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Prognostic significance of preoperative CT-based sarcopenia in locally advanced rectal cancer: a multicenter retrospective study

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Abstract

Objectives The association between preoperative CT-based sarcopenia and prognosis in locally advanced rectal cancer (LARC) remains unclear. The aim of this study was to investigate the relationship between CT-based sarcopenia and clinical outcomes in patients with LARC.

Materials and methods This multicenter retrospective study analyzed 503 LARC patients who underwent radical resection in three tertiary hospitals in China from January 2018 to June 2021 and were pathologically confirmed. All patients were followed for a period of at least three years. Clinical, pathological, and imaging data were carefully collected. According to the sex-specific skeletal muscle index (SMI), patients were evaluated for the presence of CT-based sarcopenia. The SMI was obtained by measuring the cross-sectional muscle area and standardizing it by the height of different patients. The primary endpoint was post-operative overall survival (OS), and the secondary endpoint included disease-free survival (DFS), postoperative complications, prolonged length of stay (LOS), readmission, and cancer-specific survival (CSS).

Results This study included 503 patients [mean age: 61.5 ± 10.8 years; 353 male (70.2%)], who were divided into the non-sarcopenic group (375 patients, 74.5%) and the sarcopenic group (128 patients, 25.5%). Over a mean follow-up period of 47 months (range 4–73), a total of 108 (21.4%) deaths and 162 (32.2%) combined endpoints, including recurrence or metastasis, were observed. Multivariate Cox regression analysis revealed that CT-based sarcopenia (hazard ratio [HR], 2.41; 95% confidence interval [CI], 1.49 ~ 3.87; $P < 0.001$) was independently associated with worse OS in LARC patients over a three-year period, but was not associated with shorter DFS (HR, 1.34; 95% CI, 0.89 ~ 2.03; $P = 0.163$). CT-based sarcopenia was not significantly associated with postoperative complications of grade II or greater (odds ratio [OR]: 1.29, 95% CI: 0.62 ~ 2.68, $P = 0.496$) or prolonged LOS (OR: 1.05, 95% CI: 0.6 ~ 1.86, $P = 0.853$). However, sarcopenic patients showed a higher risk of readmission (OR: 5.53, 95% CI: 1.57 ~ 19.5, $P = 0.008$) and a significant correlation with poorer CSS (HR: 2.78, 95% CI: 1.64 ~ 4.72, $P < 0.001$). Kaplan-Meier analysis showed

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that sarcopenic LARC patients had a significantly higher cumulative hazard of OS compared to non-sarcopenic patients ($P < 0.001$, log-rank test). Similar patterns of association were observed in subgroup analyses (all P values for interaction > 0.05).

Conclusions Preoperative CT-based sarcopenia is independently associated with decreased OS, CSS, and an elevated risk of readmission in patients with LARC. These findings emphasize the importance of identifying sarcopenic patients at higher risk for adverse outcomes and suggest that interventions aimed at improving physical strength and endurance may play a critical role in informing treatment strategies and guiding clinical decisions.

Keywords Sarcopenia, Locally advanced rectal cancer, Prognosis, CT

Introduction

Colorectal cancer is the second leading cause of cancer death, the incidence of colorectal cancer is similar both male and female, with rates approximately 8.1% in male and 7.5% in female. Rectal cancer accounts for approximately one-third of all colorectal cancer cases [1–3]. Although the incidence and mortality of colorectal cancer are decreasing, the incidence of rectal cancer is increasing rapidly, and the most common type is locally advanced rectal cancer (LARC). Traditionally, neoadjuvant therapy and adjuvant therapy are recommended for patients with LARC to decrease the incidence of local recurrence. However, the treatment outcome of LARC patients is still unsatisfactory, especially with highly variability in local recurrence rate and survival rate, as well as distant metastasis can reach approximately 30% [4–6]. Therefore, in addition to the multidisciplinary team working together in diagnosis, staging and other aspects to develop the best treatment strategy, it is also of great clinical significance to timely identify preoperative risk factors, risk stratification of patients, and accurate high-individual treatment.

Sarcopenia is a progressive condition defined by a widespread decline in skeletal muscle mass and strength, leading to functional impairments and a significant reduction in quality of life [7–11]. In clinical practice, the evaluation of sarcopenia is essential for identifying nutritional deficiencies, diagnosing malnutrition-related disorders, and assessing responses to interventions. As a prognostic marker, sarcopenia informs individualized treatment plans, aids in patient-specific management, and supports population-level research on improving nutrition and physical activity. Affecting individuals of diverse ages and backgrounds, sarcopenia is often associated with a constellation of symptoms, including slow walk, falls, fracture, and disability [7]. The pathophysiological mechanisms of sarcopenia are complicated and have not been fully elucidated, but they include myofiber metabolism disorders, satellite cells differentiation abnormalities, and changes in blood biochemistry and intestinal microbiome, among other factors [12–16]. Among various diagnostic methods, CT-based sarcopenia, which involves analyzing cross-sectional muscle areas obtained during routine imaging, is the most widely used parameter for sarcopenia assessment in clinical research [17]. Management of sarcopenia focuses on early diagnosis, timely intervention, and prevention of complications. Treatments may involve both pharmacological and non-pharmacological approaches tailored to the individual's needs [18–21]. Sarcopenia has a profound impact on daily living, disease prognosis, and social interactions. Its prognosis depends on disease severity, timely diagnosis, and treatment adherence. Current research is dedicated to uncovering the mechanisms of sarcopenia, developing new therapies, and improving patient outcomes.

Nevertheless, only few studies have researched the association between preoperative CT-based sarcopenia and clinical outcome of LARC patients, and the results remain controversial. This limited evidence highlights the need for further research to better understand how CT-based sarcopenia impacts the prognosis of LARC patients and its broader clinical implications. The primary objective of this study is to bridge this knowledge gap by providing a comprehensive analysis of the association between CT-based sarcopenia and patient outcomes.

Materials and methods

Subjects

From January 2018 to June 2021, 586 consecutive LARC patients underwent radical surgery in three tertiary hospitals in China and pathologically confirmed were enrolled in this multicenter retrospective research. The study protocol has been approved by the ethics committee of the Shengjing Hospital of China Medical University (ethical no.2023PS1097K), Chaoyang Central Hospital (ethical (2024) Ethical Review No. (07)), and the First Affiliated Hospital of Jinzhou Medical University (ethical no. KYLL2024437). And the requirement for informed consent was waived. LARC was defined as a stage II or III rectal tumors according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, which determined based on preoperative CT of the chest and abdomen and pelvis magnetic resonance imaging (MRI), and it located within 15 cm of the anal verge. All patients underwent total mesorectal excision (TME). All patients were required to be at least 18 years old and not

to have undergone any other form of treatment prior to the MRI scan. All patients were followed up for at least three years, and underwent postoperative imaging and clinically relevant examinations. Patients with residual tumor and/or circumferential resection margin involvement were excluded. In this study, we collected clinical characteristics, treatment regimens, pathological indicators and preoperative serum carcinoembryonic antigen (CEA) of the patients.

