	
Neck	1.41 (0.81–2.44)		1.19 (0.68–2.07)	
Trunk	0.96 (0.58–1.59)		1.09 (0.65–1.82)	
Up limb	0.74 (0.44–1.26)		0.96 (0.56–1.63)	
Overlapping	0.001 (0–1000+)		0.001 (0–1000+)	
Histologic subtype				0.376
Superficial spreading melanoma	1		1	
Nodular melanoma	7.66 (6.11–9.60)		0.95 (0.72–1.20)	
Other uncommon melanomas	1.64 (1.13–2.39)		0.73 (0.49–1.07)	
Unspecific	1.31 (1.07–1.59)		0.89 (0.73–1.10)	
Clark level		<0.001		<0.001
II	1		1	
III	3.07 (2.15–4.38)		1.73 (1.19–2.50)	
IV	12.22 (8.97–16.67)		2.50 (1.74–3.60)	
V	63.4 (44.01–91.20)		3.80 (2.42–5.97)	
Ulceration		<0.001		<0.001
No	1		1	
Yes	12.74 (10.83–15.00)		2.77 (2.28–3.37)	
Thickness		<0.001		<0.001
≤1	1		1	
1.01–2.0	7.37 (5.78–9.41)		3.54 (2.68–4.68)	
2.01–4.0	18.29 (14.36–23.30)		4.87 (3.58–6.63)	
>4.0	43.42 (34.16–55.20)		8.04 (5.77–11.20)	
N stage		<0.001		<0.001
N0	1		1	
N1	9.96 (8.09–12.26)		2.30 (1.83–2.89)	
N2	17.15 (13.54–21.72)		3.43 (2.64–4.46)	
N3	40.00 (30.79–51.95)		5.63 (4.17–7.59)	

