Risk factors, prognostic predictors, and nomograms for liver metastasis in patients with pancreatic cancer: a population-based study.

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Research Article

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Abstract

Background

Liver metastasis (LM) is a significant risk predictor for poor outcomes among pancreatic cancer patients. This study aimed to investigate the risk and prognostic factors of pancreatic cancer with liver metastases (PCLM) and establish diagnostic and prognostic nomograms for these entities.

Methods

Between 2010 and 2015, data on individuals with primary diagnosed PC were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. To identify independent risk factors for PCLM, univariate and multivariate logistic regression analyses were used. Prognostic factors were identified using LASSO regression and multivariate Cox regression analyses. Furthermore, two nomograms for predicting the risk and prognosis of PCLM were developed. The performance of the nomogram models was evaluated using receiver operating characteristic (ROC) curves, calibration plots, decision curve analysis (DCA), and risk subgroup classification. To compare survival results between groupings, Kaplan-Meier curves were constructed.

Results

A total of 33459 PC patients were included in the study, with 11458 patients (34.2%) having LM at the time of diagnosis. Younger than 70 years of age, primary site in the body or tail, lymph node metastasis, neuroendocrine carcinoma, larger tumor size, and higher grade are identified as independent risk factors for LM in patients with PC. The independent factors associated with poor prognosis for PCLM patients include older than 70 years, adenocarcinoma, poor or anaplastic differentiation, lung metastases, and not receiving surgery or chemotherapy. Based on their observed analysis results of ROC, calibration, DCA, and Kaplan-Meier survival curves, two nomograms can accurately predict the occurrence and prognosis of PCLM patients.

Conclusion

We developed two nomograms for predicting the risk of LM among PC patients as well as the personalized prognosis for PCLM patients that may aid clinical decision-making.

1. Introduction

Pancreatic cancer (PC) has now become a public health threat and the five-year survival rate for PC is only 10.2%, as reported by the National cancer institute (NIH) [1]. It is considered to be the second most lethal cancer-related disease after lung cancer. In 2021, 48,220 death cases were reported in the USA,

which accounted for 7.9% of all cancer deaths [1]. PC is extremely aggressive and prone to early metastases. Approximately 50% of patients are diagnosed with metastatic disease at the time of initial diagnosis[2]. Metastasis from PC commonly occurs in the liver (90%), lymph nodes (25%), lung (25%), peritoneum (20%), and bones (10%-15%)[3]. With being the most common site of metastasis for PC, LM had a significantly poorer prognosis than lung or other distant metastases[4].

Systemic chemotherapy is the standard of care for patients with metastatic pancreatic cancer (MPC). While the FOLFIRINOX (fluorouracil, irinotecan, leucovorin, oxaliplatin) and NG (nab-paclitaxel, gemcitabine) regimens have improved these patients' survival when compared to gemcitabine alone, the median overall survival (OS) of MPC remains less than 12 months[5]. The median survival period of patients with PCLM, the subtype of MPC with the poorest prognosis, was less than six months[6]. Patients with PC will generally be treated differently depending on whether they have LM or not. Furthermore, early diagnosis of LM also raises the possibilities of aggressive treatment, which may improve survival compared to routine chemotherapeutic therapies alone. Essentially, all patients with PC are at risk of developing LM. Most patients are asymptomatic and detected by CT or MRI scans at an outpatient follow-up visit. Therefore, identifying patients at high risk for liver metastases and taking early intervention is critical to an oncologist.

The clinical characteristics of PCLM remain poorly investigated because of the lack of large-scale population-based study. The SEER database is a population-based, nationwide, publicly available cancer reporting system. We can use SEER for epidemiological studies to find risk factors for LM from PC and adjust treatment patterns according to population factors [7]. Nomogram is a predictive tool that is widely used for the research of cancer prognosis. It can simplify statistical predictive models so that they can be expressed mathematically as a single probability estimate of occurrence. Furthermore, nomograms were considered as an alternative to the traditional TNM staging systems for example pancreatic cancer, breast cancer as well as hepatocellular carcinoma [8–10]. In this study, we analyzed the incidence, risk and prognosis factors for LM from PC using the SEER database. Meanwhile, we developed two nomograms for predicting the risk and prognosis of PCLM. Therefore, the objective of our study was 1) to analyze the incidence, risk, and prognosis factors for LM from PC by using SEER database; 2) to develop nomograms for predicting the risk and prognosis for PCLM patients, respectively.

2. Materials And Methods

2.1 Patient selection

The newly diagnosed patients with PC between 2010 and 2015 were retrieved from the SEER database, which was the largest cancer database in the United States. The SEER database contained information on the survival characteristics and incidence of malignant tumors attributable to 26% of the population across 18 cancer registries in the United States. Patients with PC were identified as those pathologically diagnosed with primary malignant tumors of the pancreas according to the International Classification of Diseases for Oncology codes: C25.0–C25.3, and C25.7–C25.9. Following are the inclusion and exclusion

criteria used in our study. We included: (1) PC patients diagnosed between 2010 and 2015; (2) a pathologic diagnosis of PC; (3) the status of LM is clear; (4) age at diagnosis is more than 18 years. The criteria for exclusion were as follows: (1) diagnosed at autopsy or via death certificates; (2) non-primary tumor or more than one primary; (3) survival time less than 1 month; (4) surgical procedure for the primary site and distant site is unknown; (5) incomplete or missing information concerning follow-up or other demographic and clinical characteristics; (6) unknown status of the lung, bone, or brain metastasis. The detailed selection process for the inclusion of patients was shown in **Supplementary Figure 1**. The data for this study was collected from the SEER database using SEER*Stat v8.3.8 software (seer.cancer.gov/seerstat). The SEER Research Plus Data Agreement was signed and the license for analyzing the study data was obtained in November 2021 (username: 15159-Nov2020).

2.2 Data collection

In this study, we collected information concerning the following baseline characteristics of PC patients: age at diagnosis, race, sex, and primary site, histology, pathological grade, T stage, LN metastasis, tumor size, surgery (including surgery to the primary and distant site), radiotherapy, chemotherapy, brain metastasis, bone metastasis, and lung metastasis. Variables selected to identify the risk factors of LM in PC patients are as follows: age at diagnosis, race, sex, primary site, histology, pathological grade, T stage, nodes status, tumor size. Additionally, a survival analysis was conducted in PC patients with LM to determine prognostic factors. In addition to the variables mentioned above, three treatment variables have been considered, namely surgery, radiotherapy, and chemotherapy. Patients were classified by age at diagnosis into two groups: ≤70 years, and >70 years, based on the cut-off value of the median age at diagnosis in PC. In addition, histological codes were divided into three categories mainly based on the ICD-O-3 codes: adenocarcinoma (histologic codes 8140,8480, 8500), neuroendocrine carcinoma (histologic code 8246), and others (histologic codes 8010, 8012, 8013, 8020, 8021, 8041, 8046, 8070, 8150, 8240, 8244, 8249, 8481, 8490, 8560). The tumor size was divided into three groups according to the T classification of the American Joint Committee on Cancer 8th edition: <2 cm, 2-4 cm, and >4 cm. The primary endpoints of the study were OS, defined as the time between diagnosis and death for any reason.

2.3 Statistical analysis

All statistical analysis was performed using R software (version 4.0.1), and a P value <0.05 (two sides) was considered statistically significant. We randomly assigned all PC patients into training and validation sets in R software, and compared the distributions of variables between the two sets using the Chi-square test or Fisher's exact test.

