Development of a nomogram to predict prognosis in ovarian cancer: a SEER-based study

Huizhen Sun[1#], Li Yan[2#], Hainan Chen[1], Tao Zheng[1], Yi Zhang[3], Husheng Wang[1]

[1]Department of Gynecology and Obstetrics, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Department of Radiation Oncology, Eye and ENT Hospital, Fudan University, Shanghai, China; [3]Department of Assisted Reproduction, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: H Wang, Y Zhang; (II) Administrative support: H Wang; (III) Provision of study materials or patients: H Sun; (IV) Collection and assembly of data: H Sun, T Zheng; (V) Data analysis and interpretation: L Yan, H Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Husheng Wang. Department of Obstetrics and Gynecology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China. Email: wanghusheng@xinhuamed.com.cn; Yi Zhang. Department of Assisted Reproduction, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China. Email: yizhang05@xinhuamed.com.cn.

Background: Ovarian cancer remains the most lethal gynecologic malignancy. In this study, we aimed to identify the specific risk factors affecting overall survival (OS) and develop a nomogram for prognostic prediction of ovarian cancer patients based on data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Information from the SEER database on ovarian cancer between 2004 and 2016 was screened and retrieved. Cases were randomly divided into the training cohort hand the validation cohort at a 7:3 ratio. The prognostic effects of individual variables on survival were evaluated via Kaplan-Meier method and Cox proportional hazards regression model using data from the training cohort. A nomogram was formulated to predict the 3- and 5-year OS rates of patients with ovarian cancer, and then validated both in the training cohort and the validation cohort.

Results: A total of 28,375 patients were selected from 75,921 samples (19,862 in training cohort and 8,513 in validation cohort). Cox regression analysis identified race, age laterality, histology, stage, grade, surgery, chemotherapy, radiotherapy, and marital status as independent risk factors for ovarian cancer prognosis. A nomogram was developed based on the results of multivariate analysis and validated using an internal bootstrap resampling approach, which demonstrated a sufficient level of discrimination according to the C-index (0.752, 95% CI: 0.746–0.758 in the training cohort, 0.755, 95% CI: 0.746–0.764).

Conclusions: We developed a nomogram valuable for accurate prediction of 3- and 5-year OS rates of ovarian cancer patients based on individual characteristics.

Keywords: Ovarian cancer; risk factors; prognosis; nomogram

Introduction

Ovarian cancer remains the most lethal gynecologic malignancy and the fifth leading cause of cancer-related mortality globally (1,2), with approximately 185,000 women died from the disease worldwide in 2018 (3,4). Epithelial ovarian cancer is the most common histologic type that encompasses a clinically and biologically heterogeneous class of tumors including several major subtypes (serous, mucinous, endometrioid and clear cell carcinoma (5). The

remaining ovarian cancer types are mainly thought to originate from stromal granulosa, theca, and germ cells (6,7). The high mortality rate pf ovarian cancer patients due to asymptomatic disease onset and resulting late diagnosis (stage III or IV) with bowel obstruction and systemic involvement (8). Furthermore, the effectiveness of currently available treatments diminishes over time and relapse occurs in the majority of patients (9), despite a high initial response rate to platinum and taxanes therapy following cytoreductive surgery in cases of advanced cancer (10). Ovarian cancer subsequently develops into incurable disease for which treatment options remain limited (11) and the reported 5-year survival rate is ~40% (12). Comprehensive characterization of the mechanisms underlying ovarian cancer is therefore essential for developing effective therapeutic strategies.

Prognostic nomograms are graphical calculation scales for predictive models to maximize the accuracy of individual prognosis (13,14) via Kaplan-Meier survival analysis and multivariate Cox proportional hazards model (15). Currently, nomograms are widely used to assist surgeons in developing treatment plans and evaluating prognosis for various tumor types, including hepatocellular carcinoma (16), gastric cancer (17), nasopharyngeal cancer (18) and several other cancers (19,20). In the current study, we retrieved and used information available from the Surveillance, Epidemiology, and End Results (SEER) database with a view to identifying risk factors affecting overall survival (OS) and developing a nomogram for visually predicting prognosis of patients with ovarian cancer. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1238).

Methods

Data sources

We collected clinicopathological data from 75,921 patients with ovarian cancer from 2004 to 2016 available in the SEER program of the National Cancer Institute. The SEER database consists of 18 registries covering ~28% of the US population and includes collated information on cancer incidence, prevalence, mortality, population-based variables, primary tumor characteristics and treatments, excluding chemotherapy (21,22). The program has been commonly used by researchers to search for prognostic factors associated with various cancer types (23-26).

Study population

Patients diagnosed with ovarian cancer from 2004 to 2016 were identified from the SEER database. Tumor staging was manually restaged based on the lasted AJCC criteria. The following information was obtained for each patient: race, age, tumor laterality, histology, grade, stage, surgery, radiotherapy, chemotherapy, insurance, and marital status. Patients with missing data were excluded. Eligible cases were randomly divided into the training cohort and the validation cohort at a 7:3 ratio. Ethics approval was not required because that all the data of ovarian cancer patients in our study were gained from SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The prognostic effect of each variable on survival was evaluated using the Kaplan-Meier method and log-rank test. Multivariate analyses were performed using the Cox proportional hazards regression model. Variance inflation factors (VIF) were calculated to evaluate the independence of each variable. Survival was calculated in months from the date of initial surgery to the last follow-up. Statistical analyses were performed using the software package R version 3.3.1 (http://www.r-project.org/).

