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Preoperative Score to Stratify Recurrence Risk After Curative Resection of Resectable Pancreatic Ductal Adenocarcinoma: A Retrospective Cohort Study

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Keyword:

Recurrence; Prognostic score; Stratification; Pancreatic ductal adenocarcinoma

1. Abstract

1.1. Background

Oncological survival after operation of resectable pancreatic ductal adenocarcinoma (R-PDAC) is variable depending on various factors. Preoperative risk stratification could guide decision-making in multidisciplinary treatment concepts. We develop and validate a prognostic score for disease-free survival (DFS) in R-PDAC to solve this issue.

1.2. Methods

421 R-PDAC patients between January 2012 and December 2015 were enrolled. Performance of the final model was evaluated with respect to discrimination, calibration and clinical usefulness. A prognostic score based on the final model was developed, and external validated in 290 patients.

1.3. Results

On multivariable analysis, age, carbohydrate antigen (CA)19-9, CA125, tumor size, systemic-immune-inflammation index, and lymphocyte-monocyte ratio were independently associated with DFS. Final model had acceptable calibration, discrimination and internal validity. The prognostic score could delineate low- and high-risk groups with median DFS of 19.6 and 10.1 months (P<0.0001). Tumors in high-risk group exhibited more aggressive pathobiological behaviors. Additionally, at 1-year follow-up, the restricted mean survival time was longer with adjuvant chemotherapy than those without in low-risk patients. However, no significant difference was detected in high-risk patients.

1.4. Discussion

The prognostic score could accurately predict DFS preoperatively in R-PDAC patients and provide reference for risk-adapted strategies formulation for R-PDAC management in the future.

2. Text

2.1. Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide, ranking the sixth leading cause of tumor-related deaths in China and the fourth in the Western world [1-3]. The only curable approach for PDAC is resection, however, patients underwent curative-intent operation are still at a high recurrence risk up to 80% because of the propensity of early recurrence and lack of effective systemic therapies, leading to a 5-year overall survival of only 12%-27% [4]. The National Comprehensive Cancer Network (NCCN) has set criteria to assess the resectability of PDAC based on major vascular status according to preoperative imagine [5]. Though, previous studies have supported that patients with borderline resectable or locally advanced tumors could benefit from sys-

temic treatment, [6,7] Neoadjuvant therapy recommendation for resectable tumors remained controversial. Many studies confirmed the timing of recurrence affected overall survival and proposed factors like highly evaluated CA19-9 level, large tumor size, differentiation and positive lymph nodes to predict the recurrence risk of resected PDAC (R-PDAC) [8,9]. Currently, lack of a prognosis evaluation system has hindered the establishment of tailored clinical strategies for R-PDAC. In this article, we attempt to set up a novel model which comprehensively take advantage of preoperative factors to assess the recurrence risk for resected PDAC, aiming to verify high risk patients and provide guidance for perioperative adjuvant therapy.

3. Materials and Methods

3.1. Patients

Patients undergoing curative-intent pancreatectomy from January 2012 to December 2015 in our hospital (blinded as per author guidelines) for pathologically confirmed PDAC were included as a training cohort in this study. Exclusion criteria contained distal metastasis, incomplete clinical data, history of neo-adjuvant therapy, initial invasion of major vessels (including portal vein, superior mesenteric vein/artery, common hepatic artery and celiac axis) on preoperative imagines, R1/2 resection and perioperative mortality due to postoperative complications. Consecutive patients from January 2016 to December 2018 fulfilling the same criteria consisted of a validation cohort. Eventually, 711 patients (421 for training set and 290 for validation set) were enrolled in present study (Figure 1).

