# A nomogram predicting overall survival for metastatic pancreatic cancer: SEER database analysis

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# Abstract

Background: This study's motive was to find out the determinants of average survival for sufferers with metastatic pancreatic cancer (PC) and formulate a nomogram to evaluate overall survival (OS).

Methods: A whole of 10165 sufferers with metastatic PC identified from 2010 to 2015 were recruited from the Surveillance, Epidemiology, and End Results (SEER) application. All sufferers were randomly assigned to a training set (n=7117) and an internal validation set (n=3048). A nomogram was built derived from univariate and multivariate Cox evaluation to evaluate an individual patient's 6-, 12- and 18-month OS. The nomogram's overall performance used to be assessed via concordance index (C-index), receiver operating characteristic (ROC) curves, and calibration plots.

Results: A whole of 10165 sufferers with metastatic PC identified from 2010 to 2015 had been included. Our analysis revealed that age, race, grade, N stage, bone metastasis, brain metastasis, liver metastasis, lung metastasis, surgery, and chemotherapy were identified as independent predictors for overall survival. The C-index of training set was 0.681 (95%CI:0.673-0.689) and validation set was 0.689 (95%CI:0.677-0.701). The calibration curves validated that the nomogram estimated 6-, 12- and 18-month OS precisely. Kaplan-Meier curves confirmed sizable variation in OS amongst the stratified low-, and high-risk groups (P<0.0001).

Conclusions: The nomogram efficiently forecasts OS in sufferers with metastatic PC. This predictive model may assist clinicians in risk stratification, prognosis predictions, and facilitating personalized treatment.


# Background

PC is a surprisingly fatal disorder with a five years survival rate of 10% in American, and it is turning into an increasing cause of cancer [1]. The potential treatment for PC patients is surgical resection. Due to the difficulty of early diagnosis, solely 20% of PC sufferers are possible candidates for therapeutic resection [2]. Many PC sufferers existed far away metastases at the time of analysis [3]. The primary treatment for metastatic pancreatic cancer is chemotherapy. Nevertheless, the patient's survival time is still no longer significantly improved, with a median survival time of 8.7 months [4]. Due to the heterogeneity of PC in the survival rate of sufferers, it is necessary to prepare a novel model to provide these sufferers with accurate survival predictions.

The prognostic assessment of tumors relies typically on the Joint Committee on Cancer (AJCC) eighth version staging system. The system solely considers the dimension and extension of cancer, the quantity of lymph node metastases, and the faraway metastasis [5]. However, Some vital prognostic elements have not been included in the system, e.g., tumor grade, which decreases its prediction accuracy for positive sufferers. AJCC is not suitable for individualized prediction of patients. Tumor differentiation is

related to the survival rate of PC patients [6]. Thence, an extra correct prediction system is necessary to establish to help clinicians predict personal survival.

The nomogram has been general as a dependable alternative tool that can assist clinicians in making effortless predictions about individuals [7, 8]. This study aimed to establish a prognostic nomogram mainly dependent on massive population data, which can more accurately evaluate the individualized survival rate of PC sufferers. The nomogram would assist clinicians in predicting the individualized survival time of metastatic pancreatic cancer.

## Methods

# Study populations and selection criteria

Data used were obtained from the SEER program, which included up to 97% of cancer incidence and encompassed 28% of the US population [9]. For this study, the SEER*Stat software (8.3.8) was used to extract sufferers diagnosed with metastatic PC (2010–2015) from the SEER database. A whole of 43528 patients has been firstly screened. The inclusion standards were as follows: (a) Site recode ICD-O-3/WHO 2008:Pancrease; (b) M1 stage; (c) survival time at least 30 days; (d) age between 18 and 85 years. The exclusion standards were as follows:(a) incomplete information on race, AJCC staging, tumor size, surgery, and tumor metastasis. Since the initial cohort used the 7th version of AJCC, We changed the T staging to the eighth version based on the facts about the dimension of the tumor. Since solely 7.6% of sufferers with metastatic PC experience surgery, the number of positive lymph nodes in most sufferers was unknown. Therefore, this study regards the 7th version N1 staging as the 8th version N1 or N2 staging.

Using the 'caret' package, enrolled sufferers have been randomly assorted into training and internal validation cohorts in the ratio of 7:3. Used the training cohort to select variables and build a nomogram in the research and the validation cohort to evaluate the nomogram. No moral consent used to be required in our study due to the fact SEER records had been analyzed anonymously.

# Data collection

Research information was obtained from the SEER database, including age at diagnosis, gender, tumor size, grade, TNM stage, therapy, follow-up information. The diagnosis age is parted into two sets (≤60 and >60 years), the treatment records include surgery, radiotherapy, and chemotherapy. The sites of tumor metastasis had bone, lung, liver, and brain. OS was described as the period from diagnosis to death or the ultimate follow-up.

# Statistical analysis

Categorical variables were expressed in frequency (percentage), and continuous variables were described in median (interquartile range). Cox multivariate analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) of the risk variables. The Kaplan-Meier approach was used to analyze OS.

We transformed continuous variables into categorical variables for further processing. We parted sufferers into low-risk and high-risk sets that relied on the median risk score.

