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ORIGINAL RESEARCH

Controlling Nutritional Status (CONUT) Score Is A Predictor Of Post-Operative Outcomes In Elderly Gastric Cancer Patients Undergoing Curative Gastrectomy: A Prospective Study

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Purpose: The Controlling Nutritional Status (CONUT) score is a recently developed measure that is calculated using the serum albumin level, total cholesterol level, and lymphocyte counts. The aim of this study was to examine whether the CONUT score can predict post-operative outcomes in elderly patients undergoing curative gastrectomy.

Patients and methods: Pre-operative CONUT scores were evaluated from August 2014 to September 2016 in 357 gastric cancer patients who were scheduled to undergo curative gastrectomy. The patients were divided into three groups according to pre-operative CONUT scores: normal, light, moderate, and severe. We then calculated the association between the patient's CONUT score and post-operative complications.

Results: CONUT scores were statistically associated with age ($P = 0.015$), body mass index ($P < 0.001$), pre-operative hemoglobin level ($P < 0.001$), tumor-node-metastasis stage ($P < 0.001$), surgical method ($P = 0.036$), and post-operative complications ($P < 0.001$). Multivariate analysis showed that age and the CONUT score were independent predictors of post-operative complications and 1-year survival.

Conclusion: CONUT scores can be used to predict post-operative complications and 1-year survival in elderly gastric cancer patients undergoing curative gastrectomy. They can also be used to classify the nutritional status of patients, which can be helpful for pre–and post-operative nutritional management.

Keywords: gastric cancer, nutrition, post-operative complications, CONUT score, elderly patients

Introduction

Gastric cancer is an aggressive neoplasm and is the third leading cause of cancer-related deaths worldwide.[1] The treatment of gastric cancer continues to be a big challenge. Surgical resection is currently the main treatment modality in diagnosed patients.[2] Gastrectomy is associated with several post-operative complications, such as infections, leakage, post-operative hemorrhage, delayed gastric emptying, and organ dysfunction. The presence of complications can lead to an increase in the length of post-operative recovery, with prolonged hospitalization and an increase in hospital costs.[3]

Malnutrition is a major concern for cancer patients, because it has a negative effect on malignancy progression, post-operative outcomes, response to anti-cancer

treatment, hospitalization length, and cost.[4] Controlling Nutritional Status (CONUT) score is a novel, simple evaluation measure that is calculated using serum albumin level, total cholesterol concentration, and total lymphocyte count measurement.[5] Few studies have investigated the use of the CONUT score in cancer patients. To our knowledge, this is the first study investigating the role of the CONUT score in predicting post-operative outcomes in elderly gastric cancer patients undergoing curative gastrectomy.

Materials And Methods

Patients

In this prospective study, data of patients undergoing curative gastrectomy were collected between August 2014 and September 2016. The patients were treated following the Japanese guideline for treatment of gastric cancer. All patients had undergone standard D2 lymphadenectomy.[6] The inclusion criteria were as follows: 1) proven gastric adenocarcinoma, 2) history of curative gastrectomy, 3) age ≥ 65 years, 4) no history of neoadjuvant treatment, and 5) no history of multiple organ resection. The study was approved by the ethics committee of The Second Affiliated Hospital of Wenzhou Medical University and complianced with the Declaration of Helsinki. Written Informed consent was obtained from all patients enrolled in this study.

Assessment Of CONUT Score

The pre-operative laboratory measurements included serum albumin level, total cholesterol concentration, and total peripheral lymphocyte count. The CONUT score was calculated as shown in Table 1, based on previous studies. The cut-off values were 35 g/L for serum albumin, 180 mg/dl for total cholesterol, and 1600/mm^3 for total peripheral lymphocyte count.[7,8] Patients with a score of ≥2 were considered to have malnutrition.[5,9]