A nomogram was formulated based on the results of multivariate analysis using the rms package in R version 3.3.1. The maximum score of each factor was set as 10. The performance of the nomogram was measured according to the concordance index (C-index) and assessed by comparing nomogram-predicted versus observed Kaplan-Meier estimates of survival probability. Accuracy was required to be validated by 500 times bootstrapping and 10-fold cross-validation measures internally and externally. The fitting degree was evaluated on the basis of concordance index (C-index) values and calibration plots, which were derived based on regression analysis. A probability (P) value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 75,921 ovarian cancer patients were identified from the SEER database, of which 47,546 were excluded (*Figure 1*), resulting in the final inclusion of 28,375 patients (19,862 in the training cohort, 8,513 in the validation
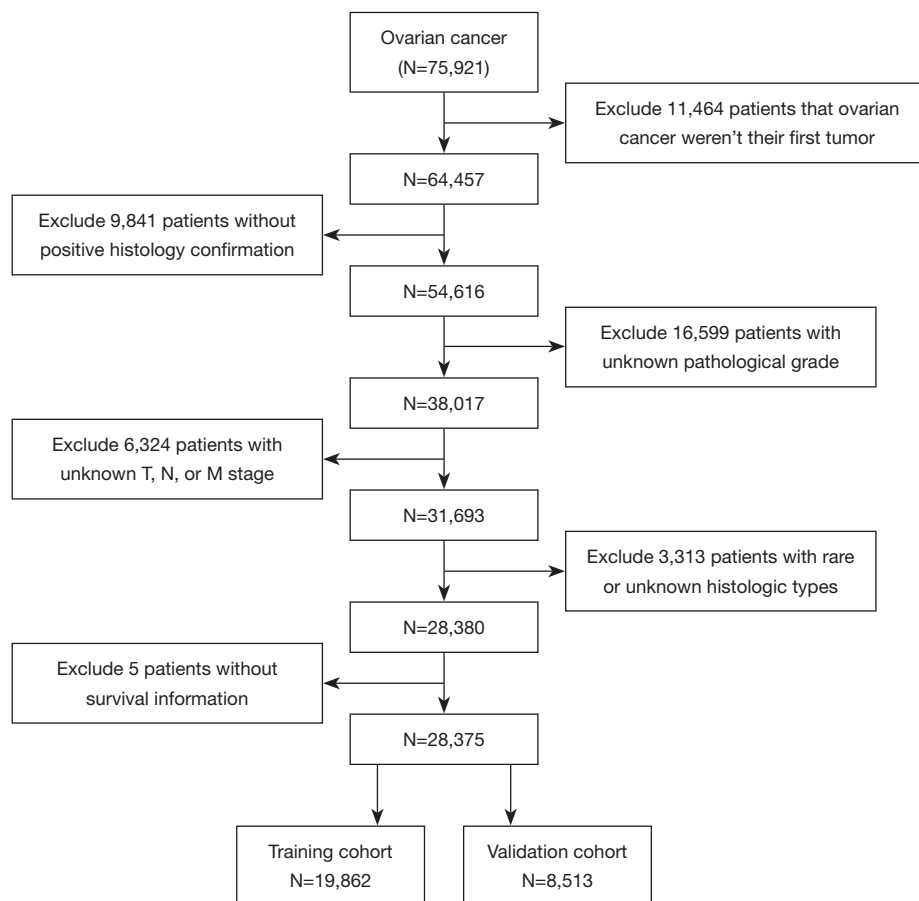
Figure 1 The flow diagram of the selection process for the study cohort.

cohort). The clinical characteristics of our study patients are summarized in *Table 1*. Tumor pathology was categorized into six groups: serous, mucinous, endometrioid, clear-cell, sex cord-stromal and germ cell carcinoma.

Survival analysis

The median follow-up period was 38 (range, 17–71) months and overall 5-year survival rate was 55.5±0.3% (*Figure 2*). All 19,862 patients in the training cohort were subjected to univariate and multivariate analyses to determine predictors of survival (*Table 2*). Specific demographic data (race and age) significantly influenced patient prognosis (*Figure 3*). Clinicopathological factors, such as laterality, histology, grade and stage (AJCC), were additionally identified as risk factors influencing patient survival (*Figure 4*). Furthermore, TNM stage shows that tumor metastasis seriously affected the survival of patients with ovarian cancer (*Figure S1*).

Survival outcomes differed in relation to the type of surgery, radiotherapy, and chemotherapy (*Figure 5*). Though patients with chemotherapy had better survival in a short time after being diagnosed, they had worse survival in a long time, perhaps due to the severe cancer condition of those patients. Finally, marital status had significant effects on survival in ovarian cancer, but insurance didn't (*Figure S2*). Cox regression analysis was performed to further explore the effects of age, race, histology, stage, laterality, grade, surgery, chemotherapy, radiotherapy, and marital status. Each of the eleven factors was an independent risk factor for prognosis (P<0.001) (*Table 2*). All VIFs are far away from 10, indicating there are no multi-collinearity problem. The developed nomogram presented in *Figure 6A* is based on the significant risk factors identified using multivariate analyses for predicting 3- and 5-year OS. To calculate OS rates, we initially identified each factor based on the points scale at the top of the nomogram and subsequently

Table 1 Clinical characteristics of patients in the training and the validation cohorts

