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Original Article

Prognostic stratification based on a novel nomogram for left-sided pancreatic adenocarcinoma after surgical resection: a multi-center study

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Abstract: Left-sided pancreatic adenocarcinoma (LPAC) has a poorer prognosis and has some distinct features compared to cancer of pancreatic head. A reliable model to predict the prognosis of LPAC following surgery is needed in clinical practice. Our study included 231 patients with resected LPAC from 3 Chinese pancreatic disease centers. Cox-regression analysis was conducted to identify independent risk factors of LAPC. Then we established a nomogram and performed C-index, receiver operating characteristic curve, calibration plot and decision curve analysis to assess its discrimination and calibration. As a result, CA19-9, surgical margin, tumor differentiation, lymph node metastasis, and postoperative adjuvant chemotherapy were identified as significant prognostic factors. Based on these predictors, a novel nomogram was constructed. The nomogram achieved high C-indexes in the training cohort (0.805) and validation cohort (0.719), which were superior than the AJCC-8 staging system and other nomograms. The area under curve of the nomogram for predicting patients survival at 1-, 2-, and 3-year in training cohort were more than 0.8. Kaplan-Meier survival curve for the subgroups stratified based on the nomogram showed a better separation than the AJCC-8 stage I, II, III, indicating a superior ability of risk stratification for our model. In summary, we constructed a nomogram which showed a better predictive ability for patients' survival with LPAC after surgical resection than the AJCC staging system and other predictive models. Our model would be helpful to discriminate high-risk LPAC and facilitate clinical decision making.

Keywords: Left-sided pancreatic adenocarcinoma, nomogram, overall survival, prognostic stratification

Introduction

Pancreatic cancer (PC) is one of the most malignant cancers in the world, accounting 4.5% of all cancer-related deaths [1]. The highly aggressive phenotype and early recurrence and metastasis of tumor are still the critical causes for the adverse prognosis [2]. PC is mainly divided into two cancer types specifically: pancreatic adenocarcinoma, which occupies 85% of cases and originates from exocrine glands of pancreas, and pancreatic neuroendocrine tumors, which are rare (less than 5%) and occurs in the endocrine tissue [3]. Left-sided pancreatic adenocarcinoma (LPAC), also known as adenocarcinoma of pancreatic body and tail, accounts for 15% of pancreatic adenocarcinoma [4]. It's more often metastasized at diagnosis and associated with poor prognosis, possibly because of delayed consultation caused by the absence of specific symptoms [4]. Pathologically, LPAC was related to the squamous subtype [5]. It enriched for genes that are involved in epithelial-mesenchymal transition

(EMT) and tumor invasion, as well as poor anti-tumor immune response [5].

Despite numerous recent progresses in the management of LPAC, there are almost no breakthroughs for effective biomarkers nor treatment strategies. The only potentially curable treatment still remains to be surgical resection [1]. The traditional tumor staging system, Tumor Node Metastasis (TNM) staging system published by the American Joint Committee on Cancer (AJCC) was regarded as one of the most staging systems for predicting PC prognosis [6]. However, it mainly emphasizes pathological outcomes but ignores some critical demographic and serological characters. Some researchers tried to improve AJCC staging system and establish new nomograms for LPAC based on the Surveillance, Epidemiology, and End Results (SEER) datasets [7, 8]. However, due to data limitation, some vital indicators including tumor markers (carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 19-9) and pathological features (perineural and lymphovascular invasion, surgical margin) were not included in their studies. Numerous literature have proved that indicators like carbohydrate antigen 19-9, perineural and lymphovascular invasion, surgical margin were the important prognostic factors of PC [1, 3]. Lack of these data will largely reduce the predictive effect of the prognostic model. Therefore, it's urgent to develop a more precise and comprehensive model for predicting the prognosis of patients with resected LPAC.

In current study, demographic, serological and pathological information of 231 patients with LPAC from 3 Chinese pancreatic disease centers were collected. Cox regression analyses were used to identified significant prognostic factors of LPAC. Built on the selected predictors, we established a novel nomogram and compared predictive power of the new-established nomogram with AJCC staging system and other nomograms published previously.

Materials and methods

Data collection

Patients who diagnosed with LPAC and underwent surgical resection from 2008 to 2019 in 3 Chinese pancreas centers in Guangdong Provincial People's Hospital, Sir Run Run Shaw Hospital, and Peking Union Medical College Hospital were enrolled into the study. The inclusion criteria were as follows: 1) primary diagnosed pancreatic adenocarcinoma pathologically and confirmed LPAC by radiographic evaluation; 2) had undergone surgical resection including Distal Pancreatectomy (DP) or Radical Antegrade Modular Pancreatosplenectomy (RAMPS); 3) $\geq$ 18 years old and $\leq$ 85 years old; 4) the score of American Society of Anesthesiologists (ASA) < III. Patients 1) with distant metastasis; 2) the clinical and pathological data was incomplete; 3) had second primary maligancy; 4) had preoperative adjuvant treatment; 5) died in one month after surgical resection were excluded from the study. Enrolled patients' demographic, serological and pathological information including gender, body mass index (BMI), age, diabetes mellitus (DM), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), jaundice, serum albumin, tumor size, surgical margin, tumor differentiation, perineural invasion, lymphovascular invasion, Lymph node metastasis (LNM), Lymph node positive rate (LNR), Postoperative adjuvant chemotherapy (PAC), and AJCC stage were manually collected. AJCC 8th edition (AJCC-8) staging system was used to determined patients' AJCC stage [9]. The primary endpoints were overall survival (OS), defined as the date of surgery to the death, and disease-free survival (DFS), defined as the recurrence or last follow-up.