In the diagnostic cohort, univariate logistic regression analysis was used to select risk factors for LM; those with a p< 0.05 were then further evaluated using multivariate logistic regression analysis to identify independent risk factors. Further, a novel diagnostic nomogram was developed using the "rms" package based on identified independent risk factors. ROC curves were generated for the nomogram, and the corresponding area under the curve (AUC) was calculated to evaluate discrimination. Moreover, DCA analysis and calibration curves were employed to evaluate the performance of the nomogram.

A two-step process was implemented in the prognostic cohort for the selection of the features in the nomogram. As a first step, the least absolute shrinkage and selection operator (LASSO) method was employed for the primary selection of useful predictive attributes in order to minimize overfitting. Then, the most significant attributes identified by LASSO regression from the training set were further investigated using multivariate Cox proportional hazards analysis. Furthermore, the variables with P value < 0.05 in the multivariate analysis were incorporated into a nomogram that aimed at predicting the OS of PCLM patients, and the individual risk score was derived using the formula of the nomogram. In addition, the AUCs of the time-dependent ROC curves of the nomogram were calculated for 6, 12, and 18 months in order to illustrate the accuracy of the prediction. Calibration and DCA curves were plotted for 6, 12, and 18 months to evaluate the nomogram. All PC patients with LM were divided into high- and low-risk groups according to the median risk score. A Kaplan-Meier survival curve with the log-rank test was used to examine the difference in OS between the two groups.

3. Results

3.1 Patients Baseline Clinical Characteristics

In total, 33459 PC patients diagnosed between 2010 and 2015 met the criteria for inclusion. There were 11458 patients (34.2%) who had liver metastases at initial diagnosis and 22001 patients who did not. The median survival time in the entire cohort was 9 months, and the median age at diagnosis was 67 years old. The clinical characteristics of PC patients with or without LM were presented in **Table 1**. In comparison to patients without liver metastases, those who experienced LM tended to be much younger (≤70 years: 65.9% vs 59.7%, p<0.001), more likely to be male (54.7% vs 49.1%, p<0.001), and had a higher black ethnicity (13.4% vs 11.8%, p<0.001). The presence of liver metastases is most common among patients with adenocarcinoma or neuroendocrine carcinoma of histology type with a body or tail of the tumor (41.5% vs 24.7%, p<0.001). Further, LM is more likely to occur in patients with lymph node metastasis (47.3% vs 43.5%, p<0.001), tumors larger than 4 cm in diameter (56.3% vs 39.7%, p<0.001), bone metastasis (5.6% vs 1.3%, p<0.001), and lung metastasis (15.3% vs 5.3%, p<0.001). In terms of treatment, patients with LM are less likely to undergo surgery of the primary site (3.5% vs 40.7%, p<0.001), radiation treatment (4.8% vs 24.7%, p<0.001), and chemotherapy (62.5 vs 59.7%, p<0.001).

3.2 Independent Risk Factors for PCLM

We enrolled and analyzed 33459 patients with PC for LM-related risk factors, and stratified 22306 and 11153 patients into the training and validation sets at a 2:1 ratio. **Supplementary Table 1** summarized the baseline characteristics of the patients in two sets. Overall, the baseline characteristics were balanced among the training and validation sets. The univariate logistic analysis revealed that all nine potential factors were significantly significant, as presented in **Table 2**. In addition, the multivariate logistic regression analysis determined that six associated factors were independent risk factors for LM in PC patients, including younger than 70 years of age, primary site in body or tail, lymph node metastasis, adenocarcinoma or neuroendocrine carcinoma, a larger tumor size, and a higher grade **(Table 2)**.

3.3 Diagnostic Nomogram Model Establishment and Validation

A nomogram model predicting the risk of LM in PC patients was constructed based on independent risk factors obtained through multivariable logistic regression **(Figure 1)**. According to ROC analysis, the AUC of the nomogram was 0.728, indicating excellent discriminatory ability **(Figure 2A)**. The observed results were highly consistent with the predicted results according to the calibration curve **(Figure 2B)**. Additionally, DCA demonstrated the effectiveness of the nomogram model for clinical practice **(Figure 2C)**. An internal validation cohort was created and the corresponding validation curves were then plotted to provide further validation of the model. The ROC analysis revealed an AUC value of 0.737 for the nomogram, showing high discrimination for the validation population as well **(Figure 2D)**. An excellent agreement was observed between the nomogram predictions and actual observations using the calibration curve, and the internal verification cohort was in agreement with the training cohort **(Figure 2E)**. In the validation cohort, DCA demonstrated a robust performance of the nomogram model in clinical practice **(Figure 2F)**.

3.4 Independent Prognostic Factors for PCLM

11458 eligible PC patients with LM were included in the study to explore prognostic factors. Supplementary Table 2 revealed that no significant differences existed between the validation and training sets. In total, 16 variables were included in the analysis. In LASSO regression analysis, age at diagnosis, histology, pathological grade, surgery of the primary site, surgery of the distant site, chemotherapy, and lung metastasis were identified as OS risk factors **(Figure 3)**. All of these seven factors were independently associated and statistically significant with OS in the multivariate analysis **(Table 3)**.

3.5 Establishment and Validation of Prognostic Nomogram Model

A nomogram was developed using the seven prognostic factors to predict the survival of PC patients with LM **(Figure 4)**. On the basis of the calibration curves of the nomograms for the probability of 6, 12, and 18-month OS in the training **(Figures 5A–C)** and validation **(Figures 6A–C)** sets, there was a strong agreement between the nomogram-estimated OS and the actual outcome. Additionally, the DCA curves indicated that the nomogram had acceptable performance in clinical practice **(Figures 5D-F, 6D-F)**. Additionally, the ROC analysis indicates that the AUCs of the nomogram for the training set at 6,12, and 18 months were 0.751, 0.749, and 0.775 **(Figure 7A)**, whereas the corresponding values for the validation set were 0.751, 0.751, and 0.784 **(Figure 7B)**, which suggests that the nomogram also provides reasonable accuracy in predicting the survival of PC patients with LM. A shorter OS was observed in the high-risk group than in the low-risk group, as evidenced by the KM curves **(Figure 7C, D)**.

4. Discussion

In 2021, about 48200 deaths from PC were reported in the USA, accounting for 7.9% of all cancer-related deaths [11]. PC is characterized by insidious symptoms and early metastasis. Diagnosis at an early stage

is difficult owing to the insidious nature of its onset. The disease has a very low survival rate because of its rapid progression and poor prognosis. It is considered to be one of the most lethal malignancies worldwide. Furthermore, PC does not respond very well to the available treatment options. Therefore, the treatment of PC remains a huge challenge for oncologists to overcome. In almost 90% of cases, distant metastasis of PC occurs in the liver[12]. These patients usually exhibit no symptoms. Once a patient with PC develops LM, a less favorable prognosis is often observed. Currently, LM is the leading cause of cancer-related death in PC patients. Therefore, it is clinically significant to identify risk factors and prognostic factors associated with PCLM patients and to intervene early in high-risk patients. In this study, we evaluated risk and prognostic factors for patients with PCLM using logistic regression and LASSO-Cox analyses, respectively. Furthermore, we incorporated the risk and prognostic factors identified as a basis for generating a diagnostic and prognostic nomogram, respectively. A score can be calculated based on information extracted from the nomograms related to diagnosis and prognosis, providing guidance for subsequent clinical evaluation and intervention.

