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Prognostic Nutritional Index as a Predictor of Prognosis in Postoperative Patients With Gastric Cancer

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Abstract. *Background/Aim: The prognostic nutritional index (PNI) has been reported as an immunonutritional index that can easily evaluate nutritional status and immunocompetence from blood tests. The purpose of this study was to investigate the usefulness of PNI as a prognostic factor in postoperative gastric cancer patients. Patients and Methods: In this retrospective cohort study, we evaluated 258 patients with pStage I-III gastric cancer who underwent radical resection at Yokohama City University Hospital, from 2015 to 2021. To examine the association with prognosis, we analyzed clinicopathological factors including PNI (<47/≥47), age (<75/≥75), sex (male/female), depth (pT1/≥pT2), lymph node metastasis (pN+/pN-), lymphatic invasion (ly+/ly-), vascular invasion (v+/v-), histological type (enteric/spread) and postoperative complications. Results: In univariate analysis, PNI (p<0.001), depth of tumor invasion (p<0.001), lymph node involvement (p<0.001), age (p=0.002), lymphatic invasion (p<0.001), vascular invasion (p<0.001), and postoperative complications (p=0.003) were associated with overall survival. In multivariate analysis, PNI (HR=2.100, 95% confidence interval 1.225-3.601, p=0.007), tumor invasion, lymph node metastasis, and postoperative complications were shown as poor prognostic factors for overall survival. Conclusion: PNI is an independent prognostic factor for overall and recurrence-free survival in postoperative gastric cancer patients. PNI could be implemented in clinical practice to identify patients at higher risk for poor outcomes.*

Gastric cancer is a cause of significant morbidity and mortality; 1,000,000 cases are diagnosed, and 800,000 cases die every year (1). The current standard of care for gastric cancer is surgery and adjuvant therapy. However, many patients experience recurrence after curative resection for gastric cancer (2). Therefore, it is crucial to identify the prognostic factors for recurrence after surgical techniques and adjuvant chemotherapy. Previous studies have investigated various prognostic factors and their efficacy has been reported (3-5). Lien YC *et al.* reported that preoperative serum albumin level was associated with resectability and survival in patients with adenocarcinoma of the gastric cardia (3). Preoperative nutritional status and the patient's immune status may be prognostic factors for the patient's long-term survival in various malignancies (3-5).

In this study, we focused on the prognostic nutritional index (PNI) as a prognostic indicator for gastric cancer. PNI has been widely used, owing to its efficiency, simplicity, and convenience, in assessing the preoperative condition and in predicting the surgical risk for gastrointestinal malignancy patients (6-8). PNI is calculated by the serum albumin concentration and the peripheral blood lymphocyte count. PNI was originally intended for use in patients with Stage IV and V (9); however, recently, it has been used more widely for preoperative risk assessment in many malignancies (10). In the present study, we aimed to investigate the validity of PNI for predicting prognosis in postoperative gastric cancer patients.

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Table I. *Comparison of overall survival rates stratified by patient characteristics.*

Characteristics	No. of patients (%)	1-year OS rate (%)	3-year OS rate (%)	5-year OS rate (%)	*p*-Value
Age (years)					<0.001
<75	179 (69.3)	96.9	82.8	78.6	
≥75	79 (30.7)	96.0	65.9	52.7	
Sex					0.416
Male	183 (70.9)	97.6	75.7	69.8	
Female	75 (29.1)	94.3	80.8	72.2	
Site of tumor					0.009
Upper	63 (24.4)	93.4	62.6	55.2	
Middle	113 (43.8)	96.0	81.3	78.1	
Lower	82 (31.8)	97.3	84.5	73.2	
T status					<0.001
T1	138 (53.5)	99.1	94.9	91.7	
T2 to T3	120 (46.5)	93.0	59.4	50.0	
Lymph node metastasis					<0.001
Negative	168 (65.1)	98.0	93.0	85.9	
Positive	90 (34.9)	93.1	53.5	46.2	
Prognostic nutritional index					<0.001
<47	75 (29.1)	91.2	60.4	50.7	
≥47	183 (70.9)	98.8	85.0	79.1	
Lymphatic invasion					<0.001
Negative	168 (65.1)	98.0	93.0	85.9	
Positive	90 (34.9)	93.1	53.5	46.2	
Vascular invasion					<0.001
Negative	154 (59.7)	98.5	90.5	85.1	
Positive	104 (40.3)	92.9	60.8	51.6	
Postoperative surgical complications					0.003
No	160 (62.0)	98.5	90.5	85.1	
Yes	98 (38.0)	92.9	60.8	51.6	
Histological type					0.106
Intestinal	137 (53.1)	97.5	83.3	75.0	
Diffuse	121 (46.9)	94.8	72.1	66.3	

OS, Overall survival.

