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Development and Validation of a Cox Regression-Based Nomogram for Predicting All-Cause Mortality in Patients with Early-Onset Cutaneous Melanoma

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Simple Summary

Early-onset cutaneous melanoma is uncommon but can lead to serious health consequences, and patients with the same disease stage may still have different survival outcomes. Therefore, more accurate methods are needed to estimate an individual patient's prognosis. In this study, we analyzed data from patients with early-onset cutaneous melanoma in the Surveillance, Epidemiology, and End Results database and developed a prediction tool based on multiple clinical and tumor-related factors. The tool showed better accuracy in predicting 3- and 5-year overall survival than the conventional American Joint Committee on Cancer staging system and showed good agreement between predicted and observed outcomes. These findings suggest that the proposed tool may help clinicians better identify patients with different levels of mortality risk and support individualized follow-up and treatment decisions.

Abstract

Background: Although the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) system is widely used for prognostic assessment in cutaneous melanoma, survival outcomes vary among patients with the same stage. We aimed to develop and validate a nomogram for individualized survival prediction in early-onset cutaneous melanoma. **Methods:** Patients with early-onset cutaneous melanoma were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Fifteen variables were analyzed using multivariable Cox regression to identify prognostic factors and construct a nomogram. Discrimination, calibration, reclassification, and clinical utility were evaluated. **Results:** The 3- and 5-year overall survival rates were 95.9% and 94.1%, respectively, with a median follow-up of 62 months. Thirteen factors independently predicted all-cause mortality (all $P < 0.05$): sex, age, tumor size, SEER stage, AJCC stage, marital status, radiotherapy, chemotherapy, surgery, regional lymph node removal, annual household income, mitotic rate, and ulceration. In the validation set, the nomogram had a higher concordance index than the AJCC system (0.902 vs. 0.862). In the testing set, the 3- and 5-year areas under the curve were 0.922 and 0.893, respectively, with good calibration. The nomogram showed incremental predictive value, positive net reclassification improvement (0.349/0.298), integrated discrimination improvement (0.060/0.084) (all $P < 0.05$), and greater net clinical benefit than the AJCC system. **Conclusions:** The SEER-derived nomogram demonstrated superior performance to the AJCC system and may support individualized mortality risk assessment and personalized follow-up and treatment in early-onset cutaneous melanoma.

Keywords: SEER; nomogram; Cox; cutaneous melanoma; early-onset

1.Introduction

According to 2024 statistics published by the American Cancer Society, melanoma ranks second only to colorectal cancer in incidence among men aged 49 and younger. For women in this same demographic, its occurrence is exceeded solely by breast and thyroid malignancies. Following a clinical diagnosis of melanoma, prognostic assessment becomes a central concern for both patients and clinicians. However, clinicians face significant challenges in estimating patient survival, particularly in predicting survival time for patients with advanced-stage disease, where uncertainty is substantially greater. Such prognostic inaccuracies often lead to difficulties in physician–patient communication and challenges in clinical decision-making. Currently, the TNM staging system established by the AJCC, according to the extent of the primary tumor (T), regional lymph node status (N), and the presence of distant metastasis (M), remains the principal standard for prognostic assessment in cutaneous melanoma. However, studies have demonstrated substantial heterogeneity in survival outcomes among patients with the same stage who receive standardized treatment, suggesting limitations of this staging system in treatment optimization and prognostic prediction[1]. The main limitations are as follows: (1) limited variable coverage, as key prognostic variables such as demographic parameters and pathological characteristics are not included; (2) a singular evaluation dimension, lacking a quantitative model that integrates multiple factors to predict individualized survival probabilities. Given that tumor biological behavior is regulated by multidimensional factors, constructing a predictive tool that integrates multiple variables is of significant value for achieving precise risk stratification and personalized medicine.

Nomograms, as integrated predictive tools, combine multiple parameters and present them through a visual interface, enabling the rapid estimation of the probability of specific clinical outcomes within a given time window. This tool not only supports prognostic risk stratification, but also provides evidence to guide individualized treatment planning and follow-up strategies. At present, it has been widely applied in prognostic assessments for various malignancies. Unlike the conventional TNM staging framework, nomograms provide the flexibility to flexibly incorporate specific prognostic factors, facilitating the creation of tailored predictive models for distinct patient cohorts and thereby driving individualized survival risk stratification and clinical guidance[2]. Drawing upon data from early-onset melanoma cohorts in the US SEER repository, this study established a predictive nomogram to estimate 3- and 5-year overall survival probabilities. The model's discriminative performance and clinical applicability were rigorously assessed and validated, offering quantitative evidence to guide therapeutic decision-making and follow-up surveillance in routine practice.

2. Materials and Methods

2.1 Data Source

The data analyzed in this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) database, specifically the Incidence - SEER Research Data, 17 Registries, November 2023 Sub (2000–2021) dataset. The data were accessed through SEER*Stat software, version 8.4.4.

Early-onset cutaneous melanoma cases diagnosed between 2000 and 2021 were identified according to predefined eligibility criteria. Patients were required to be 15–49 years of age, have a single primary cancer diagnosis, and meet the relevant International Classification of Diseases for Oncology, Third Edition (ICD-O-3) criteria. Histological subtypes were identified using the following ICD-O-3 codes: 8720/3, 8721/3, 8722/3, 8723/3, 8730/3, 8740/3, 8741/3, 8742/3, 8743/3, 8744/3, 8745/3, 8746/3, 8761/3, 8770/3, 8771/3, 8772/3, 8773/3, 8774/3, 8780/3, and 8790/3. Anatomical sites were restricted to C44, C51.0, C60.9, and C63.2. Cases were excluded if clinical information was missing or unavailable, or if the diagnosis was not microscopically confirmed or was based exclusively on autopsy findings.

2.2 Data Preparation

Following literature review, data filtration, curation, and synthesis, the final parameters and sub-classifications integrated into the statistical evaluation comprised: sex (male, female); age groups (15-39, 40-44, and 45-49 years); racial background (White, Black, and other categories including American Indian/Alaska Native and Asian/Pacific Islander); primary tumor location (head and neck, trunk, extremities); tumor size (≤ 1 cm, 1.1-1.9 cm, ≥ 2 cm); SEER staging (localized, regional, distant); AJCC classification (stages I through IV); marital status (married, single, separated/divorced/widowed); radiotherapy, chemotherapy, and surgical interventions (each categorized as yes or no); regional lymph node clearance (yes, no); median annual household income levels (low: $< \$54,999$; intermediate: $\$55,000$ - $\$94,999$; high: $> \$95,000$); mitotic rate (none, $< 1/\text{mm}^2$, $\geq 1/\text{mm}^2$); and ulceration status (absent, present). For this segment of the research, all-cause mortality served as the primary endpoint. Overall survival (OS) duration was quantified from the initial cutaneous melanoma diagnosis to either death resulting from any cause or the final censorship date.

