Original Article

The prognostic value of the controlling nutritional status (CONUT) score in predicting outcomes of esophageal cancer patients receiving radiotherapy with or without chemotherapy

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Background: Controlling nutritional status (CONUT) scores and systemic immune-inflammation index (SII) values are associated with the prognosis of several common malignancies. The current study aimed to explore the prognostic value of CONUT scores and SII values in patients with esophageal cancer (EC) receiving radical radiotherapy (RT) or concurrent chemoradiotherapy (CCRT).

Methods: We calculated the pre-RT CONUT scores and SII values of 62 patients with EC receiving RT or CCRT. Receiver operating characteristic (ROC) curves were used to determine the adequate cut-off values. The Kaplan-Meier method and Cox proportional hazard model were used to analyze the association between CONUT scores and SII values and prognosis.

Results: The 1-year progression-free survival (PFS) and 1-year overall survival (OS) rates of the 62 patients were 51.61% and 66.13%, respectively. Based on the time-dependent ROC curve for the 1-year OS of all patients, the optimal cut-off value was 622.02 for the SII and a score of 1 for the CONUT score. The univariate analysis showed that the CONUT score (P=0.036), tumor-nodal-metastasis (TNM) stage (P<0.01), and CCRT (P=0.008) significantly affected the survival of EC patients. The multifactorial analysis showed that the CONUT score (P=0.041) and TNM stage (P<0.01) were independent prognostic factors affecting clinical outcomes in patients with EC undergoing radical RT or CCRT.

Conclusions: The pre-RT CONUT score could be an effective predictor of prognosis in patients with EC receiving radical RT or CCRT; however, the pre-RT SII value had no clinical value in predicting survival in our study.

Keywords: Controlling nutritional status (CONUT); radiotherapy (RT); esophageal cancer (EC); systemic immune-inflammatory index (SII)

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Introduction

According to the latest data, esophageal cancer (EC) is the 10th most commonly diagnosed cancer and the sixth leading cause of cancer-related death worldwide (1). China has the highest incidence and mortality rate of EC, and 90% of EC patients have esophageal squamous cell carcinoma (2). However, the incidence of EC is insidious, and about 50% of EC patients are at relatively advanced stages at the time of their initial treatment or lose the opportunity to undergo surgery due to old age or underlying diseases (3).

As one of the main treatments for patients with locally advanced EC without surgical indications, radiotherapy (RT) occupies an important position in the treatment of EC (4). The probability of local RT failure is high due to RT resistance or tumor heterogeneity, and the 5-year survival rate for conventional RT in patients with non-surgical EC is only 10%; however, the relevant clinical factors affecting radiosensitivity are unclear (5,6). A growing number of recent studies (7,8) have reported that malnutrition and systemic inflammatory responses predict poor prognosis for several common cancers.

The incidence of malnutrition in patients with malignancies is as high as 40–80%, and at 67–85%, the proportion of malnutrition in patients with EC is the highest among all malignancies (7-9). Chemotherapy-induced nausea, vomiting, decreased appetite, and RT-induced esophageal mucositis can affect feeding and lead to an increased incidence of malnutrition (10). Inflammation is involved in the whole process of tumorigenesis and treatment. A study has shown that the inflammatory response of tumor patients is closely related to patient prognosis (11). Commonly used indicators to assess the nutritional and inflammatory status of the body include the controlling nutritional status (CONUT) score and the systemic immune-inflammation index (SII) (12-14).

Developed in 2005, the CONUT score is an index used to assess the nutritional status of patients. It is calculated based on the serum albumin concentration level, lymphocyte count, and cholesterol level. Previous studies have shown that the CONUT score can predict the surgical risk and immunotherapy outcomes for a variety of malignancies (15-17). A recent study noted that high CONUT scores may be a poor prognostic factor for patients with small cell lung cancer receiving RT (18).

