The Combination of Neutrophil-to-lymphocyte Ratio and Serum Carbohydrate Antigen 19-9 Level as a Prognostic Indicator in Patients with Recurrent Pancreatic Cancer

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Abstract. *Background/Aim:* We retrospectively investigated the relationship between prognosis and combined neutrophil-to-lymphocyte ratio (NLR) and serum carbohydrate antigen 19-9 (CA19-9) levels in patients with recurrent pancreatic cancer. *Patients and Methods:* We enrolled 66 patients whose pancreatic cancer recurred. *Results:* Based on ROC analysis results, the patients were divided into NLR^{High} ($NLR \geq 1.69$) or NLR^{Low} ($NLR < 1.69$), and into $CA19-9^{High}$ ($CA19-9 \geq 107.95$ U/ml) or $CA19-9^{Low}$ ($CA19-9 < 107.95$ U/ml). When the patients were grouped by combined NLR and CA19-9, their 2-year survival rates were $NLR^{Low}/CA19-9^{Low}$: 58.7%; $NLR^{Low}/CA19-9^{High}$ or $NLR^{High}/CA19-9^{Low}$ (grouped together): 11.2%; and $NLR^{High}/CA19-9^{High}$: 0% ($p < 0.0001$). Finally, in multivariate analysis, the combination of NLR and serum CA19-9 level was an independent prognostic factor in patients with recurrent pancreatic cancer. *Conclusion:* The combination of NLR and serum CA19-9 level is a useful prognostic indicator for recurrent pancreatic cancer.

Pancreatic cancer (PC) is the most aggressive malignancy, with a 5-year overall survival rate of less than 5%; worldwide, it is the seventh leading cause of cancer-related mortality (1, 2). Chemotherapy or radiation therapy had been used to treat patients with recurrent PC, but median survival time after recurrence was only 5.1–6.0 months (3, 4). However, recent progress in chemotherapy, such as nab-paclitaxel plus gemcitabine (GEM) and FOLFIRINOX, has been shown to prolong their survival (5, 6). Accurate

prediction of prognosis in these patients is needed to determine optimal treatment strategies and prepare patients' expectations.

Serum tumor markers (TMs) are recognized as prognostic indicators in various types of cancers (7-10). Among serum TMs, carbohydrate antigen 19-9 (CA19-9) is the only marker currently recommended for monitoring PC by the National Comprehensive Cancer Network guidelines. Several studies reported the relationship between CA19-9 and survival (11-14), which implies that CA 19-9 is a prognostic indicator in recurrent PC as well.

Although TMs, including CA19-9, are mainly derived from the cancer itself, prognoses of various cancers are also affected by patient-related factors, including inflammation, immunocompetence, and nutrition, with the correlation between inflammation status and cancer prognosis being of particular interest. Reportedly, systemic inflammatory responses are closely associated with development and progression of cancer by the promotion of angiogenesis and increased cancer cell proliferation (15, 16). The neutrophil-to-lymphocyte ratio (NLR), an inflammatory indicator derived from routine blood tests, is a well-recognized prognostic factor in various cancers (17-22). Garcea *et al.* reported that preoperative NLR offered important prognostic information regarding disease-free survival following curative resection of PC (23). However, the prognostic significance of CA19-9 and NLR in recurrent PC patients remains unclear. Therefore, this study aimed to evaluate the prognostic significance of NLR and serum CA19-9 level in recurrent PC patients. Furthermore, the different origins of TMs and NLR suggested that their combination might be superior to either TMs or NLR alone for predicting prognosis of patients with recurrent PC. The current study, therefore, also aimed to evaluate the prognostic significance of the combination of serum CA19-9 level and NLR in these patients.

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Patients and Methods

Patients. We retrospectively reviewed records of 103 patients who had undergone pancreaticoduodenectomy or distal pancreatectomy with regional lymphadenectomy for PC at our hospital between January 2005 and December 2016 and found 70 who had developed postoperative recurrence as of March 31, 2018. 4 patients were excluded because either their NLR or serum CA19-9 levels at the time of recurrence were unavailable. Finally, 66 patients were enrolled in this study. The subjects included 44 men and 22 women whose median age was 71.5 years (range=44-85 years) at the time of recurrence. Their median follow-up periods were 25.5 months (range=1.7-91.5 months) after surgery and 9.1 months (range=0-84.5 months) after recurrence. The clinicopathological findings were determined according to the 7th edition of General Rules for the Study of Pancreatic Cancer by Japan Pancreas Society (24). Patients were periodically checked for early recurrence by diagnostic imaging, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). We collected data of serum CA 19-9 levels, peripheral lymphocyte counts, and peripheral neutrophil counts from blood tests performed at the time of recurrence and indicated in the patients' records. The NLR was obtained by dividing the peripheral neutrophil count by the peripheral lymphocyte count.