Study design

Under the inclusion and exclusion criteria, eligible patients and corresponding clinicopathological information were reviewed retrospectively. Patients from Guangdong Provincial People's Hospital and Sir Run Run Shaw Hospital were enrolled into training cohort, while the external validation cohort comprised patients from Peking Union Medical College Hospital. Cox regression analysis was firstly used to find the independent risk factors for LPAC. A nomogram was constructed according to the significant prognostic factors and then validated in training and validation cohorts. The predictive capacity of the nomogram was compared with AJCC-8 staging system and nomograms published previously [7, 8]. The study was approved by the Medical Research Ethics Committee of Guangdong Provincial People's

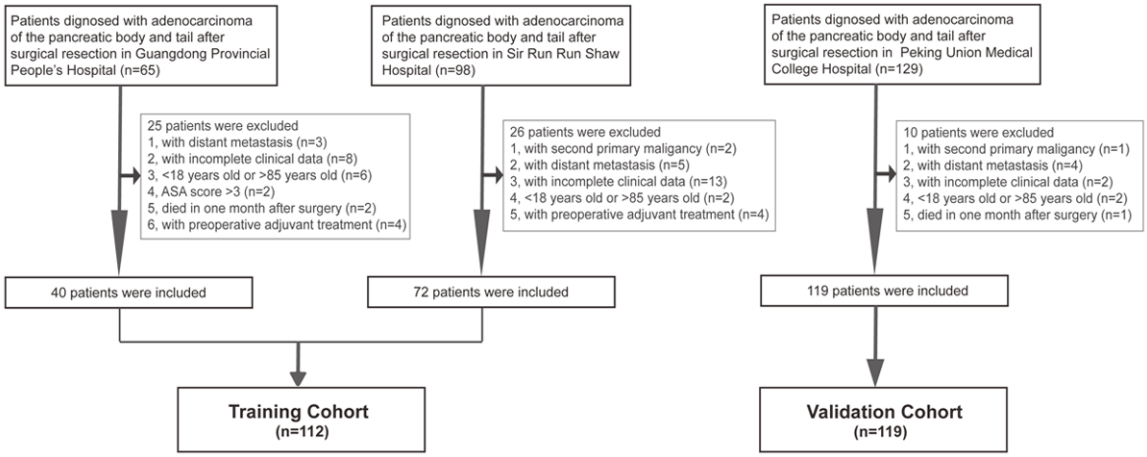

Figure 1. The flow diagram of the selection process for the training and validation cohorts.

Hospital, Sir Run Run Shaw Hospital, and Peking Union Medical College Hospital. All enrolled patients provided written informed consent. The study was executed in accordance with Declaration of Helsinki of the World Medical Association.

Statistical analysis

Some continuous variables (i.e. age, CA19-9, CA12-5, CEA, serum albumin, LNR) were converted to categorical variables. X-tile (New Haven, CT, United States) was used to defined the best cutoff values for outcome-based optimization. Categorical data were compared by using Chi-square and Fisher's exact tests. Univariate and multivariate cox proportional hazards regression was conducted to identify potential prognostic risk factors and a visual nomogram was established based on the risk factors. The discrimination performance of the nomogram was evaluated by the concordance index (C-index) and receiver operating characteristic curve (ROC) analysis. The area under curve (AUC) of ROC was performed to assess predicting ability of 1-, 2-, and 3-year survival of the nomograms. The calibration of the nomogram was estimated using calibration plots. Decision curve analysis (DCA) was performed to evaluate the net benefit and clinical performance of the nomogram. Cut-offs made by X-tile was used to divide patients into high-risk, middle-risk and low-risk subgroups. The predictive power of the nomogram among three subgroups was assessed by the Kaplan-Meier analyses and log-rank tests. R 4.0.0 version software (http://www.r-project.org/) with packages "survival", "rms", "foreign", "pROC", and "survminer" were used for statistical analyses. All tests were two-sided and *P*-value < 0.05 was considered as statistically significant.

Results

Patient characteristics and follow-up

Under the established criteria, 40 patients with LPAC after surgical resection from Guangdong Provincial People's Hospital and 72 patients from Sir Run Run Shaw Hospital were enrolled into training cohort, while 119 patients from Peking Union Medical College Hospital were enrolled into validation cohort (**Figure 1**). The median ages of patients in training and validation cohort were 64 and 62, respectively. In the training cohort, most patients (43; 38.4%) were classified as AJCC-8 stage IIA, 31 patients (27.7%) were stage IIB, 24 patients (21.4%) were stage IB, 6 patients (5.4%) were stage IA and 8 patients (7.1%) were stage III. In the validation cohort, most patients (49; 41.2%) were categorized as AJCC stage IIB, 35 patients (29.4%) were stage IIA, 23 patients (19.3%) were stage IB, 4 patients (3.4%) were stage IA and 8 patients (6.7%) were stage III. A total of 73 (65.2%) patients in training cohort and 80 (67.2%) patients validation cohort had received chemotherapy after surgical resection. A summary of other clinicopathologic characteristics of the patients was listed in **Table 1**. Continuous variables including age, CA19-9, CA12-5, CEA, serum albumin, LNR were converted to categor-

Table 1. A summary of clinicopathologic characteristics of the patients in training and validation cohorts

Characteristics	Training Cohort (n=112)	Validation Cohort (n=119)	*P*-value
Gender			0.9713
Male	59 (52.68%)	64 (53.78%)	
Female	53 (47.32%)	55 (46.22%)	
Age (Years)			0.9249
≥ 60	68 (60.71%)	74 (62.18%)	
< 60	44 (39.29%)	45 (37.82%)	
BMI (kg/m^2)			0.2789
≥ 24	35 (31.25%)	47 (39.50%)	
18.5-24	67 (59.82%)	66 (55.46%)	
< 18.5	10 (8.93%)	6 (5.04%)	
Diabetes			0.4756
Absent	82 (73.21%)	81 (68.07%)	
Present	30 (26.79%)	38 (31.93%)	
CA19-9 (U/ml)			0.3894
≥ 312	27 (24.11%)	36 (30.25%)	
< 312	85 (75.89%)	84 (69.75%)	
CA125 (U/ml)			-
≥ 26.7	25 (22.32%)	-	
< 26.7	87 (77.68%)	-	
CEA (ng/ml)			0.3733
≥ 2.10	69 (61.61%)	81 (68.07%)	
< 2.10	43 (38.39%)	38 (31.93%)	
Serum albumin (g/L)			0.1038
≥ 43.3	25 (22.32%)	39 (32.77%)	
< 43.3	87 (77.68%)	80 (67.23%)	
Jaudice			-
Absent	103 (91.96%)	-	
Present	9 (8.04%)	-	
Tumor size (cm)			0.08287
≥ 4	66 (58.93%)	64 (53.78%)	
2-4	36 (32.14%)	51 (42.86%)	
< 2	10 (8.93%)	4 (3.36%)	
Surgical margin			0.5461
R1	12 (10.71%)	9 (7.56%)	
R0	100 (89.29%)	110 (92.44%)	
Differentiation			0.5960
Well	15 (13.39%)	21 (17.65%)	
Moderately	55 (49.11%)	59 (49.58%)	
Poorly	42 (37.50%)	39 (33.27%)	
Lymphovascular invasion			0.9531
Absent	11 (9.82%)	13 (10.92%)	
Present	101 (90.18%)	106 (89.08%)	
Perineural invasion			0.2418
Absent	66 (58.93%)	80 (67.23%)	
Present	46 (41.07%)	39 (32.77%)	