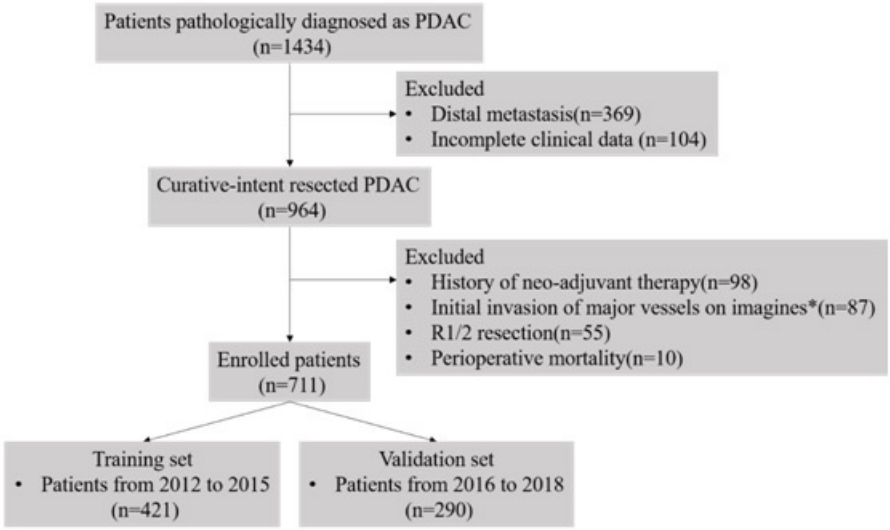

Figure 1. Flow chart of study design. PDAC: pancreatic ductal adenocarcinoma.
*Major vessels consisted of portal vein, superior mesenteric vein/artery, common hepatic artery and celiac axis.

4. Data Collection

Surgical procedures were referred to principles of surgical technique from NCCN guidelines [5]. Patients demographic characteristics comprised age, gender and body mass index (BMI). BMI was calculated as weight in kilograms (kg) divided by the height in meters squared (m^2). Preoperative clinical parameters included tumor size, tumor location, tumor markers (carbohydrate antigen (CA) 19-9, CA125 and carcinoembryonic antigen (CEA)) and inflammation-based prognostic scores (systemic-immune-inflammation index (SIII), prognostic nutritional index (PNI), systemic inflammatory response index (SIRI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR)). Tumor size and location were measured according to contrast-enhanced abdominoperineal computed tomography (CT) within 2 weeks before operation. All the laboratory data were collected using the measurements that were within 1 week before surgery. Patients with 3 or more consecutive undetectable CA19-9 values (<0.8U/ml) were identified as CA19-9 not available (Undetectable). SIII was calculated as NLR multiply by platelet count (10^9/l). PNI was calculated as 5 times lymphocyte count (10^9/l) plus serum albumin (g/l). SIRI was calculated as NLR multiply by monocyte count (10^9/l) [10,11].

5. Follow-Up

Follow-up was conducted via outpatient and visit phone call. For the follow-up management, patients were required to visit in the 1st week after hospital discharge for baseline assessment of adjuvant therapy. Physical examination, laboratory tests and radiological imagine were conducted every 3 months after surgery in the first 2 years and afterward visit was every 6 months as long as relapse was not detected. The recurrence was diagnosed according to emerging suspicious lesions and elevated CA19-9, and was confirmed by fluorodeoxyglucose positron emission tomography or biopsy if necessary. The start dates of the overall survival (OS) and disease-free survival (DFS) were the date of surgical resection. The start dates of the overall survival (OS) and disease-free survival (DFS) were the date of surgical resection. For the OS, the end point was set as the date of death or the last follow-up. For the DFS, the end point was set as the

date of recurrence in any forms, death from cancer-related cause of the date or the last follow-up.

6. Recurrence

According to previous studies, recurrence patterns were classified into 5 categories. Definition of local recurrence was recurrence in the remnant pancreas or in the surgical bed. Metastatic recurrence was grouped into 3 categories: "liver only" and "lung only" for isolated hepatic and pulmonic recurrence respectively, and "other" for other distant recurrence. The category "Local and metastatic" contained recurrence occurring in both local and distant sites.

7. Scoring System for Recurrence-Risk Stratification

Preoperative factors associated with DFS were identified using univariate and multivariate Cox proportional hazard models. A final model selection was performed by a backward stepdown selection process with the Akaike information criterion. The discriminative performance was evaluated by calculating Harrell's concordance index (C-index). 95% CI for the C-statistic was derived from one thousand random samples of the population. Calibration and goodness of fit were assessed by visual examination of calibration plot and tested with an extension of the Hosmer-Lemeshow test for survival data. A bootstrap sample method was conducted for internal validation of the final model. A nomogram derived from the final model were draw to estimate the individual post-operation DFS possibilities at 6, 12, 18 and 24 months. Based on the final model, a prognostic score was developed and weighted with β-coefficients in the final model for population level estimation. The coefficients of variables derived from Cox regression analyses in final model were multiplied by 10 and rounded to one decimal for clinical use. For better classifying patients by recurrence risk, an optimal cut-off point verified via the Lausen and Hothorn's method divided patients into two-groups according to low and high risk. C-index of the novel risk classification was also calculated. The same risk predictive algorithm derived from training set was applied in the validation cohort for external validation.

