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Integrated pretreatment stratification system for pancreatic cancer: combining anatomical resectability and tumor biological parameters

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ABSTRACT

Objective: Current clinical staging of pancreatic ductal adenocarcinoma (PDAC) relies predominantly on anatomical resectability, thus limiting its prognostic utility. We developed and validated a pretreatment prognostic grading system incorporating multidimensional parameters.

Methods: Patients with histologically confirmed PDAC undergoing curative-intent pancreatectomy were retrospectively enrolled. Independent prognostic determinants of overall survival (OS) and disease-free survival (DFS), identified through multivariable Cox proportional hazards regression, provided the basis for deriving the Tianjin Prognostic Score and its corresponding risk stratification scheme.

Results: Resectability status, lymph node metastasis indicated by imaging, pretreatment serum CA19-9 levels, and the prognostic nutritional score (PNS) independently predicted both OS and DFS. These parameters were integrated into the Tianjin Prognostic Score for PDAC prognosis stratification. The Tianjin-Grade system, subsequently established according to this score, segregated patients into 4 discrete prognostic cohorts with significantly divergent survival outcomes. This system exhibited significantly greater discriminatory ability for prognosis than conventional serum CA19-9 and resectability criteria. Notably, patients classified as having high risk or extremely high risk derived substantial survival benefits from neoadjuvant chemotherapy (NAC), whereas those with low or intermediate risk demonstrated comparable survival outcomes regardless of NAC administration.

Conclusion: The Tianjin-Grade system provides accurate pretreatment prognosis prediction in patients with PDAC through integration of anatomical and biological parameters, thus serving as a reliable tool for prognostic assessment. This system facilitates the development of personalized preoperative therapeutic strategies.

KEYWORDS

Pancreatic ductal adenocarcinoma; staging system; prognosis; recurrence; neoadjuvant chemotherapy

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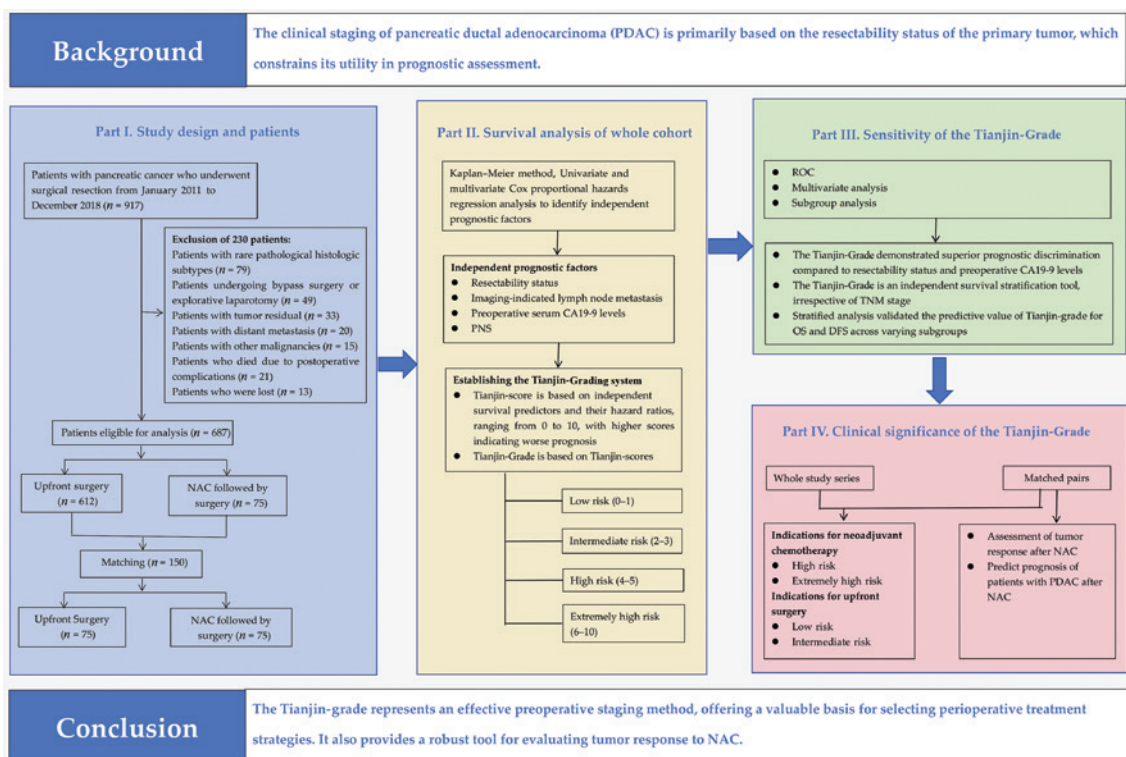
Introduction

Accurate prognosis evaluation is critical in cancer management. However, because the widely used tumor node metastasis (TNM) staging system relies on postoperative pathological data, its preoperative applicability is limited¹. Clinical TNM staging serves as a prognostic and therapeutic guide across multiple cancers, including gastric, breast, and lung cancers²⁻⁵. However, its utility for prognostic assessment in pancreatic ductal adenocarcinoma (PDAC) remains limited^{6,7}. The clinical staging of PDAC relies primarily on the resectability criteria

established by the National Comprehensive Cancer Network (NCCN) guidelines, which categorize localized PDAC into resectable, borderline resectable, and locally advanced stages according to the extent of tumor vascular involvement⁸. Because this system depends solely on anatomical factors, its prognostic predictive ability is limited.

The determination of whether a patient with PDAC should proceed with surgical resection depends on both anatomical resectability and expected survival benefits. Biological factors and the patient's physical condition, which are closely

associated with prognosis, are increasingly considered in resectability criteria⁹⁻¹³. In 2008, Katz et al.⁹ introduced biological and conditional criteria for assessing PDAC resectability. In 2017, the International Pancreatic Association (IPA) redefined resectability criteria, requiring a comprehensive evaluation across anatomical, biological, and conditional dimensions. Patients eligible for surgical resection must meet criteria in all 3 dimensions¹⁰. The IPA criteria outperform NCCN guidelines in predicting patient survival and are more rigorous in defining surgical indications^{11,12}.



Study flowchart In part I, 687 patients with pancreatic cancer undergoing surgical resection were enrolled according to the inclusion/exclusion criteria; the patients were categorized into upfront surgery and neoadjuvant chemotherapy groups according to treatment strategy. After comparison of baseline characteristics, propensity score matching (1:1 ratio) yielded 75 matched pairs per group. Part II involved univariate and multivariate survival analyses to establish the Tianjin grading system incorporating independent prognostic factors, for stratifying patients into low-, intermediate-, high-, and extremely high-risk tiers. Part III validated the prognostic relevance of the Tianjin-Grade, and demonstrated its superior predictive accuracy to serum CA19-9 and NCCN resectability criteria. The Tianjin-Grade maintained independent prognostic significance across all subgroups. Part IV explored the clinical utility of the Tianjin-Grade, which was used to guide perioperative decision-making (upfront surgery for low/intermediate-risk patients, or neoadjuvant therapy for high/extremely high-risk patients). Assessment of neoadjuvant treatment responses indicated that a decreased Tianjin-Grade post-neoadjuvant therapy correlated with better prognosis after radical resection. Therefore, the Tianjin-Grade is proposed as a multi-dimensional assessment integrating anatomical, biological, and physical condition factors for clinical decision-making in pancreatic cancer. CA, carbohydrate antigen; DFS, disease-free survival; NAC, neoadjuvant chemotherapy; NCCN, National Comprehensive Cancer Network; OS, overall survival; PNS, prognostic nutritional score; ROC, receiver operating characteristic; TNM, tumor node metastasis.

Currently, PDAC prognosis and treatment decisions increasingly rely on both anatomical and biological factors. However, no pretreatment prognostic grading system integrates both types of factors. This study was aimed at developing and validating a comprehensive grading system for PDAC that incorporates common anatomical and biological factors to guide treatment decisions.

