

The Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio Are Prognostic Factors in Patients with Locally Advanced Pancreatic Cancer Treated with Chemoradiotherapy

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See editorial on page 223.

Background/Aims: We investigated whether inflammatory markers such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) independently and in combination would be significant prognostic factors for survival in patients with locally advanced pancreatic cancer. **Methods:** A total of 497 patients with locally advanced pancreatic cancer who received neoadjuvant or definitive chemoradiotherapy from 2005 to 2015 were evaluated. We divided the patients into groups according to the median values of NLR and PLR: NLR < 1.89 (n=156), NLR ≥ 1.89 (n=341), PLR < 149 (n=248) and PLR ≥ 149 (n=249). **Results:** For NLR < 1.89 and ≥ 1.89 groups, respectively, the 1-year overall survival (OS) rates were 73.2% and 60.8% (p < 0.001) and 1-year progression-free survival (PFS) rates were 43.9% and 31.3% (p < 0.001). For PLR < 149 and ≥ 149 groups, respectively, the 1-year OS rates were 68.1% and 61.3% (p = 0.029) and 1-year PFS rates were 37.9% and 32.5% (p = 0.027). Patients with both high NLR and high PLR showed the worst OS and PFS rates compared with those with both lower NLR and lower PLR. **Conclusions:** Elevated pretreatment NLR and PLR independently and in combination significantly predicted poor OS and PFS. (*Gut Liver* 2018;12:342-352)

Key Words: Pancreatic neoplasms; Prognosis; Neutrophils; Platelet count; Lymphocyte count

INTRODUCTION

Among major solid tumors, pancreatic cancer is well known

for its poor prognosis.¹ Although surgical treatment is the treatment of choice for pancreatic cancer, only 20% of patients are candidates for curative resection.² Pancreatic cancer is considered to be resectable when the tumor is not in contact with major arteries (celiac axis, superior mesenteric artery, or common hepatic artery) or major veins (superior mesenteric vein or portal vein). If the patient has locally advanced, such as unresectable or borderline resectable, pancreatic cancer, chemotherapy or definitive or preoperative concurrent chemoradiotherapy (CCRT) is recommended, and the survival is much poorer than those with resectable tumors.³ Thus, it is important to find the prognostic factors for patients with locally advanced pancreatic cancer and set an optimal treatment plan.

Recently, the notion that the outcome of cancer patients is affected not only by tumor characteristics but also by host-related factors has gained much attention. Host factors such as age, sex, performance status, and inflammatory status have been identified as significant prognostic factors in many reports.⁴⁻⁶ As it has become apparent that cancer-associated inflammation is a key determinant of disease progression and survival for cancer patients, there has been much interest in the relationship between patient prognosis and inflammatory hematologic markers.^{7,8} Among inflammatory hematologic markers, the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) are well-known hematologic markers, and studies have suggested that NLR and PLR are associated with the outcome of cancer patients.^{5,7}

Although there are many studies reporting the significance of NLR and PLR as prognostic factors in pancreatic cancer, almost none have shown the efficacy of NLR and PLR in patients with locally advanced pancreatic cancer receiving CCRT.^{7,9-13} Thus, this study aimed to investigate whether NLR and PLR are

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associated with the survival outcomes of patients with locally advanced pancreatic cancer treated with CCRT.

MATERIALS AND METHODS

1. Patients

We retrospectively examined the medical records of patients with locally advanced pancreatic cancer who had undergone neoadjuvant or definitive CCRT from January 2005 to December 2015. All patients who had previously received any other treatment, patients who had been diagnosed with a double primary malignancy, patients with distant metastasis at diagnosis, patients who had received RT alone or under 20 Gy, patients with no follow-up imaging, and patients with a neuroendocrine tumor were excluded. Finally, 497 patients were included in the analysis. We retrospectively collected and analyzed patient data, including clinical and laboratory information including white blood cell differential counts and platelet counts. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count. All NLR and PLR values were measured before the start of treatment within 2 weeks. The resectability of pancreatic tumors was determined based on imaging studies including computed tomography (CT) and magnetic resonance imaging (MRI).

The study was approved by the Institutional Review Board of Severance Hospital (IRB No. 2017-3183-01) and performed in accordance with the principles of the Declaration of Helsinki. The informed consent was waived for this retrospective study.

2. Treatment

All patients included in this study received initial preoperative or definitive CCRT.

For RT, CT simulation was performed with intravenous contrast and four-dimensional CT when possible, and respiration training was done to minimize the respiration motion. The primary tumor and involved lymph nodes were set as the gross tumor volume (GTV). The internal target volume (ITV) was delineated when possible, and the planning target volume (PTV) was defined as the GTV or ITV plus a 5-mm margin. A total of 281 patients (56.5%) received three-dimensional conformal RT (3DCRT), and the remaining 216 patients (43.5%) received intensity-modulated radiotherapy (IMRT). The most commonly used dose scheme was 50.4 Gy in 28 patients for 3DCRT patients and 58.42 Gy in 23 fractions for IMRT patients.

For chemotherapy, various chemotherapy regimens were used: (1) 1,000 mg/m² gemcitabine weekly (days 1, 8, and 15) followed by a 1-week rest period; (2) 75 mg/m² cisplatin on day 1 of each 28-day cycle combined with weekly 1,000 mg/m² gemcitabine; (3) 500 mg/m² fluorouracil weekly; (4) 850 mg/m² capecitabine twice daily; (5) 40 mg/m² titanium silicate-1 twice daily from days 1 to 14 and from days 22 to 35; and (6) 0.5 g

tegafur/uracil three times daily. The primary aim was to administer full-dose chemotherapy.