Lymph node metastasis(LNM)			0.05982
Absent	73 (65.18%)	62 (52.10%)	
Present	39 (34.82%)	57 (47.90%)	
Lymph node positive rate (LNR)			0.7684
≥ 0.06	34 (30.36%)	33 (27.73%)	
< 0.06	78 (69.64%)	86 (72.27%)	
Postoperative adjuvant chemotherapy (PAC)			0.8495
Absent	39 (34.8%)	39 (32.8%)	
Present	73 (65.2%)	80 (67.2%)	
AJCC Stage			0.2743
IA	6 (5.4%)	4 (3.4%)	
IB	24 (21.4%)	23 (19.3%)	
IIA	43 (38.4%)	35 (29.4%)	
IIB	31 (27.7%)	49 (41.2%)	
III	8 (7.1%)	8 (6.7%)	

BMI-Body mass index; CA19-9-Carbohydrate Antigen 19-9; CA125-Carbohydrate Antigen 125; CEA-Carcinoembryonic Antigen; LNM-Lymph node metastasis; LNR-Lymph node positive rate; PAC-Postoperative adjuvant chemotherapy; AJCC-American Joint Committee on Cancer.

ical variables. Overall, the median follow-up of training and validation cohort were 16.8 months and 15.6 months. The 1-, 2-, and 3-year OS rates were 72.3%, 36.8%, 28.3% in training cohort and 75.2%, 38.3%, 30.4% in validation cohort.

Identification of independent risk factors

Univariate cox regression analysis was conducted and CA19-9, CA125, CEA, surgical margin, tumor histologic differentiation, perineural invasion, LNM, LNR, and PAC were identified as potential prognostic risk factors (*P*-value < 0.05). All significant univariable predictors were selected into multivariate cox regression analysis. It's showed that CA19-9, surgical margin, tumor histologic differentiation, LNM, and PAC were independent risk factors of patients with resected LPAC. Then the Schoenfeld residuals analyses were performed to assess whether the assumption of proportional hazards was valid (**Figure 2**). The *P*-values for CA19-9, surgical margin, differentiation, LNM, and PAC were 0.0599, 0.8258, 0.1408, 0.4489, and 0.5149, respectively. The *P*-value of the global test was 0.1089. Therefore, the selected indicators met up with the proportional hazards assumption. Further, Kaplan-Meier analyses validated that higher CA19-9, positive surgical margin and LNM were significantly associated with poorer survival, while well differentiated tumor and PAC treatment were associated with better survival (**Figure 3**). Taken together, the results in **Table 2** and **Figures 2**, **3** indicates CA19-9, surgical margin, tumor histologic differentiation, LNM, and PAC were critical prognostic predictors for LPAC.

Construction and validation of a prognostic nomogram

A prognostic nomogram was constructed based on the five significant prognostic risk factors for predicting patient survival of LPAC (**Figure 4**). In our nomogram, each risk factor was given a score based on a point scale: CA19-9 < 312 U/ml, R0 surgical margin, well differentiation, absence of LNM, and presence of PAC was given 0 points; CA19-9 ≥ 312 U/ml was given 64 points; R1 surgical margin was assigned 100 points; Moderately differentiation was given 26 points; Poorly differentiation was given 63 points; Presence of LNM was given 20 points; Absence of PAC was given 42 points. Lastly the total points could be added together and converted to obtain the 1-, 2- and 3-year survival rate.

We next used the C-index and AUC of ROC to assess the discriminatory power of the nomograms. As shown in **Table 3**, our nomogram achieved high C-indexes in both training cohort [0.805 (95% CI, 0.775-0.825)] and validation cohort [0.719 (95% CI, 0.698-0.740)]. Importantly, we found the C-index of our model was

