


Prognostic Nomogram for Patients With Pancreatic Ductal Adenocarcinoma of Pancreatic Head After Pancreaticoduodenectomy

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Hongkai Zhuang^{1,2#}, Zixuan Zhou^{1#}, Zuyi Ma^{1,2}, Shanzhou Huang¹, Yuanfeng Gong¹, Zhenchong Li¹, Chunsheng Liu¹, Shujie Wang¹, Bo Chen^{3*}, Chuanzhao Zhang^{1*} and Baohua Hou^{1*} 

¹Department of General Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China. ²Shantou University of Medical College, Shantou, China. ³Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.

ABSTRACT

BACKGROUND: The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) of pancreatic head remains poor, even after potentially curative R0 resection. The aim of this study was to develop an accurate model to predict patients' prognosis for PDAC of pancreatic head following pancreaticoduodenectomy.

METHODS: We retrospectively reviewed 112 patients with PDAC of pancreatic head after pancreaticoduodenectomy in Guangdong Provincial People's Hospital between 2014 and 2018.

RESULTS: Five prognostic factors were identified using univariate Cox regression analysis, including age, histologic grade, American Joint Committee on Cancer (AJCC) Stage 8th, total bilirubin (TBIL), CA19-9. Using all subset analysis and multivariate Cox regression analysis, we developed a nomogram consisted of age, AJCC Stage 8th, perineural invasion, TBIL, and CA19-9, which had higher C-indexes for OS (0.73) and RFS (0.69) compared with AJCC Stage 8th alone (OS: 0.66; RFS: 0.67). The area under the curve (AUC) values of the receiver operating characteristic (ROC) curve for the nomogram for OS and RFS were significantly higher than other single parameter, which are AJCC Stage 8th, age, perineural invasion, TBIL, and CA19-9. Importantly, our nomogram displayed higher C-index for OS than previous reported models, indicating a better predictive value of our model.

CONCLUSIONS: A simple and practical nomogram for patient prognosis in PDAC of pancreatic head following pancreaticoduodenectomy was established, which shows satisfactory predictive efficacy and deserves further evaluation in the future.

KEYWORDS: Nomogram, CA19-9, overall survival, recurrence-free survival, pancreatic cancer

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CORRESPONDING AUTHORS: Bo Chen, Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, NO.106 Zhongshan Er Road, Yuexiu District, Guangzhou 510080, Guangdong, China. Email: chenbo@gdph.org.cn

Chuanzhao Zhang, Department of General Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, NO. 106 Zhongshan Er Road, Yuexiu District, Guangzhou 510080, Guangdong, China. Email: 641703837@qq.com

Baohua Hou, Department of General Surgery, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, NO.106 Zhongshan Er Road, Yuexiu District, Guangzhou 510080, Guangdong, China. Email: 15917919681@163.com

Introduction

Pancreatic cancer is one of the most aggressive solid tumors, causing 4.5% of all cancer-related deaths worldwide.¹ Pancreatic duct adenocarcinoma (PDAC) accounts for more than 90% of all pancreatic cancer.² The 5-year survival rate for PDAC is only about 8%.³ For resectable PDAC of pancreatic head, pancreaticoduodenectomy remains the major treatment option.⁴ However, patients following curative resection have different outcome due to tumor heterogeneity.⁵ Therefore it is of great interest to develop accurate predictive model for PDAC patients after radical operation.

#HZ and ZZ contributed equally to this work and should be considered as co-first authors.

*Co-corresponding authors.

Currently, the stage system from the American Joint Committee on Cancer (AJCC) are widely used in clinical practice to predict the prognosis of pancreatic cancer and assist in the decision-making of treatment and surveillance. However, AJCC Stage 8th is determined mostly by anatomical features, such as tumor size, lymph node, or vascular invasion status, and metastasis, which do not include other possible prognostic factors. For example, Wang et al suggested perineural invasion as a critical predictors of PDAC.⁶ Recently, investigators tried to develop predictive nomograms for pancreatic cancer using data from the Surveillance, Epidemiology, and End Results (SEER) program database.⁷⁻¹¹ However, no study was conducted using independent data to compare the efficacy of the different models and some important serum biomarkers and perineural invasion status were not taken into account.



