# Development and validation of a novel nomogram for predicting the prognosis of patients with resected pancreatic adenocarcinoma

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**Abstract.** The survival prediction for patients with resected pancreatic adenocarcinoma by using the Tumor-Node-Metastasis (TNM) staging system remains limited. A nomogram is a efficient tool that can be used to predict the outcome of patients with various types of malignancy. The present study aimed to develop and validate a nomogram for patients with resected pancreatic adenocarcinoma. A total of 368 patients (258 in the training set and 110 in the validation set) who underwent pancreatic adenocarcinoma resection at the China National Cancer Center between January 2008 and October 2018 were included in the present study. The nomogram was established according to the results from Cox multivariate analysis, which was validated by discrimination and calibration. The area under the receiver operating characteristic curve (AUC) was determined to assess the accuracy of survival predictions. The results from multivariate analysis in the training set demonstrated that blood transfusion, T-stage, N-stage, tumor grade, capsule invasion, carbohydrate antigen 199, neutrophil percentage and adjuvant therapy were independent prognostic factors for overall survival (OS; all $P<0.05$). Subsequently, a nomogram predicting the 1-year, 3-year and 5-year OS rates, with favorable calibration, was established based on the independent prognostic factors. The concordance indices of the nomogram were higher compared with the TNM staging system in both training and validation sets. Furthermore, a clear risk stratification system based on the nomogram was used to classify patients into the three following groups: Low-risk group ($\leq168$), moderate-risk group (168-255) and high-risk group ($>255$). The risk stratification system demonstrated an improved ability in predicting the 1-year, 3-year and 5-year OS rates compared with the TNM system (AUC, 0.758, 0.709 and 0.672 vs. AUC, 0.614, 0.604 and 0.568; all $P<0.05$). The present study developed and validated a nomogram for patients with resected pancreatic adenocarcinoma by including additional independent prognostic factors, including tumor marker, immune index, surgical information, pathological data and adjuvant therapy. Taken together, the results from the present study indicated an improved performance of the nomogram in predicting the prognosis of patients with resected pancreatic adenocarcinoma compared with the TNM staging system.

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*Abbreviations:* AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; AUC, area under the curve; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242; CRP/ALB, c reactive protein/albumin; MLR, monocyte and lymphocyte ratio; NLR, neutrophil and lymphocyte ratio; NP, neutrophil percentage; OS, overall survival; PLR, platelet and lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic inflammatory reaction Index; SIRI, systemic inflammatory response index; TNM, Tumor-Node-Metastasis

## Introduction

Pancreatic adenocarcinoma is the fourth and sixth most common cause of cancer-associated mortality in the United States (7.27%; 2018) and China (2.82%; 2015), respectively (1,2). With the annual increase in the number of pancreatic adenocarcinoma-associated mortality cases, it is predicted that this malignancy will become the second leading cause of cancer-associated mortality in the United States by 2030 (3). At present, complete surgical resection remains the only therapeutic strategy for significantly prolonging the survival of patients with pancreatic adenocarcinoma (4). However, since pancreatic adenocarcinoma is diagnosed at late and advanced stages, <20% of newly diagnosed patients are eligible for potential curative surgical resection (4,5). Despite recent advancements in chemotherapy and radiotherapy, the 5-year survival rate of patients who underwent curative resection remains poor (12-27%) (6-8). It is therefore essential to develop an efficient prognostic system to predict the survival of patients with pancreatic adenocarcinoma.

The American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system (9), which is based on the histological analysis of tumor and metastasis, has been extensively used for the prognostic evaluation of patients with pancreatic adenocarcinoma (10,11). However, the current TNM staging system for pancreatic adenocarcinoma does not include certain clinicopathological factors that may affect the prognosis, including age, sex, tumor grade and carbohydrate antigen 199 (CA199) level (11-13). CA199, as a measure of tumor burden, is a diagnostic and prognostic marker (14,15). Humphris *et al* (16) reported that normal preoperative CA199 levels identified a good prognosis. Furthermore, previous studies reported that the prognosis of patients varies significantly within the same TNM stage (10,11). It is therefore essential to develop a more efficient predictive model that could be used to predict the survival of patients with pancreatic adenocarcinoma.

Nomograms are multivariate predictive models that have been extensively applied for clinical prognostic evaluation in several types of malignancy (17-20). Unlike the TNM staging system, nomograms are efficient in incorporating additional prognostic factors, allowing therefore a more accurate prediction (21,22). At present, numerous nomograms have been established for predicting the survival of patients with pancreatic adenocarcinoma; however, most of these nomograms used the demographic and pathological data from the United States, where a number of potential prognostic factors, including tumor markers and surgical information, were not included (13,23-27).

The present study aimed to develop and validate a prognostic nomogram for patients with resected pancreatic adenocarcinoma, by including additional prognostic factors based on the clinical database from the China National Cancer Center.

## Materials and methods

*Patient dataset and study design*. The present study was a retrospective study approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China). A total of 368 patients with pancreatic adenocarcinoma who underwent curative surgical resection (with an R0 margin) at the China National Cancer Center between January 2008 and October 2018 were included in the present study. The cohort was comprised of 208 (56.5%) male and 160 (43.5%) female patients with a median age of 60 years (age range, 45-72 years). The study inclusion criteria were as follows: i) Diagnosis of pancreatic adenocarcinoma; ii) patients underwent curative surgical resection with R0 resection, which was determined by no macroscopic or microscopic residual carcinoma; and iii) based on the TNM staging system, the stages of patients were T1-3N+M0 (9). The exclusion criteria were as follows: i) Patients with T4 stage or distant metastasis; ii) patients that underwent palliative surgery; iii) patients who had received preoperative chemotherapy or radiotherapy; iv) patients who had suffered from other malignancies before pancreatic adenocarcinoma and (v) patients who died due to other reasons or unexpected outcomes. Prior to radical pancreaticoduodenectomy or distal pancreatectomy with splenectomy, patients were examined with enhanced MRI and/or CT scanning to confirm the absence of locally unresectable or distant metastases. Generally, there were more people in the training set used to construct the nomogram and fewer people in the validation set. In the present study, the patients were randomly divided into study sets for model training (258 patients) and validation (110 patients) according to a ratio of 7:3.