Patients and Methods

Patients. A total of 258 patients with gastric cancer underwent gastrectomy in the Department of Surgery in Yokohama City University Hospital, Yokohama, Japan, between January 2015 and December 2021. The clinicopathological factors were determined according to the Japanese classification of Gastric Carcinoma: 3rd English edition (11). Patients with gastric adenocarcinoma classified as clinical stage I-III were undergone curative resection.

Surgery and adjuvant treatment. Total gastrectomy and distal, proximal, or partial gastrectomy were performed. Generally, pathological stage II was treated with S-1 monotherapy, whereas pathological stage III was treated with S-1 plus docetaxel or capecitabine plus oxaliplatin.

Methods. According to Onodera *et al*., the PNI was calculated preoperatively for each case using the following formula: 10 × serum albumin value (g/dl) + 0.005 × lymphocyte count in peripheral blood (9). We performed univariate analysis using Cox proportional hazards model using nine clinical background factors [PNI (>47/≤47), age (>75/≤75 years), sex (male/female), tumor depth (T1, T2 or T3), tumor location (upper, middle, lower), lymphatic invasion (negative/positive), venous invasion (negative/positive), histology (intestinal/diffuse), and postoperative complications (no/yes)] to investigate their association with overall survival (OS) and recurrence-free survival (RFS). The Cox proportional hazard model was used to perform univariate and stepwise multivariate survival analyses.

Statistical analysis. Categorical variables are presented as frequency and percentage (%). The chi-square test, Student's *t*-test, and the Mann–Whitney test were used to compare the groups. Survival curves were created by the Kaplan–Meier method, and a log-rank test was used to analyze the equality of survival curves. The univariate and multivariate hazard ratios were calculated using the Cox proportional hazard model. All significant variables in the univariate analysis were used for backward stepwise multivariate models. A *p*-value of less than 0.05 was considered to be statistically significant. The statistical analyses were performed using the SPSS software program, version 27.0 (SPSS, Chicago, IL, USA).

Results

Patients' background. A total of 258 patients with gastric cancer were evaluated in this study. The patients were aged

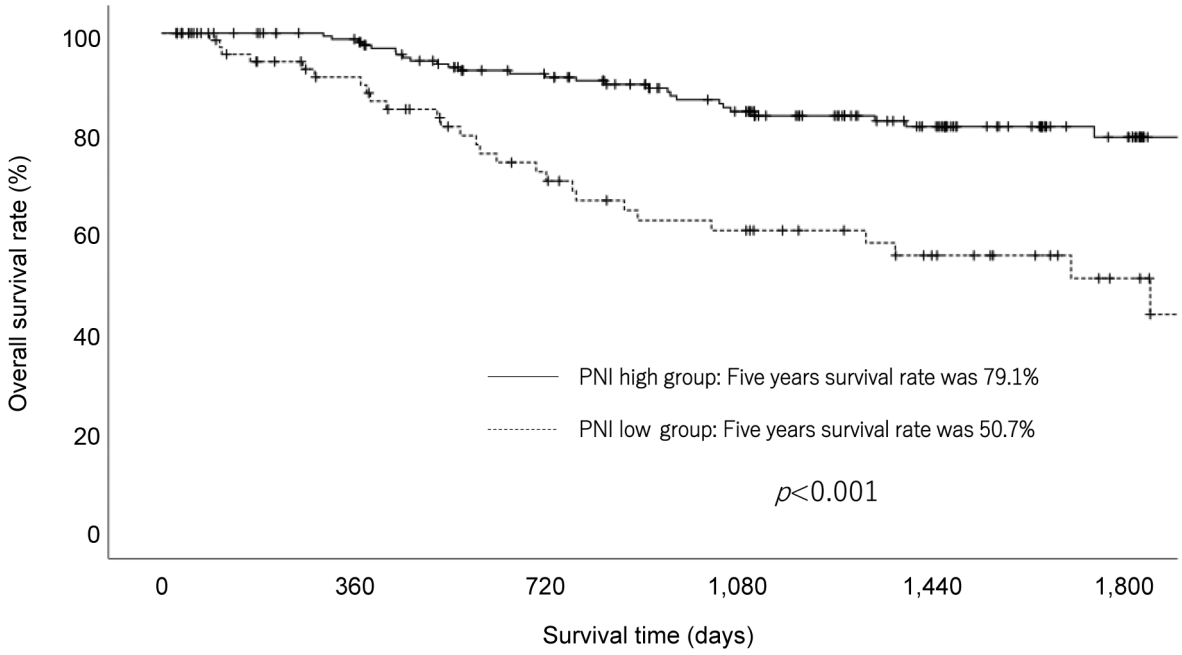

Figure 1. *The overall survival in the prognostic nutritional index (PNI) high group and the PNI low group.*