The SII is an inflammatory marker that reflects the immune and inflammatory state of the body. Many studies have reported a strong correlation between RT and the body's immune and inflammatory response (11,19,20). The SII is calculated by multiplying the neutrophil count with the platelet count, and dividing the result by the lymphocyte count.

This paper focuses on the clinical significance of CONUT scores and pre-RT SII values in EC patients undergoing RT or concurrent chemoradiotherapy (CCRT) to help identify new prognostic correlates of RT. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1193/rc).

Highlight box

Key findings

- Pre-radiotherapy (RT) controlling nutritional status (CONUT) scores could be an effective predictor of prognosis in patients with esophageal cancer receiving radical RT or concurrent chemoradiotherapy (CCRT).

What is known, and what is new?

- The CONUT score can predict the surgical risk and immunotherapy outcomes for a variety of malignancies.
- The CONUT score could be an effective predictor of prognosis in patients with EC receiving radical RT or CCRT.

What is the implication, and what should change now?

- CONUT scores could be obtained before treatment to predict the prognosis of RT and CCRT patients. Close attention should be paid to patients with high CONUT scores, and further interventions should be administered to patients to prolong their survival time.

Methods

Patients

We retrospectively studied the medical records of patients who received RT or CCRT to treat EC at the Cancer Hospital of Harbin Medical University from July 2017 to June 2020. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) be aged 18–80 years; (II) have been diagnosed with EC but have refused or been unable to tolerate surgery; (III) have histologically or cytologically confirmed EC (IV) have an Eastern Collaborative Oncology Group (ECOG) score of 0–2; and (V) have serum cholesterol data available that had been collected within 1 month before treatment. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had malignancies other than

EC; (II) did not reach the dose of radical RT for EC; and/or (III) had received a second round of RT at the esophageal site. We recommended that all the patients choose RT or CCRT based on their tolerance to the treatment and their individual willingness. All the patients were hospitalized for RT or CCRT. 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 Harbin Medical University Cancer Hospital (No. KY2023-18) and informed consent was obtained from all the patients.

Treatment

All the patients received radical RT with or without CCRT (total RT dose: 50–66 Gy; total RT frequency: 25–33 f). The CCRT regimens mainly comprised paclitaxel combined with platinum or fluoropyrimidine drug 5-fluorouracil. Ultimately, 62 patients were enrolled in this study.

Data collection

We collected basic patient information and laboratory test results through our electronic medical record system, including age, gender, ECOG score, smoking history, drinking history, body mass index (BMI), primary tumor location, pathological type, synchronous chemotherapy, and tumor-nodal-metastasis (TNM) stage. We also collected data, such as serum albumin level, lymphocyte count, and cholesterol level within 1 month prior to RT, to calculate the CONUT score (Table S1). Any patients with incomplete clinicopathological records were excluded from the study.

Short-term efficacy evaluation and follow-up

The patients' responses to treatment were evaluated using short-term efficacy criteria (21) by two experienced doctors. There were three classes of outcomes: complete remission (CR), partial remission (PR), and no remission (NR). The response rate (RR) in this study was defined as the percentage of patients who achieved CR or PR of all the patients enrolled.

We collected follow-up data for patients up to August 27, 2022 or the date of death. Progression-free survival (PFS) was defined as the time between receiving RT and disease progression, death, or the follow-up cut-off date. Overall survival (OS) was defined as the time between receiving RT and death or the follow-up cut-off date.

Statistical analysis

All the recorded data were analyzed using SPSS (version 26.0; IBM, Armonk, NY, USA) and R (version 3.6.3). The categorical variables were compared using Fisher's exact test or the Chi-squared test. Survival probabilities were estimated using the Kaplan-Meier method, and differences in the survival probabilities were analyzed using the Wilcoxon test and the log-rank test. Cox proportional hazards model was used for the univariate and multivariate analyses to investigate the effects of different factors on survival. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. P values <0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves were plotted for prediction to validate the optimal cut-off values for the pre-CONUT score and pre-RT SII value.