Data collection and follow-up

In this research, the baseline characteristics of LARC patients were carefully collected through the Neusoft HIS clinical admission records (Table 1). The data included clinical characteristics (sex, age, BMI, clinical stage, nodal status, location), treatment regimens (preoperative treatment, surgical approach, surgical procedures, postoperative chemoradiotherapy), pathological indicators (pathological staging, whether invasion of peripheral nerves and blood vessels) and preoperative serum carcinoembryonic antigen (CEA). The preoperative CEA level was measured within one week prior to surgery. For all patients who underwent neoadjuvant therapy, the measurement was conducted after completing treatment. CEA levels were classified as normal (≤ 5.0 ng/mL) or elevated (> 5.0 ng/mL). In this study, four neoadjuvant treatment protocols were employed. Long-course chemoradiotherapy consisted of 45–50.4 Gy administered in 25–28 fractions with concurrent fluorouracil or capecitabine. Short-course radiotherapy protocols delivered 25 Gy across 5 fractions. Neoadjuvant chemotherapy regimens included oxaliplatin with leucovorin and fluorouracil (FOLFOX) or oxaliplatin with capecitabine (CAPOX). Total neoadjuvant therapy incorporated long-course chemoradiotherapy combined with either induction chemotherapy (prior to chemoradiotherapy) or consolidation chemotherapy (following chemoradiotherapy). Postoperative chemotherapy regimens used in these protocols included FOLFOX, CAPOX, or capecitabine monotherapy.

Outcomes and measures

Postoperative follow-up began on day one via phone or in-person visits. Follow-ups occurred every 3–6 months for the first 2 years and every 6 months for the following 3 years. Patients were considered lost to follow-up if they missed appointments for over a year. CEA levels were measured regularly: every 3–6 months for 2 years and then every 6 months for 3 years. Imaging, including abdominal/pelvic CT and chest CT, was performed annually for at least 3 years. Colonoscopy was conducted 1year post-surgery and repeated every 2–5 years unless advanced adenomas were found. We conducted telephone communications and carefully reviewed patient medical records both outpatient and inpatient systems to collect follow-up information. We ensured that all participants were followed for a minimum of three years after undergoing radical surgery. The primary outcome we interested in was overall survival (OS), which defined as the time from surgery to death from any cause or the last follow-up. The secondary outcome included disease-free survival (DFS), readmission, length of stay, postoperative complications, and cancer-specific survival (CSS). DFS was defined as the time from surgery to the time of recurrence, or metastasis, or death for any reason, or the last follow-up. The time to the endpoint was determined by the number of months between the surgery date and the occurrence of the event. Readmission was defined as hospital readmission within 30 days after discharge [22]. Length of stay (LOS) was calculated as the number of days between admission and discharge. Since there is no universally accepted definition for prolonged length of stay (LOS), we defined prolonged LOS as exceeding the upper quartile for all cases (greater than 22 days). Postoperative complications were graded based on the Clavien-Dindo classification system [23]. In cases where multiple complications occurred, the highest Clavien-Dindo grade was used for analysis. Complications included gastrointestinal-related complications, surgical site complications, infectious complications, and other types of complications. CSS is defined as the duration of time from surgery to the date of death specifically caused by the diagnosed cancer or the last follow-up.

Evaluation and definition of CT-based sarcopenia

In this study, a single preoperative unenhanced CT image of a LARC patient was used for the analysis. The patient was positioned supine, and the image was acquired at the level of the third lumbar vertebra. Images were imported into Mimics Research version 21.0 software (Materialise, Leuven, Belgium) for image segmentation. According to the skeletal muscle threshold of -29HU to 150HU, the area (cm^2) of all abdominal muscles was automatically delineated, and the total skeletal muscle area was obtained by manual delineation adjustment. To ensure the accuracy of the analysis, image analysis was performed by researchers who were unaware of clinical outcome of LARC patients, and the skeletal muscle index (SMI) normalized the muscle status of the individual by dividing the total muscle area (cm^2) by the square of the height (m^2). SMI was also stratified according to gender, with sarcopenia defined as less than 32.5 cm^2/m^2 in female and less than 44.77 cm^2/m^2 in male [24].

Statistical analysis

Shapiro-Wilk test was used for determining whether variables were normally distributed. All normally distributed continuous variables were expressed presented

Table 1 Demographic and clinicopathological characteristics

Characteristics	Total (*n* = 503)	Non-sarcopenia (*n* = 375)	Sarcopenia (*n* = 128)	*p*
Age at surgery, mean (SD)	61.5 ± 10.8	59.4 ± 10.5	67.6 ± 9.4	**< 0.001**
Sex, n (%)				**0.003**
female	150 (29.8)	125 (33.3)	25 (19.5)	
male	353 (70.2)	250 (66.7)	103 (80.5)	
BMI, mean (SD)	23.7 ± 3.2	24.4 ± 3.1	21.5 ± 2.8	**< 0.001**
Clinical stage, n (%)				0.803
II	231 (45.9)	171 (45.6)	60 (46.9)	
III	272 (54.1)	204 (54.4)	68 (53.1)	
Clinical T stage, n (%)				0.086
cT2	25 (5.0)	21 (5.6)	4 (3.1)	
cT3	433 (86.1)	326 (86.9)	107 (83.6)	
cT4	45 (8.9)	28 (7.5)	17 (13.3)	
Lymph node status, n (%)				0.649
negative	231 (45.9)	170 (45.3)	61 (47.7)	
positive	272 (54.1)	205 (54.7)	67 (52.3)	
location, n (%)				0.988
<5 cm	187 (37.2)	140 (37.3)	47 (36.7)	
>10 cm	73 (14.5)	54 (14.4)	19 (14.8)	
5–10 cm	243 (48.3)	181 (48.3)	62 (48.4)	
Preoperative serum CEA, n (%)				0.15
<5	344 (68.4)	263 (70.1)	81 (63.3)	
≥5	159 (31.6)	112 (29.9)	47 (36.7)	
Surgical approach, n (%)				0.104
laparoscope	441 (87.7)	334 (89.1)	107 (83.6)	
open	62 (12.3)	41 (10.9)	21 (16.4)	
Neoadjuvant therapy, n (%)				0.626
No	373 (74.2)	276 (73.6)	97 (75.8)	
Yes	130 (25.8)	99 (26.4)	31 (24.2)	
Adjuvant chemotherapy, n (%)				**< 0.001**
No	129 (25.6)	81 (21.6)	48 (37.5)	
Yes	374 (74.4)	294 (78.4)	80 (62.5)	
Adjuvant radiotherapy, n (%)				0.861
No	410 (81.5)	305 (81.3)	105 (82)	
Yes	93 (18.5)	70 (18.7)	23 (18)	
pN stage, n (%)				0.519
0	257 (51.1)	187 (49.9)	70 (54.7)	
1	196 (39.0)	148 (39.5)	48 (37.5)	
2	50 (9.9)	40 (10.7)	10 (7.8)	
pT stage, n (%)				**0.019**
0	10 (2.0)	6 (1.6)	4 (3.1)	
1	5 (1.0)	4 (1.1)	1 (0.8)	
2	57 (11.3)	47 (12.5)	10 (7.8)	
3	405 (80.5)	305 (81.3)	100 (78.1)	
4	26 (5.2)	13 (3.5)	13 (10.2)	
Lymphovascular invasion, n (%)				0.148
negative	439 (87.3)	332 (88.5)	107 (83.6)	
positive	64 (12.7)	43 (11.5)	21 (16.4)	
Perineural invasion, n (%)				0.964
negative	378 (75.1)	282 (75.2)	96 (75)	
positive	125 (24.9)	93 (24.8)	32 (25)	
Neoadjuvant therapy regimen, n (%)				0.427
Neoadjuvant chemotherapy	91 (70.0)	72 (72.7)	19 (61.3)	

