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Significance of the inflammation-based prognostic score in recurrent pancreatic cancer

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ABSTRACT

Background: Although the prognosis of recurrent pancreatic cancer (RPC) is improving with the appearance of new anticancer drugs, prognostic indicators for RPC are still poorly understood. The aim of this study was to evaluate significance of the inflammation-based prognostic score, including modified Glasgow Prognostic Score (mGPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and Prognostic Nutritional Index (PNI), in patients with RPC.
Methods: This study reviewed 263 patients of pancreatic ductal adenocarcinoma at our institution between 2006 and 2015. A receiver operating characteristics curve analysis was performed to determine the cut-off values. The prognostic significance of the inflammation-based prognostic scores were evaluated by a multivariate analysis.
Results: 172 patients (65.4%) who had recurrence was included in this study. The optimal PNI for predicting 1-year survival after recurrence was 40 with higher area under receiver operating characteristics curve value (0.704) in comparison with other inflammation-based prognostic scores. A univariate and multivariate analysis revealed that liver metastasis ($P < 0.001$) and PNI < 40 ($P < 0.001$) were independently associated with the survival time after recurrence. When each of the two predictors was counted as one point and the points were calculated for all cases, a good stratified survival curve was obtained, showing the shorter survival in the higher points: median survival times of 2, 1, and 0 points were 4.3, 11.1, and 21.2 months, respectively ($P < 0.001$).
Conclusions: Inflammation-based prognostic scores, especially PNI is useful clinical biomarker for predicting the survival time after recurrence in patients with pancreatic adenocarcinoma.

Introduction

Although survival of pancreatic ductal adenocarcinoma (PDAC) has been prolonged with the progress of multidisciplinary treatment [1], an appreciable proportion of patients develop recurrence even after curative treatment. Recently, the prognosis of unresectable or recurrent pancreatic cancer (RPC) is improving with the appearance of novel anti-cancer drugs such as fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) [2], and nanoalbumin-paclitaxel (nab-PTX) [3]. In management of recurrent patients, predicting the life expectancy and planning the optimal treatment strategy are thought to lead to an improvement in the patient's prognosis. To date, there is no well validated and widely accepted prognostic model in daily clinical practice for RPC.

It is well known that systemic inflammatory response plays an important role in cancer progression [4]. With the recognition of the prognostic importance of the systemic inflammatory response in cancer, a variety of inflammation-based prognostic scores have been developed [5–9]. As inflammation-based prognostic scores, modified Glasgow Prognostic Score (mGPS) consisted of albumin value and C-reaction protein [5], neutrophil-to-lymphocyte ratio (NLR) [7], platelet-to-lymphocyte ratio (PLR) [9], lymphocyte-to-

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monocyte ratio (LMR) [8], and prognostic nutrition index (PNI) consisted of lymphocyte count and albumin value [6] have been reported for survival predictors of various cancers. In primary PDAC, these markers were also identified as the independent predictors of the postoperative prognosis [5,6,10,11]. However, no reports have investigated the role of the inflammation-based prognostic scores in patients with RPC, and its usefulness was still unknown.

The object of this study was to systematically evaluate significance of representative inflammation-based prognostic scores including mGPS, NLR, PLR, LMR, and PNI in patients with RPC.

Patients and methods

Patients

Between January 2006 to December 2015, a total of 286 consecutive patients were histopathologically diagnosed as PDAC and underwent pancreatectomy in Nara Medical University Hospital. Among them, 16 patients of para-aortic lymph node metastasis, 5 patients of R2 resection, and 2 patients who died in a short period postoperatively due to perioperative morbidity were excluded. As a result, remaining 263 patients were reviewed retrospectively and analyzed. Of the 263 patients, 175 patients (66.5%) had recurrence in the follow-up period. Since hematologic data at the recurrence time were not available in 3 cases, 172 patients were finally enrolled as RPC in this study. This study was approved by the Local Ethics Committee on Clinical Investigation of Nara Medical University. Written informed consent was obtained from all of the patients.

The following clinicopathological characteristics were obtained retrospectively from the patients' medical records: age, sex, location of primary tumor, resectability status at initial diagnosis, histologic differentiation, tumor depth, nodal involvement, tumor stage, pre- and postoperative treatment, perioperative blood transfusion, pattern of recurrence. Tumors were classified according to the TNM staging system of the Union for International Cancer Control version 7th. Resectability status was defined according to the National Comprehensive Cancer Network Guidelines Version 2. 2016. An R0 resection was designated as surgical margins free of microscopic or macroscopic tumor involvement.