All clinicopathological characteristics were collected from the medical record database of the China National Cancer Center and included the following: Age at the time of diagnosis, sex, clinical symptoms (pain, jaundice, digestive symptoms and weight loss), past medical history (diabetes and hypertension) and life style (smoking status and alcohol consumption). The laboratory data included CA199, carbohydrate antigen 242 (CA242), neutrophil percentage (NP), alanine aminotransferase, aspartate aminotransferase, total bilirubin, prognostic nutritional index (PNI), platelet and lymphocyte ratio (PLR), neutrophil and lymphocyte ratio (NLR), monocyte and lymphocyte ratio (MLR), systemic inflammatory reaction index (SII), systemic inflammatory response index (SIRI) and c reactive protein/albumin (CRP/ALB), which were collected 2 weeks prior to radical surgery. The PNI was calculated based on the serum albumin and lymphocyte counts, by using the following equation: $PNI=10$ x albumin (g/dl) + 0.005 x lymphocyte count (/mm$^3$). The SII and SIRI were calculated based on neutrophil, lymphocyte, monocyte and platelet counts, using the following equation: $SII=$ platelet count x neutrophil count/lymphocyte count; $SIRI=$ neutrophil count x monocyte count/lymphocyte count. The remaining data were calculated as follows: $PLR=$ platelet count/lymphocyte count; $NLR=$ neutrophil count/lymphocyte count; $MLR=$ monocyte count/lymphocyte count.

The American Society of Anesthesiologists classification (ASA class) and information about blood transfusion, total retrieved lymph nodes, tumor information (location, tumor grade, and lymphovascular, perineural and capsule invasions) and adjuvant therapy were also included in the present study. The tumor stage and nodal involvement in the present study were defined according to the 8th edition TNM staging system (28).

*Follow-up analysis*. The primary endpoint of the present study was the overall survival (OS), which was measured from the date of radical surgery to the mortality due to pancreatic adenocarcinoma, or to the last follow-up (updated in May 2019). The follow-up procedure was as follows: Once every three months within the first two years following surgery and continual procedures every six months thereafter, in which the postoperative treatment information and survival conditions were recorded. Long-term prognostic data were collected from the patients' clinical records or contact with the patients' relatives via telephone. Patients who died after the surgery (within 1 month following surgery) were excluded from the present study. A total of three patients were lost due to perioperative mortality.

*Statistical analysis*. X-tile software (v.3.6.1; Yale School of Medicine) (29) was used to identify the optimal cut-off values of the potential prognostic factors, including NP, PNI, PLR, NLR, MLR, SII, SIRI and CRP/ALB. X-tile software can divide marker data into two populations: low and high. All possible

Table I. Clinicopathological characteristics of patients in the training and validation sets.

| Characteristic | Training set | | Validation set | | P-value |
|---|---|---|---|---|---|
| | Patient, n | % | Patient, n | % | |
| Sex | | | | | 0.675 |
| Male | 144 | 55.8 | 64 | 58.2 | |
| Female | 114 | 44.2 | 46 | 41.8 | |
| Age, years | | | | | 0.265 |
| ≤60 | 136 | 52.7 | 51 | 46.4 | |
| >60 | 122 | 47.3 | 59 | 53.6 | |
| Symptom | | | | | 0.108 |
| No | 39 | 15.5 | 24 | 22.6 | |
| Yes | 212 | 84.5 | 82 | 77.4 | |
| Pain | | | | | 0.195 |
| No | 104 | 41.6 | 52 | 49.1 | |
| Yes | 146 | 58.4 | 54 | 50.9 | |
| Jaundice | | | | | 0.452 |
| No | 182 | 72.8 | 73 | 68.9 | |
| Yes | 68 | 27.2 | 33 | 31.1 | |
| Digestive symptoms | | | | | 0.023 |
| No | 202 | 80.8 | 74 | 69.8 | |
| Yes | 48 | 19.2 | 32 | 30.2 | |
| Weight loss | | | | | 0.420 |
| No | 152 | 60.6 | 69 | 65.1 | |
| Yes | 99 | 39.4 | 37 | 34.9 | |
| Diabetes | | | | | 0.342 |
| No | 189 | 73.3 | 85 | 78.0 | |
| Yes | 69 | 26.7 | 24 | 22.0 | |
| Hypertension | | | | | 0.131 |
| No | 197 | 76.4 | 75 | 68.8 | |
| Yes | 61 | 23.6 | 34 | 31.2 | |
| Smoke | | | | | 0.231 |
| No | 193 | 76.0 | 77 | 70.0 | |
| Yes | 61 | 24.0 | 33 | 30.0 | |
| Alcohol | | | | | 0.218 |
| No | 204 | 80.3 | 82 | 74.5 | |
| Yes | 50 | 19.7 | 28 | 25.5 | |
| ASA class | | | | | 0.405 |
| ≤2 | 188 | 74.6 | 85 | 78.7 | |
| >2 | 64 | 25.4 | 23 | 21.3 | |
| Blood transfusion | | | | | 0.372 |
| No | 155 | 61.5 | 61 | 56.5 | |
| Yes | 97 | 38.5 | 47 | 43.5 | |
| Tumor location | | | | | 0.348 |
| Head and neck | 124 | 48.1 | 47 | 42.7 | |
| Body and tail | 134 | 51.9 | 63 | 57.3 | |
| T stage | | | | | 0.917 |
| T1 | 33 | 13.1 | 15 | 13.9 | |
| T2 | 139 | 55.2 | 56 | 56.5 | |
| T3 | 80 | 31.7 | 35 | 29.6 | |
| N stage | | | | | 0.961 |
| N0 | 142 | 56.3 | 61 | 53.7 | |
| N1 | 84 | 33.3 | 35 | 34.3 | |
| N2 | 26 | 10.4 | 10 | 12.0 | |