Characteristics	Total, n (%)	Training cohort, n (%)	Validation cohort, n (%)	P
Total No.	28,375	19,862	8,513	
Race				0.443
White	23,597 (83.2)	16,536 (83.3)	7,061 (82.9)	
Black	1,898 (6.7)	1,324 (6.7)	574 (6.7)	
Others	2,880 (10.1)	2,002 (10.1)	878 (10.3)	
Age, years				0.307
≤30	1,086 (3.8)	750 (3.8)	336 (3.9)	
31–40	1,585 (5.6)	1,104 (5.6)	481 (5.7)	
41–50	4,942 (17.4)	3,452 (17.4)	1,490 (17.5)	
51–60	8,039 (28.3)	5,614 (28.3)	2,425 (28.5)	
61–70	7,083 (25)	4,976 (25.1)	2,107 (24.8)	
71–80	4,160 (14.7)	2,915 (14.7)	1,245 (14.6)	
>80	1,480 (5.2)	1,051 (5.3)	429 (5.0)	
Laterality				0.070
Unilateral	16,007 (56.4)	11,274 (56.8)	4,733 (55.6)	
Bilateral	12,368 (43.6)	8,588 (43.2)	3,780 (44.4)	
Histology				0.876
Serous carcinoma	18,538 (65.3)	12,958 (65.2)	5,580 (65.5)	
Mucinous carcinoma	2,285 (8.1)	1,606 (8.1)	679 (8.0)	
Endometrioid carcinoma	4,580 (16.1)	3,203 (16.1)	1,377 (16.2)	
Clear cell carcinoma	2,032 (7.2)	1,432 (7.2)	600 (7.0)	
Sex cord-gonadal stromal tumor	209 (0.7)	154 (0.8)	55 (0.6)	
Germ cell tumor	731 (2.6)	509 (2.6)	222 (2.6)	
Grade				0.907
Well differentiated	3,491 (12.3)	2,435 (12.3)	1,056 (12.4)	
Moderately differentiated	5,526 (19.5)	3,861 (19.4)	1,665 (19.6)	
Poorly differentiated	12,127 (42.7)	8,530 (42.9)	3,597 (42.3)	
Undifferentiated	7,231 (25.5)	5,036 (25.4)	2,195 (25.8)	
Stage				0.857
I	8,228 (29.0)	5,752 (29.0)	2,476 (29.1)	
II	2,875 (10.1)	2,037 (10.3)	838 (9.8)	
III	12,247 (43.2)	8,533 (43)	3,714 (43.6)	
IV	5,025 (17.7)	3,540 (17.8)	1,485 (17.4)	

Table 1 (*cobtinued*)

Table 1 (*cobtinued*)

Characteristics	Total, n (%)	Training cohort, n (%)	Validation cohort, n (%)	P
T stage				0.889
T0	16 (0.1)	12 (0.1)	4 (0.0)	
T1	8,707 (30.7)	6,080 (30.6)	2,627 (30.9)	
T2	3,818 (13.5)	2,703 (13.6)	1,115 (13.1)	
T3	15,834 (55.8)	11,067 (55.7)	4,767 (56.0)	
N stage				0.320
N0	21,674 (76.4)	15,204 (76.5)	6,470 (76.0)	
N1	6,701 (23.6)	4,658 (23.5)	2,043 (24.0)	
M stage				0.588
M0	23,350 (82.3)	16,322 (82.2)	7,028 (82.6)	
M1	5,025 (17.7)	3,540 (17.8)	1,485 (17.4)	
Surgery				0.551
Not performed	490 (1.7)	337 (1.7)	153 (1.8)	
Performed	27,885 (98.3)	19,525 (98.3)	8,360 (98.2)	
Radiotherapy				0.553
Not performed	28,061 (98.9)	19,647 (98.9)	8,414 (98.8)	
Performed	314 (1.1)	215 (1.1)	99 (1.2)	
Chemotherapy				0.297
No/unknown	7,269 (25.6)	5,053 (25.4)	2,216 (26.0)	
Performed	21,106 (74.4)	14,809 (74.6)	6,297 (74.0)	
Insurance status				0.726
None or unknown	7,237 (25.5)	5,054 (25.4)	2,183 (25.6)	
Any	21,138 (74.5)	14,808 (74.6)	6,330 (74.4)	
Marital status				0.011
Not married	13,138 (46.3)	9,294 (46.8)	3,844 (45.2)	
Married	15,237 (53.7)	10,568 (53.2)	4,669 (54.8)	

summed the points of each factor. Finally, 3- and 5-year OS rates were obtained based on the bottom point scale of the nomogram. The calibration plots based on bootstrap resampling validation are illustrated in *Figure 6B,C*. The C-index of the nomogram was 0.752 (95% CI: 0.746–0.758).

We further validated the nomogram using the data of the validation cohort. The calibration plots based on bootstrap resampling validation are illustrated in *Figure 6D,E*. The C-index was 0.755 (95% CI: 0.746–0.764), indicating good agreement between the nomogram and actual observation

for predicting 3- and 5-year OS rates of patients with ovarian cancer.

In general, the OS rates were better for younger patients and poorer for black women. Advanced stage, paired site and high grade had a negative influence on OS. In terms of histological subtype, the germ cell tumor type was associated with best prognosis in general, followed by endometrial carcinoma, sex cord-gonadal stromal tumor, serous carcinoma, clear cell carcinoma, and mucinous carcinoma. Survival was superior in patients who underwent
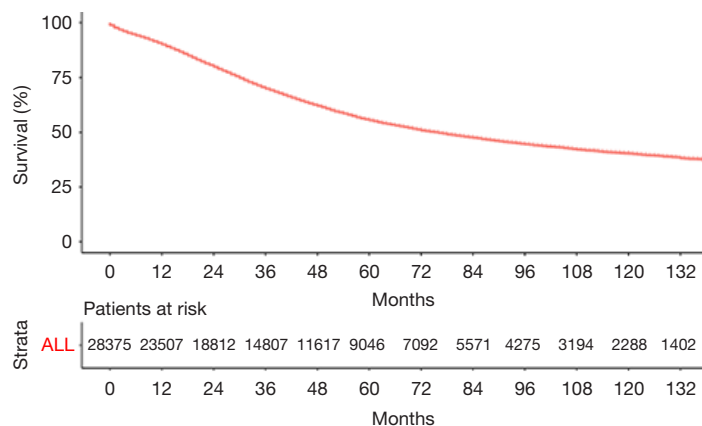
Figure 2 Overall Kaplan-Meier survival curve of all included patients.