We also collected the results of blood tests performed at the time of pretreatment and recurrence, including the serum levels of albumin, C-reactive protein, carbohydrate antigen (CA) 19-9, and neutrophil, lymphocyte, monocyte, and platelet counts in the peripheral blood. The mGPS was determined on the basis of previous study [5]. The NLR was calculated as the neutrophil count divided by the lymphocyte count. The PLR was calculated as platelet count divided by lymphocyte count. The LMR was calculated as lymphocyte count divided by monocyte count. The PNI was calculated using the following formula: 10 × serum albumin value (g/dL) + 0.005 × total lymphocyte counts in the peripheral blood (/mm^3). The predictive values of the inflammation-based prognostic scores at recurrence were evaluated by receiver operating characteristic (ROC) analysis. The accuracy of predicting prognosis was assessed by calculating the area under the curve (AUC). The cut-off values of CA19-9 at recurrence was determined of below 37 U/ml as normal range.

Perioperative management and oncologic follow-up

Neoadjuvant chemoradiotherapy (NACRT) and adjuvant chemotherapy protocols in our institute have been previously described [12,13]. Since September 2008, all patients have been subjected to NACRT to achieve local control and a complete cure. In brief, the NACRT regimen consists of gemcitabine (GEM) and concomitant radiation of 54 Gy. Systemic GEM at 1000 mg/m^2 administered weekly. Surgery was performed within three to five weeks after the completion of NACRT. Surgery involved subtotal stomach-preserving pancreatoduodenectomy (SSPPD), distal pancreatectomy (DP) with or without celiac axis resection, and total pancreatectomy (TP). Regional lymph node dissection was performed in most patients.

As postoperative adjuvant therapy, patients received combination therapy of weekly hepatic arterial infusion of high-dose 5-fluorouracil and systemic infusion of GEM as previously described [13]. Some patients received adjuvant chemotherapy with GEM or S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) alone based on the patient's condition or choice. Adjuvant chemotherapy was deemed completed when the planned number or cycles of chemotherapy had been reached: WHF/GEM, 9 infusions of WHF and 18 administrations of GEM; GEM, 18 administrations of GEM; S-1, 16 weeks of oral administration.

The patients were followed-up every 3 months for up to 2 years after initial operation by CT or MRI with blood examination. Follow up was performed at least every 3–4 months between 3 and 5 years after, and then every 6 months thereafter. The recurrence of PDAC was defined as diagnosis by imaging studies (CT, MRI, and so on), regardless of laboratory examination. The pattern of recurrence was classified as liver, lung, local, peritoneum, and lymph node, according to the site of recurrence.

Statistical analysis

The final follow-up date was December 31, 2017. Overall survival was defined as the period from initial treatment to cause-specific

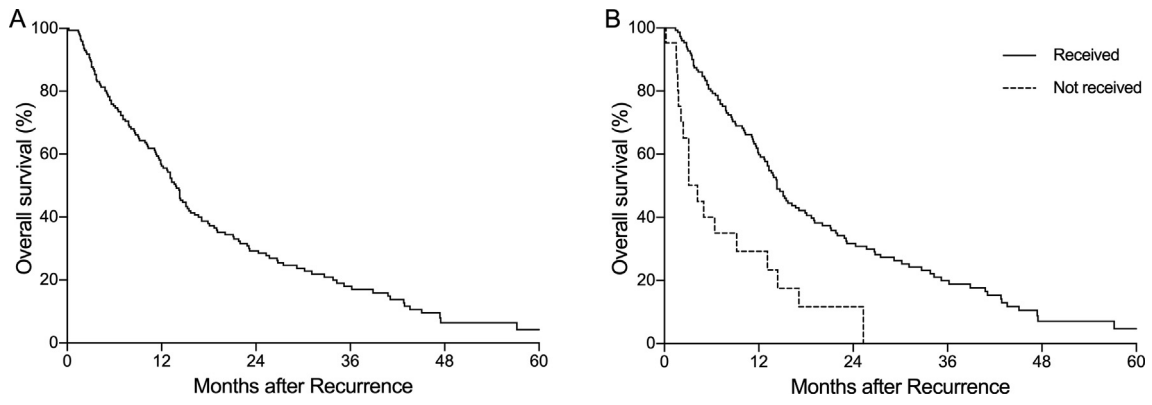

Fig. 1. Kaplan-Meier estimates of the post-recurrence survival. (A) All patient (B) Survival curves according to the presence of chemotherapy for recurrence.

death or censored until the date of last follow-up. Recurrence-free survival was calculated from the time of surgery to the first detection of recurrence. Post-recurrence survival was defined as the interval from documented recurrence to time of death or last follow-up. Kaplan–Meier survival calculations and the corresponding log-rank tests were carried out to determine differences in survival rates. Categorical variables were presented as number and percentage, and groups were compered using χ-squared test or Fisher's exact test. Continuous variables were expressed as median, and were compered using Mann-Whitney *U* test. The univariate and multivariate hazard ratios (HRs) were calculated using a Cox proportional hazard model. A P value < 0.05 was considered statistically significant. All statistical analysis was performed by using JMP software ver. 13.2 (SAS Institute Inc. Cary, NC, USA).

