The prognostic nomograms in patients with nodular melanoma: a SEER population-based study

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Abstract

Nodular melanoma (NM) is one of the most common subtype of malignant melanoma, usually with bad prognosis. In this study, we aim to develop a nomogram to predict 3-year and 5-year overall survival (OS) and cancer-specific survival (CSS) in patients with nodular melanoma. Patients diagnosed as NM were extracted from the Surveillance, Epidemiology, and End Results (SEER) database between 2010–2015, and then they were randomly assigned to the training and validation cohorts. Several independent risk factors were found and merged to generate a nomogram using univariate and multivariate COX risk regression methods. To determine the nomogram's predictive ability, the receiver operating characteristic (ROC) curve, concordance index (C-index), area under curve (AUC) and calibration curves were calculated. In clinical practice, decision curve analysis (DCA) was employed to measure nomograms. A total of 8050 eligible patients were randomly assigned to one of two groups: 70% training (n = 5635) or 30% validation (n = 2415). The Nomogram's construct was applied with the selected independent factors, and the validation indexes revealed that the nomogram had strong discriminative power. In the training cohort of OS, the C-index was 0.746, and in the validation cohort of OS, it was 0.745. In the training cohort of CSS, the C-index was 0.777, whereas in the validation cohort, it was 0.775. The AUCs for the 3- and 5-year OS rates, as well as the CSS rates, were above 0.78, and the calibration curves exhibited strong nomogram predictive power. The created nomograms could provide net clinical benefit, according to DCA. Our study has developed a nomogram to more accurately and comprehensively predict 3-year and 5-year OS and CSS in patients with nodular melanoma, which is critical for clinicians to make early assessments, improve individualized treatment, identify relevant prognostic factors, and improve survival of the affected population.

Introduction

Melanoma is a cancerous tumor that develops from the melanocytes. Melanocytes are found in the epidermis's basal layer, so 95% of melanomas are found in the skin. Melanomas can also be found in mucous membranes and other melanocyte-containing tissues, but they are less common. In the United States, melanoma is the fifth most common cancer in men and the sixth most common cancer in women[1]. Melanoma mortality has changed in recent years, we should pay more attention to the diagnosis and prognosis of the melanoma population, and screen for relevant prognostic factors to help diagnose melanoma early and improve the survival rate of the affected population.

Cutaneous melanoma (CM) is often classified according to superficial spreading melanoma (SSM), acral melanoma (ALM), nodular melanoma (NM), and lentigo malignant melanoma (LMM). NM is more aggressive than other types and usually presents as a darker, well-defined, uniformly pigmented nodule with or without ulceration. Most NMs usually develop rapidly within months to years after diagnosis. Studies have shown that NM have worse prognosis and lower 5-year and 10-year survival rates[2] than the others. It is necessary to analyze the related factors of NM to help better understand and treat NM.

Several clinical and histopathological findings have been reported as important prognostic factors in melanoma patients, such as: tumor thickness (Breslow depth), presence or absence of ulcers, anatomical location, and American Joint Committee on Cancer (AJCC) stage, treatment[3]. We selected relevant prognostic factors for NM patients from the SEER database, such as age, gender, race, primary site, ulceration, TNM stage, AJCC stage, SEER stage, Breslow depth and treatment plan for independent factor analysis. More patients could benefit from our research.

A nomogram is a visual calculation method that combines multiple independent correlated variables to predict survival or disease risk. Many doctors and researchers apply nomograms to analyze the clinical characteristics of diseases and judge prognosis[4]. The incidence of nodular melanoma ranks second in melanoma, and the prognosis is poorer. We believe that it is necessary to study the independent factors related to the prognosis of NM to help the diagnosis and treatment of NM patients. Therefore, the aim of this study was to identify clinicopathological factors associated with prognosis based on data from the SEER database. In particular, we sought to construct and validate nomograms for predicting individual 3- and 5-year OS and CSS rates in NM patients.

Materials And Methods

Data source and selection of Variables

The Surveillance, Epidemiology, and End Results(SEER) is one of the largest cancer database available to the public, covering approximately 28% of the US population. According to the International Classification of Diseases for Oncology(ICD-O-3) histology/behavior ,patients diagnosed as “8721/3:Nodular melanoma” between 2010 and 2015 were retrospectively extracted from SEER Research data,18 Registries Nov 2019 Sub[2000–2017] with SEER* Stat software (Version 8.3.6); Clinical information of each patient to be collected includes age, sex, race, primary site, T-stage, N-stage, M-stage, AJCC-stage, SEER-stage, ulceration, Breslow thickness, treatment, survival status, and survival time. The exclusion criteria for this study were as follows: race unknown; no positive histology; primary site unknown; T0 or T-stage unknown; N-stage unknown; AJCC-stage unknown; SEER-stage unknown; ulceration unknown; Breslow thickness unknown; treatment unknown. We eventually got 8050 patients based on the above inclusion and exclusion criteria. Patients were randomized into a training cohort(n = 5635) and a validation cohort(n = 2415) in a 7:3 ratio (Fig. 1). The SEER database agreement has been signed and provided permission to access SEER information (accession username: 22369-Nov2020). This study was undertaken without institutional review board approval or informed consent since the SEER database is publicly accessible.

With Xtile software (Yale University, New Haven, Connecticut, USA)[5], we used the optimal cutoff values to convert continuous variables into categorical variables. In this study, the optimal cutoff values by age were categorized into < 70, 70–84 and > 84 years old (Fig. 2). As reported in previous studies, the cutoff values for Breslow thickness were 0.01–0.99 mm, 1.00–2.00 mm, 2.01-4.00 mm, and > 4.00 mm[3,6].

Data analysis

All statistical analysis in our study was performed with R software version 4.1.3(https://www.r-project.org/). Descriptive statistics were used to analyze the demographic features of patients as well as clinical features. Using R software, the training and validation cohorts were randomly assigned, and the chi-square test was utilized to compare the associations between them. The Kaplan-Meier method and the log-rank test were used to determine the connection between clinical variables and OS and CSS, while univariate and multivariate cox regression analysis were performed to evaluate prognostic factors. Furthermore, we created a nomogram for predicting OS and CSS using a multivariate Cox proportional hazard model. C-index, calibration curves (bootstrap 1,000 resampling validation), receiver operating characteristic (ROC) curves and calculated areas under the receiver operating characteristic curve (AUC) values were used to evaluate the predictive capacity of the nomograms. The clinical value of the model was evaluated using decision curve analyses (DCAs).

Results

Demographic and clinicopathological characteristics

At last, a total of 8050 patients with nodular melanoma were available from the SEER database during the period 2010–2015. They were randomly divided into a training cohort and a validation cohort in a 7:3 ratio. The training cohort had the largest proportion of people in the “<70 years old” group (n = 3115,55%), was predominantly male (n = 3585,63.6%), and was mostly White (n = 5539,98.3%); As for the primary sites, We categorized them into four categories: head, face, and neck, trunk, extremities, and others (including melanomas located in the mucosa such as the gastrointestinal tract, external genitalia and some skin overlap areas). The most common primary site in our study was limbic melanoma (n = 2534,45%). T4 (n = 1903,33.8%), N0 (n = 4200,74.5%), and M0 (n = 5377,95.4%) were the most common T stage, N stage, and M stage, respectively. In AJCC stage, stage II was predominant (n = 2783 ,49.4%); SEER stage was divided into localized, regional, and distant, with local staging being the most frequent (n = 3645,64.7%). The number of patients with and without ulceration was approximately equal; The most common depth of nodular melanoma is > 4mm. In terms of treatment, the majority of patients underwent surgery (n = 5506 ,97.7%). The validation cohort's population distribution was fairly comparable to the training cohort's, implying that the overall demographic characteristics were similar. All p-values were more > 0.1, indicating that patients in the training and validation cohorts were assigned at random. More detailed information is provided in Table 1.