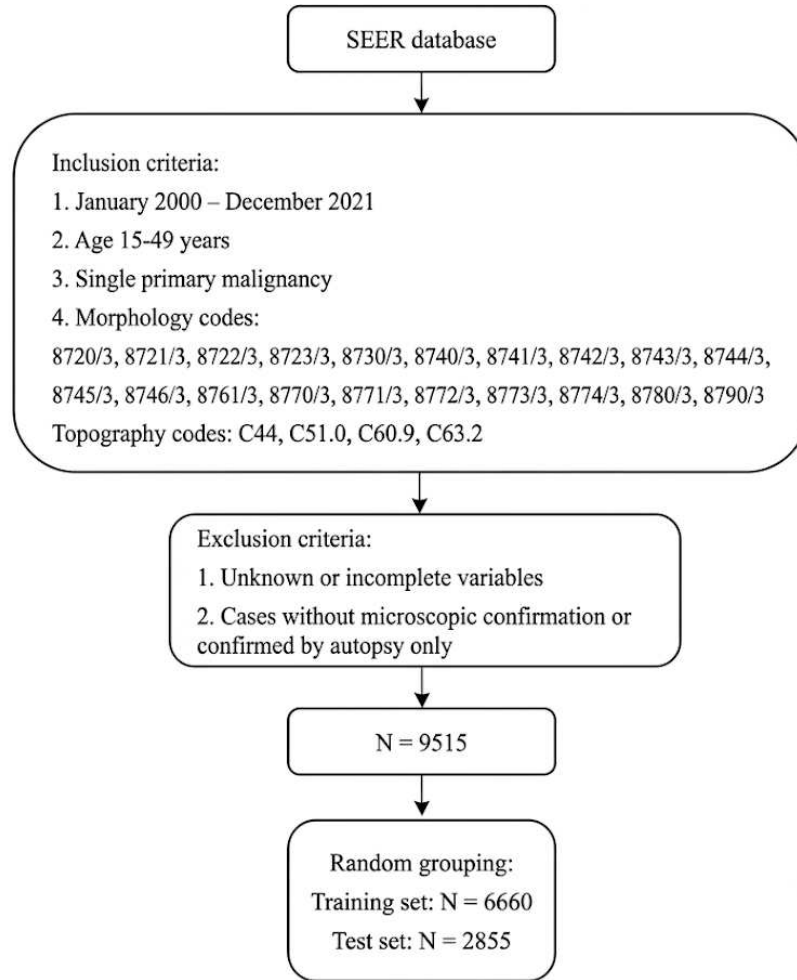


Figure 1. Screening Process for Cases of Early-Onset Cutaneous Melanoma

2.3 Statistical Analysis

1) Survival analysis

Categorical data are summarized using relative frequencies (percentages). Kaplan-Meier survival curves were generated to estimate 3- and 5-year overall survival probabilities for individuals with early-onset cutaneous melanoma. Furthermore, the log-rank test was utilized to determine the statistical significance of survival variations across different strata.

2) Variable Selection and Predictive Model Development

Patient records were randomly allocated into a training cohort and a validation cohort at a 7:3 ratio via R software. Initially, bidirectional stepwise selection was executed on the training set to screen candidate features. These filtered covariates were subsequently integrated into a multivariable Cox proportional hazards regression model to isolate independent prognostic indicators of all-cause mortality for early-onset cutaneous melanoma ($P < 0.05$). Guided by

these confirmed factors, a personalized nomogram was established to predict 3- and 5-year all-cause mortality probabilities.

3) Model Validation

The testing dataset served to internally validate the nomogram across multiple metrics:

(1) Discrimination: We derived the C-index and ROC-derived AUC values to contrast the model's performance with traditional AJCC staging. C-index scores span 0.5 to 1.0, with values exceeding 0.7 representing acceptable discrimination and those ≥ 0.9 indicating superior efficacy. The AUC functions as an indicator of predictive accuracy, following valuation thresholds analogous to the C-index.

(2) Calibration Performance: Bootstrap resampling (500 iterations) is applied to plot and evaluate calibration curves, with the x-axis representing model predicted probabilities and the y-axis representing actual observed probabilities. The calibration accuracy of the model's predicted probabilities is assessed by comparing the degree of deviation between the fitted curve (solid black line) and the ideal calibration line (dashed red line).

(3) Model improvement: We examined the superior predictive value of the nomogram versus AJCC staging through Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) indices. NRI determined whether the proposed model improved patient reclassification precision compared to the established system, evaluating the overall accuracy gains of risk category shifts[3]. In contrast, IDI focuses on individual-level probability variations between the novel and conventional frameworks, measuring how effectively the new model enhances discrimination capability regarding patients with versus without the outcome event[4]. The specific calculation formulas for NRI (Net Reclassification Improvement) and IDI (Integrated Discrimination Improvement) are as follows: $NRI = (Sensitivity_{new_model} + Specificity_{new_model}) - (Sensitivity_{old_model} + Specificity_{old_model})$; $IDI = (P_{new,events} - P_{old,events}) - (P_{new,non-events} - P_{old,non-events})$. Where: $P_{new,events}$: represents the mean predicted probability of outcome for the new model, $P_{old,events}$: represents the mean predicted probability of outcome for the old model, $P_{new,non-events}$: represents the mean predicted probability of non-outcome for the new model, $P_{old,non-events}$: represents the mean predicted probability of non-outcome for the old model. Directional interpretation of NRI and IDI: A positive value (>0) indicates that the new model has better predictive performance than the original model. A value of zero ($=0$) suggests no difference in predictive performance between the two models. A negative value (<0) indicates that the new model has inferior predictive performance relative to the original model.

(4) Clinical utility assessment: Decision curve analysis (DCA), a novel approach for evaluating clinical prediction models, was first introduced by Andrew Vickers in 2006[5]. DCA, also known as a clinical decision curve, assesses clinical usefulness by quantifying the model's net benefit. Unlike traditional ROC curves, which primarily focus on accuracy-related metrics such as sensitivity and specificity, DCA incorporates clinical decision preferences by

using the concept of threshold probability. In this way, model performance is closely linked to real-world clinical decision needs[6, 7]. In this study, DCA was subsequently implemented to appraise the clinical net benefit yielded by the established predictive models.

All computations and statistical evaluations were executed via SPSS software (v26.0; IBM Corp., Armonk, NY, USA) and R environment (v4.1.1; <https://www.R-project.org>). A two-sided P-value threshold below 0.05 was adopted to indicate statistical significance across all analyses.

3. Results

3.1 Baseline Characteristics

A cohort of 9,515 early-onset cutaneous melanoma cases satisfying the selection criteria was extracted from the SEER database for the years 2000–2021. Via R, subjects were split at a 7:3 ratio into a training subset (n = 6,660, 70%) for constructing the nomogram and a testing subset (n = 2,855, 30%) for evaluation. Across the entire study group, there were 4,074 male subjects (42.82%) and 5,441 female subjects (57.18%). Age distribution categories consisted of 15–39 years (n = 4,580, 48.13%), 40–44 years (n = 2,091, 21.98%), and 45–49 years (n = 2,844, 29.89%). Primary tumor locations comprised the head and neck (n = 1,476, 15.51%), trunk (n = 3,570, 37.52%), and limbs (n = 4,469, 46.97%). Table 1 outlines the complete baseline demographic and clinical features of the total cohort, training group, and validation group.

