Original Article

Development and validation of a nomogram to predict overall survival of conjunctival melanoma: a population-based study

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Background: Conjunctival melanoma (CM) is a rare, invasive tumor in the eye that readily metastasizes and spreads. Based on some significant clinicopathological information, we aimed to develop a prognostic model to predict the overall survival (OS) of CM patients.

Methods: Data of patients diagnosed with CM from 2000 to 2019 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Significant prognostic factors were extracted and integrated based on competing risk regression to build a nomogram. Harrell's concordance index (C-index), receiver operating characteristic (ROC) curve, and calibration plots were used to evaluate the performance of the nomogram.

Results: The study included 272 patients with CM, with a median age of 63 years. A nomogram was developed using age and tumor-node-metastasis (TNM) stage as variables. The model's C-index was 0.755, and the area under the curve (AUC) was 0.774, 0.812, and 0.815 at 5, 8, and 10 years, respectively. The calibration plot used to predict CM demonstrated good consistency between the predicted OS probability and the actual OS probability.

Conclusions: We have developed a nomogram model to predict the OS of patients with CM, which can predict the survival of these patients. The model's prognostic value is higher than that of the American Joint Committee on Cancer (AJCC) staging system alone. This tool can help evaluate the tumor-specific prognosis, identify patients at high risk of cancer-specific death, and guide clinical decision-making.

Keywords: Conjunctival melanoma (CM); nomogram; overall survival (OS); prognosis; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Conjunctival melanoma (CM) is a rare invasive ocular surface malignant tumor, accounting for about 2–5% of all ocular tumors (1). The incidence of CM is much lower than that of uveal melanoma, accounting for 5–7% of ocular melanoma (1). Epidemiologic studies in the United States and Europe have shown that the incidence of CM is approximately 0.2–0.8 per million per year (2-4). Differences in the incidence of CM between different regions may be related to ultraviolet exposure (5,6).

Most CM originate from primary acquired melanosis (PAM) or conjunctival nevus (7-9). It may originate from any part of the conjunctiva and rapidly invade other structures of the eye. Uncontrolled disease usually metastasizes to the ear, nose, neck, lung, liver, skin, and even brain (10). Existing statistical data show that CM shows a 10-year local recurrence rate in 50% of cases, and distant metastasis is diagnosed in 26% of cases (11).

There have been some studies that reported the treatment and survival period of CM (4,12-15), but because of its low incidence rate and few previous studies, there is no effective method to accurately predict the survival of CM patients. By adjusting age, sex, the Surveillance, Epidemiology, and End Results (SEER) registration, race/ethnicity, grade, The International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology/behavior, diagnosis confirmation, chemotherapy record, radiotherapy sequence, and radiotherapy record, for the first time, we established and verified a nomogram model for reliably predicting overall survival (OS) in CM patients and compared it with the American Joint Committee on Cancer (AJCC) staging system. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1277/rc).

Highlight box

Key findings

- In the current study, a nomogram model for reliably predicting overall survival (OS) in conjunctival melanoma (CM) patients was constructed.

What is known and what is new?

- American Joint Committee on Cancer (AJCC) staging system can also predict the survival of patients well, but it does not include other factors such as age.
- This study combined the data in the Surveillance, Epidemiology, and End Results database to build a nomogram, which better predicts the OS of CM patients in 5, 8, and 10 years.

What is the implication, and what should change now?

- The model's prognostic value is higher than that of the AJCC staging system alone. This tool can help evaluate the tumor-specific prognosis, identify patients at high risk of cancer-specific death, and guide clinical decision-making.

Methods

Data source and patient selection

SEER*Stat software version 8.4.0.1 was used to select patients from the Incidence-SEER 17 Regs Research database based on our application on November, 2022 to build the cohort. The inclusion criteria were as follows: patients diagnosed with CM between 2000 and 2019 and confirmed by pathology, with a histology code (morphology code 8720–8799) according to the ICD-O-3, and an ICD-O-3 site code of C69.0 (conjunctival). We included only patients with one malignant primary tumor of CM and excluded those with incomplete survival data or a survival time of less than 1 month, as well as patients with unknown AJCC stage [according to the 6th edition of AJCC tumor-node-metastasis (TNM) classification], laterality, or race. The flow chart of the patient selection process is illustrated in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables

Variables in the selected cohort were: baseline demographics (year of diagnosis, age at diagnosis, sex, race, insurance status, marital status), tumor features (primary site, laterality, T stage, N stage, M stage, AJCC stage, histological type, metastasis at diagnosis), therapy (surgery, radiation, chemotherapy), and survival variables (months of survival, vital status, cause-specific classification of death). We used a cut-off age of 65 years based on a previous study (16). OS was the study endpoint and it was defined as the time from diagnosis to death attributed to CM.