Materials and methods

Study design and patients

This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (approval number EK20250247). All procedures involving human participants were in accordance with the ethical guidelines outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before surgery, including a statement regarding the collection of clinicopathological data and samples for scientific purposes. Through our institute's pancreatic cancer database, a total of 836 patients who underwent surgical resection for pancreatic cancer at Tianjin Medical University Cancer Institute and Hospital between January 2011 and December 2018 were eligible to participate in this study. The inclusion criteria comprised (i) patients diagnosed with PDAC, (ii) patients who underwent curative intent pancreatic resection, and (iii) patients with complete clinical and pathological examination results. The exclusion criteria included (i) patients with rare histopathologic subtypes, such as adenosquamous carcinomas, acinar cell carcinomas, and intraductal papillary mucinous neoplasms or mucinous cystic neoplasms with invasive cancer; (ii) patients who underwent bypass surgery or explorative laparotomy without resection; (iii) patients with macroscopic or microscopic residual tumors; (iv) patients with distant metastasis; (v) patients who died because of postoperative complications; (vi) patients with a history of other malignancy; and (vii) patients lost to follow-up.

Data collection

Clinicopathological data, including sex, age at surgery, pretreatment serum levels of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), lymphocyte and neutrophil counts, C-reactive protein levels, platelet count, albumin and prealbumin levels, tumor location, tumor size, lymph node

metastasis indicated by imaging, resectability status, differentiation, TNM stage, postoperative surgical complications, and adjuvant chemotherapy details were extracted from our institute's pancreatic cancer database. Postoperative complications included hemorrhage, anastomotic leakage, pancreatic fistulas, chyle leaks, and abdominal infection.

In a prior study, we introduced a prognostic nutritional score (PNS) based on lymphocyte count, platelet count, and prealbumin levels to reflect patients' immune and nutritional status¹⁴. Pretreatment evaluation of lymph node metastasis relies on computed tomography (CT) or PET-CT scans. Resectability status is determined through multidisciplinary discussions, according to NCCN guidelines for pancreatic adenocarcinoma. Tumors were staged according to the eighth edition of the Union for International Cancer Control (UICC) TNM classification system. Pretreatment serum CA19-9 and CEA levels were evaluated within 1 week before surgery or neoadjuvant chemotherapy (NAC). For patients with obstructive jaundice, CA19-9 levels were re-assessed after biliary drainage. Tumor responses to NAC were assessed according to RECIST 1.0 criteria. Resectability status and the Tianjin-Grade were reassessed after NAC.

Follow-up

Patients were followed up every 3 months for the first 2 years, every 6 months for years 3–5, and annually thereafter until the end of follow-up or death. Each visit included a physical examination, serum CA19-9 and CEA tests, and abdominal ultrasound; chest and abdominal CT scans were performed every 6 months. For suspected recurrence or metastasis, additional imaging was conducted as needed. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up, and disease-free survival (DFS) was defined as the interval from diagnosis to tumor recurrence or last follow-up. The median follow-up duration was 51 months (range: 3–126) for OS and 49 months (range: 2–126) for DFS. The last follow-up date was December 30, 2023.

Statistical analysis

Quantitative parameters are expressed as medians with interquartile ranges (IQRs) and were compared with the Mann–Whitney *U* test. Categorical variables are presented as absolute values and percentages, and were compared with

the chi-square test or Fisher's exact test. OS and DFS curves were generated with the Kaplan–Meier method, and differences between curves were evaluated with the log-rank test. Independent prognostic factors were identified through Cox proportional hazards regression analysis. The Tianjin-score was developed according to risk factors and their hazard ratios from multivariate analysis. The performance of the Tianjin-score in predicting survival was compared with NCCN resectability criteria and serum CA19-9 levels through receiver operating characteristic (ROC) curve analysis. Comparisons between ROC curves were conducted with the Z test.

Patients were categorized into 2 groups according to their initial treatment strategy: an upfront surgery group and NAC group. To decrease bias from differing covariate distributions, propensity score matching with the nearest-neighbor method was applied. Survival outcomes were compared between the matched groups. To formally test whether the effect of NAC differed across Tianjin-Grade subgroups, we introduced an interaction term between treatment strategy (NAC vs. upfront surgery) and Tianjin-Grade into the multivariable Cox proportional hazards model. A significant interaction effect would indicate that the treatment benefit was modified by the Tianjin-Grade. Subgroup analyses were conducted with Cox proportional hazards regression to compare OS and DFS between patients receiving NAC and those undergoing upfront surgery, with stratification based on predefined prognostic factors.

All statistical analyses were performed in SPSS version 24.0 and MedCalc v.20.0. A two-tailed *P*-value < 0.05 was considered statistically significant. For pairwise comparisons of survival outcomes across Tianjin-Grade subgroups, the significance threshold was adjusted with Bonferroni correction to *P* < 0.0083 to account for multiple comparisons.

Results

Clinicopathological features and treatment

The study's exclusion criteria are outlined in **Figure S1**. After exclusion of 230 patients, 687 individuals were deemed eligible for inclusion. The demographic, clinical, and tumor characteristics are summarized in **Table 1**. All patients underwent R0 resection: 440 patients (64.0%) underwent pancreaticoduodenectomy, 243 patients (35.4%) underwent distal pancreatectomy, and only 4 patients (0.6%) underwent total pancreatectomy. Additionally, 21 patients underwent resection

and reconstruction of the superior mesenteric vein or portal vein. Seventy-five patients received NAC with either mFOLF-IRINOX (comprising 5-fluorouracil, leucovorin, gemcitabine, and oxaliplatin) or albumin-bound paclitaxel combined with gemcitabine. Postoperative adjuvant chemotherapy was administered to 357 patients (52.0%) with various regimens, including mFOLFIRINOX; gemcitabine plus capecitabine; gemcitabine plus S-1; S-1 alone; and gemcitabine alone. Postoperative complications were observed in 186 patients (27.1%), all of whom recovered with conservative management.

Survival analysis of patients with PDAC

Independent prognostic indicators for OS included resectability status, lymph node metastasis indicated by imaging, preoperative serum CA19-9 levels, and PNS (**Tables 2 and 3**). For DFS, unfavorable prognostic factors included locally advanced disease, borderline resectable status, lymph node metastasis indicated by imaging, elevated preoperative serum CA19-9 levels, and a PNS of 2-3 (**Tables 2 and 3**). Kaplan–Meier curves stratifying patients by these independent prognostic factors are shown in **Figure 1**.

Tianjin-grading system

A novel prognostic scoring system, the Tianjin-score, was developed on the basis of independent survival predictors, and assigned points to risk factors and their hazard ratios (**Table 3**). For example, a preoperative serum CA19-9 level of 200–1,000 U/mL combined with a PNS of 1 received 1 point, whereas borderline resectable status, lymph node metastasis indicated by imaging, CA19-9 ≥ 1,000 U/mL, and PNS of 2 each received 2 points. Locally advanced disease and PNS of 3 were assigned 3 points each (**Table 4**). Total scores ranged from 0 to 10, with higher scores indicating poorer prognosis. Survival analysis demonstrated declines in median OS from 49.0 months (score 0) to 12.0 months (score 10), and in median DFS from 24.0 months to 2.0 months (**Figure 2A, B**). Patients with scores ≥ 6 were grouped because of their similarly poor outcomes. Further survival analysis revealed overlapping outcomes for scores 0–1, 2–3, and 4–5, thus leading to the creation of the Tianjin grading system. The Tianjin-Grade includes low-risk (0–1), intermediate-risk (2–3), high-risk (4–5), and extremely high-risk (6–10) categories. Stratified survival curves showed a decline