Results

Baseline characteristics of patients

A total of 62 patients who met the inclusion criteria were enrolled in this study, and their characteristics are shown in *Table 1*. The patients were all male (100%), and had a median age of 61 years (range, 42–85 years). Of the 62 patients, 37 (59.68%) had a history of smoking, 40 (64.52%) had a history of alcohol consumption, 19 (30.65%) received CCRT, and 25 (40.32%) had an ECOG score ≥1. Based on the BMI assessment, 28 patients (45.16%) were allocated to the low-BMI group (BMI: <22.61 kg/m^2), and 34 patients (54.84%) were allocated to the high-BMI group (BMI: ≥22.61 kg/m^2). The locations of the primary tumor were as follows: cervical esophagus, n=2 (3.23%); upper thoracic segment, n=10 (16.13%); middle thoracic segment, n=20 (32.26%); and lower thoracic segment, n=30 (48.39%). In terms of the pathological type, 60 patients had squamous cell carcinoma (96.77%), one patient had adenocarcinoma (1.6%), and one patient had melanoma (1.6%). None of the patients had RT or CCRT treatment-related deaths.

Identification of optimal cut-off values for pre-CONUT and pre-RT SII value

Based on the time-dependent ROC curves of the 62 patients with 1-year OS, the optimal cut-off value for the pre-RT SII value was 622.02 [area under the curve (AUC): 0.566, 95% CI: 0.415–0.717; sensitivity: 0.409; specificity: 0.775], and the optimal cut-off value for the CONUT score

Table 1 Baseline characteristics of the included patients

Variables	Value
Age (years), median [range]	61 [42–85]
<61	27
≥61	35
Gender	
Male	62
Female	0
ECOG	
0	37
1	22
2	3
Smoking history	
Yes	36
No	26
Drinking history	
Yes	40
No	22
BMI (kg/m^2)	
Median [range]	22.61 [15.75–36.46]
<22.61	33
≥22.61	29
Location of primary tumor	
Cervical esophagus	2
Upper thoracic	10
Middle thoracic	20
Lower thoracic	30
Esophagogastric junction	0
Pathological type	
Adenocarcinoma	1
Squamous cell carcinoma	60
Other	1
Chemotherapy	
CCRT	19
No	43
TNM	
I + II	32
III + IV	30
SII	
Median [range]	598.06 [74.60–3,883.44]
<622.02	43
≥622.02	19
CONUT score	
Median [range]	0.95 [0–5]
0	25
1	19
2	16
3	1
4	0
5	1

ECOG, Eastern Collaborative Oncology Group; BMI, body mass index; CCRT, concurrent chemoradiotherapy; TNM, tumor-nodal-metastasis; SII, systemic immune-inflammation index; CONUT, controlling nutritional status.

was 1 (AUC: 0.607, 95% CI: 0.458–0.756; sensitivity: 0.455; specificity: 0.775). The threshold value was 1 (AUC: 0.607, 95% CI: 0.458–0.756; sensitivity: 0.455; specificity: 0.775) (*Figure 1*). For the subsequent data analysis, the patients were divided into the low CONUT group (a CONUT score ≤1) and the high CONUT group (a CONUT score >1), and the low pre-RT SII group (a SII value <622.02), and the high pre-RT SII group (a SII value ≥622.02).

Correlation between the CONUT score and clinicopathological parameters

We evaluated the relationship between CONUT scores and clinicopathological parameters in patients with EC undergoing RT or CCRT (*Table 2*). There were no statistically significant differences between the high and low CONUT score groups in terms of age, performance status (PS), smoking history, alcohol consumption history, BMI, primary tumor site, previous treatment history, pre-RT SII value, and tumor stage (P>0.05).

