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# Sarcopenia is associated with prognosis in patients with esophageal squamous cell cancer after radiotherapy or chemoradiotherapy

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## Abstract

**Background:** This study aimed to determine the prognostic value of the sarcopenia on the progression free survival (PFS) and overall survival (OS) of esophageal squamous cell cancer (ESCC) patients who received radiotherapy (RT) or chemoradiotherapy (CRT).

**Methods:** Data on clinicopathological characteristics and nutritional parameters were analyzed and correlated with PFS and OS, retrospectively. Skeletal muscle, subcutaneous, visceral and total fat tissue cross-sectional areas were evaluated on CT images at the midpoint of the 3rd lumbar vertebrae. A total of 213 patients were enrolled in this study.

**Results:** Sarcopenia was significantly associated with subcutaneous fat content. The univariate analysis demonstrated that OS was superior in patients with non-sarcopenia, non-alcohol, NRI  $\geq 100$ , albumin  $\geq 40$  g/L, TATI  $> 83.0$ , SATI  $> 27.8$ , VATI  $> 49$ , non-anemia, cervical and upper-thoracic ESCC, T stage 1–2, N stage 0–1 and TNM stage I–II. In the multivariate analysis, sarcopenia, albumin, N stage and TNM stage were identified as independent prognostic factors of survival. This study demonstrated that sarcopenia was related to worse PFS and OS in patients with ESCC who received RT or CRT.

**Conclusions:** Sarcopenia is considered to be a useful predictor in patients with ESCC who received RT or CRT. This study also provided a conceptual basis for further prospective research on the application of the sarcopenia for patients receiving RT or CRT for intermediate- and advanced-stage ESCC.

**Keywords:** Esophageal squamous cell cancer, Sarcopenia, Body composition, Chemoradiotherapy, Prognosis

## Introduction

The esophageal cancer is one of the leading causes of mortality among the digestive tract cancers [1]. The main histology type is Esophageal Squamous Cell Carcinoma (ESCC), which accounts for 90% of esophageal

cancers worldwide [2]. Since most patients are diagnosed in advanced stages and unable to undergo surgery, the reference treatment for patients with ESCC is chemoradiotherapy (CRT) [2, 3]. However, the prognosis remains disappointing with 5 years of survival rates following CRT or CT of around 30% [4].

Most of patients with advanced ESCC are affected by cancer-related cachexia, which results in wasting of skeletal muscle mass with or without loss of fat mass [5]. Meanwhile, CRT treatment-related dysphagia, nausea or vomiting also induce the deterioration of cachexia, leading to a change in body composition and malnutrition [6, 7]. Moreover, nutritional support was

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reported to improve weight gain, overall survival rate and quality of life in patients [1, 8, 9]. Hence, identifying convenient and effective nutritional prognostic factors before treatment is of great importance.

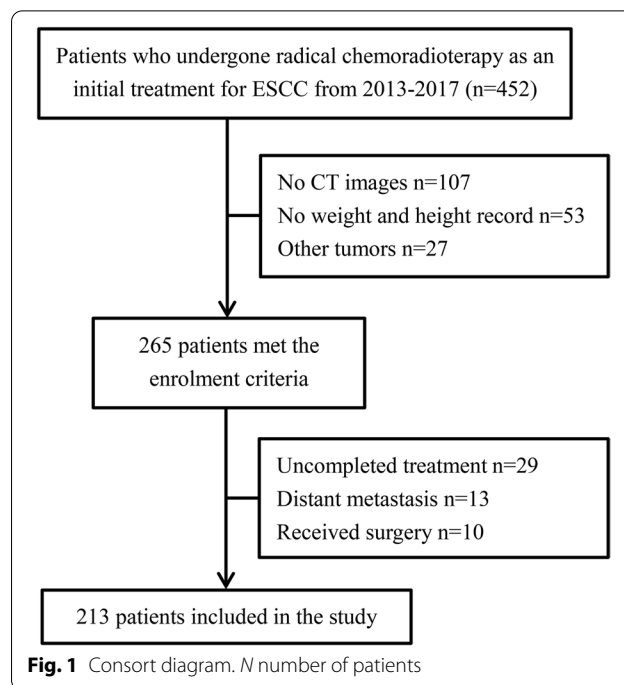
Sarcopenia reduces physical activity, which leads to decreased energy and poor prognosis. To this end, the important role of sarcopenia has reached consistent recognition and the Asian Working Group for Sarcopenia (AWGS) 2019 consensus was developed [10]. Large amounts of evidence indicate that sarcopenia independently correlate with poorer OS in malignant tumors, including head and neck cancer [11], lung cancer [12, 13], colorectal cancer [14, 15], gastric cancer [16], and renal cell cancer [17]. Sarcopenia is associated with mortality, and lower OS in patients with ESCC. Esophagus is an important digestive organ, the occurrence of esophageal tumor seriously affects the nutritional status of patients, and then reduces the prognosis of patients. Some studies also suggested that sarcopenia is associated with impaired OS after surgery for oesophageal cancer [1, 18], however, the prognostic value of sarcopenia for patients with ESCC who received RT or CRT has not been demonstrated yet.

In this study, we investigate sarcopenia before treatment and its association with nutritional status, and survival of patients, and thus evaluated the prognostic value of sarcopenia for survival through univariate and multivariate analyses in ESCC patients who received RT or CRT.

