Impact of Body Composition on Clinical Outcomes in Patients with Esophageal Squamous Cell Carcinoma Receiving Neoadjuvant Immunotherapy Plus Chemotherapy

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AIM: Some studies have reported that body composition profiles affect clinical outcomes of multidisciplinary treatments in several types of cancers; however, a paucity of data exists on the association in neoadjuvant immunotherapy. In the present study, we aimed to investigate the effect of body composition on the clinical outcomes of patients with esophageal squamous cell carcinoma (ESCC) receiving neoadjuvant immunotherapy plus chemotherapy (nICT).

METHODS: Clinicopathological data and computed tomography (CT) images of 85 patients with locally advanced ESCC who underwent esophagectomy after nICT were collected. At diagnosis and before surgery, the CT scan of the third lumbar vertebra was chosen to evaluate the skeletal muscle index (SMI), skeletal muscle radiodensity (SMD), the subcutaneous and the visceral adiposity index. The relationships between body composition and tumor response after nICT and postoperative complications were analyzed.

RESULTS: The clinical stage (Odds Ratio (OR) 0.345, 95% confidence interval (CI) 0.141–0.844, $p = 0.020$) and change in SMI (ΔSMI, OR 1.394, 95% CI 1.061–1.832, $p = 0.017$) were associated with tumor remission after nICT. Moreover, the multivariate logistic analysis revealed that ΔSMI (OR 0.598, 95% CI 0.433–0.828, $p = 0.002$) was associated with the incidence of postoperative complications. Patients with ΔSMI <-1 had a higher rate of postoperative complications (56% vs 15%, $p < 0.001$).

CONCLUSIONS: For ESCC, ΔSMI is associated with the pathological response after nICT and postoperative complications. Further analysis is needed to clarify whether nutritional intervention during neoadjuvant therapy increases SMI and thus improves clinical outcomes.

Keywords: esophageal squamous cell carcinoma; body composition; neoadjuvant immunotherapy; postoperative complications; skeletal muscle index

Introduction

Esophageal carcinoma (EC) is one of the deadliest types of cancer and ranks sixth among all malignant tumors worldwide in terms of mortality rates [1]. In China, esophageal squamous cell carcinoma (ESCC) is the predominant histopathological subtype of EC, constituting approximately 90% of all reported cases [2]. Esophagectomy is a crucial therapeutic for locally advanced ESCC, playing a significant role in its treatment. However, the 5-year survival of surgery alone for esophageal cancer is not satisfactory. In patients with advanced localized ESCC, neoadjuvant therapy (NT) could reduce tumor loading, afford operation possibility, and prolong the prognosis of ESCC patients after surgery. Consequently, the integration of neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy with surgical procedures has been explored and recommended as a standard treatment plan by guidelines [3].

Increasingly, the utilization of immune checkpoint inhibitors (ICIs) has emerged as indispensable in the treatment of advanced ESCC owing to their remarkable therapeutic efficacy. Several studies, including CheckMate 649, KEYNOTE-590, and ESCORT-1st, have reported that the concurrent application of immunotherapy and chemotherapy for advanced ESCC results in notable improvements in overall survival (OS) compared to chemotherapy alone [4, 5, 6]. According to the findings of the NICE study, neoadjuvant immunotherapy plus chemotherapy (nICT) has achieved favorable therapeutic effects, with a pathological complete response (pCR) rate of 39.2% [7]. A preliminary investigation involving 16 individuals diagnosed with locally advanced ESCC also suggested that nICT demonstrates favorable effectiveness and tolerability [8]. Therefore, nICT may serve as a strategic choice for managing advanced ESCC.

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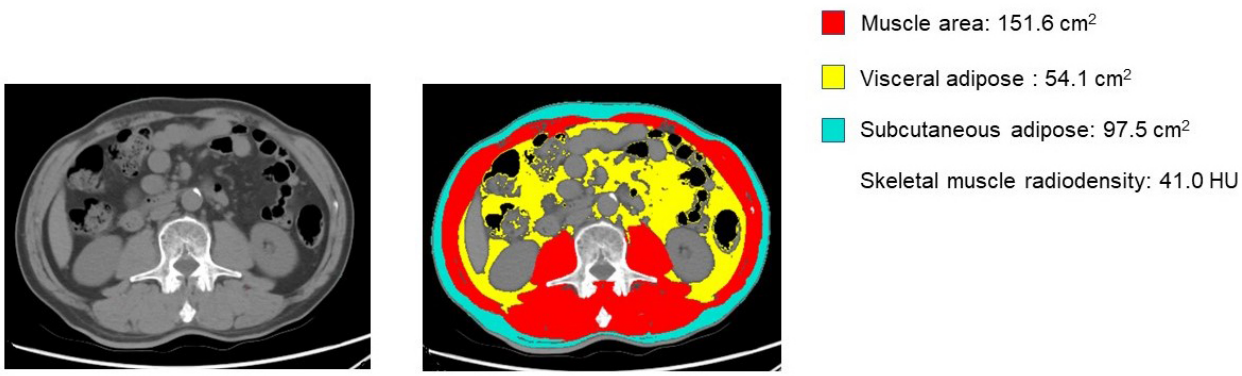