Table 1 Assessment Of Nutrition Status Based On CONUT Score

Parameter	Degree Of Malnutrition			
	Normal	Light	Moderate	Severe
Serum albumin (mg/dL)	> 35	30–34.9	25–29	< 25
Albumin score	0	2	4	6
Total Lymphocyte (/mL)	>1600	1200–1599	800–1199	< 800
Lymphocyte Score	0	1	2	3
Total Cholesterol (mg/dL)	> 180	140–180	100–139	< 100
Cholesterol Score	0	1	2	3
Total Score	0-1	2–4	5–8	9–12

Data Collection

The data were collected from a prospectively maintained computer database. We retrieved data on the following demographic and clinicopathological features: age, sex, body mass index (BMI), hemoglobin concentration, diabetes, American Society of Anesthesiologists (ASA) grade, and tumor-node-metastasis (TNM) stage. We also retrieved the following surgical data: surgical method, surgery duration, type of gastrectomy (subtotal or total gastrectomy), type of anastomosis (Roux-En-Y, Billroth I, or Billroth II), and post-operative complications. The Clavien-Dindo classification method was used to classify post-operative complications and to avoid bias. Grade I complications were not analyzed in this study. No deaths were recorded in this patient group during the study period.

Statistical Analysis

SPSS Statistics software, version 22.0 (IBM Corporation, Armonk, NY, USA), was used for data analysis. Continuous variables following normal distribution were presented as mean and standard deviation (SD). Non-normally distributed variables were presented as median and interquartile range (IQR). Normally distributed and continuous variables were compared using the X2 test, while non-normally distributed variables were compared using the Mann–Whitney *U*-test. Univariate analysis was performed to find the potential risk factors, and multivariate analysis was then performed to identify independent predictors. A *P*-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

In the study, we enrolled 357 patients who met our inclusion criteria. According to the CONUT Score, we classified patients into three degrees: normal (0–1), light malnutrition (2–4), moderately or severe malnutrition (≥ 5). We analysed the correlations of nutrition status with Postoperative Complications and 1-year survival using logistic regression (Figure 1). Mean age of the patients was 73.29 ± 5.24 years. Most patients were male 275 (77%). Mean BMI of the patients was 21.61 ± 3.24, and 12.9% of patients had pre-operative diabetes. Mean pre-operative hemoglobin level was 107.2 ± 21.07. ASA grades of the included patients was as follows (in the descending order): II (245, 68.6%), III (86, 24.1%), I (24, 6.72%), and IV (2, 0.56%). TNM classification showed that most patients had stage III disease (151, 42.3%), followed by stage I (119, 33.3%) and stage

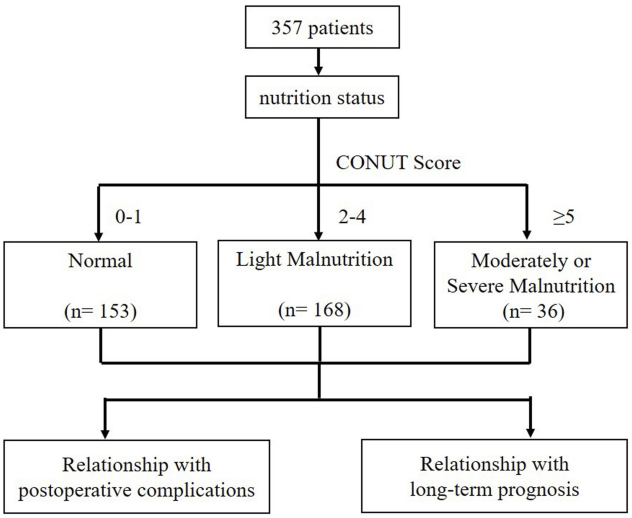

Figure 1 Block flow chart of experimental grouping.

II (87, 24.4%) disease. Regarding surgery, 79.3% of patients opted for open surgery, of which 56.9% underwent subtotal gastrectomy; the rest (43.1%) underwent total gastrectomy. In total, 47.1% of patients underwent Roux-En-Y anastomosis, 34.5% underwent Billroth I anastomosis, and the remaining 18.5% underwent Billroth II anastomosis. In most patients, the tumor location was the antrum (207, 58%), followed by the body (76, 21.3%), fundus (67, 18.8%), and pylorus (7, 1.9%). Mean surgery time was 202.6 ± 55.65 mins.