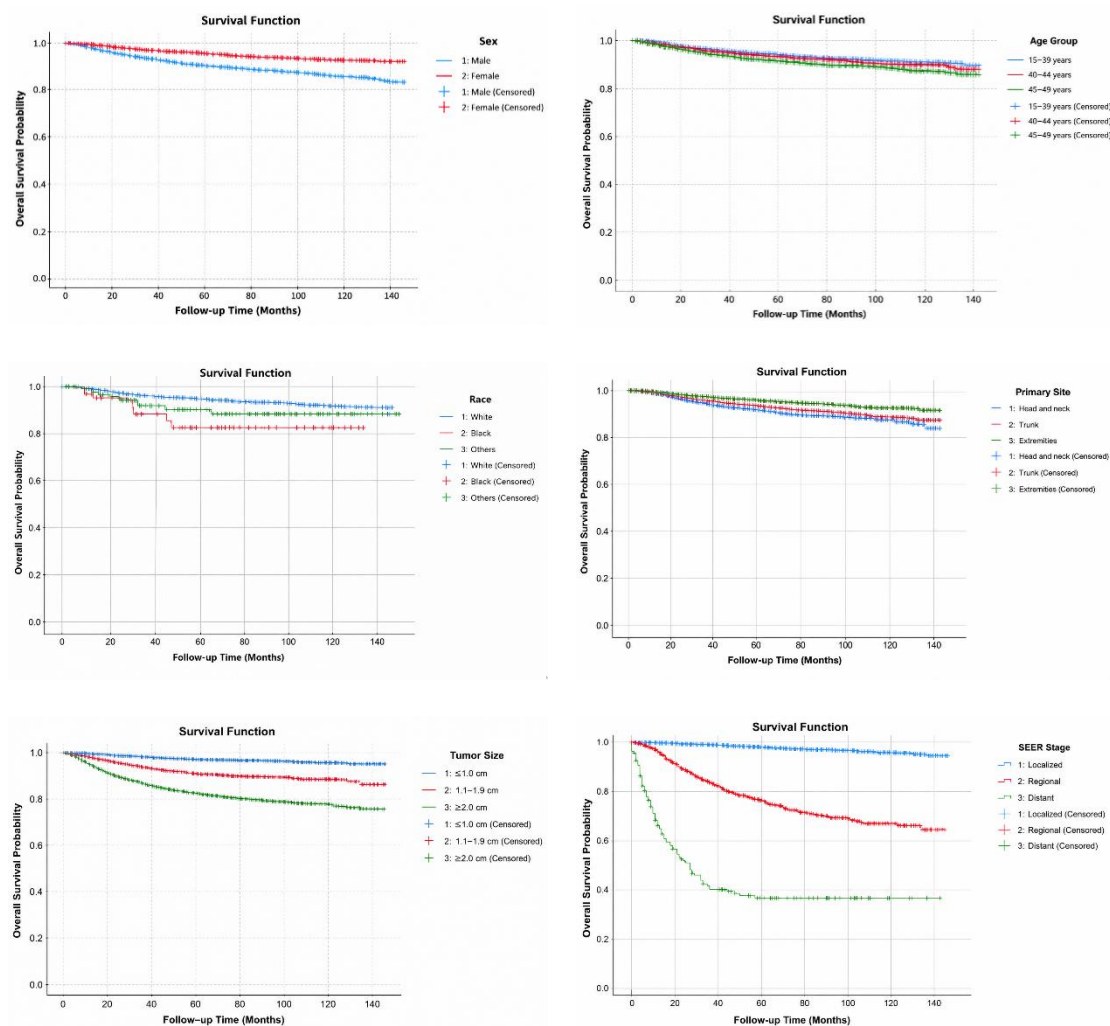
Table 1. Baseline patient demographics and clinical attributes

Variable	Overall Cohort (N = 9,515) n (%)	Training Cohort (N = 6,660) n (%)	Validation Cohort (N = 2,855) n (%)	<i>P</i>
Sex				0.737
Male	4,074 (42.82)	2,859 (42.93)	1,215 (42.56)	
Female	5,441 (57.18)	3,801 (57.07)	1,640 (57.44)	
Age, years				0.499
15–39	4,580 (48.13)	3,226 (48.44)	1,354 (47.43)	
40–44	2,091 (21.98)	1,443 (21.67)	648 (22.70)	
45–49	2,844 (29.89)	1,991 (29.89)	853 (29.88)	
Race				0.215
White	9,325 (98.00)	6,525 (97.97)	2,800 (98.07)	
Black	43 (0.45)	26 (0.39)	17 (0.60)	
Others	147 (1.54)	109 (1.64)	38 (1.33)	
Primary Site				0.084
Head and neck	1,476 (15.51)	1,069 (16.05)	407 (14.26)	
Trunk	3,570 (37.52)	2,479 (37.22)	1,091 (38.21)	
Extremities	4,469 (46.97)	3,112 (46.73)	1,357 (47.53)	
Tumor Size				0.143
≤1.0 cm	6,347 (66.71)	4,401 (66.08)	1,946 (68.16)	
1.1–1.9 cm	1,947 (20.46)	1,388 (20.84)	559 (19.58)	
≥2.0 cm	1,221 (12.83)	871 (13.08)	350 (12.26)	
SEER Stage				0.728
Localized	8,094 (85.07)	5,661 (85.00)	2,433 (85.22)	
Regional	1,259 (13.23)	881 (13.23)	378 (13.24)	
Distant	162 (1.70)	118 (1.77)	44 (1.54)	
AJCC Stage				0.156
I	7,209 (75.76)	5,018 (75.35)	2,191 (76.74)	
II	993 (10.44)	724 (10.87)	269 (9.42)	
III	1,197 (12.58)	833 (12.51)	364 (12.75)	

Variable	Overall Cohort (N = 9,515) n (%)	Training Cohort (N = 6,660) n (%)	Validation Cohort (N = 2,855) n (%)	P
IV	116 (1.22)	85 (1.28)	31 (1.09)	
Marital Status				0.263
Married	5,805 (61.01)	4,028 (60.48)	1,777 (62.24)	
Single	3,062 (32.18)	2,175 (32.66)	887 (31.07)	
Separated/Divorced/Widowed	648 (6.81)	457 (6.86)	191 (6.69)	
Radiotherapy				0.363
Yes	134 (1.41)	89 (1.34)	45 (1.58)	
No	9,381 (98.59)	6,571 (98.66)	2,810 (98.42)	
Chemotherapy				0.679
Yes	209 (2.20)	149 (2.24)	60 (2.10)	
No	9,306 (97.80)	6,511 (97.76)	2,795 (97.90)	
Surgery				0.331
Yes	9,438 (99.19)	6,610 (99.25)	2,828 (99.05)	
No	77 (0.81)	50 (0.75)	27 (0.95)	
Regional Lymph Node Dissection				0.282
Yes	4,656 (48.93)	3,283 (49.29)	1,373 (48.09)	
No	4,859 (51.07)	3,377 (50.71)	1482 (51.91)	
Median Household Income				0.099
Low income	700 (7.36)	465 (6.98)	235 (8.23)	
Medium income	6,257 (65.76)	4,402 (66.10)	1,855 (64.97)	
High income	2,558 (26.88)	1,793 (26.92)	765 (26.80)	
Mitotic Rate				0.468
None	3,684 (38.72)	2,555 (38.36)	1,129 (39.54)	
< 1/mm ²	1,051 (11.05)	732 (10.99)	319 (11.17)	
≥ 1/mm ²	4,780 (50.24)	3,373 (50.65)	1,407 (49.28)	
Ulceration Status				0.647
Absent	8,255 (86.76)	5,785 (86.86)	2,470 (86.51)	
Present	1,260 (13.24)	875 (13.14)	385 (13.49)	

3.2 Kaplan–Meier Survival Analysis

With a median tracking duration of 62 months, the 3-year and 5-year overall survival rates for early-onset cutaneous melanoma cases reached 95.9% and 94.1%, respectively. Screening via univariate analysis revealed that gender, age categories, race, anatomical site, tumor size, SEER and AJCC stages, marital status, radiation therapy, chemotherapy, surgery, regional lymph node clearance, median family income, mitotic features, and ulceration were all statistically significant prognostic predictors (all $P < 0.05$). Figure 2 depicts the corresponding Kaplan-Meier survival curves, whereas detailed survival percentages and between-group significance testing from log-rank assessments are presented in Table 2.