The 'rms' package was used to build a nomogram based on the risk determinants recognized in the multiple Cox analysis. The performance of the nomogram was measured by the consistency index and evaluated by the calibration curve[10]. Furthermore, the accuracy of 6-, 12-, and 18-month survival of nomogram was assessed by the area under the ROC curve (AUC). All statistical analyses were executed by R project v.4.1.0. Two-tailed $p < 0.05$ was viewed as statistically tremendous.

## Results

# Patients traits

A whole of 10,165 patients with metastatic PC met the criteria and was enrolled in the analysis. The demographic and clinicopathological traits of sufferers are shown in Table 1. 7117 and 3048 sufferers have been parted into the training and internal validation cohorts, respectively. The median survival time of these groups was both 5 (2–12) months. Totaly, 4651 (45.8%) were female, and the most frequent tumor location was pancreatic body tail (4282,42.1%). Tumor size in 5046 (49.6%) patients exceeds 4 cm, 651 (6.4%) sufferers with ≤ 2 cm, and 4468 (44.0%) between 2 and 4 cm. 7925 (78.0%) patients had liver metastases. In the treatment information, 6820 (67.1%) received chemotherapy, 674 (6.6%) received radiotherapy, and 771 (7.6%) received surgery.

Table 1
Demographic and clinicopathological characteristics of PC patients with distant metastasis

| Variables | All patients (N = 10165) | Training cohort (n = 7117) | Validation cohort (n = 3048) |
|---|---|---|---|
| | n(%) | n(%) | n(%) |
| Age | 3220 (32.7%) | 2251 (31.6%) | 969 (31.8%) |
| ≤60 | 6945 (68.3%) | 4866 (68.4%) | 2079 (68.2%) |
| >60 | | | |
| Race | 8082 (79.5%) | 5662 (79.6%) | 2420 (79.4%) |
| White | 1363 (13.4%) | 940 (13.2%) | 423 (13.9%) |
| Black | 720 (7.1%) | 515 (7.2%) | 205 (6.7%) |
| Other | | | |
| Sex | 5514 (54.2%) | 3813 (53.6%) | 1701 (55.8%) |
| Male | 4651 (45.8%) | 3304 (46.4%) | 1347 (44.2%) |
| Female | | | |
| T stage(8th) | 576 (5.7%) | 401 (5.6%) | 175 (5.7%) |
| T1 | 3763 (37.0%) | 2652 (37.3%) | 1111 (36.5%) |
| T2 | 3655 (35.9%) | 2527 (35.5%) | 1128 (37.0%) |
| T3 | 2171 (21.4%) | 1537 (21.6%) | 634 (20.8%) |
| T4 | | | |
| N stage(8th) | 6047 (59.5%) | 4191 (58.9%) | 1856 (60.9%) |
| N0 | 4118 (40.5%) | 2926 (41.1%) | 1192 (39.1%) |
| N1/N2 | | | |
| Tumor size | 651 (6.4%) | 451 (6.3%) | 200 (6.6%) |
| ≤2cm | 4468 (44.0%) | 3146 (44.2%) | 1322 (43.4%) |
| 2cm ~ 4cm | 5046 (49.6%) | 3520 (49.5%) | 1526 (50.0%) |
| >4cm | | | |

| Variables | All patients (N = 10165) | Training cohort (n = 7117) | Validation cohort (n = 3048) |
|---|---|---|---|
| | n(%) | n(%) | n(%) |
| Tumor location | 3939 (38.8%) | 2770 (38.9%) | 1169 (38.4%) |
| Head | 4282 (42.1%) | 2973 (41.8%) | 1309 (42.9%) |
| Bodytail | 1944 (19.1%) | 1374 (19.3%) | 570 (18.7%) |
| Other | | | |
| Grade | 416 (4.1%) | 305 (4.3%) | 111 (3.7%) |
| G1 | 1168 (11.5%) | 798 (11.2%) | 370 (12.1%) |
| G2 | 1473 (14.5%) | 1010 (14.2%) | 463 (15.2%) |
| G3/G4 | 7108 (69.9%) | 5004 (70.3%) | 2104 (69.0%) |
| Unknown | | | |
| Surgery | 771 (7.6%) | 527 (7.4%) | 244 (8.0%) |
| Yes | 9394 (92.4%) | 6590 (92.6%) | 2804 (92.0%) |
| No | | | |
| Radiation | 674 (6.6%) | 472 (6.6%) | 202 (6.6%) |
| Yes | 9491 (93.4%) | 6645 (93.4%) | 2846 (93.4%) |
| No/NA | | | |
| Chemotherapy | 6820 (67.1%) | 4773 (67.1%) | 2047 (67.2%) |
| Yes | 3345 (32.9%) | 2344 (32.9%) | 1001 (32.8%) |
| No | | | |
| Bone metastasis | 642 (6.3%) | 466 (6.5%) | 176 (5.8%) |
| Yes | 9523 (93.7%) | 6651 (93.5%) | 2872 (94.2%) |
| No | | | |
| Brain metastasis | 59 (0.6%) | 37 (0.5%) | 22 (0.7%) |
| Yes | 10106 (99.4%) | 7080 (99.6%) | 3026 (99.3%) |
| No | | | |

| Variables | All patients (N = 10165) | Training cohort (n = 7117) | Validation cohort (n = 3048) |
|---|---|---|---|
| | n(%) | n(%) | n(%) |
| Liver metastasis | 7925 (78.0%) | 5561 (78.1%) | 2364 (77.6%) |
| Yes | 2240 (22.0%) | 1556 (21.9%) | 684 (22.4%) |
| No | | | |
| Lung metastasis | 1782 (17.5%) | 1249 (17.5%) | 533 (17.5%) |
| Yes | 8383 (82.5%) | 5868 (82.5%) | 2515 (82.5%) |
| No | | | |
| First malignant tumor | 8545 (84.1%) | 5990 (84.2%) | 2555 (83.8%) |
| Yes | 1620 (15.9%) | 1127 (15.8%) | 493 (16.2%) |
| No | | | |

