Original Article

Prognostic significance of preoperative Naples prognostic score on short- and long-term outcomes after pancreatoduodenectomy for ampullary carcinoma

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Background: The Naples prognostic score (NPS) is an effective and objective tool to assess the immune–nutritional status of patients with malignant tumors. The aim of this study was to investigate the clinical significance of preoperative NPS on short- and long-term outcomes after pancreatoduodenectomy (PD) for ampullary carcinoma.

Methods: We retrospectively analyzed 404 consecutive patients with ampullary carcinoma who underwent PD between January 2012 and June 2018. Preoperative NPS was calculated from serum albumin and total cholesterol concentrations, and the neutrophil–lymphocyte ratio and lymphocyte-monocyte ratio (LMR). Patients were then divided into three groups according to their NPS. Clinicopathological variables, postoperative outcomes, and survival data were compared between the three groups. Univariate and multivariate Cox analysis of overall survival (OS) and recurrence-free survival (RFS) were also conducted, and time-dependent receiver operating characteristic (ROC) curves were created to evaluate the discriminatory ability of the prognostic scoring systems.

Results: Patients with higher NPS had worse prognosis, and significant OS difference (group 0 *vs.* 1, P=0.02; group 1 *vs.* 2, P<0.001; group 0 *vs.* 2, P<0.001) and RFS difference (group 0 *vs.* 1, P=0.088; group 1 *vs.* 2, P<0.001; group 0 *vs.* 2, P<0.001). Multivariate analysis revealed that NPS was an independent significant predictor of OS (grade 2 *vs.* grade 1 or 0, hazard ratio: 3.067; P<0.001) and RFS (grade 2 *vs.* grade 1 or 0, hazard ratio: 2.732; P<0.001). The time-dependent receiver operating curve analysis showed that NPS had better prognostic performance for OS and RFS than other prognostic models. Additionally, significant differences in the incidence of postoperative morbidity were observed between the three groups, and the NPS was an independent risk factor of overall postoperative complications (grade 2 *vs.* grade 1 or 0, odds ratio: 1.692; P=0.02).

Conclusions: The NPS was an independent predictor of overall- and RFS in patients undergoing PD for ampullary carcinoma, and was independently associated with the incidence of postoperative complications.

Keywords: Naples prognostic score (NPS); ampullary carcinoma; prognostic factor; immune-nutritional status; postoperative outcomes

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Introduction

Ampullary carcinoma is a relatively rare malignant tumor representing approximately 8% of all malignant periampullary tumors and accounting for 30–40% of surgically resectable periampullary cancers (1-6). Compared with other periampullary tumors, the clinical symptoms of ampullary cancer usually occur earlier, which may explain the better prognosis. As reported previously (2,4,5), the 5-year overall survival (OS) rate of ampullary carcinomas is approximately 40–65% in resectable patients. Studies have suggested that many factors affect the prognosis of ampullary cancer, including the TNM stage, tumor subtypes, surgical margins, adjuvant chemotherapy (2-4,7); however, it remains necessary and urgent to study additional prognostic factors to accurately predict the prognosis of ampullary cancer.

Recently, nutritional and immune status as host-related factors, have attracted attention for predicting surgical outcomes in various cancers. The Controlling Nutritional Status (CONUT) score (8,9), prognostic nutritional index (PNI) (10,11), and Glasgow prognostic score (GPS) (12,13) were confirmed prognostic factors in malignant tumors. The Naples prognostic score (NPS), proposed by Galizia *et al.* (14), consists of serum albumin and total cholesterol concentrations, neutrophil–lymphocyte ratio (NLR), and lymphocyte-monocyte ratio (LMR). However, currently, the correlation between NPS and short- and long-term prognosis of patients undergoing pancreatoduodenectomy (PD) for ampullary carcinoma remains unknown.

In this study, our aim was to assess the prognostic significance of preoperative NPS on short-and long-term outcomes after PD for ampullary cancer.

We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-741/rc).

Methods

Patient cohort

A total of 465 patients who underwent PD for ampullary carcinoma between January 2012 and June 2018 at the Tongji Medical Hospital of Tongji Medical College of Huazhong University of Science and Technology were enrolled in the present study. Patients with incomplete data (n=20), neo-adjuvant therapy (n=5), nutritional and immune interventions before admission (n=16) and unknown histological characteristics were excluded from the study (n=20). Finally, 404 patients were included in the OS analysis data set. Patients who died within 90 days of surgery and who had positive resection margin were excluded, and 375 patients were enrolled in the recurrence-free survival (RFS) analysis data set (*Figure 1*). After discharge, adjuvant chemotherapy was administered to all patients unless the patient's condition was intolerant to chemotherapy, or the patient was lost to follow-up or for other reasons. Regimens utilized for ampullary cancer were typically either S1-based or gemcitabine (Gem)-based. Patients were followed-up every 3 months for the first 2 years and then every 6 months for a total of 5 years. Patients were examined for recurrence using tumor markers and computed tomography every 3 months. If recurrence was suspected, recurrent ampullary carcinoma was diagnosed by a biopsy specimen or exfoliative cytology of the abdominal cavity. The enrolled patients were followed until death or June 30, 2020, whichever came first. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We obtained written informed consent from the patients for participation, and the study was approved by the ethics committee of Tongji Medical Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20190418).

NPS and other prognostic scoring systems

The NPS model was proposed by Galizia and his colleagues (14), consists of four parameters, namely serum albumin and total cholesterol concentrations, NLR, and LMR. Albumin concentration <4 g/dL is assigned a score of 1 and concentration ≥4 g/dL is assigned a score of 0. Total cholesterol concentration <180 mg/dL is assigned a score of 1, while total cholesterol ≥180 mg/dL is assigned a score of 0. NLR ≥2.96 is assigned a score of 1, while NLR <2.96 is assigned a score of 0. LMR <4.44 is assigned a score of 1, while LMR ≥4.44 is assigned a score of 0. The sum of the four parameters' scores is the NPS score. All patients in this study were divided into three groups according to their NPS scores. Patients with a score of 0, 1 or 2, or 3 or 4 were assigned to groups 0, 1, and 2, respectively.

