Clinical implications of the Naples prognostic score in patients with resected pancreatic cancer

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Synopsis

We assessed the clinical impact of the Naples prognostic score (NPS) on short- and long-term outcomes in patients with resected pancreatic cancer. The NPS is a simple scoring system and an independent preoperative predictor of survival.

ABSTRACT

Background. Nutritional and immunological statuses are attracting increasing attention for their ability to predict surgical outcomes in various cancers. The Naples prognostic score (NPS) consists of the serum albumin level, total cholesterol level, neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) and could be useful for predicting survival.

Methods. We retrospectively analyzed 196 patients with pancreatic cancer who underwent curative R0/R1 resection with a surgery-first strategy between June 2003 and August 2016. The NPSs of the patients were calculated with preoperative data, and the patients were then divided into 3 groups based on their NPS. Clinicopathological characteristics, surgical outcomes, and long-term survival were compared, and a multivariate analysis of overall survival was conducted.

Results. Of a total of 196 patients, 22 were classified into Group 0 (NPS 0), 113 were classified into Group 1 (NPS 1 or 2), and 61 were classified into Group 2 (NPS 3 or 4). The median survival time was 103.4 months in Group 0, 33.3 months in Group 1 and 21.3 months in Group 2. Significant survival differences were observed among the 3 groups (Group 1 vs. 2, Group 0 vs. 2, P = 0.0380, P = 0.0022, respectively). In a

multivariate analysis, the NPS was identified as an independent prognostic factor (HR = 1.78; P = 0.0131); however, there were no significant differences in the incidence of postoperative morbidity among the NPS groups.

Conclusions. The NPS could be an easy scoring system and an independent preoperative predictor of survival.

INTRODUCTION

Pancreatic cancer is one of the most aggressive malignancies and is ranked as the fourth leading cause of cancer-related mortality worldwide.[1] The rates of morbidity and mortality after surgery are high, with a recurrence rate of 80% and a 5-year survival rate of 10 to 20%.[2-4] Therefore, it is important to identify a preoperative prognostic marker that could assist in identifying patients who would benefit from surgery. Histological prognostic factors, such as metastatic lymph node ratio, resection margins, portal vein invasion and tumor differentiation, have been demonstrated to predict survival in patients with pancreatic cancer.[5-8] However, these histological factors are available for assessment only after surgery.

It is now widely recognized that the outcomes of cancer patients are not merely dependent on tumor characteristics; several host-related factors play important roles as well.[9] Recently, nutritional and immunological status, which can be measured easily, were shown to affect the surgical prognosis in many types of cancer.[10,11] Pretreatment serum levels of inflammatory indicators, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), are

associated with prognosis.[12-14] Additionally, simple scoring systems, such as the prognostic nutritional index (PNI), the Glasgow prognostic score (GPS), and the controlling nutritional status (CONUT), that represent preoperative nutritional and immunological status are also widely used to predict outcomes.[15,16] The Naples prognostic score (NPS) is among these scoring systems and incorporates several nutritional and immunological markers including the serum albumin level, total cholesterol level, NLR, and LMR. It was first described by Gennaro et al.[17] as an independent prognostic factor in patients undergoing surgery for colorectal cancer. However, its role in the management of pancreatic cancer is unknown.

In the current study, we aimed to assess the correlation between the NPS and clinicopathological characteristics, postoperative complications, and prognosis in pancreatic cancer patients who underwent curative R0/R1 resection with a surgery-first strategy.