Table I. Continued.

| Characteristic | Training set | | Validation set | | P-value |
|---|---|---|---|---|---|
| | Patient, n | % | Patient, n | % | |
| Lymph nodes, n | | | | | 0.798 |
| ≤6 | 69 | 25.7 | 31 | 27.4 | |
| >6 | 171 | 74.3 | 82 | 72.6 | |
| Tumor grade | | | | | 0.473 |
| Poorly | 37 | 14.9 | 17 | 16.4 | |
| Moderately | 174 | 69.9 | 78 | 69.1 | |
| Well | 38 | 15.3 | 11 | 14.5 | |
| Lymphovascular invasion | | | | | 0.973 |
| No | 174 | 74.0 | 82 | 73.9 | |
| Yes | 61 | 26.0 | 29 | 26.1 | |
| Perineural invasion | | | | | 0.965 |
| No | 95 | 39.7 | 44 | 40.0 | |
| Yes | 144 | 60.3 | 66 | 60.0 | |
| Capsule invasion | | | | | 0.508 |
| No | 70 | 27.7 | 33 | 31.1 | |
| Yes | 183 | 72.3 | 73 | 68.9 | |
| CEA, ng/ml | | | | | 0.370 |
| ≤5 | 158 | 63.7 | 64 | 58.7 | |
| >5 | 90 | 36.3 | 45 | 41.3 | |
| CA199, U/ml | | | | | 0.907 |
| ≤37 | 56 | 22.6 | 24 | 22.0 | |
| >37 | 192 | 77.4 | 85 | 78.0 | |
| CA242, IU/ml | | | | | 0.174 |
| ≤20 | 96 | 38.7 | 34 | 31.2 | |
| >20 | 152 | 61.3 | 75 | 68.8 | |
| NP | | | | | 0.686 |
| ≤0.700 | 180 | 72.0 | 80 | 74.1 | |
| >0.700 | 70 | 38.0 | 28 | 25.9 | |
| ALT, U/l | | | | | 0.712 |
| ≤40 | 145 | 63.9 | 66 | 66.0 | |
| >40 | 82 | 36.1 | 34 | 34.0 | |
| AST, U/l | | | | | 0.960 |
| ≤40 | 156 | 68.7 | 69 | 69.0 | |
| >40 | 71 | 31.3 | 31 | 31.0 | |
| TBIL, $\mu$mol/l | | | | | 0.232 |
| ≤17.1 | 143 | 63.0 | 56 | 56.0 | |
| >17.1 | 84 | 37.0 | 44 | 44.0 | |
| PNI | | | | | 0.402 |
| ≤52 | 156 | 68.7 | 64 | 64.0 | |
| >52 | 71 | 31.3 | 36 | 36.0 | |
| PLR | | | | | 0.234 |
| ≤210.082 | 222 | 88.8 | 91 | 84.3 | |
| >210.082 | 28 | 11.2 | 17 | 15.7 | |
| NLR | | | | | 0.405 |
| ≤2.751 | 162 | 64.8 | 65 | 60.2 | |
| >2.751 | 88 | 35.2 | 43 | 39.8 | |
| MLR | | | | | 0.341 |
| ≤0.279 | 163 | 65.2 | 76 | 70.4 | |
| >0.279 | 87 | 34.8 | 32 | 29.6 | |

Table I. Continued.

| Characteristic | Training set | | Validation set | | P-value |
|---|---|---|---|---|---|
| | Patient, n | % | Patient, n | % | |
| SII | | | | | 0.770 |
| ≤718.312 | 198 | 79.2 | 87 | 80.6 | |
| >718.312 | 52 | 20.8 | 21 | 19.4 | |
| SIRI | | | | | 0.120 |
| ≤0.782 | 110 | 43.0 | 38 | 35.2 | |
| >0.782 | 140 | 56.0 | 70 | 64.8 | |
| CRP/ALB | | | | | 0.700 |
| ≤0.142% | 51 | 38.1 | 23 | 41.1 | |
| >0.142% | 83 | 61.9 | 33 | 58.9 | |
| Adjuvant therapy | | | | | 0.279 |
| No | 128 | 50.2 | 62 | 56.4 | |
| Yes | 127 | 49.8 | 48 | 43.6 | |

In the present study, patients who lacked the results of 1-2 factors but had other available factors were also included. ASA class, American Society of Anesthesiologists classification; T, tumor; N, node; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242; NP, neutrophil percentage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; PNI, prognostic nutritional index; PLR, platelet and lymphocyte ratio; NLR, neutrophil and lymphocyte ratio; MLR, monocyte and lymphocyte ratio; SII, systemic inflammatory reaction Index; SIRI, systemic inflammatory response index; CRP/ALB, c reactive protein/albumin.

divisions of the marker data were assessed by a variety of standard statistical tests, including the log-rank test for survival and means tests for associations between other marker data. Then the program selected the optimal division of the data (29). $\chi^2$ test was used to compare the categorical characteristics between the two disjoint sets. Cox proportional hazard univariate and multivariate regression analyses were used to evaluate the independent prognostic predictors for OS in the training set.