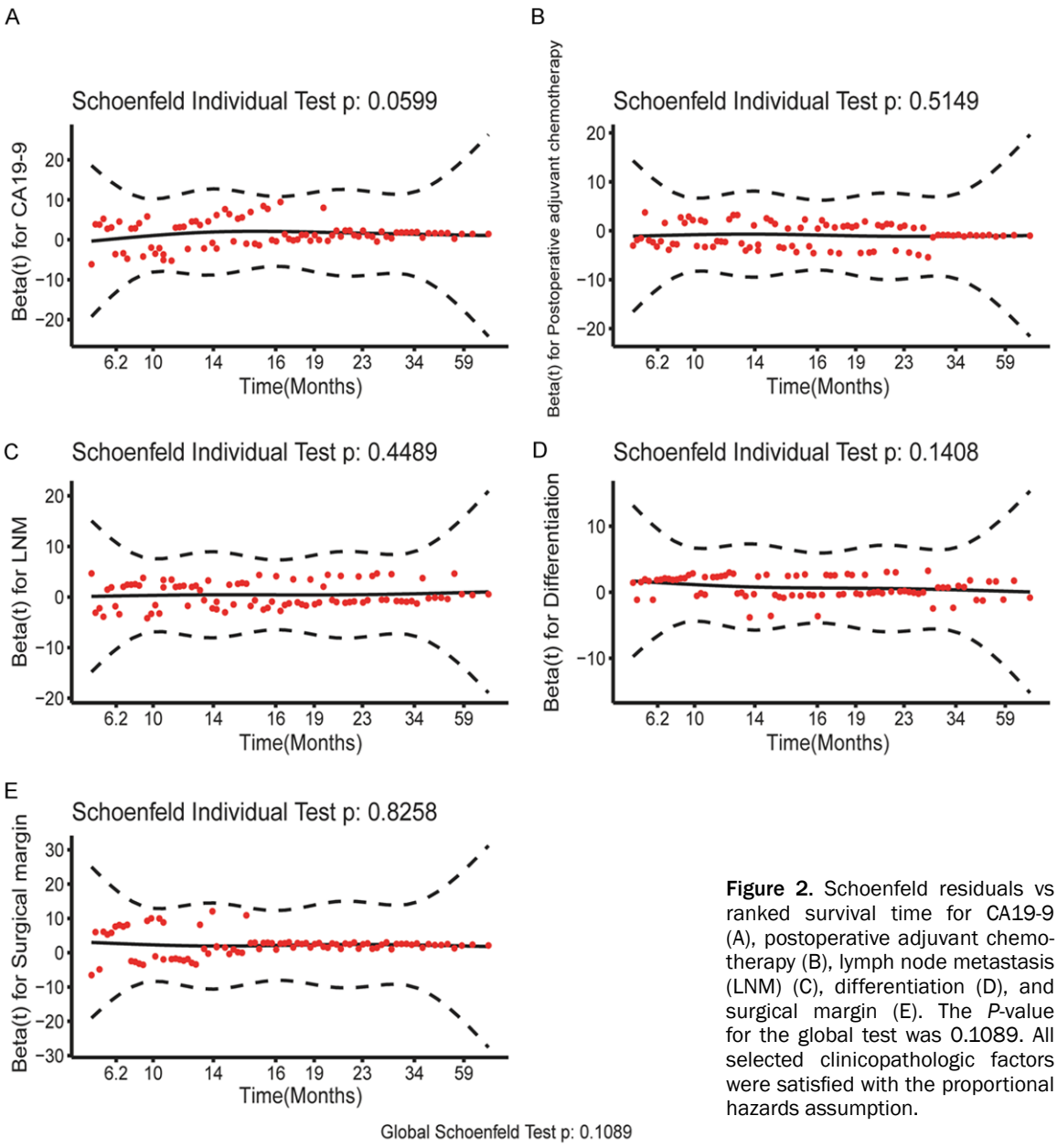

Figure 2. Schoenfeld residuals vs ranked survival time for CA19-9 (A), postoperative adjuvant chemotherapy (B), lymph node metastasis (LNM) (C), differentiation (D), and surgical margin (E). The *P*-value for the global test was 0.1089. All selected clinicopathologic factors were satisfied with the proportional hazards assumption.

higher than the AJCC-8 staging system and other predictive models. The AUC value of our nomogram for predicting 1-, 2-, and 3-year survival were 0.843, 0.818, 0.813 in training cohort and 0.722, 0.675, 0.667 in validation cohort, which were also higher than the AJCC-8 staging system and other predictive models (**Table 3**; **Figure 5D**, **5E**).

The calibration curves for predicting 1-, 2-, and 3-year survival probabilities matched with the actual survival rates well (**Figure 6**). And DCA were performed to evaluate the net benefit and clinical performance. The results showed that the nomogram had a better net benefit with a wider range of threshold probabilities than AJCC-8 staging system in training cohort for both 1-, 2-, and 3-year survival (**Figure 7A-C**), indicating a better clinical benefit for both patients and clinicians. Taken together, the results in **Table 3** and **Figures 4-7** suggested the nomogram we developed had an effective predictive value and has extra yield compared to the AJCC-8 staging system.

Prognostic stratification based on the nomogram for LPAC

To explore the ability for stratify high-risk patients of our nomogram, all patients were

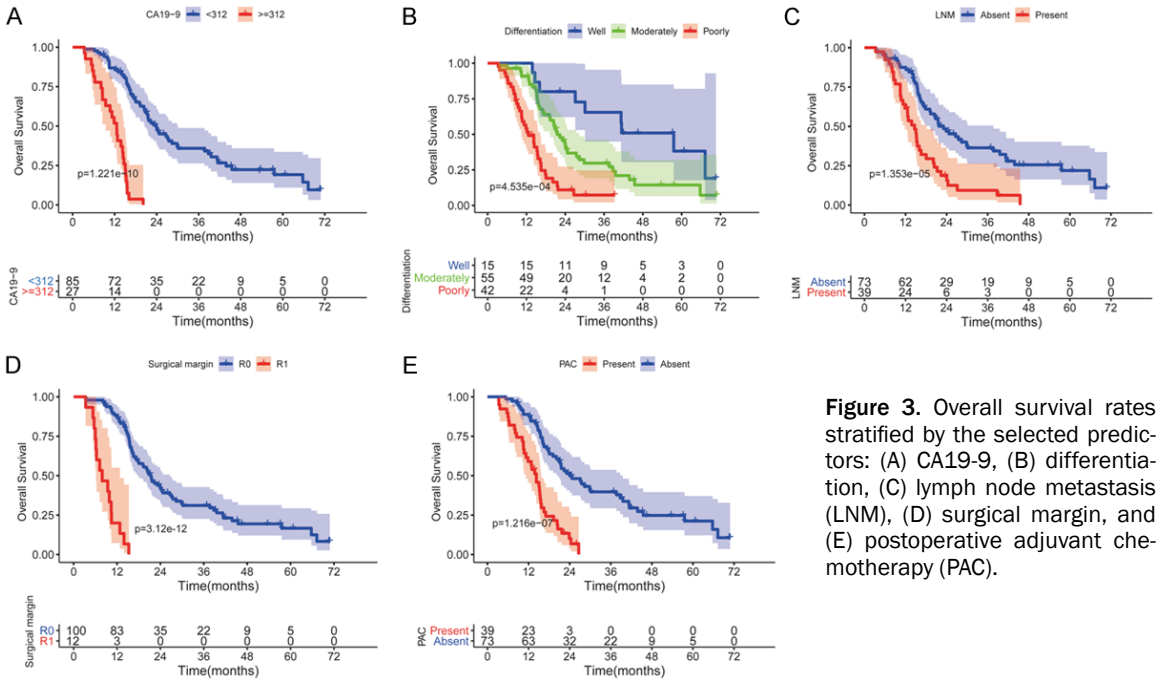

Figure 3. Overall survival rates stratified by the selected predictors: (A) CA19-9, (B) differentiation, (C) lymph node metastasis (LNM), (D) surgical margin, and (E) postoperative adjuvant chemotherapy (PAC).

divided into high-risk, middle-risk and low-risk subgroups based on the cut-off made by X-tile: high-risk ≥ 160; low risk < 80; and 80 ≤ middle-risk < 160. Kaplan-Meier analysis was conducted to determine OS and DFS among three subgroups (**Figure 8A** and **8B**). We found the high-risk group had the worst survival rate while the low-risk group had the best survival rate, indicating an adverse outcome for high-risk LPAC. Meanwhile, the OS and DFS of patients of AJCC-8 stage I, II, III were also displayed in **Figure 8C** and **8D**. Compared with AJCC-8 staging system, our nomogram presented a superior ability to classify the risk stratification of patients with LPAC, as the survival curve for the three subgroups had better separation than the survival curve for the AJCC-8 stage I, II, III.

