Prognostic impact of the Controlling Nutritional Status score in patients with esophageal cancer treated with immune checkpoint inhibitor

Lele Chang
Harbin Medical University Cancer Hospital
Qian Cheng
Harbin Medical University Cancer Hospital
Qian Ma
Harbin Medical University Cancer Hospital
Lei He
Harbin Medical University Cancer Hospital
Qingwei Li
Harbin Medical University Cancer Hospital
Ji Tao (taoji66@163.com)
Harbin Medical University Cancer Hospital

Case Report

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Abstract

Background: In recent years, a growing number of clinical studies have shown that immune checkpoint inhibitor (ICI) can increase the remission rate and improve the prognosis of patients with esophageal cancer. The Controlling Nutritional Status (CONUT) score is a novel nutritional indicator that can predict the prognosis of certain malignancies. However, no one has yet pointed to its role in ICI treatment in patients with esophageal cancer. The aim of this study was to investigate the clinical significance of CONUT score in patients with esophageal cancer receiving immune checkpoint inhibitor treatment.

Methods: We retrospectively analyzed the clinical data of 69 patients with advanced esophageal cancer treated with ICI. Based on the receiver operating characteristic (ROC) curve, we chose 1 as the optimal cut-off value (AUC; 0.619, 95%CI: 0.477-0.762; sensitivity 0.565; specificity 0.696), and divided 69 patients into the low CONUT and the high CONUT groups. We assessed the relationship between clinicopathological factors including CONUT score, systemic immune-inflammatory index (SII), and neutrophil-to-lymphocyte ratio (NLR) and the prognosis.

Results: In univariate analysis, we found that the CONUT score, NLR could predict progression-free survival (PFS) and overall survival (OS) ($P<0.05$); in multivariate analysis, the CONUT score and SII, NLR were an independent prognostic factor for OS ($P<0.05$). Furthermore, among patients treated with ICI, a high CONUT score was associated with a significantly worse PFS and OS compared with a low CONUT group.

Conclusion: The CONUT can be used to predict the efficacy and prognosis of ICI therapy in patients with esophageal cancer. Our studies have shown that the CONUT score can be used as an effective indicator for the prognosis of patients with esophageal cancer receiving ICI.

Introduction

As one of the most common malignant tumors in the world, esophageal cancer ranks seventh and sixth in terms of morbidity and mortality [1], and the five-year survival rate is extremely low [2].For patients with early esophageal cancer, timely diagnosis and radical surgery can effectively control the progression of cancer to a certain extent; while for patients with advanced esophageal cancer, cytotoxic chemotherapy is the main treatment method. Recently, various molecularly targeted drugs have achieved good results in the treatment of patients with esophageal cancer [3, 4]. In addition, immunotherapy, including ICI, has greatly advanced the treatment of esophageal cancer. [5–9].

The first ICI nivolumab, a programmed cell death-1 (PD-1) inhibitor, to show effectiveness in the treatment of esophageal cancer. The ATTRACTION-1 study, an open-label, multicenter Phase II study, administered nivolumab to patients with advanced esophageal cancer who had previously failed or were intolerant of chemotherapy showed a favorable response rate (ORR) and median overall survival (mOS) was significantly improved [5].Results from the ATTRACTION-3 study demonstrated that nivolumab conferred a survival benefit regardless of tumor programmed death ligand-1 (PD-L1) expression [8]. The KEYNOTE-

028 study showed that pembrolizumab can achieve an ORR of 30% in overall patients, with a mOS of 7 months and a median progression-free survival (mPFS) of 1.8 months [10]. The KEYNOTE-180 study showed higher OS in PD-L1-positive patients [11].

There is increasing evidence that the presence of systemic inflammatory responses and malnutrition is associated with poorer prognosis in various malignancies [12–14]. Recently, several inflammation-based markers, such as NLR, SII, Godzilla Prognostic Score (GPS), were reported to be prognostic factors for immunotherapy in various malignancies [15–19], including esophageal cancer [20–23]. The CONUT, which consists of serum albumin, peripheral lymphocyte count, and serum total cholesterol, was used to assess early nutritional status. [24, 25]. The relationship between the CONUT score and the perioperative surgical risk and postoperative prognosis of malignancies such as gastric, esophageal, pancreatic, liver, cervical, and bladder cancers has been reported [26–31]. Studies have shown that the CONUT score is related to the prognosis of cancer patients receiving chemotherapy. However, its effectiveness in patients receiving ICI has not been studied [32–34]. The primary objective of this study was to investigate the clinical significance of the CONUT score in patients with esophageal cancer who were treated with ICI.

Methods

Patients

This retrospective study included data of patients diagnosed with esophageal cancer at the Harbin Medical University Cancer Hospital between January 2017 and October 2020. The inclusion criteria were as follows: 1) patients aged 18–80 years; 2) histologically or cytologically confirmed unresectable locally advanced/recurrent or distant metastatic esophageal cancer; unresectable locally advanced patients who cannot receive curative treatment (including curative chemoradiotherapy or radical radiotherapy, etc.); patients who have progressed or relapsed after neoadjuvant or adjuvant therapy; 3) Eastern Cooperative Oncology Group (ECOG) score 0–2; and 4) patients receiving ICI therapy. The exclusion criteria include: 1) history or coexisting with another malignant tumors; 2) patients with acute inflammation, hematological diseases or autoimmune diseases; and 3) the serum level of cholesterol data not available. Finally, 69 patients were included in this study.