As revealed by the diagnostic nomogram, patients with less than 70 years of age, tumors of the body and tail, neuroendocrine cancer, poor or anaplastic differentiation, lymph node metastases, and large tumor size were more likely to develop liver metastases. Younger patients were significantly more likely than older patients to suffer from LM in our study. According to some studies, patients at younger ages have tumors with higher and more aggressive histopathology[13, 14]. The presence of numerous genetic alterations in younger patients further supports the hypothesis that immature tumor cells are more prone to causing DNA damage. Therefore, younger patients may at greater risk for developing metastasis. As explained in many previous reports[15, 16], our results suggested that primary tumors located in the tail and body of the pancreas are more prone to metastasize to the liver than primary tumors located in the head of the pancreas. Most commonly, larger or more advanced tumors are found within the body or tail of the pancreas than within the head, perhaps due to the absence of obstructive jaundice, which may increase the risk of liver metastases in these patients. Even though pancreatic neuroendocrine tumors usually progress slowly with little inertia, some patients still develop metastases during the course of the disease, particularly liver metastases. Our findings indicated that pancreatic neuroendocrine tumors have a higher risk of LM than pancreatic adenocarcinoma. In a recent study, the DNA of neutrophil extracellular traps (NETs) was found to play a crucial role in promoting LM in pancreatic neuroendocrine, a mechanism that differs from previous studies concerning cytokines and chemokines, integrin complexes, metabolic programming, and proliferation signaling [27, 28]. Poorly differentiated tumor cells are typically more aggressive[17], which may explain partially our findings that poor differentiation was significantly associated with a higher risk of LM. There has been scientific evidence showing that LN metastasis is a common sign before distant metastasis[18, 19], suggesting that patients with PC and LN metastasis should pay greater attention to distant metastases. On the other hand, tumor size, which has proven to be a strong and consistent indicator of both distant metastasis and poorer prognosis[20, 21], was found to be directly correlate with the invasion of cancer cells into the liver. Larger tumors tend to be more aggressive and susceptible to involving adjacent organs and blood vessels, which may indicate a greater tumor burden in PC patients. Therefore, clinicians must maintain a keen awareness of these risk factors

when treating patients with PC. MRI/PET-CT scans should be recommended for these patients with potential risks at an early stage.

In addition, survival analysis was performed. Our research suggested that patients older than 70 years, with adenocarcinoma, poor or anaplastic differentiation, accompanied lung metastases, and no surgery or chemotherapy might indicate a poor prognosis for PCLM patients. The prognosis of older PC patients has been generally reported to be poorer than that of younger patients [22, 23]. Our study indicated that patients diagnosed with PCLM who are older are also more likely to have a shorter survival time. Additionally, the results of several previous studies demonstrated that older PCLM patients had a worse prognosis[24, 25]. Despite our inability to gather additional relevant information derived from the database, we hypothesized that it was likely related to impaired performance and reduced immunity in elderly individuals. Adenocarcinoma constitutes the most common histological subtype of PC. In our study, adenocarcinomas comprised 76.3% of the patients with PCLM, which represents the most prevalent histological subtype. The adenocarcinoma subtype also proved to be a significant independent predictor of poorer OS in patients with PCLM in our study. Among PC patients with adenocarcinoma, the overall survival rate is the lowest and the prognosis is poor [26, 27], which is similar to our findings. It has been suggested that non-adenocarcinoma tumors are distinct from adenocarcinoma neoplasms of the pancreas as far as their morphology and biology is concerned[28]. Further research is needed to clarify the specific mechanisms involved. Poor or anaplastic differentiation was associated with a poorer prognosis, since it has been observed to be strongly associated with a worse prognosis in multiple cancers[29, 30], reflecting the nature of the tumor. We found the accompanied lung metastasis might indicate poor prognosis to PC patients with LM. Lung metastasis worsens the prognosis of patients with PCLM, which is consistent with the results of previous studies on PC [31, 32].

Currently, there is no standard treatment option for patients with PCLM. Systemic treatment with chemotherapy is the main treatment. Recent studies have reported several palliative chemotherapy options for patients with MPC, including fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine and nab-paclitaxel, which improved median OS to 11 and 8.5 months, respectively, compared to 6.7-7 months for gemcitabine alone [5]. Patients with PCLM continue to have a poor prognosis due to secondary chemoresistance [33], highlighting the urgent need for new treatment strategies. Treatment options for PCLM may continue to involve a combination of systemic chemotherapy, novel targeted therapies and immune checkpoint inhibitors in the near future [34].

In international guidelines, surgery for the treatment of patients with PCLM is not recommended. However, with an improvement in the surgical safety of resection and the unrelenting pursuit of better survival rates in PCLM patients, surgery for resection of the primary tumor in selected cases has become increasingly common, and retrospective studies indicate that this may improve survival. In our study, we demonstrate that resection of the primary tumor or metastatic site can prolong survival in PCLM patients. Such treatment options should be considered for carefully selected patients. In previous studies, surgical resection of the tumor or metastatic lesions was reported to improve quality of life and prolong survival. In a propensity-matched analysis of the SEER database, cancer-directed surgery reliably increased

median OS from 5 to 10 months for patients with pancreatic ductal adenocarcinoma with LM [35]. Furthermore, several types of pancreatic neuroendocrine tumors (PNETs) are treated with cancer-directed surgery regardless of LM[36]. Up to 30% of patients with PNET develop LM at the time of diagnosis [37], and it is recommended to perform Type I/II LM resection on G1/G2 PNETs [38]. Four decades ago, surgery was primarily used as a palliative treatment for colorectal cancer liver metastasis (CRLM) [38]. At present, resection surgery is considered the standard of care for CRLM. A quarter of CRC patients present with LM during the course of their disease, and surgical resection is considered the preferred curative option[39]. Patients with PC commonly develop subclinical metastasis, which must be addressed macroscopically as well as microscopically. Therefore, surgical therapy involving the primary site or a distant site should be recommended when PCLM patients are carefully selected by a multidisciplinary team at a high-volume PC center. Hence, we concluded that surgical therapy cannot impair chemotherapy and should be part of a more comprehensive treatment program. Multi-center randomized controlled studies are required to confirm updated standards of care in this field. We provide a set of targets and hypotheses to guide this research agenda.

Further developments include local ablative therapies such as microwave ablation (MWA) and radiofrequency ablation (RFA), transarterial chemoembolization (TACE), stereotactic body radiotherapy (SBRT) and selective internal radiation therapy (SIRT), which have been demonstrated for the treatment of LM in a variety of tumor types[39]. Nevertheless, these therapies have not been adequately evaluated in the setting of MPC and therefore should be considered as alternative treatments to surgery and systemic therapy. In conclusion, advances in systemic and local therapeutic approaches, coupled with an integrated multidisciplinary approach, hold promise for improving the quality of life and health of patients suffering from this dismal disease.

There are several limitations to the present study that should be noted. Firstly, as part of this study, a retrospective analysis of the SEER database is conducted with potential selection bias and low granularity of the data. Several potentially prognostic variables, such as chemotherapy regimens, metastasis extent, and tumor markers such as CA19-9, as well as the patient's physical condition, preoperative conditions, and complications postoperatively, were not provided, which limits the estimation of their role in the nomogram. Second, our study was limited to patients who had only LM at diagnosis, and those with LM occurring at a later stage were not included. Thirdly, due to the heterogeneity of data, we evaluated the nomogram only through our internal validation method; no publicly available data was enrolled for external validation in order to avoid selective bias. Lastly, despite the fact that the nomogram has achieved acceptable predictive performance and a relatively complete evaluation in order to accurately estimate the risk and prognosis of PCLM, further investigation should be conducted.

