Preoperative Prognostic Nutritional Index Predicts Long-term Outcome in Gastric Cancer: A Propensity Score-matched Analysis

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Abstract. *Background/Aim:* Recent evidence suggests that preoperative malnutrition may lead to poor survival in cancer patients. This study aimed to determine the ability of the prognostic nutritional index (PNI) to predict survival in gastric cancer patients. *Patients and Methods:* Two hundred and eighteen patients who had undergone laparoscopic gastrectomy were retrospectively reviewed via propensity score-matched analysis. *Results:* In multivariate analysis of overall patients, pTNM stage, carcinoembryonic antigen, and PNI were independent predictors of overall survival (OS), and pTNM stage and PNI were independent predictors of cancer-specific survival (CSS). Among the 92 non-elderly patients, pTNM stage and PNI were independent predictors of OS, and pTNM stage, PNI, and adjuvant chemotherapy were independent predictors of CSS in multivariate analysis. On the other hand, among the 126 elderly patients, low PNI value was identified as a significant predictor of shorter OS in univariate analysis. *Conclusion:* PNI is associated with OS and CSS in gastric cancer patients, especially non-elderly patients.

The tumor-node-metastasis (TNM) staging system is known to be a significant parameter for predicting the clinical course of patients with cancer (1). Despite its widespread use, the TNM classification merely focuses on tumor extension, irrespective of the biological behavior of the tumor or the host antitumor response. Recent studies reported that a preoperative malnutrition and immunosuppressive status can

lead to poor survival in patients with cancer (2, 3). Several scoring tools for assessing preoperative nutritional status are now available. The prognostic nutritional index (PNI), which is based on the level of lymphocytes and albuminemia, is a useful parameter to indicate the immune and nutritional status of patients with different types of malignant tumors (4-7). The PNI is associated with the prognosis of patients with cancer because serum albumin is a potential indicator not only of the nutrition and systemic inflammatory response, but also of the antitumor immune response, and lymphocytes play a crucial role in the host cellular adaptive immune response (8). Therefore, the PNI can be considered a good indicator of prognosis, as well as, the immune and nutritional status in patients with cancer.

In this study, propensity score-matched (PSM) analysis was used to determine the ability of the PNI to predict survival, especially age-stratified long-term survival, in patients with gastric cancer.

Patients and Methods

Patients. A database of medical records from 449 consecutive patients who had undergone gastrectomy for gastric cancer at our institution between January 2009 and December 2016 was retrospectively reviewed. The inclusion criteria were as follows: 1) age 20-89 years, 2) histologically confirmed gastric adenocarcinoma, 3) no distant metastasis, 4) an Eastern Cooperative Oncology Group performance status of 0-2, and 5) curative gastrectomy with R0 resection. Patients were excluded if they had T4b disease; remnant gastric cancer; an emergency gastrectomy for bleeding or perforation; post-neoadjuvant chemotherapy; and hematological, inflammatory, or autoimmune disorders. In total, 368 patients were enrolled in the study (Figure 1).

All patients underwent laparoscopic or laparoscopy-assisted gastrectomy. The extent of gastrectomy and lymph node dissection was determined according to the Japanese gastric cancer treatment guidelines (version 3) (9). Five-fluorouracil-based adjuvant chemotherapy regimens (cisplatin plus tegafur/gimeracil/oteracil or capecitabine) were recommended to the majority of patients with advanced gastric cancer.

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Figure 1. Study flow diagram.

The patients' clinical characteristics, laboratory data, treatment data, and pathological data were collected from reviewing medical records. Tumor stage was determined according to the American Joint Committee on Cancer TNM staging system (7th edition) (1).

The observation period was from the date of surgery until the date of death, loss to follow-up, or withdrawal of consent. Overall survival (OS) and cancer-specific survival (CSS) were evaluated following gastrectomy. OS was calculated from the date of primary gastrectomy to the date of death from any cause or last follow-up. CSS was calculated from the date of primary gastrectomy to the date of cancer-specific death or withdrawal of consent.

Patients were stratified into two groups according to age: <70 years (non-elderly) and ≥ 70 years (elderly).

