Development of A Nomogram to Predict Survival Outcome Among Epithelial Ovarian Cancer Patients With Site-Distant Metastases: A Population-Based Study

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Research article

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Abstract

Objective. The incidence of initial diagnosis with distant metastasis in patients with epithelial ovarian cancer is not rare, for which the available prognostic evaluation criteria is absent. This study aimed to develop a nomogram score to predict long-term prognosis.

Methods. This study analyzed patients with epithelial ovarian cancer from the Surveillance, Epidemiology, and End Results (SEER) database between 1975 and 2016. Multivariable logistic and Cox regression were performed to identify survival trajectories. A nomogram score was used to predict long-term survival probability.

Results. A total of 131050 patients were included, 18.2%, 7.8% and 66.1% had localized, regional and distant metastases, respectively. Metastases were inversely associated with high probability of 5-year overall survival outcome, localized (OR, 4.62; 95%CI, 4.45-4.80), regional (OR, 2.47; 95%CI, 2.36-2.59) compared with distant metastases. Survival was poorer among regional (HR, 1.72; 95%CI, 1.65-1.79) and distant (HR, 3.39; 95%CI, 3.29-3.49) metastases at diagnosis. For incidence, 0.9%, 6.7%, 5.8% and 0.2% had bone, liver, lung and brain metastases in the all-cause mortality cohort respectively, 1.6%, 9.9%, 8.8% and 0.3% had bone, liver, lung and brain metastases in the cancer-specific mortality cohort respectively. The median survival among the all-cause mortality cohort was 21.0 months, cancer-specific mortality cohort was 15.0 months. Organ-specific metastases were independently associated with survival prognosis.

Conclusions. Nomogram score in estimating the long-term prognosis is feasible, for which contribute to directing clinical treatment and prognosis assessment in patient harboring site-distant metastases.

Highlights

1. Long-term prognosis among patients diagnosed with site-distant metastases via nomogram score assessment is feasible.
2. Site-distant metastases are at high risk of 5-year survival probability.
3. Organ-specific and solitary organ-specific metastases are associated with an excess risk of prognosis.

1. Introduction

Epithelial ovarian cancer is a deadly malignant disease[1]. According to the Surveillance, Epidemiology, and End Results (SEER) cancer statistics review (1975–2015), with more than twenty-thousand cases and fourteen-thousand deaths annually[2]. Although with the continuous advancement of surgical techniques and the improvement of chemotherapy drugs, the overall survival rate of patients with epithelial ovarian cancer has improved in the past 50 years, but the five-year overall survival rate is still less than 50%[3–5]. Numerous studies have investigated the association among potential survival

trajectories as to prognosis of ovarian cancer[6]. However, the predictors of long-term survival are not well elucidated.

Sites-distant metastases seem to represent a significant cause of morbidity and mortality among patients with epithelial ovarian cancer[7–9]. Previous studies from case report and single institution experiences have yielded varying conclusions, especially robust population-based estimates relating to the incidence of sites-distant metastases at diagnosis are common. However, populations-level estimation for prognosis among patients with newly diagnosed epithelial ovarian cancer and sites-distant metastases are also lacking.

In autopsy studies, patients with epithelial ovarian cancer are inclined to liver, lung, bone and/or brain metastases, not all of which are clinically apparent prior to death[9–11]. Thus, in patients with both localized and/or organ specific distant metastases, the risk of prognostic factors should be reassessment. Furthermore, patients diagnosed to have localized and/or distant metastases are suitable candidates for studies on postoperative adjuvant treatment, also which can help surgeons choose appropriate surgical measures for patients in advance.

Based on a lack of proven benefit, the purpose of this study was to use the SEER database to summarize the incidence proportion of organ specific distant metastases. Based on a nomogram score, we also sought to predict survival time, in which depend on independent risk factors that contribute to prognosis.

