

Prediction Model for Overall Survival in Patients with Epithelial Ovarian Cancer Undergoing Surgery and Systemic Therapy Based on the 2010–2021 SEER Database

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Purpose: Epithelial ovarian cancer (EOC) is a common gynecological malignancy, and accurate survival prediction after treatment remains challenging. Our aim was to construct a nomogram that effectively evaluates the overall survival (OS) of patients with EOC after surgery and systemic therapy.

Patients and Methods: Patients with EOC who underwent surgery and systemic therapy and were enrolled in the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2021 were divided into training and test sets in a 7:3 ratio for internal validation. Univariate Cox regression analysis, least absolute shrinkage and selection operator (LASSO), and multivariate Cox regression analysis were used to screen independent risk factors and construct a nomogram to predict OS. Model discrimination was assessed using the time-dependent area under the receiver operating characteristic curve (AUC). Calibration curves were plotted to evaluate agreement between predicted and observed survival, and clinical utility was assessed using decision curve analysis (DCA).

Results: A total of 17,285 EOC patients who underwent surgery and systemic therapy were included, with a median follow-up of 69 months. During follow-up, 4799 patients had died and 7282 remained alive. The final model included thirteen variables: age, race, marital status, histological classification, tumor size, CA125, T/N stage, cancer summary stage, FIGO stage, time from diagnosis to treatment, treatment sequence, and the extent of regional lymph node dissection. The 5-year AUC of the prediction model was 0.77 (95% CI: 0.76–0.78) in the training cohort and 0.77 (95% CI: 0.75–0.79) in the test cohort. The Brier scores ranged from 0.051 to 0.193 in training and test sets. These results indicate that the model possesses acceptable discriminatory capability and stability.

Conclusion: We developed a nomogram based on clinical variables to provide individualized estimation of OS in EOC patients who underwent surgery and systemic therapy.

Keywords: epithelial ovarian cancer, nomograms, SEER database, surgery and systemic therapy, overall survival

Introduction

Ovarian cancer is a commonly diagnosed cancer and cause of cancer death among women worldwide.¹ According to the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review (1975–2015), there are more than 20,000 cases and 14,000 deaths each year.² The main histological type of ovarian cancer is epithelial origin.³ Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer, and although the overall survival (OS) of patients with EOC has improved over the past 50 years with the continuous advancement of surgical techniques and improved chemotherapy drugs, the 5-year survival rate is only 46%.⁴

In the management of EOC, surgical treatment and systemic therapy are the two principal therapeutic modalities.⁵ Surgical treatment remains essential for tumor burden reduction and disease staging, contributing to improved prognosis in many patients; however, its benefits are often influenced by disease extent, patient condition, and perioperative risks.⁶ Systemic treatment, including platinum-based chemotherapy and emerging targeted agents, provides a non-invasive means to control microscopic and residual disease and reduce recurrence risk, yet it may be limited by drug toxicity and resistance.⁷ Given these complementary strengths and weaknesses, the combination of surgical and systemic therapy has become a widely adopted clinical approach.⁸ Surgery combined with systemic therapy effectively reduces tumor burden and controls systemic disease; however, the approach has a longer duration, and requires good patient tolerance.⁹

Currently, the International Federation of Gynecology and Obstetrics (FIGO) staging system remains the cornerstone for prognostic assessment in EOC.¹⁰ However, substantial heterogeneity in survival outcomes still exists among patients within the same stage, suggesting that traditional staging alone may be insufficient for accurate individualized prognostic evaluation.⁹ Treatment-related factors (eg, treatment strategy, time from diagnosis to treatment) may provide additional prognostic information beyond traditional clinicopathological variables by reflecting treatment strategies and the timeliness of care. If patients with a high risk of death can be distinguished after surgery and systemic therapy, it will help determine whether more aggressive treatment and closer follow-up should be implemented.

A large number of studies have investigated the relationship between the potential survival outcomes and the prognosis of ovarian cancer.¹¹ Wang et al used multivariate Cox regression analysis to construct a nomogram for predicting survival in patients with distant ovarian cancer metastasis.¹² The C-index for OS was 0.79, which outperformed the FIGO 2018 staging criteria. Song et al used multivariate logistic regression analysis to construct a nomogram for predicting the risk of early mortality in patients with advanced EOC. The area under the curve (AUC) was greater than 0.87, demonstrating good predictive ability and clinical utility.¹³ However, most existing prognostic models were developed using relatively limited datasets or focused mainly on tumor-related variables, without fully incorporating treatment-related factors that may influence survival outcomes. Therefore, it is necessary to construct a comprehensive

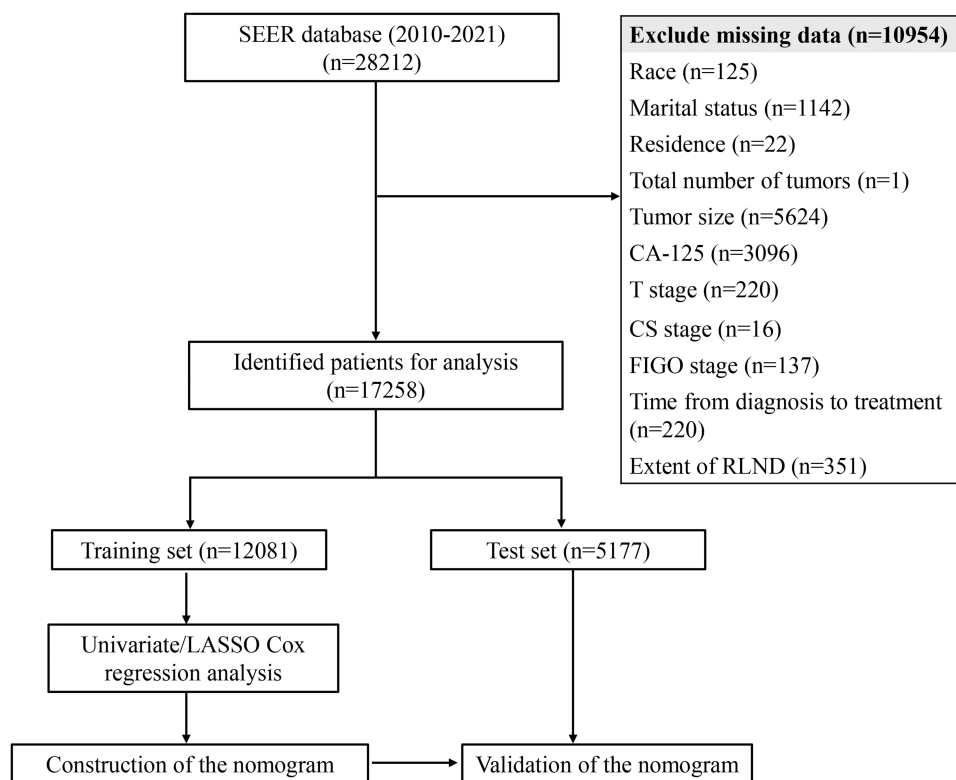


Figure 1 Flowchart of patient selection.

prediction tool that integrates clinical characteristics and treatment process to more accurately assess postoperative prognosis and guide individualized treatment strategies.

The purpose of this study was to summarize the independent risk factors for patients with EOC after surgery and systemic therapy using the SEER database covering the years 2010–2021. We developed and validated a nomogram based on least absolute shrinkage and selection operator (LASSO)-Cox regression analysis to predict OS in patients with EOC who received surgery and systemic therapy. LASSO was used to select the most informative predictors and reduce multicollinearity, thereby improving the robustness of the multivariable Cox model.

Materials and Methods

Study Population

Patient data were obtained from the SEER database, comprising 17,258 individuals diagnosed with EOC. The inclusion criteria were as follows: (1) patients with EOC confirmed by pathological diagnosis and meeting the criteria for international classification of disease (ICD) classification, including serous ovarian cancer (SOC), mucinous ovarian cancer (MOC), endometrioid ovarian cancer (ENOC), and clear cell ovarian cancer (CCC); (2) patients with ovarian cancer enrolled from 2010 to 2021; (3) patients with ovarian cancer who underwent surgery; (4) patients with ovarian cancer who received systemic therapy before or after surgery. Exclusion criteria: (1) patients with missing information on race, marital status, and place of residence; (2) patients with unknown total number of primary/malignant tumors; (3) patients with missing information on tumor size, T stage, disease stage, and FIGO stage; (4) patients with missing information on the time from diagnosis to treatment; (5) patients with missing information on the extent of regional lymph node dissection (RLND). [Figure 1](#) shows a flow chart of patient selection. Cases with missing information in key variables were excluded using a sequential screening procedure. Once a case was excluded due to missing data in an earlier variable, it was not included in subsequent exclusion steps.

This study is based on data from the SEER database, which is publicly available and contains de-identified information. According to the “Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects” issued by China on February 18, 2023, this study meets the ethical review exemption criteria (Article 32, item 1 and 2): (1) it uses legally obtained publicly available data, or data generated through observation without interfering with public activities; (2) it uses anonymized information data. Therefore, no ethical approval or informed consent is required.

