A Novel Nomogram to predict survival of patients with choroidal melanoma

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Research article

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Abstract

Aim

The purpose of this study is to develop and validate a prediction model of overall survival (OS) in choroidal melanoma patients.

Methods

A total of 3415 patients with choroidal melanoma from 2004 to 2015 were collected from the Surveillance, Epidemiology, and End Results database. A novel nomogram was built based on independent risk factors evaluated by Cox proportional hazards regression model. And internal validations were performed to assess the performance of our nomogram by concordance index (C-index), calibration plot and decision curve analysis (DCA).

Results

Seven factors (age at diagnosis, race, sex, American Joint Committee for Cancer (AJCC) primary tumor (T) category, histological type, marital status and total number of primary tumors) were prognostic factors of OS. These factors were used to conduct a prediction model. The predictive accuracy of the nomogram for the OS has been stable at about 0.72 from 36 to 60 months evaluated by C-index. The calibration plots showed that the OS was also consistent between prediction and actual observation. Moreover, the DCA indicated our nomogram had better net benefit than the T-category.

Conclusion

The nomogram predicting the OS of choroidal melanoma may assist clinicians to decide treatment options individually.

1. Introduction

Uveal melanoma (UM) is not only the most common intraocular malignant tumor in adults but also the second most common melanoma[1, 2]. According to different primary sites, UM can be divided into the iris, ciliary body and choroidal tumors, among which choroidal melanoma accounts for more than 90%[3]. Unlike cutaneous melanomas, nearly half of choroidal melanoma develops hematogenous metastasis, whose median survival is only 3.6 months[4]. And although the latest immunotherapy has been successful in treating patients with cutaneous melanoma, its effect on UM is very limited[5, 6]. Due to a high rate of distant metastasis, limited treatment and poor prognosis, it is urgently needed to further understand choroidal melanoma.

So far, multiple clinicopathological variables such as pathologic and genetic factors, are used to predict prognosis and guide clinical management. The increasing tumor size, largest basal tumor diameter, tumor thickness, ciliary body involvement and extraocular spread are all considered as important clinical characteristics[3, 7]. When the thickness of the choroidal melanoma is less than 3 mm, the 10-year mortality rate is about 12%. And when it is greater than 8 mm, the 10-year mortality rate can be as high as 49%. Hence, the American Joint Committee on Cancer (AJCC) combined these clinical features to evaluate tumor staging for predicting poor prognosis. Also, chromosome abnormalities monosomy 3, loss of 6q and additional copies of 8q are all closely related to the poor outcome of patients with choroidal melanoma[8, 9]. However, a comprehensive prediction model including various prognostic factors for the survival of choroidal melanoma patients is still lacking.

With the promotion of precision medicine, the prognostic models of cancer have been widely used to assist in decision-making and manage patient prognosis. One method is the nomogram. According to the regression coefficient of each variable in the multivariate regression model, each subtype of variables is scored by the nomogram. And then a total score can be calculated. Finally, the possibility of an individual occurrence of outcome events can be predicted by nomogram through analyzing the relationship between the total score and the outcome event. In this study, we will conduct and validate a nomogram to predict the overall survival (OS) of choroidal melanoma patients.

2. Material And Methods

2.1 Patient selection

In this study, all cases were obtained by the SEER*Stat software (version 8.3.6) from the Surveillance, Epidemiology, and End Results (SEER) database, which covers publicly cancer data of 28% of the United States population[10]. The inclusion criteria were: 1. primary site record C69.3: choroid, based on the Third Edition of International Classification of Diseases for Oncology (ICD-O-3); 2. histological type limited to common histological types of choroidal melanoma (ICD-O-3 codes: 8720/3, 8770/3, 8771/3 and 8772/3). The exclusion criteria were: unknown/ incomplete information on variables including survival time, age at diagnosis, sex, race, AJCC classification of primary tumor (T), histological type, marital status and total number of primary tumors.