Conclusions

In this study, we used univariate and multivariate logistic regression analyses to identify the risk factors for PCLM, followed by LASSO-Cox regression analyses in order to identify prognostic factors, from which

two nomograms were constructed. These nomograms facilitate clinicians' ability to identify high-risk patients and provide them with various treatment options based on those risks.

Conclusions

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Declarations

Authors' contributions

Jing Wang, and Biyang Cao designed the research. Biyang Cao, Yixin Kang Chenchen Wu performed the research and analyzed results. Biyang Cao wrote the paper. Jing Wang, Chenchen Wu and Letian Zhang edited the manuscript and provided critical comments. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics statement

Our research is based on the National Cancer Institute's SEER program. For this study, we signed the SEER research data agreement to access SEER information, using reference number 15159-Nov2020. Data were obtained following the approved guidelines. The Office for Human Research Protection considered this research to be on nonhuman subjects because the subjects were patients who had been researched by the United States Department of Health and Human Services and were publicly accessible and de-identified. Thus, no institutional review board approval was required.

Conflict of Interest: None

Consent for publication: Written informed consent for publication was obtained from all participants.

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Abbreviations

Pancreatic cancer liver metastasis（PCLM）; pancreatic cancer (PC); liver metastasis (LM); overall survival (OS); Surveillance, Epidemiology, and End Results (SEER); 95% confidence interval [CI]; decision curve analyses (DCAs); receiver operating characteristic (ROC); least absolute shrinkage and selection operator (LASSO); colorectal cancer liver metastasis (CRLM); pancreatic neuroendocrine tumors (PNETs); transarterial chemoembolization (TACE); microwave ablation (MWA); radiofrequency ablation (RFA)； stereotactic body radiotherapy (SBRT).

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Tables

Table 1. Clinical characteristics for patients diagnosed with pancreatic cancer with and without liver metastasis in SEER database (2010-2015).

Variable	levels	Total (N=33459)	With LM (N=11458)	Without LM (N=22001)	P-value
Age at diagnosis (years)	≤70	20680 (61.8%)	7552 (65.9%)	13128 (59.7%)	<.001
	>70	12779 (38.2%)	3906 (34.1%)	8873 (40.3%)	
Sex	Female	16390 (49.0%)	5195 (45.3%)	11195 (50.9%)	<.001
	Male	17069 (51.0%)	6263 (54.7%)	10806 (49.1%)	
Race	White	26459 (79.1%)	9048 (79%)	17411 (79.1%)	<.001
	Black	4139 (12.4%)	1533 (13.4%)	2606 (11.8%)	
	Other	2861 (8.6%)	877 (7.7%)	1984 (9%)	
Primary site	Head	17950 (53.6%)	4441 (38.8%)	13509 (61.4%)	<.001
	Body/tail	10200 (30.5%)	4762 (41.5%)	5438 (24.7%)	
	Other	5309 (15.9%)	2255 (19.7%)	3054 (13.9%)	
Histology	Adenocarcinoma	22948 (68.6%)	8746 (76.3%)	14202 (64.6%)	<.001
	Neuroendocrine carcinoma	1585 (4.7%)	615 (5.4%)	970 (4.4%)	
	Other	8926 (26.7%)	2097 (18.3%)	6829 (31%)	
Pathological grade	Well/Moderate	8293 (24.8%)	1185 (10.3%)	7108 (32.3%)	<.001
	Poor/Anaplastic	5105 (15.3%)	1367 (11.9%)	3738 (17%)	
	Unspecific	20061 (60.0%)	8906 (77.7%)	11155 (50.7%)	
T stage	T1	2063 (6.2%)	362 (3.2%)	1701 (7.7%)	<.001
	T2	8383 (25.1%)	3934 (34.3%)	4449 (20.2%)	

Variable	levels	Total (N=33459)	With LM (N=11458)	Without LM (N=22001)	P-value
	T3	14526 (43.4%)	3541 (30.9%)	10985 (49.9%)	
	T4	6635 (19.8%)	2116 (18.5%)	4519 (20.5%)	
	TX	1852 (5.5%)	1505 (13.1%)	347 (1.6%)	
LN metastasis	No	18469 (55.2%)	6044 (52.7%)	12425 (56.5%)	<.001
	Yes	14990 (44.8%)	5414 (47.3%)	9576(43.5%)	
Tumor size (cm)	<2	3617 (10.8%)	664 (5.8%)	2953 (13.4%)	<.001
	2-4	14644 (43.8%)	4338 (37.9%)	10306 (46.8%)	
	>4	15198 (45.4%)	6456 (56.3%)	8742 (39.7%)	
Surg Prim	No	24100 (72.0%)	11054 (96.5%)	13046 (59.3%)	<.001
	Yes	9359 (28.0%)	404 (3.5%)	8955 (40.7%)	
Surg Dis	No	32408 (96.9%)	11102 (96.9%)	21306 (96.8%)	.822
	Yes	1051 (3.1%)	356 (3.1%)	695 (3.2%)	
Radiation	No	27483 (82.1%)	10909 (95.2%)	16574 (75.3%)	<.001
	Yes	5976 (17.9%)	549 (4.8%)	5427 (24.7%)	
Chemotherapy	No	13156 (39.3%)	4298 (37.5%)	8858 (40.3%)	<.001
	Yes	20303 (60.7%)	7160 (62.5%)	13143 (59.7%)	
Bone metastasis	No	32524 (97.2%)	10812 (94.4%)	21712 (98.7%)	<.001
	Yes	935 (2.8%)	646 (5.6%)	289 (1.3%)	

Variable	levels	Total (N=33459)	With LM (N=11458)	Without LM (N=22001)	P-value
Brain metastasis	No	33365 (99.7%)	11405 (99.5%)	21960 (99.8%)	<.001
	Yes	94 (0.3%)	53 (0.5%)	41 (0.2%)	
Lung metastasis	No	30546 (91.3%)	9701 (84.7%)	20845 (94.7%)	<.001
	Yes	2913 (8.7%)	1757 (15.3%)	1156 (5.3%)	
Vital status	Alive	6025 (18.0%)	804 (7%)	5221 (23.7%)	<.001
	Dead	27434 (82.0%)	10654 (93%)	16780 (76.3%)	

LN, lymph node; LM, liver metastasis; Surg Prim, surgical treatments of the primary site; Surg Dis, *surgical treatments of the distant site*

Table 2. Univariate and multivariate logistic analyses of liver metastasis in pancreatic cancer patients.

Variable	levels	Without LM (N=14608)	With LM (N=7698)	Univariate analysis	Multivariate analysis
Age at diagnosis (years)	≤70	8783 (60.1%)	5032 (65.4%)		
	>70	5825 (39.9%)	2666 (34.6%)	0.80 (0.75-0.85, p<.001)	0.72 (0.68-0.77, p<.001)
Sex	Female	7393 (50.6%)	3485 (45.3%)		
	Male	7215 (49.4%)	4213 (54.7%)	1.24 (1.17-1.31, p<.001)	1.16 (0.89-1.23, p=.056)
Race	White	11590 (79.3%)	6048 (78.6%)		
	Black	1730 (11.8%)	1047 (13.6%)	1.16 (1.07-1.26, p<.001)	1.07 (0.97-1.17, p=.186)
	Other	1288 (8.8%)	603 (7.8%)	0.90 (0.81-0.99, p=.036)	0.93 (0.83-1.04, p=.228)
Primary site	Head	8939 (61.2%)	3003 (39%)		
	Body/tail	3604 (24.7%)	3212 (41.7%)	2.65 (2.49-2.83, p<.001)	2.30 (2.14-2.47, p<.001)
	Other	2065 (14.1%)	1483 (19.3%)	2.14 (1.98-2.31, p<.001)	1.76 (1.61-1.92, p<.001)
Histology	Adenocarcinoma	9394 (64.3%)	5867 (76.2%)		
	Neuroendocrine carcinoma	640 (4.4%)	411 (5.3%)	1.03 (0.90-1.17, p=.670)	1.28 (1.10-1.49, p=.001)
	Other	4574 (31.3%)	1420 (18.4%)	0.50 (0.46-0.53, p<.001)	0.61 (0.56-0.66, p<.001)
Pathological grade	Well/Moderate	4727 (32.4%)	799 (10.4%)		
	Poor/Anaplastic	2476 (16.9%)	919 (11.9%)	2.20 (1.97-2.44, p<.001)	2.26 (2.01-2.53, p<.001)
	Unspecific	7405 (50.7%)	5980 (77.7%)	4.78 (4.40-5.19, p<.001)	4.23 (3.86-4.64, p<.001)
T stage	T1	1131 (7.7%)	245 (3.2%)		