# Univariate and multivariate analysis of results of elements on OS

We carried out Cox regression evaluation to determine major prognostic elements related to OS. In Table 2, univariate analysis confirmed that clinicopathological traits were predictive threat elements ($p < 0.05$). Clinical traits include age, race, grade, tumor size, T and N stage, bone metastasis, brain metastasis, liver metastasis, and lung metastasis. Pathological features include grade. Moreover, Chemoradiotherapy and surgery were prognostic protective factors ($p < 0.001$). Gender and first malignant tumor are not predictive factors ($p > 0.05$).

Table 2
Cohort univariate and multivariate analysis results

| Variable | Variable lever | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Age | ≤60 | Reference | 1.296 ~ 1.441 | < 0.001 | Reference | 1.224 ~ 1.363 | < 0.001 |
| | > 60 | 1.266 | | | 1.291 | | |
| Gender | Male | Reference | 0.916 ~ 1.010 | 0.121 | Reference | | |
| | Female | 0.962 | | | | | |
| Race | White | Reference | 1.007 ~ 1.164 | 0.031 | Reference | 1.013 ~ 1.170 | 0.022 |
| | Black | 1.083 | | 0.803 | 1.089 | | 0.900 |
| | Other | 0.988 | 0.893 ~ 1.087 | | 1.006 | 0.915 ~ 1.107 | |
| Tumor location | Head | Reference | 0.969 ~ 1.080 | 0.411 | Reference | | |
| | Bodytail | 1.023 | | 0.538 | | | |
| | Other | 1.022 | 0.955 ~ 1.093 | | | | |
| Grade | G1 | Reference | 2.002 ~ 2.774 | < 0.001 | Reference | 2.035 ~ 2.828 | < 0.001 |
| | G2 | 2.356 | | | 2.399 | | |
| | G3/G4 | 3.280 | 2.797 ~ 3.845 | < 0.001 | 3.313 | 2.818 ~ 3.895 | < 0.001 |
| Tumor size | ≤2cm | Reference | 1.080 ~ 1.334 | < 0.001 | Reference | 0.784 ~ 1.432 | 0.707 |
| | 2-4cm | 1.200 | | | 1.060 | | 0.340 |
| | > 4cm | 1.251 | 1.126 ~ 1.389 | < 0.001 | 1.154 | 0.860 ~ 1.549 | |
| T stage(8th) | T1 | Reference | 1.090 ~ 1.365 | < 0.001 | Reference | 0.985 ~ 1.506 | 0.454 |
| | T2 | 1.220 | | | 1.218 | | 0.508 |
| | T3 | 1.256 | 1.122 ~ 1.406 | < 0.001 | 1.192 | 0.968 ~ 1.466 | 0.369 |
| | T4 | 1.314 | 1.168 ~ 1.477 | < 0.001 | 1.237 | 1.002 ~ 1.528 | |
| N stage(8th) | N0 | Reference | 0.895 ~ 0.988 | 0.015 | Reference | 1.030 ~ 1.140 | 0.002 |
| | N1/N2 | 0.940 | | | 1.084 | | |
| Surgery | No | Reference | 0.288 ~ 0.359 | < 0.001 | Reference | 0.301 ~ 0.383 | < 0.001 |
| | Yes | 0.322 | | | 0.340 | | |

| Variable | Variable lever | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95%CI | p-value | HR | 95%CI | p-value |
| Radiation | No/NA | Reference | 0.750 ~ 0.913 | < 0.001 | Reference | 0.827 ~ 1.014 | 0.090 |
| | Yes | 0.827 | | | 0.915 | | |
| Chemotherapy | No | Reference | 0.571 ~ 0.634 | < 0.001 | Reference | 0.453 ~ 0.505 | < 0.001 |
| | Yes | 0.602 | | | 0.479 | | |
| Bone metastasis | No | Reference | 1.116 ~ 1.355 | < 0.001 | Reference | 1.050 ~ 1.280 | 0.004 |
| | Yes | 1.229 | | | 1.159 | | |
| Brain metastasis | No | Reference | 1.240 ~ 2.388 | 0.001 | Reference | 1.183 ~ 2.314 | 0.003 |
| | Yes | 1.720 | | | 1.655 | | |
| Liver metastasis | No | Reference | 1.108 ~ 1.246 | < 0.001 | Reference | 1.145 ~ 1.295 | < 0.001 |
| | Yes | 1.175 | | | 1.218 | | |
| Lung metastasis | No | Reference | 1.119 ~ 1.270 | < 0.001 | Reference | 1.060 ~ 1.209 | < 0.001 |
| | Yes | 1.192 | | | 1.132 | | |
| First malignant tumor | No | Reference | 0.907 ~ 1.036 | 0.358 | Reference | | |
| | Yes | 0.969 | | | | | |

