Nomograms Predicting Overall Survival and Cancer Special Survival for Cervical Cancer in stage IIIC1

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Research Article

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Abstract

Background

The purpose of this study is to explore the factors that affect the prognosis of overall survival (OS) and cancer special survival (CSS) in cervical cancer with stage IIIC1 and establish nomogram models to predict this prognosis.

Methods

Data from The Surveil-lance, Epidemiology, and End Results (SEER) Program meeting the inclusion criterions were classified into training group, and data of validation were obtained from the First Affiliated Hospital of Anhui Medical University from 2010 to 2019. The incidence, Kaplan-Meier curves, OS and CSS of stage IIIC1 were evaluated according to the training group. Nomograms were established according to the results of univariate and multivariate Cox regression models. Harrell's C-index and receiver operating characteristic curve (ROC) were calculated to measure the accuracy of the prediction models. Calibration plots show the relationship between the predicted probability and the actual outcome. Decision-curve analysis (DCA) was applied to evaluate the clinical applicability of the constructed nomogram.

Results

The incidence of pelvic lymph node metastasis, a high-risk factor for prognosis in cervical cancer, decreased slightly over time. There are eight independent prognostic variables for OS, including age, race, histology, differentiation, extension range, tumor size, radiation recode and surgery, but seven for CSS with age excluded. Nomograms of OS and CSS were established based on the results. The C-index for the nomograms of OS and CSS were 0.692, 0.689 respectively when random sampling of SEER data sets, and 0.706, 0.737 respectively when random sampling of external data sets. AUCs for the nomogram of OS were 0.648, 0.644 respectively, and 0.683, 0.675 for the nomogram of CSS. Calibration plots for the nomograms were almost identical to the actual observations. The DCA also proved the value of the two models.

Conclusion

Age, race, histology, differentiation, extension range, tumor size, radiation recode and surgery were all independent prognosis factors for OS. Only age excepts in CSS. OS and CSS nomograms were established in our study based on the result of multivariate Cox proportional hazard regression, and both own good predictive and clinical application value after validation.

1. Background

Cervical cancer is the most common malignant tumor among female reproductive system, and the fourth most common malignant tumor in women, after breast cancer, colorectal cancer and lung cancer[1]. In 2018, approximately 570,000 women were diagnosed cervical cancer and 311,000 women died from it[1].

Carcinogenic human papillomavirus persistent infection is the main cause of cervical cancer development[2].Fortunately due to HPV vaccine, a drug protecting from cervical precancerous lesions, the incidence and mortality of cervical cancer in developed countries are gradually decreasing[3]. However, in developing countries, cervical cancer is still one of the most common cancers and the main dead cause of cancer in women[4]. For example, in China, the incidence and mortality of cervical cancer are increasing significantly, especially among young women[5]. Due to the huge economic burden of cervical cancer screening and vaccination programs, many women are still suffering from HPV infection and its related cervical cancer[6].

International Federation of Obstetrics and Gynecology (FIGO) stage is a systematic stage based on clinical examination[7]. In 2018, FIGO made important adjustments to the cervical cancer stage system[7]. Compared to the 2014 FIGO stage, with the following changes: (a) Horizontal infiltration width no longer affects stage; (b) One more stage IB3 is added in stage IB: In the revised system for stage IB disease, for every 2 cm increase in tumor size, the substage increases. Tumor smaller than 2 cm are classified as IB1, tumor greater than or equal to 2 cm and less than 4 cm are classified as IB2, tumors greater than or equal to 4 cm are classified as IB3; (c) pelvic lymph node metastasis or paraaortic lymph node metastasis are directly classified as stage IIIC1/2[7, 8].

The FIGO stage system is most frequently used to assess the prognosis of patients with cervical cancer. The new FIGO stage reflects the important impact of lymph node metastasis on the prognosis of cervical cancer patient[9]. However, in the same stage, the survival rate is heterogeneous. The FIGO stage system's prediction of prognosis is not comprehensive enough, and the accuracy needs to be improved[10, 11].

It is a trend to use nomogram for building cancer prediction model, because nomograms simplify a large number of complex factors into a single simple numerical estimation model to predict the probability of events[11]. At present, there are few prognostic analyses involving stage IIIC1 in cervical cancer, and no nomogram has been established for patients with stage IIIC1.

The purpose of this study is to explore the factors that affect the prognosis of stage IIIC1 and establish nomogram models to predict the prognosis of stage IIIC1.

2. Materials And Methods

2.1 Data Source

This is a retrospective observational study with data from The Surveil-lance, Epidemiology, and End Results (SEER) Program. The SEER database is a publicly available, federally funded cancer reporting system[12]. All cases extracted from the SEER database do not contain any personally identifying information.

There was one external validation set to validate the nomogram in the present analysis, whose data were obtained from the First Affiliated Hospital of Anhui Medical University from 2010 to 2019, all patients

pathologically diagnosed with cervical cancer. The data are available to every researcher since all the patients were authorized by Anhui Medical University Ethics Committee when they signed to obey the data use agreement.

2.2 Inclusion criterions

Inclusion criterions were that cervical cancer was pathologically diagnosed by SEER database from 2004 to 2015, and it was the first primary tumor; all patients underwent surgery and was evaluated positive for pelvic lymph node metastasis; there is no spreading to adjacent pelvic organs or distant organs; information about race, differentiation, surgery, marriage, tumor size, extension range was complete; histopathological diagnosis is squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma utilizing ICD-O-3 codes, poorly/ moderate/ well differentiation (demonstrated in Figure 1). Selecting the patients with negative lymph nodes in the same way to compare with pelvic lymph node metastasis. External validation set was selected by the same criterions, except that the marital status is unknown.

2.3 Statistical analysis

Categorical variables were described by count and percentage. Kaplan-Meier curves and log-rank tests were used to draw overall survival (OS) curves and cancer special survival (CSS) curves in different lymph nodes situation. Also, univariate and multivariate Cox regression models were employed to estimate hazard ratio (HR) and exact 95% confidence intervals (CIs) to analyze the prognostic factors for IIIC1 stage in cervical cancer. The OS was the primary endpoint outcome from the date of diagnosis to the date of death or the latest follow-up. The CSS was the special endpoint outcome from the date of diagnosis to the date of death from cervical cancer or the latest follow-up.