Prognostic factors for predicting OS and CSS

Age ($p < 0.001$), sex($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), M stage ($p < 0.001$), AJCC stage ($p < 0.001$), SEER stage ($p < 0.001$), ulceration ($p < 0.001$), Breslow thickness ($p < 0.001$), and treatment ($p < 0.001$) were all shown to be linked with OS in the univariate analysis. Only age, gender, M stage, AJCC stage, SEER stage, ulceration, and treatment revealed a link with OS in the multivariate analysis (Table 2).

In CSS, univariate and multivariate analyses yielded results that were broadly consistent with OS (Table 3).

Survival Analyses

Kaplan-Meier curves suggest that patients of advanced age have a worse prognosis, female patients have a better prognosis compared to males, while patients with a primary site on the extremities or trunk have a better prognosis, higher levels of TNM stage, AJCC stage and SEER stage have a worse prognosis, consistent with previous experience; With ulceration and deeper infiltration is also associated with shorter OS and CSS, and patients who have received surgery have a longer OS and CSS (Fig. 3 and Fig. 4).

Construction and validation of nomogram

Significant independent risk factors derived from the multivariate analysis were used to construct a nomogram to predict patients' OS and CSS (Fig. 5). The scale at the top of the nomogram provides a score for each prognostic variable, and ultimately the sum of all scores corresponds to the proportion at the bottom of the nomogram. The nomogram for OS prediction shows that prognosis is mainly influenced by age, followed by tumor stage, surgery, ulceration, and sex. Similarly, the nomogram for CSS showed that age, tumor stage, and surgery were also important factors influencing prognosis. The nomograms were then verified by c-index, calibration curves (Fig. 6) or ROC curves (Fig. 7), and DCA curves were used to evaluate clinical efficacy. The c-indexes for OS and CSS for the training cohort were 0.746 and 0.777, respectively, corresponding to 0.745 for OS and 0.775 for CSS in the validation cohort. The 3-year and 5-year OS AUC for the training cohort were 0.778 and 0.779, and the corresponding values for the validation cohort were 0.774 and 0.786, respectively; the 3-year and 5-year CSS AUC were 0.794 and 0.789, and for the validation cohort were 0.818 and 0.796, respectively. All calibration curves exhibit satisfactory performance. And the DCA curves (Fig. 8) show that two models generate net profits in both the training and validation cohorts.

Discussion

In our study, based on univariate cox proportional hazards regression, we found that age, gender, anatomical site, T stage, N stage, M stage, AJCC stage, SEER stage, Breslow depth, ulceration and treatment were associated with OS and CSS in NM patients. However, in multivariable cox proportional hazards regression, T and N stages were not strongly associated with prognostic factors for OS and CSS rates in NM patients. At the same time, we constructed a nomogram to quantitatively predict individual 3- and 5-year OS and CSS rates through patient-related and tumor-related factors. Our nomograms can be used to estimate patients’ outcomes and make individualized decisions about monitoring and treatment.

Most studies have confirmed that advanced age is a relevant risk factor for the prognosis of NM, which is consistent with the results obtained in our study. One study analyzed the peak age of nodular melanoma at 65 to 69 years of age. However, the age cutoffs varied across studies. Therefore, in this study, the age was divided into < 70 years, 70–84 years and > 84 years by X-Tile software as cut-off points, which could

better distinguish the survival rate of some variables. A study of 3076 patients[7] found that with increasing age, Breslow depth, the presence of ulceration, and the proportion of males also increased, suggesting that age is associated with other risk factors. Complications in the elderly population may also be an important factor affecting the prognosis of melanoma, but other complications of patients were not recorded in the SEER database, so it was not possible to analyze and study this, which is also one of the limitations of this study. At the same time, we found that gender was also a relevant prognostic factor, with most studies showing that being female was a protective factor for melanoma survival, with higher 3- and 5-year survival in women. One study[8] found that the 5- and 10-year overall survival rates for men were 69% and 61%, respectively, compared with 82% and 75% for women. This is similar to our findings. Race, which has been shown in other studies to be associated with melanoma prognosis[9]. But this was not reflected in our study. We believe that this is related to the fact that the majority of patients included in the database are Caucasian, and we also consider that different subtypes of melanoma may behave differently for an independent factor of race. Other studies have analyzed differences in survival between different ethnic groups and have been correlated with melanocyte distribution, sunlight exposure time, and genetic mutations in different ethnic groups. Further studies are needed to explore the relationship between survival and ethnicity in different subtypes of melanoma[10].

Location is also a fairly important prognostic factor in some studies, with extremities having better survival than trunk locations[11]. However, other studies have shown that the survival rate of the proximal site is worse than that of the distal site[12]. Most studies concluded that melanoma located in the head and neck had a worse prognosis, with a 1.84-fold higher risk of death in patients with CMM of the head and neck compared with patients of the extremities in multivariate analysis[13]. In our study, NM with primary sites of the trunk and extremities had a higher survival rate, and NM in the head and neck site had a lower survival rate, similar to the findings of some of these studies. Studies have confirmed that the thickness of the tumor, that is, the Breslow depth, is directly proportional to the mortality of melanoma, and the deeper the Breslow depth, the higher the positive rate of sentinel lymph node biopsy, that is, the easier it is to metastasize[14,15]. This is the same result as our study. Ulceration are an important factor in rapid tumor growth secondary to ischemia, so tumors with ulceration are thought to be more aggressive[16]. Most studies have shown that ulceration is a significant predictor of reduced overall survival[17] and a significant predictor of recurrence[18] in multivariate analysis. This was also verified in our study. The T, N, M stage, AJCC stage and SEER stage mentioned in our study are also important prognostic factors after univariate analysis, but T and N stage have little significance in multivariate analysis. The results were slightly different, and further research is needed. This is similar to the results of previous studies. Surgery is the main treatment for melanoma. Surgical methods include local excision, local wide excision, lymph node dissection, or sentinel lymph node biopsy[19]. At present, a variety of new treatment options have emerged, and adjuvant therapy is recommended for some patients with stage II and patients with stage III and IV. However, currently used chemotherapy drugs are of limited value for most patients with stage IV melanoma. Adjuvant therapies include: immunotherapy (melanoma vaccine, interferon, interleukin-2), chemotherapy, radiotherapy, and biological chemotherapy. Since no other new

treatment options were included in the SEER database, we used surgical treatment as the analysis indicator. Other studies have also confirmed that surgical treatment is a good prognostic factor, which is the same as our findings.

In this study, we used a huge database, adding more possible prognostic related factors such as: age, sex, race, anatomical site, TNM stage, SEER stage, AJCC stage, depth, ulcer and treatment, these factors are readily available in clinical work and better represent the clinical and pathological features of NM. Our nomogram shows good discriminative power in predicting prognosis, and is more comprehensive than previously constructed nomograms. In the present study, both the internal and external C-index were above 0.78, showing a pleasing discriminative ability to provide patients with prognostic information in a personalized manner. Likewise, AUCs also implies good discriminative ability. The calibration curve shows that the predicted values of the nomogram have high agreement. In addition, DCA was performed to provide the clinical net benefit of the predictive model. In the present study, all results indicated that the DCA curves of the 3- and 5-year OS rates of the new model yielded a significant net clinical benefit.