Variables related to OS in the preliminary statistical analysis were included in the multivariate analysis. The multivariate analysis revealed that age, race, grade, N stage, surgery, chemotherapy, bone metastasis, brain metastasis, liver metastasis, and lung metastasis remained independent factors associated with OS. Elderly patients (HR = 1.291, 95%CI: 1.224–1.363), advanced grade (HR = 2.399 for moderately differentiated 95%CI: 2.035–2.828; HR = 3.313 for poorly differentiated and undifferentiated, 95%CI: 2.818–3.895), race (HR = 1.089 for black race, 95%CI: 1.013–1.170), advanced stage of N (HR = 1.084, 95%CI: 1.030–1.140), bone metastasis (HR = 1.159, 95%CI: 1.050–1.280), brain metastasis (HR = 1.655, 95%CI: 1.183–2.314), liver metastasis (HR = 1.218, 95%CI: 1.145–1.295), lung metastasis (HR = 1.132, 95%CI:1.060–1.209) suffered from greater inferior survival. On the other hand, sufferers with surgery (HR = 0.340, 95%CI: 0.301–0.383), chemotherapy (HR = 0.479, 95%CI: 0.453–0.505) experienced better survival. In Figue 1, the Kaplan-Meier survival curve confirmed that the OS differences of these factors in stratification were statistically significant ($p < 0.05$).

# Construction and validation of nomogram

All prognostic factors recognized from the training cohort were included in the building of a nomogram. The nomogram was constructed relied on the multivariate model to predict 6-, 12-, and 18-month survival rates (Fig. 2). The C-index of the nomogram was 0.681 (95%CI:0.673–0.689) in the training cohort.

Similarly, the C-index was 0.689 (95%CI:0.677–0.701) in the validation cohort. Calibration curves for 6-, 12- and 18-month survival rates showed a superior consistency between the nomogram-predicted survival and the authentic survival in two cohorts (Fig. 3). Furthermore, We also identified the accuracy of the nomogram via analyzing the AUC value (Fig. 4). For the training set, the AUC values of the nomogram for predicting 6-, 12-, and 18-month OS rates were 0.737, 0.723, and 0.727, respectively, for the validation cohort and were 0.748, 0.727, and 0.722.

According to the total hazard score obtained by the nomogram, the two groups of sufferers had been divided into low-risk and high-risk cohorts. The Kaplan-Meier survival curves based on hazard stratification were proved in Fig. 5. Compared with the sufferers in the low-risk set, the high-risk set presented lower significant OS in the training and validation sets.

# Discussion

At diagnosis, 50% of sufferers with PC accompanied by metastasis, and 30% were in the locally advanced stage [11]. Approximately 70% of PC sufferers die from metastatic disease, and 25% die without metastasis [12]. It is critical to set up an effective prognostic system to evaluate the survival rate of metastatic PC. Some previously reported nomograms were limited to sufferers with resectable PC [8, 13]. Hence, we hope to construct a predictive nomogram for metastatic PC.

In this research, 10165 patients with metastatic PC were accepted from the SEER database and analyzed to construct the OS-prediction nomogram. After researching multiple variables, including clinicopathological data and therapy, we formulated a nomogram, together with ten independent prognostic factors (age at diagnosis, race, grade, N stage, surgery, chemotherapy, bone metastasis, liver metastasis, brain metastasis, lung metastasis). The nomogram predicted OS at 6-, 12- and 18-month with excessive accuracy. Meanwhile, these prognostic factors are readily available in medical practice. In addition, the ROC curve confirmed that the nomogram exhibited a high potential in predicting OS. The nomogram is helpful for the popularization of consultation and personalized therapy for patients with metastatic PC.

71% of patients with PC were diagnosed over 60 years old, and the increase in age may contribute to the patient's mortality[14]. The outcomes of our study exhibit that pancreatic cancer patients over 60 have worse OS, which is similar to other studies[15, 16]. Our nomogram also demonstrated that the magnitude of inferior prognosis as the grade of the tumor increased. Resembled reviews indicate that tumor differentiation is a risk factor predicting survival[17]. Song's study suggested that sufferers with cancer in the head of the pancreas might have a worse survival rate [18].

Moreover, Patrick et al. proved that radiotherapy could benefit patients with unresectable pancreatic cancer[19]. However, this study observed that radiotherapy is no longer a risk factor for prognosis through multivariate analysis. Adjuvant chemotherapy can considerably enhance the survival of PC patients[20]. This study also proves that chemotherapy is an influential protective factor for metastatic PC. Primary

tumor resection raises the OS in sufferers with metastatic PC based on chemotherapy [21]. Our research also proved that the implementation of surgery could notably enhance the survival of metastatic PC. Therefore, our nomogram included these therapeutic interventions. In this study, 7925 (78.0%) patients were accompanied by liver metastases. The brain is the minor metastatic location for PC patients, and cancer metastasis to the brain means that the patient has a worse survival.