Results

Patient characteristics

The median overall survival of all 263 patients was 41.2 months (4.1–138.5), and the median recurrence-free survival was 22.0 months (1.1–120.2). Thirty-three patients (12.5%) recurred within 12 months after the initial treatment.

The sites of recurrence were as follows: liver, $n = 51$ (29.7%); lung, $n = 48$ (27.9%); local, $n = 48$ (27.9%); peritoneum, $n = 38$ (22.1%); lymph nodes, $n = 22$ (12.8%); and bone, $n = 1$ (0.6%). Thirty-three patients (19.2%) had at least two concurrent sites of the recurrence.

After the diagnosis of recurrence, a total of 151 patients (87.8%) received systemic chemotherapy. The first line chemotherapy

Table 1
Clinicopathological characteristics at recurrence and median survival time after recurrence.

Variables		*n*	MST (months)	*p*
Age, years	≥ 70	85 (49)	13.8	0.923
	< 70	87 (51)	14.2	
Sex	Male	102 (59)	12.0	0.279
	Female	70 (41)	15.1	
Location of primary tumor	Ph	106 (62)	13.9	0.999
	Pb/ Pt	66 (38)	13.6	
Resectability of primary tumor	Resectable	118 (69)	15.1	0.013
	BR/ UR-LA	54 (31)	11.1	
Neoadjuvant therapy	Received	98 (57)	14.4	0.778
	Not received	74 (43)	13.1	
Adjuvant chemotherapy	Completed	97 (56)	21.8	<0.001
	Incompleted	75 (44)	8.5	
Perioperative blood transfusion	Performed	48 (28)	10.3	0.013
	Not performed	124 (72)	14.7	
Histologic differentiation	Differentiated	149 (87)	14.3	0.083
	Undifferentiated	23 (13)	13.3	
Tumor depth of primary tumor	T1-2	19 (11)	21.2	0.115
	T3-4	153 (89)	12.1	
Nodal involvement of primary tumor	N0	102 (59)	14.3	0.255
	N1	70 (41)	12.2	
Resection status	R0	145 (84)	13.9	0.764
	R1	27 (16)	13.1	
CA19-9[a], U/mL	≥ 37	109 (55)	10.3	<0.001
	< 37	60 (44)	24.3	
Duration from surgery to recurrence, months	≥ 12	107 (62)	16.2	<0.001
	< 12	65 (38)	10.2	
mGPS	0–1	157 (91)	14.3	<0.001
	2	15 (9)	3.1	
NLR	≥ 3.0	60 (35.9)	6.8	0.002
	< 3.0	112 (65.1)	15.5	
PLR	≥ 121	51 (29.7)	11.9	0.008
	< 121	121 (70.3)	18.1	
LMR	≥ 3.25	61 (35.5)	17.1	0.035
	< 3.25	111 (64.5)	11.4	
PNI	≥ 40	125 (73)	16.2	<0.001
	< 40	47 (27)	6.1	
Liver metastasis	Present	51 (30)	7.8	<0.001
	Absent	121 (70)	15.5	
Lung metastasis	Present	48 (28)	25.3	<0.001
	Absent	124 (72)	12.0	
Local recurrence	Present	48 (28)	13.3	0.852
	Absent	124 (72)	14.3	
Peritoneal metastasis	Present	38 (22)	5.4	0.007
	Absent	134 (78)	14.3	
Lymph node metastasis	Present	22 (13)	13.1	0.989
	Absent	150 (87)	13.9	
Multiple organ metastasis	Present	33 (19)	6.5	0.010
	Absent	139 (81)	14.3	
Chemotherapy for recurrence	Received	151 (88)	14.3	<0.001
	Not received	21 (12)	4.2	

MST: median survival time, Ph: pancreas head, Pb: pancreas body, Pt: pancreas tail, BR: borderline resectable, UR-LA: unresectable locally advanced, CA19-9: carbohydrate antigen 19-9, mGPS: modified Glasgow Prognostic Score, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio.
LMR: lymphocyte-to-monocyte ratio, PNI: prognostic nutrition index.
[a] Data not available for three patients. Values in parentheses are percentages.

regimens included S-1 monotherapy ($n = 58$, median post-recurrence survival time 21.2 months), a combination of GEM and S-1 ($n = 39$, 13.9 months), a combination of GEM and nab-PTX ($n = 22$, 13.3 months) and the others ($n = 32$, 10.1 months). There were no statistical differences in survival between first-line chemotherapy regimens ($P = 0.056$). Two cases of local recurrence and 12 cases of lung metastasis underwent resection of recurrence sites. Twenty-four patients were not subjected to treatment by poor general condition or patient choice, and best supportive care was provided to them.