from 31 to 88 years old, 183 were males and 75 females. Total gastrectomy and distal, proximal, or partial gastrectomy were performed on 66, 180 and 11 patients, respectively. D1+ and D2 lymph node dissection was performed on 139 and 112 patients, respectively. The cutoff value for the PNI was set to 47 according to the OS rate and previous reports (Table I). All patients were classified into two groups, PNI low group [<47; n=75 (29.1%)] and PNI high group [≥47; n=183 (70.9%)]. The analysis of the patient background characteristics revealed statistically significant differences between the PNI low and PNI high groups regarding the following variables: median age (67 years *vs*. 72 years, p=0.001), preoperative hemoglobin (11.0 g/dl *vs*. 13.5 mg/dl, p=0.001), and preoperative C-reactive protein (0.14 mg/dl *vs*. 0.92 mg/dl, p<0.001).

Survival analysis. The 9 clinicopathologic factors based on patient, operation, and tumor findings were analyzed as shown in Table I. OS was compared between the groups using the log-rank test. There were significant differences in age (<75 *vs*. ≥75), site of tumor (upper, middle, lower third), UICC T status (T1 *vs*. T2 to T3), lymph node metastasis, lymphatic invasion, vascular invasion, postoperative surgical complication and the PNI (<47 *vs*. ≥47). The 3-year and 5-year OS rates were 85.0 and 79.1% in the PNI high group and 60.4% and 44.7% in the PNI-low group, respectively (both p<0.001). The OS curves are shown in Figure 1. Univariate analyses for overall survival revealed that the PNI, age, T status, lymph node metastasis, lymphatic invasion, vascular invasion, and postoperative surgical complication were significantly associated with OS. According to the multivariate analysis (Table II), the PNI was an independent predictor of OS [hazard ratio (HR)=3.452, 95% confidence interval (CI)=2.042-5.836, p=0.007]. Univariate analyses for RFS demonstrated that PNI also was a significant prognostic factor (Table III). The 5-year RFS rate was significantly higher in the PNI-high compared to the PNI-low group (79.1% *vs*. 50.7%, p<0.001) (Figure 2). The PNI was selected for the final multivariate analysis model [HR=1.962, 95% CI=1.185-3.249, p=0.009] (Table III). Between PNI high and low groups, a comparison of patterns of recurrence showed a significant difference in peritoneal recurrence (7.7% *vs*. 20.0% p=0.004) (Table IV).

Perioperative clinical course. The total rates of postoperative surgical complications in the PNI high and low groups did not differ to a statistically significant extent (38.7% *vs*. 37.7%, p=0.889). Similarly, no difference was observed regarding anastomosis leakage (12.0% *vs*. 7.1%, p=0.223), pneumonia (4.0% *vs*. 6.6%, p=0.564), and abdominal abscess (2.7% *vs*. 3.3%, p=1.00) between two groups. The proportion of Stage II and III cases was significantly lower in the high PNI group, compared to that in the low PNI group [58/183 (32%) *vs*. 49/75 (65%), p<0.001]. Among stage II and III cases, the introduction rate of postoperative adjuvant chemotherapy rate was higher in the PNI high group, compared to the PNI low group (77% *vs*. 47%, p=0.0395).

Table II. *Uni- and multi-variate Cox proportional hazards analysis of clinicopathological factors for overall survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (years)				0.002			
<75	179	1.000					
≥75	79	2.288	1.351-3.875				
Sex				0.467			
Male	183	1.000					
Female	75	1.252	0.683-2.293				
T status				<0.001			0.005
T1	138	1.000			1.000		
T2 or T3	120	8.932	4.043-19.730		3.566	1.461-8.702	
Lymph node metastasis				<0.001			<0.001
Negative	168	1.000			1.000		
Positive	90	6.583	3.588-12.079		3.149	1.614-6.141	
Prognostic Nutritional Index				<0.001			0.007
>47	183	1.000			1.000		
<47	75	3.452	2.042-5.836		2.100	1.225-3.601	
Lymphatic invasion				<0.001			
Negative	149	1.000					
Positive	109	4.790	2.610-8.792				
Vascular invasion				<0.001			
Negative	154	1.000					
Positive	104	4.915	2.681-9.010				
Histological type				0.140			
Intestinal	137	1.000					
Diffuse	121	1.489	0.877-2.529				
Postoperative complications				0.003			0.068
No	160	1.000			1.000		
Yes	98	2.273	1.334-3.873		1.649	0.963-2.821	