2. Methods

2.1 *Population-based study inclusion and exclusion criteria*

The SEER database includes information on epithelial ovarian cancer incidence, outcome, and treatment for approximately thirty percent of the US population[12]. The SEER registries collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, and first course of treatment, and they follow up with patients for vital status. Within the SEER 18 registries in the November 2016 data submission, we identified 148597 patients diagnosed as ovarian cancer from 1973 to 2016. Inclusion criteria: (1) Epithelial ovarian cancer confirmed by pathologic diagnosis, meeting the criteria of International Classification of Diseases for Oncology, 3rd ed[8]. The primary site was C56.9 ovary, (2) Patients who had intact clinical information and survival outcomes, (3) Evidence of distant metastases at newly diagnosis, based on the commonly used International Federation of Gynecology and Obstetrics (FIGO) staging system, distant metastases included FIGO III-A, III-B, III-C, III-NOS and IV. Likewise, due to that the database included distant metastases variables, which contributed to the presence of metastatic position like bone, liver, brain and lung at time of diagnosis. Exclusion criteria: (1) Patients who were diagnosed at autopsy or via death certificate, (2) Patients with carcinoma for whom the presence or absence of distant metastases at diagnosis were unknown, (3) Patients who had unknown follow-up records.

2.2 *Follow-up information and classification*

Patients were stratified by sites of distant metastases, as well as other variables included age, race/ethnicity, marital status, etc. The clinicopathologic variables in the study are shown in Table s1.

2.3 *Incidence and survival analysis*

The incidence proportions were calculated for patients with organ specific metastases identified at diagnosis. The primary endpoint was overall survival, defined as the time from newly diagnosis to death or loss of follow-up. Survival time was stratified as time (t) less than or equal to or more than sixty months (cut-off point,5-year). In addition to all-cause mortality, a separate analysis as to ovary cancer with distant metastases survival time including overall survival (OS) and cancer-specific survival (CSS) were conducted among women diagnosed after 2010, used to assess the risk of distant metastases related to survival outcome.

2.4 *Statistical analysis*

Stepwise multivariable logistic and Cox regression were performed to identify survival trajectories associated with increased all-cause mortality and the presence of distant metastases. Survival estimation was performed using the Kaplan-Meier method and compared using the log-rank test. A nomogram was conducted based on the results of multivariate logistic regression analysis herein. Patients were randomly divided into the training and validation samples. The predictive performance of the nomogram was evaluated via concordance index and calibration curve. To accurately decrease the overfit bias, 1000 bootstrap samples was performed. All analyses were performed using R software, version 3.6.2 (https://www.r-project.org/). $P < 0.05$ was considered statistical significance.

3. Results

A total of 131050 women with epithelial ovarian cancer were included in this analyses (Figs. 1). 18.2%, 7.8% and 66.1% had localized, regional and distant metastases, respectively. Among the cohort with metastatic disease, 18.6%, 81.4% were aged ≤ 50 and > 50 years, respectively. 30.0%, 70.0% were survived > 60 and ≤ 60 months, respectively. Compared to less than 5-year overall survival patients, most survivors with long-term (> 60 months) were more likely to be diagnosed with localized metastases, as well as younger age, lower grade and accepting surgery (Tables1).

Table 1
Incidence proportion and median survival in patients with metastases at diagnosis

Metastases subtype	Incidence Proportion of all-cause mortality cohort, %	median survival (IQR), month	Incidence Proportion of cancer-specific mortality cohort, %	median survival (IQR), month
Bone	0.9	5.0(1.0–11.0)	1.6	4.0(1.0–9.0)
Liver	6.7	9.0(2.0–25.0)	9.9	6.0(1.0–19.0)
Lung	5.8	9.0(2.0–24.0)	8.8	6.0(1.0–21.0)
Brain	0.2	3.5(1.0–11.0)	0.3	3.0(1.0–7.0)
Lymph	0.9	4.0(1.0–7.0)	0.5	1.5(1.0-5.75)
Bone only	0.4	7.0(2.0-19.5)	0.6	6.0(2.0-14.5)
Liver only	0.1	10.0(2.0–28.0)	6.9	7.0(1.0–20.0)
Lung only	3.9	11.0(2.0–25.0)	5.8	8.0(1.0–22.0)
Lymph only	0.5	5.0(2.0–8.0)	0.2	2.0(1.0-4.5)
Brain only	4.8	4.0(2.0–12.0)	0.2	2.5(2.0-7.75)

Abbreviations: IQR, interquartile range.