Variable	levels	Without LM (N=14608)	With LM (N=7698)	Univariate analysis	Multivariate analysis
	T2	2901 (19.9%)	2653 (34.5%)	4.22 (3.65-4.90, p<.001)	1.53 (0.89-1.86, p=.080)
	T3	7325 (50.1%)	2402 (31.2%)	1.51 (1.31-1.75, p<.001)	0.81 (0.64-1.02, p=.054)
	T4	3019 (20.7%)	1411 (18.3%)	2.16 (1.86-2.52, p<.001)	0.72 (0.56-1.01, p=.051)
	TX	232 (1.6%)	987 (12.8%)	9.4 (6.4-9.7, p<.001)	7.18 (5.52-9.35, p<.001)
LN metastasis	No	8213 (56.2%)	4046 (52.6%)		
	Yes	6395 (43.8%)	3652 (47.4%)	1.16 (1.10-1.23, p<.001)	1.38 (1.30-1.47, p<.001)
Tumor size (cm)	<2	1966 (13.5%)	460 (6%)		
	2-4	6800 (46.5%)	2939 (38.2%)	1.85 (1.66-2.06, p<.001)	1.29 (1.08-1.55, p=.006)
	>4	5842 (40%)	4299 (55.8%)	3.15 (2.82-3.51, p<.001)	2.05 (1.71-2.46, p<.001)

LN, lymph node; LM, liver metastasis

Table 3. Multivariate Cox analysis of the training cohort based on the results of Lasso regression.

Variable	Levels	All	Multivariate analysis
Age at diagnosis (years)	≤70	4812 (62.5%)	
	>70	2886 (37.5%)	1.29 (1.23-1.36, p<.001)
Histology	Adenocarcinoma	5867 (76.2%)	
	Neuroendocrine carcinoma	411 (5.3%)	0.31 (0.28-0.35, p<.001)
	Other	1420 (18.4%)	0.79 (0.75-0.85, p<.001)
Pathological grade	Well/Moderate	799 (10.4%)	
	Poor/Anaplastic	919 (11.9%)	1.72 (1.55-1.91, p<.001)
	Unspecific	5980 (77.7%)	1.48 (1.36-1.61, p<.001)
Surg Prim	No	7429 (96.5%)	
	Yes	269 (3.5%)	0.37 (0.31-0.43, p<.001)
Surg Dis	No	7450 (96.8%)	
	Yes	248 (3.2%)	0.80 (0.69-0.93, p=.004)
Chemotherapy	No	2934 (38.1%)	
	Yes	4764 (61.9%)	0.43 (0.41-0.45, p<.001)
Lung metastasis	No	6510 (84.6%)	
	Yes	1188 (15.4%)	1.35 (1.27-1.44, p<.001)

Surg Prim, surgical treatments of the primary site; Surg Dis, *surgical treatments of the distant site*