Discussion

The aim of the present study was to examine the usefulness of PNI as a predictor of prognosis in postoperative gastric cancer patients. The major finding was that PNI was an independent predictive factor of OS in postoperative gastric cancer patients, suggesting that PNI should be included in the routine assessment of gastric cancer patients.

In the present study, PNI was an effective prognostic factor for patients with gastric cancer undergoing gastrectomy. Similar results were observed in the previous studies. Jiang *et al*. evaluated the clinical impacts of PNI in gastric cancer patients undergoing total gastrectomy. They used a cutoff value of 46 to divide patients into PNI-low and high group and demonstrated that the 5-year OS rate of the PNI-low group was significantly lower than that of the PNI-high group (6). Nozoe *et al*. investigated the prognostic value of PNI in patients with gastric cancer who had been treated by resection and lymph node dissection. In their report, the mean PNI value (49.7) of the study population was set as the cutoff to divide patients into high and low groups. They demonstrated that the 5-year OS rates in PNI-low group were significantly lower than those in PNI high group (67.7% *vs*. 86.5%) (8). In all these studies, the 5-year survival rates varied; however, they were significantly lower in the PNI-low group than in the PNI-high group.

There are several reasons that could explain the correlation between PNI and prognosis found in this study. First, PNI status may have affected the rate of induction of postoperative adjuvant therapy. In our study, the proportion of patients requiring postoperative chemotherapy who actually received it was significantly lower in PNI-low. It is possible that patients with low PNI had a lower rate of induction of postoperative therapy and did not benefit from postoperative therapy. In fact, the rate of peritoneal recurrence was higher in patients with low PNI. Previous studies have shown that adjuvant S-1 therapy reduces peritoneal recurrence, and a low PNI may prevent the induction of S-1, resulting in peritoneal recurrence and a poor prognosis (12, 13). Further investigation is needed to determine what causes may influence the initiation of adjuvant therapy. The second reason is that differences in perioperative complication rates between high and low PNI groups may have influenced prognosis. Previous studies