Data collection

We collected the basic clinical information of these patients, mainly including: age, sex, ECOG performance status (PS), smoking history, drinking history, Body Mass Index (BMI), the location of primary tumor, pathological type, ICI treatments cycle, squamous cell carcinoma antigen (SCC-Ag), and number of prior treatments. In addition, we also evaluate NLR, SII. The time-dependent receiver operating characteristic (ROC) curves for 1-year OS showed that the optimal cut-off values for NLR and SII were 2.24 and 837.05, respectively (Fig. 1). We collected data including the serum albumin, total cholesterol, and peripheral blood lymphocyte count within 1 month before the first ICI treatment, as the assessment of the CONUT score (Table 1). A study of the cut-off value of CONUT score based on the 1-year OS time-dependent ROC curve showed that the most suitable cut-off value for CONUT score was 1 (AUC; 0.619,

95%CI: 0.477–0.762; sensitivity 0.565; specificity 0.696) (Fig. 1). Therefore, we chose the optimal cut-off value of the CONUT score as 1, and divided 69 patients into the low CONUT score group (CONUT ≤ 1) and the high CONUT score group (CONUT > 1). NLR was calculated by dividing the neutrophil count by the lymphocyte count. SII was calculated by multiplying the platelet count by the neutrophil count divided by the lymphocyte count. We collected patient follow-up data until December 9, 2021 or the date of death.

Informed consent was waived due to retrospective retrieval of patient data. Ethical approval was obtained before the study began from the Ethics Committee of Harbin Medical University Cancer Hospital.

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

Variable	Range	Score
Serum albumin (g/dL)	≥ 3.50	0
	3.00–3.49	2
	2.50–3.49	4
	< 2.50	6
Cholesterol (mg/dL)	≥ 180	0
	140–179	1
	100–139	2
	< 100	3
Cholesterol (mg/dL)	≥ 1600	0
	1200–1599	1
	800–1199	2
	< 800	3
CONUT, Controlling Nutritional Status		

Tumor assessment

To assess treatment response, planned computed tomography or magnetic resonance imaging was performed every 3 months according to the RECIST criteria 1.1 or clinical deterioration in patients. To eliminate the influence of immunotherapy pseudo-progression, we selected the response rate (RR) and the disease control rate (DCR) after 12 weeks of treatment. The RR was defined as the ratio of the sum of complete response (CR) plus partial response (PR). The DCR was defined as the ratio of the sum of CR and PR and stable disease (SD). The PFS was defined as the time from the first treatment cycle with ICI agent to radiographically recorded disease progression or death or the last follow-up. The OS was defined

as the time from the first treatment with ICI agent to death, or was censored at the date of last patient contact.

Statistical analyses

All of the statistical analyses were performed using SPSS v23.0 (IBM, Armonk, NY, USA) and R software programs. The Fisher's exact test was used to compare categorical data. The Kaplan-Meier method was used to estimate survival probabilities, and differences in survival probabilities were analyzed using the Wilcoxon test and the log-rank test. Cox multivariate regression analysis was performed, Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. And P value of < 0.05 were considered to indicate statistical significance.

Results

Patients' characteristics

Table 2
Patient characteristics treated with ICI

Variable	Value
Age (years old)	
Median [range]	60[44–78]
< 52	9
≥ 52	60
Gender	
Male	67
Female	2
PS	
0	48
1	21
Smoking history	
Yes	37
No	32
Drinking history	
Yes	46
No	23
BMI (kg/m²)	
< 21.87	30
≥21.87	39
The location of primary tumor	
Cervical esophagus	2
Upper thoracic	11
Middle thoracic	32
Lower thoracic	24
Esophagogastric junction	0

PS, performance status; BMI, Body Mass Index; ICI, Immune checkpoint inhibitors; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate; CONUT, Controlling Nutritional Status.

Variable	Value
Pathological type	
Adenocarcinoma	0
Squamous cell carcinoma	69
Radiotherapy or not	
Yes	31
No	38
ICI treatments cycle	
< 6	60
≥6	9
Number of prior treatments	
0	59
1	8
≥2	2
Squamous cell carcinoma antigen (μg/L)	
< 2.6	49
≥2.6	20
SII	
Median [range]	637.41[145.41-3987.28]
< 837.05	45
≥837.05	24
NLR	
Median [range]	2.43[0.77–20.44]
< 2.24	28
≥ 2.24	41
CONUT score	
Median [range]	1.62[0–7]

PS, performance status; BMI, Body Mass Index; ICI, Immune checkpoint inhibitors; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate; CONUT, Controlling Nutritional Status.

Variable	Value
0	18
1	24
2	11
3	7
4	4
5	3
6	0
7	2
8	0
9	0

PS, performance status; BMI, Body Mass Index; ICI, Immune checkpoint inhibitors; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate; CONUT, Controlling Nutritional Status.

