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

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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 χ² 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).
Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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/m², d1; capecitabine: 2000 mg/m²/d, d1-d14), oxaliplatin plus 5-Fu plus leucovorin (FOLFOX, oxaliplatin: 130 mg/m², d1; 5-Fu: 2400 mg/m², continuous 46 h; leucovorin: 400 mg/m², d1), oxaliplatin plus S-1 (SOX, oxaliplatin: 130 mg/m², d1; S-1: 80 mg/m²/d, d1-d14). Four patients received other neoadjuvant chemotherapy regimens, such as epirubicin plus oxaliplatin plus 5-Fu (EOF), epirubicin plus oxaliplatin plus capecitabine, 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 $\chi^2$ 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).

| 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).

| Parameters                  | Values | CONUT score | ≤3 (n=182) | ≥4 (n=85) | P-value |
|-----------------------------|--------|-------------|------------|-----------|---------|
| Gender                      | Female | 71 (26.1)   | 49         | 19        | 0.425   |
|                             | Male   | 201 (73.9)  | 133        | 66        |         |
| Age (yr)                    | <65    | 171 (62.9)  | 124        | 44        | 0.010   |
|                             | ≥65    | 101 (37.1)  | 58         | 41        |         |
| ECOG                        | 0      | 112 (41.2)  | 76         | 34        | 0.786   |
|                             | 1, 2   | 160 (58.8)  | 106        | 51        |         |
| BMI (kg/m²)                 | <18.5  | 32 (11.8)   | 18         | 13        | 0.204   |
|                             | ≥18.5  | 234 (86.0)  | 161        | 71        |         |
| Primary tumor site          | Upper  | 45 (16.5)   | 31         | 13        | 0.706   |
|                             | Middle | 54 (19.9)   | 39         | 15        |         |
|                             | Lower  | 150 (55.1)  | 99         | 48        |         |
|                             | More than 2 sites | 23 (8.5) | 13         | 9         |         |
| Tumor size (cm)             | <4     | 128 (47.1)  | 85         | 39        | 0.912   |
|                             | ≥4     | 135 (49.6)  | 91         | 43        |         |
| Gastrectomy                 | Total  | 105 (38.6)  | 70         | 33        | 0.737   |
|                             | Subtotal | 132 (48.5) | 90         | 39        |         |
|                             | Combined resection | 35 (12.9) | 22         | 13        |         |
| Differentiation             | Well   | 39 (14.3)   | 23         | 15        | 0.477   |
|                             | Poorly | 207 (76.1)  | 135        | 68        |         |
| yp T stage                  | T0     | 21 (7.7)    | 19         | 2         | 0.025   |
|                             | 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                  | NO     | 94 (34.6)   | 64         | 29        | 0.867   |
|                             | N1-3   | 178 (65.4)  | 118        | 56        |         |

(continued to the next page)
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).

### 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* | P-value |
|-------------------------------------------|---------------------------------------------|---------------|---------|
| ypT stage**                              |                              | ≤3 (n=182) | ≥4 (n=85) |
| T0N0M0                                    | 13 (4.8)                                  | 12            | 1       |
| 0                                         | 1 (0.4)                                    | 0             | 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.

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.
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
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).

**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                                            | 4.700               | 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) | 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                                              | 1.331               | 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.

**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, 1.085–2.213; 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).
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 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.
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.

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