Table 1 Patient characteristics and outcomes stratified by Tianjin-Grade

Characteristics	Entire cohort (<i>n</i> = 687)	Tianjin-Grade				<i>P</i>
		Low risk (<i>n</i> = 161)	Intermediate risk (<i>n</i> = 257)	High risk (<i>n</i> = 164)	Extremely high risk (<i>n</i> = 105)	
Baseline features						
Sex, No. (%)						0.520
Male	395 (57.5)	94 (58.4)	140 (54.5)	95 (57.9)	66 (62.9)	
Female	292 (42.5)	67 (41.6)	117 (45.5)	69 (42.1)	39 (37.1)	
Age, years, median (IQR)	61 (55–67)	60 (54–66)	61 (55–67)	60 (54–67)	63 (58–67)	0.226
Age, years, No. (%)						0.817
< 70	592 (86.2)	133 (85.7)	219 (85.2)	145 (88.4)	90 (85.7)	
≥ 70	95 (13.8)	23 (14.3)	38 (14.8)	19 (11.6)	15 (14.3)	
Blood examination results						
Baseline CA19-9, U/mL, median (IQR)	158.6 (42.8–507.4)	51.3 (16.3–138.9)	127.4 (37.9–356.2)	355.5 (119.3–1,254.5)	925.0 (247.2–1,557.5)	< 0.001
Baseline CA19-9, U/mL, No. (%)						< 0.001
< 200	377 (54.9)	145 (90.1)	155 (60.3)	58 (35.4)	19 (18.1)	
200–1,000	201 (29.3)	16 (9.9)	87 (33.9)	63 (38.4)	35 (33.3)	
≥ 1,000	109 (15.9)	0 (0)	15 (5.8)	43 (26.2)	51 (48.6)	
Baseline CEA, ng/mL, median (IQR)	3.9 (2.5–9.5)	3.3 (2.2–10.9)	3.1 (1.7–10.0)	3.8 (1.7–6.3)	4.6 (2.9–10.8)	0.440
Baseline CEA, ng/mL, No. (%)						< 0.001
≤ 5	478 (69.6)	129 (80.1)	196 (76.3)	99 (60.4)	54 (51.4)	
> 5	209 (30.4)	32 (19.9)	61 (23.7)	65 (39.6)	51 (48.6)	
Lymphocytes, × 10 ⁹ /L, median (IQR)	1.5 (1.2–1.9)	2.0 (1.7–2.3)	1.5 (1.2–1.9)	1.4 (1.1–1.7)	1.3 (1.1–1.5)	< 0.001
Lymphocytes, × 10 ⁹ /L, No. (%)						< 0.001
< 1.6	372 (54.1)	13 (8.1)	149 (58.0)	122 (74.4)	88 (83.8)	
≥ 1.6	315 (45.9)	148 (91.9)	108 (42.0)	42 (25.6)	17 (16.2)	
Platelets, × 10 ⁹ /L, median (IQR)	221.0 (181.0–276.0)	235.0 (191.5–289.0)	228.0 (190.5–279.0)	215.5 (174.3–277.3)	189.0 (145.0–242.5)	< 0.001
Platelets, × 10 ⁹ /L, No. (%)						< 0.001
≥ 160	597 (86.9)	157 (97.5)	231 (89.9)	141 (86.0)	68 (64.8)	
< 160	90 (13.1)	4 (2.5)	26 (10.1)	23 (14.0)	37 (35.2)	
Prealbumin, g/L, median (IQR)	0.20 (0.16–0.24)	0.24 (0.20–0.26)	0.20 (0.16–0.24)	0.19 (0.15–0.22)	0.19 (0.16–0.22)	< 0.001
Prealbumin, g/L, No. (%)						< 0.001
≥ 0.23	192 (27.9)	83 (51.6)	68 (26.5)	24 (14.6)	17 (16.2)	
< 0.23	495 (72.1)	78 (48.4)	189 (73.5)	140 (85.4)	88 (83.8)	

Table 1 Continued

Characteristics	Entire cohort (n = 687)	Tianjin-Grade				P
		Low risk (n = 161)	Intermediate risk (n = 257)	High risk (n = 164)	Extremely high risk (n = 105)	
Baseline PNS, No. (%)						< 0.001
0	110 (16.0)	66 (41.0)	31 (12.1)	10 (6.1)	3 (2.9)	
1	253 (36.8)	95 (59.0)	100 (38.9)	40 (24.4)	18 (17.1)	
2	269 (39.2)	0 (0)	116 (45.1)	97 (59.1)	56 (53.3)	
3	55 (8.0)	0 (0)	10 (3.9)	17 (10.4)	28 (26.7)	
Imaging examination results						
Tumor location <i>in pancreas</i> , No. (%)						0.217
Head	443 (64.5)	102 (63.4)	171 (66.5)	111 (67.7)	59 (56.2)	
Body and tail	244 (35.5)	59 (36.6)	86 (33.5)	53 (32.3)	46 (43.8)	
Tumor size, No. (%)						0.128
< 4 cm	478 (69.6)	116 (72.0)	188 (73.2)	109 (66.5)	65 (61.9)	
≥ 4 cm	209 (30.4)	45 (28.0)	69 (26.8)	55 (33.5)	40 (38.1)	
Lymph node metastasis, No. (%)						< 0.001
Yes	229 (33.3)	0 (0)	45 (17.5)	100 (61.0)	84 (80.0)	
No	458 (66.7)	161 (100.0)	212 (82.5)	64 (39.0)	21 (20.0)	
Resectability status, No. (%)						< 0.001
Resectable	523 (76.1)	161 (100.0)	226 (87.9)	116 (70.7)	20 (19.0)	
Borderline resectable	148 (21.5)	0 (0)	31 (12.1)	45 (27.4)	72 (68.6)	
Locally advanced	16 (2.3)	0 (0)	0 (0)	3 (1.8)	13 (12.4)	
Treatment characteristic						
Type of treatment, No. (%)						< 0.001
NAC + surgery	75 (10.9)	7 (4.3)	17 (6.6)	25 (15.2)	26 (24.8)	
Upfront surgery	612 (89.1)	154 (95.7)	240 (93.4)	139 (84.8)	79 (75.2)	
Surgical procedure, No. (%)						0.061
PD	440 (64.0)	103 (64.0)	172 (66.9)	108 (65.9)	57 (54.3)	
DP	243 (35.4)	58 (36.0)	84 (32.7)	53 (32.3)	48 (45.7)	
TP	4 (0.6)	0 (0)	1 (0.4)	3 (1.8)	0 (0)	
Postoperative adjuvant chemotherapy, No. (%)	357 (52.0)	85 (52.8)	136 (52.9)	80 (48.8)	56 (53.3)	0.830
Surgical complications, No. (%)	186 (27.1)	33 (20.5)	64 (24.9)	52 (31.7)	37 (35.2)	0.024
Pathological outcomes						
Tumor differentiation, No. (%)						0.003
Good and moderate	308 (44.8)	86 (53.4)	121 (47.1)	68 (41.5)	33 (31.4)	
Poor	379 (55.2)	75 (46.6)	136 (52.9)	96 (58.5)	72 (68.6)	

Table 1 Continued

Characteristics	Entire cohort (n = 687)	Tianjin-Grade				P
		Low risk (n = 161)	Intermediate risk (n = 257)	High risk (n = 164)	Extremely high risk (n = 105)	
TNM stage, No. (%)						< 0.001
I	271 (39.4)	99 (61.5)	115 (44.7)	34 (20.7)	23 (21.9)	
II	316 (46.0)	56 (34.8)	112 (43.6)	92 (56.1)	56 (53.3)	
III	100 (14.6)	6 (3.7)	30 (11.7)	38 (23.2)	26 (24.8)	
Perineural invasion, No. (%)	406 (59.1)	83 (51.6)	164 (63.8)	88 (53.7)	71 (67.6)	0.010
Lymphovascular invasion, No. (%)	164 (23.9)	22 (13.7)	56 (21.8)	50 (30.5)	36 (34.3)	< 0.001
Survival outcome						
OS, months, median (95% CI)	22.0 (20.2–23.8)	39.0 (31.3–46.7)	25.0 (21.7–28.4)	17.0 (14.3–19.7)	12.0 (10.2–13.8)	< 0.001
DFS, months, median (95% CI)	11.0 (9.9–12.1)	22.0 (18.3–25.7)	12.0 (9.5–14.5)	9.0 (6.4–11.6)	5.0 (4.0–6.0)	< 0.001
OS, % (95% CI)						< 0.001
1 year	72.7 (69.4–76.2)	87.9 (82.9–93.1)	79.9 (75.1–85.0)	63.3 (56.3–73.1)	46.6 (37.9–57.4)	
3 year	32.1 (28.4–26.2)	52.6 (44.9–61.8)	35.6 (29.6–42.8)	22.5 (16.1–31.5)	–	
5 year	19.0 (15.6–23.3)	33.9 (25.7–44.8)	21.5 (16.0–28.9)	9.1 (4.4–18.9)	–	
DFS, % (95% CI)						< 0.001
1 year	45.1 (41.3–48.9)	67.8 (60.9–75.5)	49.9 (44.0–56.5)	34.2 (27.5–42.5)	12.1 (7.1–20.5)	
3 year	21.6 (18.4–25.3)	35.6 (28.2–44.7)	24.0 (18.8–30.5)	15.2 (9.9–23.3)	–	
5 year	14.8 (11.8–18.5)	27.4 (20.2–37.1)	14.4 (9.8–21.2)	–	–	

