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Original Article

Predicting early recurrence for resected pancreatic ductal adenocarcinoma: a multicenter retrospective study in China

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Abstract: A precise classification of early recurrence (ER) after radical surgery of pancreatic ductal adenocarcinoma (PDAC) has not been standardized. We aim to develop an optimal cut-off based on scientific evidence to distinguish early and late recurrence (LR) for PDAC after radical surgery and develop a predictive model for ER of PDAC. The best threshold for recurrence-free survival (RFS) was assessed with a minimum *P*-value method, and patients were categorized into ER and LR groups. We used a logistic regression model to assess potential risk factors for ER and develop a predictive model for ER risk. The best threshold between high-risk and intermediate-high-risk groups was identified by using the receiver operating characteristic curve. Among 3,279 patients included, 1,234 (37.6%) experienced ER. The RFS of 9 months is the optimal threshold to distinguish ER and LR. Univariable and multivariable analysis identified four preoperative risk factors for ER, including larger tumor maximal diameter on computed tomography (CT), enlarged lymph nodes on CT, carbohydrate antigen (CA) 125 > 35 U/ml, and CA19-9 > 235 U/ml. The concordance index (C-index) for the predictive model in the training cohort and the validation cohort was 0.651 (95% confidence interval (CI): 0.624-0.678), and 0.636 (95% CI: 0.593-0.679), respectively, showing promising predictive ability. The high-risk group had a score above 203, and the corresponding risk of ER for this group was 56.7%. An RFS of 9 months is the best threshold to distinguish ER and LR. The model can accurately predict the risk of ER in PDAC after radical resection, and risk grouping can predict the patients who could benefit from upfront surgery.

Keywords: Early recurrence, pancreatic ductal adenocarcinoma, predictive model

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains the most lethal solid tumor with overall 5-year survival of 10% [1]. Because of the lack of typical clinical symptoms and sensitive biomarker in the early phase of PDAC, only 20% of patients are assessed as surgical resectable at initial diagnosis. Although current guidelines recommend surgery as the first choice for resectable pancreatic cancer, the prognosis of some patients is not satisfactory with 80% of patients experiencing recurrence and about 30% of patients dying within one year after radical surgery [2]. Increasing evidence has shown that early recurrence (ER) is mainly attributed to occult metastasis already existed at the time of surgery [3], indicating that patients with ER may benefit from neoadjuvant therapy rather than upfront surgery. Therefore, it would be clinically important to identify the patients with resectable pancreatic cancer who are likely to develop ER after radical surgery.

Although ER of PDAC has gained more attention in recent years, the precise definition of ER is still debating. Some studies defined recurrence within 6 months postoperatively as ER [4-8], but some other studies defined recurrence within 12 months postoperatively as ER [9-12]. There are several problems with the definition of ER as following: inconsistent criteria, single-center, and small sample size. Therefore, there is a need to further define clinically meaningful ER criteria that reflect patient prognosis based on large multi-center studies.

China Pancreatic Data Center (CPDC) is a national multi-center PDAC patient database. In this study, we aimed to categorize the risk of ER and develop a predictive model for ER of PDAC based on the CPDC database. We analyzed the data from 2016 to 2019 in the CPDC database to define ER using the minimum *P*-value method and divided the patients into ER and LR groups. Next, we compared the differences in clinicopathologic characteristics between the two groups and used multivariable regression to determine the independent risk factors associated with ER to establish a predictive model for ER of PDAC.

Methods and material

CPDC and study population

CPDC was initiated by the Pancreatology Research Group of the Surgical Branch of the Chinese Medical Association in 2017. It is the first multi-center, shared, professional, and big data platform in China. A total of 79 surgical medical centers in China participated in the development of the database, which included all patients with pathologically diagnosed PDAC since 2016 with a one-year update period. Each medical center performs its follow-up and submits its data to the CPDC, which aggregates and updates the follow-up data annually. The official website of CPDC is https://chinacpdc.org.cn/#/web/home and the application for registration was required to use the database.

The information was collected from patients of PDAC who underwent radical surgery from 2016 to 2019 in the CDPC database. The inclusion criteria were as follows: 1) The pathological diagnosis was PDAC. 2) There was at least one postoperative follow-up. The exclusion criteria were as follows: 1) use of neoadjuvant therapy; 2) non-radical surgery; 3) confirmed distant metastasis during surgery (stage M1); 4) positive resection margin (R2); 5) unknown survival data; 6) death within a month after surgery. Finally, the data of 3,279 patients with resected PDAC were enrolled in the study. The flow chart of this study was shown in **Figure 1**.

Data collections

Pre- and post-operative demographic, clinicopathological and therapeutic variables were obtained from the CPDC database. Preoperative carbohydrate antigen (CA) 19-9 and CA125 values were included in our analysis. CA19-9 values detected when patients developed jaundice (total bilirubin > 5 mg/dL) were not included in the analysis. When the value of CA19-9 less than 1.0 U/ml, it was considered negative for Lewis antigen and the patient was not included into the analysis. R0 is defined as the distance from the tumor cells to the nearest resection margin exceeding 0 mm, while the resection margin where the tumor cells are observed under the microscope is defined as R1. Postoperative recurrence time was defined as the time when the first follow-up cross-sectional imaging study (CT, PET/CT, or MRI) showed recurrence [13]. The main indicators of this study were RFS, post-recurrence survival (PRS), and overall survival (OS). RFS was described as the time from radical resection to first recurrence or, if recurrence had not yet occurred postoperatively, to final follow-up. Similarly, the time from first postoperative recurrence to final follow-up or death was defined as PRS, and the time from radical resection to final follow-up or death was defined as OS.

Statistical analysis

We applied the chi-square test to analyze categorical variables and the Student's t-test or Mann-Whitney U-test to analyze continuous variables. Median survival was calculated using Kaplan-Meier curve. Comparisons between subgroups were performed by applying the minimum *P*-value method. A log-rank test was conducted on the PRS of each subgroup to determine the optimal cut-off value for RFS at the lowest *P*-value, and the population was divided into ER and LR groups based on this cut-off value.

The receiver operating characteristics (ROC) curve was used to determine the best cut-off values for the continuous variable as risk factors for ER. In the ROC curve, the position nearest to the top left corner of the figure is the optimal threshold. Variables with a *P*-value less than 0.1 in the univariate logistic analysis were enrolled as covariates in multivariate logistic regression analysis. Odds ratios (OR) with 95% confidence intervals (CIs) were identified by using multivariate logistic regression analysis. All *P* values were two sides test and a *P*-value less than 0.05 was regarded as statistically significant. Seventy percent of the patients in the database were randomly included in the training cohort to build the predictive model and thirty percent of the patients in the validation cohort. All preoperative independent significant factors were used to build a predictive model

