

# Validation and modification of the AJCC 8th TNM staging system for pancreatic ductal adenocarcinoma in a Chinese cohort: A nationwide pancreas data center analysis

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## Abstract

**Objective:** To validate the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for pancreatic ductal adenocarcinoma (PDAC) in a Chinese cohort of radically resected patients and to develop a refined staging system for PDAC.

**Methods:** Data were collected from the China Pancreas Data Center (CPDC) for patients with resected PDAC in 2016 and 2017, and cancer-specific survival (CSS) was evaluated using the Kaplan-Meier method and log-rank test. Univariate and multivariate analyses based on Cox regression were performed to identify prognostic factors. The recursive partitioning analysis (RPA), Kaplan-Meier method, and log-rank test were performed on the training dataset to generate a proposed modification for the 8th TNM staging system utilizing the preoperative carbohydrate antigen (CA)19-9 level. Validation was performed for both staging systems in the validation cohort.

**Results:** A total of 1,676 PDAC patients were retrieved, and the median CSS was significantly different between the 8th TNM groupings, with no significant difference in survival between stage IB and IIA. The analysis of T and N stages demonstrated a better prognostic value in the N category. Multivariate analysis showed that the preoperative serum CA19-9 level was the strongest prognostic indicator among all the independent risk factors. All patients with CA19-9 >500 U/mL had similar survival, and we proposed a new staging system by combining IB and IIA and stratifying all patients with high CA19-9 into stage III. The modified staging system had a better performance for predicting CSS than the 8th AJCC staging scheme.

**Conclusions:** The 8th AJCC staging system for PDAC is suitable for a Chinese cohort of resected patients, and the N category has a better prognostic value than the T category. Our modified staging system has superior accuracy in predicting survival than the 8th AJCC TNM staging system.

**Keywords:** CA19-9; cancer-specific survival; CPDC; pancreatic ductal adenocarcinoma; prognosis; TNM staging

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## Introduction

Despite advances in multimodality treatment, pancreatic

ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with a 5-year survival rate of less than 8%, and it is expected to be the second greatest cause of

cancer-related death in 2030 (1,2). Surgical resection remains the only potential cure for PDAC, but only 20% of PDAC patients are eligible for surgical operation, and postoperative long-term survival can be achieved in only 20% of patients undergoing successful resection and adjuvant therapy (3,4).

The poor survival of PDAC patients requires the development of an accurate staging system to guide treatment and predict prognosis. The American Joint Committee on Cancer (AJCC) TNM staging system is the most widely used indicator for such purposes, and it is based on three factors: tumor size and extension (T), lymph node metastasis (N), and distant metastasis (M). In 2016, the AJCC released the 8th TNM staging system for PDAC. Since then, several studies have validated the predictive value of this system in clinical use and proposed modifications for the AJCC 8th edition staging system (5-14). However, most of these studies are based on Western cohorts, and whether the modified staging system is suitable for the Chinese population remains unclear.

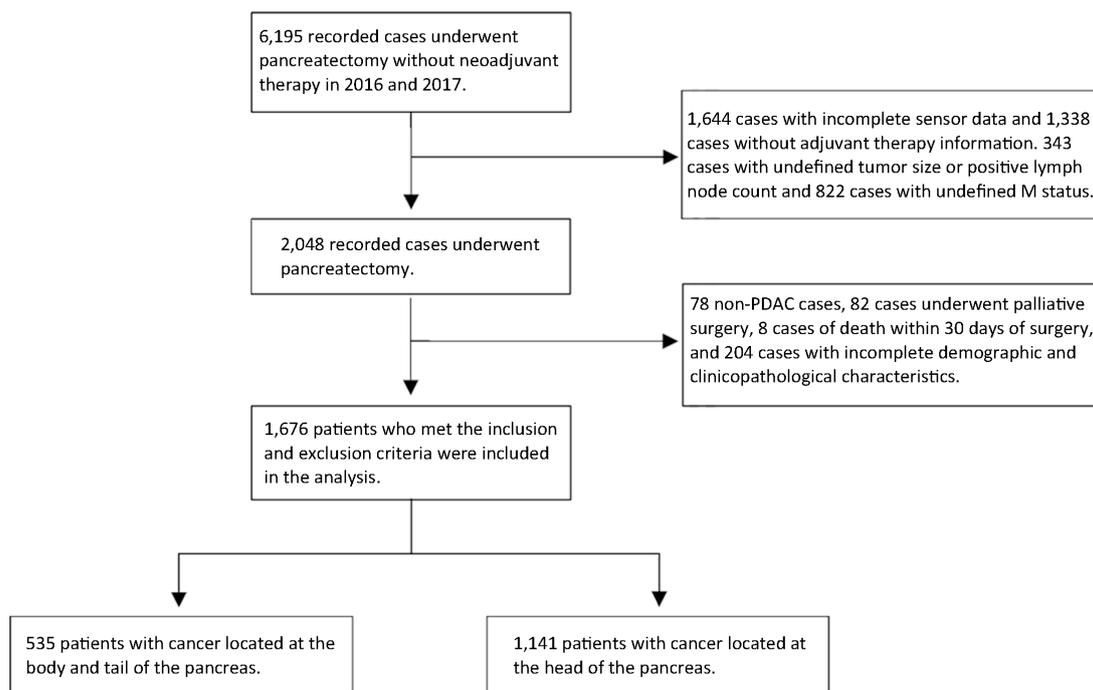
Therefore, this study aimed to validate the AJCC 8th staging system for PDAC using a cohort from the China Pancreas Data Center (CPDC) and to propose a modification for the 8th TNM staging system by incorporating the preoperative level of CA19-9.

## Materials and methods

### Patients and data source

A multicenter web-based registry called the CPDC was initiated by the Chinese Society of Surgery and became the first multidisciplinary and specialized oncology big data center in China. Data in CPDC were collected from 90 tertiary hospitals in 31 provinces across China, and these hospitals represent the top hospitals in pancreatic disease diagnosis and treatment in China. The CPDC started data collection in 2016, and patients were followed up and registered yearly by participating hospitals. Data used in this study were retrieved from the CPDC database. This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (PUMCH). The requirement of informed consent was waived because of the retrospective nature of this study. The inclusion criteria were as follows: 1) pathologically confirmed PDAC; 2) underwent curative intent surgical resection in 2016 and 2017; and 3) had complete clinicopathological and follow-up information. The exclusion criteria were as follows: 1) neoadjuvant treatment or 2) death within 30 d of surgery.

