jgc | Journal of Gastric Cancer

Original Article

Check for updates

Correspondence to
Weilin Wang
Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital, Zhejiang University, School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, China.
E-mail: wam@zju.edu.cn

ORCID iDs
Hailong Jin 🔴
https://orcid.org/0000-0002-8195-6578
Kankai Zhu 🔴
https://orcid.org/0000-0002-2513-6540
Weilin Wang 🔴
https://orcid.org/0000-0001-9432-2649

Author Contributions
Conceptualization: J.H., Z.K., W.W.; Data curation: J.H., Z.K.; Formal analysis: J.H., Z.K.; Writing - original draft: J.H., Z.K.; Writing - review & editing: J.H., Z.K., W.W.

The Predictive Values of Pretreatment Controlling Nutritional Status (CONUT) Score in Estimating Short- and Long-term Outcomes for Patients with Gastric Cancer Treated with Neoadjuvant Chemotherapy and Curative Gastrectomy

Hailong Jin 🔴 [1], **Kankai Zhu** 🔴 [1], **Weilin Wang** 🔴 [2,3,4,5,6]

[1]Department of Gastrointestinal Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[2]Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, China
[3]Key Laboratory of Precision Diagnosis and Treatment for Hepatobiliary and Pancreatic Tumor of Zhejiang Province, Hangzhou, China
[4]Research Center of Diagnosis and Treatment Technology for Hepatocellular Carcinoma of Zhejiang Province, Hangzhou, China
[5]Clinical Medicine Innovation Center of Precision Diagnosis and Treatment for Hepatobiliary and Pancreatic Disease of Zhejiang University, Hangzhou, China
[6]Clinical Research Center of Hepatobiliary and Pancreatic Diseases of Zhejiang Province, Hangzhou, China

ABSTRACT

Purpose: Previous studies have demonstrated the usefulness of the controlling nutritional status (CONUT) score in nutritional assessment and survival prediction of patients with various malignancies. However, its value in advanced gastric cancer (GC) treated with neoadjuvant chemotherapy and curative gastrectomy remains unclear.
Materials and Methods: The CONUT score at different time points (pretreatment, preoperative, and postoperative) of 272 patients with advanced GC were retrospectively calculated from August 2004 to October 2015. The χ^2 test or Mann-Whitney U test was used to estimate the relationships between the CONUT score and clinical characteristics as well as short-term outcomes, while the Cox proportional hazard model was used to estimate long-term outcomes. Survival curves were estimated by using the Kaplan-Meier method and log-rank test.
Results: The proportion of moderate or severe malnutrition among all patients was not significantly changed from pretreatment (13.5%) to pre-operation (11.7%) but increased dramatically postoperatively (47.5%). The pretreatment CONUT-high score (≥4) was significantly associated with older age (P=0.010), deeper tumor invasion (P=0.025), and lower pathological complete response rate (CONUT-high vs. CONUT-low: 1.2% vs. 6.6%, P=0.107). Pretreatment CONUT-high score patients had worse progression-free survival (P=0.032) and overall survival (OS) (P=0.026). Adjusted for pathologic node status, the pretreatment CONUT-high score was strongly associated with worse OS in pathologic node-positive patients (P=0.039).

Generated by 🔴 xmlinkpress

Conclusions: The pretreatment CONUT score might be a straightforward index for immune-nutritional status assessment, while being a reliable prognostic indicator in patients with advanced GC receiving neoadjuvant chemotherapy and curative gastrectomy. Moreover, lower pretreatment CONUT scores might indicate better chemotherapy responses.

Keywords: Controlling nutritional status; Gastric cancer; Neoadjuvant chemotherapy; Gastrectomy; Prognosis

INTRODUCTION

According to GLOBOCAN 2018, gastric cancer (GC) was reported to reach the fifth highest incidence and the third highest mortality worldwide [1]. The latest cancer statistics in China showed that approximately 680,000 new cases were diagnosed, while 500,000 deaths were estimated due to GC in 2015 [2].

Despite significant improvements in the diagnostic and therapeutic modalities for patients with GC, the 5-year overall survival (OS) remains poor, especially in the advanced stage [3,4]. Although surgery is considered as the main curative approach for GC, perioperative chemotherapy has been widely used to improve the prognosis [5,6]. Therefore, it is crucial to identify the prognostic indicators using pretreatment clinical parameters, instead of pathological parameters, for risk stratification and subsequent individual therapy.

Several factors can lead to malnutrition in patients with advanced GC undergoing treatment, for example, dyscrasia, gastric outlet obstruction, gastric bleeding, and gastrointestinal adverse events induced by perioperative chemotherapy. Recently, the immune-nutritional status was associated with the patient outcome, especially in those inflammatory or neoplastic patients who exhibited accelerated metabolism [7]. The prognostic nutritional index (PNI) or the controlling nutritional status (CONUT) score, which represents the immunological and nutritional status deriving from peripheral blood parameters, has been not only related to short-term outcomes, such as surgical complications [8,9], but also patients' long-term prognosis in various malignancies [10-15]. Our previous study has also demonstrated that pretreatment PNI was a useful tool for survival prediction in patients with advanced GC treated with neoadjuvant chemotherapy [16].