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; IQR, interquartile range; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; TP, total pancreatectomy; OS, overall survival; DFS, disease-free survival; NAC, neoadjuvant chemotherapy.

in OS (39.0 to 12.0 months) and DFS (22.0 to 5.0 months) from low- to extremely high-risk groups (Figure 2C, D). The differences in survival among the Tianjin-Grade subgroups were statistically significant, with a *P*-value < 0.0083 (according to log-rank test with Bonferroni correction).

Sensitivity of the Tianjin-Grade

The Tianjin-Grade, compared with resectability status and preoperative CA19-9 levels, demonstrated superior prognostic discrimination, with higher time-dependent area under the curves (AUCs) at 1, 3, and 5 years (Table S1, Figure S2). Multivariate analysis confirmed the Tianjin-Grade as an independent survival stratification tool, regardless of TNM stage, differentiation, surgical complications, or adjuvant chemotherapy (Table 5). Stratified analysis further validated its

predictive value for OS and DFS across varying clinicopathological subgroups (Tables S2 and S3, Figures S3 and S4).

Clinical significance of the Tianjin-Grade

Patients were divided into NAC and upfront surgery groups (baseline clinical characteristics summarized in the left column of Table S4 compared with resectability status and preoperative CA19-9 levels). Although OS and DFS did not significantly differ between groups (Figure S5A, B), subgroup analysis based on Tianjin-Grade risk categories revealed that high-risk and extremely high-risk patients in the NAC group had significantly better outcomes than those undergoing upfront surgery (Figure S5G–J). In contrast, no significant differences were observed in the low- and intermediate-risk subgroups (Figure S5C–F). A formal test for interaction

Table 2 Univariate analysis of overall survival and disease-free survival for patients with PDAC with pretreatment factors

Variables	Overall survival			Disease-free survival		
	MST (mo)	HR (95% CI)	<i>P</i>	MDT (mo)	HR (95% CI)	<i>P</i>
Sex						
Male	20.0	1 (ref)		10.0	1 (ref)	
Female	24.0	0.931 (0.774–1.120)	0.450	11.0	0.965 (0.811–1.148)	0.685
Age (years)						
< 70	22.0	1 (ref)		11.0	1 (ref)	
≥ 70	16.0	1.369 (1.061–1.765)	0.016	8.0	1.166 (0.911–1.494)	0.223
Baseline CA19-9 (U/mL)						
< 200	26.0	1 (ref)		15.0	1 (ref)	
200–1,000	20.0	1.320 (1.071–1.628)	0.009	10.0	1.339 (1.100–1.630)	0.004
≥ 1,000	14.0	2.017 (1.577–2.582)	< 0.001	6.0	2.247 (1.778–2.838)	< 0.001
Baseline CEA (ng/mL)						
≤ 5	24.0	1 (ref)		12.0	1 (ref)	
> 5	18.0	1.341 (1.010–1.633)	0.004	8.0	1.321 (1.097–1.591)	0.003
Baseline PNS						
0	42.0	1 (ref)		20.0	1 (ref)	
1	24.0	1.524 (1.121–2.071)	0.007	13.0	1.328 (1.010–1.748)	0.043
2	19.0	2.180 (1.616–2.941)	< 0.001	9.0	1.936 (1.480–2.532)	< 0.001
3	12.0	3.638 (2.444–5.416)	< 0.001	6.0	2.688 (1.856–3.893)	< 0.001
Tumor location in pancreas						
Head	22.0	1 (ref)		11.0	1 (ref)	
Body and tail	21.0	0.983 (0.811–1.191)	0.860	11.0	0.971 (0.811–1.163)	0.751
Tumor size on baseline CT						
< 4 cm	22.0	1 (ref)		11.0	1 (ref)	
≥ 4 cm	20.0	1.087 (0.890–1.326)	0.414	9.0	1.097 (0.911–1.321)	0.330
Lymph node metastasis diagnosed on baseline CT						
No	25.0	1 (ref)		14.0	1 (ref)	
Yes	15.0	1.977 (1.631–2.397)	< 0.001	6.0	1.802 (1.504–2.159)	< 0.001
Resectability status						
Resectable	24.0	1 (ref)		13.0	1 (ref)	
Borderline resectable	17.0	1.547 (1.249–1.917)	< 0.001	8.0	1.558 (1.271–1.910)	< 0.001
Locally advanced	6.0	4.208 (2.501–7.081)	< 0.001	3.0	3.920 (2.330–6.595)	< 0.001

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; MST, median overall survival time; MDT, median disease-free survival time; mo, month; PDAC, pancreatic ductal adenocarcinoma; PNS, prognostic nutritional score; ref, reference category.

Table 3 Multivariate analysis of overall survival and disease-free survival for patients with PDAC

Variable	Category	Overall survival			Disease-free survival			Risk points
		HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>	
Resectability status	Locally advanced/ resectable	3.352	2.364–5.055	< 0.001	2.655	1.675–4.334	< 0.001	3
	Borderline resectable/ resectable	1.534	1.175–2.094	< 0.001	1.514	1.255–2.167	< 0.001	2
Lymph node metastasis diagnosed on baseline CT	Yes/no	1.918	1.551–2.371	< 0.001	1.566	1.300–1.887	< 0.001	2
Baseline CA19-9 (U/mL)	> 1,000/< 200	1.693	1.338–2.170	0.007	1.817	1.424–2.319	< 0.001	2
	200–1,000/< 200	1.227	1.095–1.420	0.039	1.292	1.058–1.482	0.025	1
Baseline PNS	3/0	2.956	1.917–4.434	< 0.001	2.590	1.592–3.586	< 0.001	3
	2/0	2.027	1.499–2.741	< 0.001	1.790	1.365–2.346	< 0.001	2
	1/0	1.468	1.078–1.998	0.015	1.318	1.078–1.797	0.016	1

CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; PDAC, pancreatic ductal adenocarcinoma; PNS, prognostic nutritional score.

between treatment strategy and Tianjin-Grade was significant for both OS ($P < 0.001$) and DFS ($P < 0.001$), thus confirming that the benefit of NAC was indeed modified by the pretreatment risk stratification (Table 6).

To mitigate potential biases from imbalanced clinical data, propensity score matching was performed, thus yielding 75 well-matched pairs. After matching, all baseline covariates were balanced between groups (Table S4, Figure S6). The NAC group demonstrated superior OS and DFS to the upfront surgery group, particularly among high-risk and extremely high-risk patients. No significant survival differences were observed in the low- and intermediate-risk subgroups (Figure 3, Table S5). The interaction between treatment strategy and Tianjin-Grade remained significant for both OS ($P = 0.001$) and DFS ($P < 0.001$), thereby reaffirming that pretreatment risk categories influenced the therapeutic benefit of NAC (Table 6). Furthermore, multivariable Cox regression models, adjusted for age, tumor differentiation, TNM stage, surgical complication, and use of postoperative adjuvant chemotherapy, were used to evaluate the survival benefit of NAC within each Tianjin-Grade subgroup. The low-risk Tianjin-Grade subgroup comprised 13 patients, including only 2 patients >70 years old, with stage II ($n = 1$) and stage I ($n = 12$) disease, and no surgical complications. Therefore, the analysis was adjusted solely for tumor differentiation and postoperative adjuvant chemotherapy. The results remained consistent: NAC was significantly associated with improved OS and DFS in the high-risk and extremely high-risk groups (Table 7).