Table 2 Univariate and multivariate analyses of survival for ovarian cancer patients

Characteristics	Univariate analyses		Multivariate analysis		VIF
	HR (95% CI)	P	HR (95% CI)	P	
Total No.					
Race		<0.001		<0.001	1.022
White	Reference		Reference		
Black	1.166 (1.073–1.267)	<0.001	1.190 (1.094–1.295)	<0.001	
Others	0.718 (0.662–0.779)	<0.001	0.904 (0.833–0.982)	0.017	
Age, years		<0.001		<0.001	1.193
≤30	Reference		Reference		
31–40	2.204 (1.716–2.830)	<0.001	1.323 (1.014–1.726)	0.039	
41–50	3.260 (2.602–4.084)	<0.001	1.390 (1.086–1.778)	0.009	
51–60	4.154 (3.328–5.186)	<0.001	1.639 (1.284–2.093)	<0.001	
61–70	5.651 (4.528–7.053)	<0.001	1.950 (1.528–2.490)	<0.001	
71–80	7.917 (6.335–9.895)	<0.001	2.613 (2.044–3.341)	<0.001	
>80	12.19 (9.688–15.33)	<0.001	4.326 (3.363–5.564)	<0.001	
Laterality		<0.001		<0.001	1.332
Unilateral	Reference		Reference		
Bilateral	2.112 (2.022–2.205)	<0.001	1.203 (1.148–1.261)	<0.001	
Histology		<0.001		<0.001	1.522
Serous carcinoma	Reference		Reference		
Mucinous carcinoma	0.403 (0.365–0.445)	<0.001	1.608 (1.432–1.804)	<0.001	
Endometrioid carcinoma	0.308 (0.285–0.332)	<0.001	0.835 (0.768–0.908)	<0.001	
Clear cell carcinoma	0.515 (0.467–0.567)	<0.001	1.439 (1.297–1.597)	<0.001	
Sex cord-gonadal stromal tumor	0.188 (0.121–0.292)	<0.001	0.785 (0.503–1.223)	0.285	
Germ cell tumor	0.058 (0.039–0.088)	<0.001	0.285 (0.182–0.446)	<0.001	

Table 2 (*cobtinued*)

Table 2 (*cobtinued*)

Characteristics	Univariate analyses		Multivariate analysis		VIF
	HR (95% CI)	P	HR (95% CI)	P	
Grade		<0.001		<0.001	1.296
Well differentiated	Reference		Reference		
Moderately differentiated	2.147 (1.920–2.400)	<0.001	1.571 (1.403–1.761)	<0.001	
Poorly differentiated	4.063 (3.671–4.498)	<0.001	1.750 (1.567–1.955)	<0.001	
Undifferentiated	3.940 (3.543–4.381)	<0.001	1.668 (1.486–1.874)	<0.001	
Stage		<0.001		<0.001	1.694
I	Reference		Reference		
II	2.238 (2.006–2.496)	<0.001	2.020 (1.801–2.265)	<0.001	
III	5.970 (5.533–6.442)	<0.001	5.168 (4.717–5.661)	<0.001	
IV	9.299 (8.572–10.088)	<0.001	7.649 (6.939–8.431)	<0.001	
T stage		<0.001	Not included		
T0	Reference				
T1	0.136 (0.065–0.286)	0.000			
T2	0.353 (0.168–0.743)	0.066			
T3	0.855 (0.407–1.794)	0.910			
N stage		<0.001	Not included		
N0	Reference				
N1	1.889 (1.804–1.979)	<0.001			
M stage		<0.001	Not included		
M0	Reference				
M1	2.737 (2.609–2.871)	<0.001			
Surgery		<0.001		<0.001	1.022
Not performed	Reference		Reference		
Performed	0.188 (0.166–0.214)	<0.001	0.367 (0.322–0.417)	<0.001	
Radiotherapy		0.0021		0.001	1.004
Not performed	Reference		Reference		
Performed	1.355 (1.126–1.632)	0.001	1.369 (1.136–1.650)	0.001	
Chemotherapy		<0.001		<0.001	1.189
No/Unknown	Reference		Reference		
Performed	1.376 (1.305–1.449)	<0.001	0.746 (0.705–0.789)	<0.001	
Insurance status		0.146	Not included	<0.001	
None or unknown	Reference				
Any	0.966 (0.922–1.012)	0.146			
Marital status		<0.001		<0.001	1.015
Not married	Reference		Reference		
Married	0.892 (0.854–0.931)	<0.001	0.878 (0.84–0.917)	<0.001	
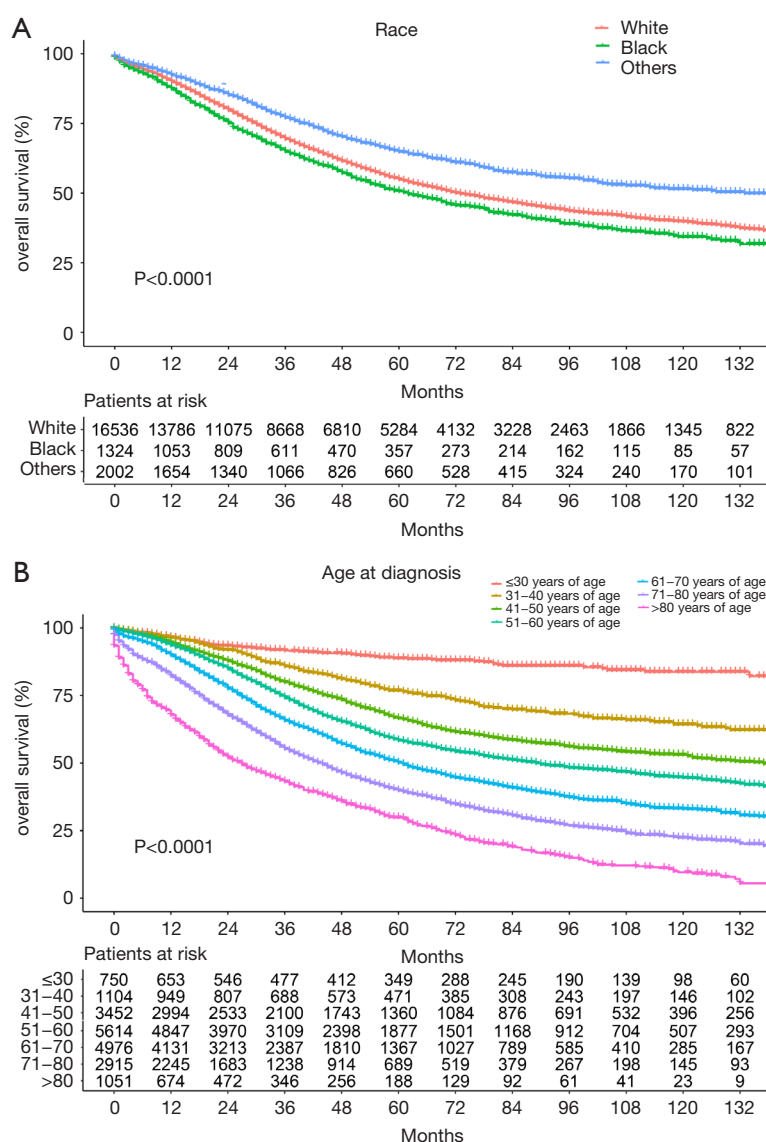
Figure 3 Overall Kaplan-Meier survival curves for patients according to (A) race and (B) age at diagnosis.