2.2 Construction and verification of nomogram

We enrolled 3415 eligible patients from the SEER database from 2004 to 2015, and employed univariable and multivariable cox regression analyses to selected variables and build regression models. The hazard ratio (HR) was calculated to show the contribution degree of each variable. And the nomogram was established for predicting outcomes of choroidal melanoma patients based on the multivariate cox regression model. For the most efficient use of datasets, we used bootstrap resampling for internal validation. The concordance index (C-index) was used to test the discrimination of models and the calibration plot was conducted to evaluate the calibration of models. Furthermore, the clinical net benefit of prediction models was measured by the decision curve analysis (DCA).

2.3 Statistical analysis

In this study, the following variables were used: age at diagnosis, race, sex, AJCC classification of T, histological type, marital status and total number of primary tumors. Age at diagnosis was reclassified as “< 50”, “50–59”, “60–69”, “70–79” and “>=80”. The race was divided into “white” and “other”. The T-category was reclassified into “T1”, “T2”, “T3” and “T4”. In marital status, “Single”, “Widowed”, “Separated” and “Divorced” were all regrouped as “other”, and “Married” and “Unmarried or Domestic Partner” were divided into “Married or Unmarried Partner”. The OS was endpoints in this study. All statistical analyses were performed based on R statistical software (version 3.6.2). Extension packages, including “readxl”, “survival”, “rms”, “foreign”, “dplyr”, “pec” and “survminer” were also used. In addition, the DCA was performed based on the source file “stdca.r”. All statistical tests were two-tailed and P-value ≤ 0.05 was considered statistically significant.

3. Results

3.1 patient characteristics

The demographics and clinicopathological characteristics of patients are shown in Table 1. In all eligible cases, 60–69 years old (896, 26.24%), male (1786, 52.30%), white (3334, 97.63%) and T2 (1454, 42.58%) accounted for a higher proportion.

3.2 Identification of independent prognostic factors of choroidal melanoma

The cox proportional hazards models were applied to select risk and protective factors of choroidal melanoma. Univariate cox regression analyses indicated seven prognostic factors (age at diagnosis, race, sex, T-category, histological type, marital status and total number of primary tumors) of OS.

Moreover, as shown in Fig. 1, multivariable cox regression analysis indicated age at diagnosis (HR = 1.535, 95% confidence interval [CI] = 1.454 − 1.622), white person (HR = 1.908, 95% CI = 1.142–3.186), male (HR = 1.333, 95% CI = 1.161–1.530), malignant melanoma (HR = 0.621, 95% CI = 0.457–0.845), mixed epithelioid and spindle cell melanoma (HR = 1.193, 95% CI = 0.845–1.685), spindle cell melanoma (HR = 0.391, 95% CI = 0.252–0.608), T2 category (HR = 1.347, 95% CI = 1.142 − 1.588), T3 category (HR = 2.542, 95% CI = 2.078–3.110), T4 category (HR = 3.621, 95% CI = 2.802–4.678), married or unmarried partner (HR = 0.718, 95% CI = 0.624 − 0.826) and more than one primary tumors (HR = 0.634, 95% CI = 0.529 − 0.759) were prognostic factors for OS.

Forest plot of prognostic factors of OS based on multivariate cox regression analysis. OS: overall survival

3.3 Construction of nomogram

The nomogram calculating 3- and 5- years OS of choroidal melanoma patients were developed based on the multivariate cox regression analyses. For example, if a 73 years old white married female patient had

only epithelioid cell melanoma with T2 category, she would get 212 points according to our nomogram. This means the third-year survival rate of her is around 77% and the fifth-year survival rate is about 62%. The nomograms were shown in Fig. 2.

Nomogram predicting 3 and 5-year OS of choroidal melanoma patients. OS: overall survival

3.4 Verification of nomogram

For the most use of the dataset, we employed bootstrap resampling to validate the nomogram. When compared with simple T-category, the c-index showed our nomogram presented good discrimination with 1000 bootstraps from 36 months to 60 months (Fig. 3A). The calibration plots also indicated that the nomogram had good calibration (Fig. 3B). Moreover, the nomogram has shown better clinical net benefit in both 3 and 5 years of OS prediction than the T-category by DCA (Fig. 3C).

