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Pre-treatment neutrophil to lymphocyte ratio as a predictive marker for pathological response to preoperative chemoradiotherapy in pancreatic cancer

SHINICHIRO HASEGAWA[1,2], HIDETOSHI EGUCHI[1], AKIRA TOMOKUNI[1], YOSHITO TOMIMARU[1], TADAFUMI ASAOKA[1], HIROSHI WADA[1], NAOKI HAMA[1], KOICHI KAWAMOTO[1], SHOGO KOBAYASHI[1], SHIGERU MARUBASHI[1], MASAMITSU KONNNO[2], HIDESHI ISHII[2,3], MASAKI MORI[1], YUICHIRO DOKI[1] and HIROAKI NAGANO[1]

Departments of [1]Gastroenterological Surgery, [2]Frontier Science for Cancer and Chemotherapy, and [3]Cancer Profiling Discovery, Osaka University Graduate School of Medicine, Suita, Osaka 565-0871, Japan

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Abstract. An elevated neutrophil to lymphocyte ratio (NLR) has been reported to be associated with the pathological response to neoadjuvant therapies in numerous types of cancer. The aim of the current study was to clarify the association between pre-treatment NLR and the pathological response to preoperative chemoradiotherapy in pancreatic cancer patients. This retrospective analysis included data from 56 consecutive patients whose tumors were completely surgically resected. All patients received preoperative therapy, consisting of gemcitabine-based chemotherapy (alone or in combination with S-1) combined with 40 or 50.4 Gy irradiation, prior to surgery. Predictive factors, including NLR, platelet to lymphocyte ratio (PLR), modified Glasgow prognostic score and prognostic nutrition index, were measured prior to treatment. A comparison was made between those who responded well pathologically (good response group, Evans classification IIb/III) and those with a poor response (Evans I/IIa). NLR was determined to be significantly higher in the poor response group. Multivariate analysis identified an elevated NLR as an independent risk factor for the poor pathological response [odds ratio (OR), 5.35; P=0.0257]. The pre-treatment NLR (≥2.2/<2.2) was found to be a statistically significant predictive indicator of pathological response (P=0.00699). The results demonstrate that pre-treatment NLR may be a useful predictive marker for the pathological response to preoperative therapy in pancreatic cancer patients.

Correspondence to: Dr Hiroaki Nagano, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: hnagano@gesurg.med.osaka-u.ac.jp

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Introduction

Pancreatic cancer has the poorest prognosis of any major malignancy (5-year survival rate, 6%) (1). At present, surgical resection represents the only potentially curative treatment strategy in these patients, however, the 5-year survival rate following surgical resection remains low, at 5.5-21% (2,3). Gemcitabine (GEM)-based chemotherapy forms the core of multimodal therapy and has improved the prognosis of patients with pancreatic cancer (3). Multimodal therapies including preoperative treatments have been investigated, and studies indicate that preoperative chemoradiotherapy followed by surgery may improve the clinical outcome by reducing the frequency of local recurrence and increasing the 5-year survival rate in pancreatic cancer patients (4-8). However, in cases where preoperative therapy is not sufficiently effective and extensive tumor growth occurs, chemotherapy may unnecessarily increase the time between diagnosis and surgery, and may result in the patient missing the opportunity for surgical resection. Therefore, it is essential to identify the specific pre-treatment prognostic factors that can determine which patients will benefit from preoperative therapy.

To date, the identified prognostic factors predominantly consist of various pathological characteristics of the resected tumor specimen, including tumor size (9), histological grade, vascular invasion (10), lymph node metastases (11) and intrapancreatic perineural invasion (12). However, each of these factors can only be determined following surgical resection.

There is increasing evidence demonstrating that inflammatory cells in the tumor microenvironment are important in the development of tumors; blood cell counts in peripheral blood, which in part reflect immune function in cancer patients, are considered part of the internal environment (13-20). A number of prognostic factors based on cancer-associated systemic inflammation have been investigated, including the following: Serum C-reactive protein (CRP) combined with albumin levels (modified Glasgow prognostic score; mGPS) (21); Albumin level in combination with lymphocyte

count (Onodera's prognostic nutritional index; PNI) (22); the neutrophil to lymphocyte ratio (NLR) (23), combining neutrophil and lymphocyte counts; and the platelet to lymphocyte ratio (PLR) (24), combining platelet and lymphocyte counts. However it is unknown whether such prognostic markers correlate with the outcome of preoperative therapy in pancreatic cancer patients.