Preoperative nutritional parameters. All laboratory data used for calculating preoperative nutritional parameters were obtained within 1 week before surgery. The following items were selected as concise constitutional evaluation methods: body mass index (BMI) (body weight [kg]/height [m²]) and the PNI ($10 \times$ serum albumin [g/dl] + $0.005 \times$ total lymphocyte count in peripheral blood [mm³]) (4).

A receiver operating characteristic (ROC) curve of the preoperative PNI was generated for the multiple logistic regression analysis of OS and CSS. The area under the ROC curve (AUC) estimation method was used to assess the ability of the preoperative PNI to predict OS and CSS. The optimal cut-off value for the preoperative PNI was set at 44.3 in this study, based on OS (sensitivity, 77.8%; specificity, 56.3%; AUC=0.681) and CSS (sensitivity, 73.2%; specificity, 52.5%; AUC=0.592). Patients were categorized as having a low (<44.3) or high PNI value (≥ 44.3) (Figure 2a-b).

Ethics approval and consent to participate. This study was approved by the Ethical Review Board of Shimane University Faculty of Medicine (Shimane, Japan). Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived, due to the retrospective nature of this study.

Statistical analyses. Continuous variables were expressed as the mean $\pm$ standard deviation or median and range. Comparisons were performed using the Chi-square test or Student's *t*-test for

Figure 2. Receiver operating characteristic curves for (a) overall survival and (b) cancer-specific survival. Receiver operating characteristic curves were plotted to determine the optimal cutoff value for the prognostic nutritional index.

categorical variables and the Mann-Whitney *U*-test for non-normally distributed continuous variables. OS and CSS were calculated using the Kaplan–Meier method and compared by the log-rank test. Univariate analysis was performed to identify factors associated with OS and CSS. Variables with a $p < 0.05$ in the univariate analysis were included in the multivariate analysis using a Cox proportional hazards model to determine the independent prognostic factors. Potential prognostic factors included age (<70 vs. ≥ 70 years), sex (female vs. male), BMI (<18.5 vs. ≥ 18.5 kg/m²), tumor size (<5.0 vs. ≥ 5.0 cm), cancer cell differentiation (well- vs. moderately/poorly differentiated), pathological TNM (pTNM) stage (Stage I, II vs. III), preoperative serum carcinoembryonic antigen (CEA) level (<5.0 vs. ≥ 5.0 ng/ml), the PNI (<44.3 vs. ≥ 44.3), and postoperative adjuvant chemotherapy (“no” vs. “yes”).

All statistical analyses were conducted using JMP software for Windows (version 11; SAS Institute, Cary, NC, USA). A two-sided $p < 0.05$ was considered statistically significant. To reduce bias due to different distributions of covariables between groups of patients with a low and high PNI, PSM analysis was performed using R statistical package (version 3.1.3) (<http://www.r-project.org>). The following covariables were matched: tumor depth, lymph node metastasis, and pTNM stage.

Results

Clinicopathological characteristics of overall patients with gastric cancer. The associations between the PNI and the clinicopathological characteristics of the entire cohort of

368 patients with gastric adenocarcinoma are summarized in Table I. Based on a PNI cutoff value of 44.3, 109 patients (29.6%) were classified as having a low PNI and the remaining 259 patients (70.4%) were classified as having a high PNI. PNI values were significantly associated with age ($p < 0.001$), BMI ($p < 0.001$), white blood cell count ($p = 0.004$), red blood cell count ($p < 0.001$), tumor size ($p < 0.001$), tumor depth ($p < 0.001$), lymph node metastasis ($p = 0.010$), pTNM stage ($p < 0.001$), intraoperative bleeding ($p = 0.029$), serum albumin concentration ($p < 0.001$), and C-reactive protein (CRP) level ($p < 0.001$).

Clinicopathological characteristics of propensity score matched patients with gastric cancer. After applying PSM analysis, the distributions of confounding variables (tumor depth, lymph node metastasis, and pTNM stage) were adequately balanced between the low and high PNI groups. This allowed us to generate 109 matched pairs with a standardized or individualized follow-up, which were used in subsequent analyses as indicated. PNI values were significantly associated with age ($p < 0.001$), BMI ($p = 0.012$), white blood cell count ($p = 0.002$), red blood cell count ($p < 0.001$), tumor size ($p = 0.001$), serum albumin concentration ($p < 0.001$), CRP level ($p < 0.001$), and adjuvant chemotherapy ($p = 0.035$) (Table II).