In this study, the nomogram presented accurate discrimination, with a C-index of 0.681. The calibration curves of each training and validation set showed the goodness of match for predicting survival. Nomogram's 6-, 12-, and 18-month OS expected was very close to the actual OS, respectively. In addition, the Kaplan-Meier survival curves stratified by nomogram showed a statistically significant difference in the two cohorts. Our nomogram constructed based on a large number of SEER databases could reflect a broader range of applicability. This nomogram can be used as a visualization tool to assist clinicians in individual prognostic predictions and treatment decisions for metastatic PC.

Some limitations existed in this study. First, there are no essential prognostic factors such as CA19-9 in the SEER database. Secondly, this study was unable to obtain specific information about surgery and chemotherapy. This study was based on retrospective data, and further prospective studies are needed to confirm the validity of our predictive model.

# Conclusion

We used the SEER database to evaluate the clinicopathological factors of OS in patients with metastatic PC. In addition, nomograms for forecasting 6-, 12- and 18 months have also been built. Our nomogram showed correct performance and can be regarded as a new visualization tool for individual survival.

# Abbreviations

PC: Pancreatic cancer; OS: Overall survival; SEER: Surveillance, Epidemiology, and

End Results; AJCC: American Joint Commission on Cancer; HR: Hazard ratio; CI: Confidence interval; ROC: Receiver operating characteristic; TNM: Tumor-Node-Metastasis; CA19–9: Carbohydrate antigen19–9

# Declarations


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None


### Authors' contributions

TY and HSW: Study ideas, manuscript review. KL: Data acquisition, statistical data analysis and interpretation, manuscript preparation. JSC: Data acquisition, statistical data analysis, and manuscript review. HXZ: Statistical data analysis, and explanation. JWB: Data acquisition, statistical dataanalysis.

TYC: Data acquisition. SBC: Manuscript editing. KL and JSC contributed equally. The author(s) read and approved the final manuscript.


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### Availability of data and materials

The data used and analyzed in our study can be obtained from the author upon reasonable request.

### Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

All authors' publishing consent has been obtained.

### Competing interests

The authors declare that this manuscript has no conflict of interest with them.