Outcomes of patients in the NAC group

The mean tumor size decreased from 4.1 ± 1.7 cm to 3.5 ± 1.4 cm after NAC. Of the 75 patients, 53 (70.7%) showed decreased tumor size, 14 (18.7%) achieved partial response according to RECIST 1.0 criteria, 58 (77.3%) maintained stable disease, and 3 (4.0%) experienced progression. On the basis of NCCN criteria, only 10 patients (13.3%) transitioned to resectable status, but Tianjin-Grade identified downgrading in 28 patients (37.3%). The patients were divided into a decreased group and a stable/increased group according to whether the Tianjin-Grade decreased after NAC. The baseline characteristics of both groups before NAC are presented in Table S6. Except for the higher Tianjin-Grade and higher CA19-9 levels in the decreased group, the 2 groups showed no statistically significant differences in other baseline factors and were comparable. Patients exhibiting a decreased Tianjin-Grade after NAC had significantly longer survival than those with stable disease or disease progression (median OS: 37.0 vs. 20.0 months, $P = 0.016$; median DFS: 23.0 vs. 10.0 months, $P = 0.033$, Figure 4).

Discussion

Importance of clinical staging in PDAC

Accurate clinical staging in PDAC is essential for identifying patients most likely to benefit from upfront surgery from those better served by NAC. This study introduced a novel and

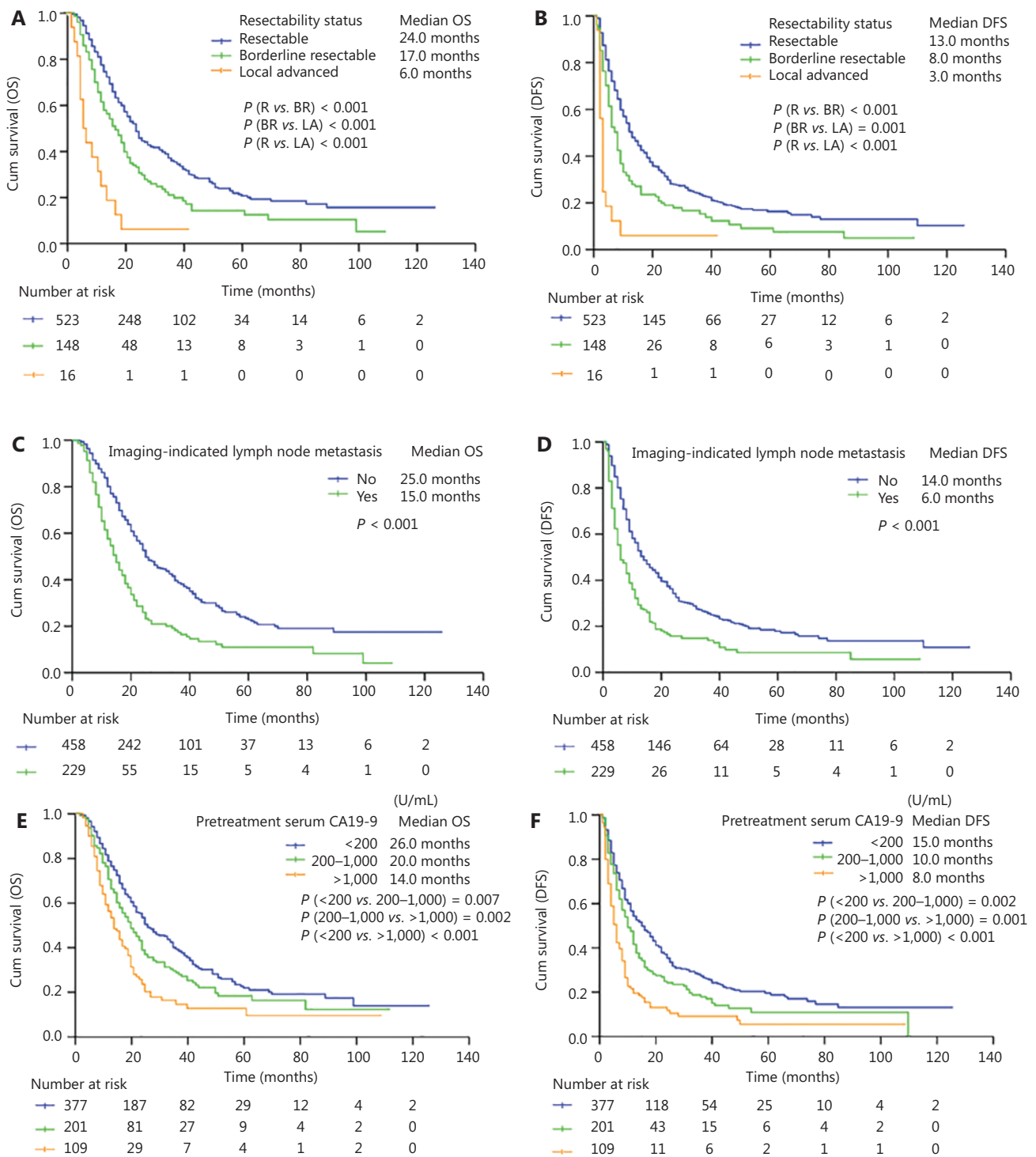


Figure 1 Continued

comprehensive clinical staging system, the Tianjin grading system, which integrates tumor resectability, imaging-detected lymph node metastasis, pretreatment CA19-9 levels, and the

PNS. The system effectively stratified patients into 4 distinct risk categories (low, intermediate, high, and extremely high risk), and demonstrated valuable prognostic implications for OS and DFS.

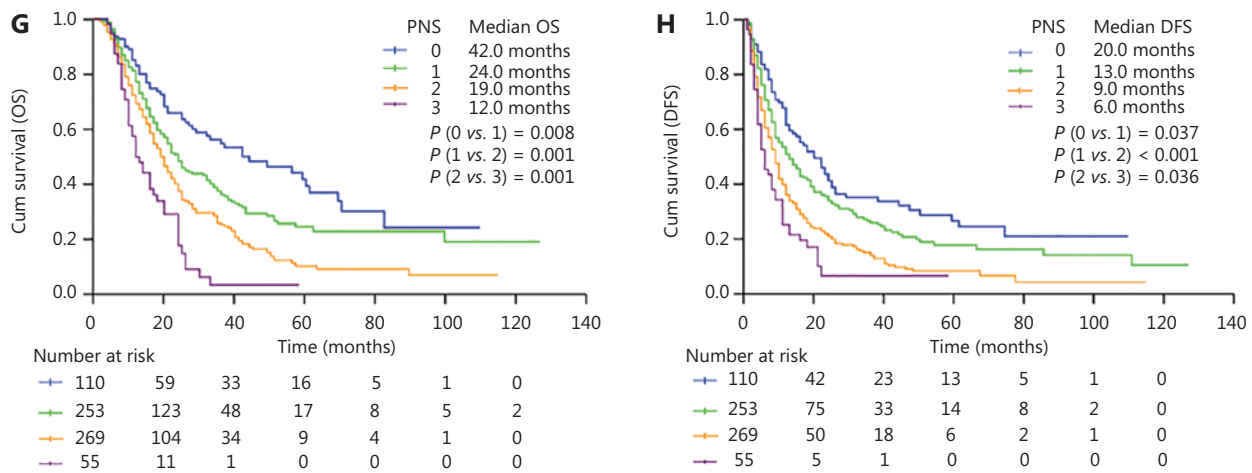


Figure 1 Kaplan–Meier curves of OS and DFS according to independent prognostic factors. (A) OS according to resectability status. (B) DFS according to resectability status. (C) OS according to lymph node metastasis identified through imaging. (D) DFS according to lymph node metastasis identified through imaging. (E) OS according to pretreatment serum CA19-9. (F) DFS according to pretreatment serum CA19-9. (G) OS according to PNS. (H) DFS according to PNS. BR, borderline resectable; CA19-9, carbohydrate antigen 19-9; Cum, cumulative survival; DFS, disease-free survival; LA, locally advanced; OS, overall survival; PNS, prognostic nutritional score; R, resectable.