Significant prognosis factors of OS and CSS in the Cox proportional hazards regression model were used to build the nomograms to predict the 3- , 5-year OS and CSS rates. Harrell's C-index and receiver operating characteristic curve (ROC) were calculated to measure the accuracy of the prediction models. Calibration plots show the relationship between the predicted probability and the actual outcome. Finally, decision-curve analysis (DCA) was applied to evaluate the clinical applicability of the constructed nomogram with quantifying the net improved benefits at various threshold probabilities. All statistical analyses and plots were performed in SPSS 23.0 and R version 3.6.2 (http://www.R-project ct.org/). P value of <0.05 was considered significant.

3. Results

3.1 Incidence and survival analysis

From 2004 to 2015, 1838 cervical cancer patients appeared pelvic lymph nodes metastasis (20.34%). Firstly, after being compared it seems that the incidence of lymph node metastasis in cervical cancer from 2004 to 2015 has decreased slightly over time as shown in Figure 2A. After log-rank test, either OS

or CSS, pelvic lymph node metastasis was a high-risk factor for prognosis in cervical cancer (both $p<0.001$), and Kaplan-Meier survival curves also confirmed the effect of lymph node metastasis on prognosis, as shown in Figure 2B, 2C.

3.2 Patients Characteristics

In the training cohort, a total of 1838 cervical cancer patients between 2004 and 2015 were involved. As for validation cohort, 148 patients met the criterions in the First Affiliated Hospital of Anhui Medical University between 2009 and 2019, 125 of them in active follow-up, 15.54% lost to follow-up. The majority in training cohort were younger women (94.61%), and all were younger women in validation cohort. As for tumor characteristics, squamous cell carcinoma, confined to the cervix uteri/uterus and with tumor size≥4 was the majority in both cohorts. However, the poorly differentiated distributions were 53.80%, 22.40% respectively in training and validation cohort. Details were listed in Table 1. OS rate of training and validation cohorts were 33.00%, 32.80% respectively. And CSS rate of training and validation cohorts were 24.80%, 25.60% respectively.

3.3 Prognostic factors of OS and CSS

Univariate and multivariate Cox proportional hazard regression were used for calculating the prognostic factors of OS and CSS. Results of univariate Cox proportional hazard regression were shown in Table 2, and multivariate Cox proportional hazard regression were shown in forest plot (Figure 3A, 3B). Age, race, histology, differentiation, extension range, tumor size, radiotherapy and surgery were all independent prognosis factors for OS. Independent prognosis factors for CSS were same to OS except age.

3.4 Nomogram

Based on the prognostic factors of OS and CSS derived from the Cox proportional hazard regression, OS and CSS nomograms were respectively established, and shown in Figure 4. The C-index for the nomograms of OS and CSS were 0.692, 0.689 respectively when random sampling of SEER data sets, and 0.706, 0.737 respectively when random sampling of external data sets. Calibration plots for the nomograms displayed that the predicted 3-, 5-year OS and CSS probabilities for the training and validation sets were almost identical to the actual observations, as displayed in Figure 5. As shown in Figure 6 about ROC curves for the nomogram prediction models, the 3- and 5-year AUCs for the nomogram of OS were 0.648, 0.644 respectively, and 0.683, 0.675 for the nomogram of CSS, indicating a good model discrimination ability. The DCA also proved the value of the two models. The net benefit of our prognosis models was larger than that in other two scenarios (all screening or none-screening) in a wide range of threshold probabilities as displayed in Figure 7.

4. Discussion

Research discovers that pelvic lymph node metastasis is a high-risk factor for cervical cancer patients, and has got consistent approval by lots of studies[13, 14]. Until 2018, FIGO agreed that lymph node

metastasis had the greatest effect on prognosis, except for spreading to adjacent pelvic organs or distant organs. However, study by Xiaoliang Liu found that even in stage IIIC1, the survival rate also is heterogeneous, and tumor size, extension range, etc. have significant effect on prognosis of stage IIIC1[15]. Therefore, we included 10 variables from the SEER database to analyze the factors which affect the prognosis of stage IIIC1. Furthermore, previous studies demonstrated that these 10 variables were significantly associated with the prognosis of cervical cancer. For this reason, univariate and multivariate Cox proportional hazard regression were performed for all these 10 variables[15-17].

Then, we established OS and CSS nomograms based on the result of multivariate Cox proportional hazard regression. The factors in OS nomogram include age, race, tumor size, differentiation, histology, extension range, surgery, radiotherapy. For nomogram of CSS, only age is excluded. In previous studies on prognostic analysis of cervical cancer, elderly patients always have the shorter overall survival due to weak immune systems, and aging organ is related to poor prognosis[18, 19]. But it was not an independent prognosis factor for CSS in stage IIIC1 according to our analysis. As we can see in Table S1, the possibility of death from cervical cancer was obviously lower in elderly patients. Therefore, the effect of age on CSS needs more detailed study.

Our nomograms are well innovated and practical. Firstly, although nomograms for cervical cancer have been widely used[17, 20], there is still no one for stage IIIC1 in cervical cancer. Secondly, contrast to FIGO stage, patient demographics (age, race), tumor characteristics (tumor size, histology, differentiation, extension range) and treatment (surgery, radiotherapy) which were independent prognosis factors for OS or CSS were included in our nomograms. Further, these variables were easily obtained in clinical. So, our nomograms could reduce the bias caused by patient demographics and different treatment when predicting prognosis of cervical cancer. Thirdly, our nomograms were verified by external data sets. This process can test the predictive ability of nomogram in different groups of people, and judge its applicability to various groups of people[21].

The C-indexes of nomograms trended to be between 0.65 and 0.75, which were acceptable[22, 23]. And the C-indexes of random sampling of SEER and external data sets all reached this area, indicating that our nomograms have favourable discrimination ability. Besides, whether the nomograms are incorrectly estimated or over-fitting can be measured according to calibration plots. When the plot completely meets the 45-degree line, the prediction model is considered to have a fine calibration[24]. And our calibration plots fit well with the 45-degree line. It means our nomograms have good calibration in 3- and 5-year OS and CSS prediction. In addition, DCA was used to evaluate the clinical applicability of the constructed nomogram when quantifying the net improvement benefits under different threshold probabilities[25]. After validation, DCA confirmed that our nomograms have a better clinical benefit and utility in predicting the survive of cervical cancer in stage IIIC1.