A total of 1,676 PDAC patients who met the criteria above were finally included. The detailed enrollment procedure is shown in *Figure 1*. The following data were



**Figure 1** Flow chart of PDAC patients included in this study. PDAC, pancreatic ductal adenocarcinoma.

retrieved for each patient: sex, age (year), body mass index (BMI, kg/m<sup>2</sup>), differentiation grade, preoperative serum total bilirubin (TBIL, μmol/L), preoperative serum carbohydrate antigen 19-9 (CA19-9, U/mL), preoperative serum carcinoembryonic antigen (CEA, ng/mL), surgical approach, tumor size (cm), T stage, tumor site, the number of positive lymph nodes (LNs positive), the number of examined lymph nodes (LNs examined), resection margin status, follow-up time, and survival information. The 8th edition N stage was derived from the number of positive lymph nodes. Resection margin status was defined as R0 if no cancer cells were found within 0 mm of the resection margin microscopically and R1 if cancer cells were visible microscopically within the resection margin. No M1 or R2 resection disease was found in the final cohort.

**Statistical analysis**

The primary outcome was cancer-specific survival (CSS), which was calculated from the date of surgery to the date of death or the last follow-up date. Continuous variables are presented as the medians and interquartile ranges (IQRs), while categorical variables are presented as frequencies. Survival curves were calculated using the Kaplan-Meier method, and the differences in survival between groups were evaluated by the log-rank test. The cutoff points of continuous variables for survival were determined and validated using X-tile software (Yale University, New Haven, CT, USA). Univariate and multivariate analyses were performed and hazard ratios (HRs) and 95% confidence interval (95% CI) were determined by a Cox proportional hazards regression model to identify independent prognostic factors. Then, the data were randomly divided into training and validation sets at a 2:1 ratio. To develop a refined staging system that incorporated CA19-9 together with the 8th AJCC stage, recursive partitioning analysis (RPA) combined with the Kaplan-Meier method and log-rank test was performed to derive new stages in the training set. The predictive performance of the modified staging system was measured by the concordance probability estimate (CPE), concordance index (C-index) and decision curve analysis (DCA), with a CPE and C-index larger than 0.5 indicating good prediction abilities. All statistical analyses were performed using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria) and X-tile software. A two-sided P-value of <0.05 was considered statistically significant.

**Results**

**Baseline characteristics**

A total of 1,676 patients with complete clinical and survival data from the CPDC database were retrieved, and their baseline demographic and clinicopathological characteristics are shown in *Table 1*. The median age was 63.00 (IQR, 56.00–68.00) years, and 1,018 (60.7%) patients were male. While 535 (31.9%) patients had cancer located at the body and tail of the pancreas, 1,141 (68.1%) patients had pancreatic head cancer. The median tumor size was 3.00 (IQR, 2.50–4.00) cm. The median values of CEA and CA19-9 were 3.26 (IQR, 2.00–5.61) ng/mL and 158.95 (IQR, 39.27–519.68) U/mL, respectively. The median

**Table 1** Baseline demographic and clinicopathological characteristics (N=1,676)

Characteristics	n (%)
Gender	
Female	658 (39.3)
Male	1,018 (60.7)
Age (year) [median (IQR)]	63.00 (56.00, 68.00)
BMI (kg/m <sup>2</sup> ) [median (IQR)]	22.41 (20.45, 24.22)
TBIL (μmol/L) [median (IQR)]	19.50 (11.00, 112.60)
CA19-9 (U/mL) [median (IQR)]	158.95 (39.27, 519.68)
CEA (ng/mL) [median (IQR)]	3.26 (2.00, 5.61)
Tumor size (cm) [median (IQR)]	3.00 (2.50, 4.00)
Site of tumor	
Body and tail of pancreas	535 (31.9)
Head of pancreas	1,141 (68.1)
Differentiation	
I	74 (4.4)
II	792 (47.3)
III	807 (48.2)
IV	3 (0.2)
LNs positive [median (IQR)]	0 (0, 1.00)
LNs examined [median (IQR)]	10.00 (5.00, 16.00)
Margin	
R0	1,502 (89.6)
R1	174 (10.4)
Adjuvant therapy	
No	945 (56.4)
Yes	731 (43.6)

IQR, interquartile range; BMI, body mass index; TBIL, total bilirubin; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LN, lymph node.

number of LNs examined was 10.00 (IQR, 5.00–16.00). The median follow-up period and the median CSS for all 1,676 patients were 23 months and 24 months, respectively.

### Evaluation of AJCC stage classification for CSS

Table 2 shows the detailed stage classification which stratified patients according to the AJCC 8th staging system. Stage IA was found in 210 (12.5%) patients, stage IB in 477 (28.5%) patients, stage IIA in 176 (10.5%) patients, stage IIB in 498 (29.7%) patients, and stage III in 315 (18.8%) patients. Due to the short follow-up period, the median CSS for IA patients was not shown, and the median CSS calculated using the Kaplan-Meier method was as follows: stage IB, 30 months; stage IIA, 32 months; stage IIB, 19 months; and stage III, 16 months. Kaplan-Meier survival curves are shown in Figure 2 with a significant difference in prognosis among different stages (log-rank  $P < 0.001$ ). When comparing CSS between each two stages, a significant difference between each group was

**Table 2** Staging and median CSS of PDAC patients based on the AJCC 8th staging system (N=1,676)

Classifications	n (%)	Median CSS (month)	95% CI
TNM grouping			
IA	210 (12.5)	NA	NA
IB	477 (28.5)	30	27–NA
IIA	176 (10.5)	32	21–NA
IIB	498 (29.7)	19	17–21
III	315 (18.8)	16	14–17
T stage (N0)			
T1	210 (12.5)	NA	NA
T2	477 (28.5)	30	27–NA
T3	176 (10.5)	32	21–NA
T4	96 (5.7)	17	15–24
T stage			
T1	317 (18.9)	35	26–NA
T2	861 (51.4)	24	21–28
T3	300 (17.9)	21	19–32
T4	198 (11.8)	16	15–20
N stage			
N0	959 (57.2)	32	28–39
N1	575 (34.3)	19	17–20
N2	142 (8.5)	14	11–17

CSS, cancer specific survival; PDAC, pancreatic ductal adenocarcinoma; AJCC, American Joint Committee on Cancer; 95% CI, 95% confidence interval; NA, not available.

found, except for that between stage IB and IIA, with a log-rank P-value of 0.030 between IB and IA, 0.400 between IIA and IB, 0.008 between IIB and IIA, and 0.027 between III and IIB.

