

The Nomograms for Predicting Cancer-specific Survival in Patients With Ovarian Cancer After Surgery

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Research Article

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Abstract

Objectives: Clear cell adenocarcinoma of the ovary (CCAO) and mixed cell adenocarcinoma of the ovary (MACO) were one of the gynecological malignancies.

Methods: Univariate and multivariate cox regression analysis were used to determine prognostic factors. Drawing nomograms, the receiver operating characteristic (ROC) curve and the calibration curve was applied to evaluate the agreement of the nomogram. The survival analysis was constructed to the high-risk factors.

Results: The nomogram was constructed and had a better discrimination. The calibration curves indicated that the nomograms had good calibration capabilities. 4 or more regional lymph nodes removed by surgery was beneficial to the patient's prognosis.

Conclusions: Our study analyzed the prognosis of CCAO or MACO patients, and constructed a predictive nomogram with good accuracy.

Introduction

Ovarian clear cell carcinoma of the ovary (CCCO) is a rare histologic subtype of ovarian cancer. It is often misdiagnosed and missed due to the lack of typical clinical manifestations and specific diagnostic methods. Simultaneously, the clinical prognosis is poor because it is too late to find out. At present, surgical treatment is the main clinical treatment, supplemented by comprehensive treatment of chemotherapy and neoadjuvant chemotherapy[1–3]. Patients with CCCO should be treated strictly by AJCC staging surgery[4]. Tumor reduction surgery was positively correlated with postoperative survival, while the size of residual tumor lesions was negatively correlated with survival rate[5]. However, there is currently a lack of clinically established prognostic models for patients with CCCO after surgical treatment, and the impact of postoperative lymph node dissection on the prognosis has not been established.

This study used SEER*Stat software to retrospectively analyze the National Cancer Institute database (The Surveillance, Epidemiology, and End Results, SEER), referred to as SEER database, and selected 5906 postoperative patients diagnosed as clear cell adenocarcinoma of the ovary (CCAO) or mixed cell adenocarcinoma of the ovary (MCAO) from 2010 to 2015 to explore the relevant factors of their prognosis, constructing a nomogram of 3-year and 5-year cancer-specific survival (CSS) rate to provide strong evidence for prognostic analysis after clinical surgery. CSS rate refers to the survival rate of patients after surgical treatment.

Patients And Methods

Data Collection

The SEER database is a public database that collects information on millions of patients with malignant tumors in some states and counties of the United States, including the incidence Status, treatment status, prognosis and death. In this study, a total of 1127 cases for CCAO and 1064 cases for MCAO were selected for retrospective analysis using SEER*Stat software. The inclusion and exclusion criteria were as follows. Inclusion criteria: (1) All included are primary ovarian tumors, (2) The pathological tissue ICD-O-3 classification were 8130 (CCAO) and 8323 (MCAO), (3) The diagnosis period was 2010 to 2015 years, (4) All patients were treated with surgery. Exclusion criteria: (1) Incomplete information such as tumor differentiation and staging information and corresponding variable indicators; (2) Incomplete follow-up information; (3) Carcinoma in situ; (4) The patients died within 1 month.

Statistical analysis

The influencing factors of CCAO or MCAO were selected in this study including age, race, laterality, grade, the seventh edition of American Joint Committee on Cancer (AJCC) staging for the extent of tumor (T), extent of spread to lymph nodes (N), and presence of metastasis (M), regional lymph nodes surgery, CSS rate, survival status. The grade included the following types: well-differentiated (G1), moderately-differentiated (G2), poorly-differentiated (G3), and undifferentiated (G4). The cox proportional hazard regression model was used for univariate and multivariate analysis, and the independent factors affecting the prognosis of CCAO or MCAO were obtained. Drawing a nomogram to predict 3-year and 5-year CSS rate, using receiver operating characteristic (ROC) curve to evaluate the predictive ability of the model. Calibration curve were respectively adopted to evaluate the relationship between the actual results of the model and the expected results probability of association in the nomogram. The Kaplan-Meier plotter analysis was to explore the CSS rate of the risk factors. All data analyses were conducted using R software (version 3.6.0; <http://www.r-project.org/>). P value of less than 0.05 was considered to statistical significance.