Among the 66 patients included in this study, 50 patients (75.8%) underwent chemotherapy to treat their recurrent PC, including 38 who received GEM-based regimen (GEM alone or GEM plus S-1 or GEM plus nab-paclitaxel), 11 who received S-1 alone and 1 who received uracil-tegafur as first-line therapy, and 15 who also received secondary treatment (FOLFIRINOX, n=1; GEM plus nab-paclitaxel, n=1; GEM plus S-1, n=4; GEM plus oxaliplatin, n=2; GEM alone, n=5; S-1, n=2). Sixteen (24.2%) of 66 patients were treated with best supportive care without chemotherapy. Recurrences within 12 months after surgery were classified as early recurrences, and those occurring later than 12 months after surgery were considered late recurrences, according to a previous report (25).

The Tottori University Hospital Ethics Committee approved this study (No. 17A135); informed consent requirements were waived for this retrospective study.

Statistical analysis. The Chi-square test and Fisher's exact probability tests were used to evaluate differences between two groups. Optimal cutoff values for NLR and serum CA19-9 levels with respect to survival were calculated using receiver operating characteristic (ROC) analysis. Survival curves after recurrence were constructed by the Kaplan-Meier method, and the prognostic differences among survival curves were examined with log-rank tests. We used univariate and multivariate analyses of factors considered prognostic of overall survival, with Cox's proportional hazards model. p -Value<0.05 was considered significant. All statistical analyses were performed using SPSS software (Version 24, SPSS Inc., Chicago, IL, USA).

Results

Mean NLR and serum CA19-9 level at the time of recurrence were 2.42 ± 2.57 and 945.0 ± 2816.1 U/ml, respectively. No significant correlation between NLR and serum CA19-9 level was found (Figure 1).

Figure 1. Graph of neutrophil-to-lymphocyte ratio (NLR) and serum carbohydrate antigen 19-9 (CA19-9) level at the time of recurrence. We observed no significant correlation between NLR and serum CA19-9 level.

In ROC analyses of NLR and serum CA19-9 level, optimal cut-off values (highest Youden indices) for 2-year survival were NLR: 1.69, and CA19-9: 107.95 U/ml. Based on these results, patients were grouped as: NLR^{High} (NLR ≥ 1.69 ; n=36) or NLR^{Low} (NLR <1.69; n=30); and as CA19-9^{High} (CA19-9 ≥ 107.95 U/ml; n=37) or CA19-9^{Low} (CA19-9 <107.95 U/ml; n=29). Table I shows correlations among NLR, serum CA19-9 level, and clinicopathological characteristics in patients with recurrent PC. Significant associations were observed between NLR and lymph node metastasis ($p=0.006$), and between serum CA19-9 level and vascular involvement ($p=0.03$). Two-year survival rates significantly varied by both NLR (NLR^{High} group: 3.4%, NLR^{Low} group: 40.2%, $p<0.001$; Figure 2a), and CA19-9 (CA19-9^{High} group: 3.6%, CA19-9^{Low}: 39.4%, $p<0.001$; Figure 2b).

The prognostic significance of the combination of NLR and serum CA19-9 level was then determined by dividing the patients into three groups: NLR^{Low}/CA19-9^{Low} (Group A, n=17); NLR^{Low}/CA19-9^{High} or NLR^{High}/CA19-9^{Low} (Group B, n=25); and NLR^{High}/CA19-9^{High} (Group C, n=24). To this end, the patients in Groups A, B, and C were assigned 0, 1, and 2, respectively, according to the previous study (26). The AUCs for 2-year survival were NLR: 0.647 ($p=0.059$), serum CA19-9 level: 0.672 ($p=0.027$), and combination of NLR and serum CA19-9 level: 0.772 ($p<0.001$), which indicates that the combination of NLR and serum CA19-9 level is more useful than either indicator alone for predicting 2-year survival in these patients (Figure 3). Two-year survival rates were Group A: 58.7%, Group B: 11.2%, and Group C: 0% ($p<0.0001$; Figure 4). Finally, in multivariate analysis, the combination of NLR and serum CA19-9 level was an independent prognostic factor for patients with recurrent PC (Table II).

Table I. Relationships among NLR, serum CA19-9 level, and clinicopathological variables in recurrent pancreatic cancer patients.