3.1 *Risk of long-term overall survival based on the nomogram scores*

After multivariable logistics regression analysis, metastases were inversely associated with risk of 5-year overall survival, localized (OR, 4.62; 95%CI, 4.45–4.80), regional (OR, 2.47; 95%CI, 2.36–2.59) compared with distant metastases (Tables2). After Cox regression analysis, the presence of metastases was one of the independent risk factors of all-cause mortality (Tables5). Compared with localized metastases, survival was poorer among regional (HR, 1.72; 95%CI, 1.65–1.79) and distant (HR, 3.39; 95%CI, 3.29–3.49) metastases at diagnosis. These independent associated risk factors were used to form a 5-year overall survival prediction nomogram (Fig. 1). The nomogram score demonstrated robust accuracy in estimating the risk of 5-year overall survival probability, with an unadjusted C index of 0.78. In addition, calibration plot also showed ideal agreement as to metastases, as well as other risk factors, contributing to the estimation of long-term survival (≥ 5-year) prediction.

Table 2
Multivariate logistic regression analysis of survival in OS and CSS mortality cohort

Variable	OS				CSS			
	HR	95%CI lower	95%CI upper	P value	HR	95%CI lower	95%CI upper	P value
Age, y								
< 50	1[ref]	NA	NA		1[ref]	NA	NA	
>=50	1.58	1.49	1.67	< 0.01	0.71	0.65	0.78	< 0.01
Race								
white	1[ref]	NA	NA		1[ref]	NA	NA	
non-white	0.97	0.93	1.01	0.12	1.34	1.25	1.44	< 0.01
Grade								
I/II	1[ref]	NA	NA		1[ref]	NA	NA	
III/IV	1.53	1.43	1.64	< 0.01	0.93	0.83	1.04	0.18
unknown	1.57	1.46	1.69	< 0.01	0.93	0.82	1.05	0.23
Histology								
serous	1[ref]	NA	NA		1[ref]	NA	NA	
non-serous	1.37	1.32	1.42	< 0.01	1.50	1.39	1.62	< 0.01
FIGO								
I	1[ref]	NA	NA		1[ref]	NA	NA	
II	2.29	2.06	2.53	< 0.01	1.16	0.98	1.37	NA
III	4.47	4.13	4.85	< 0.01	1.13	0.99	1.28	NA
IV	5.09	4.67	5.54	< 0.01	1.34	1.16	1.54	< 0.01
unknown	3.70	3.34	4.09	< 0.01	3.12	2.66	3.67	< 0.01
Metastases								
bone								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	0.82	0.72	0.94	< 0.01	0.74	0.58	0.95	0.02
brain								

Abbreviations: OS, overall survival. CSS, cancer specific survival.

Variable	OS				CSS			
	HR	95%CI lower	95%CI upper	P value	HR	95%CI lower	95%CI upper	P value
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	0.74	0.57	0.96	0.03	0.76	0.46	1.26	0.29
liver								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	0.82	0.77	0.87	< 0.01	0.79	0.70	0.89	< 0.01
lung								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	0.93	0.87	0.99	0.02	1.01	0.89	1.14	0.91
lymph								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	1.19	0.91	1.55	0.21	0.68	0.44	1.08	0.11
Insurance								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	1.12	1.07	1.18	< 0.01	2.01	1.82	2.22	< 0.01
surgery								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	4.06	3.87	4.26	< 0.01	2.22	2.01	2.45	< 0.01
Martial								
yes	1[ref]	NA	NA		1[ref]	NA	NA	
no	1.03	0.99	1.07	0.17	1.72	1.60	1.86	< 0.01

Abbreviations: OS, overall survival. CSS, cancer specific survival.