Post-recurrence survival and prognostic significance of the inflammation based prognostic score

At the final follow-up, 140 (81.4%) patients had died, and 32 (18.6%) remained alive. Among them, 137 (97.9%) patients were cause-specific death, and remaining 3 patients died of pneumonia. Overall, the median post-recurrence survival was 13.8 months (0.2–81.3), and the 1-, 2- and 3-year post-recurrence survival rates were 56.2, 29.3 and 18.0%, respectively (Fig. 1A). In addition, there were significant difference in survival curves of chemotherapy-received group and non-received group (Fig. 1B, $P < 0.001$).

In the present study, the cut-off value of NLR, PLR, LMR, and PNI at recurrence were determined by ROC curve based on prognostic outcomes of 1-year after recurrence set with reference to the median survival time after recurrence in this cohort, and were defined as 3.0, 121, 3.25, and 40, respectively. Although there were no significant differences in each ROC curves (P = 0.248), the AUC of NLR, PLR, LMR, and PNI were 0.610, 0.645, 0.639, and 0.704, respectively. As a result, the AUC of the PNI at recurrence was higher than the other inflammation-based prognostic scores (with a sensitivity of 86.7%, a specificity of 45.2%, AUC = 0.704).

The associations between the clinicopathological characteristics and the survival time after recurrence are also shown in Table 1. The patients with higher mGPS, NLR and PLR group had a significantly shorter survival time than those with lower group. The survival time was significantly shorter in the patients with a lower LMR and PNI than in those with higher group. According to the survival analysis, other factors including borderline or unresectable at initial diagnosis, incompletion of adjuvant chemotherapy, perioperative blood transfusion, higher CA19-9 level, recurrence including liver metastasis, recurrence including peritoneal metastasis, multiple organ metastasis, and no chemotherapy for recurrence, were also associated with a shorter survival time after recurrence.

To evaluate the significance of the inflammation-based prognostic scores for RPC, we performed univariate and multivariate Cox regression analyses using a model including mGPS and PNI at recurrence and recurrence pattern. Among various clinicopathological factors, incompletion of adjuvant chemotherapy, perioperative blood transfusion, higher CA19-9 level, higher mGPS level, lower PNI level, liver metastasis, peritoneal metastasis, and no chemotherapy for recurrence were significant prognostic factor. When adjusted for these factors in multivariate analysis, incompletion of adjuvant chemotherapy, higher CA19-9 level, lower PNI, liver metastasis, and no chemotherapy for recurrence were the independent prognostic factor associated with the post-recurrence survival (Table 2).

Prediction model using the inflammation based prognostic score

When each of the two predictors, lower PNI level at recurrence and liver metastasis, was counted as one point and the points were calculated for all 172 cases, a good stratified survival curve was obtained, showing the shorter survival in the higher points: median survival times of 2, 1, and 0 points were 4.3, 11.1, and 21.2 months, respectively (Fig. 2A, $P < 0.001$). Furthermore, the similarly stratified curves were shown both in the subgroup who underwent the chemotherapy (Fig. 2B, $P < 0.001$) and the group who did not undergo the chemotherapy for recurrence (Fig. 2C, $P = 0.002$).

Relationship between PNI and clinicopathological factors

Next, to explore the relationship between PNI at recurrence and clinicopathological characteristics, we compered the higher PNI (≥40) group and the lower PNI (<40) group (Table 3). While pretreatment lymphocyte count and albumin value were equivalent among the groups, there was a significant decrease of each parameters in the lower PNI group at recurrence. There was no

Table 2
Univariate and multivariate analysis of the survival time after recurrence.

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age at recurrence, years, ≥ 70	1.017 (0.727-1.423)	0.923		
Gender, Male	1.206 (0.859-1.704)	0.279		
Location of primary tumor, Ph	0.999 (0.710–1.419	0.998		
Resectability, Borderline or Unresectable-locally advanced	1.568 (1.086-2.233)	0.017	1.403 (0.955-2.098)	0.085
Neoadjuvant therapy, Not received	0.952 (0.678-1.343)	0.779		
Adjuvant chemotherapy, incompleted	3.133 (2.193-4.492)	<0.001	1.960 (1.252-3.073)	0.003
Perioperative blood transfusion, Performed	1.571 (1.087-2.237)	0.017	0.956 (0.624-1.433)	0.544
Histologic differentiation, Undifferentiated	1.496 (0.921-2.321)	0.100		
Tumor depth of primary tumor, T3-4	1.578 (0.926-2.939)	0.097		
Nodal involvement of primary tumor, N1	1.217 (0.863-1.706)	0.259		
Resection status, R1	0.931 (0.565-1.457)	0.763		
Duration from surgery to recurrence, months, < 12	1.966 (1.410-2.815)	<0.001		
Liver metastasis, Present	2.359 (1.614-3.417)	<0.001	2.225 (1.428-3.459)	<0.001
Lung metastasis, Present	0.485 (0.319-0.717)	<0.001	0.890 (0.560-1.383)	0.610
Local recurrence, Present	0.964 (0.649-1.399)	0.852		
Peritoneal metastasis, Present	1.693 (1.136-2.463)	0.011	1.308 (0.806-2.082)	0.272
Lymph node metastasis, Present	0.997 (0.587-1.594)	0.989		
CA19-9 at recurrence, U/ml, > 37	2.361 (1.631-3.489)	<0.001	1.848 (1.222-2.842)	0.003
mGPS at recurrence, 2	2.905 (1.622-4.834)	<0.001	1.075 (0.543-2.036)	0.828
PNI at recurrence, < 40	2.621 (1.793-3.777)	<0.001	2.019 (1.348-3.239)	<0.001
Chemotherapy for recurrence, Not received	2.954 (1.723-4.781)	<0.001	3.085 (1.679-5.366)	<0.001