Statistical analysis

We used univariate Cox regression analysis to identify potential prognostic factors. When the P value is lower than 0.05, it is included in the multiple Cox proportional risk regression model. Unless otherwise stated, categorical variables report integers and proportions, and continuous

variables report the median of the quartile range. All results are expressed in hazard ratio (HR) and 95% confidence interval (CI). Then, we built a nomogram by combining meaningful variables (P<0.05). Nomogram predicted the OS of CM patients in 5, 8, and 10 years. The nomogram has been tested through 1,000 bootstrap resampling for the validation of the nomogram. Calculate Harrell's concordance index (C-index) and receiver operating characteristic (ROC) to evaluate the accuracy of the model, and then use the calibration chart to evaluate the consistency between the predicted results and the actual results of the 5-, 8-, and 10-year survival time. If the model is well calibrated, the predicted value should be 45° diagonal.

Finally, we stratified patients according to the scores predicted by the nomogram in the dataset, divided patients into low- and high-risk groups, and plotted Kaplan-Meier (KM) curves to further assess calibration. SPSS 26 and R version 4.1.3 were used for statistical analysis. The significance level of all tests was set at 0.05 on a bilateral basis.

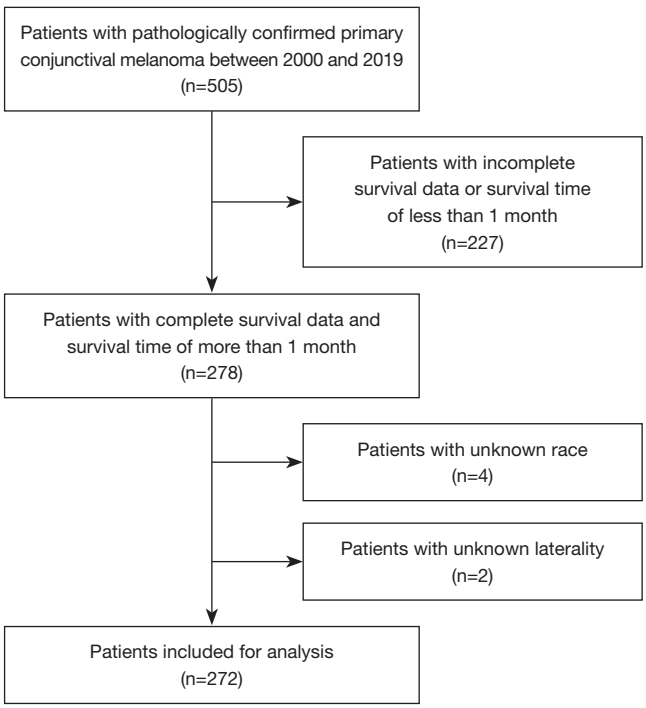

Figure 1 Flow chart of cases selection from SEER database. SEER, Surveillance, Epidemiology, and End Results.

Results

Patient characteristics

A total of 272 eligible patients with primary CM were identified from the SEER database between 2000 and 2019 and included in the analysis. The demography of patients is shown in *Table 1*. The average age is 60.4 years old. The median age of patients at diagnosis is 63 years old [interquartile range (IQR), 50–74 years old]. Among them, 141 (51.8%) were males and 131 (48.2%) were females.

Table 1 Baseline characteristics and Cox regression analyses for OS

Characteristics	Values	Univariable analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)					
<65	148 (54.4)	Ref.		Ref.	
≥65	124 (45.6)	4.6 (2.9–7.3)	<0.001***	4.4 (2.74–7.2)	<0.001***
Sex					
Male	141 (51.8)	Ref.			
Female	131 (48.2)	0.67 (0.44–1)	0.057		
Marital					
Married	146 (53.7)	Ref.			
Unmarried†	91 (33.5)	1.1 (0.72–1.8)	0.608		
Unknown	35 (12.9)	1.0 (0.54–1.9)	0.953		

Table 1 (*continued*)