Table 1 (continued)

Characteristics	Total (*n* = 503)	Non-sarcopenia (*n* = 375)	Sarcopenia (*n* = 128)	*p*	
Long-course chemoradiotherapy	19 (14.6)	13 (13.1)	6 (19.4)		
Short-course radiotherapy	2 (1.5)	1 (1)	1 (3.2)		
Total neoadjuvant therapy	18 (13.8)	13 (13.1)	5 (16.1)		
Adjuvant chemotherapy regimen, n (%)				**< 0.001**	
CAPOX	324 (86.6)	264 (89.8)	60 (75)		
Capecitabine	36 (9.6)	23 (7.8)	13 (16.2)		
FOLFOX	14 (3.7)	7 (2.4)	7 (8.8)		
Cancer related death, n (%)				0.685	
No	17 (15.7)	9 (14.5)	8 (17.4)		
Yes	91 (84.3)	53 (85.5)	38 (82.6)		
Length of stay, Median (IQR)	19.0 (15.5, 22.0)	18.0 (15.0, 22.0)	20.0 (16.0, 23.0)	0.42	
Prolonged length of stay (> 22 days), n (%)					0.256
No		384 (76.3)	291 (77.6)	93 (72.7)	
Yes		119 (23.7)	84 (22.4)	35 (27.3)	
Readmission, n (%)				**0.008**	
No	487 (96.8)	368 (98.1)	119 (93)		
Yes	16 (3.2)	7 (1.9)	9 (7)		
Surgical procedure, n (%)				**0.001**	
Dixon	403 (80.1)	309 (82.4)	94 (73.4)		
Hartmann	20 (4.0)	8 (2.1)	12 (9.4)		
Miles	70 (13.9)	53 (14.1)	17 (13.3)		
Other[a]	10 (2.0)	5 (1.3)	5 (3.9)		
Number of complications, n (%)				0.104	
1	85 (86.7)	59 (89.4)	25 (80.6)		
2	11 (11.3)	7 (10.6)	4 (12.9)		
3	2 (2.1)	0 (0)	2 (6.5)		
Clavien-Dindo (highest grade complication), n (%)				0.222	
I	42 (42.9)	31 (46.3)	11 (35.5)		
II	46 (46.9)	31 (46.3)	15 (48.4)		
III	8 (8.2)	5 (7.5)	3 (9.7)		
IV	2 (2.0)	0 (0)	2 (6.5)		

CEA carcinoembryonic antigen, pN pathological nodal stage, pT pathological tumor stage.

[a] Combined resection of adjacent organs or anatomical structures affected by tumor invasion

as mean ± standard deviations. Categorical variables were presented as frequencies (%). Independent samples Student's t-test was performed with among continuous variables groups and categorical data were compared by chi-square or Fisher's exact test. Non-normally distributed data were analyzed using non-parametric tests.

Long-term survival was assessed with Kaplan–Meier analysis according to the muscle status and evaluated with the log-rank test. Logistic regression analysis was used to evaluate the association between CT-based sarcopenia and postoperative complications, prolonged LOS, and readmission. The Cox proportional hazards model was applied to assess the relationship between CT-based sarcopenia and long-term survival. Confounders that were selected on the basis of clinical interest, all significant covariates in the univariate analysis, or their associations with the outcomes of interest or a change in effect estimate of more than 10%. Potential multi-collinearity was tested using the variance inflation factor (VIF), with VIF > = 5 indicating the presence of multi-collinearity. Interaction and stratified analyses were conducted according to subgroup variables. Interaction across subgroups was tested using the likelihood ratio test. We constructed 3 models: model I, factors were selected based on common clinical variables, such as age and gender. In model II, factors were selected if they changed the effect estimate by at least 10% in addition to common clinical variables. In model III, factors were included based on common clinical variables, *p*-values less than 0.05 in univariate analysis, or a 10% or greater change in the effect estimate.

All analyses were performed using R Statistical Software Version 4.2.2. A two-sided *P* value < 0.05 was considered statistically significant.

Results

Patient clinical characteristics

A total of 586 LARC patients pathological confirmed initially enrolled in this research, while a further 83 patients were excluded (lost follow up, $n = 73$; lack of complete clinical data, $n = 10$; Fig. 1). Consequently, 503 patients, comprising 353 male and 150 female, with a median follow-up period of 47 months (range 4–73 months) and categorized into two groups based on the presence or absence of CT-based sarcopenia.

In general, there was a higher proportion of male among patients with CT-based sarcopenia ($P = 0.003$). The sarcopenic group was significantly older than the non-sarcopenic group (67.6 ± 9.4 vs. 59.4 ± 10.5, $P < 0.001$), while BMI was significantly lower than those without CT-based sarcopenia (21.5 ± 2.8 vs. 24.4 ± 3.1, $P < 0.001$). Sarcopenic patients also presented a lower proportion of postoperative chemotherapy ($P < 0.001$) and more readmission ($P = 0.008$). Significant differences were observed between the two groups in terms of adjuvant chemotherapy regimens ($P < 0.001$), and surgical procedure ($P = 0.001$). Despite no difference in the proportion of clinical T stage ($P = 0.086$), the sarcopenic group had a higher pathological T stage ($P = 0.019$). However, there were no differences in height, clinical stage, location, and other factors between the two groups (all P value > 0.05).

Association between CT-based Sarcopenia and locally advanced rectal cancer

After completing the three-year follow-up period, a total of 108 (21.4%) deaths and 162 (32.2%) combined including recurrence or metastasis endpoints were observed. Kaplan-Meier analysis showed that sarcopenic LARC patients had a significantly higher cumulative hazard of OS compared to non-sarcopenic patients ($P < 0.001$, log-rank test) (Fig. 2A). Table 2 provided the results from the univariate Cox regression analyses regarding OS. It demonstrated that age, clinical stage, clinical T stage, lymph node status, neoadjuvant therapy, and pN stage were related to hazard of OS (all P value < 0.05). There is a significant independent negative correlation between CT-based sarcopenia and hazard of OS in the unadjusted model (HR, 2.51; 95% CI, 1.72 ~ 3.68; $P < 0.001$). When

