

# Prognostic nutritional index is an independent prognostic factor for gastric cancer patients with peritoneal dissemination

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## Abstract

**Objective:** The predictive and prognostic role of prognostic nutritional index (PNI) in gastric cancer patients with peritoneal dissemination remains unclear. This study aims to explore the role of the PNI in predicting outcomes of gastric cancer patients with peritoneal dissemination.

**Methods:** A total of 660 patients diagnosed with gastric adenocarcinoma with peritoneal metastasis between January 2000 and April 2014 at Sun Yat-sen University Cancer Center and the Sixth Affiliated Hospital of Sun Yat-sen University were retrospectively analyzed. The clinicopathologic characteristics and clinical outcomes of patients with peritoneal dissemination were analyzed.

**Results:** Compared with PNI-high group, PNI-low group was correlated with advanced age ( $P=0.036$ ), worse performance status ( $P<0.001$ ), higher frequency of ascites ( $P<0.001$ ) and higher frequency of multisite distant metastasis ( $P<0.001$ ). Kaplan-Meier survival curves showed that PNI-high group had a significantly longer median overall survival than PNI-low group (13.13 vs. 9.03 months,  $P<0.001$ ). Multivariate survival analysis revealed that Borrmann type IV ( $P=0.014$ ), presence of ascites ( $P=0.017$ ) and lower PNI ( $P=0.041$ ) were independent poor prognostic factors, and palliative surgery ( $P<0.001$ ) and first-line chemotherapy ( $P<0.001$ ) were good prognostic factors. For patients receiving palliative surgery, the postoperative morbidity rates in the PNI-low group and PNI-high group were 9.1% and 9.9%, respectively ( $P=0.797$ ). The postoperative mortality rate was not significantly different between PNI-low and PNI-high groups (2.3% vs. 0.9%,  $P=0.362$ ).

**Conclusions:** PNI is a useful and practical tool for evaluating the nutritional status of gastric cancer patients with peritoneal dissemination, and is an independent prognostic factor for these patients.

**Keywords:** Prognostic nutritional index (PNI); gastric cancer; peritoneal dissemination; survival

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## Introduction

Gastric cancer is the fourth most common cancer and the third leading cause of cancer-related death worldwide (1).

With early diagnosis, advances in surgery and standard chemotherapy, the overall survival (OS) of gastric cancer patients is increasing, particularly in Japan and Korea (2-4). However, most gastric cancer patients in China are

diagnosed at an advanced stage (5).

Among the metastasis patterns of gastric cancer, peritoneal dissemination is the most common and lethal cause, which is considered the terminal period of gastric cancer (6). Gastric cancer patients with peritoneal dissemination often develop oral intake deficiency, overconsumption, bleeding, ascites and cancer pain, which cause debilitating malnutrition and immunological deterioration. Moreover, the worsened nutritional status can lead to development of the tumor by suppressing the immunity of the patients (7). Therefore, nutritional status plays a significant role in the OS of gastric cancer patients. Several studies demonstrated that various factors regarding the nutritional status are correlated with prognosis of gastric cancer patients (7-12). The prognostic nutritional index (PNI) is calculated by serum albumin and total lymphocyte count, including nutritional parameters and immune competence testing (13,14). It has been proposed as a simple and useful marker under the cutoff value of 45 to predict postoperative complication and the OS outcome after resection of gastric cancer and other malignancies (7,10,15-19).

Recently, Sachlova *et al.* reported that PNI represents a useful tool for evaluating the prognosis of patients with metastatic gastric cancer (12). However, the predictive and prognostic role of PNI in gastric cancer patients with peritoneal dissemination remains unclear. Therefore, the aim of this study was to explore the role of PNI in predicting the outcomes of gastric cancer patients with peritoneal dissemination.