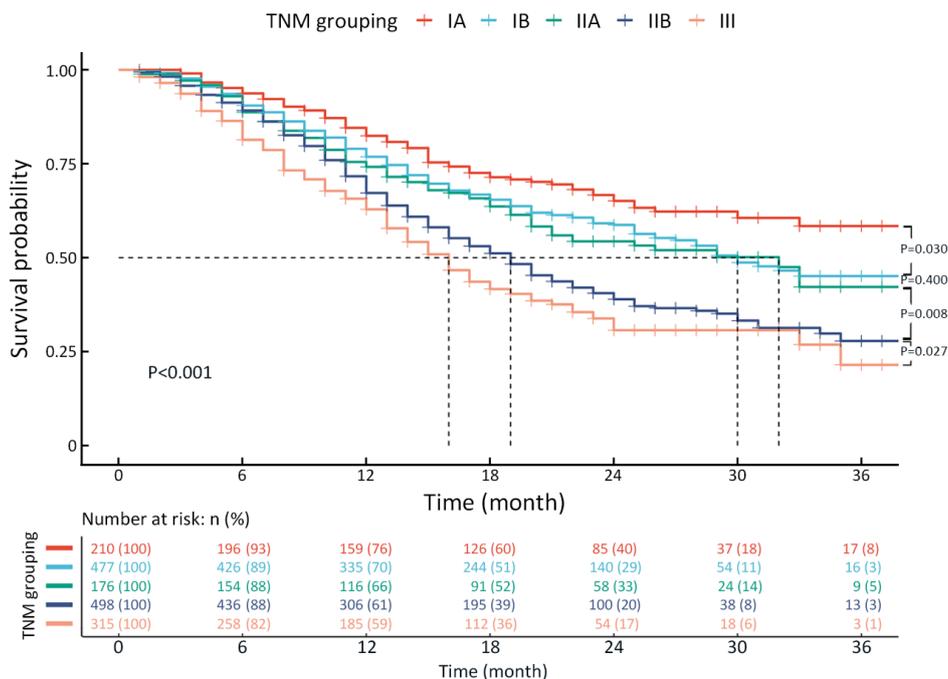
### Prognostic values of T and N staging for CSS

Of all 1,676 patients with curative resection, 959 (57.2%) patients had no lymph node metastasis. According to the 8th edition, under the N0 setting, there were 210 (12.5%) patients with T1, 477 (28.5%) patients with T2, 176 (10.5%) patients with T3, and 96 (5.7%) patients with T4 cancer. The median CSS for T2, T3, and T4 patients was 30, 32, and 17 months, respectively (Table 2). The log-rank test for the survival of each T category showed significant differences between T1 and T2 and T3 and T4 but not between T2 and T3 (Figure 3A). The same trend was found when T stage was analyzed without N0 setting (Figure 3B), and CSS for overall T stage was 35 months for T1, 24 months for T2, 21 months for T3, and 16 months for T4. The log-rank P-value was 0.002 between T1 and T2, 0.590 between T2 and T3, and 0.011 between T3 and T4.

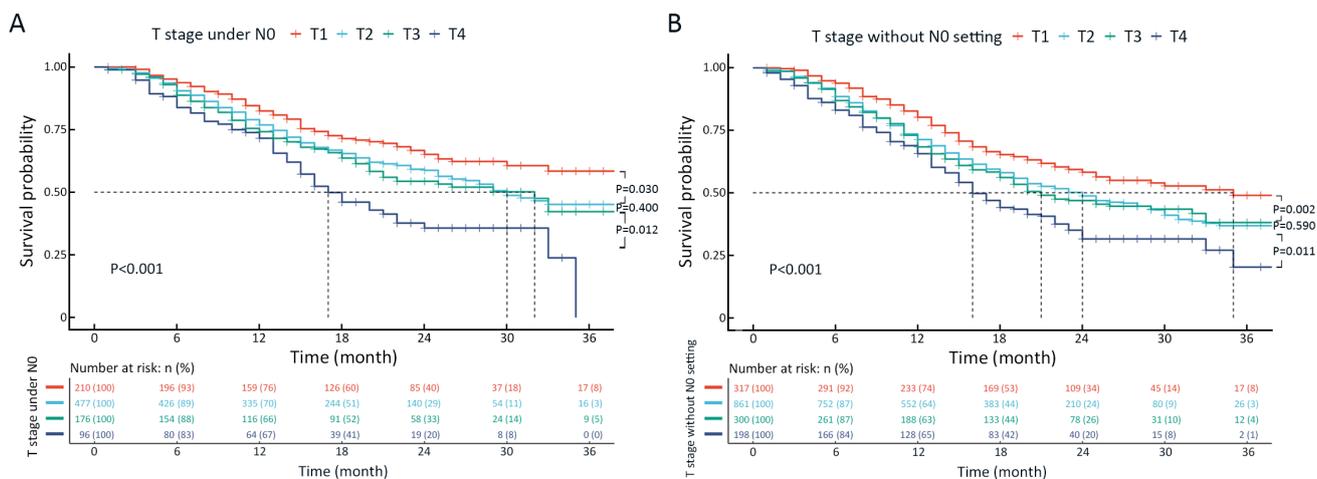
A total of 717 (42.8%) patients had node-positive disease, with 575 (34.3%) and 142 (8.5%) patients classified as N1 and N2, respectively. The N classification in the 8th TNM staging system was discriminative for the entire cohort (Figure 4,  $P < 0.001$ ), with a median CSS of 32 months for N0 tumors, 19 months for N1 tumors, and 13 months for N2 tumors.

### Prognostic indicators for resected PDAC patients

Cox regression analysis showed that older age ( $> 65$  years, HR=1.22; 95% CI: 1.05–1.40,  $P = 0.007$ ), higher preoperative TBIL ( $> 128.29$   $\mu\text{mol/L}$ , HR=1.50; 95% CI: 1.29–1.76,  $P < 0.001$ ), higher preoperative serum CA19-9 ( $> 500$  U/mL, HR=1.64; 95% CI: 1.41–1.91,  $P < 0.001$ ), higher preoperative serum CEA ( $> 2.98$  ng/mL, HR=1.45; 95% CI: 1.25–1.67,  $P < 0.001$ ), pancreatic head cancers (HR=1.23; 95% CI: 1.05–1.43,  $P = 0.009$ ), advanced differentiation (HR=1.67; 95% CI: 1.47–1.90,  $P < 0.001$ ), T stage (HR=1.22; 95% CI: 1.13–1.31,  $P < 0.001$ ), N stage (HR=1.53; 95% CI: 1.38–1.69,  $P < 0.001$ ), and R1 resection margin (HR=1.67; 95% CI: 1.36–2.03,  $P < 0.001$ ) were associated with worse survival, while larger BMI ( $> 19$  kg/m<sup>2</sup>, HR=1.33; 95% CI: 1.10–1.62,  $P = 0.004$ ) and adjuvant therapy (HR=1.34; 95% CI: 1.16–1.55,  $P < 0.001$ ) were considered protective factors. Multivariate analysis showed that significant predictors of mortality were higher