METHODS

Patients

We retrospectively assessed a total of 425 patients with resected pancreatic cancer between June 2003 and August 2016 at the Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine. Among the 425 patients, 173 patients did not have sufficient data and were excluded from the analysis. Additionally, 56 patients who underwent neoadjuvant therapy were excluded. Finally, 196 patients were analyzed in this study. Among the patients enrolled in this study, 191 had invasive ductal carcinomas, and 5 had acinar cell carcinomas. Extensive radical resections (D2) were performed in all patients. Gemcitabine and/or S-1, which is an oral 5-fluorouracil prodrug tegafur combined with oteracil and gimeracil, were administered as adjuvant chemotherapy to all patients unless contraindicated by the patient's condition or for other reasons. Gemcitabine (1000 mg/m^2) was administered weekly for 3 weeks, followed by 1 week of no treatment. Oral S-1 was administered for 4 weeks followed by 2 weeks of no treatment or for 2 weeks followed by 1 week of no treatment. Chemotherapy was initiated within 2 months of the operation in all the patients who were considered eligible

for the treatment. All patients were examined for recurrence using tumor markers and computed tomography every 3 or 6 months. Recurrent pancreatic cancer was treated in consideration of the condition or recurrence pattern of the patient. The ethics committee of the hospital approved this study, and informed consent was obtained from all patients for the subsequent use of their clinical data.

Data collection

The following preoperative data were routinely collected 2 or 3 days before surgery: body mass index, CA19-9 levels, serum albumin, total cholesterol, absolute neutrophil count, absolute lymphocyte count, and absolute monocyte count. The NPS was calculated based on serum albumin, total cholesterol, NLR, and LMR, as previously reported by Galizia, et al (Supplementary Figure 1).[17] Albumin concentrations < 4.0 mg/dl were scored as 1, and concentrations ≥ 4.0 mg/dl were scored as 0. Total cholesterol ≤ 180 mg/dl was scored as 1, and total cholesterol > 180 mg/dl was scored as 0. An NLR > 2.96 was scored as 1, and an NLR ≤ 2.96 was scored as 0. An LMR ≤ 4.44 was scored as 1, and an LMR > 4.44 was scored as 0. The NPS was defined as the sum of the

aforementioned scores. The patients were divided into 3 groups based on their NPS score: patients with a score of 0 were assigned to Group 0, patients with a score of 1 or 2 were assigned to Group 1, and patients with a score of 3 or 4 were assigned to Group 2. Pathological findings were assessed by the 7th edition of the General Rules for the Study of Pancreatic Cancer.[18]

Statistical analysis

Continuous data were compared by t tests, and categorical data were compared using a chi-square test. Survival was estimated with the Kaplan-Meier method, and survival estimates were compared by using log-rank tests. Overall survival and recurrence-free survival were calculated from the date of the surgery to the date of the event (death or recurrence of cancer, respectively). In cases without recurrence or death, patients were censored at the date of the last follow-up. A Cox proportional-hazard regression analysis was used for univariate and multivariate analysis. Variables with $P < 0.05$ in univariate analysis were included in the multivariate analysis. To evaluate the discriminatory ability of the prognostic scoring systems, receiver operating characteristics

(ROC) curves were generated, and differences among the areas under the curve (AUC) were compared. All statistical analyses were conducted using JMP version 13.0 software (SAS Institute, Cary, NC, USA). The threshold for significance was $P < 0.05$.

RESULTS

Patient characteristics

The baseline demographic characteristics of the 196 patients included in this study are summarized in Table 1. Of the 196 patients, the mean age at diagnosis was 64.2 ± 10.3 years, and the study included 126 male and 70 female subjects. The mean body mass index was 21.6 ± 3.17. Tumors were located in the pancreatic head in 147 patients and in the body and tail in 49 patients. We performed 138 pancreatic head resections, including 60 pancreaticoduodenectomies, 15 pylorus-preserving pancreaticoduodenectomies and 63 subtotal stomach-preserving pancreaticoduodenectomies. Moreover, we performed 45 distal pancreatectomies and 11 total pancreatectomies. The conclusive stages of the 196 patients according to the UICC classification were IA in 6 cases, IB in 2 cases, IIA in 57 cases, IIB in 108 cases, III in 2 cases, and IV in 21 cases. Among the 196 patients, 72 patients underwent adjuvant chemotherapy; 38 of the patients received S-1, 18 received gemcitabine, and 4 received gemcitabine and S-1. Out of all of the included patients, 22 patients were classified into Group 0 (NPS 0), 113 were classified into Group 1 (NPS 1 or 2), and 61 were classified into Group 2 (NPS 3 or 4) based on the Naples prognostic

scoring system.