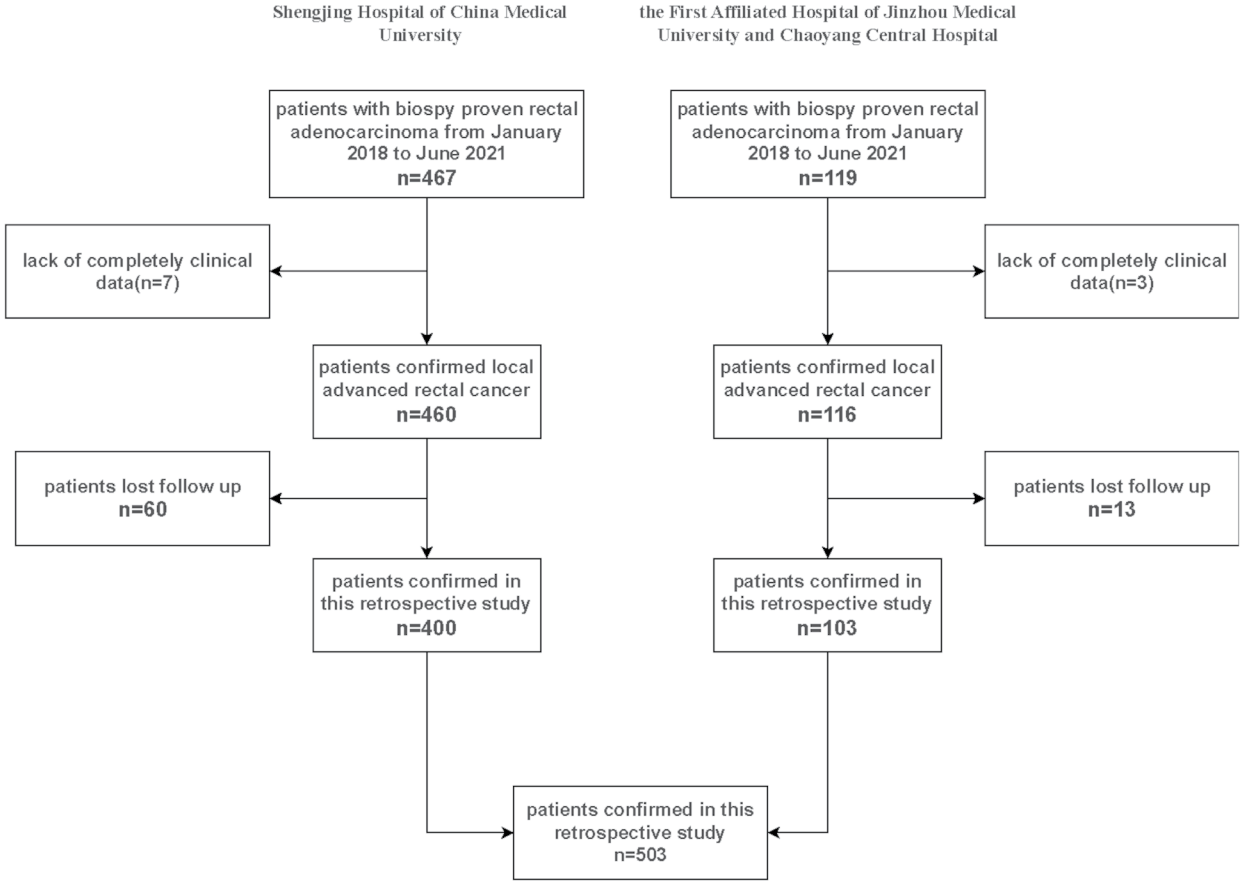

Fig. 1 patients flow chart

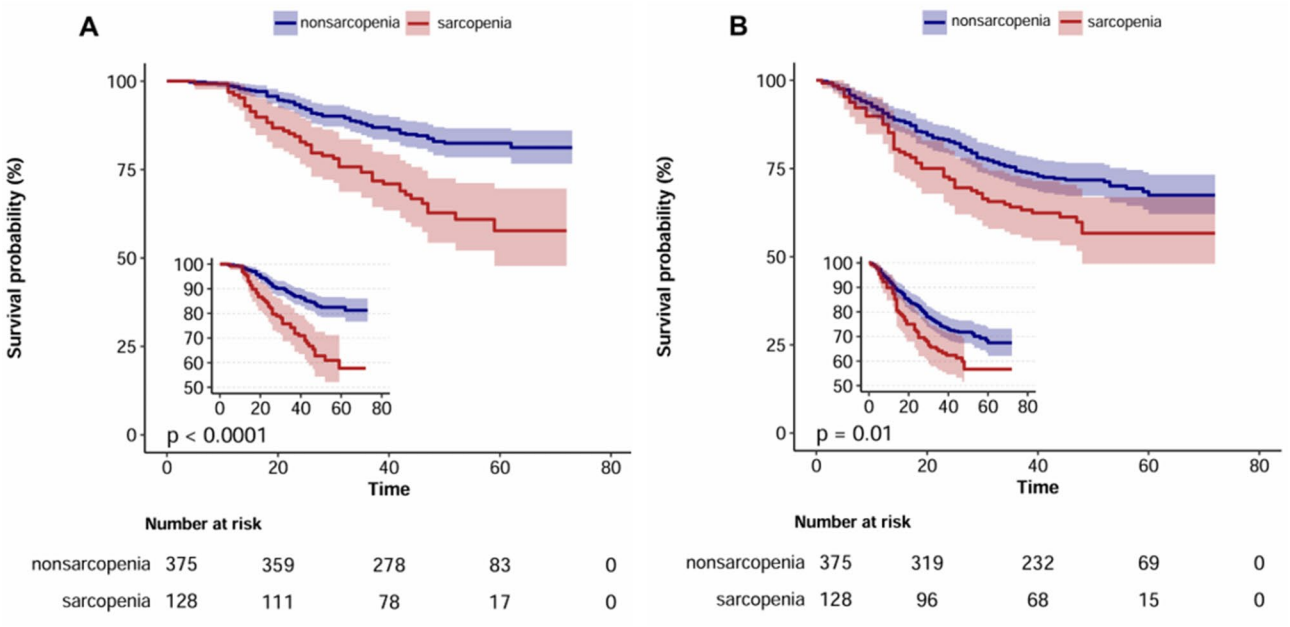

Fig. 2 Kaplan–Meier curves of cumulative incidence of (**A**) overall survival and (**B**) disease-free survival according to presence or absence of sarcopenia

adjusted for sex, age in model I, sarcopenic participants had a 2.24 times greater risk for OS compared to those non-sarcopenic patients (HR, 2.24, 95% CI, 1.48 ~ 3.39, $P < 0.001$, Table 3). When model II further adjusted for BMI, this independent association remained significant (HR, 2.56, 95% CI, 1.63 ~ 4.02, $P < 0.001$). After adjustment for other potential confounders including clinical T stage, clinical stage, pN stage, lymph node status, neoadjuvant therapy, and surgical procedure, this relationship remained stable as well (HR, 2.41, 95% CI, 1.49 ~ 3.87, $P < 0.001$, model III).