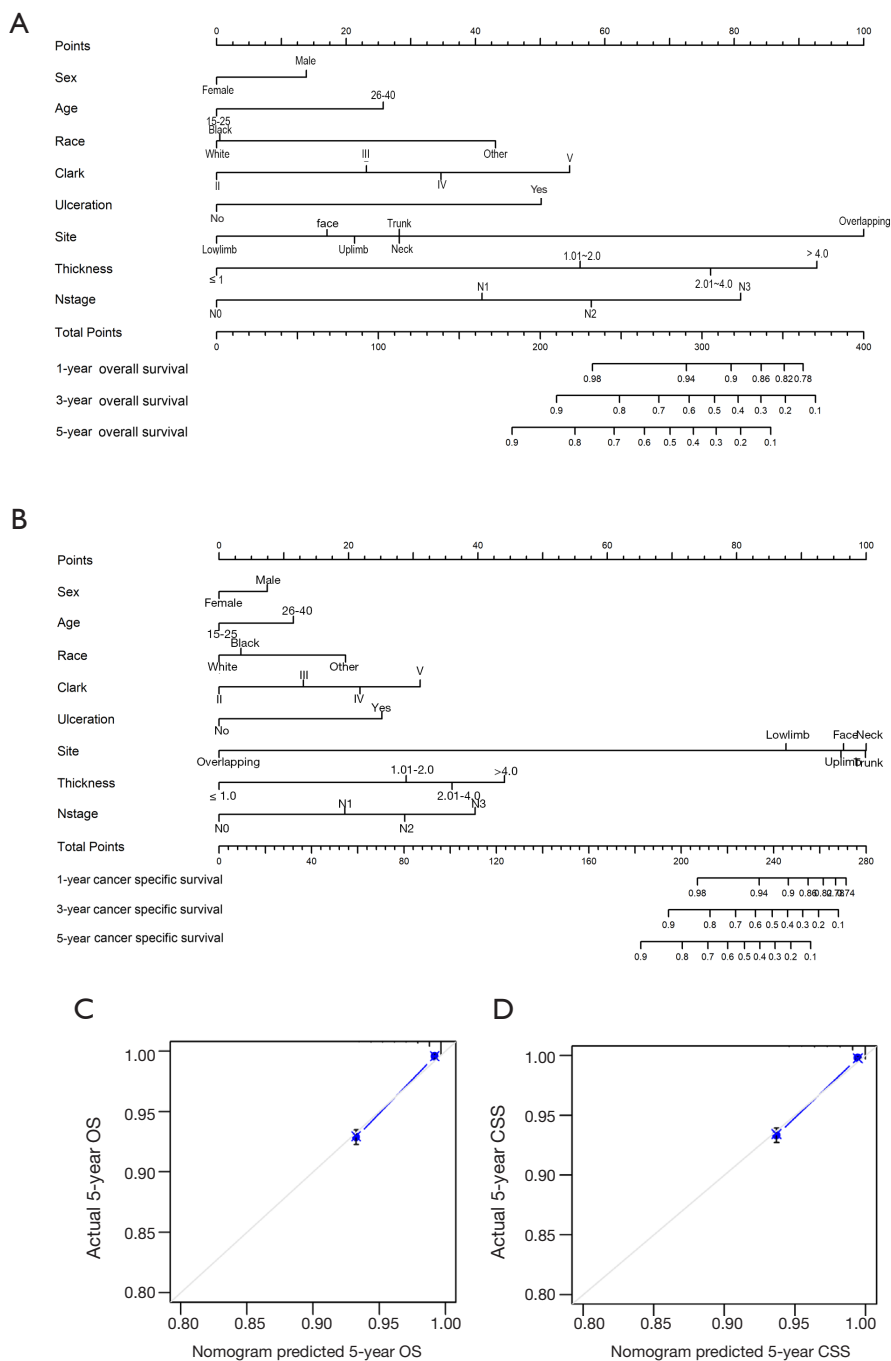


Figure 1 Nomograms with clinicopathological characteristics to predict OS (A) and CSS (B) of adolescent and young adult patients with CM. Calibration curves for 5-year OS (C) and 5-year CSS (D) using nomograms are shown. OS, overall survival; CSS, cancer specific survival; CM, cutaneous melanoma.

stage III. The nomograms developed in our study include not only AJCC staging system but also demographic characteristics. Furthermore, different from TNM staging system, the nomograms can provide quantified prognosis

evaluation for individual patients. Though nomograms have been validated to compare favorably to the traditional TNM staging systems in many cancers, this graphical tool is still not convenient enough to be applied in clinical

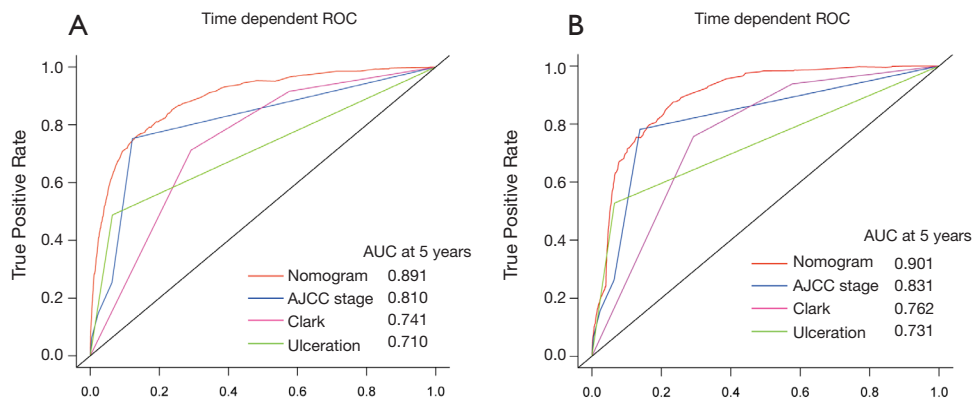


Figure 2 Time-dependent ROC curves at 5 year compare the prognostic accuracy in predicting OS (A) and CSS (B) of the nomograms with other clinicopathological features. OS, overall survival; CSS, cancer specific survival; ROC, receiver operating characteristic.