Association Of Clinicopathological Features With The CONUT Score

Statistical analysis of the association between the CONUT score and clinicopathological features showed that sex (P = 0.087), diabetes (P = 0.241), type of anastomosis (P = 0.063), type of gastrectomy (P = 0.393), tumor location (P = 0.086), and surgery time (P = 0.903) were not significantly associated with the CONUT score. However, we found that age (P = 0.015), BMI (P < 0.001), hemoglobin level (P < 0.001), TNM stage (P = 0.013), and surgical method (P = 0.036) were significantly associated with the CONUT score. We further analyzed the significant variables by performing a univariate analysis, to study their role as risk factors for post-operative outcomes (Table 2).

Association Of Post-Operative Outcomes With The CONUT Score

Results of the statistical analysis for the association between the CONUT score and post-operative outcomes are shown in Table 3. The post-operative complications in our cohort were as follows: delayed gastric emptying (9 patients), ileus (12), pneumonia (21), anastomosis leakage (2), wound infection (4), anastomosis stenosis (2), ascites (7), deep venous thrombosis (3), pleural effusion (39), small bowel obstruction (7), lymph node leakage (2), pulmonary embolism (2), pleural effusion (39), intra-abdominal bleeding (5), intra-abdominal infection (19), septic shock (2), and multiple organ failure (19). Post-operative complications were significantly associated with the CONUT score (P < 0.001). Mean post-operative hospitalization length was 18.15 ± 10.12 days (P = 0.290); post-operative hospitalization length and lymph node metastasis (P = 0.132) were not significantly associated with the CONUT score. The CONUT score was significantly associated with 1-year survival.

Univariate And Multivariate Analysis For Post-Operative Complications And 1-Year Survival

On univariate analysis, we found that age (P = 0.022) and the CONUT score (P < 0.001) were significant risk factors for post-operative complications. Subsequent multivariate analysis showed that age (P < 0.001) and the CONUT score (P < 0.001) were independent predictors of post-operative complications in our cohort (Table 4).

Factors that could be associated with 1-year survival were analyzed by univariate and multivariate analysis. On univariate analysis, we found that age (P < 0.001), BMI (P = 0.044), TNM stage (P = 0.039), and the CONUT score (P = 0.030) were significant risk factors for 1-year survival. On multivariate analysis, we found that age (P < 0.001), TNM stage (P = 0.036), and the CONUT score (P = 0.021) were independent predictors of 1-year survival (Table 5).

Discussion

Patient's nutrition, inflammation, and immune status can influence tumor progression.[10,11] Surgical treatment is considered successful when there are no post-operative complications.[12] Post-operative short-term outcomes and long-term survival in gastric cancer patients are of great concern for both surgeons and patients. It has been found that, compared with younger patients, elderly patients have later disease and poorer surgical tolerance, which are often associated with a worse long-term and short-term prognosis.[13,14] Therefore, early identification of a population with poor post-operative prognosis could be important.

Table 2 Clinicopathological Features Of Patients According To Nutritional Status

Factors	Total	Normal (n= 153)	Light Malnutrition (n= 168)	Moderately Or Severe Malnutrition (n= 36)	*P*-Value
Age (years)	73.29 (5.24)	71.84 (4.77)	72.20 (4.77)	73.91 (5.79)	0.015*
Gender					
Female	82	41	33	8	0.087
Male	275	112	135	28	
BMI	21.61 (3.24)	21.76 (3.42)	22.16 (2.31)	20.93 (2.94)	<0.001*
Diabetes					
No	311	136	144	31	0.241
Yes	46	17	24	5	
ASA grade					
I	24	13	10	1	0.199
II	245	109	113	23	
III	86	31	43	12	
IV	2	0	2	0	
Preoperation	107.2 (21.07)	127.4 (16.42)	109.71 (19.9)	95.47 (22.73)	<0.001*
Hemoglobin (IQR)					
TNM					
I	119	64	49	6	0.013
II	87	33	44	10	
III	151	56	75	20	
Surgical method					
Laparotomy	283	114	137	32	0.036
Laparoscopy	74	39	31	4	
Type of anastomosis					
Roux-en-Y	168	69	83	16	0.063
Billroth I	123	62	50	11	
Billroth II	66	22	35	9	
Type of gastrectomy					
Subtotal	203	89	96	18	0.393
Total	154	64	72	18	
Tumor location					
Fundus	67	32	30	5	0.286
Body	76	30	40	6	
Antrum	207	90	92	25	
Pylorus	7	1	6	0	
Surgery time (minutes)	202.6 (55.65)	203.2 (47.1)	203.86 (57.70)	196.81 (45.2)	0.903