Multivariate analysis was performed to identify the independent prognostic factors, in order to establish the nomogram by using the rms package within R project software. Based on the hazard ratio of the corresponding characteristics in the Cox regression model, each independent prognostic factor was scored using the 'nomogram' function within R project (21). Validations were performed in the validation set using two parameters of the nomogram, discrimination and calibration. The concordance (C)-index was implemented to assess discrimination, whereas calibration curves were generated using bootstrap resampling (1,000 resamples). The area under the receiver operating characteristic curve (AUC) was determined to assess the accuracy of survival predictions. The Kaplan-Meier method was used to analyze the survival curves, and differences were estimated using log-rank test.

Statistical analyses were performed using SPSS software (version 25.0; IBM Corp.), GraphPad Prism software (version 7.00; GraphPad Software Inc.) and R software (version 3.5.2; http://www.r-project.org). Two-tailed P<0.05 was considered to indicate a significant difference.

## Results

*Patient characteristics.* A total of 368 patients with resected pancreatic adenocarcinoma were randomly divided into the

training set (258 patients) and the validation set (110 patients). As presented in Table I, the optimal cut-off values identified using X-tile software were as follows: 0.700 for NP, 52 for PNI, 210.082 for PLR, 2.751 for NLR, 0.279 for MLP, 718.312 for SII, 0.782 for SIRI and 0.142% for CRP/ALB. Based on these values, patients were subsequently divided into low and high expression groups. The mean follow-up period of the training set was 44.4 months (range, 2-104.9 months), while the 1-year, 3-year and 5-year OS rates were 72.3, 41.4 and 26.4%, respectively. The mean follow-up period of the validation set was 40.1 months (range, 1.5-102.8 months), while the 1-year, 3-year and 5-year OS rates were 66.4, 38.8 and 25.6%, respectively. The clinicopathological characteristics of patients from the training and validation sets are presented in Table I. No significant difference was observed between the two groups for each characteristic.

*Independent prognostic factors in the training set.* The results from univariate and multivariate regression analyses for the training set are presented in Table II. Results from univariate analysis demonstrated that OS was significantly associated with sex, symptom, weight loss, ASA class, blood transfusion, tumor location, T stage, N stage, tumor grade, capsule invasion, CA199, CA242, NP, NLR, SII and adjuvant therapy (all P<0.05). Furthermore, following multivariate analysis, blood transfusion, T stage, N stage, tumor grade, capsule invasion, CA199, NP and adjuvant therapy were identified as significant independent prognostic factors for patients with resected pancreatic adenocarcinoma (all P<0.05).

*Development and validation of the nomogram.* A nomogram predicting the 1-year, 3-year and 5-year OS rates of patients with pancreatic adenocarcinoma was constructed based on

Table II. Univariate and multivariate analyses on clinicopathological characteristics of patients in the training set.

| Characteristics | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Sex | | | | |
| Female | Reference | | Reference | |
| Male | 1.370 (1.025-1.832) | 0.033 | 1.333 (0.903-1.966) | 0.148 |
| Symptom | | | | |
| Yes | Reference | | Reference | |
| No | 0.654 (0.438-0.978) | 0.039 | 0.833 (0.489-1.420) | 0.501 |
| Weight loss | | | | |
| Yes | Reference | | Reference | |
| No | 0.734 (0.548-0.983) | 0.038 | 0.804 (0.532-1.215) | 0.300 |
| ASA class | | | | |
| >2 | Reference | | Reference | |
| ≤2 | 0.689 (0.485-0.978) | 0.037 | 1.119 (0.686-1.827) | 0.652 |
| Blood transfusion | | | | |
| Yes | Reference | | Reference | |
| No | 0.644 (0.469-0.884) | 0.007 | 0.594 (0.384-0.920) | 0.020 |
| Tumor location | | | | |
| Body and tail | Reference | | Reference | |
| Head and neck | 0.720 (0.539-0.961) | 0.026 | 0.853 (0.522-1.394) | 0.525 |
| T stage | | | | |
| T3 | Reference | | Reference | |
| T2 | 0.589 (0.431-0.807) | 0.001 | 0.513 (0.326-0.808) | 0.003 |
| T1 | 0.494 (0.300-0.814) | 0.006 | 0.451 (0.215-0.946) | 0.035 |
| N stage | | | | |
| N2 | Reference | | Reference | |
| N1 | 0.704 (0.425-1.167) | 0.174 | 0.592 (0.317-1.106) | 0.100 |
| N0 | 0.417 (0.254-0.685) | 0.001 | 0.400 (0.212-0.754) | 0.005 |
| Tumor grade | | | | |
| Well | Reference | | Reference | |
| Moderately | 2.464 (1.462-4.155) | 0.001 | 2.894 (1.383-6.057) | 0.005 |
| Poorly | 4.102 (2.255-7.460) | 0.000 | 3.904 (1.671-9.121) | 0.002 |
| Capsule invasion | | | | |
| Yes | Reference | | Reference | |
| No | 0.585 (0.405-0.843) | 0.004 | 0.496 (0.297-0.829) | 0.007 |
| CA199, U/ml | | | | |
| >37 | Reference | | Reference | |
| ≤37 | 0.477 (0.318-0.717) | 0.000 | 0.430 (0.230-0.802) | 0.008 |
| CA242, IU/ml | | | | |
| >20 | Reference | | Reference | |
| ≤20 | 0.524 (0.362-0.758) | 0.001 | 0.961 (0.573-1.611) | 0.880 |
| NP | | | | |
| >0.700 | Reference | | Reference | |
| ≤0.700 | 0.577 (0.402-0.827) | 0.003 | 0.361 (0.198-0.657) | 0.001 |
| NLR | | | | |
| >2.751 | Reference | | Reference | |
| ≤2.751 | 0.653 (0.475-0.897) | 0.008 | 1.301 (0.723-2.343) | 0.380 |
| SII | | | | |
| >718.312 | Reference | | Reference | |
| ≤718.312 | 0.665 (0.464-0.952) | 0.026 | 1.097 (0.614-1.960) | 0.754 |