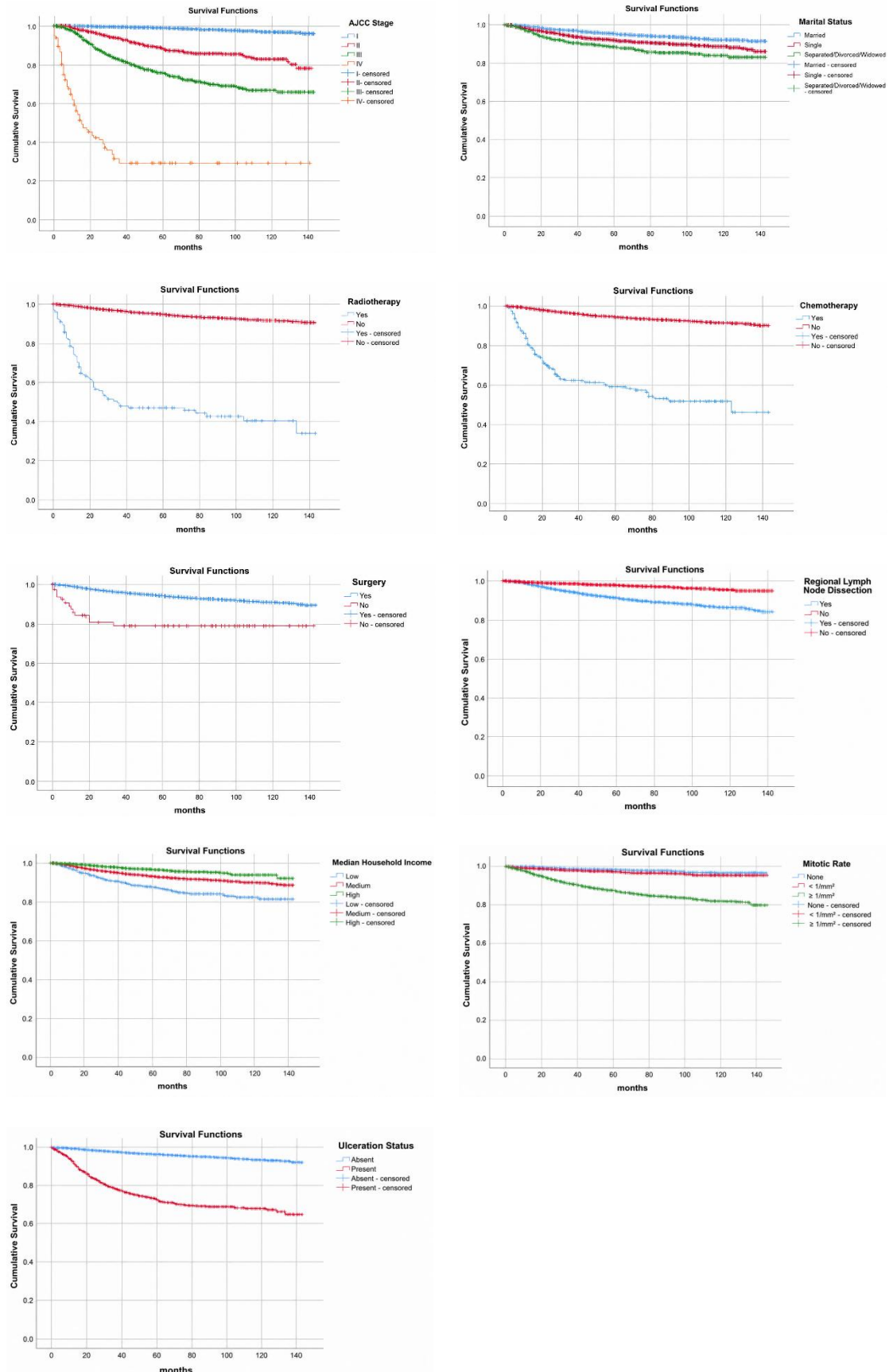


Figure 2 . Kaplan-Meier survival plots of the early-onset cutaneous melanoma cohort

Table 2 . Overall Survival Rates According to Baseline Characteristics

Variable	3-year OS (%)	5-year OS (%)	P value
Overall Population	95.9	94.1	
Sex			< 0.001
Male	93.9	91.2	
Female	97.4	96.4	
Age (years)			0.002
15-39	96.6	95.0	
40-44	95.8	94.2	
45-49	94.9	92.8	
Race			0.037
White	96.0	94.2	
Black	90.8	83.5	
Other	92.5	88.9	
Primary Site			< 0.001
Head and Neck	94.5	92.3	
Trunk	95.6	93.5	
Extremities	96.7	95.3	
Tumor Size			< 0.001
≤ 1 cm	98.4	97.4	
1.1-1.9 cm	94.5	91.6	
≥ 2 cm	85.0	81.3	
SEER Stage			< 0.001
Localized	98.9	98.0	
Regional	83.6	76.6	
Distant	40.7	37.4	
AJCC Stage			< 0.001
I	99.4	98.9	
II	93.4	88.4	
III	82.8	76.0	

Variable	3-year OS (%)	5-year OS (%)	P value
IV	29.3	-	
Marital Status			< 0.001
Married	97.1	95.5	
Single	94.5	92.5	
Separated/Divorced/Widowed	91.4	89.1	
Radiotherapy			< 0.001
Yes	47.9	45.8	
No	96.6	94.8	
Chemotherapy			< 0.001
Yes	62.4	59.2	
No	96.7	94.9	
Surgery			< 0.001
Yes	96.0	94.2	
No	79.6	-	
Regional Lymph Node Dissection			< 0.001
Yes	93.7	90.8	
No	98.0	97.3	
Median Household Income			< 0.001
Low income	91.4	88.6	
Middle income	95.7	94.0	
High income	97.8	96.4	
Mitotic Rate			< 0.001
None	99.2	98.9	
< 1 / mm ²	98.9	97.8	
≥ 1 / mm ²	92.7	89.7	
Ulceration Status			< 0.001
Absent	98.2	97.0	
Present	80.8	75.4	

3.3 Identification of Prognostic Factors and Development of the Predictive Model

Utilizing the training set, we evaluated fifteen clinical and demographic features (sex, age, race, tumor site and size, SEER and AJCC stages, marital status, receipt of radiotherapy, chemotherapy, or surgery, regional lymph node clearance, median family income, mitotic features, and ulceration) via bidirectional stepwise selection. These chosen variables were further analyzed within a multivariable Cox proportional hazards framework to determine independent prognostic factors for all-cause survival outcomes in early-onset cutaneous melanoma cases ($P < 0.05$).