Table I. Baseline characteristics of PNI stratified overall patients.

Characteristics	Total patients	PNI		p-Value
		<44.3 (n=109)	≥44.3 (n=259)	
Age (years)		78 (46-91)	69 (36-89)	<0.001
Gender				0.124
Male	254	69	185	
Female	114	40	74	
BMI		21.4 (13.9-30.7)	22.6 (16.5-32.8)	<0.001
WBC (μl)		5320 (1830-9750)	5760 (510-10300)	0.004
RBC (×10 ⁴ μl)		366 (223-520)	439 (203-579)	<0.001
Location of tumor				0.187
EGJ	11	2	9	
U	70	23	47	
M	162	40	122	
L	125	44	81	
Tumor size (mm)		55 (7-170)	36 (3-180)	<0.001
Procedure				0.090
LTG	82	31	51	
LPG	37	7	30	
L(A)DG	249	71	178	
Differentiation				0.123
Well	71	14	57	
Moderate	134	42	92	
Poor	163	53	110	
Depth of tumor				<0.001
T1a-1b	190	40	150	
2	48	12	36	
3	54	23	31	
4a-4b	74	34	40	
Lymph node metastasis			0.010	
N0	244	59	185	
N1	40	14	26	
N2	42	19	23	
N3	42	17	25	
pTNM stage				<0.001
Ia-Ib	217	45	172	
IIa-IIb	65	26	39	
IIIa-IIIc	86	38	48	
Operation time (min)		399 (177-911)	398 (218-836)	0.542
Intraoperative bleeding (ml)		100 (0-5850)	20 (0-3600)	0.029
Albumin (g/dl)		3.4 (1.5-4.0)	4.2 (3.5-5.1)	<0.001
CRP (mg/l)		0.22 (0.01-7.09)	0.06 (0.002-6.31)	<0.001
CEA (ng/ml)				0.117
<5	286	79	207	
≥5	82	30	52	
Adjuvant chemotherapy			0.541	
Yes	100	32	68	
No	268	77	191	

PNI: Prognostic nutritional index; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; EGJ: esophagogastric junction; U: upper; M: middle; L: lower; Differentiation: tumor differentiation; LTG: laparoscopic total gastrectomy; LPG: laparoscopic proximal gastrectomy; L(A)DG: laparoscopic (assisted) distal gastrectomy; pTNM stage: pathological TNM stage; CRP: C-reactive protein; CEA: carcinoembryonic antigen.

Cox regression analysis of postoperative survival in the entire cohort of propensity score matched patients with gastric cancer. In the PSM dataset, univariate analysis identified advanced pTNM stage ($p<0.001$), a high serum

CEA level ($p=0.017$), a low PNI value ($p<0.001$), and a high CRP level ($p=0.034$) as significant risk factors for shorter OS. In the multivariate analysis, pTNM stage (hazard ratio [HR]=2.959, 95% confidence interval [CI]=1.793-5.004;

Table II. Baseline characteristics of PNI stratified propensity score matched overall patients.

Characteristics	Total patients	PNI		p-Value
		<44.3 (n=109)	≥44.3 (n=109)	
Age (years)		78 (46-91)	68 (36-89)	<0.001
Gender				0.315
Male	145	69	76	
Female	77	40	33	
BMI		21.4 (13.9-30.7)	22.4 (16.8-32.8)	0.012
WBC (μl)		5320 (1830-9750)	5890 (3080-10300)	0.002
RBC (×10 ⁴ μl)		366 (223-520)	432 (279-548)	<0.001
Location of tumor				0.333
EGJ	6	2	4	
U	41	23	18	
M	91	40	51	
L	80	44	36	
Tumor size (mm)		55 (7-170)	40 (5-180)	0.001
Procedure				0.954
LTG	60	31	29	
LPG	14	7	7	
L(A)DG	144	71	73	
Differentiation				0.919
Well	27	14	13	
Moderate	82	42	40	
Poor	109	53	56	
Depth of tumor				0.937
T1a-1b	80	40	40	
2	27	12	15	
3	45	23	22	
4a-4b	66	34	32	
Lymph node metastasis				0.813
N0	120	59	61	
N1	30	14	16	
N2	33	19	14	
N3	35	17	18	
pTNM stage				0.963
Ia-Ib	92	45	47	
IIa-IIb	51	26	25	
IIIa-IIIc	75	38	37	
Operation time (min)		399 (177-911)	392 (218-836)	0.466
Intraoperative bleeding (ml)		100 (0-5850)	90 (0-3600)	0.577
Albumin (g/dl)		3.4 (1.5-4.0)	4.2 (3.5-5.1)	<0.001
CRP (mg/l)		0.22(0.01-7.09)	0.08 (0.01-3.30)	<0.001
CEA (ng/ml)				0.204
<5	166	79	87	
≥5	52	30	22	
Adjuvant chemotherapy				0.035
Yes	79	32	47	
No	139	77	62	