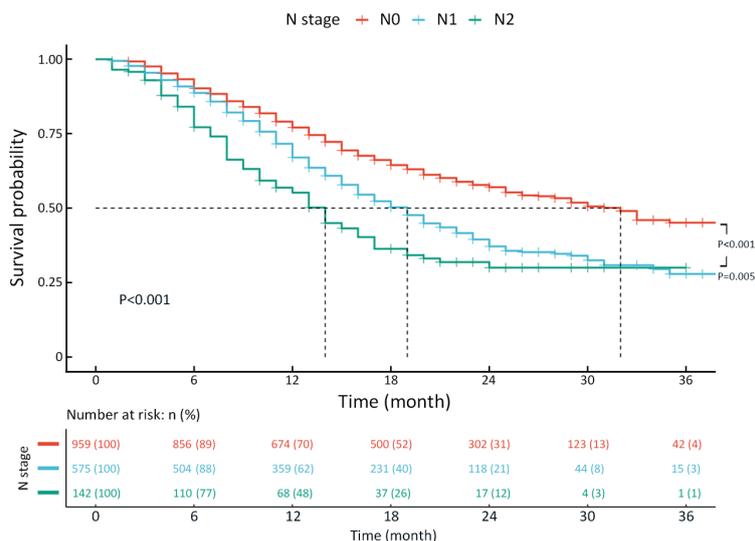
**Figure 2** Comparison of CSS among different stages according to the AJCC 8th TNM system ( $P<0.001$ ). CSS, cancer-specific survival; AJCC, American Joint Committee on Cancer.



**Figure 3** Prognostic values of T staging for CSS. (A) CSS for T stage in 959 patients with curative resection for node-negative pancreatic cancer ( $P<0.001$ ); (B) CSS for overall T stage ( $P<0.001$ ). T stage was defined by the AJCC 8th TNM staging system. CSS, cancer-specific survival; AJCC, American Joint Committee on Cancer.

preoperative serum TBIL ( $>128.29 \mu\text{mol/L}$ , HR=1.32, 95% CI: 1.11–1.56;  $P=0.002$ ), higher preoperative serum CA19-9 ( $>500 \text{ U/mL}$ , HR=1.40, 95% CI: 1.20–1.64;  $P<0.001$ ), higher preoperative serum CEA ( $>2.98 \text{ ng/mL}$ , HR=1.18, 95% CI: 1.01–1.37;  $P=0.032$ ), advanced differentiation (HR=1.64, 95% CI: 1.44–1.86;  $P<0.001$ ), T stage (HR=1.16, 95% CI: 1.07–1.26;  $P<0.001$ ), N stage

(HR=1.40, 95% CI: 1.26–1.56;  $P<0.001$ ), and R1 resection margin (HR=1.69, 95% CI: 1.38–2.09;  $P<0.001$ ), while adjuvant therapy (HR=0.64, 95% CI: 0.56–0.75;  $P<0.001$ ) was a factor associated with improved prognosis. Notably, preoperative serum CA19-9 was the strongest prognostic indicator among all preoperative factors, with an HR of 1.40 (Table 3).



**Figure 4** Prognostic values of N staging for CSS in patients who underwent curative resection with N stage PDAC defined by the AJCC 8th TNM staging system ( $P < 0.001$ ). CSS, cancer-specific survival; PDAC, pancreatic ductal adenocarcinoma; AJCC, American Joint Committee on Cancer.

#### Modification of the 8th AJCC staging system based on preoperative CA19-9

Because the preoperative serum CA19-9 value was a strong predictor for CSS in PDAC, we identified 500 U/mL as the cutoff point for the preoperative level of CA19-9. In the entire cohort, 1,244 patients had preoperative CA19-9  $\leq 500$  U/mL, while 432 patients had preoperative CA19-9  $> 500$  U/mL. With this cutoff point, each TNM stage was divided into two subgroups: “H” for CA19-9  $> 500$  U/mL and “L” for CA19-9  $\leq 500$  U/mL, and 10 subgroups were obtained as follows: IAH, IAL, IBH, IBL, IAH, IAL, IIBH, IIBL, IIH and IIIL. A significant difference in survival was found between the two subgroups within each TNM stage, except for that between IIH and IIIL (Figure 5A–E). However, CSS was not significantly different between all “H” subgroups (Figure 5F,  $P = 0.063$ ).

Next, the entire cohort was randomly divided into training and validation sets at a 2:1 ratio. The baseline characteristics of the two cohorts are shown in Supplementary Table S1. RPA of the training set showed that all “H” subgroups could be assembled into one stage (Supplementary Figure S1), which was named the H group, and the survival curve of the H group was similar to that of subgroup IIIL, with  $P = 0.980$  in the training set (Figure 6A,B). However, the survival difference between H stage and subgroup IIBL was statistically significant ( $P = 0.035$ , Figure 6C), and no significant difference was found

between IBL and IIAL (Figure 6D). Therefore, we named IAL “nIA”, combined IBL and IIAL into one stage named “nIB”, renamed IIBL “nII”, and then merged the H stage with IIIL to form a new stage, “nIII” (Figure 7).

#### Validation of modified staging system

The modified staging system was then validated with the CPE in the validation set against the original 8th TNM staging system. Our new staging system achieved a CPE of 0.590, which was superior to that of the 8th AJCC staging system (CPE, 0.575).

