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The Prognostic Nutritional Index as a Predictor of Gastric Cancer Progression and Recurrence

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Background: Gastric cancer can recur soon after treatment. We evaluated the prognostic nutritional index (PNI), a predictor of postoperative complications, and examined the association of PNI with progression and recurrence of gastric cancer.

Methods: We retrospectively investigated data from 697 patients who had undergone surgery for gastric carcinoma (excluding those with stage IV disease) and analyzed associations of age, sex, performance status (PS), American Society of Anesthesiologists (ASA) classification, diabetes, depth of main tumor (T), lymph node metastasis, postoperative complications, recurrence, and survival with PNI. We also performed multivariate analysis to identify factors associated with survival.

Results: PNI significantly decreased with age and was significantly lower in women. PNI was significantly positively correlated with PS. PNI was significantly lower for ≥T2 cancers and in patients with lymph node metastasis. There was no association between postoperative complications and PNI. PNI was significantly lower for patients who developed recurrence than for those who did not. The survival rate was examined for groups with a PNI of ≥45 (high PNI) and <45 (low PNI). Both 5-year overall survival (OS) and cancer-specific survival (CS) were significantly worse for the low PNI group. Multivariate analysis showed that PNI was an independent predictor of OS and CS.

Conclusions: PNI was associated with progression and recurrence of gastric cancer.

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Key words: gastric cancer, prognostic nutritional index (PNI), surgery

Introduction

Recent research confirmed an association between outcomes and systemic inflammatory reaction in cancer patients. The presence of a systemic inflammatory reaction is not only an indicator of nutrition and cachexia[1], it is also a useful prognostic factor that differs in mechanism from tumor markers for various carcinomas[2]. While many tumor markers directly reflect substances released from tumors, a systemic inflammatory reaction indicates that a tumor has activated the immune system, which leads to release of inflammatory cytokines into the bloodstream (which act as intercellular signal transmitters) and changes in blood biochemical data (that are cause-specific)[3].

A well-established marker of a systemic inflammatory reaction is the Glasgow Prognostic Score (GPS)[4,5], which was originally reported by McMillan et al. in 2004. Onodera et al. proposed the Onodera Prognostic Nutritional Index (PNI)[6], which uses serum albumin level and lymphocyte count to calculate an index of preoperative nutrition. The PNI has been repurposed as an index of systemic inflammatory reaction for cancer patients, especially by researchers outside Japan[7,8]. We examined whether PNI is useful for predicting cancer progression and recurrence in patients with gastric cancer.

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Table 1 Patient characteristics

		All cases n = 697
Age		66.3±11.6
Sex	Male	474
	Female	223
PS	0	590
	1	94
	2	13
ASA	1	484
	2	173
	3	40
Diabetes	Yes	85
	No	612
Depth	T1	375
	T2	241
	T3	80
	T4	1
Lymph node metastasis	N0	494
	N1	119
	N2	77
	N3	7
Postoperative complications	Yes	146
(Clavien-Dindo Grade II or higher)	No	551
Recurrence	Yes	98
	No	599
PNI		49.1±6.8

Patients and Methods

Patients

We retrospectively reviewed the medical records of 697 consecutive patients who underwent surgical treatment of gastric cancer, excluding those with stage IV disease, from November 1995 to June 2014 in the Nippon Medical School Musashikosugi Hospital Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery. Baseline clinical variables, including age, sex, performance status (PS), American Society of Anesthesiologists (ASA) classification, diabetes status, pathological staging (TNM), postoperative complications (defined as grade II or worse complications on the Clavien-Dindo classification[9]), and preoperative PNI, were collected from medical records. The TNM of gastric cancer was classified according to the 15th edition of the Japanese Gastric Cancer Association TNM classification system. Cancer-specific survival (CS) and overall survival (OS) were defined as the intervals from surgery to death from gastric cancer and to death from any cause, respectively, or the last follow-up. The overall median duration of follow-up was 65 months.

The patients included 474 men (68.0%), and the average age was 66.3 years (range, 24-90 years). Tumor invasion depth was T1 for 375 cases (53.8%) and ≥T2 for 322 cases (46.2%). Lymph node metastasis was present in 494 cases (70.9%). Postoperative complications developed in 146 patients (20.9%), and 98 patients (14.1%) experienced cancer recurrence (**Table 1**). We examined associations of age, sex, PS, ASA classification, diabetes status, depth of main tumor (T), lymph node metastasis, postoperative complications, cancer recurrence, and survival rates with PNI. Furthermore, to identify factors associated with OS and cancer-specific survival (CS), we performed multivariate analysis of age, gender, PS, ASA classification, tumor invasion depth (T), presence of lymph node metastasis, presence of postoperative complications, and PNI. This study was conducted in accordance with the principles of the Helsinki Declaration, and the study protocol was approved by the Ethics Committees of Hasuda Hospital (Approval No. 202112-01).