Fig. 1. The portal phase computed tomography image of the third lumbar vertebra (L3) level was used to measure the body composition. Red: Skeletal muscle; Yellow: Visceral adipose tissue; Blue: Subcutaneous adipose tissue. HU, Hounsfield unit.

Malignant tumors frequently lead to the loss of skeletal muscle mass and alterations in body composition, which are commonly linked to unfavorable prognosis, particularly in individuals with ESCC [9]. Several studies have shown that sarcopenia, a condition characterized by a gradual and widespread reduction in both muscle mass and strength, is linked to pulmonary complications or anastomotic leakage, whereas others have shown no associations [10, 11]. Sandini *et al*. [12] reported that a rise in muscle tissue during neoadjuvant chemotherapy for advanced pancreatic cancer is correlated with an increased probability of undergoing surgical resection. These findings indicate that patients' nutritional status may impact neoadjuvant chemotherapy's efficacy. Aoyama S *et al*. [13] documented that reducing body weight during NT was an independent risk factor for complications after surgery. However, a retrospective study indicated that sarcopenia did not increase the incidence of morbidity or mortality in ESCC patients receiving neoadjuvant chemoradiotherapy [14]. Therefore, the influence of body composition on postoperative complications among ESCC patients receiving neoadjuvant therapy needs further exploration.

Furthermore, the impact of body composition on clinical outcomes in patients with ESCC treated with nICT remains uncertain. Few studies have explored whether body composition can predict pathologic response and surgical complications in ESCC patients undergoing neoadjuvant immunotherapy. Hence, this study sought to evaluate the relevance of body composition in tumor response and postoperative complications among ESCC patients who underwent nICT.

Materials and Methods

Study Subjects and Data Collection

From February 2021 to June 2023, a retrospective analysis was conducted on individuals with ESCC who underwent nICT followed by esophagectomy at the Department of Thoracic Surgery, the First Affiliated Hospital of Anhui Medical University. The inclusion criteria were as follows: (1) patients were between the ages of 18 and 75 years; (2) patients were pathologically diagnosed with ESCC; (3) patients had not received chemotherapy (or radiotherapy) or any other anticancer treatment within the past 6 months; (4) patients had a clinical stage of cT2–4, a lymph node N0~N3, and no distant metastasis (M0); and (5) patients had computed tomography (CT) images available at both the time of diagnosis and before surgery. The exclusion criteria comprised: (1) concurrent malignancy in other organs; (2) presence of distant metastases; and (3) prior history of endoscopic submucosal dissection (ESD) or esophagectomy. Ultimately, this study involved a total of 85 patients. The study was conducted in accordance with the Declaration of Helsinki and received approval from The Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval number: 2023493). Due to the retrospective design of the study, the Ethics Committee waived the requirement for informed consent. Demographic information, nICT regimens, operative records, tumor profiles, pathologic response to nICT, and postoperative complications were collected by reviewing patient medical records.

Patient Therapy

Before surgery, patients who were diagnosed with locally advanced ESCC had received nICT for a period of 2–4 cycles. The neoadjuvant therapy protocol consisted of administering camrelizumab, an intravenous PD-1 inhibitor, along with dual-drug chemotherapy containing platinum and paclitaxel. The treatment cycle occurred every 3 weeks. Camrelizumab (200 mg) was administered at each dose. The platinum-based chemotherapy regimen was 75 mg/m^2 cisplatin D1 or 80 mg/m^2 nedaplatin D1. The dosage for the paclitaxel treatment was either 260 mg/m^2 of albumin-bound paclitaxel on day 1, 175 mg/m^2 of paclitaxel on day 1, or 175 mg/m^2 of paclitaxel liposome on day 1 [8, 15, 16]. CT scans were obtained every 6–8 weeks to assess the response to nICT. The operation proceeded at least 4 weeks after the nICT was finished. After receiving nICT, the surgical procedure involved an open or video-assisted thoracoscopic esophagectomy with at least a two-field lymphadenectomy.