PNI: Prognostic nutritional index; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; EGJ: esophagogastric junction; U: upper; M: middle; L: lower; Differentiation: tumor differentiation; LTG: laparoscopic total gastrectomy; LPG: laparoscopic proximal gastrectomy; L(A)DG: laparoscopic (assisted) distal gastrectomy; pTNM stage: pathological TNM stage; CRP: C-reactive protein; CEA: carcinoembryonic antigen.

$p < 0.001$), CEA level (HR=1.817, 95%CI=1.068-3.023; $p = 0.028$), and the PNI (HR=3.289, 95%CI=1.869-6.003; $p < 0.001$) were confirmed as independent prognostic factors for OS in PSM patients (Table III).

In the univariate analysis, a large tumor size ($p = 0.025$), advanced pTNM stage ($p < 0.001$), a low PNI value ($p = 0.049$), a high serum CEA level ($p = 0.040$), and adjuvant chemotherapy ($p = 0.008$) were significantly associated with CSS. In the

Table III. Univariate and multivariate analyses for overall survival and cancer-specific survival in propensity score matched overall patients.

Variables	Patients (n=218)	Category or characteristics	Overall survival			Cancer-specific survival		
			Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis
			HR	95%CI		HR	95%CI	
Age	92/126	(<70/≥70)	1.475	0.884-2.538	0.139	0.709	0.355-1.410	0.325
Gender	73/145	(Female/male)	1.701	0.993-3.058	0.053	1.414	0.690-3.116	0.353
BMI	190/28	(≥18.5/<18.5)	1.149	0.529-2.212	0.706	1.052	0.414-3.548	0.924
Tumor size	107/111	(<5/≥5)	1.6	0.969-2.695	0.066	2.263	1.107-4.977	0.025
Differentiation	109/109	(Well & mod/poor)	1.409	0.856-2.352	0.178	1.533	0.770-3.161	0.226
pTNM Stage	143/75	(I, II/III)	2.674	1.629-4.419	<0.001	10.13	4.473-27.161	<0.001
CEA	166/52	(<5.0/≥5.0)	1.917	1.131-3.174	0.017	2.136	1.036-4.254	0.04
PNI	109/109	(≥44.3/<44.3)	2.885	1.699-5.116	<0.001	2.000	0.999-4.197	0.049
CRP	173/45	(<0.5/≥0.5)	1.843	1.050-3.114	0.034	1.311	0.553-2.786	0.515
Adjuvant chemotherapy	139/79	(No/Yes)	1.017	0.613-1.727	0.948	2.528	1.268-5.218	0.008
						1.052	0.485-2.364	0.899

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; Differentiation: tumor differentiation; pTNM stage: pathological TNM stage; CEA: carcinoembryonic antigen, PNI: prognostic nutritional index; CRP: C-reactive protein.

multivariate analysis, pTNM stage (HR=14.003, 95%CI=5.033-44.487; $p<0.001$) and the PNI (HR=2.794, 95%CI=1.352-6.039; $p<0.001$) were confirmed as independent prognostic factors for CSS in PSM patients (Table III).

Postoperative survival analysis stratified by the PNI in the entire cohort of propensity score-matched patients with gastric cancer. In the PSM dataset, Kaplan–Meier analysis and the log-rank test demonstrated that patients with a low PNI value had a significantly poorer prognosis in terms of OS and CSS than those with a high PNI value ($p<0.001$ and $p=0.008$, respectively). The 5-year OS and CSS rates for patients with a low and high PNI value were 50.9% and 80.4% and 73.6% and 84.2%, respectively (Figure 3a-b).