Table 4 Components of the Tianjin grading system and their corresponding scores

Risk factors	Score			
	0	1	2	3
Resectability status	R	–	BR	LA
Lymph node metastasis indicated by imaging	No	–	Yes	–
Baseline CA19-9 (U/mL)	< 200	200–1,000	> 1,000	–
Baseline PNS	0	1	2	3

R, resectable; BR, borderline resectable; LA, locally advanced; CA19-9, carbohydrate antigen 19-9; PNS, prognostic nutritional score. Tianjin-score range: 0–10.

Although the NCCN criteria remain the standard for assessing surgical resectability⁸, they focus on anatomical features and lack detailed prognostic and biological information. Consequently, patients classified as having “resectable” tumors according to current standards may experience early recurrence post-surgery, whereas certain patients classified as having borderline or locally advanced disease could achieve long-term survival with appropriate NAC followed by surgery^{15,16}. Hence, clinical decision-making should be informed by more comprehensive prognostic evaluations rather than anatomical factors alone. The Tianjin grading system uniquely addresses this gap by integrating biological markers and

patient-specific conditions to enhance risk stratification and treatment personalization.

Novelty of the Tianjin grading system vs. existing models

Compared with previously established staging tools¹⁷⁻²⁰, such as the Heidelberg Prognostic Pancreatic Cancer (HELPP) score and the ABC staging system, the Tianjin grading system offers notable advancements. Although the HELPP score has good prognostic value, it lacks integration of critical anatomical indicators such as tumor resectability¹⁷. The ABC system effectively incorporates anatomical, biological, and conditional aspects, but does not include lymph node metastasis or nutritional status, both of which are critical predictors of prognosis in patients with PDAC¹⁸. The Tianjin system addresses these limitations by providing a more holistic approach combining anatomical evaluation of resectability with biological indicators (serum CA19-9 and lymph node metastasis indicated by imaging) and patient-specific factors (assessed through the PNS), thereby substantially enhancing prognostic accuracy and clinical utility.

An additional innovative aspect of this study is its focus on Asian populations, particularly representing the demographic of Chinese patients with PDAC. Most existing staging and prognostic tools have been derived predominantly from

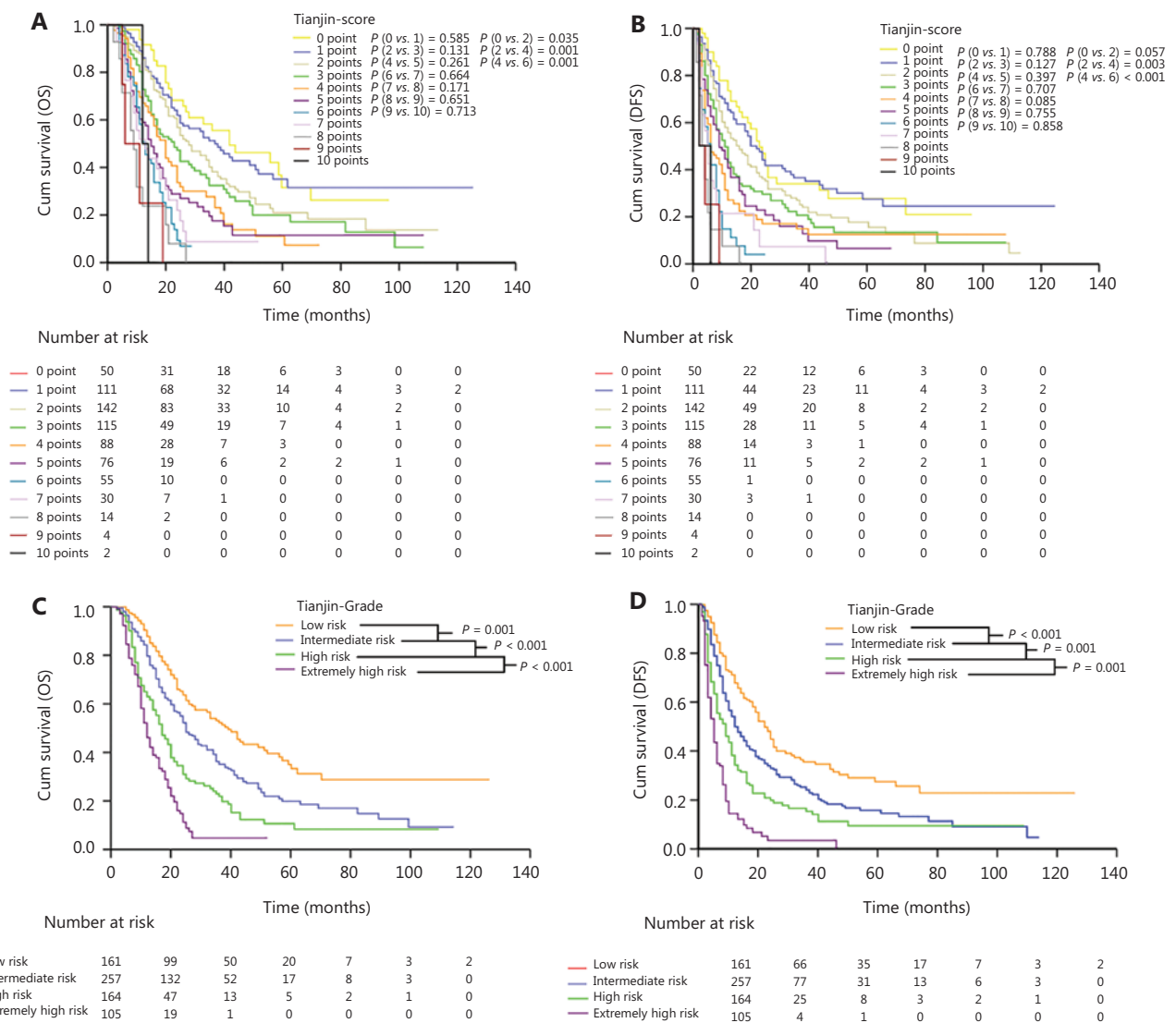


Figure 2 Kaplan-Meier curves of OS and DFS according to the Tianjin-grading system. (A) OS according to the Tianjin-Score. (B) DFS according to the Tianjin-Score. (C) OS according to the Tianjin-Grade. (D) DFS according to the Tianjin-Grade. Cum, cumulative survival; DFS, disease-free survival; OS, overall survival.

Western cohorts¹⁷⁻²⁰, and therefore have potentially limited applicability to Asian populations, because of differences in genetics, tumor biology, and treatment responses. Because the Tianjin grading system was specifically developed and validated within a Chinese cohort, it is particularly suitable and potentially has enhanced accuracy for Asian populations.

The Tianjin grading system also demonstrated substantial innovation in clinical practicality and ease of implementation. In contrast to certain existing staging systems that require complex or less commonly available diagnostic techniques (such as routine PET-CT scans or extensive genomic profiling), the Tianjin grading system uses readily accessible and

routinely performed clinical assessments, including enhanced CT imaging, standard laboratory tests for CA19-9, and basic nutritional assessments. This accessibility ensures ease of use across diverse clinical settings, thus enhancing its real-world utility and widespread applicability, particularly in resource-limited environments.

Biological and patient-specific factors as novel components

One innovative aspect of the Tianjin grading system is its rigorous integration of biological factors and patient condition

Table 5 Multivariate survival analysis of the prognostic value of the Tianjin-Grade vs. known prognostic factors

Variables	Category	Overall survival			Disease-free survival		
		HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Tianjin-Grade	Extremely high-risk/low-risk	4.369	3.165–6.032	< 0.001	4.198	3.091–5.701	< 0.001
	High-risk/low-risk	2.347	1.745–3.155	< 0.001	2.051	1.556–2.703	< 0.001
	Intermediate-risk/low-risk	1.616	1.239–2.107	< 0.001	1.531	1.199–1.954	0.001
TNM stage	III/I	1.504	1.130–2.002	0.005	1.569	1.195–2.060	0.001
	II/I	1.208	0.980–1.490	0.077	1.173	0.962–1.430	0.114
Tumor differentiation	Poor/well and moderate	1.537	1.273–1.855	< 0.001	1.515	1.270–1.807	< 0.001
Surgical complication	Present/absent	1.267	1.031–1.558	0.025	1.153	0.950–1.400	0.150
Postoperative adjuvant chemotherapy	Yes/no	0.521	0.433–0.627	< 0.001	0.678	0.569–0.807	< 0.001

CI, confidence interval; HR, hazard ratio; TNM, tumor node metastasis.