In 2005, a study demonstrated the CONUT score, comprising the serum albumin level, total peripheral lymphocyte count, and total cholesterol level, as a convenient screening tool for the early detection and monitoring of the malnutrition status of hospitalized patients and as an effective prognostic biomarker [17-19]. Importantly, another study that enrolled a large cohort from China showed that the CONUT score is superior to PNI in predicting the prognosis of patients with stage II-III GC receiving radical gastrectomy and postoperative chemotherapy [20]. However, there is a paucity of studies evaluating these indexes in cancer patients undergoing neoadjuvant treatment. A Japanese study reported the preoperative CONUT score predicting survival in 417 colorectal cancer patients with curative resection; however, the proportion of total patients who underwent neoadjuvant chemotherapy was only 3% (13/417) [21]. Another study consisting of approximately 25% (46/185) patients receiving preoperative treatment showed that the pretreatment CONUT score was an independent predictor in terms of prognosis in patients with resectable thoracic esophageal squamous cell carcinoma (ESCC); a subgroup analysis showed that the survival was poorer in

the CONUT-high score group among preoperatively treated patients [22]. Recently, Hikage *et al.* [23] reported that compared with pretreatment and preoperative CONUT scores, those calculated 14 days postoperatively, were considered independent survival predictors in patients with esophageal cancer receiving neoadjuvant treatment, but the study sample was relatively small.

Therefore, our study was designed to explore the potential relationship between the longitudinal CONUT score at different time points and postoperative complications or prognosis in patients with advanced GC receiving perioperative chemotherapy and curative gastrectomy.

MATERIALS AND METHODS

Study population

We retrospectively collected the data of patients endoscopically and histopathologically diagnosed with gastric adenocarcinoma in the Department of Gastrointestinal Surgery, the First Affiliated Hospital, Zhejiang University, School of Medicine, between August 2004 and October 2015. The inclusion criteria were as follows: 1) patients aged 18–80 years; 2) those with a primary tumor that invades or penetrates the serosa with or without regional lymph nodes metastasis upon computed tomography or magnetic resonance imaging before initial treatment; 3) Eastern Cooperative Oncology Group score 0–2; and 4) patients who received radical gastrectomy. The exclusion criteria included 1) prior stomach surgery; 2) prior treatment for GC including but not limited to chemotherapy or radiotherapy; 3) history or coexisting with another malignancy except cured basal cell carcinoma of skin and cured carcinoma in-situ of the uterine cervix; 4) presence of acute inflammatory, hematological disorders, or autoimmune diseases; and 5) distant metastases. Finally, 272 patients were included in the analysis, and the pathological TNM staging was classified according to the 7th edition of the American Joint of Committee on Cancer [24].

Perioperative management

We used fluorouracil-based and oxaliplatin-based chemotherapy regimens in neoadjuvant settings every 21 days: oxaliplatin plus capecitabine (XELOX, oxaliplatin: 130 mg/m^2, d1; capecitabine: 2000 mg/m^2/d, d1-d14), oxaliplatin plus 5-Fu plus leucovorin (FOLFOX, oxaliplatin: 130 mg/m^2, d1; 5-Fu: 2400 mg/m^2, continuous 46 h; leucovorin: 400 mg/m^2, d1), oxaliplatin plus S-1 (SOX, oxaliplatin: 130 mg/m^2, d1; S-1: 80 mg/m^2/d, d1-d14). Four patients received other neoadjuvant chemotherapy regimens, such as epirubicin plus oxaliplatin plus 5-Fu (EOF), epirubicin plus oxaliplatin plus capecitabin, or paclitaxel plus S-1 (PS1) for the initiation treatment, which was the consultation between surgeons and patients. Generally, upon the progress of the tumor, the patients would switch to receive paclitaxel-based or irinotecan-based chemotherapy regimens. After the completion of the last cycle of neoadjuvant chemotherapy, gastrectomy with D2 or D2 plus lymphadenectomy was performed within 2 weeks, and adjuvant chemotherapy continued after surgery within 4–6 weeks depending on the patients' desire and physical conditions.

Postoperative complication

The definition and their grade of postoperative complications were based on the Clavien-Dindo classification [25]. The complications included anastomotic leakage, pancreatic fistula, duodenal stump fistula, lymphorrhea, gastroplegia, bowel obstruction, bleeding, ascites, pleural effusion, pulmonary infection, pulmonary embolism, cardiovascular morbidity, acute

cerebral infarction, cholecystitis, and surgical site infection. Of those, 2 complications (0.7%) were classified as grade I, 30 (11.0%) as grade II, 6 (2.2%) as grade III, and 4 (1.5%) as grade IV; the incidences in our study were consistent with the previous study [26].

CONUT score and other peripheral blood parameters

The blood samples were collected at three time points: 1) within 2 weeks before initial chemotherapy; 2) within 1 week before surgery; 3) at least 7 days after surgery when the patient was discharged from the hospital. The laboratory data included carcinoembryonic antigen (CEA), serum albumin level, total peripheral lymphocyte count, and the total cholesterol level. The cut-off value of CEA was identified as 5.0 ng/mL [27]. The CONUT score was summarized in **Table 1** [17]. The optimal cut-off value for the CONUT score was set at 4 based on the receiver operating characteristic (ROC) curve to predict the actual 3-year progression-free survival (PFS) and OS, with a sensitivity of 40.2% and a specificity of 72.6%. The body mass index (BMI) was calculated and 18.5 kg/m^2 was selected as the cut-off value, as generally adopted in previous published studies [18].

Ethical statement

Due to the retrospective retrieval of the patients' data, the informed consent was waived remitted. Ethical approval was obtained before the study began from the Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine.

Statistical analysis

The differences between the groups were examined using the χ^2 test or Mann-Whitney U test for categorical variables. Continuous variables were described as mean ± standard deviation or median (range, minimum-maximum). The follow-up data were updated in February 2020. The PFS was calculated from the date of initiation of neoadjuvant chemotherapy to the data of objective tumor progression or recurrence, or death from any cause, whichever occurred first. The OS was calculated from the date of initiation of neoadjuvant chemotherapy to the date of death due to any cause. Kaplan-Meier curves with the log-rank test was used to compare the survival difference. The factors with P-value <0.1 in the univariate analysis were entered into the final multivariate model with the backward likelihood method to determine the independent prognostic factors.