3. Response assessment

Routine follow-up was performed at 1 and 3 months after CCRT and routinely after that. The Response Evaluation Criteria in Solid Tumors were used to evaluate the treatment response. The progression of the disease was observed based on imaging studies such as CT or MRI. The recurrence of tumor, increased size of primary tumor, or development of regional or distant metastasis was defined as progression.

4. Statistical analysis

The primary endpoint of our study was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), local failure-free rate (LFFR), and distant failure-free rate (DFFR). All endpoints were calculated from the first date of treatment to the date of the event. The Kaplan-Meier methods and log-rank test were used to calculate the cumulative probabilities of OS, PFS, LFFR, and DFFR. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Multivariate analysis was performed using the statistically significant factors proven using univariate analysis. The SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for all analyses.

RESULTS

1. Patient and tumor characteristics

Patient and tumor characteristics are shown in Table 1. We divided the patients into groups based on receiver operating characteristics value for the pretreatment NLR and the median value for PLR. The value of NLR and PLR before treatment were 1.89 and 149 respectively. For the two groups divided by the receiver operating characteristics value of NLR, characteristics such as age, sex, Eastern Cooperative Oncology Group (ECOG) status, pathology, tumor stage (T stage), node stage (N stage), chemotherapy regimen, resectability and RT dose did not show significant difference between the two groups. However, there were more patients with tumor size >3.1 cm and less patients with pancreatic head tumor in the higher NLR group. Regarding the two groups divided by the median value of PLR, most patient and tumor characteristics did not differ, except for the subsite and T stage. More patients had a pancreas head tumor in the higher PLR group. However, more patients had T4 stage disease in the lower PLR group.

2. Overall survival

The median follow-up was 19.3 months (range, 4.8 to 128.5 months). The median OS was 15.7 months. The OS was significantly lower in the NLR \geq 1.89 group than the NLR <1.89 group (Fig. 1A). The 1-year OS rates were 73.2% and 60.8% for

Table 1. Patient and Tumor Characteristics

Characteristic	Total (n=497)	NLR<1.89 (n=156)	NLR≥1.89 (n=341)	p-value	PLR<149 (n=248)	PLR≥149 (n=249)	p-value
Age, yr	64 (35–88)	62 (35–83)	64 (35–88)	0.198	63 (35–88)	64 (35–87)	0.682
≤64	272 (54.7)	92 (59.0)	180 (52.8)		138 (55.6)	134 (53.8)	
>64	225 (45.3)	64 (41.0)	161 (47.2)		110 (44.4)	115 (46.2)	
Sex				0.091			0.687
Female	202 (40.6)	72 (46.2)	130 (38.1)		103 (41.5)	99 (39.8)	
Male	295 (59.4)	84 (53.8)	211 (61.9)		145 (58.5)	150 (60.2)	
ECOG				0.924*			0.374*
ECOG 0	131 (26.4)	41 (26.3)	90 (26.4)		71 (28.6)	60 (24.1)	
ECOG 1	358 (72.0)	113 (72.4)	245 (71.8)		172 (69.4)	186 (74.7)	
ECOG 2	8 (1.6)	2 (1.3)	6 (1.8)		5 (2.0)	3 (1.2)	
Pathology				0.157*			0.517*
Adenoca	413 (83.1)	135 (86.5)	278 (81.5)		209 (84.3)	204 (81.9)	
Adenosquamous carcinoma	5 (1.0)	0	5 (1.5)		3 (1.2)	2 (0.8)	
Poor differentiated	5 (1.0)	0	5 (1.5)		1 (0.4)	4 (1.6)	
Unknown	74 (14.9)	21 (13.5)	53 (15.5)		35 (14.1)	39 (15.7)	
Subsite				0.014			0.003
Head	345 (69.4)	120 (76.9)	225 (66.0)		157 (63.3)	188 (75.5)	
Not head	152 (30.6)	36 (23.1)	116 (34.0)		91 (36.7)	61 (24.5)	
Clinical T stage				0.277*			0.013*
T1	7 (1.4)	4 (2.6)	3 (0.9)		3 (1.2)	4 (1.6)	
T2	33 (6.6)	8 (5.1)	25 (7.3)		12 (4.8)	21 (8.4)	
T3	204 (41.0)	69 (44.2)	135 (39.6)		89 (35.9)	115 (46.2)	
T4	253 (50.9)	75 (48.1)	178 (52.2)		144 (58.1)	109 (43.8)	
Clinical N stage				0.584			0.826
N0	297 (59.8)	96 (61.5)	201 (58.9)		147 (59.3)	150 (60.2)	
N1	200 (40.2)	60 (38.5)	140 (41.1)		101 (40.7)	99 (39.8)	
Tumor size, cm	3.10 (1.20–9.00)	3.00 (1.20–6.00)	3.30 (1.20–9.00)	0.006	3.20 (1.20–9.00)	3.00 (1.20–9.00)	0.346
≤3.1	251 (50.5)	93 (59.6)	158 (46.3)		120 (48.4)	131 (52.6)	
>3.1	246 (49.5)	63 (40.4)	183 (53.7)		128 (51.6)	118 (47.4)	
Resectability				0.132			0.049
Unresectable	378 (76.1)	112 (71.8)	266 (78.0)		198 (79.8)	180 (72.3)	
Borderline	119 (23.9)	44 (28.2)	75 (22.0)		50 (20.2)	69 (27.7)	
Chemotherapy regimen				0.668			0.501
Gemcitabine based	251 (50.5)	81 (51.9)	170 (49.9)		129 (52.0)	122 (49.0)	
Not gemcitabine based	246 (49.5)	75 (48.1)	171 (50.1)		119 (48.0)	127 (51.0)	
CA 19-9	304.5 (0–20,000)	211.80 (0.10–20,000)	374.00 (0–20000)	0.031	305.0 (0.10–20,000)	304.0 (0–20,000)	0.893
≤304.5	247 (49.9)	89 (57.1)	158 (46.6)		122 (49.6)	125 (50.2)	
>304.5	248 (50.1)	67 (42.9)	181 (53.4)		124 (50.4)	124 (49.8)	
RT modality				0.876			0.826
3DCRT	281 (56.5)	89 (57.1)	192 (56.3)		139 (56.0)	142 (57.0)	
IMRT+TOMO	216 (43.5)	67 (42.9)	149 (43.7)		109 (44.0)	107 (43.0)	
TD EQD2	49.56 (24.42–64.31)	49.56 (38.44–62.00)	49.56 (24.42–64.31)		49.56 (24.42–64.31)	49.56 (42.47–62.00)	

