Original Article

Controlling Nutritional Status score predict the individualized survival of patients with gastric cancer

Xishan Zhu MD, PhD[1], Ye Zhao MD, PhD[2], Feiyan Ma MD, PhD[3], Shikai Wu MD, PhD[1]

[1]Oncology Department, Peking University, First Hospital, Beijing, China
[2]Pathology Department, Peking University, First Hospital, Beijing, China
[3]Radiotherapy Department, Chengde Medical College, Baoding No.1 Middle Hospital, Baoding, China

Background and Objectives: The present study aimed to determine the correlation between Controlling Nutritional Status (CONUT) score and prognosis in gastric cancer patients undergoing total gastrectomy. **Methods and Study Design:** The clinical data of 245 gastric cancer patients who underwent total gastrectomy in Peking University, First Hospital between January1st 2005 and December 30th 2015 were retrospectively collected. According to the CONUT level, they were divided into high CONUT (>3) group and low CONUT (≤3) group. The relationship between CONUT and the disease-free survival (DFS) and overall survival (OS) were analyzed by statistical analysis. **Results:** The results showed that the optimal cutoff value for CONUT to predict the 5-year survival was 3 and CONUT had a higher area under the ROC curve (AUC) for 5-year disease free survival (DFS) and overall survival (OS) prediction. Additionally, when age was considered as a stratified factor, univariate analyses demonstrated that high CONUT correlated with shorter DFS in non-elderly (<65) patients and shorter DFS and OS in elderly (≥65) patients. **Conclusions:** High CONUT was significantly correlated with older age, advanced TNM-stage, higher Ki-67 and pathological subtype. Patients with high pre-operative high CONUT levels should be given more observation and constant follow-up after surgery.

Key Words: Controlling Nutritional Status (CONUT), gastric cancer, disease-free survival (DFS), overall survival (OS), cancer prognosis

INTRODUCTION

Tumor microenvironment plays an important role in tumorigenesis. The relationship between the systemic inflammatory state represented by inflammatory factors and malignant tumors is the focus of attention in current research. Chronic inflammatory states can subtly promote the occurrence, migration, invasion and transfer of cancer cells.[1-4] More and more researches confirmed the important role of systemic inflammatory response and malnutrition in cancer progression and the mechanism involved has been fully recognized.[5-7]

Controlling Nutritional Status (CONUT) score is an automatic tool to assess nutritional status, taking into account laboratory information, including serum albumin, total cholesterol level, and total lymphocyte count.[8] The CONUT score has been used to objectively evaluate nutritional status in patients with inflammatory disease, chronic heart failure, and chronic liver disease.[9-12] Recently, the CONUT score was shown to be a predictive or prognostic marker in patients with malignancy, including colorectal, esophageal cancer, and hepatocellular carcinoma.[13-15]

Gastric cancer is associated with high morbidity and mortality rates worldwide. Identifying individuals at high risk is important for surveillance and prevention of gastric cancer. Gastric cancer is a group of heterogeneous tumors based on distinctive morphological and molecular genetic features which closely correlates with the nutritional con-

ditions, peripheral blood cells might reflect the inflammatory and immune response of patients to malignant tumors and are critical for determining the treatment response and clinical outcomes of patients.16

The present study aimed to evaluate the prognostic impact of CONUT in patients with gastric cancer after radical gastrectomy. These results may reveal the important role of nutrition-based factors in gastric cancer after radical gastrectomy and may also help to evaluate patient prognosis.

METHODS
Patients
A retrospective analysis was conducted of 245 gastric cancer patients underwent total gastrectomy with R0 resection in Peking University, First Hospital between January 1st 2005 and December 30th 2015. R0 resection is defined as complete resection with negative margin. The inclusion criteria were included: 1) gastric cancer confirmed by histology and pathology; 2) clinical stage con-

firmed according to the 8th edition; 3) ECOG (Eastern Cooperative Oncology Group) performance status score of 0–1; 4) proportion of body/mass ≥20.0 kg/m^2; 5) without history of other cancer; 6) no neo-adjuvant radiotherapy or chemotherapy; 7) available blood tests results collected before surgery. The exclusion criteria were included: 1) receiving any kinds of therapies before the operation; 2) pre-operative death; 3) loss of follow-up; 4) no pre-operative blood cell counts records; 5) concurrent infection; 6) autoimmune disease.