The C-index evaluating the nomogram predicting (A) OS of choroidal melanoma patients from 36 months to 60 months by bootstrap resampling. Calibration plots for validation of the nomogram predicting (B) 3 and 5-year OS of choroidal melanoma patients. Decision curve analyses for validation of the nomogram predicting (C) 3 and 5-year OS of choroidal melanoma patients. The gray line: none of the patients died. The black line: all patients died. The black dotted line: model of nomogram. The red dotted line: model of T-category. OS: overall survival; C-index: concordance index.

4. Discussion

UM is a kind of rare malignant tumor, with around 1500 new cases each year in American. The 5-year relative survival of ocular melanoma is 78.4%. However, once patients develop distant metastases occurred, the reported 5-year survival rate would be around 16% [11]. Hence, the accurate prediction of patient outcome is critical to the selection of the optimal therapeutic strategy and improving the survival of patients. Here, we built and validated nomogram predicting the OS of choroidal melanoma in the light of the SEER database.

Mariani et al[12] developed a nomogram for liver metastasis in patients with UM and found the interval between the diagnosed and liver metastases < 6 months, more than 10 metastases of liver, a maximum liver metastasis area over 1200 mm^2 and lactate dehydrogenase (LDH) value > 1.5 were risk prognostic predictors for patients. However, this study only retrospectively enrolled 224 patients from a single center. Valpione et al[13] also conducted a prognostic nomogram for metastatic UM including two cohorts and 254 patients and reported area of liver involvement, the increased value of serum LDH and a World Health Organization performance status between 2 and 3 were prognostic risk factors. Although more and more scholars have begun to pay attention to the prediction of tumor survival rate, the prediction model of the survival rate of choroidal melanoma is still lacking.

Over the last decades, the incidence rate of UM has been increasing, especially among white people[14, 15]. However, for this rare disease, few studies have analyzed the prognostic differences between

different races. Cormeier et al[16] reported that non-Caucasians are more likely to be in advanced stages of cutaneous melanoma than whites. Interestingly, a study shows that there is no difference in mortality among different races in UM[17]. And in our study, we found white is an independent prognostic risk factor in both univariate and multivariate regression. The result may be influenced by the small sample size of non-Caucasians patients, and need to be verified by a larger sample size cohort study.

Multiple primary cancers are relatively uncommon[18], and whether patients with UM are more likely to have multiple primary cancers remains controversial[19, 20]. In our study, we discovered that choroidal melanoma patients with multiple primary cancers are a protective factor for the first time. Marzena et al[21] once reported choroidal melanoma patients with a family history of cancer, higher education, living in cities, previous surgery history except for UM, and female pregnancy two or less than two were more likely to be detected with multiple primary cancers. And these factors may be useful for early detection or treatment and prolong survival.

However, there were still some limitations to this study. The genetic (chromosome abnormalities monosomy 3, loss of 6q and additional copies of 8q) and genomic abnormalities are also predictors of patient outcome[22–24]. Besides, many circulating biochemical markers, yet to be studied, may play important roles in predicting the prognosis of choroidal melanoma as well[25, 26]. Unfortunately, due to the lack of these data in the SEER database, these factors cannot be included in this retrospective study. We also need to use an external cohort to verify the transportability and generalizability of the nomograms[27], and this will be our next research direction. Besides, due to the latest data having not been updated, our study only adopted the 7th AJCC TNM staging. Furthermore, our nomogram will be optimized on the basis of the 8th AJCC TNM staging.

5. Conclusion

In conclusion, we found that old white unmarried male patients with T4 category choroidal melanoma had shorter OS. Furthermore, we developed and validated two nomograms based on these variables to predict 3 and 5- year OS of patients with choroidal melanoma. And our prognostic models may assist clinical medical decision-making and managing patient prognosis.

Abbreviations

OS
overall survival
C-index
concordance index
DCA
decision curve analysis
AJCC
American Joint Committee for Cancer

T
tumor category
UM
Uveal melanoma
SEER
The Surveillance, Epidemiology, and End Results database
ICD-O-3
Third Edition of International Classification of Diseases for Oncology
HR
hazard ratio
CI
confidence interval
LDH
lactate dehydrogenase

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this study, because the data used in this study were obtained from the SEER database in a publicly available manner.

Consent for publication

Not applicable.

Conflicts of interest

The authors declare that they have no competing interests.