A two-sided P-value <0.05 was considered as statistically significant. All statistical analyses were operated using the SPSS ver.25.0 software (SPSS, Chicago, IL, USA).

Table 1. Assessment of the nutritional status according to the CONUT score

Parameters	Malnutrition degree			
	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.50	3.00–3.49	2.50–2.99	<2.50
Alb score	0	2	4	6
Total lymphocyte count (/mm³)	≥1,600	1,200–1,599	800–1,199	<800
TLC score	0	1	2	3
T-cho (mg/dL)	≥180	140–179	100–139	<100
T-cho score	0	1	2	3
CONUT score (total)	0–1	2–4	5–8	9–12
Classification (total score)	≥4 High CONUT group			
	≤3 Low CONUT group			

CONUT is calculated as the sum of the Alb score, TLC score, and T-cho score.
CONUT = controlling nutritional status; Alb = albumin; TLC = total lymphocyte count; T-cho = total cholesterol.

RESULTS

Patient characteristics

Of the 272 enrolled patients, the median age was 61 years (range, 32–80 years), and 201 (73.9%) patients were men and 71 (26.1%) were women. The median number of neoadjuvant chemotherapy cycles was 3 (range, 1–8). A total of 105 (38.6%) patients received total gastrectomy, 132 (48.5%) received subtotal gastrectomy, and 35 (12.9%) underwent combined resection. Total tumor diameter was 4.0±2.5 cm. A total of 42 (15.4%) patients exhibited postoperative complications, while 10 patients were grade III-IV. No patient died of severe complications. A total of 178 (65.4%) patients had pathological lymph node metastasis; the total number of lymph nodes achieved was 34.5±13.2 and the number of lymph nodes metastasis was 4.5±6.7. The yp TNM classifications (the yp prefix was used to indicate cases in which staging was performed following preoperative therapy) were as follows: 13 patients showed no residual tumor cells with a pathological complete response (pCR), and 1 patient had stage 0, 35 had stage I, 65 had stage II, and 148 had stage III (**Table 2**).

Table 2. Associations between pretreatment CONUT score and clinicopathological parameters in advanced gastric cancer patients treated with neoadjuvant chemotherapy and curative gastrectomy (n=272)

Parameters	Values	CONUT score[*]		
		≤3 (n=182)	≥4 (n=85)	P-value
Gender				0.425
Female	71 (26.1)	49	19	
Male	201 (73.9)	133	66	
Age (yr)				0.010
<65	171 (62.9)	124	44	
≥65	101 (37.1)	58	41	
ECOG				0.786
0	112 (41.2)	76	34	
1, 2	160 (58.8)	106	51	
BMI (kg/m²)[†]				0.204
<18.5	32 (11.8)	18	13	
≥18.5	234 (86.0)	161	71	
Primary tumor site				0.706
Upper	45 (16.5)	31	13	
Middle	54 (19.9)	39	15	
Lower	150 (55.1)	99	48	
More than 2 sites	23 (8.5)	13	9	
Tumor size (cm)[‡]				0.912
<4	128 (47.1)	85	39	
≥4	135 (49.6)	91	43	
Gastrectomy				0.737
Total	105 (38.6)	70	33	
Subtotal	132 (48.5)	90	39	
Combined resection	35 (12.9)	22	13	
Differentiation[§]				0.477
Well	39 (14.3)	23	15	
Poorly	207 (76.1)	135	68	
yp[‖] T stage[¶]				0.025[‖]
T0	21 (7.7)	19	2	
Tis	1 (0.4)	1	0	
T1	18 (6.6)	14	3	
T2	42 (15.4)	28	13	
T3	2 (0.7)	0	2	
T4	186 (68.4)	118	65	
yp[‖] N stage				0.867
N0	94 (34.6)	64	29	
N1-3	178 (65.4)	118	56	

Table 2. (Continued) Associations between pretreatment CONUT score and clinicopathological parameters in advanced gastric cancer patients treated with neoadjuvant chemotherapy and curative gastrectomy (n=272)

Parameters	Values	CONUT score[*]		
		≤3 (n=182)	≥4 (n=85)	P-value
yp[‖] TNM stage[**]				0.335[‖‖‖]
T0N0M0	13 (4.8)	12	1	
0	1 (0.4)	1	0	
I	35 (12.9)	24	10	
II	65 (23.9)	40	24	
III	148 (54.4)	96	49	
pCR				0.107
Yes	13 (4.8)	12	1	
No	259 (95.2)	170	84	
Post-operation chemotherapy[††]				0.798
Absent	20 (7.4)	13	7	
Present	241 (88.6)	160	76	
Postoperative complications[‡‡]				0.818
No	227 (83.5)	152	70	
Yes	42 (15.4)	28	14	
Severe complications (Clavien-Dindo ≥III)[‡‡]				1.000
No	259 (95.2)	173	81	
Yes	10 (3.7)	7	3	
Pretreatment CEA (ng/mL)[§§]				0.680
≤5	194 (71.3)	129	62	
>5	65 (23.9)	45	19	

Values are presented as number (%).
CONUT = controlling nutritional status; ECOG = eastern cooperative oncology group; BMI = body mass index; Tis = tumor in situ; TNM = tumor-node-metastasis; pCR = pathological complete response (T0N0M0); CEA = carcinoembryonic antigen.
[*]Total cholesterol of 5 patients was not available, CONUT could not be calculated. [†]BMI: the data of 6 patients were not available. [‡]Tumor size: 21 patients found no residual tumor in the resection specimens, while the data of 9 patients were not available. [§]Differentiation: well includes well and moderately differentiated adenocarcinoma, poorly includes poorly differentiated adenocarcinoma, ring cell carcinoma, squamous carcinoma, and mucinous adenocarcinoma. A total of 21 patients found no residual tumor in the resection specimens, while the data of 5 patients were not available. [‖]The yp prefix was used to indicate the cases in which staging was performed following preoperative therapy.
[¶]yp T stage: the data of 2 patients were not available because rare tumor cells were residual. [**]yp TNM stage: 10 patients couldn't be classified according to the 7th TNM classification, 3 patients were T0N1M0, 4 patients were T0N2M0, 1 patient was T0N3M0, and 2 patients were TxN0M0. [††]Post-operation chemotherapy: the data of 11 patients were not available. [‡‡]Postoperative complications: the data of 3 patients were not available. [§§]CEA: The data of 13 patients were not available. [‖‖]The Mann-Whitney U test was used.