It is worth noting that the tumor size shared the largest contribution to nomograms, whether OS or CSS. The influence of tumor size on prognosis has been confirmed in various cancers, including thyroid cancer, breast cancer[26, 27]. In cervical cancer, the influence of tumor size on prognosis in stage IB and stage □

has been confirmed and shown in FIGO stage[28, 29]. According to multivariate Cox proportional hazard regression, as the tumor size increases, the prognosis of patients with stage IIIC1 becomes significantly worse. Furthermore, the HR was worse than any other factors included in the nomograms. Meanwhile, imaging can be evidence of FIGO stage[7]. Studies on the application of imaging to assess the tumor size of cervical cancer before surgery show that the diagnostic power of imaging is obviously stronger than clinical assessment[30], especially MRI, depending on its superior contrast resolution, which can visualize tumor volume and size[31]. We can conclude that compared to other pathological characteristics, the effect of tumor size on prognosis in cervical cancer holds unity across all stages. Further research revealed the value of tumor size as prognostic indicator. Therefore, we suggest that IIIC1 can be further divided into three sub stages according to tumor size.

Even though the nomograms were verified by external data set, our study still has some limitations. Firstly, as a retrospective study, this research filtered data from data sets and excluded patients with missing data on the collected variables, leading to a selection bias. Secondly, some key indicators are in lack, especially dosage of radiotherapy and details of chemotherapy project, etc. For example, only “Yes” and “No” showed in SEER database about chemotherapy, leading to the weaken impact of chemotherapy on survival. Thirdly, insufficient sample size of external data set and missing part of data caused inadequate verification.

5. Conclusion

In conclusion, age, race, histology, differentiation, extension range, tumor size, radiation recode and surgery were all independent prognosis factors for OS, and race, histology, differentiation, extension range, tumor size, radiation recode, surgery for CSS. In addition, OS and CSS nomograms were established in our study based on the result of multivariate Cox proportional hazard regression, and both own good predictive and clinical application value after validation. Especially, tumor size shared the largest contribution to nomograms.

Abbreviations

FIGO: International Federation of Obstetrics and Gynecology; SEER: The Surveil-lance, Epidemiology, and End Results; OS: Overall Survival; CSS: Cancer Special Survival; HR: Hazard Ratio; Cis: Confidence Intervals; ROC: Receiver Operating Characteristic; DCA: Decision-Curve Analysis

Declarations

Ethics approval and consent to participate

All cases extracted from the SEER database do not contain any personally identifying information. The external validation set are available to every researcher since all the patients were authorized by Anhui Medical University Ethics Committee when they signed to obey the data use agreement.

Consent for publication

Not applicable.

Availability of data and materials

One of the data of this study are available from the Surveillance, Epidemiology, and

End Results (SEER) database(https://seer.cancer.gov/, accession numbers were 10086-Nov2019). The external data were obtained from the First Affiliated Hospital of Anhui Medical University.

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There is no fund in this study.

Competing Interests

The authors declared that no competing interest exists.

Authors' contributions

YFF, YW, ML designed the study. YFF, YW conducted the data analysis and YFF

wrote the manuscript. SWW, YQX, and YYL collected the data. All authors

were involved in interpreting the data and revising the manuscript. All

authors agreed with the final publication. The author(s) read and approved

the final manuscript

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References

1. Arbyn, M., et al., Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health, 2020. 8(2): p. e191-e203.
2. Arbyn, M., et al., Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev, 2018. 5: p. CD009069.
3. Siegel, R.L., K.D. Miller, and A. Jemal, Cancer statistics, 2018. CA Cancer J Clin, 2018. 68(1): p. 7-30.

4. Bray, F., et al., Long-term Realism and Cost-effectiveness: Primary Prevention in Combatting Cancer and Associated Inequalities Worldwide. J Natl Cancer Inst, 2015. 107(12): p. djv273.
5. Hu, Z. and D. Ma, The precision prevention and therapy of HPV-related cervical cancer: new concepts and clinical implications. Cancer Med, 2018. 7(10): p. 5217-5236.
6. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012 a synthetic analysis. Lancet Glob Health. 2016;4(9)e609-e616. doi10.1016S2214-109X(16)30143-7.
7. Bhatla, N., et al., Cancer of the cervix uteri. Int J Gynaecol Obstet, 2018. 143 Suppl 2: p. 22-36.
8. Oncology, F.C.o.G., FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet, 2014. 125(2): p. 97-8.
9. Waggoner, S.E., Cervical cancer. The Lancet, 2003. 361(9376): p. 2217-2225.
10. Wang, C., et al., A Prognostic Nomogram for Cervical Cancer after Surgery from SEER Database. J Cancer, 2018. 9(21): p. 3923-3928.
11. Wan, G., et al., Nomogram prediction of individual prognosis of patients with hepatocellular carcinoma. BMC Cancer, 2017. 17(1): p. 91.
12. Doll, K.M., A. Rademaker, and J.A. Sosa, Practical Guide to Surgical Data Sets: Surveillance, Epidemiology, and End Results (SEER) Database. JAMA Surg, 2018. 153(6): p. 588-589.
13. Sevin BU, Lu Y, Bloch DA, Nadji M, Koechli OR, Averette HE. Surgically defined prognostic parameters in patients with early cervical carcinoma. A multivariate survival tree analysis. Cancer. 1996;78(7)1438-1446.
14. Gien, L.T. and A. Covens, Lymph node assessment in cervical cancer: prognostic and therapeutic implications. J Surg Oncol, 2009. 99(4): p. 242-7.
15. Liu, X., et al., A Risk Stratification for Patients with Cervical Cancer in Stage IIIC1 of the 2018 FIGO Staging System. Sci Rep, 2020. 10(1): p. 362.
16. Matsuo, K., et al., Validation of the 2018 FIGO cervical cancer staging system. Gynecol Oncol, 2019. 152(1): p. 87-93.
17. Xie, G., et al., Calculating the overall survival probability in patients with cervical cancer: a nomogram and decision curve analysis-based study. BMC Cancer, 2020. 20(1): p. 833.
18. Quinn, B.A., et al., Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment and overall survival. Brachytherapy, 2019. 18(1): p. 29-37.
19. McComas, K.N., et al., The variable impact of positive lymph nodes in cervical cancer: Implications of the new FIGO staging system. Gynecol Oncol, 2020. 156(1): p. 85-92.
20. Marchetti, C., et al., Survival Nomograms after Curative Neoadjuvant Chemotherapy and Radical Surgery for Stage IB2-IIIB Cervical Cancer. Cancer Res Treat, 2018. 50(3): p. 768-776.
21. Iasonos, A., et al., How to build and interpret a nomogram for cancer prognosis. J Clin Oncol, 2008. 26(8): p. 1364-70.