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In the current study, we utilized the data from our institution to evaluate an entire set of possible prognostic factors in patients with PDAC of pancreatic head and to generate a sample and reliable nomogram. We also compared the efficacy of our model and previous reported models.

Materials and Methods

Patient data

We retrospectively collected and analyzed 112 patients with PDAC of pancreatic head from January 2014 to May 2018 who underwent pancreaticoduodenectomy with R0 resection at Guangdong Provincial people's Hospital. All the patients had received the optimal chemotherapy provided by multiple disciplinary teams by synthesizing the patients' tumor burden, physical and financial condition. The exclusion criteria included: (a) refusal to follow-up; (b) patients diagnosed with preoperative infection, hematological or inflammatory diseases; (c) patients with history of other malignant cancers; (d) no informed consent; (e) patients with unknown origins or distant metastasis. The protocol of this study was approved by the Clinical Research Ethic Committee of Guangdong Provincial people's Hospital and all informed consents were obtained (No.GDREC2016099A).

The patients' clinicopathological characteristics were collected from medical records, including gender, age, AJCC Stage 8th, neoadjuvant chemotherapy, postoperative adjuvant chemotherapy, preoperative biliary drainage, histologic grade, vascular invasion, perineural invasion, peripancreatic fat invasion, and blood test within preoperative 7 days (neutrophils, platelets, lymphocytes, alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, total bilirubin (TBIL), CA19-9, CA12-5).

Follow-up

All the patients with PDAC in our hospital were followed up by our team. A telephone follow-up was made every 3 months and the follow-up ended with the patient's dead. Patients routinely underwent enhanced abdominal computed tomography (CT) scans or magnetic resonance imaging (MRI) in every 3 months within first 1 year and every 6 months thereafter. The OS was defined as the period from the period between surgery and confirmed death or final follow-up. The RFS was defined as the period between surgery and tumor relapse or final follow-up.

Statistical analysis

R 3.5.2 project was used for analysis. The optimal cut-off value for blood test (neutrophils, platelets, lymphocytes, alanine aminotransferase [ALT], aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, total bilirubin (TBIL), CA19-9, CA12-5) was calculated by the X-tile 3.6.1 software (Yale University, New Haven, CT, USA).¹² Univariate Cox regression analysis was used to figure out prognostic factors for OS

and RFS of PDAC of pancreatic head. Hazard ratio and 95% Confidence interval (95% confidence interval [CI]) were calculated. And all subset regression analysis and multivariate Cox regression analysis was used to develop a prognostic model to predict OS for PDAC of pancreatic head. Log-rank test and Kaplan-Meier method were used to analyze and conduct survival curves. For all analysis, P value $< .05$ was considered to be statistically significant.

A nomogram based on the results of all subset regression analysis and multivariate Cox regression analysis was developed using R package rms. The predictive performance of the nomogram was assessed by C-index and calibration curve and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

Results

Clinicopathological characteristics

According to the criteria mentioned above, 112 patients with PDAC of pancreatic head were collected. The detailed clinicopathological characteristics were summarized in Table 1. Among the 112 patients included, 65 (58.0%) were male. The median age of the patients was 60 (ranging from 38 to 84) years. The median OS and RFS was 2.02 (ranging from 0.08 to 4.60) years and 1.33 (ranging from 0.06 to 4.20) years. Moreover, the 1-, 2-, and 3-year OS rates were 80.4%, 51.8%, and 26.8%, while the 1-, 2-, and 3-year RFS rates were 61.6%, 41.1%, and 21.4%. And 52 (46.4%) patients died before the last follow-up, while 63 (56.3%) patients suffered from recurrence before the last follow-up. According to histologic grade, the number of the cases of well, moderate and poor differentiation were 10 (8.93%), 86 (76.8%), and 16 (14.3%), respectively. Based on the AJCC Stage 8th, the number of the cases in stage IA, IB, IIA, IIB, III were 20 (17.9%), 21 (18.8%), 18 (16.1%), 47 (42.0%), and 6 (5.4%), respectively.

