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Lymphocyte–to–Monocyte Ratio and Prognostic Nutritional Index Predict Poor Prognosis in Patients on Chemotherapy for Unresectable Pancreatic Cancer

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Abstract. *Background/Aim: Recently, several systemic inflammation-based scores, such as neutrophil–to–lymphocyte ratio (NLR), platelet–to–lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), modified Glasgow prognostic score (GPS), and prognostic nutritional index (PNI), have been proposed as prognostic factors for several cancers. In this study, we aimed to determine the influence of systemic inflammation-based scores and nutrition status on the outcome in patients receiving chemotherapy for unresectable pancreatic cancer. Patients and Methods: A total of 93 consecutive patients who underwent chemotherapy for unresectable pancreatic cancer at Osaka Medical College Hospital, Takatsuki, Japan, between January 2008 and December 2014 were eligible for this study. The outcomes assessment included one- and two-year overall survival (OS) rates, according to changes in LMR and PNI prior to, and following chemotherapy. Results: LMR<3.4 (OR=5.02, 95%CI=1.559-19.85, p=0.005) and PNI<43 (OR=3.53, 95%CI=1.057-14.21, p=0.03) independently predicted a poor outcome in patients receiving chemotherapy for unresectable pancreatic cancer using multivariate analysis. According to changes in LMR and PNI prior to, and following chemotherapy, compared to patients who maintained LMR≥3.4, patients whose LMR decreased from ≥3.4 to <3.4 had significantly lower OS rates (p<0.001). Similarly, compared to patients who maintained PNI≥43, patients whose PNI deteriorated had significantly lower OS rates (56.2% versus 25.8% at one year, and 12.5% versus 0% at two years; p=0.003). Conclusion: LMR<3.4 and PNI<43 are identified as independent predictors of poor outcome in patients receiving chemotherapy for unresectable pancreatic cancer. LMR and PNI may help clinicians identify patients at high risk for poor prognosis.*

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Pancreatic cancer is one of the most dismal malignancies worldwide), and more than 80% of patients are diagnosed at an inoperable stage (1). Current available prognostic factors, such as pathological findings and CA19-9, are very useful and reliable (2). However, these factors are insufficient in predicting outcomes in patients with unresectable pancreatic cancer.

Recently, several systemic inflammation-based scores, such as Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), modified Glasgow prognostic score (GPS), and prognostic nutritional index (PNI), have been proposed as prognostic factors for several cancers (3-8). These scores can be readily calculated from simple, low cost, and easily accessible blood tests. However, associations between these systemic inflammation-based scores and prognosis of patients receiving chemotherapy for unresectable pancreatic cancer are seldom discussed. To select optimal therapeutic strategies and predict the prognosis of individual patients, particularly those with unresectable pancreatic cancer, identification of reliable markers, based on biological reaction to tumors, is absolutely imperative. Additionally, markers should reflect the physical reaction against the tumor as much as possible. For these reasons, an inclusion of immunological and nutritional status of patients is preferable. In this study, we aimed to determine the influence of systemic inflammation-based scores and nutrition status on the outcome of patients receiving chemotherapy for unresectable pancreatic cancer.

Patients and Methods

Patients and assessment. A total of 93 consecutive patients who underwent chemotherapy for unresectable pancreatic cancer at the Osaka Medical College Hospital, Takatsuki, Japan, between January 2008 and December 2014 were eligible for this study. All patients who were enrolled in this study were diagnosed with pancreatic

cancer based on pathologic examination of the liver or peritoneal metastasis *via* staging laparotomy, endoscopic ultrasound-guided fine needle aspiration, and cytology of ascites fluid. Exclusion criteria were: i) inability to receive at least one cycle of chemotherapy due to side effects (n=10) and ii) a previous chemotherapy or neoadjuvant chemo-radiotherapy for pancreatic cancer. Patients who refused chemotherapy and those with a poor performance status (*i.e.*, Eastern Cooperative Oncology Group score>2) were also excluded from this study (9).