The CONUT score was calculated as described previously (15), and the score consists of albumin and total cholesterol concentrations and the lymphocyte count, the cut-off value of the CONUT was set at 4 scores. As reported previously (10), the PNI was calculated as follows: 10 × albumin value (in grams per deciliter) + 0.005 × total lymphocyte count (TLC) in the peripheral blood, the cut-

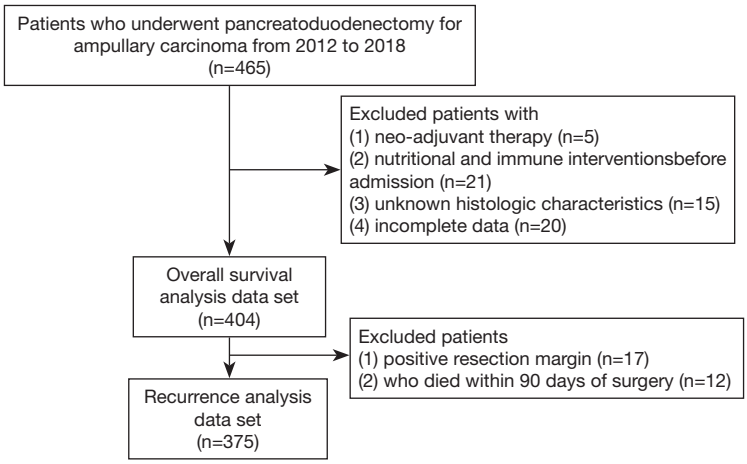

Figure 1 Flow diagram of study population selected.

off value of the PNI for clinically significant malnutrition was also set at below 45 in our study. The systemic inflammation score (SIS) score was calculated for each patient as described previously (16), and the score consists of albumin concentration and LMR. The Nutritional Risk Index (NRI) was calculated using the formula: NRI = (15.9 × serum albumin g/dL) + (41.7 × current weight/usual weight). The usual weight was defined as the stable weight 6 months before the illness, the cut-off value of the NRI for clinically significant malnutrition was set at below 97.5 in our study. Pathological TNM stage was determined according to the 8th edition of the Cancer Staging Manual of the American Joint Commission on Cancer (17).

Data collection

The following clinical characteristics and pathological findings were collected from patients' medical records. Baseline characteristics: age, sex, body mass index (BMI), co-morbidities, American Society of Anesthesiologists (ASA) class, preoperative biliary drainage, serum albumin, total cholesterol, total bilirubin, carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and neutrophil, lymphocyte, and monocyte counts. Pathological findings: histological subtype (intestinal, pancreatobiliary, and ambiguous type), T stage, tumor size, tumor grade, lymph node metastasis, vascular invasion, perineural invasion, surgical margin, and TNM stage. Intraoperative parameters: operative time, blood loss, transfusion, and surgical procedure.

Definition of postoperative outcomes

Major postoperative complications were defined as grade III or higher in the Clavien–Dindo classification (18). Pancreatic fistula (19), delayed gastric emptying (20), biliary leak (21), and postoperative hemorrhage (22) were defined by the definition of the International Study Group of Pancreatic Surgery. OS was calculated from date of surgery to the date of death and RFS was calculated from the date of surgery to the date of cancer recurrence.

Surgical procedure

Standard PD was performed by authors R Qin and F Zhu. Organs resection: The scope of the resection included the pancreatic head and uncinate process, as well as the distal stomach, gallbladder, common bile duct, and lymph nodes and the entire duodenum and proximal jejunum. Digestive tract reconstruction: we performed pancreaticojejunostomy by the imbedding pancreaticojejunostomy method, as reported previously (23). Pancreatogastrostomies were performed by embedding the pancreatic remnant into the stomach. An end-to-side hepaticojejunostomy was performed 15 cm away from the pancreaticojejunostomy, and antecolic side-to-side gastroenterostomy was performed with the staple technique, 40 cm away from the hepaticojejunostomy.

Statistical methods

Categorical variables were expressed as frequencies and percentages, and differences in variables between the groups

were compared using Pearson's chi square or Fisher's exact tests. Continuous variables were expressed as medians and interquartile ranges (IQR) and were compared using Mann-Whitney U and Kruskal-Wallis tests. Some variables were dichotomized using median values or normal values. Survival was estimated with the Kaplan-Meier method and log-rank tests. Cox proportional-hazard regression analysis was used for univariate and multivariate analysis. Variables with P<0.1 on the univariate analysis were included in the multivariate analysis. To evaluate the discriminatory ability of the prognostic scoring systems, we created time-dependent receiver operating characteristic (ROC) curves. We then calculated the areas under the curve (AUCs), and higher AUC values indicated better predictive ability. For all tests, differences with P values <0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) and the statistical package R (version 3.3.1, R Project for Statistical Computing, Vienna, Austria).

Results

Patients' characteristics

The clinicopathological characteristics of the 404 patients included in this study are summarized in *Table 1*. Of the 404 patients, the median age was 58 years (IQR: 50–64 years), namely 228 (56.4%) male and 176 (43.6%) female subjects; the median BMI was 21.7 kg/m^2 (IQR: 19.9–23.4 kg/m^2). The median total bilirubin concentration was 61 mmol/L (IQR: 17–152 mmol/L), and preoperative biliary drainage was performed in 148 (36.6%) patients. Of the 404 patients, 160 (39.6%) underwent laparoscopic pancreaticoduodenectomies. The conclusive stages of the 404 patients who underwent resection according to the AJCC classification were stage I in 181 (44.8%) cases, stage II in 111 (27.5%) cases, and stage III in 112 (27.7%) cases; 175 (43.3%) patients underwent adjuvant chemotherapy. Among the included patients, 85 (21.0%) patients were classified into group 0 (NPS 0), 195 (48.3%) into group 1 (NPS 1 or 2), and 124 (30.7%) into group 2 (NPS 3 or 4).

Correlation between preoperative NPS and patients' clinicopathological characteristics

The results of the analysis of the associations between NPS and clinicopathological characteristics are shown in *Table 2*. A significantly higher NPS was observed in patients with elevated bilirubin (P<0.001), CA19-9 (P<0.001), and CA125 concentrations (P=0.047), and in those who underwent preoperative biliary drainage (P=0.001); however, there were no significant differences for age, sex, ASA class, co-morbidities, BMI, and CEA concentrations between the three groups. In addition, significant differences were found for histological subtype (P=0.005), tumor grade (P=0.01), vascular invasion (P=0.004), TNM stage (P=0.028), and adjuvant therapy (P=0.018) among the three groups; however, there was no difference regarding tumor size, T stage, lymph node metastasis, perineural invasion, or positive margins between the three groups.

Postoperative complications

In total, 160 patients (39.6%) developed postoperative complications, namely pancreatic fistula (n=85; 21.0%), postoperative bleeding (n=46; 11.4%), delayed gastric emptying (n=69; 17.1%), intra-abdominal abscess (n=46; 11.4%), bile leakage (n=9; 2.2%), and pulmonary infection (n=26; 6.4%); 69 cases (17.1%) had grade ≥III postoperative complications. The median postoperative hospital stay was 18 days (IQR: 15–22 days), and 12 patients (3.0%) died within 90 days after surgery.

We investigated the associations between the NPS and postoperative complications. The incidence of overall postoperative complications (P=0.038), pancreatic fistula (P=0.004), intra-abdominal abscess (P=0.024), pulmonary infection (P=0.002), and the postoperative hospital stay (P<0.001) was closely associated with the NPS. However, there were no significant differences in grade ≥III postoperative complications, bile leakage, postoperative hemorrhage, and delayed gastric emptying among 3 groups. Furthermore, the NPS was an independent risk factor of overall postoperative complications (grade 2 *vs.* grade 1 or 0, odds ratio: 1.692; P=0.02). The results of the analysis of the associations between the NPS and postoperative complications are shown in *Table 3* and Table S1.