The present study aimed to determine whether the presence of systemic inflammation predicts the outcome of preoperative treatments in patients with pancreatic cancer.

Materials and methods

Patient population. The present retrospective analysis included data from 56 consecutive patients with histologically confirmed pancreatic ductal adenocarcinoma, whose tumors were completely resected by surgery (R0) at Osaka University Hospital (Suita, Osaka, Japan) between March 2007 and October 2012. None of the patients had received any prior treatments, and all were newly diagnosed. During this period, patients with any T stage (cT1-4) and degree of lymph node involvement, including regional and distant lymph nodes (N1 and M1 lym), but without distant organ metastasis, received chemoradiotherapy prior to surgery. All patients had sufficient renal, hepatic, cardiac and bone marrow reserve and were able to tolerate the planned chemotherapy and subsequent surgical procedures.

The disease stages of all patients were determined prior to preoperative therapy and following surgery, according to the International Union Against Cancer criteria (25). Pre-treatment clinical staging was based on computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging, and positron emission tomography (PET) scanning. Lymph nodes measuring ≥1.0 cm in maximum transverse diameter on CT scans were diagnosed as metastasis-positive; if lymph nodes were visible but measured <1.0 cm, they were regarded as metastasis-positive only when the PET scan revealed focal prominent 18-fluorodeoxyglucose uptake. The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine. Written informed consent was obtained from all patients.

Hematological examination. Routine laboratory tests for leukocyte, neutrophil, lymphocyte, platelet, C-reactive protein (CRP), albumin, carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA) and DUPAN-2 levels were conducted prior to surgery and the commencement of preoperative therapy. The latex immunonephelometry method was applied to measure the serum concentration of CRP (normal range, 0-0.3 mg/dl) using a JCA-BM6070 automated biochemical analyzer (JEOL Ltd., Tokyo, Japan) and CRP-EX (LSI Medience Corporation, Tokyo, Japan). The chemiluminescence enzyme immunoassay method was applied to measure serum levels of CA19-9, CEA and DUPAN-2 using Lumipulse G1200 (Fujirebio, Inc., Tokyo, Japan), Access CEA reagent and the UniCel DXI 800 immunoassay system (Beckman Coulter, Inc., Brea,CA, USA). Serum levels <37 U/ml for CA19-9, <5 ng/ml for CEA and <150 U/ml for DUPAN-2 were considered as normal levels in the present study. Based on the mGPS (21), which combines CRP and albumin concentrations,

Table I. Clinicopathological characteristics of the included patients (n=56).

Parameter	Value
Age (years)	65.6±10.8
Gender, n	
Male	34
Female	22
White blood cells (/μl)[a]	5425.7±1450.4
Neutrophil (%)[a]	60.6±9.4
Lymphocyte (%)[a]	27.6±7.9
Platelets (10^4/μl)[a]	22.1±6.8
C-reactive protein (mg/dl)[a]	0.36±0.67
Albumin (g/dl)[a]	3.8±0.3
Carbohydrate antigen 19-9 (U/ml)[a]	328.0±391.9
Carcinoembryonic antigen (ng/ml)[a]	5.6±14.8
DUPAN-2 (U/ml)[a]	1951.7±7451.4
Neutrophil to lymphocyte ratio[a]	2.6±1.6
Platelet to lymphocyte ratio[a]	165.8±70.2
Modified Glasgow prognostic score, n	
1+2	6
0	50
Prognostic nutrition index[a]	44.9±4.7
Location, n	
Pancreatic head	47
Pancreatic body	3
Pancreatic tail	6
cT stage, n	
T1	3
T2	1
T3	51
T4	1
cN status, n	
Positive	4
Negative	52
cStage, n	
I	4
IIA	46
IIB	4
III	1
IV	1
Maximal diameter (mm)[a]	21.3±13.6
Histology, n	
Well-differentiated	1
Moderately differentiated	54
Poorly differentiated	1
pT stage, n	
T1	14
T2	5
T3	37
T4	0
pN status, n	
Positive	17
Negative	39

Table I. Continued.

Parameter	Value
pStage, n	
I	14
IIA	26
IIB	15
III	0
IV	1
Evans grade, n	
I	10
IIa	30
IIb	14
III	2
Adjuvant therapy, n	
Yes	42
No	14
Recurrence, n	
Yes	34
No	22

[a]Data presented as mean ± standard deviation. T, tumor invasion depth; N, lymph node metastasis.

patients who had both elevated CRP levels (>1 mg/dl) and albumin levels <3.5 g/dl were assigned a score of 2. Patients with only elevated CRP (>1 mg/dl) were assigned a score of 1. Patients with neither of these abnormalities were assigned a score of 0. The PNI was calculated using the following formula: PNI = [albumin (g/dl) x 10] + [0.005 x total lymphocyte count (/μl)] (22,26).