Table 1. General characteristics of patients (n = 85).

Characteristics	Value
Age (years), median (IQR)	67 (59, 71)
Gender, No. (%)	
Male	69 (81.2)
Female	16 (18.8)
ECOG PS, No. (%)	
0	63 (74.1)
1	22 (25.9)
Tumor location, No. (%)	
Upper	8 (9.4)
Middle	54 (63.5)
Lower	23 (27.1)
Clinical TNM stage, No. (%)	
II	37 (43.5)
III	40 (47.1)
IV	8 (9.4)
Minimally invasive esophagectomy, No. (%)	
Yes	77 (90.6)
No	8 (9.4)
yp TNM stage, No. (%)	
pCR	12 (14.1)
I	33 (38.8)
II	13 (15.3)
III	23 (27.1)
IV	4 (4.7)
Tumor regression grade, No. (%)	
TR (grade 2/3)	38 (44.7)
non-TR (grade 0/1)	47 (55.3)
R category, No. (%)	
R0	79 (92.9)
R1	6 (7.1)
Postoperative complication, No. (%)	
Yes	23 (27.1)
No	62 (72.9)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; pCR, pathological complete response; PS, Performance Status; TR, tumor remission; non-TR, non-tumor remission.

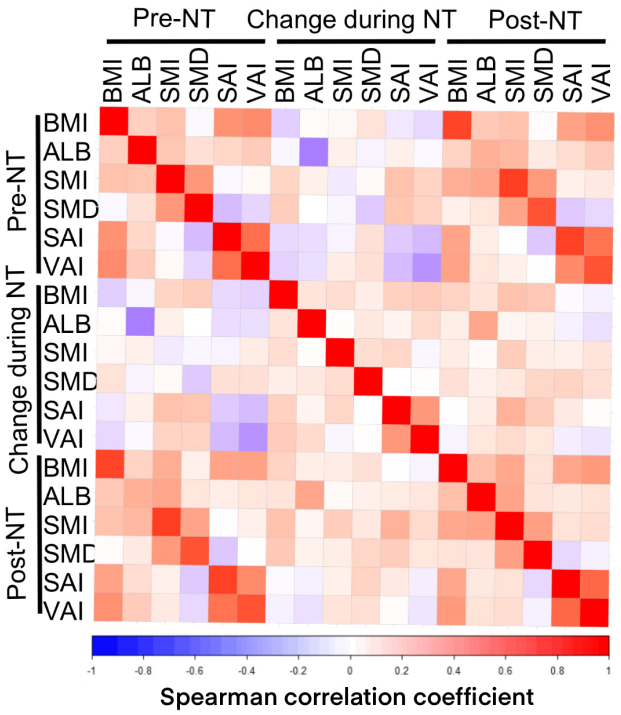

Fig. 2. Correlations between different body compositions during neoadjuvant treatment. Red indicates positive correlations (Spearman correlation coefficient >0), while blue indicates negative correlations (Spearman correlation coefficient <0), and the intensity of color indicates coefficient value. ALB, albumin; BMI, body mass index; NT, neoadjuvant therapy; SAI, subcutaneous adipose index; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; VAI, visceral adipose index.

Body Composition

A CT scan of the third lumbar vertebra (L3) was chosen to evaluate muscle and adipose tissue since this specific anatomical site is strongly linked to whole-body muscle and fat mass [17]. Quantification was performed for skeletal muscle area within the standard Hounsfield unit (HU) range of –29 to 150 HU, for visceral adipose tissue within the range of –15 to 50 HU, and subcutaneous adipose tissue within the range of –190 to 30 HU (Fig. 1). SliceOmatic version 5.0 (TomoVision, Montreal, Quebec, Canada) was used to analyze CT images containing no patient information [18]. After dividing the measured value of each body component by the square meter of height, an index was obtained for the skeletal muscle index (SMI), visceral adipose index (VAI), and subcutaneous adipose index (SAI) [19]. The software was used to calculate the skeletal muscle radiodensity (SMD) as the average radiation attenuation value of the whole muscle area. Body mass index (BMI) was calculated with dividing weight by the square of height. The changes in BMI, SMI, SMD, VAI, and SAI before and after neoadjuvant therapy are represented by ΔBMI, ΔSMI, ΔSMD, ΔVAI, and ΔSAI, respectively.