## Materials and methods

### Patients

The records of all 213 ESCC patients were confirmed by pathology and collected from Shandong Cancer Hospital between June 2013 and December 2017 in accordance with the STROBE statement. Patients were included in this study if they had RT or CRT. The exclusion criteria were as follows: (1) history of other malignancies, (2) incomplete medical records (such as no electronic CT image data, height or weight information etc.), (3) distant metastasis. A consort flow diagram of patient selection is shown in Fig. 1. The 7th edition of the American Joint Committee on Cancer TNM staging system was used to determine the clinical or pathological stage. This retrospective study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute. Formal written informed consent was waived by the Ethics Committee of Shandong Cancer Hospital and Institute owing to its retrospective study design, and all data were kept confidential.



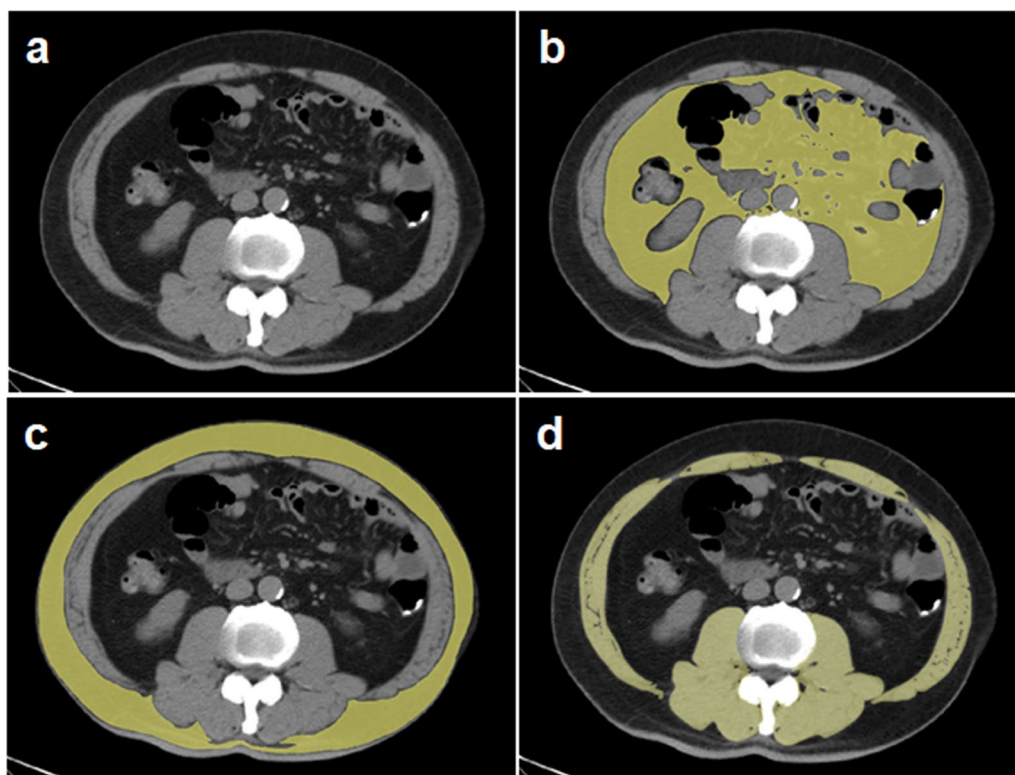
**Fig. 1** Consort diagram. *N* number of patients

### Treatment

Patients received the same radiotherapy with photons (6 MV) to a total dose of 50–70 Gy (median 60 Gy) with 1.8–2.0 Gy/day, 5 days per week. 63 patients received RT, 112 patients received concurrent CRT and 38 patients received sequential CRT. 150 patients receiving chemotherapy treated with platinum-based chemotherapy (median of 3 cycles, range 1–6 cycles).

### Image analysis of subcutaneous and visceral fat mass and skeletal muscles

In all patients, computer tomography scans were acquired less than 2 weeks prior to RT or CRT. Skeletal muscle, subcutaneous fat, visceral fat and total fat area were measured at the midpoint of the third lumbar vertebrae (L3) as described previously (Fig. 2A–D) [7, 19, 20]. L3 was chosen because tissue in this region has been found to be most correlated with whole body composition [7, 21]. In briefly, images from computed tomography (Somatom AR.C; Siemens, Erlangen, Germany) scans on participants in the supine position were used for analysis. Visceral and subcutaneous fat area were calculated using a software OsiriX (Pixmeo, Geneva, Switzerland) [1, 21] and with a threshold within –190 to –30, –150 to –50 Hounsfield units (HUs), respectively. The Hounsfield unit thresholds of –29 to 150 were then set for skeletal muscles including the rectus abdominis, transverse abdominal, psoas, paraspinal, internal and



**Fig. 2** Body composition measurements using computed tomography at the level of third lumbar vertebrae. (A) Original computed tomography images for measurements. (B) Delineation of visceral fat area with a threshold of  $-150$  to  $-50$  HU. (C) Delineation of subcutaneous fat area with a threshold of  $-190$  to  $-30$  HU. (D) Delineation of total skeletal muscle area with a threshold of  $-29$  to  $+150$  HU

external oblique muscles. Regions of the subcutaneous, visceral fat and skeletal muscles area was defined by tracing its contour on each scan, and manual corrections were performed when necessary [1, 21]. Sarcopenia has been defined as a skeletal muscle index (SMI) of  $\leq 41$   $\text{cm}^2/\text{m}^2$  for women and  $\leq 53$   $\text{cm}^2/\text{m}^2$  in case of a body mass index (BMI) of  $\geq 25$   $\text{kg}/\text{m}^2$  or  $\leq 43$   $\text{cm}^2/\text{m}^2$  in case of a BMI of  $< 25$   $\text{kg}/\text{m}^2$  for men [7].