3.2 *Incidence and median survival of patients with metastases*

Among the patients in the all-cause mortality cohort(n = 33727) and cancer-specific mortality cohort (n = 15742) with metastases at diagnosis were identified. For incidence, 0.9%, 6.7%, 5.8% and 0.2% had bone, liver, lung and brain metastases in the all-cause mortality cohort respectively, 1.6%, 9.9%, 8.8% and 0.3% had bone, liver, lung and brain metastases in the cancer-specific mortality cohort respectively. The

incidence proportion of patients with organ-specific or solitary metastases at diagnosis provided in Table 1. As stratified by organ-site metastases, presented in Tables3. The median survival among the all-cause mortality cohort was 21.0 months, cancer-specific mortality cohort was 15.0 months. As stratified by organ-specific metastases and solitary organ metastases, patients with solitary lung metastases showed the longest median survival (11.0months) and patients with brain metastases had the shortest median survival (3.5months) in the all-cause mortality cohort. Patients with solitary lung metastases showed the longest median survival (8.0months) and patients with solitary lymph metastases experienced the shortest median survival (1.5months).

3.3 *Risk factors screening for predicting long-term survival possibility*

After multivariable adjustment, the risk of 5-year overall survival was significantly associated with lung metastases (OR,0.69;95%CI,0.52–0.92), age (OR,1.26; 95%CI,1.16–1.38), race (OR,0.82;95%CI,0.76–0.89), grade (OR,1.29;95%CI,1.17–1.41), histology (OR,0.89;95%CI,0.82–0.97), surgery (OR,0.16;95%CI,0.13–0.21), insurance (OR,0.79;95%CI,0.71–0.87) and martial (OR,0.96;95%CI,0.88–1.04) among the all-cause mortality cohort. Among the all-cause mortality cohort, we observed similar, although not statistically significant, association for organ-specific metastases. lung metastases were associated with a significant decrease in long-term survival possibility (Tables4).

3.4 *Development and validation of a prognosis predicting nomogram*

On multivariable cox regression for all-cause mortality and cancer-specific mortality, organ-specific metastases were independently associated with survival prognosis (Table 2). These independent associated risk factors were performed to form a prognosis (3-year/5-year overall survival) estimation nomogram. Among the all-cause mortality cohort, 70% of patients were used for training, 30% of patients were used for validation. So did the cancer-specific mortality cohort. The nomogram score demonstrated good accuracy in estimating the prognosis of 3-year and 5-year overall survival. In the all-cause mortality training and validation cohort, a bootstrap-corrected C index was 0.79,0.78, respectively. The calibration plot also showed robust result of the estimation (Fig. 2). In the cancer-specific mortality training and validation cohort, the nomogram displayed C index was 0.75, 0.74, respectively. So did the stable calibration curve (Fig. 3).

4. Discussion

Epithelial ovarian cancer is the most common pathological type in ovarian malignant tumors[5]. Based on the SEER cancer registry data analysis, the potential factors of long-term survival were comprehensively understood in this study. Taken the 5-year over survival as a cut-off point, we observed that site of metastases and organ-specific metastases strongly were associated with overall survival in the all-cause mortality cohort and cancer-specific mortality cohort, these survival trajectories potentially contributed to patients prognosis with distant metastases, especially among patients with organ-specific metastases at diagnosis. Likewise, consistence with previous study, other survival trajectories such as race, ovarian

involvement, histology, age (taken menopause age as borderline), insurance and marital status, which were commonly relevant to the long-term prognosis[13–15]. In addition, this study explored the risk of 5-year overall survival among patients with localized, regional and distant metastases, our data demonstrated that distant metastases were significantly associated with long-term survival (> 5 years). Collectively, tumor migration may contribute to the worse long-term survival in patients with site-distant metastases at initial diagnosis. To the best of our knowledge, this is the largest population-based study exploring prognosis in patients with epithelial ovarian cancer diagnosed with tumor metastases at diagnosis.