Kaplan-Meier analysis showed that sarcopenic LARC patients had a significantly higher cumulative hazard of DFS compared to non-sarcopenic patients ($P = 0.01$, log-rank test) (Fig. 2B). Table 2 displayed the results of the univariate cox regression analyses for DFS. In univariate analysis, results demonstrated that clinical stage, clinical T stage, lymph node status, location, preoperative serum CEA, neoadjuvant therapy, pN stage, lymphovascular invasion, perineural invasion and were related to DFS (all P value < 0.05). In the unadjusted model, there is a significant independent negative correlation between CT-based sarcopenia and hazard of DFS (HR, 1.54; 95% CI, 1.11 ~ 2.14; $P = 0.011$). After adjusted for sex, age in model I, sarcopenic participants increased 50% risk for DFS compared to those without sarcopenia (HR, 1.5, 95% CI, 1.05 ~ 2.15, $P = 0.025$, Table 3). When model II further adjusted for clinical stage, neoadjuvant therapy, pN stage, lymphovascular invasion, this association remained independent (HR, 1.48, 95% CI, 1.02 ~ 2.15, $P = 0.037$). After adjusting for other potential confounding factors, including BMI, clinical T stage, lymph node status, tumor location, preoperative serum CEA levels, perineural invasion, and surgical procedure, this correlation is no longer significant (HR, 1.34, 95% CI, 0.89 ~ 2.03, $P = 0.163$, model III).

In total, 98 patients experienced 113 postoperative complications, with 11 patients reporting two complications and 2 patients reporting three complications (Table S1). Among the cohort, 91 cancer-related deaths and 17 non-cancer-related deaths were recorded. Statistical analysis revealed no significant difference between the two groups regarding median LOS or prolonged LOS. Table S3 showed that there was no statistically significant association between CT-based sarcopenia and postoperative complications of grade II or greater (OR: 1.29, 95% CI: 0.62 ~ 2.68, $P = 0.496$, model III). Similarly, Table S5 found no significant relationship between CT-based sarcopenia and prolonged length of stay (OR: 1.05, 95% CI: 0.6 ~ 1.86, $P = 0.853$, model III). However, Table S7 revealed that sarcopenic patients had a 5.53 times higher risk of readmission compared to non-sarcopenic patients (OR: 5.53, 95% CI: 1.57 ~ 19.5, $P = 0.008$, model III). Table S9, on the other hand, reported a statistically significant correlation between CT-based sarcopenia and CSS (HR: 2.78, 95% CI: 1.64 ~ 4.72, $P < 0.001$, model III). Kaplan-Meier analysis showed that sarcopenic LARC patients had a significantly higher cumulative hazard of CSS compared to non-sarcopenic patients ($P < 0.001$, log-rank test) (Figure S1).

Table 2 Unadjusted Cox regression analyses for OS and DFS

factor	OS		DFS	
	HR (95%CI) *p*		HR (95%CI) *p*	
Age at surgery	1.03 (1.01,1.05)	**0.009**	1.0061 (0.9914,1.021)	0.416
sex: male vs. female	1.31 (0.85,2.03)	0.22	1.22 (0.86,1.73)	0.256
BMI	0.99 (0.9331,1.0505)	0.741	0.98 (0.94,1.03)	0.5
sarcopenia	2.51 (1.72,3.68)	**< 0.001**	1.54 (1.11,2.14)	**0.011**
Clinical stage: III vs. II	2.16 (1.43,3.27)	**< 0.001**	2.25 (1.61,3.15)	**< 0.001**
Clinical T stage: ref.=2				
3	2.93 (0.72,11.88)	0.133	2.22 (0.82,6)	0.116
4	5.61 (1.29,24.41)	**0.022**	3.36 (1.15,9.85)	**0.027**
Lymph node status:	1.98 (1.32,2.97)	**< 0.001**	2.03 (1.46,2.83)	**< 0.001**
location: ref.=<5 cm				
>10 cm	0.51 (0.25,1.05)	0.066	0.56 (0.32,0.99)	**0.046**
5–10 cm	0.97 (0.65,1.44)	0.869	1.0095 (0.7285,1.3987)	0.955
Preoperative.serum.CEA: ≥5 vs. < 5	1.33 (0.9,1.97)	0.153	1.48 (1.08,2.04)	**0.014**
Surgical approach: open vs. laparoscope	1.33 (0.79,2.23)	0.287	1.37 (0.9,2.08)	0.146
Neoadjuvant therapy	1.65 (1.11,2.45)	**0.013**	1.44 (1.04,2.01)	**0.03**
Adjuvant chemotherapy:	0.8 (0.53,1.21)	0.293	1.02 (0.72,1.45)	0.897
Adjuvant radiotherapy:	1.22 (0.77,1.94)	0.393	1.19 (0.81,1.75)	0.366
pN.stage: ref.=0				
1	1.41 (0.91,2.17)	0.121	1.82 (1.29,2.57)	**< 0.001**
2	4.09 (2.49,6.7)	**< 0.001**	3.76 (2.44,5.8)	**< 0.001**
pT.stage: ref.=0				
1	0 (0,Inf)	0.994	0 (0,Inf)	0.992
2	1.43 (0.18,11.43)	0.736	2.31 (0.3,17.81)	0.42
3	2.36 (0.33,16.96)	0.393	3.97 (0.56,28.43)	0.169
4	5.29 (0.68,41.37)	0.112	7.4 (0.97,56.64)	0.054
Lymphovascular invasion:	1.57 (0.96,2.58)	0.073	2.11 (1.44,3.09)	**< 0.001**
Perineural invasion:	1.49 (1,2.24)	0.051	1.62 (1.16,2.25)	**0.004**
Surgical procedure: ref.=Dixon	3.28 (1.69,6.36)	**< 0.001**	2.43 (1.34,4.41)	**0.003**
Hartmann	1.83 (1.13,2.98)	**0.015**	1.52 (1,2.3)	**0.048**
Miles	3.35 (1.35,8.3)	**0.009**	4.48 (2.18,9.19)	**< 0.001**
other				

Subgroup analyses

Moreover, subgroup and interaction analyses were performed to clarify whether the associations between CT-based sarcopenia and OS was consistent across different subgroups of LARC patients (Fig. 3), no significant modification was found after adjusted for age, BMI, clinical stage, clinical T stage, lymph node status, pN stage, neoadjuvant therapy, and surgical procedure according to multivariable cox regression analysis Model **III** (*P* values for interaction were all > 0.05). CT-based sarcopenia remained related to worse OS in participants older than 75 years old (HR: 4.05, 95%CI: 0.62 ~ 26.37), with BMI

Table 3 Cox regression analyses for OS and DFS in different models

sarcopenia	Unadjusted model	Model I	Model II	Model III
	HR (95%CI) *p*	HR (95%CI) *p*	HR (95%CI) *p*	HR (95%CI) *p*
OS	2.51 < 0.001 (1.72,3.68)	2.24 < 0.001 (1.48 ~ 3.39)	2.56 < 0.001 (1.63 ~ 4.02)	2.41 < 0.001 (1.49 ~ 3.87)
DFS	1.54 0.011 (1.11,2.14)	1.5 0.025 (1.05 ~ 2.15)	1.48 0.037 (1.02 ~ 2.15)	1.34 0.163 (0.89 ~ 2.03)