Data Collection

The information of patients with EOC was extracted from the SEER database. Demographic information included: age, race, marital status, residence, income, clinical characteristics included: histology, number of tumors, first malignant tumor status, tumor size, CA125, tumor-node-metastasis (TNM) stage, cancer summary (CS) stage, FIGO stage, time interval from diagnosis to treatment, extent of RLND, treatment sequence, and whether cytoreduction was performed. We introduced the variable “RX Summ–Systemic/Sur Seq (2007+)” to assess the effectiveness of treatment sequence as a predictor. We defined the treatment sequence based on the response codes of this variable: adjuvant sequence (surgery-systemic therapy), neoadjuvant sequence (systemic therapy-surgery), and perioperative sequence (systemic therapy-surgery-systemic therapy). Systemic therapy includes chemotherapy, hormone therapy, biological response modifiers/immunotherapy, and transplantation/endocrine-related treatments. Regarding the definition of EOC, according to the third edition of the ICD-O-3 developed by the International Agency for Research on Cancer (IARC), four histologic categories were included: SOC (8441/3, 8442/3, 8460/3, 8461/3, 9014/3), MOC (8470/3, 8471/3, 8472/3, 8480/3, 8481/3), ENOC (8380/3, 8381/3, 8382/3, 8383/3) and CCC (8310/3, 8313/3). The field codes for each variable in the SEER database are listed in [Table S1](#). Categorical variables were coded appropriately, while continuous variables were retained in their original scale for regression analysis.

Table 1 Characteristics of Patients with EOC

Variables	All Set (n=17258)	Training Set (n=12081)	Test Set (n=5177)	P
Age category				0.358
<40	827 (4.79%)	569 (4.71%)	258 (4.98%)	
40–50	2527 (14.64%)	1781 (14.74%)	746 (14.41%)	
50–60	4892 (28.35%)	3472 (28.74%)	1420 (27.43%)	
60–70	5189 (30.07%)	3624 (30.00%)	1565 (30.23%)	
70–80	2992 (17.34%)	2056 (17.02%)	936 (18.08%)	
≥80	831 (4.82%)	579 (4.79%)	252 (4.87%)	
Race				0.215
White	14111 (81.76%)	9850 (81.53%)	4261 (82.31%)	
Black	1011 (5.86%)	732 (6.06%)	279 (5.39%)	
Others	2136 (12.38%)	1499 (12.41%)	637 (12.30%)	
Marital				0.118
Married or Partner	10021 (58.07%)	6979 (57.77%)	3042 (58.76%)	
Single	3453 (20.01%)	2467 (20.42%)	986 (19.05%)	
Living alone	3784 (21.93%)	2635 (21.81%)	1149 (22.19%)	
Residence				0.950
Big urban	10880 (63.04%)	7618 (63.06%)	3262 (63.01%)	
Small urban	4776 (27.67%)	3347 (27.70%)	1429 (27.60%)	
Rural	1602 (9.28%)	1116 (9.24%)	486 (9.39%)	
Income				0.200
<5K	838 (4.86%)	564 (4.67%)	274 (5.29%)	
5–10K	13170 (76.31%)	9247 (76.54%)	3923 (75.78%)	
≥10K	3250 (18.83%)	2270 (18.79%)	980 (18.93%)	
Histology				0.142
SOC	12061 (69.89%)	8412 (69.63%)	3649 (70.48%)	
MOC	761 (4.41%)	532 (4.40%)	229 (4.42%)	
ENOC	2475 (14.34%)	1720 (14.24%)	755 (14.58%)	
CCC	1961 (11.36%)	1417 (11.73%)	544 (10.51%)	
Tumors number				0.103
1	13,731 (79.56%)	9604 (79.50%)	4127 (79.72%)	
2	2952 (17.11%)	2052 (16.99%)	900 (17.38%)	
≥3	575 (3.33%)	425 (3.52%)	150 (2.90%)	
First Malignant: Yes	15207 (88.12%)	10,660 (88.24%)	4547 (87.83%)	0.465
Tumors size	90.00 [52.00,135.00]	90.00 [53.00,135.00]	90.00 [50.00,135.00]	0.277
Tumors size category				0.137
<3cm	2085 (12.08%)	1444 (11.95%)	641 (12.38%)	
3–5cm	1737 (10.06%)	1176 (9.73%)	561 (10.84%)	
5–10cm	5530 (32.04%)	3924 (32.48%)	1606 (31.02%)	
10–15cm	4427 (25.65%)	3102 (25.68%)	1325 (25.59%)	
15–20cm	2266 (13.13%)	1573 (13.02%)	693 (13.39%)	
≥20cm	1213 (7.03%)	862 (7.14%)	351 (6.78%)	
CA125: Positive	15360 (89.00%)	10,730 (88.82%)	4630 (89.43%)	0.246
T				0.117
T1	4350 (25.21%)	3094 (25.61%)	1256 (24.26%)	
T2	2599 (15.06%)	1791 (14.82%)	808 (15.61%)	
T3	10309 (59.73%)	7196 (59.56%)	3113 (60.13%)	
N				0.879
N0	12428 (72.01%)	8710 (72.10%)	3718 (71.82%)	
N1	4108 (23.80%)	2871 (23.76%)	1237 (23.89%)	
NX	722 (4.18%)	500 (4.14%)	222 (4.29%)	

(Continued)

Table 1 (Continued).

Variables	All Set (n=17258)	Training Set (n=12081)	Test Set (n=5177)	P
M:MI	3473 (20.12%)	2428 (20.10%)	1045 (20.19%)	0.912
CS stage				0.293
Localized	2262 (13.11%)	1615 (13.37%)	647 (12.50%)	
Regional	4504 (26.10%)	3138 (25.97%)	1366 (26.39%)	
Distant	10492 (60.79%)	7328 (60.66%)	3164 (61.12%)	
FIGO stage				0.259
I stage	3980 (23.06%)	2828 (23.41%)	1152 (22.25%)	
II stage	1991 (11.54%)	1367 (11.32%)	624 (12.05%)	
III stage	7824 (45.34%)	5459 (45.19%)	2365 (45.68%)	
IV stage	3463 (20.07%)	2427 (20.09%)	1036 (20.01%)	
Time interval from diagnosis to treatment	2.00 [0.00,18.00]	1.00 [0.00,18.00]	2.00 [0.00,18.00]	0.614
Interval category				0.885
0	8411 (48.74%)	5910 (48.92%)	2501 (48.31%)	
≤7	1728 (10.01%)	1207 (9.99%)	521 (10.06%)	
7–14	2038 (11.81%)	1403 (11.61%)	635 (12.27%)	
14–21	1653 (9.58%)	1163 (9.63%)	490 (9.46%)	
21–28	1235 (7.16%)	866 (7.17%)	369 (7.13%)	
>28	2193 (12.71%)	1532 (12.68%)	661 (12.77%)	
Treatment sequence				0.094
Adjuvant sequence	13789 (79.90%)	9666 (80.01%)	4123 (79.64%)	
Neoadjuvant sequence	1069 (6.19%)	718 (5.94%)	351 (6.78%)	
Perioperative sequence	2400 (13.91%)	1697 (14.05%)	703 (13.58%)	
Cytoreduction: Yes	13085 (75.82%)	9135 (75.61%)	3950 (76.30%)	0.346
Extent of RLND				0.745
0	6858 (39.74%)	4784 (39.60%)	2074 (40.06%)	
1–3	2046 (11.86%)	1426 (11.80%)	620 (11.98%)	
≥4	8354 (48.41%)	5871 (48.60%)	2483 (47.96%)	

Abbreviations: EOC, epithelial ovarian cancer; SOC, serous ovarian cancer; MOC, mucinous ovarian cancer; ENOC, endometrioid ovarian cancer; CCC, clear cell ovarian cancer; CS, cancer summary; RLND, regional lymph node dissection; FIGO, International Federation of Gynecology and Obstetrics.

Nomogram Development and Performance Evaluation

The selected patients obtained after screening were randomly assigned to the training set and the test set based on a 7:3 ratio using a fixed random seed (20240613). Univariate Cox analysis with a liberal threshold ($P < 0.1$) was first applied as a preliminary screening step to reduce the number of candidate predictors before LASSO regression. The LASSO algorithm is a powerful machine learning method that can be used to regress high-dimensional data.¹⁴ The above candidate variables were entered into the LASSO regression model for dimensionality reduction and feature selection. Ten-fold cross-validation was applied to determine the optimal penalty parameter (λ), and the λ value corresponding to the minimum mean squared error plus one standard error ($\lambda = \text{MSE} + 1\text{SE}$) was selected to identify the key variables associated with OS. Then, the variables screened out by LASSO regression were further included in the multivariate Cox regression analysis, and independent risk factors with a $P < 0.05$ were retained. A nomogram was constructed based on these variables to estimate the 1-year, 3-year, 5-year and 10-year OS. This endpoint was selected because it is objectively and reliably recorded in the SEER database. According to the regression formula, the risk score of each patient was then calculated to predict OS.