Association between preoperative Naples prognostic score and clinicopathological characteristics

The associations between the NPS and clinicopathological characteristics were analyzed in Table 2. Regarding the preoperative clinical variables, the male patients (P = 0.0168) and patients with a pancreatic head tumor (P = 0.0022) had significantly higher NPS scores; however, there were no significant differences in age, body mass index, or CA19-9 levels among the three groups. On the other hand, a significantly higher NPS score was observed in the patients who had invasion into the serosa (P = 0.0121), invasion into the bile duct (P < 0.0001) or invasion into the duodenum (P < 0.0001) as a postoperative pathological factor. However, there was no difference in tumor size; invasion into the retroperitoneum, portal venous system, regional artery, nerve plexus, lymphatic system, venous system, or perineural space; lymph node metastasis; UICC stage; or residual tumor status among the 3 NPS groups. Arterial reconstructions were performed in patients with invasion into the right hepatic artery, common hepatic artery

or superior mesenteric artery.

Overall and recurrence-free survival based on Naples prognostic score

Overall and recurrence-free survival curves were statistically analyzed and are depicted in Figure 1. Regarding overall survival, the median overall survival time of each NPS group was 103.4 months in Group 0, 33.3 months in Group 1 and 21.3 months in Group 2. Statistically, there was a significant survival difference among the 3 groups (Group 0 vs. 1, Group 1 vs. 2, Group 0 vs. 2, P = 0.0653, P = 0.0380, P = 0.0022, respectively) (Figure 1A). Additionally, the median recurrence-free survival time of each NPS group was 40.2 months in Group 0, 12.9 months in Group 1 and 12.6 months in Group 2. Significant survival differences were observed between Group 0 and Group 1 and between Group 0 and Group 2 (P = 0.0408, P = 0.0258, respectively) (Figure 1B). Among patients without adjuvant chemotherapy, the median overall survival time was significantly different between Group 0 and Group 1 and between Group 1 and Group 2 (P = 0.0088, P = 0.0060, respectively) (Supplementary Figure 2). Among patients with adjuvant chemotherapy, the median overall survival time was also significantly different

between Group 0 and Group 1 and between Group 0 and Group 2 (P = 0.0363, P = 0.0457, respectively) (Supplementary Figure 3).

Univariate and multivariate analysis of prognostic factors in pancreatic cancer

Univariate analysis identified the following as significant prognostic factors for overall survival: tumor size, lymph node metastasis, peritoneal cytology, residual tumor status, adjuvant chemotherapy, the NPS, and histopathologically confirmed invasion into the bile duct, portal venous system, regional artery, nerve plexus, lymphatic system, venous system, or perineural space. In the multivariate analysis, invasion into the portal venous system (HR = 1.94, 95% CI = 1.23-3.08, P = 0.0046), lymph node metastasis (HR = 1.99, 95% CI = 1.18-3.53, P = 0.0096), peritoneal cytology (HR = 1.83, 95% CI = 1.06-3.05, P = 0.0305), adjuvant chemotherapy (HR = 2.71, 95% CI = 1.75-4.29, P < 0.0001) and NPS (HR = 1.82, 95% CI = 1.15-2.84, P = 0.0104) were identified as independent prognostic factors (Table 3).

Surgical outcomes

In total, 68 patients (34.7%) had grade III or higher postoperative complications, including pancreatic fistula (n = 39; 21.0%), intra-abdominal bleeding (n = 4; 2.0%), bile leakage (n = 4; 2.0%), delayed gastric emptying (n = 20; 10.2%), infectious complications (n = 20; 10.2%), and portal vein thrombosis (n = 5; 2.5%). None of the postoperative complications were significantly associated with the NPS groups (Table 4). In addition, estimated blood loss, operative time, and postoperative hospital stay were not significantly different among the NPS groups.

