Original Article

Nutritional statuses before and after chemotherapy predict the prognosis of Chinese patients after gastrectomy for gastric cancer

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Background and Objectives: Nutritional parameters may predict the prognosis of patients with gastric cancer. This study investigated whether changes in nutritional parameters before and after chemotherapy were associated with survival among patients who underwent gastrectomy for gastric cancer. **Methods and Study Design:** We retrospectively reviewed data from 77 Chinese patients who had undergone gastrectomy for stage III gastric cancer at a single center. Laboratory data from before and after chemotherapy were collected regarding peripheral albumin, prealbumin, total protein, hemoglobin, and total cholesterol concentrations. The prognostic nutritional index (PNI) values were calculated and compared before and after chemotherapy. The relationships between survival and the pre-chemotherapy and post-chemotherapy nutritional statuses were evaluated. **Results:** Among the 77 patients, survival was associated with the staging, the pre-chemotherapy PNI values, and the post-chemotherapy body mass index (BMI) values. Significantly better overall survival was associated with a high pre-chemotherapy PNI value (hazard ratio [HR]: 0.485, 95% confidence interval (CI): 0.255–0.920) and a normal post-chemotherapy BMI value (HR: 0.475, 95% CI: 0.249–0.907). Even better survival was associated with the co-existence of a high pre-chemotherapy PNI value and a normal post-chemotherapy BMI value (vs. one or more abnormal parameter, HR: 0.337, 95% CI: 0.167–0.679). **Conclusions:** Chinese patients who underwent gastrectomy for gastric cancer had nutritional statuses that deteriorated after adjuvant chemotherapy. High pre-chemotherapy PNI values and normal post-chemotherapy BMI values were associated with better survival outcomes. Thus, low pre-chemotherapy PNI values and/or low post-chemotherapy BMI values may predict poor outcomes among these patients.

Key Words: nutritional status, gastric cancer, surgery, adjuvant chemotherapy, prognosis

INTRODUCTION

In 2015, gastric cancer was the second most common cancer and the third leading cause of cancer mortality in China.[1] Both insufficient perioperative nutritional support and side effects of adjuvant chemotherapy can lead to inadequate energy intake that causes weight loss and affects survival.[2,3] A low body mass index (BMI) is an independent risk factor for poor survival among gastric cancer patients,[4] although BMI does not reflect long-term living conditions and is a relatively poor indicator of postoperative nutritional status among patients with gastric cancer.[5,6] Recent studies have indicated that the prognostic nutritional index (PNI) is another independent prognostic factor for gastric cancer,[7] as high PNI values are associated with prolonged survival and low PNI values are associated with shorter survival.[8] However, few reports have considered both postoperative PNI and BMI as prognostic factors for gastric cancer. Therefore, we retrospective evaluated 77 Chinese patients who underwent gastrectomy for stage III gastric cancer and explored whether changes in PNI and BMI before and after chemotherapy were associated with survival outcomes.

METHODS

Patients

All selected patients received information regarding the study and consented to the use of their data. The pathological and clinical records were complete for all patients. Patients were excluded if they had received preoperative chemotherapy or radiotherapy or been diagnosed with multiple primary tumors. The patients' records were reviewed and telephone follow-ups were performed until the end of December 2017, and no patients were lost to

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follow-up. The observation period started at the beginning of the patient's first postoperative chemotherapy cycle, and the patient was then followed until the first instance of death or the last follow-up (maximum follow-up: 64 months).

The 77 patients had undergone surgery for gastric cancer and completed courses of adjuvant chemotherapy at the Affiliated Hospital of Jiangnan University, Jiangsu Province, between July 2015 and December 2017. The surgical treatments involved partial gastrectomy (15 patients) or total gastrectomy (62 patients). All patients had histologically diagnosed gastric adenocarcinoma with local lymph node metastasis, which was classified as pathological stage III disease.

Testing

Data were collected from before the first chemotherapy cycle and after the last chemotherapy cycle regarding anthropomorphic characteristics, complete blood count, and a basic metabolic profile. The PNI was calculated as serum albumin concentration (g/L) + 5 × peripheral lymphocyte count ($\times 10^9$/L). Cell counts were performed using a fully automated blood cell counter (Beckman Coulter), and metabolic parameters were evaluated using a fully automated biochemistry analyzer (Roche Diagnostics). The diluent for the blood cell count assay was purchased from Nanjing Weidi Chemical Company. Cholesterol and albumin concentrations were measured using a Cobas 8000 modular analyzer and related reagents (Roche Diagnostics). Prealbumin was evaluated using turbidimetric inhibition immunoassay kits produced by Shenzhen Mindray Bio-Medical Electronics Company.