surgery and chemotherapy and inferior in those subjected to radiotherapy. With the aid of the newly developed nomogram, it was possible to effectively predict prognosis according to individual patient characteristics.

Discussion

Despite considerable progress in the development of both surgical procedures and novel medicines, the overall survival rates of ovarian cancer patients remain extremely low. International Federation of Gynecology and Obstetrics stage and residual tumor after debulking surgery are

the most widely reported prognostic factors (27), but are insufficient for effective prognosis. A nomogram, commonly used in clinical oncology, is a convenient tool that quantifies risk by incorporating and illustrating the relative importance of various prognostic factors (28). The current study used data from more than 20,000 cases of ovarian cancer for developing a nomogram to predict the 3- and 5-year OS rates based on 10 significant factors (age, race, histology, stage, laterality, grade, surgery, chemotherapy, radiotherapy, and marital status) with the aim of effectively predicting prognosis according to specific characteristics. To our knowledge, no other researchers to
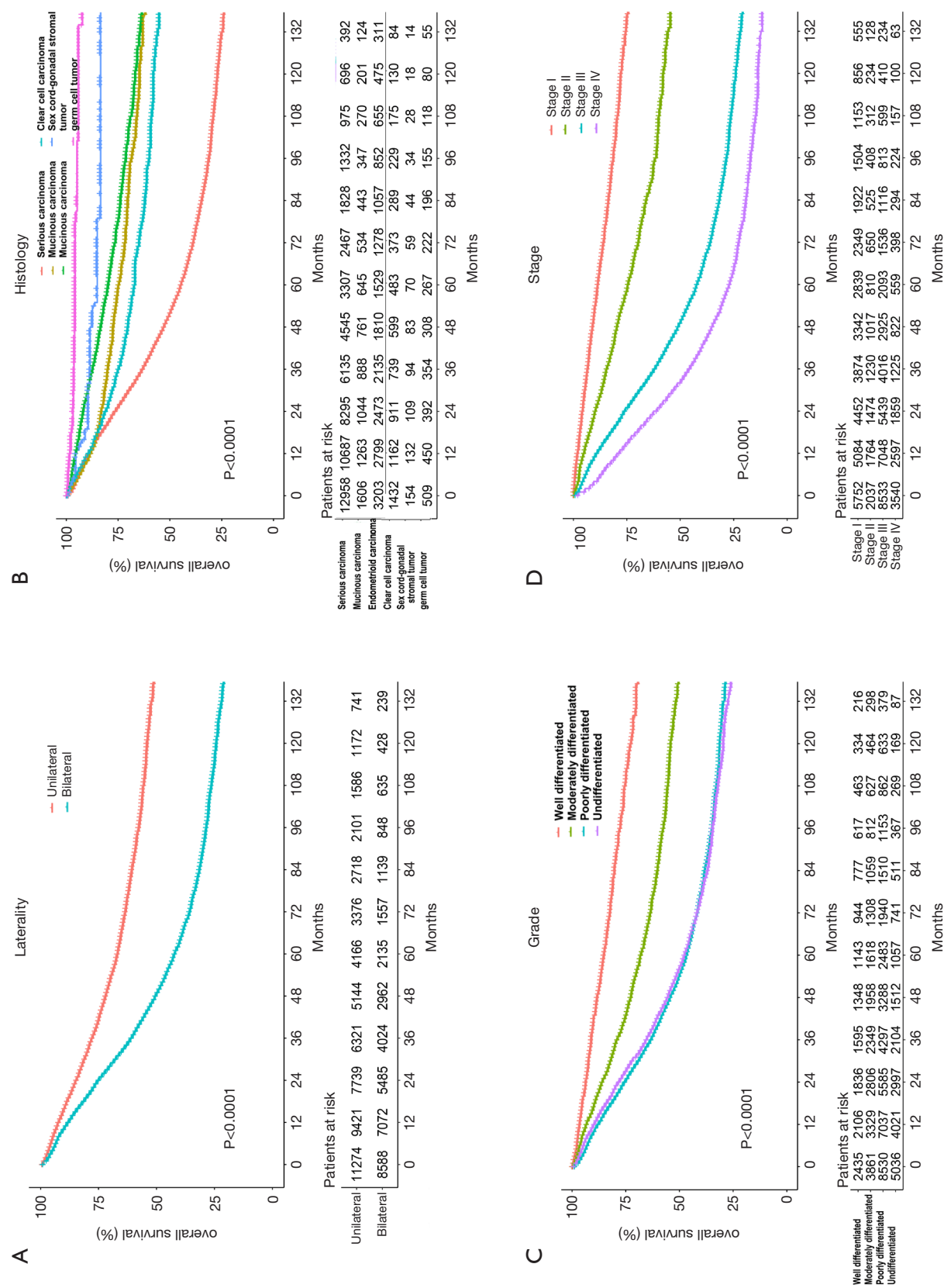
Figure 4 Overall Kaplan-Meier survival curves for patients according to (A) laterality, (B) histology, (C) grade, and (D) stage.
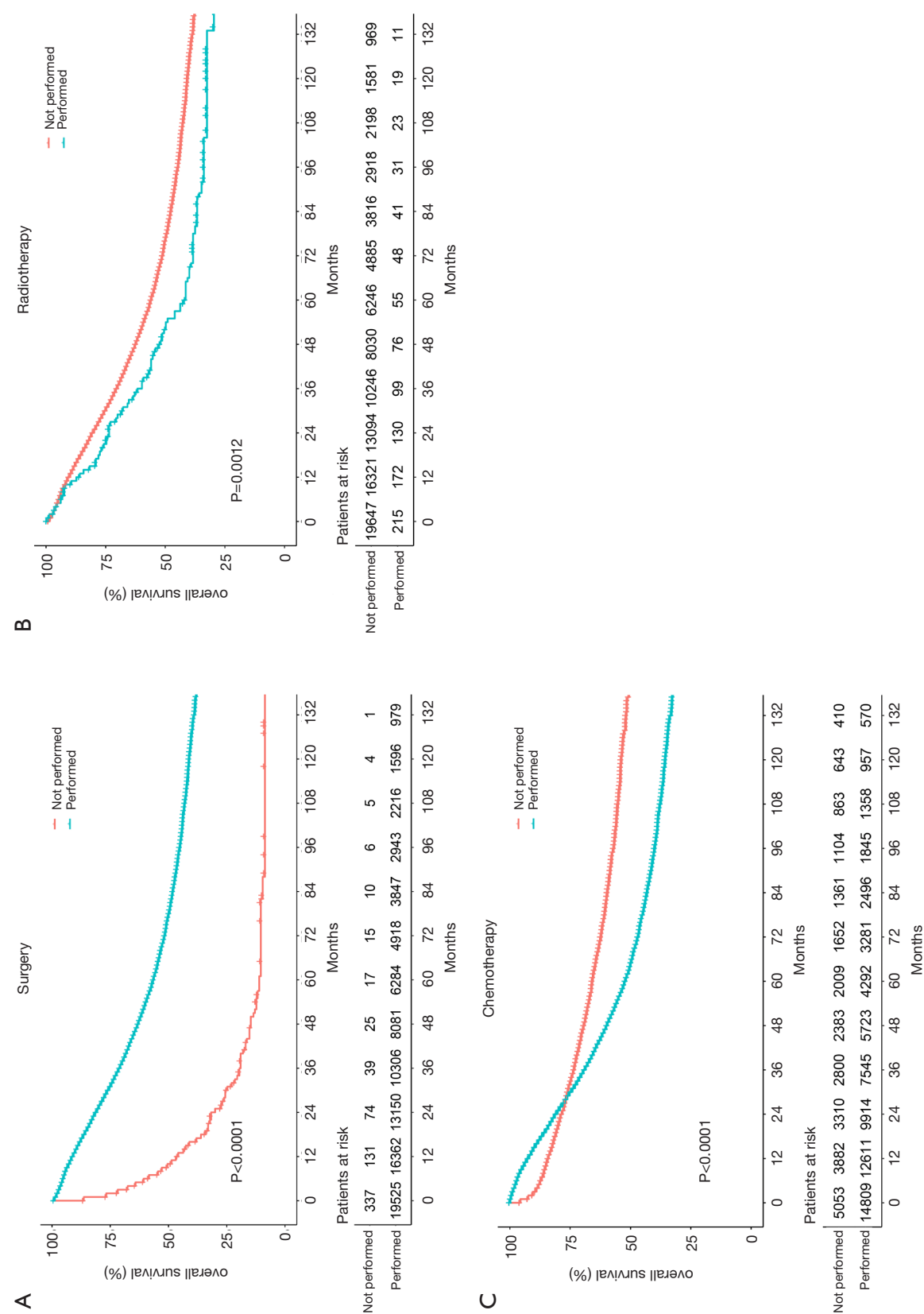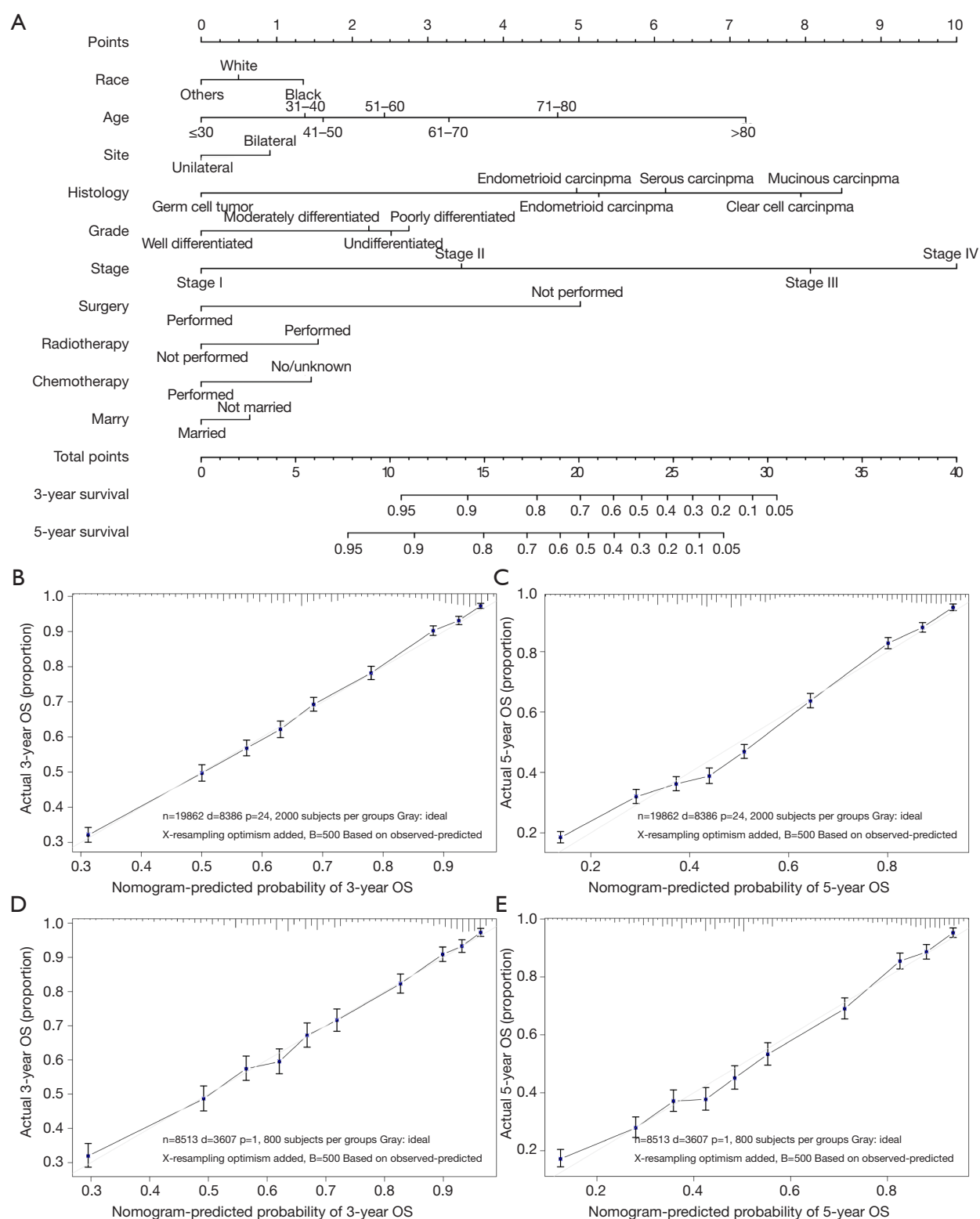
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Figure 5 Overall Kaplan-Meier survival curves for patients according to (A) surgery, (B) radiotherapy, (C) chemotherapy.