Table II. Continued.

| Characteristics | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Adjuvant therapy | | | | |
| Yes | Reference | | Reference | |
| No | 1.433 (1.067-1.925) | 0.017 | 1.931 (1.297-2.875) | 0.001 |

HR, hazard ratio; CI, confidence interval; ASA class, American Society of Anesthesiologists classification; T, tumor; N, node; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242; NP, neutrophil percentage; NLR, neutrophil and lymphocyte ratio; SII, systemic inflammatory reaction index.
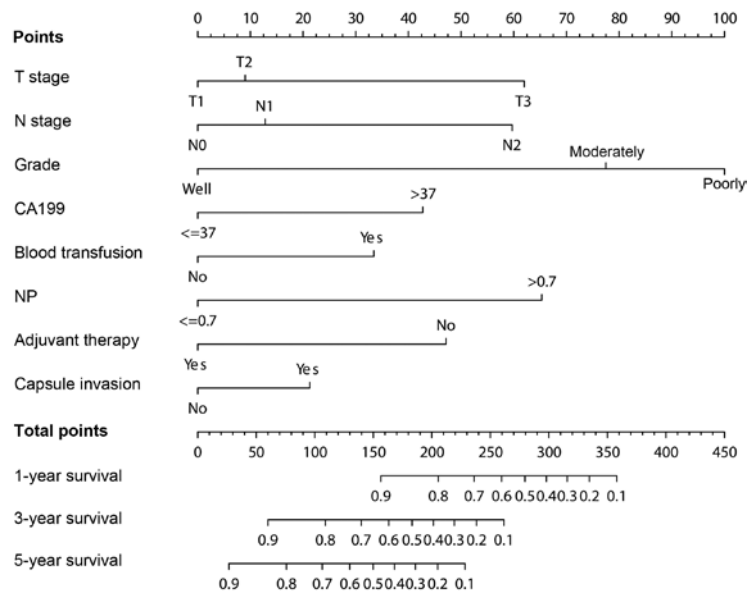


Figure 1. Nomogram predicting the 1-year, 3-year and 5-year overall survival of patients with resected pancreatic adenocarcinoma. T, tumor; N, node; CA199, carbohydrate antigen 199; NP, neutrophil percentage.

the independent prognostic factors identified from the Cox multivariate regression model in the training set (Fig. 1). Each subtype within these indicators was allocated a score according to the 'Points' in the nomogram. Next, the predicted survival probabilities for each patient was calculated using the nomogram. For example, the total points of patients were calculated by summing up the score for each indicator first. Then the right position in the total points axis was found and a perpendicular line drawn to the survival probabilities axis. Finally, the predicted survival probabilities at 1-year, 3-year and 5-year were obtained.

As presented in Table III, the C-indices for the 1-year, 3-year and 5-year OS prediction in the training set were 0.824 [95% confidential interval (CI), 0.775-0.873], 0.782 (95% CI, 0.745-0.823) and 0.770 (95% CI, 0.731-0.810), respectively. The C-indices for the 1-year, 3-year and 5-year OS prediction in the validation set were 0.779 (95% CI, 0.705-0.853), 0.778 (95% CI, 0.718-0.838) and 0.766 (95% CI, 0.709-0.823), respectively. The C-indices of both training and validation sets were higher in the nomogram compared with the TNM staging system. Furthermore, the calibration curves for the probability

of 1-year, 3-year and 5-year OS demonstrated a positive association between the predicted and observed values in the validation set (Fig. 2).

*Survival analysis according to the risk stratification system based on the nomogram.* A clear risk stratification system of OS rates was established using the predicted probabilities obtained from the nomogram. The score for each independent prognostic factor is presented in Table IV. Total scores for each patient was defined as the sum of each score for each indicator in the nomogram. According to the optimal cut-off values of total scores, patients were classified into three groups as follows: Low-risk group (≤168, n=124), moderate-risk group (168-255, n=126) and high-risk group (>255, n=118), where each group represented a distinct prognosis. Patients were categorized according to the TNM staging system and the risk stratification system, and the risk stratification system based on the nomogram had the ability to delineate three different prognosis groups (P<0.01; Fig. 3). The AUC values of the risk stratification system for predicting the 1-year, 3-year and 5-year OS rates were 0.758, 0.709 and 0.672, respectively,

Table III. C-indexes for the nomogram and TNM staging system.