Results

Patient characteristics

In this study, a total of 2191 patients were diagnosed with CCAO (1127 cases) and MCAO (1064 cases). For CCAO and MCAO patients, most of them were under 70 years old (CCAO: 88.46%; MCAO: 83.17%), most of them were white people (CCAO: 74.18%; MCAO: 85.34%). Most of them occurred on one side of the ovary (CCAO: 89.17%; MCAO: 66.35%), and the grade was mostly Poorly-undifferentiated (CCAO: 53.33%; MCAO: 41.45%), 69.39% of CCAO and 60.62% of MCAO patients received 4 or more regional lymph nodes surgery. (Table 1)

Table 1
Basic clinical information for CCAO and MCAO patients in this study

Characteristics	CCAO	MCAO
	1127(100%)	1064(100%)
Age		
< 40	49 (4.35%)	56 (5.26%)
40–49	236 (20.94%)	221 (20.77%)
50–59	391 (34.69%)	341 (32.05%)
60–69	321 (28.48%)	267 (25.09%)
70–79	98 (8.70%)	135 (12.69%)
>=80	32 (2.84%)	44 (4.14%)
Race		
Black	53 (4.70%)	50 (4.70%)
White	836 (74.18%)	908 (85.34%)
Other	238 (21.12%)	106 (9.96%)
Laterality		
Left	515 (45.70%)	351 (32.99%)
Right	490 (43.48%)	355 (33.36%)
Bilateral	122 (10.83%)	358 (33.65%)
Grade		
Well differentiated	17 (1.51%)	119 (11.18%)
Moderately differentiated	109 (9.67%)	186 (17.48%)
Poorly differentiated	601 (53.33%)	441 (41.45%)
Undifferentiated	400 (35.49%)	318 (29.89%)
AJCC T		
T1a	391 (34.69%)	220 (20.68%)
T1b	18 (1.60%)	19 (1.79%)
T1c	355 (31.50%)	204 (19.17%)
T2a	34 (3.02%)	59 (5.55%)
T2b	61 (5.41%)	59 (5.55%)

Characteristics	CCAO	MCAO
T2c	67 (5.94%)	100 (9.40%)
T3a	35 (3.11%)	44 (4.14%)
T3b	32 (2.84%)	51 (4.79%)
T3c	134 (11.89%)	308 (28.95%)
AJCC N		
N0	990 (87.84%)	866 (81.39%)
N1	137 (12.16%)	198 (18.61%)
AJCC M		
M0	1067 (94.68%)	960 (90.23%)
M1	60 (5.32%)	104 (9.77%)
Scope regional lymph nodes surgery		
None	252 (22.36%)	298 (28.01%)
1 to 3 regional lymph nodes removed	93 (8.25%)	121 (11.37%)
4 or more regional lymph nodes removed	782 (69.39%)	645 (60.62%)

Cox regression analysis results

For CCAO patients, we screened out seven independent prognostic factors by univariate and multivariate cox regression analysis. Age, race, laterality, AJCC T, AJCC N, AJCC M and regional lymph nodes surgery were closely related to CSS in CCAO patients (Table 2). For MCAO patients, we obtained five independent prognostic factors by the above methods, such as grade, AJCC T, AJCC N, AJCC M, regional lymph nodes surgery (Table 3).

Table 2
 Prediction factors for CCAO patient cancer-specific survival by univariate and multivariate Cox regression analysis

Characteristics	Clear cell adenocarcinoma of ovary			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
< 40	Reference		Reference	
40–49	0.522(0.315–0.864)	0.012	0.592(0.353–0.992)	0.047
50–59	0.381 (0.233–0.624)	< 0.001	0.433(0.259–0.723)	0.001
60–69	0.423(0.257–0.696)	< 0.001	0.408(0.243–0.687)	< 0.001
70–79	0.478(0.262–0.870)	0.016	0.454(0.244–0.846)	0.013
>=80	0.836(0.416–1.681)	0.616	0.676(0.332–1.374)	0.279
Race				
Black	Reference		Reference	
White	0.431(0.277–0.671)	< 0.001	0.582(0.363–0.932)	0.024
Other	0.410(0.249–0.677)	< 0.001	0.505(0.299–0.852)	0.010
Laterality				
Left	Reference		Reference	
Right	1.033(0.782–1.366)	0.817	1.094(0.824–1.454)	0.534
Bilateral	3.948(2.879–5.412)	< 0.001	1.764(1.231–2.527)	0.002
Grade				
Well differentiated	Reference			
Moderately differentiated	1.231(0.288–5.267)	0.780		