We collected the clinicopathological data and laboratory records from the patient's case history. The patients were followed up in Peking University, First Hospital and end points for the investigation were disease-free survival (DFS) and overall survival (OS). OS was defined as the length of time from randomization to death for any reasons after total gastrectomy. DFS was defined as the time between the beginning of randomization to the recurrence of the disease or death for any causes. The end point follow-up was placed on March 2020.

Patients gave their written informed consent. The study protocol was approved by the institutional committee on human research of the Institutional Review Board (IRB) of Peking University, First Hospital.

Controlling Nutritional Status (CONUT) score
Pre-operative blood samples were obtained within 2 weeks before surgery. The preoperative CONUT score was calculated using albumin level, total lymphocyte count, and total cholesterol level in each patient. (1) A lbumin concentrations ≥3.5, 3.0-3.49, 2.5-2.99, and <2.5 g/dL were scored as 0, 2, 4, and 6 points, respectively. (2) Total lymphocyte counts ≥1,600, 1,200-1,599, 800-1,199, and <800/mm^3 were scored as 0, 1, 2, and 3 points, respectively. (3) Total cholesterol concentrations ≥180, 140-179, 100-139, and <100 mg/dL were scored as 0, 1, 2, and 3 points, respectively. The CONUT score was defined as the sum of (1), (2), and (3) (Table 1). In this study, patients were divided into 2 groups: low CONUT group (score <3) and high CONUT group (score ≥ 3).

Statistical analyses
Statistical analysis was performed using SPSS 20.0 software, chi-square test was used for comparison of probability calculation. The spearman test was used for correlation analysis. Survival rate was calculated by Kaplan-Meier survival curve, log-rank test was used for univariate analysis, and COX regression was used for multivariate analysis. $p<0.05$ meant the difference was statistically significant.

RESULTS
Correlations between the CONUT and clinical characteristics
The CONUT ranged from 1.47 to 6.58, with a median level of 3.68 and the optimal cut-off point of the CONUT was 3.15 in our research. So, the patients were divided into low CONUT (CONUT≤3 n=104, 42.4%) and high CONUT groups (CONUT>3, n=141, 57.6%). Correlations of clinical characteristics of the pre-operative CONUT are summarized in Table 2. Pre-operative CONUT level was associated with TNM stage ($p=0.011$), tumor differentiation ($p=0.027$), patients age ($p=0.037$) and pathological subtype ($p=0.033$).

Correlations of the CONUT score with survival
In the univariate analysis, high CONUT, patient age, Ki-67 status, T stage, N stage and pathological subtype were related with DFS and OS. In the multivariate analysis, high CONUT ($p=0.027$), patient age ($p=0.028$), Ki-67 status ($p=0.024$), N stage ($p=0.029$) and pathological subtype ($p=0.028$) were independent predictors of DFS, while high CONUT ($p=0.033$), patient age ($p=0.021$) and N stage ($p=0.031$) were correlated with OS (Tables 3 and 4).

Correlations of the CONUT score with gastric cancer pathological subtype
Since there are 3 pathological subtypes for gastric cancer, the prognostic value of CONUT was subsequently analyzed in these 3 subgroups. The results revealed obvious associations of high CONUT score and worse outcomes in the Signet ring carcinoma subgroup (Tables 5 and 6).

Relationships between CONUT and clinicopathological features in non-elderly patients
There was a significant correlation between CONUT and cancer differentiation ($p=0.032$), TNM stage ($p=0.017$) and T stage ($p=0.022$) in non-elderly patients (<65) (Table 6). Univariate analysis showed that high CONUT (HR 2.917; 95% CI 1.702-4.132; p=0.039) was important risk factors for poor prognosis; In multivariate analysis, high CONUT (HR 2.259; 95% CI 1.121-3.397; $p=0.043$) was independently related to poor survival time (Table 8). In a comparative study of CONUT value and survival analysis in non-elderly patients after total gastrectomy, high CONUT and short disease-free survival were statistically associated ($p=0.017$), but high CONUT and short overall survival time was not statistically correlated (Table 9).