Variables (n)	NLR ^{Low} , n (%) 30 (100%)	NLR ^{High} , n (%) 36 (100%)	p-Value	CA19-9 ^{Low} , n (%) 29 (100%)	CA19-9 ^{High} , n (%) 37 (100%)	p-Value
Age (years)						
<70 (27)	13 (43.3%)	14 (38.9%)	0.715	15 (51.7%)	12 (32.4%)	0.114
≥70 (39)	17 (56.7%)	22 (61.1%)		14 (48.3%)	25 (67.6%)	
Gender						
Male (44)	19 (63.3%)	25 (69.4%)	0.6	19 (65.5%)	25 (67.6%)	0.861
Female (22)	11 (36.7%)	11 (30.6%)		10 (34.5%)	12 (32.4%)	
Primary Tumor size (mm) ^a						
<29.5 (35)	18 (60.0%)	17 (50.0%)	0.423	17 (60.7%)	18 (50.0%)	0.393
≥29.5 (29)	12 (40.0%)	17 (50.0%)		11 (39.3%)	18 (50.0%)	
Tumor location						
Head (45)	19 (63.3%)	26 (72.2%)	0.44	19 (65.5%)	26 (70.3%)	0.681
Body and tail (21)	11 (36.7%)	10 (27.8%)		10 (34.5%)	11 (29.7%)	
Lymph node metastasis						
Absent (19)	14 (46.7%)	5 (13.9%)	0.006	12 (41.4%)	7 (18.9%)	0.058
Present (47)	16 (53.3%)	31 (86.1%)		17 (58.6%)	30 (81.1%)	
Lymphatic involvement ^b						
Ly 0/1 (24)	12 (41.4%)	12 (33.3%)	0.504	14 (48.3%)	10 (27.8%)	0.089
Ly 2/3 (41)	17 (58.6%)	24 (66.7%)		15 (51.7%)	26 (72.2%)	
Vascular involvement ^c						
V 0/1 (31)	16 (53.3%)	15 (41.7%)	0.344	18 (62.1%)	13 (35.1%)	0.03
V 2/3 (35)	14 (46.7%)	21 (58.3%)		11 (37.9%)	24 (64.9%)	
Perineural invasion ^d						
Ne 0/1 (9)	6 (20.0%)	3 (8.3%)	0.28	3 (10.3%)	6 (16.2%)	0.72
Ne 2/3 (57)	24 (80.0%)	33 (91.7%)		26 (89.7%)	31 (83.8%)	
Time to recurrence after pancreatectomy						
<12 months; early (40)	16 (53.3%)	24 (66.7%)	0.27	15 (51.7%)	25 (67.6%)	0.191
≥12 months; late (26)	14 (46.7%)	12 (33.3%)		14 (48.3%)	12 (32.4%)	

NLR^{Low}: <1.69; NLR^{High}: ≥1.69; CA19-9^{Low}: <107.95; CA19-9^{High}: ≥107.95. ^adata not available for 2 patients; ^bLymphatic involvement: ly 0-3, grade of lymphatic vessel invasion; data not available for 1 patient; ^cVascular involvement: v 0-3, grade of venous invasion; ^dPerineural invasion: ne 0-3, grade of perineural invasion.

Discussion

The present study demonstrates that both NLR and serum CA19-9 level at the time of PC recurrence are useful for predicting prognosis and supports the notion that both tumor-related markers and patient-related inflammation markers affect prognosis.

Neutrophils play important roles in systemic inflammatory response, which affects both tumor development and metastasis. In response to cytokine stimulation, neutrophils can diverge towards antitumor (N1) or protumor (N2) phenotypes (27). In the acute inflammation state, neutrophils are activated to exert an antitumor effect, whereas in chronic inflammation, neutrophils may promote tumor growth and metastasis. Inflammatory cytokines such as G-CSF, IL-6, and TGF-β1 can induce the N2 phenotype in bone marrow and tumor microenvironments (28). In addition, priming with IFN-γ and TNF-α can convert the phenotype from N2 to N1 (29). Thereby, neutrophils may exert either an antitumor or

protumor function, depending on the profile of inflammatory cytokines. Increased serum concentration of IL-6 was reported in patients with PC (30, 31), which suggests that most of the increased numbers of neutrophils observed in patients with recurrent PC are of the N2 phenotype and may exert a protumor effect. In addition, neutrophils can reportedly induce tumor progression *via* releasing matrix metalloproteinase-9, which activates angiogenic factors (32, 33). This relationship could explain the correlation between high NLR and poor prognosis in the current study.

High NLR also reflects low lymphocyte count, which is also reportedly related to poor prognosis in various cancers, including PC (34-36). Lymphocytes include CD4⁺ and CD8⁺ T cells, NK cells, NKT cells, gamma-delta T cells, and B cells, which are closely associated with tumor immunity. Therefore, low numbers of those cells are likely associated with impaired tumor immunity, which in turn results in tumor progression. In fact, several studies have associated tumor-infiltrating lymphocytes, such as CD4⁺ and CD8⁺

Figure 2. Survival curves of patients with recurrent pancreatic cancer according to NLR (a) and serum CA19-9 level (b).