8. Statistical Analysis

Continuous and categorical data are expressed as means with standard deviation or medians with inter-quartile range (IQR) and percentage, respectively. Baseline characteristics comparison according to the cohorts and postoperative outcomes comparison between two risk groups in different cohorts were conducted using Chi-squared test for categorical data, and the Mann-Whitney U-test for continuous data. DFS and OS were depicted using Kaplan–Meier method and described with median and 95% confidence intervals (95% CI). Restricted mean survival time (RMST) was calculated as a milestone treatment effect measurement to assess adjuvant chemotherapy efficacy when the proportionality assumption of Cox proportional hazard model was rejected. All the analysis was performed using R (version 3.5.2; http://r-project.org) and SPSS software (IBM SPSS Statistics 21.0). A P value <0.05 was considered statistically significant and all tests were two-sided.

9. Results

9.1. Baseline Clinicopathological Features

A total of 711 patients with histopathologically diagnosed PDAC and underwent curative-intent surgery from January 2012 to December 2018 were included. Preoperative demographic and clinical characteristics of the overall patients (n=711), training cohort (n=421) and validation cohort (n=290) were listed in Table 1. Baseline parameters comparisons showed significant difference between the two cohorts in age, NLR, differentiation, lymph-vascular invasion, perineural invasion and lymph node metastasis.

Table 1: Baseline demographic and clinicopathological data according to the cohort set.

	Overall Patients (n=711)	Training Set (n=421)	Validation Set (n=290)	P-value
Gender, n(%)				0.295
Male	256 (36.0%)	145 (34.4%)	111 (38.3%)	
Female	455 (64.0%)	276 (65.6%)	179 (61.7%)	
Age (mean±SD, years)	63.4 ±8.9	64.1 ±8.9	62.4 ±8.9	0.009
BMI (mean±SD, Kg/m^2)	22.9 ±3.0	22.9 ±3.0	22.8 ±3.0	0.685
CA19-9 (median with IQR, U/mL)	136.1 (38.6-370.6)	134.6 (38.7-347.9)	140.6 (37.6-417.1)	0.426
Undetectable, n(%)	46(6.5%)	28(6.7%)	18(6.2%)	0.872
CA125 (median with IQR, U/mL)	14.8 (10.0-23.7)	14.9 (10.6-25.2)	14.7 (9.1-22.9)	0.327
CEA (median with IQR, ng/mL)	3.2 (2.1-5.3)	3.2 (2.1-5.1)	3.2 (2.1-5.7)	0.790
Tumor size (mean±SD, cm)	3.1 ±1.3	3.0 ±1.2	3.2 ±1.4	0.190
Tumor location, n(%)				0.182
Head/neck	469 (66.0%)	286 (67.9%)	183 (63.1%)	
Body/tail	242 (34.0%)	135 (32.1%)	107 (36.9%)	
SIII (mean±SD)	564.8±396.3	547.6±381.2	590.0±416.8	0.161
PNI (mean±SD)	46.5±7.4	46.6±6.9	46.3±8.1	0.592
SIRI (mean±SD)	1.3±1.0	1.3±1.0	1.3±1.0	0.580
NLR (median with IQR)	2.5 (1.9-3.4)	2.4 (1.8-3.3)	2.7 (2.0-3.5)	0.024
PLR (mean±SD)	152.9±83.3	151.4±75.0	155.2±94.2	0.550
LMR (median with IQR)	3.5 (2.6-4.9)	3.4 (2.5-4.8)	3.7 (2.7-5.1)	0.543
Differentiation				0.025
Well-moderate	215 (30.2%)	141 (33.5%)	74 (25.5%)	

Poor	496 (69.8%)	280 (66.5%)	216 (74.5%)	
LVI	202 (28.4%)	85 (20.2%)	117 (40.3%)	<0.001
Peritoneal nerve invasion	585 (82.3%)	378 (89.8%)	207 (71.4%)	<0.001
Resection margin (R0)	631 (88.7%)	380 (90.3%)	251 (86.6%)	0.147
LNM	297 (41.8%)	188 (44.7%)	109 (37.6%)	0.064
T stage				0.876
T1	173 (24.3%)	105 (24.9%)	68 (23.4%)	
T2	434 (61.1%)	256 (60.8%)	178 (61.4%)	
T3	104 (14.6%)	60 (14.3%)	44 (15.2%)	
Adjuvant chemotherapy	503 (70.7%)	291 (69.1%)	212 (73.1%)	0.276
Recurrence	541 (76.1%)	290 (68.9%)	251 (86.6%)	<0.001

SD: standard deviation; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; IQR: inter-quarter range; CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; SIII: systemic-immune-inflammation index; PNI: prognostic nutritional index; SIRI: systemic inflammatory response index; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; LVI: lymph-vascular invasion; LNM: lymph node metastasis.

