

Original Article

Prognostic value of preoperative prognostic nutritional index in stage III gastric cancer after curative resection: a retrospective cohort study

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Background and Objectives: Nutrition and inflammation play a crucial role in the development of cancer. The prognostic value of the prognostic nutritional index (PNI) has been confirmed in some types of human cancers. This study analyzed the prognostic significance of the preoperative PNI in patients with stage III gastric cancer after curative surgery. **Methods and Study Design:** In this retrospective study, we enrolled 274 patients who underwent curative operation for stage III gastric cancer. The correlation between the preoperative PNI and overall survival (OS) was analyzed using Kaplan–Meier curves and multivariate Cox regression analyses. **Results:** The patients with a high PNI had a significantly higher median OS than did those with a low PNI (46.8 months vs 24.1 months, $p=0.01$). In the subgroup analysis, the survival benefit of the PNI was limited to the patients with poorly differentiated gastric cancer (high PNI, 46.8 months; low PNI, 21.8 months, $p=0.004$) and was not observed in those with well and moderately differentiated cancer (high PNI, 30.3 months; low PNI, 26.7 months, $p=0.30$). In the multivariate analysis, the PNI was an independent prognostic factor for OS. **Conclusions:** The PNI can be used as an independent prognostic biomarker for operable advanced gastric cancer.

Key Words: prognostic nutritional index, survival, advanced gastric cancer, serum albumin, lymphocytes

INTRODUCTION

Gastric cancer is the second most common cancer and the third leading cause of cancer-related death in China.¹ Curative resection remains the most preferred treatment approach for operable gastric cancer, considerably improving postoperative survival.^{2,3} However, many patients with gastric cancer still experience recurrence and metastasis after curative operation, particularly those with advanced cancer.^{4,5} The classification of patients with malignancy can help predict survival and thus improve clinical outcomes though the implementation of individualized therapies.⁶ Therefore, various tumor-related biomarkers have been considered crucial for predicting cancer recurrence and survival, such as the tumor stage, pathological differentiation, resection margin, and nodal involvement.⁷ However, such biomarkers can be evaluated only through postoperative histological evaluation and operative findings.⁸⁻¹⁰ The prognosis of patients with gastric cancer is associated not only with tumor-related factors but also with the patient's conditions, including inflammation, immunity, and nutritional status.^{11,12}

Patients with advanced malignancies are often malnourished, and the preoperative nutritional status is associated with postoperative complications, tumor progression, and clinical outcomes.^{13,14} Malnutrition can result in increased susceptibility to infections, loss of lean body mass, delayed wound healing, and complicated inpatient course.^{15,16} In addition, malnutrition can impair immune function, thus contributing to tumor development.¹⁷

Moreover, the systemic inflammatory response has been considered to be pathogenic with progressive nutritional decline in patients with cancer, which has also been associated with tumor development.¹⁸

The prognostic nutritional index (PNI), a simple, cost-effective, and convenient tool for assessing the nutritional and immunological status, is widely utilized to evaluate the prognosis of various types of malignancies including gastric cancer.¹⁹⁻²¹ However, no study has yet evaluated the association of the preoperative PNI with the survival of patients with operable advanced gastric cancer. In this study, we examined the prognostic significance of the preoperative PNI in patients who underwent curative surgery for stage III gastric cancer.

METHODS

Patients

In this retrospective study, we enrolled 274 patients who underwent curative resection for histologically confirmed stage III gastric cancer at the Department of General Sur-

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gery in First Affiliated Hospital of Jinan University between June 1, 2010, and June 1, 2015. The inclusion criteria were histologically confirmed stage III gastric cancer, age older than 18 years, and life expectancy of more than 6 months. Patients who had preoperative acute and severe comorbidities, such as systemic infection, autoimmune diseases, and inflammation, and had received adjuvant treatments, such as preoperative chemotherapy, were excluded. The clinical and histopathological characteristics of all patients, including sex, age, tumor site, tumor size, tumor stage, lymph node status, TNM staging, and pathological differentiation, were collected through review of clinical records by one surgeon and were verified by another surgeon. Histopathological and clinical staging were evaluated through postoperative histopathological examination and clinical assessment, respectively, according to the UICC TNM classification. Blood routine test and biochemistry were conducted on the day before surgery to obtain the absolute neutrophil, lymphocyte, monocyte, and platelet counts and the serum albumin concentration. The neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR) were calculated. The PNI was calculated using the following formula: $10 \times \text{serum albumin concentration (g/dL)} + 0.005 \times \text{lymphocyte count (number/mm}^2\text{)}$.