Clinical Outcomes

The Japanese Classification of Esophageal Cancer criteria were used to measure the pathological response after nICT, which included the following categories: Grade 0 indicates the absence of recognizable cytological or histological therapeutic impact; Grade 1a indicates that viable cancer cells constituted two-thirds of the tumor tissue; Grade 1b indicates that viable cancer cells accounted for one to two-thirds of the tumor tissue; Grade 2 indicates that viable cancer cells accounted for less than one-third of the tumor tissue; and Grade 3 indicates that the absence of viable cancer cells [20]. This study classified grade 0/1a/1b as non-tumor remission (non-TR) and considered grade 2/3 as tumor remission (TR). The classification of tumor stages, which included the clinical stage and pathologic stage after nICT, was determined using the tumor staging system

Table 2. Changes of body composition and albumin in neoadjuvant therapy.

Outcomes	Median (IQR)	Spearman's rank correlation	*p* value
BMI (kg/m^2)		0.882	0.012
Pre-NT	21.48 (19.42, 24.33)		
Post-NT	21.72 (20.22, 24.41)		
ΔBMI	0.34 (–0.54, 1.16)		
ALB (g/L)		0.410	0.159
Pre-NT	42.90 (39.95, 44.70)		
Post-NT	43.20 (41.30, 43.30)		
ΔALB	0.70 (–1.70, 3.00)		
SMI (cm^2/m^2)		0.901	0.146
Pre-NT	45.10 (42.25, 49.70)		
Post-NT	44.80 (42.17, 48.83)		
ΔSMI	–0.12 (–1.57, 0.40)		
SMD (HU)		0.835	0.026
Pre-NT	37.45 (33.88, 41.49)		
Post-NT	36.70 (32.84, 41.20)		
ΔSMD	–0.30 (–1.05, 0.65)		
SAI (cm^2/m^2)		0.891	0.126
Pre-NT	25.80 (20.55, 34.14)		
Post-NT	26.02 (21.05, 34.14)		
ΔSAI	0.10 (–0.70, 3.06)		
VAI (cm^2/m^2)		0.832	0.076
Pre-NT	22.30 (17.79, 29.05)		
Post-NT	25.03 (18.80, 30.94)		
ΔVAI	–0.30 (–1.00, 2.93)		

ALB, albumin; BMI, body mass index; NT, neoadjuvant therapy; SMI, skeletal muscle index; SMD, skeletal muscle radiodensity; SAI, subcutaneous adipose index; VAI, visceral adipose index.

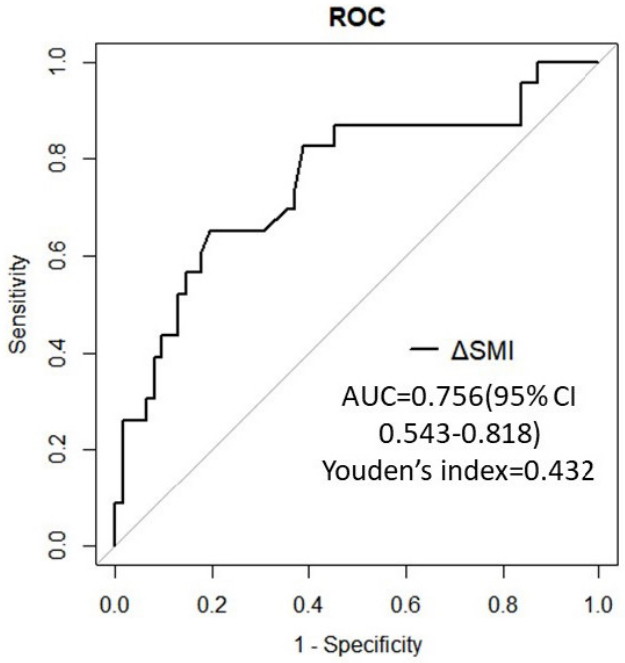

Fig. 3. Areas under the receiver operating characteristic (ROC) curves for postoperative complications. AUC, area under the curve; CI, confidence interval.

of the American Joint Committee on Cancer (AJCC) (8th edition) [21]. Postoperative complications were diagnosed according to the criteria established by the Esophagectomy Complications Consensus Group. The severity of complications was classified according to the Clavien–Dindo classification, and complications of Grade II or greater were considered significant for this analysis [22].