Model I: adjusted for sex, age

Model II: adjusted for sex, age, BMI in OS; adjusted for sex, age, clinical stage, neoadjuvant therapy, pN stage, lymphovascular invasion in DFS

Model III: adjusted for age, sex, BMI, clinical stage, clinical T stage, lymph node status, pN stage, neoadjuvant therapy, and surgical procedure in OS; adjusted for sex, age, BMI, clinical stage, clinical T stage, lymph node status, location, preoperative serum CEA, neoadjuvant therapy, pN stage, lymphovascular invasion, perineural invasion, and surgical procedure in DFS

greater than 25 (HR: 3.51, 95%CI: 1.11 ~ 11.07), in female (HR: 3.7, 95%CI: 1.33 ~ 10.3), and in patients who undergoing neoadjuvant therapy (HR: 3.5, 95%CI: 1.42 ~ 8.62). We excluded sex and neoadjuvant therapy as it is the categorical factor in the subgroup analysis. Besides, we also conducted subgroup and interaction analyses between CT-based sarcopenia and DFS across different subgroups (Fig. 4), no significant modification was found after adjusted for age, BMI, clinical stage, clinical T stage, location, preoperative serum CEA, neoadjuvant therapy, pN stage, lymphovascular invasion, perineural invasion and surgical procedure (*P* values for interaction were all > 0.05). CT-based sarcopenia remained related to OS in patients older than 75 years old (HR: 2.24, 95%CI: 0.39 ~ 12.81), with BMI greater than 25 (HR: 3.3, 95%CI: 1.03 ~ 10.62), in female (HR: 1.92, 95%CI: 0.75 ~ 4.91, and in patients who undergoing neoadjuvant therapy (HR: 3.11, 95%CI: 1.36 ~ 7.11). We also excluded sex and neoadjuvant therapy as it is the categorical factor in the subgroup analysis.

Discussion

In this study, we investigated the correlation between preoperative CT-based sarcopenia and clinical outcomes in patients with LARC. During 3 years follow-up, after adjustment for potential confounders, the occurrence of preoperative CT-based sarcopenia was independently correlated with worse OS, CSS and readmission, but not DFS, postoperative complications of grade II or greater, and prolonged LOS in LARC patients. To the best of our knowledge, this research is the largest multicenter study of clinical outcomes in patients with preoperative CT-based sarcopenia and LARC.

Previous studies on sarcopenia and LARC clinical outcome have been few and results are inconsistent. In a study of 122 patients, lower pretreatment muscle mass was correlated with DFS (HR, 2.611, 95% CI, 1.129 ~ 6.040, *P* = 0.025) and CSS (HR, 3.124, 95% CI, 1.030 ~ 9.472, *P* = 0.044) [25]. In a single center retrospective research of 628 LARC patients, Chiloiro et al. [26] showed that sarcopenia was only related to radiotherapy interruption (OR, 0.73, 95% CI, 0.55 ~ 0.94, *P* = 0.019), 23% patients were unable to tolerate the full course of radiotherapy. Higher BMI was also associated with radiotherapy interruption, and sarcopenia was associated with local control but not with OS and DFS. In another study, Choi et al. indicated that sarcopenia measured before LARC treatment, but not after completion of preoperative neoadjuvant therapy, adversely effected OS in LARC patients (HR, 3.558, 95% CI, 1.311 ~ 9.655, *P* = 0.013) [27]. In this study, nearly a third of patients received short-course radiation therapy. In general, LARC patients undergoing long-term chemoradiotherapy usually need 4–6 weeks, and surgery is performed about 8 weeks after completion of treatment. In contrast, LARC patients who have completed short-course radiotherapy usually have surgery 1 week after completion of treatment. Therefore, in the above studies, there was a large gap between the diagnosis of sarcopenia and the operation, and preoperative neoadjuvant therapy itself would increase the incidence of sarcopenia in cancer patients [28, 29]. Thus, to some extent, muscle loss during neoadjuvant therapy is not clearly indicated. According to Miyamoto and colleagues, muscle loss of more than 5% during palliative chemotherapy in unresectable colorectal cancer patients was correlated with worse OS (HR, 2.07, 95% CI, 1.19 ~ 3.61) [30]. Levolger et al. noted that muscle loss during chemoradiotherapy was related to worse DFS and metastasis-free survival in relevant patients, but was not significantly associated with OS [31]. However, it should be pointed out that in this study, more than 30% of the patients were accompanied by distant metastasis. Although the patients included in this study underwent radical surgery, stage IV patients have the worse prognosis compared with non-metastatic patients. At the same time, it should be pointed out that advanced cancer patients are often in a state of cachexia, and it inevitably accelerates their muscle loss [9]. Given that some patients did not undergo neoadjuvant therapy, this study puts more emphasis on the impact of preoperative muscle status on survival outcomes. In this multicenter study of 503 LARC patients, after three model comparisons and adjustment for potential confounders, preoperative CT-based sarcopenia was correlated with worse OS (HR,