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Authors’ contributions

YY, XTH conceived of and designed the study protocol. WZY, WTT, ZLP collected the data. WZY, WWJ, CYZ, GLX and ZMY were involved in the analysis. WZY, WTT and GLX wrote the first draft of the

manuscript. YY, XTH and ZMY reviewed and revised the manuscript and produced the final version. All authors read and approved the final manuscript.

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Tables

Table 1
patient characteristics

Variables	No.	%
Cases evaluated	3415	100
Age at diagnosis		
< 50	653	19.12
50–59	867	25.39
60–69	896	26.24
70–79	653	19.12
>= 80	346	10.13
Sex		
Male	1786	52.30
Female	1629	47.70
Race		
White	3334	97.63
Other	81	2.37
Histological type		
Malignant melanoma, NOS	2868	83.98
Mixed epithelioid and spindle cell melanoma	253	7.41
Epithelioid cell melanoma	97	2.84
Spindle cell melanoma	197	5.77
T-category		
T1	1238	36.25
T2	1454	42.58
T3	519	15.20
T4	204	5.97
Marital status		
Married or Unmarried Partner	2272	66.53
Other	1143	33.47
Number of primary malignant tumors		

Variables	No.	%
1	2742	80.29
>=2	673	19.71

Table 2
Univariate Cox regression analysis for overall survival

Univariate analysis		
	HR (95% CI)	**P value**
Age at diagnosis		
< 50	1 (Reference)	
50–59	1.586 (1.237–2.034)	< 0.001
60–69	1.859 (1.457–2.371)	< 0.001
70–79	2.839 (2.230–3.614)	< 0.001
>= 80	5.708 (4.451–7.320)	< 0.001
Sex		
Female	1 (Reference)	
Male	1.177 (1.031–1.344)	0.016
Race		
Other	1 (Reference)	
White	1.512 (0.908–2.519)	0.112
Histological type		
Epithelioid cell melanoma	1 (Reference)	
Malignant melanoma	0.399 (0.295–0.540)	< 0.001
Mixed epithelioid and spindle cell melanoma	0.995 (0.706–1.401)	0.976
Spindle cell melanoma	0.272 (0.175–0.421)	< 0.001
T-category		
T1	1 (Reference)	
T2	1.375 (1.166–1.620)	< 0.001
T3	2.638 (2.166–3.214)	< 0.001
T4	4.080 (3.184–5.229)	< 0.001
Marital status		
Other	1 (Reference)	
Married or Unmarried Partner	0.668 (0.585–0.764)	< 0.001

Univariate analysis		
Number of primary malignant tumors		
>=2	1 (Reference)	
1	1.336 (1.118–1.596)	0.001