Discussion

As a highly aggressive cancer, LPAC may easily relapse and progress even after curative-intent resection. It is of great value to develop a prognostic model for predicting patient survival and identity high-risk patients. In the current study, we performed analyses based on multi-center dataset and identified CA19-9, surgical margin, tumor histologic differentiation, LNM, and PAC as independent prognostic factors of LPAC. Further, we established a novel nomogram, which displayed a high C-indexes and AUC value and had more powerful predictive ability than the AJCC-8 staging system. Besides, we divided the patients into subgroups based on the nomogram and stratify the high-risk and low-risk LPAC patients, which would help oncologist better arrange the follow up and make individualized treating strategy.

Serum CA19-9 level has a high sensitivity (approximately 80%) in the diagnosis of PC and currently it is the most commonly used and effective biomarker for PC [10]. It has been reported that preoperative CA19-9 level could reflect tumor stage, tumor resectability, pathological grade and LNM in PC patients to some extent [11, 12]. In addition, the response of CA19-9 was also a great indicator of curative effect of chemotherapy and surgery [13-15]. Previous studies have proved that a low CA19-9 level (< 250 U/mL) was associated with better survival in patients with resected LPAC [16]. In the present study, we demonstrated serum CA19-9 level ≥ 312 U/ml was the independent prognostic risk factors of LPAC and first added CA19-9 into a predictive model for resected LPAC. Of note, CA19-9 may also be a promising target for treating PC. CA19-9 conjugating targeting therapy, CA19-9 antibody-dependent cell-mediated cytotoxicity, inhibition of CA19-9 biosynthetic enzymes, and blockade of CA19-

Table 2. Univariate and multivariate cox regression analysis for overall survival

Patient characteristics		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender	Male/Female	1.133 (0.7341-1.749)	0.572		
Age	≥ 60/< 60	1.138 (0.7392-1.751)	0.558		
BMI	≥ 24/18.5-24/< 18.5	0.9501 (0.6705-1.346)	0.774		
Diabetes	Present/Absent	1.017 (0.6196-1.668)	0.948		
CA19-9	≥ 312/< 312	7.6 (4.293-13.45)	3.39E-12	3.8450 (1.9634-7.5299)	8.59E-05
CA125	≥ 26.7/< 26.7	2.033 (1.244-3.322)	0.00462	1.5928 (0.9519-2.6652)	0.076359
CEA	≥ 2.10/< 2.10	2.494 (1.564-3.977)	0.000124	1.4099 (0.8281-2.4005)	0.205805
Albumin	≥ 43.3/< 43.3	1.557 (0.9472-2.559)	0.0808		
Jaundice	Present/Absent	0.7001 (0.2832-1.731)	0.44		
Tumor size	≥ 4/2-4/< 2	1.165 (0.8418-1.613)	0.356		
Surgical margin	R1/R0	12.63 (6.344-25.14)	5.24E-13	9.6355 (4.6746-19.8612)	8.32E-10
Differentiation	Poorly/Moderately/Well	2.714 (1.888-3.902)	6.93E-08	1.9926 (1.3651-2.9084)	0.000353
Lymphovascular invasion	Present/Absent	0.672 (0.3238-1.394)	0.286		
Perineural invasion	Present/Absent	1.691 (1.083-2.641)	0.0208	1.1259 (0.6836-1.8545)	0.641343
Lymph node metastasis (LNM)	Present/Absent	2.601 (1.666-4.063)	2.62E-05	3.4018 (1.0396-11.1318)	0.042956
Lymph node positive rate (LNR)	≥ 0.06/< 0.06	2.362 (1.506-3.704)	0.000182	0.4472 (0.1305-1.5325)	0.20033
Postoperative adjuvant chemotherapy (PAC)	Present/Absent	0.2703 (0.1674-0.4365)	8.74E-08	0.3996 (0.2406-0.6638)	0.000395

BMI-Body mass index; CA19-9-Carbohydrate Antigen 19-9; CA125-Carbohydrate Antigen 125; CEA-Carcinoembryonic Antigen; LNM-Lymph node metastasis; LNR-Lymph node positive rate; PAC-Postoperative adjuvant chemotherapy.

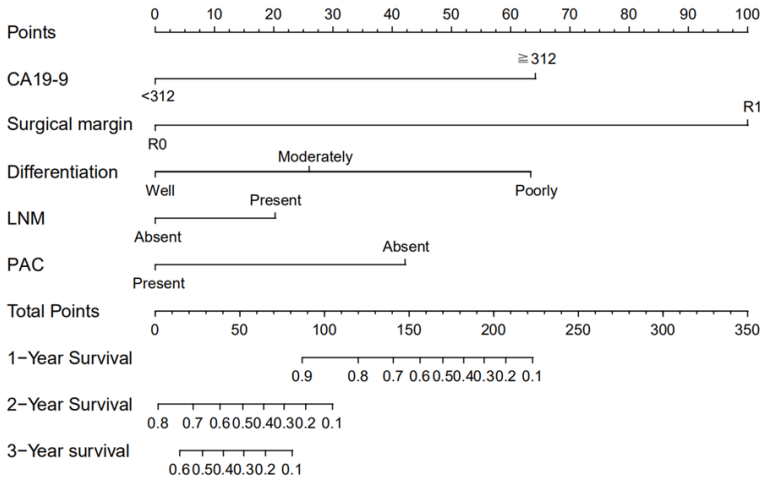

Figure 4. Nomogram to predict 1-, 2-, and 3-year survival of patients with left-sided pancreatic adenocarcinoma after surgical resection. (CA19-9 < 312 U/ml, R0 surgical margin, well differentiation, absence of LNM, and presence of PAC = 0 points; CA19-9 ≥ 312 U/ml = 64 points; R1 surgical margin = 100 points; Moderately differentiation = 26 points; Poorly differentiation = 63 points; Presence of LNM = 20 points; Absence of PAC = 42 points). LNM-lymph node metastasis; PAC-postoperative adjuvant chemotherapy.