22. Polterauer, S., et al., Nomogram prediction for overall survival of patients diagnosed with cervical cancer. Br J Cancer, 2012. 107(6): p. 918-24.
23. Jiang, S., et al., Prognosis and nomogram for predicting postoperative survival of duodenal adenocarcinoma: A retrospective study in China and the SEER database. Sci Rep, 2018. 8(1): p. 7940.
24. Van Calster, B., et al., A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol, 2016. 74: p. 167-76.
25. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. JAMA. 2015;313(4)409-410. doi10.1001jama.2015.37.
26. Foulkes, W.D., J.S. Reis-Filho, and S.A. Narod, Tumor size and survival in breast cancer--a reappraisal. Nat Rev Clin Oncol, 2010. 7(6): p. 348-53.
27. Nguyen, X.V., et al., Effect of Tumor Size on Risk of Metastatic Disease and Survival for Thyroid Cancer: Implications for Biopsy Guidelines. Thyroid, 2018. 28(3): p. 295-300.
28. Landoni, F., et al., Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. The Lancet, 1997. 350(9077): p. 535-540.
29. Wagner, A.E., et al., Impact of tumor size on survival in cancer of the cervix and validation of stage IIA1 and IIA2 subdivisions. Gynecol Oncol, 2013. 129(3): p. 517-21.
30. Mitchell, D.G., et al., Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. J Clin Oncol, 2006. 24(36): p. 5687-94.
31. Nag, S., et al., Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. Int J Radiat Oncol Biol Phys, 2004. 60(4): p. 1160-72.

Tables

Table 1. Patient characteristics in training cohort and validation cohort				
	Training cohort（N=1838）		Validation cohort（N=125）	
Age	N	Percent	N	Percent
X≥70	99	5.39	0	0.00
X＜70	1739	94.61	125	100.00
Race				
White	1460	79.40	0	0.00
Black	140	7.60	0	0.00
Others	238	12.90	125	100.00
Marital status				
Married	938	51.00	unknow	
Single	696	37.90	unknow	
Divorce	204	11.10	unknow	
Histology				
squamous cell carcinoma	1260	68.60	99	79.20
adenocarcinoma	413	22.50	25	20.00
adenosquamous	165	9.00	1	0.80
Differentiation				
Poorly differentiated	988	53.80	28	22.40
Moderate/ Well differentiation	850	46.20	97	77.60
Extension range				
Confined to the cervix uteri/uterus	1117	60.80	91	72.80
Extension beyond uterus	721	39.20	34	27.20
Tumor size（cm）				
X<2	217	11.80	6	4.80
2≤X<4	614	33.40	47	37.60
X≥4	1007	54.80	72	57.60
Radiation recode				
Yes	1520	82.70	92	73.60

No	318	17.30	33	26.40
Chemotherapy recode				
Yes	1416	77.00	116	92.80
No	422	23.00	9	7.20
Surgery				
Preserve uterus	165	9.00	0	0.00
Hysterectomy	1673	91.00	125	100.00
Survival state				
Survive	1232	67.00	84	67.20
Dead of other cause	150	8.20	9	7.20
Dead of cervical cancer	456	24.80	32	25.60

Table 2. Univariate analysis of OS and CSS in the training cohort				
Characteristics	OS		CSS	
	Hazard ratios (95% CI)	P	Hazard ratios (95% CI)	P
Age				
X<70	Reference		Reference	
X≥70	2.636(2.030-3.423)	0.000	1.354(0.925-1.981)	0.119
Race				
White	Reference		Reference	
Black	1.457(1.122-1.892)	0.005	1.636(1.207-2.217)	0.002
Others	0.906(0.703-1.166)	0.442	0.854(0.632-1.153)	0.303
Marriage				
Married	Reference		Reference	
Single	1.116(0.939-1.326)	0.212	0.957(0.779-1.175)	0.673
Divorce	1.295(1.014-1.655)	0.038	1.163(0.871-1.552)	0.305
Histology				
Squamous cell carcinoma	Reference		Reference	
Adenocarcinoma	1.394(1.160-1.674)	0.000	1.545(1.241-1.923)	0.000
Adenosquamous	1.354(1.037-1.767)	0.026	1.281(0.941-1.745)	0.116
Differentiation				
Poorly differentiated	Reference		Reference	
Moderate/Well differentiation	0.735(0.625-0.865)	0.000	0.741(0.614-0.893)	0.007
Extension range				
Confined to the cervix uteri/uterus	Reference		Reference	
Extension beyond uterus	2.315(1.972-2.717)	0.000	1.800(1.486-2.180)	0.000
Tumor size（cm）				
X<2	Reference		Reference	
2≤X<4	2.312(1.516-3.525)	0.000	2.385(1.387-4.101)	0.002
X≥4	4.538(3.031-6.793)	0.000	4.220(2.495-7.139)	0.000

Radiation recode				
Yes	Reference		Reference	
No	1.506(1.242-1.828)	0.000	1.364(1.044-1.782)	0.023
Chemotherapy recode				
Yes	Reference		Reference	
No	1.055(0.877-1.270)	0.570	0.826(0.637-1.072)	0.151
Surgery				
Hysterectomy	Reference		Reference	
Preserve uterus	0.662(0.515-0.851)	0.001	0.671(0.503-0.896)	0.010

