



Impact of Skeletal Muscle Loss and Sarcopenia on Outcomes of Locally Advanced Esophageal Cancer during Neoadjuvant Chemoradiation

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ABSTRACT

Background. The impact of changes in skeletal muscle and sarcopenia on outcomes during neoadjuvant chemoradiotherapy (NACR) for patients with esophageal cancer remains controversial.

Patients and Methods. We retrospectively analyzed the data of patients with locally advanced esophageal squamous cell cancer who received NACR followed by esophagectomy between June 2013 and December 2021. The images at third lumbar vertebra were analyzed to measure the cross-sectional area and calculate skeletal muscle index (SMI) before and after NACR. SMI less than 52.4 cm²/m² for men and less than 38.5 cm²/m² for women were defined as sarcopenia. The nonlinearity of the effect of percent changes in SMI (Δ SMI%) to survival outcomes was assessed by restricted cubic splines.

Results. Overall, data of 367 patients were analyzed. The survival outcomes between sarcopenia and non-sarcopenia groups had no significant differences before NACR. However, patients in post-NACR sarcopenia group showed poor overall survival (OS) benefit ($P = 0.016$) and poor disease-free survival (DFS) ($P = 0.043$). Severe postoperative complication rates were 11.9% in post-NACR sarcopenia group and 5.0% in post-NACR non-sarcopenia group ($P = 0.019$).

There was a significant non-linear relationship between Δ SMI% and survival outcomes ($P < 0.05$ for non-linear). On the multivariable analysis of OS, Δ SMI% $> 12\%$ was the independent prognostic factor (HR 1.76, 95% CI 1.03–2.99, $P = 0.039$) and significant difference was also found on DFS analysis ($P = 0.025$).

Conclusions. Patients with post-neoadjuvant chemoradiotherapy sarcopenia have worse survival and adverse short-term outcomes. Moreover, greater loss in SMI is associated with increased risks of death and disease progression during neoadjuvant chemoradiotherapy, with maximum impact noted with SMI loss greater than 12%.

Keywords Chemoradiotherapy · Esophageal cancer · Sarcopenia · Skeletal muscle index

In recent years, multimodal therapy based on surgery has shown many significant improvements in perioperative and long-term survival outcomes for patients with locally advanced esophageal cancer.¹ Neoadjuvant chemoradiotherapy (NACR) followed by esophagectomy is strongly recommended,² with the newly published CROSS trial reporting a 10-year survival of 38% in patients treated with NACR.³ Notwithstanding this welcome progress, esophageal cancer still is associated with higher disease recurrence rates, as well as with challenges to physical recovery from neoadjuvant therapy and enhancing long-term quality of life. Many studies reporting nutrition-related indicators such as the Naples prognostic score (NPS), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have emphasized the clinical influence of nutrition and patients' physical condition on oncologic and operative outcomes in esophageal cancer.^{4,5}

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Sarcopenia, defined by an unintentional loss of skeletal muscle mass, is now commonly described in oncology patients, especially those with gastrointestinal cancer, and is indicated with poor survival benefit.^{6,7} For patients with esophageal cancer, sarcopenia is reported in a range of 14–80%.⁷ Progressing to sarcopenia is multivariable with dysphagia, less nutrient intake, higher metabolic rate, and dietary changes all contributory. Among patients with locally advanced esophageal cancer, the addition of neoadjuvant therapy may influence patients' nutritional status. Notwithstanding, many studies only involved time-specific body compositions, few involved it dynamically during neoadjuvant therapy.^{8–13} In recent years, many studies indicated that skeletal muscle index (SMI) loss after neoadjuvant therapy might affect the patients' survival benefit, however, the results are varied.^{14–19}

This study aimed, first, to investigate whether sarcopenia affected survival outcomes and postoperative outcomes among patients with locally advanced esophageal squamous cell cancer treated with neoadjuvant chemoradiation in a high-volume center. Second, this study aimed to systematically examine changes in SMI including loss and increase after neoadjuvant chemoradiation, and to evaluate the impact of these changes on outcomes.

PATIENTS AND METHODS

Patients

Study Design

This was a single-center retrospective cohort study. The Institutional Review Board (IRB) of West China hospital approved our study (IRB no. 2022-853), and the writing of informed consent was waived. The data were retrieved from the hospital information system (HIS) and picture archiving and communication system (PACS). This study was followed with the STROBE statement.²⁰

Inclusion and Exclusion Criteria

We retrospectively enrolled all consecutive patients with esophageal cancer who underwent neoadjuvant therapy followed by esophagectomy between June 2013 and December 2021. The inclusion criteria were locally advanced esophageal squamous cell cancer with resectable tumor, clinical stages T2–4aN0–2M0, patient age 18–80 years old with ability to undergo surgery, completed 2 cycles of neoadjuvant chemotherapy, completed a total radiation dose of 40–50.4 Gy, and undergoing minimally invasive McKeown surgery.