Multicollinearity among predictors was further assessed using the generalized variance inflation factor (GVIF), and the adjusted measure $\text{GVIF}^{1/(2 \times \text{df})}$ was used for categorical variables. Values ≥ 5 were considered indicative of potential multicollinearity. The proportional hazards assumption was assessed using Schoenfeld residual tests. The area under the receiver operating characteristic curve (ROC) was used to compare the predictive accuracy of the nomogram. Calibration curves were constructed using bootstrap resampling ($B = 500$) with optimism correction, dividing predicted

Table 2 Univariate Cox Regression Analysis for OS in Patients with EOC

Variable	Alive (n=7282)	Dead (n=4799)	Univariate Cox Regression Analysis	
			HR [95% CI]	P
Age category				
<40	424 (5.82%)	145 (3.02%)	Ref	
40–50	1213 (16.66%)	568 (11.84%)	1.20[1.00,1.44]	<0.05
50–60	2232 (30.65%)	1240 (25.84%)	1.42[1.19,1.68]	<0.001
60–70	2126 (29.20%)	1498 (31.21%)	1.77[1.50,2.10]	<0.001
70–80	1054 (14.47%)	1002 (20.88%)	2.46[2.06,2.93]	<0.001
≥80	233 (3.20%)	346 (7.21%)	3.17[2.61,3.85]	<0.001
Race				
White	5865 (80.54%)	3985 (83.04%)	Ref	
Black	410 (5.63%)	322 (6.71%)	1.28[1.14,1.44]	<0.001
Others	1007 (13.83%)	492 (10.25%)	0.85[0.78,0.94]	<0.001
Marital				
Married or Partner	4330 (59.46%)	2649 (55.20%)	Ref	
Single	1529 (21.00%)	938(19.55%)	1.03[0.96,1.11]	0.398
Living alone	1423 (19.54%)	1212 (25.26%)	1.33[1.24,1.42]	<0.001
Residence				
Big urban	4701 (64.56%)	2917 (60.78%)	Ref	
Small urban	1952 (26.81%)	1395 (29.07%)	1.11[1.04,1.19]	0.001
Rural	629 (8.64%)	487 (10.15%)	1.09[0.99,1.20]	0.077
Income				
<5K	298 (4.09%)	266 (5.54%)	Ref	
5–10K	5397 (74.11%)	3850 (80.23%)	0.91[0.80,1.03]	0.142
≥10K	1587 (21.79%)	683 (14.23%)	0.80[0.69,0.92]	<0.01
Histology				
SOC	4460 (61.25%)	3952 (82.35%)		
MOC	363 (4.98%)	169 (3.52%)	0.62[0.53,0.72]	<0.001
ENOC	1415 (19.43%)	305 (6.36%)	0.30[0.27,0.34]	<0.001
CCC	1044 (14.34%)	373 (7.77%)	0.53[0.48,0.59]	<0.001
Tumors number				
1	5768 (79.21%)	3836 (79.93%)	Ref	
2	1266 (17.39%)	786 (16.38%)	0.86[0.80,0.93]	<0.001
≥3	248 (3.41%)	177 (3.69%)	0.91[0.79,1.06]	0.246
First Malignant: Yes	6449 (88.56%)	4211 (87.75%)	0.94[0.86,1.03]	0.182
Tumors size	100.00 [60.00,140.00]	80.00 [47.00,120.00]		
Tumors size category				
<3cm	807 (11.08%)	637 (13.27%)	Ref	
3–5cm	578 (7.94%)	598 (12.46%)	1.19[1.06,1.33]	<0.01
5–10cm	2191 (30.09%)	1733(36.11%)	1.00[0.91,1.09]	0.928
10–15cm	2032 (27.90%)	1070 (22.30%)	0.74[0.67,0.81]	<0.001
15–20cm	1081 (14.84%)	492 (10.25%)	0.63[0.56,0.71]	<0.001
≥20cm	593 (8.14%)	269 (5.61%)	0.62[0.54,0.72]	<0.001
CA125: Positive	6227 (85.51%)	4503 (93.83%)	2.28[2.02,2.56]	<0.001
T				
T1	2643 (36.29%)	451 (9.40%)	Ref	
T2	1290 (17.71%)	501 (10.44%)	2.06[1.81,2.34]	<0.001
T3	3349 (45.99%)	3847 (80.16%)	5.20[4.72,5.74]	<0.001
N				
N0	5634 (77.37%)	3076 (64.10%)	-	-
N1	1419 (19.49%)	1452 (30.26%)	1.58[1.49,1.69]	<0.001
NX	229 (3.14%)	271 (5.65%)	2.41[2.13,2.73]	<0.001

(Continued)

Table 2 (Continued).

Variable	Alive (n=7282)	Dead (n=4799)	Univariate Cox Regression Analysis	
			HR [95% CI]	P
M:MI	1013 (13.91%)	1415 (29.49%)	2.40[2.25,2.55]	<0.001
CS stage				
Localized	1441 (19.79%)	174 (3.63%)	Ref	
Regional	2425 (33.30%)	713 (14.86%)	1.93[1.64,2.28]	<0.001
Distant	3416 (46.91%)	3912 (81.52%)	6.60[5.67,7.68]	<0.001
FIGO stage				
I stage	2466 (33.86%)	362 (7.54%)	Ref	
II stage	1043 (14.32%)	324 (6.75%)	1.96[1.69,2.28]	<0.001
III stage	2764 (37.96%)	2695 (56.16%)	5.12[4.58,5.71]	<0.001
IV stage	1009 (13.86%)	1418 (29.55%)	7.86[7.00,8.83]	<0.001
Time interval from diagnosis to treatment	0.00 [0.00,15.00]	8.00 [0.00,20.00]		
Interval category				
0	4144 (56.91%)	1766 (36.80%)	Ref	
≤7	588 (8.07%)	619 (12.90%)	2.06[1.88,2.25]	<0.001
7–14	665 (9.13%)	738 (15.38%)	2.25[2.06,2.45]	<0.001
14–21	563 (7.73%)	600 (12.50%)	2.34[2.14,2.57]	<0.001
21–28	465 (6.39%)	401 (8.36%)	2.20[1.98,2.45]	<0.001
>28	857 (11.77%)	675 (14.07%)	2.03[1.85,2.21]	<0.001
Treatment sequence				
Adjuvant sequence	6189 (84.99%)	3477 (72.45%)	Ref	
Neoadjuvant sequence	254 (3.49%)	464 (9.67%)	2.76[2.50,3.04]	<0.001
Perioperative sequence	839 (11.52%)	858 (17.88%)	2.20[2.04,2.37]	<0.001
Cytoreduction: Yes	4934 (67.76%)	4201 (87.54%)	1.53[1.40,1.66]	<0.001
Extent of RLND				
0	2410 (33.10%)	2374 (49.47%)	Ref	
1–3	838 (11.51%)	588 (12.25%)	0.78[0.72,0.86]	<0.001
≥4	4034 (55.40%)	1837 (38.28%)	0.45[0.43,0.48]	<0.001

Abbreviations: OS, overall survival; EOC, epithelial ovarian cancer; SOC, serous ovarian cancer; MOC, mucinous ovarian cancer; ENOC, endometrioid ovarian cancer; CCC, clear cell ovarian cancer; CS, cancer summary; RLND, regional lymph node dissection; HR, hazard ratios; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

probabilities into 10 groups to assess the agreement between predicted and observed outcomes. Kaplan-Meier (KM) curve was used to assess clinical applicability. Decision curve analysis (DCA) was performed to evaluate the potential clinical utility of the prediction model. The analysis estimates the net benefit across a range of threshold probabilities (pt), which represent the risk level at which a patient or clinician would choose to initiate an intervention. Net benefit was calculated using the following formula:

$$\text{Net benefit untreated} = \frac{\text{TN}}{n} - \frac{\text{FN}}{n} \left(\frac{p_t}{1 - p_t} \right)$$

where TN and FN denote the numbers of true-positive and false-positive cases, respectively, and N is the total number of patients. Patients with predicted risk exceeding the selected threshold probability were considered eligible for intervention. The net benefit of the prediction model was compared with two reference strategies: treating all patients and treating no patients. DCA was generated by plotting net benefit against a range of threshold probabilities to determine whether the model provided superior clinical benefit across clinically relevant risk thresholds.¹⁵

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD), and differences between groups were compared using Student's *t*-test. Categorical variables were expressed as frequencies and percentages (%), and differences were compared using chi-square test. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using Cox and LASSO hazard regression models. *P* < 0.05 was defined as significant. All analyses were performed using