Our study has some limitations. First, the nomogram data comes from the SEER database, which contains only about 30% of the U.S. population, which is mostly Caucasian. Therefore, ethnicity and population are more limited, and although the data volume is large, the population category is relatively single. We need to augment data from other populations to more fully characterize the disease in NM. These should be factored into future forecasting models. Second, we did not include other prognostic factors such as marital status, economic status, education, complications, novel treatment modalities, mitotic index, presence and number of tumor-infiltrating lymphocytes (TILs), Capillary invasion, presence of microscopic satellites, and presence of perineural invasion. vi If this information is incorporated into the model, it will make nomogram predictions more accurate and personalized in the future. Finally, patients were divided into two groups, 70% of which were used for construction and the remaining 30% for validation of nomograms. The C-index, AUC, calibration curve and DCA performed well, but further studies are needed to externally validate the proposed nomogram.

Conclusion

In conclusion, we combined demographic and clinicopathological characteristics from the SEER database to build an efficient nomogram to predict prognostic factors in NM patients. The graph can help clinicians more accurately predict the 3- and 5-year OS and CSS rates of a single patient, and provide guidance for patient treatment, monitoring, and follow-up.

Declarations

Data availability statement

All data generated or analysed during this study are included in this published article.

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Author contributions

W.X and J.Z.Z designed the study. Y.J.L was in charge of data collection and processing. The manuscript was written by W.X and Y.J.L and was evaluated and modified by J.Z.Z. The final manuscript was read and approved by all writers.

Competing interests

The authors declare no competing interests.

References

1. Leiter, U., Keim, U. & Garbe, C. Epidemiology of Skin Cancer: Update 2019. Adv Exp Med Biol **1268**, 123–139. https://doi.org/10.1007/978-3-030-46227-7_6 (2020).
2. Kuno, Y., Ishihara, K., Yamazaki, N. & Mukai, K. Clinical and pathological features of cutaneous malignant melanoma: a retrospective analysis of 124 Japanese patients. Jpn J Clin Oncol **26**, 144–151. https://doi.org/10.1093/oxfordjournals.jjco.a023198 (1996).
3. Gershenwald, J.E., *et al.* Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin **67**, 472–492. https://doi.org/10.3322/caac.21409 (2017).
4. Iasonos, A., Schrag, D., Raj, G.V. & Panageas, K.S. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol **26**, 1364–1370. https://doi.org/10.1200/JCO.2007.12.9791 (2008).
5. Camp, R.L., Dolled-Filhart, M. & Rimm, D.L. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res **10**, 7252–7259. https://doi.org/10.1158/1078-0432.CCR-04-0713 (2004).
6. Garbe, C., *et al.* European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics - Update 2019. Eur J Cancer **126**, 141–158. https://doi.org/10.1016/j.ejca.2019.11.014 (2020).
7. Chao, C., *et al.* Correlation between prognostic factors and increasing age in melanoma. Ann Surg Oncol **11**, 259–264. https://doi.org/10.1245/aso.2004.04.015 (2004).
8. MacKie, R.M., *et al.* Cutaneous malignant melanoma in Scotland: incidence, survival, and mortality, 1979-94. The Scottish Melanoma Group. BMJ **315**, 1117–1121. https://doi.org/10.1136/bmj.315.7116.1117 (1997).
9. Che, G., *et al.* Trends in incidence and survival in patients with melanoma, 1974–2013. Am J Cancer Res **9**, 1396–1414. (2019).
10. Enninga, E.A.L., *et al.* Survival of cutaneous melanoma based on sex, age, and stage in the United States, 1992–2011. Cancer Med **6**, 2203–2212. https://doi.org/10.1002/cam4.1152 (2017).

11. Cochran, A.J., Elashoff, D., Morton, D.L. & Elashoff, R. Individualized prognosis for melanoma patients. Hum Pathol **31**, 327–331. https://doi.org/10.1016/s0046-8177(00)80246-4 (2000).
12. Hsueh, E.C., Lucci, A., Qi, K. & Morton, D.L. Survival of patients with melanoma of the lower extremity decreases with distance from the trunk. Cancer **85**, 383–388. (1999).
13. Lachiewicz, A.M., Berwick, M., Wiggins, C.L. & Thomas, N.E. Survival differences between patients with scalp or neck melanoma and those with melanoma of other sites in the Surveillance, Epidemiology, and End Results (SEER) program. Arch Dermatol **144**, 515–521. https://doi.org/10.1001/archderm.144.4.515 (2008).
14. Breslow, A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg **172**, 902–908. https://doi.org/10.1097/00000658-197011000-00017 (1970).
15. Rousseau, D.L., Jr., *et al.* Revised American Joint Committee on Cancer staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. Ann Surg Oncol **10**, 569–574. https://doi.org/10.1245/aso.2003.09.016 (2003).
16. Crowson, A.N., Magro, C.M. & Mihm, M.C. Prognosticators of melanoma, the melanoma report, and the sentinel lymph node. *Mod Pathol* **19 Suppl 2**, S71-87. https://doi.org/10.1038/modpathol.3800517 (2006).
17. Retsas, S., Henry, K., Mohammed, M.Q. & MacRae, K. Prognostic factors of cutaneous melanoma and a new staging system proposed by the American Joint Committee on Cancer (AJCC): validation in a cohort of 1284 patients. Eur J Cancer **38**, 511–516. https://doi.org/10.1016/s0959-8049(01)00394-x (2002).
18. Lassau, N., *et al.* Prognostic value of angiogenesis evaluated with high-frequency and color Doppler sonography for preoperative assessment of melanomas. AJR Am J Roentgenol **178**, 1547–1551. https://doi.org/10.2214/ajr.178.6.1781547 (2002).
19. Saltman, B.E., *et al.* Prognostic implication of sentinel lymph node biopsy in cutaneous head and neck melanoma. Head Neck **32**, 1686–1692. https://doi.org/10.1002/hed.21390 (2010).

Tables

Table 1. The demographics and clinical features for nodular melanoma in different cohorts

characteristics	Training cohort(N=5635)	Validation cohort(N=2415)	P-value
Age			
<70 years old	3115 (55.3%)	1345 (55.7%)	0.286
70-84 years old	1805 (32.0%)	739 (30.6%)	
>84 years old	715 (12.7%)	331 (13.7%)	
Sex			
Male	3585 (63.6%)	1525 (63.2%)	0.714
Female	2050 (36.4%)	890 (36.8%)	
Race			
Black	42 (0.7%)	17 (0.7%)	0.757
White	5539 (98.3%)	2379 (98.5%)	
Others	54 (1.0%)	19 (0.8%)	
Primary Site			
Head Neck and Face	1419 (25.2%)	601 (24.9%)	0.116
Trunk	1611 (28.6%)	747 (30.9%)	
Extremities	2534 (45.0%)	1040 (43.1%)	
Others	71 (1.3%)	27(1.1%)	
T stage			
T1	676 (12.0%)	286 (11.8%)	0.983
T2	1261 (22.4%)	533 (22.1%)	
T3	1794 (31.8%)	770 (31.9%)	
T4	1903 (33.8%)	826 (34.2%)	
N stage			
N0	4200 (74.5%)	1806 (74.8%)	0.414
N1	744 (13.2%)	316 (13.1%)	
N2	399 (7.1%)	186 (7.7%)	
N3	292 (5.2%)	107 (4.4%)	
M stage			

