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Case Report

The prognostic value of preoperative pre-albumin and PNI for overall survival in gastric cancer patients

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Abstract: Background: The presence of malnutrition and systematic inflammatory response can cause a shorter survival and higher possible complications in patients with malignancy. Routine peripheral blood tests and liver function tests reflecting immune and nutritional status, were reported to be the predictors of overall survival (OS) in some tumor patients. Aims: This retrospective study aimed to assess the prognostic value of preoperative pre-albumin, albumin, hemoglobin and prognostic nutritional index (PNI) for OS in gastric cancer (GC) patients. Methods: A total of 368 patients who were diagnosed with GC and underwent surgery between December 2010 and December 2012 were followed-up until October 2016. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values of pre-albumin, albumin and PNI. Then, a score system including pre-albumin and PNI was constructed. Kaplan-Meier curves and Cox regression analyses were used to calculate OS characteristics. Results: The cutoff values of pre-albumin, albumin and PNI were 192.5 mg/L, 42 g/L and 48.37, respectively by ROC curve analysis. The Kaplan-Meier survival curves revealed that GC patients with hemoglobin ≥ 120 g/L (P = 0.006), albumin ≥ 42 g/L (P = 0.034), pre-albumin ≥ 192.5 mg/L (P = 0.000), tumor size < 5 cm (P = 0.000), PNI ≥ 48.37 (P = 0.001) and well differentiation grade (P = 0.026) had longer OS. Additionally, pre-albumin, PNI and TNM stage were demonstrated to be independent risk factors for the overall survival, and the area under the ROC curve of the new score model was 0.637 (95% confidence interval: 0.581-0.694), showing a reliable ability to evaluate the prognostic value of GC patients. Conclusions: Preoperative pre-albumin and PNI were independent prognostic factors and the new score model in our study may serve as a reliable index to predict the prognosis of GC patients.

Keywords: Gastric cancer, pre-albumin, prognostic nutritional index, overall survival

Introduction

Gastric cancer is the fourth most prevalent malignant cancer worldwide [1], almost two thirds of the cases occur in developing countries [2]. The GC patients are commonly diagnosed at refractory advanced stage leading into poor prognosis [3]. Therefore, it is important to find appropriate prognostic factors which can help to improve diagnosis and therapy of GC patients.

Studies have shown that the presence of malnutrition and systematic inflammatory response can cause a shorter survival and higher possible complications in patients with malignancy [4, 5]. Peripheral blood tests and liver function tests were reported to be the predictors of OS in some tumors, such as colorectal cancer, breast cancer, hepatocellular carcinoma and gastric cancer [6-9]. Among them, serum albumin has a long half-life (nearly 20 days) and is associated with postoperative morbidity and the survival of patients [10-12]. While pre-albumin, which is synthesized in the liver has a shorter half-life (nearly 2 days), and is more sensitive during the perioperative period [13, 14]. According to the related research, pre-albumin is a remarkable prognostic factor for evaluating outcomes of colon [15], esophagus [16], ovarian [17] and lung cancers [18, 19], but few studies were republished to access the prediction of pre-albumin for survival outcome in GC patients.

The Prognostic Nutritional Index (PNI) is calculated by two indexes, lymphocytes and serum albumin, which can reflect nutrition and immune

function, therefore some researchers reported that PNI can predict long-term outcomes of GC patients.

In this study, we collected information regarding basic patient characteristics and preoperative laboratory tests, including pre-albumin and PNI, and explored their prognostic values of OS in GC patients.

Materials and methods

Ethics

This study was approved by the Ethics Committee of the *Affiliated Wuxi People's Hospital of Nanjing Medical University*. Written informed consent was obtained from each patient. The study complied was performed in accordance with the guidelines of Declaration of Helsink.

Patients

Clinico-pathological data of 368 patients, who were diagnosed with gastric cancer and underwent radical total or subtotal gastrectomy in the *Affiliated Wuxi People's Hospital of Nanjing Medical University* between December 2010 and December 2012, were analyzed retrospectively in this study. Information was collected regarding basic patient characteristics. The disease progression in the GC patients was classified using the guidelines outlined in the seventh edition of the American Joint Committee on cancer (AJCC) about tumor-node-metastasis (TNM) staging [21].