Univariate Cox regression analysis of prognostic factors

Using the X-tile 3.6.1 software for survival analysis, we determined the optimal cut-off value for parameters including age, neutrophil, platelet, lymphocyte, ALT, ALP, AST, TBIL, albumin, CA125, and CA19-9, as displayed in Table 1. We next performed univariate Cox regression analysis and found that age, histologic grade, AJCC Stage 8th, perineural invasion, TBIL, and CA19-9 were unfavorable prognostic factors for OS. And AJCC Stage 8th, perineural invasion, peripancreatic fat invasion, and CA19-9 were unfavorable prognostic factors for RFS in PDAC of pancreatic head.

A novel prognostic nomogram for OS

Based on the result of univariate Cox regression analysis for OS, we performed all subset analysis to integrate the significant prognostic factors in different combination to establish a

Table 1. Clinicopathological characteristics of patients with PDAC of pancreatic head: univariate Cox analysis.

CHARACTERISTIC	PATIENTS (N= 112)	OS			RFS		
		HR	95% CI	PVALUE	HR	95% CI	PVALUE
Gender (Female/male)	47/65	1.34	0.76-2.36	.31	1.15	0.69-1.90	.59
Age (≤ 58 / > 58 years)	47/65	2.18	1.19-3.99	.011	1.34	0.81-2.24	.26
Neoadjuvant chemotherapy (Yes/No)	12/100	1.84	0.86-3.91	.11	1.41	0.67-2.97	.36
Adjuvant chemotherapy (yes/no)	49/63	1.07	0.62-1.85	.82	1.27	0.77-2.08	.35
Preoperative biliary drainage (Yes/No)	31/81	1.45	0.82-2.57	.21	1.43	0.84-2.41	.19
Histologic grade (Well/Moderate/Poor)	10/86/16	1.82	1.01-3.30	.047	1.62	0.95-2.76	.07
AJCC Stage 8th (IA/IB/IIA/IIB/III)	20/21/18/47/6	1.83	1.40-2.41	1.28E-05	1.87	1.47-2.39	5.07E-07
Vascular cancer embolus (yes/no)	27/85	1.61	0.89-2.91	.11	1.44	0.84-2.50	.19
Perineural invasion (yes/no)	71/41	2.32	1.23-4.36	.0089	2.21	1.25-3.91	.0065
Peripancreatic fat invasion (Yes/No)	75/37	1.74	0.94-3.21	.078	2.04	1.14-3.65	.016
Neutrophil (≤ 5.0 / $> 5.0 \times 10^9/L$)	79/33	1.46	0.84-2.52	.18	1.23	0.74-2.03	.43
Platelet (≤ 300 / > 300)	68/44	0.79	0.93-1.01	.45	0.79	0.45-1.39	.41
Lymphocyte (≤ 0.86 / $> 0.86 \times 10^9/L$)	14/98	1.37	0.58-3.21	.47	1.73	0.75-4.02	.2
ALT (≤ 32 / > 32 U/L)	25/87	1.56	0.76-3.20	.23	1.77	0.90-3.48	.1
ALP (≤ 99 / > 99 U/L)	18/94	2.11	0.84-5.31	.11	2.24	0.96-5.20	.06
AST (≤ 30 / > 30 U/L)	23/89	1.37	0.67-2.82	.39	1.69	0.83-3.42	.15
TBIL (≤ 303.26 / > 303.26 $\mu\text{mol/L}$)	27/85	2.05	1.14-3.67	.016	1.51	0.87-2.6	.14
Albumin (≤ 34.4 / > 34.4 g/L)	42/70	1.46	0.81-2.64	.21	1.34	0.79-2.26	.28
CEA (≤ 4.5 / > 4.5 ng/mL)	51/61	0.92	0.76-1.10	.35	0.93	0.81-1.09	.38
CA12-5 (≤ 42.0 / > 42.0 U/L)	98/14	1.91	0.89-4.08	.096	1.71	0.84-3.47	.14
CA19-9 (< 749.1 / ≥ 749.1 U/L)	94/18	2.59	1.36-4.91	.0036	2.19	1.20-3.98	.01

Bold indicates P value < 0.05 was considered statistically significant. AJCC, American Joint Committee on Cancer; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; CEA, carcinoembryonic antigen; HR, hazard ratio; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival; TBIL, total bilirubin.