## Patients and methods

### Patients

Between January 2000 and April 2014, a total of 660 patients were diagnosed with gastric adenocarcinoma with peritoneal metastasis at Sun Yat-sen University Cancer Center and the Sixth Affiliated Hospital of Sun Yat-sen University. The diagnosis of peritoneal dissemination was mainly through imaging test. Some patients were diagnosed with peritoneal dissemination by laparoscopic staging or laparotomy. The treatment, including palliative surgery and chemotherapy, was performed after obtaining written informed consent from all patients. The first-line chemotherapy regimens included a variety of agents, such as taxane, irinotecan, 5-fluorouracil, oxaliplatin and capecitabine. In the present study, postoperative morbidity

was defined as the incidence rate of the postoperative complication and postoperative mortality was defined as death occurred in 30 d after operation. And this study was also approved by the independent Institute Research Ethics Committee at the Sun Yat-sen University Cancer Center and the Sixth Affiliated Hospital of Sun Yat-sen University. We conducted this retrospective research according to the principles expressed in the Declaration of Helsinki.

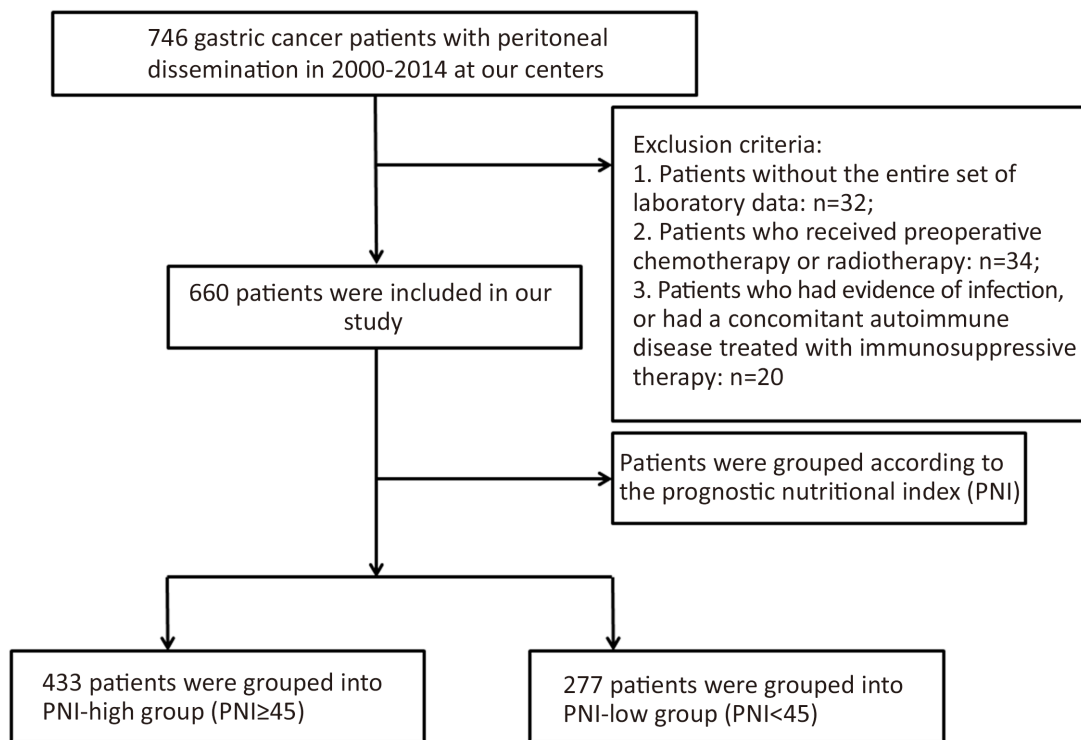
Information regarding patient demographics was collected for analysis. Only patients with an entire set of laboratory data were included in this study. Patients were excluded if they had evidence of infection, or a concomitant autoimmune disease treated with immunosuppressive therapy which affected their total lymphocyte count. Patients who received preoperative chemotherapy or radiotherapy were also excluded in this study (*Figure 1*).

### Prognostic nutritional index (PNI)

The PNI was calculated as described previously using the following formula:  $10 \times$  serum albumin concentration (g/dL) +  $0.005 \times$  lymphocyte count (number/mm<sup>2</sup>) in peripheral blood (14). All nutritional factors were measured a few days before palliative surgery or first-line chemotherapy. The cutoff value in present study was set as 45, because PNI < 45 is defined as moderate to severe malnutrition. Therefore, the patients in this study were grouped into PNI-low group (PNI < 45) and PNI-high group (PNI ≥ 45).