#### Clinical definitions

We calculated BMI ( $\text{kg}/\text{m}^2$ ) values by based on a direct measurement of weight ( $\text{kg}$ )/height<sup>2</sup> ( $\text{m}^2$ ) at diagnosis, we divided patients into obesity (BMI  $\geq 24$ ) and no obesity groups (BMI  $< 24$ ) according to previous study [22]. Anemia was defined as serum hemoglobin (Hb) levels  $\leq 12$  g/dL in women and  $\leq 13$  g/dL in men according to Chinese criterion [23]. Serum albumin was divided into normal and low albumin groups according to the normal value defined by laboratory in our hospital. Patients in this cohort were divided into two groups based on median tumor length ( $\leq 4$  cm and  $> 4$  cm). The age was categorized according to previous study [24]. Nutritional Risk Index (NRI) was then calculated using the following

formula:  $\text{NRI} = (1.519 \times \text{albumin g/dL}) + 41.7 \times (\text{present body weight/ideal body weight})$  [25]. The ideal body weight was calculated using the Lorentz formula [26]. The nutritional status of each patient was stratified according to the calculated NRI: NRI score  $\geq 100$ : no risk;  $< 100$ : have risk [8].

#### Follow-up

OS was computed from the day of the pathological diagnosis of ESCC until death or the last follow-up. The second endpoint was PFS, defined as the time between day 1 and the first event of local failure, metastatic recurrence, progression, or death. Patients lost to follow-up were “censored” at the date of the last clinic visit.

Patients were followed up in the hospital once every 3 months for the first 2 years, once every 6 months for the third year, and once yearly from the fourth year. During the re-examination, the patient received blood routine examination, liver and kidney function, tumor markers and other laboratory tests, as well as chest and abdomen computed tomography examination. Bone emission computed tomography was performed every 6 months.

### Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. A  $\chi^2$  test or Fisher's exact test was performed for comparing patient baseline characteristics. PFS and OS were calculated using Kaplan–Meier analysis method and log-rank tests. The Cox regression model was used for univariate and multivariate analysis. After the univariate analysis, those variables with  $p < 0.2$  were taken part in the multivariate analysis and Cox stepwise forward regression analysis and Wald test were conducted.  $p < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

A total number of 213 patients with ESCC undergoing CRT or CT were assessed. Baseline characteristics of all included patients are shown in Table 1. The study group consisted of 160 men (75.1%) and 53 women (24.9%), from 44 to 85 years (median 67). 114 patients (53.5%) had a history of smoking. 100 patients (46.9%) in our cohort had a history of alcohol use. The most common location of primary tumors was the middle second of the thoracic esophagus (40.4%). The length of tumor lesions ranged from 1.0 to 10.5 cm (median 4.5). The median BMI was 22.5 kg/m<sup>2</sup> (range 14.5–31.2 kg/m<sup>2</sup>). The SMI exhibited a normal distribution (Fig. 3), and the mean SMI was 37.3 ± 8.7. The number of patients in the sarcopenia group and non-sarcopenia group was 170 (79.8%) and 43 (20.2%), respectively.

### Sarcopenia and prognosis of ESCC

The median follow-up duration was 35 (range, 4–77) months. The median OS of the 213 patients was 35 months and the 1-, 3-, and 5-year OS rates were 93.9%, 49.8%, and 9.4%, respectively. The 5-year OS in the sarcopenia group was significantly shorter (2.3%) than that in the non-sarcopenia group (7.0%;  $p = 0.016$ ; Fig. 4B). The median PFS of the 213 patients was 26 months and the 1-, 3-, and 5-year PFS rates were 77.9%, 32.4%, and 1.9%, respectively. The 3-year PFS in the sarcopenia group was significantly shorter (27.0%) than that in the non-sarcopenia group (48.8%;  $p = 0.018$ ; Fig. 5C).

### Univariate and multivariate analyses of OS of 213 patients

In the univariate analysis (Table 2), nutritional parameters including serum albumin  $\geq 40$  g/L, non-sarcopenia, TNM stage I-II and N stage 0–1 were strongly associated with an improved OS. Non-alcohol, NRI  $\geq 100$ , non-anemia, TATI  $> 83.0$ , SATI  $> 27.8$ , VATI  $> 49.0$ , cervical and