Statistical analysis

All experiments were performed at least three times and the mean value was used. Statistical analyses were performed using SPSS software (version 23.0, IBM Corp., Armonk, NY), and the chi-squared test was used to compare categorical variables. Differences in survival outcomes were evaluated using the Kaplan-Meier method and log-rank test. Multivariable analysis by Cox proportional-hazard model was used to determine the independence of the prognostic factors. Differences were considered statistically significant at p-values of <0.05.

RESULTS

Clinical characteristics

The patients included 59 men and 18 women with a mean age of 62.58±8.97 years. The average number of chemotherapy cycles was 6.77±4.14, and all patients completed >2 chemotherapy cycles. Comparisons of the patients' characteristics and test results revealed significant differences in the proportions of normal and abnormal red blood cell counts and blood urea nitrogen concentrations (Table 1).

Determining a cut-of value for the PNI

There are no clear data regarding the optimal PNI cut-off value for prognostication, although a value of 49 (postoperative) was reported by Murakami Y et al.[9] and a value of 46.7 was reported by Lee et al.[10] We created a receiver operating characteristic curve and identified the optimal cut-off value as 42.3 for our patients, which provided an area under the curve of 0.560 (p=0.013), 87% sensitivity, and 66% specificity. Thus, the patients were grouped according whether they had high PNI values (≥42.3) or low PNI values (<42.3) (Figure 1).

Nutritional parameters and survival

The patients' nutritional parameters were also used to create high and low groups at the time points before and after chemotherapy. Significant differences were observed in terms of the pre-chemotherapy PNI values and the post-chemotherapy BMI values (Tables 2). No other significant differences were observed (Supplementary tables 1-3).

The shortest follow-up time was 30 months and the longest follow-up time was 64 months. The group with high pre-chemotherapy PNI values had significantly better overall survival than the group with low pre-chemotherapy PNI values (hazard ratio [HR]: 0.485, 95% CI: 0.255–0.920; p=0.027) (Figure 2A). The group with normal post-chemotherapy BMI values also had significantly better overall survival (HR: 0.475, 95% CI: 0.249–0.907; p=0.019) (Figure 2B). Moreover, even better overall survival was associated with the co-existence of a high pre-chemotherapy PNI value and a normal post-chemotherapy BMI value (HR: 0.337, 95% CI: 0.167–0.679; p=0.002) (Figure 2C).

Table 1. Clinicopathological features of seventy-seven patients with gastric cancer

Basic feature	Normal cases before chemotherapy (%)	Abnormal cases before chemotherapy (%)	Normal cases after chemotherapy (%)	Abnormal cases after chemotherapy (%)	χ^2	p-value
RBC ($\times 10^{12}$/L)	24 (31.2)	53 (68.8)	10 (13.0)	67 (87.0)	7.398	0.007**
Hemoglobin (mol/L)	29 (37.7)	48 (62.3)	22 (28.6)	55 (71.4)	1.437	0.231
Lymphocyte ($\times 10^9$/L)	73 (94.8)	4 (5.2)	67 (87.0)	10 (13.0)	2.829	0.093
Prealbumin (mg/L)	46 (59.7)	31 (40.3)	41 (53.2)	36 (46.8)	0.660	0.416
Transferrin (g/L)	54 (70.1)	23 (29.9)	56 (72.7)	21 (27.3)	0.127	0.721
Total protein (g/L)	40 (51.9)	37 (48.1)	38 (49.4)	39 (50.6)	0.104	0.747
Total cholesterol (mmol/L)	51 (66.2)	26 (33.8)	58 (75.3)	19 (24.7)	1.538	0.215
Albumin (g/L)	66 (85.7)	11 (14.3)	57 (74.0)	20 (26.0)	3.271	0.070
BUN (mmol/L)	74 (96.1)	3 (3.9)	63 (81.8)	14 (18.2)	8.001	0.005**
BMI (kg/m^2)	59 (76.6)	18 (23.4)	53 (68.8)	24 (31.2)	2.340	0.126

*p<0.05; **p <0.01; ***p<0.001.