The baseline characteristics of the 69 patients are summarized in Table 2. The median age of patients was 60 years (range, 44–78 years), and 67 patients (97.1%) were male. Thirty-seven patients (53.6%) had a history of smoking, and 46 patients (66.7%) had a history of drinking. Twenty-one patients (30.4%) had an ECOG PS of 1. According to the assessment of BMI, 30 patients (43.5%) were divided into low BMI group (BMI < 21.87Kg/m^2), and 39 patients (56.5%) were divided into high BMI group (BMI ≥ 21.87Kg/m^2). The location of the primary tumor in all patients was as follows: cervical esophagus, n = 2 (2.9%); upper thoracic, n = 11 (15.9%); middle thoracic, n = 32 (46.4%); lower thoracic, n = 24 (34.8%); esophagogastric junction, n = 0 (0%). The pathological type of all patients (100%) was squamous cell carcinoma. Thirty-one patients (44.9%) received radiotherapy and all patients (100%) received chemotherapy. Nine patients (13.0%) used ICI for more than 6 cycles. ICI was administered to 59 patients (85.5%) for the first treatment; 8 (11.6%) for the second treatment; and 2 (2.9%) for the third and subsequent treatment. According to the assessment of SCC-Ag, 49 patients (71.0%) were classified into the low SCC group (< 2.6μg/L), while 20 patients (29.0%) were classified into the high SCC group (≥ 2.6μg/L). The mean SII was 637.41 (range, 145.41-3987.28). Forty-five patients (65.2%) were classified as the low SII group (< 837.05). The mean NLR was 2.43 (range 0.77–20.44). Forty-one patients (59.4%) were classified in the high NLR group (≥ 2.24). The mean CONUT score was 1.62 (range, 0–7), of which 42 (60.9%) were classified as the low CONUT (CONUT ≤ 1).

Associations between CONUT score and clinicopathological parameters in esophageal cancer patients treated with ICI

We assessed the associations between CONUT score and clinicopathological parameters in esophageal cancer patients treated with ICI (Table 3). There were no significant differences in age, gender, PS, smoking history, drinking history, BMI, the location of primary tumor, radiotherapy history, ICI treatment cycle, number of prior treatments, SCC, and SII between the high and low CONUT groups. In addition, patients with the low NLR in the low CONUT group were significantly higher than those in the high CONUT group [23/42 (54.76%) *vs.* 5/27 (18.52%); respectively; P = 0.003].

The response and survival in esophageal cancer patients treated with ICI

The clinical responses of the 69 patients were as follows: PR, n = 28; CR, n = 6; SD, n = 14; and progress disease (PD), n = 21. Therefore, the RR was 49.28% (34/69), and the DCR was 69.57% (48/69). The DCR of the high SII group was significantly lower than that of the low SII group (78.26% vs. 52.17%, P = 0.050) (Table 4). The RR of the high NLR group was significantly lower than that of the low NLR group (67.86% and 36.59%, P = 0.015). The DCR of the high NLR group was significantly lower than that of the low NLR group (92.86% and 53.66%, P = 0.000). The DCR was worse in the high CONUT group than the low CONUT group (80.95% vs 51.85%, P = 0.016). Other factors were not related to RR or DCR.

The PFS and OS of all esophageal cancer patients treated with ICI are shown in Fig. 2. The 1-year PFS rate and mPFS were 49.28% and not reached, respectively. The 1-year OS rate and mOS were 66.67% and 18.3 months, respectively.

Table 3
Associations between CONUT score and clinicopathological parameters in esophageal cancer patients treated with ICI

Variable	Group	Total	Low CONUT(≤ 1)	High CONUT(>1)	P value*
Age (years old)	< 52	9	**4**	**5**	0.299
	≥ 52	60	**38**	**22**	
Gender	Male	67	**40**	**27**	0.517
	Female	2	**2**	**0**	
PS	0	48	**33**	**18**	0.116
	1	21	**9**	**12**	
Smoking history	Yes	37	**24**	**13**	0.621
	No	32	**18**	**14**	
Drinking history	Yes	46	**29**	**17**	0.612
	No	23	**13**	**10**	
BMI (kg/m²)	< 21.87	30	**15**	**15**	0.137
	≥ 21.87	39	**27**	**12**	
The location of primary tumor	Middle thoracic	32	**21**	**11**	0.471
	Non- Middle thoracic	37	**21**	**16**	
Radiotherapy or not	Yes	31	**16**	**15**	0.216
	No	38	**26**	**12**	
ICI treatments cycle	< 6	60	**35**	**25**	0.466
	≥ 6	9	**7**	**2**	
Number of prior treatments	0	59	**36**	**23**	0.432
	≥ 1	10	**6**	**4**	
SCC-Ag(μg/L)	< 2.6	49	**32**	**17**	0.283
	≥ 2.6	20	**10**	**10**	

*, Fisher's exact test. CONUT, Controlling Nutritional Status; PS, performance status; BMI, Body Mass Index; ICI, Immune checkpoint inhibitors; SCC-Ag, Squamous cell carcinoma antigen; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate.