Inclusion and exclusion criteria

The eligibility criteria included: 1) all patients were diagnosed with gastric cancer by gastroscopy; 2) they had no heart disease or other important organ dysfunction; 3) the need of surgery was definite; 4) their peripheral blood tests were obtained within one week before surgery.

Exclusion criteria from the study included the following conditions: 1) the patient had previous malignant tumors or multiple primary cancers, 2) the patient had received radiotherapy or chemotherapy before the operation, 3) the patient had some disease which can affect the counting of peripheral blood cells, such as liver cirrhosis, infection and so on 4) the patient died within 30 days after surgery in the process of follow-up.

Definition of prognostic nutritional index and the new score model

The prognostic nutritional index (PNI) was calculated using the following formula: serum albumin (g/L) + 5× total lymphocyte count (×109/L) [22]. The cutoff values of PNI, prealbumin and albumin were determined by ROC curve for the prediction of survival outcomes based on the Youden index [maximum (sensitivity + specificity -1) [23].

The new score model (PNI-prealbumin) was calculated as follows: the patients with both an elevated PNI (≥ 48.37) and prealbumin (≥ 192.5) were assigned a score of 2; the patients with only one elevated value were assigned a score of 1; the patients with no elevated values were assigned a score of 0.

Follow-up and treatment

The study collected a total of 488 cases of gastric cancer patient with complete information. After surgery, they accepted 4-6 cycles of first-line adjuvant combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or a prodrug of 5-fluorouracil (capecitabine; CapeOX). Their follow-up dates were obtained through telephones and outpatient visit. Enrolled patients were prospectively followed-up until December 2017. Follow-up was performed in regular intervals (every 3 months for the first 2 years after operation, every 6 months in years 3-5, and every 12 months after 5 years). According to the inclusion and exclusion criteria, 368 patients were included in the final analysis of this study.

Statistical analysis

All statistical analyses were conducted using SPSS software (version 16.0). The associations between pre-albumin levels and clinico-pathological features were explored and assessed by the χ^2 tests or the Fisher exact test, as appropriate. For analysis of overall survival, Kaplan-Meier curves were constructed and statistical analysis was carried out using the log-rank test. Both univariate and multivariate survival analysis were performed using the Cox proportional hazard model. A comparison of the new score