Figure 6 A nomogram for prediction of 3- and 5-year OS rates of patients with ovarian cancer (A). Calibration curve of the nomogram predicting (B) 3-year and (C) 5-year OS rates of patients with ovarian cancer in the training cohort. (D) 3-year and (E) 5-year OS rates of patients with ovarian cancer in the validation cohort.

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date have conducted a comprehensive nomogram analysis based on the SEER database for predicting outcomes in ovarian cancer patients. The discrimination performance of the nomogram was evaluated using an internal bootstrap resampling method. The C-index demonstrated the capability of the nomogram to predict 3- and 5-year OS rates of patients with ovarian cancer.

Platinum/taxanes therapy following cytoreductive surgery is the standard therapeutic strategy for advanced ovarian cancer. Radiotherapy was largely discontinued after the introduction of platinum-based chemotherapy. In our analysis, radiotherapy was associated with poor prognosis in ovarian cancer, similar to the earlier findings of Patel *et al.* (29) who analyzed OS for clear cell, mucinous, and endometrioid histologies of stage I–III ovarian cancer from the SEER Program between 2004 and 2011. Patients receiving radiation therapy had lower cause-specific survival and ovarian cancer at 5 and 10 years. However, a number of studies have demonstrated the essential utility of radiotherapy as a feasible treatment modality for patients with persistent recurrent epithelial ovarian cancer (30), which indicated that radiotherapy is irreplaceable still and needed to be studied furthermore.

Marital status has recently been established as an independent predictor of survival in gastric cancer (17), colorectal cancer (31) and several other tumors. Determination of the relationship between marital status and survival in ovarian cancer would be beneficial for decision making by researchers, physicians as well as policy makers to improve the mortality rate. Our data showed that unmarried ovarian cancer patients (including widowed, single, divorced, and separated samples or those with domestic partners) generally have poorer prognosis although the marital status may have changed for some patients during the course of study.

The SEER database has provided the opportunity to perform large, population-based studies for many tumor types, such as laryngeal squamous cell carcinoma (32), malignant pleural mesothelioma (33), lung cancer (34) and brain cancer (35). However, several vital limitations require addressing and the results should be interpreted with caution. Firstly, our nomogram isn't validated by the data of our own department or other databases, due to the lack of another large cohort. Secondly, the current study is a retrospective design and a larger randomized controlled trial may be required to validate our findings. Thirdly, the C-index of the nomogram is not entirely reliable. Several other factors additionally influence prognosis, such as family

history and general health. Meanwhile, the follow-up period for some patients was extremely long and some factors may have changed over this time-period, such as marital status. Further systematic analyses are therefore required to improve the predictive accuracy of the nomogram.

Despite the obvious limitations of our study, the data clearly indicate that age, race, histology, stage, laterality, grade, surgery, chemotherapy, radiotherapy, and marital status are independent risk factors for survival of patients with ovarian cancer The nomogram developed could accurately predict the 3- and 5-year OS rates of our patient sample according to individual characteristics.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-1238

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1238). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data of ovarian cancer were obtained from SEER database.