Follow-up

All patients were followed up at regular intervals through outpatient visits. Patients underwent physical and laboratory examinations and imaging studies, including routine blood test, biochemistry analysis, and tumor marker analysis, every 3 months for the first 2 years, every 6 months for the next 3 years, and once annually thereafter. Enhanced abdominal computed tomography or magnetic resonance imaging scans were generally obtained every 12 months. Clinical follow-up lasted from the date of surgery to either the time of death or July 2015. This study was approved by the Institutional Review Board of First Affiliated Hospital of Jinan University (20160823).

Statistical Analysis

Statistical analyses were performed using SPSS, Version 21.0 (IBM, USA). A two-sided p value of <0.05 was considered statistically significant. Overall survival (OS) was calculated from the date of surgery to death. The χ^2 test or Fisher's exact test was used to analyze the association between qualitative variables and the PNI, whereas independent Student's t test was used to analyze quantitative values. Survival was analyzed using Kaplan–Meier curves and the log-rank test. A Cox regression model was used to assess the hazard ratio and conduct multivariate analysis.

RESULTS

The baseline clinicopathological characteristics of the 274 patients who underwent curative resection for histologically confirmed stage III gastric cancer are listed in Table 1. Of the 274 patients, 192 were men and 82 were women, and their average age was with 61 ± 3.2 years. The most frequently involved tumor site was the stomach body, accounting for tumors in 125 of the 274 patients. Accord-

ing to TNM staging, 90 patients had T1 or T2 tumor, and 184 patients had T3 or T4 tumor. Regarding pathology, 160 patients had well and moderately differentiated adenocarcinoma, whereas 114 patients had poorly differentiated tumors. The median NLR, LMR, PLR, and PNI of all the patients were 2.75 (0.81–5.63), 3.53 (1.24–7.51), 152 (81–183), and 46.3 (18.2–62.7), respectively, which were considered the cutoff values. Moreover, no significant association was observed between the PNI and the clinicopathological characteristics, except for lymph node involvement, NLR, LMR, and PLR.

Prognostic significance of the PNI in stage III gastric cancer

The median follow-up period was 21.4 (6.1–79.6) months. Lymph node involvement, pathological differentiation, NLR, PLR, LMR, and PNI were significantly correlated with OS (Table 2). The patients with a PNI of ≥ 46.3 in peripheral blood had significantly higher postoperative median OS than did those with a PNI of <46.3 (46.83 months vs 24.13 months, $p=0.01$, Table 2, Figure 1).

In the subgroup analysis, for poorly differentiated gastric cancer, the patients with a high PNI of ≥ 46.3 had significantly longer median OS than did those with a PNI of <46.3 (46.8 months vs 21.8 months, $p=0.00$). However, no significant correlation was observed between the PNI and OS of patients with well and moderately differentiated gastric cancer (30.3 months vs 26.7 months, $p=0.30$, Figure 2).

In the multivariate analysis, we included age, sex, tumor size, tumor invasion depth, lymph node involvement, histological differentiation type, NLR, PLR, LMR, and PNI in the Cox regression model to identify independent prognostic factors for operable stage III gastric cancer. The results showed that the PNI (hazard ratio, 0.46; 95% CI, 0.29–0.74; $p<0.05$), lymph node involvement (hazard ratio, 1.05; 95% CI, 0.691–1.604; $p<0.05$), and histological differentiation (hazard ratio, 1.30; 95% CI, 0.82–2.05; $p<0.05$) were independent prognostic factors (Table 2).

DISCUSSION

In this study, we retrospectively examined the PNI of a large cohort of patients who underwent curative resection for operable advanced gastric cancer and its association with the prognosis of cancer. We found that a lower preoperative PNI was significantly correlated with a shorter OS, and that PNI was an independent prognostic predictor of OS in patients with operable stage III gastric cancer. Furthermore, in subgroup analyses, the association of the PNI with prognosis was limited to patients with well and moderately differentiated tumors. Therefore, we confirmed that the preoperative PNI can be examined for optimal preoperative risk stratification of individual patients, and the preoperative PNI can serve as a biomarker for predicting the prognosis of patients with advanced gastric cancer after curative resection.