Figures

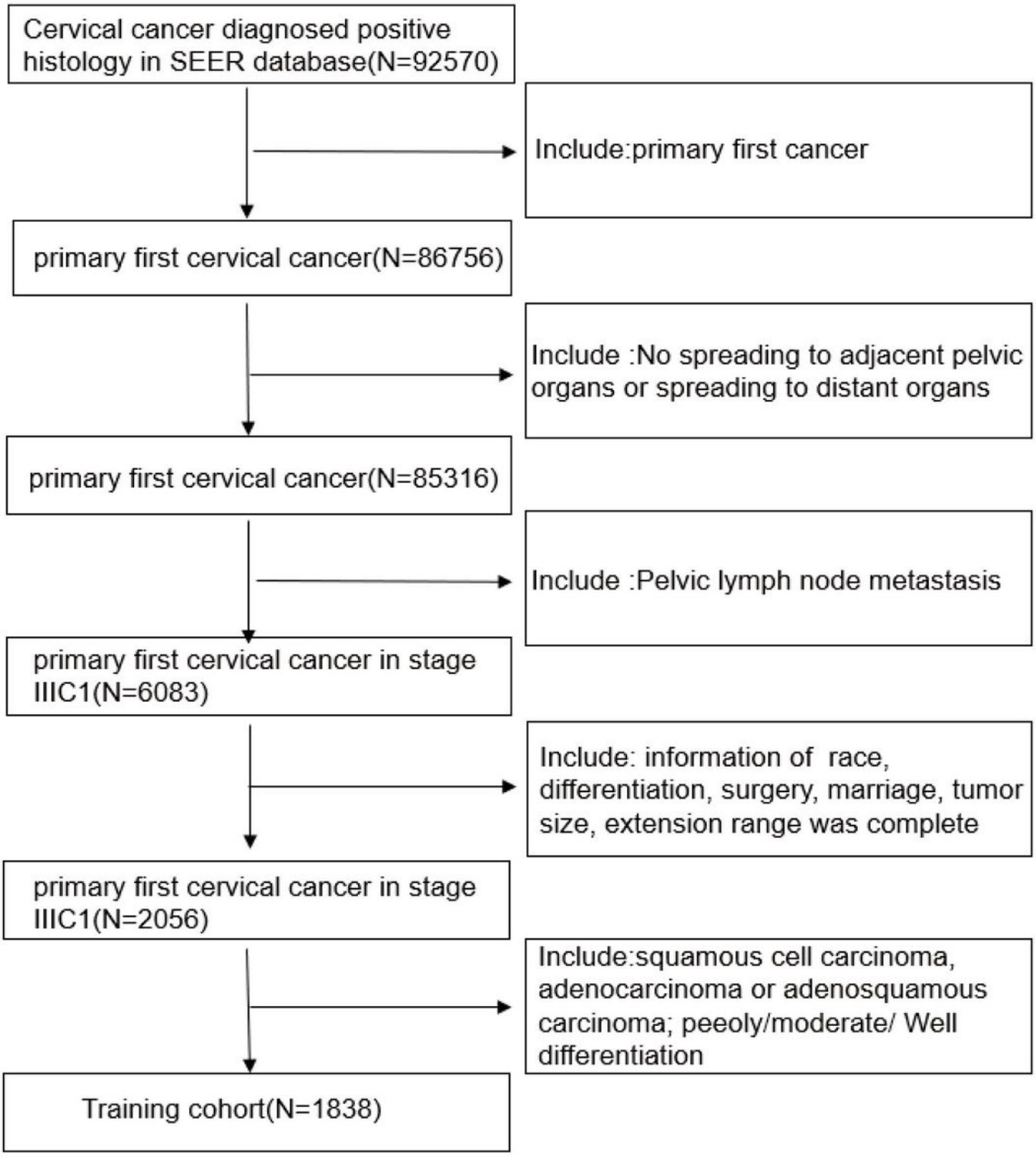

Figure 1

Study selection

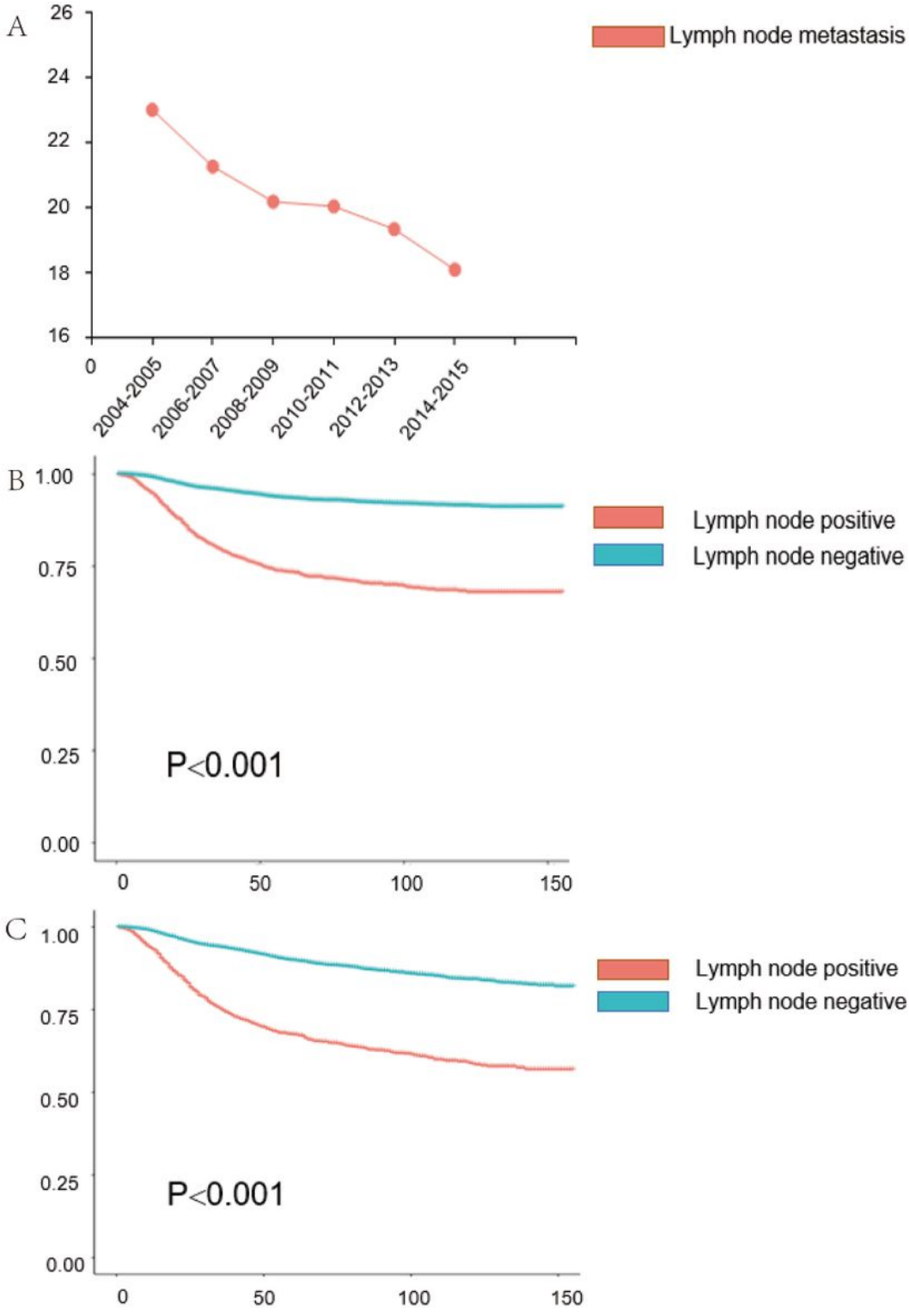

Figure 2

(A) Incidence of lymph node metastasis; (B) Kaplan-Meier survival curves of OS between lymph node metastasis and prognosis; (C) Kaplan-Meier survival curves of CSS between lymph node metastasis and prognosis.