Clinicopathological characteristics after applying propensity score matched analysis in age-stratified patients. After applying PSM analysis, tumor depth, lymph node metastasis, and pTNM stage were not significantly different between the low and high PNI groups in age-stratified patients. Finally, 92 non-elderly patients (42.2%) and 126 elderly patients (57.8%) were selected for analysis.

PNI values were significantly associated with age ($p=0.004$), BMI ($p=0.046$), white blood cell count ($p=0.017$), red blood cell count ($p<0.001$), tumor size ($p=0.016$), serum albumin concentration ($p<0.001$), and CRP level ($p<0.001$) in the 92 non-elderly patients with gastric cancer (Table IV).

Conversely, PNI values were significantly associated with age ($p=0.024$), red blood cell count ($p<0.001$), serum albumin concentration ($p<0.001$), and CRP levels ($p=0.012$) in the 126 elderly patients with gastric cancer (Table IV).

Cox regression analysis of postoperative survival in non-elderly patients. In the 92 non-elderly patients, univariate analysis identified advanced pTNM stage ($p<0.001$) and a low PNI value ($p<0.001$) as significant risk factors for shorter OS. In the multivariate analysis, pTNM stage (HR=10.784, 95%CI=4.014-33.398; $p<0.001$) and the PNI (HR=6.178, 95%CI=2.353-17.905; $p<0.001$) were confirmed as independent prognostic factors for OS (Table V).

Univariate analysis identified a large tumor size ($p=0.041$), advanced pTNM stage ($p<0.001$), a low PNI value ($p=0.011$), and adjuvant chemotherapy ($p=0.018$) as significant risk factors for shorter CSS. In the multivariate analysis, pTNM stage (HR=145.018, 95%CI=20.010-1,566.193; $p<0.001$), the PNI (HR=4.751, 95%CI=1.571-16.442; $p<0.001$), and adjuvant chemotherapy (HR=6.310, 95%CI=1.214-33.210; $p=0.029$) were confirmed as independent prognostic factors for CSS (Table V).

Cox regression analysis of postoperative survival in elderly patients. In the 126 elderly patients, univariate analysis identified a low PNI value (HR=2.234, 95%CI=1.138-4.790;

Figure 3. Kaplan–Meier curves of postoperative survival. (a) Overall survival and (b) cancer-specific survival according to the prognostic nutritional index (PNI) values in the propensity score-matched analysis of all patients.

$p=0.019$) as a significant risk factor for shorter OS and advanced pTNM stage ($HR=5.839$, $95\%CI=2.032-20.903$; $p<0.001$) as a significant risk factor for shorter CSS (Table VI).

Postoperative survival analysis stratified by the PNI in non-elderly patients with gastric cancer. Kaplan–Meier analysis and the log-rank test demonstrated that patients with a low PNI value had a significantly poorer prognosis in terms of OS and CSS than those with a high PNI value ($p<0.001$ and $p=0.003$, respectively). The 5-year OS and CSS rates for patients with a low and high PNI value were 46.6% and 88.1% and 54.7% and 85.7%, respectively (Figure 4a-b).

Postoperative survival analysis stratified by the PNI in elderly patients with gastric cancer. Kaplan–Meier analysis and the log-rank test demonstrated that patients with a low PNI value had a significantly poorer prognosis in terms of OS, but not CSS, than those with a high PNI value ($p=0.015$ and $p=0.250$, respectively). The 5-year OS and CSS rates for patients with a low and high PNI value were 52.5% and 71.5% and 82.5% and 82.3%, respectively (Figure 5a-b).

Age-stratified PNI values in 218 propensity score matched patients with gastric cancer. In the age-stratified analysis, the PNI value was significantly lower in elderly patients than in non-elderly patients ($p<0.001$). The mean PNI values for non-elderly and elderly patients were 47.97 ± 8.31 and 42.95 ± 6.56 , respectively (Figure 6).