Characteristics	Clear cell adenocarcinoma of ovary			
Poorly differentiated	1.935(0.480–7.805)	0.354		
Undifferentiated	1.518(0.373–6.175)	0.560		
AJCC T				
T1a	Reference		Reference	
T1b	0.537(0.074–3.898)	0.538	0.337(0.045–2.501)	0.288
T1c	1.281(0.847–1.937)	0.241	1.210(0.797–1.837)	0.371
T2a	3.571(1.882–6.776)	< 0.001	3.298(1.733–6.278)	< 0.001
T2b	3.893(2.289–6.620)	< 0.001	3.321(1.934–5.704)	< 0.001
T2c	3.678(2.216–6.104)	< 0.001	3.332(1.993–5.573)	< 0.001
T3a	7.612(4.515–12.832)	< 0.001	5.327(3.104–9.142)	< 0.001
T3b	6.971(3.919–12.400)	< 0.001	5.071(2.809–9.155)	< 0.001
T3c	8.174(5.625–11.877)	< 0.001	3.482(2.203–5.504)	< 0.001
AJCC N				
N0	Reference		Reference	
N1	3.515(2.678–4.614)	< 0.001	1.925(1.380–2.684)	< 0.001
AJCC M				
M0	Reference		Reference	
M1	5.215(3.717–7.318)	< 0.001	2.377(1.632–3.464)	< 0.001
Scope regional lymph nodes surgery				
None	Reference		Reference	
1 to 3 regional lymph nodes removed	1.220(0.811–1.834)	0.340	1.045(0.673–1.622)	0.845

Characteristics	Clear cell adenocarcinoma of ovary			
4 or more regional lymph nodes removed	0.552(0.419–0.727)	< 0.001	0.641(0.468–0.877)	0.005

Table 3

Prediction factors for MCAO patient cancer-specific survival by univariate and multivariate Cox regression analysis

Characteristics	Mixed cell adenocarcinoma of ovary			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
< 40	Reference		Reference	
40–49	0.690(0.393–1.212)	0.197	0.598(0.335–1.067)	0.082
50–59	0.784(0.460–1.336)	0.371	0.659(0.379–1.143)	0.138
60–69	0.849(0.493–1.460)	0.553	0.630(0.361–1.098)	0.103
70–79	1.609(0.929–2.788)	0.090	0.975(0.554–1.717)	0.930
>=80	2.519(1.351–4.696)	0.004	1.601(0.834–3.075)	0.157
Race				
Black	Reference		Reference	
White	0.508(0.337–0.767)	0.001	0.751(0.491–1.148)	0.186
Other	0.466(0.269–0.807)	0.006	0.864(0.487–1.534)	0.618
Laterality				
Left	Reference		Reference	
Right	1.336(0.986–1.810)	0.062	1.190(0.873–1.622)	0.271
Bilateral	2.135(1.614–2.824)	< 0.001	1.145(0.844–1.554)	0.385
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.842(0.931–3.645)	0.079	1.571(0.784–3.148)	0.202

Characteristics	Mixed cell adenocarcinoma of ovary			
	Univariate analysis		Multivariate analysis	
Poorly differentiated	4.487(2.437–8.262)	< 0.001	2.225(1.175–4.213)	0.014
Undifferentiated	4.423(2.375–8.236)	< 0.001	1.979(1.029–3.806)	0.041
AJCC T				
T1a	Reference		Reference	
T1b	1.265(0.386–4.147)	0.698	1.415(0.420–4.760)	0.575
T1c	0.683(0.388–1.202)	0.186	0.591(0.333–1.049)	0.072
T2a	1.924(1.020–3.629)	0.043	1.596(0.835–3.052)	0.157
T2b	1.755(0.879–3.504)	0.110	1.528(0.755–3.093)	0.238
T2c	2.064(1.227–3.472)	0.006	1.425(0.825–2.461)	0.205
T3a	4.850(2.816–8.352)	< 0.001	3.326(1.882–5.880)	< 0.001
T3b	4.191(2.450–7.170)	< 0.001	2.858(1.590–5.138)	< 0.001
T3c	4.989(3.375–7.375)	< 0.001	2.414(1.516–3.842)	< 0.001
AJCC N				
N0	Reference		Reference	
N1	2.520(1.985–3.200)	< 0.001	1.732(1.296–2.316)	< 0.001
AJCC M				
M0	Reference		Reference	
M1	3.746(2.860–4.908)	< 0.001	1.750(1.296–2.362)	< 0.001
Scope regional lymph nodes surgery				
None	Reference		Reference	
1 to 3 regional lymph nodes removed	0.794(0.558–1.131)	0.202	0.665(0.459–0.963)	0.031