Multivariable Cox modeling revealed that sex, age, tumor size, SEER staging, AJCC classification, marital status, receipt of radiotherapy, chemotherapy, or surgical treatment, regional lymph node dissection, household income, mitotic status, and ulceration status served as independent prognostic indicators for all-cause mortality in early-onset cutaneous melanoma ($P < 0.05$). Specifically, age 45-49 years (vs. 15-39 years: HR = 1.30, 95% CI: 1.03-1.65; $P = 0.028$), tumor size 1.1-1.9 cm (vs. ≤ 1 cm: HR = 1.56, 95% CI: 1.20-2.02; $P < 0.001$), tumor size ≥ 2 cm (vs. ≤ 1 cm: HR = 1.84, 95% CI: 1.42-2.39; $P < 0.001$), regional metastasis (vs. localized: HR = 1.95, 95% CI: 1.19-3.19; $P = 0.008$), distant metastasis (vs. localized: HR = 2.58, 95% CI: 1.23-5.43; $P = 0.012$), Stage II (vs. Stage I: HR = 3.44, 95% CI: 2.29-5.15; $P < 0.001$), Stage III (vs. Stage I: HR = 4.30, 95% CI: 2.37-7.80; $P < 0.001$), Stage IV (vs. Stage I: HR = 8.69, 95% CI: 3.80-19.84; $P < 0.001$), single status (vs. married: HR = 1.56, 95% CI: 1.25-1.95; $P < 0.001$), separated/divorced/widowed status (vs. married: HR = 1.50, 95% CI: 1.07-2.09; $P = 0.018$), no surgery (vs. surgery: HR = 4.54, 95% CI: 2.44-8.42; $P < 0.001$), no regional lymph node dissection (vs. regional lymph node dissection: HR = 1.63, 95% CI: 1.20-2.21; $P = 0.002$), mitotic rate $\geq 1 / \text{mm}^2$ (vs. none: HR = 1.87, 95% CI: 1.26-2.78; $P = 0.002$), and presence of ulceration (vs. absence: HR = 1.74, 95% CI: 1.38-2.20; $P < 0.001$) were identified as independent risk factors for all-cause mortality. In contrast, female sex (vs. male: HR = 0.70, 95% CI: 0.57-0.87; $P = 0.001$), no radiotherapy (vs. radiotherapy: HR = 0.49, 95% CI: 0.35-0.70; $P < 0.001$), no chemotherapy (vs. chemotherapy: HR = 0.61, 95% CI: 0.45-0.83; $P = 0.002$), and high income (vs. low income: HR = 0.48, 95% CI: 0.32-0.72; $P < 0.001$) served as independent protective factors against all-cause mortality (details in Table 3).

Table 3. Outcomes of multivariable Cox proportional hazards regression analysis (Training Set)

Variable	HR	95% CI	P
Sex			
Male	1 (Reference)		
Female	0.70	0.57-0.87	0.001
Age (years)			
15-39	1 (Reference)		
40-44	1.19	0.91-1.57	0.210
45-49	1.30	1.03-1.65	0.028
Primary Site			
Head and Neck	1 (Reference)		
Trunk	0.98	0.74-1.29	0.866
Extremities	0.77	0.58-1.03	0.078
Tumor Size			
≤ 1 cm	1 (Reference)		
1.1-1.9 cm	1.56	1.20-2.02	< 0.001
≥ 2 cm	1.84	1.42-2.39	< 0.001
SEER Stage			
Localized	1 (Reference)		
Regional	1.95	1.19-3.19	0.008
Distant	2.58	1.23-5.43	0.012
AJCC Stage			
I	1 (Reference)		
II	3.44	2.29-5.15	< 0.001
III	4.30	2.37-7.80	< 0.001
IV	8.69	3.80-19.84	< 0.001
Marital Status			
Married	1 (Reference)		
Single	1.56	1.25-1.95	< 0.001
Separated/Divorced/Widowed	1.50	1.07-2.09	0.018

Variable	HR	95% CI	P
Radiotherapy			
Yes	1 (Reference)		
No	0.49	0.35-0.70	< 0.001
Chemotherapy			
Yes	1 (Reference)		
No	0.61	0.45-0.83	0.002
Surgery			
Yes	1 (Reference)		
No	4.54	2.44-8.42	< 0.001
Regional Lymph Node Dissection			
Yes	1 (Reference)		
No	1.63	1.20-2.21	0.002
Median Household Income			
Low income	1 (Reference)		
Middle income	0.74	0.54-1.01	0.060
High income	0.48	0.32-0.72	< 0.001
Mitotic Rate			
None	1 (Reference)		
< 1 / mm ²	1.29	0.73-2.26	0.381
≥ 1 / mm ²	1.87	1.26-2.78	0.002
Ulceration Status			
Absent	1 (Reference)		
Present	1.74	1.38-2.20	< 0.001

Note: HR, hazard ratio; CI, confidence interval.

To forecast 3- and 5-year overall survival outcomes visually, a personalized nomogram was constructed (Figure 3) incorporating the validated multivariable Cox predictors: sex, age, tumor size, SEER classification, AJCC stage, marital status, radiotherapy, chemotherapy, surgery, lymph node dissection, median income, mitosis, and ulceration. Application of the nomogram proceeds sequentially: first, find the corresponding score for every variable along the top Points line; second, accumulate all individual points to establish a total score; and third, map this overall score down to the lower 3-Year and 5-Year OS axes to extract the predicted survival probabilities.