Table 1. Assessment of undernutrition status by the CONUT score

Parameters	Range (Score)			
Serum albumin (g/dL)	≥3.5 (1)	3.0-3.49 (2)	2.5-2.9 (4)	<2.5 (6)
Serum total cholesterol (mg/dL)	≥180 (0)	140-180 (1)	100-139 (2)	<100 (3)
Lymphocyte count (/mm^3)	≥1600 (0)	1200-1599 (1)	800-1199 (2)	<800 (3)
CONUT score	0~1	2~4	5~8	9~12
Nutritional stratification	Normal	Mild	Moderate	Severe

Table 2. Relationship between CONUT and clinicopathological features in 245 gastric cancer patients after total gastrectomy

Characteristics	Total patients	CONUT >3 (n=141)	CONUT ≤3 (n=104)	p value
Age (Years)				0.037
<65	162	92	70	
≥65	83	49	34	
Gender				0.432
Male	179	97	82	
Female	66	44	22	
Ki-67 status				0.043
Negative	126	66	60	
Positive	119	75	44	
Differentiation				0.027
Well	24	8	16	
Moderate	137	79	58	
Poor	84	54	30	
pT stage				0.483
T1	52	32	20	
T2	57	36	21	
T3	64	34	30	
T4	72	41	31	
p N stage				0.036
N0	73	48	25	
N1	49	25	24	
N2	71	38	33	
N3	52	30	22	
TNM stage				0.011
I	33	22	11	
II	66	25	41	
III	92	61	31	
IV	54	33	21	
Ajuvant chemotherapy				0.923
Yes	108	49	59	
N0	137	92	45	
Laboratory findings				
TC (mmol/L, mean)	4.77	4.52	4.83	0.025
TG (mmol/L, mean)	1.27	1.07	1.32	0.031
HDL-C (mmol/L, mean)	1.23	1.11	1.27	0.018
LDL-C (mmol/L, mean)	2.97	2.84	3.02	0.429
Albumin (g/L)	36.4	34.1	27.3	<0.001
Lymphocyte count (10^9/L)	1.55	1.29	1.76	0.042
Pathological subtype				0.033
Adenocarcinoma	183	105	78	
Signet ring cell carcinoma	50	32	18	
Mucinous adenocarcinoma	12	4	8	

TC: total cholesterol; TG: Triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HC: hemoglobin concentration; CONUT: Controlling Nutritional Status score.

Table 3. Analyses regarding the prognostic factors for disease free survival

Variable	Univariate HR	95%CI	p value	Multivariate HR	95%CI	p value
CONUT (>3 vs ≤3)	3.223	1.002-5.444	0.019	3.116	1.235-4.997	0.027
Age (<65 vs ≥65)	1.376	1.218-1.534	0.019	1.423	1.034-1.812	0.028
Ki-67 status (<14% vs ≥14%)	1.665	1.226-2.104	0.013	1.762	1.234-2.290	0.024
pT stage	1.982	0.649-3.315	0.041	1.229	0.562-1.896	0.195
pN stage	1.794	0.364-3.224	0.044	1.783	1.337-2.229	0.029
Pathological subtype	2.917	1.421-4.413	0.032	2.611	1.3427-3.880	0.028

Relationships between CONUT and clinicopathological features in elderly patients

In elderly patients (≥65), there was a significant correlation between CONUT and cancer differentiation (p=0.032), TNM stage (p=0.023) and pathological subtype (p=0.028) (Table 7). Univariate analysis showed that high CONUT (HR 2.617; 95% CI 1.692-3.542; p=0.017) were important risk factors for poor prognosis; In multivariate analysis, high CONUT (HR 3.021 95% CI 1.644-4.398; p=0.024) were independently associated with poor survival time (Table 8). In a comparative study of CONUT value and survival analysis in elderly patients after