M0	5377 (95.4%)	2325 (96.3%)	0.0958
M1	258 (4.6%)	90 (3.7%)	
AJCC stage			
I	1299 (23.1%)	558 (23.1%)	0.383
II	2783 (49.4%)	1211 (50.2%)	
III	1295 (23.0%)	556 (23.0%)	
IV	258 (4.6%)	90 (3.7%)	
Seer Stage			
Localized	3645 (64.7%)	1567 (64.9%)	0.219
Regional	1644 (29.2%)	723 (29.9%)	
Distant	346 (6.1%)	125 (5.2%)	
Ulceration			
Absent	2776 (49.3%)	1228 (50.9%)	0.195
Present	2859 (50.7%)	1187 (49.1%)	
Breslow thickness			
<1.00mm	594 (10.5%)	244 (10.1%)	0.919
1.00-2.00mm	1366 (24.2%)	580 (24.0%)	
2.01-4.00mm	1779 (31.6%)	767 (31.7%)	
>4.00mm	1896 (33.6%)	824 (34.1%)	
Treatment			
Non-surgery	129 (2.3%)	48 (2.0%)	0.444
Surgery	5506 (97.7%)	2367 (98.0%)	

Table 2. Univariate and multivariate Cox proportional hazards regression analyses of variables associated with overall survival.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Age						
<70 years old	1	Reference		1	Reference	
70-84 years old	2.07	1.92-2.24	<0.001	2.1	1.95 - 2.27	<0.001
>84 years old	4.6	4.22-5.02	<0.001	4.62	4.22 - 5.06	<0.001
Sex						
Female	1	Reference		1	Reference	
Male	1.29	1.2-1.39	<0.001	1.25	1.17 - 1.35	<0.001
Race						
Black	1	Reference				
Others	0.73	0.43-1.22	0.226			
White	0.8	0.55-1.15	0.229			
Primary Site						
Extremities	1	Reference				
Head Neck and Face	1.32	1.22-1.43	<0.001			
Trunk	1.05	0.97-1.14	0.23			
Others	1.32	1.22-1.43	<0.001			
T stage						
T1	1	Reference		1	Reference	
T2	0.81	0.7-0.93	0.002	0.95	0.65 - 1.39	0.7958
T3	1.24	1.09-1.4	0.001	0.76	0.33 - 1.76	0.529
T4	2.29	2.04-2.58	<0.001	2.91	0.91 - 9.27	0.0713
N stage						
N0	1	Reference		1	Reference	
N1	1.3	1.18-1.43	<0.001	0.76	0.6 - 0.97	0.0265
N2	1.74	1.55-1.95	<0.001	0.96	0.75 - 1.23	0.7443
N3	2.61	2.3-2.97	<0.001	1.41	1.1 - 1.81	0.0071
M stage						

M0	1	Reference		1	Reference	
M1	4.53	4.01-5.11	<0.001	2.87	2.03 - 4.04	<0.001
AJCC stage						
I	1	Reference		1	Reference	
II	2.14	1.94-2.38	<0.001	1.31	1.12 - 1.54	<0.001
III	2.68	2.4-2.99	<0.001	1.67	1.24 - 2.25	<0.001
IV	8.85	7.63-10.26	<0.001	2.87	2.03 - 4.04	<0.001
SEER stage						
Distant	1	Reference		1	Reference	
Localized	0.23	0.21-0.26	<0.001	0.53	0.41 - 0.69	<0.001
Regional	0.4	0.36-0.45	<0.001	0.75	0.59 - 0.96	0.0205
Ulceration						
Absent	1	Reference		1	Reference	
Present	2.18	2.03-2.33	<0.001	1.57	1.46 - 1.69	<0.001
Breslow thickness						
<1.00mm	1	Reference		1	Reference	
1.00-2.00mm	0.75	0.65-0.86	<0.001	0.76	0.52 - 1.11	0.1553
2.01-4.00mm	1.18	1.03-1.34	0.013	1.01	0.44 - 2.33	0.9811
>4.00mm	2.16	1.91-2.44	<0.001	0.39	0.12 - 1.23	0.1067
Treatment						
Non-surgery	1	Reference		1	Reference	
Surgery	0.36	0.3-0.43	<0.001	0.48	0.4 - 0.58	<0.001

Table 3. Univariate and multivariate Cox proportional hazards regression analyses of variables associated with cancer-specific survival.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Age						
<70 years old	1	Reference		1	Reference	
70-84 years old	1.64	1.49-1.81	<0.001	1.72	1.56 - 1.9	<0.001
>84 years old	3.6	3.16-4.1	<0.001	3.69	3.22 - 4.23	<0.001
Sex						
Female	1	Reference		1	Reference	
Male	1.38	1.25-1.51	<0.001	1.27	1.15 - 1.4	<0.001
Race						
Black	1	Reference				
White	0.6	0.4-0.9	0.013			
Others	0.65	0.36-1.18	0.156			
Primary Site						
Extremities	1	Reference		1	Reference	
Head Neck and Face	1.33	1.19-1.49	<0.001	1.17	1.04 - 1.31	0.0084
Trunk	1.26	1.13-1.39	<0.001	1.29	1.16 - 1.44	<0.001
Others	2.84	2.11-3.81	<0.001	1.74	1.29 - 2.34	<0.001
T stage						
T1	1	Reference		1	Reference	
T2	0.76	0.63-0.93	0.007	0.81	0.48 - 1.38	0.4408
T3	1.31	1.1-1.56	0.002	0.53	0.15 - 1.84	0.3152
T4	2.89	2.45-3.4	<0.001	2.8	0.61 - 12.98	0.1871
N stage						
N0	1	Reference		1	Reference	
N1	1.99	1.77-2.24	<0.001	0.66	0.51 - 0.86	0.0021
N2	2.67	2.33-3.06	<0.001	0.84	0.64 - 1.1	0.2097
N3	4.31	3.74-4.97	<0.001	1.23	0.94 - 1.62	0.1301
M stage						

M0	1	Reference		1	Reference	
M1	6.86	6-7.85	<0.001	1.77	1.3 - 2.41	<0.001
AJCC stage						
I	1	Reference		1	Reference	
II	2.68	2.28-3.16	<0.001	1.69	1.34 - 2.11	<0.001
III+IV	6.27	5.34-7.35	<0.001	2.77	1.92 - 3.99	<0.001
SEER stage						
Distant	1	Reference		1	Reference	
Localized	0.13	0.11-0.14	<0.001	0.43	0.31 - 0.58	<0.001
Regional	0.34	0.3-0.39	<0.001	0.74	0.57 - 0.97	0.0282
Ulceration						
Absent	1	Reference		1	Reference	
Present	2.72	2.48-2.99	<0.001	1.74	1.57 - 1.92	<0.001
Breslow thickness						
<1.00mm	1	Reference		1	Reference	
1.00-2.00mm	0.7	0.58-0.86	<0.001	0.75	0.44 - 1.28	0.2971
2.01-4.00mm	1.24	1.04-1.49	0.017	1.26	0.36 - 4.43	0.7134
>4.00mm	2.7	2.28-3.2	<0.001	0.36	0.08 - 1.67	0.1916
Treatment						
Non-surgery	1	Reference		1	Reference	
Surgery	0.33	0.26-0.42	<0.001	0.42	0.33 - 0.54	<0.001