ROC curves of the inflammatory indicators

ROC curves were generated for the survival status at 2 years after surgery. The AUCs were 0.6379 (95% CI, 0.5431-0.7231) for the NPS, 0.5606 (95% CI, 0.4665-0.6506) for the CONUT, 0.5246 (95% CI, 0.4596-0.5888) for the mGPS, 0.5238 (95% CI, 0.4574-0.5893) for the prognostic index (PI) and 0.5852 (95% CI, 0.4883-0.6759) for the PNI. The NPS exhibited a significantly greater AUC value than the CONUT, mGPS and PI (P = 0.0421, P = 0.0320, P = 0.0330, respectively) (Supplementary Figure 4). No significant difference was observed between the NPS and the PNI (P = 0.2362).

DISCUSSION

In this study, we assessed the value of the NPS in patients with resected pancreatic cancer. We found that the NPS was strongly correlated with both overall and recurrence-free survival. However, the NPS did not affect surgical outcomes after pancreatectomy.

The immune system plays an important role in cancer as it can destroy cancer cells or establish a tumor microenvironment that facilitates cancer cell proliferation.[19] Inflammation-related prognostic scores utilizing blood count parameters, such as the NLR, LMR, and PLR, have gained increasing attention in relation to various malignancies, including pancreatic cancer.[12-14] However, a single marker can be influenced by the host's situation and could even be misleading when the cut-off value is arbitrarily decided. We previously reported the possible use of the GPS or CONUT score as a prognostic marker for pancreatic cancer,[20,21] but to date, few studies have evaluated the combination of these inflammatory markers.

The NPS includes the serum albumin level, total cholesterol level, NLR, and LMR. Serum albumin levels are used in many nutritional scoring systems. Some proinflammatory substances, such as cytokines, reduce the concentration of albumin,

which is why albumin levels can be used as a marker of systemic inflammation.[22] However, albumin levels change easily in hospitalized patients because of changes in body fluid levels. In addition, serum cholesterol levels have been reported to correlate with the progression of cancer.[23] Lymphocytes play a fundamental role in cell-mediated immunity by initiating a cytotoxic immune response and inhibiting cancer cell proliferation, invasion, and migration.[24] For example, lymphopenia has been associated with poor cancer survival in multiple studies.[25,26] Neutrophils are recruited by cancer cells via intercellular adhesion molecule-1, thereby enhancing cell arrest in the capillaries,[27] and neutrophils are known as key mediators in promoting tumor-related angiogenesis via circulating vascular endothelial growth factor.[28] Moreover, monocytes play an important role in tumor progression. Tumor-associated macrophages (TAMs), which are associated with peripheral blood monocytes, have been found to be correlated with poor survival in several malignancies.[29,30] The NPS includes all of the aforementioned prognostic biomarkers and reflects both nutritional status and inflammatory status. Therefore, the NPS is expected to be a more promising biomarker than the previously mentioned single parameters.

A prior study concerning the NPS in patients with colorectal cancer showed that patients with the worst NPS experienced postoperative complications more frequently.[17] However, the NPS did not affect the postoperative morbidity in the present study. One reason for this result was the difference in tumor locations among the NPS groups. The differences in tumor locations led to different operative procedures, including pancreatic head resection or distal pancreatectomy. Moreover, Probst et al showed that none of the nutritional assessment scores reflected malnutrition that was relevant to complications after pancreatic surgery.[31] As we previously reported,[21] the immune-nutritional status might be a relatively insignificant prognostic factor for postoperative complications in pancreatic cancer. Morbidity after pancreatectomy does not depend on nutritional status but depends on other factors such as the hardness of the pancreas, the influence of pancreatitis and the operative procedure.