Table 4. Analyses regarding the prognostic factors for overall survival

Variable	Univariate			Multivariate		
	HR	95%CI	p value	HR	95%CI	p value
CONUT (>3 vs ≤3)	2.761	1.121-4.401	0.026	2.031	1.117-2.945	0.033
Age (<65 vs ≥65)	1.872	1.109-2.635	0.042	1.33	1.101-1.559	0.021
Ki-67 status (<14% vs ≥14%)	1.023	1.004-1.042	0.046	0.862	0.367-1.357	0.261
pT stage	1.304	1.112-1.496	0.035	1.761	0.963-2.559	0.437
pN stage	1.822	1.207-2.557	0.029	1.296	1.103-1.489	0.031
Pathological subtype	1.126	1.002-1.25	0.038	1.611	0.367-2.855	0.302

Table 5. Analyses results of CONUT for the prediction of disease free survival and overall survival in different breast cancer subtypes

	DFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Adenocarcinoma	1.452 (0.672-2.232)	0.223			1.408 (0.873-1.943)	0.439		
CONUT <3								
CONUT ≥3								
Signet ring carcinoma	1.631 (1.141-2.121)	0.021	1.462 (1.208-1.716)	0.027	2.012 (1.562-2.462)	0.012	1.782 (0.457-3.107)	0.009
CONUT <3								
CONUT ≥3								
Mucinous adenocarcinoma	2.231 (0.981-3.481)	0.562			1.762	0.381		
CONUT <3								
CONUT ≥3								

total gastrectomy, there were statistical correlation between high CONUT and short disease-free survival time (p=0.028) and short overall survival time as well (p=0.042) (Table 9).

Statistical analysis of CONUT on survival parameters
We then analyzed the pre-operative CONUT values of 245 patients and divided them into CONUT >3 and CONUT ≤3 groups. As shown in Figures 1, in non-elderly patients (<65), high CONUT is an independent prognostic factor for a short DFS; in elderly patients (≥65), high CONUT is an independent prognostic factor for a short DFS and OS (Figure 2).

DISCUSSION
The prognosis of gastric cancer is related to the pathological stage, location, tissue type, biological behavior and treatment. Surgery is the main treatment for this malignant tumor, but even after radical resection, a considerable number of patients will relapse. The prognosis of gastric cancer varies greatly, therefore, finding reliable prognostic factors to stratify patients more accurately is the most important method to improve the clinical prognosis.[17-20] The CONUT score is an efficient tool for early detection and continuous control of under-nutrition in hospitalized patients, allowing nutritional status to be monitored in all inpatients.[21] This score is derived from 3 parameters; namely, serum concentrations of albumin (an indicator of protein reserve), total cholesterol (a caloric depletion parameter), and total lymphocyte count (an indicator of loss of immune defenses caused by malnutrition).[22] Thus, the combination of these three parameters could integrate the accuracy of each parameter to assess

for the general condition. Among the three components of CONUT, serum albumin concentration is the most important parameter, which is twice the weight of the other two. It is a reliable indicator not only for nutritional score but also for systemic inflammation. Our study demonstrated that low serum albumin was associated with poor survival, what is more, low peripheral lymphocyte count was an indicator for the inadequate host immune response and was correlated with undesirable prognosis in gastric cancer after total gastrectomy.

Although the original CONUT score article described four categories, the cut-off values of the CONUT score used in the literature differs between and different cancers.[23,24] The cut-off value of pre-operative CONUT was defined to be 3 after analysis and calculation in this study. Our results suggested that high CONUT score was associated with more advanced tumor characteristics, including advanced TNM stage, Ki-67 status, and pathological subtype. This study confirmed that there is a certain relationship between pre-operative CONUT and survival prognosis of gastric cancer after total gastrectomy. The inflammation and immune status of tumor patients is a dynamic process that always changing, so, a dynamic detection of CONUT may better reflect the balance between inflammation and anti-tumor immunity. The mechanism of CONUT in the poor prognosis of gastric cancer after total gastrectomy may related to the immunosuppression or excessive inflammation caused by the residual tumor, postoperative stress and complications.