Variable	Group	Total	Low CONUT(≤ 1)	High CONUT(>1)	P value*
SII	< 837.05	45	**30**	**15**	0.203
	≥ 837.05	24	**12**	**12**	
NLR	< 2.24	28	**23**	**5**	0.003
	≥ 2.24	41	**19**	**22**	

*, Fisher's exact test. CONUT, Controlling Nutritional Status; PS, performance status; BMI, Body Mass Index; ICI, Immune checkpoint inhibitors; SCC-Ag, Squamous cell carcinoma antigen; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate.

Table 4
Response and disease control rate in esophageal cancer patients treated with ICI

Variable	RR	DCR
Age (< 52 VS. ≥52)	33.33% VS. 51.67%	44.44% VS. 73.33%
Gender (male VS. female)	50.75% VS. 0.00%	70.15% VS. 50.00%
PS (0 VS. 1)	45.83% VS.57.14%	72.92% VS. 61.90%
Smoking history (Yes VS. No)	45.95% VS. 53.13%	67.57% VS. 71.88%
Drinking history (Yes VS. No)	54.35% VS.39.13%	71.74% VS. 65.22%
BMI (< 21.87 VS. ≥21.87)	46.67% VS. 51.28%	63.33% VS. 74.36%
The location of primary tumor (M VS. Non- M)	43.75% VS. 54.05%	68.75% VS. 70.27%
Pathological type (SCC VS. Non-SCC)	49.28% VS. 0.00%	69.56% VS. 0.00%
Radiotherapy or not (Yes VS. No)	48.39% VS. 50.00%	70.97% VS. 68.42%
Number of ICI treatments (< 6 VS. ≥6)	46.67% VS. 66.67%	65.00% VS. 100.00%
Number of prior treatments (0 VS. ≥1)	54.24% VS. 20.00%	76.27% VS. 30.00%
SCC-Ag (< 2.6 VS. ≥2.6)	53.06% VS. 40.00%	73.47% VS. 60.00%
SII (< 837.05 VS. ≥837.05)	56.52% VS. 34.78%	78.26% VS. 52.17%*
NLR (< 2.24 VS. ≥2.24)	67.86% VS. 36.59%**	92.86% VS. 53.66%***
CONUT score (≤ 1 VS. >1)	57.14% VS. 37.04%	80.95% VS. 51.85%****

*, P = 0.050; **, P = 0.015; ***, P = 0.000; ****, P = 0.016 (Fisher's exact test). CONUT, Controlling Nutritional Status; PS, performance status; BMI, Body Mass Index; M, Middle thoracic; Non- M, Non-Middle thoracic; SCC, Squamous cell carcinoma; Non-SCC, Non- Squamous cell carcinoma; ICI, Immune checkpoint inhibitors; SCC-Ag, Squamous cell carcinoma antigen; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate.

Based on the univariate analysis, we found that the presence of prior therapy and non-mid-thoracic esophageal cancer were significantly associated with shorter PFS.According to the Kaplan-Meier survival analysis, 1-year PFS rate of patients with middle thoracic esophageal cancer was 62.50%, while the 1-year PFS rate of patients with non-middle thoracic esophageal cancer was 37.84% (P = 0.043). The 1-year PFS rate was 55.93% in no prior treatment patients, while that of the patients with prior treatment was 10.00% (P = 0.008). The 1-year PFS rates of the high NLR group and the low NLR group were 34.15% and 71.43%, respectively (P = 0.003). The 1-year PFS rates of the low CONUT and high CONUT groups were 60.00% and 29.17%, respectively (P = 0.028) (Table 5). The PFS curves in ICI patients according to SII, NLR and CONUT scores are shown in Fig. 3.

Table 5
Results of the univariate analysis of factors predicting the PFS and OS

Variable	PFS		OS	
	1-year survival rate	P value*	1-year survival rate	P value*
Age (< 52 VS. ≥52)	33.33% VS. 50.82%	0.308	33.33% VS. 71.67%	0.024
Gender (male VS. female)	49.25% VS. 50.00%	0.984	67.16% VS. 50.00%	0.614
PS (0 VS. 1)	54.17% VS. 38.10%	0.223	70.83% VS. 57.14%	0.270
Smoking history (Yes VS. No)	51.35% VS. 46.88%	0.713	64.86% VS. 68.75%	0.735
Drinking history (Yes VS. No)	52.17% VS. 43.48%	0.499	67.39% VS. 65.21%	0.858
BMI(< 21.87 VS. ≥21.87)	40.00% VS. 56.41%	0.111	56.67% VS. 74.36%	0.087
The location of primary tumor (M VS. Non- M)	62.50% VS. 37.84%	0.043	68.75% VS. 64.86%	0.735
Radiotherapy or not (Yes VS. No)	61.29% VS. 39.47%	0.073	67.74% VS. 65.79%	0.865
Number of ICI treatments (< 6 VS. ≥6)	48.33% VS. 55.56%	0.688	61.67% VS. 100.0%	0.024
Number of prior treatments (0 VS. ≥1)	55.93% VS. 10.00%	0.008	72.88% VS. 30.00%	0.008
SCC-Ag (< 2.6 VS. ≥2.6)	55.10% VS. 35.00%	0.133	73.47% VS. 50.00%	0.063
SII (< 837.05 VS. ≥837.05)	57.14% VS. 37.04%	0.106	82.22% VS. 37.50%	0.001
NLR (< 2.24 VS. ≥2.24)	71.43% VS. 34.15%	0.003	92.86% VS. 48.78%	0.000
CONUT score (≤ 1 VS. >1)	60.00% VS. 29.17%	0.028	76.19% VS. 51.85%	0.038