Overall and RFS according to the NPS

OS and RFS curves were statistically analyzed, and the results are shown in *Figure 2*. The median OS time for each NPS group was 94.6 months in group 0, 89.6 months in group 1, and 24.2 months in group 2. Regarding OS, there was a significant survival difference between the three groups (group 0 *vs.* 1, P=0.02; group 1 *vs.* 2, P<0.001;

Table 1 Clinicopathological characteristics of 404 patients underwent pancreatoduodenectomy for ampullary carcinoma

Factors	Values
Age, years	58 [50–64]
Sex (male)	228 (56.4)
Body mass index, kg/m^2	21.7 [19.9–23.4]
ASA class	
I	51 (12.6)
II	314 (77.7)
III	39 (9.7)
Co-morbidities	95 (23.5)
Preoperative biliary drainage	148 (36.6)
Total bilirubin, μmol/L	61 [17–152]
Albumin, mg/dL	3.7 [3.3–4.0]
Cholesterol, mg/dL	188 [150–233]
NLR	2.45 [1.78–3.72]
LMR	2.97 [2.13–4.25]
CA19-9, U/mL	57 [17–210]
CA125, U/mL	13.7 [10.3–21.1]
CEA, ng/mL	2.6 [1.7–4.0]
Estimated blood loss, ml	200 [100–400]
Operative time, minutes	283 [211–370]
Surgical procedure	
LPD	160 (39.6)
OPD	244 (60.4)
Histological subtype	
Intestinal	140 (34.7)
Pancreatobiliary	247 (61.1)
Ambiguous	17 (4.2)
Tumor size, cm	2.0 [1.5–2.7]
T stage	
T1	92 (22.8)
T2	138 (34.2)
T3	162 (40.1)
T4	12 (3.0)
Lymph node metastasis, positive	108 (26.7)
Vascular invasion, positive	33 (8.2)
Perineural invasion	18 (4.5)
Tumor grade	
well	77 (19.1)
moderately	288 (71.3)
poorly	39 (9.7)
Positive resection margin	17 (4.2)
TNM stage	
I	181 (44.8)
II	111 (27.5)
III	112 (27.7)
Adjuvant therapy	175 (43.3)
Naples prognostic score	
Group 0	85 (21.0)
Group 1	195 (48.3)
Group 2	124 (30.7)

Categorical variables were expressed as n (%), continuous variables are expressed as medians and interquartile ranges [IQR]. ASA, American Society of Anesthesiologists; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CA19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; LPD, laparoscopic pancreatoduodenectomy; OPD, open pancreatoduodenectomy.

group 0 *vs.* 2, P<0.001). In comparison, the median RFS time for each NPS group was 81.2 months in group 0, 73.0 months in group 1, and 20.5 months in group 2. There was a significant survival difference between the three groups (group 0 *vs.* 1, P=0.088; group 1 *vs.* 2, P<0.001; group 0 *vs.* 2, P<0.001).

Univariate and multivariate analyses of prognostic factors in ampullary cancer

A total of 404 patients who underwent PD were included in the OS data set. The median OS was 74.1 months. The results of Univariate and Multivariate Cox proportional hazards regression model for prognostic factors for OS are shown in *Table 4*. In the multivariate analysis, NPS (grade 2 *vs.* grade 1 or 0, HR =3.067, 95% CI: 2.203–4.274; P<0.001) was an independent prognostic factor in patients who underwent PD for ampullary carcinoma. In addition,

Table 2 The relationships between Naples prognostic score and clinicopathological characteristics in 404 patients underwent pancreatoduodenectomy for ampullary carcinoma

Variables	Group 0, N=85	Group 1, N=195	Group 2, N=124	P value
Age, years	55 [50–63]	58 [51–64]	58 [50–65]	0.309
Sex (male)	45 (52.9)	115 (59.0)	68 (54.8)	0.588
Body mass index, kg/m^2	21.9 [20.2–23.2]	21.8 [20.2–23.7]	21.1 [19.3–23.4]	0.072
ASA class				
I/II	81 (95.3)	177 (90.8)	107 (86.3)	0.092
III	4 (4.7)	18 (9.2)	17 (13.7)	
Co-morbidities	19 (22.4)	47 (24.1)	29 (23.4)	0.95
Preoperative biliary drainage	21 (24.7)	66 (33.8)	61 (49.2)	0.001
Total bilirubin, μmol/L	27.0 [11.4–74.2]	57.2 [16.4–138.7]	126.5 [44.1–192.5]	<0.001
CA19-9, U/mL	25.4 [10.2–68.7]	54.8 [15.5–182.9]	104.5 [35.1–451.6]	<0.001
CA125, U/mL	13.3 [9.3–17.1]	13.7 [10.7–21.3]	15.2 [10.2–24.2]	0.047
CEA, ng/mL	2.4 [1.7–3.5]	2.5 [1.7–4.0]	2.8 [1.7–4.4]	0.401
Histological subtype				
Intestinal	60 (70.6)	128 (65.6)	59 (47.6)	0.005
Pancreatobiliary	23 (27.1)	59 (30.3)	58 (46.8)	
Ambiguous	2 (2.4)	8 (4.1)	7 (5.6)	
Tumor size, cm	2.0 [1.5–2.5]	1.8 [1.5–2.5]	2.0 [1.5–3.0]	0.326
T stage				
T1/T2	57 (67.1)	108 (55.4)	65 (52.4)	0.092
T3/T4	28 (32.9)	87 (44.6)	59 (47.6)	
Lymph node metastasis, positive	22 (25.9)	47 (24.1)	39 (31.5)	0.345
Vascular invasion, positive	2 (2.4)	13 (6.7)	18 (14.5)	0.004
Perineural invasion	3 (3.5)	7 (3.6)	8 (6.5)	0.433
Tumor grade				
Well	26 (30.6)	36 (18.5)	15 (12.1)	0.01
Moderately	53 (62.4)	136 (69.7)	99 (79.8)	
Poorly	6 (7.1)	23 (11.8)	10 (8.1)	
Positive resection margin	2 (2.4)	9 (4.6)	6 (4.8)	0.629
TNM stage				
I	48 (56.5)	88 (45.1)	45 (36.3)	0.028
II	15 (17.6)	59 (30.3)	37 (29.8)	
III	22 (25.9)	48 (24.6)	42 (33.9)	
Adjuvant therapy	47 (55.3)	84 (43.1)	44 (35.5)	0.018

Categorical variables were expressed as n (%), continuous variables are expressed as medians and interquartile ranges [IQR]. ASA, American Society of Anesthesiologists; CA19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen.