Table 6 Multivariable Cox proportional hazards model incorporating an interaction term between treatment strategy (NAC vs. upfront surgery) and Tianjin-Grade

Category	Overall survival			Disease-free survival		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Entire study series						
Treatment strategy (NAC/upfront surgery)	0.545	0.395–0.750	< 0.001	0.511	0.380–0.688	< 0.001
Tianjin-Grade						
Extremely high-risk/low-risk	5.182	3.792–7.083	< 0.001	5.438	4.037–7.326	< 0.001
High-risk/low-risk	2.738	2.063–3.633	< 0.001	2.488	1.911–3.240	< 0.001
Intermediate-risk/low-risk	1.569	1.209–2.037	< 0.001	1.550	1.219–1.970	< 0.001
Matched pairs						
Treatment strategy (NAC/upfront surgery)	0.489	0.322–0.741	0.001	0.440	0.297–0.651	< 0.001
Tianjin Grade						
Extremely high-risk/low-risk	8.623	3.487–21.328	< 0.001	6.763	3.055–14.969	< 0.001
High-risk/low-risk	3.163	1.306–7.662	0.011	2.594	1.190–5.652	0.016
Intermediate-risk/low-risk	1.540	0.627–3.780	0.346	1.495	0.685–3.262	0.312

CI, confidence interval; HR, hazard ratio; NAC, neoadjuvant chemotherapy.

assessments, which have been underrepresented in, or entirely omitted from, established criteria¹⁰. By using widely available contrast-enhanced CT to detect lymph node involvement, despite certain limitations^{21,22}, the predictive results of this system demonstrated a high degree of consistency with the pathological findings. In this study, 82.5% of cases with positive findings on CT scans were confirmed according to pathology.

Additionally, the use of the PNS, a novel measure capturing immune-nutritional status through lymphocyte count, platelet count, and prealbumin levels, addresses critical limitations of conventional assessment tools¹⁴. Although ECOG performance status remains widely used, its discriminatory ability is limited in patients with pancreatic cancer receiving intensive treatments (particularly surgical resection), most of whom have ECOG scores of 0–1¹⁸. Herein, the PNS outperformed

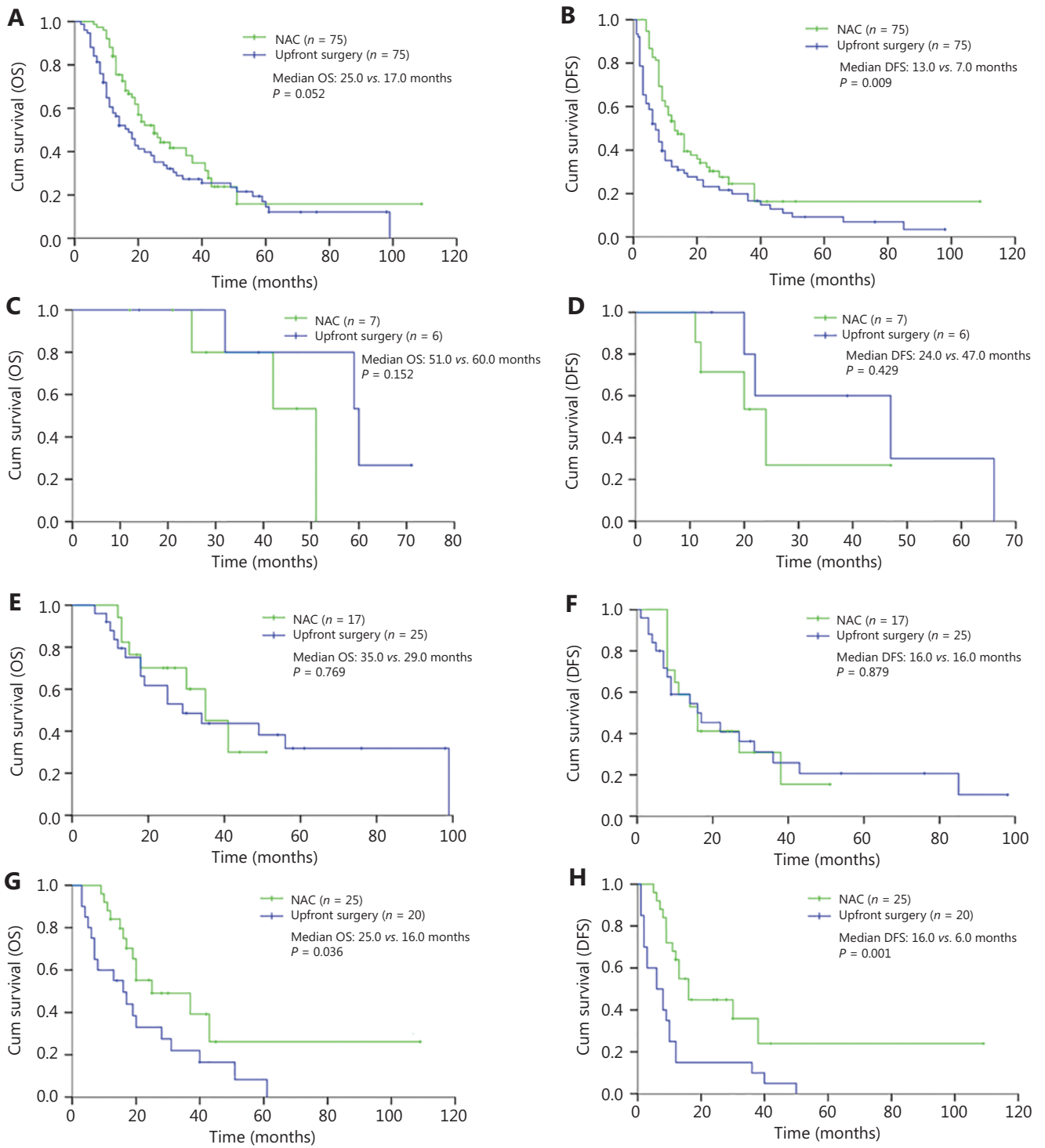


Figure 3 Continued

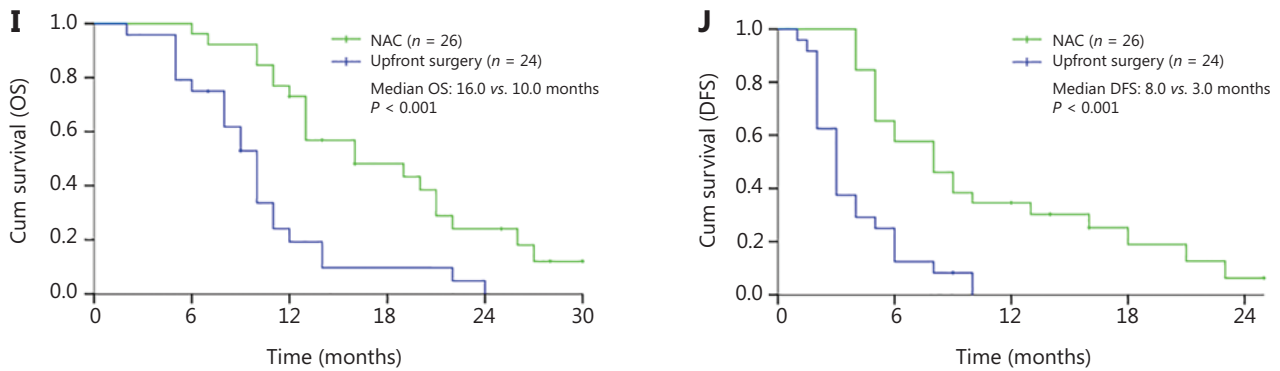


Figure 3 Comparison of survival curves between matched patients with different Tianjin-Grades who received NAC and those who underwent upfront surgery. (A) OS curves of all matched patients. (B) DFS curves of all matched patients. (C) OS curves of low-risk patients. (D) DFS curves of low-risk patients. (E) OS curves of intermediate-risk patients. (F) DFS curves of intermediate-risk patients. (G) OS curves of high-risk patients. (H) DFS curves of high-risk patients. (I) OS curves of extremely high-risk patients. (J) DFS curves of extremely high-risk patients. Cum, cumulative survival; DFS, disease-free survival; NAC, neoadjuvant chemotherapy; OS, overall survival.