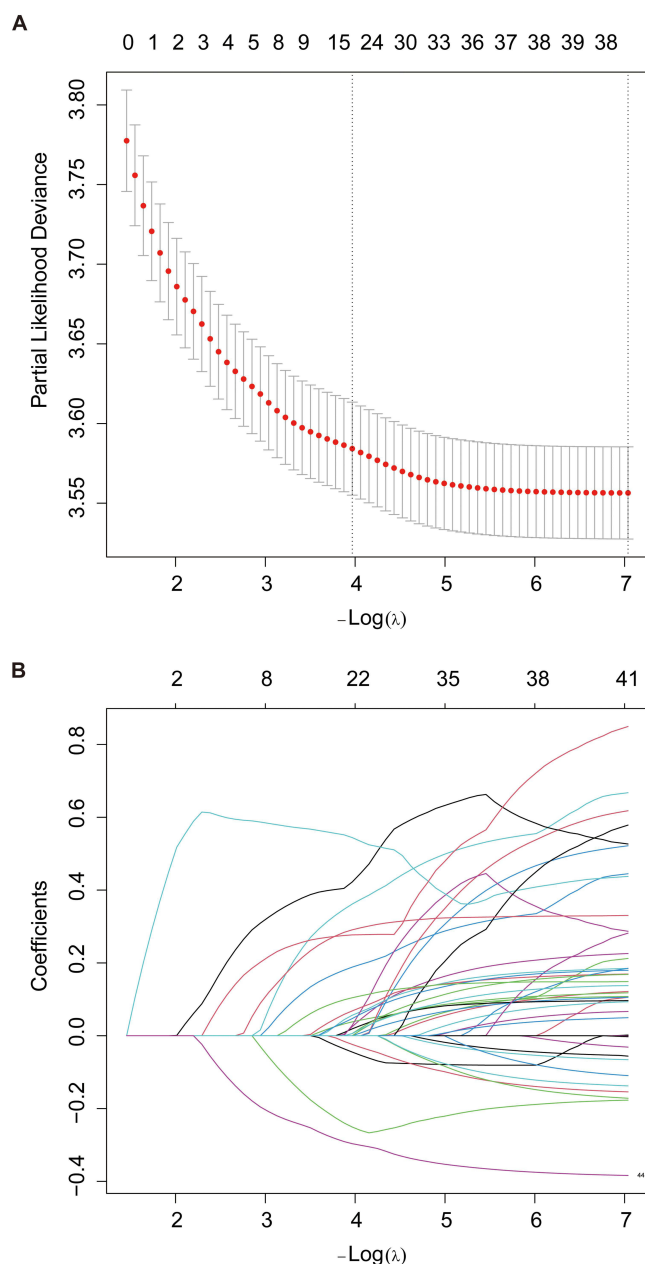


Figure 2 Variable selection based on LASSO Cox regression algorithm. **(A)** Selection of adjustment parameter (λ). LASSO Cox regression model was adopted, and penalized parameter adjustment was performed by 10-fold cross validation based on the minimum standard. The partial likelihood deviation was plotted against $\log(\lambda)$. A vertical dashed line was drawn at the optimal λ value based on the minimum standard. **(B)** LASSO coefficient curve for all extracted variables.

R software, version 4.0.4 (<https://www.r-project.org/>). Cox proportional hazards regression analysis was performed using the “survival” package and the “survminer” package. The “glmnet” package was used to perform LASSO Cox regression analysis. Time-dependent ROC curves were generated using the “timeROC” package in R. Nomogram construction and calibration curves were constructed using the “rms” package. The observed survival probabilities for right-censored data were estimated using the KM method. $P < 0.05$ was considered statistically significant.

Results

Characteristics of Patients

A total of 17,258 EOC patients who received surgery and systemic therapy were included, which were divided into training set ($n=12,081$) and test set ($n=5177$) in a ratio of 7:3. Table 1 summarizes the clinical characteristics of the

Table 3 Multivariate Cox Regression Analysis for OS in Patients with EOC

Variable	HR [95% CI]	P
Age category		
<40	Ref	
40–50	1.12[0.93,1.34]	0.242
50–60	1.24[1.04,1.48]	<0.05
60–70	1.38[1.16,1.65]	<0.001
70–80	1.74[1.46,2.09]	<0.001
≥80	2.18[1.78,2.67]	<0.001
Race		
White	Ref	
Black	1.27[1.14,1.43]	<0.001
Others	1.01[0.92,1.11]	0.794
Marital		
Married or Partner	Ref	
Single	1.16[1.08,1.26]	<0.001
Living alone	1.12[1.04,1.20]	<0.01
Histology		
SOC		
MOC	1.99[1.68,2.35]	<0.001
ENOC	0.84[0.74,0.96]	<0.01
CCC	1.71[1.52,1.93]	<0.001
Tumors size category		
<3cm	Ref	
3–5cm	1.09[0.98,1.22]	0.123
5–10cm	0.99[0.90,1.09]	0.852
10–15cm	0.84[0.76,0.93]	<0.001
15–20cm	0.83[0.73,0.93]	<0.01
≥20cm	0.88[0.76,1.02]	0.080
CA125: Positive	1.22[1.08,1.38]	<0.01
T		
T1	Ref	
T2	1.26[0.97,1.62]	0.079
T3	1.62[1.29,2.03]	<0.001
N		
N0	Ref	
N1	1.19[1.11,1.29]	<0.001
NX	1.15[1.01,1.30]	<0.05
CS stage		
Localized	Ref	
Regional	1.25[1.02,1.53]	<0.05
Distant	1.58[1.21,2.06]	<0.001
FIGO stage		
I stage	Ref	
II stage	1.46[1.07,1.98]	<0.05
III stage	1.96[1.49,2.57]	<0.001
IV stage	2.56[1.94,3.39]	<0.001
Interval category		
0	Ref	
≤7	1.19[1.09,1.31]	<0.001
7–14	1.20[1.09,1.31]	<0.001
14–21	1.15[1.04,1.27]	<0.01
21–28	1.08[0.96,1.21]	0.207
>28	0.99[0.90,1.09]	0.839

(Continued)

Table 3 (Continued).

Variable	HR [95% CI]	P
Treatment sequence		
Adjuvant sequence	Ref	
Neoadjuvant sequence	1.39[1.26,1.55]	<0.001
Perioperative sequence	1.15[1.06,1.25]	<0.001
Extent of RLND		
0	Ref	
1–3	0.86[0.79,0.95]	<0.01
≥4	0.68[0.63,0.73]	<0.001

Abbreviations: OS, overall survival; EOC, epithelial ovarian cancer; SOC, serous ovarian cancer; MOC, mucinous ovarian cancer; ENOC, endometrioid ovarian cancer; CCC, clear cell ovarian cancer; CS, cancer summary; RLND, regional lymph node dissection; HR, hazard ratios; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

patients enrolled in training set and test set. No significant differences were found in all characteristics between the training set and test set ($P>0.05$). During the follow-up period, 4799 deaths were observed, while 7282 patients remained alive. Among the 17,258 patients, the average age was 59.87 ± 12.11 years, and whites (81.76%) accounted for the majority. Regarding the histological classification of EOC, SOC was the predominant subtype, accounting for 69.89% of cases, followed by ENOC (14.34%), CCC (11.36%), and MOC (4.41%).

Most of the tumors were T3 stage (59.73%), N0 stage (72.01%), and distant metastasis (60.79%). In terms of FIGO staging distribution, most patients were diagnosed at stage III (45.34%), with decreasing proportions at stage I (23.06%), stage IV (20.07%), and stage II (11.54%). Regarding the sequence of surgery and systemic therapy, most patients received adjuvant sequence (79.90%), followed by neoadjuvant sequence (13.91%) and perioperative sequence (6.19%).

The median OS for the entire cohort was 77 months (95% CI: 74–79), compared with 78 months (95% CI: 75–81) in the training set and 75 months (95% CI: 71–79) in the test set. The median follow-up time was 69 months (95% CI: 68–70) for the entire cohort, 69 months (95% CI: 67–81) for the training set, and 71 months (95% CI: 69–73) for the test set.

Risk Factor Analysis for OS

We then divided the population of the training set into a survival group ($n=7282$) and a death group ($n=4799$). The results of univariate Cox regression analysis showed that age, race, marital status, residence, income, histological classification, number of tumors, tumor size, CA125, TNM, CS stage, FIGO stage, time from diagnosis to treatment, treatment sequence, cytoreduction, and the extent of RLND were associated with OS in EOC (Table 2). Among them, patients with older age, black race, living alone, living in small cities/villages, income <5000, CA125 positive, T3, NX, distant metastasis, FIGO stage IV, and certain treatment sequence had a higher risk of death. It should be noted that the observed differences between treatment sequence may reflect underlying baseline disease severity or patient selection rather than a direct causal effect of the treatment itself.

Establishing a Nomogram for Predicting OS in Patients with EOC

Figure 2 shows the variable selection process using LASSO regression in the training set. A total of 13 predictors were identified by LASSO, including age, race, marital status, histological classification, tumor size, CA125, T stage, N stage, CS stage, FIGO stage, time from diagnosis to treatment, treatment sequence, and extent of RLND. These predictors were subsequently incorporated into a multivariable Cox proportional hazards model to construct the nomogram (Table 3 and Figure 3). The corresponding regression coefficients for each variable in the final model are presented in Table S2. In addition, all predictors in the final model had $GVIF^{1/(2 \times df)}$ values below 5, indicating that no significant multicollinearity was present among the included staging variables (Table 4).

