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L3-SMI as a predictor of overall survival in oesophageal cancer patients receiving PD-1 inhibitors combined with chemotherapy

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ABSTRACT

Background: Programmed death ligand-1 (PD-1), as an immunotherapy target, has been increasingly used in tumour therapies. But as reactions and outcomes to PD-1 inhibitors combined with chemotherapy vary individually, it is primarily important to identify an ideal indicator for predicting the therapeutic effectiveness in individual patients. Oesophageal cancer (EC) patients often have difficulty eating due to tumour blockage of the oesophagus, leading to malnutrition and muscle loss. Sarcopenia is one of the influencing factors for poor prognosis in tumour patients, but its role in PD-1 inhibitors combined with chemotherapy of EC patients is not fully clarified. In this study, we aimed to explore the prognostic significance of Sarcopenia measured by CT in EC patients treated with PD-1 antibody combined with chemotherapy.

Methods: The third lumbar skeletal muscle mass index (L3-SMI) was obtained from 83 EC patients before and 3 months after administration of PD-1 inhibitors combined with chemotherapy using conventional CT scans.

Results: Baseline L3-SMI and 3-month L3-SMI values were found not suitable for predicting the overall survival (OS) of EC patients ($p=0.32$ & $p=0.055$). Longitudinal change in L3-SMI (ΔL3-SMI) during PD-1 inhibitors combined with chemotherapy was identified as a relevant marker of OS in univariable analysis (HR: 0.98, 95% CI: 0.96–1.00, $p=0.042$) and multivariable analysis (HR: 0.96, 95% CI: 0.93–0.99, $p=0.02$). L3-SMI-positive patients generally had better OS ($p=0.041$).

Conclusion: Excessive muscle loss rather than muscle loss before and after administration of PD-1 inhibitors combined with chemotherapy is an important prognostic factor for therapeutic outcomes and OS in EC patients.

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Oesophageal cancer; programmed death ligand-1; sarcopenia; L3-SMI; PD-1 inhibitor combined with chemotherapy

Introduction

Oesophageal cancer (EC) is a common digestive system malignant tumour with a high mortality rate due to its typical clinical feature of progressive dysphagia [1]. Immunosuppressants, especially programmed death ligand-1 (PD-1) inhibitors, have been extensively available for the treatment of EC to ameliorate the poor prognosis of EC patients [2]. PD-1 is a novel member of the immune protein superfamily and its membrane protein comprises 288 amino acid residues. This immune regulation targeting PD-1 is of great significance in combating tumours, infections, autoimmune diseases, and organ transplant survival [3]. PD-1 inhibitors have been utilized extensively in the treatment of EC patients and exhibit a demonstrable effect on the therapeutic outcome [4]. Although PD-1 inhibitors combined with chemotherapy improve overall survival (OS) in EC patients and are used as the standard treatment for EC, EC remains an invasive and fatal disease. Most advanced EC patients often fail to ingest sufficient nutrients due to swallowing difficulty during the treatment process, knowing that malnutrition and cachexia are closely bound up with poor prognosis in EC patients [5–7].

As an important indicator of malnutrition, sarcopenia has aroused increasing attention from clinicians and cancer researchers [8]. Sarcopenia is known as a syndrome that is prone to fracture, joint injury, and

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even organ injuries due to the continuous decrease in skeletal muscle mass, strength and function [9]. Sarcopenia is related to various diseases, such as autoimmune diseases, rheumatic diseases, aging, and disability [10–12]. In addition, Sarcopenia is a critical element for the increase of undesirable outcomes such as weakness and even death of various cancer patients [13].

In line with these trends, there have been various studies on the impact of sarcopenia on the survival expectations of EC [14–16], but there exist controversies. While some studies have demonstrated that sarcopenia is a risk factor for poor survival, some other studies hold the opposite view. Additionally, the role of sarcopenia as a prognostic indicator for PD-1 inhibitors combined with chemotherapy of EC patients has not yet been clarified. In the present study, we intend to determine whether sarcopenia assessed by CT-based analysis could predict the therapeutic effect and OS in EC patients receiving PD-1 inhibitors combined with chemotherapy by analysing the clinicopathological characteristics and laboratory test values, and discuss their correlations with sarcopenia.

Materials and methods

Data collection and patient characteristics

This study was approved by the Ethics Committee of Wenzhou Medical University (NO.KY2023-R155) and all patients participating in this study signed a written informed consent form. Besides, this study conducted in accordance with the ethical standards stipulated in the Declaration of Helsinki.