9/E-selectin-mediated migration are still under investigation [10].

One of the most important and difficult thing for surgical operation for LPAC is to achieve a negative surgical margin, since LPAC may often adhere to or invade major vessels or retroperitoneal tissues [17]. The margin status had been proven to influence the local recurrence rate of PC [18]. Our study found R1 surgical margin was an important prognostic risk factors of LPAC and it was given the highest points in our nomogram, indicating a positive margin significantly impaired patient prognosis. RAMPS procedure invented by Strasberg was a modified procedure of DPS to treat tumors of pancreatic body and tail and was characterized by deeper removal of retroperitoneal nerve and lymph nodes [19]. Previous studies showed RAMPS provided benefits for patients with LPAC to obtain negative surgical margin, which might improve patients RFS following operation [20]. However, for the patients who could not obtain negative margin, it will be of interest to explore the effect of more aggressive treatments in the future, such as intraoperative radiotherapy [21].

Currently, standard therapeutic strategies for patients with resectable PC is surgical resection combined with adjuvant chemotherapy. The main chemotherapy regimens are modified FOLFIRINOX (including 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin) or gemcitabine plus nab-paclitaxel regimen [1]. A phase 3 study compared FOLFIRINOX with the gemcitabine monotherapy in 342 patients with PC and found the FOLFIRINOX regimen prolonged median OS from 6.8 to 11.1 months [22]. Results from another first-line phase 3 trial compared gemcitabine plus nab-paclitaxel with gemcitabine monotherapy and revealed a median OS of 8.5 months in the combination group, which was better than 6.7 months in the monotherapy group [23]. We also confirmed that PAC was a protective factor in our study. While adjuvant chemotherapy is the cornerstone of management after surgery, the selection of specific chemotherapy regimen remains controversial. Though the efficacy of FOLFIRINOX and gemcitabine plus nab-paclitaxel have never been compared directly in clinical trials, some real-world studies showed that the younger and fitter patients might prefer to receive FOLFIRINOX regimen and tend to have better OS [24, 25].

Apart from the common clinicopathological factors, recently large-scale sequencing studies have showed that some molecular biomarkers may play important role in tumor formation and progression of PC [26-28]. Compared with PC from the head, LPAC was significantly enriched for genes involved in hypoxia response, epithelial-tomesenchymal transition (EMT), metabolic reprogramming, TP63 expression, squamous differentiation and inflammation [5]. Some molecular biomarkers like S100A2 were proven to accelerate tumor invasion and be associated with poor prognosis, especially in LPAC [5, 29]. Further studies are needed to validate these findings and determine whether these biomarkers or which of them may contribute to the predictive model.

Overall, our predictive model has some particular advantages as following: 1) it has a higher

Table 3. Comparison of the C-index and AUC values between nomograms and AJCC-8 staging

Patients		Overall Survival				
		C-index (95% CI)	AUC for survival rate			*P*-value
			1-year	2-year	3-year	
Training Cohort	Nomogram	0.805 (0.775-0.825)	0.843	0.818	0.813	
	He's nomogram	0.706 (0.681-0.731)	0.717	0.691	0.732	< 0.05
	Zou's nomogram	0.727 (0.702-0.752)	0.701	0.739	0.725	< 0.05
	AJCC-8 staging	0.608 (0.586-0.630)	0.694	0.693	0.711	< 0.01
Validation Cohort	Nomogram	0.719 (0.698-0.740)	0.722	0.675	0.667	
	He's nomogram	0.674 (0.656-0.692)	0.670	0.591	0.624	< 0.05
	Zou's nomogram	0.638 (0.614-0.662)	0.662	0.594	0.613	< 0.05
	AJCC-8 staging	0.589 (0.566-0.612)	0.590	0.578	0.601	< 0.01

AUC-Area Under Curve; AJCC-American Joint Committee on Cancer.

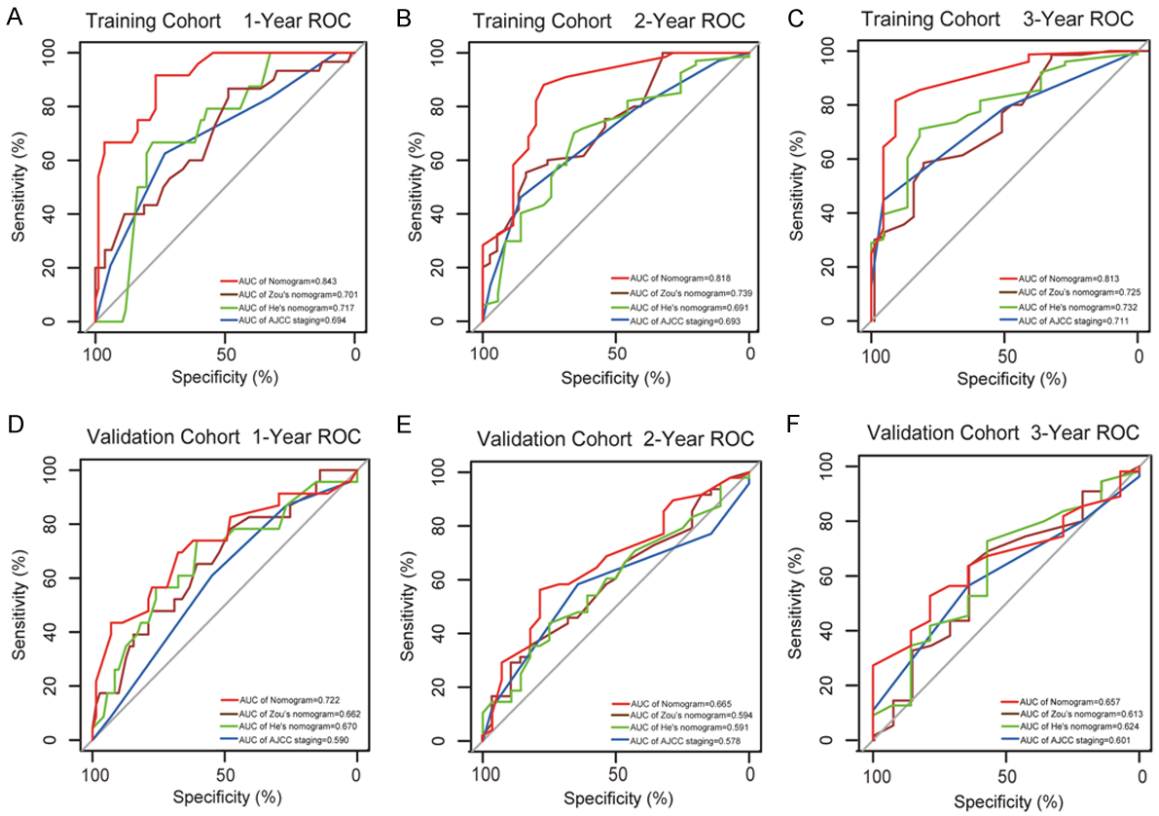

Figure 5. Comparison of the Receiver Operating Characteristic (ROC) curves of the nomograms and the AJCC-8 staging system for 1-, 2-, and 3-year overall survival (OS) prediction in the training cohort (A-C) and validation cohort (D-F).