In the past few decades, many clinicopathological biomarkers have been identified to efficiently predict recurrence and survival in gastric cancer through the continuous efforts of researchers.[25-27] However, expensive and

Table 6. Relationship between CONUT and clinicopathological features in 162 non-elderly (<65) gastric cancer patients after total gastrectomy

Characteristics	Total patients	CONUT		
		>3 (n=90)	≤3 (n=72)	p value
Gender				0.562
Male	108	49	59	
Female	54	41	13	
Vessel invasion				0.305
Negative	89	46	43	
Positive	73	44	29	
Differentiation				0.032
Well	11	3	8	
Moderate	87	47	40	
Poor	64	40	24	
pT stage				0.022
T1	34	20	14	
T2	28	13	15	
T3	39	20	19	
T4	61	37	24	
pN stage				0.328
N0	49	37	12	
N1	34	14	20	
N2	60	30	30	
N3	19	9	10	
TNM stage				0.017
I	28	20	8	
II	51	22	29	
III	63	42	21	
IV	20	6	14	
Ajuvant chemotherapy				0.652
Yes	65	27	38	
No	97	63	34	
Tumor location				0.731
Upper	46	25	21	
Middle	18	6	12	
Lower	92	55	37	
Whole	6	4	2	
Pathological type				0.062
Adenocarcinoma	121	67	54	
Signet ring cell carcinoma	32	21	11	
Mucinous adenocarcinoma	9	2	7	

technical limitations have prevented their clinical spread. Blood-based biomarkers are now recognized to be attractive practical tools due to the advantages of being easily accessible, routinely tested, relatively noninvasive and inexpensive.[28] We here in this study showed TNM stage, patients age, lymph node metastasis, tumor differentiation and a high CONUT were significant risk factors for a poor prognosis by univariate analyses and TNM stage, patients age and a high CONUT were found to be independently associated with poor survival in multivariate analysis. When we divide the patients into non-elderly and elderly groups, significant associations were found between the CONUT and factors such as lymphocyte invasion, cancer differentiation, TNM stage and tumor infiltration in non-elderly patients and the lower CONUT was correlated with shorter DFS in non-elderly patients; while in elderly patients, lymphocyte invasion, cancer differentiation and TNM stage were also statistically significant and the high CONUT was correlated with shorter DFS and OS.

Based on the above results, it is thought that the pre-operative CONUT score may be useful in the stratification of risk and tailoring individualized treatments. In clinical practice, patients with high CONUT score should receive more effective adjuvant therapy and shorten the follow-up interval. Furthermore, considering the promising results of targeted nutritional intervention, patients with high CONUT score may benefit from preoperative nutritional intervention.[29-34] The pre-operative CONUT can better reflect the surgical risk and nutritional status of gastric cancer patients. High CONUT is an independent risk factor for poor prognosis in gastric cancer patients. Therefore, patients with low pre-operative CONUT levels should be observed more closely after surgery to avoid the occurrence of post-operative complications in the near future. At the same time, more detailed and closed long-term follow-up should be placed on these patients in order to obtain the opportunity to intervene in the relapse or metastasis as early as possible.

Our study had some limitations. First, this study has several limitations. First, a bias may exist, because the data were obtained from only a single institution. Second, we divided patients into two groups with high and low CONUT scores using a cut-off value of 3; however, cut-off values for CONUT scores have varied among reports, and the optimal cut-off value remains unclear. Third,

Table 7. Relationship between CONUT and clinicopathological features in 83 elderly (≥65) gastric cancer patients after total gastrectomy