### Statistical analysis

The categorical variables were presented as numbers and percentages, and Chi-square tests were used to compare categorical variables. OS was calculated from the diagnosis of peritoneal metastasis to death from any cause. Unadjusted Kaplan-Meier survival curves with log-rank testing were generated to compare the survival benefits. In the present study, median OS time was used to compare the survival benefits indirectly. Prognostic factors were analyzed by searching the clinicopathological factors in univariate analysis, and the variables with P < 0.05 in the univariate analysis entered into multivariate analysis using Cox proportional hazard regression models. The forward selection method was used for multivariate Cox proportional analysis. The hazard ratio (HR) and 95% confidence interval (95% CI) were used to estimate the role of each predictor of survival. Two-sided P < 0.05 was



**Figure 1** The flow chart of this study.

considered statistically significant. All of the above statistical analyses were performed by SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA).

All of the regular follow-up assessments were completed by November 2015, and the median follow-up was 12.3 months (range, 0.3–56.1 months).

## Results

### Patient characteristics

The baseline characteristics of 660 gastric cancer patients with peritoneal dissemination are shown in *Table 1*. There were 433 patients in the PNI-high group and 227 patients in the PNI-low group. Compared with PNI-high group, PNI-low group was likely to be older (11.5% *vs.* 6.7%,  $P=0.036$ ), to have worse performance status (PS) (8.8% *vs.* 1.8%,  $P<0.001$ ), higher frequency of ascites (62.1% *vs.* 39.7%,  $P<0.001$ ), higher frequency of multisite distant metastasis (42.3% *vs.* 29.1%,  $P<0.001$ ), less palliative surgery (59.0% *vs.* 76.0%,  $P<0.001$ ) and first-line chemotherapy (62.6% *vs.* 70.0%,  $P=0.044$ ). The other baseline characteristics between the two groups had no difference.

### Overall survival

The median OS was 13.13 (95% CI, 11.35–14.92) months in the PNI-high group and 9.03 (95% CI, 7.85–10.22) months in the PNI-low group (*Figure 2*). The OS difference between the groups was significant ( $P<0.001$ ).

Patients receiving first-line chemotherapy had a significantly longer median OS of 13.57 (95% CI, 11.91–15.23) months compared with 6.70 (95% CI, 5.76–7.64) months in patients who did not ( $P<0.001$ ) (*Figure 3*).

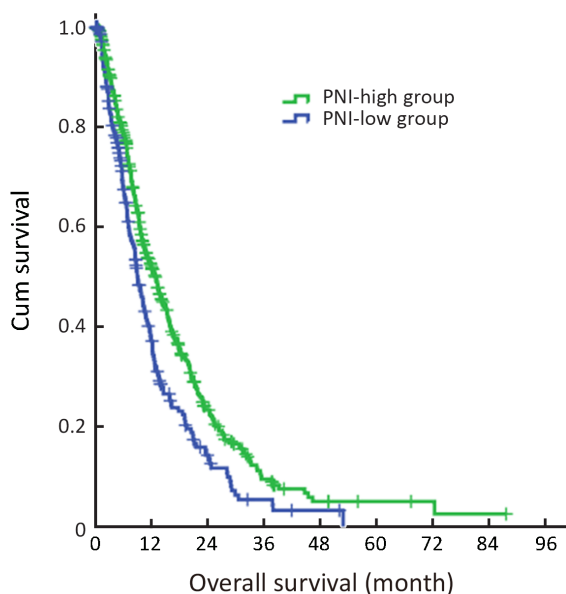
In the subgroup analysis, for patients receiving palliative surgery, patients in the PNI-high group had a significantly longer median OS than patients in the PNI-low group [14.03 (95% CI, 11.80–16.26) months *vs.* 10.13 (95% CI, 8.20–12.06) months;  $P=0.009$ ] (*Figure 4A*). However, for patients not receiving palliative surgery, the median OS between PNI-high and PNI-low groups was not significantly different [9.07 (95% CI, 7.42–10.72) months *vs.* 7.97 (95% CI, 5.92–10.01) months;  $P=0.051$ ] (*Figure 4B*).