Characteristics	Mixed cell adenocarcinoma of ovary			
	Univariate analysis		Multivariate analysis	
4 or more regional lymph nodes removed	0.480(0.378–0.610)	< 0.001	0.568(0.433–0.746)	< 0.001

Nomogram construction

The above independent influencing factors were screened out and assigned, and the maximum amount of change was assigned as 100 points, and then the scores corresponding to the individual indicators of each research object were obtained. Finally, the total score was obtained by summarizing the scores of each of the selected variables. The total score could be used to find the 3-year and 5-year CSS. Two Nomograms predicting CSS for CCAO(Fig. 1A) or MCAO (Fig. 1B) patients were established as follows. For example: a CCAO patient, age was 55 years old (about 2 points), race was black people (about 25 points), laterality was bilateral tumor (about 21 points), AJCC T stage was T1c (about 46 points), AJCC N stage was N0 stage (0 point), AJCC M stage was M0 (0 point), 1 to 3 regional lymph nodes removed by surgery (about 20 points), we could get a total score of 114 points, then 3-year CSS of the patient was between 60–70%, 3-year CSS of the patient was between 50–60%.

Validation and calibration of nomogram

The AUCs of the Nomogram predicting CSS demonstrated a good discriminative ability for CCAO patients (3-year CSS AUC: 0.764, Fig. 2A;5-year CSS AUC:0.759, Fig. 2B) or MCAO patients (3-year CSS AUC: 0.744, Fig. 2C; 5-year CSS AUC:0.796, Fig. 2D). These results indicated that the discrimination performed a good prediction capability in the 3-year and 5-year CSS nomogram for CCAO (Fig. 3A) or MCAO (Fig. 3B) patients. The calibration curves of the prediction nomogram using to predict the 3-year and 5-year CSS in CCAO (Fig. 3C) or MCAO (Fig. 3D) patients, which presented the predicted values were consistent with the actual values, demonstrated a good agreement.

Survival analysis of risk factors

We conducted risk stratification analysis based on the high-risk factors in the cox regression analysis. All patients were divided into two groups: high-risk patients (CCOA: 560/1127,49.7%; MCAO:527/1064,49.5%) and low-risk patients (CCOA:567/1127,50.3%; MCAO:537/1064,50.5%). The survival curves demonstrated that the risk stratification could well differentiate CSS in CCOA (Fig. 4A) and MCAO (Fig. 4B) patients ($p < 0.05$).

Discussion

CCCO was a type of epithelial ovarian cancer, which was highly malignant and had a poor prognosis[6]. Studies showed that the incidence of Asians was significantly higher than that of other races[7, 8]. The median age of this disease was 55 years old[9]. In our study, both CCAO and MCAO patients were selected for surgical treatment, whose age were between 50–59 years old (CCAO: 34.69%, MCAO:

32.05%), and most of them were white people. For CCAO patients, who younger than 40 years old were apt to own a poor prognosis, while there is no statistical difference between the age and poor prognosis for MCAO patients. Interestingly, bilateral ovarian disease of the patients with CCAO increased their poor prognosis. As the level of AJCC T staging increasing of CCAO or MCAO patients, the risk of adverse prognosis improved. Lymph node metastasis and distant organ metastasis were the important factors for its adverse outcome. Importantly, Multi-regional lymph node surgical removal (4 or more regional) could improve a good survival outcome for CCAO patient. In MCAO patients, the worse of the grade, the worse of the survival prognosis. Regional lymph node dissection could improve their poor prognosis. Many studies have shown that lymphadenectomy was very controversial for their prognosis[10–12], but we recommend that patients with CCAO or MCAO could undergo lymphadenectomy during surgery.