Data are presented median (range) or number (%).

NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group; CA, carbohydrate antigen; RT, radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; TOMO, tomotherapy; TD, total dose; EQD2, equivalent dose in 2 Gy fractions.

*Fisher exact test.

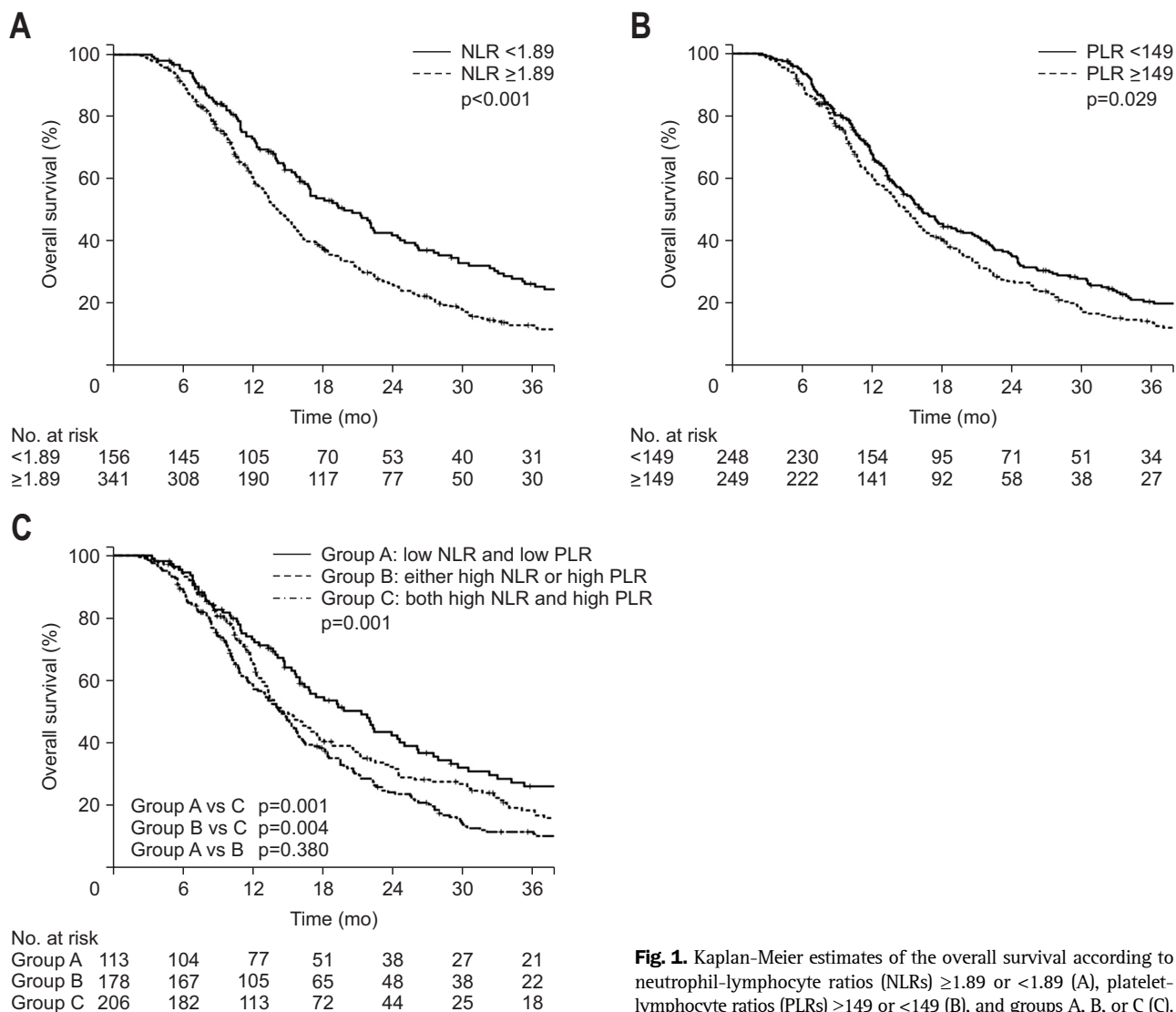


Fig. 1. Kaplan-Meier estimates of the overall survival according to neutrophil-lymphocyte ratios (NLRs) ≥1.89 or <1.89 (A), platelet-lymphocyte ratios (PLRs) ≥149 or <149 (B), and groups A, B, or C (C).