Figures

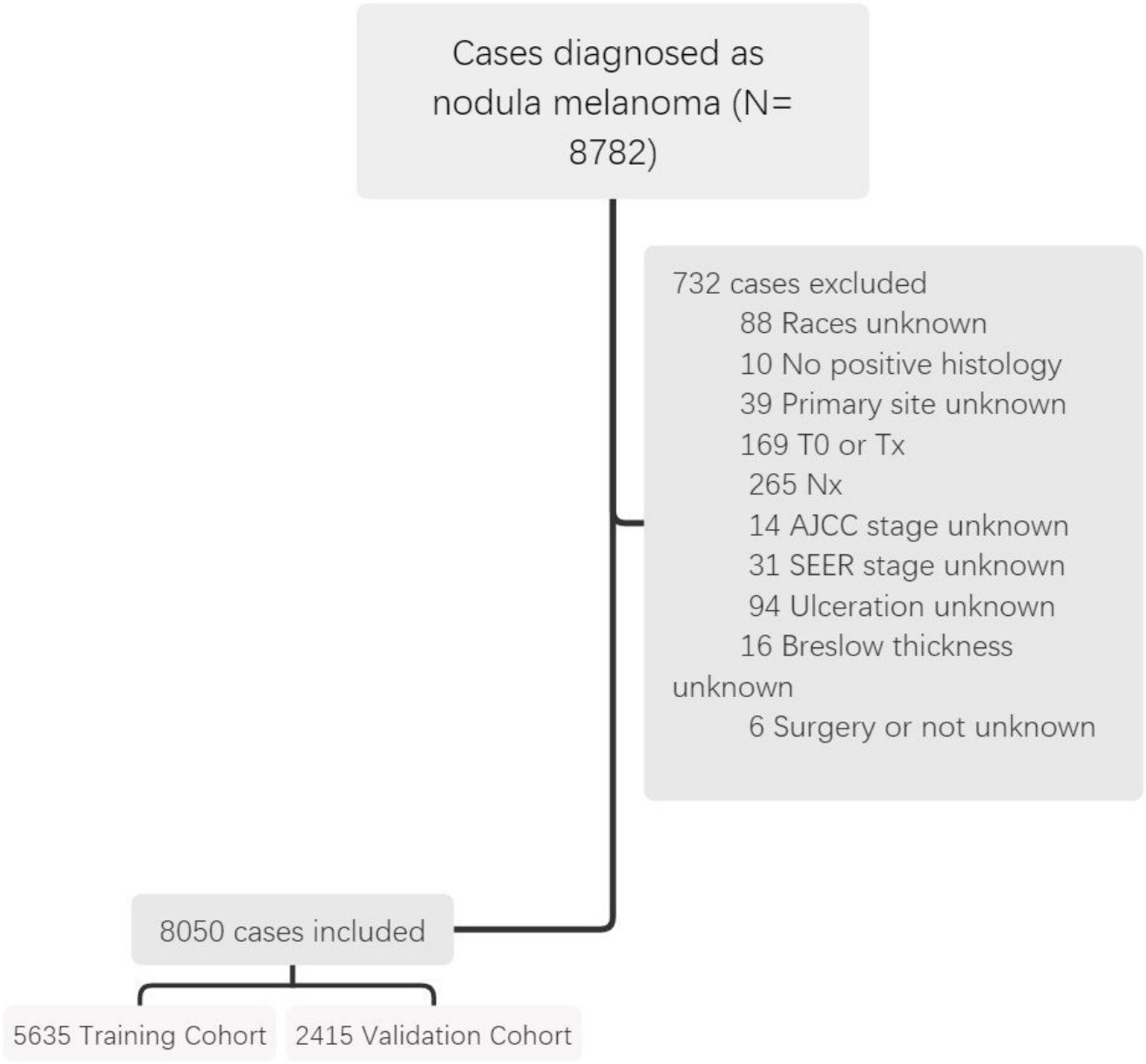


Figure 1

Flowchart showing the study screening process.