Gastric cancer is frequently associated with preoperative malnutrition, which results from tumor progression; decreased oral intake; and abdominal pain.^{22,23} Tumor cells can express cytokines, such as the tumor necrosis factor- α , which plays a key role in the pathogenesis of malnutrition and selectively inhibits the genetic ex-

Table 1. Correlation between the percentage of PNI and clinicpathologic characteristics

Characteristic	PNI		<i>p</i>
	<46.3 (n=198)	≥46.3 (n=76)	
Age(years)			0.81
≥60	97	36	
<60	101	40	
Gender			0.16
Male	134	58	
Female	64	18	
Tumor site			0.80
Gastric cardia	52	23	
Gastric body	92	33	
Gastric antrum	54	20	
Tumor size (cm)			0.65
≥5	63	22	
<5	135	54	
Tumor invasion depth			0.99
T1+T2	65	25	
T3+T4	133	51	
Lymph node involvement			<0.00
N0	103	22	
N1	95	54	
Pathological differentiation			0.917
Well/Moderate	116	44	
Poor	82	32	
NLR			<0.00
≥2.75	126	19	
<2.75	72	57	
LMR			0.006
≥3.53	88	48	
<3.53	110	28	
PLR			<0.00
≥152	131	23	
<152	67	53	

PNI: prognostic nutritional index; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; PLR: platelet/lymphocyte ratio.

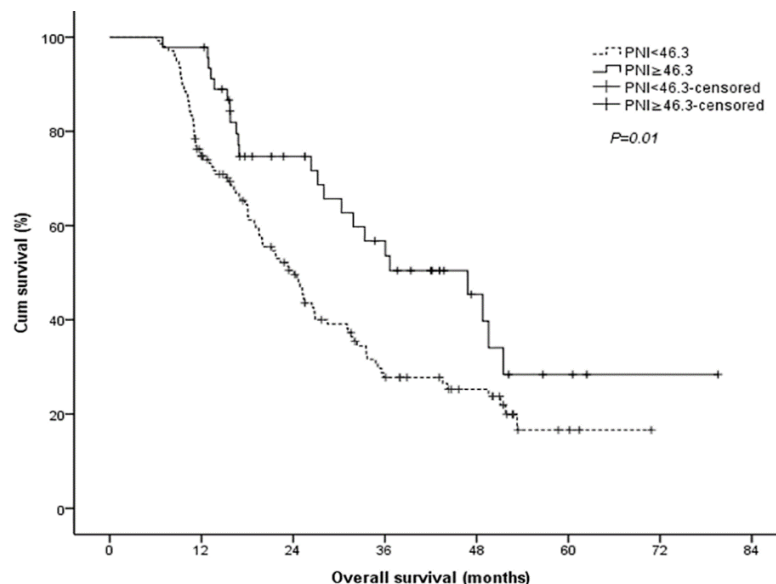


Figure 1. Kaplan–Meier estimates of overall survival. Panel shows the association between PNI and overall survival (median survival in PNI≥46.3, 46.8 months; in PNI<46.3, 24.1 months, *p*=0.01).

pression of albumin prior to weight loss.²⁴ Albumin, the main component of plasma proteins, can preserve the colloid osmotic pressure and reflect the nutritional status.²⁵ Hypoalbuminemia exerts negative effects on tissue healing and collagen synthesis in surgical wounds or

anastomoses and host immune responses.^{26,27} Therefore, malnutrition is associated with poor quality of life or prognosis of patients with cancer. Inflammation is considered to be one of the crucial contributors to cancer progression and metastasis.²⁸ Lymphocytes account for

Table 2. The prognostic characteristics of patients underwent radical operation for stage III gastric cancer

	Univariate			Multivariate		
	n	MS (months)	<i>p</i>	HR	95% CI	<i>p</i>
Age (years)			0.94			
≥60	133	25.4				
<60	141	26.7				
Gender			0.94			
Male	192	24.7				
Female	82	31.1				
Tumor site			0.85			
Gastric cardia	75	24.7				
Gastric body	125	26.8				
Gastric antrum	74	31.1				
Tumor size (cm)			0.18			
≥5	85	24.1				
<5	189	28.5				
Tumor invasion depth			0.49			
T1+T2	90	28.0				
T3+T4	184	24.9				
Lymph node involvement			0.04	1.05	0.69-1.60	0.04
N0	135	35.1				
N1	149	24.131				
Pathological differentiation			0.02	1.30	0.82-2.05	0.00
Well/Moderate	160	27.2				
Poor	114	25.2				
NLR			0.02			
≥2.75	145	21.7				
<2.75	129	31.1				
PLR			0.00			
≥152	154	16.6				
<152	120	31.6				
LMR			0.04			
≥3.53	136	36.1				
< 3.53	138	24.5				
PNI			0.01	0.46	0.29-0.74	0.00
≥46.3	76	46.8				
< 46.3	198	24.1				

MS: median survival; CI: confidence interval; HR: hazard ratio; PNI: prognostic nutritional index; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; PLR: platelet/lymphocyte ratio.