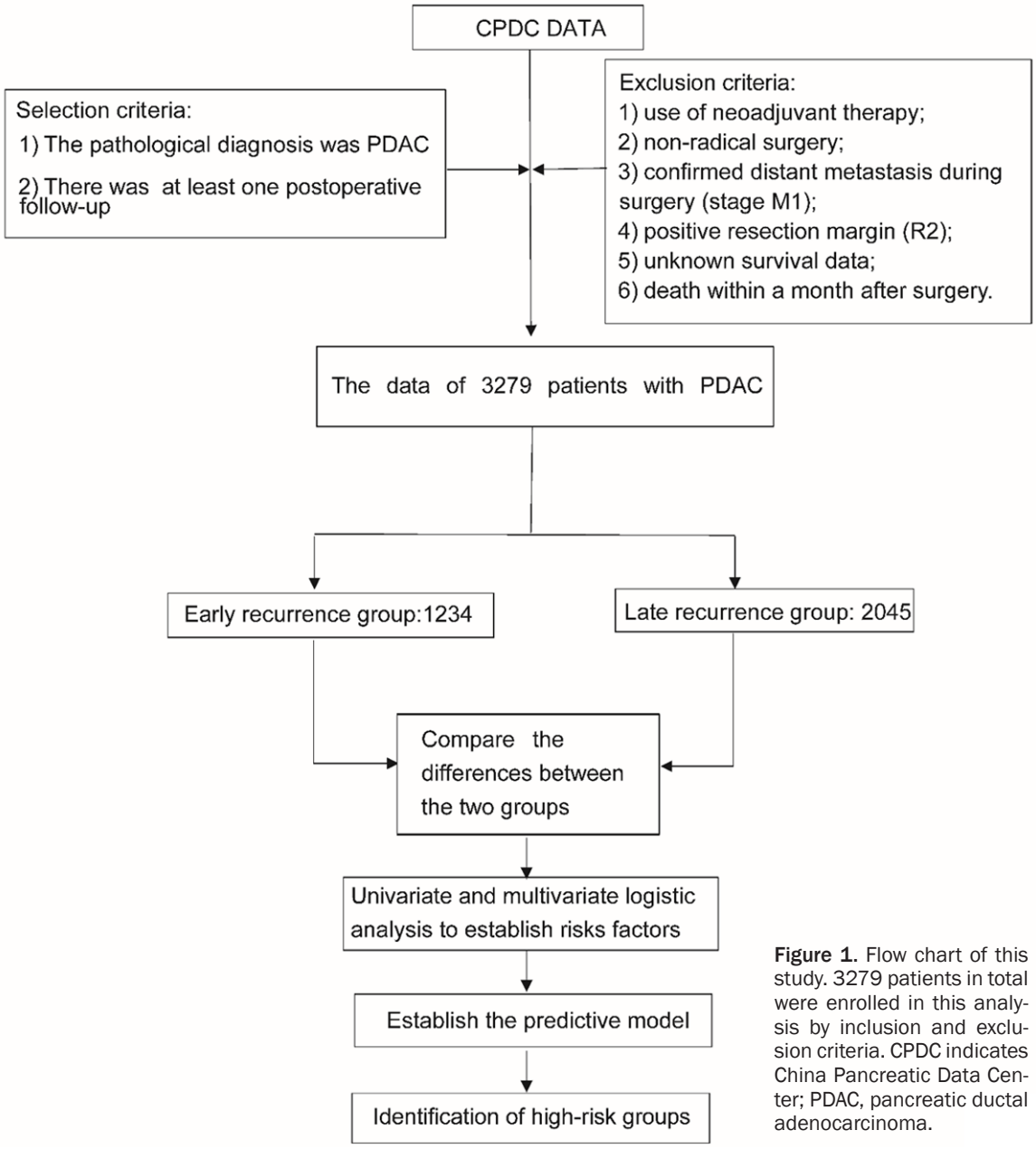

Figure 1. Flow chart of this study. 3279 patients in total were enrolled in this analysis by inclusion and exclusion criteria. CPDC indicates China Pancreatic Data Center; PDAC, pancreatic ductal adenocarcinoma.

for ER. We quantified the discriminatory performance of the ER nomogram by measuring the C-index on the training and validation populations. Calibration curves were drawn to evaluate the stability of the ER nomograms. All analysis was performed using the SPSS version 22.0 (IBM, Armonk, NY, USA) and R software (Version 3.6.1; https://www.R-project.org).

Results

Demographics and clinical characteristics

Our study population enrolled 3,279 patients, and their baseline demographics and clinical characteristics were shown in **Table 1**. The median follow-up time of the patients included in this study was 24.3 months (95% CI, 23.5-25.0). Until the last follow-up in 2019, 1860 of the 3279 patients relapsed. Median RFS and median OS were 8.5 months (95% CI, 8.2-8.9), 21.8 months (95% CI, 20.3-23.2), respectively.

Defining the time of ER

Among the 1,860 patients who had recurrence after surgery, PRS was unavailable in 356 patients, and a total of 1,504 patients who had a definite PRS was included for defining the time of ER (**Table 2**). Kaplan-Meier analysis

Table 1. Demographics, clinicopathologic, and treatment characteristics of included patients

Variable	All Patients (n = 3279)
Age, median (IQR)	62 (55-68)
Female, n (%)	1383 (42.2%)
BMI, kg/m^2, median (IQR)	22.5 (20.5-22.4)
Jaundice, n (%)	999 (30.6%)
Weight loss, n (%)	669 (20.4%)
Diabetes, n (%)	611 (18.8%)
Smoking, n (%)	955 (29.2%)
Drinking: n (%)	567 (17.4%)
Tumor location, n (%)	
Head	2130 (65.0%)
Body & tail	1149 (35.0%)
CT lymph nodes metastasis, n (%)	839 (26.9%)
CT tumor size, cm, median (IQR)	3.0 (2.4-4.0)
CA19-9, U/mL, median (IQR)	165.4 (42.7-532.1)
CA125, U/mL, median (IQR)	17.3 (11.46-29.8)
CEA, U/L, median (IQR)	3.3 (2.07-5.79)
Operation, n (%)	
Open	2805 (85.6%)
Minimal invasive	474 (14.4%)
Operative time, minutes, median (IQR)	280 (200-360)
Vascular invasion, n (%)	667 (20.6%)
Intraoperative bleeding, ml, median (IQR)	300 (200-500)
Capsular invasion, n (%)	1915 (60.5%)
Vessel carcinoma embolus, n (%)	620 (19.7%)
Perineural invasion, n (%)	2189 (68.7%)
Resection margin, n (%)	
R0	2884 (90.0%)
R1	319 (10.0%)
Examined lymph nodes number, median (IQR)	10 (5-17)
Positive lymph nodes ratio	
≤ 0.2	2658 (82.6%)
> 0.2	559 (17.4%)
Pathology tumor size, cm, median (IQR)	3.0 (2.5-4)
Tumor differentiation	
Well/moderate	1551 (48.1%)
Poor	1676 (51.9%)
Clinically relevant pancreatic fistula, n (%)	210 (6.4%)
Abdominal infection, n (%)	344 (10.5%)
Biliary fistula, n (%)	65 (2.0%)
Delayed gastric emptying, n (%)	597 (18.2%)
Adjuvant chemotherapy, n (%)	1420 (43.4%)

BMI indicates body mass index; IQR, interquartile range; CT, computed tomography; CA, carbohydrate antigen; CEA, carcinoembryonic antigen.

showed that 9 months was the optimal time for ER (**Figure 2A**), so we defined ER as 9 months after radical resection. A total of 1,234 patients experienced ER. The median RFS (4.7 months; 95% CI, 4.4-5.0) in the ER group was shorter compared to the median RFS (13.9 months; 95% CI, 13.4-14.4) in the LR group (**Figure 2B**). Similarly, the median PRS (5.3 months; 95% CI, 4.8-5.7) in the ER group (**Figure 2C**) was shorter compared to the median PRS (7.1 months; 95% CI, 5.9-8.3) in the LR group. Median OS was notably shorter in patients with ER (10.6 months; 95% CI, 10.2-11.0) compared to patients with LR (24.2 months; 95% CI, 22.6-25.7) (**Figure 2D**).