Our study reported the incidence and median survival time of different organ-specific metastases. Consistent with some but not all prior studies[8,11,16], liver metastases showed the highest incidence in all-cause death cohorts, followed by lung metastases, and bone metastases and brain metastases had relatively low incidence.

However, in solitary organ metastasis, the incidence of brain and lung metastases were relatively high. In the cancer-specific death cohort, we found that the same rules followed, except that the incidence of solitary lung metastasis and liver metastasis were higher than the former cohort. Curiously, despite the high incidence of lung and liver metastases, the median survival time for these patients was relatively longer. Up to now, there is no standard treatment plan for distant metastasis. The main treatment is to control the primary disease. The choice of treatment plan needs to fully evaluate the patient's condition[17,18]. The multidisciplinary combined treatment mode can improve the patient's quality of life and survival time to varying degrees. In general, although the incidence of organ-specific metastasis is not high in the entire cohort, which have potential impact on the prognosis of patients, so attention should be paid to the decision of the treatment plan for patients with distant metastases at the initial diagnosis.

In previous studies, the prognostic assessment of patients with epithelial ovarian cancer usually used postoperative FIGO staging, pathological tissue typing, and lymph node metastasis as evaluation criteria[19–21]. However, with the optimization and improvement of treatment methods, more and more patients already have site-distant metastases at the time of initial diagnosis, so it is necessary to fully evaluate the prognosis of patients by combining the risk of different site metastases. Our study found that organ metastasis had a significant impact on the 5-year overall survival time of patients, especially lung, liver and bone metastases, consistent with previous reports[17,22,23].

Compared with lymph node metastasis, patients with organ metastasis have a relatively lower 5-year survival time and worse prognosis. Therefore, our study adopted the nomogram scoring standard to quantify the metastasis of different organs, and assign points based on the specific location of the metastasis at the initial diagnosis of the patient, so as to effectively evaluate the 3-year survival time and 5-year survival time. In the process of establishing the nomogram, we used regression analysis to screen out 14 variables significantly related to prognosis. The model was robust through 1000 consecutive iteration tests. At the same time, the calibration curve also showed that the predicted value and the actual consistency.

The use of the nomogram score in estimating the risk of a patient harboring organ-specific metastases to direct clinical treatment and prognosis assessment is a novel concept. Because there are many factors affecting the prognosis of patients, the risk of metastases is worth considering. Other factors such as age, race, surgery, pathological type, FIGO stage, insurance, and marital status also should be considered. In short, we have established a visual prognostic evaluation model, as well as beneficial reference value for guiding patients' treatment and prognosis.

Our research also has the following limitations. First, we use the SEER database to assess the prognostic risk of patients. To the best of our knowledge, tumor metastases that affect the prognosis of patients should also consider many factors such as retroperitoneal lymph nodes and chemotherapy. This information cannot be obtained from the database. Second, there are some patients who may be at risk of distant metastasis during treatment. We cannot accurately obtain detailed information about these patients, so the risk of recurrence cannot be assessed. Third, laboratory indicators such as CA125 are related to the prognosis of ovarian cancer patients, but the database has only partial records, so it was not included in this study. Finally, we cannot obtain a detailed treatment plan for the patient, so we cannot assess the potential influencing factors of the prognosis assessment.

Despite the above limitations, our study depended on the visual scale of organ metastasis scale for the first time to quantitatively evaluate the 5-year survival risk of patients, for which accurately predict the 3-year survival time and 5-year survival time of patients with different organ metastases. For patients with initial diagnosis of organ metastasis, the prognostic evaluation criteria should focus on organ-specific metastasis at diagnosis, which is worthy of further research and confirmation.

Declarations

Author contributions

Wu Ren and Shixuan Wang developed the original concept and study design. Bo Wang generated the initial draft of the manuscript. All authors contributed to the interpretation of the findings and approved the final manuscript version.

Conflict of interest statement

The authors declare that they have no potential conflict of interest.