Diagnosis of unresectable pancreatic cancer and distant metastases were considered as indications for chemotherapy. All patients received at least one cycle of chemotherapy. Complete blood count and serum biochemical examination were routinely assessed prior to and one month after the beginning of chemotherapy. Written informed consent for the use of clinical data in the medical records system for research purposes was given by all patients included in this study.

Inflammation-based prognostic markers (7). Data on inflammation-based prognostic markers, such as PLR, LMR, and NLR, were derived from the absolute numbers of circulating platelets, lymphocytes, monocytes, and neutrophils, respectively. Onodera's PNI was calculated as [(10×albumin) + (0.005×absolute number of circulating lymphocytes)] (10). Patients were assigned a modified GPS (mGPS) of 2 when both elevated C-reactive protein (CRP) levels (>0.5 mg/dL) and hypoalbuminemia (<3.5 g/dL) were present, while those with only one abnormality were assigned an mGPS of 1, and those with a normal CRP and albumin were assigned an mGPS of 0 (11).

Assessment of resectability. Confirmation of resectability based on computed tomography was performed according to the recent NCCN definition and the consensus statement of the International Study Group of Pancreatic Surgery (12). Briefly, unresectable pancreatic cancer indicated the presence of distant metastases and/or more than 180-degree involvement of the circumference of the superior mesenteric artery (SMA), celiac artery (CA), and first jejunal artery (J1A) (13-15).

Chemotherapy regimens. A single course of Gemcitabine (GEM) involved intravenous infusion at a dose of 1000 mg/m^2, administered once a week for three consecutive weeks, followed by one week of rest. Similarly, the course of Tegafur/gimeracil/oteracil (also known as S-1) involved 100 mg/m^2 intravenous infusion daily for four weeks followed by two weeks of rest. The regimen for Folfirinox was repeated every two weeks as follows: i) two hour-intravenous infusion of oxaliplatin at 85 mg/m^2 and l-leucovorin at 200 mg/m^2, and at the same time, irinotecan intravenous infusion for 90 minutes at 180 mg/m^2 and ii) an intravenous bolus of 5-FU at 400 mg/m^2 followed by continuous intravenous infusion of 5-FU over 46 hours at 2400 mg/m^2. Pre-medications in all patients included the 5-HT3 receptor antagonist, dexamethasone, and selective neurokinin 1 receptor antagonist. G-CSF 150 μg was administered daily (16).

Criteria for tumor response. Assessment for tumor response was based on Response Evaluation Criteria in Solid Tumors guidelines (RECIST, version 1.1), classified as partial remission (PR, ≥30% decrease), stable disease (SD, <20% increase and <30% decrease), or progressive disease (PD, ≥20% increase) (17). When response was assessed as PD, we offered the alternative of palliative treatment or second-line chemotherapy after explaining the prognosis and clinical advantages/disadvantages to the patients.

Statistical analysis. Continuous variables were expressed as median values and were compared to one another using Fisher's exact test for nonparametric data. Using the data obtained from blood collection, factors found to significantly influence a poor outcome by univariate analysis were included in the multivariate logistic regression analysis to determine the adjusted odds ratio (OR). Overall survival (OS) and progression-free survival (PFS) rates were calculated using the Kaplan–Meier method implementing the log-rank test to analyze any differences. All analyses were performed using the JMP version 9.0 software package (SAS Institute, Cary, NC, USA), and values of $p<0.05$ were considered statistically significant.