**Table 1** Baseline characteristics

Characteristic	Non-sarcopenia n = 43, 20.2%	Sarcopenia n = 170, 79.8%	p value
Age, years			0.163
> 65	21	103	
$\geq 65$	22	67	
Gender			0.064
Male	37	123	
Female	6	47	
Smoking			0.307
Yes	26	88	
No	17	82	
Alcohol			0.781
Yes	21	79	
No	22	91	
BMI, kg/m <sup>2</sup>			0.145
$\geq 24$	19	55	
< 24	24	115	
NRI			0.234
$\geq 100$		38	137
< 100		5	33
Anemia			0.325
Yes	12	61	
No	31	109	
Albumin			0.306
< 40	7	40	
$\geq 40$	36	130	
SATI (cm <sup>2</sup> /m <sup>2</sup> )			<b>0.009</b>
$\leq 27.8$	14	93	
$> 27.8$	29	77	
VATI (cm <sup>2</sup> /m <sup>2</sup> )			0.633
$\leq 49.0$	20	86	
$> 49.0$	23	84	
TATI (cm <sup>2</sup> /m <sup>2</sup> )			0.133
$\leq 83.0$	17	89	
$> 83.0$	26	81	
Location			0.063
Neck/upper	25	72	
Middle/lower	18	98	
Length (cm)			0.116
$\leq 4$	17	90	
$> 4$	26	80	
Treatment strategies			0.678
RT	8	55	
CRT	36	114	
TNM stage			0.871
I–II	16	61	
III–IV	27	109	
T stage			0.961
T1–2	9	35	
T3–4	34	135	
N stage			0.683
N0–1	14	61	
N2–3	29	109	

P value highlighted in bold indicated  $p < 0.05$

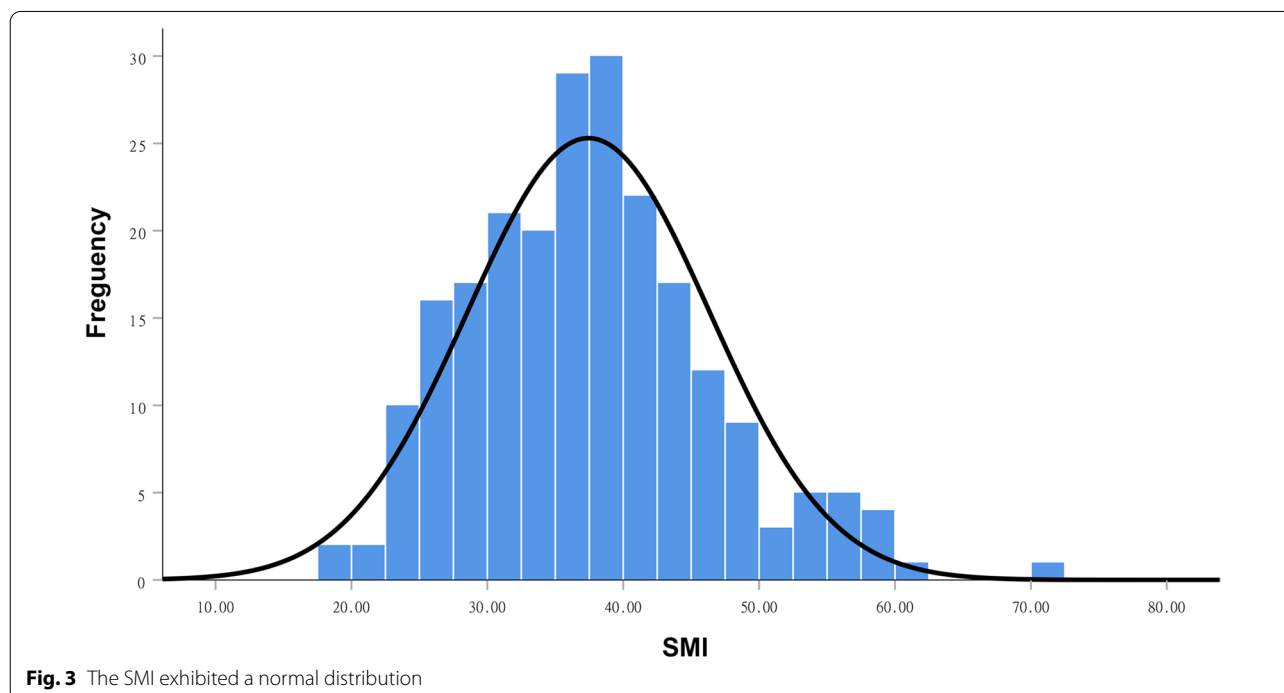
upper-thoracic locations and T stage 1–2 were the clinicopathological and prognostic factors for longer OS.

The median OS (95% CI) in patients with alcohol history was shorter than those without alcohol history [33 versus 43 months, respectively (HR 1.372, 95% CI 1.036–1.817;  $p=0.027$ ; Table 2)]. Patients with high NRI had better survival rates than those with low NRI [41 versus 32 months, respectively (HR 0.610, 95% CI 0.426–0.874;  $p=0.007$ )]. Patients with anemia had a shorter time than those with non-anemia [35 versus 41 months, respectively (HR 1.439, 95% CI 1.073–1.928;  $p=0.015$ )]. Patients with high serum albumin had better survival rates than those with low serum albumin [41 versus 32 months, respectively (HR 0.582, 95% CI 0.416–0.813;  $p=0.002$ ; Table 2, Fig. 4A)]. The median OS in patients in the non-sarcopenia group was longer than that in the patients in the sarcopenia group [47 versus 35 months, respectively (HR 1.457, 95% CI 1.024–2.074;  $p=0.036$ ; Fig. 4B)]. Patients with high TATI had better survival rates than those with low TATI [45 versus 32 months, respectively (HR 0.689, 95% CI 0.520–0.913;  $p=0.01$ )]. Patients with high SATI had a longer time than those with low SATI [45 versus 33 months, respectively (HR 0.707, 95% CI 0.533–0.937;  $p=0.016$ )]. Patients with high VATI had a longer time than those with low VATI [45 versus 32 months, respectively (HR 0.659, 95% CI 0.497–0.872;  $p=0.004$ )]. Patients with N stage 2–3 ESCC had a shorter time than those with stage 0–1 [29 versus