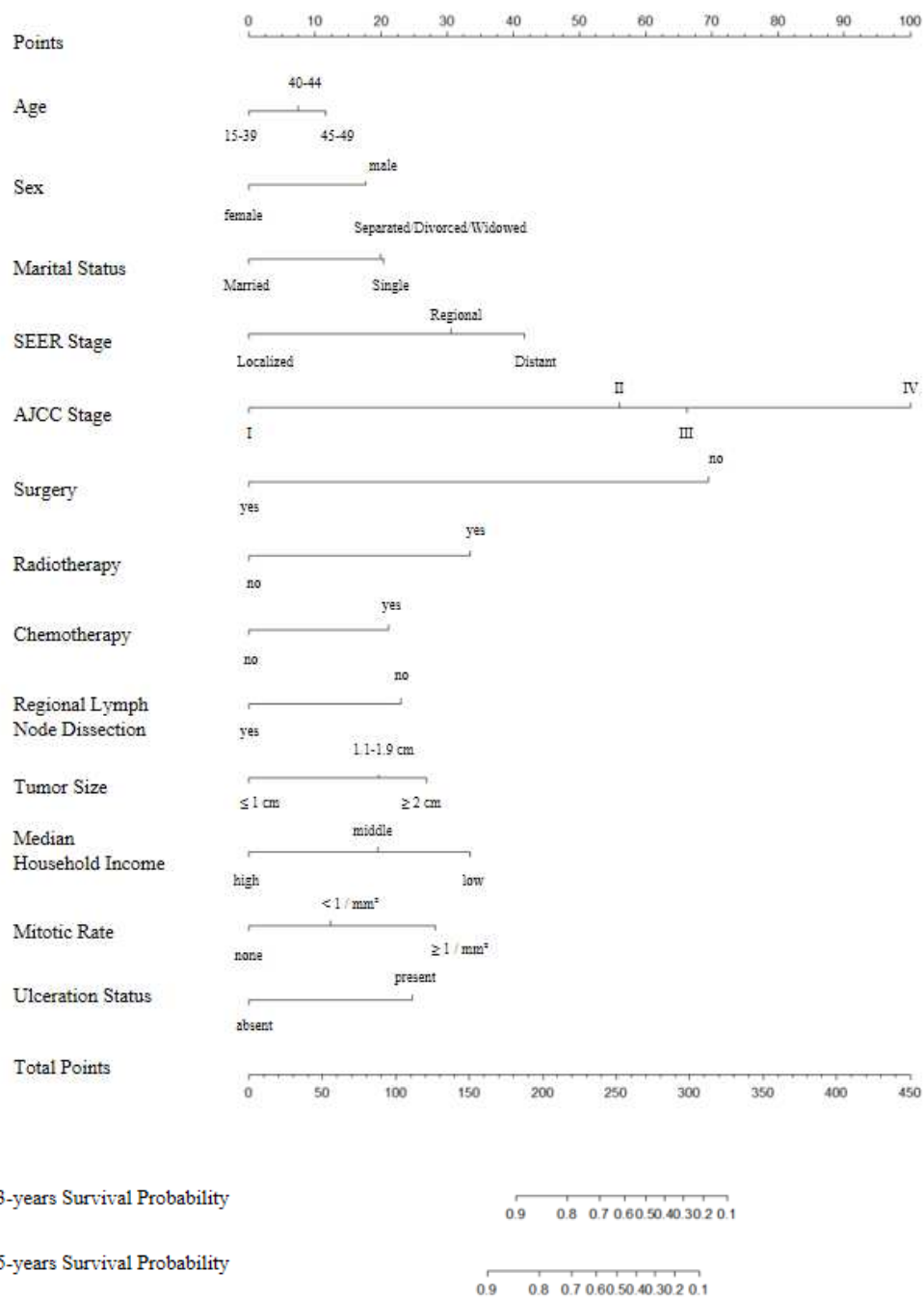


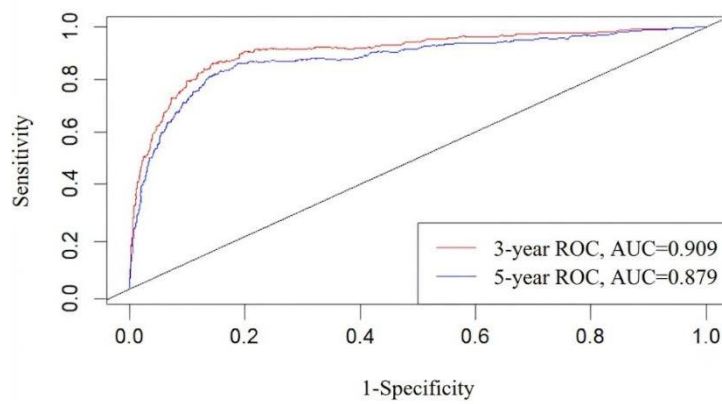
Figure 3. Nomogram for predicting the prognosis of early-onset cutaneous melanoma.

3.4 Validation of the Predictive Model

1) Discriminative Performance

Receiver operating characteristic (ROC) evaluations revealed that the training set's concordance index (C-index) favored the nomogram over the conventional AJCC criteria (0.883 vs. 0.838). A comparable superiority emerged in the validation cohort, yielding a C-index of 0.902 for the alternative model compared to 0.862 for the standard classification. In terms of prognostic capability, the nomogram achieved 3-year AUCs of 0.909 (training) and 0.922 (testing), alongside 5-year AUCs of 0.879 and 0.893. These metrics demonstrate that the nomogram model possesses superior discriminative efficiency and predictive accuracy relative to standard AJCC staging (Figure 4).

(a)



(b)

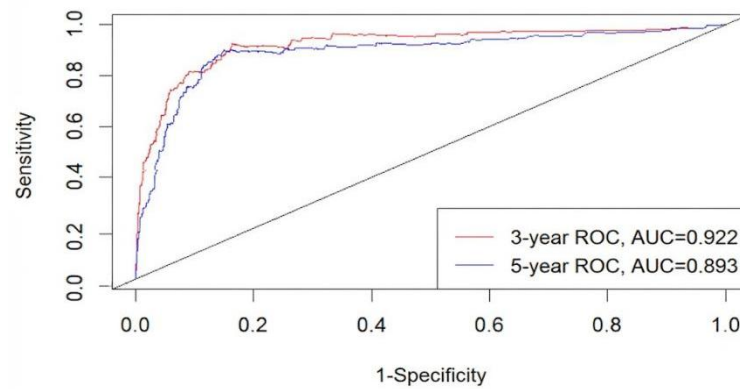


Figure 4. ROC Curves for Early-Onset Cutaneous Melanoma

Note: (a) Training cohort; (b) Testing cohort.

2) Calibration evaluation

As illustrated by the calibration curves, strong concordance was achieved between the estimated and actual 3-year and 5-year survival rates in training and validation sets alike, with the plotted lines closely paralleling the benchmark reference. These findings validate the excellent calibration performance inherent to the model (Figure 5).

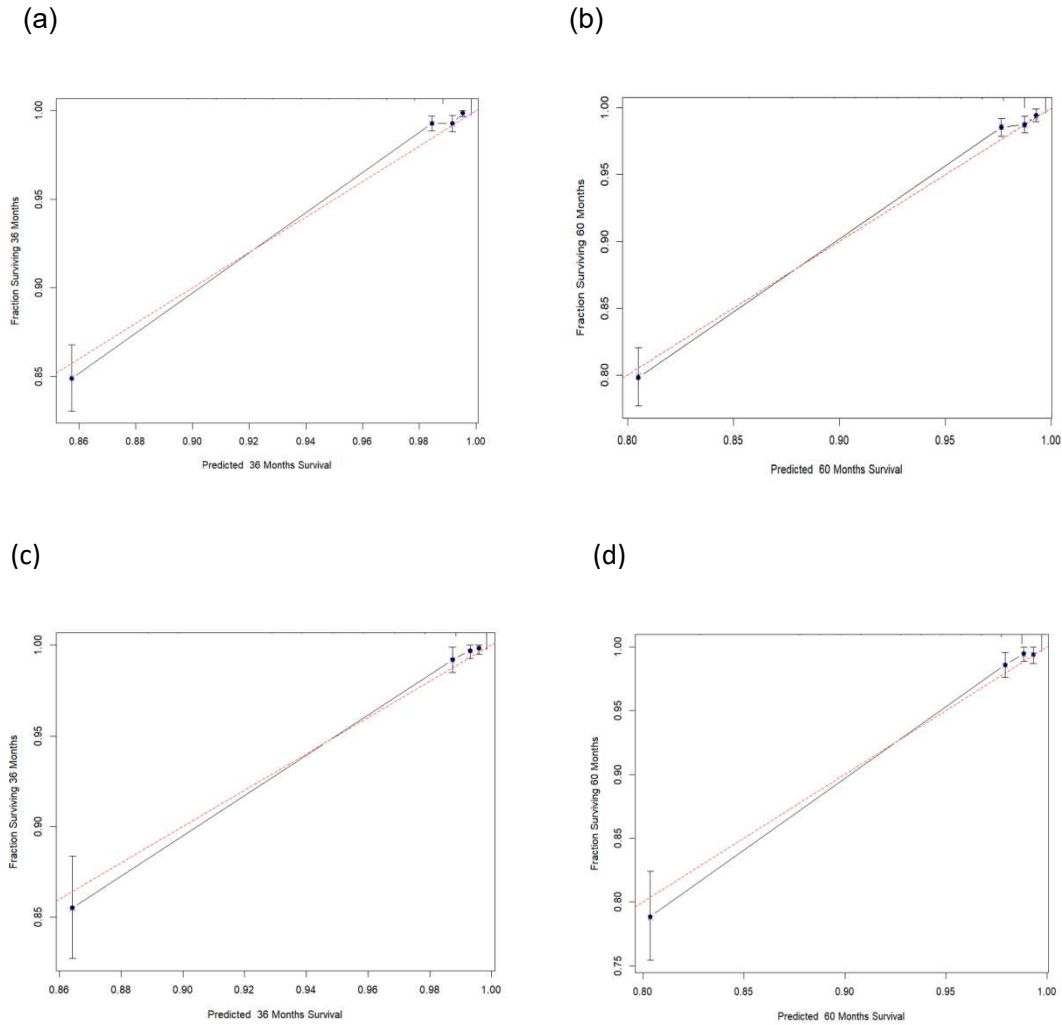


Figure 5. Calibration curves for early-onset cutaneous melanoma.

Note: Calibration plots for survival probability: (a) 3-year, training set; (b) 5-year, training set; (c) 3-year, validation set; (d) 5-year, validation set.

