The Clinical Influence of the CONUT Score on Survival of Patients With Gastric Cancer Receiving Curative Treatment

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Abstract. *Background:* We investigated the influence of the preoperative Controlling Nutritional Status (CONUT) score on survival and recurrence of gastric cancer in patients after curative treatment. *Patients and Methods:* This study included 331 patients who underwent curative surgery followed by adjuvant treatment for gastric cancer between 2013 and 2017. The risk factors for overall survival (OS) and recurrence-free survival (RFS) were identified. *Results:* Based on the 1-, 3- and 5-year survival rates, a CONUT score of 2 was regarded as the optimal cut-off value for classification. The 3- and 5-year OS rates were 93.6% and 88.6%, respectively in the low-CONUT group, and 82.7% and 73.6% in high-CONUT group ($p=0.022$). The 3- and 5-year RFS rates were 78.8% and 68.7%, respectively, in the low-CONUT group, and 89.3% and 86.6%, respectively, in the high-CONUT group ($p=0.05$). A multivariate analysis showed that the CONUT score was a significant independent predictive factor for OS and RFS. *Conclusion:* The CONUT score was a predictive factor for survival in patients who underwent curative treatment for gastric cancer. It is necessary to develop an effective plan for perioperative care and surgical strategy according to the CONUT score.

Gastric cancer is the third-most common cancer and the second leading cause of cancer-related death in the world

This article is freely accessible online.

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Key Words: Gastric cancer, CONUT score, survival.

(1, 2). Gastrectomy with D2 lymphadenectomy and perioperative adjuvant treatment is a standard treatment for resectable gastric cancer. However, even when patients receive curative treatment, more than half develop recurrent disease (3-5). Thus, to further improve the chance of survival, it is necessary to establish new approaches for treatment.

Previous studies showed that perioperative malnutrition affected short-term oncological outcomes, including postoperative surgical complications, the incidence of adverse events in patients who received adjuvant treatment, and the continuation of adjuvant treatment (6-9). Moreover, perioperative malnutrition also affected the long-term oncological outcomes in gastric cancer (10, 11). To evaluate the perioperative nutritional status and detect malnutrition, several markers of nutritional status, including the Geriatric Nutritional Risk Index, subjective global assessment, and mini nutritional assessment, were developed and are clinically used in gastrointestinal cancer treatment (12-14).

Recently, the controlling nutritional status (CONUT) score has been developed and used in screening of the perioperative nutritional status and assessment of malnutrition in cancer treatment (15). The CONUT score is calculated from the serum albumin concentration, the total peripheral lymphocyte count, and the total cholesterol concentration. Recent studies on the CONUT score in various malignancies have demonstrated that a high CONUT score is associated with poor oncological outcomes for many tumor types, including gastrointestinal tumors (16, 17). However, while the CONUT score has clinical advantages, such as cost effectiveness and simplicity, few studies have evaluated its prognostic value in patients with gastric cancer (18, 19). Therefore, we clarified whether or not the long-term oncological outcomes were affected by the CONUT score in patients with gastric cancer who underwent curative treatment.

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

Characteristics	Subgroup	No. of patients (%)	Survival rate, %			p-Value
			1-Year	3-Year	5-Year	
Age	<65 Years	237 (71.6%)	97.0	88.1	82.3	0.260
	≥65 Years	94 (28.4%)	98.9	94.7	84.9	
Gender	Male	219 (66.2%)	97.3	88.5	82.2	0.223
	Female	112 (33.8%)	98.2	92.8	86.5	
Pathological type	Intestinal	172 (52.0%)	98.8	93.6	87.5	0.038
	Diffuse	159 (48.0%)	96.2	85.4	79.6	
Pathological T status	T1	206 (62.2%)	99.0	95.6	92.1	<0.001
	T2 to T4	125 (37.1%)	96.0	80.8	69.9	
Pathological lymph node metastasis	Negative	233 (70.4%)	98.3	96.1	92.1	<0.001
	Positive	98 (39.6%)	95.9	74.3	63.5	
CONUT score	<2	221 (66.8%)	98.2	93.6	88.6	<0.001
	≥2	110 (33.2%)	96.4	82.7	73.6	
Lymphatic invasion	Negative	226 (68.3%)	97.3	92.9	89.7	<0.001
	Positive	105 (31.7%)	98.1	82.7	67.8	
Vascular invasion	Negative	192 (58.0%)	98.4	95.8	90.8	<0.001
	Positive	139 (42.0%)	96.4	81.2	72.3	
Postoperative surgical complications	No	281 (84.9%)	97.5	90.0	83.6	0.675
	Yes	50 (15.1%)	98.0	87.8	80.0	