The optimal cut-off value of CA19-9 for predicting ER

Given the significant impact of CA19-9 on the prognosis of pancreatic cancer patients [9, 14, 15], we analyzed the relationship between CA19-9 and ER. Of the entire cohort of 3,279 patients, 135 patients as Lewis antigen-negative were excluded, 144 patients were excluded for the onset of jaundice (total bilirubin > 5 mg/dL), and 43 patients had missing data of CA19-9. Of the 3279 patients, 2960 were available for analysis with preoperative CA 19-9 (median 171.8 U/ml, interquartile range (IQR) 48.9-533.5). The area under the ROC curve (AUC) for preoperative CA 19-9 was 0.565 (95% CI, 0.541-0.590) and 235 U/ml was the best threshold for predicting ER with a specificity of 65.5% and a sensitivity of 45.9%. 42.9% (543/1265) patients with preoperative CA 19-9 value more than 235 U/ml had ER, compared to 32.3% (547/1695) patients with preoperative CA 19-9 less than or equal to 235 U/ml (P < 0.001) (**Figure 3A**). Patients with preoperative CA 19-9 more than 235 U/ml experienced a significantly shorter median RFS (12.5 months; 95% CI, 11.6-13.5) compared to those with preoperative CA 19-9 less than or equal to U/ml (17.4 months; 95% CI, 15.8-18.9) (P < 0.001) (**Figure 3B**). Median

Table 2. Evaluated cut-off value for defining early and late recurrence based on the prognosis after recurrence

Evaluated Cut-off	*P* Value	Potential Early Recurrence Cohort				Potential Late Recurrence Cohort			
		N	RFS (mo)	PRS (mo)	OS (mo)	n	RFS (mo)	PRS (mo)	OS (mo)
3 mo	9.4×10^{-2}	247	1.7	5.4	7.4	1257	8.8	6.1	16.9
4 mo	1.7×10^{-2}	373	2.4	5.5	8.2	1131	9.5	6.1	18.3
5 mo	1.0×10^{-2}	475	2.9	5.5	8.4	1029	10.2	6.1	19.1
6 mo	1.0×10^{-3}	573	3.3	5.5	8.9	931	11.1	6.1	20.2
7 mo	4.6×10^{-5}	701	3.8	5.2	9.7	803	12.0	6.5	21.3
8 mo	2.8×10^{-5}	810	4.3	5.4	10.2	694	12.8	6.9	23.0
9 mo	**5.0×10^{-6}**	**898**	**4.7**	**5.3**	**10.6**	**606**	**13.9**	**7.1**	**24.2**
10 mo	4.0×10^{-5}	979	5.1	5.4	11.0	525	14.7	7.5	25.6
11 mo	8.1×10^{-5}	1034	5.4	5.5	11.5	470	15.5	7.5	26.6
12 mo	1.5×10^{-5}	1102	5.8	5.5	11.9	402	16.4	8.1	28.1
13 mo	2.0×10^{-5}	1164	6.1	5.5	12.5	340	17.6	9.1	30.8
14 mo	1.6×10^{-4}	1207	6.2	5.6	12.8	297	18.7	8.3	30.8
15 mo	1.6×10^{-4}	1253	6.5	5.6	13.2	251	19.9	8.5	31.4
16 mo	2.4×10^{-4}	1291	6.6	5.6	13.4	213	20.7	8.7	32.7
17 mo	2.4×10^{-4}	1315	6.7	5.7	13.6	189	21.7	9.5	34.2
18 mo	4.0×10^{-4}	1342	6.8	5.7	13.9	162	22.4	10.1	34.5

Shown in bold is the optimal cut-off value with the minimal *P*-value. RFS indicates recurrence-free survival; PRS, post-recurrence survival; OS, overall survival.

OS (18.1 months; 95% CI, 16.6-19.5) was remarkably shorter in patients with preoperative CA 19-9 more than 235 U/ml compared to those with preoperative CA 19-9 less than or equal to 235 U/ml (29.1 months; 95% CI, 26.1-32.1) ($P < 0.001$) (**Figure 3C**).

Predictors associated with ER of PDAC

The clinicopathological characteristics of ER and LR groups are presented in **Table 3**. Univariate and multivariate analysis identified preoperative and intra-&postoperative risk factors associated with ER of PDAC (**Table 4**). Four preoperative variables were identified as significantly associated with ER., including larger tumors on preoperative CT, preoperative CA19-9 > 235 U/ml (OR, 1.420; 95% CI, 1.181-1.707; $P < 0.001$), regional lymph node enlargement (OR, 2.075; 95% CI, 1.719-2.506; $P < 0.001$) and preoperative CA125 > 35 U/ml (OR, 1.782; 95% CI, 1.428-2.223; $P < 0.001$). Eleven intraoperative and postoperative variables were independently associated with ER, including age > 65 (OR, 1.188; 95% CI, 1.008-1.400; $P = 0.040$), minimal invasive surgery (OR, 0.699; 95% CI, 0.551-0.886; $P = 0.003$), operative time > 360 minutes (OR, 1.368; 95% CI, 1.122-1.667; $P = 0.002$), vascular invasion (OR, 1.304; 95% CI, 1.060-1.603; $P = 0.012$), intraoperative bleeding > 400 ml (OR; 1.358; 95% CI, 1.132-1.628; $P = 0.001$), R1 resection margin (OR, 1.301; 95% CI, 1.004-1.685; $P = 0.047$), larger tumor size, positive lymph nodes ratio > 0.2 (OR, 1.409; 95% CI, 1.150-1.728; $P = 0.001$), poor tumor differentiation (OR, 1.824; 95% CI, 1.547-2.150; $P < 0.001$), abdominal infection (OR, 1.286; 95% CI, 1.006-1.643; $P = 0.044$), and delayed gastric emptying (OR, 1.306; 95% CI, 1.063-1.605; $P = 0.011$).