48 months, respectively (HR 1.501, 95% CI 1.120–2.013;  $p=0.007$ ; Fig. 4C)]. Patients with TNM stage III–IV ESCC had a shorter time than those with stage I–II [28 versus 51 months, respectively (HR 1.421, 95% CI 1.226–1.647;  $p<0.001$ ; Fig. 4D)]. Patients with T stage 3–4 ESCC had a shorter survival time than those with stage 1–2 [34 versus 51 months, respectively (HR 1.291, 95% CI 1.084–1.539;  $p=0.004$ )]. Patients with middle and lower-thoracic ESCC lived for a shorter OS time than those with cervical and upper-thoracic ESCC [33 (29.35–36.65) months versus 47 (41.57–52.43) months, respectively (HR 1.698, 95% CI 1.203–2.125;  $p=0.001$ )]. Multivariate analysis (Table 2) revealed that serum albumin [HR 0.658 (0.470–0.923);  $p=0.023$ ], sarcopenia [HR 1.638 (1.113–2.410);  $p=0.016$ ], TNM stage [HR 2.439 (1.710–3.228);  $p<0.0001$ ], and N stage [HR 0.483 (0.262–0.890);  $p<0.0001$ ] were independent prognostic factors for OS in ESCC patients.

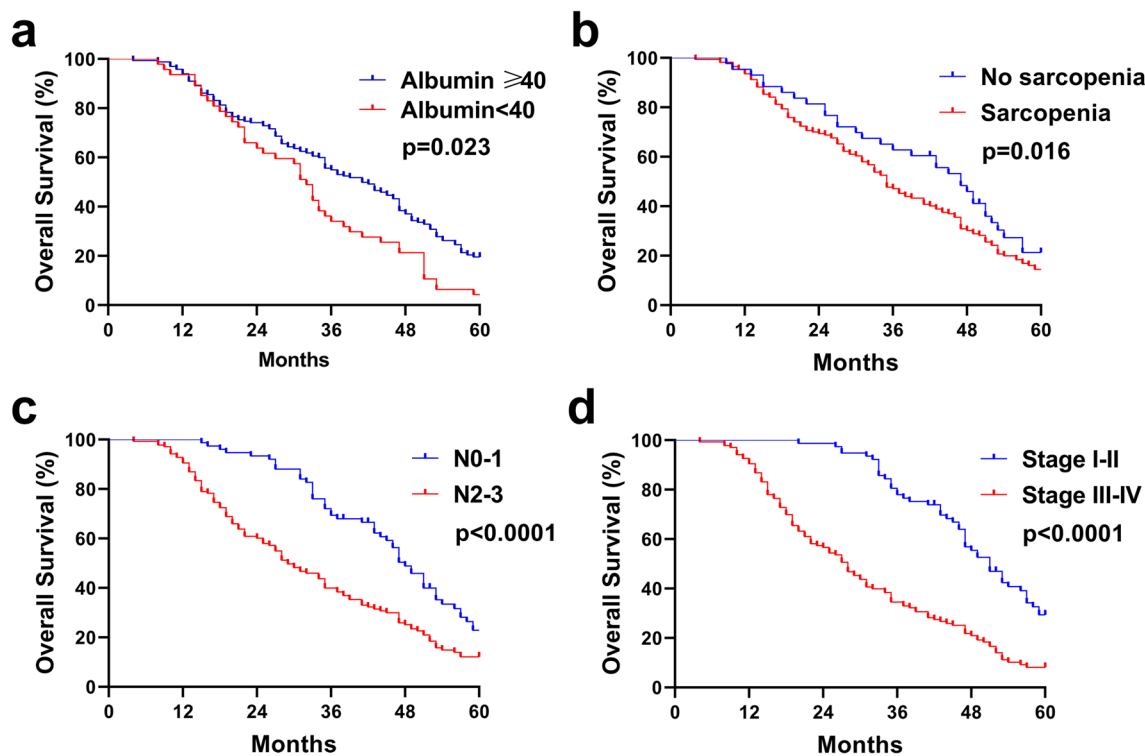
#### Univariate and multivariate analyses of PFS of 213 patients

Univariate analysis (Table 3) of predictive factors of PFS showed that non-alcohol history, non-anemia, non-sarcopenia, VATI > 49, cervical and upper-thoracic locations and TNM stage I–II were strongly correlated with a longer PFS. NRI  $\geq 100$ , serum albumin  $\geq 40$  g/L, TATI > 83, SATI > 27.8, T stage 1–2 and N stage 0–1 were the clinicopathological features that predicted a better PFS.