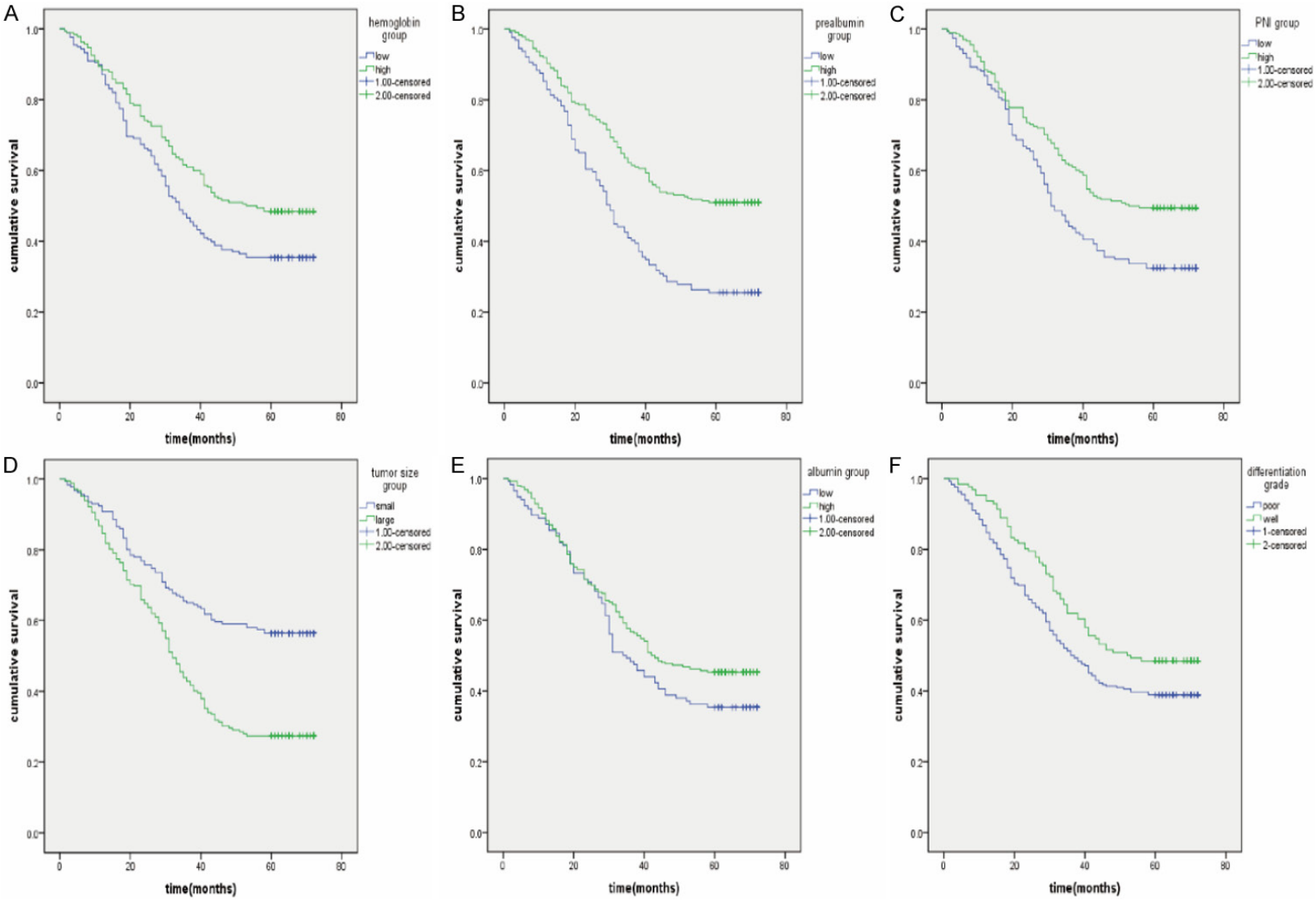

Figure 1. The Kaplan-Meier survival curves for patients in high hemoglobin and low hemoglobin, high pre-albumin and low pre-albumin, high PNI and low PNI, high PNI, large tumor size and small tumor size, high albumin and low albumin, well differentiation grade and poor differentiation grade. The *p* value of log rank test of (A-F) was 0.006, 0.034, 0.000, 0.000, 0.001 and 0.026, respectively.

model and other serum indexes was also performed according to the area under the ROC curve (AUC). For all tests, P < 0.05 was considered to be statistically significant.

Results

Patients' characteristics

Based on the cut-off values of PNI, pre-albumin and albumin, the patients were divided into low and high level groups for further analysis. Overall, 279 (75.8%) patients were males and 89 (24.2%) were females. The median age of patients was 64 years old (range, 28-83). The median follow-up months were 41 (range, 1.5-72).

Cutoff values of prognostic factors

Using the ROC curve, we determined that the recommended cutoff values of PNI, albumin and pre-albumin were 48.37 [sensitivity, 66.5; specificity, 51.7; area under the curve (AUC), 0.589; P = 0.004]; 42 g/L [sensitivity, 58.7; specificity, 46.9; area under the curve (AUC), 0.621; P = 0.037] and 192.5 mg/L [sensitivity, 78.7; specificity, 45.1; area under the curve (AUC), 0.611; P = 0.000], respectively (**Figure 2**).

Relationship of baseline pre-albumin levels and PNI with clinico-pathologic characteristics

The association was shown in **Table 1**. The serum pre-albumin was not significantly correlated with differentiation grade or tumor location; however, the association between pre-albumin and gender (P = 0.002), age (P = 0.006), hemoglobin (P < 0.001), albumin (P < 0.001), tumor size (P < 0.001), complications and TNM stage (P = 0.018) were significant. PNI was correlated with age (P < 0.001), hemoglobin (P < 0.001), albumin (P < 0.001), tumor location (P < 0.05) and complications (P < 0.05).