predictive efficacy compared to the AJCC-8 staging system and other models by including more parameters; 2) it is a simple and reproducible model, which is developed based on datasets from multi-centers; 3) it helps stratify high-risk patients, who may need early intervention. Inevitably, our study had some limitations. First, this is a retrospective study so that future prospective studies are needed to verify our nomogram. Second, the molecular phenotypes of tumors are not included in our analysis. It will be very helpful to add the molecular phenotypes or genetic information to build a prognostic model in the future.

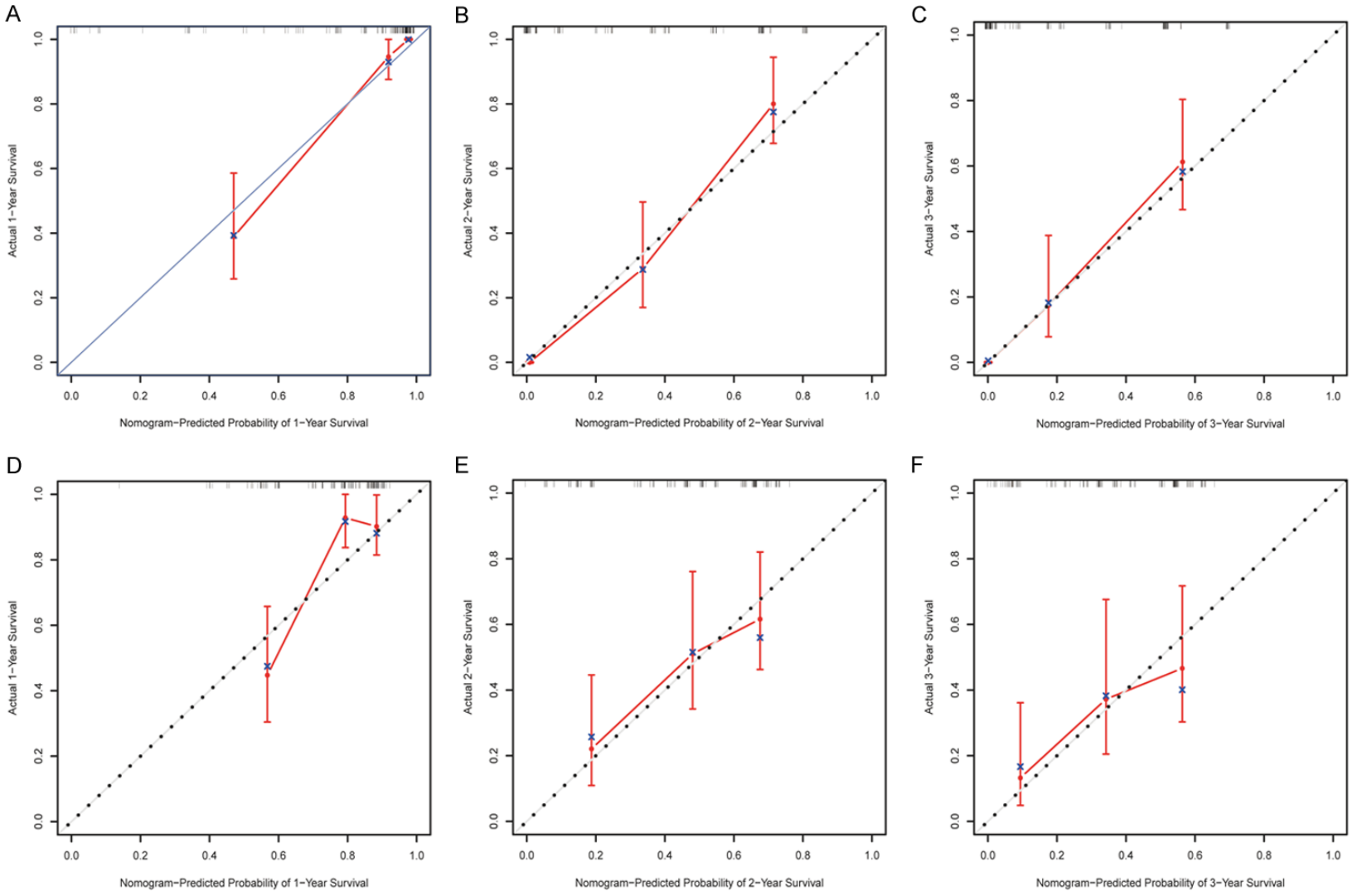

Figure 6. Calibration plots of the nomogram for 1-, 2-, and 3-year overall survival (OS) prediction in the training cohort (A-C) and validation cohort (D-F).

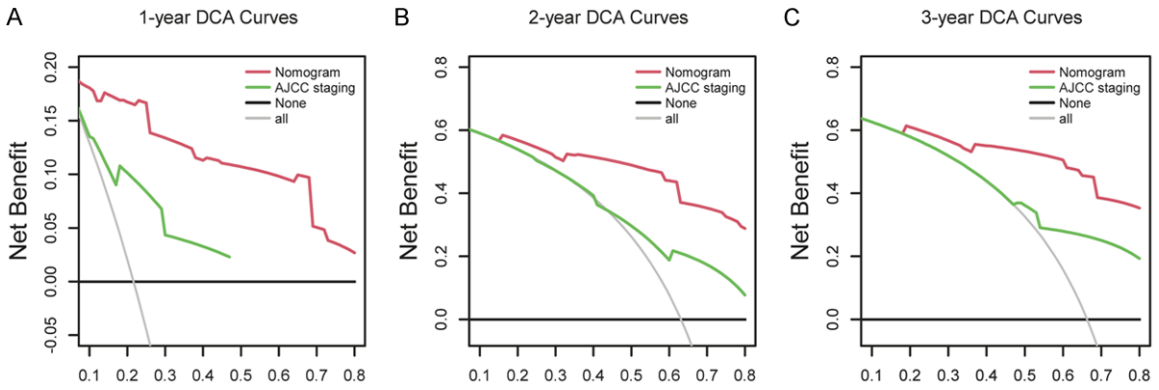

Figure 7. Decision curve analysis of the nomogram for 1-, 2-, and 3-year overall survival (OS) prediction of patients in the training cohort (A-C). The nomogram had a better net benefit with a wider range of threshold probabilities than AJCC-8 staging system for both 1-, 2-, and 3-year OS.