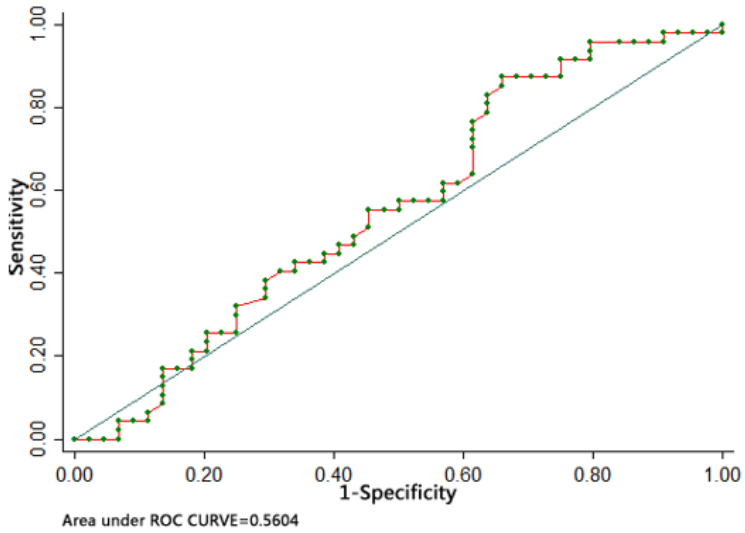

Figure 1. Determination of PNI cut-off value. PNI cut-off value. Note: sensitivity=0.87, 1-specificity=0.34, optimal cutoff value ≥42.3.