The median OS in the PNI-high group was significantly longer than that in the PNI-low group both for patients receiving first-line chemotherapy [15.40 (95% CI,

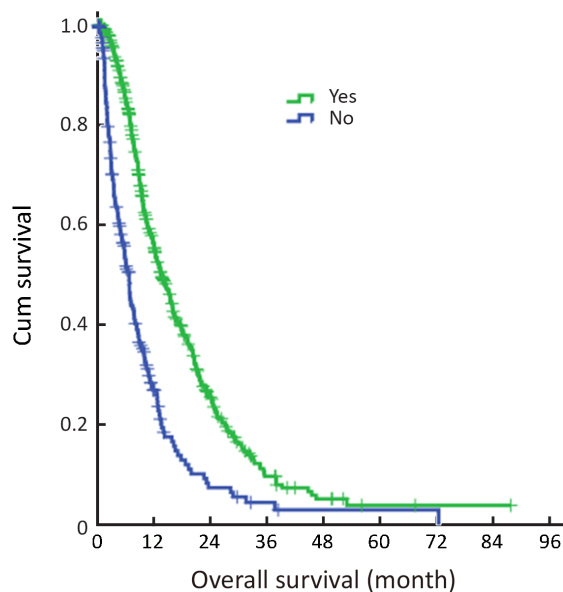
**Table 1** Clinicopathological characteristics of 660 gastric cancer patients with peritoneal dissemination according to prognostic score index

Characteristics	n (%)		P
	PNI-high group* (N=433)	PNI-low group** (N=227)	
Age (year)			0.036
<70	404 (93.3)	201 (88.5)	
≥70	29 (6.7)	26 (11.5)	
Gender			0.395
Male	242 (55.9)	119 (52.4)	
Female	191 (44.1)	108 (47.6)	
ECOG PS			<0.001
<2	381 (88.0)	204 (89.9)	
≥2	8 (1.8)	20 (8.8)	
Unkonwn	44 (10.2)	3 (1.3)	
Weight loss (kg)			0.141
<5	82 (18.9)	62 (27.3)	
≥5	19 (4.4)	24 (10.6)	
Unknown	332 (76.7)	141 (62.1)	
Tumor location			0.766
Cardia	118 (27.3)	65 (28.6)	
Non-cardia	301 (69.5)	157 (69.2)	
Unknown	14 (3.2)	5 (2.2)	
Borrmann type IV			0.053
Yes	65 (15.0)	48 (21.1)	
No	362 (83.6)	178 (78.4)	
Unkonwn	6 (1.4)	1 (0.5)	
SRCC			0.704
Yes	150 (34.6)	83 (36.6)	
No	272 (62.8)	141 (62.1)	
Unkonwn	11 (2.6)	3 (1.3)	
Ascites			<0.001
Yes	172 (39.7)	141 (62.1)	
No	261 (60.3)	86 (37.9)	
Multisite distant metastasis			<0.001
Yes	126 (29.1)	96 (42.3)	
No	306 (70.7)	131 (57.7)	
Unkonwn	1 (0.2)	0 (0)	
Palliative surgery#			<0.001
Yes	329 (76.0)	134 (59.0)	
No	104 (24.0)	93 (41.0)	
First-line chemotherapy			0.044
Yes	303 (70.0)	142 (62.6)	
No	128 (29.6)	85 (37.4)	
Unkonwn	2 (0.4)	0 (0)	