*, Wilcoxon test. CONUT, Controlling Nutritional Status; PS, performance status; BMI, Body Mass Index; M, Middle thoracic; Non- M, Non- Middle thoracic; ICI, Immune checkpoint inhibitors; SCC-Ag, Squamous cell carcinoma antigen; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate.

Based on univariate analysis of OS-related factors showed that patients with not less than 6 cycles of immunotherapy and no prior treatment were associated with longer OS. In a Kaplan-Meier survival analysis showed that the 1-year OS rate of esophageal cancer patients with not less than 6 cycles immunotherapy was 100.00%, while the 1-year OS rate of patients with less than 6 cycles immunotherapy was 61.67% (P = 0.024). The 1-year OS rate was 72.88% in patients with no prior treatment, compared with 30.00% in patients with prior treatment (P = 0.008). The 1-year OS rate of patients in the high SII group was 37.50%, and the 1-year OS rate of the patients in the low SII group was 82.22% (P = 0.001). The 1-year OS rates of patients in the low NLR group and the high NLR group were 92.86% and 48.78%, respectively (P = 0.000). The 1-year OS rates of patients in the low and high CONUT groups were 76.19% and 51.85%, respectively (P = 0.038) (Table 5). The OS curves in ICI patients according to SII, NLR and CONUT scores are shown in Fig. 4. A multivariate analysis revealed that the CONUT score, NLR, and SII were the independent prognostic factors in esophageal cancer patients treated with ICI (HR, 2.056; 95% CI, 1.031–4.098, P = 0.041; HR, 2.830; 95% CI, 1.235–6.482, P = 0.014; HR, 2.487; 95% CI, 1.245–4.969, P = 0.010; respectively) (Table 6).

Table 6
Results of the multivariate Cox regression analysis of factors predicting the PFS and OS

Variable	PFS		OS	
	Hazard ratio (95%)	P value*	Hazard ratio (95%)	P value*
SII (< 837.05 *VS.* ≥837.05)	1.644(0.590–4.579)	0.341	2.487(1.245–4.969)	0.010
NLR (< 2.24 *VS.* ≥2.24)	1.098(0.382–3.157)	0.862	2.830(1.235–6.482)	0.014
CONUT score (≤ 1 *VS.* >1)	1.299(0.521–3.239)	0.575	2.056(1.031–4.098)	0.041

*, a proportional regression hazard model. CONUT, Controlling Nutritional Status; SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate.

Discussion

This is the first study to examine the relationship between ICI therapy and the nutritional status in patients with esophageal cancer. In our study, ICI-treated esophageal cancer patients in the high CONUT group (CONUT > 1) had significantly worse OS and PFS compared to the low CONUT group (CONUT ≤ 1). We also found that the CONUT score was an independent predictor of ICI treatment effect and OS. We therefore believe that the CONUT score may serve as a potential early predictive marker in esophageal cancer patients who want to benefit from ICI therapy.

The CONUT scores included serum albumin and total cholesterol and total lymphocyte count in peripheral blood. Serum albumin mainly reflects the body's ability to synthesize protein, serum total cholesterol reflects the body's ability to metabolize lipids, and the total lymphocyte count in peripheral blood reflects the body's immune function [35]. Subjective Global Assessment (SGA) and the Full Nutritional Assessment are relatively complex, while the CONUT score provides an easier and more

objective assessment of a patient's nutritional status [36]. Thus, a higher CONUT scores could reflect not only malnutrition, but also systemic inflammation and an impaired immune responses. In addition, the CONUT scores can be retrospectively studied in relation to clinical outcomes. Therefore, we retrospectively investigated the relationship between the CONUT scores and patient outcomes. We found that the proportion of patients with a lower CONUT score in the low NLR group tended to be significantly higher than the proportion of patients with a low CONUT score in the high NLR group (Table 3). One possible explanation is that both the COUNT score and the NLR are related to the total lymphocyte count in peripheral blood.

Previous studies have reported the influence of the CONUT score on preoperative prognosis [27, 28]. Studies have shown that the CONUT score is an independent prognostic factor for relapse-free survival (RFS) and OS in patients with resectable thoracic esophageal squamous cell carcinoma (ESCC) [35].Recently, it was reported [37] that the CONUT score could be used to predict the prognosis of non-small cell lung cancer patients receiving pembrolizumab. In this report, compared with the high CONUT score group (CONUT > 2), the low CONUT score group (CONUT $\leq$ 2) was associated with significantly longer PFS and OS. And they found that the CONUT score were independent prognostic factors of OS ($P < 0.05$). However, this retrospective study had a small number of patients and may be biased. Currently, there are no relevant reports on the CONUT score in predicting treatment outcome in patients with esophageal cancer treated with ICI. In the present study, we show for the first time that patients with esophageal cancer with the high CONUT score treated with ICI had significantly worse OS and PFS compared with patients with the low CONUT score.