satisfactory nomogram for PDAC of the pancreatic head (Figure 1A). And we found the nomogram consisted of age, AJCC Stage 8th, perineural invasion, TBIL, and CA19-9 is an appropriate model (Figure 1). We then calculated the score of each patient based on this nomogram and the optimal cut-off value of the nomogram based score for OS (145). The whole cohort was divided into a high-score group (score > 145) and a low-score group (score < 145) based on the optimal cut-off value. The KM survival analysis for OS and RFS respectively showed a significant difference between high- and low-score groups (Figure 2A and B). In particular, 1-, 2-, and 3-year OS rates in low-score group and high-score group were 84.9% vs 59.5%, 77.9% vs 10.4%, and 66.8% vs 0%, respectively. And 1- and 2-year RFS rates in low-score group and high-score group were 76.1% vs 28.2% and 63.0% vs 0%, respectively. The C-indexes for OS and RFS prediction with the nomogram were

0.73 (95% CI: 0.66-0.80) and 0.69 (95% CI: 0.62-0.76), respectively, which are significantly higher than the C-index for AJCC Stage 8th (OS: 0.66, RFS: 0.67) ($P < .05$) (Table 2). These suggested the established nomogram had more powerful efficacy of discrimination for OS and RFS than that of AJCC Stage 8th.

Calibration curves for 1-, 2-, and 3-year OS and RFS in training cohort presented good agreement between the nomogram-predicted and actual observed survival probability [Figures 3A-C and 4A-C]. Besides, comparisons of the discriminatory ability between the nomograms and other single parameter through the ROC curve analysis were also shown in Figures 3D-F and 4D-F. The AUC values of the nomogram for predicting 1-, 2-, and 3-year OS and RFS were significantly higher than other single parameter, which are AJCC Stage 8th, age, perineural invasion, TBIL, and CA19-9 [Figures 3D-F and 4D-F].

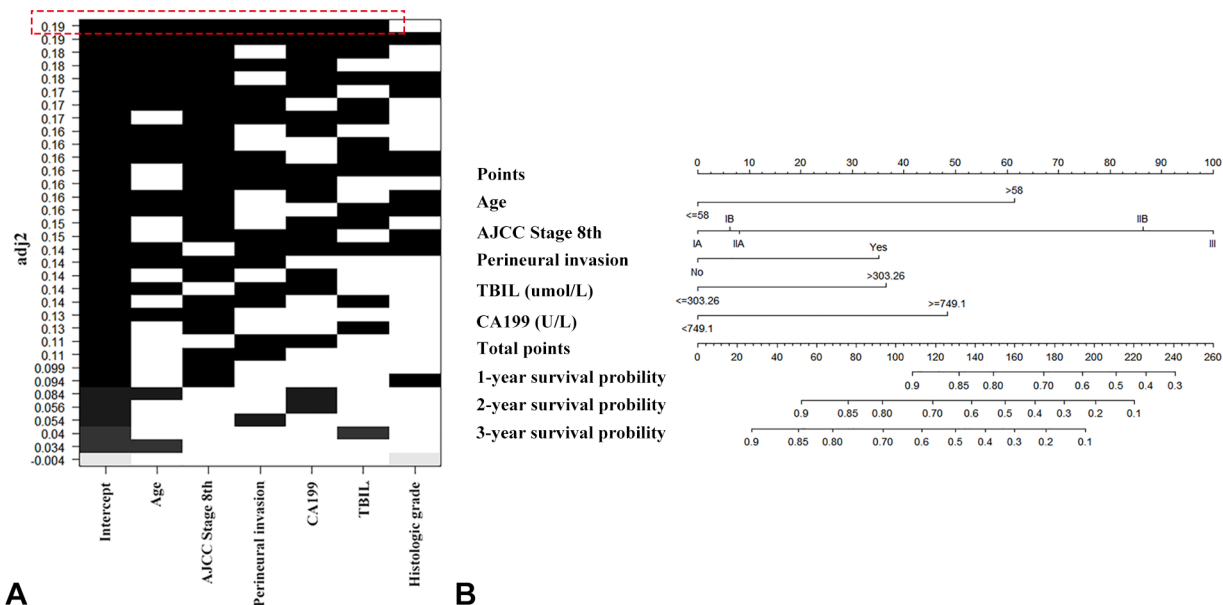


Figure 1. Construction an appropriate prognostic nomogram for PDAC of pancreatic head. (A) All subset regression analysis to figure out prognostic factors for an appropriate model to predict OS for PDAC of pancreatic head. (B) A predictive nomogram based on age, AJCC Stage 8th, perineural invasion, TBIL, and CA199. AJCC indicates American Joint Committee on Cancer; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; TBIL, total bilirubin.