Statistical Analyses

The data are presented as absolute numbers and percentages, means and standard deviations (SDs) for normally distributed variables, or medians and interquartile ranges (IQRs) for nonparametric variables. Normality was assessed using the Shapiro–Wilk test. Categorical variables were analyzed using the chi-square test or Fisher's exact test, while continuous variables were analyzed using the Student's *t*-test or Wilcoxon signed rank test. The chi-square test was used when the theoretical frequency $T \geq 5$ and sample size $N \geq 40$. When $1 \leq T < 5$ and $N \geq 40$, the test is performed using a continuity-corrected chi-square. Fisher's exact test was used when $T < 1$ or $N < 40$. Spearman's rank correlation was used to analyze correlations among parameters. A logistic regression model was employed for both the univariate and multivariate analyses. Statistical significance was defined as a two-sided *p* value

Table 3. Association between pathological response and general data or body composition.

Factors	Non-TR (n = 47)	TR (n = 38)	χ^2/Z	*p* value
Age, y, (IQR)	67 (59, 71)	67 (59, 71)	–0.089	0.929
Gender, No. (%)			0.223	0.636
Male	39 (83.0)	30 (78.9)		
Female	8 (17.0)	8 (22.1)		
ECOG, No. (%)			0.007	0.935
0	35 (74.4)	28 (73.7)		
1	12 (25.6)	10 (26.3)		
Tumor location, No. (%)				0.667**
Upper	4 (8.5)	4 (10.5)		
Middle	32 (68.1)	22 (57.9)		
Lower	11 (23.4)	12 (31.6)		
Clinical TNM stage, No. (%)				0.026**
II	15 (31.9)	22 (57.9)		
III	25 (53.2)	15 (39.5)		
IV	7 (14.7)	1 (2.6)		
Postoperative complication, No. (%)				
Yes	33 (70.2)	29 (85.0)	0.397	0.529
No	14 (29.8)	9 (15.0)		
BMI, Mean (SD), kg/m^2				
Pre-NT	21.5 (2.58)	22.23 (3.31)	–1.142	0.27
ΔBMI	0.01 (1.31)	0.84 (1.29)	–2.918	0.005
ALB, Mean (SD), g/L				
Pre-NT	42.21 (3.33)	42.62 (4.01)	–0.506	0.614
ΔALB	0.31 (4.46)	1.05 (3.63)	–0.849	0.407
SMI, Median (IQR), cm^2/m^2				
Pre-NT	43.56 (41.3, 46.12)	46.94 (42.87, 54.3)	–3.187	0.001
ΔSMI	–0.7 (–2.1, 0)	0.3 (–0.38, 1.13)	–2.679	0.001
SMD, Mean (SD), HU				
Pre-NT	35.87 (6.28)	39.46 (5.86)	–2.698	0.008
ΔSMD*	–0.7 (–1.6, –0.1)	0.18 (–0.67, 0.96)	–2.312	0.021
SAI, Median (IQR), cm^2/m^2				
Pre-NT	25.8 (20.6, 32.4)	26.05 (19.58, 37.87)	–0.296	0.767
ΔSAI	–0.3 (–0.7, 2.18)	0.3 (–0.76, 4.22)	–1.167	0.243
VAI, Median (IQR), cm^2/m^2				
Pre-NT	21.5 (18.5, 26.3)	24.36 (16.86, 36.59)	–0.990	0.322
ΔVAI	–0.4 (–1, 2.89)	–0.15 (–1.73, 3.33)	–0.053	0.958

* Median (IQR); ** Calculated by Fisher's exact test. TR, tumor remission; SD, standard deviation.

less than 0.05. Statistical analyses were performed with SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

This study included 85 patients with ESCC who received nICT and underwent esophagectomy at the First Affiliated Hospital of Anhui Medical University between February 2021 and June 2023 (Table 1). Among them, 69 patients were male (81.2%), and 16 were female (18.8%). The median age at diagnosis was 67 years. At initial presentation, the vast majority of patients exhibited clinical stage II or III disease (90.6%). After nICT, most patients (90.6%) successfully underwent minimally invasive esophagectomy. R0 resection was achieved in 79 patients (92.9%). pCR was observed in 12 cases (14.1%), while 33 cases (38.8%) were classified as ypI stage, 13 cases (15.3%) as ypII stage, 23 cases (27.1%) as ypIII stage and 4 cases (4.7%) as ypIV stage in the postoperative pathological stages. Following neoadjuvant therapy, 38 cases (44.7%) exhibited TR, while 47 cases (55.3%) exhibited non-TR based on the set threshold. The characteristics of this study population are summarized in Table 1.