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Figures

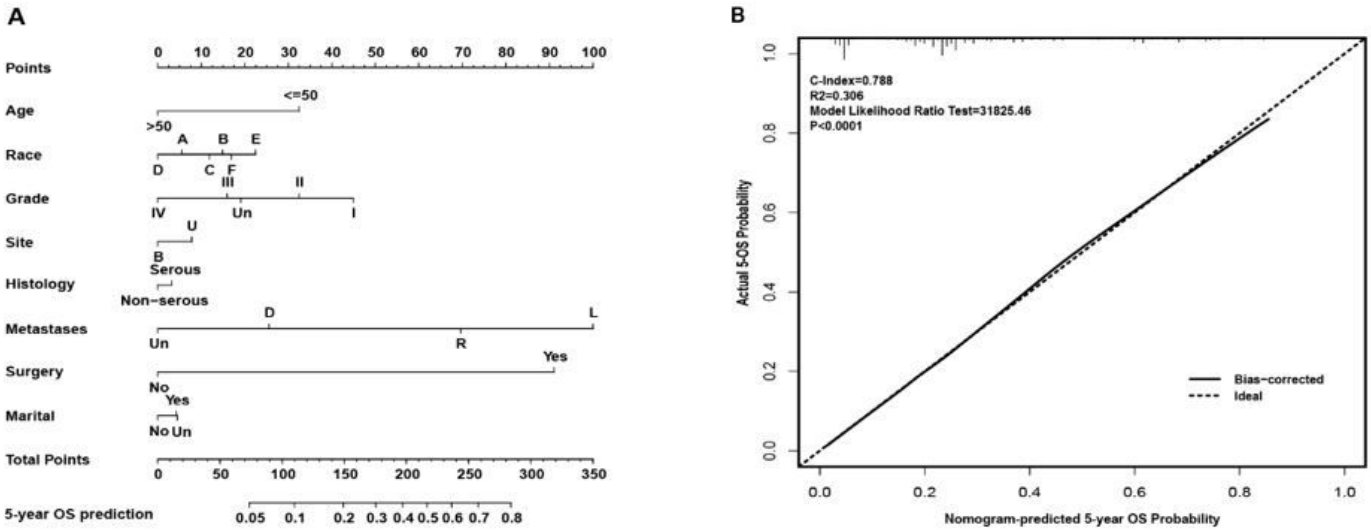

Figure 1

Nomogram score for 5-year OS probability estimation A. Nomogram to estimate the risk of 5-year OS in patients with sites-distant metastases. B. The calibration curve for predicting 5-year OS survival. Nomogram-predicted risk of overall survival is showed on the x-axis, actual overall survival is mirrored on the y-axis. Abbreviations: In the figure A, Race A, B, C, D, E, F represent Hispanic (All Races), Non-Hispanic American Indian/Alaska Native, Non-Hispanic Asian or Pacific Islander, Non-Hispanic Black, Non-Hispanic

Unknown Race, respectively. U: unilateral ovary, B: bilateral ovary. L: localized metastases, R: regional metastases, D: distant metastases. Un: unknown. OS: overall survival.