Relevant case data of EC patients receiving PD-1 inhibitors combined with chemotherapy from 2011 to 2023 were collected, and the included patients were followed up through outpatient follow-up visits or telephone interviews. Of the 282 EC patients who received PD-1 inhibitors combined with chemotherapy, 83 had abdominal CT images before and 3 months after treatment and complete follow-up data is available, and were utilized to impact of sarcopenia on EC patients treated with PD-1 inhibitor combined with chemotherapy. The details are presented in Table 1. Besides, their pre-treatment laboratory data will be used to explore the correlation between laboratory data and OS in EC patients receiving PD-1 treatment.

The clinicopathologic features of the included patients and the laboratory examination results were obtained before using PD-1 inhibitors combined with chemotherapy. The laboratory testing data included white blood cell (WBC), lymphocyte (LYM), neutrophil (NEU) and platelet (PLT) counts and haemoglobin (Hb) levels.

Definition of sarcopenia and assessment of skeletal muscle composition

The skeletal muscle composition was evaluated before and three months after administration of PD-1 inhibitors combined with chemotherapy by measuring the cross-sectional area (cm^2) of skeletal muscles in the L3 central plane on axial CT scanning using specific software (Supplement Figure 1). The skeletal muscle index (SMI) was calculated using the following equation: SMI = muscle area over the square of the corresponding patient height (m^2).

Evaluation of the efficacy of PD-1 inhibitors combined with chemotherapy

Three months after the initiation of PD-1 inhibitors combined with chemotherapy, tumour responses in individual patients were evaluated by CT scanning or endoscopy. Evaluate tumour response by measuring the change in the longest diameter of the tumour using enhanced CT before and after treatment, and calculate the tumour reduction rate for evaluating the efficacy of PD-1 inhibitors combined with chemotherapy in accordance with the applicable iRECIST standards [17]. Tumour responses were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) in accordance with the applicable iRECIST standards. The complete reduction of the lesion is called complete remission (CR). If the tumour size shrinks by at least 30%, it is considered that PR has occurred. PD is

Table 1. Univariate and multivariate Cox regression analyses for the prediction of overall survival.

	Univariate Cox-Regression		*Multivariate Cox-Regression*	
Parameter	p-value	Hazard-Ratio(95%CI)	p-value	Hazard-Ratio(95%CI)
ΔL3SMI	0.042	0.98 (0.96–1,00)	0.020	0.96 (0.93–0.99)
Baseline L3SMI	0.77	1.00 (0.99–1.00)	0.137	0.98 (0.96–1.01)
Age	0.08	0.97 (0.95–1.00)	0.035	0.97 (0.94–1.00)
BMI	0.63	0.97 (0.85–1.10)	0.534	0.96 (0.83–1.10)
ΔBMI	0.81	0.96 (0.72–1.3)	0.190	1.22 (0.91–1.63)
Tumour reduction rate	<0.001	0.46 (0.43–0.63)	<0.001	0.42 (0.29–0.60)

BMI: Body Mass Index.

defined as an increase in tumour size of at least 20%. If a patient with breast cancer has experienced reactions beyond the definition of CR, PR, or PD, it is considered that his condition is stable (SD). Disease control (DC) includes CR, PR, and SD, while PD patients were sorted out as non-DC. The time from the treatment to death was delineated as the total OS period.

Statistical analysis

Comparison of normally distributed variables was performed by Shapiro Wilk test, and comparison of abnormally distributed variables was performed by Wilcoxon rank sum test. Box plots display a graphical summary of the median, quartiles, and ranges. Random forest is an ensemble algorithm with high accuracy and generalization performance, widely utilized in feature selection [18]. Therefore, we screened factors influencing poor prognosis by Random Forest. The impact of L3-SMI on OS was assessed by the Kaplan–Meier curve test. Statistical differences between subgroups were evaluated by the Log-rank test. Univariate and multivariate analyses were performed utilizing the Cox proportional hazards regression model to further test the prognostic value of variables. All statistical analyses were conducted using R version 1.2.5033 (RStudio Inc., Boston, MA, USA) and SPSS 23 (SPSS, Chicago, IL, USA). P value < 0.05 was regarded as statistically significant.