Body Composition Parameters

Table 2 summarizes the BMI, SAI, VAI, SMI, and SMD at diagnosis and before surgery. BMI slightly increased throughout neoadjuvant treatment (from 21.48 to 21.72 kg/m^2, $p = 0.012$). Among the changes in body composition during nICT, the SMD was significantly lower than before treatment (from 37.45 to 36.70 HU, $p = 0.026$). In con-

Table 4. Univariate and multivariate analysis for pathological response.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	0.998 (0.944–1.05)	0.931		
Gender				
Male	Ref.			
Female	1.3 (0.431–3.93)	0.637		
ECOG				
0	Ref.			
1	1.042 (0.387–2.77)	0.935		
Tumor location				
Upper	Ref.			
Middle	0.687 (0.148–3.19)	0.622		
Lower	1.091 (0.21–5.67)	0.916		
Clinical TNM stage				
II	Ref.			
III				
IV	0.365 (0.173–0.771)	0.008	0.345 (0.141–0.844)	0.020
Before NT				
Pre-NT BMI	1.091 (0.941–1.27)	0.255		
Pre-NT ALB	1.031 (0.916–1.17)	0.610		
Pre-NT SMI	1.143 (1.055–1.26)	0.002	1.155 (1.030–1.295)	0.08
Pre-NT SMD	1.106 (1.027–1.2)	0.012	1.061 (0.954–1.180)	0.274
Pre-NT SAI	1.009 (0.98–1.04)	0.540		
Pre-NT VAI	1.013 (0.988–1.04)	0.331		
Change during NT				
ΔBMI	1.653 (1.167–2.46)	0.008	1.255 (0.832–1.895)	0.279
ΔALB	1.048 (0.943–1.17)	0.395		
ΔSMI	1.262 (1.025–1.61)	0.040	1.394 (1.061–1.832)	0.017
ΔSMD	1.083 (0.952–1.26)	0.253		
ΔSAI	1.005 (0.94–1.08)	0.882		
ΔVAI	1.017 (0.959–1.08)	0.581		

OR, Odds Ratio; Ref, Reference; CI, confidence interval.

trast, the other parameters did not significantly change during nICT. The correlations between various body composition parameters are shown in Fig. 2. Our findings revealed positive correlations between the SMI, SAI, VAI, and BMI at initial diagnosis and before surgery. In contrast, no correlations were found between the SMD and BMI.

Correlation between Body Composition and Pathologic Response to nICT

The patients in the non-TR group had a more advanced clinical stage than those in the TR group. No significant differences were identified in sex, age, Eastern Cooperative Oncology Group (ECOG) score, tumor site, or postoperative complications between the two groups. Regarding body composition, the patients in the non-TR group had lower SMI (median 43.56 vs. 46.94, $p = 0.001$) and SMD (median 35.87 vs. 39.46, $p = 0.008$) at diagnosis. Throughout the nICT, the SMI and SMD of patients in the non-TR group decreased, whereas those in the TR group slightly increased (ΔSMI –0.7 vs. 0.3, $p = 0.001$; ΔSMD –0.7 vs. 0.18, $p = 0.021$). The difference in the ΔBMI (median: 0.01 vs. 0.84, $p = 0.005$) between the patients in the non-TR and TR group was also statistical significance (Table 3). Moreover, the logistic regression model revealed that the ΔSMI (Odds Ratio [OR] 1.394, 95% confidence interval [CI] 1.061–1.832, $p = 0.017$) and clinical stage (OR 0.345, 95% CI 0.141–0.844, $p = 0.020$) were the factors independently associated with the pathological response to nICT (Table 4).

Influence of the ΔSMI on Postoperative Complications

Postoperative complications, including pneumonia, anastomotic leakage, recurrent nerve palsy, chylothorax, pleural effusion, and pneumothorax, were recorded. Twenty-eight postoperative events occurred in 23 patients. Table 5 illustrates the correlations between body composition and postoperative complications. Univariate logistic analyses revealed that the difference in the ΔSMI was statistically significant (OR: 0.591, 95% CI 0.418–0.78, $p = 0.001$). After adjusting for age, sex, ECOG score, and clinical stage, the multivariate logistic analysis demonstrated that the ΔSMI remained associated with the occurrence of postoperative complications (OR 0.598, 95% CI 0.433–0.828; $p = 0.002$).