Discussion

There is growing concern regarding prognostic factors for accurately identifying cancer patients at high-risk of

recurrence or metastasis, which may allow us to successfully manage these patients and improve survival (10-12). Recent evidence suggests that long-term survival in patients with cancer is determined not only by tumor-related factors, but also by host-related factors. In particular, nutritional status, cancer-related inflammation, and several nutritional-based indices, including the PNI, Controlling Nutritional Status, BMI, Glasgow Prognostic Score, and preoperative body weight loss, have proved to have important prognostic value in various types of malignancies, including gastrointestinal cancer (13-15). The PNI, which is based on serum albumin and absolute peripheral lymphocyte count, was originally used to predict perioperative immuno-nutritional status and postoperative complications after gastrointestinal surgery. The PNI is simply calculated and is easily implemented through the following scoring system: >50 (good nutrition), $45-50$ (mild malnutrition), $40-45$ (moderate malnutrition), and <40 (severe malnutrition) (7). Serum albumin is produced by hepatocytes and is regulated by inflammatory cytokines, including interleukin-6, tumor necrosis factor- α , and oxidative stress, which are surrogate biomarkers of the more aggressive behavior of the tumor. These proinflammatory cytokines are produced by the tumor itself or the host and play a crucial role in carcinogenesis, cancer progression, and angiogenesis (16-18). Therefore, low albumin levels may lead to impaired immune function and reduced response to treatment in patients with cancer. Lymphocytes play a critical role in the antitumor effect by initiating cytotoxic immune responses. Therefore, lymphocytopenia may serve as an indicator of an impaired tumor-associated immune system and thus promote tumor progression (19-20). However, few studies have evaluated the impact of preoperative nutritional status on long-term

Table IV. Baseline characteristics of age stratified propensity matched gastric cancer patients.

Characteristics	Non-elderly patients				Elderly patients			
	PNI				PNI			
	Total patients	<44.3 (n=32)	≥44.3 (n=60)	p-Value	Total patients	<44.3 (n=77)	≥44.3 (n=49)	p-Value
Age (years)		65 (46-69)	60 (36-69)	0.004		81 (70-91)	78 (70-89)	0.024
Gender				0.503				0.069
Male	62	23	39		83	46	37	
Female	30	9	21		43	31	12	
BMI		21 (13.9-29.8)	22.3 (16.8-32.8)	0.046		21.6 (14.9-30.7)	22.9 (17.9-28.4)	0.079
WBC (μl)		5290 (1830-9380)	6095 (3160-9280)	0.017		5320 (2880-9750)	5550 (3080-10300)	0.269
RBC (×10 ⁴ μl)		376.5 (248-484)	446.5 (328-548)	<0.001		365 (223-520)	398 (279-536)	<0.001
Location of tumor				0.3669				0.255
EGJ	2	0	2		4	2	2	
U	16	8	8		25	15	10	
M	43	15	28		48	25	23	
L	31	9	22		49	35	14	
Tumor size (mm)		51 (13-120)	35 (8-170)	0.016		58 (7-170)	52 (5-180)	0.158
Procedure				0.140				0.440
LTG	24	12	12		36	19	17	
LPG	7	3	4		7	4	3	
L(A)DG	61	17	44		83	54	29	
Differentiation				0.201				0.442
Well	10	6	4		17	8	9	
Moderate	30	9	21		52	33	19	
Poor	52	17	35		57	36	21	
Depth of tumor				0.270				0.663
T1a-1b	37	12	25		43	28	15	
2	13	2	11		14	10	4	
3	14	5	9		31	18	13	
4a-4b	28	13	15		38	21	17	
Lymph node metastasis				0.489				0.893
N0	53	17	36		67	42	25	
N1	10	2	8		20	12	8	
N2	11	5	6		22	14	8	
N3	18	8	10		17	9	8	
Pathological stage				0.484				0.590
Ia-Ib	45	14	31		47	31	16	
IIa-IIb	17	5	12		34	21	13	
IIIa-IIIc	30	13	17		45	225	20	
Operation time (min)		416 (177-911)	389 (275-836)	0.974		389 (204-714)	392 (218-701)	0.501
Intraoperative blood loss (ml) 55 (0-2600)		50 (0-2230)		0.916		120 (0-5850)	100 (00-3600)	0.954
Albumin (g/dl)		3.4 (1.5-3.9)	4.3 (3.6-5.1)	<0.001		3.4 (1.7-4.0)	4.0 (3.5-4.9)	<0.001
CRP (mg/l)		0.275 (0.01-7.09)	0.06 (0.01-1.03)	<0.001		0.22 (0.01-6.25)	0.10 (0.01-3.30)	0.012
CEA (ng/ml)				0.961				0.287
<5	75	26	49		91	53	38	
≥5	17	6	11		35	24	11	
Adjuvant chemotherapy			0.789					0.064
Yes	42	14	28		37	18	19	
No	50	18	32		89	59	30	