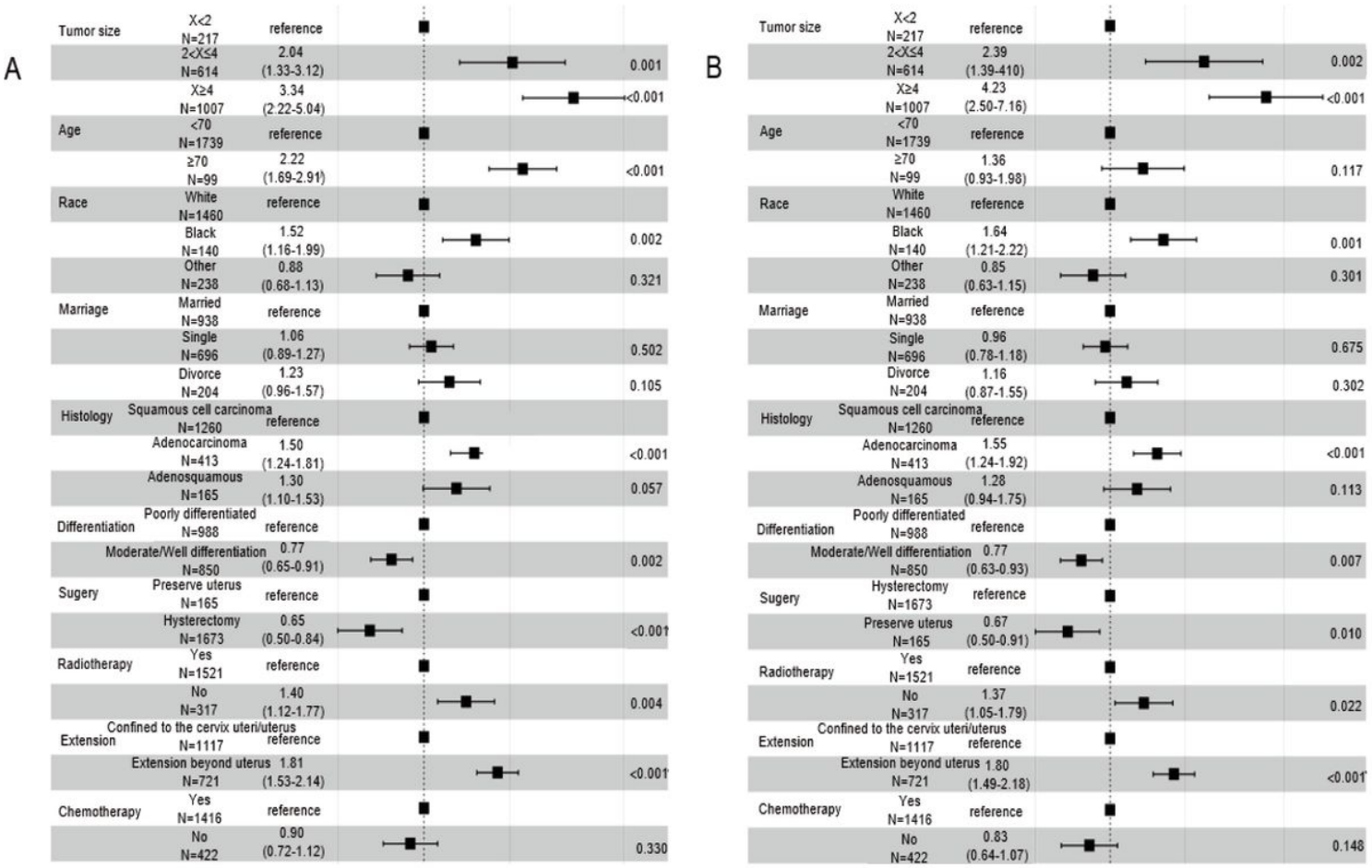

Figure 3

(A) Forest plot of OS depicting the effects of different prognostic factors; (B) Forest lpot of CSS depicting the effects of different prognostic factors.