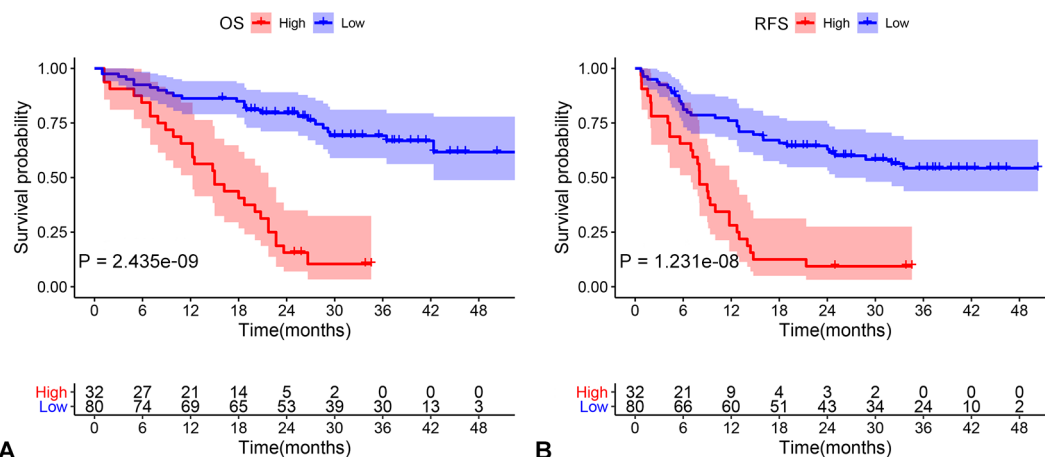


Figure 2. Kaplan-Meier survival curves for OS and RFS of patient with PDAC of pancreatic head after pancreaticoduodenectomy according to the nomogram score. Patients with PDAC of pancreatic head with score > 145 were inclined to significantly worse OS (A) and RFS (B). The P value were analyzed by the log-rank test. OS indicates overall survival; PDAC, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival.

Table 2. Discriminatory capabilities of nomogram and AJCC Stage 8th in patients with PDAC of pancreatic head: C-index in OS and RFS prediction.

	OS		RFS	
	C-INDEX	95% CI	C-INDEX	95% CI
Nomogram	0.73	0.66-0.80	0.69	0.62-0.76
AJCC Stage 8th	0.66	0.59-0.73	0.67	0.60-0.74
Nomogram by Li et al	0.68	0.61-0.75		
Nomogram by He et al	0.6	0.51-0.69		

AJCC, American Joint Committee on Cancer; C-index, concordance index; CI, Confidence interval; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival.

