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ORIGINAL RESEARCH

Controlling Nutritional Status (CONUT) Score Is a Prognostic Factor for Patients with Gastric Cancer Treated by Perioperative FLOT

Baran Akagunduz[1] · **Metin Demir**[2] · **Muhammet Mustafa Atcı**[3]

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Abstract

Purpose The aim of this study was to show that the Controlling Nutritional Status (CONUT) score has predictive value in gastric cancer (GC) patients treated with perioperative fluorouracil, leucovorin, oxaliplatin, or docetaxel (FLOT).

Methods A total of 161 GC patients treated with perioperative FLOT in our center were included in the study. The ideal cutoff values for the CONUT score were obtained using the receiver operating characteristic (ROC) curve analysis, and the patients were divided into low (≤3) and high (> 3) CONUT groups. The associations of CONUT with clinicopathological factors and survival were evaluated retrospectively.

Results The median follow-up time was 11.2 months (2.3–32.3 months). The median overall survival (OS) for the entire population was 14.7 months (95% CI 13.5–15.9 months). Median OS was not reached in the low-CONUT group, but it was 14.2 months (95% CI 12.6–15.9) in the high-CONUT group and the difference was statistically significant ($p = 0.002$). The univariate Cox proportional hazards model revealed that OS was significantly associated with Eastern Cooperative Oncology Group (ECOG) status ($p < 0.001$), T4b stage (p 0.03), modified Glasgow Prognostic Scores (mGPS) (p 0.005), prognostic index (PI) (p 0.011), prognostic nutritional index (PNI) ($p < 0.001$), CONUT score (p 0.003), and mucinous histology (p 0.004). In multivariate analysis, ECOG performance status (p 0.029), PNI (p 0.001), CONUT score (p 0.040), and mucinous histology (p 0.001) were still identified as independent prognostic factors for OS.

Conclusions Our study demonstrated the prognostic significance of the CONUT score in GC patients treated with perioperative FLOT.

Keywords CONUT · Prognostic factor · Gastric cancer · Perioperative FLOT

Introduction

Gastric cancer (GC) is the fifth most frequent cancer worldwide and the third leading cause of cancer-related mortality [1]. Gastrectomy and lymphadenectomy with perioperative therapies are the mainstay of the treatment. Perioperative treatment was advised for patients with borderline resectable or locally advanced GC to reduce tumor size, eliminate micrometastases, and increase R0 resection rates [2]. The use of perioperative chemotherapy in the treatment of gastric cancer established a need for more precise long-term survival predictions for these patients. Many attempts have been made to identify the prognostic markers for GC using other clinical, physiological, or pathological parameters. The neutrophil-lymphocyte ratio (NLR), modified Glasgow Prognostic Scores (mGPS), advanced lung cancer inflammation index [ALI], prognostic index (PI), and prognostic nutritional index (PNI) were documented to have some values in prognosis prediction [3–5]. Additionally, recent studies reported that the rate of metastatic lymph node may be prognostic in patients with GC receiving neoadjuvant/perioperative systemic treatment [6–8]. However, there is no consensus about their

✉ Baran Akagunduz
drbaran04@hotmail.com

Metin Demir
dr_metindemir@hotmail.com

Muhammet Mustafa Atcı
dr_mmatci@hotmail.com

[1] Department of Medical Oncology, Erzincan Binali Yildirim University Medical School, 2400 Erzincan, Turkey

[2] Department of Medical Oncology, Erzurum State Hospital, 25000 Erzurum, Turkey

[3] Department of Medical Oncology, Cemil Taşçıoğlu State Hospital, Prof. Dr, 34000 Istanbul, Turkey

usefulness for GC patients. The Controlling Nutritional Status (CONUT) score is a new immuno-nutritional biomarker that is generated using total lymphocyte count, serum albumin concentration, and total serum cholesterol concentration [9]. In several types of cancer, the CONUT score has a substantial association with survival and prognosis [10]. The CONUT score was reported to be a predictive factor for overall survival (OS) after curative resection in GC patients [11–13].

Recent studies demonstrated that the FLOT regimen consists of fluorouracil plus leucovorin, oxaliplatin, and docetaxel which is a promising combination chemotherapy for resectable GC patients in perioperative settings [14]. Although FLOT treatment is effective in GC patients, data about pre-treatment biomarkers to predict prognosis is still missing. In this study, we aimed to reveal the prognostic importance of the pretreatment CONUT score in GC patients receiving perioperative FLOT treatment.

Materials and Methods

Patients and Data Collection

This study included GC patients who were treated with perioperative (preoperative and postoperative 4 cycles) FLOT regimen consisting of 5-fluorouracil (2600 mg/m^2 as a 24-h infusion), leucovorin (200 mg/m^2), oxaliplatin (85 mg/m^2), and docetaxel (50 mg/m^2), and were followed up in Erzincan Binali Yıldırım University Mengucek Gazi Research Hospital from January 2017 and January 2021. Data of 161 GC patients were reviewed retrospectively. After receiving neoadjuvant FLOT therapy, imaging examination was performed by computed tomography or magnetic resonance imaging. Response Evaluation and Criteria in Solid Tumors 1.1 (RECIST) was used to assess treatment response [15]. All patients underwent curative gastrectomy. Exclusion criteria were missing data for prognostic index calculations, additional comorbidities that would affect the laboratory parameters, presence of metastatic disease, progression after preoperative FLOT, and previous history of other malignancies. Age, height, weight, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), histology, tumor site, tumor type, clinical T stage, and clinical N stage were all documented from patient charts as clinical and pathological data. Medical data were also used to acquire pre-FLOT laboratory findings such as absolute neutrophil count, absolute lymphocyte count, serum albumin level, and serum total cholesterol levels.

PNI was calculated using the following formula: 10 × albumin concentration (g/dl) + 0.005 × total lymphocyte count (/mm^3). mGPS was calculated as follows: score 0, CRP ≤10 mg/L; score 1, CRP > 10 mg/L and albumin ≥3.5 g/dL; and score 2, CRP > 1.0 mg/dL and albumin < 3.5 g/dL. NLR was computed by dividing the neutrophil count by the lymphocyte count. PI was scored as follows: score 0, CRP ≤ 10 mg/L and WBC ≤ 10 × 10^9; score 1, CRP ≤ 10 mg/L and WBC > 10 × 10^9; score 1, CRP > 10 mg/L and WBC ≤ 10 × 10^9 and score 2; CRP > 10 mg/L and WBC > 10 × 10^9. The value of ALI was computed as BMI × serum albumin/NLR. The CONUT score was calculated by measuring serum albumin, total cholesterol levels, and total lymphocyte count (Table 1).

Ethical Approval

The institutional and national research committees' ethical standards, as well as the 1964 Declaration of Helsinki and its later revisions or comparable ethical standards, were followed in all studies involving human participants.

Table 1 Definition of the CONUT score

Parameter	None	Light	Moderate	Severe
Serum albumin (d/dl) score	≥3.5 0	3.0–3.49 2	2.5–2.9 4	<2.5 6
Total lymphocyte (count/mm^3) score	≥1600 0	1200–1599 1	800–1199 2	<800 3
Total cholesterol (mg/dl) score	≥180 0	140–180 1	100–139 2	<100 3
CONUT score (total)	0–1	2–4	5–8	9–12
Assessment	Low	Intermediate	High	

CONUT Controlling Nutritional Status

The study protocol was approved by the local ethics committee.

Statistical Analyses

OS was defined as the period from the time of diagnosis until death and the last follow-up period for living patients. Descriptive statistics were conducted using percentages for clinical and demographic features. To compare these variables in various groups, the chi-square test or Fisher's exact test was utilized. The power of the CONUT score and other prognostic indices in predicting overall survival was analyzed using ROC curve analysis. A significant cutoff point was observed, and the sensitivity, specificity, and positive and negative predictive values were detected. Kaplan-Meier survival estimates were calculated. The effects of low and high CONUT scores on overall survival were investigated using the log rank test. The possible factors identified with univariate analyses, which have a p value of <0.20, were further entered into Cox regression analysis, with enter selection, to determine independent predictors of survival. Strongly correlated variables were excluded, and only those with clinical significance were included. A p value of <0.05 was used to infer statistical significance. Statistical analyses were performed using the SPSS Software Version 26.

Results

Optimal Cutoff Values of CONUT Score and Other Indices

The ROC curve showed the most appropriate cutoff value to be 3.5 (AUC = 0.805; 95% CI 0.74–0.87, $p < 0.001$). ROC analysis also provided 90% sensitivity and 54% specificity for this cutoff value. Therefore, we established 3.5 as the cutoff value and classified the patients into two different groups as low-Conut (≤3) and high-Conut (>3) (Fig. 1). The AUC value of CONUT was greater (0.81; p 0.001) than that of PNI, PI, NLR, ALI, and mGPS (Table 2).

Relationships Between CONUT Score and Clinicopathological Variables

The median age of 161 patients was 58.7 (32–80). There was a male predominance in the study population (68.3%). The CONUT score ranged from 0 to 12, with the majority of patients scoring 0–6 (n = 122, 75.8%) (Fig. 2). Based on the CONUT score, our cohort was divided into two groups: 56 patients (34.7%) were classified as low (≤3), and 105 patients (65.3%) were classified as high (>3). A high CONUT score was significantly related with signet ring cell and mucinous histology, poor differentiated histology, T4 tumor, and exitus status. In terms of other clinical and pathological indicators, there was no significant difference between the high and low CONUT score groups (Table 3).

CONUT Score and Survival Outcomes

The median follow-up time was 11.2 months (2.3–32.3 months). Median OS for the entire population was 14.7 months (95% CI 13.5–15.9 months) (Fig. 3). Median OS was not reached in the low-Conut (≤3) group, but it was 14.2 months (95% CI 12.6–15.9) in the high-Conut (3<) group; the difference was statistically significant ($p = 0.002$) (Fig. 4).

The univariate Cox proportional hazard model demonstrated that ECOG status (HR 2.58; 95% CI 1.54–4.29; $p < 0.001$), T4b stage (HR 6.2; 95% CI 1.26–30.5; p 0.03), mGPS (HR 1.46; 95% CI 1.12–1.91; p 0.005), PI (HR 1.62; 95% CI 1.12–2.34; p 0.011), PNI (HR 0.95; 95% CI 0.93–0.96; $p < 0.001$), CONUT score (HR 3.28; 95% CI 1.50–7.16; p 0.003), and mucinous histology (HR 6.1; 95% CI 1.8–20.6; p 0.004) were significantly associated with OS (Table 4). In multivariate analysis, ECOG performance status (HR 2.01; 95% CI 1.06–3.73; p 0.029), PNI (HR 0.93; 95% CI 0.91–0.96; p 0.001), CONUT score (HR 2.40; 95% CI 1.03–5.544; p 0.040), and mucinous histology (HR 9.44; 95% CI 2.42–36.9; p 0.001) were still identified as independent prognostic factors for OS.

Discussion

GC is one of the most aggressive malignancies with the high risk of mortality. As a result of recent studies, FLOT therapy is becoming the primary treatment in the perioperative setting [16]. Many factors, however, influence the short- and long-term prognoses of GC patients. The prognostic markers for predicting GC perioperative and long-term survival include stage, histological differentiation, and histological form [17]. However, indicators that can predict prognosis in the pretreatment period and be used in clinical practice are needed. Yılmaz et al. demonstrated that the ratio of

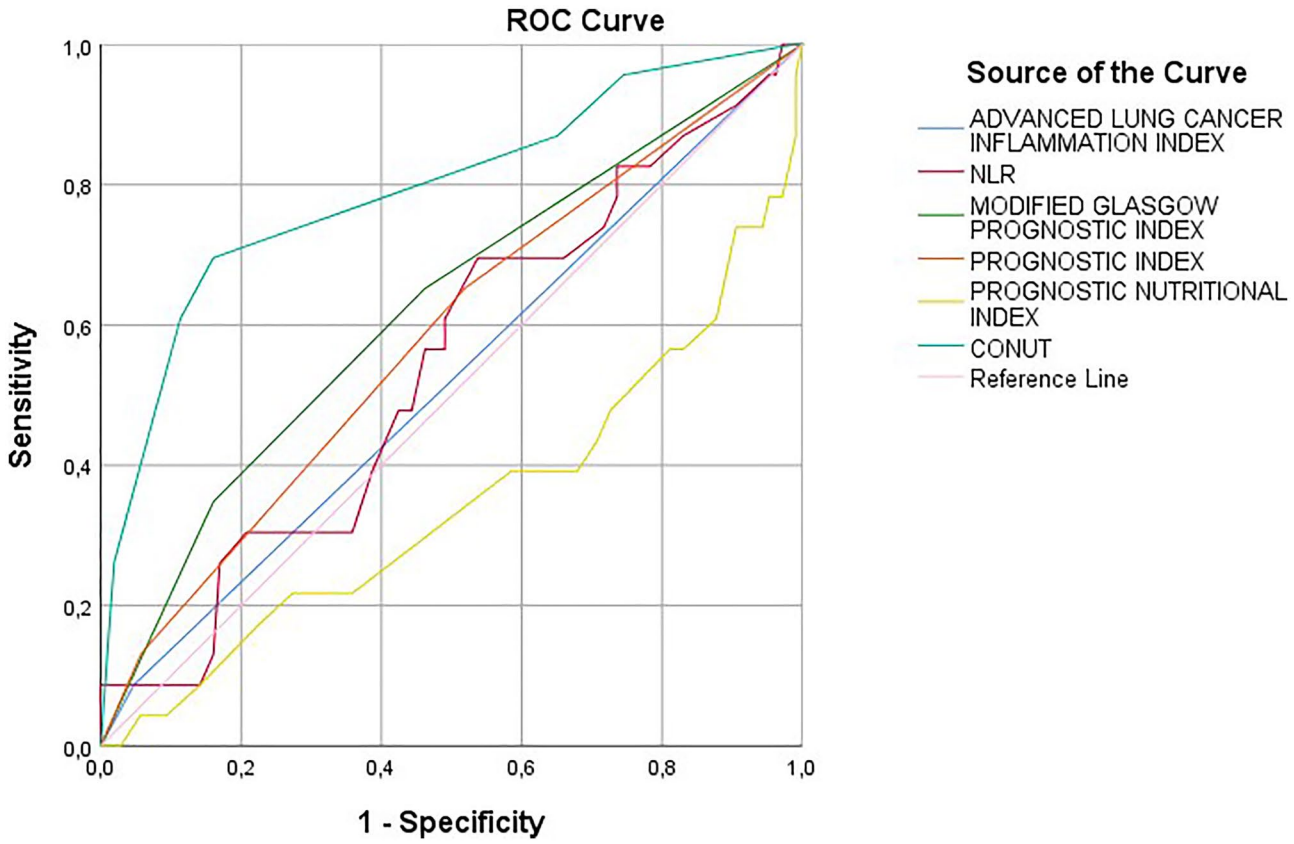

Fig. 1 ROC curve for the CONUT score and other prognostic indices

hemoglobin to red cell distribution width predicts survival in GC patients treated with neoadjuvant FLOT [18].

The total serum albumin concentration, cholesterol concentration, and total lymphocyte count in peripheral blood are used to calculate the CONUT score, which indicates protein storage, calorie deficiency, and reduced immune responses, respectively. Cholesterol is a component of cellular membranes that plays an important role in immunity. Cholesterol has a number of biological activities, including membrane fluidity and membrane protein activity, which may be linked to cancer initiation and progression, as well as immune response. As a result, immunocompetent cells gain the ability to mount an immune response against tumor spread [19]. Hypocholesterolemia may thus play a role in a poor cancer prognosis. Lymphocytes are critical in the host's anticancer defense by causing apoptosis and suppressing cancer cell proliferation, invasion, and migration. [20]. As a result, lymphocytopenia can contribute to tumor growth. Hypoalbuminemia can be caused by malnutrition or hypercatabolism, but it can also be caused by systemic inflammation, which can lead to hypercytokinemia and a weakened immune response against cancer cells [21]. As a result, the CONUT score measures not only nutritional status but also systemic inflammation and immunological

Table 2 Comparison of the AUCs for the prognostic indices

Index	AUC	95% CI	*p* value
CONUT	**0.81**	0.74–0.87	**<0.001**
ALI	0.51	0.42–0.60	0.771
NLR	0.53	0.43–0.62	0.590
mGPS	**0.62**	0.53–0.71	**0.010**
PI	0.55	0.46–0.64	0.293
PNI	**0.36**	0.26–0.45	**0.002**

ALI advanced lung cancer inflammation index, *CONUT* Controlling Nutritional Status, *mGPS* modified Glasgow Prognostic Scores, *NLR* neutrophil-lymphocyte ratio, *PI* prognostic index, *PNI* prognostic nutritional index

*$p<0.005$

response [22]. The CONUT score was found to be prognostic in GC patients treated with perioperative FLOT for OS in this study. To our knowledge, this is the first study to evaluate the prognostic value of pre-FLOT CONUT score in GC patients.

The CONUT score has been shown in a recent study to be a valuable biomarker for estimating nutritional status and predicting OS in patients with GC [23]. In this study, propensity score matching was used to examine the prognostic significance of the CONUT score with low (≤ 2) and high (≥ 3) scores in patients who had gastrectomy. Jeon et al. demonstrated that in the stage II patients with GC, light CONUT score and moderate CONUT score were significantly associated with poor prognosis (HR, 2.230; 95% CI, 1.067–4.664; $p = 0.033$, HR, 5.077; 95% CI, 1.647–15.650; $p = 0.005$ respectively) [24]. Kuroda et al. showed that CONUT was useful for predicting long-term outcome in pathological stage I–II, but not pathological stage III GC patients [12]. A recent meta-analysis demonstrated that in patients with GC, the CONUT score is an independent predictive indicator of survival and surgical complications, and it is linked to clinicopathological characteristics. Additionally, this meta-analysis showed that more advanced tumor characteristics including advanced T and N stage, advanced TNM stages, and positive microvascular invasion were significantly associated with a high CONUT score [25]. Our findings indicated that a high CONUT score was linked to a later T stage, a higher grade, and mucinous histology. In the present study, we also found that PNI was an independent prognostic factor for OS. A previous study found that the preoperative PNI value, which serves as a relevant nutritional indicator, might predict OS in patients with GC independently [26]. Park et al. demonstrated that preoperative low PNI score was related to poor prognosis in patients with stage II and stage III GC [27].

We found that mucinous pathology was an independent prognostic factor in our study population. Tseng et al. demonstrated that mucinous histology is diagnosed at a more advanced stage, resulting in a worse prognosis [28].

Despite the fact that our study was the first to show CONUT score as an independent predictive factor for OS in GC patients who had a perioperative FLOT regimen, it had some significant limitations. First of all, our study was retrospective and included patients at a single institution. High and low groups of CONUT are different in terms of some clinicopathological features, and this may affect the prognosis. Disease-free survival data and treatment used in progression were not assessed. Finally, with only 11.2 months of follow-up, it is possible that reliable conclusions about long-term survival cannot be drawn.

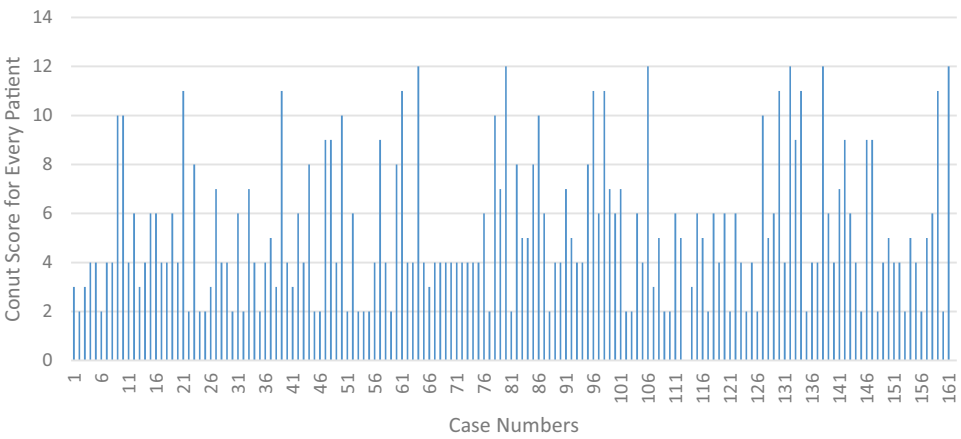

Fig. 2 The distribution of the CONUT score

Table 3 Patient and tumor characteristics according to low and high CONUT scores

	Low Conut (≤3)		High Conut (>3)		
	N	%	N	%	p
Gender					
Male	36	64.3	74	70.5	
Female	20	35.7	31	29.5	*0.421*
ECOG					
0–1	52	92.9	91	86.6	
≥2	4	7.1	14	13.4	*0.332*
Histology					
Adenocarcinoma	49	87.5	72	68.6	
Signet ring cell	6	10.7	30	28.6	***0.028***
Mucinous	1	1.8	3	2.9	
Grade					
1	2	3.6	7	6.7	
2	34	60.7	44	41.9	***0.040***
3	20	35.7	54	51.4	
Tumor location					
Cardia	22	39.3	29	27.7	
Corpus	9	16.1	21	20	
Antrum	15	26.8	35	33.3	
Esophago-gastric					
Junction	9	16.1	7	12.4	
Diffuse	1	1.8	13	6.7	*0.382*
Lauren classification					
Diffuse	8	14.3	13	12.4	
Intestinal	48	85.7	92	87.6	*0.731*
Clinic T stage					
T2	2	3.6	13	12.4	
T3	46	82.1	51	48.6	***0.010***
T4a	8	14.3	39	37.1	
T4b	0	0	2	1.9	
Clinic N stage					
N0	4	7.1	3	2.9	
N1	17	30.4	28	26.7	*0.529*
N2	13	23.2	33	31.4	
N3a	19	33.9	38	36.2	
N3b	3	5.4	3	2.9	
Response to neoadjuvant treatment					
Complete remission	12	21.4	15	14.3	
Partial response	34	60.7	55	52.4	*0.175*
Stable disease	8	14.3	24	22.9	
Progressive disease	2	3.6	11	10.5	
Status					
Exitus	7	12.5	64	61	
Alive	49	87.5	41	39	***<0.001***

*$p<0.005$

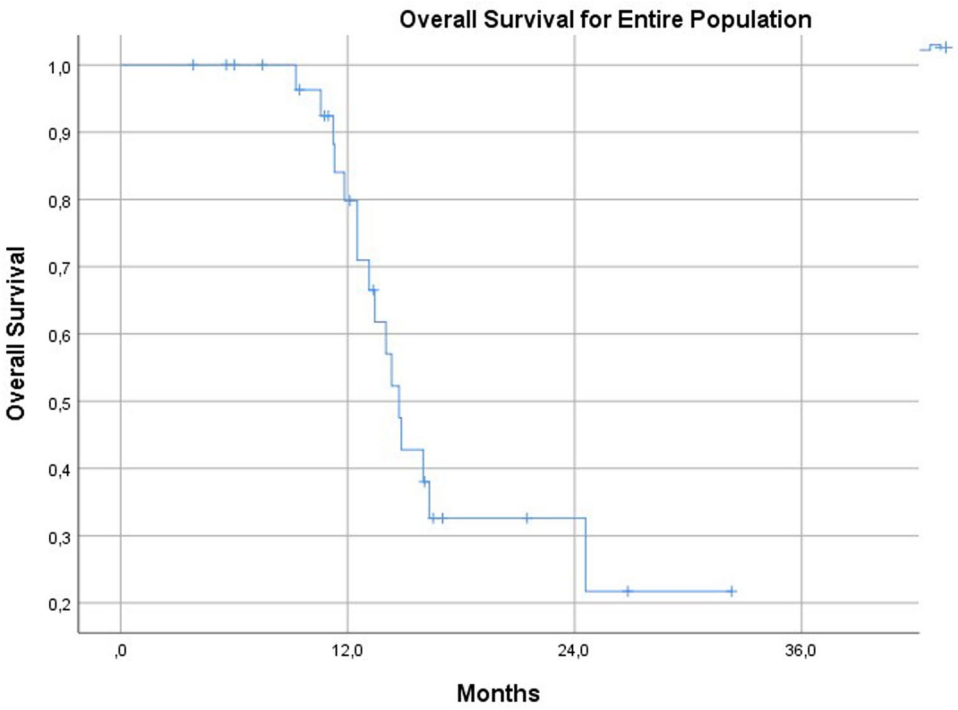

Fig. 3 Overall survival curve for the entire population

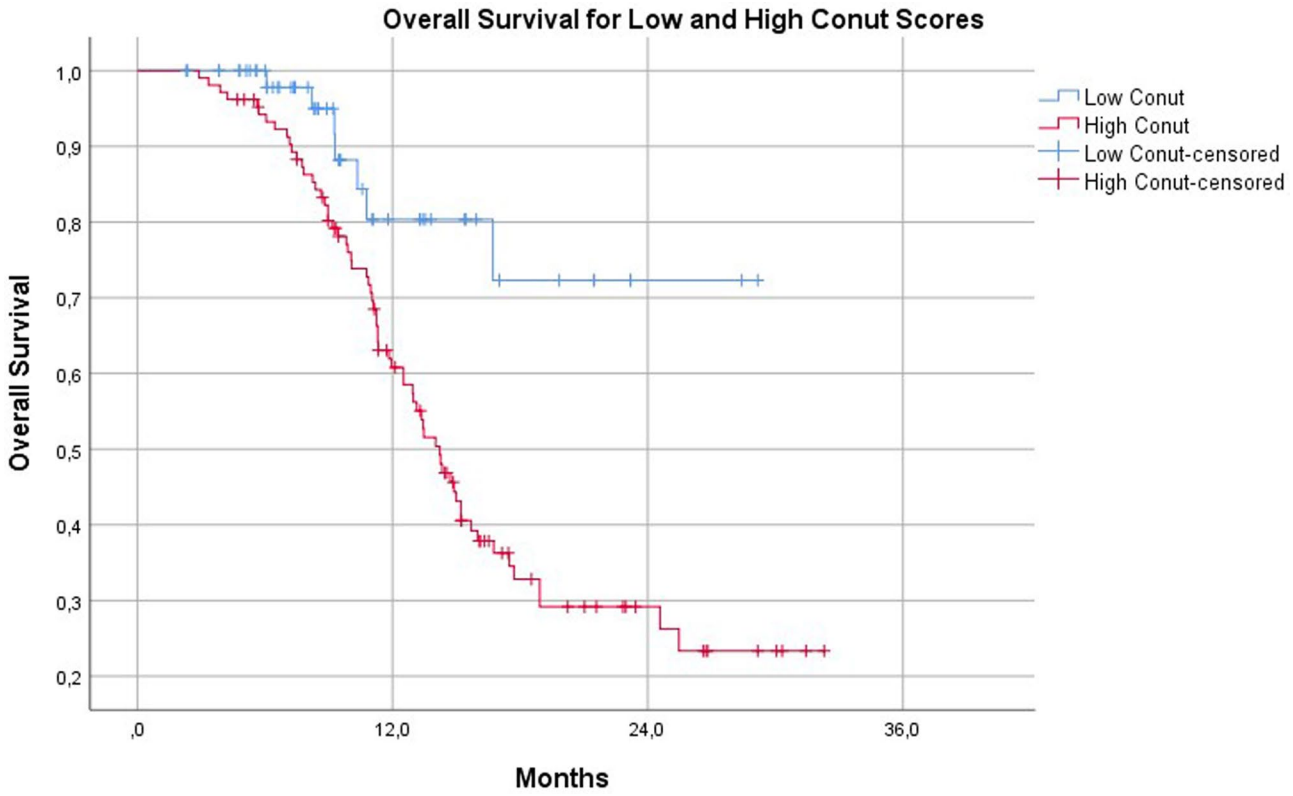

Fig. 4 Overall survival curve for low and high-Conut groups

Table 4 Univariate and multivariate analysis for OS

	Univariate				Multivariate			
	HR	95,0% CI for HR		*p*	HR	95,0% CI for HR		*p*
Age of diagnosis	1	0.99	1.03	*0.5*				
Weight	1.01	0.99	1.03	*0.43*				
BMI	1.01	0.95	1.08	*0.71*				
Gender	0.75	0.44	1.27	*0.28*				
ECOG								
0–1								
≥2	2.58	1.54	4.29	***<0.001***	2.010	1.06	3.73	**0.029**
Clinic T stage								
T2								
T3	1.15	0.52	2.6	*0.731*	1.155	0.48	2.79	*0.754*
T4a	1.01	0.47	2.4	*0.988*	0.511	0.18	1.44	*0.200*
T4b	6.2	1.26	30.5	***0.030***	2.277	0.16	32.23	*0.546*
Clinic N stage								
N0								
N1	3.5	0.47	26.1	*0.221*	2.1	0.27	163	*0.482*
N2	3.2	0.43	23.5	*0.265*	1.71	0.21	13.74	*0.617*
N3a	3.2	0.43	23.7	*0.265*	1.09	0.13	9.24	*0.940*
N3b	6.2	0.64	60.0	*0.119*	4.27	0.25	74.18	*0.322*
ALI								
	1.27	0.63	2.56	*0.511*				
NLR	1.1	0.92	131	*0.327*				
mGPS	1.46	1.12	1.91	***0.005***	1.21	0.71	2.06	*0.498*
PI	1.62	1.12	2.34	***0.011***	0.94	0.48	1.86	*0.857*
PNI	0.95	0.93	0.96	***<0.001***	0.93	0.91	0.96	***<0.001***
CONUT	1.49	1.26	1.75	***<0.001***				
LDH	1.00	0.99	1.00	*0.950*				
Grade								
1								
2	1.35	0.4	4.45	*0.620*				
3	1.68	0.52	5.46	*0.397*				
CONUT (categorical)								
Low								
High	3.28	1.50	7.16	***.003***	2.40	1.03	.54	***0.040***
Tumor type								
Diffuse								
Intestinal	1.27	0.63	2.56	*0.514*				
Histology								
Adenocarcinoma								
Signet ring cell	1.54	0.93	2.53	0.090	1.64	0.92	2.9	*0.095*
Mucinous	6.1	1.8	20.6	**0.004**	9.44	2.42	36.9	***0.001***

ALI advanced lung cancer inflammation index, *BMI* body mass index, *CONUT* Controlling Nutritional Status, *LDH* lactate dehydrogenase, *mGPS* modified Glasgow Prognostic Scores, *NLR* neutrophil-lymphocyte ratio, *PI* prognostic index, *PNI* prognostic nutritional index

*$p<0.005$

Conclusions

GC is a common and highly lethal malignancy of the gastrointestinal tract. Systemic inflammation and nutritional status play an important role in the pathogenesis of GC such as many other cancers. Our study demonstrated the prognostic significance of the pretreatment CONUT score in GC patients treated with perioperative FLOT, for the first time. The CONUT score is a simple, useful, and low-cost marker that can be used in clinical practice.

Author Contribution Concept—BA, MD, MMA; design—BA, MD, MMA; supervision—BA, MD; resources—BA, MD, MMA; materials—BA, MD, MMA; data collection and/or processing—BA; analysis and/or interpretation—BA; literature search—BA, MMA; writing manuscript—BA; critical review—BA; other—BA.

Availability of Data and Materials None

Code Availability Non-available

Declarations

Ethics Approval This study was ethically approved.

Consent to Participate Retrospective study design.

Consent for Publication Retrospective study design.

Conflict of Interest The authors declare no competing interests.

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