9.2. Survival Analysis According to Cohorts

The median DFS for training set and validation set were 13.5 and 11.8 months (P=0.311), respectively. In the training set, the 6-, 12-,18- and 24-months DFS rates were 96.2%, 81.3%, 65.1% and 52.3%, respectively. In the validation set, the 6-, 12-,18- and 24-months DFS rates were 94.5%, 76.1%, 59.5% and 46.6%, respectively. The median OS for training set and validation set were 24.9 and 21.8 months (P=0.034), respectively.

9.3. Preoperative Risk Factors and Establishment of Prognostic Nomogram

9 out of 14 evaluated preoperative factors were associated with DFS in the univariate Cox analysis (P<0.1), which consist of age, CA19-9, CA125, tumor size on preoperative imagine, SIII, NLR, PLR and LMR (Table 2). Ultimate results of multivariate analysis confirmed 6 factors: age, CA19-9, CA125, tumor size, SIII and LMR as independent risk factors for DFS (Table 2). C-index of final multivariate model was 0.64 with 95%CI: 0.61-0.68, suggesting acceptable discrimination ability. The model showed a good calibration at 6, 12, 18 and 24 months through Hosmer-Lemeshow test (P=0.996, P=0.720, P=0.092, and P=0.142, respectively). The calibration plot comparing predicted and observed DFS probability at 6,12,18, and 24 months displayed good fitness in training set **(**Figure 2). Uncertainties around HR were calculated using bootstrapping procedure to verify the robustness of final multivariate model in internal validation process (Table 2). We built a novel nomogram integrating all preoperative risk factors in the final model for 6-,12-, 18- and 24-month DFS (Figure 3).

Table 2: Univariate and multivariate analysis of factors associated with disease-free survival in training cohort.

Factors	Recurrence, n (%)	Univariate analysis				Multivariate analysis			
		HR	CI (95%)	P	HR	CI (95%)	P	BCA HR (95%)	Prognostic score
Age, years	290(68.9%)	1.013	1.000-1.026	0.047	1.014	1.001-1.027	0.041	1.000-1.030	0.1
Gender									
Male	96(66.2%)	Ref	-	-					
Female	194(70.3%)	1.136	0.889-1.452	0.307					
BMI	-	1.005	0.964-1.049	0.802					
CA19-9, U/ml									
≤60	58(52.7%)	Ref.	-	-	Ref.	-	-	-	0
60<, ≤480	151(74.0%)	0.520	0.315-0.858	0.010	1.622	1.190-2.213	0.002	1.177-2.173	4.8
>480	60(75.9%)	0.905	0.573-1.429	0.668	2.072	1.415-3.036	<0.001	1.385-3.178	7.3
Undetectable	21(75.0%)	1.265	0.769-2.079	0.355	1.644	0.973-2.778	0.063	0.934-2.805	5.0
CA125, U/ml									
≤10	57(60.6%)	Ref.	-	-	Ref.	-	-	-	0
10<, ≤33	178(70.6%)	0.503	0.346-0.730	<0.001	1.381	1.020-1.871	0.037	1.052-1.874	3.2
>33	55(73.3%)	0.742	0.548-1.005	0.054	1.468	0.982-2.195	0.061	0.981-2.322	3.8
CEA, ng/mL	-	1.011	0.989-1.033	0.341					
Tumor size, cm									
≤2	63(59.4%)	Ref.	-	-	Ref.	-	-	-	-3.6
2<, ≤3	109(65.7%)	0.553	0.379-0.807	0.002	1.430	1.043-1.961	0.026	1.074-1.956	0
3<, ≤4	71(79.8%)	0.748	0.531-1.054	0.097	1.683	1.181-2.399	0.004	1.219-2.415	1.6
>4	47(78.3%)	1.045	0.722-1.512	0.815	1.793	1.208-2.661	0.004	1.219-2.731	2.3

Tumor location									
Head/neck	197(68.9%)	Ref.	-	-					
Body/tail	93(68.9%)	1.104	0.862-1.413	0.433					
SIII									
≤475.6	134(60.9%)	Ref.	-	-	Ref.	-	-	-	0
>475.6	156(70.9%)	1.459	1.158-1.839	0.001	1.307	1.008-1.694	0.043	1.017-1.731	2.7
PNI	-	0.988	0.971-1.006	0.201					
≤40.85	81(19.2%)	Ref.	-	-					
>40.85	340(80.8%)	0.724	0.548-0.956	0.023					
SIRI	-								
≤0.85	164(39.0%)	Ref.	-	-					
>0.85	257(61.0%)	1.474	1.156-1.879	0.002					
NLR	-								
≤3.15	298(70.8%)	Ref.	-	-					
>3.15	123(29.2%)	1.401	1.094-1.793	0.007					
PLR	-								
≤175.3	296(70.3%)	Ref.	-	-					
>175.3	125(29.7%)	1.441	1.129-1.839	0.003					
LMR									
≤3.42	157(75.5%)	Ref.	-	-	Ref.	-	-	-	0
>3.42	133(62.4%)	0.721	0.572-0.908	0.005	0.803	0.619-1.044	0.101	0.623-1.018	-2.2