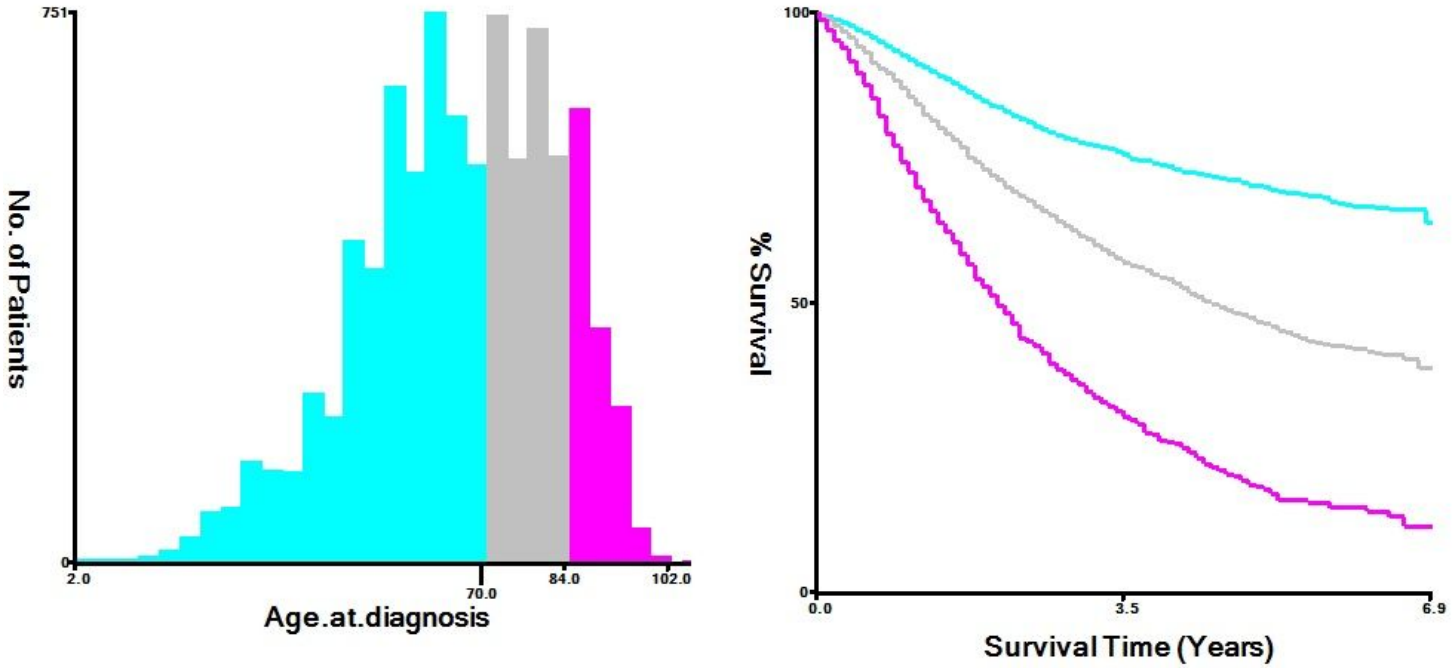


Figure 2

The optimal cut-off values for age

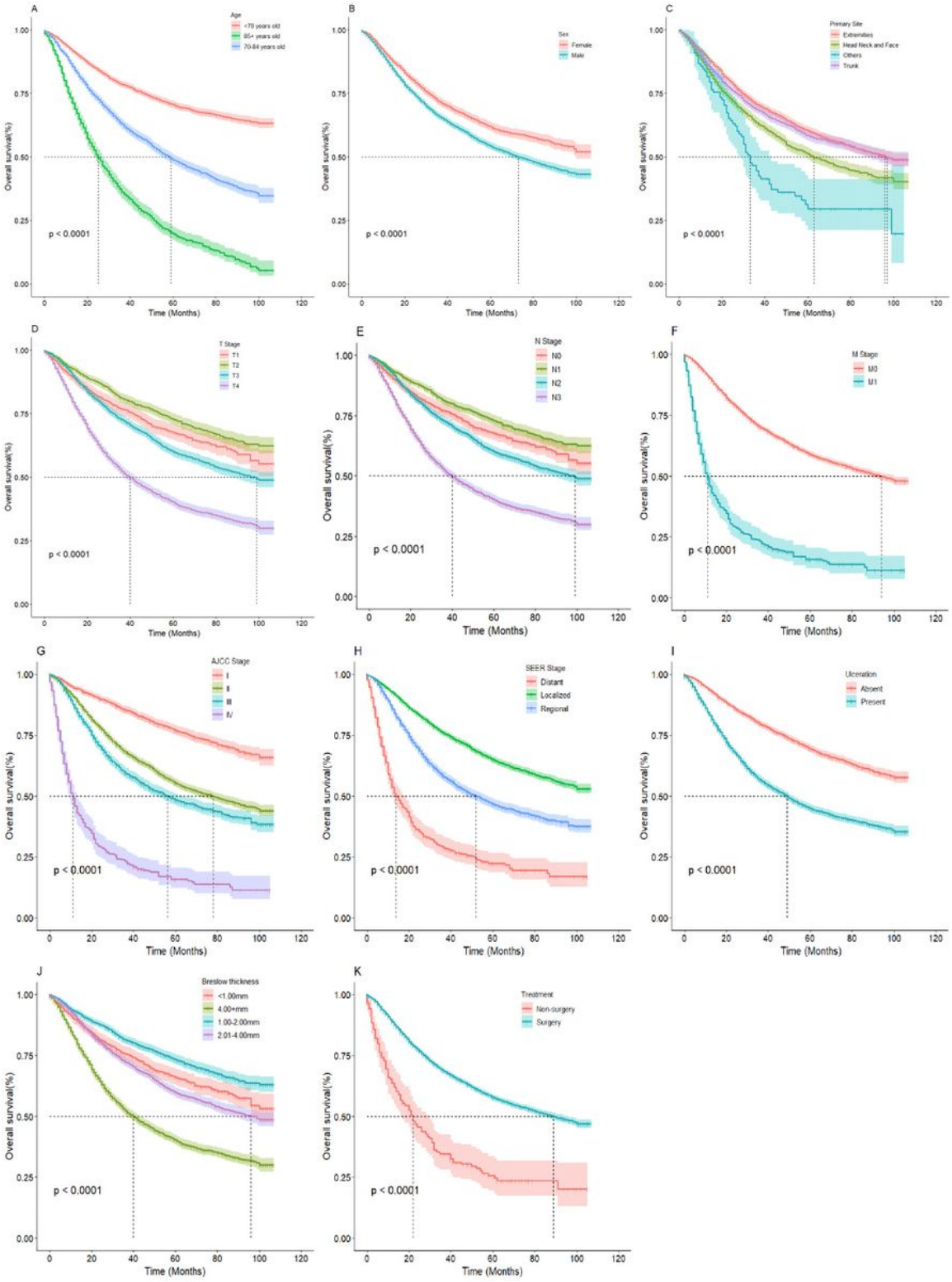


Figure 3

Kaplan–Meier curves of overall survival for patients based on : (A) Age; (B) Sex; (C) Primary site; (D-F) T N M stage; (G)AJCC stage; (H) SEER stage; (I) Ulceration; (J) Breslow thickness; (K) Treatment

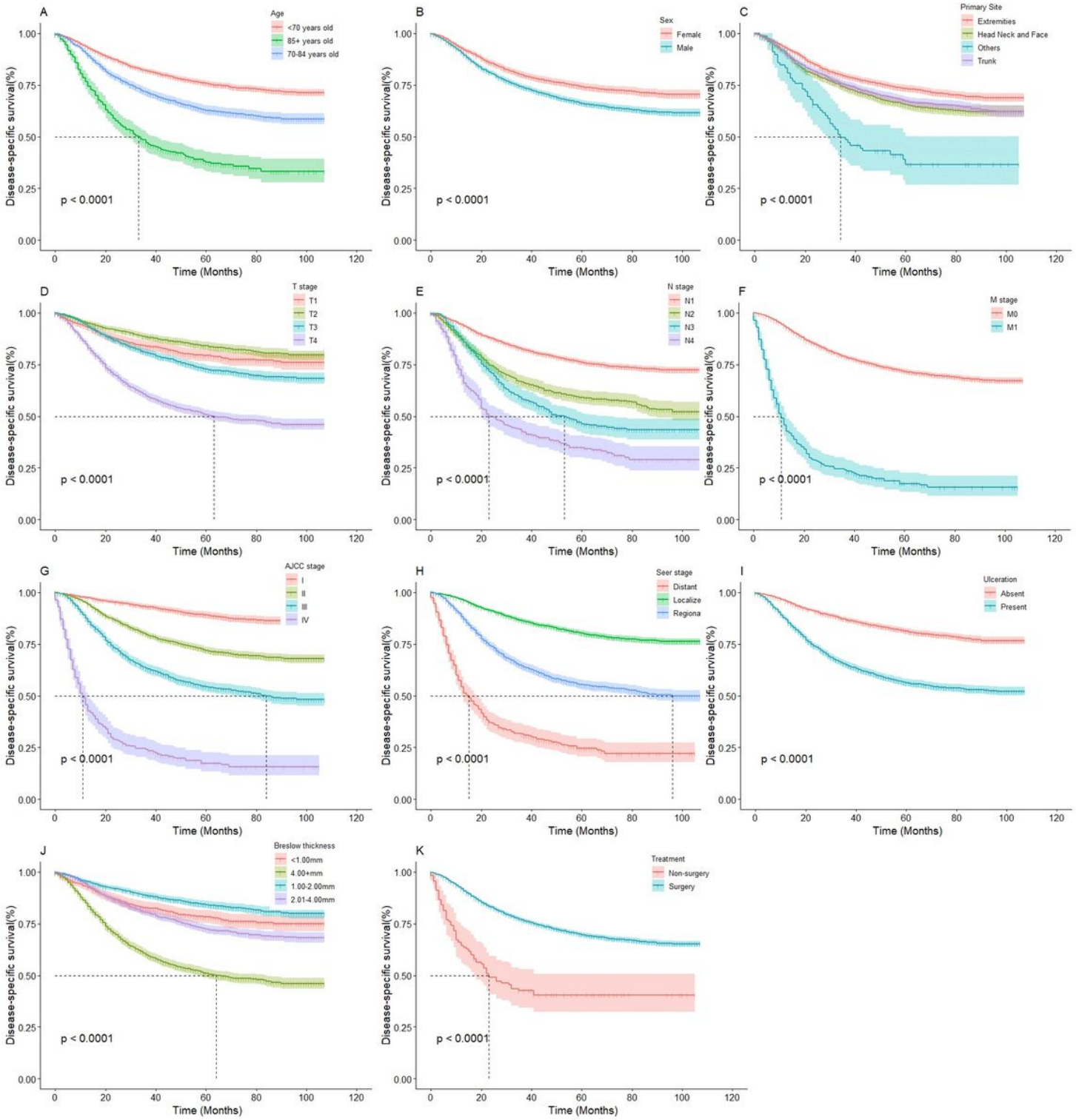
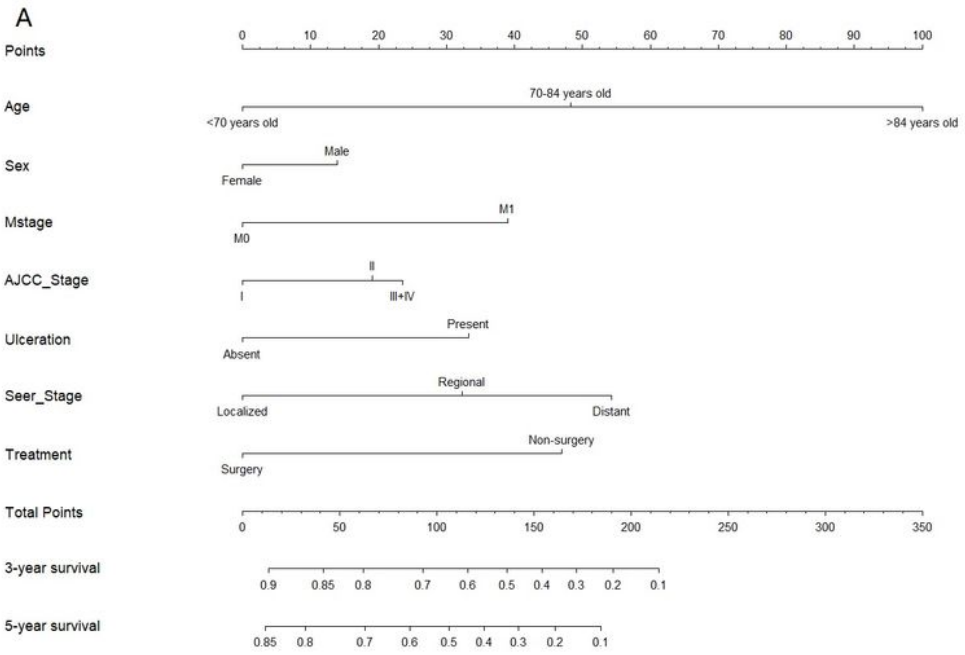