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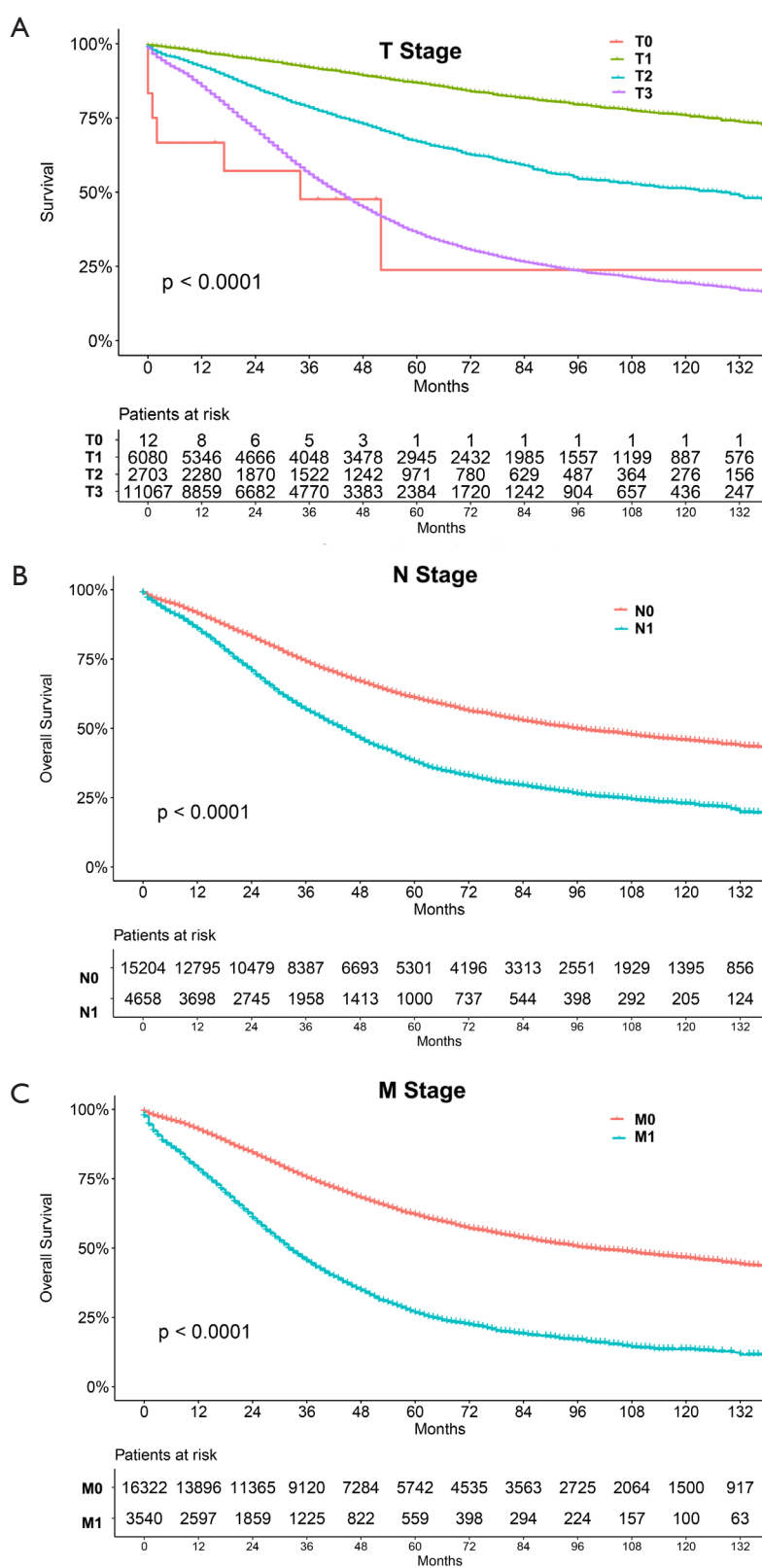
Figure S1 Overall Kaplan-Meier survival curves for patients according to (A) T stage, (B) N stage, (C) C stage.
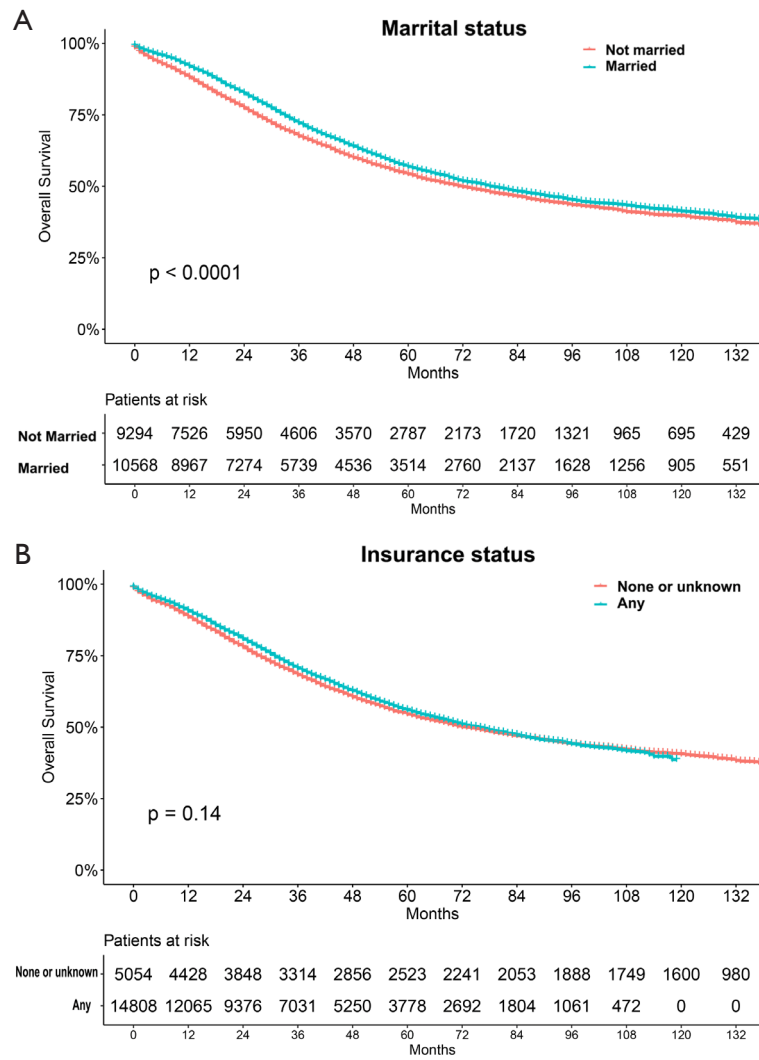
Figure S2 Overall Kaplan-Meier survival curves for patients according to (A) marital status and (B) insurance status.