Establish and validate ER predictive model based on preoperative parameters

Because of missing complete four parameters, 909 cases were excluded for the establishment of the predictive model, and a total of 2370 cases were included. The model incorporating the preoperative predictors described above was developed (70% of the overall population was randomly selected as a training set) and presented as the nomogram (**Figure 4A**). The risk factors such as tumor size in CT, lymph node enlargement on CT, CA19-9, and CA125 were associated with ER. For example, a 60-year-old patient with pancreatic tumor size of 50 mm (score = 62), lymph node enlargement (score = 100), CA19-9 values of 500 ng/ml

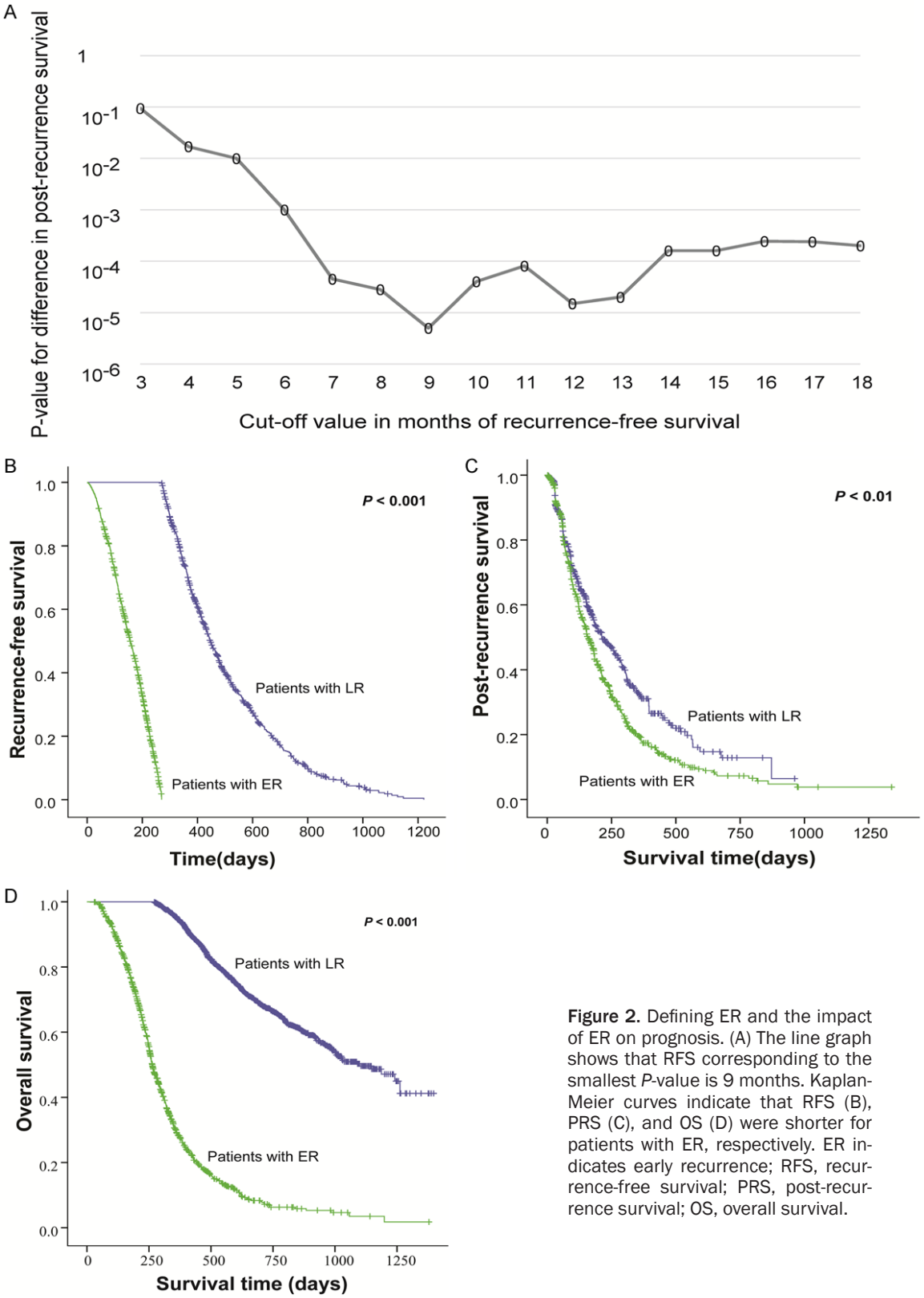

Figure 2. Defining ER and the impact of ER on prognosis. (A) The line graph shows that RFS corresponding to the smallest *P*-value is 9 months. Kaplan-Meier curves indicate that RFS (B), PRS (C), and OS (D) were shorter for patients with ER, respectively. ER indicates early recurrence; RFS, recurrence-free survival; PRS, post-recurrence survival; OS, overall survival.

(score = 73), CA125 values of 20 ng/ml (score = 0), would have an estimated risk of ER at 56%. The calibration curves for the ER risk nomogram in the training cohort and validation cohort demonstrated good agreement (**Figure 4B**, **4C**). The C-index for predicting nomograms in the training cohort and the validation cohort was 0.651 (95% CI: 0.624-0.678), and 0.636