PNI: Prognostic nutritional index; BMI: body mass index; WBC: white blood cell; RBC: red blood cell; EGJ: esophagogastric junction; U: upper; M: middle; L: lower; Differentiation: tumor differentiation; LTG: laparoscopic total gastrectomy; LPG: laparoscopic proximal gastrectomy; L(A)DG: laparoscopic (assisted) distal gastrectomy; pTNM stage: pathological TNM stage; CRP: C-reactive protein; CEA: carcinoembryonic antigen.

Table V. Univariate and multivariate analyses for overall survival and cancer-specific survival in non-elderly patients.

Variables	Patients (n=92)	Category or characteristics	Overall survival			Cancer-specific survival		
			Univariate analysis			Multivariate analysis		
			HR	95%CI	p-Value	HR	95%CI	p-Value
Gender	30/62	(Female/male)	2.211	0.816-7.694	0.125	1.292	0.478-4.070	0.625
BMI	13/79	(≥18.5/<18.5)	1.678	0.482-4.545	0.379	1.492	0.344-4.585	0.548
Tumor size	58/34	(<5/≥5)	2.407	0.988-5.972	0.053	2.758	1.044-7.716	0.041
Differentiation	40/52	(Well & mod/poor)	1.214	0.510-3.075	0.665	1.355	0.514-3.944	0.545
pTNM Stage	62/30	(I, II/III)	8.321	3.291-23.900	<0.001	10.784	4.014-33.398	<0.001
CEA	75/17	(<5.0/≥5.0)	1.972	0.742-4.778	0.164	2.194	0.749-5.822	0.143
PNI	32/60	(≥44.3/<44.3)	4.571	1.866-11.966	<0.001	6.178	2.353-17.905	<0.001
CRP	76-16	(<0.5/≥0.5)	2.138	0.684-5.692	0.176	1.858	0.518-5.355	0.311
Adjuvant chemotherapy	50/42	(No/Yes)	0.909	0.247-1.480	0.271	3.371	1.221-10.839	0.018
						6.310	1.214-33.210	0.029

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; Differentiation: tumor differentiation; pTNM stage: pathological TNM stage; CEA: carcinoembryonic antigen, PNI: prognostic nutritional index; CRP: C-reactive protein.

Table VI. Univariate and multivariate analyses for overall survival and cancer-specific survival in elderly patients.

Variables	Patients (n=126)	Category or characteristics	Overall survival			Cancer-specific survival		
			Univariate analysis			Multivariate analysis		
			HR	95%CI	p-Value	HR	95%CI	p-Value
Gender	43/83	(Female/male)	1.533	0.809-3.068	0.195	1.374	0.496-4.384	0.551
BMI	111/15	(≥18.5/<18.5)	0.927	0.318-2.152	0.872	0.468	0.026-2.307	0.410
Tumor size	49/77	(<5/≥5)	1.226	0.655-2.401	0.531	2.725	0.878-11.888	0.086
Differentiation	69/57	(Well & mod/poor)	1.66	0.903-3.106	0.103	1.625	0.605-4.550	0.334
pTNM Stage	81/45	(I, II/III)	1.624	0.873-2.983	0.124	5.839	2.032-20.903	<0.001
CEA	91/35	(<5.0/≥5.0)	1.756	0.922-3.240	0.085	2.207	0.789-5.923	0.127
PNI	77/49	(≥44.3/<44.3)	2.234	1.138-4.790	0.019	2.234	1.138-4.790	0.019
CRP	97/29	(<0.5/≥0.5)	1.738	0.888-3.247	0.103	1.121	0.313-3.219	0.845
Adjuvant chemotherapy	89/37	(No/Yes)	1.202	0.631-2.442	0.586	2.043	0.751-5.553	0.158

HR: Hazard ratio; CI: confidence interval; BMI: body mass index; Differentiation: tumor differentiation; pTNM stage: pathological TNM stage; CEA: carcinoembryonic antigen, PNI: prognostic nutritional index; CRP: C-reactive protein.