HR: hazard ratio; CI: confidence interval; BCA: bootstrap confidence interval; Ref.: reference; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; SIII: systemic-immune-inflammation index; PNI: prognostic nutritional index; SIRI: systemic inflammatory response index; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio.

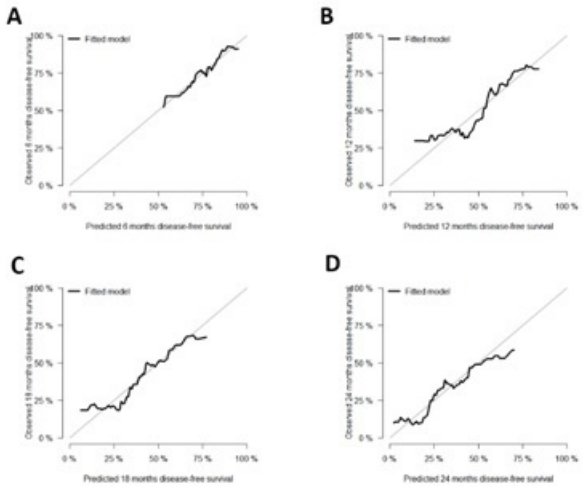

Figure 2. Calibration plots at 6-(A), 12-(B), 18-(C) and 24-(D) months for the final multivariate model in training cohort.

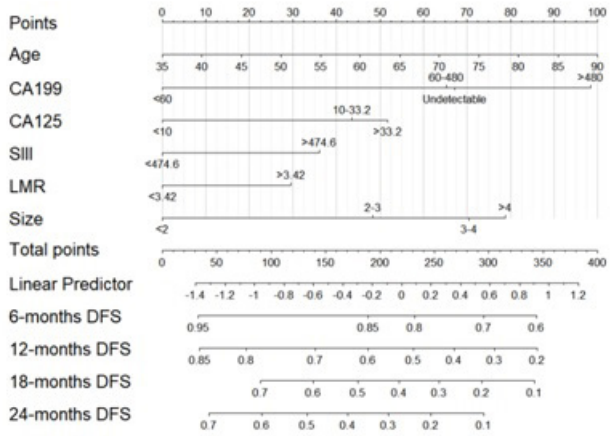

Figure 3. Prognostic nomogram to predict individual disease-free survival probability in patients with resectable pancreatic ductal adenocarcinoma after curable resection. Patients score points for preoperative characteristics. CA199: carbohydrate antigen 19-9; SIII: systemic-immune-inflammation index; LMR: lymphocyte-monocyte ratio; DFS: disease-free survival.

9.4. Prognostic Score for Recurrence-Risk Stratification

All variables comprised in the scoring system were weighted according to the β-parameter estimation issued from the final Cox model. The coefficients of factors in Cox regression analyses were multiplied by 10 and rounded to one decimal for clinical use and listed detailed in Table 2. The code of score could be read as follows: Prognostic scores=(0.1* age in year)+ (CA19-9, if ≤60=0; if 60<, ≤480=4.8 ;if >480=7.3; if Undetectable = 5.0, U/ml) +(CA125, if ≤10=0; if 10<, ≤33=3.2; if >33=3.8, U/ml)+ (tumor size in cm, if ≤2=-3.6; if 2<, ≤3=0; if 3<, ≤4=1.6; if >4=2.3)+(SIII, if ≤475.6=0; if >475.6=2.7)+(LMR, if ≤3.42=0; if >3.42=-2.2). The Lausen and Hothorn test was conducted in training set to determine an optimal cut-off point for stratifying patients into two-risk groups with different recurrence risk: low-risk group (N= 223, score≤13.6) and high-risk (N=198, score>13.6, HR=2.57, 95% CI 2.02-3.28, p<0.0001). Kaplan-Meier curves of DFS by two-risk groups approach in training cohort were depicted in Figure 4A. The median DFS were 19.6 (95% CI 15.6-23.9) and 10.1 (95% CI 8.2-11.3) months for the low-risk and high-risk group, respectively (p<0.0001). C-index for the two-risk classification in the training cohort was 0.61 (95% CI 0.57-0.54). A similar discrimination ability was confirmed in the validation cohort (C-index 0.63, 95% CI 0.60-0.67) for the final model. Calibration plots and Hosmer-Lemeshow tests showed a good calibration at 6, 12, 18 and 24 months (P=0.912, P=0.701, P=0.330, and P=0.169, respectively. The discrimination ability of the risk score algorithm developed using the training cohort was externally confirmed, with median DFS estimated to 16.3 (95% CI 13.2-19.1) months for the low-risk group and 9.0 (95% CI 7.3-10.8) months for the high-risk group (HR=1.81, 95% CI 1.40-2.34, p<0.0001, Figure 4B) and with a similar C-index estimation (C-index 0.59, 95%CI:0.55-0.62) when compared with the training cohort.