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# Figures

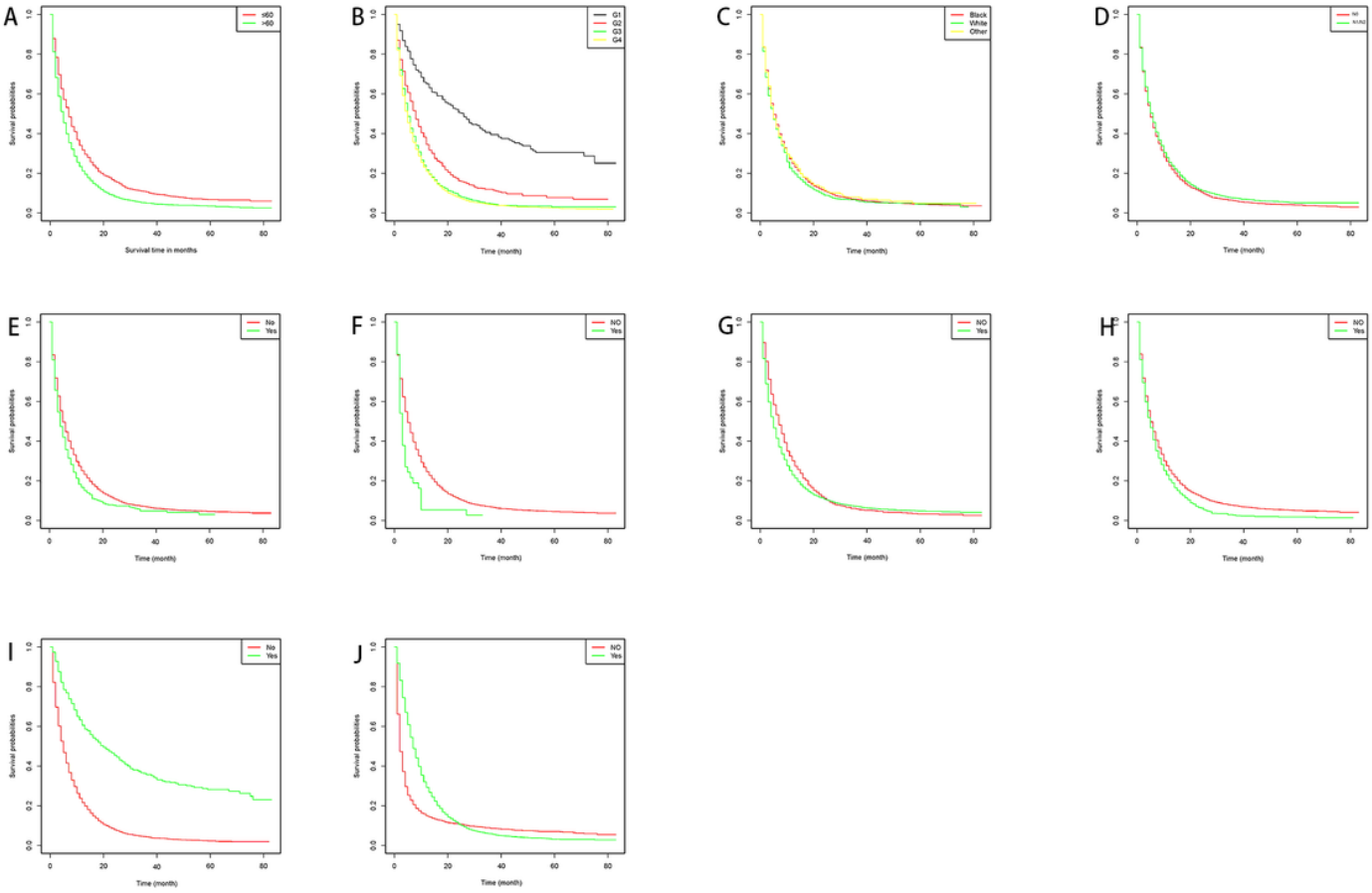



**Figure 1**

Kaplan-Meier OS curves stratified by patient characteristics: (A) Age; (B) ; (Grade) ;C (Race); D (N stage); E (Bone metastasis); F (Brain metastasis); G (Liver metastasis); H (Lung metastasis); I (Surgery); J (Chemotherapy). Abbreviations: G1 Well differentiated, G2 Moderately differentiated, G3 Poorly differentiated, G4 Undifferentiated

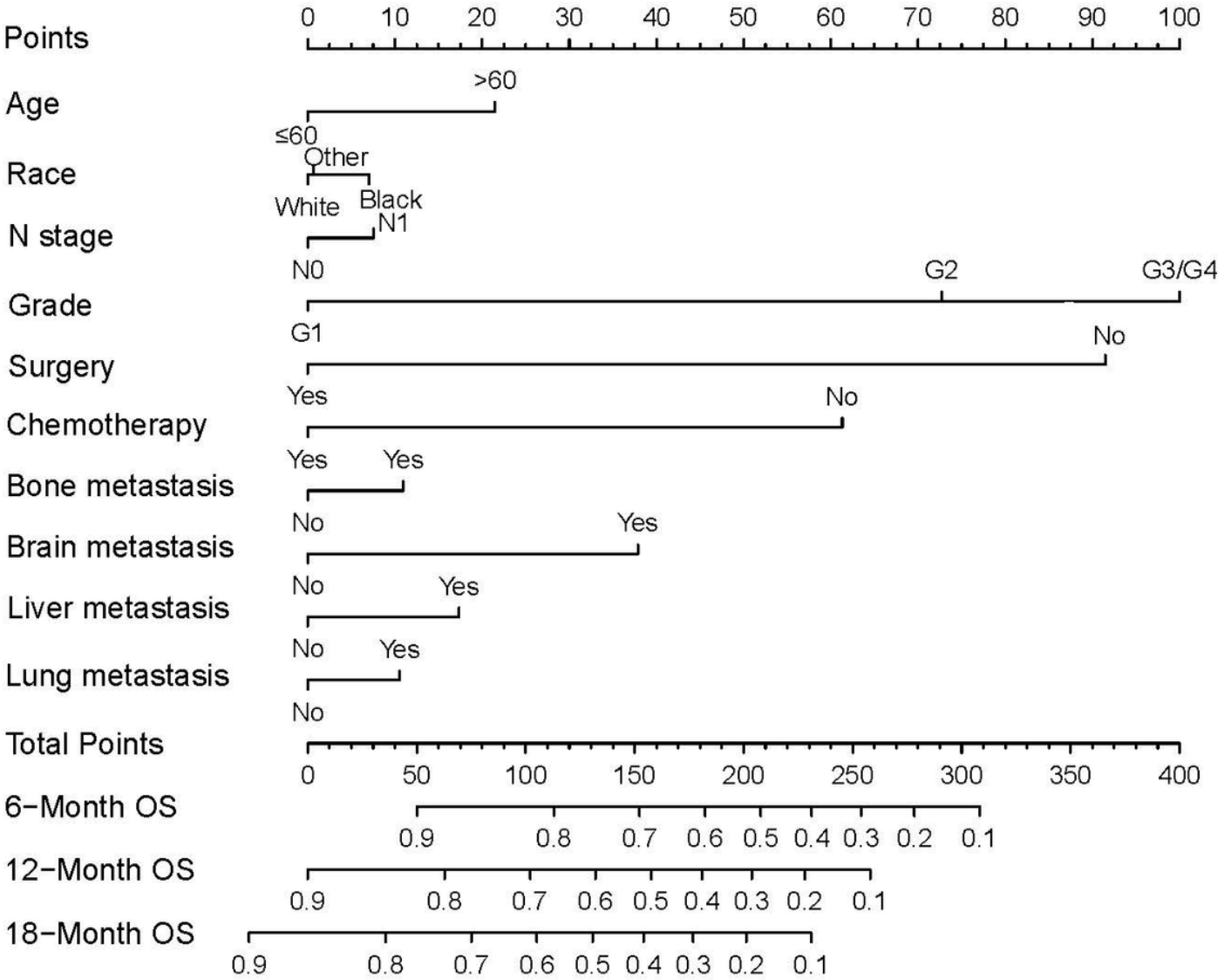
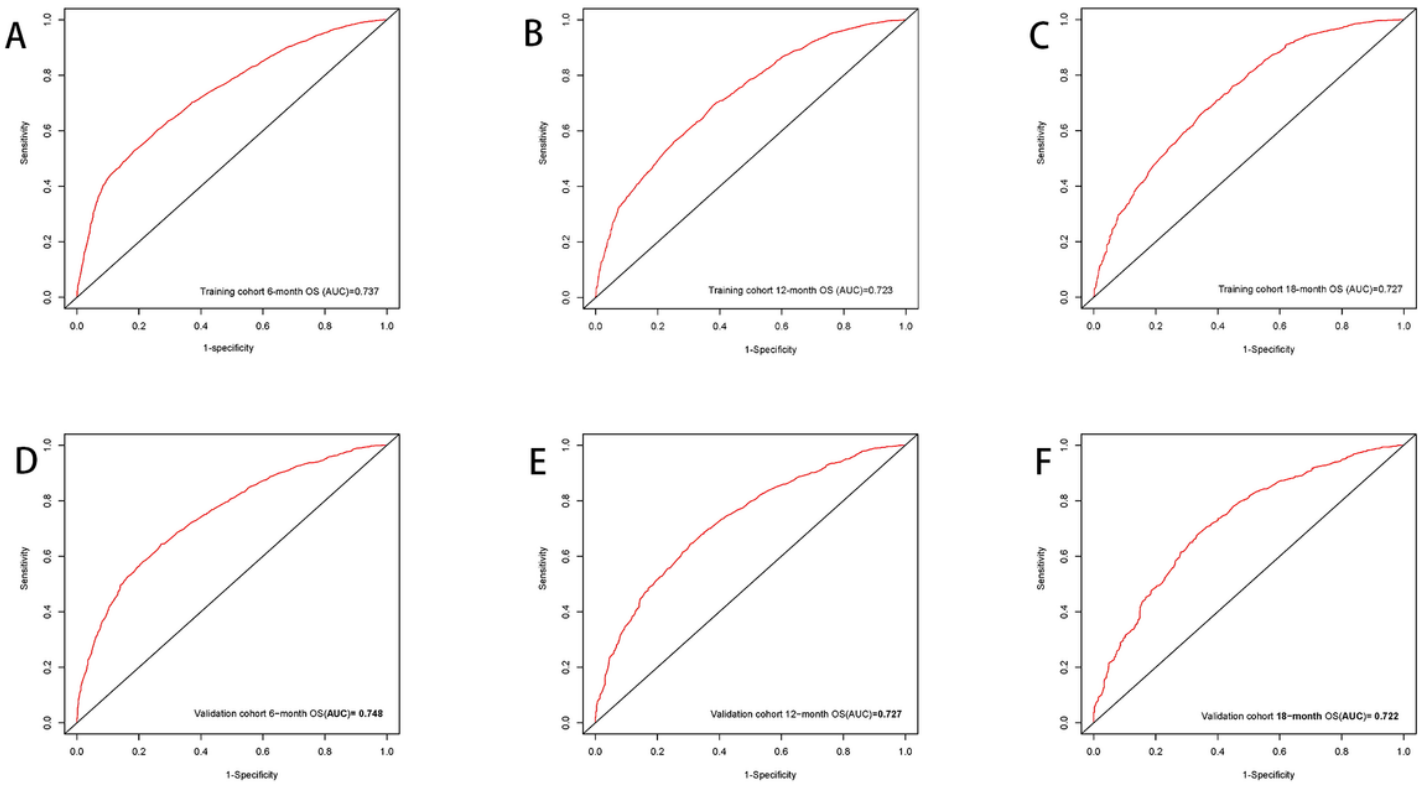