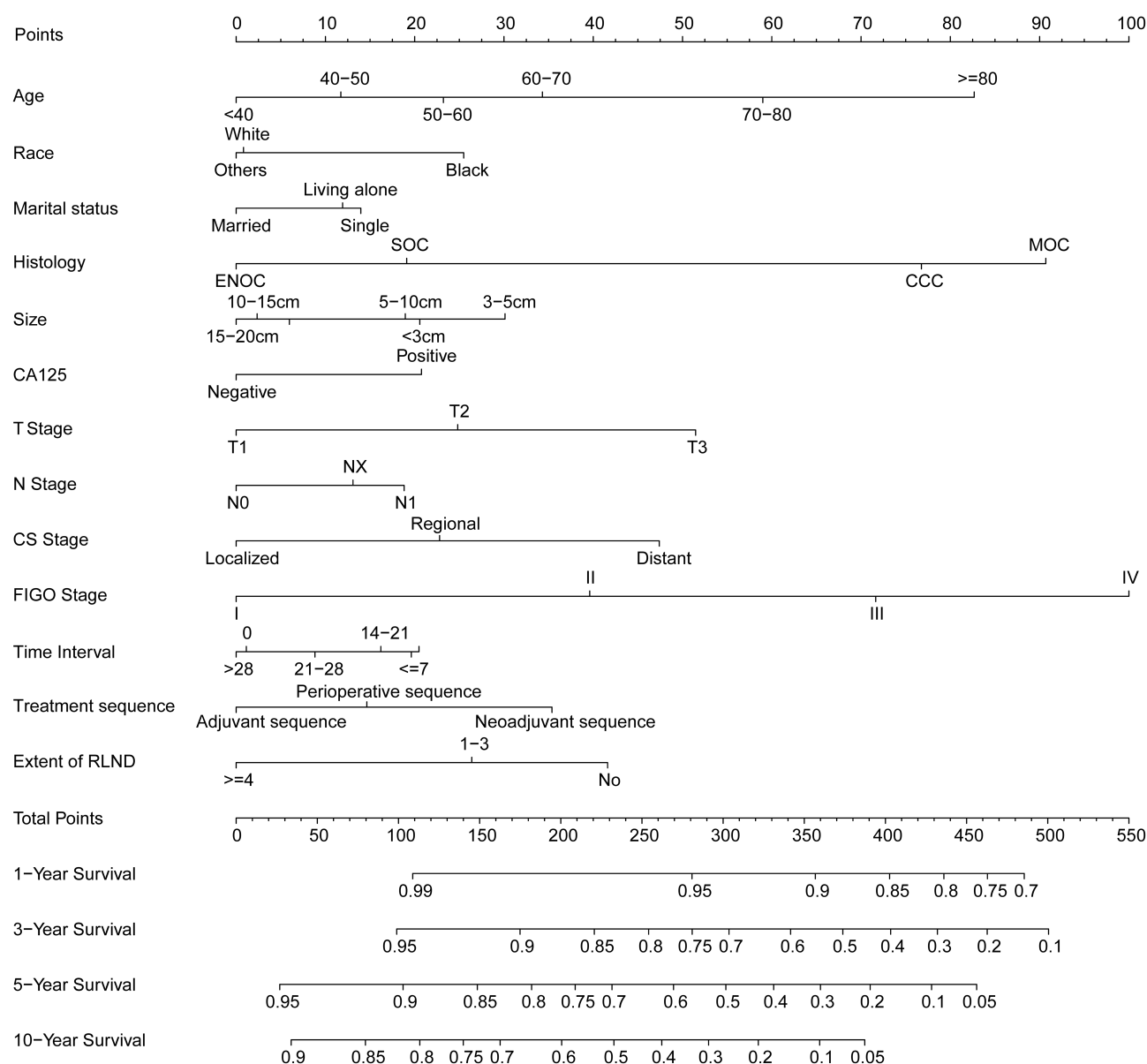


Figure 3 Nomogram of OS of patients with EOC after surgical treatment and systemic therapy in the training set.

Performance Evaluation of Nomogram

Figure 4 shows the ROC curve of the prediction model. The AUC of the training set (1 year: 0.73 [95% CI:0.70–0.75], 3 years: 0.75 [95% CI:0.74–0.76], 5 years: 0.77 [95% CI:0.76–0.78], 10 years: 0.81 [95% CI:0.79–0.83]) and the test set (1 year: 0.72 [95% CI:0.69–0.75], 3 years: 0.76 [95% CI:0.74–0.77], 5 years: 0.77 [95% CI:0.75–0.79], 10 years: 0.81 [95% CI:0.79–0.84]). These results suggest that the model has fair to good discrimination. The calibration curves showed that the predicted probabilities were generally consistent with the observed outcomes in both the training and test cohorts (Figures 5 and 6). The Brier scores across different time points were relatively low, ranging from 0.051 to 0.193 in the training cohort and from 0.056 to 0.193 in the test cohort, suggesting acceptable predictive performance. In addition, the DCA results showed that the prediction model had clinical benefits, and the benefits increased over time (Figures 7 and 8).

We calculated the prognostic index (PI) for each patient and performed risk stratification based on the estimated relative risk derived from the model, dividing patients into low-risk and high-risk groups. KM survival analysis showed that the OS of the low-risk group was better than that of the high-risk group (Figure 9), indicating good discriminatory

Table 4 Assessment of Multicollinearity Among Variables Using the GVIF

Variable	GVIF	df	GVIF ^{1/(2*df)}
Age	1.16	1	1.08
Race	1.08	2	1.02
Marital status	1.14	2	1.03
Histology	1.56	3	1.08
Size	1.18	4	1.02
CA125	1.11	1	1.05
T stage	17.84	16	2.06
N stage	1.56	2	1.12
CS stage	8.46	2	1.71
FIGO stage	25.42	3	1.71
Time interval	1.40	5	1.03
Treatment sequence	1.34	2	1.08
Extent of RLND	1.47	2	1.10

Abbreviations: GVIF, generalized variance inflation factor; FIGO, International Federation of Gynecology and Obstetrics; RLND, regional lymph node dissection.

performance of the model. Schoenfeld residual tests indicated that several variables showed statistical deviations from the proportional hazards assumption ([Table S3](#)). Inspection of the Schoenfeld residual plots suggested that these deviations were generally modest, with residual curves largely parallel to the zero line. ([Figure S1](#)).

Discussion

There are currently three common treatment methods for EOC: adjuvant sequence, neoadjuvant sequence, and perioperative sequence. Aggressive surgery to achieve the maximum cytoreductive and systemic therapy effects will inevitably increase the incidence of postoperative complications and mortality. The incidence of postoperative mortality after initial cytoreductive surgery for advanced EOC ranges from 0% to 6.7%, and the average postoperative mortality incidence is 2.8%.¹⁶ However, the risk of death in EOC patients after surgery and systemic therapy remains unclear. In recent years, nomograms have been widely used to predict the risk and prognosis of malignant tumors.¹⁷ Our study demonstrated that age, race, marital status, histological classification, tumor size, CA125, T stage, N stage, CS stage, FIGO stage, time from diagnosis to treatment, treatment sequence, and extent of RLND are predictive factors for OS in EOC patients who underwent surgery and systemic therapy.

Previous studies have demonstrated that age is associated with the prognosis of EOC treated with surgery and systemic therapy. Hanatani et al have shown that EOC patients under 40 years of age may have longer survival time.¹⁸ Elderly women with advanced EOC who underwent cytoreductive surgery appear to have a worse prognosis than younger women.¹⁹ Increased comorbidities and poorer performance status in the elderly may explain the poorer cytoreductive surgery rates, treatment, and survival outcomes. In addition, a study found that patients aged ≥ 70 years had a 1.4-fold increased risk of cancer-specific death (95% CI: 1.2–1.5) after adjusting for potential confounders.²⁰ In our study, advanced age was associated with increased risk of death in EOC patients treated with surgery and systemic therapy, which is consistent with the above findings. Beyond age, disease stage is also a critical determinant of prognosis in EOC patients. Our study showed that patients with T3/N1/distant metastasis/FIGO stage IV had a higher risk of postoperative death, and the survival rate of ovarian cancer was inversely correlated with the CS stage. This is consistent with current clinical evidence. Baldwin et al calculated the relative survival rate within 10 years through the SEER database and found that the 5-year relative survival rate of FIGO stage I patients was 89%, 70% for stage II patients, 36% for stage III patients, and 17% for stage IV patients.²¹ Together, these findings highlight the need for stratified management strategies based on age and stage to optimize outcomes in EOC patients undergoing surgery and systemic therapy. In addition, our analysis showed that larger tumor size was associated with a lower risk of death, which appears