Notes: The values given are number of patients unless indicated otherwise. * Statistically significant ($P< 0.05$).
Abbreviations: BMI, body mass index; TNM, Tumor Node Metastasis; ASA, American Society of Anaesthesiologists; IQR, interquartile range.

In the present study, we found that the CONUT score can be used as a predictor for post-operative complications and 1-year survival in elderly gastric cancer patients undergoing curative gastrectomy. The CONUT score is calculated from three parameters: serum albumin level, total cholesterol concentration, and peripheral lymphocyte count.[15] Serum albumin is an indicator of protein reserves.[16] Total peripheral lymphocyte count is an indicator of immunological status.[17] Moreover, previous studies have found that T cells play a key role in the immune response against cancers.[18] Menges et al[19] found that lymphopenia is caused by a systemic

Table 3 The Relationship Between Postoperative Outcomes And Nutritional Status

Factors	Total	Normal	Light Malnutrition	Moderate Or Severe malnutrition	*P*–value
Postoperative complications					
Clavien-Dindo Grade II	96	41	44	11	0.535
Delayed gastric emptying	9	2	5	2	
Ileus	12	7	4	1	
Pneumonia	22	1	17	4	
Anastomosis leakage	2	1	1	0	
Wound infection	4	2	2	0	
Anastomosis stenosis	2	2	0	0	
Ascites	7	4	2	1	
Deep venous thrombosis	3	2	1	0	
Small bowel obstruction	7	5	0	2	
Lymph node Leakage	2	0	2	0	
Pulmonary Embolism	2	1	1	0	
Pleural effusion	39	5	30	4	
Clavien-Dindo Grade III	24	11	13	0	0.460
Intra-abdominal bleeding	5	2	3	0	
Intra-abdominal infection	19	9	10	0	
Clavien-Dindo Grade IV	2	1	1	0	0.674
Septic shock	2	1	0	1	
Clavien-Dindo Grade V	1	0	0	1	0.551
Multiple Organ Failure	1	0	0	1	
Total complications	113	29	68	16	< 0.001
Lymph Node Metastasis	93	77	91	25	*0.132
Post-operative hospital stays (days)	18.15 (10.12)	15.69 (9.07)	18.70 (10.78)	17.92 (8.62)	0.290
30–days readmission	3	2	0	10	0.393
One Year survival					
Alive	331	149	152	30	0.002*
Dead	26	4	16	6	

Notes: Data are expressed as number of patients, * Statistically significant ($P< 0.05$).

inflammatory response resulting from a decrease in innate cellular immunity, which is indicated by a significant decrease in the number of T-4 helper lymphocytes and natural killer cells.[19] A decrease in T cell count was shown to be correlated with poor prognosis because of inadequate host immunity against cancer.[18] A low serum cholesterol level is associated with negative clinical outcomes in cancer patients.[20,21] In cancerous tissues, there is an increased expression of the mRNA coding the low-density lipoprotein cholesterol receptor.[22] This in turn increases the low-density lipoprotein cholesterol intake of the tumor tissue, causing a decrease in the serum cholesterol level.[22] The cholesterol is used to accelerate tumor growth.[23] This explains why cholesterol levels increase after surgery. A decrease in serum cholesterol level not only reflects a decrease in the caloric intake but also a decline in the cholesterol levels of the cell membrane, which is associated with a poor prognosis.[24]