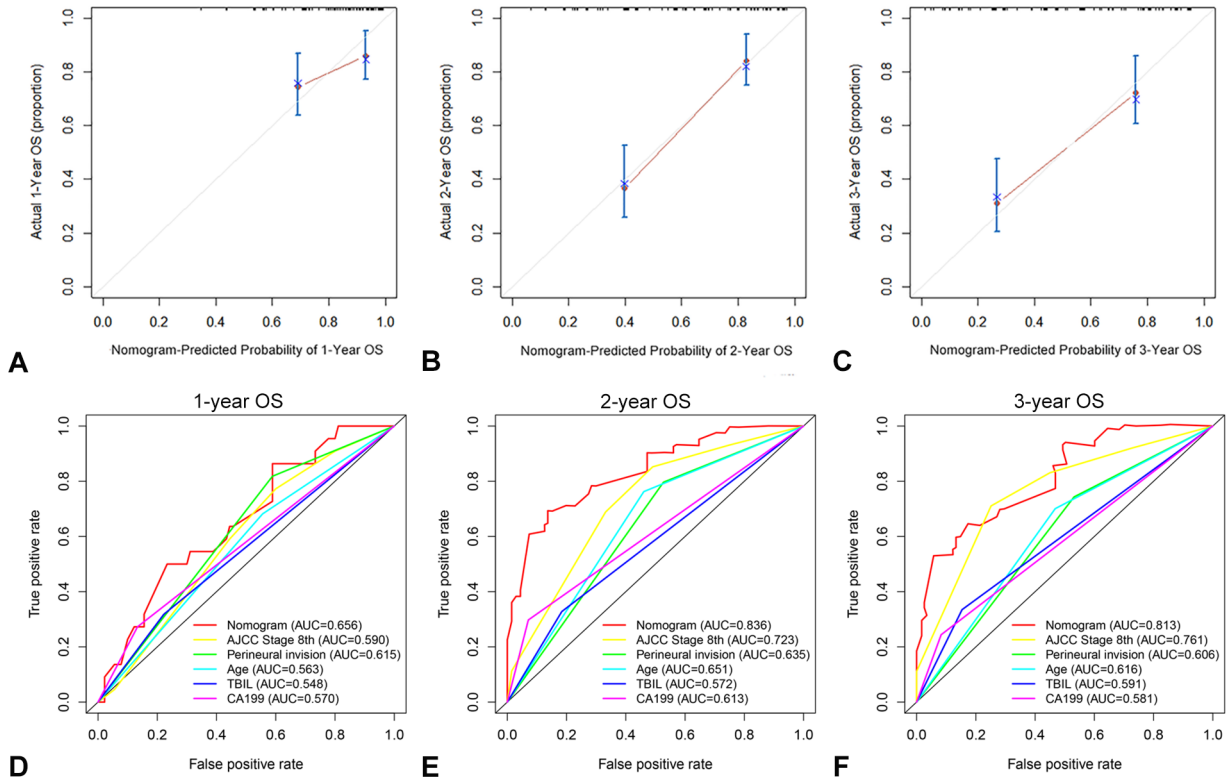


Figure 3. Evaluation of the fitting degree and predictive accuracy of the nomogram for OS prediction. (A-C) Calibration plot for 1-, 2-, and 3-year OS of the established nomogram. (D-F) ROC analysis for 1-, 2-, and 3-year OS of the nomogram and other single parameter, which are AJCC Stage 8th, age, perineural invasion, TBIL, and CA19-9. AJCC, American Joint Committee on Cancer; OS, overall survival; ROC, receiver operating characteristic; TBIL, total bilirubin.