Table 3 The relationships between Naples prognostic score and postoperative short outcomes in 404 patients underwent pancreatoduodenectomy for ampullary carcinoma

Variables	Total patients, N=404	Group 0, N=85	Group 1, N=195	Group 2, N=124	P value
Overall postoperative complications	160 (39.6)	27 (31.8)	73 (37.4)	60 (48.4)	0.038
Major postoperative complications (CD ≥ IIIa)	69 (17.1)	10 (11.8)	30 (15.4)	29 (23.4)	0.062
Pancreatic fistula					
Grade A	46 (11.4)	9 (10.6)	20 (10.3)	17 (13.7)	0.004
Grade B	32 (7.9)	7 (8.2)	19 (9.7)	6 (4.8)	
Grade C	7 (1.7)	0 (0.0)	0 (0.0)	7 (5.6)	
Bile leakage	9 (2.2)	0 (0.0)	5 (2.6)	4 (3.2)	0.272
Postoperative hemorrhage	46 (11.4)	8 (9.4)	22 (11.3)	16 (12.9)	0.736
Delayed gastric emptying					
Grade A	35 (8.7)	9 (10.6)	14 (7.2)	12 (9.7)	0.838
Grade B	26 (6.4)	6 (7.1)	13 (6.7)	7 (5.6)	
Grade C	8 (2.0)	1 (1.2)	3 (1.5)	4 (3.2)	
Intra-abdominal abscess	46 (11.4)	6 (7.1)	18 (9.2)	22 (17.7)	0.024
Pulmonary infection	26 (6.4)	2 (2.4)	8 (4.1)	16 (12.9)	0.002
90-days mortality	12 (3.0)	1 (1.2)	2 (1.0)	9 (7.3)	0.003
Postoperative hospital stay, days	18 [15–22]	16 [14–19]	19 [15–21]	20 [16–25]	<0.001

Categorical variables were expressed as n (%), continuous variables are expressed as medians and interquartile ranges [IQR]. CD, Clavien-Dindo classification.

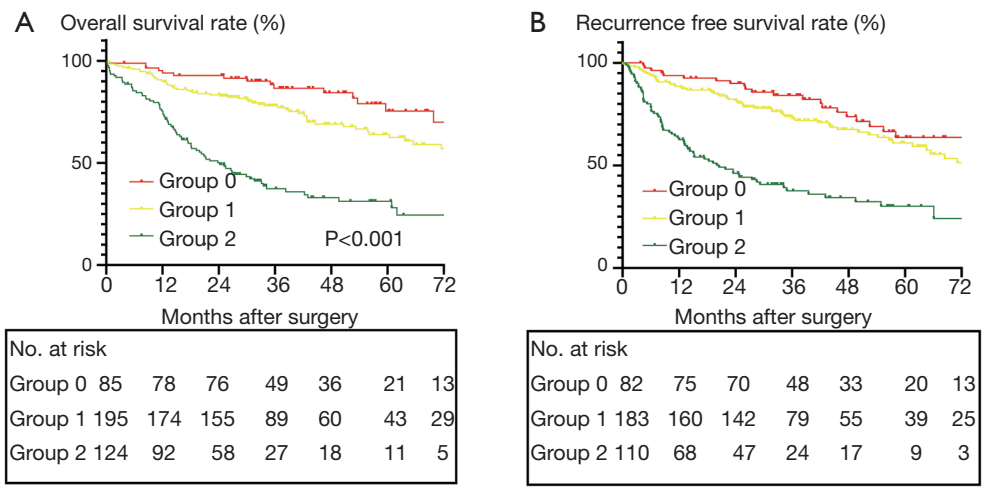

Figure 2 Kaplan-Meier curves for overall survival (A) and recurrence-free survival (B). (A) Significant overall survival difference were observed between the three groups (group 0 *vs.* 1, P=0.02; group 1 *vs.* 2, P<0.001; group 0 *vs.* 2, P<0.001). (B) There was a significant recurrence-free survival difference between group 1 and group 2, and between group 0 and group 2 (P<0.001, P<0.001, respectively), no significant difference between group 0 and group 1 (P=0.088).

Table 4 Univariate and multivariate Cox proportional hazard regression analysis of prognostic factors for OS in patients who underwent pancreatoduodenectomy for ampullary carcinoma

Factors	No. patients	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age (>65 *vs.* ≤65 years)	71/333	1.220 (0.823–1.805)	0.322		
Sex (male *vs.* female)	228/176	1.122 (0.817–1.540)	0.477		
Co-morbidities (+ *vs.* –)	95/309	0.581 (0.381–0.886)	0.012		
BMI (>25 *vs.* ≤25 kg/m^2)	48/356	1.057 (0.654–1.709)	0.820		
ASA class (III *vs.* I or II)	39/365	1.399 (0.855–2.288)	0.182		
Operative time (>283 *vs.* ≤283 minutes)	182/222	1.279 (0.935–1.750)	0.124		
Estimated blood loss (>200 *vs.* ≤200 mL)	131/273	1.381 (1.003–1.900)	0.048		
Transfusion (+ *vs.* –)	185/219	1.434 (1.047–1.964)	0.031		
CA19-9 (>37 *vs.* ≤37 U/mL)	232/172	1.428 (1.035–1.972)	0.030		
CA125 (>35 *vs.* ≤35 U/mL)	44/360	1.211 (0.765–1.919)	0.397		
CEA (>5 *vs.* ≤5 ng/mL)	65/339	1.630 (1.103–2.408)	0.012		
Jaundice (+ *vs.* –)	254/150	1.561 (1.109–2.196)	0.012		
Histological subtype (pancreatobiliary *vs.* intestinal)	140/264	2.745 (1.997–3.773)	<0.001	2.115 (1.515–2.952)	<0.001
T stage (T3/T4 *vs.* T1/T2)	174/230	2.237 (1.629–3.077)	<0.001	1.712 (1.235–2.375)	0.001
Lymph node metastasis (+ *vs.* –)	108/296	2.162 (1.560–2.997)	<0.001		
Vascular invasion (+ *vs.* –)	33/371	2.554 (1.639–3.979)	<0.001		
Perineural invasion (+ *vs.* –)	18/386	2.033 (1.064–3.885)	0.026		
Tumor grade (poorly *vs.* moderately or well)	39/365	2.000 (1.258–3.185)	0.003		
Resection margins (+ *vs.* –)	17/387	4.362 (2.531–7.518)	<0.001	2.178 (1.208–3.925)	0.01
TNM stage (III *vs.* I or II)	112/292	2.342 (1.698–3.236)	<0.001	2.037 (1.441–2.874)	<0.001
Adjuvant therapy (+ *vs.* –)	175/229	0.578 (0.416–0.804)	0.001	0.558 (0.399–0.779)	0.001
Postoperative complications (+ *vs.* –)	160/244	1.823 (1.334–2.491)	<0.001	1.616 (1.173–2.228)	0.003
SIS (2 *vs.*1 or 0)	127/277	1.672 (1.215–2.299)	0.002		
CONUT (>4 *vs.* ≤4)	66/338	2.545 (1.795–3.610)	<0.001		
PNI (<45 *vs.* ≥45)	231/173	1.773 (1.264–2.488)	0.001		
NRI (<97.5 *vs.* ≥97.5)	170/234	1.560 (1.142–2.132)	0.005		
NPS (grade 2 *vs.* grade 0 or 1)	124/280	3.788 (2.755–5.208)	<0.001	3.067 (2.203–4.274)	<0.001