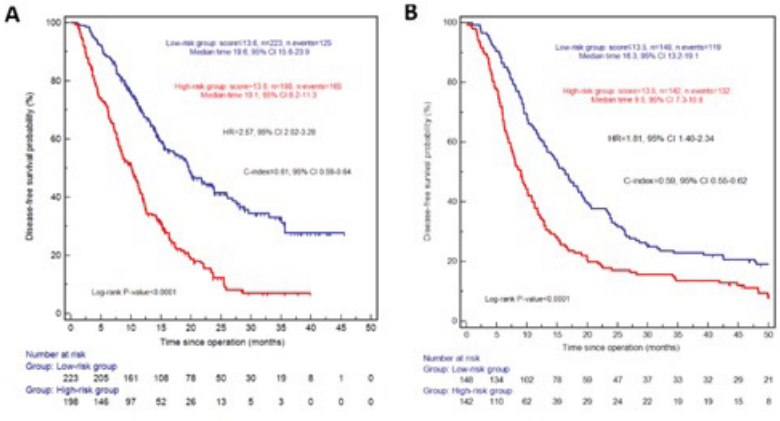

Figure 4. Kaplan-Meier curves of disease-free survival in the training (A) and validation cohorts (B) refer to prognostic score groups based on the Hothorn and Lausen optimal cut point. HR: hazard ratio; CI: confidence interval.

9.5. Postoperative Clinicopathologic Outcomes According to Two-Risk Groups

As expected, tumors in high-risk group exhibited more aggressive pathobiological behaviors, including poorer differentiation, higher T stages, more lymphovascular invasion (LVI), perineural invasion (PNI) and lymph node metastasis (LNM) in both training and validation cohorts (Table 3). Additionally, observed recurrence patterns were notably different. Patients in the low-risk group presented more often with local only recurrence (9.0% vs. 2.2%, P=0.033, Table 3). On the contrary, liver only recurrence (43.2% vs. 65.9%, P<0.001) was more prevalent among patients in high-risk group. Similar trends were also seen in the validation cohort (Table 3). Significant DFS difference was observed in favor of adjuvant chemotherapy over none in the low-risk group both in training and validation cohorts (Figure 5A). The 12-month RMST of patients receiving adjuvant chemotherapy was 10.9 (95% CI 10.6-11.3) months versus 9.6 (95% CI 8.8-10.3) months for patients without receiving chemotherapy, with an obviously difference of 1.3 (95% CI 0.5-2.2) months statistically (P=0.0016) in the training cohort. When extended at 24 months, the RMST of patients receiving adjuvant chemotherapy was 10.6 (95% CI 10.1-11.1) months versus 8.8 (95% CI 7.6-9.9) months for patients without receiving chemotherapy, with a difference of 1.8 (95% CI 0.6-3.1) months statistically (P=0.0044). Similar significant trends were also observed in the validation cohort (Figure 5C). On the contrary, there were no differential effects on DFS of adjuvant chemotherapy in high-risk group. In the training cohort, the RMST of patients receiving adjuvant chemotherapy at 12 months (8.8, 95% CI 8.2-9.4 months) was slightly longer than that of patients without receiving chemotherapy (7.6, 95% CI 6.6-8.6 months, P=0.0444), but when extended at 24 months, the RMST showed no difference (Figure 5B). In the validation cohort, the RMST at both 12 and 24 months showed no difference between patients with and without adjuvant chemotherapy (Figure 5D).