Preoperative therapy and postoperative follow-up. The preoperative treatment consisted of GEM-based chemotherapy [GEM alone (600-1,000 mg/m^2) or GEM plus S-1 (60-80 mg/m^2), a fourth-generation oral fluoropyrimidine] combined with 40 or 50.4 Gy irradiation, as reported previously (4,27). Based on the CONKO-001 study (3), gemcitabine-based adjuvant chemotherapy has been routinely administered since 2007. Postoperative follow-up consisted of a routine physical examination and laboratory tests, including assessment of serum levels of CEA, CA19-9 and DUPAN-2. Chest X-ray and CT/ultrasonography of the abdomen were performed every 3 months, and the presence or absence of cancer recurrence was carefully monitored. Recurrence was defined as the detection of a new abnormal finding or the gradual enlargement of an abnormal finding during any imaging study. The median follow-up period of the 56 patients was 27.1 months (range, 6.1-80.2 months).

Evaluation of response to preoperative therapies. The preoperative treatment effect was determined based on the examination of hematoxylin-eosin (Sigma-Aldrich, St. Louis, MO, USA) stained permanent sections by a gastrointestinal pathologist; samples were scored using a previously published grading system, Evans classification (28). A minimal pathological response was defined as a treatment effect score of grade I or grade IIa (≥90% or 50-89% viable tumor cells, respectively,

Table II. Comparison of clinical and histopathological factors between poor response group (Evans I+IIa) and good response group (Evans IIb+III).

	Evans grade		
Parameter	I/IIa (n=40)	IIb/III (n=16)	P-value
Age (years)[a]	65.9±10.0	64.7±12.9	NS
Gender, n			NS
Male	25	9	
Female	15	7	
CA19-9 (U/ml)[a]	313.6±377.3	365.3±439.3	NS
CEA (ng/ml)[a]	6.4±17.4	3.4±1.8	NS
DUPAN-II (U/ml)[a]	2231.2±8717.9	1233.0±1971.5	NS
NLR[a]	2.9±1.8	1.9±0.6	0.0481
PLR[a]	172.9±73.4	147.3±59.2	NS
mGPS, n			NS
1+2	5	0	
0	35	16	
PNI[a]	44.2±4.4	46.8±5.1	NS
Location, n			NS
Pancreatic head	28	8	
Pancreatic body	8	6	
Pancreatic tail	4	2	
cT stage, n			NS
T1	3	0	
T2	1	0	
T3	35	16	
T4	1	0	
cN status, n			NS
Positive	4	0	
Negative	36	16	
cStage, n			NS
I	4	0	
IIA	31	15	
IIB	4	0	
III	1	0	
IV	0	1	
Maximal diameter (mm)[a]	22.3±14.9	18.8±9.4	NS
Histology, n			NS
Well	1	0	
Moderate	38	16	
Poor	1	0	
pT stage, n			0.0611
T1	7	7	
T2	3	2	
T3	30	7	
T4	0	0	
pN status, n			NS
Positive	13	3	
Negative	27	13	
pStage, n			NS
I	7	7	
IIA	20	6	

Table II. Continued.

Parameter	Evans grade I/IIa (n=40)	Evans grade IIb/III (n=16)	P-value
pStage, n			NS
IIB	12	3	
III	0	0	
IV	1	0	
Adjuvant therapy, n			NS
Yes	28	14	
No	12	2	NS
Recurrence, n			0.0695
Yes	21	13	
No	19	3	

[a]Data presented as mean ± standard deviation. NS, not significant; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; mGPS, modified Glasgow prognostic score; PNI, prognostic nutrition index; Well, well-differentiated; Moderate, moderately differentiated; Poor, poorly differentiated.

Table III. Predictive factors for the pathological response in clinical information.