Results

Characteristic of patients

The characteristics of 83 EC patients receiving PD-1 inhibitors combined with chemotherapy for studying the correlations between muscle content and prognosis are detailed in Supplementary Table 1. The cohort consisted of 97.6% male patients, with a median age of 68 years. Among the 83 patients, 1.3% had tumours located in the upper oesophagus, 56.6% in the middle, 30.1% in the lower, and the remaining patients had tumours in multiple oesophageal regions. Of them, 96.4% of patients had lymph node metastasis (LNM), and 37.3% of patients had distant metastasis. About 63.9% of patients received other treatments before the combination therapy, such as radiotherapy, chemotherapy, and palliative treatment.

Sarcopenia related to the therapeutic outcomes of PD-1 inhibitors combined with chemotherapy in the treatment of EC patients

The third lumbar Skeletal Muscle Index (L3-SMI) is an important indicator for determining skeletal muscle composition and was used in this study. Subsequently, we evaluated whether L3-SMI prognosticated the therapeutic outcomes of the combination therapy in 83 EC patients and divided them into a DC group ($n = 63$) and a non-DC group ($n = 20$). Comparison of the initial L3-SMI showed no significant difference between DC and non-DC groups (Figure 1(a,d)). In addition, according to the median baseline L3-SMI (69.1697cm^2/m), patients were further divided into the muscle reduction subgroup and the muscle non-reduction subgroup through a chi-square test. It was found that the baseline L3-SMI was not a crucial factor for therapeutic outcomes (Figure 1(e)), indicating that muscle deficiency before the combination therapy may not be an accurate predictor of therapeutic efficacy. Next, we evaluated the skeletal muscle composition of EC patients 3 months after the combination treatment to explore the correlation between skeletal muscle composition and disease control in EC patients before and after the combination treatment. It was found that there was no significant difference in L3-SMI between patients in the DC group and those in non-DC at 3 months (Figure 1(c)). Furthermore, according to the median 3-month L3-SMI (65.3621cm^2/m), patients were further divided into the muscle reduction subgroup and the muscle non-reduction subgroup through a chi-square test, indicating that the 3-month L3-SMI was not a crucial factor for therapeutic outcomes (Figure 1(f)). Additionally, we investigated the individual longitudinal course of the combination chemotherapy for EC patients by analysing the increase or decrease of L3-SMI values within three months(ΔL3-SMI). Interestingly, compared with the patients in non-DC group, some patients in the DC group had lost less muscle within 3 months and there was a significant statistical difference between the two groups ($p = 0.031$) (Figure 1(b)), indicating that ΔL3-SMI was an indicator of adverse therapeutic efficacy in the combination treatment of EC. In summary, ΔL3-SMI stands for sarcopenia, related to the therapeutic outcomes of PD-1 inhibitors combined with chemotherapy in the treatment of EC patients.

Sarcopenia is an adverse prognostic factor for PD-1 inhibitors combined with chemotherapy of oesophageal cancer patients

The aim of the present study was to determine whether the initial SMI or its long-term change during PD-1 inhibitors combined with chemotherapy may also have a prognostic correlation with OS. Firstly, we used a random forest algorithm to screen factors that may affect prognosis and observed that baseline SMI,