Up to February 2020, three patients (1.1%) were lost to follow-up. A total of 141 (51.8%) patients experienced disease progression and 139 (51.1%) patients died. The median PFS was 54 months (range, 2–169 months), and median OS was 57 months (range, 7–169 months). The 1-year, 3-year, and 5-year survival rates were 84.9%, 59.6%, and 51.0% for PFS, respectively, and 95.2%, 65.8%, and 54.6% for OS, respectively.

Change of perioperative CONUT score and their correlations with survival

Due to our retrospective design, the pretreatment data of five patients and preoperative data of seven patients were not available. For the postoperative CONUT score, only patients with serologic indices obtained at least 7 days after surgery were collected, excluding the influence of stress and inflammatory response caused by surgery; finally, 219 patients were enrolled for further analysis. According to the nutrition status assessment as shown in **Table 1**, the proportion of moderate or severe malnutrition among all patients was not significantly changed from pretreatment (13.5%) to pre-operation (11.7%), but increased dramatically postoperatively (47.5%) (**Fig. 1**).
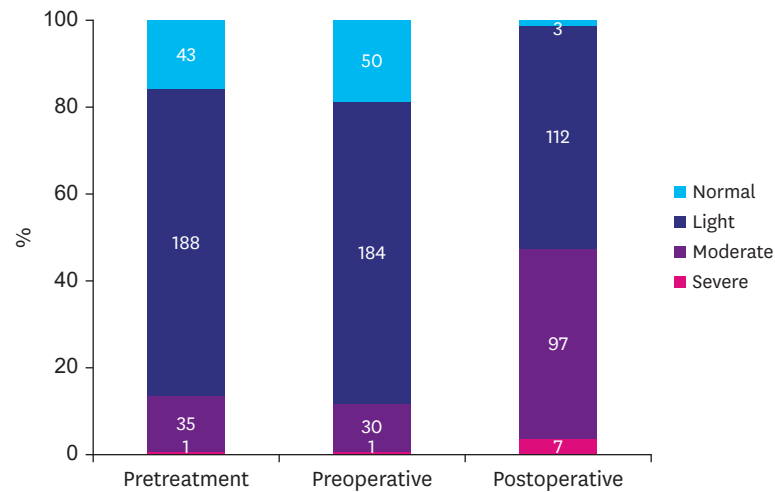
Fig. 1. Longitudinal controlling nutritional status score according to the nutrition score-based malnutrition groups at different time points.

No prognostic significance was found between the moderate or severe malnutrition group and normal or light malnutrition group both for PFS (pretreatment: P=0.565, preoperative: P=0.324, postoperative: P=0.352, Kaplan-Meier with log-rank test) and OS (pretreatment: P=0.482, preoperative: P=0.446; postoperative: P=0.464, Kaplan-Meier with log-rank test) at different time points. The ROC curve identified 4 as the optimal cut-off value for the CONUT score; further analysis revealed that only the pretreatment CONUT score showed significant prognostic values (Kaplan-Meier with log-rank test, for PFS pretreatment: P=0.032, preoperative: P=0.360, postoperative: P=0.382; for OS pretreatment: P=0.026, preoperative: P=0.382, postoperative: P=0.425).

Association between pretreatment CONUT score and clinicopathological factors

Table 2 shows the comparison of the clinicopathological parameters between the patients based on the pretreatment CONUT score. We found that the CONUT-high score was significantly associated with older age (48.2% vs. 31.9%, P=0.010), deeper tumor invasion (P=0.025), and lower pCR rate (1.2% vs. 6.6%, P=0.107). No significant association was found between the CONUT score and postoperative complications (P=0.818), as well as the degree of severe complications (P=1.000).

Association between clinicopathological factors and survival

The pretreatment BMI, tumor size, degree of differentiation, yp T stage, yp N stage, yp TNM stage, and pretreatment CONUT score were significantly associated with PFS. Considering that the yp T/yp N stage were significantly correlated with yp TNM stage, we excluded the TNM stage in the final multivariate model. The results showed that poor differentiation (HR, 2.091; 95% confidence interval [CI], 1.078–4.056; P=0.029), deep tumor invasion (HR, 2.309; 95% CI, 1.266–4.211; P=0.006), presence of pathologic lymph node metastasis (HR, 3.225; 95% CI, 1.879–5.536; P<0.001), and a high pretreatment CONUT score (HR, 1.615; 95% CI, 1.112–2.347; P=0.012) were independently associated with worse PFS (**Table 3**).