Results

LMR and PNI are independent indicators of poor prognosis for unresectable pancreatic cancer. Among the 83 patients enrolled in this study, 49 (59.0%) died within one year following the beginning of chemotherapy. The univariate analysis showed that the factors that influenced poor outcomes in patients receiving chemotherapy for unresectable pancreatic cancer were LMR<3.4 ($p=0.003$), NLR≥2.6 ($p=0.02$), and PNI<43 ($p=0.02$) (Table I). The multivariate analysis showed that LMR<3.4 (OR=5.02, 95%CI=1.559-19.85, $p=0.005$) and PNI<43 (OR=3.53, 95%CI=1.057-14.21, $p=0.03$) independently predicted a poor outcome in patients receiving chemotherapy for unresectable pancreatic cancer (Table II). Figure 1 showed OS rates according to the number of patients with LMR<3.4 and PNI<43. The one-year and two-year OS rates in patients without risk factors for poor outcome were 52.2% and 4.5%, respectively, compared to the 18.1% one-year OS and 6.0% two-year OS in patients with one risk factor, and 0% one-year OS in patients with two risk factors ($p=0.002$).

Changing of LMR during chemotherapy reflected prognosis of unresectable pancreatic cancer. Next, OS rates were compared among four groups of patients, categorized according to changes in LMR and PNI prior to, and following chemotherapy. The one-year and two-year OS rates in patients with LMR≥3.4 one month after starting chemotherapy were 56.7% and 10.8%, respectively, compared to the 17.3% one-year OS and 0% two-year OS in patients with LMR<3.4 one month after starting chemotherapy (Figure 2A, $p<0.001$). Comparison of OS rates among patients categorized according to changes in LMR one month after starting chemotherapy is shown in Figure 2B. Compared to patients who maintained LMR≥3.4, patients whose LMR decreased from ≥3.4 to <3.4 had significantly lower OS rates (65.5% *versus* 24.1% after one year and 6.9% *versus* 0% after two years; $p<0.001$). Compared to patients whose LMR increased from <3.4 to ≥3.4, patients who maintained an LMR<3.4 had significantly

Table I. *Univariate analysis of factors affecting poor prognosis in patients with unresectable pancreatic cancer.*

	One-year survival (n=34)	Death within one year (n=49)	*p*-Value
Age (≤69)	18	24	0.82
Gender M/F	20/14	37/12	0.14
WBC ≥8000	7	7	0.55
Neutrophil ≥4,000	13	23	0.5
Lymphocytes ≥1,200	23	28	0.36
Monocytes ≥250	26	41	0.57
Total protein ≥7.0	18	28	0.82
Albumin <3.5	3	11	0.13
CRP ≥1.0	8	19	0.16
LMR <3.4	30	28	0.003
PLR <325	32	40	0.18
NLR ≥2.6	15	35	0.02
CRP/Albumin ≥0.22	8	21	0.1
PNI <43	30	33	0.03
mGPS 0/1/2	23/8/3	21/20/8	0.08
CEA ≥13	5	15	0.12
CA19-9 ≥37	30	37	0.17
Distant meta (+)	15	30	0.17
First chemotherapy TS-1/GEM/FOLFIRINOX	9/19/6	24/22/3	0.06

Table II. *Multivariate analysis of factors that predict poor prognosis in patients with unresectable pancreatic cancer.*

	Odds ratio	95% CI	*p*-Value
LMR <3.4	5.02	1.559-19.85	0.005
NLR ≥2.6	2.009	0.722-5.583	0.179
PNI <43	3.53	1.057-14.21	0.03

Table III. *Evaluation of the possibility to continue chemotherapy according to the LMR or PNI values one month later.*

	Cessation of chemotherapy	Continue chemotherapy	*p*-Value
LMR <3.4 (n=46)	13	33	0.002
LMR ≥3.4 (n=37)	1	36	
	Cessation of chemotherapy	Continue chemotherapy	*p*-Value
PNI <43 (n=46)	12	34	0.01
PNI ≥43 (n=37)	2	35	

lower OS rates (25.0% *versus* 5.8% after one year and 12.5% *versus* 0% after two years; $p=0.02$).