Statistical Analysis

All statistical analyses were performed using the JMP statistical software program (Cary, NC, USA). Continuous variables are expressed as averages and ranges. The two-tailed Student *t*-test and Mann-Whitney *U* test were used to compare continuous variables. The χ^2 test was used for comparisons among groups. Survival rates were

Table 2 Associations of patient characteristics with PNI

		PNI	*P* value
Age	Old	45.3±7.2	<0.01
	Middle aged	49.2±6.6	
	Young	51.9±6.4	
Sex	Male	49.7±6.8	<0.01
	Female	47.9±6.6	
PS	0	50.2±6.0	<0.01
	1	45.3±6.8	
	2	38.3±11.7	
ASA	1	49.6±6.3	0.0798
	2	47.8±7.1	
	3	46.8±9.5	
Diabetes	Yes	49.6±6.2	0.7358
	No	49.0±6.8	
Depth	T1	51.1±5.7	<0.01
	T2 or higher	46.8±7.1	
Lymph node metastasis	N (–)	49.9±6.3	<0.01
	N (+)	47.2±7.5	
Postoperative complications	Yes	48.6±7.8	0.7882
(Clavien-Dindo Grade II or higher)	No	49.2±6.4	
Recurrence	Yes	46.2±6.9	<0.01
	No	49.7±6.6	

estimated with the Kaplan-Meier method, and the log-rank test was used to compare curves. Hazard ratios and 95% confidence intervals were estimated by using multivariate Cox regression models. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal threshold of the PNI with respect to tumor depth, lymph node metastasis, and recurrence. A P value of less than 0.05 was considered statistically significant.

Results

PNI significantly decreased with increasing age: PNI was 51.9 for young patients (<50 years), 49.2 for middle-aged patients (50-79 years), and 45.3 for old patients (≥80 years) ($p < 0.01$). Moreover, PNI was 49.7 for men and 47.9 for women ($p < 0.01$). PNI was associated with PS: PNI values were 50.2, 45.3, and 38.3 for PS values of 0, 1, and 2, respectively ($p < 0.01$). The trend was similar for the ASA classification, but the differences were not significant. There was no significant association between PNI and diabetes status. However, PNI was 51.1 for a tumor depth of T1 and 46.8 for a tumor depth of T2 or higher; thus, it was significantly lower for a tumor depth of T2 or higher ($p < 0.01$). PNI was also significantly lower for patients with lymph node metastasis: 49.9 for patients without metastasis and 47.2 for patients with metastasis ($p < 0.01$).

The presence of postoperative complications was not associated with PNI. However, when examined in association with cancer recurrence, PNI was significantly lower in patients who developed recurrence: 46.2 for those with recurrence and 49.7 for those without recurrence ($p < 0.01$) (**Table 2**). The ROC curve for the cut-off value of PNI in terms of T, lymph node metastasis, and cancer recurrence (**Fig. 1**) yielded cut-off values of 45.7, 48.3, and 48.3, respectively. Onodera et al. reported that resection and anastomosis of the gastrointestinal tract were safe when PNI was ≥45. The cut-off values obtained in the present study were similar. Thus, we set the present PNI cut-off value to 45. When patients were divided into a high PNI group (PNI ≥45) and low PNI group (PNI <45), 5-year OS was 76.7% for the former and 49.0% for the latter, indicating that outcomes were significantly worse for those with a low PNI ($p < 0.01$) (**Fig. 2**). Moreover, the 5-year CS was 87.0% for the high PNI group and 61.0% for the low PNI group, indicating that outcomes were significantly worse in the low PNI group ($p < 0.01$) (**Fig. 3**).

To identify factors associated with survival rate, we analyzed OS and CS in relation to age (≥70/<70 years), sex (female/male), PS (PS2/PS01), ASA (ASA3/ASA12), depth (≥T2/T1), lymph node metastasis (yes/no), postoperative complications (yes/no), and PNI (<45/≥45). Univariate analysis of OS confirmed significant differences in age, PS, depth, lymph node metastasis, postop-