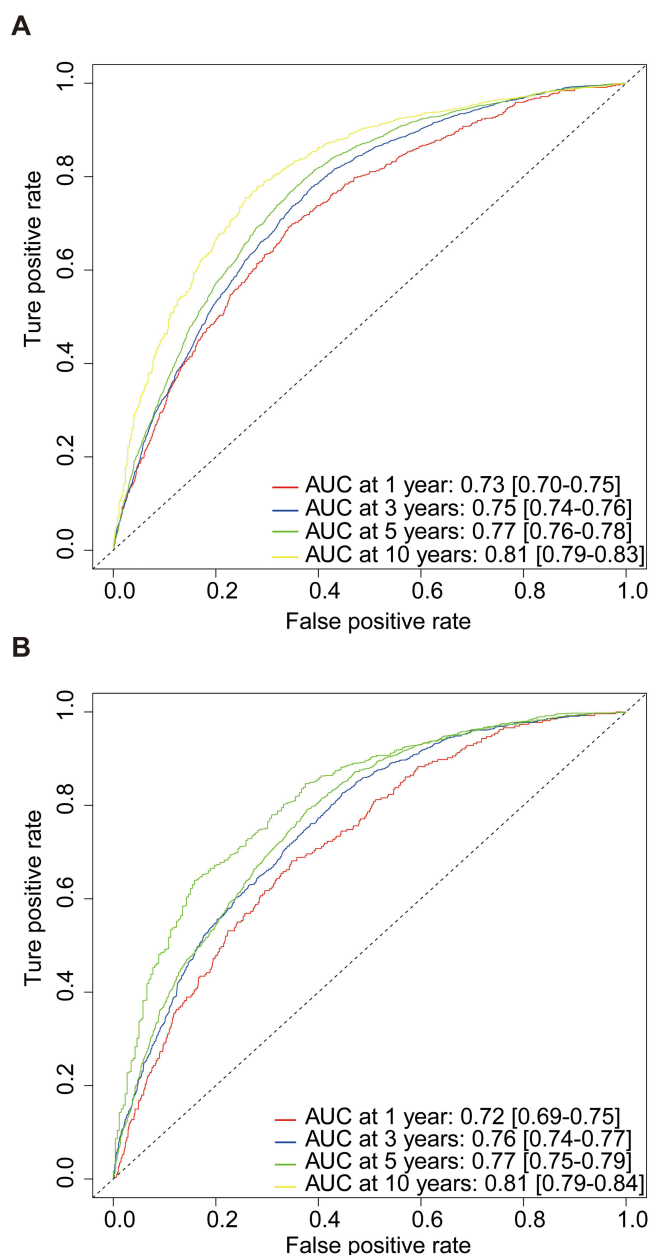


Figure 4 ROC curve of nomogram. **(A)** AUC of the training set for predicting 1/3/5/10-year OS; **(B)** AUC of the test set for predicting 1/3/5/10-year OS. **Abbreviation:** AUC, area under the curve.

counterintuitive. However, in EOC, the size of the primary tumor does not necessarily reflect the overall disease burden or extent of peritoneal dissemination. Moreover, patients with advanced-stage disease may present with relatively small primary tumors but widespread metastatic involvement, which may partly explain this finding.

In our study, the histologic type of epithelial ovarian tumors was associated with OS, and the risk of death was ranked from low to high for ENOC, SOC, CCC, and MOC. Therefore, patients with MOC in this study had the highest risk of death. In the univariate analysis, MOC appeared to have a better prognosis than SOC; however, this analysis does not account for potential confounding factors. After adjustment in the multivariate Cox model, MOC was associated with a higher risk of death, suggesting that the initial finding may have been influenced by differences in baseline characteristics. Consistently, Song et al found that patients with MOC had the highest risk of early death regardless of FIGO stage III or IV epithelial ovarian tumors¹³ Primary MOC has become the focus of research in recent years due to its

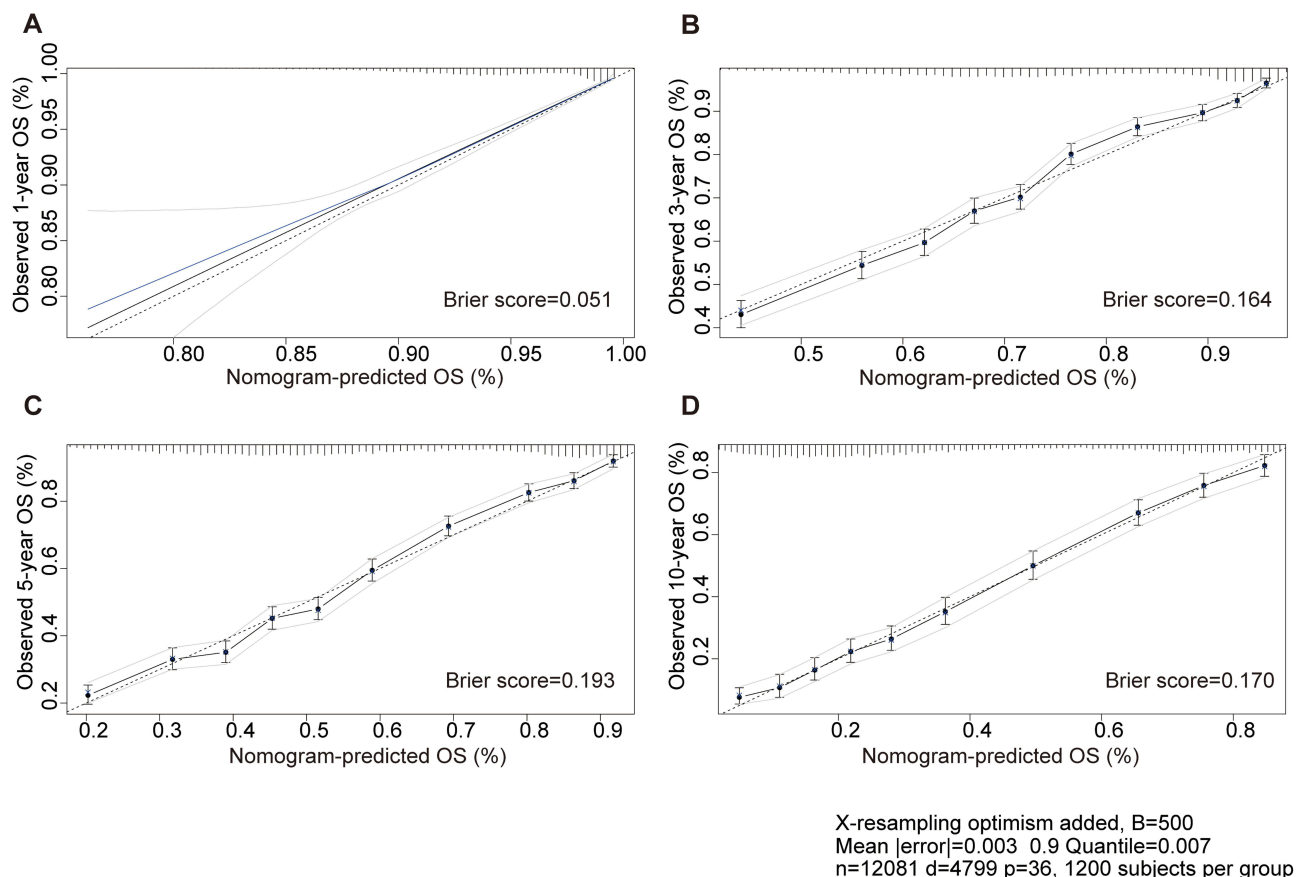


Figure 5 Calibration curve of the nomogram in the training set. (A) 1-year OS; (B) 3-year OS; (C) 5-year OS; (D) 10-year OS. The curves were generated using 500 bootstrap resamples to estimate and correct for optimism. The X-axis represents predicted probabilities, and the Y-axis represents observed probabilities. The black line shows the model-predicted probabilities, the dashed line represents perfect calibration, and the blue line indicates optimism-corrected predictions; gray lines indicate 95% bootstrap confidence limits.

unique biological characteristics and differences in response to treatment. The prognosis of MOC is worse than that of high-grade SOC, which is at least partly attributed to the lower sensitivity of MOC to platinum drugs. A retrospective study found that the response rate of patients with advanced MOC to first-line platinum chemotherapy was 39%, while the response rate of patients with SOC was 70%.²² In the study of stage III epithelial ovarian tumors, it was found that MOC and CCC had poorer progression-free survival (PFS) and OS compared with SOC.²³ Overall, MOC has a relatively poor response to systemic therapy. Although it is an EOC, the histological molecular structure of MOC is different from other subtypes. SOC is mainly caused by P53 mutations, while MOC is mainly caused by K-ras mutations.²⁴ Regarding the effectiveness of platinum-based chemotherapy, better results were observed in advanced SOC compared with MOC.²² These may explain why different histological subtypes affect the risk of early death.