CI: confidence interval, *Ph*: pancreas head, *BR*: borderline resectable, *UR-LA*: unresectable locally advanced, *CA19-9*: carbohydrate antigen 19-9, *mGPS*: modified Glasgow Prognostic Score, *PNI*: prognostic nutrition index.

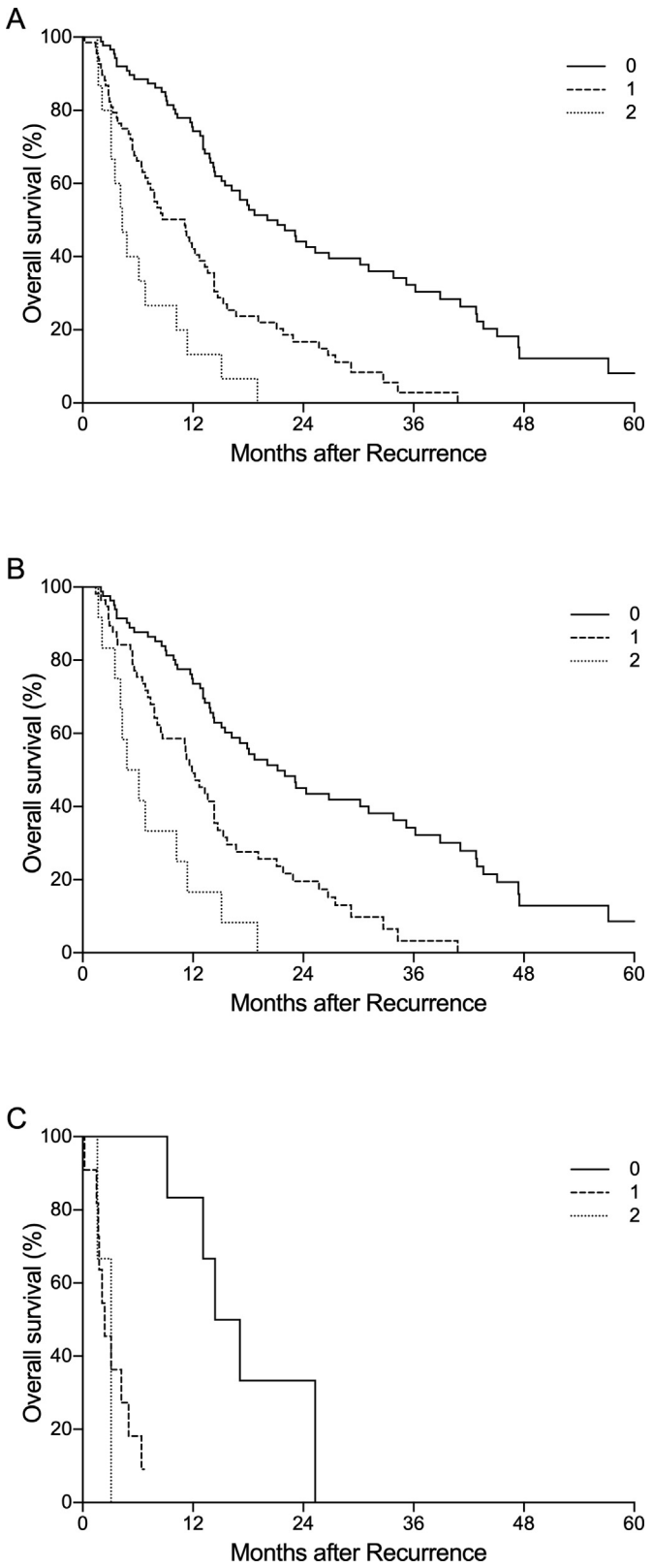

Fig. 2. A combined analysis of the PNI and liver metastasis. 0: The subgroup of non-liver metastasis together with PNI ≥40, 1: The subgroup of either liver metastasis or PNI <40, 2: The subgroup of both liver metastasis and PNI <40. (A) All patients. The PNI ≥40 together with non-liver metastasis is associated with a probability of the longest survival time. (B) The subgroup who underwent the chemotherapy for recurrence. (C) The subgroup who did not undergo the chemotherapy for recurrence.

significant association between the status of the PNI and CA19-9 at recurrence. Although the proportion of pancreas head cancer at initial diagnosis was significantly higher in lower PNI group, there were no significant differences in the other tumor related factors including CA19-9 value at recurrence and pattern of recurrence. The proportion of patients who underwent neoadjuvant therapy was significantly higher in the lower PNI group, and the completion rate of adjuvant chemotherapy was significantly higher in the higher PNI group. Moreover, the implementation rate of chemotherapy for recurrence was significantly lower in the lower PNI group.