The NPS reflects the nutritional and inflammatory status as well as the CONUT score or the GPS. We have previously reported the importance of the CONUT score and the GPS in pancreatic cancer,[20,21] and the NPS was better predictor of survival than these indices. These findings implied that nutritional status is associated with the long-term

outcome. In addition, patients with pancreatic cancer often have preoperative inflammatory diseases such as cholangitis and pancreatitis. In such a clinical setting, Aziz et al reported that preoperative biliary drainage for obstructive jaundice improved immune-nutritional status.[32] This finding suggested that early nutritional support and inflammation control might lead to better patient outcomes. In this regard, the NPS can be calculated easily with a blood test and could preoperatively detect patients with a poor prognosis. Even though adjuvant chemotherapy was also a strong prognostic factor, the NPS can predict survival after surgery regardless of the use of adjuvant chemotherapy.

Strijker et al reviewed clinical prediction models for survival after surgery for resectable pancreatic cancer.[33] Prediction models enable clinicians and patients to calculate the risks and to consider treatment options such as neoadjuvant therapy and adjuvant therapy. However, most prediction models for resectable pancreatic cancer have not been externally validated yet, including the NPS. External validation of our findings in other populations is essential, and further studies are required to select treatment options for patients with a poor prognosis.

Our study has certain limitations, including its retrospective nature, which is

inevitably associated with limited availability of laboratory values at various preoperative time points. Second, our study was a single-center study that included a small number of patients; therefore, a large-scale prospective validation study is required. Finally, we could not assess whether recurrent pancreatic cancer was treated via systemic chemotherapy, radiological therapy, surgical intervention, or best supportive care.

In conclusion, the NPS could be an easy scoring system and an independent preoperative predictor of survival in patients with resected pancreatic cancer. This finding emphasizes the importance of inflammatory biomarkers and the role of the immune system in pancreatic cancer. Further prospective evaluations of the NPS are needed to validate our findings.

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FIGURE LEGENDS

Figure 1.

A, Kaplan-Maier curves of overall survival for each NPS group. B, Kaplan-Maier curves of recurrence-free survival for each NPS group.

Supplementary Figure 1.

Calculation of the Naples prognostic score.

Supplementary Figure 2.

Kaplan-Maier curves of overall survival and recurrence-free survival in patients without adjuvant chemotherapy.

Supplementary Figure 3.

Kaplan-Maier curves of overall survival and recurrence-free survival in patients with adjuvant chemotherapy.

Supplementary Figure 4.

Receiver operating characteristic curves of the prognostic indicators.

TABLE 1. Patient Characteristics

Variables	
Age, mean ± SD (years)	64.2 ± 10.3
Sex	
Male	126 (64.3%)
Female	70 (35.7%)
Body mass index, mean ± SD	21.6 ± 3.17
Tumor location	
Head	147 (75.0%)
Body or tail	49 (25.0%)
Operative procedure	
PD	60 (30.6%)
PPPD	15 (7.7%)
SSPPD	63 (32.2%)
DP	45 (22.9%)
TP	11 (5.6%)
Others	2 (1.0%)
UICC stage	
IA	6 (3.1%)
IB	2 (1.0%)
IIA	57 (29.1%)
IIB	108 (55.1%)
III	2 (1.0%)
IV	21 (10.7%)
Adjuvant chemotherapy	72 (36.7%)
S-1	38 (19.4%)
GEM	18 (9.2%)
GS	4 (2.0%)
Others	12 (6.1%)
Naples prognostic score	
Group 0	22 (11.2%)
Group 1	113 (57.7%)

Group 2	61 (31.1%)

PD; Pancreaticoduodenectomy, PPPD; Pylorus-preserving pancreaticoduodenectomy, SSPPD; Subtotal stomach-preserving pancreaticoduodenectomy, DP; Distal pancreatectomy, TP; Total pancreatectomy, GEM; Gemcitabine, GS; Gemcitabine + S-1

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TABLE 2. Association of Naples Prognostic Score and Clinicopathological Characteristics in 196 Patients with Resected Pancreatic Cancer