Figures

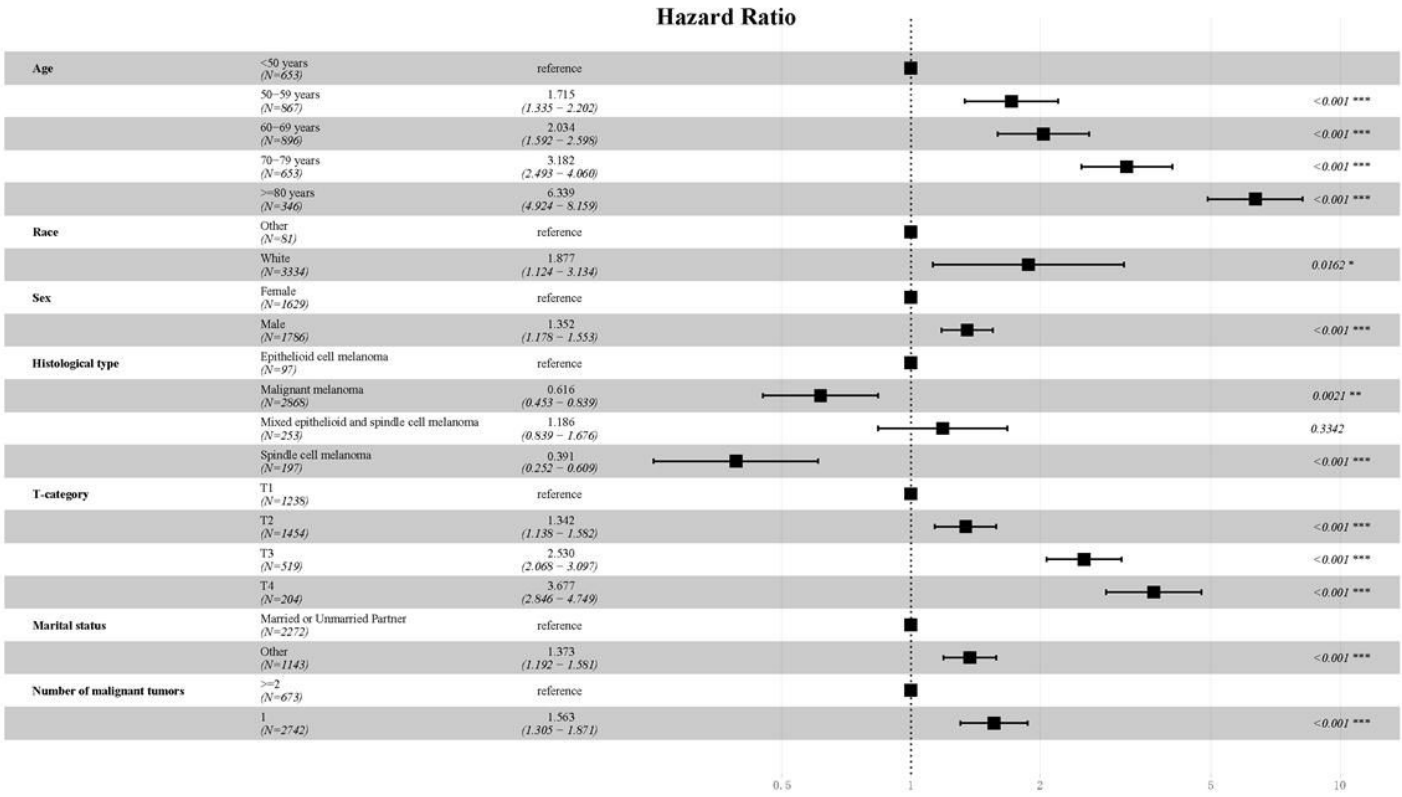

Figure 1

Effect of various factors on choroidal melanoma

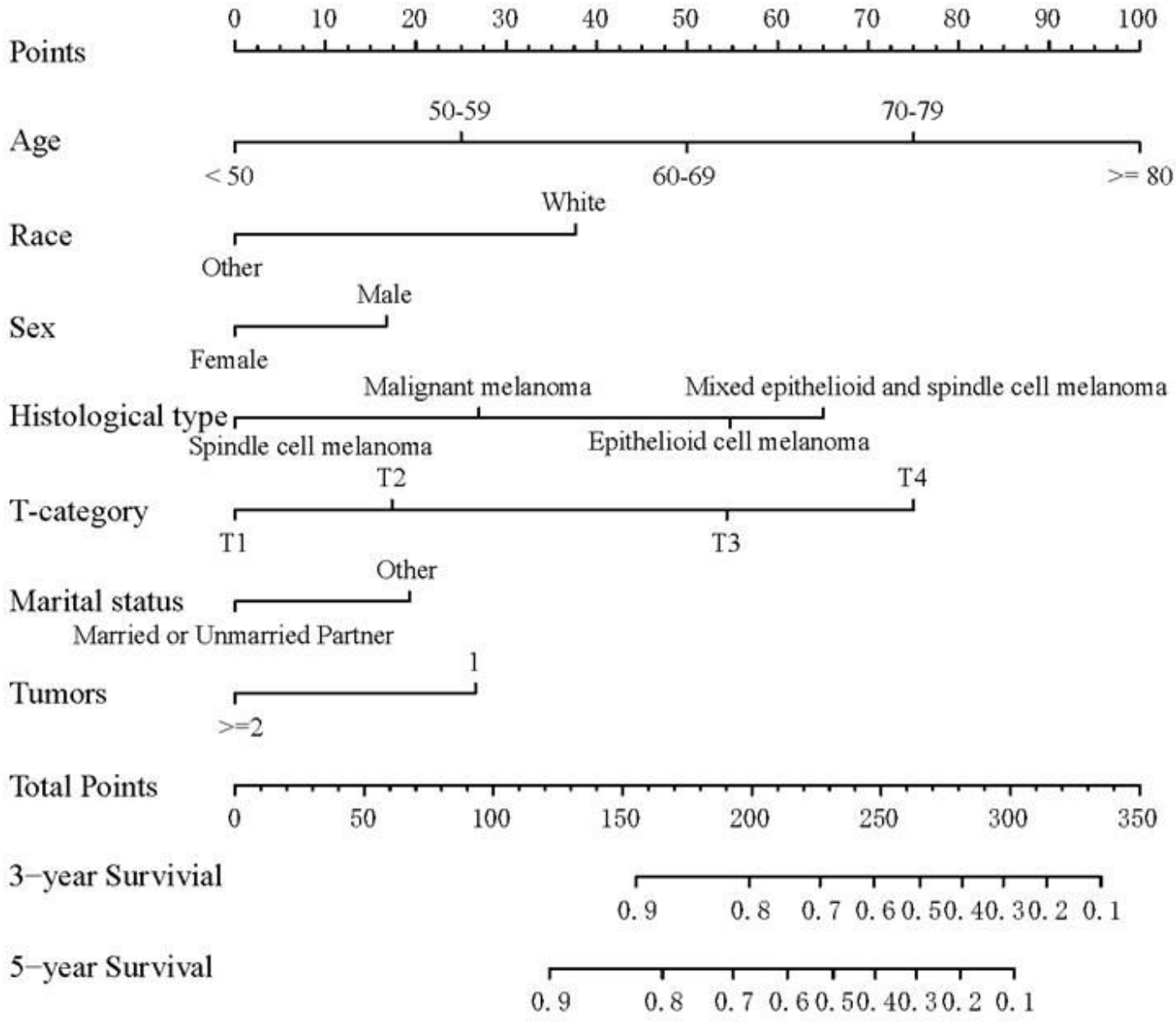