Discussion

Previously, there were several reports of prognostic factors for initial unresectable and metastatic pancreatic cancer [14,15]. However, prognostic factors of RPC after multidisciplinary treatment are still poorly understood. Previous studies showed that the systemic inflammatory response could influence the surgical complications and outcome of chemotherapy in pancreatic cancer [6,10,11,16]. There were several reports on impact of various inflammation-based prognostic scores as the prognostic factor for pre- and postoperative resectable PDAC [17,18]. To our knowledge, the present study represents the first analysis to evaluate the impact of various indicators based on the systemic inflammatory factors for RPC after multidisciplinary treatment. Our study revealed that treatment history for primary tumor, pattern of recurrence, treatment for recurrence and the inflammation-based prognostic scores were important prognostic factors of RPC.

As predicted, the post-recurrence survival time was better for patients with PNI ≥40 than for patients with PNI <40. Our study also demonstrated that CA19-9 at the time of recurrence and liver metastasis were associated with poor prognosis after recurrence according to multivariate analysis. Previous studies reported the importance of CA19-9 and the pattern of recurrence in RPC [19,20]. However, approximately 5–10% of the general population is Lewis antigen A and B-negative, which means that they do not synthesize the CA19-9 antigen and will not have elevated levels, even with PDAC. There was no significant association between PNI and CA19-9 or recurrence patterns in our study, suggesting that PNI was tumor-independent prognostic factors. Moreover, the subgroup of non-liver metastasis together with PNI ≥40 at the time of recurrence were associated with a probability of better prognosis. Although chemotherapy for recurrence has the highest hazard ratio in multivariate analysis, the presence of liver metastasis and PNI at recurrence have the advantage that the prognosis can be predicted before starting the treatment of recurrence. Therefore, we chose these factors in order to predict prognosis at the recurrence and for decision-making of treatment strategy. Data suggested that the prognosis after recurrence may be dependent on tumor-related as well as patient-related factors. Therefore, therapeutic strategies for both factors are needed for improving the prognosis after recurrence.

In this study, the PNI had the highest prognostic accuracy among various inflammation-based prognostic scores, and that was an independent prognostic factor in RPC. The PNI is considered to be an indicator not only for systemic inflammation, but also the patient's nutritional status. Although the underlying mechanisms for the prognostic significance of PNI in RPC remain unclear, one possible explanation is that systemic inflammation response may reflect tumor burden and aggressive behavior. Low PNI implies a combination of lymphocytopenia and hypoalbuminaemia. It is known that systemic inflammation, some cytokines and other chemical messengers promote cancer cell proliferation, tumor angiogenesis and metastasis [4,21,22]. Among them, lymphocytes

Table 3
Relationship between PNI and clinicopathological characteristics at recurrence.

Variables		PNI ≥40	PNI <40	*p*
Age, years	Median, range	70 (34-88)	70 (47-82)	0.868
Sex	Male	76 (61)	26 (55)	0.514
Pretreatment lymphocyte[a],/mm^3	Median, range	1209 (118-3596)	1000 (342-4582)	0.132
Pretreatment albumin[a], g/dL	Median, range	3.9 (2.7-4.8)	3.8 (2.7-5.1)	0.234
Lymphocyte at recurrence,/mm^3	Median, range	1400 (500-3784)	700 (264-2500)	<0.001
Albumin at recurrence, g/dL	Median, range	4.1 (3.0-5.1)	3.0 (1.8-3.7)	<0.001
Location of primary tumor	Ph	68 (54)	38 (81)	0.002
Resectability of primary tumor	Resectable	85 (68)	33 (70)	0.781
Neoadjuvant therapy	Received	79 (63)	19 (40)	0.007
Adjuvant chemotherapy	Completed	81 (65)	16 (34)	<0.001
Perioperative blood transfusion	Performed	34 (27)	14 (30)	0.736
Histologic differentiation	Differentiated	106 (85)	43 (91)	0.251
Tumor depth of primary tumor	T3-4	111 (89)	42 (89)	0.917
Nodal involvement	N0	77 (62)	25 (53)	0.317
Resection status	R0	106 (85)	39 (83)	0.769
Metastasis	Liver	36 (29)	15 (32)	0.690
	Lung	38 (30)	10 (21)	0.235
	Local	33 (26)	15 (32)	0.472
	Peritoneum	23 (18)	15 (32)	0.057
	Lymph node	12 (10)	10 (21)	0.096
Multiple organ metastasis	Present	24 (19)	9 (19)	0.994
CA19−9, U/mL	Median, range	62 (1-4264)	108 (1-11668)	0.142
Chemotherapy for recurrence	Received	115 (92)	36 (77)	0.006