The Kaplan-Meier survival curves of patients

The Kaplan-Meier survival curves for patients in the high hemoglobin group and low hemoglobin group (A), high pre-albumin group and low pre-albumingroup (B), high PNI group and low PNI group (C), large tumor size group and small tumor size group (D), high albumin group and low albumin group (E) and well differentiation grade group and poor differentiation grade group (F) were shown as follows (**Figure 1**). The patients with hemoglobin ≥ 120 g/L (P = 0.006), albumin ≥ 42 g/L (P = 0.034), pre-albumin ≥ 192.5 mg/L (P = 0.000), tumor size < 5 cm (P = 0.000), PNI ≥ 48.37 (P = 0.001) and well differentiation grade (P = 0.026) had longer OS.

The risk factors for overall survival

As indicated by a univariate analysis, hemoglobin, albumin, pre-albumin, tumor size and PNI all significantly impacted the overall survival (**Table 2**). Multivariate survival analysis showed that the TNM stage, PNI and the pre-albumin levels were independent risk factors for the overall survival.

Predictive value of the new score model

To further evaluate the prognostic values of the prognostic scores, ROC analysis was performed (**Figure 3**). The PNI-prealbumin score had a higher AUC value (0.637; P = 0.000) than PNI (area under the curve (AUC), 0.586; P = 0.005), albumin (area under the curve (AUC), 0.544; P = 0.151) and pre-albumin (area under the curve (AUC), 0.619; P = 0.000).

Discussion

Preoperative nutritional status and systematic inflammatory response have significant impact on patients' quality of life and overall survival [24]. Recently, growing interest has focused on using albumin, pre-albumin and lymphocytes to assess nutritional status. This study showed that pre-albumin was an independent factor for predicting postoperative survival outcomes, therefore pre-albumin may have a more sensitive value for predicting OS than albumin. Moreover, from the relationship of baseline pre-albumin levels with clinico-pathologic characteristics, serum pre-albumin was significantly correlated with complications of patients after surgery, and some studies show that pre-albumin has a predictive value of mortality in patients undergoing radiotherapy for head and neck cancer or cardiac surgery, medical complications in severe anorexia nervosa [25-28]. Thus if we can provide potential nutrition support before surgery, the low preoperative pre-albumin level of patients may be improved, which could reduce postoperative complica-