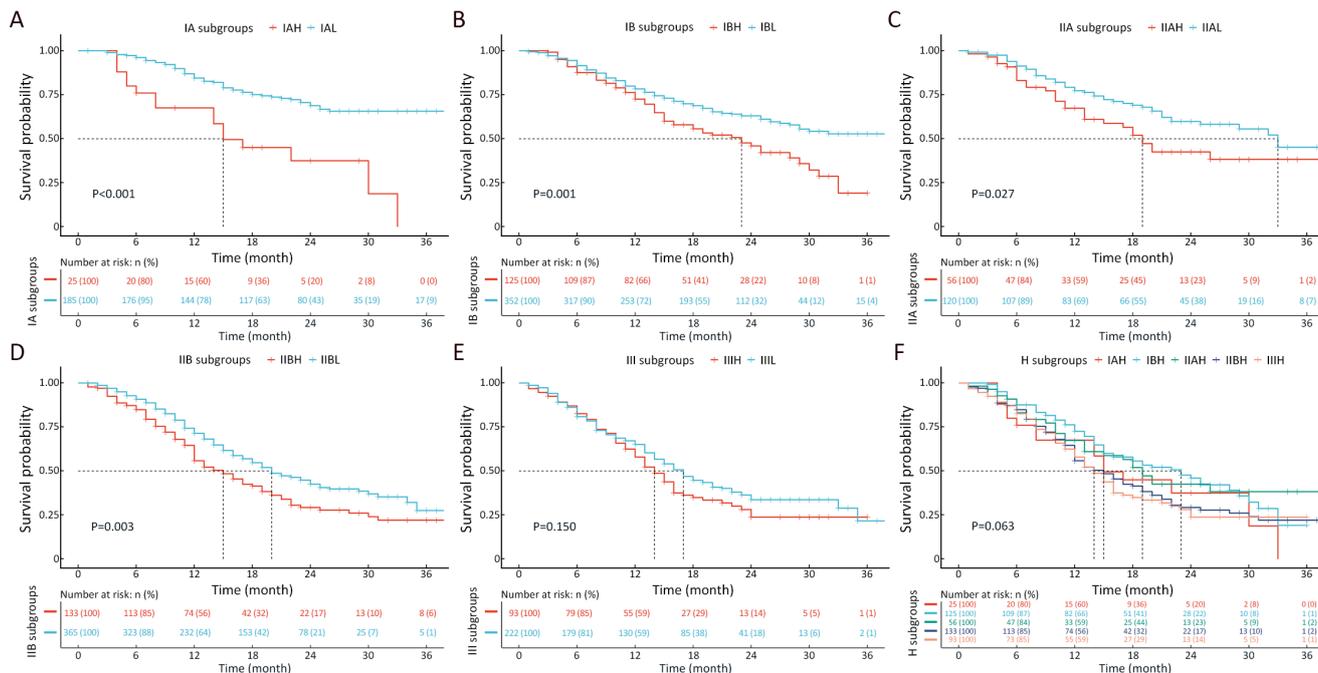
The accuracy of both staging systems was examined in the validation cohort. For the modified staging system, the C-indexes for 1-, 2-, and 3-year CSS were 0.576 (95% CI: 0.520–0.632), 0.615 (95% CI: 0.555–0.674) and 0.815 (95% CI: 0.722–0.909), respectively. For the AJCC 8th staging system, these values were 0.554 (95% CI: 0.497–0.611), 0.601 (95% CI: 0.541–0.660) and 0.742 (95% CI: 0.622–0.862), respectively (Table 4, Supplementary Figure S2). Then, the difference in the C-index between the two staging systems at 1, 2, and 3 years was examined separately. Our modified system exhibited a higher C-index at all time points, and statistical significance was found at 3 years of CSS in the validation cohort.

DCA was also performed. Although the two systems exhibited comparable predictive power for predicting 1- and 2-year CSS, the modified staging scheme had slightly better accuracy than the original TNM system, and it

**Table 3** Cox regression univariate and multivariate analysis of CSS in resected PDAC patients

Variables	No. of patients (N=1,676) [n (%)]	Univariate analysis	Multivariate analysis		
		P	P	HR	95% CI
Age (year)		0.007	0.102	1.13	0.98–1.30
≤65	1,060 (63.2)				
>65	616 (36.8)				
BMI (kg/m <sup>2</sup> )		0.004	0.054	0.83	0.68–1.00
≤19	221 (13.2)				
>19	1,455 (86.8)				
TBIL (μmol/L)		<0.001	0.002	1.32	1.11–1.56
≤128.29	1,300 (77.6)				
>128.29	376 (22.4)				
CA19-9 (U/mL)		<0.001	<0.001	1.40	1.20–1.64
≤500	1,244 (74.2)				
>500	432 (25.8)				
CEA (ng/mL)		<0.001	0.032	1.18	1.01–1.37
≤2.98	747 (44.6)				
>2.98	929 (55.4)				
Site of tumor		0.009	0.169	1.13	0.95–1.34
Body/tail of pancreas	535 (31.9)				
Head of pancreas	1,141 (68.1)				
Differentiation		<0.001	<0.001	1.64	1.44–1.86
Well	74 (4.4)				
Moderate	792 (47.3)				
Poor	807 (48.2)				
Undifferentiated	3 (0.2)				
T stage		<0.001	<0.001	1.16	1.07–1.26
T1	317 (18.9)				
T2	861 (51.4)				
T3	300 (17.9)				
T4	198 (11.8)				
N stage		<0.001	<0.001	1.40	1.26–1.56
N0	959 (57.2)				
N1	575 (34.3)				
N2	142 (8.5)				
Margin		<0.001	<0.001	1.69	1.38–2.09
R0	1,502 (89.6)				
R1	174 (10.4)				
Adjuvant therapy		<0.001	<0.001	0.64	0.56–0.75
No	945 (56.4)				
Yes	731 (43.6)				

CSS, cancer specific survival; PDAC, pancreatic ductal adenocarcinoma; BMI, body mass index; TBIL, total bilirubin; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LN, lymph node; HR, hazard ratio; 95% CI, 95% confidence interval.



**Figure 5** Survival difference stratified by CA19-9 level. (A–E) Survival was significantly different between the “H” and “L” subgroups within each TNM stage, except for that between IIIL and IIIL; (F) Survival was not significantly different between all the “H” subgroups.