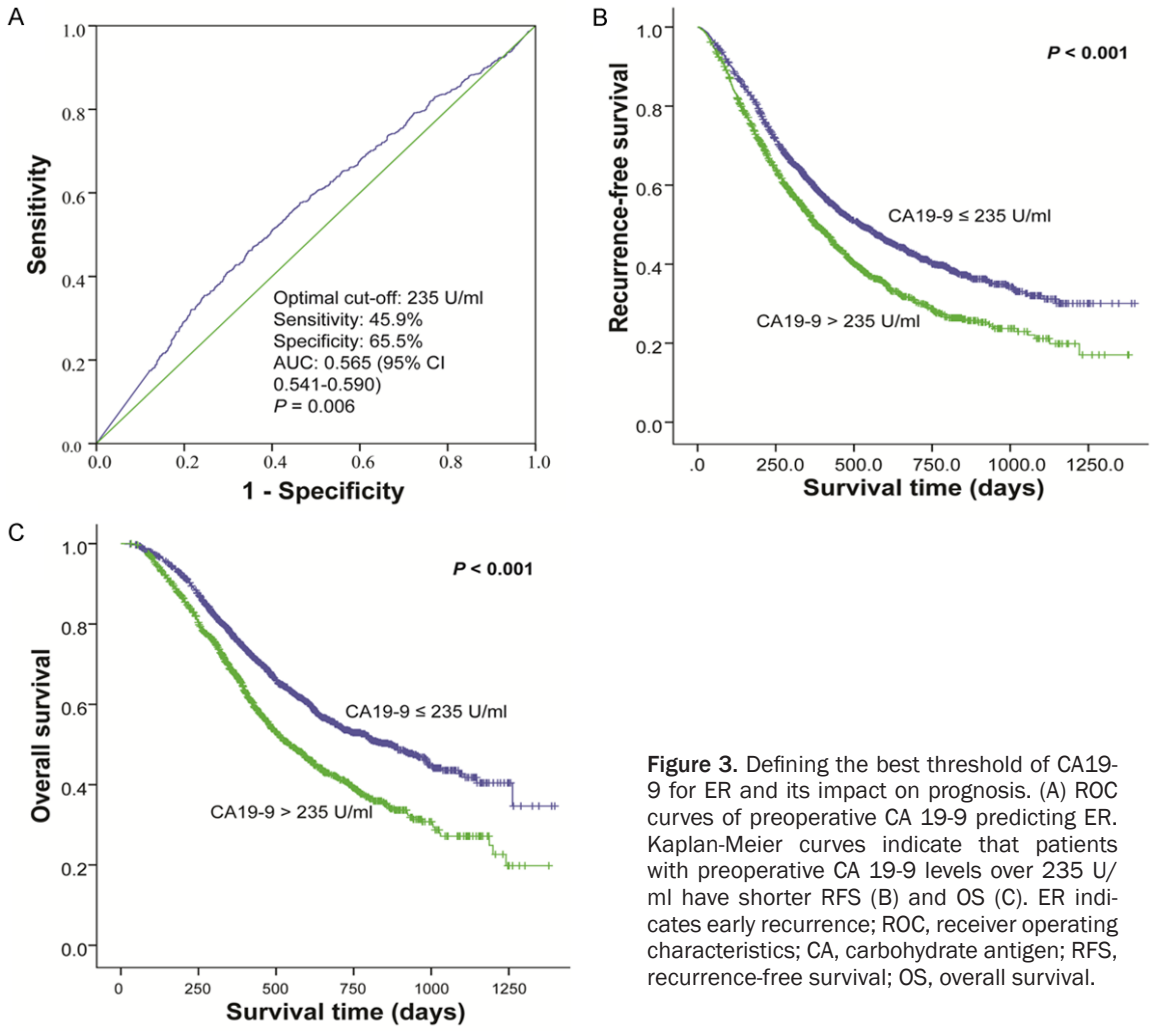

Figure 3. Defining the best threshold of CA19-9 for ER and its impact on prognosis. (A) ROC curves of preoperative CA 19-9 predicting ER. Kaplan-Meier curves indicate that patients with preoperative CA 19-9 levels over 235 U/ml have shorter RFS (B) and OS (C). ER indicates early recurrence; ROC, receiver operating characteristics; CA, carbohydrate antigen; RFS, recurrence-free survival; OS, overall survival.

(95% CI: 0.593-0.679), respectively, suggesting good discrimination of the model.

Establish a high-risk group of ER of PDAC

By calculating a total preoperative score for each PDAC patient in this study, we used ROC curves twice to define high-risk and intermediate-low-risk groups. The first ROC curve represented the score of 115.5 as the best threshold value to differentiate the low-risk group and intermediate-high-risk group with an AUC of 0.649 (95% CI, 0.626-0.672) (**Figure 5A**). For the intermediate-high-risk group, we made the second ROC curve and found that the score of 203.5 was the optimal threshold value to differentiate intermediate-risk group and high-risk group with an AUC of 0.578 (95% CI, 0.543-0.612) (**Figure 5B**). For the total population, the cut-off value of 203.5 has a sensitivity of 58.6% and a specificity of 64.7% and was selected to define high-risk and intermediate-low-risk groups. The different hazard level grouping was presented in **Figure 5C**. 82.4% (1,954/2,370) of the patients were in the intermediate-low-risk group (0-203 scores) and 32.5% (635/1,954) of them experienced ER, While 17.6% (416/2,370) of the patients was in the high-risk group (> 203 scores) and 56.7% (236/416) of them experienced ER. A part of the cases in the database was anatomically borderline resectable but not labeled, which can be deduced from the vascular invasion status. To clarify whether most of the patients in the high-risk group we selected were anatomically borderline resectable which would diminish the value of this model, we performed a chi-square test for vascular invasion in two groups. The results showed that there is no significant difference between the two groups ($P = 0.486$) (**Table 5**).

Discussion

In this study, we analyzed more than 3,200 patients with resected PDAC in the CPDC data-

Table 3. Differences of demographics, clinicopathologic, and treatment characteristics between early recurrence (< 9 months) and late recurrence (> 9 months) cohorts

Variable	Early Recurrence (n = 1234)	Late Recurrence (n = 2045)	*P* Value
Age, median (IQR)	63 (55-69)	62 (55-68)	0.049
Female, n (%)	518 (42.0%)	865 (42.3%)	0.857
BMI, kg/m^2, median (IQR)	22.5 (20.3-24.2)	22.6 (20.6-24.5)	0.038
Jaundice, n (%)	385 (31.3%)	614 (30.1%)	0.469
Weight loss, n (%)	259 (21.0%)	410 (20.1%)	0.512
Diabetes, n (%)	247 (20.2%)	364 (17.9%)	0.115
Smoking, n (%)	365 (29.6%)	590 (28.9%)	0.674
Drinking, n (%)	205 (16.7%)	362 (17.8%)	0.435
Tumor location, n (%)			0.525
Head	810 (65.6%)	1320 (64.5%)	
Body & tail	424 (34.4%)	725 (35.5%)	
CT lymph nodes metastasis, n (%)	419 (35.7%)	420 (21.6%)	< 0.001
CT tumor size, cm, median (IQR)	3.0 (2.5-4.0)	3.0 (2.1-4.0)	< 0.001
CA19-9, U/mL, median (IQR)	219.7 (54.4-708.8)	136.5 (36.7-441.1)	< 0.001
CA125, U/mL, median (IQR)	21.0 (13.3-39.8)	15.9 (10.7-24.9)	< 0.001
CEA, U/L, median (IQR)	3.5 (2.2-6.6)	3.2 (2.0-5.5)	< 0.001
Operation, n (%)			< 0.001
Open	1093 (88.6%)	1712 (83.7%)	
Minimal invasive	141 (11.4%)	333 (16.3%)	
Operative time, minutes, median (IQR)	300 (220-364)	270 (200-360)	<0.001
Vascular invasion, n (%)	288 (23.6%)	379 (18.8%)	0.001
Intraoperative bleeding, ml, median (IQR)	300 (200-500)	250 (150-400)	<0.001
Capsular invasion, n (%)	779 (65.4%)	1136 (57.6%)	< 0.001
Vessel carcinoma embolus, n (%)	241 (20.4%)	379 (19.3)	0.477
Perineural invasion, n (%)	868 (72.4%)	1321 (66.4%)	< 0.001
Resection margin, n (%)			0.008
R0	1065 (88.2%)	1819 (91.1%)	
R1	142 (11.8%)	177 (8.9%)	
Lymph nodes number, n (%)	10 (4-17)	10 (6-17)	0.25
Positive lymph nodes ratio			< 0.001
≤ 0.2	958 (78.9%)	1700 (84.9%)	
> 0.2	256 (21.1%)	303 (15.1%)	
Pathology tumor size, cm, median (IQR)	3.5 (2.5-4.5)	3.0 (2.3-4.0)	< 0.001
Tumor differentiation			< 0.001
Well/moderate	461 (37.7%)	1090 (54.4%)	
Poor	762 (62.3%)	914 (45.6%)	
Clinically relevant pancreatic fistula, n (%)	84 (6.8%)	126 (6.2%)	0.469
Abdominal infection, n (%)	157 (12.7%)	187 (9.2%)	0.001
Biliary fistula, n (%)	27 (2.2%)	38 (1.9%)	0.514
Delayed gastric emptying, n (%)	267 (21.6%)	330 (16.2%)	< 0.001
Adjuvant chemotherapy, n (%)	543 (44.0%)	877 (42.9%)	0.531

BMI indicates body mass index; IQR, interquartile range; CT, computed tomography; CA, carbohydrate antigen; CEA, carcinoembryonic antigen.

base and determined that 9 months was the best cut-off value to define ER based on PRS. Univariable and multivariable analysis identified four preoperative risk factors, including larger tumor maximal diameter, enlarged lymph nodes, CA 125 more than 35 U/ml, and CA

Table 4. Univariable and multivariable analysis for associations between pre- and intra & postoperative risk factors with early recurrence (< 9 months) of resected PDAC