Table 7 Multivariate analysis with Cox proportional hazards model to assess the survival benefit of NAC across Tianjin-Grade subgroups

Category	Overall survival			Disease-free survival		
	HR	95% CI	P	HR	95% CI	P
Low-risk						
Treatment strategy (NAC/upfront surgery)	6.822	0.544–85.586	0.137	2.044	0.432–9.664	0.367
Tumor differentiation (poor/well and moderate)	1.010	0.075–13.636	0.994	1.138	0.183–7.071	0.889
Postoperative adjuvant chemotherapy (yes/no)	0.222	0.027–1.789	0.157	0.320	0.041–2.488	0.276
Intermediate-risk						
Treatment strategy (NAC/upfront surgery)	1.517	0.527–4.365	0.439	1.165	0.467–2.908	0.743
Age (≥ 70/< 70 years)	4.725	0.561–39.800	0.153	1.254	0.289–5.434	0.762
Tumor differentiation (poor/well and moderate)	1.074	0.406–2.840	0.885	1.283	0.555–2.966	0.560
TNM stage (III/II/I)	1.087	0.483–2.445	0.840	1.034	0.518–2.067	0.924
Postoperative adjuvant chemotherapy (yes/no)	0.144	0.045–0.462	0.001	0.435	0.177–1.071	0.070
Surgical complication (present/absent)	1.637	0.428–6.256	0.471	1.482	0.398–5.514	0.557
High-risk						
Treatment strategy (NAC/upfront surgery)	0.335	0.133–0.843	0.020	0.308	0.118–0.805	0.016
Age (≥ 70/< 70 years)	2.425	0.705–8.337	0.160	2.299	0.702–7.525	0.169
Tumor differentiation (poor/well and moderate)	1.006	0.425–2.382	0.990	1.350	0.605–3.011	0.463
TNM stage (III/II/I)	1.093	0.573–2.083	0.788	1.124	0.569–2.217	0.738
Postoperative adjuvant chemotherapy (yes/no)	0.386	0.163–0.914	0.031	0.460	0.205–1.028	0.059
Surgical complication (present/absent)	2.233	0.718–6.944	0.165	1.061	0.373–3.016	0.912

Table 7 Continued

Category	Overall survival			Disease-free survival		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Extremely high-risk						
Treatment strategy (NAC/upfront surgery)	0.243	0.093–0.637	0.004	0.313	0.139–0.723	0.007
Age (≥ 70 / < 70 years)	1.626	0.585–4.521	0.351	1.189	0.491–2.881	0.701
Tumor differentiation (poor/well and moderate)	1.404	0.649–3.039	0.389	1.733	0.815–3.681	0.153
TNM stage (III/II/I)	1.253	0.789–1.988	0.339	1.109	0.651–1.629	0.902
Postoperative adjuvant chemotherapy (yes/no)	0.475	0.236–0.957	0.037	0.385	0.193–0.768	0.007
Surgical complication (present/absent)	1.807	0.773–4.228	0.172	1.060	0.477–2.354	0.886

CI, confidence interval; HR, hazard ratio; NAC, neoadjuvant chemotherapy; TNM, tumor node metastasis.

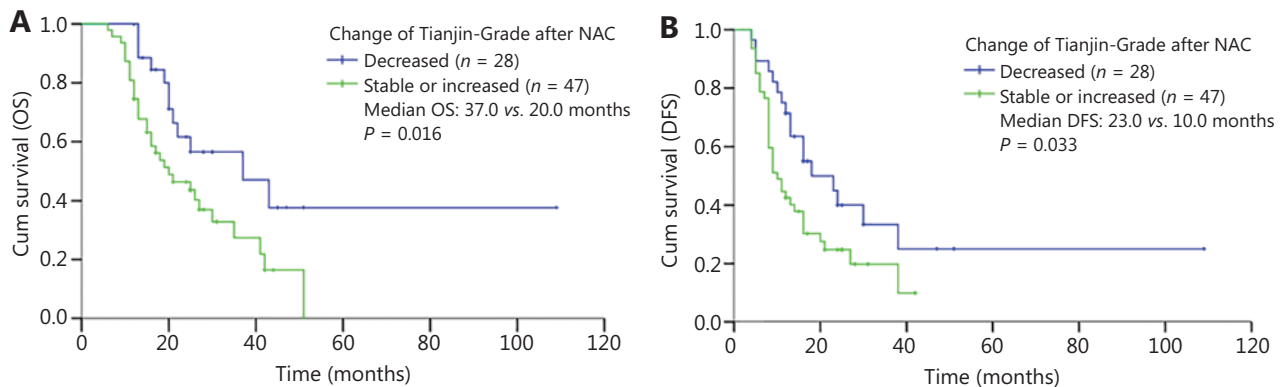


Figure 4 Patients with decreased Tianjin-Grades after NAC, compared with those with stable or increased grades, demonstrated significant survival improvements. (A) Overall survival curves. (B) Disease-free survival curves. Cum, cumulative survival; DFS, disease-free survival; NAC, neoadjuvant chemotherapy; OS, overall survival.

traditional tools such as the ECOG score, and provided superior discriminatory power in evaluating patients' overall physical readiness for major surgical interventions and NAC.

Advantages and clinical implications of the Tianjin grading system

The Tianjin grading system presents several notable advantages that distinguish it from conventional methods: (1) comprehensive multidimensional evaluation incorporating anatomical, biological, and conditional indicators; (2) clear and actionable risk stratification that aids in personalized clinical decision-making; (3) objective guidance for choosing between upfront surgery or NAC, particularly in identifying high- and extremely high-risk groups of patients likely to markedly

benefit from neoadjuvant interventions; and (4) superior ability to evaluate tumor response to NAC beyond conventional RECIST 1.0 and NCCN criteria, thereby accounting for the fibrotic nature and limited size variability of PDAC tumors after chemotherapy²³⁻²⁹.

Study limitations and future directions

Despite these advancements, several study limitations must be acknowledged. Although propensity score matching was used to balance baseline characteristics between groups, the potential for selection bias could not be entirely excluded. Additionally, the retrospective single-center design necessitates validation through prospective multicenter studies. Furthermore, the inclusion of only surgical patients restricts

the generalizability of the findings to non-surgical populations, and the relatively limited NAC cohort further underscores the need for validation in larger samples.

Conclusions

In summary, the Tianjin grading system represents a substantial innovation in PDAC clinical staging by providing a robust, multidimensional framework that enhances risk stratification and therapeutic decision-making. This novel tool demonstrates significant potential to transform clinical practice by more accurately identifying patients likely to benefit from NAC or upfront surgery, and effectively evaluating treatment responses. Specifically designed and validated within the Chinese population, this tool addresses a critical gap by offering enhanced accuracy and applicability for Asian patients. Its practicality and ease of clinical implementation further reinforce its value in routine patient care. Future prospective studies are warranted to validate and refine the Tianjin grading system's predictive ability across larger, more diverse patient cohorts.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yuexiang Liang, Song Gao, Jun Yu, Kuirong Jiang, Chuntao Gao, Jihui Hao.

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Contributed data or analysis tools: Yiping Zou, Quan Man, Hongwei Wang, Shaofei Chang, Zhifei Li.

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Wrote the paper: Yuexiang Liang, Song Gao.

Data availability statement

The data that support the findings of this study are available from the corresponding author.

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