Table 5. Univariate and multivariate analysis for overall postoperative complications.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.028 (0.966–1.1)	0.409		
Gender				
Male	Ref.			
Female	0.327 (0.049–1.31)	0.162		
ECOG				
0	Ref.			
1	1.015 (0.321–2.93)	0.979		
Tumor location				
Upper	Ref.			
Middle	3.5 (0.561–68.05)	0.258		
Lower	1.474 (0.176–31.5)	0.747		
yp TNM stage				
pCR/I/II	Ref.			
III/IV	0.919 (0.311–2.53)	0.873		
R category				
R0	Ref.			
R1	1.93 (0.289–38.08)	0.559		
Change during NT				
ΔBMI	0.738 (0.495–1.06)	0.114		
ΔALB	1.021 (0.908–1.15)	0.735		
ΔSMI	0.591 (0.418–0.78)	0.001	0.598 (0.433–0.828)	0.002
ΔSMD	0.936 (0.817–1.07)	0.326		
ΔSAI	1.023 (0.95–1.1)	0.554		
ΔVAI	0.994 (0.929–1.06)	0.852		
After NT				
Post-NT BMI	0.88 (0.73–1.04)	0.157		
Post-NT ALB	0.996 (0.879–1.14)	0.950		
Post-NT SMI	0.974 (0.897–1.05)	0.511		
Post-NT SMD	0.995 (0.919–1.08)	0.902		
Post-NT SAI	0.98 (0.937–1.02)	0.305		
Post-NT VAI	0.996 (0.961–1.03)	0.782		

CI, confidence interval; OR, Odds Ratio; Ref, Reference.

The area under the curve (AUC) of the ΔSMI for postoperative complications prediction was 0.756 (95% CI 0.543–0.818) (Fig. 3). Based on the Youden index, the cutoff value of the ΔSMI was –1 (sensitivity 60.9%, specificity 82.3%). Postoperative complications, particularly pneumonia, were more frequent in the ΔSMI <–1 group (Table 6). Patients who had a ΔSMI <–1 experienced a prolonged drainage tube removal time (mean: 9.0 vs. 8.0, $p = 0.041$) and an increased duration of postoperative hospital stay (mean:8.0 vs. 7.0, $p = 0.03$). Therefore, the ΔSMI served as an independent predictor for evaluating the medical outcomes of patients with ESCC who underwent nICT.

Discussion

In the current study, we measured the area of skeletal muscle, subcutaneous and visceral adiposity, as well as skeletal muscle radiodensity using CT images of L3 vertebral body sections, and examined the correlation between body composition and tumor response and surgical results following nICT for patients with ESCC in China. Our research revealed that the ΔSMI is a robust predictor of pathological response, demonstrating notably greater ΔSMI values in the patients with tumor regression than those without. Furthermore, the ΔSMI was strongly correlated with a greater occurrence of postoperative complications. A ΔSMI <–1 was strongly linked to a longer removal time for drainage tubes; extended hospital stays after surgery, and an increased incidence of postoperative complications. These findings indicated that assessing muscle parameters may be a straightforward and efficient approach for evaluating the treatment response of nICT-treated ESCC patients.

The importance of body composition and its influence on clinical outcomes after neoadjuvant treatment across different types of cancers has been well documented in previous studies. Lin *et al*. [23] demonstrated a correlation between the initial SMD and alterations in SMI during neoadjuvant chemotherapy with pathological response. The adverse effects of a reduction in skeletal muscle on the clini-

Table 6. Surgical outcomes in patients with low and high ΔSMI.

Outcomes	ΔSMI <–1 (n = 25)	ΔSMI ≥–1 (n = 60)	χ^2/Z	*p* value
Overall complications, No. (%)	14 (56)	9 (15)	15.030	<0.001
Pneumonia, No. (%)	5 (20)	0 (0)	9.393	0.002
Anastomotic leakage, No. (%)	3 (12)	5 (8.3)	0.014	0.905
Postoperative hospital stays (days), median (IQR)	9.0 (7.5–14.5)	8.0 (7.0–9.75)	–2.172	0.030
Drainage tube removed time (days), median (IQR)	8.0 (6.5–11)	7.0 (6.0–8.75)	–2.046	0.041

cal prognosis of individuals with EC receiving multimodal treatments have also been discussed in the literature. For example, Ishida *et al*. [24] found that a low muscle index before neoadjuvant chemotherapy was correlated with an unfavorable pathological response to chemotherapy in EC patients. Sato *et al*. [25] reported that, in patients with unresectable EC, individuals with skeletal muscle loss had lower response rates to chemoradiotherapy. Recently, immunotherapy has led to significant improvements in treating patients with advanced ESCC. Nonetheless, the relationship between body composition and the response to nICT in ESCC patients remains unknown. Previous studies have shown that skeletal muscle loss is correlated with immunotherapy efficacy in treating advanced cancer [26, 27]. Our research revealed that pretreatment SMI, SMD, and ΔSMI were associated with the tumor response to nICT in univariate analysis. However, according to the multivariate analysis, the ΔSMI was the sole independent predictor of pathological response.