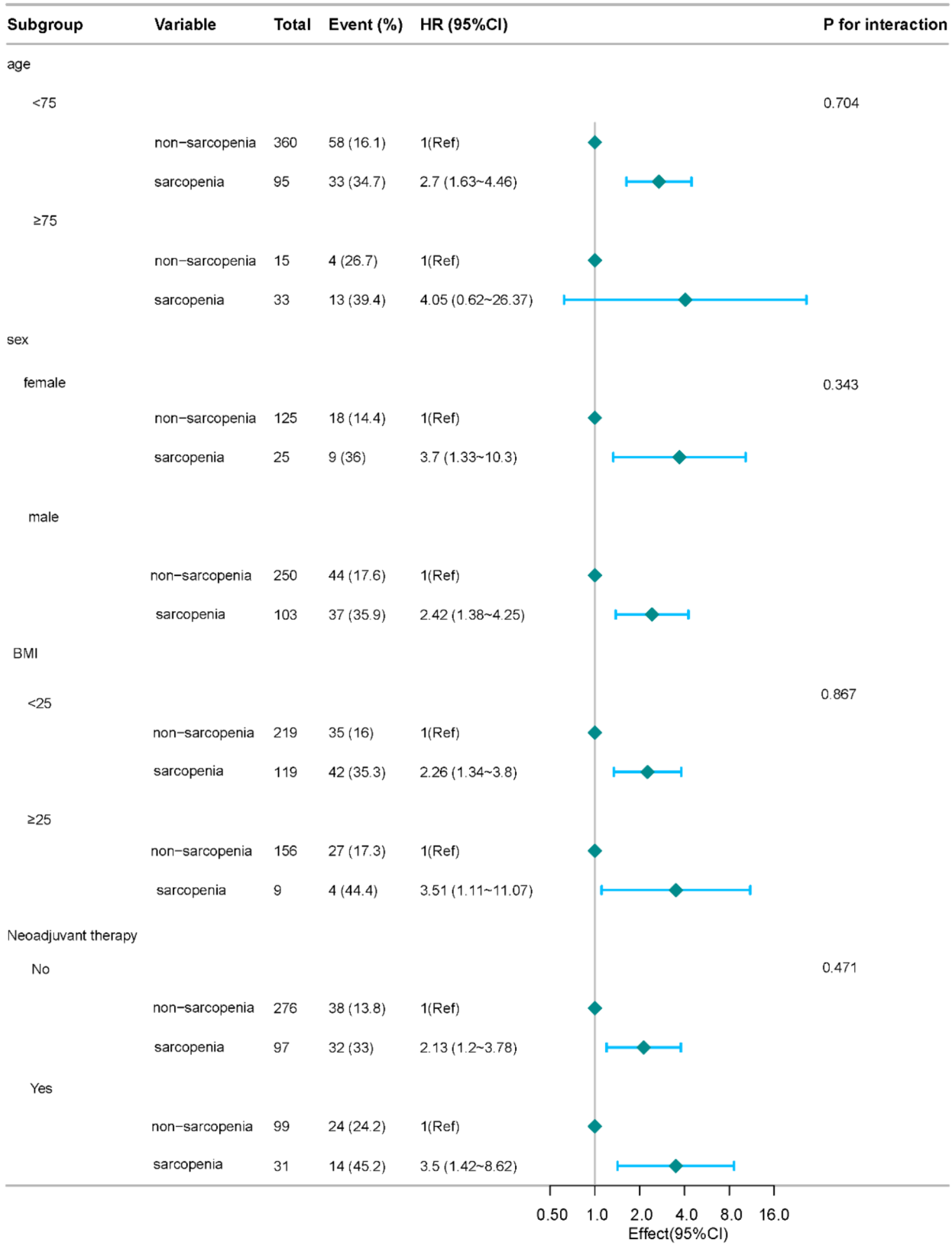

Fig. 3 Associations between sarcopenia and OS in different subgroups of LARC patients. Sarcopenia was adjusted for age, BMI, clinical stage, clinical T stage, lymph node status, pN stage, surgical procedure except for the sex and. neoadjuvant therapy. HR, hazards ratio; 95% CI, 95% confidence interval

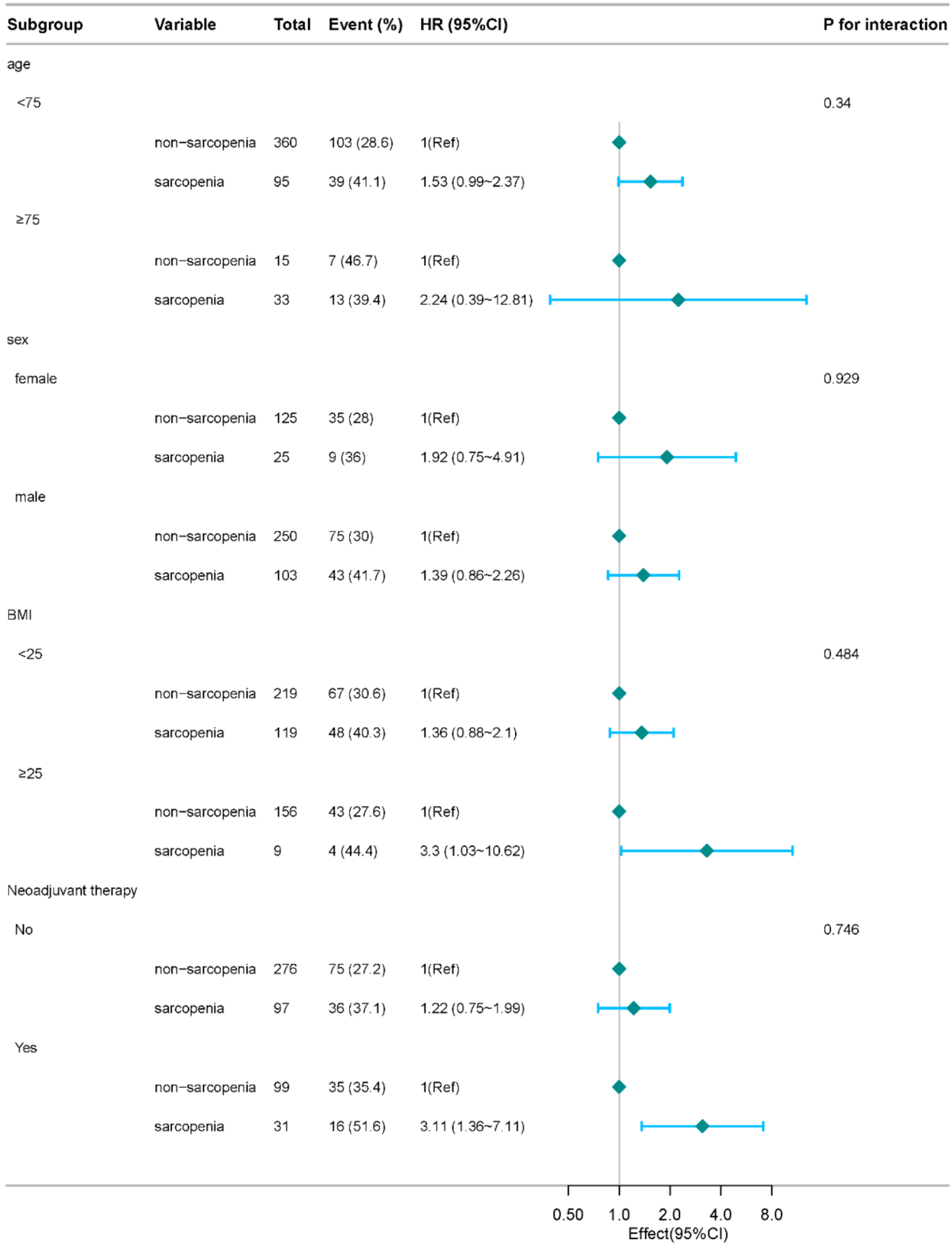

Fig. 4 Associations between sarcopenia and DFS in different subgroups of LARC patients. Sarcopenia was adjusted for age, BMI, clinical stage, clinical T stage, location, preoperative serum CEA, surgical procedure, pN stage, lymphovascular invasion, perineural invasion except for the sex and neoadjuvant therapy. HR, hazards ratio; 95% CI, 95% confidence interval

2.41, 95% CI, 1.49 ~ 3.87, $P < 0.001$) in LARC patients but not to DFS (HR, 1.34, 95%CI, 0.89 ~ 2.03, $P = 0.163$).