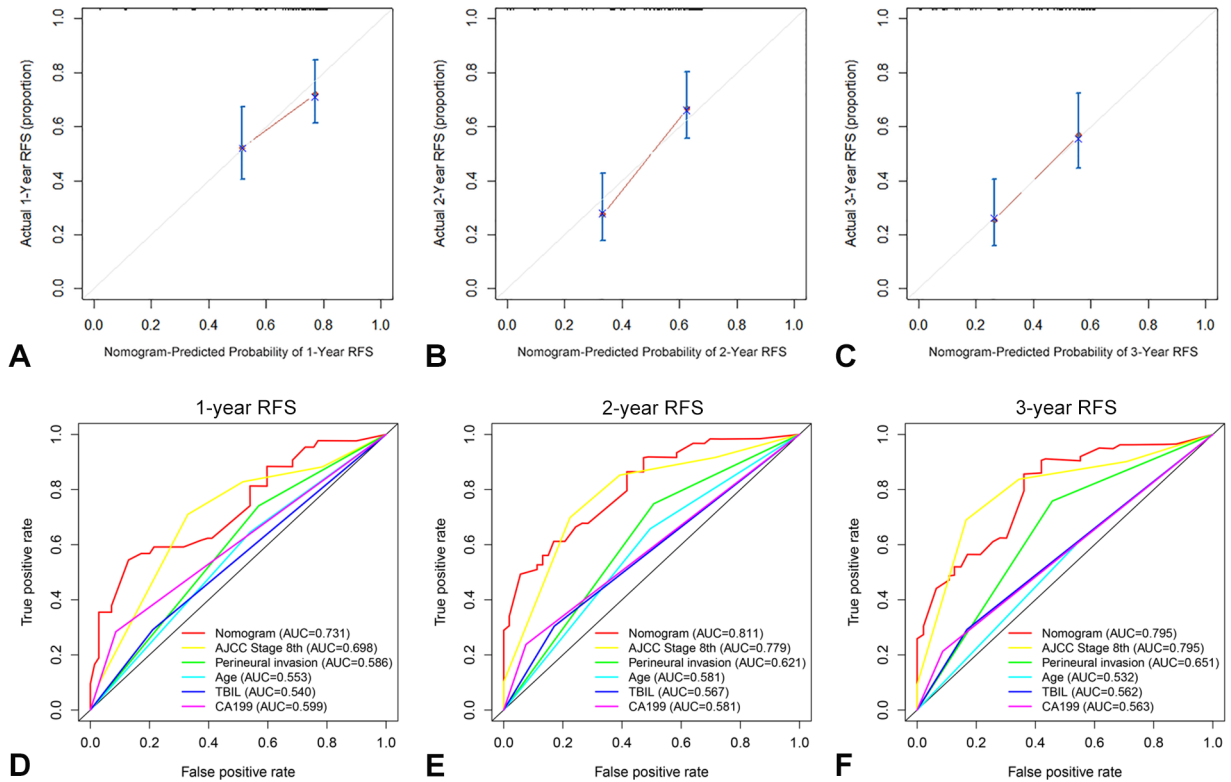


Figure 4. Evaluation of the fitting degree and predictive accuracy of the nomogram for RFS prediction. (A-C) Calibration plot for 1-, 2-, and 3-year RFS of the established nomogram. (D-F) ROC analysis for 1-, 2-, and 3-year RFS of the nomogram and other single parameter, which are AJCC Stage 8th, age, perineural invasion, TBIL, and CA19-9. AJCC, American Joint Committee on Cancer; RFS, recurrence-free survival; ROC, receiver operating characteristic; TBIL, total bilirubin.

Comparison among different prognostic models for PDAC of pancreatic head

We further compared our prognostic models with other reported models for pancreatic head cancer using the data from our institute.^{7,11} The results showed the C-index of these two previously reported nomogram for OS were 0.68 (95% CI: 0.61-0.75) and 0.60 (95% CI: 0.51-0.69), both of which were statistically lower than C-index of our nomogram (C-index=0.73, 95% CI: 0.66-0.80) (Table 2).

Discussion

Pancreatic ductal adenocarcinoma (PDAC) of the pancreatic head is one of the most aggressive cancers and also one of the most difficult cancers to cure.¹³ In the current study, we utilized the retrospective data of patients with PDAC of pancreatic head following pancreaticoduodenectomy in our hospital to assess the impact of clinicopathological characteristics on patients' prognosis. Moreover, a well-calibrated prognostic nomogram was constructed to predict OS and RFS in patients with PDAC of pancreatic head. The established nomogram showed superior predictive performance compared with AJCC Stage 8th, which was confirmed by the higher C-indexes and AUC values for OS and RFS. Taken together, the current nomogram presents satisfactory predictive power for PDAC of pancreatic head following curative operation. Our study may facilitate clinicians to identify more "aggressive" tumors and choose more individually appropriate therapy.

We introduced serum parameters including TBIL and CA19-9 to develop the prognostic model. CA19-9, a sialylated Lewis blood group antigen, is normally embedded on cell surfaces as gangliosides and mucins on epithelial of the pancreatic ducts and biliary tract.¹⁴ It is widely considered as a useful diagnostic and prognostic biomarkers for PDAC.¹⁵ Gu et al reported that elevated CA19-9 was correlated with poor survival, which HRs reaching 9.95.^{16,17} The sensitivity and specificity of CA19-9 for diagnosing PDAC could reach 80% and 80%-90%, respectively.¹⁸ In the current study, we also confirmed that patients with higher CA19-9 levels (≥ 749.1 U/L) had worse OS and RFS than those with low CA19-9 levels (< 749.1 U/L). Though some previous studies failed to find a significant association between TBIL and survival of patients with PDAC, our study demonstrated that TBIL was a valuable predictor for PDAC of pancreatic head following operation in our study, which was consistent with the studies by Zhang et al¹⁹ and Yoon et al.²⁰ Actually, hyperbilirubinemia reflects malignant tumor features including bile duct compression and invasion, which significantly associated with poor prognosis of patients with PDAC of pancreatic head.²¹ Thus, preoperative biliary drainage might decrease the level of TBIL but contributed little to the prognosis of patients.²² It should be pointed out that CA19-9 level may be affected by elevated TBIL. Indeed, we found in our study that CA19-9 were weakly associated with TBIL (Cor=0.23, $P=.015$) (Figure S1). Consistently, Liu et al²³ also identified the association between