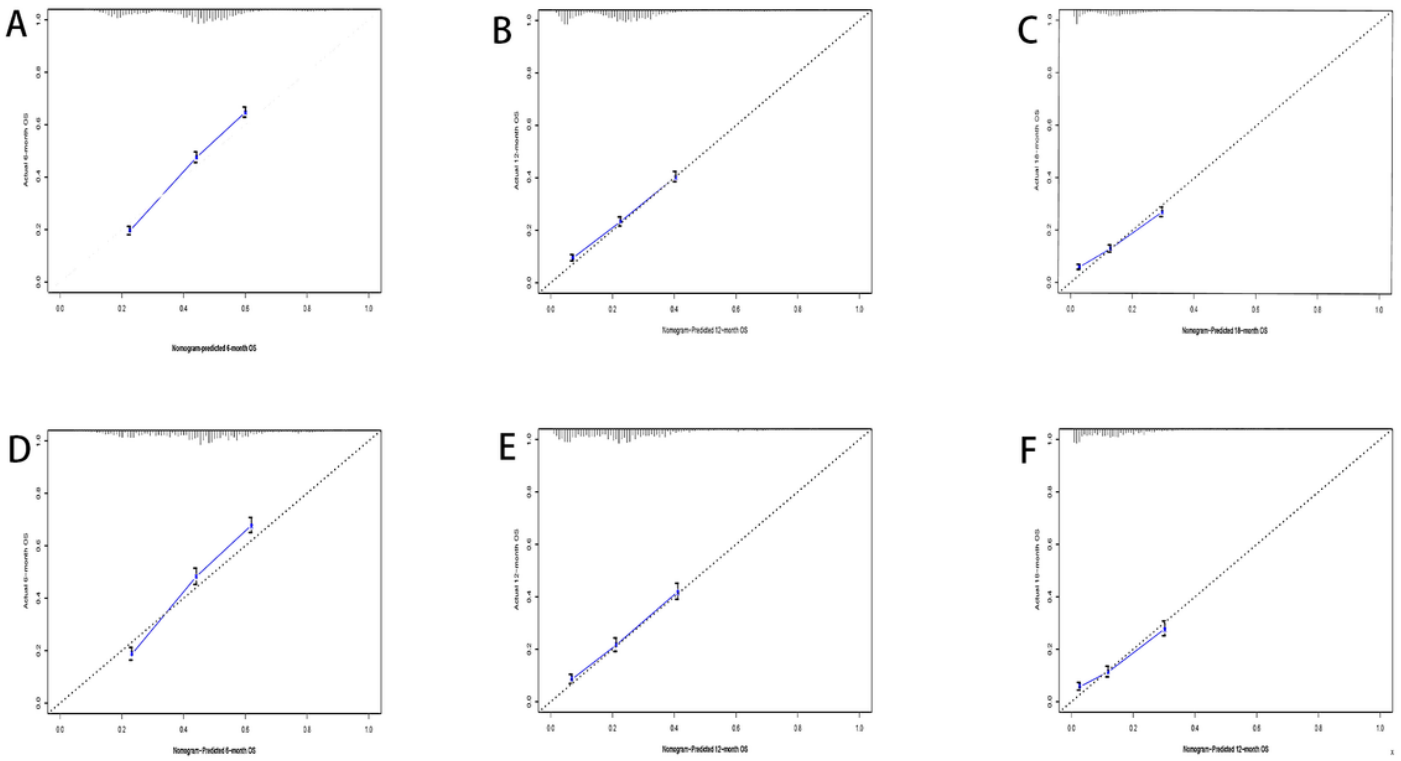

**Figure 2**

Nomogram for predicting 6-, 12-, 18-months OS of patients. The nomogram is used by adding the points identified on the scale for 10 variables to achieve the total points, and a vertical line is drawn downward to the survival axes to determine the probability of 6-,12- and 18-years OS.



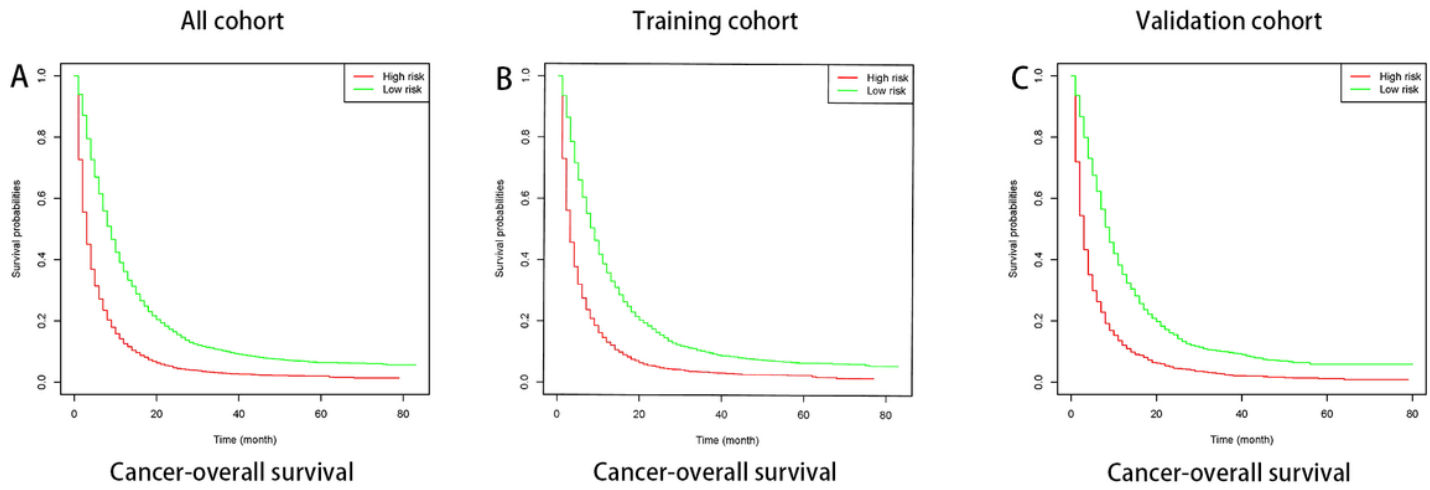

## Figure 3

Calibration plots of nomogram for 6-, 12- and 18-month OS prediction of the training set (A, B, C) and validation set (D, E, F). X-axis represents the nomogram-predicted OS probability and Y-axis represents the actually observed OS probability. The diagonal line indicates the perfect nomogram reference. Dots with bars represent nomogram-predicted probabilities together with 95% confidence interval.




## Figure 4

ROC curves of the training cohort(A, B and C) and the validation cohort(D, E and F).




## Figure 5

Kaplan-Meier curves of OS for patients in the low- and high-risk groups. A:6-months; B:12-months; C:18-months; OS Overall survival.

# Supplementary Files

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

- Nomogram.xlsx