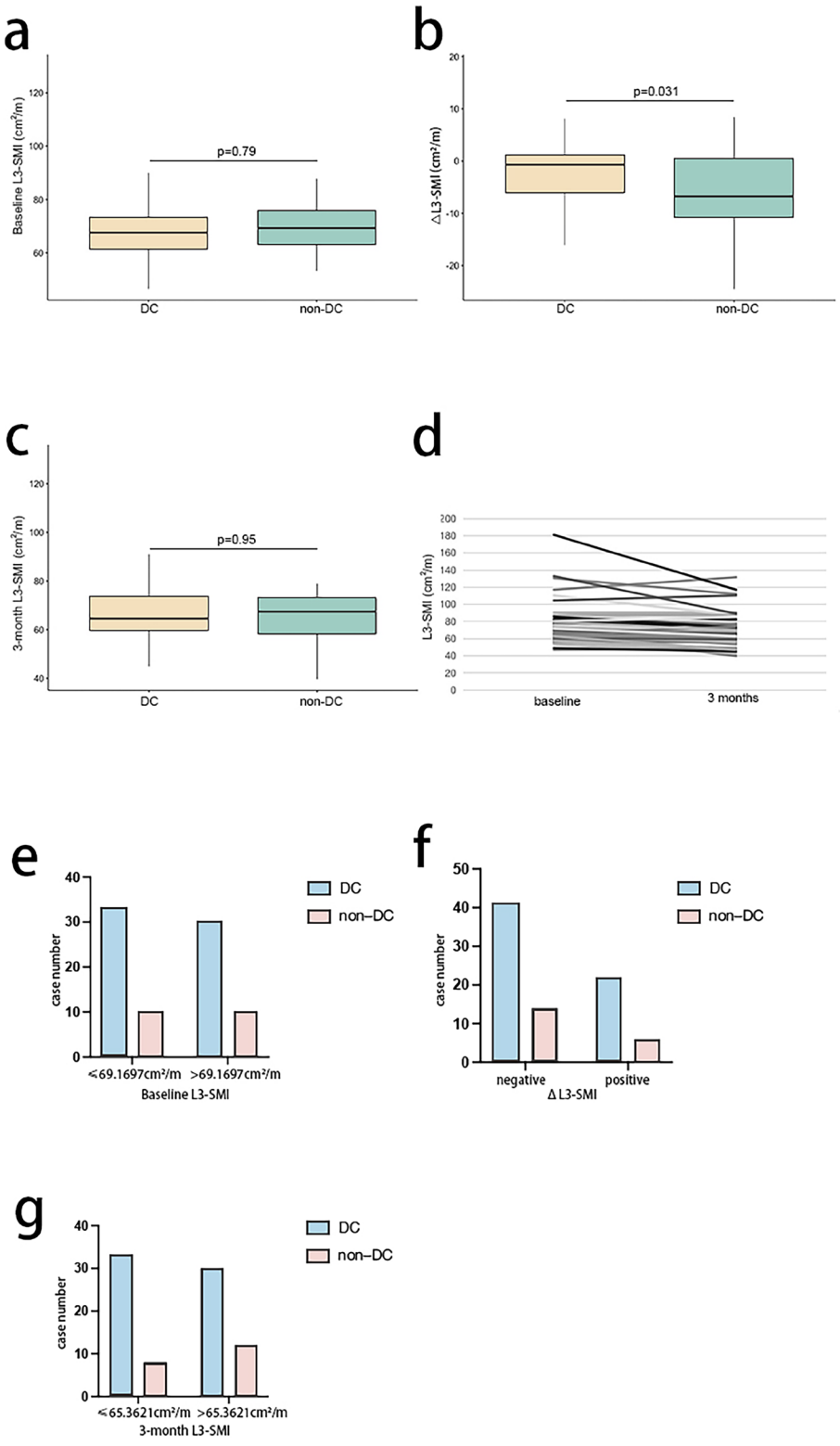

Figure 1. Sarcopenia related to the therapeutic outcomes of PD-1 inhibitors combined with chemotherapy in the treatment of EC patients. (a) Comparison of baseline L3-SMI in esophageal cancer patients with and without PD-1 inhibitors combined with chemotherapy efficacy; divided patients into DC group ($n=63$) and non-DC group ($n=20$) based on treatment efficacy. (b) Comparison of ΔL3-SMI in oesophageal cancer patients with and without PD-1 inhibitors combined with chemotherapy efficacy; divided patients into DC group ($n=63$) and non-DC group ($n=20$) based on treatment efficacy. (c) Comparison of 3-month L3-SMI in oesophageal cancer patients with and without PD-1 inhibitors combined with chemotherapy; divided patients into DC group ($n=63$) and non-DC group ($n=20$) based on treatment efficacy. (d) Overall longitudinal L3-SMI values between baseline CT scans and at 3 months are unaltered. (e) Efficacy between baseline L3-SMI > 69.1697cm2/m vs. baseline L3-SMI ≤69.1697cm2/m; grouping through chi square test. (f) Efficacy between ΔL3-SMI positive vs. ΔL3-SMI negative; patients were divided into two subgroups based on the increase or decrease of ΔL3-SMI. (g) Efficacy between 3-month L3-SMI >65.3621cm^2/m vs. 3-month L3-SMI ≤65.3621cm^2/m; grouping through chi square test.