Characteristics	Total patients	CONUT >3 (n=51)	CONUT ≤3 (n=32)	p value
Gender				0.814
Male	71	48	23	
Female	12	3	9	
Vessel invasion				0.072
Negative	37	20	17	
Positive	46	31	15	
Differentiation				0.032
Well	13	5	8	
Moderate	50	32	18	
Poor	20	14	6	
pT stage				0.456
T1	18	12	6	
T2	29	23	6	
T3	25	14	11	
T4	11	4	7	
pN stage				0.017
N0	24	11	13	
N1	15	11	4	
N2	11	8	3	
N3	33	21	12	
TNM stage				0.023
I	5	2	3	
II	15	3	12	
III	29	19	10	
IV	34	27	7	
Ajuvant chemotherapy				0.762
Yes	43	22	21	
No	40	29	11	
Tumor location				0.923
Upper	28	16	12	
Middle	19	12	7	
Lower	32	23	9	
Whole	4	2	2	
Pathological subtype				0.028
Adenocarcinoma	62	38	24	
Signet ring cell carcinoma	18	11	7	
Mucinous adenocarcinoma	3	2	1	

Table 8. Prognostic role of CONUT on gastric cancer after total gastrectomy

Variable	Patients	Characteristics	Univariate HR	Univariate 95%CI	Univariate p value	Multivariate HR	Multivariate 95%CI	Multivariate p value
<65 years CONUT	141/104	>3/≤3	2.917	1.702-4.132	0.039	2.259	1.121-3.397	0.043
≥65 years CONUT	51/32	>3/≤3	2.617	1.692-3.542	0.017	3.021	1.644-4.398	0.024

Table 9. Prognostic role of CONUT for cancer-specific survival in gastric cancer patients after total gastrectomy

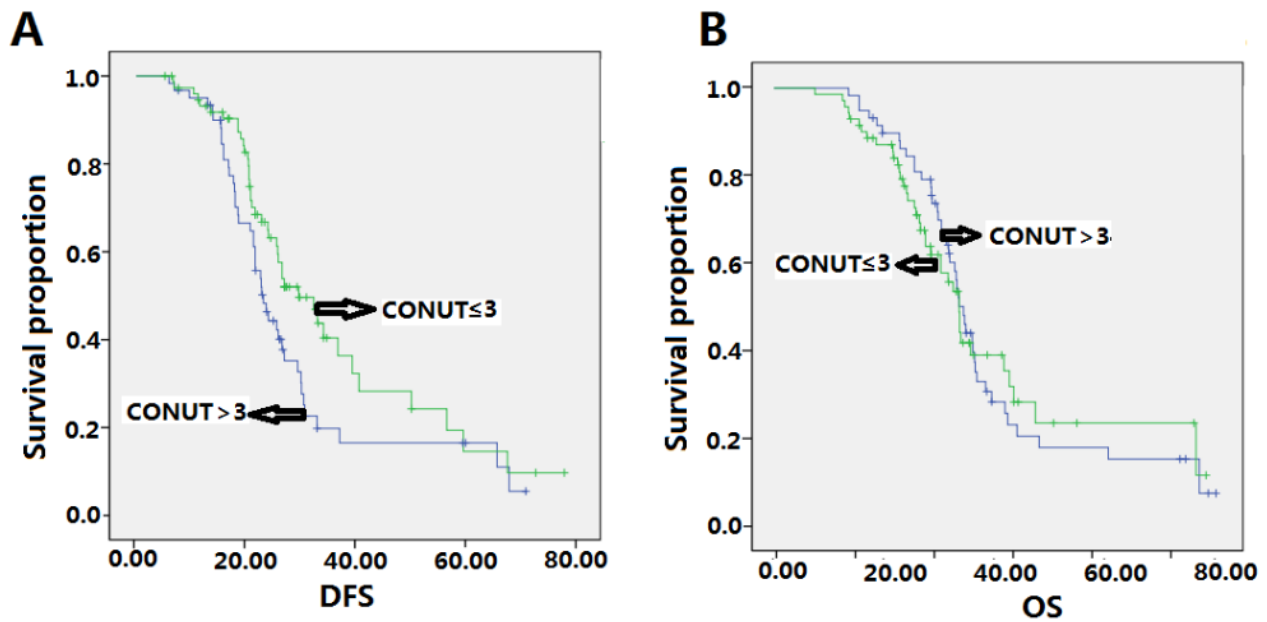| Characteristics	Patients	DFS（M）	p value	χ^2	OS (M)	p value	χ^2
<65 years							
CONUT			0.017	4.124		0.371	2.651
>3	90	27.2			37.8		
≤3	72	31.5			38.4		
≥65 years							
CONUT			0.028	3.327		0.042	3.971
>3	51	24.8			30.1		
≤3	32	30.5			33.2		