| Characteristics | 1-year OS | | 3-year OS | | 5-year OS | |
|---|---|---|---|---|---|---|
| | C-index | 95% CI | C-index | 95% CI | C-index | 95% CI |
| Training set | | | | | | |
| Nomogram | 0.824 | 0.775-0.873 | 0.782 | 0.742-0.823 | 0.770 | 0.731-0.810 |
| TNM system | 0.667 | 0.591-0.742 | 0.648 | 0.589-0.706 | 0.642 | 0.585-0.699 |
| Validation set | | | | | | |
| Nomogram | 0.779 | 0.705-0.853 | 0.778 | 0.718-0.838 | 0.766 | 0.709-0.823 |
| TNM system | 0.695 | 0.603-0.787 | 0.672 | 0.595-0.749 | 0.669 | 0.594-0.744 |

C, concordance; TNM, tumor-node-metastasis; OS, overall survival; CI, confidence interval.
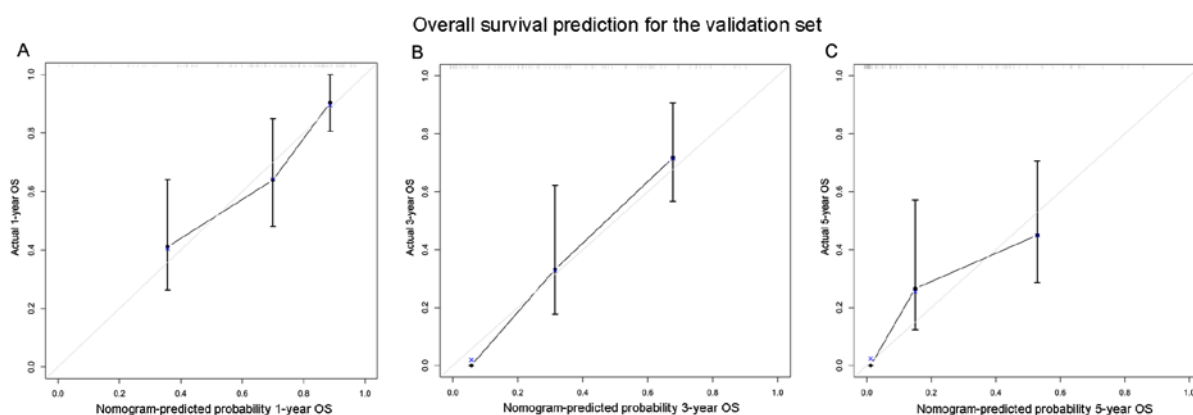


Figure 2. Calibration curves predicting the OS at (A) 1-year, (B) 3-year and (C) 5-year for the validation set. The plots along the 45° line indicates an appropriate calibration model, in which the predicted probabilities were identical to the actual outcomes. OS, overall survival.

whereas the AUC values for the current TNM staging system are 0.614, 0.604 and 0.568, respectively (28) (Fig. 4).

## Discussion

The AJCC TNM staging system is currently the most extensively used system to predict the prognosis of several types of cancer, including pancreatic adenocarcinoma (30). Numerous studies suggested that T and N stages might not be the only clinical factors that can be used to determine the prognosis of patients with pancreatic adenocarcinoma (9,13,14,31). Since implementing the traditional TNM staging system for patients with resected pancreatic adenocarcinoma is considered as imprecise, it is therefore essential to develop a more accurate survival predictive model (13,14,31,32). In order to address the limitations of the TNM staging system, the present study developed and validated a survival predictive nomogram for patients with resected pancreatic adenocarcinoma, by including additional independent prognostic factors.

Nomogram is a graphical representation of a statistical predictive model, which can predict patients' individualized risk for a specific survival outcome (21). At present, a number of prognostic nomograms have been developed to diagnose several types of cancer, such as non-small-cell lung cancer and gastroenteropancreatic neuroendocrine neoplasms (21,33,34).

The first nomogram for patients with pancreatic adenocarcinoma was established in 2004 by Memorial Sloan-Kettering Cancer Center (MSKCC) (23), which provided more accurate survival predictions compared with the TNM staging system when validated by external patient cohorts (13,35). However, tumor markers, adjuvant therapy and other potential prognostic factors were not considered in the MSKCC study. Furthermore, in the MSKCC nomogram, patients with T1 stage were assigned with higher scores than patients with T2 and T3 stages, which is different from clinical data from patients, limiting the popularization of MSKCC nomogram (31). Furthermore, other available nomograms are not specific to patients with resected pancreatic adenocarcinoma (24,26,33,36), whereas the nomogram established in the present study was specifically targeted for patients with resected pancreatic adenocarcinoma. The present nomogram included T stage, N stage, tumor grade, capsule invasion, CA199, NP, blood transfusion and adjuvant therapy, which demonstrated an improved performance in predicting the prognosis of patients compared with the TNM staging system. To the best of our knowledge, the present study was the first to describe a nomogram that included capsule invasion, NP and blood transfusion to predict the OS of patients with resected pancreatic adenocarcinoma.

T and N stages were included in the present nomogram, as they have previously been considered as key independent

Table IV. Score of characteristics in the nomogram.

| Characteristic | Score |
| --- | --- |
| Blood transfusion | |
| No | 0 |
| Yes | 33.3 |
| NP | |
| ≤0.7 | 0 |
| >0.7 | 65.1 |
| CA199, U/ml | |
| ≤37 | 0 |
| >37 | 42.6 |
| T stage | |
| T1 | 0 |
| T2 | 9 |
| T3 | 62.1 |
| N stage | |
| N0 | 0 |
| N1 | 12.6 |
| N2 | 59.8 |
| Tumor grade | |
| Poorly | 100.0 |
| Moderately | 77.5 |
| Well | 0 |
| Adjuvant therapy | |
| No | 47.4 |
| Yes | 0 |
| Capsule invasion | |
| No | 0 |
| Yes | 21.2 |