ICI is a cancer therapy that targets co-inhibitory signaling on the surface of T cells, resulting in long-lasting antitumor responses by disabling the braking mechanism of the immune system [38]. Phase II clinical trials ATTRACTION-1 study and KEYNOTE-180 study showed the efficacy and safety of ICI as third-line treatment of advanced esophageal cancer [5, 11]. In 2019, the phase III KEYNOTE-181 [7] study showed that among patients with a PD-L1 combined positive score (CPS) $\geq$ 10, the mOS in the pembrolizumab group was 9.3 months, compared with 6.7 months in the chemotherapy group, and there was no significant difference in PFS between two groups. Subgroup analysis found that Asian patients benefited more from pembrolizumab treatment. The results of the ATTRACTION-3 study showed that [8], regardless of the level of PD-L1 expression in patients, the nivolumab group could improve the OS of patients by 2.5 months and reduce the risk of death by 23%. More and more studies have demonstrated the safety and efficacy of ICI in patients with advanced esophageal cancer. ONO4538 is a phase II clinical study [6] to investigate the efficacy of nivolumab in patients with advanced ESCC who are refractory or intolerant to fluoropyrimidine, platinum and taxane chemotherapy. The results showed an OS of 10.8 months and a PFS of 2.8 months, suggesting that nivolumab may be a potential treatment option for patients with advanced ESCC who are refractory or intolerant. At this stage, we still need to further explore the role and mechanism of ICI in patients with esophageal cancer, so that more advanced esophageal cancer patients can benefit from ICI.

As immunotherapy plays an increasingly important role in cancer treatment, the research on tumor biomarkers related to its therapeutic effect is also continuously applied. Biomarkers currently used to assess whether there is a good response to immunotherapy mainly include PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI). The expression of MHC-II molecules [39], CD8 expression in tumor-infiltrating lymphocytes (TIL) and lack of DNA mismatch repair system [40] have also recently been shown to be biomarkers. Neoantigen [41] is another biomarker that has been used to predict the effect of anti-PD-1 therapy in esophageal cancer. However, the correlation between these biomarkers has not yet been investigated, so we plan to study the correlation of various biomarkers in ICI treatment in the future.

This study has certain limitations. First, because this study was a single-institution retrospective study, the number of patients treated with ICI was relatively small. In addition, many patients are lost because serum total cholesterol levels are not considered important in esophageal cancer chemotherapy treatment. Third, the current retrospective study cannot include factors that may influence inflammation and nutritional status. Therefore, we need prospective studies to overcome these problems.

In conclusion, the CONUT score can be used as a biomarker to predict the efficacy and prognosis of esophageal cancer patients receiving ICI therapy, and can be used to guide advanced esophageal cancer patients who want to benefit from ICI therapy.

Declarations

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Date Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics Statement

This study was reviewed and approved by the Board of Directors of Harbin Medical University Cancer Hospital. Written informed consent has been obtained from study participants for the publication of any potentially identifiable images or data contained herein.