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Characteristics	Values	Univariable analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Race					
White	250 (91.9)	Ref.			
Black	6 (2.2)	0.83 (0.21–3.4)	0.8		
Others‡	16 (5.9)	1.64 (0.79–3.4)	0.18		
Laterality					
Left	138 (50.7)	Ref.			
Right	134 (49.3)	1.1 (0.74–1.7)	0.594		
T stage					
T1	29 (10.7)	Ref.		Ref.	
T2	136 (50.0)	1.8 (0.69–4.4)	0.238	2.1 (0.82–5.4)	0.123
T3	84 (30.9)	2.3 (0.90–6.0)	0.083	3.1 (1.19–8.1)	0.021*
T4	23 (8.5)	9.9 (3.67–26.8)	<0.001***	7.7 (2.79–21.0)	<0.001***
N stage					
N0	266 (97.8)	Ref.		Ref.	
N1	6 (2.2)	8.4 (3.4–21)	<0.001***	7.4 (2.00–27.1)	0.003**
M stage					
M0	265 (97.4)	Ref.		Ref.	
M1	7 (2.6)	8.3 (3.6–19)	<0.001***	8.1 (2.52–25.9)	<0.001***
Surgery					
No	17 (6.3)	Ref.			
Yes	255 (93.8)	0.94 (0.41–2.2)	0.89		
Radiotherapy					
No	256 (94.1)	Ref.			
Yes	16 (5.9)	1.9 (0.9–3.8)	0.094		
Chemotherapy					
No	228 (83.8)	Ref.			
Yes	44 (16.2)	1.3 (0.75–2.1)	0.381		
OS (months)					
Mean (SD)	91.7 (51.0)				
Median [IQR]	87.5 [54, 134]				

Values are expressed in n (%) unless otherwise stated. †, unmarried: separated/divorced/widowed; ‡, others: Asian, Pacific Islander, and American Indian/Alaska. *, P<0.05; **, P<0.01; ***, P<0.001. OS, overall survival; HR, hazard ratio; CI, confidence interval; ref., reference; SD, standard deviation; IQR, interquartile range.

Of the 272 patients, 250 (91.9%) were white, 6 (2.2%) were black and 16 (5.9%) were Asian, Pacific Islander, or American Indian/Alaska Native. Race data were collected by the SEER database. All patients were unilateral CM, and the involvement rate of left or right eyes was similar. Most of the patients (93.8%) underwent surgery, only 5.9% of patients were treated with radiotherapy and 16.2% of patient were treated with chemotherapy. The mean survival time of all patients was 91.7 months, the median survival time was 87.5 months (IQR, 54–134 months). The analysis of OS was drawn into the KM curve (*Figure 2*).

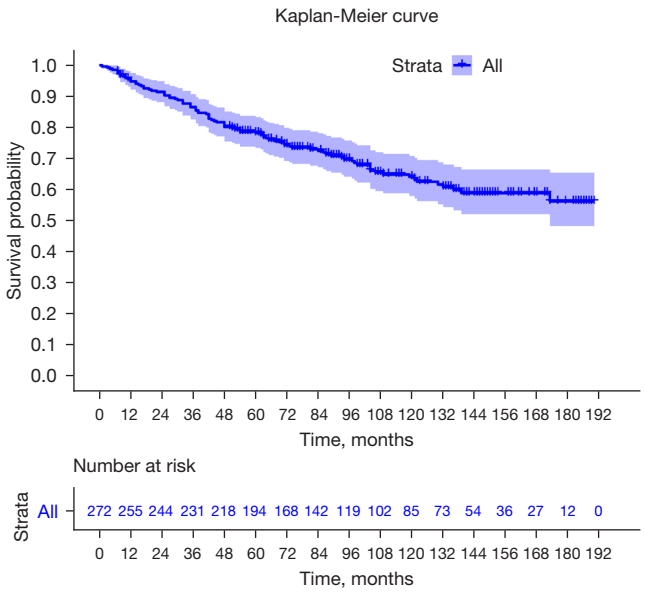

Figure 2 Kaplan-Meier curve showing OS rates in the overall patient population (n=272). OS, overall survival.

In order to determine the prognostic factors related to OS, we used univariate and multivariate analyses based on competitive risk model. In univariate analysis, age (P<0.001), sex (P=0.057), T (P<0.001), N (P<0.001), M (P<0.001), and radiotherapy (P<0.001) are important factors affecting prognosis. Multivariate analysis showed that age (P<0.001), T phase (P<0.001), N phase (P<0.001), and M phase (P<0.001) were independent prognostic factors for OS in CM patients.