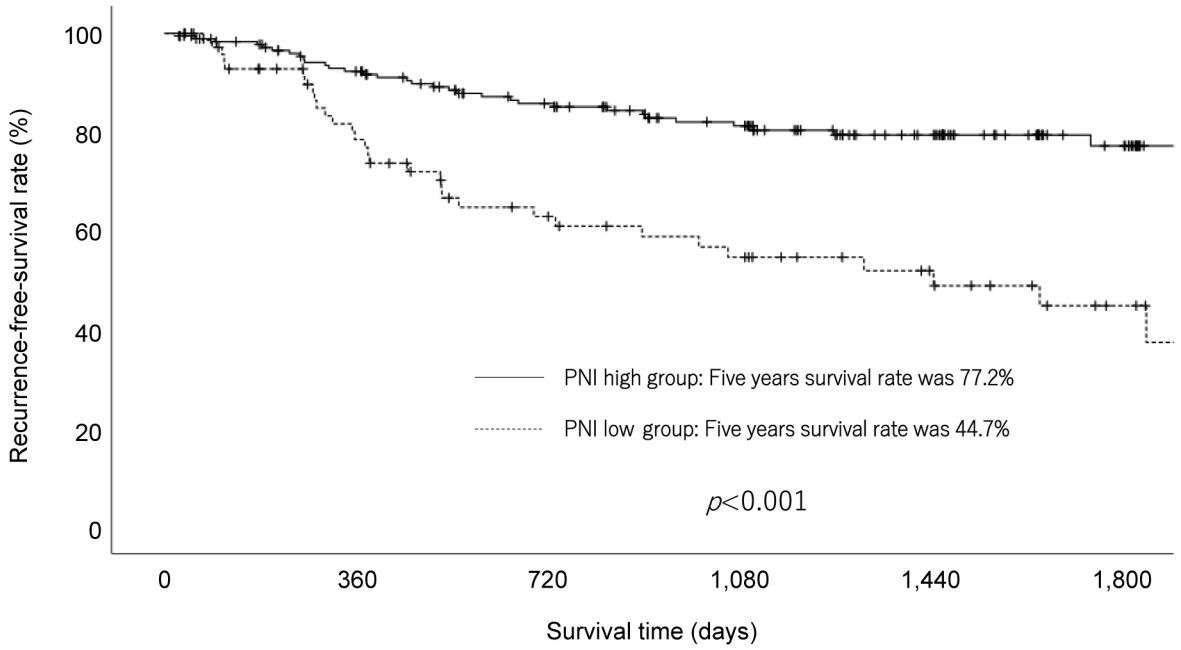

Figure 2. *The recurrence-free survival in the prognostic nutritional index (PNI) high group and the PNI low group.*

Table III. *Uni- and multi- variate Cox proportional hazards analysis of clinicopathological factors for recurrence-free survival.*

Factors	No	Univariate analysis			Multivariate analysis		
		HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (years)				0.008			
<75	179	1.000					
≥75	79	1.941	1.186-3.175				
Sex				0.301			
Male	183	1.000					
Female	75	1.347	0.766-2.370				
T status				<0.001			0.008
T1	138	1.000			1.000		
T2 or T3	120	7.642	3.892-15.005		2.847	1.322-6.131	
Lymph node metastasis				<0.001			<0.001
Negative	168	1.000			1.000		
Positive	90	7.642	4.333-13.476		4.029	2.145-7.568	
Prognostic Nutritional Index				<0.001			0.009
>47	183	1.000			1.000		
≥47	75	3.284	2.016-5.348		1.962	1.185-3.249	
Lymphatic invasion				<0.001			
Negative	149	1.000					
Positive	109	4.285	2.483-7.392				
Vascular invasion				<0.001			
Negative	154	1.000					
Positive	104	5.112	2.935-8.903				
Histological type				0.368			
Intestinal	137	1.000					
Diffuse	121	1.251	0.768-2.038				
Postoperative complications				0.001			0.043
No	160	1.000			1.000		
Yes	98	2.234	1.367-3.650		1.669	1.017-2.738	

Table IV. *Patterns of recurrence according to prognostic nutritional index.*

	Prognostic nutritional index				*p*-Value
	≥47 (n=183)		<47 (n=75)		
	Number	%	Number	%	
Peritoneal recurrence	14		15		0.004
Hematological recurrence	16		11		0.158
Lymph node recurrence	10		4		0.966
Local recurrence	5		6		0.057

demonstrated the clinical relation between PNI and postoperative complications (14, 15). So far, the patients with postoperative complications have had significantly poor prognosis. For example, Hirahara *et al*. evaluated the PNI status and postoperative complications after laparoscopic gastrectomy cancer patients. They found that PNI low patients had more postoperative complications and poor survival. Therefore, PNI status is associated with the occurrence of postoperative complications and, consequently, with poor prognosis.

The optimal cutoff value of the PNI to predict the long-term outcomes remains unclear. Nozoe *et al*. have demonstrated that the PNI provides useful information regarding the clinical outcomes of patients with gastric carcinoma. They used the mean PNI value (49.7) among the study patients as a threshold to divide PNI low and high groups and showed that the 5-year survival rate was significantly lower in patients with low PNI than in patients with high PNI (67.7% *vs*. 86.5%, $p<0.001$) (8). Migita *et al*. have set the cutoff value at 48, with a sensitivity and specificity for predicting the 5-year OS were 82.3% and 57.9%, respectively. They showed the 5-year OS rate was 85.7 % in the PNI-high group and 54.5% in the PNI-low group ($p<0.001$) (7). Nan Jiang *et al*. performed a ROC curve analysis and found PNI 46 as the optimal cutoff value. When the PNI was 46, the Youden index was maximal. They demonstrated that the 5-year OS rate was 54.1% in the PNI-high group and 21.1% in the PNI-low group ($p<0.001$) (6). Each report used similar cutoffs and the results were comparable. In the present study, the cutoff was set at 47 based on previous literature, and similar findings were obtained.

This study had several limitations. First, it was the retrospective study. A randomized, prospective cohort, multicenter study is needed to generalize the results and clarify the underlying mechanisms. Second, the study was limited to Asian patients, most of which were Japanese. It is not clear whether the results of this study will be applicable to a multiracial population. Third, the number of patients was small. Therefore, several possible factors such as postoperative therapy and peritoneal metastases could not be included in the multivariate analysis. Finally, the optimal cutoff value for true PNI remains unclear. In this study, we defined a PNI of less than 47 as clinically significant nutritional immune status.