Ph: pancreas head, *CA19-9*: carbohydrate antigen 19-9, *PNI*: prognostic nutrition index.
[a] Data before initial treatment of primary tumor. Values in parentheses of categorical variables are percentages.

play a central role in anticancer immunity, and lymphocytopenia reflects the impairment of cellular adaptive immunity against cancer cells. Therefore, lymphocytopenia is thought to be a biological marker of immune suppression. Furthermore, PDAC is thought to be associated with the most significant lymphocytopenia compared to the other gastrointestinal tumors [23]. On the other hand, albumin is one of the most reliable indicators of mid- and long-term nutritional status [24]. Hypoalbuminaemia is associated with poor tissue healing, decreased collagen synthesis in surgical wounds and at anastomoses, and impairment of immune responses such as macrophage activation and granuloma formation [25–28]. Therefore, compromised immunonutritional status is an important factor that can lead to increased spread of the tumor. Another explanation is that PNI reflects the tolerability to systemic chemotherapy. Our study revealed that implementation rate of chemotherapy for recurrence in the low PNI group was significantly worse compared to the higher PNI group. Our previous study also showed that lower PNI was critical risk factor for the failure to complete adjuvant chemotherapy [29]. Ikeya et al. also reported the association between the inflammation-based prognostic scores and continuity of chemotherapy among patients with unresectable colorectal cancer, suggesting that patients with a high PNI were able to continue to a long-term treatment because of an adequate physical reserve [30].

In this study, we observed that the PNI at recurrence was significantly associated with patients' performance status, primary tumor location, completion rate of adjuvant chemotherapy and blood transfusion, while there were no associations between PNI and any other patients' and tumor factors including pattern of recurrence. These findings suggest that low PNI at recurrence may be result of the decrease of the lymphocyte and albumin due to chronic physical exhaustion following to more invasive treatment. Therefore, since keeping or enhancing PNI level may lead to adequate long-term treatment after recurrence, continuous intervention such as long-term nutritional support or monitoring may be crucial to improve patient prognosis even after the completion of multidisciplinary treatment for resectable pancreatic cancer. However, since there are limited medical evidence to support our hypothesis, further studies are needed.

The current study has some limitations. This was a retrospective cohort study at single institution. In addition, there was some heterogeneity of multidisciplinary treatment including first-line chemotherapy after recurrence and patient selection, and the number of enrolled patients was relatively small. Therefore, biases inherent to retrospective studies could not be completely avoided. However, our results strongly support the idea that PNI can be a promising prognostic biomarker for RPC and may have critical implications for the future therapeutic strategies. To verify the usefulness of PNI in treating patients with RPC, further prospective studies are required.

In conclusion, the inflammation-based prognostic scores, especially PNI, were useful predictive indicators for recurrent pancreatic cancer. Therefore, measuring these indicators at recurrence could be helpful in prediction of prognosis and decision-making of treatment strategy in daily clinical practice.

Author contributions

KN and MS designed the study. KN performed the statistical analyses and drafted the first version of the manuscript. KN, MS, TA, MN, KN and NI contributed to the writing of the manuscript. All the authors approved the final version of the manuscript.

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References

[1] Picozzi VJ, Oh SY, Edwards A, Mandelson MT, Dorer R, Rocha FG, et al. Five-year actual overall survival in resected pancreatic cancer: a contemporary single-institution experience from a multidisciplinary perspective. Ann Surg Oncol 2017;24:1722–30.
[2] Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
[3] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.