Associations between the CONUT score and clinicopathological parameters with short-term efficacy evaluation

The clinical responses of the 62 patients were as follows:

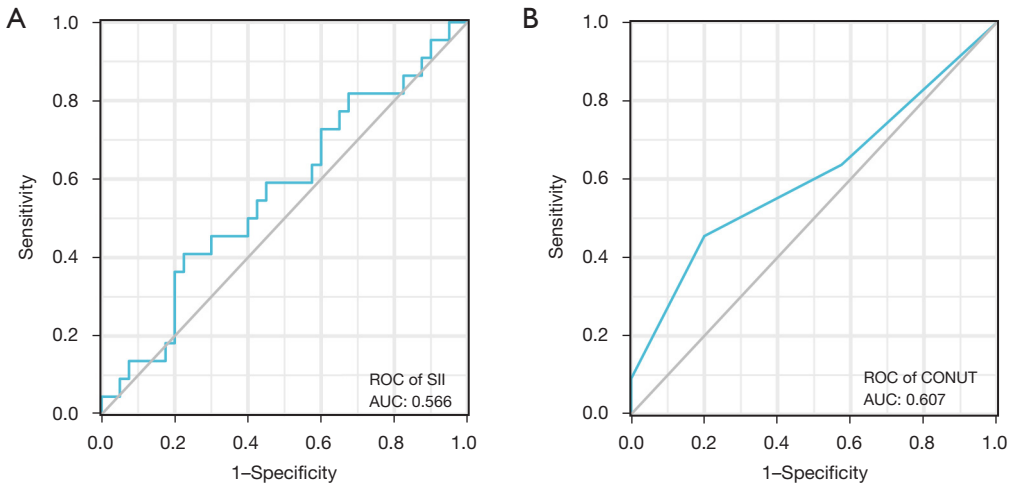

Figure 1 The time-dependent ROC curves for the CONUT score and the SII value for predicting the prognosis of esophageal cancer patients. (A) The ROC curves for discriminating between outcomes using the SII, AUC =0.566; (B). The ROC curves for discriminating between outcomes using the CONUT score, AUC =0.607. ROC, receiver operating characteristic; SII, systemic immune-inflammatory index; AUC, area under the curve; CONUT, controlling nutritional status.

Table 2 Correlations between the CONUT score and clinicopathological parameters

Variables	Group	Total	Low CONUT (≤1)	High CONUT (>1)	P value*
Age (years)	<61	27	21	6	0.299
	≥61	35	23	12	
ECOG	<1	37	28	9	0.320
	≥1	25	16	9	
Smoking history	Yes	36	22	14	0.053
	No	26	22	4	
Drinking history	Yes	40	25	15	0.078
	No	22	19	3	
BMI (kg/m^2)	<22.61	33	22	11	0.426
	≥22.61	29	22	7	
The location of primary tumor	Middle thoracic	20	14	6	0.908
	Non-middle thoracic	42	30	12	
Number of prior treatments	0	23	17	6	0.695
	≥1	39	27	12	
SII	<622.02	43	33	10	0.132
	≥622.02	19	11	8	
TNM	I + II	32	23	9	0.871
	III + IV	30	21	9	

*, Fisher's exact test or chi-square test. CONUT, controlling nutritional status; ECOG, Eastern Collaborative Oncology Group; BMI, body mass index; SII, systemic immune-inflammation index; TNM, tumor-nodal-metastasis.

two patients achieved CR; 26 patients achieved PR; and 34 patients showed NR. Thus, the RR was 45.16% (28/62), and the NR was 54.84% (34/62). The RR was worse in the high CONUT group than in the low CONUT group (38.89% *vs.* 47.73%), and the RR was higher in the low pre-RT SII group than the high SII group (48.84% *vs.* 36.84%), but none of the P values were statistically significant. The RR was significantly lower in the low age group than the high age group (37.04% *vs.* 51.43%), but the analysis showed the same absence of statistically significant P values (*Table 3*).