Figures

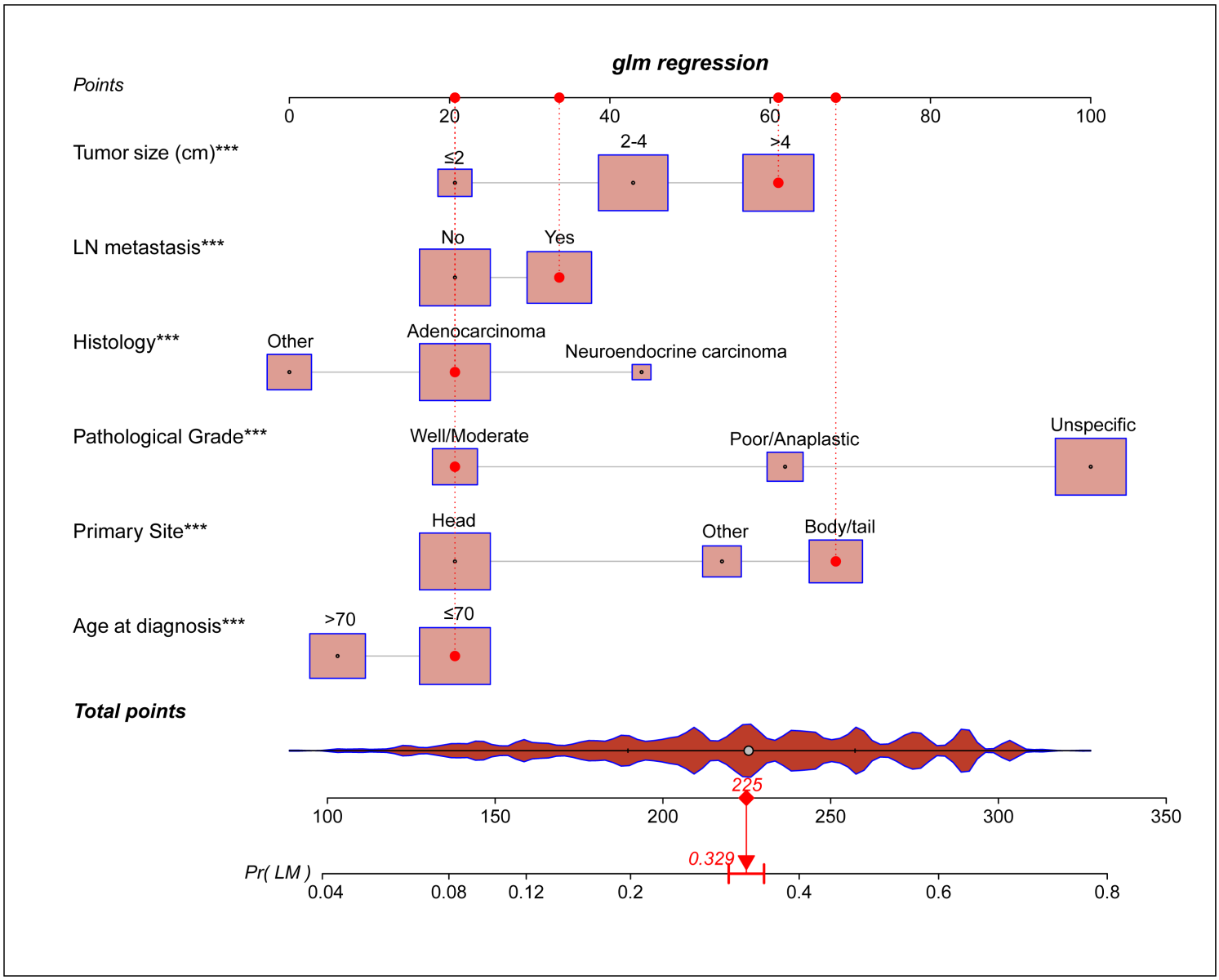

Figure 1

Nomogram for predicting LM from PC patients

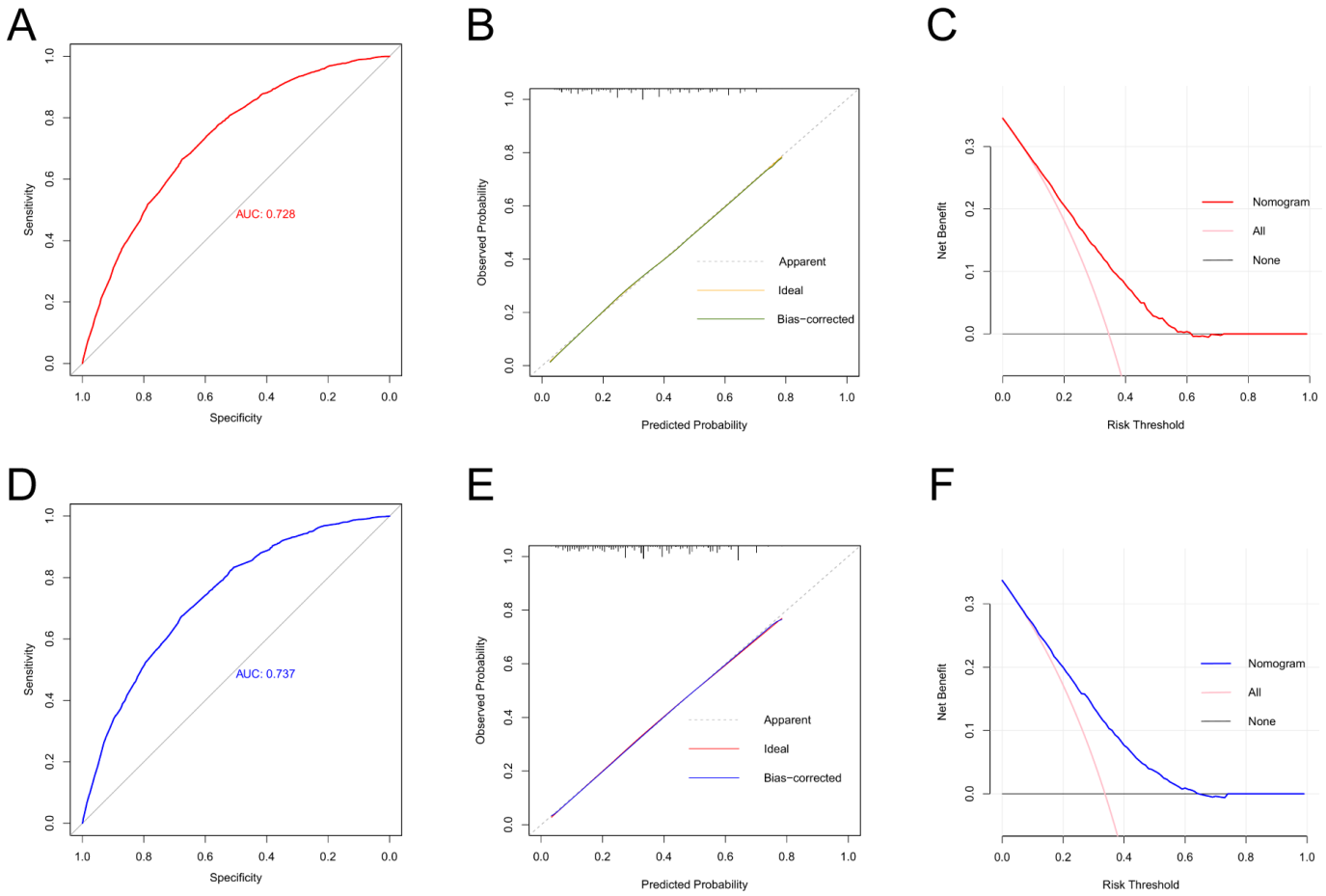

Figure 2

Validation of the diagnostic nomogram in the training and valiation sets The receiver operating characteristic curve (A), calibration curve (B), and decision curve analysis (C) of the training set; the receiver operating characteristic curve (D), calibration curve (E), and decision curve analysis (F) of the valiation set.

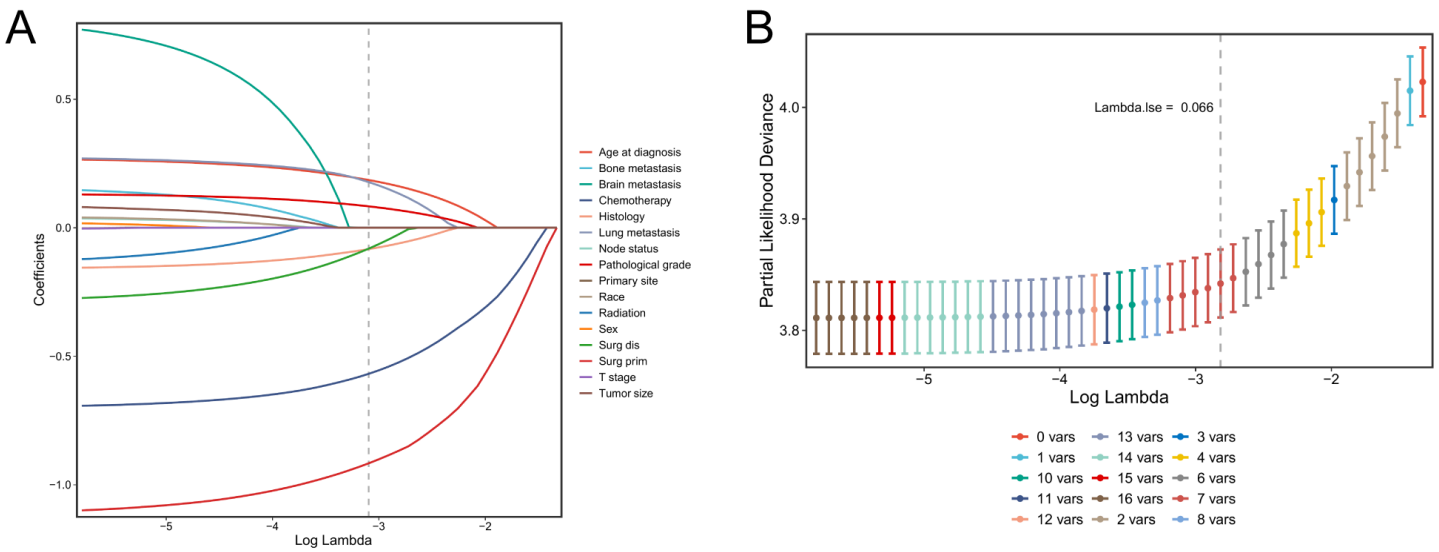

Figure 3

The LASSO regression used to select prognostic factors for OS (A) LASSO coefficient profiles of 16 variables for OS; (B) LASSO Cox analysis identified 7 variables for OS. The LASSO regression analysis run in R runs 10 times K cross-validation for centralization and normalization of included variables and then selects the most appropriate lambda value depending on the type measure of -2log-likelihood and binomial family. “Lambda.lse” gives a model with good performance but the least number of independent variables.