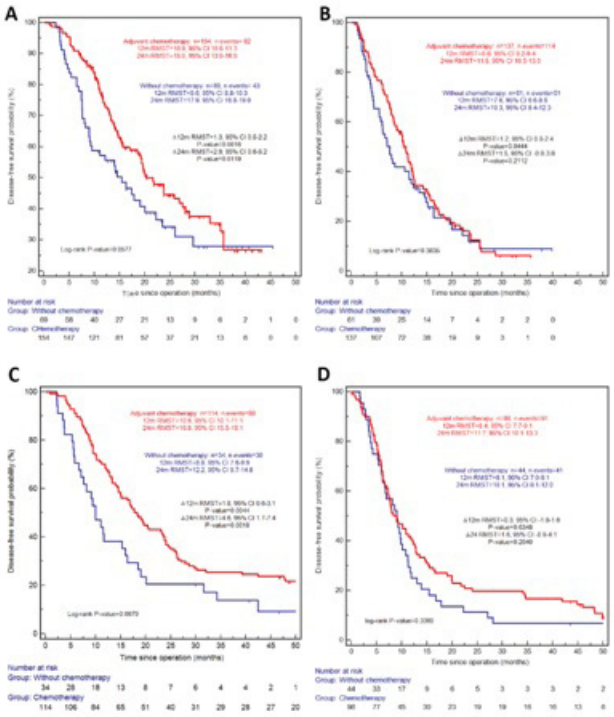

Figure 5. Kaplan-Meier curves for disease-free survival by adjuvant chemotherapy in two risk groups of training cohort (A for low risk group, B for high risk group) and validation cohort (C for low risk group, D for high risk group). RMST: restricted mean survival time; CI: confidence interval.

Table 3: Comparison of postoperative outcomes between risk groups in the training and validation cohort.

Factors	Training set(n=421)			Validation set(n=290)		
	Low-risk (n=223)	High-risk (n=198)	P	Low-riskn (n=148)	High-risk (n=142)	P
Differentiation			0.033			0.006
Well-moderate	85 (38.1%)	56 (28.3%)		48 (32.4%)	26 (18.3%)	
Poor	138 (61.9%)	142 (71.7%)		100 (67.6%)	116 (81.7%)	
LVI	33 (14.8%)	52 (26.3%)	0.003	50 (33.8%)	67 (47.2%)	0.020
PNI	197 (88.3%)	181 (91.4%)	0.299	101 (68.2%)	106 (74.6%)	0.228
Resection margin (R0)	206 (92.4%)	174 (87.9%)	0.120	129 (87.2%)	122 (85.9%)	0.756

LNM	87 (39.0%)	101 (51.0%)	0.013	46 (31.1%)	63 (44.4%)	0.020
T stage			<0.001			<0.001
T1	94 (42.2%)	11 (5.6%)		53 (35.8%)	15 (10.6%)	
T2	115 (51.6%)	141 (71.2%)		83 (56.1%)	95 (66.9%)	
T3	14 (6.3%)	46 (23.2%)		12 (8.1%)	32 (22.5%)	
Adjuvant chemotherapy	154 (69.1%)	137 (69.2%)	1.000	114 (77.0%)	98 (69.0%)	0.124
Chemotherapy regimens			0.417			0.375
None	69(30.9%)	61(30.8%)		34(23.0%)	44(31.0%)	
Gemcitabine	57(25.6%)	43(21.7%)		27(18.2%)	23(16.2%)	
S-1	17(7.6%)	24(12.1%)		15(10.1%)	17(12.0%)	
Combined †	80(35.9%)	70(35.4%)		72(48.6%)	58(40.8%)	
Recurrence	125(56.1%)	165(83.3%)	<0.001	119(80.4%)	132(93.0%)	0.002
Recurrence patterns						
Local only	15 (6.7%)	5 (2.5%)	0.043	8 (5.4%)	2 (1.4%)	0.104
Metastatic only	105 (47.1%)	146 (73.7%)	<0.001	111 (75.0%)	127 (89.4%)	0.001
Liver only	51 (22.9%)	95 (48.0%)	<0.001	77 (52.0%)	90 (63.4%)	0.051
Lung only	21 (9.4%)	14 (7.1%)	0.384	16 (10.8%)	14 (9.9%)	0.790
Others	47 (21.1%)	49 (24.7%)	0.370	27 (18.2%)	36 (25.4%)	0.142
Local + Metastatic	10 (4.5%)	9 (4.5%)	0.976	3 (2.0%)	0 (0)	0.248

LVI: lymph-vascular invasion; PNI: peritoneal nerve invasion; LNM: lymph node metastasis;

† Including gemcitabine + capecitabine, gemcitabine + S-1 and gemcitabine + oxaliplatin;

10. Discussion

Previous studies have focused on exploring preoperative parameters with good predictive ability to recognize patients with high-risk features ahead of operation, aiming to formulate pertinently effective systemic therapy strategy [8,12]. However, identifying and systemically quantifying of indicators to establish a convenient system that meet clinical application still remained a problem to be solved. Naru Kim et al [13]. Have proposed a predictive nomogram for early recurrence for R-PDAC consist of 7 parameters in a retrospective study, however, the enrolling of R1 resections might be detriment to accuracy of final model. In this study, we proposed a novel scoring system based upon preoperative parameters to predict the postoperative DFS rates of R-PDAC at 6-, 12-, 18- and 24-month by only including R0 resections and draw nomogram for visually presentation. Consulting the interoperability in clinical application, we set a cut-off point to stratify patients into two-risk groups according to the final scores. DFS for low-risk group is significantly longer than high-risk group. Furthermore, exploration on histological tumor characteristics verified that high-risk group possessed more malignant biological behaviors.