**Fig. 3** The SMI exhibited a normal distribution





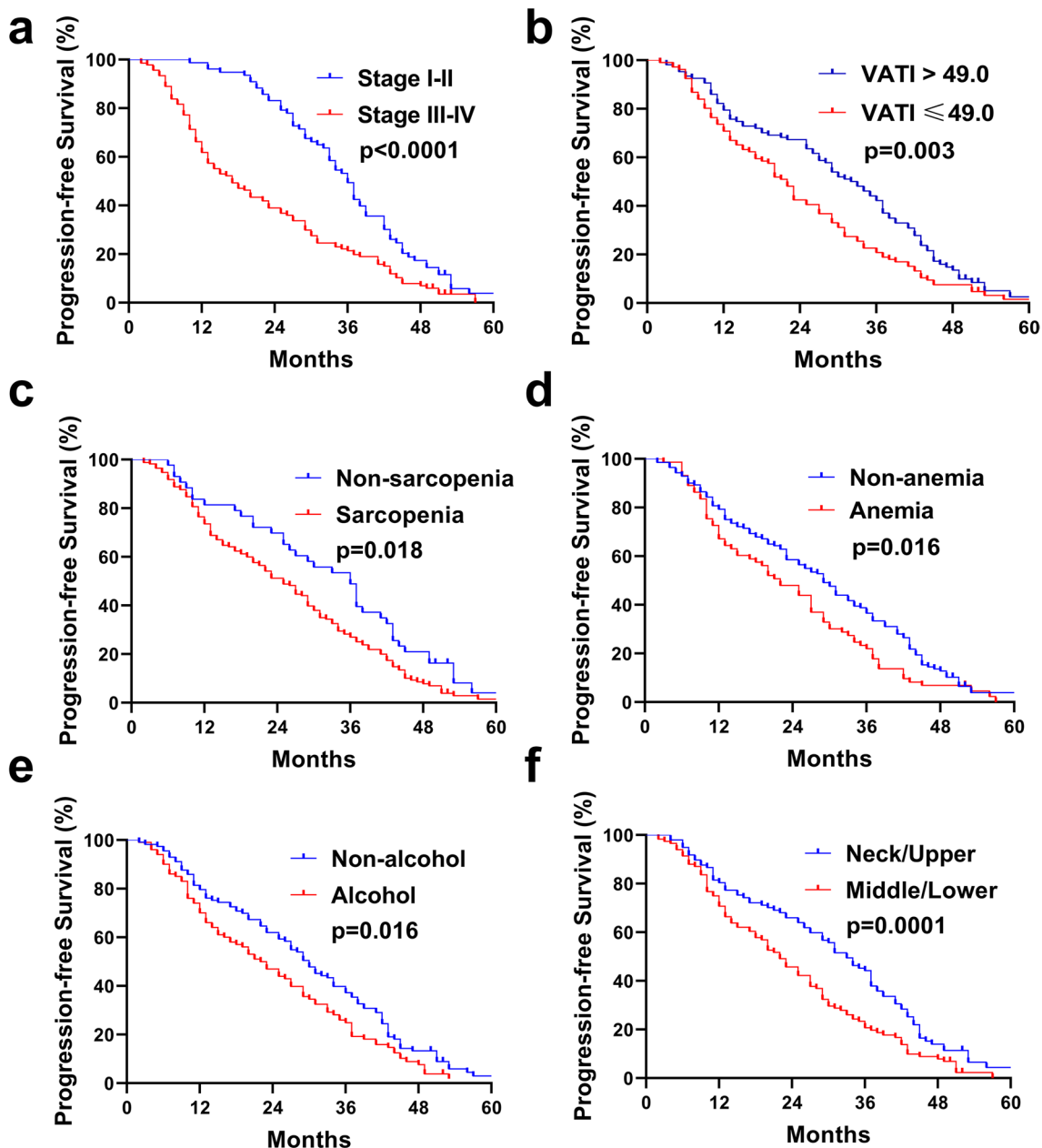
**Fig. 4** Kaplan–Meier survival curves. (A) OS of patients with albumin  $\geq 40$  or  $< 40$ . (B) OS of patients according to sarcopenia. (C) OS of patients according to N stage. (D) OS of patients according to TNM stage

In the multivariate analysis (Table 3), Patients with TNM stage III–IV ESCC lived for a shorter PFS time than those with stage I–II [17 versus 36 months, respectively (HR 1.384, 95% CI 1.193–1.605;  $p < 0.0001$ ; Fig. 5A)]. Patients with VATI  $> 49.0$  had better survival rates than those with low VATI  $\leq 49.0$  [33 versus 22 months, respectively (HR 0.667, 95% CI 0.497–0.895;  $p = 0.003$ ; Fig. 5B)]. The median PFS in patients in the non-sarcopenia group was longer than that in patients in the sarcopenia group [36 (29.58–42.43) months versus 25 (21.20–28.80) months, respectively (HR 1.509, 95% CI 1.052–2.164;  $p = 0.018$ ; Fig. 5C)]. Patients of ESCC with anemia had a shorter PFS time than those with non-anemia [22 versus 29 months, respectively (HR 1.428, 95% CI 1.043–1.954;  $p = 0.016$ ; Fig. 5D)]. Patients of ESCC with alcohol history had a shorter PFS duration than those with non-alcohol history [22 versus 30 months, respectively (HR 1.539, 95% CI 1.144–2.070;  $p = 0.016$ ; Fig. 5E)]. Patients with middle and lower-thoracic ESCC had a shorter PFS duration than those with cervical and upper-thoracic ESCC [22 versus 33 months, respectively (HR 1.352, 95% CI 1.008–1.812;  $p = 0.0001$ ; Fig. 5F)].

## Discussion

Our study demonstrated that sarcopenia, serum albumin  $< 40$  g/L, N stage 2–3 and TNM stage III–IV are independently associated with poor OS in 213 ESCC patients who received RT or CRT in this analysis. The predictors of sarcopenia can be identified easily on any preoperative computer tomography images and might be helpful in the difficult triage before those treatments.