3-month L3-SMI, and ΔL3-SMI may have a certain impact on prognosis (Figure 2). Additionally, further analysis revealed that the %IncMSE of ΔL3-SMI was −1.7307552 and IncNodePurity was 3.230781219, suggesting that ΔL3-SMI may hold a decisive function in the overall prognosis of the combination treatment for EC patients (Figure 2(a,b)). Using the median L3-SMI as a subgroup criterion, we further compared the CT scan values of L3-SMI before or 3 months after the combination treatment to screen decisive factors affecting OS. Patients with a baseline L3-SMI greater than the median value were classified as the non-muscle loss group, and those with a baseline L3-SMI smaller than the median value were classified as the muscle loss group. It was found that there was no significant difference in OS before treatment between the two groups ($p = 0.32$) (Figure 3(a)), pointing out that baseline L3-SMI did not hold a major role in predicting the prognosis of EC patients. Interestingly, at 3 months after there was still no statistical significance in OS between the two groups 3 months after the combination treatment ($p = 0.055$) (Figure 3(b)), prompting 3-month L3-SMI was not the main influencing factor of prognosis. Subsequently, we analysed the correlation between changes in L3-SMI within 3 months after the combination chemotherapy and the patient OS and found a statistical significance between ΔL3-SMI and OS of patients ($p = 0.041$) (Figure 3(c)), showing that OS of L3-SMI positive patients was significantly better than that of ΔL3-SMI negative patients and demonstrating ΔL3-SMI was an adverse prognostic factor of prognosis. Additionally, we also divided patients into DC group and non-DC group to compare the relationship between tumour response and OS and found that the efficacy evaluation at 3 months cannot predict OS ($p = 0.26$) (Figure 3(d)).

Finally, we further analysed the univariate and multivariate Cox analysis results of OS (Table 1). Univariate analysis showed that ΔL3-SMI had a prognostic impact on OS (HR: 0.98, 95% CI: 0.96–1.00, $p = 0.042$). Besides, tumour reduction rate had a prognostic impact on OS as well (HR: 0.46, 95% CI: 0.43–0.63, $p < 0.001$). In addition, BMI (HR = 0.97, 95% CI 0.85–1.1, $p = 0.63$), ΔBMI (HR = 0.96, 95% CI 0.73–1.3, $p = 0.81$), and baseline L3-SMI (HR = 1.00, 95% CI 0.99–1.00, $p = 0.77$) were not significantly correlated with OS. Importantly, the prognostic correlation of ΔL3-SMI (HR: 0.96, 95% CI: 0.93–0.99, $p = 0.020$) and tumour reduction rate (HR: 0.43, 95% CI: 0.29–0.60, $p < 0.001$) were independent of the confounding variables mentioned above in multivariate Cox Regression analysis, that is, ΔL3-SMI, as well as tumour reduction rate, were independent prognostic factors for EC patients treated with PD-1 inhibitors combined with chemotherapy.

Correlation between clinical pathology, laboratory data and prognosis

With the aim of better exploring the correlation between laboratory features and the prognosis of patients after PD-1 inhibitors combined with chemotherapy, we collected laboratory features of the aforementioned patients ($n = 83$) before receiving PD-1 inhibitors combined with chemotherapy (Supplementary Table 1). The univariate and multivariate analysis results of laboratory data and prognosis are summarized in Table 2. Univariate analysis showed no significant difference in the clinical pathological features and laboratory features, such as LNM, the pathological type of EC, WBC, LYM, NEU and PLT counts, and Hb level. Besides, multivariate Cox analysis