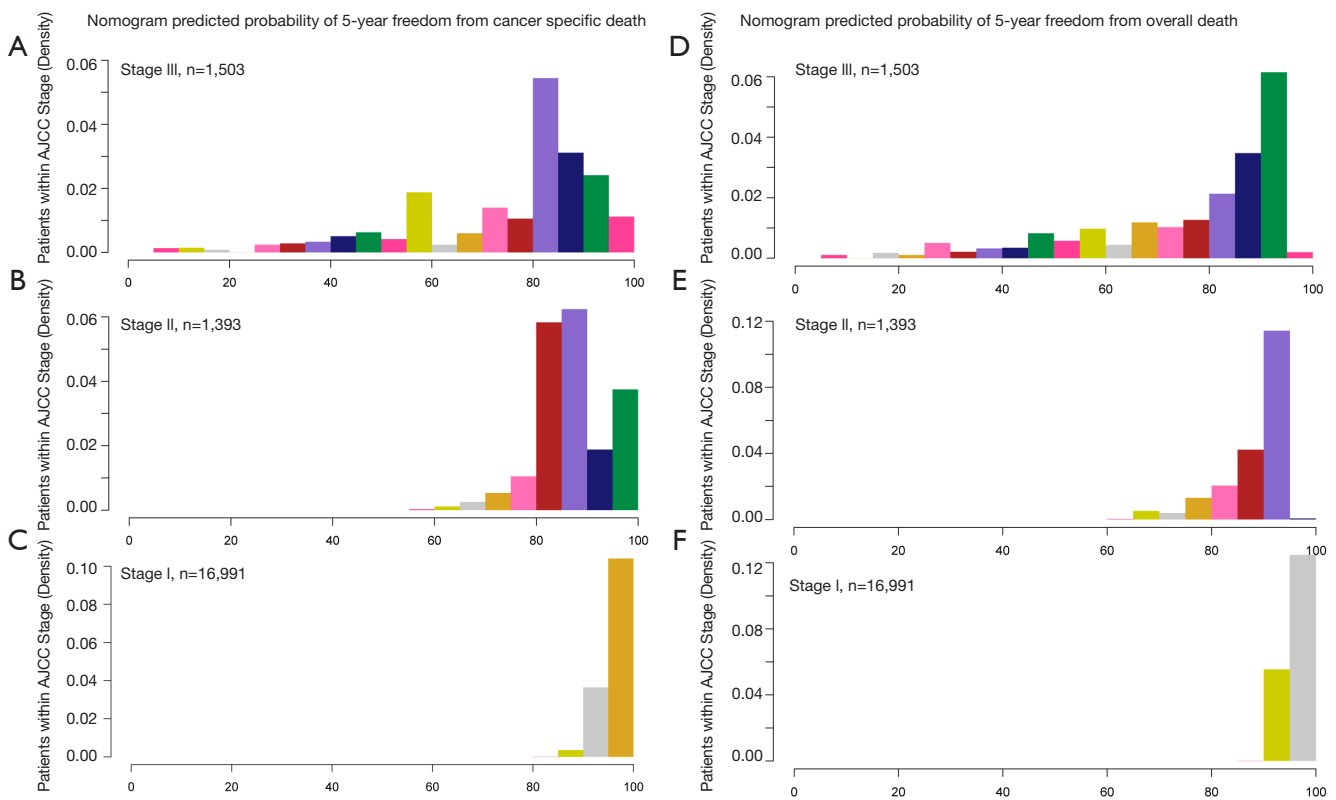


Figure 3 Histogram of nomogram-predicted freedom from cancer specific death (A,B,C) and overall death (D,E,F) within each AJCC stage. AJCC, American Joint Committee on Cancer.

practice. Therefore, we developed a user-friendly web-based nomogram to facilitate its feasibility in clinical practice. By typing in the clinicopathologic features of any individual patient, doctors can estimate the survival precisely.

Though the first web-based prognostic nomograms

targeting adolescent and young adult patients has been built, there are still several limitations in our study. Firstly, SEER database lacks several important clinical information including tumor grade, comorbidity and disease-free survival. Secondly, this study only included young patients

Probability of Survival	
OS	38.6302%
CSS	34.9705%

Figure 4 Print screen from the web-based nomograms, predicting OS and CSS in a fictional patient. The nomograms are available at <http://youthcm.site/>. Choose or enter the value for each variable, and then press the “Calculate” button. OS, overall survival; CSS, cancer specific survival.

receiving surgical resection and thus this model cannot be applied to the elderly or patients with distant metastasis. Thirdly, external validation is needed to verify whether our predictive model is universally applicable.

Conclusions

In conclusion, we have developed precise user-friendly web-based nomograms to predict OS and CSS in adolescent and young adult CM patients based on a large population cohort. It is hoped that this personalized predictive tool can be applied to treatment and follow-up related decision making.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-1295>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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