Previous studies have shown that the CONUT score is associated with post-operative complications in colorectal cancer.[25,26] Recently, Hirahara et al[27] reported that the CONUT score is an independent predictor of survival in patients with esophageal cancer undergoing curative thoracoscopic esophagostomy. Furthermore, Tokunaga et al[25] showed that the CONUT score predicts overall survival, relapse-free survival, and severe post-operative complications when patients are classified into three groups: normal, light, and moderate/severe CONUT score. To our knowledge, this is the first time that the CONUT score has been used to predict the long–and short-term prognosis in patients with

Table 4 Univariate And Multivariate Analysis Of Factors Associated With Postoperative Complications

Factors	Univariate					Multivariate		
	Complications	No Complications	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Age	74.45 (5.68)	71.75 (4.81)	1.105	1.057–1.155	0.022*	1.094	1.045.-1.145	< 0.001*
BMI	21.95 (3.45)	22.55 (3.13)	0.944	0.880–1.012	0.347			
Hemoglobin	113.60 (21.5)	116.94 (21.88)	0.993	0.983–1.003	0.561			
TNM								
I	33	86						
II	23	64	1.275	0.981–1.657	0.104			
III	57	94						
Surgical Method								
Laparoscopy	24	50	1.070	0.618–1.852	0.809			
Open	89	194						
CONUT Score								
Normal	29	124						
Light Malnutrition	68	100	2.99	1.832–4.891	< 0.001*	2.695	1.631–4.451	< 0.001*
Moderate/Severe Malnutrition	16	20						

Notes: *Statistically significant ($P < 0.05$), Data are expressed as number of patients.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index, CONUT Score, Controlling Nutritional Status.

gastric cancer. Except for TNM staging and tumor typing,[28] the body's nutritional state, inflammation, and the immune status are closely related to the disease's prognosis.[10,29] Perioperative nutritional support in patients with malnutrition-based cancer can improve the nutritional status, enhance tolerance during treatment, and positively affect post-operative survival.[30,31] Early identification and treatment of malnutrition by using the CONUT score in elderly patients undergoing curative gastrectomy may improve the surgical outcomes and reduce the post-operative complications.

This study has several limitations. First, a bias may exist, because the data were obtained from only a single

Table 5 Univariate And Multivariate Analysis Of Factors Associated With 1-Year Survival

Factors	Univariate					Multivariate		
	Alive	Dead	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Age	72.18 (4.96)	78.00 (5.84)	1.225	1.130–1.328	< 0.001*	1.214	1.116.-1.321	< 0.001*
BMI	22.45 (3.21)	21.26 (3.52)	0.900	0.802–1.010	0.044*	0.967	0.845 −1.107	0.072
Hemoglobin	116.53 (21.76)	107.65 (18.53)	0.982	0.965–1.000	0.815			
TNM								
≤ II	196	10	2.232	1.023–5.274	0.039*	2.398	0.982–5.853	0.036*
> II	135	16						
Surgical Method								
Laparoscopy	74	12	0.297	0.069–1.289	0.087			
Open	257	24						
CONUT Score								
Normal	149	4						
Light Malnutrition	152	16	4.503	1.518–13.354	0.030*	2.909	0.909–9.311	0.021*
Moderate/Severe Malnutrition	30	6						

Notes: *Statistically significant ($P < 0.05$), Data are expressed as number of patients.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index, CONUT Score, Controlling Nutritional Status.

institution. Second, although two researchers were responsible for data collection, artificial errors are unavoidable. Thus, a further validation, with larger, multi-center data sets, is needed to evaluate the role of the CONUT score in predicting the prognosis of gastric cancer patients.

Conclusion

The CONUT score is a simple, easy, and feasible score that reflects the nutritional and inflammatory status of a patient. Our study indicates that the CONUT score can help clinicians to predict post-operative complications and 1-year survival in elderly gastric cancer patients. Management of nutritional status may be crucial for survival in gastric cancer patients.

Ethics Approval And Consent To Participate

All participants provided their written informed consent, and the protocol for this study was approved by the ethics committee of The Second Affiliated Hospital of Wenzhou Medical University and conformed to the tenets of the Declaration of Helsinki.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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