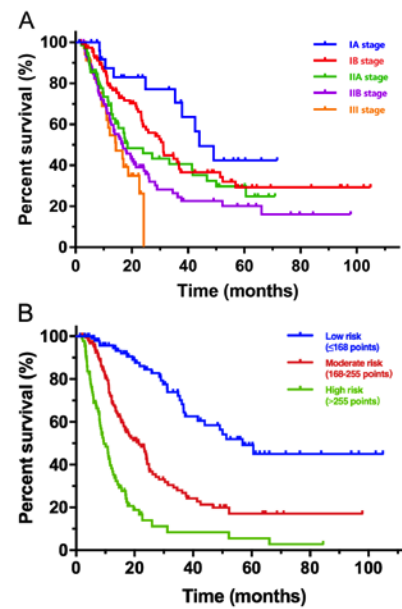NP, neutrophil percentage; CA199, carbohydrate antigen 199; T, tumor.



Figure 3. Kaplan-Meier survival curves for patients with resected pancreatic adenocarcinoma, according to (A) the TNM staging system and (B) the risk stratification system based on the developed nomogram. TNM, tumor-node-metastasis.

prognostic factors for pancreatic adenocarcinoma (9-11,14). In particular, T4 stage is associated with the presence of tumors involved in the coeliac axis or superior mesenteric artery (28). In addition, since patients with T4 stage tumors may not be able to undergo surgery, patients with T4 stage pancreatic adenocarcinoma were not included in the study.

Consistent with previous findings, the results of the present study demonstrated that, in addition to the T and N stages, tumor grade may also act as an independent predictor for patients with resected pancreatic adenocarcinoma (14,31,37). For example, it has been reported that well-differentiated tumors are significantly associated with longer survival rates (14,37,38). The nomogram developed in the present study demonstrated the magnitude of poor prognosis as tumor grade changed from well to poorly differentiated. It has been reported that tumor grade incorporation into the current TNM system enables accurate prognosis prediction within particular clinical stages (30), which has been validated by two subsequent studies (11,37). In the present study, patients with distinct tumor grades were assigned to different points

in the nomogram, even if they were classified within the same TNM stage. These observations partly illustrated the higher power of the nomogram for predicting the survival of patients compared with the TNM staging system.

Consistent with previous findings (39-41), the results from the present study demonstrated that presence of capsule invasion was an independent poor prognostic factor for OS in patients with resected pancreatic adenocarcinoma. In another study, Mannell et al (39) reported that the malignant invasion of the pancreatic capsule was significantly associated with poor prognosis. Furthermore, it has been demonstrated that the incidence of capsule invasion has a tendency to increase in relation to tumor size (40). This phenomenon may explain why capsule invasion is considered a poor prognosis factor.

CA199 is a well-established marker used to determine tumor burden, and the most frequently used tumor marker for pancreatic adenocarcinoma (14,42,43). CA199 has been reported as a diagnostic and a prognostic marker (14-16). Evaluation of preoperative CA199 is positively associated with tumor resectability and postoperative prognosis (14,16,44,45). Furthermore, postoperative CA199 levels have been reported to predict OS and disease-free survival following cancer resection and adjuvant chemotherapy (45-49). Consistent with the results from the present study, a previous report demonstrated that CA199 can predict the prognosis of patients with resected pancreatic adenocarcinoma when combined with PLR (45). A 10-year follow-up study on a large patient population indicated that CA199 is an independent prognostic factor for advanced pancreatic adenocarcinoma (50).

In the nomogram developed in the present study, blood transfusion was a prognostic factor that could have been easily ignored. Previous studies reported that blood transfusion is associated with the survival outcome of patients following pancreatic resection (51-53). Furthermore, a previous study identified blood transfusion as a significant negative predictor
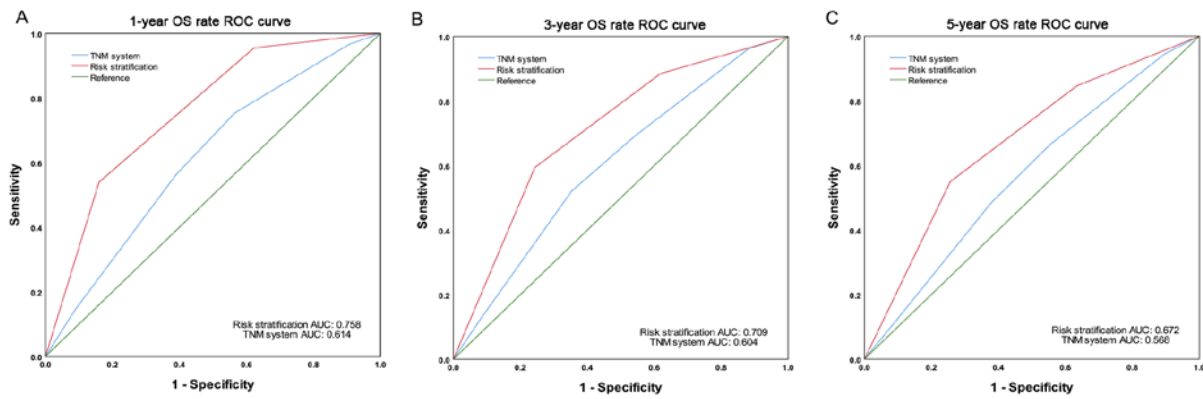
Figure 4. Comparisons of the ROC curves of the risk stratification system, based on the developed nomogram and the TNM staging systems for (A) 1-year, (B) 3-year and (C) 5-year OS prediction. ROC, receiver operating characteristic; TNM, tumor-node-metastasis; OS, overall survival; AUC, area under the curve.