Variables	Group 0 (n = 22)	Group 1 (n = 113)	Group 2 (n = 61)	P value
Age, years	61.1 ± 9.8	64.6 ± 10.1	64.6 ± 10.7	0.3281
Sex				0.0168*
Male	8 (36.4)	75 (67.6)	41 (67.2)	
Female	14 (63.6)	36 (32.4)	20 (32.8)	
Body mass index	20.4 ± 0.96	21.5 ± 0.41	20.7 ± 0.63	0.4034
Tumor Location				0.0022*
Head	13 (59.1)	77 (69.4)	55 (90.2)	
Body or tail	9 (40.9)	34 (30.6)	6 (9.8)	
CA19-9				0.1302
≤ 37 IU/ml	10 (45.5)	29 (25.7)	46 (75.4)	
> 37 IU/ml	12 (54.5)	84 (74.3)	15 (24.6)	
Tumor Size				0.6825
≤ 20 mm	7 (31.8)	31 (27.4)	14 (22.9)	
> 20 mm	15 (68.2)	82 (72.6)	47 (77.1)	
Serosa invasion				0.0121*
(+)	13 (59.1)	90 (79.7)	54 (88.5)	
(-)	9 (40.9)	23 (20.3)	7 (11.5)	
Retroperitoneum invasion				0.0608
(+)	19 (86.4)	99 (87.6)	45 (73.8)	
(-)	3 (13.6)	14 (12.4)	16 (26.2)	
Bile duct invasion				<.0001*
(+)	7 (31.8)	46 (40.7)	44 (72.1)	
(-)	15 (68.2)	67 (59.3)	17 (27.9)	
Duodenum invasion				<.0001*
(+)	6 (27.3)	36 (31.9)	40 (65.6)	
(-)	16 (72.7)	77 (68.1)	21 (34.4)	
Portal venous system invasion				0.3431
(+)	8 (36.4)	46 (40.7)	18 (29.5)	
(-)	14 (63.6)	67 (59.3)	43 (70.5)	
Regional artery invasion				0.7926
(+)	2 (9.1)	13 (11.5)	5 (8.3)	
(-)	20 (90.1)	100 (88.5)	55 (91.7)	

Nerve plexus invasion				0.6995
(+)	3 (13.6)	20 (17.7)	13 (21.3)	
(-)	19 (86.4)	93 (82.3)	48 (78.7)	
Lymphatic invasion				0.7959
(+)	19 (90.5)	90 (84.9)	44 (86.3)	
(-)	2 (9.5)	16 (15.1)	7 (13.7)	
Venous invasion				0.9006
(+)	12 (57.1)	64 (60.4)	29 (56.9)	
(-)	9 (42.9)	42 (39.6)	22 (43.1)	
Perineural invasion				0.1349
(+)	17 (80.9)	88 (83.0)	48 (94.1)	
(-)	4 (19.1)	18 (17.0)	3 (5.9)	
Lymph node metastasis				0.099
(+)	11 (50.0)	79 (71.2)	45 (73.8)	
(-)	11 (50.0)	32 (28.8)	16 (26.2)	
Peritoneal cytology				0.3743
(+)	3 (13.6)	17 (15.0)	14 (22.9)	
(-)	19 (86.4)	96 (85.0)	47 (77.1)	
UICC stage				0.8913
I or II	20 (90.9)	99 (87.6)	54 (88.5)	
III or IV	2 (9.1)	14 (12.4)	7 (11.5)	
Residual tumor				0.0989
R1	2 (9.1)	30 (27.3)	20 (32.8)	
R0	20 (90.9)	80 (72.7)	41 (67.2)	
Adjuvant chemotherapy	8 (36.3)	30 (26.5)	18 (29.5)	0.6353