The pretreatment BMI, tumor size, degree of differentiation, yp T stage, yp N stage, yp TNM stage, post-operation chemotherapy, and pretreatment CONUT score were significantly associated with the OS. The presence of postoperative complications displayed a trend of

Journal of Gastric Cancer

Table 3. Cox proportional hazard model for progression-free survival among the 272 advanced gastric cancer patients

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender (ref: male)						
Female	1.036	0.712–1.507	0.855			
Age (yr) (ref: <65)						
≥65	0.759	0.535–1.075	0.120			
Pretreatment BMI (kg/m²) (ref: ≥18.5)						
<18.5	1.947	1.241–3.053	0.004	1.329	0.784–2.254	0.291
Tumor size (cm) (ref: <4)						
≥4	2.195	1.548–3.112	<0.001	1.449	0.988–2.126	0.058
Degree of differentiation (ref: well)						
Poorly	2.242	1.265–3.972	0.006	2.091	1.078–4.056	0.029
yp* T stage (ref: Tis and T0-2)						
T3-4	4.170	2.558–6.799	<0.001	2.309	1.266–4.211	0.006
yp* N stage (ref: N0)						
N1-3	5.524	3.321–9.186	<0.001	3.225	1.879–5.536	<0.001
yp* TNM stage (ref: T0N0M0, 0 and I)						
II-III	23.509	5.815–95.038	<0.001	NA	NA	NA
Post-operation chemotherapy (ref: present)						
Absent	1.687	0.983–2.895	0.058	1.749	0.951–3.217	0.072
Postoperative complications (ref: no)						
Yes	1.398	0.906–2.157	0.131			
Severe complications (Clavien-Dindo ≥III) (ref: no)						
Yes	1.478	0.691–3.164	0.314			
Pretreatment CONUT score (ref: ≤3)						
≥4	1.455	1.028–2.058	0.034	1.615	1.112–2.347	0.012
Pretreatment CEA (ng/mL) (ref: ≤5)						
>5	1.231	0.843–1.799	0.282			

Considering that the yp T/yp N stages were significantly associated with the yp TNM stage, we didn't include the TNM stage in the final multivariate analysis.
Cox proportional multivariate hazards model was performed with the backward likelihood method.
HR = hazard ratio; CI = confidence interval; ref = reference; BMI = body mass index; Tis = tumor in situ; TNM = tumor-node-metastasis; CONUT = controlling nutritional status; CEA = carcinoembryonic antigen; NA = not applicable.
*The yp prefix was used to indicate cases in which staging was performed following preoperative therapy.

worse OS (HR, 1.455; 95% CI, 0.942–2.247; P=0.091). A multivariate model showed that poor differentiation (HR, 1.970; 95% CI, 1.013–3.835; P=0.046), deep tumor invasion (HR, 2.316; 95% CI, 1.271–4.221; P=0.006), presence of pathologic lymph node metastasis (HR, 3.131; 95% CI, 1.823–5.379; P<0.001), presence of postoperative complications (HR, 1.772; 95% CI, 1.082–2.903; P=0.023), and high pretreatment CONUT scores (HR, 1.618; 95% CI, 1.111–2.356; P=0.012) were independently associated with worse OS (**Table 4**).

Association between the pretreatment CONUT score and survival

The pretreatment CONUT score can be used to effectively differentiate the patient survival. The 3-year PFS rates were 64.3% in the CONUT-low score group and 50.6% in the CONUT-high score group (HR, 1.451; 95% CI, 1.004–2.098; P=0.032), and the 3-year OS rates were 69.8% and 56.5% (HR, 1.476; 95% CI, 1.016–2.144; P=0.026), respectively (**Fig. 2A and B**). Adjusted for pathologic node status, the CONUT-high score patients had a worse 3-year OS in the pathologic node-positive group compared with the CONUT-low score patients (HR, 1.476; 95% CI, 0.985–2.213; P=0.039), and a worse 3-year PFS (HR, 1.427; 95% CI, 0.959–2.124; P=0.056) although the P-value was not strongly significant (**Fig. 2C and D**). The adjusted PFS and OS curves for yp TNM stage showed no survival significance for stage III patients (HR, 1.357; 95% CI, 0.901–2.045; P=0.117 for PFS; HR, 1.405; 95% CI, 0.925–2.133; P=0.085 for OS) (**Fig. 2E and F**).

jgc Journal of Gastric Cancer

Table 4. Cox proportional hazard model for overall survival among the 272 advanced gastric cancer patients

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender (ref: male)						
Female	1.094	0.751–1.595	0.638			
Age (yr) (ref: <65)						
≥65	0.811	0.572–1.151	0.241			
Pretreatment BMI (kg/m²) (ref: ≥18.5)						
<18.5	2.015	1.283–3.164	0.002	1.456	0.858–2.471	0.163
Tumor size (cm) (ref: <4)						
≥4	2.099	1.479–2.979	<0.001	1.402	0.954–2.061	0.085
Degree of differentiation (ref: well)						
Poorly	2.174	1.226–3.854	0.008	1.970	1.013–3.835	0.046
yp* T stage (ref: Tis and T0-2)						
T3-4	4.022	2.470–6.548	<0.001	2.316	1.271–4.221	0.006
yp* N stage (ref: N0)						
N1-3	5.216	3.136–8.676	<0.001	3.131	1.823–5.379	<0.001
yp* TNM stage (ref: T0N0M0, 0 and I)						
II-III	22.321	5.522–90.226	<0.001	NA	NA	NA
Post-operation chemotherapy (ref: present)						
Absent	1.801	1.048–3.096	0.033	1.824	0.974–3.415	0.060
Postoperative complications (ref: no)						
Yes	1.455	0.942–2.247	0.091	1.772	1.082–2.903	0.023
Severe complications (Clavien-Dindo ≥III) (ref: no)						
Yes	1.506	0.703–3.225	0.292			
Pretreatment CONUT score (ref: ≤3)						
≥4	1.479	1.043–2.097	0.028	1.618	1.111–2.356	0.012
Pretreatment CEA (ng/mL) (ref: ≤5)						
>5	1.202	0.822–1.758	0.342			

Considering that the yp T/yp N stages were significantly associated with the yp TNM stage, we did not include the TNM stage in the final multivariate analysis. The Cox proportional multivariate hazards model was performed with the backward likelihood method.
HR = hazard ratio; CI = confidence interval; ref = reference; BMI = body mass index; Tis = tumor in situ; TNM = tumor-node-metastasis; CONUT = controlling nutritional status; CEA = carcinoembryonic antigen; NA = not applicable.
*The yp prefix was used to indicate the cases in which staging was performed following preoperative therapy.