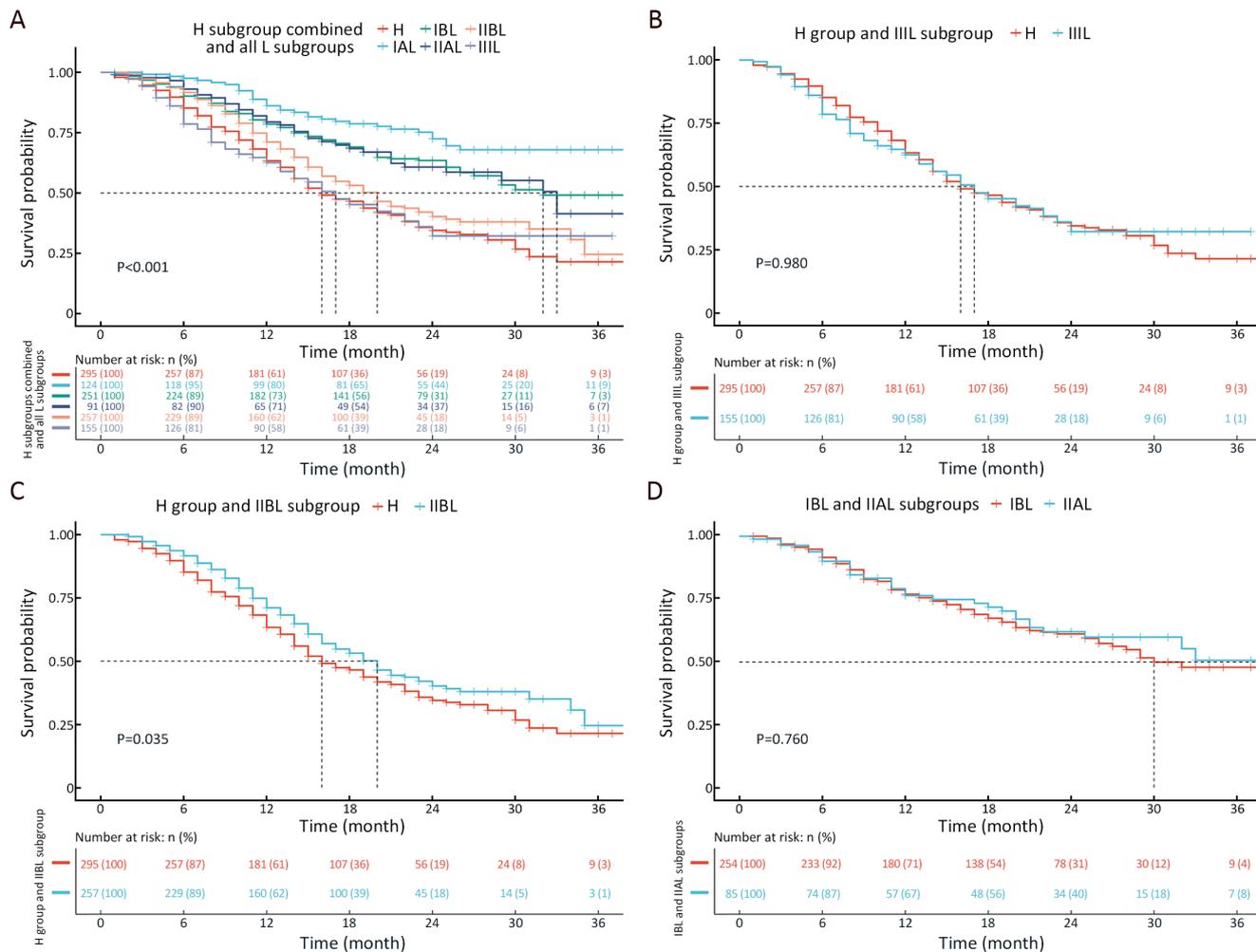
yielded preferable net benefit along with a wider range of threshold probability for predicting 3-year survival compared to the AJCC 8th TNM staging system in the validation cohorts (Figure 8). A higher threshold probability represented superior estimations of decision outcomes. These results coincide with our C-index validation.

**Discussion**

Cancer staging is very important to predict patient prognosis and guide clinical treatment approaches. The 8th TNM staging system for PDAC published by the AJCC in 2016 has shown improved prognostic performance against the 7th edition (5-9,14). The pancreas is a thin belt-like organ without a capsule, and PDAC often extends to the surface of the pancreas, leading to various definitions of conventional T3 (extended to peripancreatic tissues) (15). The revised T system discarded the ambiguous description of T3 and was based mainly on tumor size, bringing better reproducibility for the 8th TNM staging system. Regarding the discriminatory power of the T category, many studies have found better prognostic value of the new T stage under the N0 setting (7,9). However, in the present study, significant differences in prognosis were found

between each T stage, except for that between T2 and T3, resulting in insignificant discriminatory power between stage IB and IIA. This problem can also be observed in our validation using the 2014–2015 SEER dataset (Supplementary Figure S3) as well as in two international multicenter validation studies (5,6).

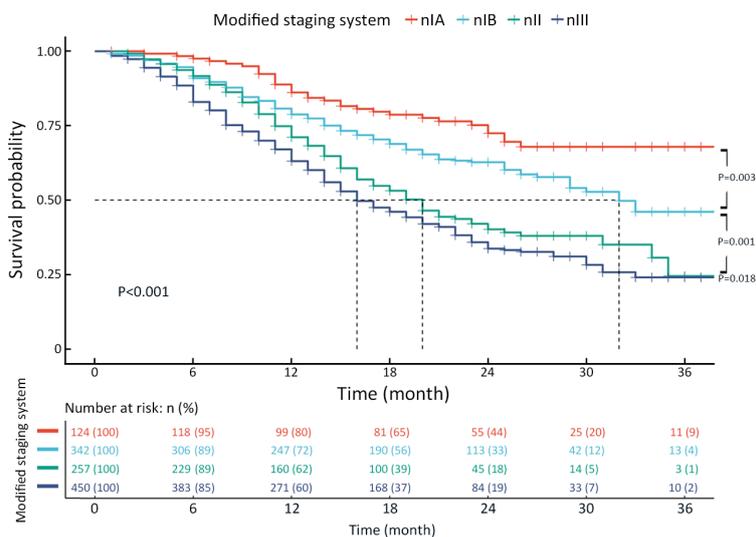
LN metastasis is negatively correlated with the survival of pancreatic cancer patients (16,17). LN-positive disease was defined as N1 in the 7th edition and was further divided into N1 (1–3 positive LNs) and N2 (≥4 positive LNs) in the 8th edition. This new feature helps stratify the survival of patients based on how far the disease has spread. The same N classification method is used for other cancers with different cutoff points (3,18). Shin *et al.* validated the 8th TNM staging system using data from Korean patients and found an insignificant difference in the median OS between pN1 and pN2 (18.1 months vs. 16.9 months; P=0.10) (8). However, in this study, we found good discriminatory power between N stages, consistent with most validation studies (5-7,9,12,14). The different prognostic performance between the T and N staging systems suggests that LN metastasis could better stratify patient outcome than tumor size, and it is necessary to add other factors into the T system or reevaluate “extra-pancreatic extension”.



**Figure 6** Modification of the AJCC 8th TNM staging system for PDAC. (A,B) After combining all the “H” subgroups into one stage, the survival curve of the new H stage was similar to that of subgroup IIIL, and no significant difference in CSS was found between IBL and IIAL in training set (P=0.980); (C) Survival difference between H stage and subgroup IIBL was statistically significant (P=0.035); (D) No significant difference was found between IBL and IIAL (P=0.760). AJCC, American Joint Committee on Cancer; PDAC, pancreatic ductal adenocarcinoma.

To date, several modifications for the 8th AJCC staging system for PDAC have been proposed. Chen *et al.* developed a refined staging system using SEER data for resectable PDAC patients, which incorporated post-operative tumor grade (19). Shi *et al.* maintained the T, N, and M definitions of the current 8th staging scheme but regrouped the substages into a new staging system (10). However, these modifications were not designed specifically for resected patients or were complex and thus have not been widely accepted among patients and clinicians. To our knowledge, no modification of the AJCC 8th staging system for PDAC has been proposed to incorporate preoperative biochemical variables.