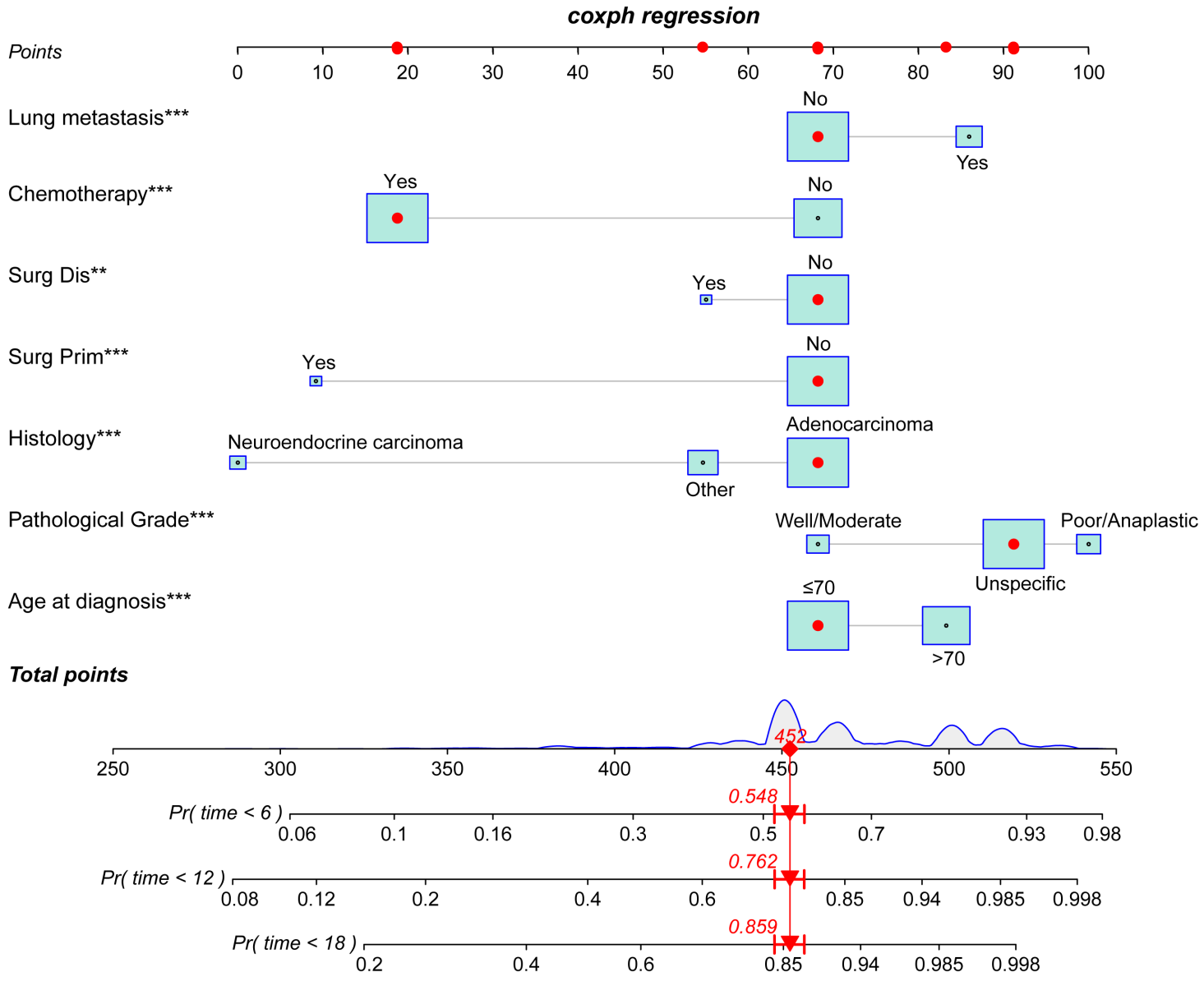

Figure 4

A prognostic nomogram for PC patients with LM

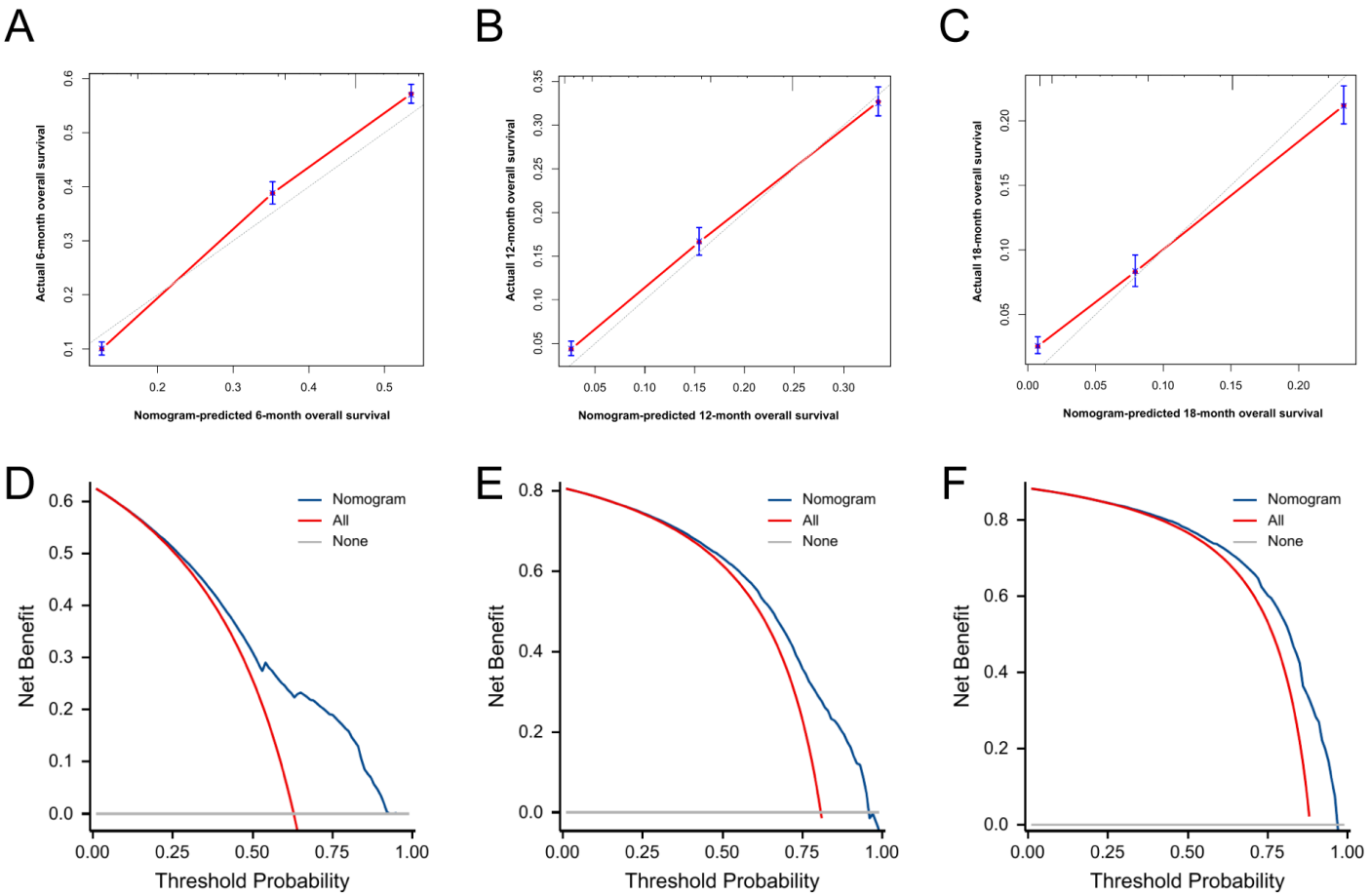

Figure 5

The calibration curves of the nomogram for the 6 (A), 12 (B), and 18 months (C) in the training set. The decision curve analysis of the nomogram for the 6 (D), 12 (E), and 18 months (F) in the training set.