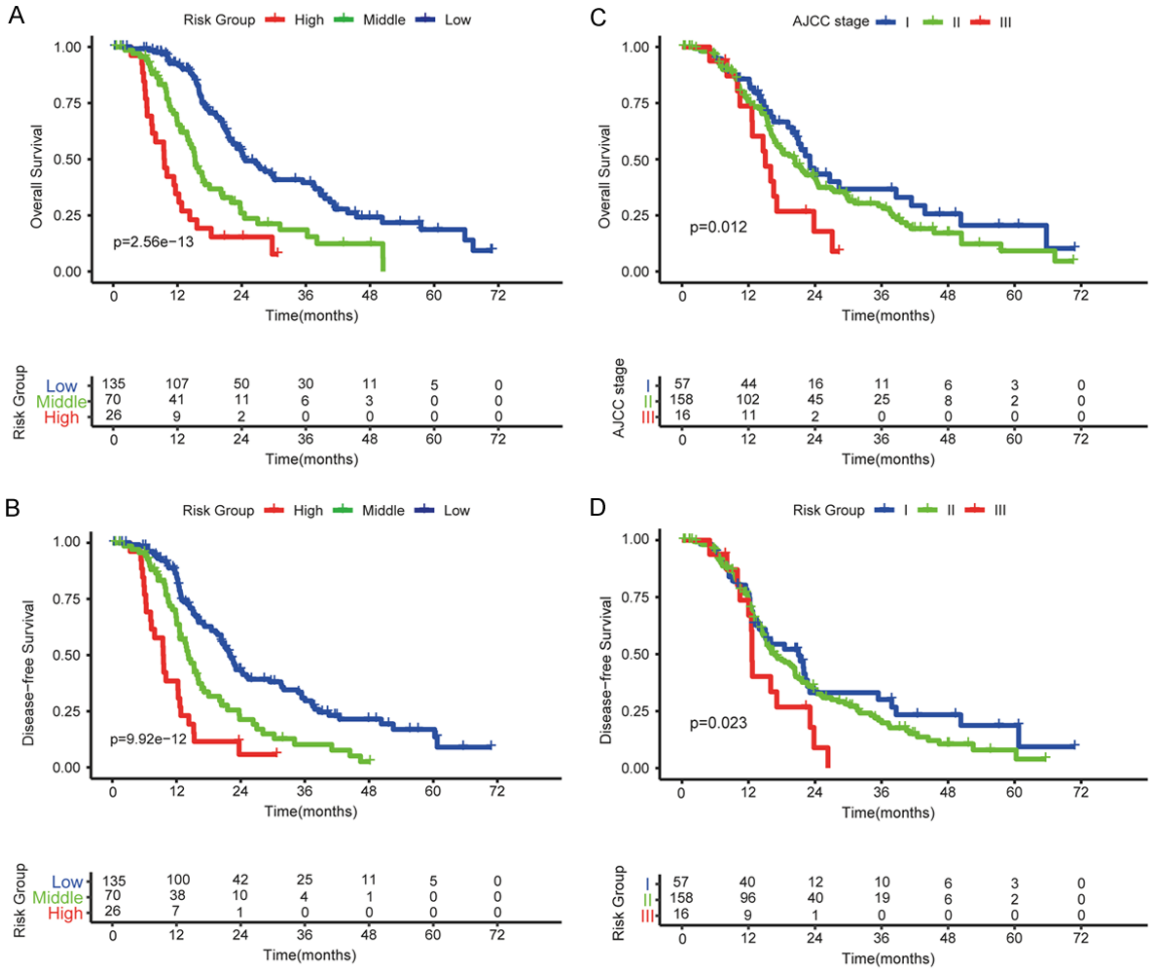

Figure 8. (A, B) Kaplan-Meier analysis was performed to evaluate overall survival (OS) (A) and disease-free survival (DFS) (B) among three subgroups stratified by the risk scores. (C, D) Kaplan-Meier analysis was performed to evaluate OS (C) and DFS (D) among patients of AJCC-8 stage I, II, III. The survival curves for the three subgroups stratified by the risk scores had better separation than those for the AJCC-8 stage I, II, III.

In summary, we identified CA19-9, surgical margin, differentiation, LNM, and PAC as the independent risk factors of LPAC after surgical resection. And we built a comprehensive and

effective prognostic model for LPAC based on these factors, which helped stratify high-risk patients and facilitated clinical decision-making.

Ethics approval and consent to participate

The study was approved by the Medical Research Ethics Committee of Guangdong Provincial People's Hospital, Sir Run Run Shaw Hospital, and Peking Union Medical College Hospital.

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Disclosure of conflict of interest

None.

Abbreviations

PC, Pancreatic Cancer; LPAC, Left-sided Pancreatic Adenocarcinoma; EMT, Epithelial-mesenchymal Transition; TNM, Tumor-node-metastasis; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results; DP, Distal Pancreatectomy; RAMPS, Radical Antegrade Modular Pancreatosplenectomy; ASA, American Society of Anesthesiologists; BMI, Body Mass Index; DM, Diabetes Mellitus; CA19-9, Carbohydrate Antigen 19-9; CA125, Carbohydrate Antigen 125; CEA, Carcinoembryonic Antigen; LNM, Lymph Node Metastasis; LNR, Lymph Node Positive Rate; PAC, Postoperative Adjuvant Chemotherapy; OS, Overall Survival; DFS, Disease-free Survival; ROC, Receiver Operating Characteristic; AUC, Area Under Curve; DCA, Decision Curve Analysis.

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