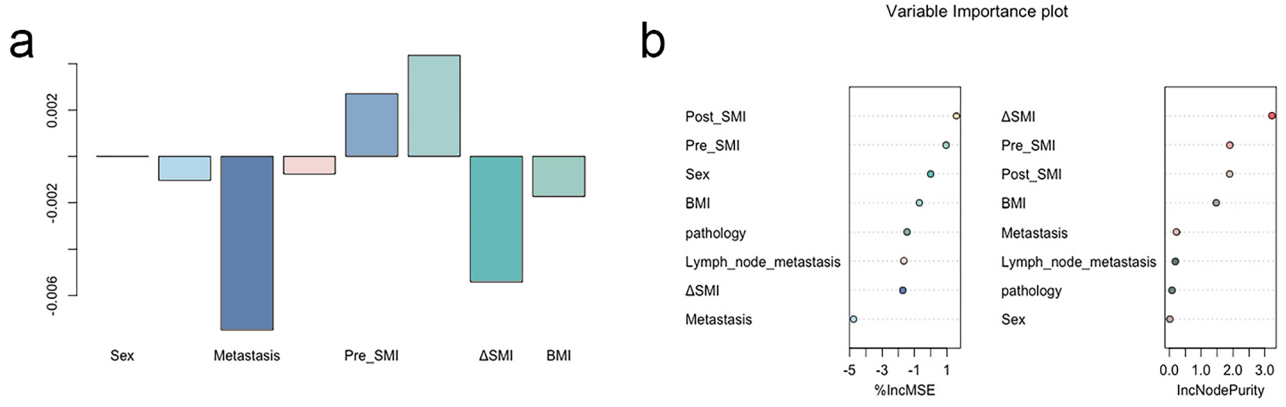

Figure 2. Sarcopenia is an adverse prognostic factor for PD-1 inhibitors combined with chemotherapy of oesophageal cancer patients. (a) Screening prognostic factors in a random Forest model. (b) Variable importance plot of prognosis. (c) Partial dependence on ΔL3-SMI.

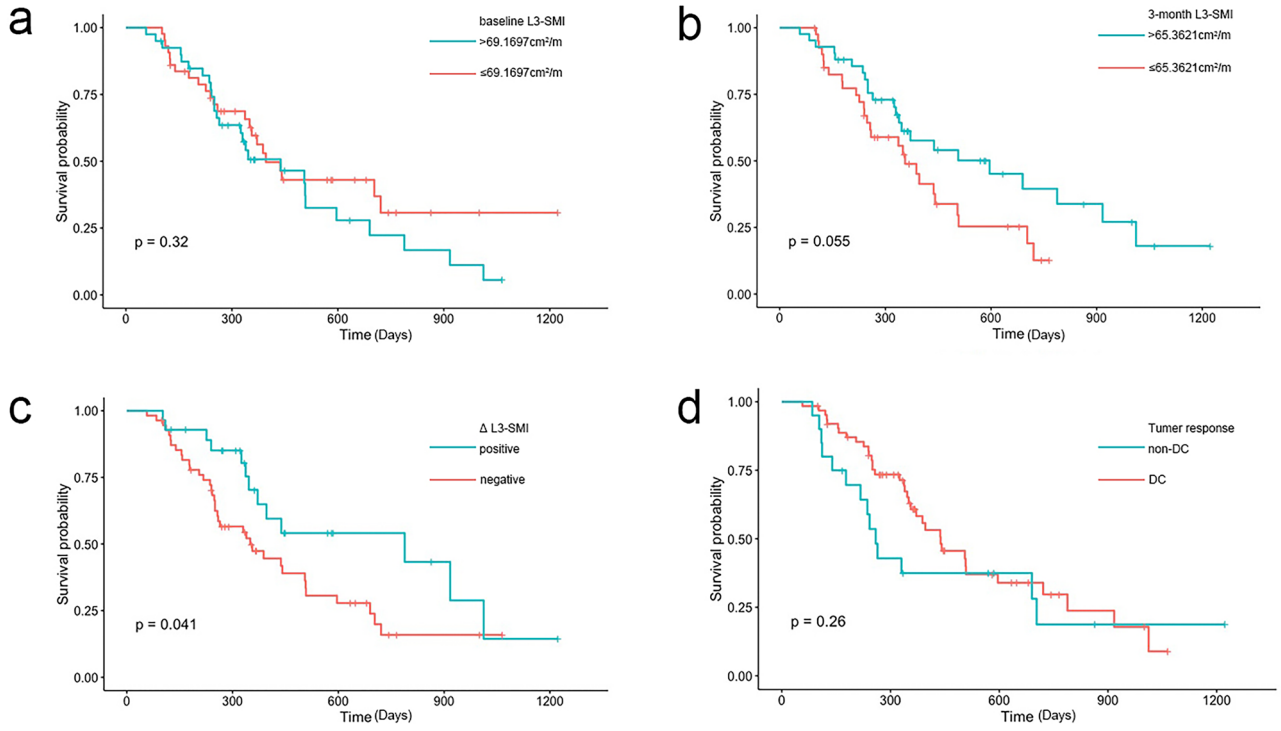

Figure 3. Sarcopenia is an adverse prognostic factor for PD-1 inhibitors combined with chemotherapy of oesophageal cancer patients. (a) OS between baseline L3-SMI > 69.1697cm^2/m vs. baseline L3-SMI ≤69.1697cm^2/m; grouping through chi square test. (b) OS between 3-month L3-SMI >65.3621cm^2/m vs. 3-month L3-SMI ≤65.3621cm^2/m; grouping through chi square test. (c) OS between ΔL3-SMI positive vs. ΔL3-SMI negative; patients were divided into two subgroups based on the increase or decrease of ΔL3-SMI.