Nomogram construction

The nomogram for predicting the OS of CM patients for 5, 8, and 10 years is constructed by incorporating four independent prognostic factors: T stage, N stage, M stage, and age (*Figure 3*). From the nomogram, patients with higher M stage have worse prognosis [M1; P<0.001; HR (95% CI), 8.1 (2.52–25.9)], and each subtype of these four

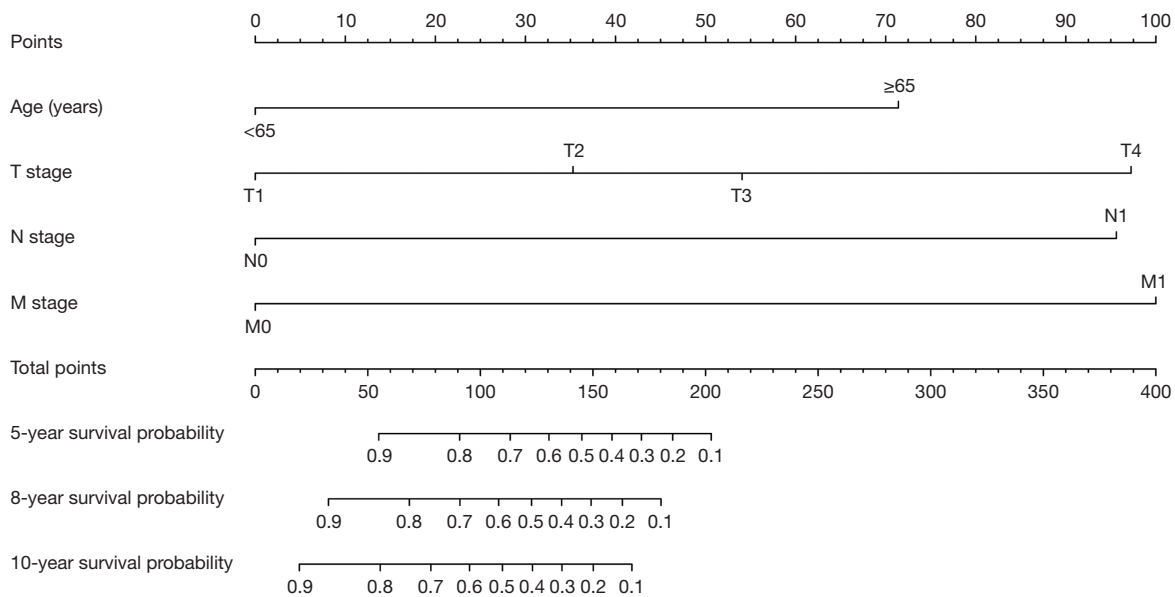

Figure 3 Prognostic nomogram predicting the probability of 5-, 8-, and 10-year OS in patients with CM. The total scores of independent prognostic factors projected to the bottom scale represent the probabilities of 5-, 8-, and 10-year OS. Y, year; OS, overall survival; CM, conjunctival melanoma.