CONUT: Controlling Nutritional Status.

Patients and Methods

Patients. Patients who underwent curative resection for gastric cancer at Kanagawa Cancer Center from 2013 to 2017 were selected based on medical records. The inclusion criteria were as follows: (i) histologically proven adenocarcinoma, (ii) clinical stage I-III disease, according to the fifth edition of the General Rules for Gastric Cancer published by the Japanese Gastric Cancer Association (20), and (iii) complete (R0) resection of gastric cancer with radical lymph node dissection.

Surgical procedure and adjuvant treatment. All patients underwent distal or total gastrectomy with lymphadenectomy. D1+ nodal dissection was performed for clinical stage IA disease, while D2 dissection was performed for clinical stage ≥IB disease. Patients diagnosed with pathological stage II or III disease received adjuvant chemotherapy for 1 year.

Evaluations and statistical analyses. The CONUT score was calculated using three parameters: Serum albumin, total cholesterol level, and total lymphocyte count. Serum albumin was categorized and scored as: score 0: 3.5-4.5 g/dl, score 2: 3.0-3.49 g/dl, score 4: 2.5-2.9 g/dl, and score 6: <2.5 g/dl. Total lymphocyte count was categorized and scored as: score 0: >1,600/ml, score 1: 1,200-1,599/ml, score 2: 800-1,199/ml, and score 3: <800/ml. Cholesterol was categorized and scored as: score 0: >180 mg/dl, score 1: 140-180 mg/dl, score 2: 100-139 mg/dl, and score 3: <100 mg/dl. Blood samples were collected at day 1-7 before surgery. These individual scores were summed to provide a total CONUT score. The significance of differences in CONUT score and clinicopathological parameters was determined using the chi-squared test. Recurrence-free survival (RFS) was defined as the period between surgery and recurrence or death, whichever

came first. Overall survival (OS) was defined as the period between surgery and death. The Kaplan-Meier method was used to calculate the OS and RFS curves. Univariate and multivariate survival analyses were performed using a Cox proportional hazards model. *p*-Values of 0.05 or less were considered to indicate statistical significance. The SPSS software program (v27.0 J Win; IBM, Armonk, NY, USA) was used for all statistical analyses. This study was approved by the IRB of Kanagawa Cancer Center (2019-eki-176).

Results

Patients. A total of 331 patients were evaluated. The cut-off value for the CONUT score was set at 2 based on the 3- and 5-year OS rates (Table I) and the results of previous studies (16-19). The study population included 221 patients with a CONUT score of <2 (low-CONUT group) and 110 with a CONUT score of ≥2 (high-CONUT group). Significant differences were observed in the following background characteristics of the low-CONUT and high-CONUT groups: median age [65 (range=36-84) *versus* 71 years (range=36-87) years; *p*<0.001]; preoperative albumin [26.3 (range=12.8-41.8) *versus* 22.7 (range=10.8-47) mg/dl; *p*<0.001], and preoperative C-reactive protein [0.15 (range=0.01-3.17 mg/l) *versus* 0.28 (range=0.3-55) mg/l; *p*=0.006]. The high-CONUT group included a larger percentage of elderly patients and patients with a hyper-inflammatory status before surgery.

Survival analysis and patterns of recurrence. The clinicopathological factors were categorized and analyzed

Table II. Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival.