Patients with LARC often have both sarcopenia and low BMI, which may be associated with cancer-related cachexia [27, 31]. Our study also showed that patients with CT-based sarcopenia had lower BMI ($P < 0.001$). In this study, univariate analysis showed that BMI had no significant impact on OS or DFS. A research demonstrated that higher BMI may elevate the risk of mortality in stage IV colorectal cancer patients [32]. Choi et al. reported that BMI had no prognostic significance for DFS (HR, 1.00, 95%CI, 0.911 ~ 1.096, $P = 0.992$) and OS (HR, 0.972, 95%CI, 0.832 ~ 1.135, $P = 0.720$) [27]. Levolger showed BMI was not significantly related to DFS and distant metastasis-free survival [31] (HR, 1.10, 95% CI, 0.99 ~ 1.22, $P = 0.084$). BMI was grouped according to 25 kg/m^2 in our study and the results indicated that the correlation between CT-based sarcopenia and OS and DFS remained consistent, and there was no interaction between BMI and CT-based sarcopenia, which further increased the robustness of the study conclusions. Of course, given the different definitions of low BMI, further research is needed. Since sarcopenia is a systemic disease correlated with aging, the proportion of male suffered from sarcopenia could reach twice that of women, we also performed subgroup analysis according to age and sex, and the results showed that the association of CT-based sarcopenia with OS and DFS was consistent in all subgroups, the findings from the subgroup analysis were consistent with the overall results.

It is crucial to understand why the detrimental effects of CT-based sarcopenia have only been shown in relation to OS, but not DFS. Although the timing of muscle area measurements was different, Choi et al. noted that there was a significant correlation between sarcopenia and OS ($P = 0.004$), but it was not associated with DFS or postoperative complication rates [27]. In another study that included 132 LARC patients, sarcopenia was identified as an independent predictor of OS (HR, 3.71; 95% CI, 1.28 ~ 10.75), but not associated with progression-free survival in multivariate analyses ($P = 0.386$) [33]. Chung et al. [29], in a study involving 93 patients with LARC who underwent preoperative chemoradiotherapy followed by CT scans after neoadjuvant therapy cessation, found no significant correlation between sarcopenia, whether diagnosed pre- or post-neoadjuvant therapy, and DFS ($P > 0.05$). Similarly, Chiloiro et al. [26], in a retrospective single-center study, reported no significant association between lower SMI and DFS (HR: 0.74, 95% CI: 0.51 ~ 1.07, $P = 0.11$). In contrast, Nie et al. [34] employed sex-specific SMI thresholds to assess sarcopenia in rectal cancer patients and identified higher SMI as a significant protective factor for DFS (HR: 0.595, 95% CI: 0.387 ~ 0.913, $P = 0.018$). This finding suggests that greater muscle mass may enhance disease-free survival, potentially by improving physical resilience or tolerance to treatments. The discrepancies between these studies could be attributed to differences in diagnostic criteria for sarcopenia, regional and ethnic variations in body composition, inconsistencies in the timing of CT measurements, and variations in study design, sample size, and statistical methodologies. Moreover, the retrospective nature of most studies and the lack of standardized cut-off values for SMI further complicate comparisons across studies. These findings emphasize the importance of establishing unified diagnostic standards for sarcopenia and conducting prospective multicenter studies to explore its prognostic significance in rectal cancer patients with greater precision.

Our study found no association between CT-measured sarcopenia and Grade II or higher postoperative complications or LOS in LARC patients. This result aligns with the findings of Arayne et al. [35], who observed no link between sarcopenia and postoperative complications or LOS in rectal cancer patients. Conversely, Jeroen et al. [36]. reported that reduced skeletal muscle mass predicted postoperative complications and LOS in colorectal cancer patients, likely reflecting differences in surgical techniques between colon and rectal cancer. Womer et al. [37] used psoas muscle area to evaluate sarcopenia and found that patients with smaller psoas areas had higher rates of major complications. However, their findings were only significant when imaging was conducted within 90 days of surgery. Our study, which focused on Grade II or higher complications for clinical significance, may explain the observed differences. Similarly, Choi et al. [27] reported no significant association between sarcopenia and postoperative morbidity, suggesting that experienced surgeons may play a role in minimizing complications. Interestingly, our study identified a significant association between sarcopenia and readmission (OR: 5.53, 95% CI: 1.57 ~ 19.5, $P = 0.008$), consistent with the findings of Chai et al. [38] in a cohort of 228 colorectal cancer patients. However, Jochum et al. [39], with a smaller sample size of 47 LARC patients, found no significant increase in readmission rates, likely due to limited statistical power. Additionally, our study showed that sarcopenia was significantly CSS, which is consistent with the results of a cohort of 708 patients ($P = 0.049$) [40]. On the other hand, Nilsson et al. found no link between sarcopenia and CSS in anal cancer, potentially due to biological and surgical differences between anal and rectal cancers [41].

In addition, regardless of treatment, a significant proportion of LARC patients still have accelerated skeletal muscle loss. The reasons for this are various, and the most likely and most common reason is cachexia caused by cancer itself [42]. This may also be the reason why

excessive muscle loss can lead to poor patient survival. Therefore, considering the important role that excessive muscle loss plays in the survival of LARC patients, the results of this study can guide clinicians to stop or reverse muscle loss in LARC patients before surgery. Therefore, clinicians can use endurance and resistance exercise intervention before any treatment to maintain the mass and function of patients' skeletal muscle, so as to obtain the better prognosis.

There are some limitations to this study. First, there were many censors in the Kaplan-Meier curve describing survival outcomes up to during 73 months follow-up. The data was censored not because patients were lost to follow-up, but because the study was terminated and we were unable to confirm the event. Given the long duration of the follow-up period and the inevitable censor events after 73 months, especially after 73 months, interpretation of the survival curve may be somewhat difficult and needs to be carried out with caution. However, since this is rough, uncensored data for most of the 73 months, it would be meaningful to compare data for these time periods. Second, considering that this study is retrospective and observational, we still cannot control all confounding factors despite the use of multi-factor regression analysis, multi-model comparison and sensitivity analysis, and our study has the limitations of observational research itself. As over 14% of patients were excluded from the two cohorts due to incomplete follow-up or other reasons, it may impact the generalizability of our findings and should be considered when interpreting the results. These limitations highlight the necessity for future prospective cohort studies to validate and expand upon these results.

Conclusion

Our research indicated that preoperative CT-based sarcopenia was an independent predictor of OS, CSS and readmission in patients with LARC, but not DFS, postoperative complications of grade II or greater, and prolonged LOS. Our findings may assist clinicians in identifying LARC patients with a poor prognosis, enabling future interventions aimed at improving endurance and physical strength, thereby supporting clinical decision-making and the development of treatment strategies.

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
Author Contributions Statement: JZ, YG, ZL, and SP contributed to the conception of the work. JZ and YG drafted the manuscript. JZ, YG, YW, QW, CZ, WC, XL, and XZ contributed to data collection. JZ and YG performed the image and statistical analysis. ZL and SP reviewed the manuscript. All authors provided final approval and accepted responsibility for all aspects of the work. All authors have read and approved the final version of the manuscript.

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Data availability
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the Shengjing Hospital of China Medical University (ethical no.2023PS1097K), Chaoyang Central Hospital (ethical (2024) Ethical Review No. (07)), and the First Affiliated Hospital of Jinzhou Medical University (ethical no. KYLL2024437) and in conformity to the Declaration of Helsinki. The need for informed consent of participants in this study was waived by ethics committee of Shengjing Hospital of China Medical University (ethical no.2023PS1097K), Chaoyang Central Hospital (ethical (2024) Ethical Review No. (07)), and the First Affiliated Hospital of Jinzhou Medical University (ethical no. KYLL2024437).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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