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Figures

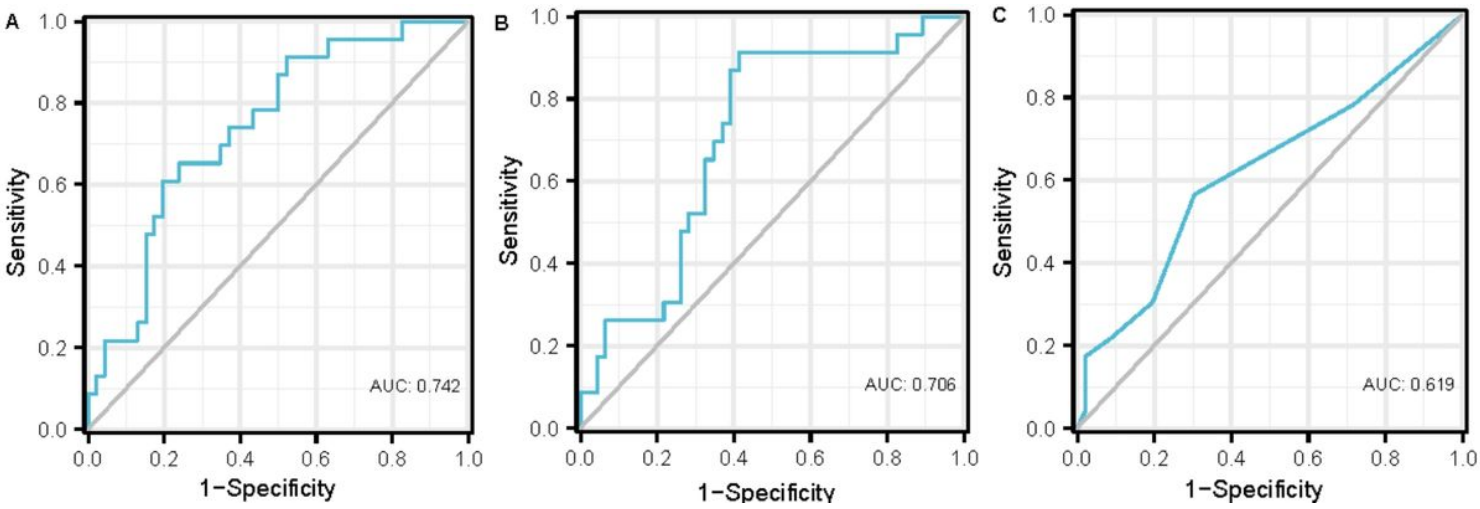

Figure 1

The time-dependent receiver operating characteristic (ROC) curve for 1-year overall survival (OS). ROC according to systemic immune-inflammatory index (SII) (A). Area under the curve (AUC) =0.742. ROC according to neutrophil-to-lymphocyte ratio (NLR) (B). AUC=0.706. ROC according to controlling Nutritional Status (CONUT) (C). AUC=0.619.

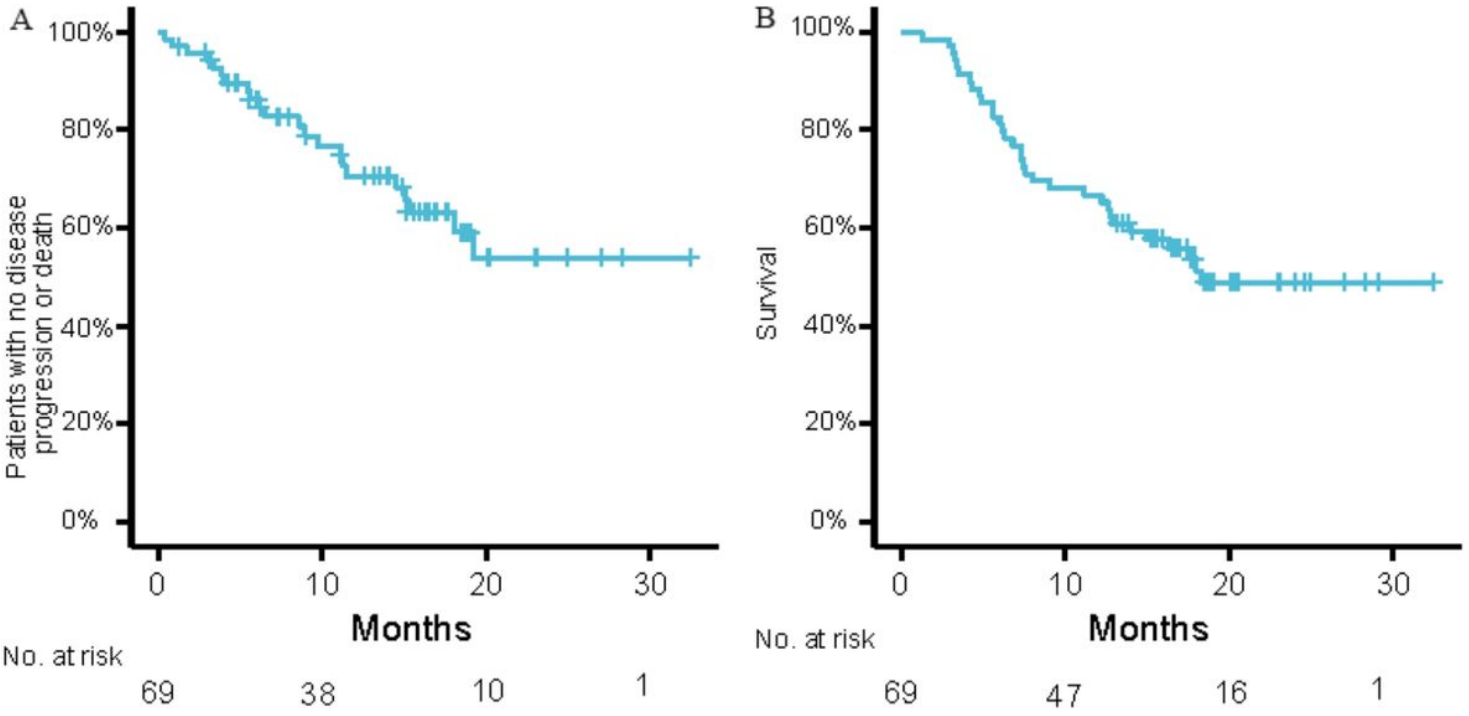

Figure 2

Survival curves of the esophageal cancer patients treated with ICI. Kaplan-Meier estimates of progression-free survival（PFS） (**A**) and overall survival（OS） (**B**).