Table 3 Associations of the CONUT score and clinicopathological parameters with short-term efficacy evaluation

Variables	RR (%)
Age (<61 *vs.* ≥61 years)	37.04 *vs.* 51.43
ECOG (0 *vs.* ≥1)	40.54 *vs.* 52.00
Smoking history (yes *vs.* no)	50.00 *vs.* 42.50
Drinking history (yes *vs.* no)	44.00 *vs.* 45.95
BMI (<22.61 *vs.* ≥22.61 kg/m^2)	48.48 *vs.* 41.38
The location of primary tumor (M *vs.* Non-M)	45.00 *vs.* 47.50
CCRT (yes *vs.* no)	52.63 *vs.* 41.86
SII (<622.02 *vs.* ≥622.02)	48.84 *vs.* 36.84
TNM stage (I + II *vs.* III + IV)	46.88 *vs.* 43.33
CONUT score (≤1 *vs.* >1)	47.73 *vs.* 38.89

Fisher's exact test or chi-square test. CONUT, controlling nutritional status; RR, response rate; ECOG, Eastern Collaborative Oncology Group; BMI, body mass index; M, middle thoracic; Non-M, non-middle thoracic; CCRT, concurrent chemoradiotherapy; SII, systemic immune-inflammation index; TNM, tumor-nodal-metastasis.

Univariate and multivariate analysis of predictors of PFS and OS in patients with EC receiving RT or CCRT

The PFS and OS of all the EC patients who received RT or CCRT are shown in *Figure 2*. The 1-year PFS rate and median PFS rate were 51.61% and 33.7 months, respectively, and the 1-year OS rate and median OS rate were 66.13% and 45.5 months, respectively. The univariate analysis showed that TNM stage and CCRT were significant prognostic factors for PFS. The PFS curves for patients based on the CONUT scores versus pre-RT SII values are shown in *Figure 3*. According to the Kaplan-Meier survival analysis, the 1-year PFS rate was significantly better in the group receiving CCRT than the RT alone group (69.57% *vs.* 40.00%, P=0.008). The 1-year PFS rates for patients with TNM stage (III + IV) versus TNM stage (I + II) were 78.12% and 23.33%, respectively (P<0.01) (*Table 4*). The multifactorial analysis showed that TNM stage and CONUT score were independent prognostic factors for PFS in EC patients treated with radical RT (HR: 2.713; 95% CI: 1.435–5.132, P=0.020; HR: 2.011; 95% CI: 1.068–3.787, P=0.030, respectively) (*Table 5*).

The univariate analysis based on the factors associated with OS showed that the 1-year OS rates were 72.72% and 44.44% in the low CONUT and high CONUT groups,

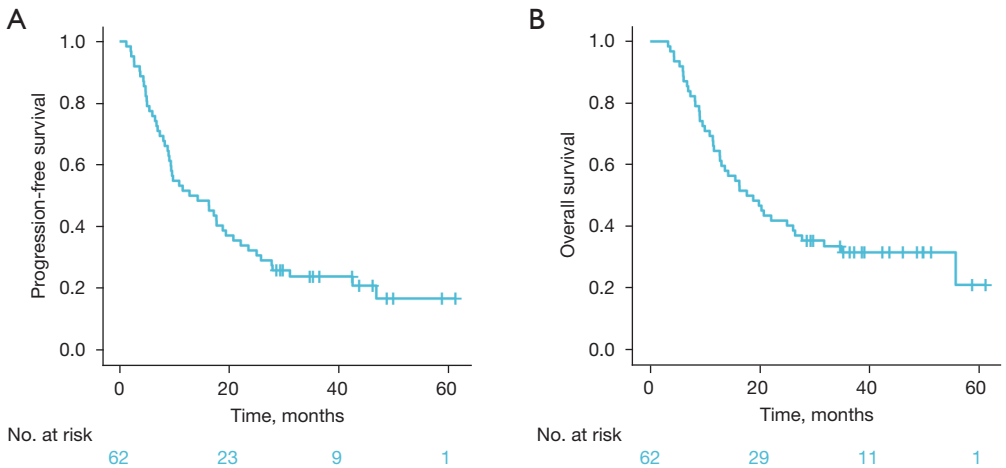

Figure 2 The Kaplan-Meier curve for the PFS (A) and OS (B) of patients with esophageal cancer treated with radical radiotherapy or concurrent chemoradiotherapy. PFS, progression-free survival; OS, overall survival.