CA19-9; Carbohydrate antigen 19-9, *; Statistically significant

TABLE 3. Univariate and Multivariate Cox Proportional-hazard Regression Analysis of Overall Survival of Patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥ 70 years vs. < 70 years)	1.21 (0.79-1.83)	0.3667		
Sex (male vs. female)	0.78 (0.52-1.16)	0.2166		
Tumor location (head vs. body or tail)	1.23 (0.80-1.95)	0.3552		
Tumor size (≤ 20 mm vs. > 20 mm)	0.48 (1.31-3.52)	0.0014	1.12 (0.66-1.96)	0.6795
Serosa invasion (+ vs. -)	1.13 (0.72-1.83)	0.5969		
Retroperitoneum invasion (+ vs. -)	0.91 (0.57-1.52)	0.7024		
Bile duct invasion (+ vs. -)	1.55 (1.05-2.30)	0.0261	1.03 (0.65-1.64)	0.9076
Duodenum invasion (+ vs. -)	1.41 (0.95-2.07)	0.0891		
Portal venous system invasion (+ vs. -)	2.24 (1.52-3.31)	<.0001	1.94 (1.23-3.08)	0.0046*
Regional artery invasion (+ vs. -)	1.97 (1.05-3.41)	0.0359	0.78 (0.39-1.46)	0.4504
Nerve plexus invasion (+ vs. -)	2.04 (1.26-3.20)	0.0047	1.26 (0.70-2.20)	0.4335
Lymphatic invasion (+ vs. -)	3.39 (1.68-8.09)	0.0002	1.75 (0.77-4.55)	0.1883
Venous invasion (+ vs. -)	1.86 (1.25-2.84)	0.0023	0.96 (0.60-1.57)	0.8820
Perineural invasion (+ vs. -)	3.64 (1.73-9.36)	0.0002	1.58 (0.67-4.37)	0.3112
Lymph node metastasis (+ vs. -)	2.71 (1.68-4.60)	<.0001	1.99 (1.18-3.53)	0.0096*
Peritoneal cytology (+ vs. -)	1.93 (1.15-3.09)	0.0146	1.83 (1.06-3.05)	0.0305*
UICC stage (III or IV vs. I or II)	2.75 (1.61-4.46)	0.0004	1.39 (0.76-2.44)	0.2786
Residual tumor (R1 vs. R0)	2.14 (1.37-3.26)	0.0011	1.55 (0.93-2.53)	0.0942
CA19-9 (≥ 37 IU/ml vs. < 37 IU/ml)	1.37 (0.88-2.19)	0.1690		

Adjuvant chemotherapy (- vs. +)	2.66 (1.75-4.16)	<.0001	2.71 (1.75-4.29)	<.0001*
NPS (Grade 2 vs. Grade 0/1)	1.73 (1.14-2.59)	0.0109	1.82 (1.15-2.84)	0.0104*

CA19-9; Carbohydrate antigen 19-9; NPS; Naples prognostic score, *; Statistically significant

TABLE 4. Association of Naples Prognostic Score and Surgical Outcome

	Grade 0 (n = 22)	Grade 1 (n = 113)	Grade 2 (n = 61)	P value
Operative time (min)	384.7 ± 28.9	423.8 ± 12.9	457.9 ± 17.4	0.0755
Estimated blood loss (ml)	822.4 ± 200.1	1009.4 ± 89.1	1159.9 ± 120.2	0.3201
Postoperative complications (CD ≥ III)	8 (38.1)	43 (40.6)	17 (33.3)	0.6828
ISGPF grade ≥ B	6 (28.6)	25 (23.6)	8 (15.7)	0.5167
Bile leakage	0 (0)	1 (0.9)	3 (5.8)	0.1124
Intra-abdominal bleeding	0 (0)	3 (2.8)	1 (1.9)	0.7168
Delayed gastric emptying	1 (4.8)	12 (11.3)	7 (13.7)	0.5488
Infectious complications	1 (4.8)	11 (10.4)	8 (15.7)	0.3728
Portal vein thrombosis	1 (4.8)	3 (2.8)	1 (1.9)	0.8074
Postoperative hospital stay (day)	34.8 ± 5.5	37.8 ± 2.5	37.4 ± 3.5	0.8806

CD; Clavien-Dindo grade, ISGPF; International Study Group for Pancreatic Fistula