Figure 4

Kaplan–Meier curves of cancer-specific survival for patients based on : (A) Age; (B) Sex; (C) Primary site; (D-F) T N M stage; (G)AJCC stage; (H) SEER stage; (I) Ulceration; (J) Breslow thickness; (K) Treatment



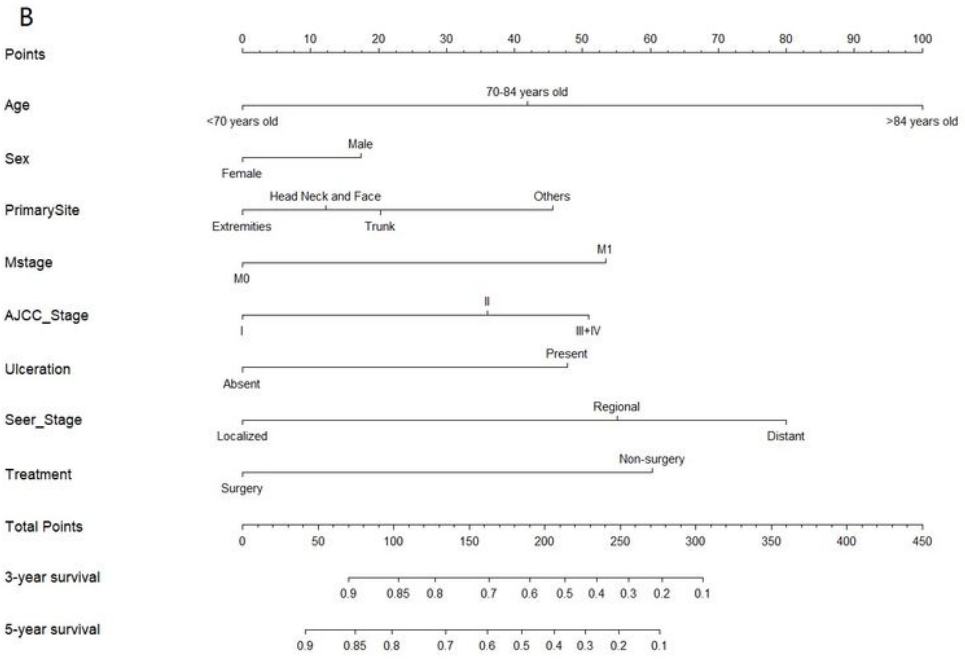


Figure 5

Nomograms predicting 3- and 5-year OS (A) and CSS (B) of nodular melanoma.

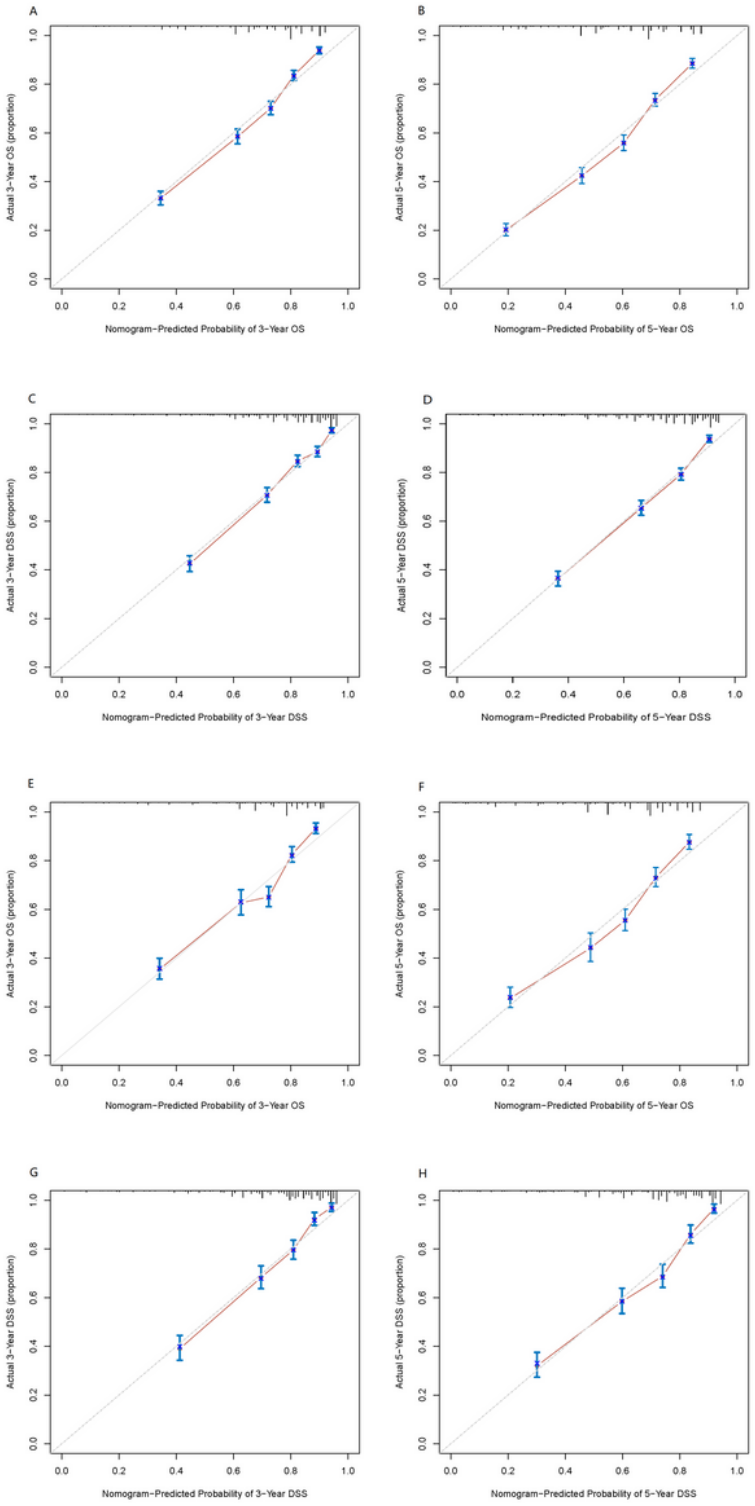


Figure 6

Calibration curves of the nomograms for 3- and 5-year OS and CSS prediction of the training cohort (A–D) and validation cohort (E–H).