of survival, whereas adjuvant chemotherapy is associated with significantly longer survival (53). These findings are consistent with the results from the present study. Furthermore, intraoperative transfusion, lymph node metastasis and lymph node ratio have been reported as independent prognostic factors in predicting tumor recurrence (54). However, how intraoperative transfusion may have a negative impact on the recurrence and OS of patients with cancer remains unclear. It has been hypothesized that blood transfusion may suppress the immune system of the recipient, resulting therefore in early tumor recurrence (55). Conversely, it has been speculated that patients requiring blood transfusion may have been associated with perioperative complications, which may influence survival more than the transfusion itself (56). Prospective studies are therefore required to determine the clinical impact and underlying mechanism of transfusion in patients with pancreatic adenocarcinoma. However, blood transfusion should be avoided by following the established operative procedures, in order to minimize intraoperative bleeding.

Adjuvant therapy has been reported to be associated with the prognosis of patients following pancreatic adenocarcinoma resection (57-61). Although adjuvant therapy is not a pathological factor, it is considered to significantly affect survival (59-61). It was therefore included in the nomogram developed in the present study. A systematic review reported that despite curative-intent resection, the prognosis of patients with recurrence remains poor, which leads therefore to adjuvant therapy (61). Consistent with the results from the present study, Corsini *et al* (60) reported that patients with pancreatic adenocarcinoma who receive adjuvant therapy following successful resection have better survival rates. These findings were described in numerous studies (57-59). Subsequently, according to the present study and previous reports, it is suggested that patients with pancreatic adenocarcinoma should undergo postoperative chemotherapy.

It has been demonstrated that NP may act as a prognostic factor for patients with resected pancreatic adenocarcinoma. Previous studies reported the association between inflammation and various types of malignancy, such as renal cell carcinoma, pancreatic cancer (62-65), and cancer-associated inflammation is ranked as the seventh most common hallmark of tumor development (66). Based on systemic inflammation analyses, several prognostic factors, including NLR, MLR

and PNI, have the ability to predict the prognosis of patients with resectable pancreatic adenocarcinoma (67-69). Consistent with these findings, the present study identified NLR as a prognostic factor for pancreatic cancer following univariate analysis; however, multivariate analysis failed to validate NLR role as an independent prognostic factor. Furthermore, the association between NP and the prognosis of patients with pancreatic adenocarcinoma has been well established. For example, pretreatment with NP has been reported to act as an independent prognostic factor for patients with advanced cancer who exhibit adverse outcomes (70). NP has also been considered as an independent prognostic factor in patients with nasopharyngeal carcinoma (71). Previous studies suggested that neutrophils, which serve a crucial role in the inflammatory tumor microenvironment, could mediate the pro-tumor effects via different molecular mechanisms (72,73). In addition, neutrophils are associated with increased tumor burden and tumor aggressiveness, which may reflect the prognosis of patients with various types of cancer (70). The results from the present study demonstrated that NP may be considered as a novel prognostic indicator for predicting survival outcome of patients with pancreatic cancer. However, whether NP, as an immune index, may be used as a prognostic marker for patients with resected pancreatic adenocarcinoma requires further investigation using larger-scale cohort studies.

Validation is essential to assure that the nomogram is universally applicable (21). In the present study, the calibration plots in the validation set exhibited a positive association between the predicted nomogram and the actual survival rate, which demonstrated the repeatability and reliability of the present nomogram. Furthermore, the C-indices in both training and validation sets were significantly higher in the nomogram compared with the TNM staging system. In addition, a clear risk stratification system of OS rates was established by using the total scores obtained from the nomogram. In the present study, the AUC values indicated that the risk stratification system based on the nomogram demonstrated improved ability in predicting the 1-year, 3-year and 5-year OS rates compared with the TNM system.

To the best of our knowledge, the present study was the first to describe a nomogram that included tumor marker, immune index, surgical information, pathological data and adjuvant therapy to predict the OS of patients with resected

pancreatic adenocarcinoma. The present nomogram demonstrated favorable discrimination and calibration in the training and validation sets. It may therefore be used as a practical tool to predict the prognosis of patients.

The present study presented some limitations. Firstly, this study lacked an external validation. In the present study, 70% of patients were randomly assigned into the training set to develop the nomogram, whereas 30% of patients were assigned into the validation set to validate the nomogram. Although this is a generally accepted method for nomogram development and validation, external validation based on other populations is required to estimate the model accuracy. Secondly, although the validation results demonstrated that the nomogram may be able to predict the prognosis of patients, this nomogram did not include all potential prognostic factors such as preoperative treatment, familial pancreatic adenocarcinoma, the number of harvested lymph nodes etc. Thirdly, due to the complexity of adjuvant therapy, specific adjuvant therapy options were not subdivided in the present study, which may have influenced the accuracy of the prediction.

In conclusion, the present study successfully developed and validated a nomogram that could be used for the prognosis prediction of patients with resected pancreatic adenocarcinoma, based on the database from the China National Cancer Center. Compared with the TNM staging system, the present nomogram was more performant at predicting prognosis of patients. This nomogram requires further external validation before its use in clinical practice.

## Acknowledgements

## Funding

## Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

## Authors' contributions

HR and CFW conceived and designed the present study. HR and CRW drafted the initial manuscript and performed statistical analysis. HR, CRW and SA acquired the data. SA performed the statistical analysis. HR and CFW analyzed and interpreted the data. All authors contributed to data analysis. All authors drafted and critically revised the paper for important intellectual content. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The present study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China).

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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