Though the NCCN guideline [5] recommended neo-adjuvant for high-risk R-PDAC, the description of high-risk patients was ambiguous. The present study defined high-risk patients with 6 quantified parameters and provided clinical evidence for neo-adjuvant therapy in such group. It has been confirmed that neo-therapy allowed initial treatment of occult metastases, downstages large tumors and improves rates of negative margin, hence, prolonging life expectancy for patients in advanced stage disease [7,14,15]. With the status of neo-adjuvant therapy evolving, growing number of prospective studies are conducted to explore the effect of neo-adjuvant therapy on resectable PDAC candidate for upfront surgery, considering the inaccuracy of preoperative imagine, substantial rates of R1 resection and the fact that part of patients failed to recover qualified for subsequent therapy from complications of pancreatectomy [16]. The results from a meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer stressed that neo-adjuvant treatment appeared to improve overall survival, which is accordance with the current result from ESPAC-5F trial that neo-adjuvant therapy group owned obvious survival advantage at 1 year (77% vs. 42%) [16]. We evaluated the effect of adjuvant treatment regard of the two-risk classification and found that only in low-risk group can adjuvant chemotherapy significantly improve RMST of DFS at the landmarks of 12- and 24-month. DFS for patients received adjuvant chemotherapy didn't differ from that without adjuvant chemotherapy in high-risk group, suggesting that perioperative adjuvant therapy for patients with high-risk feature of recurrence was essential. In addition, the definition of high-risk group could serve as inclusion criteria in future clinical trials. Age, CA19-9, CA125, tumor size, SIII, and LMR were identified independently associated with DFS. It was reported in several previous studies that older age, high serum CA19-9 level and large tumor size were risk factors for prognosis of PDAC [8,17-20]. And this study confirmed these features independently related to shorter DFS of R-PDAC. CA125 was employed as a biomarker for numerous cancers, especially for ovarian cancer, and its serum level would not be influenced by serum bilirubin levels [21,22]. Elevated CA125 was observed in approximately 45% patients with pancreatic cancer [19]. However, few studies found correlation between preoperative

CA125 and recurrence. In this study, we identified CA125 could serve as independent risk factors for DFS of R-PDAC. The inflammatory response played a critical role in tumor invasion, progression, and metastasis by promoting tumor angiogenesis and decreasing anticancer effects [23]. Cancer-related inflammation is considered as the seventh hallmark of cancer and many studies have verified that inflammation scores calculated by inflammatory cell counts such as NLR, PLR and SIRI could help to predict cancer prognosis [11,24,25]. Differing from that SIRI reported as predictor for recurrence of PDAC [11], we only identified SIII and LMR as risk factors for DFS. There existed several limitations in presented study. First, the retrospective nature might bring to selection bias since we merely enrolled patients with complete clinical data. Second, the resectability status were estimated rely on imageological examination, however, tumor contact with major venous like superior mesenteric vein or portal vein <180° might increase R1 resection rates to some degree and deteriorate prognosis. For this concern, we excluded patients have any tumor contact with major vessels and the R0 resection rates was similar between the two risk groups. In addition, there might existed imprecise impact about the enrolled parameter tumor size and CA19-9. The tumor size was directly assessed on CT or MRI imagines, wherein artificial errors might present. The CA19-9 level could be affected by the presence of jaundice and it was noteworthy that about 2-4% patients were Lewis' negative. We reviewed all the patients' imagines and evaluated patients with undetectable CA19-9 levels as an individual variable. Finally, given that sample size of the external validation was merely 290, validation in large sample should be necessary.

11. Conclusions

In conclusion, we presented a preoperative clinical prognostic score for histological tumor characteristics prediction and recurrence risk classification of curative-intent resected PDAC. The novel system was capable of clinical screening of patients at high risk of recurrence and provide the reference for risk-adapted strategies definition in future. Furthermore, this system could be utilized as a patient selection tool in future clinical trials to reduce heterogeneity among treatment cohorts in terms of risk profile.

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