Characteristic	Subgroup	n	Univariate analysis			Multivariate analysis		
			OR	95% CI	p-Value	OR	95% CI	p-Value
Age	<65 Years	237	1.000					
	≥65 Years	94	1.377	0.721-2.631	0.332			
Gender	Male	219	1.000					
	Female	112	1.385	0.749-2.562	0.299			
Pathological type	Intestinal	172	1.000					
	Diffuse	159	1.672	0.957-2.922	0.071			
Pathological T status	T1	206	1.000					
	T2 to T4	125	4.226	2.336-7.643	<0.001			
Lymph node metastasis	Negative	233	1.000			1.000		
	Positive	98	5.417	3.043-9.646	<0.001	3.464	1.864-6.440	<0.001
CONUT score	<2	221	1.000			1.000		
	≥2	110	2.898	1.664-5.045	<0.001	1.949	1.100-3.451	0.022
Lymphatic invasion	Negative	226	1.000					
	Positive	105	3.189	1.829-5.559	<0.001			
Vascular invasion	Negative	192	1.000			1.000		
	Positive	139	4.239	2.290-7.846	<0.001	2.640	1.376-5.066	0.003
Postoperative complications	No	281	1.000					
	Yes	50	1.221	0.594-2.510	0.586			

CI: Confidence interval; CONUT: Controlling Nutritional Status; OR: odds ratio.

Figure 1. Overall survival of patients according to Controlling Nutritional Status (CONUT) score.

for prognostic significance (Table II). The univariate analyses of factors associated with OS identified T factor, vascular invasion, lymphatic invasion, lymph node metastasis, and CONUT score as significant prognostic factors. We therefore included the CONUT score in the final

multivariate analysis model. The 3- and 5-year OS rates following surgery were 93.6% and 88.6%, respectively, for the low-CONUT group and 82.7% and 73.6% for the high-CONUT group ($p=0.022$). The OS curves are shown in Figure 1. Univariate analyses of factors associated with RFS

Table III. Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for recurrence-free survival.

Characteristic	Subgroup	n	Univariate analysis			Multivariate analysis		
			OR	95% CI	p-Value	OR	95% CI	p-Value
Age	<65 Years	237	1.000					
	≥65 Years	94	1.283	0.702-2.346	0.418			
Gender	Male	219	1.000					
	Female	112	1.234	0.700-2.177	0.467			
Pathological type	Intestinal	172	1.000					
	Diffuse	159	1.501	0.889-2.533	0.129			
Pathological T status	T1	206	1.000					
	T2 to T4	125	3.608	2.092-6.224	<0.001			
Lymph node metastasis	Negative	233	1.000			1.000		
	Positive	98	4.462	2.622-7.592	<0.001	3.119	1.757-5.536	<0.001
CONUT score	<2	221	1.000			1.000		
	≥2	110	2.450	1.456-4.121	<0.001	1.713	1.000-2.933	0.050
Lymphatic invasion	Negative	226	1.000					
	Positive	105	2.945	1.746-4.967	<0.001			
Vascular invasion	Negative	192	1.000			1.000		
	Positive	139	3.220	1.856-5.589	<0.001	2.100	1.168-3.775	0.013
Postoperative complications	No	281	1.000					
	Yes	50	1.304	0.722-1.394	0.323			

CI: Confidence interval; CONUT: Controlling Nutritional Status; OR: odds ratio.

Figure 2. Recurrence-free survival of patients according to Controlling Nutritional Status (CONUT) score.

revealed that the CONUT score was a significant prognostic factor. This was therefore included as a significant prognostic factor in the final multivariate analysis model (Table III). The 3- and 5-year RFS rates after surgery were 78.8% and 68.7%, respectively, in the low-CONUT group,

and 89.3% and 86.6% in the high-CONUT group ($p=0.05$). The RFS curves are shown in Figure 2. When first relapse was compared between the two groups (Table IV), the incidence of local recurrence tended to be higher in the high-CONUT group.

Table IV. Patterns of recurrence for patients with Controlling Nutritional Status (CONUT) score <2 and those with score ≥2.