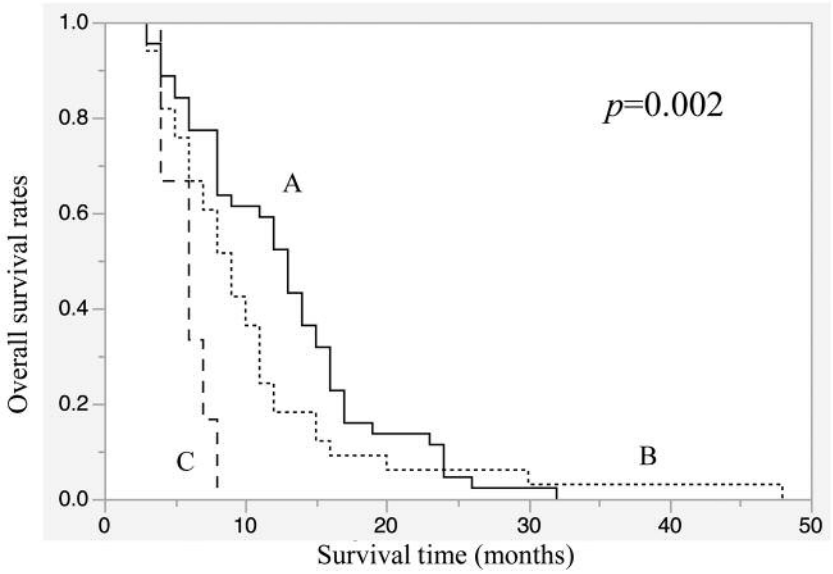
Also, Changing of PNI during chemotherapy was reflected prognosis of unresectable pancreatic cancer. The one and two-year OS rates in patients with PNI ≥43 one month after starting chemotherapy were 54.0% and 10.8%, respectively, compared to the 19.5% one-year OS and 0% two-year OS in patients with PNI<43 one month after starting chemotherapy (Figure 3A, $p=0.0009$). Comparison of the OS rates among patients categorized according to changes in PNI one month after starting chemotherapy is shown in Figure 3B. Compared to patients who maintained PNI≥43, patients whose PNI deteriorated had significantly lower OS rates (56.2% *versus* 25.8% at one year, and 12.5% *versus* 0% at two years; $p=0.003$). There were no significant differences in OS rates between patients whose PNI increased from <43 to ≥43, and in those who maintained a PNI<43 ($p=0.3$).

LMR and PNI could be indicator for continuing of unresectable pancreatic cancer chemotherapy. There were 14 patients who were compelled by their primary doctors to stop chemotherapy one month after initiation for a variety of reasons, including side effects (particularly neutropenia), disease progression, and own wishes. One month after the initiation of chemotherapy, patients with LMR<3.4 or PNI<43 were not able to receive subsequent doses compared to patients with LMR≥3.4 (Table III, $p=0.002$) and those with PNI≥43 (Table III, $p=0.01$), respectively.

Discussion

Increasing evidence for a positive relationship between inflammation and nutrition and cancer progression and development, with several markers proposed as prognostic factors for different types of cancers (3-8). These markers, including NLR, PLR, LMR, modified GPS, and PNI, can easily be calculated from routine blood samples. LMR has been demonstrated to be an independent prognostic factor for cancer-specific survival in patients with a variety of malignancies (18-20), similar to PNI (1, 21, 22). However, to the best of our knowledge, our findings here produce the first report that evaluates the prognostic significance of inflammatory markers and nutrition factors in patients receiving chemotherapy for unresectable pancreatic cancer. Our results demonstrate that low LMR and PNI values are significantly associated with poor prognosis in this population of patients.

Low LMR is often accompanied by relative lymphocytopenia and elevated monocytes. Tumor-infiltrating lymphocytes (TILs) from the peripheral blood are the most important adaptive immune cells that induce cytotoxic cell death and suppress tumor cell proliferation and migration (23). Therefore, decreased lymphocytes in the peripheral blood may lead to downregulation of the



A: 0 risk factor: 1- and 2-year survival rates were 52.2% and 4.5%, respectively
B: 1 risk factor: 1- and 2-year survival rates were 18.1% and 6.0%, respectively
C: 2 risk factors: 1-year survival rate was 0%

Figure 1. *Overall survival according to the number of independent risk factors for poor prognosis in patients receiving chemotherapy for unresectable pancreatic cancer.*

immune response to tumor cells. In fact, the relationship between lymphocytopenia and poor prognosis has been reported in extranodal natural killer/T-cell lymphoma and nasopharyngeal carcinoma (15, 24), as well as in pancreatic cancer (25).