Table 2. Univariate and multivariate Cox regression analyses for laboratory test analysis. BMI: Body-Mass-Index.

	Univariate Cox-Regression		*Multivariate Cox-Regression*	
Parameter	*p*-value	Hazard-Ratio(95%CI)	*p*-value	Hazard-Ratio(95%CI)
Lymph node metastasis	0.17	0.36 (0.085–1.5)	0.107	0.23 (0.04–1.37)
Type of pathology	0.069	1.70 (0.96–3.00)	0.099	1.82 (0.89–3.69)
White blood cell (*10^9/L)	0.300	0.94 (0.83–1.10)	0.278	0.81 (0.55–1.19)
Lymphocyte (*10^9/L)	0.091	0.71 (0.48–1.10)	0.464	0.76 (0.36–1.59)
Neutrophils (*10^9/L)	0.880	0.99 (0.85–1.10)	0.322	1.25 (0.80–1.96)
Platelet (*10^9/L)	0.940	1.00 (1.00–1.00)	0.825	1.00 (1.00–1.00)
Haemoglobin (g/L)	0.250	1.00 (1.00–1.00)	0.108	1.01 (1.00–1.02)

showed no significant correlation between these parameters and the OS of the EC patients.

Discussion

In this study, we identified the impact of sarcopenia as a predictor of efficacy and survival in EC patients receiving PD-1 inhibitors combined with chemotherapy. The results obtained in this study may help provide new perspectives for the therapeutic modalities of EC patients and particularly benefit from the determination of OS in EC patients with PD-1 inhibitors combined with chemotherapy.

In recent years, as anti-tumour Immunosuppressive drugs, PD-1 inhibitors have been consented to the treatment of more tumours, including EC [5,19]. Compared with classical radiotherapy and chemotherapy, PD-1 inhibitors have better therapeutic effects and fewer uncomfortable adverse effects [20]. However, due to individual differences, only some cancer patients benefit from PD-1 inhibitors combined with chemotherapy, while the rapid progress of the disease and poor prognosis occurred in the remaining individuals [21]. With the aim of predicting the treatment response of different cancer patients, the expression level of PD-1/PD-L1 inhibitors is widely taken as a biomarker [22]. The expression level of PD-1/PD-L1 inhibitors is not suitable for making a prediction about the treatment effect of cancer in some solid tumours, such as melanoma, hepatocellular carcinoma, and small-cell lung cancer [23–25]. Therefore, there is an urgent need for more reliable biomarkers to make a prediction

about the therapeutic impact of PD-1 inhibitors. EC patients often experience malnutrition and sarcopenia due to symptoms such as swallowing difficulty [26]. Numerous studies have been reported to explore the impact of sarcopenia on EC, but the findings and conclusions are controversial [14,16,27,28]. Grotenhuis et al. reported that sarcopenia could not be used as a prognostic indicator for EC patients after surgical resection [28], while Watanabe et al. demonstrated that sarcopenia represented a poor prognosis for EC patients [14]. However, few studies have collected data from EC patients receiving PD-1 inhibitors combined with chemotherapy or addressed the prognosis and therapeutic efficacy of PD-1 inhibitors combined with chemotherapy in treating EC patients. There are different methods for measuring muscle mass, with bioelectrical impedance analysis or ultrasound being the most normally carried out [29]. As almost all EC patients regularly undergo CT examination, we decided to calculate L3-SMI based on CT images to obtain muscle mass (sarcopenia). In this study, we demonstrated a significant correlation between the therapeutic effect and changes in skeletal muscle in EC patients during PD-1 inhibitors combined with chemotherapy. The baseline L3-SMI or 3-month L3-SMI in the study was not found to be correlated with the therapeutic effect of the combination treatment on EC patients. In addition, change in muscle mass was found to have certain predictive value for the survival prognosis of EC patients receiving PD-1 inhibitors combined with chemotherapy. Although we did not find the exact correlation between baseline L3-SMI and 3-month L3-SMI and patients' survival time, the survival time of patients in the ΔL3-SMI positive subgroup was significantly longer than that of patients in the ΔL3-SMI negative subgroup. Moreover, we further analysed the univariate and multivariate Cox analysis results of OS and discovered that ΔL3-SMI, as an independent prognostic indicator, held a crucial function on OS, demonstrating that ΔL3-SMI is an important indicator for predicting survival time in EC patients. Interestingly, tumour reduction rate has also been found to be an independent factor in the prognosis of EC patients through the univariate and multivariate Cox analysis.