Treatment strategies for EOC are largely influenced by FIGO stage and histological subtype. Nevertheless, the main treatment option remains a combination of cytoreductive surgery and systemic therapy. In our analysis, patients receiving perioperative or neoadjuvant sequences were associated with higher mortality, but these findings reflect associations in an observational dataset and should not be interpreted as causal. The observed differences likely reflect baseline disease severity and patient condition rather than treatment efficacy. However, the role of neoadjuvant therapy in MOC remains insufficiently studied.²⁵ Evidence suggests that neoadjuvant therapy may increase the rate of optimal cytoreduction in certain populations, but survival benefits compared with primary surgery remain uncertain.^{26–28} For patients who are otherwise healthy and eligible for surgery, primary cytoreductive surgery is generally preferred.^{29,30} Neoadjuvant therapy may still be considered for patients with FIGO stage IV disease, or those in stage III who cannot achieve optimal cytoreduction or have significant comorbidities.³¹ Additionally, the variable “time from diagnosis to treatment” displayed

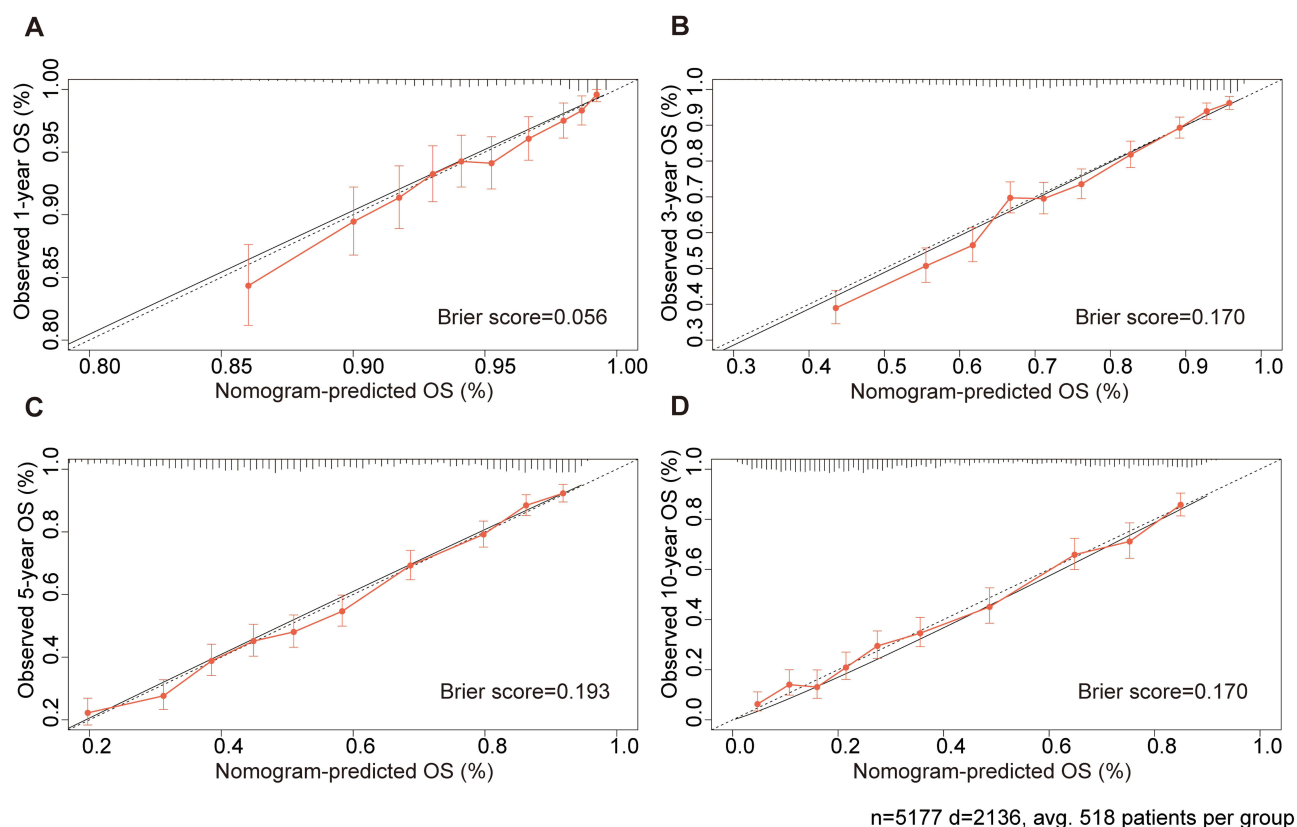


Figure 6 Calibration curve of nomogram in the test set. (A) 1-year OS; (B) 3-year OS; (C) 5-year OS; (D) 10-year OS. The X-axis represents predicted probabilities, and the Y-axis represents observed probabilities. The black line indicates the observed probabilities, the dashed line represents perfect calibration, and the Orange curve shows the model-predicted probabilities.

a non-linear association with survival. This pattern may be influenced by coding limitations in the SEER database and residual confounding factors, such as baseline health status and tumor burden. Different intervals likely reflect distinct clinical pathways rather than direct effects of treatment timing.

In our cohort, most patients were aged ≥ 50 years, and 65.41% of patients were classified as FIGO stage III–IV. The superior OS observed in the adjuvant sequence group may be partly attributed to patient selection bias, as patients who choose to undergo primary cytoreduction surgery are usually in better clinical condition and more likely to achieve optimal cytoreduction. In contrast, patients who receive neoadjuvant /perioperative sequence may have more advanced disease, higher tumor burden, or impaired performance status, which leads to a worse prognosis. In addition, delayed cytoreduction and variable efficacy of NACT may further reduce the potential survival benefit of the neoadjuvant sequence group. Therefore, clinical treatment decisions need to comprehensively consider stage, histological subtype, patient functional status, and surgical feasibility to achieve individualized treatment.

Although this study revealed the effect of different treatment sequences on the OS of patients with ovarian cancer, there are still some limitations. First, the study adopted a retrospective design, and there is an inevitable selection bias, especially in the grouping of treatment methods, which may be affected by the patient's basic status and subjective clinical judgment. Although most patients had ovarian cancer as their first primary malignancy, a small proportion had multiple primary cancers, which may introduce potential selection bias. Secondly, some clinical variables (such as performance status score, BRCA gene mutation, and intraoperative residual lesion size) are missing or incompletely recorded, which limits our more detailed analysis of prognostic factors. In addition, due to the lack of long-term follow-up data, we cannot fully evaluate the impact of neoadjuvant sequence on PFS or long-term complications. Finally, due to data and study design limitations, direct comparison with established prognostic tools and external or temporal validation were not performed. Future studies can use clinical data to validate the current model to assess its credibility.

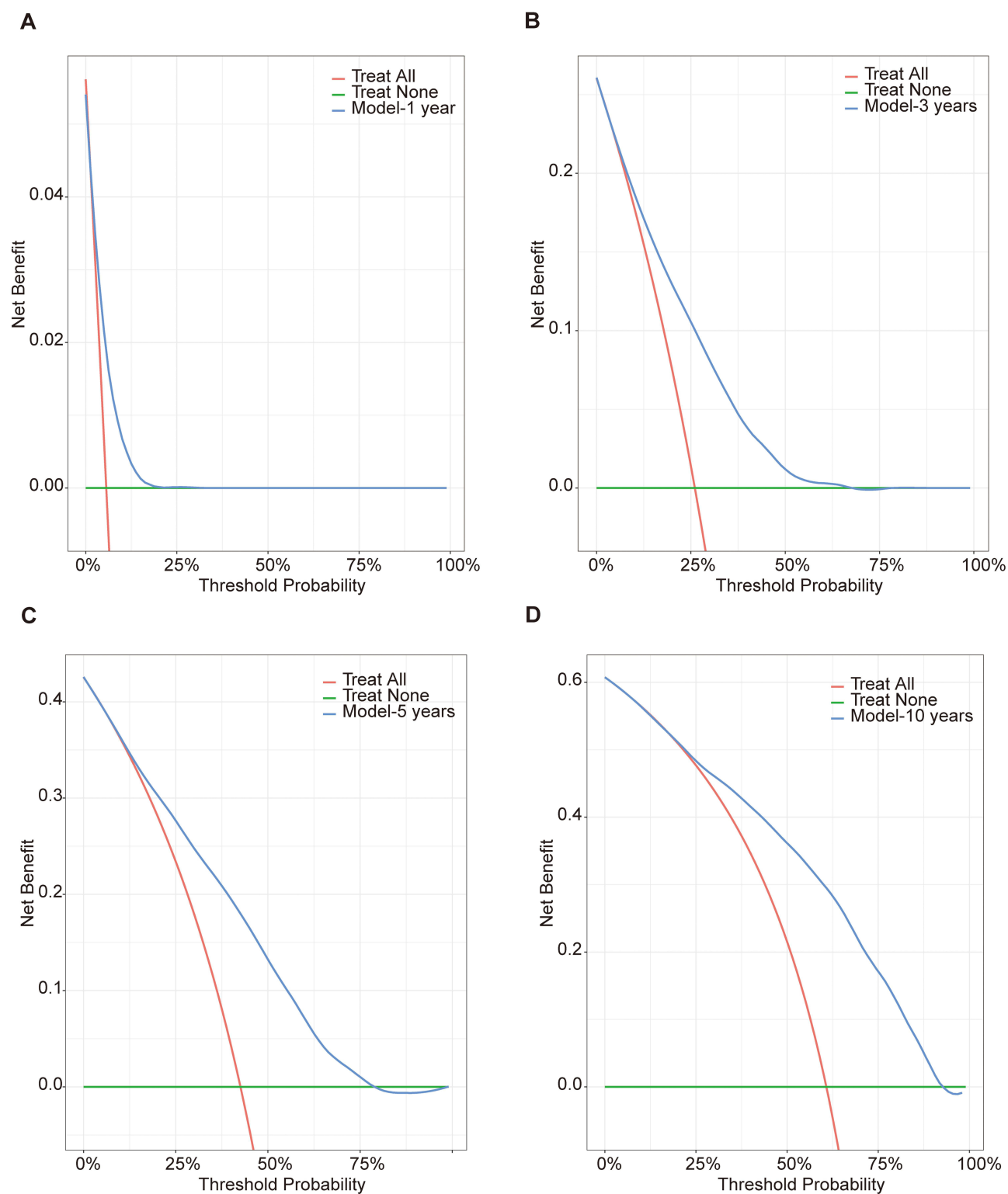


Figure 7 DCA curve of nomogram in the training set. (A) 1-year OS; (B) 3-year OS; (C) 5-year OS; (D) 10-year OS.