Cancer patients are likely to have severe nutrition and metabolism problems prior to any treatment [26]. Malnutrition has been suggested to be associated with possible mechanisms including abnormal protein and energy metabolism of tumor cells and aberrant inflammation and immunity, as well as cancer-related symptoms, such as fatigue, pain, coughing and loss of appetite. Malnutrition has been more prevalent among ESCC patients, of whom approximately 60% experienced baseline nutrition problems [22, 23, 25]. Our results agreed well with those previous studies. Sarcopenia is a common index reflecting systemic nutritional status of patients due to cancer progression [7, 27]. A similar study conducted by Mallet et al. [2] found that sarcopenia was an independent predictor of shorter OS in patients with locally advanced esophageal cancer. The research demonstrated that, besides sarcopenia, other factors including BMI, and NRI



**Fig. 5** Kaplan–Meier survival curves. **(A)** PFS of patients according to TNM stage. **(B)** PFS of patients with VATI ≤ 49 or > 49. **(C)** PFS of patients according to sarcopenia. **(D)** PFS of patients according to anemia. **(E)** PFS of patients according to alcohol. **(F)** PFS of patients according to tumor location

were significant but not independent predictors of OS in patients with locally advanced esophageal cancer. The difference between our and Mallet’s study is that pathology type of tumor in patients we selected was ESCC considering the heterogeneity of subtypes of esophageal cancer. Furthermore, other nutritional factors including hemoglobin, SATI, VATI, and TATI were calculated and compared with sarcopenia, which was not performed in

previous study mentioned above. The results of our study showed that sarcopenia, together with albumin, TNM stage and N stage, were independent predictors for OS in ESCC patients who received RT or CRT. In patients stratified by the sarcopenia index, variables including age, gender, smoking, alcohol, BMI, NRI, anemia, albumin, VATI, TATI, primary tumor locations, tumor length, treatment strategies, TNM stage, T stage, and N stage

**Table 2** Univariate and multivariate analyses of OS

Characteristic	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age ( $\geq 65$ vs. $< 65$ )	1.104	0.830–1.467	0.497			
Sex (male vs. female)	1.183	0.858–1.632	0.305			
Smoking (yes vs. no)	1.080	0.816–1.428	0.590			
Alcohol (yes vs. no)	1.372	1.036–1.817	<b>0.027</b>			
BMI ( $\geq 24$ vs. $< 24$ )	0.750	0.552–1.017	0.064			
NRI ( $\geq 100$ vs. $< 100$ )	0.610	0.426–0.874	<b>0.007</b>			
Anemia (yes vs. no)	1.439	1.073–1.928	<b>0.015</b>			
Albumin ( $\geq 40$ vs. $< 40$ )	0.582	0.416–0.813	<b>0.002</b>	0.658	0.470–0.923	<b>0.023</b>
Sarcopenia (yes vs. no)	1.457	1.024–2.074	<b>0.036</b>	1.638	1.113–2.410	<b>0.016</b>
TATI ( $> 83.0$ vs. $\leq 83.0$ )	0.689	0.520–0.913	<b>0.010</b>			
SATI ( $> 27.8$ vs. $\leq 27.8$ )	0.707	0.533–0.937	<b>0.016</b>			
VATI ( $> 49.0$ vs. $\leq 49.0$ )	0.659	0.497–0.872	<b>0.004</b>			
Location (middle/lower vs. neck/upper)	1.698	1.203–2.125	<b>0.001</b>			
Length ( $\leq 4$ vs. $> 4$ )	1.054	0.797–1.394	0.710			
Treatment (CRT vs. RT)	0.275	0.615–1.148	0.841			
RT dose ( $\leq 60$ vs. $> 60$ )	1.136	0.854–1.512	0.382			
TNM stage (III–IV vs. I–II)	1.421	1.226–1.647	<b>&lt; 0.001</b>	2.439	1.710–3.228	<b>&lt; 0.0001</b>
T stage (T3–4 vs. T1–2)	1.291	1.084–1.539	<b>0.004</b>			
N stage (N2–3 vs. N0–1)	1.501	1.120–2.013	<b>0.007</b>	2.070	1.124–3.817	<b>&lt; 0.0001</b>

HR hazard ratio, CI confidence interval, p values highlighted in bold indicated  $p < 0.05$