OS, overall survival; CA19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; NPS, Naples prognostic score; SIS, systemic inflammation score; CONUT, controlling nutritional status; PNI, prognostic nutritional index; NRI, nutritional risk index.

histological subtype (pancreatobiliary *vs.* intestinal, HR =2.115, 95% CI: 1.515–2.952; P<0.001), T stage (T3/T4 *vs.* T1/T2, HR =1.712, 95% CI:1.235–2.375; P=0.001), positive resection margins (HR =2.178, 95% CI: 1.208–3.925; P=0.01), TNM stage (III *vs.* I or II, HR =2.037, 95% CI: 1.441–2.874; P<0.001), adjuvant therapy (HR =0.558, 95% CI: 0.399–0.779; P=0.001), postoperative complications (HR =1.616, 95% CI: 1.173–2.228; P=0.003) were independent

Table 5 Univariate and multivariate Cox proportional hazard regression analysis of prognostic factors for RFS in patients who underwent pancreatoduodenectomy for ampullary carcinoma

Factors	No. patients	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age (>65 years *vs.* ≤65 years)	66/309	1.086 (0.729–1.616)	0.686		
Sex (male *vs.* female)	215/160	1.061 (0.907–1.241)	0.457		
ASA class (III *vs.* II or I)	38/337	1.449 (0.896–2.342)	0.13		
BMI (>25 *vs.* ≤25 kg/m^2)	46/329	1.049 (0.649–1.695)	0.844		
Co-morbidities (+ *vs.* –)	92/283	1.205 (0.888–1.894)	0.179		
Jaundice (+ *vs.* –)	240/135	1.685 (1.199–2.370)	0.003		
Operative time (>283 *vs.* ≤283 minutes)	169/206	1.261 (0.926–1.719)	0.141		
Estimated blood loss (>200 *vs.* ≤200 mL)	120/255	1.304 (0.949–1.792)	0.102		
Transfusion (+ *vs.* –)	171/204	1.295 (0.950–1.764)	0.102		
CA19-9 (>37 *vs.*≤37 U/mL)	213/162	1.537 (1.118–2.114)	0.008		
CA125 (>35 *vs.* ≤35 U/mL)	39/336	1.008 (0.624–1.629)	0.974		
CEA (>5 *vs.* ≤5 ng/mL)	57/318	1.311 (0.866–1.980)	0.202		
Histological subtype (pancreatobiliary *vs.* intestinal)	125/250	2.532 (1.838–3.472)	<0.001	2.093 (1.511–2.898)	<0.001
T stage (T3/T4 *vs.* T1/T2)	155/220	2.073 (1.520–2.829)	<0.001	1.692 (1.229–2.331)	0.001
Lymph node metastasis (+ *vs.* –)	92/283	1.876 (1.335–2.632)	<0.001	1.777 (1.259–2.507)	0.001
Vascular invasion (+ *vs.* –)	24/351	1.980 (1.179–3.322)	0.01		
Perineural invasion (+ *vs.* –)	17/358	2.165 (1.131–4.132)	0.02		
Tumor grade (poorly *vs.* moderately or well)	35/340	2.182 (1.370–3.476)	0.001	1.658 (1.027–2.674)	0.038
TNM stage (III *vs.* I/II)	96/279	1.842 (1.318–2.574)	<0.001		
Adjuvant therapy (– *vs.* +)	166/209	1.374 (1.003–1.882)	0.048		
Postoperative complications (+ *vs.* –)	142/233	1.551 (1.138–2.114)	0.005	1.390 (1.012–1.910)	0.042
SIS (2 *vs.*1 or 0)	116/259	1.600 (1.164–2.198)	0.004		
CONUT (>4 *vs.* ≤4)	58/317	2.232 (1.555–3.195)	<0.001		
PNI (<45 *vs.* ≥45)	214/161	1.560 (1.126–2.160)	0.008		
NRI (<97.5 *vs.* ≥97.5)	156/219	1.489 (1.094–2.027)	0.011		
NPS (grade 3 *vs.* grade 1 or 2)	110/265	3.173 (2.312–4.354)	<0.001	2.732 (1.972–3.774)	<0.001

predictive factors for OS.

Seventeen patients (4.2%) with positive resection margins and 12 patients (3.0%) who died within 90 days after surgery were excluded from the entire cohort, and the remaining 375 patients were included in the RFS data set. The median RFS was 65.5 months. The results of the univariate and multivariate Cox proportional hazards regression model for prognostic factors for RFS are shown in *Table 5*. In the multivariate analysis, NPS (grade 2 *vs.* grade 1 or 0, HR =2.732, 95% CI: 1.972–3.774; P<0.001) was an independent prognostic factor for patients undergoing surgical resection. In addition, histological subtype (pancreatobiliary *vs.* intestinal, HR =2.093, 95% CI: 1.511–2.898; P<0.001), T stage (T3/T4 *vs.* T1/T2, HR =1.692, 95% CI: 1.229–2.331; P=0.001), lymph node metastasis (HR =1.777, 95% CI: 1.259–2.507;

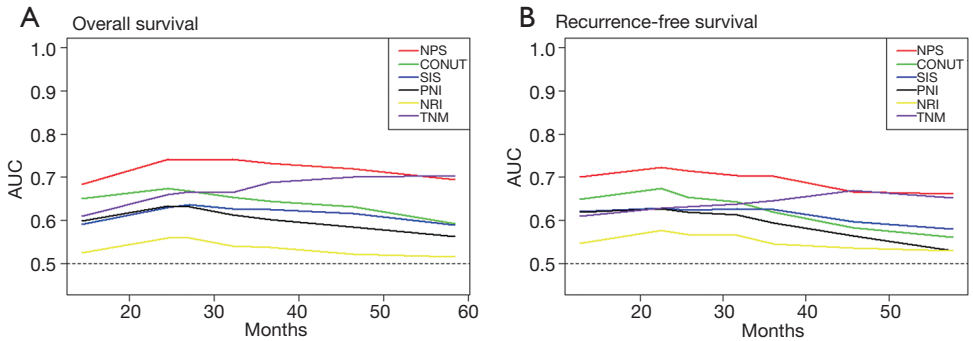

Figure 3 Comparison of the predictive accuracy of the different prognostic systems, by the time-dependent receiver operating characteristic analysis. The horizontal axis represents months after surgery, the vertical axis represents the AUC. (A) Overall survival (404 patients who underwent pancreatoduodenectomy for ampullary carcinoma). (B) Recurrence-free survival (375 patients who underwent pancreatoduodenectomy for ampullary carcinoma, excluded patients who with positive resection margin and died within 90 days of surgery). TNM stage according to the 8th edition of the Cancer Staging Manual of the American Joint Commission on Cancer. AUC, area under the curve; NPS, Naples prognostic score; SIS, systemic inflammation score; CONUT, controlling nutritional status; PNI, prognostic nutritional index; NRI, nutritional risk index.