Preoperative Risk Factors	Univariable		Multivariable	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age: > 65 versus ≤ 65 years	1.164 (1.005-1.347)	**0.043**	1.136 (0.955-1.352)	0.149
Gender: female versus male	0.987 (0.855-1.139)	0.857		
BMI: > 24 kg/m^2 versus ≤ 24 kg/m^2	0.862 (0.736-1.009)	**0.064**	0.919 (0.764-1.106)	0.372
Jaundice: yes versus no	1.058 (0.908-1.233)	0.470		
Weight loss: yes versus no	1.060 (0.890-1.263)	0.512		
Diabetes: yes versus no	1.156 (0.965-1.383)	0.115		
Chronic pancreatitis: yes versus no	1.164 (0.687-1.973)	0.572		
Smoking: yes versus no	1.034 (0.885-1.208)	0.674		
Drinking: yes versus no	0.928 (0.769-1.120)	0.435		
Tumor location: pancreatic head versus body & tail	0.953 (0.822-1.105)	0.525		
CT lymph nodes enlargement: yes versus no	2.011 (1.712-2.362)	**< 0.001**	2.070 (1.730-2.477)	**< 0.001**
CT tumor size				
≤ 2.0 cm	Reference			
> 2.0 cm, ≤ 4 cm	1.435 (1.107-1.861)	**0.006**	1.215 (0.908-1.626)	0.19
> 4.0 cm	1.982 (1.506-2.609)	**< 0.001**	1.597 (1.170-2.180)	**0.003**
CA19-9: > 235 U/mL versus ≤ 235 U/mL	1.544 (1.336-1.783)	**< 0.001**	1.441 (1.210-1.716)	**< 0.001**
CA125: > 35 U/mL versus ≤ 35 U/mL	2.241 (1.861-2.700)	**< 0.001**	1.852 (1.503-2.282)	**< 0.001**
CEA: > 5 U/L versus ≤ 5 U/L	1.393 (1.192-1.628)	**< 0.001**	1.068 (0.883-1.292)	0.495
Intra & postoperative risk factors	**Univariable**		**Multivariable**	
	OR (95% CI)	*P* Value	OR (95%)	*P* Value
Age: > 65 versus ≤ 65 years	1.164 (1.005-1.347)	**0.043**	1.188 (1.008-1.400)	**0.040**
Gender: female versus male	0.987 (0.855-1.139	0.857		
BMI: > 24 kg/m^2 versus ≤ 24 kg/m^2	0.862 (0.736-1.009)	**0.064**	0.913 (0.767-1.086)	0.302
Operation: minimal invasive versus open	0.667 (0.540-0.824)	**< 0.001**	0.699 (0.551-0.886)	**0.003**
Operative time: > 360 minutes versus ≤ 360 minutes	1.324 (1.119-1.568)	**0.001**	1.368 (1.122-1.667)	**0.002**
Vascular invasion: yes versus no	1.334 (1.122-1.586)	**0.001**	1.304 (1.060-1.603)	**0.012**
Intraoperative bleeding: > 400 ml versus ≤ 400 ml	1.589 (1.360-1.857)	**< 0.001**	1.358 (1.132-1.628)	**0.001**
Capsular invasion: yes versus no	1.388 (1.196-1.611)	**< 0.001**	1.138 (0.945-1.370)	0.172
Vessel carcinoma embolus: yes versus no	1.068 (0.891-1.279)	0.477		
Perineural invasion: yes versus no	1.324 (1.132-1.549)	**< 0.001**	1.076 (0.886-1.306)	0.461
Resection margin: R1 versus R0	1.370 (1.085-1.730)	**0.008**	1.301 (1.004-1.685)	**0.047**
Number of examined lymph nodes	1.020 (0.869-1.197)	0.810		
Positive lymph nodes ratio: > 0.2 versus ≤ 0.2	1.505 (1.252-1.810)	**< 0.001**	1.409 (1.150-1.728)	**0.001**
Pathology tumor size:				
≤ 2.0 cm	Reference			
> 2.0 cm, ≤ 4 cm	1.568 (1.290-1.906)	**< 0.001**	1.507 (1.214-1.870)	**< 0.001**
> 4.0 cm	1.838 (1.471-2.298)	**< 0.001**	1.692 (1.318-2.174)	**< 0.001**
Tumor differentiation: poor versus moderate/well	1.971 (1.705-2.279)	**< 0.001**	1.824 (1.547-2.150)	**< 0.001**
Clinically relevant pancreatic fistula: yes versus no	1.111 (0.835-1.479)	0.469		
Abdominal infection: yes versus no	1.447 (1.155-1.812)	**0.001**	1.286 (1.006-1.643)	**0.044**
Biliary fistula: yes versus no	1.180 (0.717-1.943)	0.515		
Delayed gastric emptying: yes versus no	1.433 (1.198-1.715)	**< 0.001**	1.306 (1.063-1.605)	**0.011**
Adjuvant chemotherapy: yes versus no	1.047 (0.908-1.207)	0.531		

Factors significant in univariable (*P* < 0.1) were selected for multivariable analysis and were shown in bold. PDAC indicates pancreatic ductal adenocarcinoma; BMI, body mass index; CT, computed tomography; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval.

19-9 more than 235 U/ml. Consequently, a nomogram for the prediction of ER was developed based on the four preoperative risk factors. The predictive model exhibited good performance with a C-index of 0.636 (95% CI: 0.593-0.679) in the validation cohort. The risk