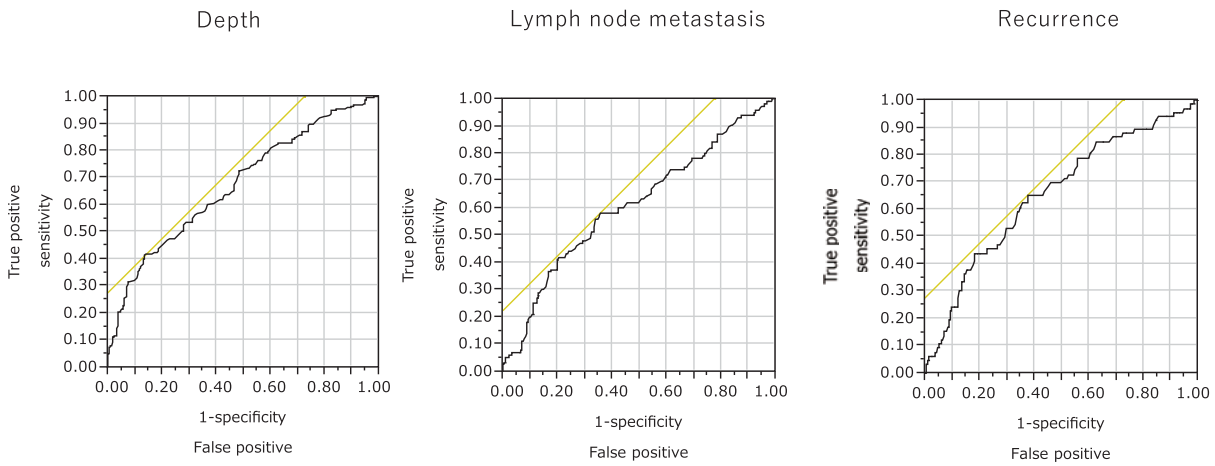

Fig. 1 Receiver operating characteristic curves for a PNI cut-off value based on tumor depth, lymph node metastasis, and cancer recurrence.

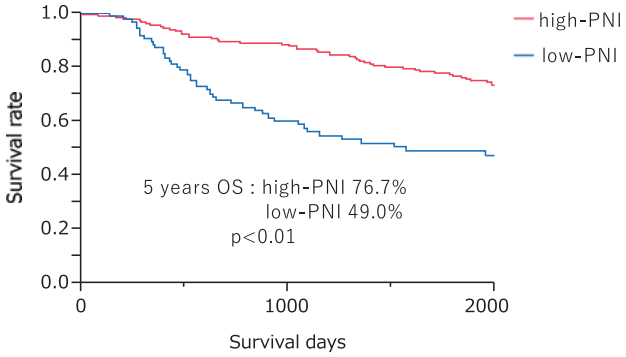

Fig. 2 Patients were classified by prognostic nutritional index (PNI) into a high PNI group (PNI ≥45) and low PNI group (PNI <45). The 5-year overall survival (OS) was 76.7% for the high PNI group and 49.0% for the low PNI group. Outcomes were significantly worse for the low PNI group ($p < 0.01$).

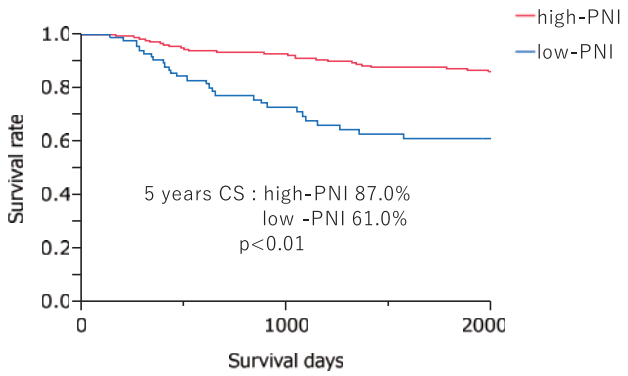

Fig. 3 Patients were classified by prognostic nutritional index (PNI) into a high PNI group (PNI ≥45) and low PNI group (PNI <45). The 5-year cancer-specific survival rate (CS) was 87.0% for the high PNI group and 61.0% for the low PNI group. Outcomes were significantly worse for the low PNI group ($p < 0.01$).

erative complications, and PNI, while multivariate analysis showed that age, lymph node metastasis, and PNI were independent prognostic factors (**Table 3**). Univariate analysis of CS confirmed significant differences in depth, lymph node metastasis, postoperative complications, and PNI, while multivariate analysis showed that depth, lymph node metastasis, and PNI were independent prognostic factors (**Table 4**).

Discussion

Numerous studies have investigated methods for predicting outcomes for patients with cancer[10]. We chose to examine PNI because there is a notable clinical advantage when cancer outcomes are predicted by an index with a mechanism that differs from those of standard tumor markers. The aims of preoperative measurement of tumor markers are to understand tumor progression and determine a suitable therapeutic approach[11]. In contrast, the aim of postoperative measurement of tumor markers is to diagnose or predict tumor recurrence and metastasis[12,13]. However, many cancer patients who present with normal preoperative tumor markers are unlikely to have tumor markers that exceed normal values, even when there is cancer recurrence or metastasis during their postoperative course. Thus, we focused on PNI, which was originally reported by Onodera et al. in 1984, as a biomarker to replace tumor markers[6]. Several markers of inflammatory reaction, and their association with cancer outcomes, have recently been reported[14]. GPS, which was originally proposed by McMillan et al. in 2004[4,5], is also a notable inflammatory reaction marker. Furthermore, associations of inflammatory reaction markers such as