Conclusion

PNI was an independent prognostic factor for overall and recurrence-free survival in postoperative patients with gastric cancer. Its implementation in clinical practice to identify patients at higher risk for poor outcomes may contribute to improved survival of postoperative gastric cancer patients.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

TI, TA made substantial contributions to the concept and design. TI, TA, made substantial contributions to the acquisition of data and the analysis and interpretation of the data. TI, TA, MJ, KK, MF, HK, SS, HT, AT, HC, KH, MN, IH, YM, KS, TO, AS, NY and YR were involved in drafting the article or revising it critically for important intellectual content. TI, TA, HC, KS, TO, AS, NY and YR give their final approval of the version to be published.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68(6)*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

3 Hashimoto I, Kano K, Onuma S, Suematsu H, Nagasawa S, Kanematsu K, Furusawa K, Hamaguchi T, Watanabe M, Hayashi

K, Furuta M, Inokuchi Y, Machida N, Aoyama T, Yamada T, Rino Y, Ogata T and Oshima T: Clinical significance of neutrophil-to-lymphocyte ratio/serum albumin ratio in patients with metastatic gastric or gastroesophageal junction cancer administered trifluridine/tipiracil. Anticancer Res *43(4)*: 1689-1697, 2023. PMID: 36974783. DOI: 10.21873/anticanres.16321

4 Aoyama T, Kazama K, Maezawa Y and Hara K: Usefulness of nutrition and inflammation assessment tools in esophageal cancer treatment. In Vivo *37(1)*: 22-35, 2023. PMID: 36593006. DOI: 10.21873/invivo.13051

5 Aoyama T, Hara K, Kazama K and Maezawa Y: Clinical impact of nutrition and inflammation assessment tools in gastric cancer treatment. Anticancer Res *42(11)*: 5167-5180, 2022. PMID: 36288879. DOI: 10.21873/anticanres.16023

6 Jiang N, Deng JY, Ding XW, Ke B, Liu N, Zhang RP and Liang H: Prognostic nutritional index predicts postoperative complications and long-term outcomes of gastric cancer. World J Gastroenterol *20(30)*: 10537-10544, 2014. PMID: 25132773. DOI: 10.3748/wjg.v20.i30.10537

7 Migita K, Takayama T, Saeki K, Matsumoto S, Wakatsuki K, Enomoto K, Tanaka T, Ito M, Kurumatani N and Nakajima Y: The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. Ann Surg Oncol *20(8)*: 2647-2654, 2013. PMID: 23463091. DOI: 10.1245/s10434-013-2926-5

8 Nozoe T, Ninomiya M, Maeda T, Matsukuma A, Nakashima H and Ezaki T: Prognostic nutritional index: a tool to predict the biological aggressiveness of gastric carcinoma. Surg Today *40(5)*: 440-443, 2010. PMID: 20425547. DOI: 10.1007/s00595-009-4065-y

9 Onodera T, Goseki N and Kosaki G: [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi *85(9)*: 1001-1005, 1984. PMID: 6438478.

10 Sun K, Chen S, Xu J, Li G and He Y: The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol *140(9)*: 1537-1549, 2014. PMID: 24878931. DOI: 10.1007/s00432-014-1714-3

11 Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer *14(2)*: 101-112, 2011. PMID: 21573743. DOI: 10.1007/s10120-011-0041-5

12 Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T and Ohashi Y: Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol *29(33)*: 4387-4393, 2011. PMID: 22010012. DOI: 10.1200/JCO.2011.36.5908

13 Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takiuchi H, Nasu J, Ohtsu A and Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group: Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol *10(11)*: 1063-1069, 2009. PMID: 19818685. DOI: 10.1016/S1470-2045(09)70259-1

14 Hirahara N, Tajima Y, Fujii Y, Kaji S, Kawabata Y, Hyakudomi R and Yamamoto T: High preoperative prognostic nutritional index is associated with less postoperative complication-related impairment of long-term survival after laparoscopic gastrectomy for gastric cancer. J Gastrointest Surg *24(12)*: 2852-2855, 2020. PMID: 32705617. DOI: 10.1007/s11605-020-04737-w

15 Mohri Y, Inoue Y, Tanaka K, Hiro J, Uchida K and Kusunoki M: Prognostic nutritional index predicts postoperative outcome in colorectal cancer. World J Surg *37(11)*: 2688-2692, 2013. PMID: 23884382. DOI: 10.1007/s00268-013-2156-9

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