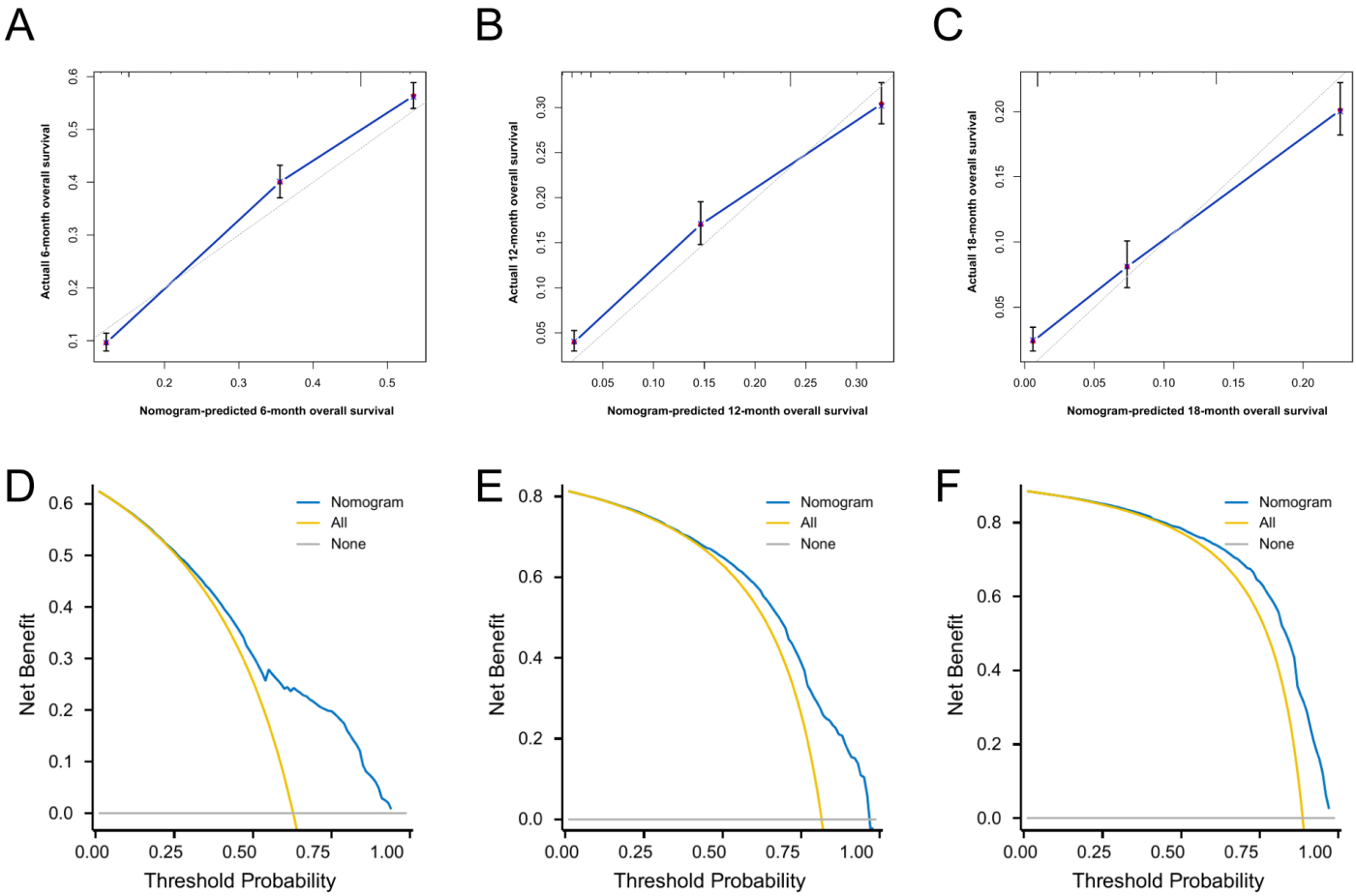

Figure 6

The calibration curves of the nomogram for the 6 (A), 12 (B), and 18 months (C) in the validation set. The decision curve analysis of the nomogram for the 6 (D), 12 (E), and 18 months (F) in the validation set.

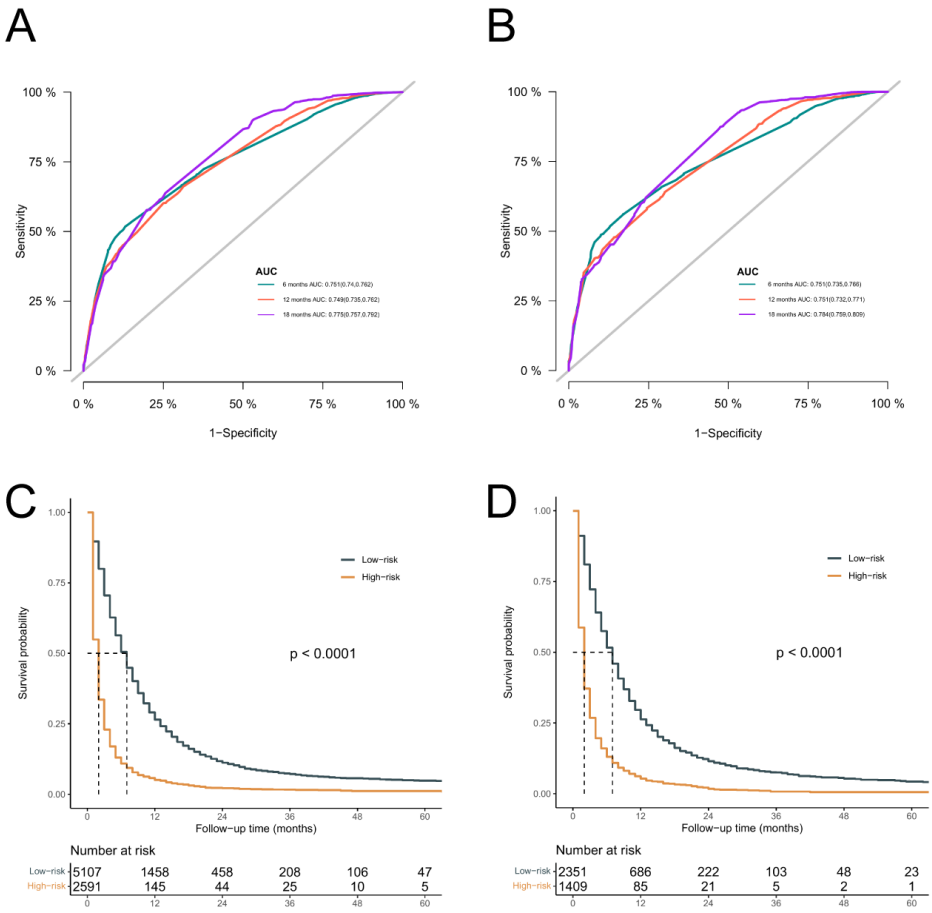

Figure 7

Time-dependent ROC curve analysis of the nomogram for the 6, 12, and 18 months in the training set (A) and the validation set (B). The Kaplan– Meier survival curves of the patients in the training set (C) and in the validation set (D).

Supplementary Files

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

- SupplementaryFigure1.pdf
- SupplementaryTable.docx