CA19-9 and TBIL in obstructive jaundice patients (e.g. gallbladder adenocarcinoma, extrahepatic cholangiocarcinoma, periampullar adenocarcinoma and pancreatic adenocarcinoma). However, Hartwig et al²⁴ and Dong et al²⁵ reported that hyperbilirubinemia did not markedly affect the level of CA19-9. And Mann et al²⁶ also demonstrated that synthesis of CA19-9 by the proliferating tumor cells contributed to the majority of CA19-9 in malignant tumors. Still, the prognostic value of CA19-9 in patients with hyperbilirubinemia should be re-considered combined with the influence of elevated TBIL. And oncologists need to evaluate cancer malignancy comprehensively by CA19-9, TBIL and other parameters. Other than vascular invasion, perineural invasion is a specific feature of PDAC that is correlated with poor prognosis and tumor recurrence.²⁷ Yang et al²⁸ reported that perineural invasion was associated with an immunosuppressive microenvironment characterized by impaired CD8⁺T cells infiltration and a reduced Th1/Th2 ratio, thereby favoring tumor progression. And Tahkola et al²⁹ also found that perineural invasion was an independent prognostic factor for PDAC, which was consistent with our study. Therefore, as an important clinicopathological characteristic and predictor, perineural invasion should be included in the new stage system or prognostic model for clinical evaluation.

Previously two predictive nomogram for PDAC of pancreatic head were established in other studies.^{7,11} Both studies were based on SEER database and mainly consider factors of tumor itself, lymph node and metastasis status without including other factors. Importantly, we compared the predictive power of these models and found our model had greatest C-index, indicating our model had better combination and better predictive efficacy. In addition, our model is sample and practical for application in clinic because all the parameters are easy to obtain. Of note, we identify high-risk patients using the nomogram, who were shown to have worse prognosis even after surgical resection. And we propose intensive and proper management for these patients. First, we recommend that patients with higher scores (>145 in the nomogram) should receive close follow-up following operation. Second, we recommend analyzing the genetic information of the high-risk tumors, especially the mutation status of critical driver genes. Third, high-risk patients should receive appropriate adjuvant therapy following operation. In particular, it will be of interest to investigate whether targeted therapy, for example, PARP inhibitor, or immune checkpoint inhibitors will have extra benefit for these high-risk patients in the context of adjuvant therapy.

The main limitation of this study is a single-center retrospective study, with a relatively small sample size. Thus, a multicenter and large cohort based study should be performed to validate our findings in the future.

Conclusion

Our study developed a novel prognostic model to predict the OS and RFS for patients with PDAC of the pancreatic head following curative operation. The established nomogram

incorporating age, AJCC Stage 8th, perineural invasion, TBIL and CA19-9 presents high predictive accuracy. Future studies are needed to further validate our findings.

Author Contributions

Conceptualization, HZ, CZ and BH; Data curation, HZ, ZZ; Formal analysis, HZ; Methodology, HZ, ZZ; Resources, BC, CZ and BH; Software, HZ, ZM, ZZ, YG, and SW; Supervision, CZ and BH; Validation, HZ, SH, ZL, and CL; Visualization, HZ; Writing—original draft, HZ; Writing—review & editing, HZ, BC, CZ and BH.

Data Availability

The datasets used in the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The protocol of this study was approved by the Clinical Research Ethic Committee of Guangdong Provincial People's Hospital.

Informed Consent

All informed consents were obtained from patients.

ORCID iD

Baohua Hou  <https://orcid.org/0000-0003-2786-3925>

Supplemental material

Supplemental material for this article is available online.

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