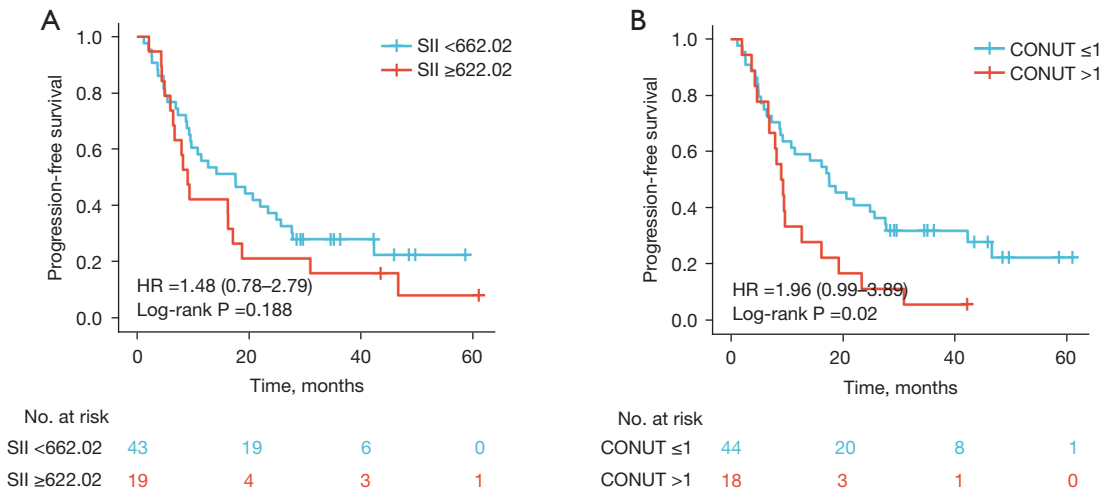

Figure 3 PFS curves in esophageal cancer patients treated with radical radiotherapy or concurrent chemoradiotherapy. (A) PFS according to the SII; (B) PFS according to the CONUT score. SII, systemic immune-inflammation index; HR, hazard ratio; CONUT, controlling nutritional status; PFS, progression-free survival.

Table 4 Univariate analysis of predictors of PFS and OS in patients with esophageal cancer receiving RT or CCRT

Variables	PFS		OS	
	1-year survival rate (%)	P value*	1-year survival rate (%)	P value*
Age (<61 *vs.* ≥61 years)	44.44 *vs.* 57.14	0.204	42.14 *vs.* 70.37	0.401
ECOG (0 *vs.* ≥1)	50.05 *vs.* 48.00	0.797	67.57 *vs.* 60.00	0.545
Smoking history (no *vs.* yes)	60.00 *vs.* 45.95	0.441	80.00 *vs.* 50.05	0.038
Drinking history (no *vs.* yes)	45.45 *vs.* 52.50	1.000	72.72 *vs.* 60.00	0.320
BMI (<22.61 *vs.* ≥22.61 kg/m^2)	54.55 *vs.* 48.27	0.449	63.64 *vs.* 62.07	0.708
The location of primary tumor (non-M *vs.* M)	45.00 *vs.* 33.34	0.590	71.42 *vs.* 45.00	0.102
CCRT (no *vs.* yes)	40.00 *vs.* 69.57	0.008	52.50 *vs.* 86.36	0.008
TNM (I + II *vs.* III + IV)	78.12 *vs.* 23.33	<0.01	90.62 *vs.* 36.67	<0.01
SII (<622.02 *vs.* ≥622.02)	55.81 *vs.* 42.11	0.172	71.43 *vs.* 52.63	0.197
CONUT score (≤1 *vs.* >1)	59.10 *vs.* 33.33	0.096	72.72 *vs.* 44.44	0.036