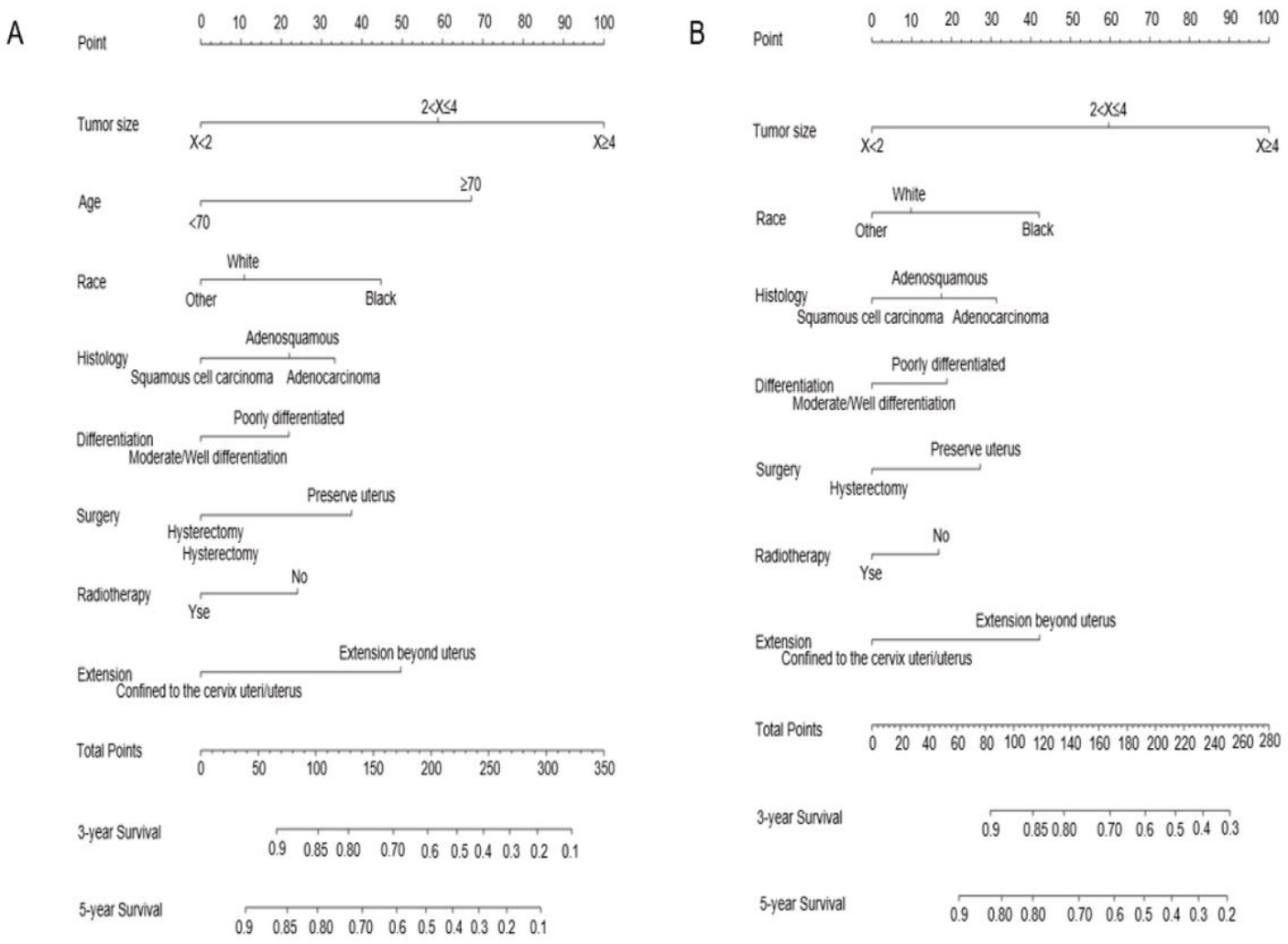

Figure 4

(A) Nomogram predict 3-and 5-year survival of OS; (B) Nomogram predict 3-and 5-year survival of CSS

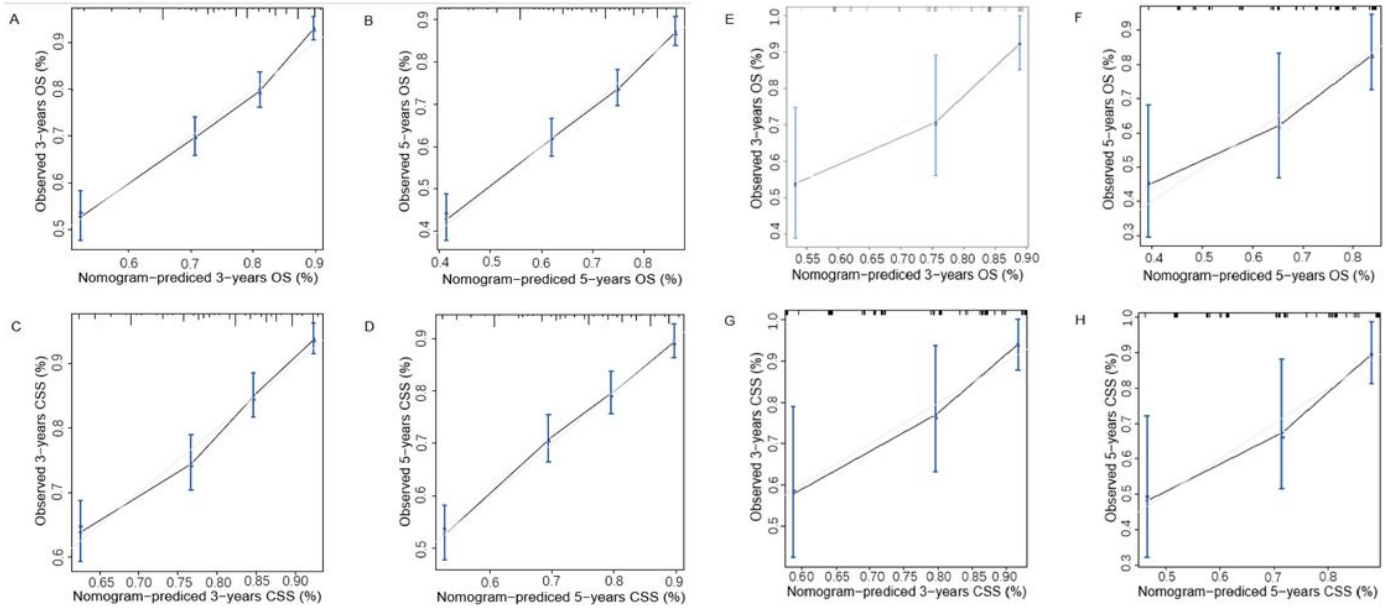

Figure 5

(A) Calibration plots for 3-year OS of the nomogram in the training cohort; (B) Calibration plots for 5-year OS of the nomogram training cohort; (C) Calibration plots for 3-year CSS of the nomogram in training cohort; (D) Calibration plots for 5-year CSS of the nomogram in training cohort; (E) Calibration plots for 3-year OS of the nomogram in validation cohort; (F) Calibration plots for 5year OS of the nomogram in validation cohort; (F) Calibration plots for 3-year CSS of the nomogram in validation cohort; (D) Calibration Plots for 5-year CSS of the nomogram in validation cohorttion.