Figure 1. Predictive analysis of CONUT on DFS and OS after total gastrectomy on 162 non-elderly (<65) patients with gastric cancer. (A) The effect of CONUT level on DFS of non-elderly patients (<65), high CONUT value is associated with shorter DFS and it has statistical significance; (B) The effect of CONUT level on OS of non-elderly patients (<65), high CONUT value is associated with shorter OS and it has no statistical significance.
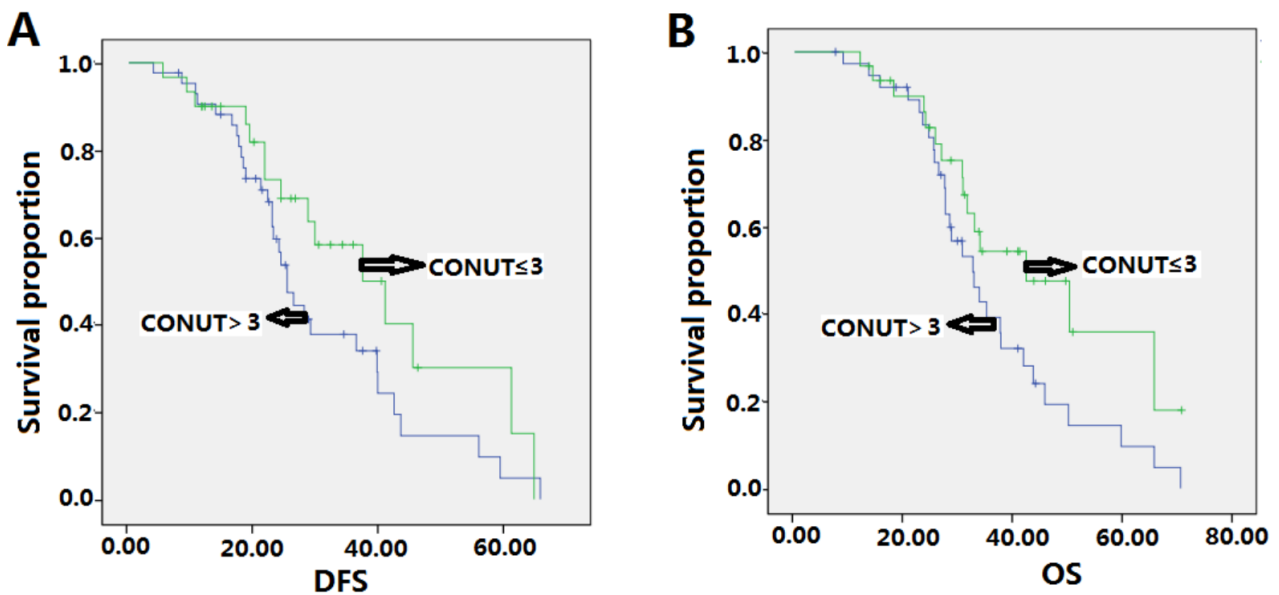

Figure 2. Predictive analysis of CONUT on DFS and OS after total gastrectomy on 83 elderly (≥65) patients with gastric cancer. (A) The effect of CONUT level on DFS of elderly patients (≥65), high CONUT value is associated with short DFS and it has statistical significance; (B) The effect of CONUT level on OS of elderly patients (≥65), high CONUT value is associated with short OS and it has statistical significance.

the number of patients included in the current study was small, and further large-scale, prospective, randomized, controlled trials are needed to confirm the results.

Conclusion

Generally speaking, the most prominent significance of this study is to find the risk factors that affect the survival time of gastric cancer after total gastrectomy from the perspective of inflammatory response and tumor immunity. The CONUT score is independently associated with DFS or OS in gastric cancer patients undergoing total gastrectomy. As a convenient, objective and noninvasive

marker, it may be useful for treatment decision-making and improving follow-up performance.

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