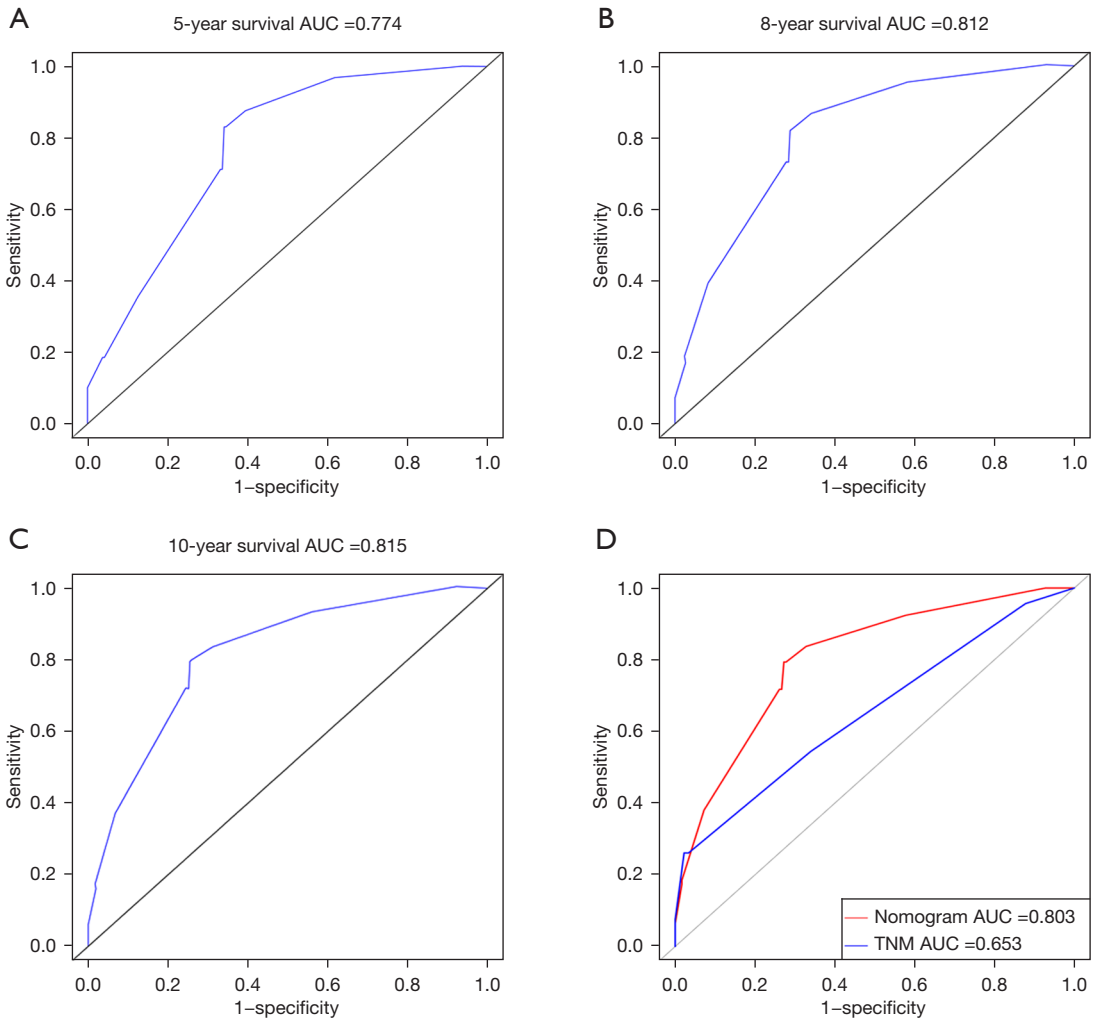

Figure 4 Validation of the nomogram. (A) ROC curves to verify accurate predictability for 5-year OS. (B) ROC curves to verify accurate predictability for 8-year OS. (C) ROC curves to verify accurate predictability for 10-year OS. (D) Comparing the AUC of the nomogram and the AUC of the TNM stage. AUC, area under the curve; TNM, tumor-node-metastasis; ROC, receiver operating characteristic; OS, overall survival.

significant independent variables is assigned a score. The total score of independent prognostic factors projected to the bottom scale represents the probability of 5, 8, and 10 years of OS.

Validation of the nomogram

The C-index of the model is 0.755 (95% CI: 0.710–0.800). The C-index of the nomogram is higher than that of the TNM stage, and the C-index of the TNM stage is 0.651 (95% CI: 0.5922–0.7098). We used the ROC curve to verify the accurate predictability of 5, 8, and 10 years of OS. The area under the curve (AUC) was 0.774, 0.812, and 0.815, respectively (*Figure 4A-4C*). And the AUC of the nomogram was higher than that of TNM staging (*Figure 4D*). To validate the nomogram, we performed 1,000 bootstrap resampling. The calibration chart used to predict CM shows that there is a good consistency between the predicted OS probability and the actual OS probability (*Figure 5*). According to the median score of the prediction model, the KM curve was drawn (*Figure 6*). The prognosis of the high-risk group was significantly worse (P<0.001).