A, Univariate analysis

Variable	OR (95% CI)	P-value
NLR (≥2.2 / <2.2)	6.84 (1.61-47.58)	0.00740
mGPS (1+2 / 0)	NA	0.0407
cT (T1,T2 / T3,T4)	NA	0.0935
cN (+ / -)	NA	0.0935

B, Multivariate analysis

Variable	OR (95% CI)	P-value
NLR (≥2.2 / <2.2)	5.35 (1.21-38.03)	0.0257
cT (T1,T2 / T3,T4)	NA	0.175
cN (+ / -)	NA	0.175

OR, odds ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; mGPS, modified Glasgow prognostic score; cT, clinical tumor invasion depth; cN, clinical node status; +, positive; -, negative; NA, not available.

remaining following therapy). Grades IIb (10-49% viable tumor cells remaining) or III (<10% viable tumor cells remaining) were considered a partial pathological response. The absence of any remaining viable tumor cells, corresponding to grade IV, was considered a complete pathological response.

Statistical analysis. Data were expressed as the mean ± standard deviation. Clinicopathological parameters were compared using the Fisher's exact test and χ^2 test, and continuous variables were compared using a Mann-Whitney U test. A receiver operating characteristic (ROC) curve was constructed to estimate the optimal cut-off value of the pre-treatment NLR. A logistic regression analysis was used to analyze the simultaneous influence of predictive factors. Odds ratios (ORs) estimated from the logistic analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). In all analyses, a $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using JMP software version 10.0.2 (SAS Institute Inc., Cary, NC, USA).

Table IV. Association between pathological response and pre-treatment NLR.

Pathological response	High NLR (≥2.2), n	Low NLR (<2.2), n	P-value
Evans grade I/IIa	20	19	0.00699
Evans grade IIb/III	2	15	

NLR, neutrophil to lymphocyte ratio.

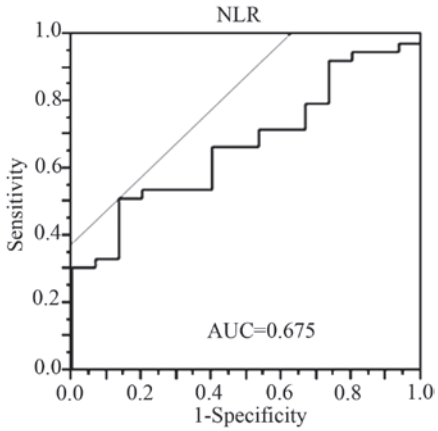

Figure 1. A receiver operating characteristic curve constructed to estimate the optimal cut-off value of the pre-treatment NLR. NLR, neutrophil to lymphocyte ratio; AUC, area under curve.

Results

Patient characteristics. The 56 patients in the current study comprised 34 (60.7%) males and 22 (39.3%) females, and the mean age was 65.6±10.8 years (range, 38-84 years). All patients who received preoperative chemoradiotherapy followed by surgery were enrolled in the study. With regard to the hematological examination, the mean NLR value among the 56 patients was 2.6±1.6, the mean PLR value was 165.8±70.2, and the mean PNI value was 44.9±4.7. In 47 patients (83.9%), the tumor was localized to the pancreatic head. Other clinical and histopathological information is listed in Table I.

Comparison of mean NLR values of the poor and good response groups. In order to assess the association between