P=0.001), tumor grade (poorly *vs.* moderately or well, HR =1.658, 95% CI: 1.027–2.674; P=0.038) and postoperative complications (HR =1.390, 95% CI: 1.012–1.910; P=0.042) were independent predictive factors for RFS.

Discriminatory ability of the prognostic scoring systems

A time-dependent ROC curves was generated for each prognostic scoring system, and the estimated AUCs and 95% CI were calculated at different time points (see *Figure 3* and Table S2). In the OS data set, the analysis of the AUCs showed that NPS exhibited significantly greater values than those with CONUT, SIS, PNI, NRI and the TNM stage at each time point, except at 5 years, when the AUC of NPS were only slightly less than that of the TNM staging. Regarding the recurrence data set, the prognostic performance of NPS was also continuously superior to other scoring systems, and after 5 years, NPS scores nearly equaled the discriminatory ability of the TNM stage.

Discussion

The NPS was designed as an objective tool to assess the immune-nutritional status of patients with malignant tumors (14,24). This retrospective study demonstrated that preoperative NPS was an independent prognostic factor for OS and RFS in patients who underwent PD for ampullary carcinoma. The time-dependent ROC analysis showed that NPS had better prognostic performance for OS and RFS than other scoring systems. In addition, we found that NPS was independently related to a higher incidence of overall postoperative complications. To the best of our knowledge, this study is the first report to identify the prognostic significance of NPS on short- and long-term outcomes in patients undergoing PD for ampullary carcinoma.

The clinical outcomes of patients with malignant tumors after curative surgery are associated with the tumor characteristics, surgical factors, and host-related factors (2,25,26). Among these factors, immune-nutritional status is widely recognized as a critical host-related factor. As previously reported (11,16,27,28), patients' immune-nutritional status was correlated with tumor progression and patient survival in various cancers. Immune-nutritional status is often assessed by evaluating blood-based parameters, such as serum albumin and total cholesterol concentrations and leukocyte counts. Considering that a single indicator is susceptible to interference from multiple non-pathological factors, various prognostic scoring systems based on the combination of multiple indicators have been proposed. Kato *et al.* (15) reported that the CONUT score was a useful prognostic predictor of OS in patients with pancreatic adenocarcinoma after pancreatectomy. Similarly, Lee *et al.* (29) showed that PNI, which is based on albumin concentration and lymphocyte count, was a strong independent predictor of survival in patients with gastric cancer. Similarly, the GPS and SIS scoring systems were also considered prognostic markers for pancreatic cancer in previous reports (13,16).

The NPS, proposed by Galizia *et al.* (14), is calculated using serum albumin and total cholesterol concentrations, and NLR and LMR. Galizia *et al.*'s study showed that NPS was closely associated with long-term outcomes in patients undergoing surgery for colorectal cancer (14). Similarly, Nakagawa and colleagues found that NPS could reflected the patient's nutritional and inflammatory status, and that NPS was an independent preoperative predictor of survival in patients with resected pancreatic cancer (24). Similarly, in our study, preoperative NPS was an independent prognostic factor for OS (grade 2 *vs.* grade 1 or 0, HR =3.067, 95% CI: 2.203–4.274; P<0.001) and RFS (grade 2 *vs.* grade 1 or 0, HR =2.732, 95% CI: 1.972–3.774; P<0.001) in patients who underwent PD for.

The cancer-related inflammatory and immune systems are closely related to carcinogenesis, progression, and metastasis (30-32). As previously reported (30), in cancer-related inflammation, effective antitumor immunity is suppressed by multiple pathways, and inflammatory cells and mediators are important constituents of the local tumor microenvironment. Among these constituents, leukocyte infiltrates are present in most malignant tumors, and these cells are involved in carcinogenesis, tumor invasion, and metastasis (33). High numbers of infiltrating lymphocytes inhibited cancer cell proliferation and invasion, which were associated with a good oncologic prognosis. Ray-Coquard *et al.* (34) showed that lymphopenia may provide a favorable microenvironment for tumor growth and invasion, as an independent prognostic factor for overall and progression-free survival in several cancers. In addition, related molecules, such as chemokines and intercellular adhesion molecule, contribute to the recruitment of neutrophils and monocytes into primary tumors (35). In turn, neutrophils as an important inflammatory cell, secrete large amounts of cytokines and chemokines, which are involved in tumor-related angiogenesis (30,35). Additionally, monocytes are closely related to tumor-associated macrophages, which are closely linked to the tumor inflammatory microenvironment, and are involved in tumor progression (36). Hence, the NLR and LMR combine the significance of lymphocytes, neutrophils, and monocytes in tumor progression, which are better prognostic indicators of survival than the single parameters mentioned above (37,38).

NPS also includes serum albumin and total cholesterol concentrations. Serum albumin is an objective indicator of nutritional status and systemic inflammation, and which is associated with postoperative outcomes in patients with malignant tumors. Elahi *et al.* (39) showed that hypoalbuminemia was associated with decreased survival in patients with advanced gastrointestinal cancer. However, serum albumin was not only affected by nutritional status and inflammation, but was related to other factors, such as changes in body fluid levels and hepatic insufficiency. In addition, cholesterol levels as an objective nutritional indicator also correlated with cancer progression (8,15). Therefore, NPS, which includes serum albumin and cholesterol concentrations, and NLR and LMR, is expected to be a better predictor of survival than PNI (consisting only of albumin concentration and lymphocyte count) and COUNT (consisting of albumin and cholesterol concentrations, and lymphocyte count). In our study, the analysis of the time-dependent ROC curves for OS and RFS showed that NPS was continuously superior to CONUT, SIS, PNI, NRI and the TNM stage at each time point, except after 5 years, the AUC of NPS was only slightly less than that of the TNM stage. Moreover, the Multivariate Cox analysis revealed that NPS was the only independent predictor of OS and RFS among these immune inflammation scoring systems mentioned above.

Advanced tumors are often accompanied by more severe nutritional-immune damage and stronger tumor related inflammatory response. Similarly, In our cohort, advanced TNM stage, higher CA19-9 and CA125 concentrations, poorly differentiated tumors, and vascular invasion were more common in group 2 than in group 1 or 0. The worst NPS was closely related to advanced cancers, which may explained that the NPS were independently correlated with survival of ampullary carcinoma in multivariate Cox analysis.