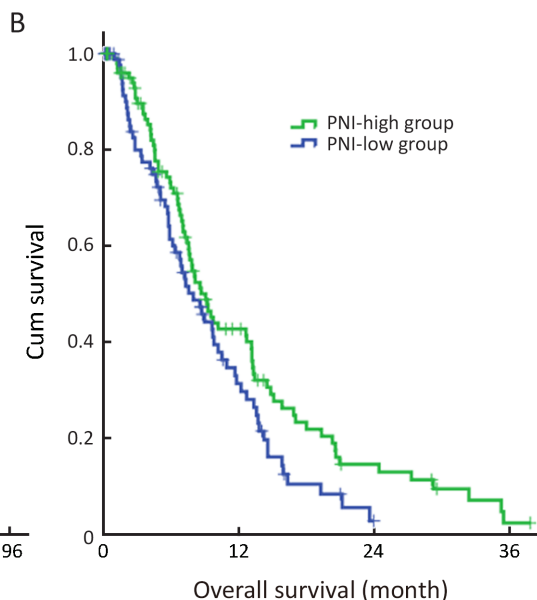
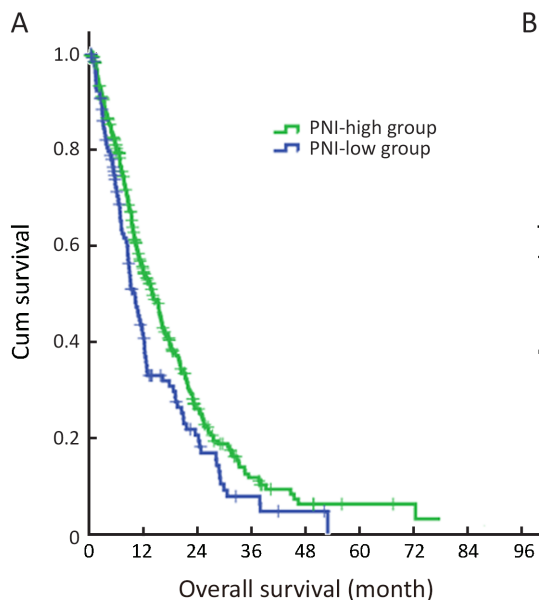
PNI, prognostic nutritional index; \*, PNI≥45; \*\*, PNI<45; ECOG PS, Eastern Cooperative Oncology Group performance status; SRCC, signet ring cell carcinoma; #, included palliative gastrectomy, by-pass surgery and open-close surgery.



**Figure 2** Kaplan-Meier survival curves of PNI-low and PNI-high groups for gastric cancer patients with peritoneal dissemination ( $P < 0.001$ ). P value is calculated by the log-rank test.



**Figure 3** Kaplan-Meier survival curves of gastric cancer patients with peritoneal dissemination according to first-line chemotherapy ( $P < 0.001$ ). P value is calculated by the log-rank test.

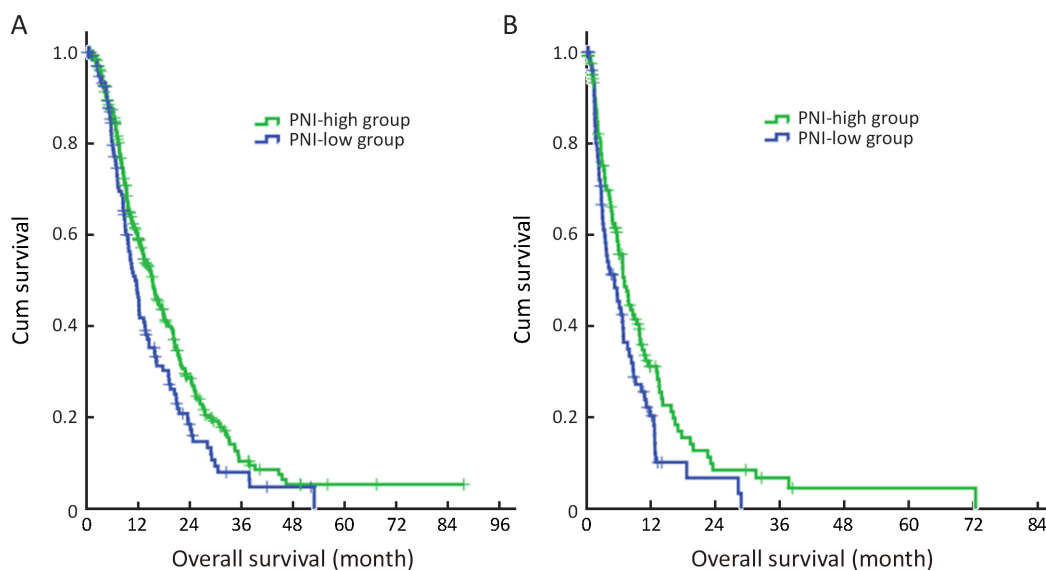


**Figure 4** Kaplan-Meier survival curves of PNI-low and PNI-high groups for gastric cancer patients with peritoneal dissemination stratified by palliative surgery. (A) Palliative surgery group ( $P = 0.009$ ); (B) Non-palliative surgery group ( $P = 0.051$ ). P values are calculated by the log-rank test.