NLR <1.89 and NLR ≥1.89 groups, respectively (p<0.001). The OS also showed a significant difference when the patients were divided by the median PLR value (Fig. 1B). The 1-year OS rates were 68.1% and 61.3% for PLR <149 and PLR ≥149 groups, respectively (p=0.029).

We divided the patients into three groups according to both the NLR and PLR. Group A included patients with both low NLR and low PLR (n=113), group B included patients with either high NLR or high PLR (n=178), and group C included patients with both high NLR and high PLR (n=206). The 1-year OS rates showed difference between the three groups: 73.3%, 65.9%, and 58.9% for groups A, B, and C, respectively (p=0.001) (Fig. 1C). Although the OS rates were not significantly different between groups A and B, the OS rate of group C was significantly lower than those of groups A and B.

As shown in Tables 2-4, univariate analysis for OS showed that age, sex, ECOG status, tumor size, resectability, CA 19-9 level, NLR, PLR, and grouping of NLR and PLR were significant

prognostic factors. Multivariate analysis was also performed and tumor size >3.1 cm (HR, 1.35; 95% CI, 1.09 to 1.66; p=0.005), CA 19-9 >304.5 U/mL (HR, 1.32; 95% CI, 1.08 to 1.61; p=0.006), NLR ≥1.89 (HR, 1.40; 95% CI, 1.12 to 1.75; p=0.003) and PLR ≥149 (HR, 1.35; 95% CI, 1.11 to 1.65; p=0.003) proved to be significant adverse factors for OS. The significant beneficial factors for OS were ECOG score 0 (HR, 0.40; 95% CI, 0.19 to 0.84; p=0.016) and ECOG score 1 (HR, 0.48; 95% CI, 0.24 to 0.98; p=0.046) compared with ECOG score 2 and borderline resectable tumor (HR, 0.62; 95% CI, 0.47 to 0.81; p<0.001). In addition, both lower NLR and lower PLR compared with both higher NLR and higher LR (HR, 0.62; 95% CI, 0.47 to 0.81; p=0.001) and either higher NLR or higher PLR compared with both higher values (HR, 0.73; 95% CI, 0.58 to 0.91; p=0.007) proved to be beneficial factors for OS.

We additionally analyzed the 1-year OS rates of different subgroups. Overall, 105 patients (21.1%) had undergone surgery after CCRT. Fifty-two patients (13.8%) in the unresectable