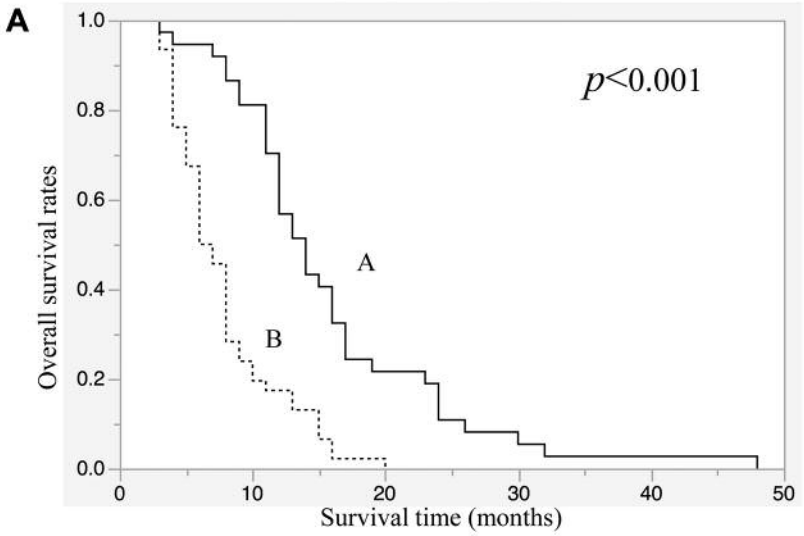
Likewise, it is important to understand the impact of monocytes on the immune response to tumor cells. Tumor-associated macrophages (TAMs), which differentiate from monocytes after recruitment into the tumor microenvironment, suppress tumor functions such as cancer-related angiogenesis, invasiveness, and immunosuppression, secondary to a wide range of inflammatory cytokines, including CSF-1 (26, 27). Indeed, Bingle and colleagues have reported an association between high macrophage density and poor clinical outcomes in various types of human cancers, including breast, lung, cervical, prostate cancer, and urothelial carcinoma of the bladder (28). Thus, it is not surprising that a high monocyte number in the peripheral blood is an adverse prognostic factor for pancreatic cancer.

Interestingly, variation of LMR value after a month from starting chemotherapy improved survival in our study patients. Even among patients with LMR<3.4 prior to chemotherapy, OS rates improved when LMR improved to ≥3.4 one month after starting chemotherapy. These results imply that inflammatory immune cells, particularly lymphocytes and monocytes in the peripheral blood, may be correlated with immune cells, such as TILs and TAMs, in the tumor microenvironment and in actual tumor progression.