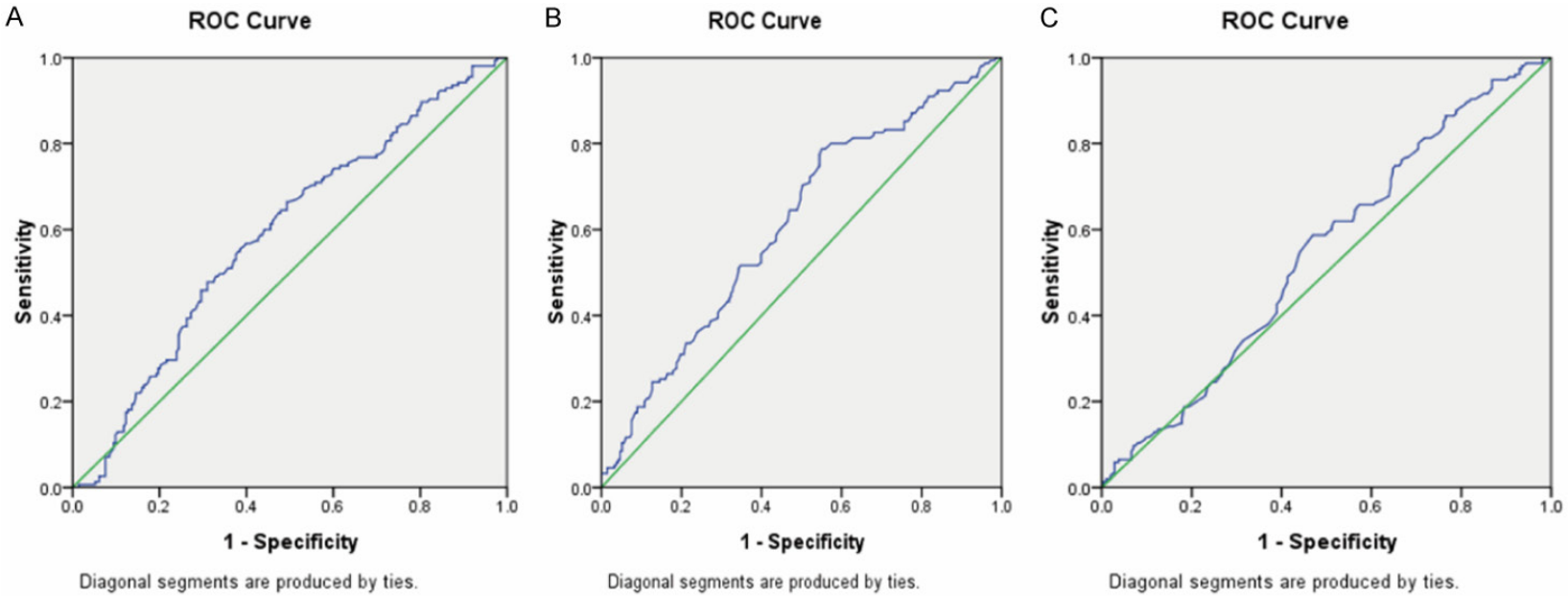

Figure 2. The ROC curve of PNI, albumin and pre-albumin.

Table 1. Relationship between the pre-albumin and PNI with clinicopathologic characteristics

Patient-related factors	pre-albumin (mg/L)		*P* value	PNI		*P* value
	< 192.5 (n = 129)	≥ 192.5 (n = 239)		< 48.37 (n = 160)	≥ 48.37 (n = 208)	
Gender			0.002*			0.396
Male	86	193		124	155	
Female	43	46		35	54	
Age (years)			0.006*			0.000*
< 60	32	91		36	87	
≥ 60	97	148		124	121	
Tumor sizes			0.000*			0.062
< 5 cm	49	137		72	114	
≥ 5 cm	80	102		88	94	
TNM stage			0.018*			0.773
I, II	42	106		63	85	
III	87	133		97	123	
Differentiation grade			0.199			0.476
Well	89	153		102	140	
Poor	40	86		58	68	
Albumin (g/L)			0.000*			0.000*
< 42	64	52		141	35	
≥ 42	65	187		19	173	
Hemoglobin (g/L)			0.000*			0.000*
< 120	85	93		109	69	
≥ 120	44	146		51	139	
Tumor location			0.068			0.013*
U	73	164		94	143	
M	23	29		28	24	
L	33	46		38	41	
Complications after surgery			0.000*			0.035*
No	108	231		142	197	
Yes	21	8		18	11	

*considered to be statistically significant.

Table 2. Univariate and Multivariate analyses of factors for prediction of overall survival

	Univariate analysis		Multivariate analysis	
	P value	χ^2 value	*HR value (95% CI)*	*P* value
Gender (male/female)	0.498			
Age (< 60 years/≥ 60 years)	0.348			
Tumor size (< 5 cm/≥ 5 cm)	0.000*	3.110	1.318 (0.970, 1.792)	0.078
TNM stage (I, II/III)	0.000*	32.936	2.792 (1.966, 3.964)	0.000*
Differentiation grade (well/poor)	0.026*	2.784	0.778 (0.579, 1.045)	0.095
Albumin (< 42 g/L/≥ 42 g/L)	0.034*	0.797	1.185 (0.816, 1.722)	0.372
Pre-albumin (< 192.5 mg/L/≥ 192.5 mg/L)	0.000*	7.439	0.664 (0.495, 0.891)	0.006*
Hemoglobin (< 120 g/L/≥ 120 g/L)	0.006*	0.013	1.017 (0.754, 1.373)	0.910
PNI (< 48.37/≥ 48.37)	0.001*	5.776	0.621 (0.422, 0.916)	0.016*