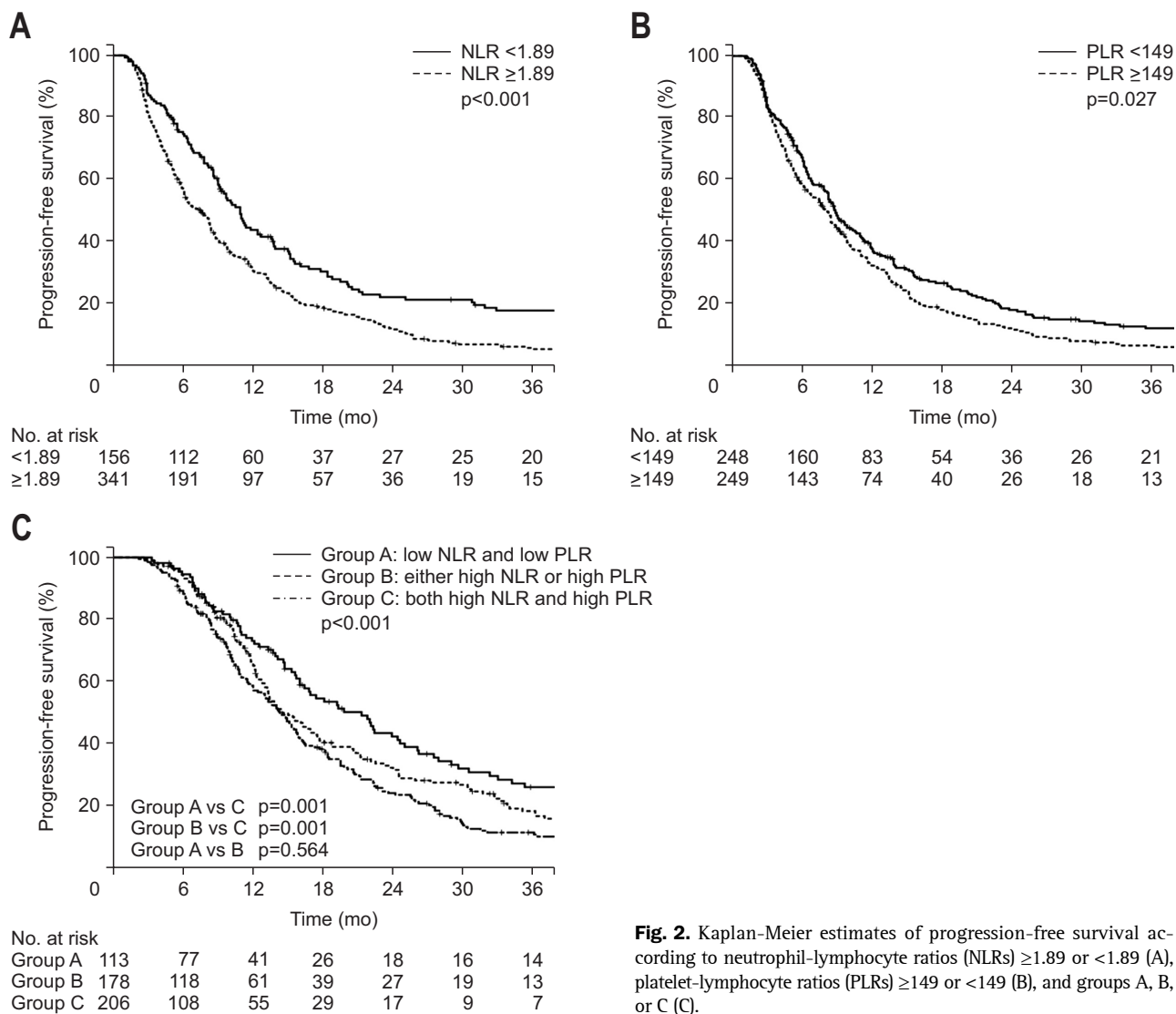


Fig. 2. Kaplan-Meier estimates of progression-free survival according to neutrophil-lymphocyte ratios (NLRs) ≥1.89 or <1.89 (A), platelet-lymphocyte ratios (PLRs) ≥149 or <149 (B), and groups A, B, or C (C).

group and 53 (44.5%) in the borderline resectable group had undergone surgery. The 1-year OS rates were 87.4% for the surgery group and 58.2% for the non-surgery group, respectively (p<0.001).

3. Progression-free survival

The PFS showed a significant difference between the groups divided by NLR and PLR values. The 1-year PFS rates were 43.9% and 31.3% for NLR <1.89 and NLR ≥1.89 groups, respectively (p<0.001) (Fig. 2A). For PLR, the 1-year PFS rates were 37.9% and 32.5% for PLR <149 and PLR ≥149 groups, respectively (p=0.027) (Fig. 2B). We also examined the PFS for groups A, B, and C, with similar results as those for OS. The 1-year PFS rates for groups A, B, and C were 41.7%, 38.5%, and 29%, respectively (p<0.001) (Fig. 2C). Although there was no significant difference in PFS between groups A and B, the PFS rate of group C was significantly lower than those of groups A and B.

On univariate analysis, sex, tumor size, CA 19-9 level, NLR,

PLR, and grouping of NLR and PLR proved to be significant prognostic factors for PFS (Table 2-4). Among these factors, tumor size >3.1 cm (HR, 1.39; 95% CI, 1.15 to 1.69; p=0.001), CA19-9 >304.5 U/mL (HR, 1.35; 95% CI, 1.11 to 1.63; p=0.002), NLR ≥1.89 (HR, 1.44; 95% CI, 1.16 to 1.78; p=0.001), and PLR ≥149 (HR, 1.28; 95% CI, 1.06 to 1.56; p=0.009) proved to be significant adverse factors for PFS. Significant favorable factors for PFS was both lower NLR and lower PLR compared with both higher NLR and higher PLR (HR, 0.63; 95% CI, 0.49 to 0.982; p=0.001) and either higher NLR or higher PLR compared with both higher values (HR, 0.69; 95% CI, 0.56 to 0.86; p=0.001).

4. Local failure-free rate and distant failure-free rate

When the patients were divided into two groups according to NLR, there was a significant difference for both LFFR and DFFR. The 1-year LFFR was 56.9% and 42.4% (p=0.03) and the 1-year DFFR was 539.2% and 44.0% (p=0.001) for NLR <1.89 and NLR ≥1.89 groups, respectively (Fig. 3).

Table 2. Univariate and Multivariate Analyses of NLR in Overall Survival and Progression-Free Survival

	Overall survival				Progression-free survival				
	UVA		MVA		UVA		MVA		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (≤64 vs >64)	1.26	1.04–1.54	0.021	1.17	0.96–1.43	0.117	1.18	0.98–1.43	0.08
Sex (female vs male)	1.33	1.09–1.63	0.006				1.25	1.03–1.52	0.025
ECOG			0.038			0.026			0.559
ECOG (ECOG 2 vs 0)	0.39	0.19–0.80	0.011	0.37	0.18–0.78	0.009	0.7	0.34–1.43	0.327
ECOG (ECOG 2 vs 1)	0.42	0.21–0.85	0.016	0.44	0.21–0.90	0.025	0.75	0.37–1.52	0.422
Pathology			0.001			0.003			0.001
Pathology (adenoca vs adenoSCCa)	0.91	0.69–1.19	0.494	0.83	0.63–1.10	0.19	0.58	0.22–1.58	0.29
Pathology (adenoca vs PD)	0.73	0.27–1.02	0.55	0.51	0.18–1.42	0.197	5.59	2.29–13.64	<0.001
Subsite (head vs other)	1.16	0.94–1.43	0.18				1.2	0.98–1.47	0.08
T stage			0.051						0.47
(T1 vs T2)	0.34	0.13–0.93	0.035				0.52	0.21–1.26	0.15
(T1 vs T3)	0.99	0.67–1.46	0.97				0.9	0.61–1.31	0.57
(T1 vs T4)	0.81	0.66–1.00	0.052				1.02	0.83–1.24	0.88
N stage (N0 vs N1)	0.99	0.81–1.21	0.9				1.05	0.87–1.27	0.63
Size (≤3.1 vs >3.1)	1.41	1.16–1.73	0.001	1.28	1.04–1.57	0.02	1.4	1.16–1.70	<0.001
Resectability (unresectable vs borderline)	0.62	0.48–0.80	<0.001	0.65	0.50–0.86	0.002	0.83	0.66–1.04	0.106
Chemotherapy (gemcitabine vs not gemcitabine)	1.028	0.84–1.26	0.783				1.17	0.97–1.42	0.098
CA 19-9 (≤304.5 vs >304.5)	1.35	1.11–1.64	0.003	1.3	1.06–1.59	0.009	1.38	1.14–1.67	0.001
NLR (<1.89 vs ≥1.89)	1.55	1.25–1.93	<0.001	1.4	1.12–1.75	0.003	1.53	1.24–1.89	<0.001
									1.44
									1.16–1.78
									0.001

NLR, neutrophil-lymphocyte ratio; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SCCa, squamous cell carcinoma; PD, poorly differentiated; CA, carbohydrate antigen.