*, Wilcoxon test. PFS, progression-free survival; OS, overall survival; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; ECOG, Eastern Collaborative Oncology Group; BMI, body mass index; M, middle thoracic; Non-M, non-middle thoracic; TNM, tumor-nodal-metastasis; SII, systemic immune-inflammation index; CONUT, controlling nutritional status.

respectively (P=0.036). Patients with TNM stage (I + II) had a significantly higher 1-year OS rate than those with TNM stage (III + IV) (90.62% *vs.* 36.67%, P<0.01). The 1-year OS rate was significantly higher in patients receiving CCRT than patients receiving RT alone (52.50% *vs.* 86.36%, P=0.008). The OS curves of the patients based on CONUT scores versus pre-RT SII values are shown in *Figure 4*. This study showed that the pre-RT SII values before RT were not associated with the prognosis of the EC patients who received RT or CCRT. The multifactorial analysis showed that the CONUT score (HR: 1.965; 95% CI: 1.030–3.751, P=0.041) and TNM stage (HR: 3.766; 95% CI: 1.858–7.632, P<0.01) were independent prognostic factors for OS among the EC patients receiving RT or CCRT (*Table 5*).

Table 5 Multivariate analysis of predictors of PFS and OS in patients with esophageal cancer receiving RT or CCRT

Variables	PFS		OS	
	Hazard ratio (95% CI)	P value*	Hazard ratio (95% CI)	P value*
CCRT (yes *vs.* no)	0.515 (0.257–1.034)	0.062	0.469 (0.216–1.018)	0.056
TNM stage (I + II *vs.* III + IV)	2.713 (1.435–5.132)	0.020	3.766 (1.858–7.632)	<0.01
CONUT score (≤1 *vs.* >1)	2.011 (1.068–3.787)	0.030	1.965 (1.030–3.751)	0.041

*, Cox proportional hazards regression models. PFS, progression-free survival; OS, overall survival; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; TNM, tumor-nodal-metastasis; CONUT, controlling nutritional status.

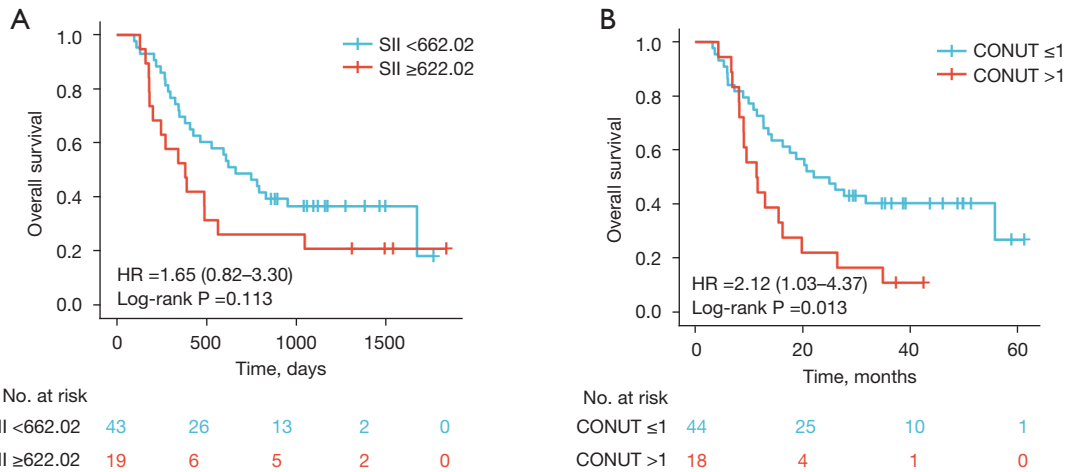

Figure 4 OS curves in esophageal cancer patients treated with radical radiotherapy or concurrent chemoradiotherapy. (A) OS according to the SII; (B) OS according to the CONUT score. SII, systemic immune-inflammation index; HR, hazard ratio; CONUT, controlling nutritional status; OS, overall survival.