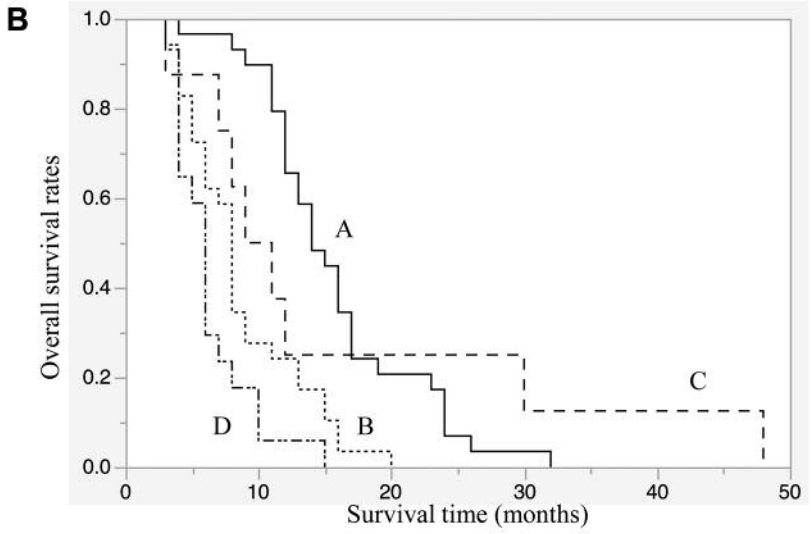
Pancreatic cancer is frequently associated with malnutrition from body weight loss due to tumor progression and decreased oral intake brought about by gastrointestinal or biliary tract obstruction and cancer-induced pain (29, 30). Low levels of albumin, total lymphocyte count, and T helper cells, as well as T cell blastogenic responses are followed by malnutrition, including an immunonutrition disorder (6, 31, 32). PNI has been used as a prognostic factor in patients with liver cirrhosis, those receiving hemodialysis, and patients with cancer (1, 21, 22). Similar to LMR, PNI may routinely be calculated from peripheral blood tests, it has a low cost and can be performed simply and quickly compared to other nutrition indices.

In this study, deterioration of PNI had a negative impact on OS, but elevation of PNI was not associated with improved OS rates. We have no clear explanation for this result. Nevertheless, maintenance of a good nutrition status for a brief period improved OS rates. Therefore, evaluation of the nutritional status and adequate nutritional support should be emphasized in patients receiving chemotherapy.

There were several limitations in this study. First, this was a retrospective study even if consecutive patients were enrolled. Second, LMR is a non-specific marker of inflammation, and results may have been affected by the presence of other systemic diseases in our cohort. Finally,



A: Patients with LMR ≥3.4 one month after starting chemotherapy (n=37):
1- and 2-year survival rates were 56.7% and 10.8%, respectively
B: Patients with LMR <3.4 one month after starting chemotherapy (n=46):
1- and 2-year survival rates were 17.3% and 0%, respectively

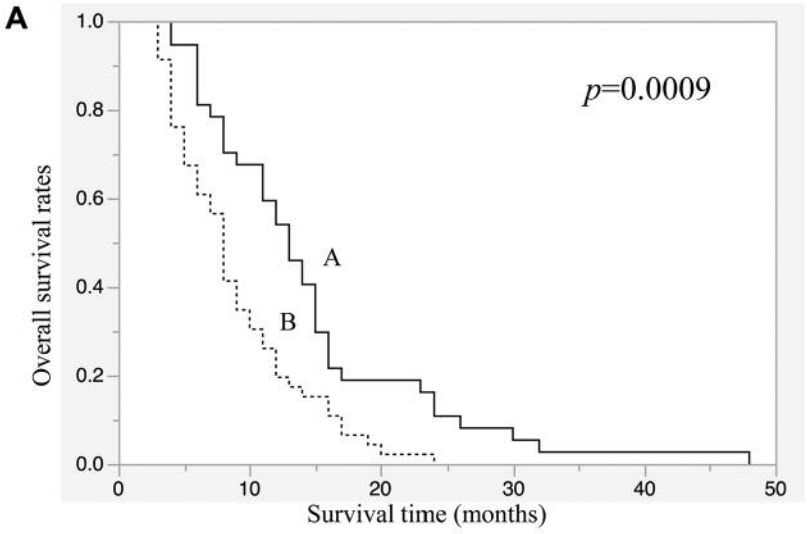


$p<0.001$ [A: LMR ≥3.4→ LMR ≥3.4 (n=29): 1- and 2-year survival rates were 65.5% and 6.9%, respectively
B: LMR ≥3.4→ LMR <3.4 (n=29): 1- and 2-year survival rates were 24.1% and 0%, respectively