According to previous studies, (14,15,24) the effect of nutritional and immune status on postoperative complications in patients with malignant tumors is controversial. Kato *et al.* (15) found that a low immune-nutritional status (high CONUT score) did not increase postoperative complications after pancreatic surgery. Similarly, Nakagawa *et al.* (24) found that NPS did not affect postoperative morbidity, and the authors considered that postoperative complications mainly depended on the operative procedural technique, and immune–nutritional status may be a relatively insignificant factor. In contrast, Galizia *et al.* (14) showed that the worst NPS was closely related to a higher incidence of postoperative complications. Similarly, we also found that NPS was an independent risk factor of overall postoperative complications in our study. Furthermore, a higher NPS influenced on postoperative complications and maybe led to unfavorable prognostic

outcomes. The postoperative complications further impair the nutritional and immune function, weaken the immune surveillance, and prolong the hospital stay, delay the postoperative chemotherapy, which is unfavorable to the prognosis of patient. In our study, both NPS and postoperative complications were the independent predictors of overall and RFS in patients underwent PD for ampullary carcinoma.

These findings imply that nutritional-immune statuses are associated with prognosis after PD for ampullary carcinoma. Therefore, preoperative adequate nutritional support involving oral or intravenous nutritional supplementation and inflammation control are considered important treatments to improve the prognosis of cancer patients. A retrospective multicenter cohort study suggested that early improvement of nutritional and immune status might lead to better prognosis in resectable pancreatic cancer patients (40). Although there was rare prospective randomized study on whether preoperative improvement of nutritional-immune status can significantly improve the prognosis, the improvement of preoperative nutritional status is considered to can reduce the body's inflammatory response and enhance the immune function to a certain extent, so as to improve surgical tolerance, reduce the incidence of postoperative complications, shorten the length of hospital stay, and enable patients to receive postoperative adjuvant treatment as soon as possible, which may be beneficial to the prognosis of patients.

A potential limitation of this study is that this was a retrospective, single-center, observational study; therefore, subject selection bias was unavoidable. In the future, prospective studies with larger sample sizes, and external validation of our findings in other populations, are essential.

Conclusions

Preoperative NPS was an independent prognostic factor for OS and RFS in patients underwent PD for ampullary carcinoma, with NPS having better prognostic performance than other immune-nutritional scoring systems. Additionally, the NPS was independently associated with the incidence of postoperative complications.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-741/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-741/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-741/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Tongji Medical Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20190418) and informed consent was taken from all individual participants.

References

1. Seo HK, Hwang DW, Lee JH, et al. Role of systemic inflammation in predicting the prognosis of ampulla of Vater carcinoma. Surg Oncol 2019;29:33-40.
2. Ramaswamy A, Bhandare M, Bal M, et al. Clinico-pathological correlates and survival outcomes in 214 resected ampullary adenocarcinomas - are outcomes different in intestinal and pancreatobiliary subtypes with adjuvant gemcitabine? HPB (Oxford) 2020;22:376-82.
3. Al Abbas AI, Falvello V, Zenati M, et al. Impact of adjuvant chemotherapy regimen on survival outcomes in immunohistochemical subtypes of ampullary carcinoma. J

Surg Oncol 2019;121:322-9.
4. Zimmermann C, Wolk S, Aust DE, et al. The pathohistological subtype strongly predicts survival in patients with ampullary carcinoma. Sci Rep 2019;9:12676.
5. Ecker BL, Vollmer CM Jr, Behrman SW, et al. Role of Adjuvant Multimodality Therapy After Curative-Intent Resection of Ampullary Carcinoma. JAMA Surg 2019;154:706-14.
6. Jiang ZQ, Varadhachary G, Wang X, et al. A retrospective study of ampullary adenocarcinomas: overall survival and responsiveness to fluoropyrimidine-based chemotherapy. Ann Oncol 2013;24:2349-53.
7. Perysinakis I, Margaris I, Kouraklis G. Ampullary cancer - a separate clinical entity? Histopathology 2014;64:759-68.
8. Iseki Y, Shibutani M, Maeda K, et al. Impact of the Preoperative Controlling Nutritional Status (CONUT) Score on the Survival after Curative Surgery for Colorectal Cancer. Plos One 2015;10:e0132488.
9. Kang HW, Seo SP, Kim WT, et al. Prognostic Impact of Nutritional Status Assessed by the Controlling Nutritional Status (CONUT) Score in Patients with Surgically Treated Renal Cell Carcinoma. Nutr Cancer 2018;70:886-94.
10. Kanda M, Fujii T, Kodera Y, et al. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg 2011;98:268-74.
11. Abe T, Nakata K, Kibe S, et al. Prognostic Value of Preoperative Nutritional and Immunological Factors in Patients with Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol 2018;25:3996-4003.
12. Polterauer S, Grimm C, Seebacher V, et al. The Inflammation-Based Glasgow Prognostic Score Predicts Survival in Patients With Cervical Cancer. Int J Gynecol Cancer 2010;20:1052-7.
13. McMillan DC, Crozier JE, Canna K, et al. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis 2007;22:881-6.
14. Galizia G, Lieto E, Auricchio A, et al. Naples Prognostic Score, Based on Nutritional and Inflammatory Status, is an Independent Predictor of Long-term Outcome in Patients Undergoing Surgery for Colorectal Cancer. Dis Colon Rectum 2017;60:1273-84.
15. Kato Y, Yamada S, Suenaga M, et al. Impact of the Controlling Nutritional Status Score on the Prognosis After Curative Resection of Pancreatic Ductal Adenocarcinoma. Pancreas 2018;47:823-9.
16. Suzuki Y, Okabayashi K, Hasegawa H, et al. Comparison of Preoperative Inflammation-based Prognostic Scores in Patients With Colorectal Cancer. Ann Surg 2018;267:527-31.
17. Chun YS, Pawlik TM, Vauthey JN. 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. Ann Surg Oncol 2018;25:845-7.
18. DeOliveira ML, Winter JM, Schafer M, et al. Assessment of Complications After Pancreatic Surgery. Ann Surg 2006;244:931-7.
19. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017;161:584-91.
20. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761-8.
21. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: A definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680-8.
22. Grützmann R, Rückert F, Hippe-Davies N, et al. Evaluation of the International Study Group of Pancreatic Surgery definition of post-pancreatectomy hemorrhage in a high-volume center. Surgery 2012;151:612-20.
23. Wang M, Xu S, Zhang H, et al. Imbedding pancreaticojejunostomy used in pure laparoscopic pancreaticoduodenectomy for nondilated pancreatic duct. Surg Endosc 2017;31:1986-92.
24. Nakagawa N, Yamada S, Sonohara F, et al. Clinical Implications of Naples Prognostic Score in Patients with Resected Pancreatic Cancer. Ann Surg Oncol 2020;27:887-95.
25. Ahmad J, Grimes N, Farid S, et al. Inflammatory response related scoring systems in assessing the prognosis of patients with pancreatic ductal adenocarcinoma: a systematic review. Hepatobiliary Pancreat Dis Int 2014;13:474-81.
26. Roberts KJ, Sutcliffe RP, Marudanayagam R, et al. Scoring System to Predict Pancreatic Fistula After Pancreaticoduodenectomy. Ann Surg 2015;261:1191-7.
27. Pokharel N, Katwal G, Adhikari SK. Comparison of preoperative Nutritional Risk Index and Body Mass Index for predicting immediate postoperative outcomes following major gastrointestinal surgery: Cohort-study. Ann Med Surg (Lond) 2019;48:53-8.
28. Ko K, Park YH, Lee JW, et al. Influence of nutritional deficiency on prognosis of renal cell carcinoma (RCC).