3) Incremental Predictive Performance

Compared with the conventional AJCC staging system, the nomogram model demonstrated net reclassification improvement (NRI) values of 0.284 (95% CI: 0.217–0.441) and 0.291 (95% CI: 0.241–0.401) for the prediction of 3-year and 5-year overall survival, respectively, in the training cohort, with corresponding integrated discrimination improvement (IDI) values of 0.052 and 0.060. In the testing cohort, the NRI values were 0.349 (95% CI: 0.163–0.527) and 0.298 (95% CI: 0.091–0.436), with corresponding IDI values of 0.060 and 0.084. Statistical significance was reached across all indices ($P < 0.05$), accompanied by positive values for both NRI and IDI. Such outcomes confirm that superior prognostic performance is conferred by the nomogram model over standard AJCC staging.

4) Clinical Utility

Decision Curve Analysis (DCA) was implemented to appraise the nomogram's clinical utility, plotting net benefit vertically against threshold probability horizontally. The two benchmarks represent extreme approaches: a zero-benefit horizontal line (no patients treated) and an oblique line (all patients treated), with a superior model staying above both lines within valid thresholds. Illustrated in Figure 6, the nomogram delivered positive net benefits across 3- and 5-year threshold ranges in training and testing groups, verifying strong clinical utility. Furthermore, superior clinical value was confirmed by higher net benefit curves that consistently exceeded those of the AJCC staging system across all threshold intervals.

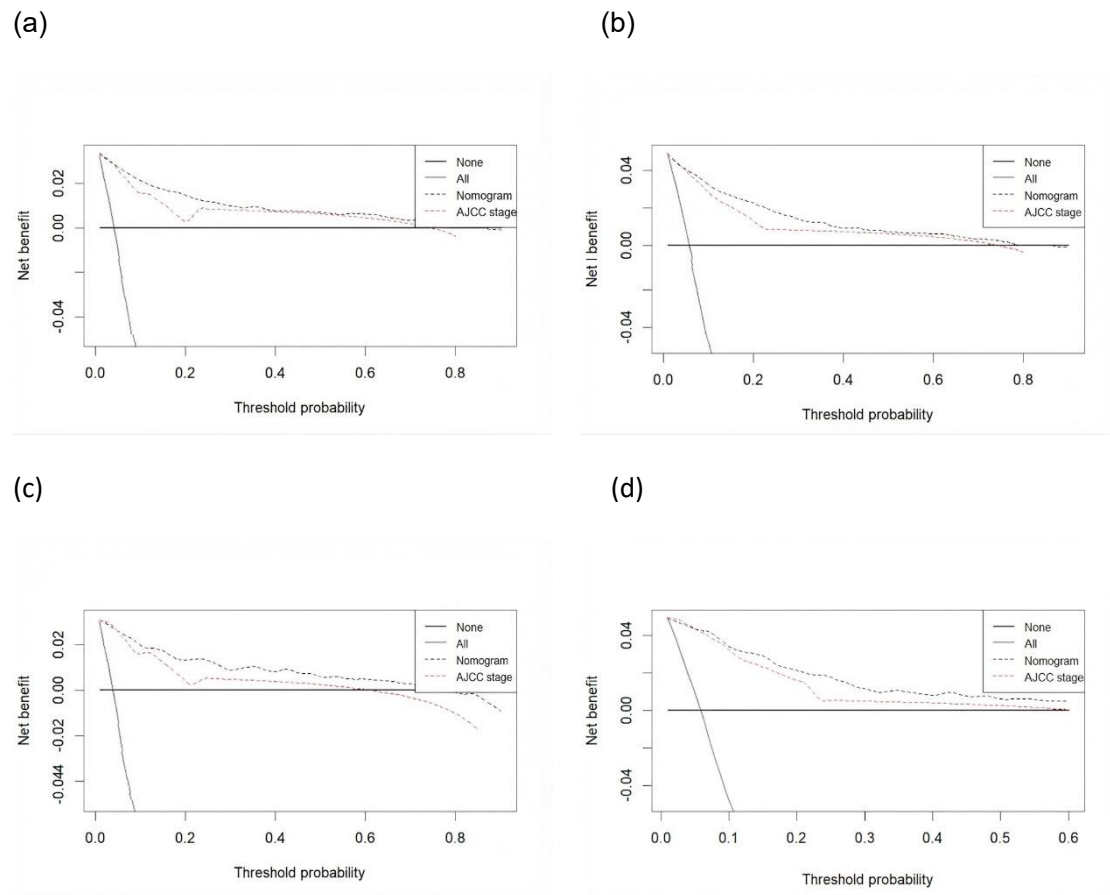


Figure 6. Evaluation of clinical net benefit via Decision Curve Analysis (DCA) for the nomogram and AJCC staging in early-onset cutaneous melanoma.

Note: Subplot layout for DCA performance: (a) 3-year, training cohort; (b) 5-year, training cohort; (c) 3-year, testing cohort; (d) 5-year, testing cohort.

4. Discussion

Cutaneous melanoma generally exhibits a favorable prognosis when diagnosed and treated at an early stage. However, the survival rate decreases significantly once metastasis occurs, leading to rapid disease progression. According to authoritative reviews from two decades ago, the 5-year survival rate for localized melanoma was as high as 98%, whereas it plummeted to 16% for metastatic disease[8]. Historically, complete surgical resection has been considered the gold standard for the treatment of stage III or IV metastatic melanoma[9]. According to the National Comprehensive Cancer Network (NCCN) Guidelines for

Melanoma, the recommended treatment for primary cutaneous melanoma includes wide excision of the primary lesion and sentinel lymph node biopsy. For patients with stage III–IV disease, systemic immunotherapy is also recommended, and in selected cases, surgical resection of metastatic lesions may be performed to improve response rates and survival outcomes[10]. With continuous advances in medicine and oncologic surgery, lymph node dissection has become an important component of the multidisciplinary management of regional metastatic melanoma[11]. During resection of metastatic lesions, complete tumor excision while minimizing postoperative impairment of quality of life is of paramount importance. Nevertheless, metastatic melanoma remains associated with a high mortality rate[11]. Therefore, accurate prediction of survival outcomes is crucial for improving the prognosis of patients with early-onset cutaneous melanoma.

In clinical practice, individualized prognostic risk assessment is critical for the early identification of high-risk patients and the implementation of precision interventions. The conventional TNM staging system, which provides only population-based risk stratification, often fails to meet the requirements for personalized management, posing challenges to its clinical utility. In this study, we developed a comprehensive and user-friendly nomogram based on a large cohort of early-onset cutaneous melanoma patients from the SEER database. By integrating multidimensional clinical parameters, this model provides a visualized assessment of survival probability, thereby combining practical utility with enhanced predictive accuracy.