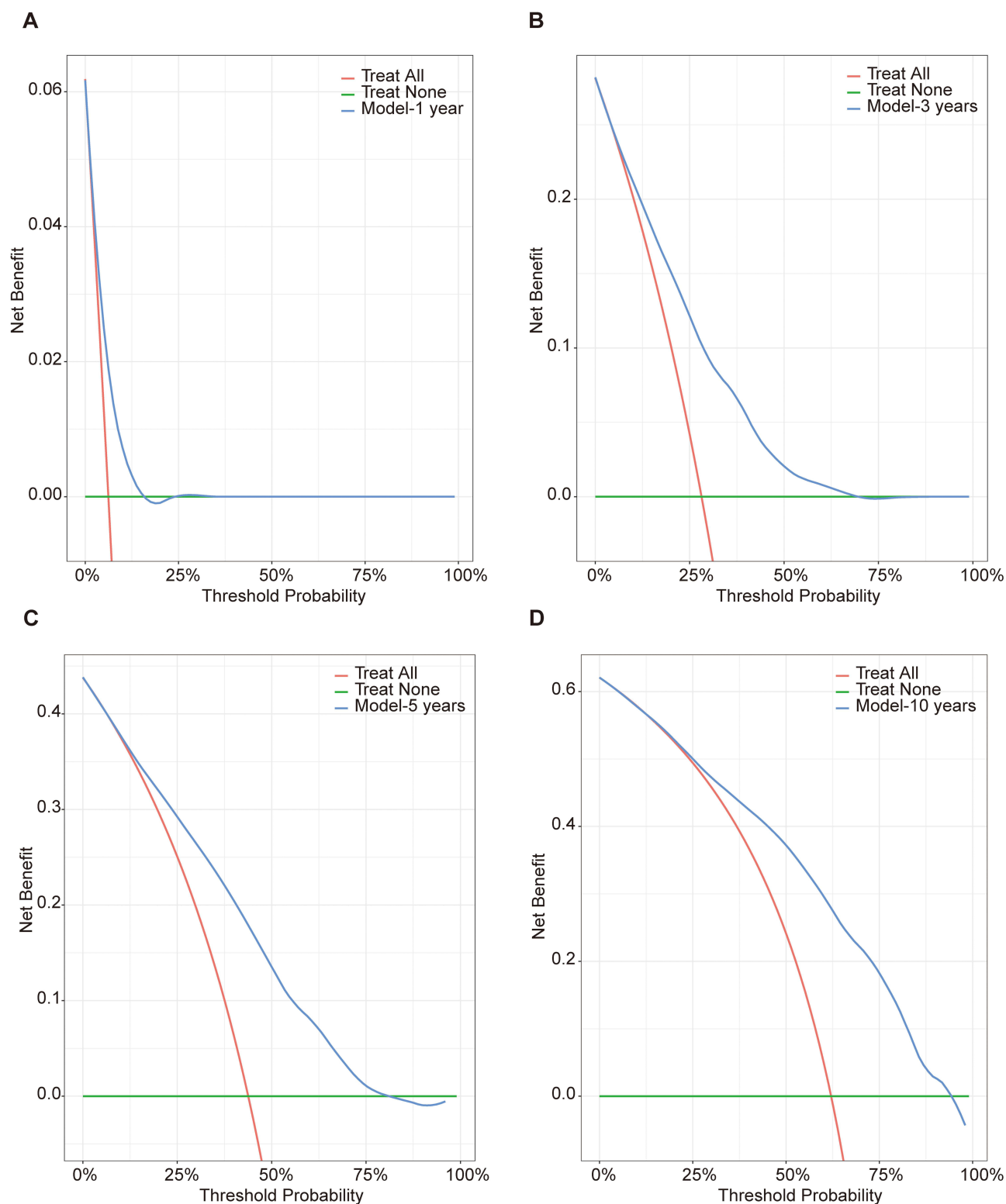


Figure 8 DCA curve of nomogram in the test set. (A) 1-year OS; (B) 3-year OS; (C) 5-year OS; (D) 10-year OS.

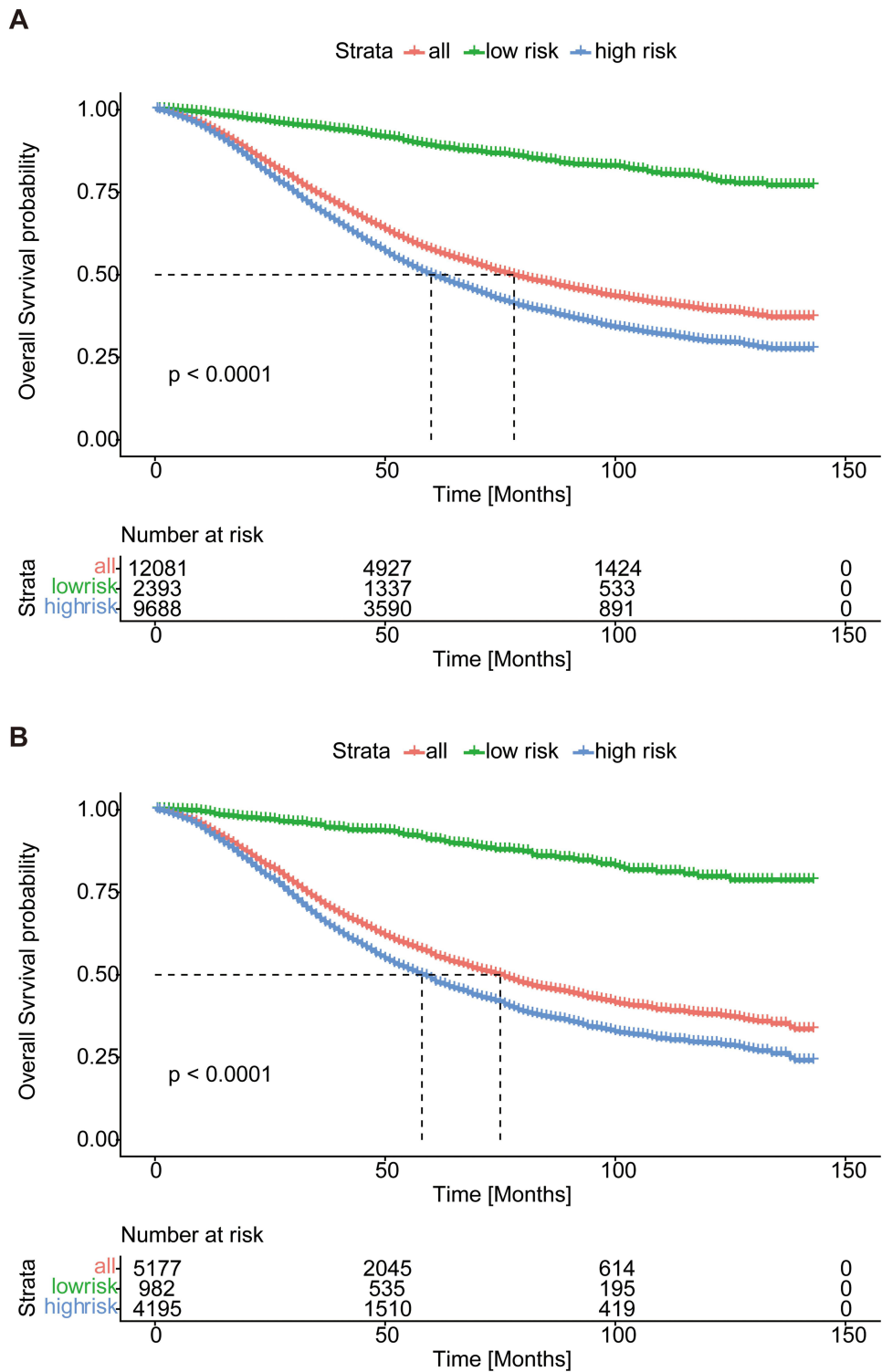


Figure 9 KM survival curve for patients stratified into low- and high-risk groups based on the model-derived risk. KM survival analysis showed that the OS of the low-risk group was better than that of the high-risk group. **(A)** training set; **(B)** test set.

Conclusion

Based on the SEER database, we developed a nomogram incorporating multiple clinical variables to estimate survival risk in patients with EOC after surgery and systemic therapy. The model demonstrated acceptable predictive performance, but further external validation is required before routine clinical use.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Since the data in the SEER database are publicly available and patient information is hidden, ethical approval and informed patient consent are not required.

Author Contributions

Hongtang Shi and Shaowei Zhan contributed equally to this work and shared the first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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