The nomogram model is currently an important tool for assessing the staging system and prognosis, and it is widely used in clinical research[13–15]. Our research comprehensively analyzed the above independent factors by establishing nomogram prediction model, using to predict the 3-year and 5-year CSS in CCAO or MCAO patients. In the nomogram, we could quickly screen out the independent risk factors. And according to their total scores added, the 3-year and 5-year CSS of patients with CCAO or MCAO after surgery were displayed, which had important clinical value.

At the same time, the ROC curve was established for the two models, which showed that the two models had better discrimination and better diagnostic effects. By drawing the calibration curve, we found that the predicted value and the actual value in the curve diagram of the two prediction models were consistent, which indicated that the prediction models had better calibration capabilities. Therefore, the establishment of the two models was satisfactory and could be used for clinical preliminary treatment evaluation. Some studies have shown that for CCAO patients, the survival rate after surgery was the key to evaluating treatment[16–18]. Our survival analysis showed that the survival time of patients with high-risk factors was shorter than that of patients with low-risk factors.

The shortcomings of this study were that the prognosis of patients was evaluated only from the perspective of surgery, and the included indicators had some limitations. At the same time, the study did not conduct external verification. Therefore, it is necessary to collect more clinical data to verify this and provide a more favorable guarantee for the implementation of precise and individualized treatment.

Declarations

Acknowledgments

None.

Conflict of interest

The authors have no competing interests to declare.

Ethics statement

The data obtained by SEER database which was a public database of each state in the United States and did not require the patient's informed consent.

Authors' contributions

Xiaobin Chen contributed to the concept, design, data collection, data analysis, chart making, writing and editing of the study.

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Figures

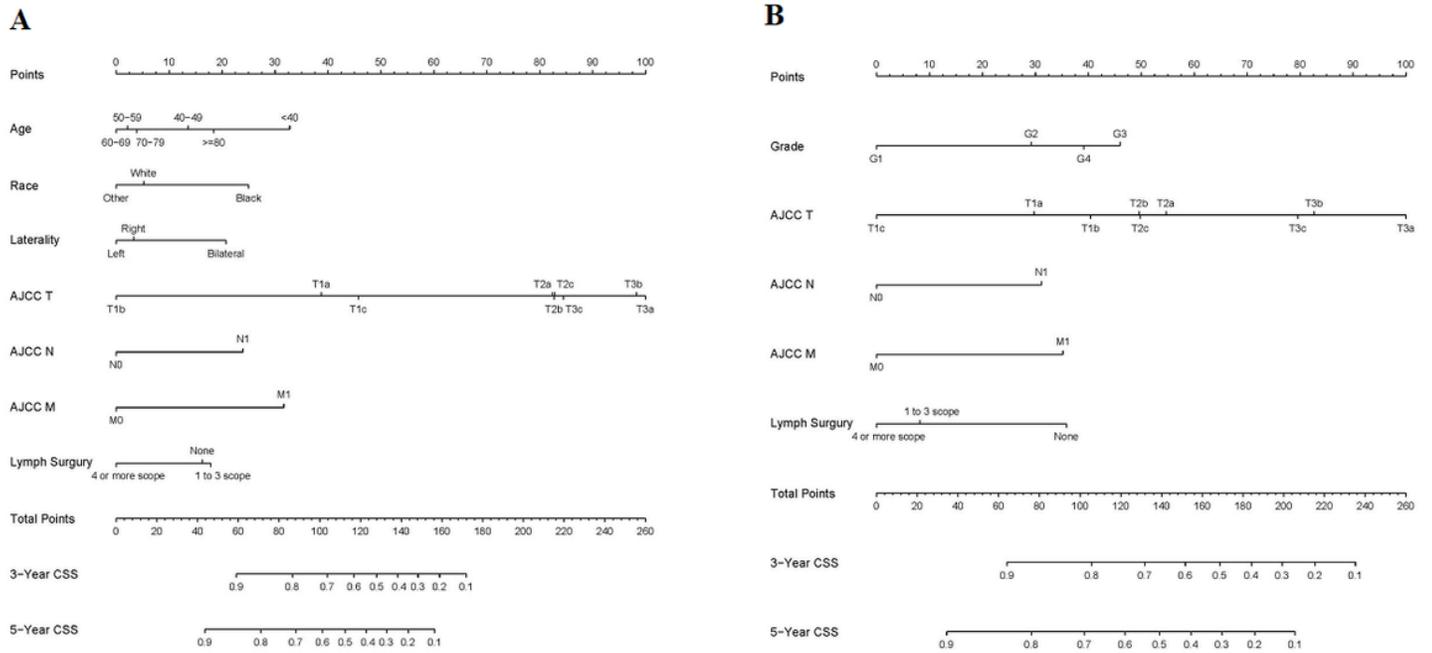


Figure 1

The Nomogram of the 3-year and 5-year CSS for CCAO(A) and MCAO(B) patients Abbreviations: lymph surgery, Scope regional lymph nodes surgery;