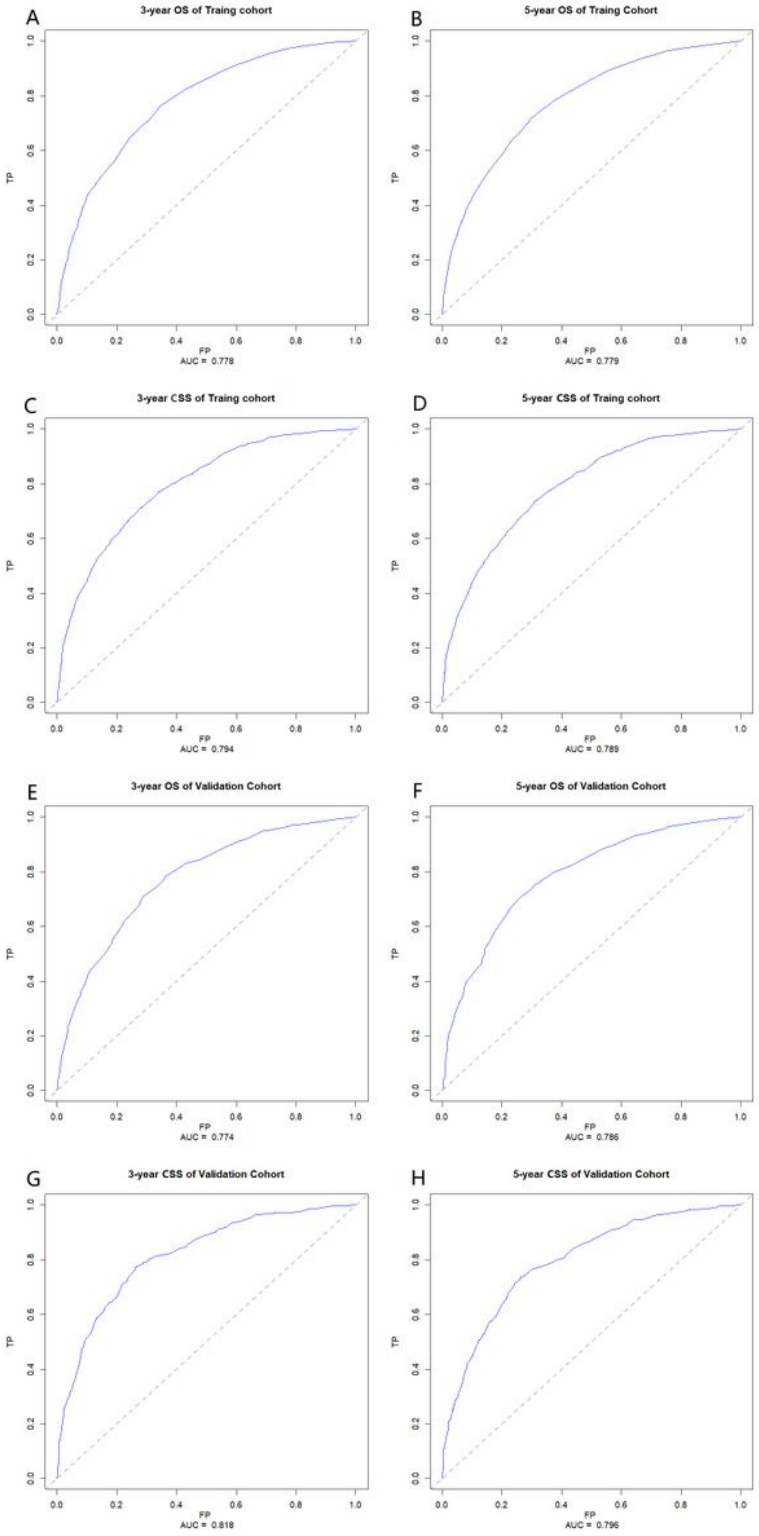


Figure 7

Comparison of the ROC curves of the nomograms for 3-year and 5-year OS and CSS prediction of the training cohort (A–D) and validation cohort (E–H).

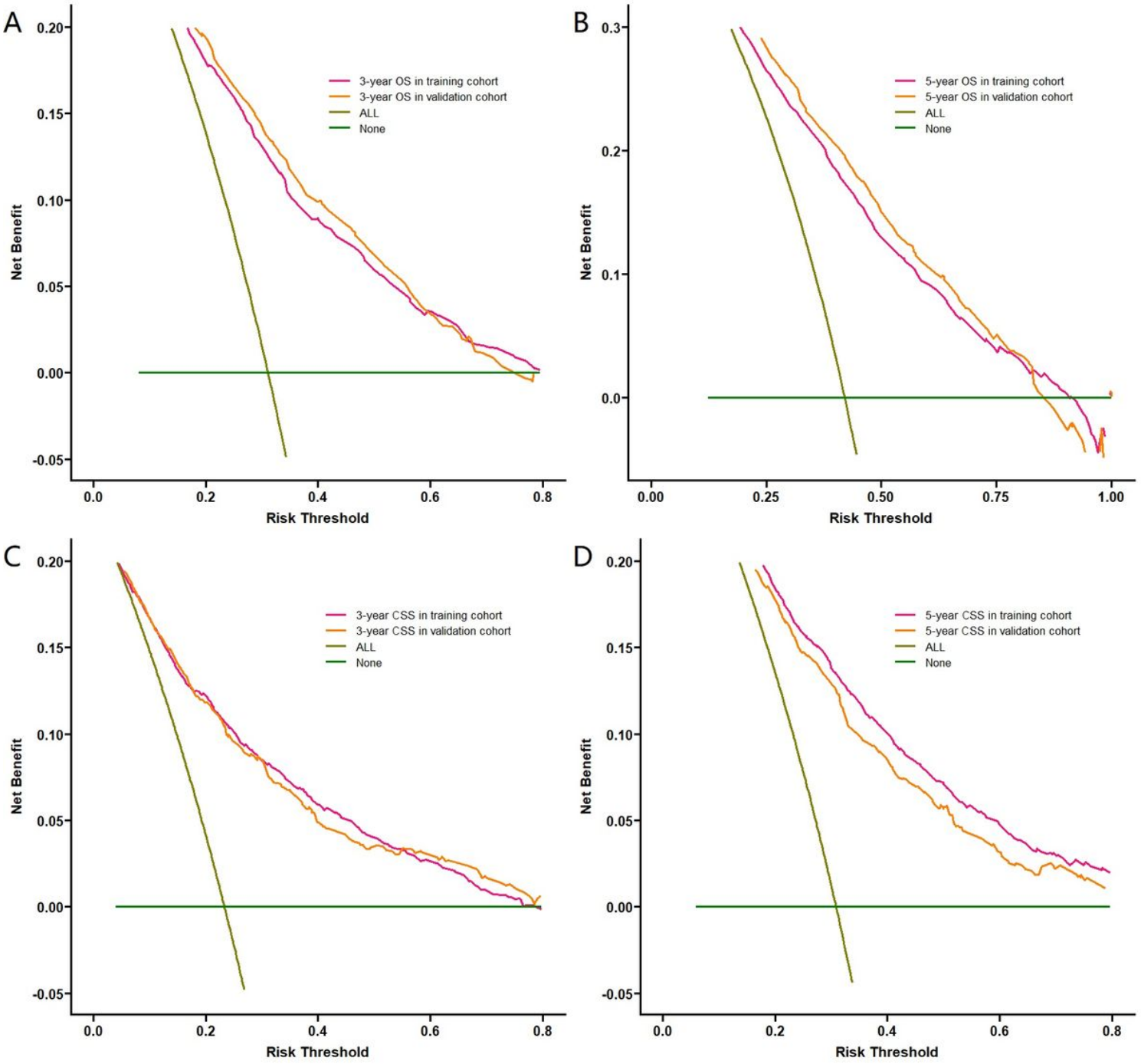


Figure 8

Comparison of the DCA curves of the nomograms for 3-year OS(A),5-year OS(B), 3-year CSS(C) and 5-year CSS(D) prediction of the training cohort and validation cohort.