Table 3. Univariate and Multivariate Analyses of PLR in Overall Survival and Progression-Free Survival

	Overall survival				Progression-free survival				
	UVA		MVA		UVA		MVA		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (≤64 vs >64)	1.26	1.04–1.54	0.021	1.19	0.98–1.46	0.076	1.18	0.98–1.43	0.08
Sex (female vs male)	1.33	1.09–1.63	0.006				1.25	1.03–1.52	0.025
ECOG			0.038			0.028			0.559
ECOG (ECOG 2 vs 0)	0.39	0.19–0.80	0.011	0.38	0.18–0.79	0.01	0.7	0.34–1.43	0.327
ECOG (ECOG 2 vs 1)	0.42	0.21–0.85	0.016	0.43	0.21–0.89	0.024	0.75	0.37–1.52	0.422
Pathology			0.001			0.002			0.001
Pathology (adenoca vs adenoSCCa)	0.91	0.69–1.19	0.494	0.8	0.61–1.06	0.118	0.58	0.22–1.58	0.29
Pathology (adenoca vs PD)	0.73	0.27–1.02	0.55	0.54	0.19–1.51	0.241	5.59	2.29–13.64	<0.001
Subsite (head vs other)	1.16	0.94–1.43	0.18				1.2	0.98–1.47	0.08
T stage			0.051						0.47
(T1 vs T2)	0.34	0.13–0.93	0.035				0.52	0.21–1.26	0.15
(T1 vs T3)	0.99	0.67–1.46	0.97				0.9	0.61–1.31	0.57
(T1 vs T4)	0.81	0.66–1.00	0.052				1.02	0.83–1.24	0.88
N stage (N0 vs N1)	0.99	0.81–1.21	0.9				1.05	0.87–1.27	0.63
Size (≤3.1 vs >3.1)	1.41	1.16–1.73	0.001	1.38	1.12–1.70	0.003	1.4	1.16–1.70	<0.001
Resectability (unresectable vs borderline)	0.62	0.48–0.80	<0.001	0.61	0.46–0.80	<0.001	0.83	0.66–1.04	0.106
Chemotherapy (gemcitabine vs not gemcitabine)	1.028	0.84–1.26	0.783				1.17	0.97–1.42	0.098
CA 19-9 (≤304.5 vs >304.5)	1.35	1.11–1.64	0.003	1.32	1.08–1.61	0.006	1.38	1.14–1.67	0.001
PLR (<149 vs ≥149)	1.24	1.02–1.50	0.029	1.35	1.11–1.65	0.003	1.24	1.02–1.49	0.028
									1.28
									1.16–1.71
									<0.001
									0.106
									0.098
									0.001
									1.34
									1.10–1.61
									0.003
									1.06–1.56
									0.009

PLR, platelet-lymphocyte ratio; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SCCa, squamous cell carcinoma; PD, poorly differentiated; CA, carbohydrate antigen.

Table 4. Univariate and Multivariate Analyses of NLR and PLR in Overall Survival and Progression-Free Survival

	Overall survival					Progression-free survival						
	UVA			MVA		UVA			MVA			
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (≤64 vs >64)	1.26	1.04-1.54	0.021	1.19	0.97-1.45	0.09	1.18	0.98-1.43	0.08	1.18	0.98-1.43	0.08
Sex (female vs male)	1.33	1.09-1.63	0.006				1.25	1.03-1.52	0.025			
ECOG			0.038			0.033			0.559			
ECOG (ECOG 2 vs 0)	0.39	0.19-0.80	0.011	0.4	0.19-0.84	0.016	0.7	0.34-1.43	0.327			
ECOG (ECOG 2 vs 1)	0.42	0.21-0.85	0.016	0.48	0.24-0.98	0.046	0.75	0.37-1.52	0.422			
Pathology			0.001			0.002			0.001			
Pathology (adenoca vs adenoSCCa)	0.91	0.69-1.19	0.494	0.8	0.61-1.06	0.129	0.58	0.22-1.58	0.29			
Pathology (adenoca vs PD)	0.73	0.27-1.02	0.55	0.51	0.18-1.43	0.203	5.59	2.29-13.64	<0.001			
Subsite (head vs other)	1.16	0.94-1.43	0.18				1.2	0.98-1.47	0.08			
T stage			0.051						0.47			
(T1 vs T2)	0.34	0.13-0.93	0.035				0.52	0.21-1.26	0.15			
(T1 vs T3)	0.99	0.67-1.46	0.97				0.9	0.61-1.31	0.57			
(T1 vs T4)	0.81	0.66-1.00	0.052				1.02	0.83-1.24	0.88			
N stage (N0 vs N1)	0.99	0.81-1.21	0.9				1.05	0.87-1.27	0.63			
Size (≤3.1 vs >3.1)	1.41	1.16-1.73	0.001	1.35	1.09-1.66	0.005	1.4	1.16-1.70	<0.001	1.39	1.15-1.69	0.001
Resectability (unresectable vs borderline)	0.62	0.48-0.80	<0.001	0.62	0.47-0.81	0.001	0.83	0.66-1.04	0.106			
Chemotherapy (gemcitabine vs not gemcitabine)	1.03	0.84-1.26	0.783				1.17	0.97-1.42	0.098			
CA 19-9 (≤304.5 vs >304.5)	1.35	1.11-1.64	0.003	1.32	1.08-1.61	0.006	1.38	1.14-1.67	0.001	1.35	1.11-1.63	0.002
NLR and PLR group			0.001			0.001			<0.001			<0.001
Group C vs group A	0.60	0.46-0.79	<0.001	0.62	0.47-0.81	0.001	0.61	0.47-0.79	<0.001	0.63	0.49-0.82	0.001
Group C vs group B	0.82	0.65-1.02	0.072	0.73	0.58-0.91	0.007	0.75	0.61-0.93	0.009	0.69	0.56-0.86	0.001

NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SCCa, squamous cell carcinoma; PD, poorly differentiated.

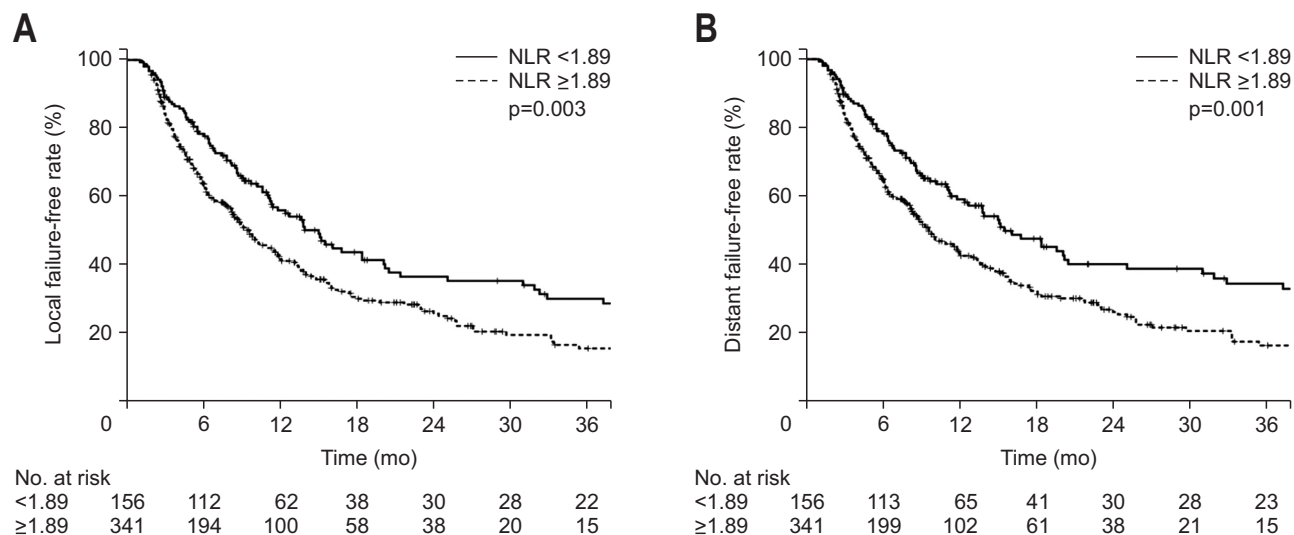


Fig. 3. Kaplan-Meier estimates of local failure-free rate (A) and distant failure-free rate (B) according to neutrophil-lymphocyte ratios (NLRs) ≥1.89 or <1.89.

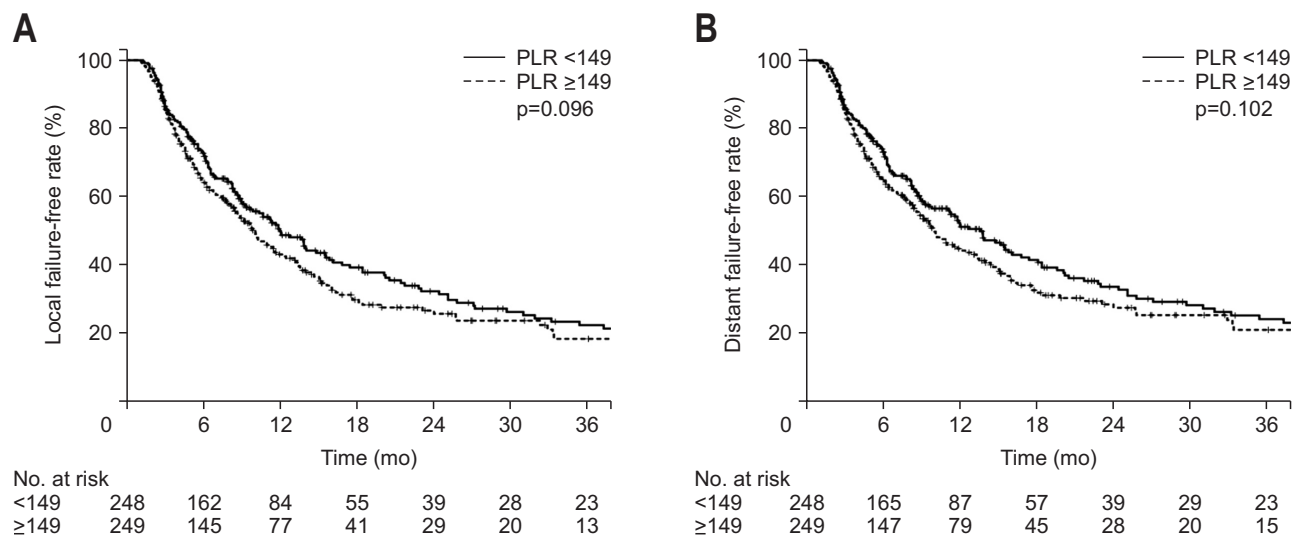


Fig. 4. Kaplan-Meier estimates of local failure-free rate (A) and distant failure-free rate (B) according to platelet-lymphocyte ratios (PLRs) ≥149 or <149.