Recurrence site	All cases (n=331), n (%)	CONUT score, n (%)		p-Value
		<2 (n=221)	≥2 (n=110)	
Peritoneal	17 (5.1%)	10 (4.5%)	7 (6.4%)	0.487
Hematological	7 (2.1%)	5 (2.3%)	2 (1.8%)	0.783
Lymph node	8 (2.4%)	4 (1.8%)	4 (3.6%)	0.315
Local	8 (2.4%)	3 (1.4%)	5 (4.5%)	0.078

The postoperative treatment course. There were some differences in the incidence of postoperative surgical complications between the high- and low-CONUT groups. With regard to surgical complications, there was a marginally significant difference in the incidence of postoperative bleeding, with the rate being higher in the high-CONUT group. The incidence of postoperative bleeding was 0.5% in low-CONUT group, while 2.7% in high-CONUT group ($p=0.074$). On the other hand, there were no differences in adjuvant treatment course. In the present study, 29.9% (99/331) of patients needed postoperative adjuvant chemotherapy. The percentage of patients who required postoperative adjuvant chemotherapy in the low-CONUT and high-CONUT groups was similar, at 29.0% (64/221) and 31.8% (35/110), respectively ($p=0.593$). Among these patients, the percentage of patients who received postoperative adjuvant chemotherapy was also similar, at 83.1% (54/65) and 80.0% (28/35), respectively ($p=0.581$).

Discussion

The present study explored whether or not the CONUT score clinically influenced the OS and RFS of patients who underwent curative gastrectomy followed by adjuvant treatment. The major finding was that the CONUT score was an independent risk factor for both OS and RFS. In addition, the CONUT score was closely related to postoperative surgical complications. Thus, the CONUT score was considered a promising clinical prognostic marker for patients who received curative treatment for gastric cancer.

In the present study, the hazard ratio (HR) of the CONUT score for OS was 1.949 [95% confidence interval (CI)=1.100-3.451, $p=0.022$], and that for RFS was 1.713 (95% CI=1.000-2.933, $p=0.050$). Similar results have been observed for other types of gastrointestinal cancer (21, 22). Toyokawa *et al.* evaluated whether or not the preoperative CONUT score was a prognostic factor in 183 esophageal cancer patients (21). Among 183 patients, 168 were assigned to the low-CONUT group and 17 were assigned to the high-

CONUT group. The 3- and 5-year OS rates were 72.0% and 63.6%, respectively, in the low-CONUT group, and 35.3% and 35.3% in the high-CONUT group ($p<0.001$). The multivariate analysis showed that a high-CONUT score was associated with a significantly poorer OS (HR=2.303, 95% CI=1.191-4.455, $p=0.013$). They concluded that the preoperative CONUT score was a prognostic marker for OS in patients who received curative treatment for esophageal cancer. In addition, Iseki *et al.* clarified the clinical influence of the preoperative CONUT score in 204 patients with colorectal cancer (22). Among 204 patients, 150 were assigned to the low-CONUT group and 54 to the high-CONUT group. The 5-year recurrence-free survival rate was 73.0% in the low-CONUT group and 53.6% in the high-CONUT group ($p=0.0018$). The 5-year cancer specific survival rate was 92.7% in the low-CONUT group and 81.0% in the high-CONUT group ($p=0.0016$). The multivariate analysis showed that a high-CONUT score was associated with significantly poorer cancer specific survival (HR=4.212, 95% CI=1.215-13.350, $p=0.025$). They concluded that the preoperative CONUT score was a useful marker for the management of patients with colorectal cancer. Given these findings, the CONUT score may be a cost-effective and broadly available prognostic marker for gastrointestinal cancer treatment.