*considered to be statistically significant.

tions and mortality. In this study, we also know that serum pre-albumin was significantly correlated with tumor size ($P < 0.001$) and TNM stage ($P < 0.05$). So the prealbumin may have a

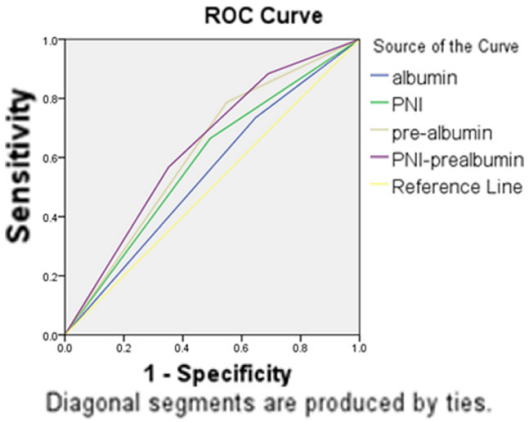

Figure 3. The ROC curve of four indexes for predicting overall survival in 368 patients with gastric cancer after resection. PNI-pre-albumin (the new score model: the combination of PNI and pre-albumin); PNI (prognostic nutritional index). The ROC curve of PNI-prealbumin: sensitivity, 88.4; specificity, 31.0; PPV, 0.385; NPV, 0.930. The ROC curve of PNI: sensitivity, 66.5; specificity, 50.7; PPV, 0.534; NPV, 0.631. The ROC curve of Prealbumin: sensitivity, 78.7; specificity 45.1; PPV, 0.350; NPV, 0.893.

significant value to determine the progression of GC patients.

Another index for assessing nutritional status and systematic inflammatory response was PNI. This study suggested the patients with a high level of PNI had a longer OS, PNI was also an independent factor for predicting postoperative survival outcomes. Related studies have shown that low PNI was associated with the depth of tumor invasion and lymph node metastasis [29], so PNI should be included in the routine assessment of gastric cancer patients. Preoperative immunonutrition significantly influences the postoperative complications and length of hospital stay [30, 31], we can adjust preoperative nutritional and immunological status to determine the optimal PNI index, which can improve the prognosis of the patients.

The Kaplan-Meier survival curves revealed that GC patients with hemoglobin < 120 g/L (P = 0.006), albumin < 42 g/L (P = 0.034), pre-albumin < 192.5 mg/L (P = 0.000), tumor size ≥ 5 cm (P = 0.000), PNI < 48.37 (P = 0.001) and poor differentiation grade (P = 0.026) had shorter OS, and we can make comprehensive assessments with these patients before surgery. For example, we can take radi or chemotherapy or provide potential nutrition support before surgery to improve the prognosis of these patients, and these patients also need more attention and care in follow up after surgery.

In this study, we construct a new score model to better evaluate the prognosis of GC patients. Multivariate survival analysis showed that the TNM stage, PNI and pre-albumin levels were independent risk factors for the over survival. Considering that the pTNM stage can only be evaluated in specimens after surgery, so the TNM stage was excluded from this score model. The PNI-prealbumin score had a higher AUC value (0.637; P = 0.000) than PNI, albumin and pre-albumin, showing a reliable discrimination ability to act as a prognostic index of GC patients. This index is also simple and inexpensive to get before surgery, so it may benefit a lot to our patients.

There are some potential limitations of this study. First, there are other potential confounding factors including specific tumor markers and inflammatory markers that are not included in this study, and there might be other reasonable cut-off levels for each ratio.

In conclusion, we found that the patients with hemoglobin ≥ 120 g/L, albumin ≥ 42 g/L, pre-albumin ≥ 192.5 mg/L , tumor size < 5 cm, PNI ≥ 48.37 and well differentiation grade (P = 0.026) had longer OS. Moreover, our study further demonstrated that preoperative pre-albumin and PNI were independent prognostic factors and the new score model may serve as a reliable index to evaluate the prognosis of gastric cancer patients.

Disclosure of conflict of interest

None.

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