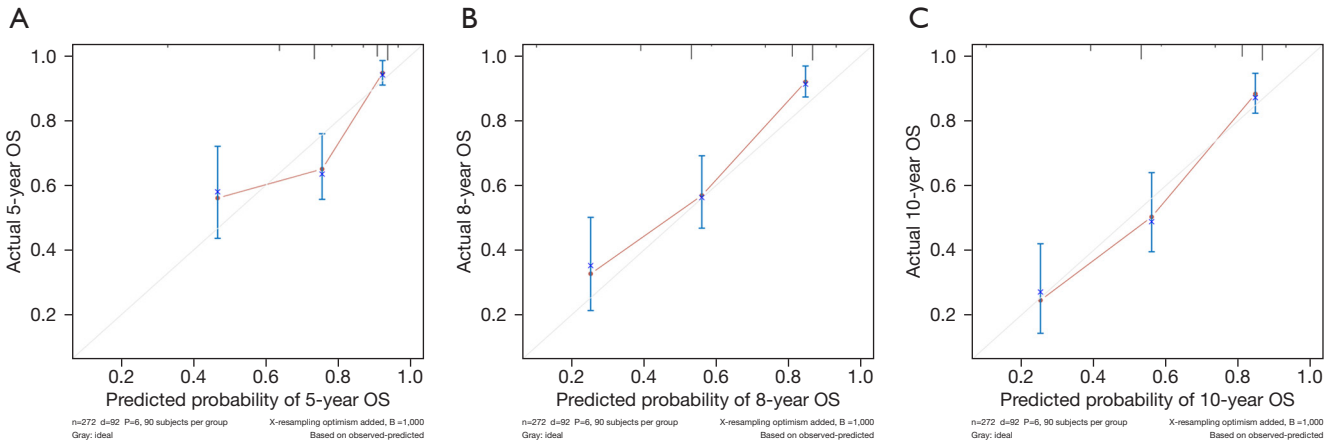

Figure 5 Calibration plot comparing predicted and actual survival probabilities: (A) at 5-year follow-up; (B) at 8-year follow-up; (C) at 10-year follow-up. The Y-axis represents the actual OS. The X-axis represents the predicted OS. The diagonal dotted line represents a perfect prediction by an ideal model. The red solid line represents the performance of the model, of which a closer fit to the diagonal dotted line represents a better prediction. The blue bar represents standard deviation. OS, overall survival; y, year.

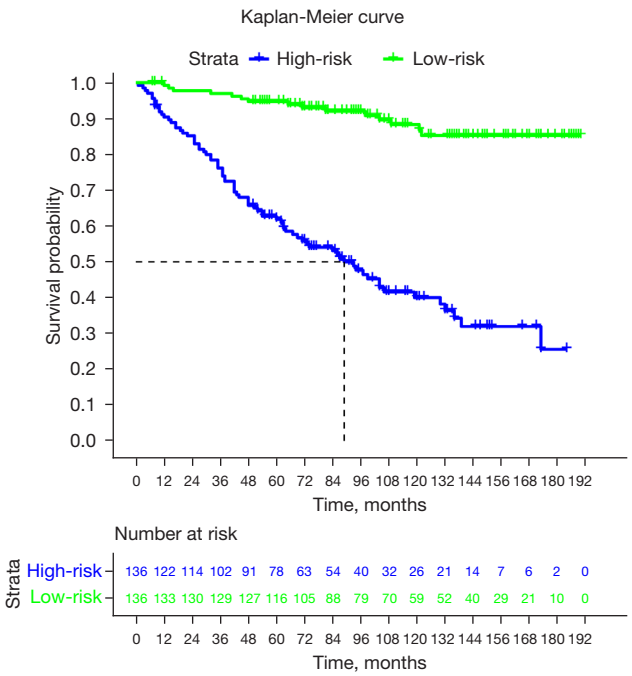

Figure 6 OS rates of high- and low-risk groups. OS, overall survival.

Discussion

CM is a rare invasive ocular surface malignancy. Surgery is an effective treatment for patients without metastasis (17), and adjunctive therapy using chemo eyedrops or irradiation reduces the chances of local recurrence (13,18,19). However, for patients with metastasis, the prognosis is poor, and there is no exact treatment plan. To address this, we developed and evaluated an individualized nomogram to predict the OS of CM patients using a large SEER cohort. Evaluation results of the model demonstrate satisfactory performance in the prognosis prediction of CM.