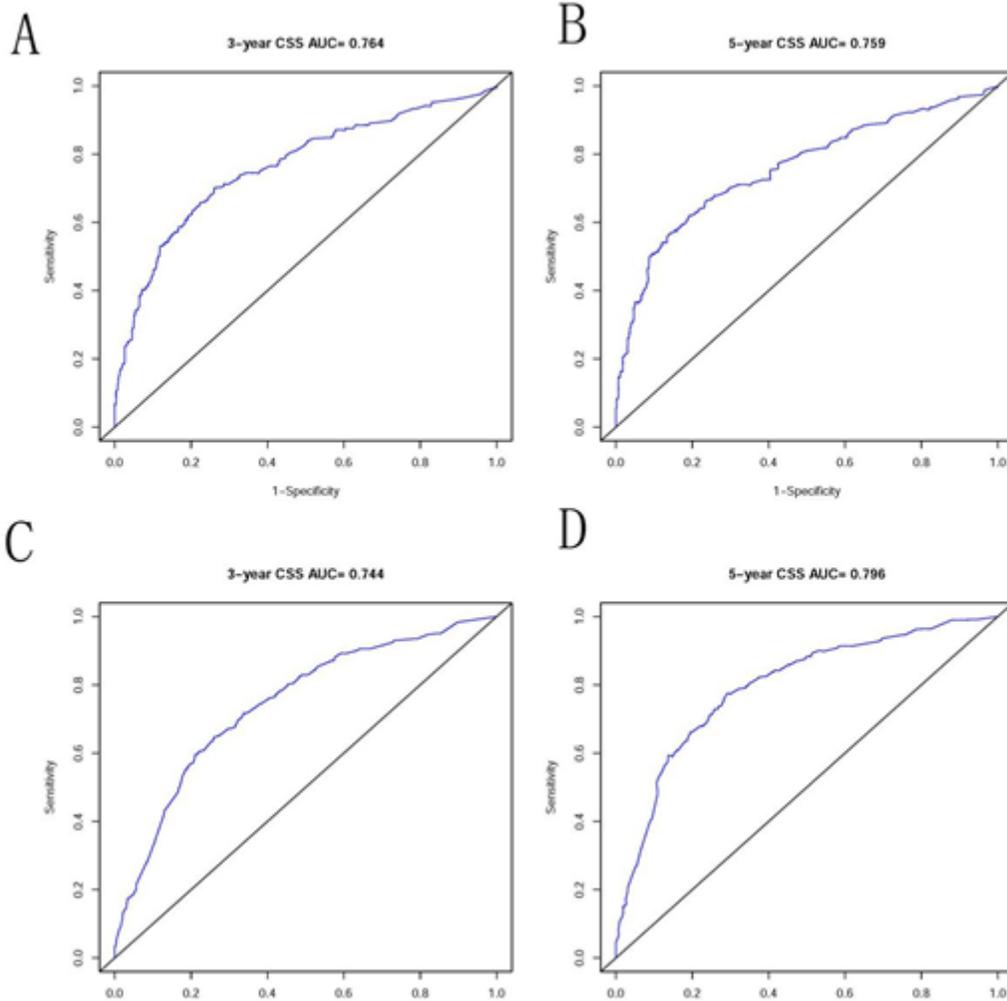


Figure 2

ROC curves of the Nomogram for predicting the prognosis at 3-year (A) and 5-year (B) CSS in CCAO patients. ROC curves of the Nomogram for predicting the prognosis at 3-year (C) and 5-year (D) CSS in MCAO patients