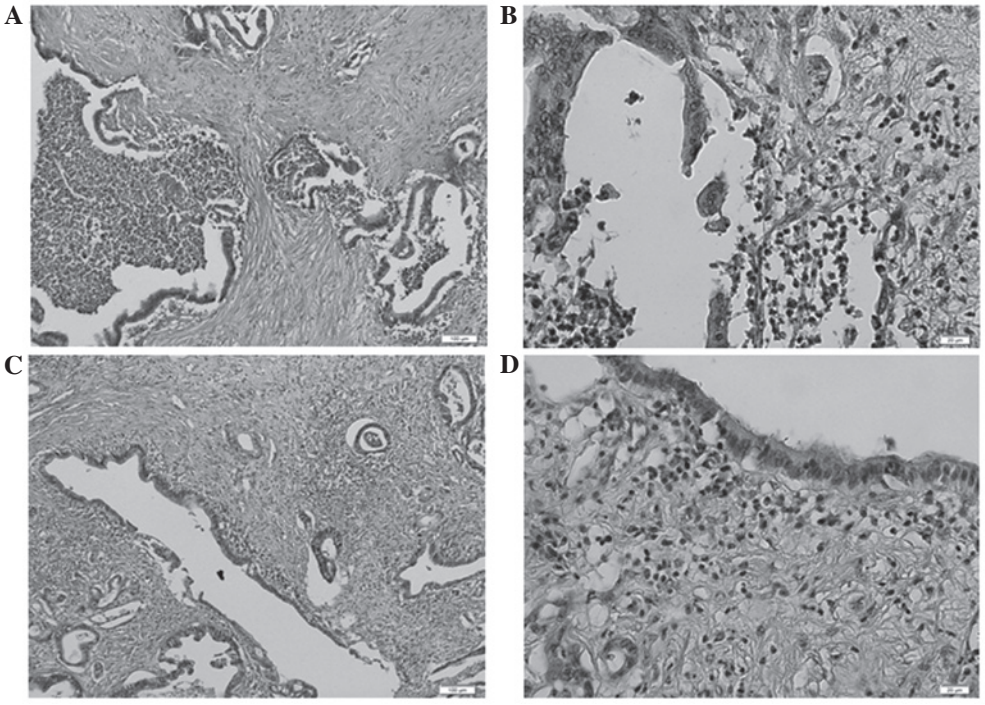

Figure 2. Representative images of patient specimens with a particularly high neutrophil to lymphocyte ratio. The pancreatic ductal adenocarcinoma tissue contained masses of neutrophils: (A) x100 magnification; (B) x400 magnification (stain, hematoxylin and eosin). Lymphoid follicles were not observed in the stromal tissue adjacent to the tumor: (C) x100 magnification; (D) x400 magnification (stain, hematoxylin and eosin).

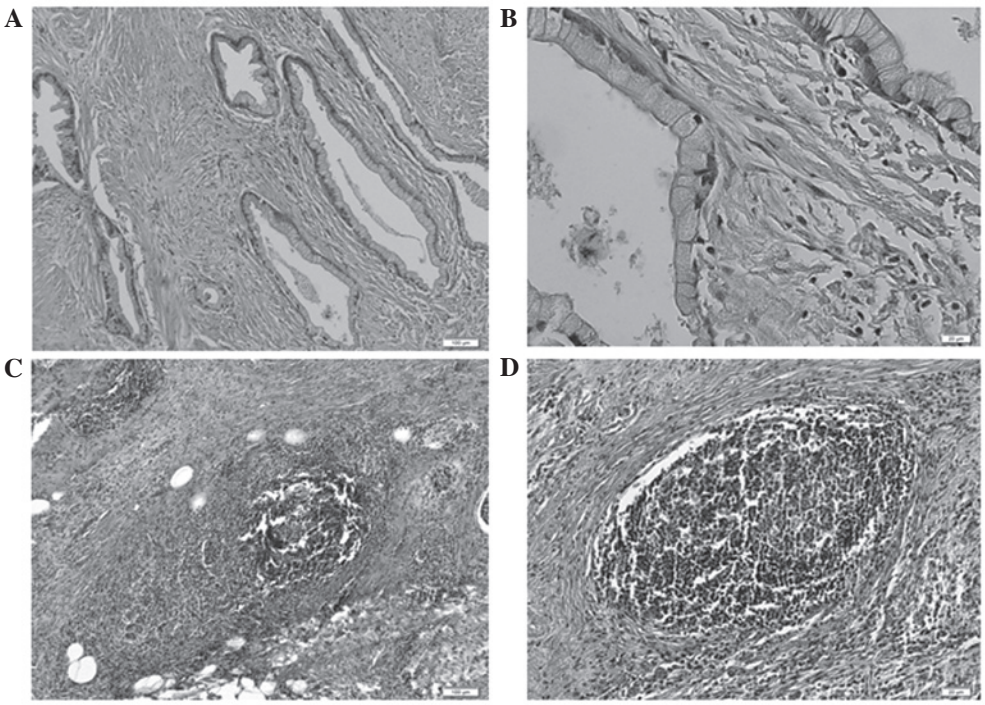

Figure 3. Representative images of patient specimens with a particularly low neutrophil to lymphocyte ratio. The pancreatic ductal adenocarcinoma did not contain any neutrophils: (A) x100 magnification; (B) x400 magnification (stain, hematoxylin and eosin). The lymphoid follicles were formed in the stromal tissue adjacent to the tumor: (C) x100 magnification; (D) x400 magnification (stain, hematoxylin and eosin).

hematological factors and the pathological response to preoperative therapies, the patients who underwent preoperative treatments were divided into a poor response group (Evans grade I or IIa) and a good response group (Evans grade IIb or III). The background clinical and histopathological factors were compared between the two groups (Table II). The mean NLR value was significantly higher in the poor response group than in the good response group, whereas the other examined factors demonstrated no significant differences between the two groups.