13.33–17.47) months *vs.* 11.67 (95% CI, 9.95–13.39) months;  $P = 0.010$ ] (*Figure 5A*) and patients not receiving first-line chemotherapy [7.03 (95% CI, 5.49–8.58) months *vs.* 5.20 (95% CI, 2.81–7.59) months;  $P = 0.019$ ] (*Figure 5B*).

#### Univariate and multivariate analysis for OS

In univariate analysis, age ( $P = 0.016$ ), PS ( $P = 0.007$ ), tumor location ( $P = 0.033$ ), Borrmann type IV ( $P = 0.003$ ), ascites



**Figure 5** Kaplan-Meier survival curves of PNI-low and PNI-high groups for gastric cancer patients with peritoneal dissemination stratified by first-line chemotherapy. (A) First-line chemotherapy group (P=0.010); (B) Non-first-line chemotherapy group (P=0.019). P values are calculated by the log-rank test.

(P<0.001), serum albumin (P=0.023), serum total lymphocyte count (P=0.007), multisite distant metastasis (P<0.001), palliative surgery (P<0.001), first-line chemotherapy (P<0.001) and PNI (P<0.001) were

significant predictors of OS (Table 2). Multivariate survival analysis demonstrated that Borrmann type IV (P=0.014), presence of ascites (P=0.017) and lower PNI (P=0.041) remained independent poor prognostic factors, and

**Table 2** Univariate and multivariate analysis of overall survival in gastric cancer patients with peritoneal dissemination

Variables	Univariate analysis			Multivariate analysis	
	N	HR (95% CI)	P	HR (95% CI)	P
Age (year) (≥70 vs. <70)	660	1.46 (1.07–1.98)	0.016		
Gender (female vs. male)	660	1.01 (0.84–1.21)	0.899		
ECOG PS (≥2 vs. <2)	613	1.87 (1.19–2.95)	0.007		
Weight loss (kg) (≥5 vs. <5)	187	0.92 (0.59–1.40)	0.681		
Tumor location (cardia vs. non-cardia)	641	0.80 (0.65–0.98)	0.033		
Borrmann type IV (no vs. yes)	653	1.42 (1.12–1.79)	0.003	1.36 (1.06–1.73)	0.014
SRCC (no vs. yes)	646	0.84 (0.69–1.02)	0.084		
Ascites (no vs. yes)	660	1.60 (1.33–1.92)	<0.001	1.29 (1.05–1.58)	0.017
Albumin (g/dL) (<4.0 vs. ≥4.0)	660	0.81 (0.68–0.97)	0.023		
TLC (mm <sup>3</sup> ) (<1,500 vs. ≥1,500)	660	0.78 (0.65–0.93)	0.007		
Multisite distant metastasis (no vs. yes)	659	1.59 (1.31–1.93)	<0.001		
Palliative surgery* (no vs. yes)	660	0.62 (0.51–0.76)	<0.001	0.63 (0.50–0.78)	<0.001
First-line chemotherapy (no vs. yes)	658	0.44 (0.36–0.53)	<0.001	0.44 (0.36–0.54)	<0.001
PNI (<45 vs. ≥45)	660	0.69 (0.57–0.84)	<0.001	0.81 (0.66–0.99)	0.041

ECOG PS, Eastern Cooperative Oncology Group performance status; SRCC, signet ring cell carcinoma; TLC, total lymphocyte count; \*, included palliative gastrectomy, by-pass surgery and open-close surgery.

palliative surgery ( $P < 0.001$ ) and first-line chemotherapy ( $P < 0.001$ ) were good prognostic factors (Table 2).

### **Postoperative morbidity and mortality**

For patients receiving palliative surgery, there was no significant difference between PNI-low group and PNI-high group regarding the postoperative morbidity rate, which were 9.0% (12/134) and 9.7% (32/329), respectively ( $P = 0.797$ ). PNI-low group had a higher postoperative mortality rate of 2.2% (3/134), compared with 0.9% (3/329) in the PNI-high group; however, the difference was not significant ( $P = 0.252$ ).