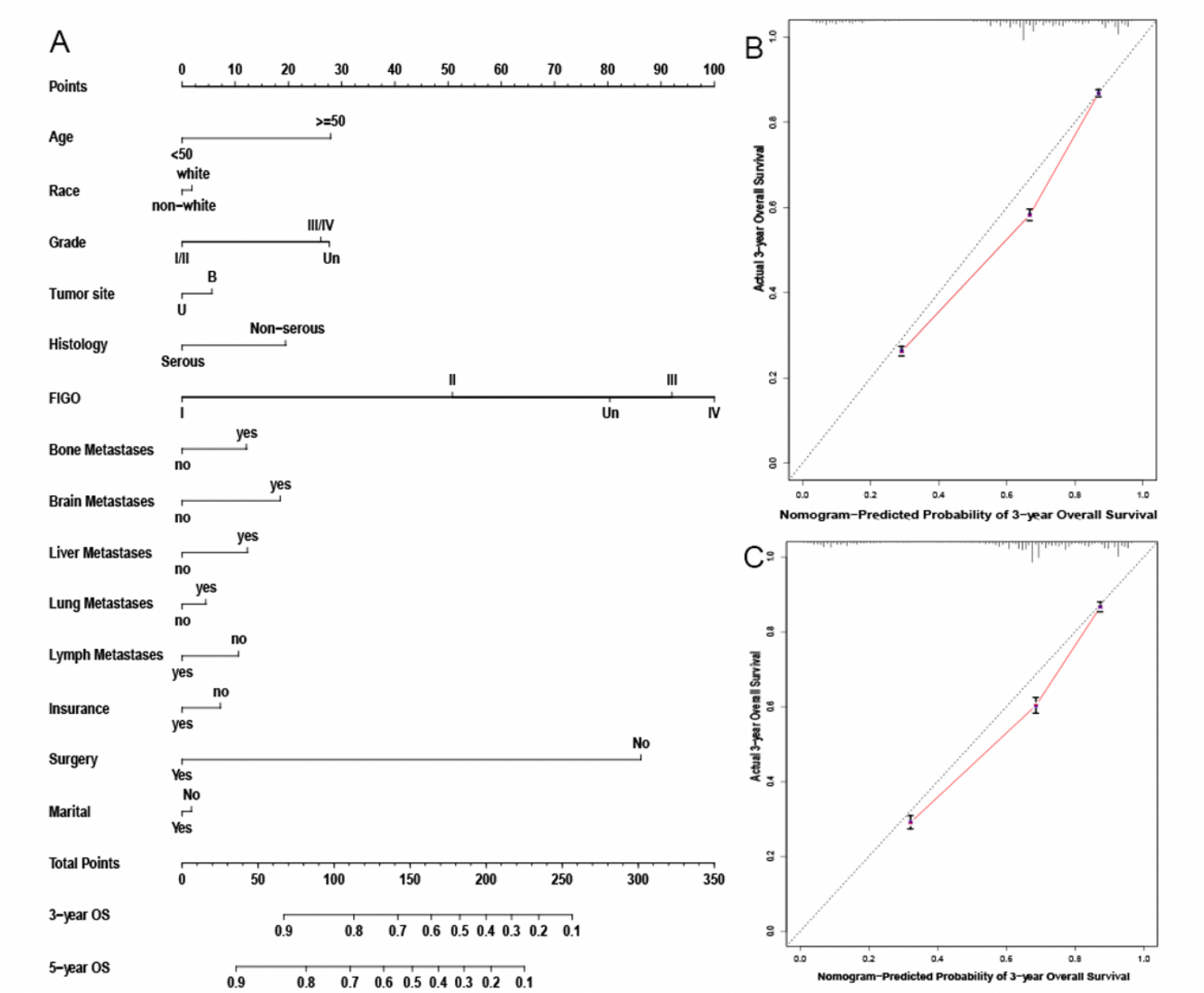

Figure 2

Nomogram estimation for 3-year/5-year overall survival in the cancer-specific mortality cohort. A. Nomogram to estimate the risk of cancer-specific overall survival in patients with sites-distant metastases. B. The calibration curve for predicting cancer-specific overall survival in the training cohort. C. The calibration curve for predicting cancer-specific overall survival in the validation cohort. Nomogram-predicted risk of overall survival is showed on the x-axis, actual overall survival is mirrored on the y-axis. Abbreviations: In the figure A, U: unilateral ovary, B: bilateral ovary. Un: unknown. OS: overall survival.