Optimal cut-off level of the pre-therapeutic NLR. An ROC curve was prepared by plotting sensitivity values against specificity values at the indicated NLR (Fig. 1). From the ROC curve, the optimal cut-off level of the pre-therapeutic NLR for predicting pathological non-responders (Evans I/IIa) was determined to be 2.2.

NLR is an independent predictive factor for pathological response. The evaluation of predictive factors for the pathological response among clinical information were assessed, including a number of prognostic markers that have been previously reported: NLR (23), PLR (24), mGPS (21) and PNI (22). Upon univariate analysis, NLR and mGPS were determined to be significantly associated with the pathological response, whilst the other prognostic markers were not (Table IIIA). Furthermore, multivariate analysis identified NLR as a significant and independent predictive factor (Table IIIB). NLR and mGPS are both closely related to inflammation; therefore, mGPS was not included in the multivariate analysis. Subsequently, the association between the blood NLR value and features of the corresponding clinical specimen were examined. Notably, numerous masses of neutrophils were detected in pancreatic ductal adenocarcinoma in cases with particularly high NLRs (Fig. 2), and the formation of lymphoid follicles in the stromal tissue adjacent to the tumor was observed in cases with particularly low NLRs (Fig. 3). This finding indicated that the NLR determined by blood examination at least partially reflected the state of the inflammation in the corresponding clinical specimens.

Finally, the predictive ability of the NLR with regard to the pathological response to preoperative therapies was evaluated. Table IV shows the prediction of pathological responses using the pre-treatment NLR values (≥2.2/<2.2). The NLR was revealed to be a significant predictive marker of pathological response (P=0.00699): The good response rates were 9.1% in patients with an NLR ≥2.2, and 44.1% in patients with an NLR <2.2.

Discussion

The NLR, which is an inexpensive and widely available blood test, has been demonstrated to be an important prognostic predictor in numerous types of cancer, including colorectal cancer (29), gastric cancer (30), ovarian cancer (31), intrahepatic cholangiocarcinoma (32), hepatocellular carcinoma (33), and pancreatic cancer (34). Furthermore, it has been reported that the NLR is correlated with the pathological response to preoperative therapy (35,36). However, there have been no reports focusing on the association between high NLR and poor response to neoadjuvant therapies in pancreatic cancer. In the present study, various pre-treatment hematological factors related to pathological response were assessed.

Biologically, the significance of high neutrophil counts in malignant tumors is based on a combination of T-cell suppression via the production of certain active substances, such as reactive oxygen species, nitric oxide and arginase (37,38), and stimulation of tumor angiogenesis through the production of IL-8, vascular endothelial growth factor, elastase and matrix metalloproteinase (39-41). By contrast, previous reports have suggested that a high number of tumor-infiltrating lymphocytes was strongly associated with favorable outcomes in patients with various types of cancer (42,43). Furthermore, lymphocytes, particularly T cells, are considered to play a central role in antitumor immunity; thus, the lymphocyte count is thought to reflect the ability of the body to eliminate tumor cells (44).

Recently, a number of combination therapies, consisting of preoperative chemoradiotherapy, surgery and postoperative chemotherapy, have been used in clinical trials, which were found to improve the poor prognosis of pancreatic cancer (27,45). In cases where combined therapies are used, it is essential to identify predictors of response to preoperative therapy in order to inform the assessment of risk and patient counselling. Similar multimodal therapies have been used for the treatment of esophageal and rectal cancers, as well as pancreatic cancer; NLR has been reported to be a useful and available predictive marker associated with pathological response to neoadjuvant chemotherapy or preoperative chemoradiotherapy in esophageal and rectal cancers, respectively (35,36). However, to the best of our knowledge, the present study is the first to demonstrate that pre-treatment NLR is significantly higher in pancreatic cancer patients who respond poorly to treatment compared with that of patients who exhibit a favorable response. NLR was identified as a significant independent risk factor among pre-treatment clinical factors, and the ratio of pathologically favorable responses was significantly lower in patients with an NLR ≥2.2 compared with that of the patients with an NLR <2.2. This finding suggests that pre-treatment NLR may be used to predict which patients will benefit from preoperative therapy.

In conclusion, pre-treatment NLR is an independent predictive marker of the pathological response to preoperative therapy in pancreatic cancer patients. However, long term analysis to investigate the association between pre-treatment NLR and disease free or overall survival has not yet been performed. Thus, further large scale, long-term studies are required to establish a cut-off value for the NLR which may be used to guide preoperative treatment choices.

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