Preoperative serum CA19-9 is a well-known biomarker for PDAC and has been widely used in the diagnosis and prognosis of PDAC (20,21). Many studies have identified serum CA19-9 as a strong predictor for the recurrence of PDAC. A recent analysis of 46 patients who underwent pancreaticoduodenectomy for PDAC in the pancreatic head showed that a high CA19-9 value ( $\geq 230$  U/mL) was correlated with worse OS, advanced pathological grade, early recurrence, and larger tumor size (22). Liu *et al.* analyzed 284 resected and 425 locally advanced pancreatic cancer patients and found that preoperative CA19-9  $\geq 1,000$  U/mL was associated with worse OS in resected patients (23). In addition, an early decrease in CA19-9 level after



**Figure 7** Difference in survival in training set according to the 8th modified TNM staging system (P<0.001).

chemotherapy was reported as a favorable factor for improved survival in advanced disease (24). However, different cutoff values were correlated with survival and recurrence in PDAC, ranging from 37 U/mL to 1,000 U/mL (25-27).

In this study, we identified 500 U/mL as the cutoff point for preoperative CA19-9 levels in patients with resected PDAC. Furthermore, univariate and multivariate analyses demonstrated that CA19-9 was the strongest prognostic indicator among all enlisted preoperative factors, and prognostic heterogeneity was monitored within each 8th AJCC stage stratified by this cutoff point, except for stage III. Based on RPA, the Kaplan-Meier method and the log-rank test, we proposed a new staging system and showed better accuracy for predicting the 3-year survival of this system than that of the 8th AJCC staging system in the validation set. Furthermore, to rule out confounders such as hyperbilirubinemia and Lewis antigen negativity, we eliminated patients with serum CA19-9 <5 U/mL (28) and serum total bilirubin levels >2.0 mg/dL (29) and obtained the same results. These results indicated that the modified

staging system outperformed the 8th AJCC staging scheme in discriminatory power.

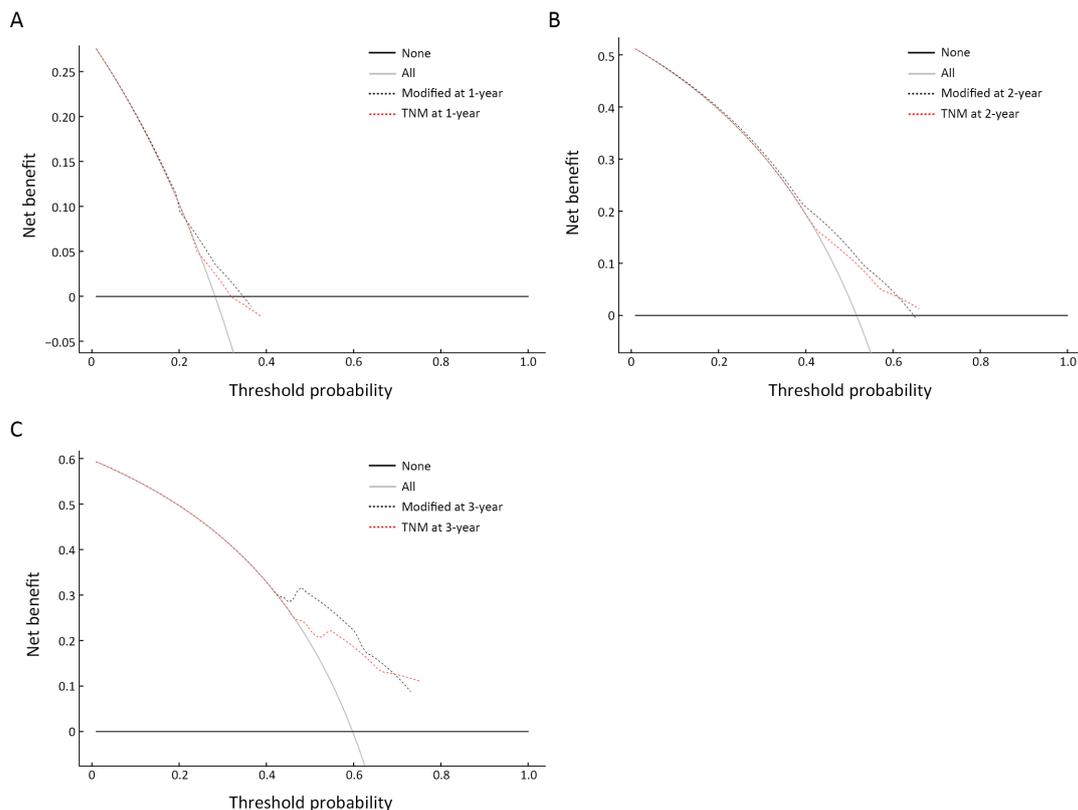
In this study, 206 patients had high preoperative CA19-9 and LN-negative disease, including 25 patients in the IAH subgroup, 125 patients in the IBH subgroup, and 56 patients in the IIAH subgroup, and patients in the IAH subgroup had the worst prognosis (15 months for IAH, 23 months for IBH, 19 months for IIAH). These results suggest that patients in stage IA with a high preoperative CA19-9 value may not benefit from surgical resection, and neoadjuvant chemotherapy or chemoradiotherapy may be suitable for these patients.

The present study has several limitations. First, data quality is the major concern of retrospective studies. Our study was based on the CPDC database, a nationwide multicenter database, which may cause heterogeneity in data collection and analysis. Second, the short follow-up time and missing data may incur bias or impair the reliability and reproducibility of our conclusion. Last, further prospective studies are needed to verify our modified the AJCC 8th staging system.

**Table 4** Comparison of C-index between our modified staging system and the AJCC 8th TNM staging system at 1-, 2-, 3-year in validation cohort

CSS	Modified		the AJCC 8th		P
	C-index	95% CI	C-index	95% CI	
1-year	0.576	0.520–0.632	0.554	0.497–0.611	0.698
2-year	0.615	0.555–0.674	0.601	0.541–0.660	0.886
3-year	0.815	0.722–0.909	0.742	0.622–0.862	0.005

AJCC, American Joint Committee on Cancer; CSS, cancer specific survival; 95% CI, 95% confidence interval.



**Figure 8** DCA showed that our modified staging scheme had better accuracy for predicting 1-year survival (A), 2-year survival (B), and 3-year survival (C), and it yielded preferable net benefit along with a wider range of threshold probability for predicting 3-year survival compared to the AJCC 8th TNM staging system in validation cohorts. DCA, decision curve analysis; AJCC, American Joint Committee on Cancer.