When the patients were divided by a PLR value of 149, there was no significant difference in either LFFR or DFFR. The 1-year LFFR was 50.2% and 43.4% ($p=0.096$) and the 1-year DFFR was 52.7% and 45.1% ($p=0.102$) for PLR <149 and PLR ≥149 groups, respectively (Fig. 4).

DISCUSSION

It is well known that tumor characteristics such as tumor size, tumor stage, and CA 19-9 level are considered meaningful factors to predict a pancreatic cancer patient's prognosis.^{14,15} Recently, other studies have suggested that inflammation is associated with a poor prognosis in cancer patients.^{16,17} This study aimed to investigate the role of NLR and PLR in predicting the

prognosis of patients with locally advanced pancreatic cancer who had undergone preoperative or definitive CCRT. Our results showed that patients with high NLR or PLR showed worse OS and PFS than those with lower NLR or PLR. When both values were taken into consideration, the group with both high NLR and high PLR showed the worst OS and PFS.

Many previous reports have shown the prognostic value of NLR and PLR and their significance as prognostic markers is becoming increasingly important. For example, a study with 403 advanced pancreatic cancer patients reported that $NLR \geq 3.1$ was a significant adverse factor for OS.¹⁸ Another study showed that $NLR \geq 3.3$ was a negative factor for 67 elderly patients with unresectable pancreatic cancer, and other studies have shown $NLR > 5$, $NLR \geq 2.551$, and $NLR \geq 2.0$ as significant prognostic values

for OS.^{7,9,11,19-21} PLR ≥ 126 was an important prognostic factor in a study involving 321 locally advanced and metastatic pancreatic cancer patients.⁴ Other studies have shown PLR ≥ 208.1 , PLR ≥ 200 , and PLR > 150 to be significant prognostic markers.^{7,9,13} Although reports concerning PLR are less common in pancreatic cancer than those relating to NLR, it has been reported to be a prognostic factor in many other malignancies.^{22,23} In our study, both NLR and PLR proved to be a useful prognostic factor for both OS and PFS.

Currently, there is no consensus on the cutoff value of NLR and PLR, and thus, various cutoff values were used in previous studies. In some studies, the receiver operating characteristic curve was used for determining the cutoff value, and in some studies, median values were used.^{4,9,18,21,24} Some other studies have used cutoff values of 5 for NLR and 150 for PLR.^{13,19,25,26} Our study set the cutoff values of NLR and PLR using their median values.

In this study, we additionally analyzed OS and PFS taking both NLR and PLR into consideration. The group of patients with both high NLR and high PLR showed the worst OS and PFS. To the best of our knowledge, this is the first study to incorporate both values into the analysis, and these results may aid in adequately determining the prognosis in patients with locally advanced pancreatic cancer.

Currently, the mechanisms responsible for high NLR and PLR being related to poor outcomes of cancer patients are not entirely understood. What is known is that inflammation status promotes tumor proliferation and helps the survival of the malignant tumor.²⁷ Furthermore, factors related to inflammation stimulate angiogenesis of the malignant tumor, invasion, and metastasis.²⁸ As NLR and PLR represent the inflammation status of the host, a high NLR and PLR can be related to a poor prognosis for cancer patients. A high NLR represents both an elevated level of neutrophils and a decreased level of lymphocytes. Lymphocytes are known to mediate the anti-tumor response and neutrophils are known to release cytokines, such as interleukins-1 and -6, and tumor necrosis factor, which promote cancer growth, angiogenesis, and metastasis.²⁹ Therefore, a high NLR, in which a decreased lymphocyte count can be connected to a decreased immune response, and an elevated neutrophil count, which can be related to tumor progression, has the potential to be a significant adverse prognostic factor for cancer patients.

There are several limitations in our study. First, as this is a retrospective study, the heterogeneity of the patients and treatment may have affected the results. Second, although neutrophil and lymphocyte counts can be influenced by infection, drugs, or other factors, we did not consider these factors, which may have biased the results. However, beyond these limitations, this study also has several strengths. Although there are many reports on inflammation and prognosis, the number of patients included in this study is one of the largest in a single institu-

tion. In addition, only the patients who received preoperative or definitive CCRT as initial treatment in our institution were included, which may have reduced some bias. Furthermore, NLR or PLR can be easily measured using peripheral blood samples, which is excellent for its usefulness as a prognostic marker.

In summary, this study showed that higher NLR or PLR is related to poor OS and PFS and high NLR is related to poor LFFR and DFFR. Furthermore, when both NLR and PLR values were high, the results were the worst for OS and PFS. Based on these results, parameters showing systemic inflammation such as NLR and PLR can be useful markers for predicting the prognosis for advanced pancreatic cancer patients. Further studies will be needed to validate the usefulness and effectiveness of these inflammatory markers in advanced pancreatic cancer patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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