DISCUSSION

The immune-nutritional status of cancer patients was considered to be closely related to the patient outcomes [7]. Moreover, chemotherapy or surgery, which was widely used for cancer treatment, can alter the host status. In the current study, a cohort of advanced GC patients who received neoadjuvant chemotherapy and sequential curative gastrectomy was investigated to provide evidence on the prognostic values of perioperative CONUT score. The previous study enrolled stage IV GC patients undergoing non-curative surgery revealed that the CONUT score showed no prognostic significance in such patients [28]. Indeed, there is a lack of of sufficient therapy strategies for stage IV cancer patients and the prognosis was rather poor. Thus, we excluded stage IV and non-curative patients. Our results showed that a high pretreatment CONUT score (≥4) was related to older age and higher ypT stages. Neither postoperative complications nor the degree of severe complications (Clavien-Dindo ≥III) had a significant correlation with the CONUT score. Yoshida et al. [8] reported that the patients with moderate or severe malnutrition based on the CONUT score had a significant high incidence of any postoperative complications and severe complications in esophageal cancer with esophagectomy; however, only 25% patients (88/352) received preoperative treatment and no subgroup analysis was conducted referring to the postoperative complications in neoadjuvant patients. It is well known that patients with complete response after neoadjuvant chemotherapy have better prognosis. Our study also showed that the patients with a low pretreatment CONUT score had a higher pCR rate compared with CONUT-high score
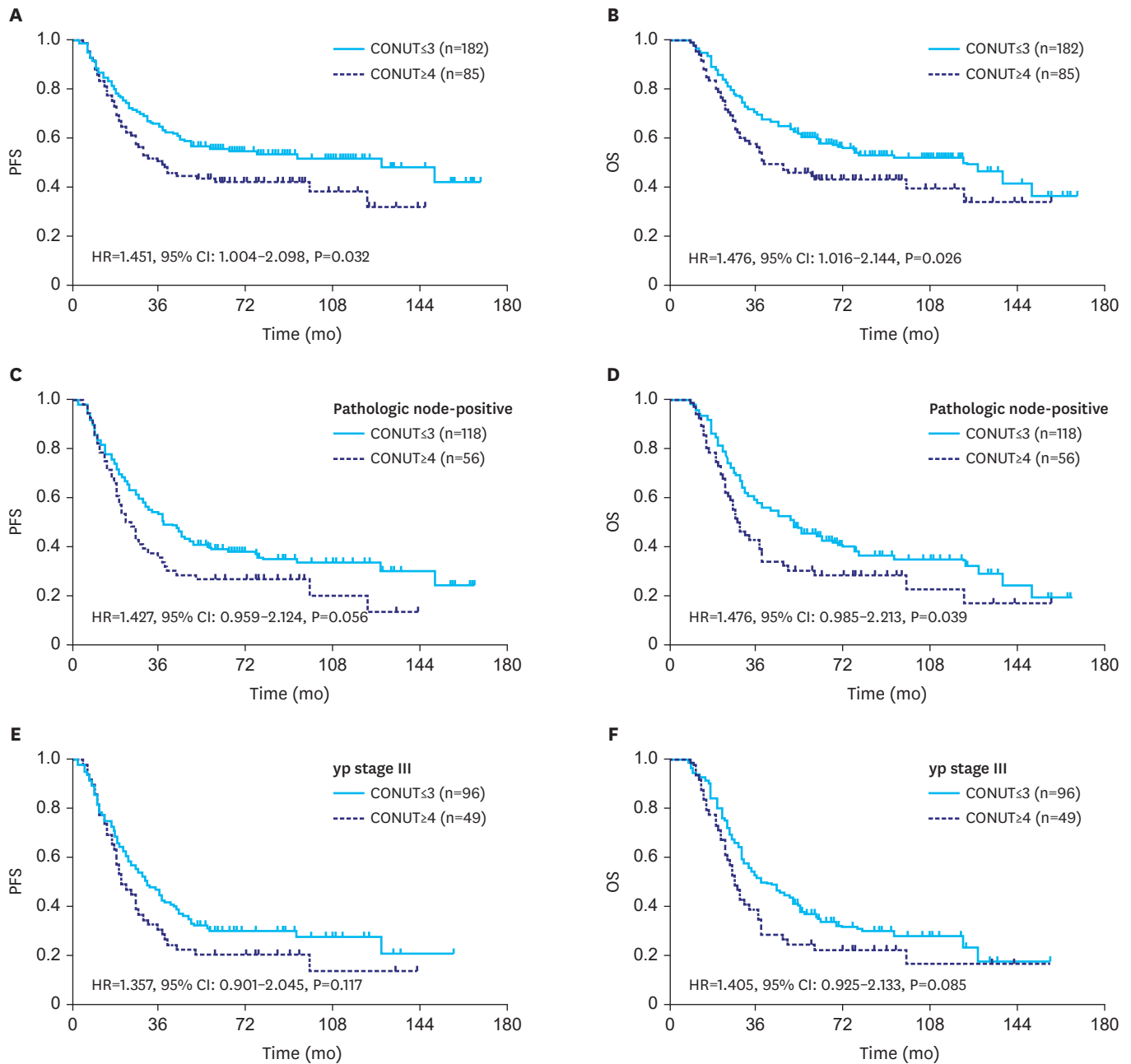
Fig. 2. The survival curve according to the pretreatment CONUT score using the Kaplan-Meier method. (A, B) PFS and OS according to the pretreatment CONUT score. (C, D) PFS and OS of the pathologic node-positive group according to the pretreatment CONUT score. (E, F) PFS and OS of the yp stage III patients according to the pretreatment CONUT score. The yp prefix was used to indicate the cases in which staging was performed following preoperative therapy. CONUT = controlling nutritional status; PFS = progression-free survival; OS = overall survival.