Oesophageal cancer patients usually experience muscle loss due to tumour blockage of the oesophagus, often resulting in sarcopenia. Sarcopenia is related to systemic inflammation and immune system activation [30,31]. Skeletal muscles intercede in anti-inflammatory reactions and hold potential anticancer functions *via* the production and release of myokines [32]. Therefore, we also analysed the impact of inflammation-related laboratory test data on the prognosis of EC patients treated with PD-1 inhibitors combined with chemotherapy. Interestingly, the results of univariate and multivariate analyses showed no significant difference between the clinicopathological features and the laboratory features such as LNM, the pathological type, WBC, LYM, NEU and PLT counts, and Hb level. The progressive loss of muscle mass leading to activation of the immune system may lead to the above results. The activation of the immune system caused by myokines such as upregulation of IL-6, IL-10, and other laboratory test data between patients with good prognosis and patients with poor prognosis made no sense [33,34]. Furthermore, some patients included in the study received radiotherapy or chemotherapy before this treatment. Radiation therapy not only kills cancer cells but also increases tumour filtration of immune cells and triggers the release of pro-inflammatory mediators, leading to the remodelling of the inflammatory microenvironment in the body [35], and chemotherapeutic drugs hold a crucial function in increasing the secretion of inflammatory mediators to reshape the tumour microenvironment *via* activating a variety of signalling pathways [36]. Therefore, radiotherapy or chemotherapy received before the treatment in EC patients may also be an important reason for the lack of significant differences in laboratory test data between patients with good and poor prognoses.

Although we have discovered the potential prognosticative function of sarcopenia in PD-1 inhibitors combined with chemotherapy of EC patients for the first time, it is worth noting that there still are some limitations in the study. Firstly, on the basis of the retrospective study design, the detection data of myokines such as IL-6 and IL-10 in the laboratory were not explored. If these laboratory test data are available, further in-depth research will be conducted. Secondly, as this study was a single-center design, it was conducted at a specific location, and the research subjects may have regional characteristics, leading to selection bias. In addition, the sample size of this study is small and there were limitations to specific populations, which may result in insufficient representativeness of the sample. Further efforts could be made to enhance the representativeness, objectivity, and generalizability of the research by expanding the scope of the study, increasing the sample size, and collaborating with multiple centres. Finally, although there was no significant difference in L3-SMI between different malignant tumours, further analysis is needed to define a more complete sarcopenia. Therefore, further clinical trials are called for fully revealing the function of sarcopenia in PD-1 inhibitors combined with chemotherapy of EC patients.

Conclusion

It was found in this study that baseline L3-SMI and 3-month L3-SMI were not influencing factors for poor OS, while ΔL3-SMI typically implied good OS. These findings may provide a new perspective to improve the treatment efficacy and prognosis of EC patients receiving PD-1 inhibitors combined with chemotherapy. Based on the research results, for patients with ΔL3-SMI negative, interventions to prevent excessive muscle loss, such as nutritional support and regular exercise, should be taken according to the relevant guidelines for nutritional adjustment of sarcopenia, which may improve the treatment efficacy and prognosis of esophageal cancer patients.

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CRediT Author Statement

Huiya Ying: Conceptualization, Methodology, Software, Investigation, Formal Analysis, Writing - Original Draft; Yuhao Chen: Data Curation, Writing - Original Draft; Yiwen Hong: Visualization, Investigation; Kanglei Ying: Resources, Supervision; Shiyu Li: Software, Validation; Yuxuan Zhang: Visualization, Writing - Review & Editing; Tianhao Mei: Data Curation; Xian Song: Data Curation; Yuanhang He: Data Curation; Chenrui Yao: Data Curation; Fujun Yu (Corresponding Author): Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing; All authors have read and approved the final work.

Ethic consent statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (NO. KY2023-R155) and conducted in accordance with the ethical standards stipulated in the Declaration of Helsinki. The patient's written informed consent has been obtained, and their anonymous information will be published in this article.

Disclosure statement

The authors declared that they have no potential competing interests in this work. We declare that we do not have any commercial or associative interest that represents potential competing interests in connection with the work submitted.

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Data availability statement

The data that support the findings of this study are available from the corresponding author Fujun Yu, upon reasonable request.

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