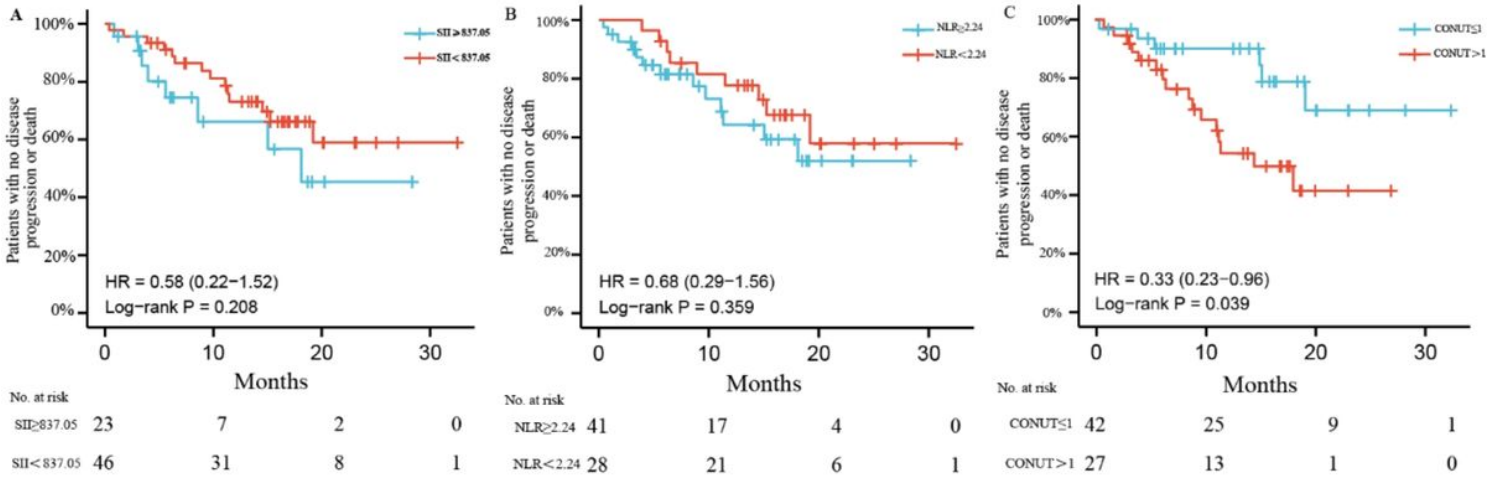

Figure 3

Progression-free survival (PFS) curves in esophageal cancer patients treated with ICI. PFS according to the SII (A); PFS according to the NLR (B); and PFS according to the CONUT score (C). SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate; CONUT, Controlling Nutritional Status.

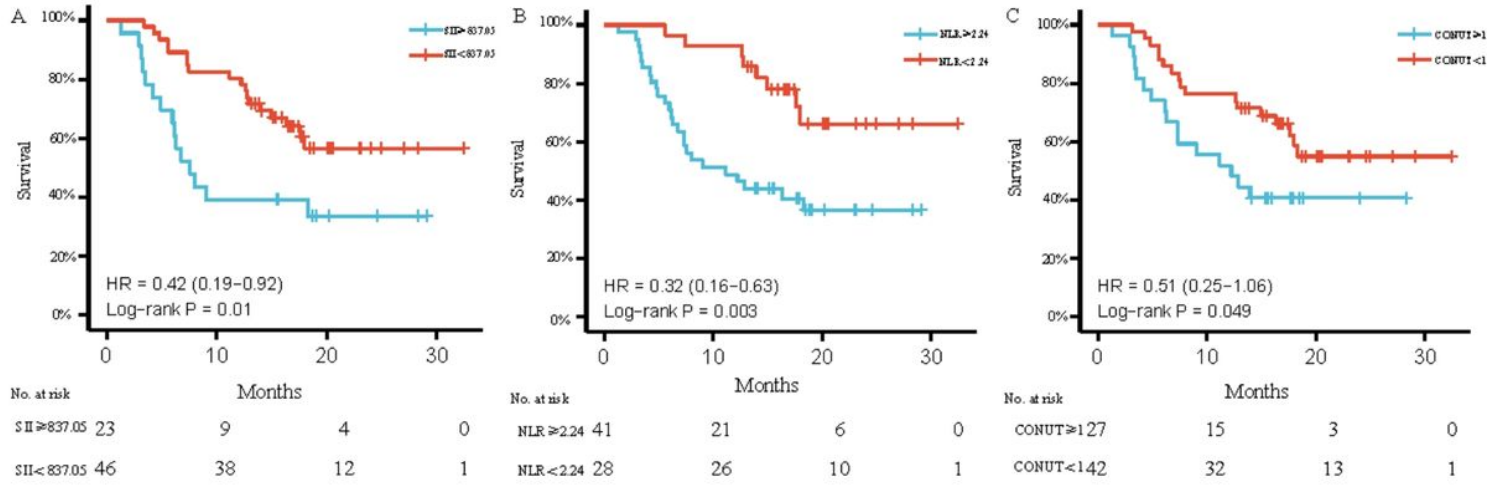

Figure 4

Overall survival (OS) curves in the esophageal cancer patients treated with ICI. OS according to the SII (A); OS according to the NLR (B); and OS according to the CONUT score (C). SII, systemic immune-inflammation index; NLR, neutrophile-to-lymphocyte rate; CONUT, Controlling Nutritional Status.