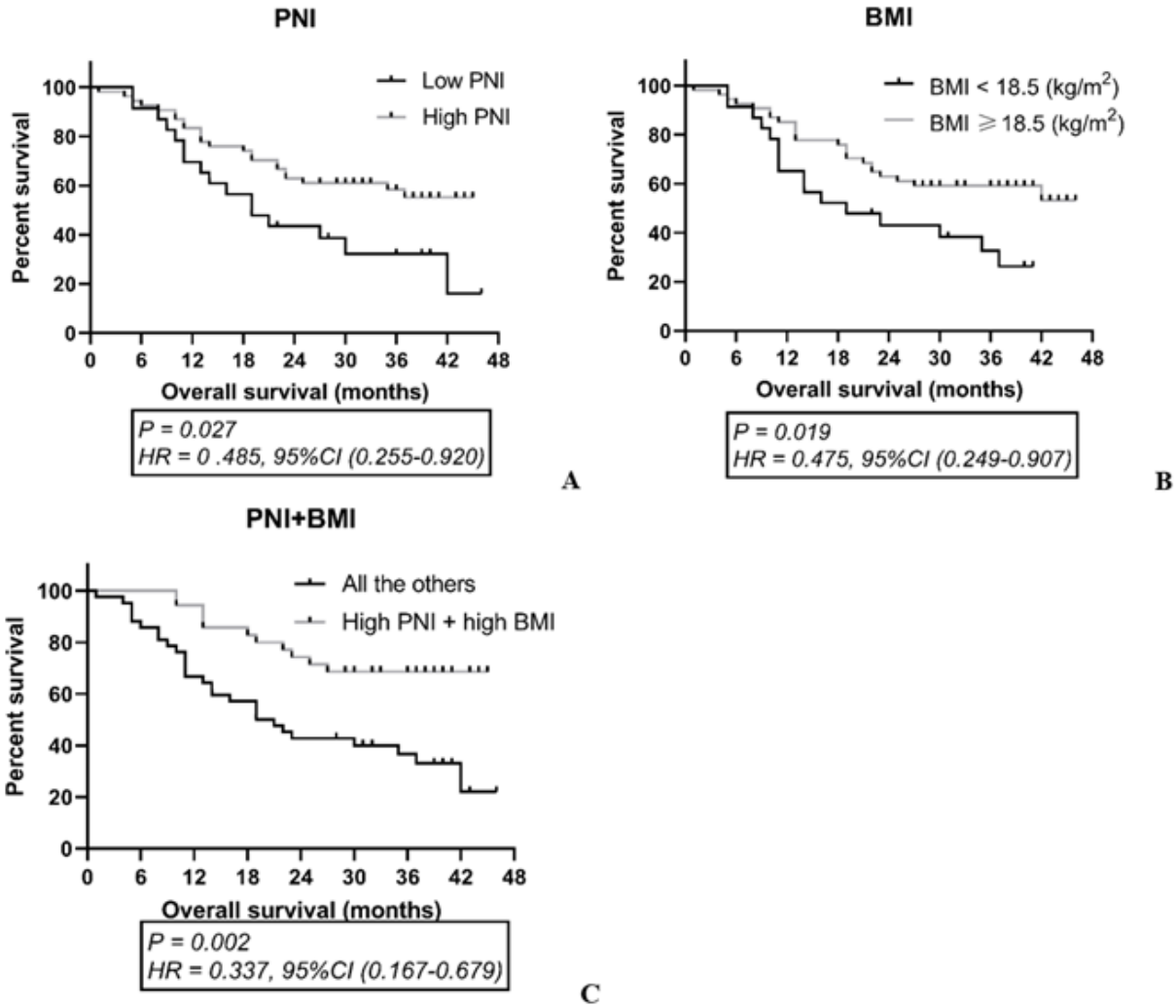

Figure 2. The relation between pre-chemotherapy PNI, post-chemotherapy BMI, and overall survival of postoperative gastric cancer patients. (A) Survival curves of gastric cancer patients grouped by PNI. (B) Survival curves of gastric cancer patients grouped by BMI. (C) Survival curves of gastric cancer patients grouped by PNI and BMI.

DISCUSSION

The present study revealed low post-chemotherapy BMI values in a high proportion of patients (31.2%), although this was lower than the malnutrition rate of 86.7% reported by Seo et al.[11] The incidence of post-chemotherapy malnutrition is relatively high among gastric cancer patients,[12] which is related to their increased pre-treatment metabolism and post-treatment reductions in energy intake that are related to dyspepsia, pain, nausea, and vomiting.[13] Moreover, cancer-associated malnutrition is

Table 2. The correlation between PNI, BMI, and survival rate of seventy-seven patients with gastric cancer of pre-chemotherapy/post-chemotherapy

Survival (months)	PNI ≥42.3 vs <42.3				BMI ≥18.5 (kg/m^2) vs <18.5 (kg/m^2)			
	Before the first chemotherapy		After the last chemotherapy		Before the first chemotherapy		After the last chemotherapy	
≥24	31	12	33	10	34	10	33	8
<24	31	3	21	13	25	8	20	16
χ^2	4.408		2.034		0.024		5.554	
p value	0.045*		0.211		1.000		0.026*	

*p<0.05; **p<0.01; ***p<0.001.

closely related to decreased food intake caused by the tumor itself, diminished anabolism induced by activated immune cells, proteolysis, lipolysis, and futile cycling.[14] Some researchers have suggested that 94.1% of malnutrition can be attributed to involuntary weight loss and low BMI.[15] The present study examined nutritional parameters before and after chemotherapy in this setting and revealed a significant change in BMI. Thus, patients who undergo adjuvant chemotherapy for gastric cancer may lose weight because of chemotherapy-induced malnutrition, which reflects their poor nutritional status. However, we did not observe any significant differences in other well-recognized nutritional parameters, such as albumin, prealbumin, total protein, or lymphocyte counts. This may be related to the small sample size, excessive weight loss during the perioperative period, and/or insufficient nutritional support during their chemotherapy, which might have manifested as persistent malnutrition.

Nutritional status is an independent prognostic factor during chemotherapy, and undernourishment is associated with disease deterioration and subsequently poor outcomes.[16] The present study revealed that postoperative BMI was significantly associated with survival, which agrees with the findings of Qin and Jiang, who reported that malnutrition decreases medication tolerance and efficacy, which affects patients' quality of life and survival.[17] The PNI has been used to predict the prognosis of gastric cancer patients, with high PNI values being associated with better outcomes.[18] Other reports have addressed the relationship between gastric cancer prognosis and the preoperative PNI value,[19] the preoperative/postoperative PNI values,[20] and the PNI, BMI, Glasgow coma scale and neutrophil/lymphocyte values.[21] Migita et al have also reported that a decreased post-chemotherapy PNI value was associated with poor outcomes.[22] Nevertheless, the PNI has some disadvantages, and more accurate prognostication can be achieved by combining it with other factors. We observed that the pre-chemotherapy PNI was closely associated with survival, although the pre-chemotherapy BMI and post-chemotherapy PNI values were not associated with survival, which may be related to the small sample size. Another possible explanation is that many patients developed hypoproteinemia during their chemotherapy or required albumin products during their hospitalization, which might not have been noted in their medical records, as albumin products could be self-administered. Furthermore, some patients may have experienced decreases in their BMI before chemotherapy, and postoperative nutritional support is easier to tolerate than nutritional support during chemotherapy. After gastrectomy, patients tend to become satiated quickly and may choose smaller but more frequent meals with enteral nutrition support. In contrast, their nutritional status during chemotherapy might be compromised because they experience nausea, vomiting, dry mouth,[23] and negative emotions.[24] Megestrol and metoclopramide are common clinical treatments to alleviate nausea and vomiting, and cyproheptadine can stimulate appetite and increase dietary intake, which may eventually lead to weight gain.[25]