Table 3 Univariate and multivariate analyses of associations of clinical characteristics with overall survival

Variable	Univariate			Multivariate		
	HR	95%CI	p value	HR	95%CI	p value
Age (≥70/<70)	2.37	1.79-3.14	<0.0001	2.22	1.59-3.11	<0.0001
Sex (female/male)	0.83	0.62-1.13	0.2463			
PS (PS2/PS01)	2.37	1.12-5.06	0.0249	1.19	0.51-2.80	0.6864
ASA (ASA3/ASA12)	1.61	0.98-2.64	0.0614			
Depth (T2 or higher/T1)	2.87	2.13-3.87	<0.0001	1.38	0.89-2.13	0.1512
Lymph node metastasis (yes/no)	4.22	3.18-5.59	<0.0001	2.54	1.70-3.79	<0.0001
Postoperative complications (yes/no)	1.83	1.34-2.50	<0.0001	1.33	0.90-1.95	0.1503
PNI (<45/≥45)	2.78	1.98-3.91	<0.0001	1.87	1.29-2.71	0.0009

HR: hazard ratio, CI: confidence interval

Table 4 Univariate and multivariate analyses of associations of clinical characteristics with cancer-specific survival

Variable	Univariate			Multivariate		
	HR	95%CI	p value	HR	95%CI	p value
Age (≥70/<70)	1.47	0.99-2.19	0.0564			
Sex (female/male)	1.35	0.90-2.03	0.1461			
PS (PS2/PS01)	1.2	0.30-4.87	0.7978			
ASA (ASA3/ASA12)	1.34	0.62-2.88	0.4593			
Depth (T2 or higher/T1)	17.81	8.25-38.46	<0.0001	8.86	2.96-26.55	<0.0001
Lymph node metastasis (yes/no)	12.16	7.54-19.61	<0.0001	3.88	2.14-7.06	<0.0001
Postoperative complications (yes/no)	1.58	1.01-2.47	0.0471	0.83	0.48-1.46	0.5211
PNI (<45/≥45)	3.4	2.09-5.54	<0.0001	1.65	1.01-2.71	0.0471

HR: hazard ratio, CI: confidence interval

neutrophil-to-lymphocyte ratio[15,16], lymphocyte-to-monocyte ratio[17,18], and C-reactive protein-to-albumin ratio (CAR)[19,20] with outcomes of cancer patients have been extensively examined. These markers are calculated by using levels of serum proteins, such as C-reactive protein or albumin, and cell counts of neutrophils, lymphocytes, or monocytes. Markers of inflammatory reaction markers of systemic inflammation caused by cancer are used to assess organ-specific blood biochemical changes caused by inflammatory cytokines[21], such as interleukin-6[22,23] (which are released by the immune system in the form of intercellular signal transmitters as the tumor-host interaction recognizes the tumor), and to indirectly measure hypercytokinemia. The Onodera index, calculated as PNI = 10 × serum albumin level (g/dL) + 0.005 × total lymphocyte count (mm^{-3}), is a simple scoring system based on serum albumin level and lymphocyte count and can assess both the nutritional status and systemic inflammatory reaction of patients. In fact, recent studies of PNI that examined the association of the latter with outcomes for cancer patients[7,8] utilized PNI in a manner not described by Onodera et al., ie, as a concrete numerical criterion for planning a safe surgery.

The present study showed that when the survival rates of a high PNI group (PNI ≥45) and low PNI group (PNI <45) were compared, both 5-year OS and 5-year CS were significantly worse for the low PNI group. The results of multivariate analysis of OS and CS showed that PNI was an independent prognostic factor. Although there are many reports on predicting outcomes of gastric cancer with PNI[24–32], few have examined independent prognostic factors in relation to both OS and CS.

Further research is necessary to determine if increasing PNI by means of a preoperative nutritional intervention improves outcomes for patients with low-PNI gastric cancer. However, if patients with low-PNI gastric cancer have a lower PNI because of cancer progression, a nutritional intervention might promote cancer progression by nourishing cancer cells. If so, preoperative chemotherapy may improve prognosis by reducing the number of cancer cells. In any case, further research is needed.

The major limitations of this study are its retrospective design and the fact that the analysis was limited to a Japanese cohort at a single center. The optimal cut-off

value for PNI may vary for studies with different endpoints and patient cohorts. To confirm the association of PNI with gastric cancer survival, prospective studies with larger samples are necessary. PNI is easy to measure before and after surgery and may help surgeons improve oncological outcomes by future potential of preoperative modulation.

In conclusion, PNI appears to be an important prognostic factor for gastric cancer.

Conflict of Interest: None declared.

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