It should be emphasized that model complexity is positively associated with predictive accuracy, and variable selection requires a careful balance between comprehensiveness and practicality. Although the inclusion of more variables may improve model performance, increased complexity may reduce its clinical applicability. Given the priority of practicality in clinical practice, variable selection in the present study focused on core indicators with high clinical relevance, strong reproducibility, and low temporal variability. After controlling for potential confounding factors, a total of 13 variables, including sex, age, tumor size, SEER stage, AJCC stage, marital status, radiotherapy status, chemotherapy status, surgery status, regional lymph node dissection, median household income, mitotic status, and ulceration status, were identified to develop prognostic models for predicting the 3-year and 5-year overall survival of patients with early-onset cutaneous melanoma. (1) Male sex, older age, and lower socioeconomic status were associated with poorer prognosis, consistent with earlier findings [12-19]. (2) The probability of adverse outcomes showed a consistent trend with the AJCC staging system. However, the nomogram revealed that patients with the same AJCC stage could exhibit different scores, indicating variations in mortality risk. This finding further validates the superiority of the nomogram over the traditional AJCC staging system in providing more refined prognostic stratification. (3) Sentinel lymph node biopsy is of great importance for the prognostic evaluation of patients, particularly for those with tumor

thickness ≥ 1.0 mm or ≥ 0.8 mm accompanied by ulceration, a mitotic rate $\geq 1/\text{mm}^2$, or other high-risk factors. In such patients, lymph node biopsy should be performed to ensure accurate staging and appropriate treatment decision-making[20]. If lymph node metastasis is identified clinically or by imaging modalities (including ultrasonography), complete lymph node dissection is considered the standard treatment[20, 21]. (4) Research indicates that the impact of radiotherapy and chemotherapy on survival outcomes in melanoma patients is limited. Specifically, radiotherapy may induce significant toxicities, while chemotherapy is generally reserved as a last-line treatment for patients who are refractory to immunotherapy and targeted therapy[20]. (5) The presence of a spouse is considered to play an important role in the prevention of skin cancer and is closely associated with the early detection of melanoma[22]. Having a partner may enhance both the accessibility of healthcare services and the level of social support. Furthermore, studies suggest that increased social support and well-being may improve immune function[23], thereby enhancing the patient's resistance to melanoma. (6) Studies have shown that the anatomical site of primary cutaneous melanoma is an important prognostic factor[24, 25]. The head and neck are chronically exposed to sunlight, whereas the trunk and extremities are typically subjected to intermittent ultraviolet radiation [26, 27]. In addition, previous studies have reported poorer survival among patients with head and neck melanoma[24]. Although the multivariable analysis in the present study showed that melanomas of the trunk and extremities had lower hazard ratios than those of the head and neck, the differences were not statistically significant. It has been suggested that head and neck melanoma is more common in older adults and male patients. Older patients may be less able to tolerate tumor burden because of poorer physical condition or the presence of chronic diseases. Furthermore, compared with younger individuals, older adults generally have longer cumulative sun exposure to the head and neck, which may explain the higher incidence of head and neck melanoma in this population. In addition, women generally pay greater attention to protecting the head and neck from ultraviolet exposure, which may help reduce the risk of head and neck melanoma[24]. Furthermore, studies have shown that even after surgical resection, patients with head and neck melanoma exhibit lower survival rates compared to those with tumors in other anatomical sites. This may be attributed to the typically older age of this patient population and their reduced tolerance to surgery or postoperative complications[28]. However, the current study focused on a younger cohort (aged under 50 years) with a predominance of female patients; consequently, anatomical site was not identified as an independent prognostic factor for cutaneous melanoma in our study.

At present, the TNM classification remains a conventional and widespread tool in clinical settings for evaluating the prognosis of malignant neoplasms. However, its limitations lie in its heavy reliance on anatomical tumor parameters while overlooking other potentially important prognostic factors. Even among patients with the same stage, substantial heterogeneity in survival outcomes remains, highlighting the limitations of this system in

individualized prognostic prediction. In the present study, key prognostic variables were identified through multivariable Cox proportional hazards regression analysis, and nomogram models were developed to predict the 3-year and 5-year overall survival of patients with early-onset cutaneous melanoma. The nomograms rank variables according to their effect sizes, thereby enabling individualized risk assessment, and their performance is closely related to the clinical relevance of the included variables. Each predictor in the model is assigned a weighted score, and the total score corresponds to a specific survival probability. By incorporating multiple variables that are highly associated with the prognosis of patients with early-onset cutaneous melanoma, this tool is able to reflect interpatient heterogeneity and quantify risk at a population level [29]. Its advantages include the following: (1) convenience, allowing rapid estimation of individualized survival probabilities; (2) accuracy, through the integration of multidimensional prognostic variables; and (3) practicality, facilitating the development of dynamic follow-up strategies.

Validation of the nomogram is a critical step to ensure its generalizability and mitigate overfitting. In this study, the developed nomogram demonstrated superior predictive accuracy and discrimination compared with the AJCC staging system, with further quantitative support from NRI and IDI analyses confirming its advantages in risk stratification. It is important to note, however, that superior statistical performance does not always equate to clinical utility; if the threshold probability deviates from clinical reality, even a statistically robust model may lead to decision-making errors due to increased false-negative risks[30]. For instance, a model with high specificity but low sensitivity and one with low specificity but high sensitivity may yield comparable C-index values. Nevertheless, when predicting high-stakes outcomes, such as mortality in melanoma patients, the clinical consequences of a false-negative (e.g., delayed treatment) are substantially more severe than those of a false-positive, thereby limiting the clinical utility of the former. To address this, we employed Decision Curve Analysis (DCA) to evaluate the clinical utility of our nomogram. The results showed that it consistently achieved higher net clinical benefit than the AJCC staging system, providing a more reliable basis for clinical decision-making.

Although the SEER database offers a substantial sample size, several inherent limitations should be noted in this study. (1) due to its retrospective design, only patients with complete information were included, which may have introduced potential selection bias. (2) Several key treatment-related variables, including radiotherapy and chemotherapy regimens, dose intensity, and long-term complications, were unavailable, precluding assessment of their specific impact on prognosis. (3) Internal validation alone was performed for the nomogram, necessitating subsequent multicenter investigations to confirm its broader applicability.

5. Conclusions

A novel prognostic nomogram predicting 3- and 5-year overall survival probabilities was formulated by synthesizing multi-attribute variables derived from SEER data—including sex, age, tumor size, SEER stage, AJCC stage, marital status, radiotherapy, chemotherapy, surgery, lymph node removal, income, mitosis, and ulceration—in early-onset cutaneous melanoma. Performance comparisons highlighted that the nomogram surpassed standard AJCC staging by delivering heightened discriminative capacity, calibration accuracy, and practical utility, alongside significant net benefit gains. Consequently, this model can be implemented for personalized survival estimation, supplying meaningful clinical guidance for prognosis evaluation and management strategies.

Declarations

Ethical Approval and Accordance: The data for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) database, a publicly available, anonymized population-based cancer registry maintained by the National Cancer Institute (NCI). The SEER database does not contain personal identifying information. Therefore, this study was deemed exempt from institutional review board (IRB) review, and formal ethical approval was not applicable. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the SEER research data use agreement.

Consent to Participate: Not applicable. Patient informed consent was not required as this study involved the retrospective analysis of de-identified, publicly available data from the SEER database.

Consent to Publish: Not applicable. No individual personal data, images, or details are included in this manuscript.

Data Availability Statement: The data analyzed in this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) database, specifically the Incidence - SEER Research Data, 17 Registries, November 2023 Sub (2000–2021) dataset, accessed through SEERStat version 8.4.4. Detailed information on the dataset is available from the SEER November 2023 Submission documentation: <https://seer.cancer.gov/data-software/documentation/seerstat/nov2023/>. Access to the SEER Research Data is provided through SEER Stat following registration and approval by the SEER Program: <https://seer.cancer.gov/data/access.html>. No accession number or other unique dataset identifier is assigned to this SEER data submission; the database name, submission

date, registry coverage, and diagnosis years identify the dataset used in this study. The raw extracted cohorts and statistical code generated during the current study are available from the corresponding author upon reasonable request.

Author Contributions: Chaodi Huang: data curation (equal); formal analysis (equal); investigation; writing – original draft. Jianguo Huang: data curation (equal); formal analysis (equal); conceptualization; methodology; project administration (equal); writing – review and editing (equal). Kaiqin Tan: data curation (equal); formal analysis (equal); project administration (equal); writing – review and editing (equal). All authors have read and agreed to the published version of the manuscript.

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