BJU Int 2013;112:775-80.
29. Lee JY, Kim HI, Kim YN, et al. Clinical Significance of the Prognostic Nutritional Index for Predicting Short- and Long-Term Surgical Outcomes After Gastrectomy: A Retrospective Analysis of 7781 Gastric Cancer Patients. Medicine (Baltimore) 2016;95:e3539.
30. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436-44.
31. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539-45.
32. Bunt SK, Yang L, Sinha P, et al. Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. Cancer Res 2007;67:10019-26.
33. Sica A, Bronte V. Altered macrophage differentiation and immune dysfunction in tumor development. J Clin Invest 2007;117:1155-66.
34. Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res 2009;69:5383-91.
35. Liang W, Ferrara N. The Complex Role of Neutrophils in Tumor Angiogenesis and Metastasis. Cancer Immunol Res 2016;4:83-91.
36. Steidl C, Lee T, Shah SP, et al. Tumor-Associated Macrophages and Survival in Classic Hodgkin's Lymphoma. N Engl J Med 2010;362:875-85.
37. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 2013;109:416-21. Erratum in: Br J Cancer 2013;109:2026.
38. Nishijima TF, Muss HB, Shachar SS, et al. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev 2015;41:971-8.
39. Elahi MM, McMillan DC, McArdle CS, et al. Score Based on Hypoalbuminemia and Elevated C-Reactive Protein Predicts Survival in Patients With Advanced Gastrointestinal Cancer. Nutr Cancer 2004;48:171-3.
40. Aziz MH, Sideras K, Aziz NA, et al. The Systemic-immune-inflammation Index Independently Predicts Survival and Recurrence in Resectable Pancreatic Cancer and its Prognostic Value Depends on Bilirubin Levels. Ann Surg 2019;270:139-46.

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Supplementary

Table S1 Risk factors associated with postoperative complications after pancreaticoduodenectomy for ampullary carcinoma

Factors	Postoperative complications			Multivariate analysis		
	Yes (n=160)	No (n=244)	P	OR	95% CI	P
Age >65 years	31 (19.4)	40 (16.4)	0.441			
Sex (male)	87 (54.4)	141 (57.8)	0.499			
Co-morbidities	38 (23.8)	57 (23.4)	0.928			
Smoking history	39 (24.4)	36 (14.8)	0.015	2.500	1.401–4.464	0.002
Jaundice	110 (68.8)	144 (59.0)	0.048			
BMI>25 kg/m^2	24 (15.0)	24 (9.8)	0.117	1.892	1.001–3.577	0.049
ASA class III	12 (7.5)	27 (11.1)	0.235			
CA19-9 >37 U/mL	102 (63.7)	130 (53.3)	0.037			
CA125 >35 U/mL	20 (12.5)	24 (9.8)	0.401			
NPS (grade 2)	60 (37.5)	64 (26.2)	0.016	1.692	1.086–2.636	0.02
Preoperative biliary drainage	60 (37.5)	88 (36.1)	0.770			
Operative time >283 minutes	82 (51.2)	140 (57.4)	0.226			
Estimated blood loss >200 mL	100 (62.5)	173 (70.9)	0.078			
Transfusion	82 (51.2)	103 (42.2)	0.075			
Surgical procedure (LPD)	49 (30.6)	111 (45.5)	0.003	0.556	0.360–0.857	0.008
Vascular invasion	17 (10.6)	16 (6.6)	0.144			
TNM stage III	46 (28.7)	66 (27.0)	0.709			
Soft pancreas	91 (56.9)	140 (57.4)	0.921			
The main pancreatic duct<3 mm	32 (20.0)	51 (20.9)	0.826			
Tumor size >2 cm	61 (38.1)	90 (36.9)	0.801			

Variables were expressed as n (%). BMI, body mass index; ASA, American Socwiety of Anesthesiologists; CA19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; NPS, Naples prognostic score; LPD, laparoscopic pancreatoduodenectomy.

Table S2 Analysis of the predictive accuracy of the different score systems on overall survival and recurrence-free survival by the time-dependent ROC

Prognostic model	AUC (95% CI)				
	1-year	2-year	3-year	4-year	5-year
Overall survival					
NPS	0.688 (0.617–0.759)	0.739 (0.685–0.792)	0.730 (0.671–0.789)	0.718 (0.655–0.782)	0.673 (0.599–0.748)
CONUT	0.661 (0.589–0.736)	0.672 (0.612–0.731)	0.645 (0.581–0.708)	0.634 (0.565–0.702)	0.573 (0.492–0.653)
SIS	0.585 (0.516–0.654)	0.625 (0.570–0.680)	0.623 (0.563–0.682)	0.605 (0.539–0.671)	0.565 (0.487–0.643)
PNI	0.584 (0.506–0.663)	0.630 (0.569–0.691)	0.600 (0.535–0.665)	0.582 (0.513–0.650)	0.538 (0.461–0.615)
NRI	0.514 (0.438–0.590)	0.559 (0.499–0.610)	0.533 (0.471–0.596)	0.522 (0.455–0.589)	0.492 (0.416–0.568)
TNM stage	0.626 (0.555–0.697)	0.661 (0.602–0.719)	0.690 (0.632–0.749)	0.689 (0.627–0.752)	0.695 (0.625–0.765)
Recurrence-free survival					
NPS	0.705 (0.638–0.671)	0.722 (0.664–0.780)	0.702 (0.641–0.764)	0.660 (0.591–0.729)	0.638 (0.562–0.714)
CONUT	0.647 (0.577–0.717)	0.677 (0.617–0.738)	0.628 (0.562–0.693)	0.581 (0.508–0.654)	0.541 (0.458–0.623)
SIS	0.612 (0.547–0.677)	0.630 (0.573–0.688)	0.627 (0.566–0.687)	0.583 (0.513–0.652)	0.551 (0.471–0.632)
PNI	0.614 (0.538–0.690)	0.629 (0.563–0.695)	0.603 (0.538–0.669)	0.558 (0.487–0.629)	0.500 (0.421–0.578)
NRI	0.539 (0.469–0.609)	0.580 (0.519–0.641)	0.551 (0.488–0.615)	0.525 (0.455–0.594)	0.501 (0.422–0.579)
TNM stage	0.604 (0.535–0.673)	0.623 (0.562–0.684)	0.643 (0.616–0.671)	0.659 (0.593–0.724)	0.655 (0.580–0.729)

ROC, receiver operating characteristic; AUC, area under the curve; NPS, Naples prognostic score; SIS, systemic inflammation score; CONUT, controlling nutritional status; PNI, prognostic nutritional index; NRI, nutritional risk index.

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