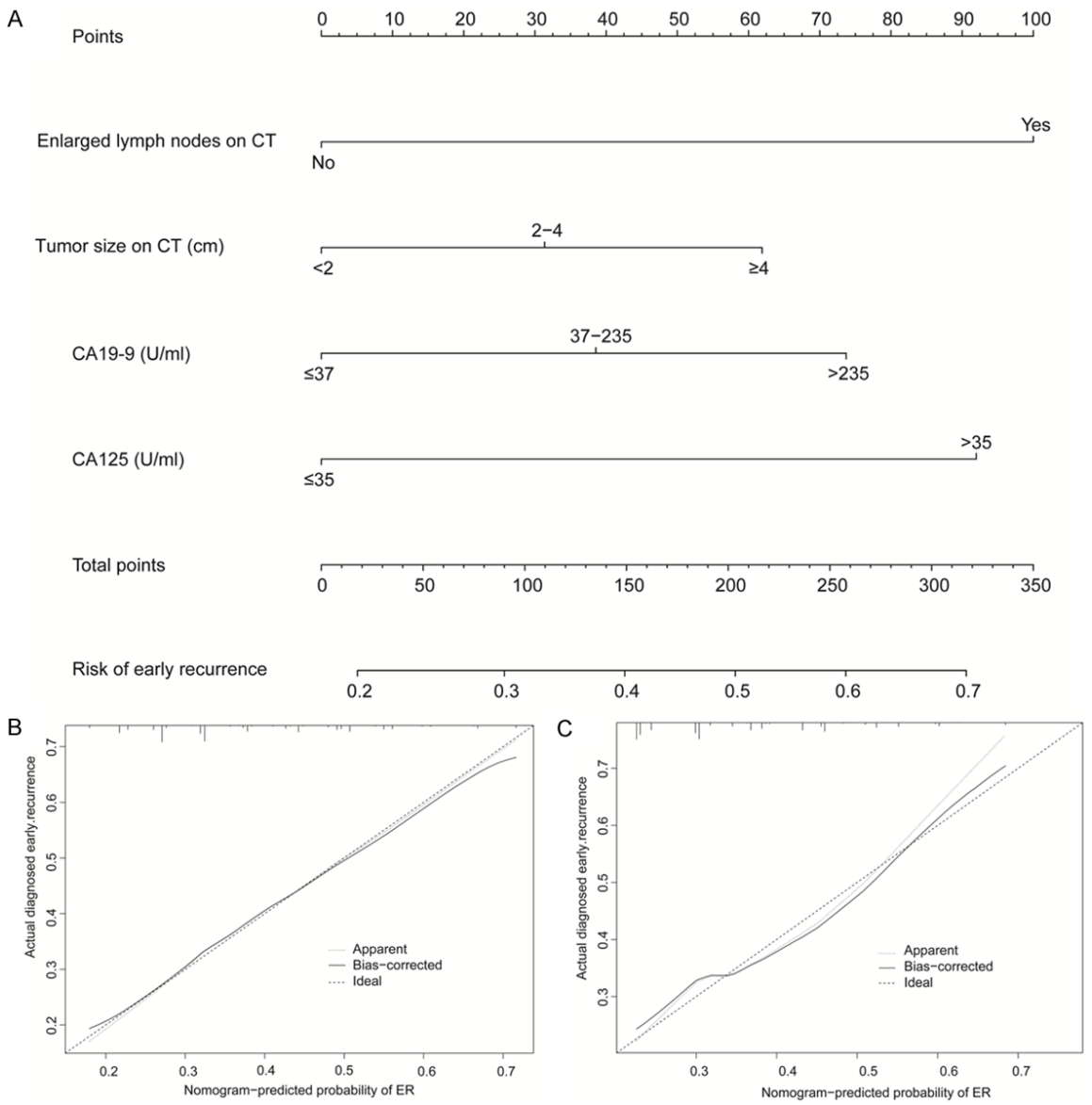

Figure 4. Development and validation of ER predictive model. (A) Establishing a predictive model of ER based on 4 independent predictors identified preoperatively. Calibration curves in the training (B) and validation (C) cohort demonstrated a good performance in predicting ER. ER indicates early recurrence.

stratification was performed and a nomogram score above 203 was defined as ER high-risk group, of which 56.7% of patients experienced ER.

In the past two decades, surgical treatment for pancreatic cancer has great improvements with increasing resection rate and surgical safety while perioperative mortality has shown a remarkable decline [16]. However, a poor understanding of the biological behavior of PDAC limits the efficacy of treatment. ER after curative-intent surgery in PDAC is the main challenge of treatment and reflects highly aggressive tumor biological behavior. Patients who develop ER after operation may not benefit from upfront surgery, and neoadjuvant strategy should be taken into consideration. Therefore, selecting patients with a high risk of ER preoperatively is particularly important.

For many years, the definition of ER of PDAC is largely depending on the researcher's preference varying from 6 to 12 months. In 2014, Yamamoto et al. [12] provided an evidence-based definition of ER and proposed that

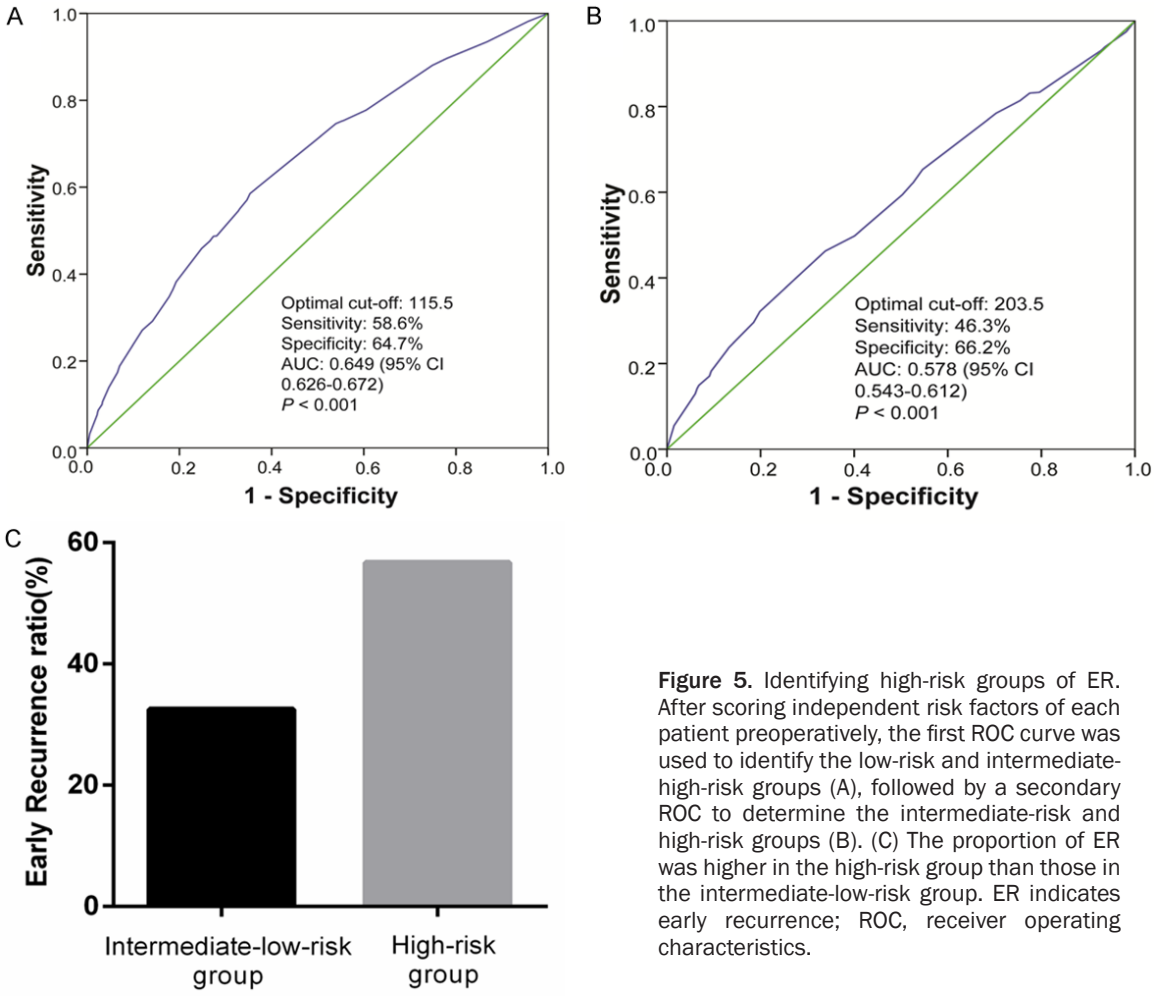

Figure 5. Identifying high-risk groups of ER. After scoring independent risk factors of each patient preoperatively, the first ROC curve was used to identify the low-risk and intermediate-high-risk groups (A), followed by a secondary ROC to determine the intermediate-risk and high-risk groups (B). (C) The proportion of ER was higher in the high-risk group than those in the intermediate-low-risk group. ER indicates early recurrence; ROC, receiver operating characteristics.

Table 5. Chi-square test for vascular invasion in ER high-risk and intermediate-low-risk groups

	ER high-risk (n = 240)	ER intermediate-low-risk (n = 1905)	*P* Value
Vascular Invasion (+)	31 (12.9%)	217 (11.4%)	0.486
Vascular Invasion (-)	209 (87.1%)	1688 (88.6%)	

ER indicates early recurrence; Vascular invasion status of 225 cases was missed.