patients, although the difference was not significant (6.6% vs. 1.2%, P=0.107); further studies including a large sample size was needed to verify this point. A multivariate model revealed that the pretreatment CONUT score was an independent predictor both for PFS and OS. A subgroup analysis showed that a strong association was observed in pathologic node-positive patients with OS, but not for those patients with a later yp TNM stage. However, the preoperative and postoperative CONUT scores showed no prognostic significance, perhaps due to the influence of nutritional support during the perioperative period, bone marrow suppression caused

by chemotherapy, and the stress of operation; all of these factors might affect the values of preoperative and postoperative CONUT, and thus, may bias our results. Taken together, the pretreatment CONUT score was a superior marker for risk stratification in GC patients, who need potential neoadjuvant chemotherapy and sequential curative gastrectomy.

The CONUT score, an immune-nutritional index, is derived from three nutritional parameters, namely the albumin level, total lymphocyte count, and total cholesterol level. These three factors were used as the indicators of protein reserves, impaired immune defense, and caloric consumption, respectively [17]. As albumin provides more weight as a malnutrition indicator, it has twice the significance when compared to the other two indices. Hypoalbuminemia was presumed to be related to poor prognoses and surgical complications in several cancers [29,30], and might be caused by the release of inflammatory cytokines, such as tumor necrosis factor-alpha or interleukin-6, as well as liver dysfunction [18]. The lymphocyte count is a determinant of cell-mediated and humoral immunity, it is thought to initiate a cytotoxic immune response through T cells, which can inhibit cancer cell proliferation, invasion, and migration [31,32]. A low peripheral total lymphocyte count has been proven to be associated with poor prognosis in kinds of malignancies [33,34], perhaps due to the insufficient host immune response caused by lymphocytopenia. As we know, cholesterol is vital for cell membrane composition, which participates in several biological signaling pathways, an increased cholesterol uptake by tumor cells might result in hypocholesteremia, which affects the ability to deliver transmembrane signals [15]. Several studies have shown that a lower serum concentration of cholesterol was related to increasing morbidity and mortality in cancer patients [35,36]. Thus, the CONUT score, which combined these three parameters, is an excellent indicator of both the nutritional and immunological status.

However, rare studies have evaluated the predictive value of perioperative CONUT score in neoadjuvant treated cancer patients [8,21-23]. As far as we know, this is the first and largest study to assess the association between the pretreatment CONUT score and short-term outcomes as well as long-term survival in advanced GC patients treated with neoadjuvant chemotherapy and sequential curative gastrectomy. Patients with a high pretreatment CONUT score may experience malnutrition caused by cancer and need more intensive therapeutic modalities.

Indeed, several limitations were present in the current study, including the enrollment of the patients just from one single institution and its retrospective design. Additionally, the ROC curve for the pretreatment CONUT score cut-off value was associated with a poor sensitivity. Thus, large scale prospective validation studies are needed in the future.

In conclusion, the pretreatment CONUT score might be an excellent prognostic predictor in advanced GC treated with neoadjuvant chemotherapy and curative gastrectomy, especially in pathologic node-positive patients. Moreover, a lower pretreatment CONUT score might indicate a better chemotherapy response. A suitable nutritional intervention approach should be taken throughout the perioperative treatment period for preventing the onset of malnutrition.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
   PUBMED | **CROSSREF**

https://doi.org/10.5230/jgc.2021.21.e14

2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-132.
   PUBMED | CROSSREF

3. Isobe Y, Nashimoto A, Akazawa K, Oda I, Hayashi K, Miyashiro I, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer 2011;14:301-316.
   PUBMED | CROSSREF

4. Strong VE, Wu AW, Selby LV, Gonen M, Hsu M, Song KY, et al. Differences in gastric cancer survival between the U.S. and China. J Surg Oncol 2015;112:31-37.
   PUBMED | CROSSREF

5. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
   PUBMED | CROSSREF

6. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-1957.
   PUBMED | CROSSREF

7. Bistrian BR, Blackburn GL, Vitale J, Cochran D, Naylor J. Prevalence of malnutrition in general medical patients. JAMA 1976;235:1567-1570.
   PUBMED | CROSSREF

8. Yoshida N, Baba Y, Shigaki H, Harada K, Iwatsuki M, Kurashige J, et al. Preoperative nutritional assessment by controlling nutritional status (CONUT) is useful to estimate postoperative morbidity after esophagectomy for esophageal cancer. World J Surg 2016;40:1910-1917.
   PUBMED | CROSSREF

9. Li L, Liu C, Yang J, Wu H, Wen T, Wang W, et al. Early postoperative controlling nutritional status (CONUT) score is associated with complication III-V after hepatectomy in hepatocellular carcinoma: A retrospective cohort study of 1,334 patients. Sci Rep 2018;8:13406.
   PUBMED | CROSSREF

10. Ryo S, Kanda M, Ito S, Mochizuki Y, Teramoto H, Ishigure K, et al. The controlling nutritional status score serves as a predictor of short- and long-term outcomes for patients with stage 2 or 3 gastric cancer: analysis of a multi-institutional data set. Ann Surg Oncol 2019;26:456-464.
    PUBMED | CROSSREF

11. Harimoto N, Yoshizumi T, Sakata K, Nagatsu A, Motomura T, Itoh S, et al. Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma. World J Surg 2017;41:2805-2812.
    PUBMED | CROSSREF