Figure 3. Receiver operating characteristic curves for NLR (a), serum CA19-9 level (b), and the combination of NLR and serum CA19-9 level (c) for the prediction of 2-year survival after recurrence of pancreatic cancer.

T cells, with poor prognosis in cancers (37-39). Furthermore, for both peripheral blood and cancer tissue, low levels of immune cells, such as NK cells, B cells, and gamma-delta T cell have been associated with poor prognosis for some cancer types (40-42). Therefore, peripheral lymphocyte count might be a good indicator of cell-mediated immune status, including both acquired and adaptive immunity, and humoral immune status against PC. Lymphocyte count is also included in the prognostic nutritional index, which is a representative indicator of nutritional status. Poor nutritional status is reportedly related to poor prognosis in cancer patients. Therefore, peripheral lymphocyte count can reflect inflammation, immunity, and nutritional status, all of which may affect prognosis of patients with recurrent PC.

Serum CA19-9 level and NLR were not significantly related in this study. Serum TMs are mainly derived from the cancers themselves, whereas NLR reflects the patient's inflammation, immunity, and nutritional status. Both tumor- and patient-centered approaches can help predict prognosis of cancer patients. In addition, the usefulness of combining several tumor- or patient-related factors to predict prognosis in patients with PC has been reported (43, 44). The different origins of TMs and NLR suggest that their combination would be superior to either serum CA19-9 level or NLR alone for predicting prognosis of patients with recurrent PC; and indeed, we found that the AUC for 2-year survival of combined serum CA19-9 level and NLR was higher than that of either of them separately. The combination of serum

Table II. Univariate and multivariate analyses of prognostic factors for overall survival in patients with recurrent pancreatic cancer.

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	p-Value	HR	95%CI	p-Value
Age (≥ 70 vs. < 70)	1.272	0.698-2.319	0.432			
Gender (male vs. female)	1.106	0.587-2.085	0.755			
Primary tumor size (≥ 29.5 mm vs. < 29.5 mm)	1.538	0.847-2.795	0.158			
Tumor location (head vs. body and tail)	1.047	0.565-1.941	0.884			
Lymph node metastasis (present vs. absent)	2.071	1.078-3.978	0.029	1.263	0.614-2.598	0.526
Lymphatic involvement (ly 0/1 vs. ly 2/3) ^a	1.520	0.807-2.861	0.195			
Vascular involvement (v 0/1 vs. v 2/3) ^b	1.952	1.078-3.534	0.027	1.253	0.661-2.377	0.490
Perineural invasion (ne 0/1 vs. ne 2/3) ^c	2.020	0.723-5.642	0.180			
Chemotherapy (present vs. absent)	0.560	0.276-1.137	0.108			
Time to recurrence after pancreatectomy (< 12 months vs. ≥ 12 months)	2.372	1.277-4.523	0.009	1.901	0.987-3.662	0.055
Combination of NLR and serum CA19-9 level			< 0.001			0.001
Group C vs. Group A	7.703	3.041-19.512	< 0.001	5.912	2.229-15.683	< 0.001
Group B vs. Group A	3.379	1.328-8.600	0.011	3.077	1.195-7.920	0.020

CI: Confidence interval; HR: hazard ratio. Group A: NLR^{Low}/CA19-9^{Low}; Group B: NLR^{Low}/CA19-9^{High} or NLR^{High}/CA19-9^{Low}; Group C: NLR^{High}/CA19-9^{High}. ^aLymphatic involvement: ly 0-3, grade of lymphatic vessel invasion; ^bVascular involvement: v 0-3, grade of venous invasion; ^cPerineural invasion: ne 0-3, grade of perineural invasion.

Figure 4. Overall survival curves after recurrence according to the combination of NLR and serum CA19-9 level. Group A: NLR^{Low}/CA19-9^{Low}; Group B: NLR^{Low}/CA19-9^{High} or NLR^{High}/CA19-9^{Low}; Group C: NLR^{High}/CA19-9^{High}.

CA19-9 level and NLR was also an independent prognostic indicator in our multivariate analysis.

This study has a certain limitations. First, it is a retrospective analysis, which could generate some bias. Second, although NLR and serum CA19-9 level were measured at the time of recurrence, the optimal time to measure them with respect to prognosis remains unclear. Third, the number of patients included in this study was small; a large-scale, prospective study is needed to verify our results.

In conclusion, the combination of NLR and serum CA19-9 level is a useful indicator of recurrent pancreatic cancer prognosis. Because peripheral blood cell count is a quick, easy, and non-invasive assay, combined NLR and serum CA19-9 level could be an inexpensive and practical marker for prognosis of patients with recurrent PC.

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