12-month has the best differential ability in OS between ER group and LR group. However, their study has a small sample size and has a bias by defining ER based on OS, since OS in the LR group is definitely longer than that in ER group. To avoid such bias, Groot et al. [9] proposed a new method to define ER based on the difference in PRS. They analyzed 957 resected PDAC patients and defined the optimal cut-off value of ER as 12 months. However, these studies were single-center studies. In the present study, by analyzing a large cohort of more than 3,200 patients with resected PDAC patients based on PRS, we calculated that 9-month was the best cut-off value to define ER. Patients with ER experienced a shorter PRS of 5.3 months, whereas patients with late recurrence had a PRS of 7.1 months. Notably, the LR group also had significantly prolonged OS. Studies showed that late recurrence patients tended to have significantly longer survival even after treatment of recurrence, suggesting that those patients need active treatment after recurrence [17, 18].

By multivariate analysis, we identified four preoperative independent risk factors for ER, including elevated CA19-9 level, elevated CA125 level, tumor size, and regional lymph node en-

largement in the CT scan. CA19-9 is the most widely recognized prognosis biomarker for PDAC. However, the relationship between CA19-9 and ER of PDAC is debated. For example, Sugiura et al. explored that preoperative CA 19-9 > 100 U/ml can predict the ER after resection of PDAC [19]. Vincent et al. showed that preoperative CA 19-9 level of > 210 U/ml and postoperative CA 19-9 level of > 37 U/ml were independently associated with ER [9]. In our study, the best threshold of preoperative CA 19-9 evaluated by the ROC curve was 235 with a sensitivity of 45.9% and a specificity of 65.5%, indicating that the CA19-9 level was not enough to predict ER. Therefore, we analyzed other biomarkers associated with PDAC such as carcinoembryonic antigen (CEA) and CA125 and it showed that CEA was not an independent risk factor but elevated CA125 (> 35 U/ml) was associated with ER. CA125 is an established biomarker for ovarian cancer and is related to peritoneal metastasis by mediating cell adhesion [20]. Einama et al. found that an elevated level of serum CA125 in pancreatic cancer patients was related to a higher recurrence rate [21]. Liu et al. demonstrated that high serum CA125 level was related to metastatic potential as well as the metastatic burden in pancreatic cancer [22]. In this study, elevated serum CA125 showed a much stronger predictive ability for ER than CA19-9. Patients with elevated CA125 levels had shortened RFS and 53.0% of them experienced ER, while patients with normal CA125 levels had only 33.5% ER rate. Elevated serum CA125 level could represent aggressive tumor feature and indicate micro-metastasis before surgery.

Moreover, we identified two accessible independent risk factors of ER based on preoperative CT scan: tumor size and regional lymph node enlargement. Tumor size measured in CT scan was frequently underestimated compared with that measured in gross pathology specimen [23, 24]. Therefore, CT tumor size has limited predictive value in prognosis. In the current study, we showed that preoperative CT tumor size could be used in predicting ER. However, it should be noted that the prognosis of pancreatic cancer is not simply deteriorating with increased tumor size [25]. Muralidhar et al. found that in lymph node-positive patients, very small tumor size was correlated with decreased OS [26]. Therefore, tumor size is not enough to predict ER, and other biological features and lymph node status should be considered. A recent study reported that lymph nodes detected by preoperative imaging had a high predictive value for pathologic involvement, especially for those without biliary obstruction [27]. In the current study, preoperative lymph node enlargement in CT scan was identified as a strong predictive factor for ER with an OR of 2.07 ($P < 0.001$). Patients with CT lymph node enlargement had a shortened OS and RFS with a higher rate of ER. Additionally, we explored the correlation between CT lymph node enlargement and pathological lymph node metastasis and found that 79.2% of patients with CT lymph node enlargement were metastasis positive. These results suggest that CT lymph node enlargement is capable of predicting lymph metastasis and ER of PDAC. CT is currently the most commonly used imaging examination for the diagnosis of PDAC and has a similar diagnostic effect as magnetic resonance imaging (MRI) in tumor diagnosis and analysis of local lymph node metastasis. However, CT has some shortcomings in the detection of micrometastasis in the liver and peritoneal implantation metastases, thus the combination of MRI, EUS, and PET-CT can be used as a supplement for predicting ER in the future study.

Several independent intra- and post-operative risk factors were identified by multivariate analysis, including minimally invasive surgery, operative time and intraoperative bleeding, resection margin, positive lymph node ratio, pathology tumor size, and tumor differentiation, as well as abdominal infection and delayed gastric emptying. However, such factors had limited value for the preoperative prediction of ER because of their intra- or postoperative nature, and we did not include them into the prediction model.

After curative-intent surgery, many patients still experience ER and the prognosis of these patients is even poorer than patients with late-stage in terms of OS [28]. How to select patients who may not benefit from upfront surgery is crucial. Therefore, we propose a nomogram scoring system for predicting ER of PDAC based on four preoperative risk factors identified by multivariate analysis: CA19-9, CA125, CT tumor size, and CT lymph node enlargement. Kim et al. developed a model for defining ER at 12 months for a single-center study of 833 patients. The tumor markers included were CA19-9 and CEA, but they accounted for a small pro-

portion in the nomogram [10]. Our multicenter, large sample study found no significant correlation between CEA and ER, while another tumor marker CA125 was significant for ER. Brennan et al. used postoperative pathologic factors to establish the probability that a patient would die after pancreatic cancer surgery, but it made it impossible to predict patient prognosis in a preoperative manner [29]. In contrast, the different weights of four risk factors for ER are well represented in the nomogram and our model allows easy calculation of the risk of ER in patients with potentially resectable PDAC. The stratification of the risk of ER before surgery by our prediction system provides important treatment strategies. For example, in patients with a low risk of ER, upfront radical surgery remains the best option. However, in patients with a high risk of ER, the benefits of upfront surgery need to be weighed against the possibility that neoadjuvant chemotherapy may be a better strategy in three ways: selection of chemosensitive patients for subsequent surgery; avoidance of unnecessary surgery in patients with poor response to chemotherapy; and earlier systemic therapy to eliminate micrometastasis.

This study has several limitations. First, although resectability was evaluated preoperatively in our database, the criteria for the judgment had bias due to the differences in surgery. Second, this study is retrospective, which will inevitably lead to selection bias. Third, the follow-up period is not long enough. Fourth, the overall adjuvant chemotherapy rate was much lower in the CPDC database than reality in China and adjuvant chemotherapy fails to show a protective effect of ER in our study. A possible explanation is that not all adjuvant chemotherapy was labeled in the database. Finally, the model proposed in this study needs further validation by multicenter prospective studies.

In conclusion, our study showed that the best threshold for distinguishing between ER and LR is a recurrence-free time of 9 months after radical surgery based on prognostic analysis after recurrence. Besides, we identified independent preoperative predictors for ER after PDAC resection, including maximum tumor diameter on the last preoperative CT, enlarged regional lymph nodes, CA 19-9 levels more than 235 U/ml, and CA 125 levels more than 35 U/ml. The scoring system for predicting ER based on four preoperative factors will be an effective tool in selecting patients with a high risk of ER and it will help us to distinguish patients who might not benefit from upfront surgery.

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Disclosure of conflict of interest

None.

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