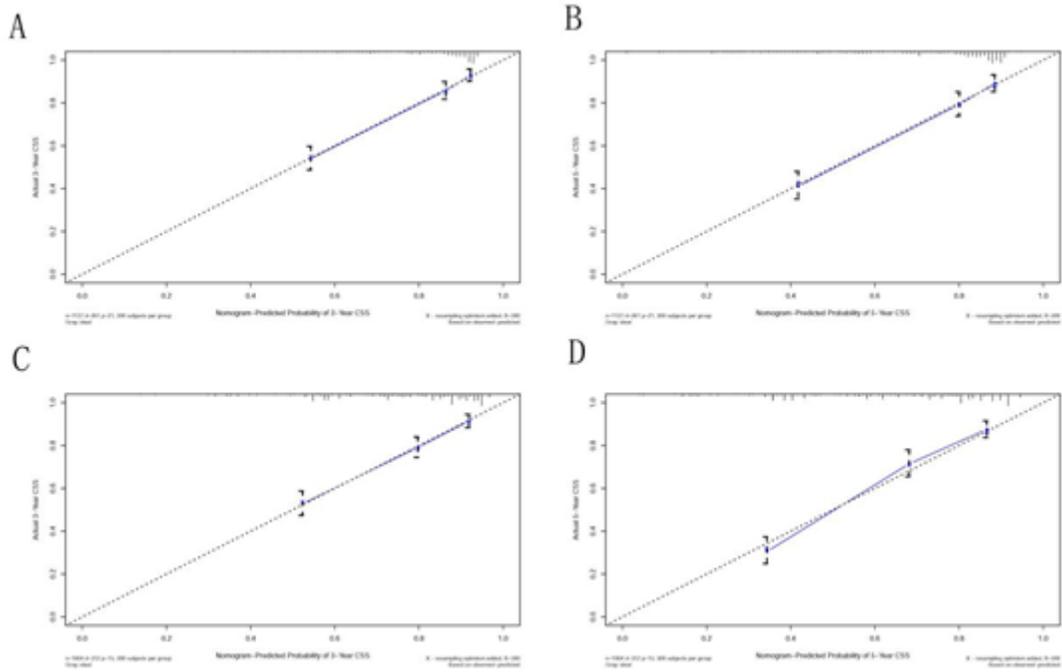


Figure 3

3-year (A) and 5-year (B) calibration curves of Nomogram for probability of CSS in CCAO patients. 3-year (C) and 5-year (D) calibration curves of Nomogram for probability of CSS in MCAO patients. (bootstrap=300 repetitions)

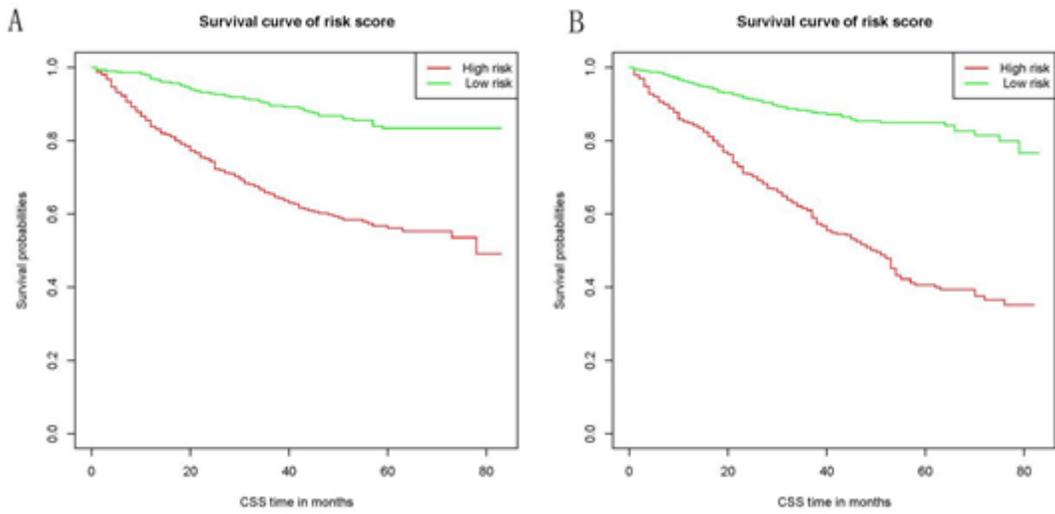


Figure 4

The survival curves of high-risk and low-risk score in CCOA (A) and MCAO (B) patients