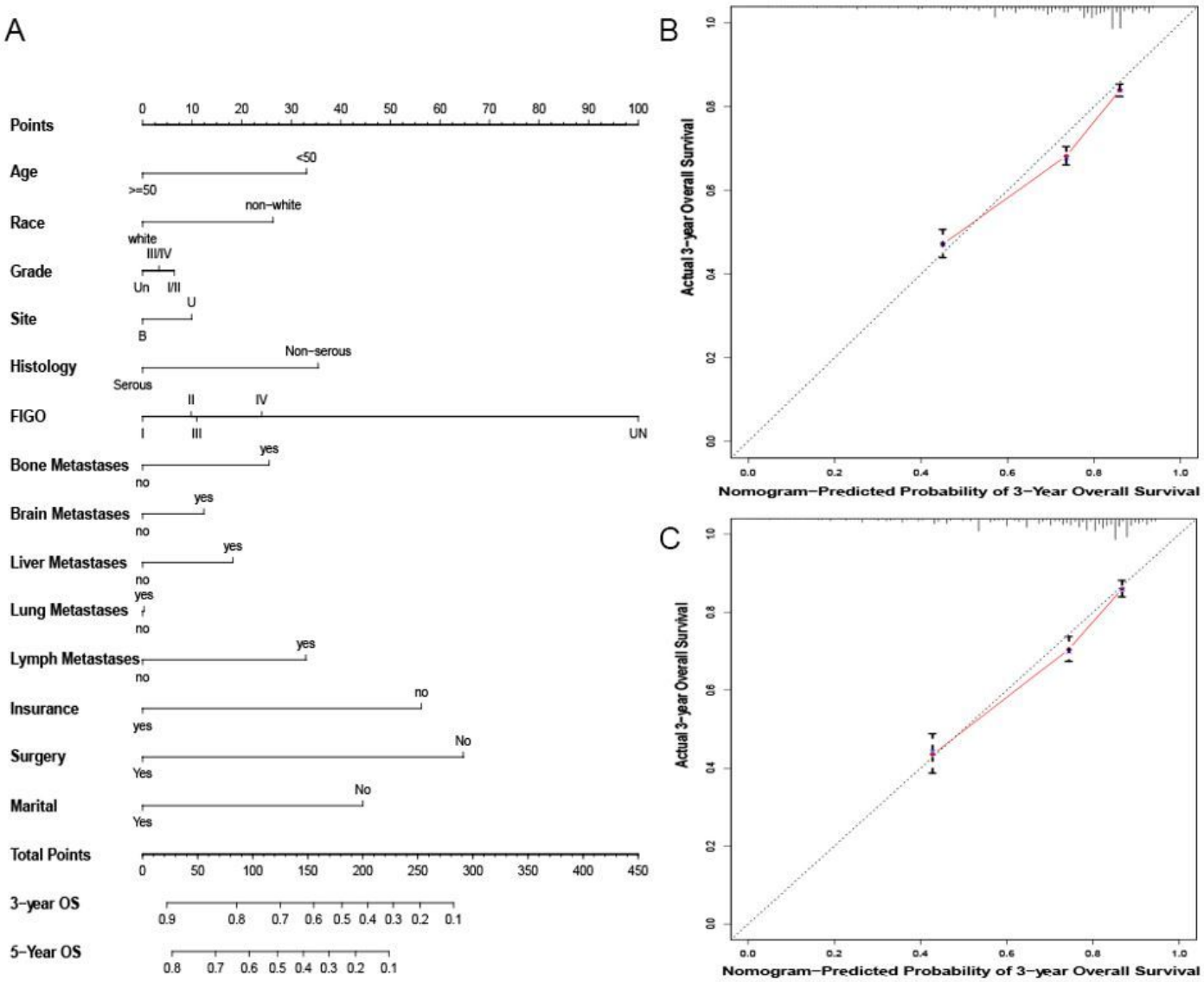

Figure 3

Nomogram estimation for 3-year/5-year overall survival in the cancer-specific mortality cohort. A. Nomogram to estimate the risk of cancer-specific overall survival in patients with sites-distant metastases. B. The calibration curve for predicting cancer-specific overall survival in the training cohort. C. The calibration curve for predicting cancer-specific overall survival in the validation cohort. Nomogram-predicted risk of overall survival is showed on the x-axis, actual overall survival is mirrored on the y-axis. Abbreviations: In the figure A, U: unilateral ovary, B: bilateral ovary. Un: unknown. OS: overall survival.

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