**Table 3** Univariate and multivariate analyses of PFS

Characteristic	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age ( $\geq 65$ vs. $< 65$ )	1.126	0.847–1.496	0.414			
Sex (male vs. female)	1.187	0.861–1.639	0.295			
Smoking (yes vs. no)	1.093	0.827–1.446	0.531			
Alcohol (yes vs. no)	1.401	1.056–1.859	<b>0.019</b>	1.539	1.144–2.070	<b>0.016</b>
BMI ( $\geq 24$ vs. $< 24$ )	0.746	0.550–1.011	0.059			
NRI ( $\geq 100$ vs. $< 100$ )	0.614	0.429–0.879	<b>0.008</b>			
Anemia (yes vs. no)	1.416	1.057–1.898	<b>0.020</b>	1.428	1.043–1.954	<b>0.016</b>
Albumin ( $\geq 40$ vs. $< 40$ )	0.589	0.421–0.822	<b>0.002</b>			
Sarcopenia (yes vs. no)	1.546	1.086–2.202	<b>0.016</b>	1.509	1.052–2.164	<b>0.018</b>
TATI ( $> 83.0$ vs. $\leq 83.0$ )	0.671	0.506–0.889	<b>0.005</b>			
SATI ( $> 27.8$ vs. $\leq 27.8$ )	0.690	0.521–0.914	<b>0.010</b>			
VATI ( $> 49.0$ vs. $\leq 49.0$ )	0.662	0.500–0.877	<b>0.004</b>	0.667	0.497–0.895	<b>0.003</b>
Location (middle/lower vs. neck/upper)	1.601	1.205–2.129	<b>0.001</b>	1.352	1.008–1.812	<b>0.001</b>
Length ( $\leq 4$ vs. $> 4$ )	1.042	0.788–1.378	0.772			
Treatment (CRT vs. RT)	0.838	0.619–1.133	0.251			
RT dose ( $\leq 60$ vs. $> 60$ )	1.158	0.870–1.542	0.314			
TNM stage (III–IV vs. I–II)	1.419	1.225–1.645	<b>&lt; 0.001</b>	1.384	1.193–1.605	<b>&lt; 0.0001</b>
T stage (T3–4 vs. T1–2)	1.269	1.066–1.510	<b>0.007</b>			
N stage (N2–3 vs. N0–1)	1.492	1.113–2.001	<b>0.008</b>			

HR hazard ratio, CI confidence interval, p values highlighted in bold indicated  $p < 0.05$



were similar between the two subgroups. Sarcopenia was significantly associated with lower SATI.

Considering the fact that the etiology of sarcopenia is currently known to be multifactorial, with contributions from systemic inflammation, reduced nutrient intake and activity levels, and increased metabolic rate [21, 24, 28], this would serve as an explanation why sarcopenia correlate with lower SATI, which usually results from the similar malnutritional factors. In this study, our findings verified the prognostic value of sarcopenia as an independent predictor of both OS and PFS in ESCC patients who received RT or CRT. Baseline nutritional status was usually evaluated with systemic inflammatory reaction biomarkers and relative parameters [2]. Studies have shown that serum albumin is related to the prognosis of cancer patients [29, 30]. Our results suggested that albumin was a predictor of OS in the univariate and multivariate analysis that was performed in this study. It could be inferred that albumin may be useful in reflecting patients' physical performance, which was possibly a crucial premise of optimal treatment and better clinical outcomes. However, some studies also suggested hypoalbuminemia might be more related to hydration or inflammation status than to malnutrition [26, 31]. In addition, alcohol,  $NRI < 100$ , anemia,  $VATI \leq 49$ ,  $TATI \leq 83$  and T stage 3–4 were significant predictor of poorer OS and PFS, respectively. Interestingly, no significant correlation between alcohol and sarcopenia was observed in this study despite of the high significance of sarcopenia in ethanol-associated cirrhosis since alcohol could mediate dysregulation of protein homeostasis and then led to sarcopenia [32]. The reason might be due to confounding effects of cancer itself and treatment. Primary tumor location was stratified into two groups in our study: (1) cervical and upper-thoracic ESCC; and (2) middle-thoracic and lower-thoracic ESCC. The primary tumor location is also important factor affecting survival outcomes. Our results suggested that primary tumor location was significant predictor of OS in the univariate analysis, and independent predictor of PFS. Patients with middle and lower-thoracic ESCC had impaired PFS and OS, which was similar with another study [33]. It could be inferred that patients with middle-thoracic and lower-thoracic ESCC may be more prone to malnutritional status due to reductions in nutrient intake resulted from esophageal obstruction. Our results also suggested that TNM stage was an independent predictor of both OS and PFS in this study. As expected, ESCC patients with TNM stage III-IV had shorter OS and PFS, which was comparable to those of previous studies on patients with ESCC who were treated with definitive radiotherapy [34]. N stage was also an independent prognostic factor of OS in this study, which agreed well with previous studies on patients with ESCC treated with definitive CRT [35].

There are limitations of present study related to somewhat smaller population in a single center, who received radiotherapy combined with chemotherapy. However, the results of this study still presented the potential of sarcopenia as a tool for predicting survival of patient independent of other factors, including albumin, N stage and TNM stage. Nevertheless, multi-center larger investigations and prospective clinical trials are needed to establish the role of the sarcopenia nutritional index for predicting clinical outcomes.

In conclusion, sarcopenia and other indexes of body composition such as lower serum albumin may be valuable to identify potential nutritional problems and poorer survival in our study. They are easily conducted on any preoperative computer tomography scan or blood examination and might be useful in patient risk stratification and help oncologists provide optimal intervention strategy before treatment initiation.

#### Abbreviations

PFS: Progression free survival; OS: Overall survival; ESCC: Esophageal squamous cell cancer; CRT: Chemoradiotherapy; BMI: Body mass index; SATI: Subcutaneous adipose tissue index; VATI: Visceral adipose tissue index; TATI: Total adipose tissue index; SMI: Skeletal muscle index.

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#### Author contributions

JQ: data collection, statistics, original draft. YS: data collection, formal analysis, resources. KZ: data collection and analysis. YT: data collection and analysis. QG: data collection, resources. KZ: conceptualization, review and editing the manuscript. JY: monitor the clinical trial. All authors read and approved the final manuscript.

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#### Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

#### Declarations

##### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute. Formal written informed consent was waived by the Ethics Committee of

Shandong Cancer Hospital and Institute owing to its retrospective study design, and all data were kept confidential.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no conflicts of interest.

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