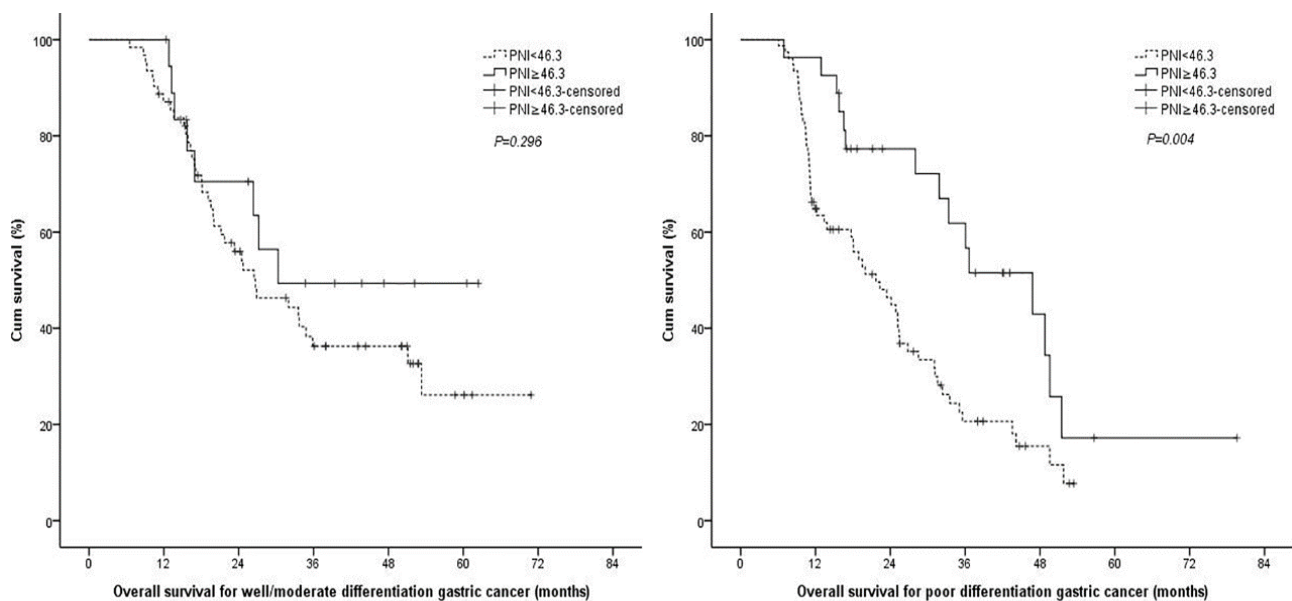


Figure 2. Histological differentiation wise survivability. Right panels showed that there was statistic significant correlation between PNI and overall survival of patients with poor differentiation gastric cancer (median survival in PNI ≥46.3, 46.8 months; in PNI <46.3, 21.8 months, *p*=0.004). The left panel show there was no significant survival association between PNI and overall survival of patients with well/moderate differentiation gastric cancer (median survival in PNI ≥46.3, 30.3 months; in PNI <46.3, 26.7 months, *p*=0.296).

the main components of inflammation and reflect the systemic inflammatory status. Lymphocytopenia is also a significant characteristic observed in patients with cancer in the setting of vascular invasion, lymph node involvement, or distant metastases and is found to be an independent indicator of the prognosis of patients with metastatic gastric cancer.²⁹⁻³¹

Several studies have reported that the PNI, an immunonutritional biomarker based on the lymphocyte count and serum albumin concentration, is a significant prognostic factor for gastric cancer.³²⁻³⁴ However, no study has yet evaluated the prognostic significance of the preoperative PNI in advanced gastric cancer after curative resection. Therefore, we conducted this retrospective study and confirmed that the PNI can serve as an independent prognostic factor for operable advanced gastric cancer. In addition, we observed a significant association of the PNI with inflammation-related prognostic biomarkers including the NLR, PLR, and LMR.

Several limitations may influence the interpretation of the results of this study. One limitation is the retrospective study design and a relatively short follow-up period. A large-scale, multicenter, prospective study should be conducted to confirm long-term results and obtain more definite evidence. Furthermore, we used the median value as the cutoff levels of the PNI in OS evaluation, whereas other studies have calculated the cutoff value by using the receiver-operator characteristic curve. Thus, the results of this study may not be comparable with those of other studies. A meta-analysis including various PNI validation studies may be required to confirm more definite cutoff values for the PNI.

In conclusion, the PNI, a simple, well-validated, and cost-effective biomarker, can be considered an independent prognostic factor for operable advanced gastric cancer.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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