The detailed mechanisms by which changes in the SMI are linked to the tumor response in patients with nICT have rarely been explored. In addition to being a locomotive organ, skeletal muscle plays a crucial role in maintaining homeostasis by releasing metabolic mediators such as cytokines. Patients with skeletal muscle loss exhibit reduced levels of serum interleukin-15 (IL-15), which functions critically in regulating CD8+ T cells and is essential for antitumor immunity [28]. Ali and Garcia [29] proposed that a reduction in skeletal muscle results in an increase in proinflammatory factors. These mediators can disrupt the immune system and the tumor microenvironment, resulting in poor responses. Severe adverse events during nICT and tumors leading to protein wasting could contribute to the reduction of skeletal muscle. Therefore, severe muscle loss may disrupt the secretion of some cytokines and impair the immune response, and thus, may be related to poor tumor regression in response to nICT. Therefore, providing nutritional support to maintain muscle mass during nICT may improve treatment outcomes. Kita *et al*. [30] revealed that enteral nutrition support prevented reduced skeletal muscle intensity during NT among individuals diagnosed with EC. More research is necessary to clarify whether nutritional support helps mitigate skeletal muscle depletion and enhance the efficacy of nICT in patients with ESCC.

Esophagectomy is a highly invasive procedure that carries a significant risk of major complications. Some studies have identified a correlation between reduced skeletal muscle mass and anastomotic leakage or pulmonary complications following esophagectomy [10, 11]. The findings of a previous study showed that the post-NT psoas muscle index was correlated with surgical complications following surgery due to EC [25]. Another study demonstrated that alterations in body composition during NT were linked to the development of postoperative complications in patients with ESCC [31]. Lin *et al*. [23] also found that patients with gastric cancer with an SMI loss >1.2 during NT had notably increased postoperative morbidity and worse recovery after surgery. Consistent with these findings, our study revealed that the ΔSMI accurately predicts postoperative complications after esophagectomy and nICT, especially for pneumonia. A ΔSMI <–1 during NT was significantly correlated with prolonged postoperative recovery. Previous studies have demonstrated that the loss of skeletal muscles is associated with weakened breathing and swallowing muscles, which may induce dysphagia, septum plugging, and atelectasis and thus result in the development of postoperative complications [32, 33]. Therefore, our findings indicated that sufficient nutritional support during NT may be necessary for improving the clinical outcomes of ESCC patients.

This study is subject to several limitations. Primarily, it was a retrospective cohort study conducted at a singular institution, potentially amplifying selection bias. Second, the patients did not receive additional nutritional support interventions during nICT. Further research is necessary to clarify whether nutritional intervention during nICT affects body composition and thus contributes to improving clinical outcomes. Third, due to the limited duration of follow-up, our analysis focused only on the short-term outcomes of nICT. In the future, we will evaluate these patients' long-term survival outcomes to verify this investigation's findings.

Conclusions

To summarize, this retrospective analysis revealed that parameters of body composition were strongly associated with tumor reactions and clinical outcomes in patients with ESCC who underwent esophagectomy following nICT. Notably, the ΔSMI is associated with the pathological response to nICT and postoperative complications, including pneumonia, in ESCC patients. However, the influence of nutritional intervention during NT on the SMI and clinical outcomes of ESCC patients receiving nICT requires further investigation.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Author Contributions

Conception and design: YZ, RZ; Administrative support: JZ, RZ; Provision of study materials or patients: YZ, NK, JZ, RZ; Acquisition and assembly of data: MX, YD, XZ, JZ; Data analysis and interpretation: YZ, MX, YL, NK; Manuscript writing: All authors; Final approval of manuscript: All authors. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of the First Affiliated Hospital of Anhui Medical University (No. 2023493). Due to the retrospective design of the study, the Ethics Committee waived the requirement for informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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