Well-nourished patients have better tolerance of chemotherapy, while a poor nutritional status may lead to muscle loss and increased chemotherapy toxicity.[26] In addition, preoperative sarcopenia predicts unfavorable long-term outcomes.[27] Providing nutrition support during chemotherapy can help improve nutritional status and cellular immunity. Furthermore, well-nourished patients are more likely to ambulate after surgery, which may help reduce muscle loss. The present study used BMI to evaluate whether malnutrition was present (based on a low BMI), which was detected for 23.4% of patients before chemotherapy and 31.2% of patients after chemotherapy. The post-chemotherapy BMI values were associated with survival outcomes, which suggests that nutritional interventions are needed to improve the nutritional status of these patients and thereby enhance their tolerance of chemotherapy. Patients with normal BMI values may still have nutritional risk factors, which suggests that chemotherapy tolerance might be improved via education regarding nutrition, eating habits, and the importance of preventing weight loss. Thus, early-stage nutritional evaluation and support may play a critical role in the comprehensive treatment of gastric cancer during the perioperative period and adjuvant chemotherapy.

The present study failed to detect significant differences in various biochemical markers of nutrition, including total protein, albumin, prealbumin, hemoglobin, and total cholesterol concentrations. This may be related to the small sample size or the variable number of chemotherapy cycles. Undernutrition could also increase adverse reactions to chemotherapy and may cause negative emotions that might motivate patients to discontinue chemotherapy.

Chemotherapy has been shown to impact the homeostasis of the gut microbiota significantly.[28] On the other hand, the gut microbiota modulate the efficacy and toxicity of several chemotherapeutic drugs through mechanisms including metabolism, immunomodulation, translocation, enzymatic degradation, and reduced diversity and ecological variation.[29] Furthermore, the dysbiosis of the gut microbiota induced by chemotherapeutic drugs

may in turn aggravate the malnutrition in patients with a malignant tumor. For example, 5-fluorouracil (5-Fu) triggered the reduction of muscle function and the concurrent dysbiosis of the gut microbiota. The fecal microbiota transplantation experiment further showed that the gut microbiota played an important role in improving muscle metabolism in 5-Fu-induced malnutrition rats.[30] Thus, in the future, we will try to improve patients' nutritional status by improving their intestinal flora, in order to improve patients' quality of life and survival.

This experimental study provides preliminary data and a theoretical basis for the relationship between nutritional status and survival among patients undergoing adjuvant chemotherapy after surgery for gastric cancer. We hope that this data may help guide appropriate nutritional support that can improve patients' quality of life and survival.

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AUTHOR DISCLOSURES

No competing interests are reported.

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Supplementary table 1. The correlation between hemoglobin, lymphocyte, and survival rate of seventy-seven patients with gastric cancer of pre-chemotherapy/post-chemotherapy

Survival (months)	Hemoglobin ≥120 g/L vs <120 g/L (male) Hemoglobin ≥110 g/L vs <110g/L (female)				Lymphocyte ≥0.8 ×10^9/L vs <0.8 ×10^9/L			
	Before the first chemotherapy		After the last chemotherapy		Before the first chemotherapy		After the last chemotherapy	
≥24	14	30	10	23	39	4	36	7
<24	15	18	12	32	34	0	31	3
χ^2	1.494		0.085		1.715		0.391	
p value	0.244		0.803		0.190		0.498	

Supplementary table 2. The correlation between albumin, total protein, and survival rate of seventy-seven patients with gastric cancer of pre-chemotherapy/post-chemotherapy

Survival (months)	Albumin ≥35 g/L vs <35 g/L				Total protein ≥65 g/L vs <65 g/L			
	Before the first chemotherapy		After the last chemotherapy		Before the first chemotherapy		After the last chemotherapy	
≥24	35	8	31	12	19	24	24	19
<24	31	3	26	8	21	13	14	30
χ^2	1.483		0.629		2.350		1.628	
p value	0.329		0.428		0.169		0.253	

Supplementary table 3. The correlation between prealbumin, total cholesterol protein, and survival rate of seventy-seven patients with gastric cancer of pre-chemotherapy/post-chemotherapy

Survival (months)	Prealbumin ≥170mg/L vs <170mg/L				Total cholesterol ≥3.9mmol/L vs <3.9mmol/L			
	Before the first chemotherapy		After the last chemotherapy		Before the first chemotherapy		After the last chemotherapy	
≥24	14	29	19	25	31	13	34	10
<24	11	23	12	21	20	13	24	9
χ^2	0.000		0.364		0.818		0.210	
p value	1.000		0.641		0.466		0.790	