Figure 2

Development of the nomogram

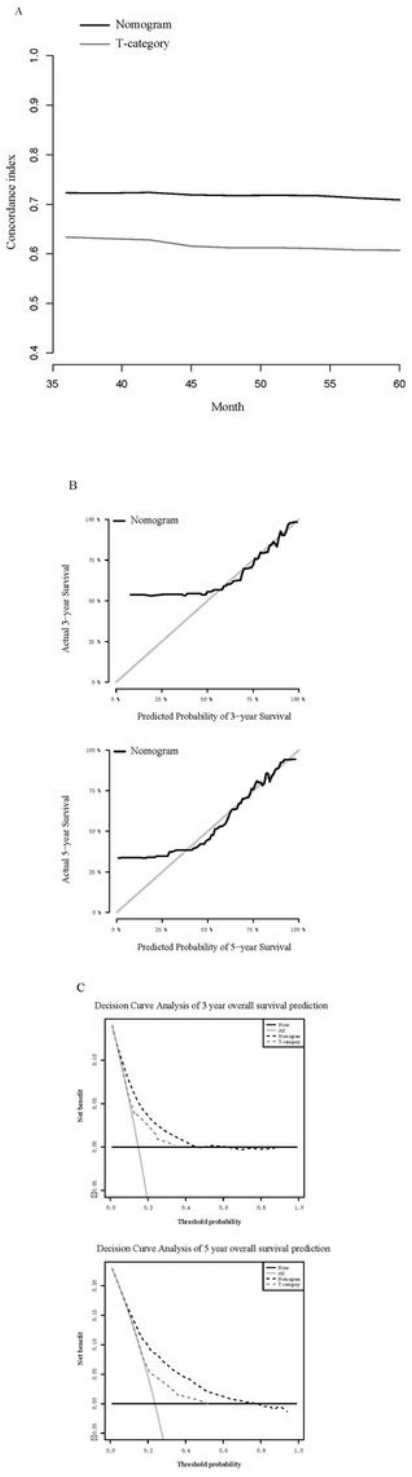

Figure 3

Validation of the nomogram