Figure 4. Kaplan-Meier curves of postoperative survival. (a) Overall survival and (b) cancer-specific survival according to the prognostic nutritional index (PNI) values in the propensity score-matched analysis of non-elderly patients.

Figure 5. Kaplan-Meier curves of postoperative survival. (a) Overall survival and (b) cancer-specific survival according to the prognostic nutritional index (PNI) values in the propensity score-matched analysis of elderly patients.

survival after gastrectomy for gastric cancer. In this study, PSM analysis was used to determine the ability of the PNI to predict long-term survival in patients with gastric cancer who underwent curative gastrectomy.

The optimal cut-off value of the PNI for predicting postoperative survival in patients with malignant tumors remains controversial and a universal cutoff value has not yet been established (4-6, 21). Therefore, we aimed to evaluate the prognostic significance of the PNI, as well as to determine an optimal cutoff value, which can better predict OS and CSS in patients with gastric cancer. ROC analysis was performed

and an optimal cutoff value for the preoperative PNI was set at 44.3 based on OS and CSS. Using this cut-off value, significant associations between a low PNI value and host- and tumor-related factors, such as advanced age, a low BMI, a deeper tumor depth, lymph node metastasis, and a more advanced pTNM stage, were confirmed in this study. In addition, PSM analysis was performed to reduce bias due to different distributions of covariables (tumor depth, lymph node metastasis, and pTNM stage) between groups of patients with a low and high PNI. In the multivariate analysis, the PNI, as well as the pTNM stage, were confirmed as

Figure 6. Box plots of the prognostic nutritional index (PNI) values according to age. In each plot, the lower and upper ends of the box represent the 25th and 75th percentiles, respectively. Capped bars represent the minimum and maximum values. The horizontal line inside the box represents the median PNI value.

independent prognostic factors for OS and CSS in patients with gastric cancer. These findings suggest that the preoperative immune and nutritional status may be a useful surrogate marker for predicting the long-term survival of patients with gastric cancer.

In our study, the mean age of patients was 70.6 years. Previous reports have defined elderly patients as aged ≥ 70 years (22-24). We therefore defined elderly patients as aged ≥ 70 years. Our study revealed that a low PNI value was an independent prognostic factor for OS and CSS in the entire cohort of patients with gastric cancer. Furthermore, a low PNI value was associated with a poorer prognosis in terms of OS, but not CSS, in elderly patients with gastric cancer. Specifically, patients with a low PNI value were more likely to die of diseases other than gastric cancer than patients with a high PNI value. Additionally, our study showed that the PNI value was significantly lower in elderly patients than in non-elderly patients with gastric cancer. These findings suggest that the PNI may be a non-specific marker of tumor progression since hypoalbuminemia and leukocytopenia are often associated with aging, irrespective of the patient having cancer (25). However, the precise mechanism(s) underlying the role of the PNI as a predictor of prognosis in patients with cancer has not yet been established.

Gastric outlet obstruction often disturbs the nutritional status of patients with advanced gastric cancer. Preoperative immuno-nutritional support through parenteral nutrition infusion with albumin may be beneficial for cancer patients with malnutrition. Recent reports suggest that immuno-nutritional support improves not only short-term survival, but

also long-term survival in gastric cancer patients with malnutrition, although the underlying mechanism(s) remain controversial (26, 27).

Several limitations need to be considered when interpreting the results of this study. First, this study was uncontrolled and retrospective in nature. Second, this was a single-center study with a relatively small sample size and short follow-up durations. Third, immune and nutritional parameters, such as interleukin-6 and tumor necrosis factor- α , were not adequately evaluated. Finally, there was insufficient evidence regarding the validity of the cut-off values for the PNI. Therefore, further studies are needed to establish appropriate cutoff values for the PNI. Large prospective randomized controlled trials should also be conducted to confirm our preliminary findings.

Despite the above limitations, PNI was confirmed to be a potentially novel prognostic factor for predicting OS and CSS under the cut-off value of 44.3 in patients with gastric cancer who underwent curative gastrectomy, especially non-elderly patients. Because the PNI is convenient, useful, and readily available at low cost, it has the potential to serve as a biomarker for predicting the survival of patients with gastric cancer.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

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