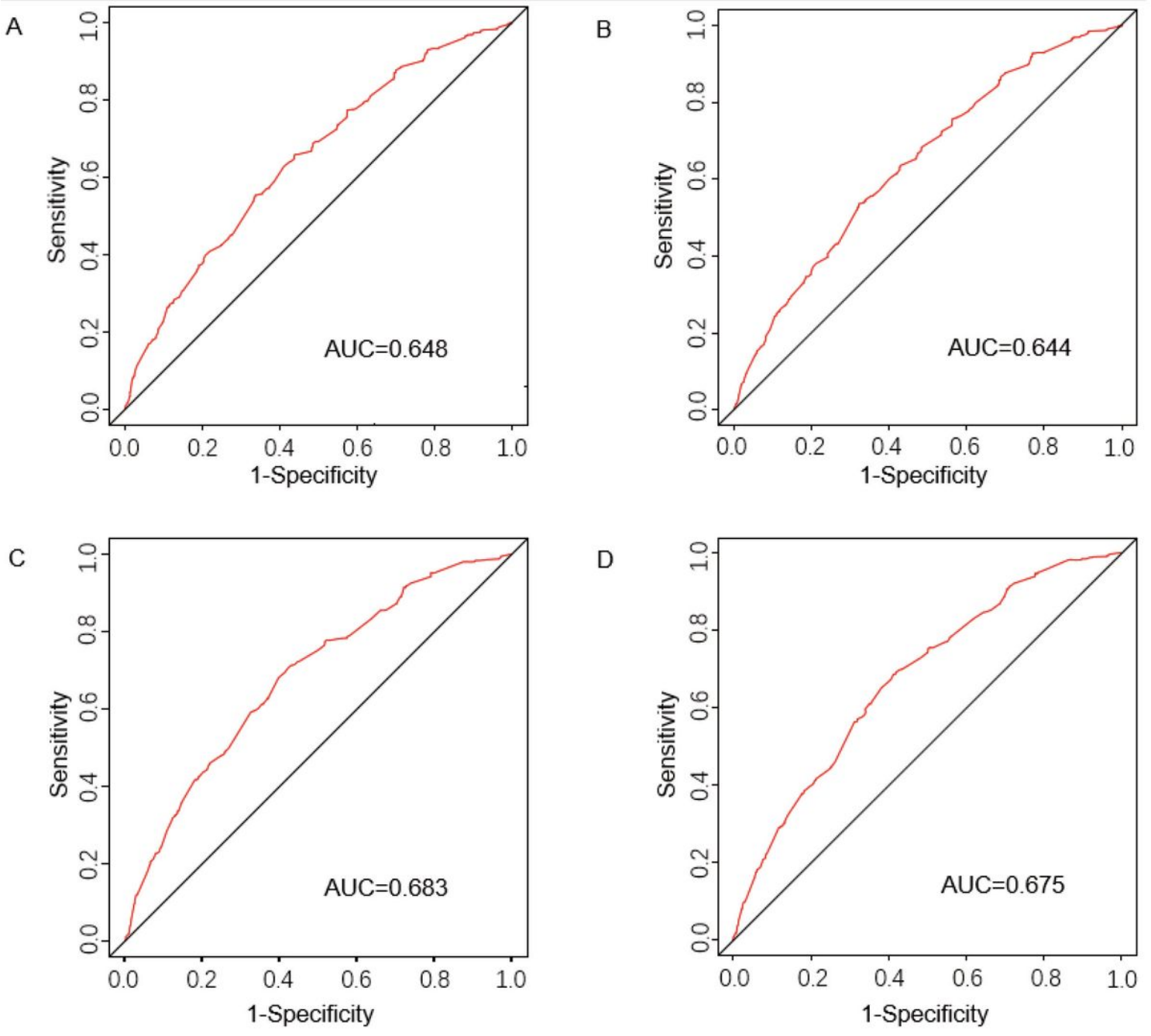

Figure 6

(A) ROC curves for 3-year OS of the nmogram; (B) ROC curves for 5-year OS of the nomogram; (C) ROC curves for 3-year CSS of the nomogram; (D) ROC curves for 5-year CSS of the nomogram.

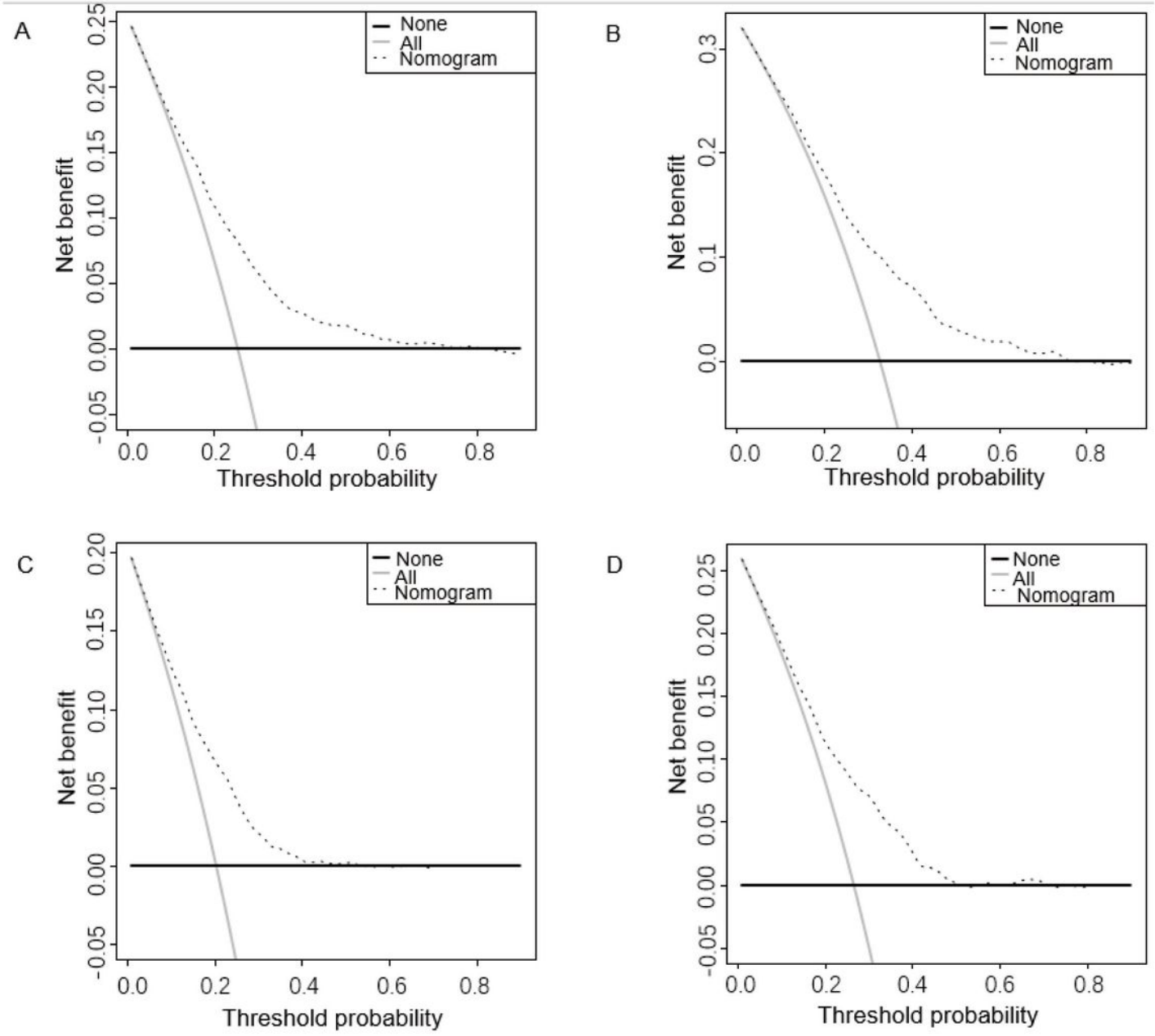

Figure 7

(A) Decision curves for 3-year OS prediction; (B) Desicion curves for 5-year OS prediction; (C) Desicion curves for 3-year CSS prediction; (D) Decision curves for 5-year CSS prediction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx