Original Article

The prognostic value of controlling nutritional status score on esophageal squamous cell carcinoma patients with neoadjuvant therapy followed by esophagectomy—a retrospective research

Pinhao Fang[1#], Jianfeng Zhou[1#], Zhiwen Liang[1#], Yushang Yang[1], Siyuan Luan[1], Xin Xiao[1], Xiaokun Li[1], Qixin Shang[1], Hanlu Zhang[1], Xiaoxi Zeng[2], Yong Yuan[1]

[1]Department of Thoracic Surgery, Med+X Center for Informatics, West China Hospital, Sichuan University, Chengdu, China; [2]Biomedical Big Data Center of West China Hospital, Med+X Center for Informatics, Sichuan University, Chengdu, China

Contributions: (I) Conception and design: Y Yuan, P Fang, J Zhou, Z Liang; (II) Administrative support: Y Yuan, P Fang, J Zhou, Z Liang; (III) Provision of study materials or patients: P Fang, J Zhou, Z Liang; (IV) Collection and assembly of data: Y Yang, S Luan, X Xiao, X Li; (V) Data analysis and interpretation: Q Shang, H Zhang, X Zeng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yong Yuan, PhD. Department of Thoracic Surgery, Med+X Center for Informatics, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu 610041, China. Email: yongyuan@scu.edu.cn.

Background: A variety of nutritional evaluation parameters has been documented as prognostic indicators in some malignancies. However, the prognostic significance of the controlling nutritional status (CONUT) score, as one of these nutritional indices, in patients with esophageal squamous cell carcinoma (ESCC) remains unclear and warrants investigation. Our study sought to elucidate the prognostic value of this nutritional index in ESCC patients who underwent neoadjuvant therapy followed by esophagectomy.

Methods: This retrospective study encompassed 314 patients diagnosed with ESCC who underwent neoadjuvant therapy followed by esophagectomy at West China Hospital of Sichuan University between August 2016 and August 2021. CONUT scores were computed at two specific time points: prior to neoadjuvant therapy initiation and before surgery, utilizing serum albumin, total lymphocyte, and cholesterol levels of ESCC patients. Furthermore, the delta CONUT (ΔCONUT) score was derived by subtracting the preoperative CONUT score from the pretreatment CONUT score. The associations between CONUT scores and various survival outcomes were evaluated using Kaplan-Meier methods and Cox regression analysis.

Results: Patients with a high preoperative CONUT score demonstrated a higher postoperative complication rate [odds ratio (OR) =2.009, 95% confidence interval (CI): 1.150–3.510, P=0.01] compared to those in the low CONUT group. Multivariate analysis revealed that a ΔCONUT score ≥0 served as an independent negative prognostic indicator for increased postoperative complications (OR =3.008, 95% CI: 1.509–5.999, P=0.002) and poorer overall survival [hazard ratio (HR) =2.388, 95% CI: 1.052–5.422, P=0.04] in ESCC patients who underwent neoadjuvant therapy combined with esophagectomy.

Conclusions: A high preoperative CONUT score and a ΔCONUT score ≥0 were indicative of a poor prognostic nutritional status in ESCC patients who had undergone neoadjuvant therapy followed by esophagectomy.

Keywords: Esophageal squamous cell carcinoma (ESCC); neoadjuvant therapy; prognosis; controlling nutritional status score (CONUT score)

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Introduction

Esophageal cancer (EC) is the ninth most common aggressive malignant tumors around the world (1,2). Esophageal squamous cell carcinoma (ESCC) represents the main pathological type of EC (3,4). Due to the aggressiveness of EC, it has a poor prognosis, and the overall five-year survival rate of EC is still lower than 30% (5,6). While esophagectomy represents a promising therapeutic avenue for patients with EC, it is notably invasive and associated with a heightened risk of postoperative complications, including anastomotic leak and pneumonia. For patients with locally advanced EC, neoadjuvant chemoradiation has emerged as a standard treatment modality. This approach holds the potential to downstage the primary tumor and extend the survival of patients diagnosed with EC (7), and neoadjuvant therapy combined with surgery emerges as the primary treatment option for patients with advanced EC (8-10).

However, many patients with EC experience weight loss and dysphagia, which are closely associated with malnutrition due to the malignant and invasive nature of EC. Additionally, neoadjuvant therapy can exacerbate nutritional or functional impairments. Various risk factors such as dyscrasia and obstruction induced by neoadjuvant therapy contribute to poor nutritional status in patients with EC (11,12). Hence, nutritional assessment and support are crucial components in optimizing multidisciplinary treatment strategies (13,14).

Recently, controlling nutritional status (CONUT) score was reported to be associated with clinical and survival outcomes in several types of cancer (15-17). The CONUT score could be easily calculated based on the albumin, lymphocyte, and cholesterol levels in peripheral blood. Previous reports had shown that CONUT score had the prognostic importance in EC patients who had only undergone esophagectomy.

Previous research demonstrated that in EC patients, CONUT was a predictor of cancer-specific survival (CSS) after esophagectomy (18). In that study, only 148 EC patients were included, and the sample size was limited. In 2016, scholars conducted a retrospective study to examine the predictive significance of pretreatment CONUT scores in patients with ESCC. However, within that research cohort, the majority of patients exclusively received surgical intervention, resulting in an insufficient sample size to adequately assess the prognostic utility of CONUT scores in EC patients who underwent neoadjuvant therapy prior to surgery (19). Therefore, this retrospective study aims to assess the clinical utility and prognostic value of the CONUT score in ESCC patients who underwent neoadjuvant therapy prior to esophagectomy. Our objective is to elucidate whether the CONUT score could serve as a valuable metric, aiding in the formulation of more effective treatment strategies and timely adjustments to therapy. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-187/rc).

Highlight box

Key findings

- This study represents the first attempt to assess the prognostic significance of controlling nutritional status (CONUT) scores at distinct time intervals and the delta CONUT (ΔCONUT) score in patients diagnosed with esophageal squamous cell carcinoma (ESCC).

What is known and what is new?

- The CONUT score has been linked to clinical and survival outcomes across various cancer types. Yet, it remains uncertain whether calculating the CONUT score could yield improved predictive capabilities concerning clinical and survival outcomes in ESCC patients who have undergone multidisciplinary treatments.
- Calculating the CONUT score at the preoperative stage could potentially serve as a superior index. Furthermore, calculating the ΔCONUT value by subtracting the preoperative CONUT score from the pretreatment CONUT score may prove beneficial in predicting both postoperative survival outcomes and overall survival in patients.

What is the implication, and what should change now?

- The CONUT score can serve not only as a predictor of tumor progression but also as a tool for identifying ESCC patients with diminished immune-nutritional status and those in need of nutritional support following neoadjuvant therapy.

Methods

Patient eligibility

The study cohort consisted of 314 individuals diagnosed with ESCC confirmed through pathological examination. Between August 2016 and August 2021, all patients underwent preoperative neoadjuvant treatment. Following completion of neoadjuvant therapy, radical esophagectomy was performed on all patients at West China Hospital, Sichuan University. Inclusion criteria comprised: (I) histologically confirmed ESCC diagnosis; (II) receipt of esophagectomy; (III) administration of neoadjuvant chemoradiotherapy or combined immunotherapy before esophagectomy; and (IV) adequate follow-up. Exclusion criteria included distant tumor metastases, receipt of adjuvant treatment, and inadequate medical records. Comprehensive medical, pathological, and clinical data of each ESCC patient were retrospectively retrieved from our database, with all patients providing informed consent. Pathological diagnosis and disease classification employed the 8th edition TNM Classification of Malignant Tumors for ESCC (20). Patients' survival outcomes were computed from the date of esophagectomy, and follow-up data were updated until September 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of West China Hospital, Sichuan University (No. 2019632) and individual consent for this retrospective analysis was waived.

Neoadjuvant chemoradiotherapy and surgery

Patients received neoadjuvant treatment according to national guidelines. Typically, the entire neoadjuvant chemotherapy regimen comprised two cycles. After completing each cycle of chemotherapy, patients were required to undergo a three-week rest period before commencing the subsequent cycle. All patients received paclitaxel (175 mg/m^2 body-surface area, D1) and cisplatin (75 mg/m^2 body-surface area, D1) intravenously during a two-cycle period. Patients also received radiotherapy with the radiation dosage of 1.8–2.0 Gy/fraction. Among all the included ESCC patients, during the therapeutic period of neoadjuvant chemotherapy, 25 patients had been synchronously treated with two cycles of immunotherapy administered by camrelizumab (200 mg, D1), tislelizumab (200 mg, D1), pembrolizumab (200 mg, D1), or sintilimab (200 mg, D1).

Surgical resection was performed approximately 6–8 weeks after the completion of neoadjuvant therapy. All patients had undergone radical esophagectomy with two or three-field lymphadenectomy, utilizing either minimally invasive or open techniques. Subsequently, conduit reconstruction via the stomach was carried out. In cases where preoperative computed tomography (CT) scans indicated potential cervical lymph node metastases, cervical lymph node dissection was performed.

CONUT score assessment

The assessment of the CONUT score in all cases was conducted via laboratory peripheral blood tests. CONUT scores were calculated at two distinct time points: before treatment initiation and before surgery. The CONUT score was derived from the cholesterol level, serum albumin level, and total lymphocyte level of each ESCC patient. The total CONUT score was categorized as either moderate malnutrition or severe malnutrition based on a predefined cutoff value set at 4. Furthermore, the delta CONUT (ΔCONUT) score was calculated as the preoperative CONUT score minus the pretreatment CONUT score. The pretreatment blood samples were obtained from patients upon their initial presentation to our institution, preceding the commencement of any treatment regimen. Subsequently, the preoperative blood samples were collected from patients following neoadjuvant therapy, one week prior to esophagectomy. Additionally, we calculated the classic nutritional index, and body mass index (BMI), at the same time points. The cutoff value for BMI was set at 18.5 kg/m^2, consistent with previous studies (21). Furthermore, we also calculated the delta BMI (ΔBMI) by preoperative BMI value subtracting pretreatment BMI value. The details of scoring system and nutritional status assessment of CONUT are shown in *Table 1*.

Statistical analysis

SPSS 26.0 software was utilized for statistical analyses. The association of CONUT score on clinical or pathologic features was calculated through Chi-square. The survival curves were achieved by Kaplan-Meier method and group comparison was conducted through long-rank test. Cox proportional hazards model was used to confirm independent prognostic factors of ESCC patients. The hazard ratio (HR) and their 95% confidence interval (CI) were also calculated and P value lower than 0.05 indicated statistical significance.

Results

Clinical characteristics based on different CONUT score

The entire cohort consisted of 314 patients, with a mean age of 62.2 years. Among them, there were 252 male patients (80.3%) with a mean age of 61.8 years (range, 44–79 years), and 62 female patients (19.7%) with a mean age of 63.1 years (range, 44–80 years). According to the

Table 1 Nutritional assessment of CONUT scoring system

Parameters	Nutritional level			
	Moderate malnutrition		Severe malnutrition	
	High grade	Low grade	High grade	Low grade
Serum albumin (g/dL)	≥3.50	3.00–3.49	2.50–2.99	<2.50
Score	0	2	4	6
Total lymphocyte (/μL)	≥1,600	1,200–1,599	800–1,199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3
Total score	≤4		>4	

CONUT, controlling nutrition status.

CONUT score, with a cutoff value set at 4, nutritional levels were categorized as moderate or severe malnutrition. Specifically, 279 patients were assigned to the pretreatment moderate malnutrition group, while 35 patients were assigned to the severe malnutrition group. Tumors located in the upper, middle, and lower thoracic esophagus were observed in 48 (15.3%), 187 (59.6%), and 79 (25.2%) of the cases, respectively. The pathological tumor T stage was ypT0, ypT1 or ypT2 for 213 patients and ypT3 or ypT4 for 101 patients. Regarding the pathological N stage, 197 patients were N negative, while 117 patients were N positive. Furthermore, there were 232 patients with ΔCONUT ≥0 and 82 patients with ΔCONUT <0. The details of patient characteristics for the three CONUT groups are presented in *Table 2* and the details of the entire cohort were demonstrated in Table S1.

CONUT score and postoperative complications

Table 3 delineated various factors, including preoperative chronic diseases and different CONUT scores of ESCC patients calculated at different time points, and examined their impact on postoperative complications. The results indicated that the complication rates following esophagectomy were significantly higher in patients with chronic obstructive pulmonary disease (COPD) [odds ratio (OR)=2.656, 95% CI: 1.043–6.764, P=0.04], high preoperative CONUT scores (OR =2.009, 95% CI: 1.150–3.510, P=0.01), and ΔCONUT ≥0 (OR =3.373, 95% CI: 1.729–6.579, P<0.001). For patients with high pretreatment CONUT scores, no significant association was found with postoperative complications. Additionally, the results of multivariate logistic regression further demonstrated that ΔCONUT ≥0 was a strong independent predictor of postoperative complications (OR =3.008, 95% CI: 1.509–5.999, P=0.002). Conversely, BMI was not identified as an independent risk factor for postoperative complications (*Table 3*).

CONUT score and survival outcomes of esophagectomy after EC neoadjuvant therapy

Figure 1 depicts the Kaplan-Meier curves for overall survival (OS) and disease-free survival (DFS) based on the cutoff value of the CONUT score. Patients with a preoperative CONUT score higher than 4 and ΔCONUT score ≥0 exhibited significantly decreased OS and DFS. However, no significant differences in OS and DFS were observed among ESCC patients with different pretreatment CONUT groups (*Figure 1*). According to the univariate analysis, several factors including sex (P=0.03), smoking status (P=0.04), tumor diameter (P=0.001), pathological T stage (P<0.001), pathological N stage (P<0.001), tumor differentiation (P<0.001), tumor regression grade (TRG) (P<0.001), pretreatment BMI (P=0.009), preoperative BMI (P=0.002), ΔBMI (P=0.02), preoperative CONUT score (P=0.01), and ΔCONUT score ≥0 (P=0.01) significantly impacted the OS of ESCC patients. Furthermore, multivariable analysis revealed that pathological N stage (HR =2.550, 95% CI: 1.404–4.631, P=0.002) and ΔCONUT score (HR =2.388, 95% CI: 1.052–5.422, P=0.04) were independent prognostic factors for OS (*Table 4*). Furthermore, the results of univariate analysis revealed that smoking status (P=0.01), tumor diameter (P<0.001), pathological T stage (P<0.001),

Table 2 Patient characteristics and CONUT

Factors	Pretreatment CONUT			Preoperative CONUT			ΔCONUT		
	Low (n=279)	High (n=35)	P	Low (n=247)	High (n=67)	P	Δ≥0 (n=232)	Δ<0 (n=82)	P
Sex			0.39			0.19			0.70
Female	57 (20.4)	5 (14.3)		45 (18.2)	17 (25.4)		47 (20.3)	15 (18.3)	
Male	222 (79.6)	30 (85.7)		202 (81.8)	50 (74.6)		185 (79.7)	67 (81.7)	
Age (years)			0.20			0.01*			0.49
>60	111 (39.8)	10 (28.6)		104 (42.1)	17 (25.4)		92 (39.7)	29 (35.4)	
≤60	168 (60.2)	25 (71.4)		143 (57.9)	50 (74.6)		140 (60.3)	53 (64.6)	
Pretreatment-BMI (kg/m^2)			0.58			–			0.29
>18.5	247 (88.5)	30 (85.7)		–	–		202 (87.1)	75 (91.5)	
≤18.5	32 (11.5)	5 (14.3)		–	–		30 (12.9)	7 (8.5)	
Preoperative-BMI (kg/m^2)			–			0.01*			0.12
>18.5	–	–		223 (90.3)	53 (79.1)		200 (86.2)	76 (92.7)	
≤18.5	–	–		24 (9.7)	14 (20.9)		32 (13.8)	6 (7.3)	
ΔBMI			–			0.31			0.48
>0	–	–		195 (78.9)	49 (73.1)		178 (76.7)	66 (80.5)	
≤0	–	–		52 (21.1)	18 (26.9)		54 (23.3)	16 (19.5)	
Smoke			0.98			0.67			0.40
No	135 (48.4)	17 (48.6)		118 (47.8)	34 (50.7)		109 (47.0)	43 (52.4)	
Yes	144 (51.6)	18 (51.4)		129 (52.2)	33 (49.3)		123 (53.0)	39 (47.6)	
Coronary artery disease			0.39			0.53			>0.99
No	264 (94.6)	35 (100.0)		236 (95.5)	63 (94.0)		221 (95.3)	78 (95.1)	
Yes	15 (5.4)	0 (0.0)		11 (4.5)	4 (6.0)		11 (4.7)	4 (4.9)	
Hypertension			0.89			0.53			0.28
No	226 (81.0)	28 (80.0)		198 (80.2)	56 (83.6)		191 (82.3)	63 (76.8)	
Yes	53 (19.0)	7 (20.0)		49 (19.8)	11 (16.4)		41 (17.7)	19 (23.2)	
COPD			>0.99			0.57			0.79
No	262 (93.9)	33 (94.3)		233 (94.3)	62 (92.5)		217 (93.5)	78 (95.1)	
Yes	17 (6.1)	2 (5.7)		14 (5.7)	5 (7.5)		15 (6.5)	4 (4.9)	
Tumor location			0.008*			0.89			0.42
Upper	46 (16.5)	2 (5.7)		39 (15.8)	9 (13.4)		37 (15.9)	11 (13.4)	
Middle	170 (60.9)	17 (48.6)		146 (59.1)	41 (61.2)		141 (60.8)	46 (56.1)	
Lower	63 (22.6)	16 (45.7)		62 (25.1)	17 (25.4)		54 (23.3)	25 (30.5)	
Tumor diameter (cm)			0.09			0.03*			0.65
≤3	184 (65.9)	28 (80.0)		174 (70.4)	38 (56.7)		155 (66.8)	57 (69.5)	
>3	95 (34.1)	7 (20.0)		73 (29.6)	29 (43.3)		77 (33.2)	25 (30.5)	
Pathological T stage			0.63			0.67			0.35
ypT 0, 1, 2	188 (67.4)	25 (71.4)		169 (68.4)	44 (65.7)		154 (66.4)	59 (72.0)	
ypT 3, 4	91 (32.6)	10 (28.6)		78 (31.6)	23 (34.3)		78 (33.6)	23 (28.0)	

Table 2 *(continued)*

Table 2 *(continued)*

Factors	Pretreatment CONUT			Preoperative CONUT			ΔCONUT		
	Low (n=279)	High (n=35)	P	Low (n=247)	High (n=67)	P	Δ≥0 (n=232)	Δ<0 (n=82)	P
Pathological N stage			0.99			0.09			0.23
ypN negative	175 (62.7)	22 (62.9)		161 (65.2)	36 (53.7)		141 (60.8)	56 (68.3)	
ypN positive	104 (37.3)	13 (37.1)		86 (34.8)	31 (46.3)		91 (39.2)	26 (31.7)	
Differentiation			0.78			0.62			0.24
Well differentiated	127 (45.5)	18 (51.4)		113 (45.7)	32 (47.8)		104 (44.8)	41 (50.0)	
Moderate differentiated	68 (24.4)	7 (20.0)		57 (23.1)	18 (26.9)		61 (26.3)	14 (17.1)	
Poor differentiated	84 (30.1)	10 (28.6)		77 (31.2)	17 (25.4)		67 (28.9)	27 (32.9)	
Preoperative treatment			>0.99			0.74			0.80
nCRT	256 (91.8)	33 (94.3)		228 (92.3)	61 (91.0)		213 (91.8)	76 (92.7)	
IMT	23 (8.2)	2 (5.7)		19 (7.7)	6 (9.0)		19 (8.2)	6 (7.3)	
TRG			0.37			0.87			0.23
0, 1	150 (53.8)	16 (45.7)		130 (52.6)	36 (53.7)		118 (50.9)	48 (58.5)	
2, 3	129 (46.2)	19 (54.3)		117 (47.4)	31 (46.3)		114 (49.1)	34 (41.5)	

Data are presented as n (%). *, P<0.05. CONUT, controlling nutritional status; BMI, body mass index; COPD, chronic obstructive pulmonary disease; nCRT, neoadjuvant chemoradiotherapy; IMT, immunotherapy; TRG, tumor regression grade.

Table 3 Logistic regression analysis for clinical factors associated with complications after surgery

Factors	Univariable analyses		Multivariable analyses	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (male/female)	1.231 (0.664–2.284)	0.51		
Age (≥60/<60 years)	1.240 (0.754–2.040)	0.40		
Smoke (yes/no)	1.430 (0.883–2.318)	0.15		
Coronary artery disease (present/absent)	0.805 (0.250–2.596)	0.72		
Hypertension (present/absent)	0.777 (0.414–1.458)	0.43		
COPD (present/absent)	2.656 (1.043–6.764)	0.04*	2.604 (0.991–6.845)	0.052
Preoperative treatment (IMT/nCRT)	2.215 (0.971–5.052)	0.06		
Pretreatment BMI (low/high)	1.844 (0.915–3.713)	0.09		
Preoperative BMI (low/high)	1.751 (0.875–3.505)	0.11		
ΔBMI (>0/≤0)	1.561 (0.896–2.720)	0.12		
Pretreatment CONUT (high/low)	0.883 (0.406–1.918)	0.75		
Preoperative CONUT (high/low)	2.009 (1.150–3.510)	0.01*	1.526 (0.853–2.730)	0.16
ΔCONUT (≥0/<0)	3.373 (1.729–6.579)	<0.001*	3.008 (1.509–5.999)	0.002*
TRG (2, 3/0, 1)	1.080 (0.669–1.743)	0.75		

*, P<0.05. OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IMT, immunotherapy; nCRT, neoadjuvant chemoradiotherapy; BMI, body mass index; CONUT, controlling nutritional status; TRG, tumor regression grade.

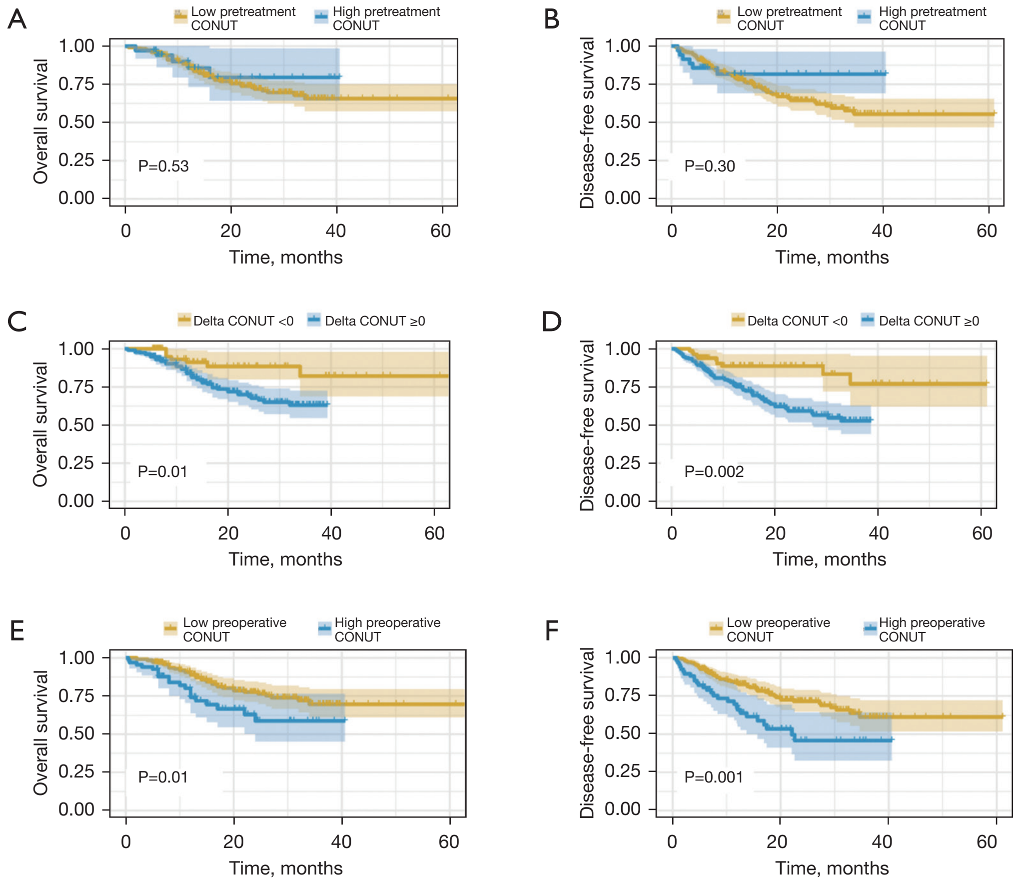

Figure 1 Survival curves stratified by CONUT score: (A) pretreatment CONUT score and overall survival; (B) pretreatment CONUT score and disease-free survival; (C) delta CONUT score and overall survival; (D) delta CONUT score and disease-free survival; (E) preoperative CONUT score and overall survival; (F) preoperative CONUT score and disease-free survival. CONUT, controlling nutritional status.

pathological N stage (P<0.001), tumor differentiation (P<0.001), TRG (P<0.001), preoperative BMI (P=0.01), ΔBMI (P=0.04), preoperative CONUT score (P=0.001), and ΔCONUT score ≥0 (P=0.002) were significantly associated with poorer DFS in ESCC patients. Additionally, smoking status (HR =1.698, 95% CI: 1.073–2.688, P=0.02), tumor diameter (HR =1.588, 95% CI: 1.007–2.506, P=0.047), pathological N stage (HR =2.335, 95% CI: 1.435–3.800, P=0.001), and ΔCONUT score (HR =2.459, 95% CI: 1.237–4.889, P=0.01) were identified as independent prognostic factors for DFS (*Table 5*).

Subgroup analysis of CONUT

Moreover, subgroup analysis was conducted to investigate the prognostic value of preoperative CONUT score (*Figure 2*) and ΔCONUT score (*Figure 3*) in ESCC patients with or without lymph node metastasis. Interestingly, the results revealed no statistical significance in patients without lymph node metastasis for OS (P=0.90). However, in ESCC patients with lymph node metastasis, a higher preoperative CONUT score was associated with poorer survival for both OS (P=0.009) and DFS (P=0.03). The ΔCONUT score was demonstrated to be associated with worse DFS regardless of lymph node metastasis.

Discussion

To our knowledge, our research encompassed a large sample size, providing valuable insights into the prognostic significance of the nutritional parameter CONUT score at different time points, including ΔCONUT score, in ESCC

Table 4 Uni- and multivariable analyses for the overall survival of 314 ESCC patients

Factors	Univariable analyses		Multivariable analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male/female)	2.608 (1.123–6.055)	0.03*	1.555 (0.585–4.131)	0.38
Age (≥60/<60 years)	1.078 (0.646–1.799)	0.77		
Smoke (yes/no)	1.719 (1.016–2.909)	0.04*	1.387 (0.746–2.581)	0.30
Coronary artery disease (present/absent)	2.733 (0.853–6.538)	0.10		
Hypertension (present/absent)	0.745 (0.368–1.512)	0.42		
COPD (present/absent)	0.545 (0.075–3.961)	0.55		
Tumor location	1.034 (0.680–1.574)	0.88		
Tumor diameter (≥3/<3 cm)	2.317 (1.403–3.825)	0.001*	1.683 (0.979–2.894)	0.06
ypT (3, 4/0, 1, 2)	2.934 (1.776–4.848)	<0.001*	1.173 (0.531–2.592)	0.69
ypN (positive/negative)	4.066 (2.398–6.897)	<0.001*	2.550 (1.404–4.631)	0.002*
Differentiation (poor/moderate or well)	1.709 (1.277–2.287)	<0.001*	1.202 (0.744–1.942)	0.45
TRG (2, 3/0, 1)	2.866 (1.670–4.921)	<0.001*	1.102 (0.432–2.815)	0.84
Preoperative treatment (IMT/nCRT)	0.970 (0.233–4.044)	0.97		
Pretreatment BMI (low/high)	2.275 (1.233–4.197)	0.009*	1.072 (0.258–4.450)	0.92
Preoperative BMI (low/high)	2.563 (1.412–4.653)	0.002*	1.440 (0.376–5.515)	0.60
ΔBMI (>0/≤0)	2.143 (1.153–3.986)	0.02*	1.876 (0.933–3.772)	0.08
Pretreatment CONUT (high/low)	0.744 (0.298–1.857)	0.53		
Preoperative CONUT (high/low)	1.967 (1.154–3.353)	0.01*	1.338 (0.756–2.368)	0.32
ΔCONUT (≥0/<0)	2.796 (1.273–6.143)	0.01*	2.388 (1.052–5.422)	0.04*

*, P<0.05. ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; TRG, tumor regression grade; IMT, immunotherapy; nCRT, neoadjuvant chemoradiotherapy; BMI, body mass index; CONUT, controlling nutritional status.

patients. Traditional nutritional indices such as BMI have been validated as indicators of body composition and have also been shown to correlate with EC progression and prognosis in previous studies (22,23). In our study, owing to its acceptable individual variability, the CONUT score was chosen as a nutritional index. We evaluated the correlation between the CONUT score, clinicopathological factors, and survival outcomes in ESCC patients who underwent neoadjuvant therapy followed by esophagectomy. The findings of our study suggested that ESCC patients with high preoperative CONUT scores were more likely to experience worse postoperative outcomes. These results align with those of leading studies in EC patients (24). Furthermore, our study demonstrated that the ΔCONUT score remained an independent prognostic factor for both OS and DFS. Additionally, we found that the ΔCONUT score was an independent risk factor for postoperative complications, with patients having a ΔCONUT score ≥0 being more prone to higher postoperative complication rates. Interestingly, pretreatment CONUT scores showed no association with the survival outcomes of ESCC patients or postoperative complication rates. These findings suggest that the CONUT score calculated at the preoperative time point may be a superior index and calculating the ΔCONUT value by preoperative CONUT value subtracting pretreatment CONUT value may be helpful in predicting both postoperative survival outcomes and patients' survival.

On the contrary, according to the results of subgroup analysis, preoperative CONUT and ΔCONUT scores were not associated with OS in ESCC patients without lymph node metastasis. However, for ESCC patients

Table 5 Uni- and multivariable analyses for the disease-free survival of 314 ESCC patients

Factors	Univariable analyses		Multivariable analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male/female)	1.865 (0.989–3.516)	0.05		
Age (≥60/<60 years)	1.060 (0.685–1.641)	0.79		
Smoke (yes/no)	1.775 (1.133–2.780)	0.01*	1.698 (1.073–2.688)	0.02*
Coronary artery disease (present/absent)	1.820 (0.734–4.513)	0.20		
Hypertension (present/absent)	0.798 (0.442–1.441)	0.46		
COPD (present/absent)	1.297 (0.471–3.568)	0.62		
Tumor location	1.064 (0.748–1.515)	0.73		
Tumor diameter (≥3/<3 cm)	2.138 (1.396–3.273)	<0.001*	1.588 (1.007–2.506)	0.047*
ypT (3, 4/0, 1, 2)	2.876 (1.877–4.408)	<0.001*	1.581 (0.812–3.081)	0.18
ypN (positive/negative)	3.372 (2.175–5.228)	<0.001*	2.335 (1.435–3.800)	0.001*
Differentiation (poor/moderate or well)	1.627 (1.270–2.083)	<0.001*	1.125 (0.755–1.678)	0.56
TRG (2, 3/0, 1)	2.565 (1.637–4.019)	<0.001*	0.974 (0.445–2.132)	0.95
Preoperative treatment (IMT/nCRT)	0.531 (0.129–2.179)	0.38		
Pretreatment BMI (low/high)	1.701 (0.958–3.020)	0.07		
Preoperative BMI (low/high)	2.055 (1.192–3.544)	0.01*	1.306 (0.726–2.347)	0.37
ΔBMI (>0/≤0)	1.768 (1.041–3.004)	0.04*	1.469 (0.832–2.593)	0.19
Pretreatment CONUT (high/low)	0.642 (0.280–1.473)	0.30		
Preoperative CONUT (high/low)	2.104 (1.338–3.311)	0.001*	1.463 (0.903–2.372)	0.12
ΔCONUT (≥0/<0)	2.813 (1.453–5.446)	0.002*	2.459 (1.237–4.889)	0.01*

*, P<0.05. ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; TRG, tumor regression grade; IMT, immunotherapy; nCRT, neoadjuvant chemoradiotherapy; BMI, body mass index; CONUT, controlling nutritional status.

with a positive N stage, the preoperative CONUT score was shown to correlate with worse prognosis. Such a discrepancy might be attributed to differences in nutritional status among diverse stages of ESCC. For ESCC patients in advanced stages, factors such as invasiveness, obstruction, dysphagia, inflammatory responses, gastrointestinal adverse events, and cachexia of ESCC may lead to the development of severe malnutrition. Consequently, the preoperative CONUT score may emerge as a more sensitive indicator in advanced ESCC patients.

Generally, patients with EC typically present with the characteristic symptom of progressive dysphagia, initially for solids and later for liquids. These symptoms often lead to frequent weight loss and are associated with poor survival outcomes (25). Esophagectomy together with neoadjuvant chemoradiation now becomes the first choice to treat patients with progressive EC (26,27). However, EC patients who finished neoadjuvant therapy were still found to have lower nutritional level (28). Due to the side effects of chemoradiation such as esophageal edema, obstruction, and inflammation, patients with EC are more prone to experiencing insufficient nutrition intake (29). Thus, patients with EC face a severe challenge in nutritional supplement. In recent years, the importance of nutritional level and dietary support has become a common recognition and covers the whole progression of EC treatment: from diagnostic phase to long-term nutrition support. Therefore, it is vital to confirm EC patients who need intensive nutritional support. On the other hand, previous studies have suggested that the progression of EC may be associated with a decline in the immune system. Malnutrition is commonly believed to be associated with

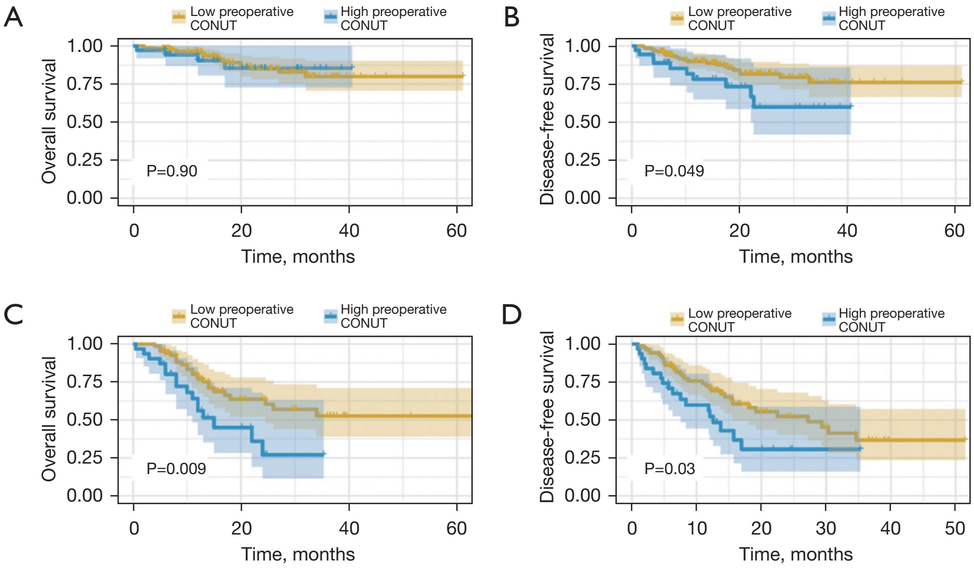

Figure 2 Survival curves stratified by preoperative CONUT score based on different tumor stages (A) overall survival of ESCC patients without lymph node metastasis; (B) disease-free survival of ESCC patients without lymph node metastasis; (C) overall survival of ESCC patients with lymph node metastasis; (D) disease-free survival of ESCC patients with lymph node metastasis. CONUT, controlling nutritional status; ESCC, esophageal squamous cell carcinoma.

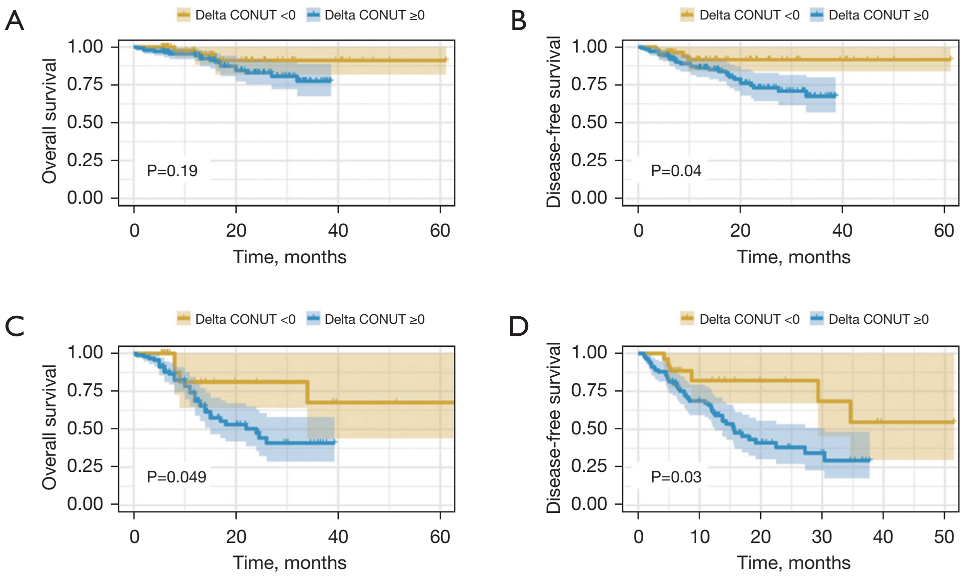

Figure 3 Survival curves stratified by delta CONUT score based on different tumor stages (A) overall survival of ESCC patients without lymph node metastasis; (B) disease-free survival of ESCC patients without lymph node metastasis; (C) overall survival of ESCC patients with lymph node metastasis; (D) disease-free survival of ESCC patients with lymph node metastasis. CONUT, controlling nutritional status; ESCC, esophageal squamous cell carcinoma.

defective immune function (30-33). Considering both immune and nutritional indexes consist of CONUT score, and the strong ability of CONUT score to predict the survival outcomes in EC patients, CONUT score could not only utilized as a detector of predicting tumor progression but also for identifying ESCC patients with decreased immune-nutritional level and for patients requiring nutritional support after neoadjuvant therapy.

Currently, two types of nutritional status evaluation systems are applied in clinical practice. One relies mostly on subjective parameters, while the other is entirely based on objective parameters. Above the evaluating systems mainly based on subjective parameters, patients are required to recall their food intake condition, or the loss of appetite during the last few months (34). However, such evaluation systems may be prone to bias due to the subjective nature of various patients' parameters, potentially leading to inaccurate results. Furthermore, while nutritional evaluation indexes based on objective parameters like BMI and serum albumin can reflect the nutritional status of patients to some extent, they may not fully capture the immune function of ESCC patients. CONUT is a simple objective parameter which is calculated through cholesterol, serum albumin and total lymphocyte level in peripheral blood that is easily obtained from a routine blood examination (35). Cholesterol has been reported to be associated with various metabolism diseases and cancers (36). Serum albumin was commonly believed as an indicator of both immune and nutritional status, and hypoalbuminemia was also reported to correlate with worse postoperative outcomes and cachexia in malignancies (37). Total lymphocyte, which was proved as an immune function detector to predict survival outcomes in various cancers (38). Therefore, based on the evidence provided, the CONUT score has been demonstrated to be a superior index in evaluating immune-nutritional function in patients with EC.

Improving the nutritional status of patients with ESCC is crucial. This is because maintaining good nutrition not only enhances patients' tolerance to treatment but also improves treatment efficacy and reduces adverse reactions during therapy. Given the strong prognostic role of the CONUT score in EC, some scholars have attempted to counter malnutrition by providing nutritional support to EC patients during the whole disease management. Oral nutritional supplements, such as liquid meal replacements, can serve as convenient and effective means of increasing calorie and protein intake in patients with compromised nutritional status. These supplements are often fortified with essential nutrients and micronutrients to address specific nutritional deficiencies (39,40). In cases where oral intake is insufficient or compromised, enteral nutrition via tube feeding may be indicated to provide adequate nutrition. Enteral feeding can be administered either nasogastrically or via gastrostomy tube, delivering a balanced formula directly into the gastrointestinal tract (41,42). Even after surgery, nutritional support remains critically important for patients with ESCC. EC patients treated with enteral nutrition support after esophagectomy experienced greater benefits in terms of immune function recovery and nutritional improvement. Furthermore, for EC patients receiving nutritional support, it was associated with a shortened duration of hospitalization (30).

Although our research demonstrated the prognostic value of CONUT score in ESCC patients, caution should be taken for the following reasons. First, the study was a single-center retrospective cohort study with a huge samples amount, all patients included were from single institution. Secondly, it is important to recognize that CONUT serves as a single assessment tool among many in evaluating the nutritional status and prognosis of patients with ESCC. It is crucial to acknowledge that the nutritional status of individuals is multifaceted and encompasses various parameters beyond those assessed by CONUT alone. The utility of CONUT may be enhanced when considered in conjunction with other relevant nutritional parameters. Finally, it is important to acknowledge that there is no consensus on the exact cutoff value of the CONUT score, and the optimal evaluation standard for CONUT scores remains unclear. Therefore, the significance of the CONUT score requires further validation through prospective studies in the future.

Conclusions

This study suggests that CONUT score can be utilized in nutritional status evaluation and CONUT score is also a robust prognostic factor of postoperative complications and long-term survival of ESCC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-187/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-187/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-187/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of West China Hospital, Sichuan University (No. 2019632) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Overall baseline characteristics of the entire cohort

Factors	N
Sex	
Female	62
Male	252
Age (years)	
Mean ± SD	62.18±7.71
>60	121
≤60	193
Pretreatment-CONUT	
Low	279
High	35
Preoperative-CONUT	
Low	247
High	67
ΔCONUT	
≥0	232
<0	82
Pretreatment-BMI (kg/m^2)	
Mean ± SD	22.28±3.22
>18.5	277
≤18.5	37
Preoperative-BMI (kg/m^2)	
Mean ± SD	22.36±3.25
>18.5	276
≤18.5	38
ΔBMI	
>0	244
≤0	70
Smoke	
No	152
Yes	162
Coronary artery disease	
No	299
Yes	15
Hypertension	
No	254
Yes	60
COPD	
No	295
Yes	19
Tumor location	
Upper	48
Middle	187
Lower	79
Tumor diameter (cm)	
≤3	212
>3	102
Pathological T stage	
ypT0	119
ypT1	49
ypT2	45
ypT3	100
ypT4	1
Pathological N stage	
ypN0	197
ypN1	82
ypN2	26
ypN3	9
Differentiation	
Well differentiated	145
Moderate differentiated	75
Poor differentiated	94
Preoperative treatment	
nCRT	289
IMT	25
TRG	
0	110
1	56
2	116
3	32

Table S1 *(continued)*

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