### **Discussion**

With a 5-year OS less than 2%, peritoneal dissemination is considered the terminal period of gastric cancer (20). Malnutrition often tortures gastric cancer patients with peritoneal dissemination, which decreases the patients' quality of life. Moreover, immunological and nutritional disorder can cause a decline in serum albumin concentration, total lymphocyte count (TLC), helper T cells, interleukins 2 and 3, and T cell blastogenic responses (7). In the present study, we noted that lower PNI, a simple inflammation-based prognostic score, was correlated significantly with advanced age, higher frequency of ascites and multisite distant metastasis, suggesting that lower PNI is correlated with a more aggressive disease phenotype. Univariate and multivariate analysis also demonstrated that PNI was an independent predictor of OS in gastric cancer patients with peritoneal dissemination, especially for patients who need to receive palliative surgery to relieve cancer-related symptoms, such as tumor bleeding, obstruction and perforation. Our results were also supported by other studies (11,21).

Until now, various indexes have been offered to assess the nutritional status in cancer patients (8,9,22,23). All the assessment indexes have their own merits, but they have also raised a series of questions. PS is a direct index to reflect the nutritional status of the patients, which is considered to be a significant prognostic factor. However, the PS assessment may be subjective and biased. In our study, multivariate analysis demonstrated that PNI is superior to PS in terms of prognostic ability.

Lien *et al.* reported that preoperative serum albumin level was correlated highly with resectability and survival in gastric cancer patients (8). Serum albumin is not only a

window to recognize the nutritional status of the patients but also a useful tool for predicting the prognostic outcome of cancer patients. However, serum albumin has its own defect in predicting the prognostic outcome of the cancer patients. First, serum albumin has a long half-life period of 20 days, and therefore cannot reflect the short-term nutrition state of the patients; second, serum albumin is easily influenced by non-nutritional factors, such as acute phase reaction, the hydration status of patients, renal function, liver function and extravascular fluid alteration. According to the multivariate analysis of our study, serum albumin did not reflect patients' outcome. Bruckner *et al.* reported that total lymphocyte count was an independent prognostic factor for patients with advanced gastric cancer (23). However, the multivariate analysis of our study showed that total lymphocyte count was not an independent prognostic factor. This indicated that total lymphocyte count was not an effective factor to predict the survival outcome of the gastric patients with peritoneal dissemination. Just as serum albumin, there may be lots of impacts influencing the PNI, too; nevertheless, our results revealed that PNI, the combination of serum albumin and total lymphocyte count, showed preponderance in predicting the outcome of gastric cancer patients with peritoneal dissemination.

Although the final results of the Regatta trial showed that palliative gastrectomy combined with chemotherapy was not superior to chemotherapy alone for advanced gastric cancer patients with a single non-curable factor (24), palliative surgery was still important for patients experiencing cancer-related symptoms, such as tumor bleeding, obstruction and perforation. The postoperative morbidity and mortality were acceptable (25). However, our results demonstrated that PNI was not a predict factor regarding postoperative complication and mortality, which was contradiction to other studies (18,26). Therefore, this indicated that PNI of gastric cancer patients with peritoneal dissemination was a prognostication of OS, but not for postoperative morbidity and mortality.

Theoretically, gastric cancer patients with malnutrition can benefit from correction of preoperative immunonutritional disorders through intravenous infusion of albumin and parenteral nutrition, but it lacks clinical trials to confirm. Qiu *et al.* reported that nutrition improvement after nutrition support indicated a survival benefit for stage IV gastric cancer patients (27). Unfortunately, their study also showed that only 30.3% of patients had the nutritional improvement after nutrition support. Furthermore, it



remains unclear whether a low PNI is a cause or a consequence of tumor progression (11). In the future, well-designed large scale randomized controlled clinical trials on the value of management in the PNI-low group are required.

This study is a substantially retrospective study with several missed data of clinicopathological characteristics of the enrolled patients, which is a potential limitation of this study. Although the data in our study were from two high-volume institutions, the results of this study should be interpreted cautiously. A large-scale prospective validation study is required to confirm the results.

## Conclusions

The present study indicated that PNI is a useful and practical tool for evaluating the nutritional status of gastric cancer patients with peritoneal dissemination, and is also an independent prognostic factor of OS for these patients.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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