Previous studies have found many factors affecting the OS of CM patients, including age, T stage, N stage, whether to transfer, whether to accept chemotherapy, radiotherapy, etc. (20-23). Michał Szymon Nowak reported the incidence and characteristics of uveal melanoma and CM in the general population in Poland from 2000 to 2017, and found that the higher death risk is related to men, age of diagnosis, chemotherapy, metastasis, local hyperplasia, and systemic tumor spread. Radiotherapy reduces the risk of death (21). Abt's retrospective study analyzed more than 40 years of data and compared the prognostic factors and survival of primary malignant tumor CM and squamous cell carcinoma of the eye. It was proposed that age at the time of diagnosis of CM was the decisive factor for survival, and male, T4 and N1 stages were also important prognostic factors for melanoma (22). Tan reviewed the patients with ocular melanoma confirmed by histology in a multi-ethnic Asian cohort in Singapore, and found that CM had an OS of 69.8% in 5 years, and the higher T stage was an important independent predictor of OS (23). It should be noted that while most of these studies utilized the Cox regression method to analyze OS, they were often limited by relatively small sample sizes. Our study found that age,

T stage, N stage, and M stage are independent prognostic factors for predicting OS in patients with CM, consistent with the findings of previous studies. AJCC staging system can also predict the survival of patients well, but it does not include other factors such as age. This study combined the data in the SEER database to build a nomogram, which better predicts the OS of CM patients in 5, 8, and 10 years. In the following nomogram evaluation, both the C-index and AUC are greater than 0.7.

Accurate risk stratification of patients with tumors such as CM is important because of the potential for heterogeneity in patient outcomes. Nomograms can provide a more personalized way to provide prognostic information to patients. However, there was no nomogram model to predict OS in patients with CM previously. For the first time, we established a nomogram model to evaluate OS in CM patients. We found that the C-index and AUC of the model were higher than that of TNM staging when age was added for prognostic analysis. To validate the nomogram, we performed 1,000 bootstrap resampling, which involved randomly selecting samples from the original dataset with replacement. This process allowed us to assess the stability and accuracy of the nomogram by evaluating its performance across multiple iterations. The calibration chart used to predict CM shows that there is a good consistency between the predicted OS probability and the actual OS probability. By establishing a nomogram, we can better predict the OS of CM patients. Based on our results, it can be inferred that the proposed nomogram is a valuable tool for predicting the OS of patients with CM using individualized patient information. More accurate survival prediction results can better provide patients with individualized treatment strategies.

However, due to the limited information of the SEER database. The nomogram should be carefully used to evaluate patient OS. Molecular biological research is an important field for the treatment of CM at present (24-27). There have been studies to detect the genetic characteristics of CM patients, and frequent mutations in BRAF (46.7%, 7/15), NRAS (26.7%, 4/15), NF1 (20%, 3/15) and TERT promoter (46.7%, 7/15) have been found in CM patients (28,29), It is also found that targeted therapy (TT) (BRAF ± MEK inhibitor) (30,31) or immune checkpoint inhibitor (ICI) [anti-programmed cell death protein 1 (PD-1) ± anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4)] can improve the survival of patients with advanced CM (28,32). However, we have not obtained such data from the SEER database. In our clinical practice, it is not easy to obtain cytogenetic data. This requires more investment and support. In addition, the cohort studied spans the years 2000 to 2019. However, current treatment modalities available for cutaneous melanoma are now often available to CM patients and have dramatically changed their chances in recent years. Patients early in the cohort were unlikely to have received current molecular therapies. We will consider these indicators and more other factors in further research to build a more advanced prediction model.

Our study, however, has several limitations. Firstly, retrospective studies based on the SEER database may have bias. Additionally, the incidence of conjunctival malignant melanoma is low. Although we had access to 19 years of data from the SEER database, the sample size is still relatively small, which may limit the predictive power of our model. Secondly, some important data, such as detailed treatment methods, molecular biology factors, which hindered further analysis. Furthermore, our nomogram was developed using the 6th edition of the AJCC TNM staging system. As the field has advanced and the 8th edition of the AJCC staging system has been introduced, further refinement of our nomogram is necessary to ensure its applicability to the current standard. Moreover, we only included patients with complete details, which may introduce selection bias. Finally, our nomogram was constructed and evaluated among patients in the SEER database, and therefore, external validation is required for other populations.

Conclusions

In conclusion, we have developed and validated a nomogram model that can predict the OS rate of patients with conjunctival malignant melanoma. The model's prognostic value is higher than that of the AJCC staging system alone. This tool can help evaluate the tumor-specific prognosis, identify patients at high risk of cancer-specific death, and guide clinical decision-making. External validation and larger prospective studies are needed to further validate the model's utility.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1277/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1277/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1277/coif). 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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