**Conclusions**

This study demonstrated that the 8th AJCC staging system for PDAC is suitable for a Chinese cohort of resected patients. Furthermore, the N category had a better prognostic value than the T category in curatively resected patients. No difference in CSS between stage IB and IIA indicated that it is plausible to combine the two groups into a single group as tumors over 2 cm without LN metastasis. CA19-9 is a robust preoperative prognostic indicator for resected patients, and our modified staging system incorporating the preoperative CA19-9 value had superior accuracy in predicting patient survival and may help in the selection of optimal patients for neoadjuvant therapy.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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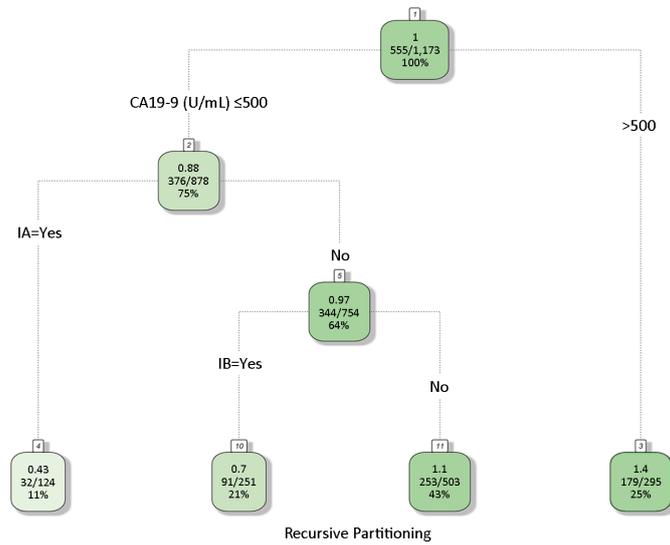
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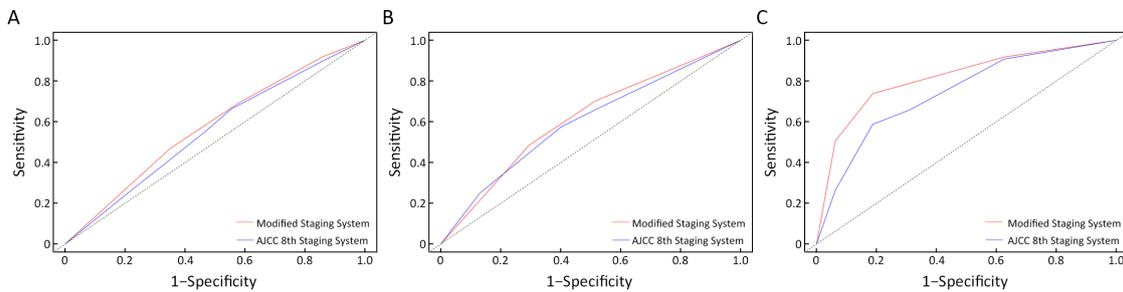
**Table S1** Baseline demographic and clinicopathological characteristics of training and validation cohort

Characteristics	Training (N=1,171) [n (%)]	Validation (N=505) [n (%)]	P
Gender			0.644
Female	455 (38.9)	203 (40.2)	
Male	716 (61.1)	302 (59.8)	
Age (year) [median (IQR)]	63.00 (56.00, 69.00)	62.00 (55.00, 67.00)	0.090
BMI (kg/m <sup>2</sup> ) [median (IQR)]	22.43 (20.53, 24.22)	22.34 (20.28, 24.22)	0.883
TBIL (μmol/L) [median (IQR)]	19.90 (11.30, 109.30)	18.10 (10.30, 116.09)	0.470
CA19-9 (U/mL) (median [IQR])	158.40 (38.89, 503.00)	160.00 (41.00, 563.20)	0.853
CEA (ng/mL) [median (IQR)]	3.24 (2.01, 5.65)	3.30 (1.92, 5.59)	0.985
Tumor size (cm) [median (IQR)]	3.00 (2.50, 4.00)	3.00 (2.50, 4.00)	0.843
Site of tumor			0.624
Body and tail of pancreas	369 (31.5)	166 (32.9)	
Head of pancreas	802 (68.5)	339 (67.1)	
Differentiation			0.641
Well	53 (4.5)	21 (4.2)	
Moderate	557 (47.6)	235 (46.5)	
Poor	558 (47.7)	249 (49.3)	
Undifferentiated	3 (0.3)	0 (0)	
LN positive [median (IQR)]	0 (0, 1.00)	0 (0, 1.00)	0.751
LN examined [median (IQR)]	10.00 (5.00, 16.00)	10.00 (5.00, 16.00)	0.771
TNM			0.621
IA	140 (12.0)	70 (13.9)	
IB	329 (28.1)	148 (29.3)	
IIA	130 (11.1)	46 (9.1)	
IIB	350 (29.9)	148 (29.3)	
III	222 (19.0)	93 (18.4)	
T stage			0.710
T1	213 (18.2)	104 (20.6)	
T2	606 (51.8)	255 (50.5)	
T3	213 (18.2)	87 (17.2)	
T4	139 (11.9)	59 (11.7)	
N stage			0.653
N0	666 (56.9)	293 (58.0)	
N1	401 (34.2)	174 (34.5)	
N2	104 (8.9)	38 (7.5)	
Margin			0.035
R0	1,062 (90.7)	440 (87.1)	
R1	109 (9.3)	65 (12.9)	
Adjuvant therapy			0.810
No	663 (56.6)	282 (55.8)	
Yes	508 (43.4)	223 (44.2)	

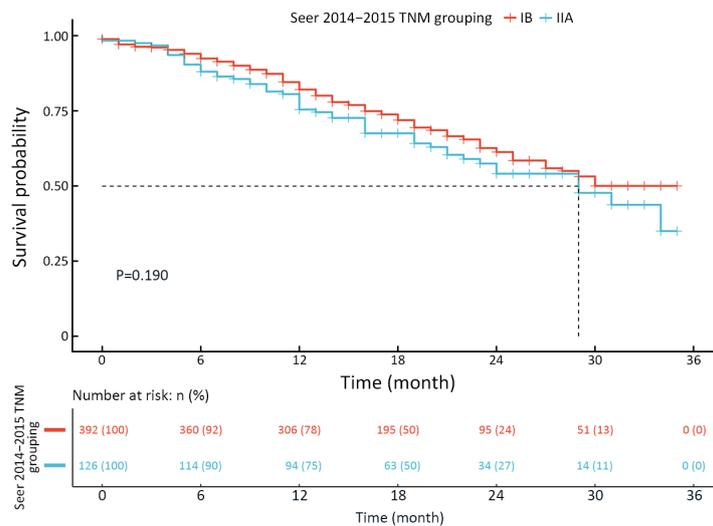
BMI, body mass index; IQR, interquartile range; TBIL, total bilirubin; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; LN, lymph node.



**Figure S1** RPA showed that all “H” subgroups could be assembled into one stage. RPA, recursive partitioning analysis; CA19-9, carbohydrate antigen 19-9.



**Figure S2** ROC curves for our modified staging system and the AJCC 8th TNM staging system at 1, 2, and 3 years. ROC, receiver operator characteristic; AJCC, American Joint Committee on Cancer.



**Figure S3** No significant difference in CSS between IB and IIA using the 2014–2015 SEER dataset ( $P=0.190$ ). CSS, cancer-specific survival.