N Engl J Med 2013;369:1691–703.
[4] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
[5] Jamieson NB, Denley SM, Logue J, MacKenzie DJ, Foulis AK, Dickson EJ, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. Ann Surg Oncol 2011;18:2318–28.
[6] Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg 2011;98:268–74.
[7] Malik HZ, Prasad KR, Halazun KJ, Aldoori A, Al-Mukhtar A, Gomez D, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. Ann Surg 2007;246:806–14.
[8] Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Friesenbichler J, et al. The lymphocyte/monocyte ratio predicts poor clinical outcome and improves the predictive accuracy in patients with soft tissue sarcomas. Int J Cancer 2014;135:362–70.
[9] Wang DS, Ren C, Qiu MZ, Luo HY, Wang ZQ, Zhang DS, et al. Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumour Biol 2012;33:749–56.
[10] Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010;200:197–203.
[11] Fujiwara Y, Misawa T, Shiba H, Shirai Y, Iwase R, Haruki K, et al. Postoperative peripheral absolute blood lymphocyte-to-monocyte ratio predicts therapeutic outcome after pancreatic resection in patients with pancreatic adenocarcinoma. Anticancer Res 2014;34:5163–8.
[12] Sho M, Akahori T, Tanaka T, Kinoshita S, Tamamoto T, Nomi T, et al. Pathological and clinical impact of neoadjuvant chemoradiotherapy using full-dose gemcitabine and concurrent radiation for resectable pancreatic cancer. J Hepatobiliary Pancreat Sci 2013;20:197–205.
[13] Sho M, Tanaka T, Yamada T, Nomi T, Akahori T, Doh J, et al. Novel postoperative adjuvant strategy prevents early hepatic recurrence after resection of pancreatic cancer. J Hepatobiliary Pancreat Sci 2011;18:235–40.
[14] Stocken DD, Hassan AB, Altman DG, Billingham LJ, Bramhall SR, Johnson PJ, et al. Modelling prognostic factors in advanced pancreatic cancer. Br J Canc 2008;99:883–93.
[15] Park I, Choi SJ, Kim YS, Ahn HK, Hong J, Sym SJ, et al. Prognostic factors for risk stratification of patients with recurrent or metastatic pancreatic adenocarcinoma who were treated with gemcitabine-based chemotherapy. Cancer Res Treat 2016;48:1264–73.
[16] Xue P, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, et al. Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. Cancer Med 2014;3:406–15.
[17] Yamada S, Fujii T, Yabusaki N, Murotani K, Iwata N, Kanda M, et al. Clinical implication of inflammation-based prognostic score in pancreatic cancer: Glasgow prognostic score is the most reliable parameter. Medicine 2016;95:e3582.
[18] Watanabe J, Otani S, Sakamoto T, Arai Y, Hanaki T, Amisaki M, et al. Prognostic indicators based on inflammatory and nutritional factors after pancreaticoduodenectomy for pancreatic cancer. Surg Today 2016;46:1258–67.
[19] Suenaga M, Fujii T, Kanda M, Takami H, Okumura N, Inokawa Y, et al. Pattern of first recurrent lesions in pancreatic cancer: hepatic relapse is associated with dismal prognosis and portal vein invasion. Hepato-Gastroenterology 2014;61:1756–61.
[20] Xue P, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, et al. Comparative outcomes between initially unresectable and recurrent cases of advanced pancreatic cancer following palliative chemotherapy. Pancreas 2014;43:411–6.
[21] Salazar-Onfray F, Lopez MN, Mendoza-Naranjo A. Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. Cytokine Growth Factor Rev 2007;18:171–82.
[22] Ebrahimi B, Tucker SL, Li D, Abbruzzese JL, Kurzrock R. Cytokines in pancreatic carcinoma: correlation with phenotypic characteristics and prognosis. Cancer 2004;101:2727–36.
[23] Romano F, Uggeri F, Crippa S, Di Stefano G, Scotti M, Scaini A, et al. Immunodeficiency in different histotypes of radically operable gastrointestinal cancers. J Exp Clin Cancer Res 2004;23:195–200.
[24] Irvin TT, Hunt TK. Effect of malnutrition on colonic healing. Ann Surg 1974;180:765–72.
[25] Ryan AM, Hearty A, Prichard RS, Cunningham A, Rowley SP, Reynolds JV. Association of hypoalbuminemia on the first postoperative day and complications following esophagectomy. J Gastrointest Surg 2007;11:1355–60.
[26] Lohsiriwat V, Lohsiriwat D, Boonnuch W, Chinswangwatanakul V, Akaraviputh T, Lert-Akayamanee N. Pre-operative hypoalbuminemia is a major risk factor for postoperative complications following rectal cancer surgery. World J Gastroenterol 2008;14:1248–51.
[27] Reynolds JV, Redmond HP, Ueno N, Steigman C, Ziegler MM, Daly JM, et al. Impairment of macrophage activation and granuloma formation by protein deprivation in mice. Cell Immunol 1992;139:493–504.
[28] Rivadeneira DE, Grobmyer SR, Naama HA, Mackrell PJ, Mestre JR, Stapleton PP, et al. Malnutrition-induced macrophage apoptosis. Surgery 2001;129:617–25.
[29] Akahori T, Sho M, Tanaka T, Kinoshita S, Nagai M, Nishiwada S, et al. Factors associated with failure to complete adjuvant chemotherapy in pancreatic cancer. Am J Surg 2016;211:787–92.
[30] Ikeya T, Shibutani M, Maeda K, Sugano K, Nagahara H, Ohtani H, et al. Maintenance of the nutritional prognostic index predicts survival in patients with unresectable metastatic colorectal cancer. J Cancer Res Clin Oncol 2015;141:307–13.