Why did the CONUT score influence the survival of patients with gastrointestinal cancer, including gastric cancer? There are several possible explanations. Firstly, there may be a relationship between the CONUT score and postoperative surgical complications. In the present study, the incidence of postoperative bleeding tended to be higher in the low-CONUT group. Similar results were observed in the previous studies. Yoshida *et al.* evaluated the relationship between the CONUT score and postoperative surgical complications in 352 esophageal cancer patients (23). They divided 352 patients into four groups according to CONUT score (normal: CONUT score 0-1, $n=205$; light: CONUT score 2-4, $n=126$; moderate: CONUT score 5-8, $n=20$; and severe: CONUT score 9-10, $n=1$). They found that there was a significant relationship between the CONUT score and postoperative surgical complications. The incidence of postoperative surgical complications (any) was 35.6% in the normal group, 39.7% in the light group, and 61.9% in the moderate to severe group, which were statistically significant differences ($p=0.024$). The incidence of Clavien-Dindo classification grade IIIb or more postoperative surgical complications was 10.2% in the normal group, 7.9% in the light group, and 23.8% in the moderate to severe group, which was also statistically significant ($p=0.034$). Furthermore, the CONUT score was an independent risk factor for postoperative complications in patients with colorectal cancer (odds ratio: 2.75, 95% CI=1.081-7.020, $p=0.034$ for any surgical complications, and 3.07, 95%

CI=1.002-9.432, $p=0.049$ for postoperative surgical complications Clavien-Dindo classification $\geq$ IIIb). The second possible explanation is that there may be a relationship between the CONUT score and the preoperative inflammation status. In the present study, there were significant differences between the low-CONUT and high-CONUT groups in the preoperative C-reactive protein status and pre-albumin status. The operative inflammation status and other nutritional status were significantly worse in the high-CONUT group. Previous studies showed that the CONUT score was strongly related to the inflammation status. Recent studies showed that tumor cells directly and/or directly affect host inflammatory cells. These host inflammatory cells promote tumor growth through the regulation of the promotion of angiogenesis, cytokine activity, and the inhibition of apoptosis (24). In addition, an elevated inflammatory response due to tumor cell activity during the perioperative period was also related to poor oncological outcomes in gastrointestinal cancer (25). However, the underlying mechanism is unclear. Thus, further studies should focus on this issue. On the other hand, we hypothesized that there may be some clinical relationship between the CONUT score and postoperative adjuvant treatment. However, there was no relationship between the CONUT score and the introduction of adjuvant treatment or toxicity. Further studies should be undertaken to clarify the relationship between the CONUT score and adjuvant treatment.

The cut-off value of the CONUT score was 2 in the present study. We set this cut-off according to 3- and 5-year overall survival rates. To apply the CONUT score to the clinical setting in gastric cancer treatment, it will be necessary to determine set the optimal cut-off value. Previous studies have set cut-off values of the CONUT score for gastrointestinal cancer. Hirahara *et al.* evaluated the clinical influence of the CONUT score in 148 patients with esophageal cancer who underwent curative surgery between 2002 and 2014 (26); they set the cut-off value at 1. Toyokawa *et al.* evaluated the clinical influence of the CONUT score in 185 patients with esophageal cancer who underwent curative surgery (22); they set the cut-off value at 3 based on a receiver operating characteristic curve analysis. In addition, Iseki *et al.* evaluated the clinical influence of the CONUT score in 204 colorectal cancer patients (19), using a cut-off value of 3. Differences in the cut-off value of the CONUT score may have occurred due to patient background characteristics, perioperative treatment, or the number of patients. Further studies are needed in order to establish the optimal cut-off value for the CONUT score for patients with gastric cancer.

In conclusion, the preoperative CONUT score was a significant prognostic factor for patients with gastric cancer who underwent gastrectomy and adjuvant treatment. The

preoperative CONUT score is a promising and potentially useful tool for developing treatment strategies to optimize the treatment of gastric cancer.

Conflicts of Interest

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

Authors' Contributions

T. Aoyama and M. Nakazono made substantial contributions to the concept and design. K. Komori, K. Kazama, I. Hashimoto, M. Nakazono, K. Hara, H. Tamagawa, and K. Segami made substantial contributions to the acquisition of data and the analysis and interpretation of data. K. Kano, S. Nagasawa, N. Yukawa, T. Ogata, Y. Rino, and T. Oshima were involved in drafting the article or revising it critically for important intellectual content. All Authors gave their final approval of the version to be published.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 21K08688.

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Received November 15, 2021

Revised December 7, 2021

Accepted December 9, 2021