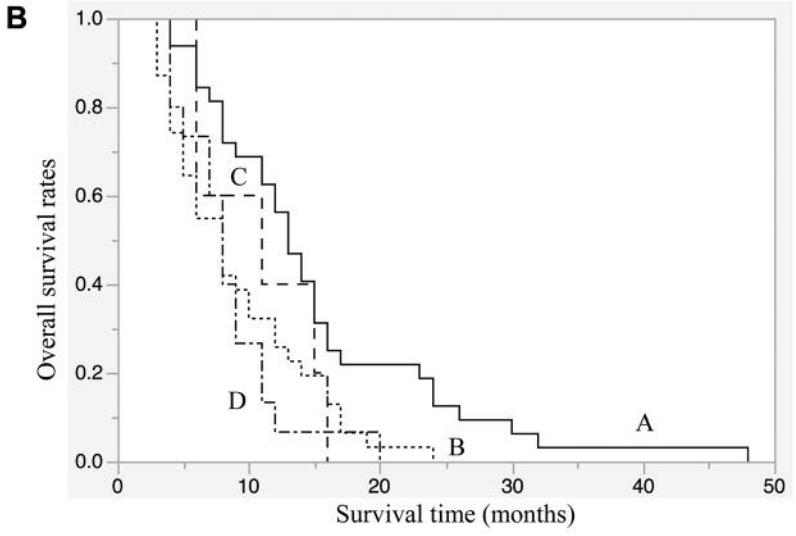
$p=0.02$ [C: LMR <3.4→ LMR ≥3.4 (n=8): 1- and 2-year survival rates were 25.0% and 12.5%, respectively
D: LMR <3.4→ LMR <3.4 (n=17): 1- and 2-year survival rates were 5.8% and 0%, respectively

Figure 2. *(A) Overall survival based on LMR value one month after starting chemotherapy in patients with unresectable pancreatic cancer. (B) Overall survival according to LMR change before, and one month after the start of chemotherapy in patients with unresectable pancreatic cancer.*

verification and investigation of specific immune cell components in the tumor microenvironment (*i.e.*, immunohistochemical staining of CD163 and CD204 against TAMs, CD4, CD8, and CD4+CD25+FoxP3+ against T cells) were not feasible in this study because our cohort comprised unresectable pancreatic cancer. Thus, to better understand the prognostic role of LMR and PNI, further prospective studies should be conducted.



A: Patients with PNI ≥43 one month after starting chemotherapy (n=37): 1- and 2-year survival rates were 54.0% and 10.8%, respectively
B: Patients with PNI <43 one month after starting chemotherapy (n=46): 1- and 2-year survival rates were 19.5% and 0%, respectively



p=0.003 [A: PNI ≥ 43→PNI ≥ 43 (n=32): 1- and 2-year survival rates were 56.2% and 12.5%, respectively
B: PNI ≥ 43→ PNI<43 (n=31): 1- and 2-year survival rates were 25.8% and 0%, respectively

p=0.3 [C: PNI<43→ PNI ≥ 43 (n=5): 1- and 2-year survival rates were 40.0% and 0%, respectively
D: PNI<43→ PNI<43 (n=15): 1- and 2-year survival rates were 13.3% and 0%, respectively

Figure 3. *(A) Overall survival based on PNI value one month after starting chemotherapy in patients with unresectable pancreatic cancer. (B) Overall survival according to PNI change one month after starting chemotherapy in patients with unresectable pancreatic cancer.*

In conclusion, LMR<3.4 and PNI<43 are identified as independent predictors of poor outcome in patients receiving chemotherapy for unresectable pancreatic cancer. LMR and PNI may help clinicians identify patients at high risk for poor prognosis.

Conflicts of Interest

The Authors state that they have no conflicts of interest and that they did not receive any financial or material support for this study.

Authors' Contributions

The conception and design of the study was done by TS and MA. Acquisition of data was done by TS, MA, YI, MH, and FH. The analysis and interpretation of the data was done by TS, KT, MA, KM, AT, FH, MH, and KU. The writing, review, and/or revision of the manuscript were done by TS, KT, and KU. The study supervision was done by KU.

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