Discussion

Cancer is recognized as a nutritional deficiency disease dysfunction (22,23). A low nutritional status in patients with malignancies causes injury-delayed healing, and immune dysfunction (22,23). A growing number of studies have found that malnutrition is associated with a poor prognosis in many patients with malignancies (24). In oncology patients, malnutrition not only decreases sensitivity to RT but also increases treatment toxicity, which in turn has a negative effect on patient survival prognosis (7,25).

The CONUT score is a readily available and easily calculated clinical index that includes the serum albumin level, lymphocyte count, and cholesterol level, and reflects not only the nutritional status but also the systemic inflammatory and immune status of patients. In recent years, many scholars have begun to pay attention to the predictive value of the CONUT score in the prognosis of EC; the subjects of these studies were mainly EC patients who received radical surgery or immune checkpoint inhibitor (ICI) therapy. In a retrospective analysis, Hirahara *et al.* found that pTNM stage (P<0.0001) and the CONUT score (P=0.0291) were independently associated with a poorer prognosis in patients with EC who underwent radical surgery, and that the CONUT score was significantly more predictive of postoperative survival in patients with EC than inflammatory markers (26). More recently, a retrospective analysis that included 69 patients showed that among the patients with EC treated with ICI therapy, the patients in the high CONUT group (>1) had significantly worse PFS and OS than those in the low CONUT group (≤1), and the multifactorial analysis revealed that the CONUT score was an independent prognostic factor for OS (P<0.05) (17).

Our study was the first clinical study to analyze the relationship between RT outcomes and CONUT scores in

patients with EC. In our study, a CONUT score >1 was an independent risk factor affecting the prognosis of patients with EC receiving radical RT or CCRT (P=0.041). The multifactorial analysis showed that the CONUT score and TNM stage were independent factors affecting the prognosis of patients with EC receiving radical RT (*Table 5*). In relation to the 62 patients' clinical responses to RT or CCRT, the RR was worse in the high CONUT group (>1) than the low CONUT group (≤1), but the difference was not statistically significant (P>0.05) (*Table 3*). Possible reasons for this result include the following: (I) to ensure consistency in the evaluation criteria, CT images (taken within 2 months of the end of RT) were compared with the volume of the RT target area in this study to evaluate short-term RT efficacy; however, efficacy may occur from several months to 6 months after RT (27); (II) some patients with early T stage did not have significant esophageal wall thickening before treatment, and thus it was difficult to accurately evaluate the treatment efficacy based on the imaging data; and (III) this study had a small sample size; thus, further analyses in large prospective studies need to be conducted to confirm the results.

As an indicator for evaluating the systemic inflammatory response, the SII has gradually received more attention due to its predictive value in RT. Wang *et al.* found that the proportion of the SII before and after RT and the SII value in the middle of RT were independent prognostic factors in esophageal squamous cell carcinoma patients receiving radical RT, while the SII value before RT was not associated with prognosis (28). These findings are similar to the findings of the present study.

The present study had several limitations. First, it was a single-center, retrospective study with a small sample size; thus, prospective studies with large samples sizes need to be conducted to validate our findings. Second, the nutritional and inflammatory indicators included in the study were all pre-RT indicators, and the malnutrition and inflammatory responses caused by radiation during RT were not taken considered. Finally, the AUC was relatively low, and a more sensitive predictive model needs to be established.

Conclusions

The CONUT score can be used as an independent prognostic factor to predict the clinical outcomes of patients with EC who receive radical RT or CCRT. Clinical staff need to pay attention to nutritional status assessments and implement timely nutritional interventions as appropriate.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1193/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1193/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1193/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1193/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 Institutional Review Board of Harbin Medical University Cancer Hospital (No. KY2023-18) and informed consent was obtained from all the patients.

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