12. Harimoto N, Yoshizumi T, Inokuchi S, Itoh S, Adachi E, Ikeda Y, et al. Prognostic significance of preoperative controlling nutritional status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma: a multi-institutional study. Ann Surg Oncol 2018;25:3316-3323.
    PUBMED | CROSSREF

13. Miyata T, Yamashita YI, Higashi T, Taki K, Izumi D, Kosumi K, et al. The Prognostic impact of controlling nutritional status (CONUT) in intrahepatic cholangiocarcinoma following curative hepatectomy: a retrospective single institution study. World J Surg 2018;42:1085-1091.
    PUBMED | CROSSREF

14. Kang HW, Seo SP, Kim WT, Yun SJ, Lee SC, Kim WJ, et al. Prognostic impact of nutritional status assessed by the controlling nutritional status (CONUT) score in patients with surgically treated renal cell carcinoma. Nutr Cancer 2018;70:886-894.
    PUBMED | CROSSREF

15. Iseki Y, Shibutani M, Maeda K, Nagahara H, Ohtani H, Sugano K, et al. Impact of the preoperative controlling nutritional status (CONUT) score on the survival after curative surgery for colorectal cancer. PLoS One 2015;10:e0132488.
    PUBMED | CROSSREF

16. Sun J, Wang D, Mei Y, Jin H, Zhu K, Liu X, et al. Value of the prognostic nutritional index in advanced gastric cancer treated with preoperative chemotherapy. J Surg Res 2017;209:37-44.
    PUBMED | CROSSREF

17. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 2005;20:38-45.
    PUBMED

18. Kuroda D, Sawayama H, Kurashige J, Iwatsuki M, Eto T, Tokunaga R, et al. Controlling nutritional status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. Gastric Cancer 2018;21:204-212.
PUBMED | CROSSREF

19. Zheng ZF, Lu J, Xie JW, Wang JB, Lin JX, Chen QY, et al. Preoperative skeletal muscle index vs the controlling nutritional status score: which is a better objective predictor of long-term survival for gastric cancer patients after radical gastrectomy? Cancer Med 2018;7:3537-3547.
PUBMED | CROSSREF

20. Liu X, Zhang D, Lin E, Chen Y, Li W, Chen Y, et al. Preoperative controlling nutritional status (CONUT) score as a predictor of long-term outcome after curative resection followed by adjuvant chemotherapy in stage II-III gastric Cancer. BMC Cancer 2018;18:699.
PUBMED | CROSSREF

21. Tokunaga R, Sakamoto Y, Nakagawa S, Ohuchi M, Izumi D, Kosumi K, et al. CONUT: a novel independent predictive score for colorectal cancer patients undergoing potentially curative resection. Int J Colorectal Dis 2017;32:99-106.
PUBMED | CROSSREF

22. Toyokawa T, Kubo N, Tamura T, Sakurai K, Amano R, Tanaka H, et al. The pretreatment controlling nutritional status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study. BMC Cancer 2016;16:722.
PUBMED | CROSSREF

23. Hikage M, Taniyama Y, Sakurai T, Sato C, Takaya K, Okamoto H, et al. The influence of the perioperative nutritional status on the survival outcomes for esophageal cancer patients with neoadjuvant chemotherapy. Ann Surg Oncol 2019;26:4744-4753.
PUBMED | CROSSREF

24. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077-3079.
PUBMED | CROSSREF

25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
PUBMED | CROSSREF

26. Hu Y, Huang C, Sun Y, Su X, Cao H, Hu J, et al. Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial. J Clin Oncol 2016;34:1350-1357.
PUBMED | CROSSREF

27. Tarantino I, Warschkow R, Worni M, Merati-Kashani K, Köberle D, Schmied BM, et al. Elevated preoperative CEA is associated with worse survival in stage I-III rectal cancer patients. Br J Cancer 2012;107:266-274.
PUBMED | CROSSREF

28. Mimatsu K, Fukino N, Ogasawara Y, Saino Y, Oida T. Utility of inflammatory marker- and nutritional status-based prognostic factors for predicting the prognosis of stage iv gastric cancer patients undergoing non-curative surgery. Anticancer Res 2017;37:4215-4222.
PUBMED

29. Oñate-Ocaña LF, Aiello-Crocifoglio V, Gallardo-Rincón D, Herrera-Goepfert R, Brom-Valladares R, Carrillo JF, et al. Serum albumin as a significant prognostic factor for patients with gastric carcinoma. Ann Surg Oncol 2007;14:381-389.
PUBMED | CROSSREF

30. Chai FY, Jiffre D. Preoperative hypoalbuminemia is an independent risk factor for the development of surgical site infection following gastrointestinal surgery. Ann Surg 2011;254:665.
PUBMED | CROSSREF

31. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-867.
PUBMED | CROSSREF

32. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-444.
PUBMED | CROSSREF

33. Schueneman AJ, Sugar EA, Uram J, Bigelow E, Herman JM, Edil BH, et al. Low total lymphocyte count is associated with poor survival in patients with resected pancreatic adenocarcinoma receiving a GM-CSF secreting pancreatic tumor vaccine. Ann Surg Oncol 2013;20 Suppl 3:S725-S730.
PUBMED | CROSSREF

34. Feng F, Zheng G, Wang Q, Liu S, Liu Z, Xu G, et al. Low lymphocyte count and high monocyte count predicts poor prognosis of gastric cancer. BMC Gastroenterol 2018;18:148.
PUBMED | CROSSREF

jgc | Journal of Gastric Cancer

35. Kitahara CM, Berrington de González A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011;29:1592-1598.
   PUBMED | **CROSSREF**

36. Jeong SM, Choi S, Kim K, Kim SM, Lee G, Son JS, et al. Association of change in total cholesterol level with mortality: a population-based study. PLoS One 2018;13:e0196030.
   PUBMED | **CROSSREF**