The exclusion criteria were presence of other malignancy or other illness that might influence body composition, distant progression after completed chemoradiotherapy, salvage esophagectomy, gastrostomy before esophagectomy, upfront colonic or jejunal interposition before surgery, cervical

esophageal tumor, and missing data on clinicopathological characteristics, complications, computed tomography (CT) images, postoperative follow-up.

Neoadjuvant Chemoradiation Regimen

Briefly, neoadjuvant chemoradiotherapy consisted of two cycles of chemotherapy with concurrent radiation. The chemotherapy regimen was paclitaxel-based platinum [cisplatin (TP) or carboplatin (TC)] or cisplatin plus 5-fluorouracil (FP). Paclitaxel [intravenous (iv) 175 mg/m²] was administered on day 1 with a combination of cisplatin (iv 25 mg/m²/day) on days 1–3 or with a combination of carboplatin (iv AUC 5) on day 1. Cisplatin (iv 25 mg/m²/day) was scheduled on days 1–3 with 5-fluorouracil (iv 500 mg/m²/day) on days 1–3. The radiation regimen, ranging from 40 to 50.4 Gy, was delivered in 23–28 fractions (1.8–2.0 Gy/frac), starting on the first day of the first chemotherapy cycle (week 1).

Surgery and Postoperative Surveillance

Esophagectomy was scheduled at 6–8 weeks after completed neoadjuvant chemoradiation, using McKeown minimally invasive surgery through chest, upper abdomen, and left neck (three incisions), and two-field lymphadenectomy (chest and upper abdomen). The follow-up visits were scheduled at 4 months postoperation and every 6 months thereafter, and contrast-enhanced CT scans were obtained.

Skeletal Muscle Index Assessment and Definition of Sarcopenia

Contrast-enhanced CT scans were routinely performed before and after NACR (all post-NACR CT scans were obtained within 1 week before surgery). The patients' staging and re-staging were analyzed through those CT scans. The images at third lumbar vertebra (L3) were analyzed by a single blinded investigator to measure the cross-sectional area (cm²) using MATLAB R2020b software (MathWorks Inc., Natick, MA, USA). Skeletal muscle index (SMI) was calculated as the ratio of the pooled cross-sectional area (at L3) to the square of the height (m²). On the basis of previous large population study, SMI less than 52.4 cm²/m² for men and less than 38.5 cm²/m² for women were defined as sarcopenia.^{21,22} The percent changes in SMI (Δ SMI %) before and after NACR was derived as follows: $(SMI_{\text{pre-NACR}} - SMI_{\text{post-NACR}}) / SMI_{\text{pre-NACR}} \times 100\%$.

Outcomes Measurement

The primary outcomes were survival benefit including overall survival (OS) and disease-free survival (DFS). The recurrence of local esophagus and locoregional lymph nodes and the metastasis of distant lymph nodes and distant organs were identified as disease-related progression.

DFS was calculated from the day of surgery to the date of disease-related progression or death. Staging was performed according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system (8th edition).

The secondary outcomes were histological tumor response and postoperative complications defined as the Clavien–Dindo (CD) classification system.²³ Pathological complete response (pCR) was defined as no tumor cells in the specimen, and no tumor cells in lymph nodes (ypT0N0). Tumor response score (TRS) was defined as follows: grade 0, grade 1, grade 2, and grade 3.²⁴ TRS 0 and TRS 1 means good response, however, TRS 2 and TRS 3 means partial response and no response, respectively.

Statistical Analysis

Data and outcomes were analyzed using GraphPad Prism version 8.0 (San Diego, CA, USA) and R version 4.2.1 (R Development Core Team, Vienna, Austria). Continuous data were expressed as mean (standard deviation, SD) or median (interquartile range, IQR), and count data were expressed as absolute numbers and percentages. The chi-squared test or Fisher's exact test were used to analyze categorical data. The Student's *t*-test or the Mann–Whitney *U* test were used to analyze continuous data. Statistical significance was considered when the two-sided probability (*p*-value) was less than 0.05. Survival curves were drawn using the Kaplan–Meier method and compared using the log-rank test. Hazard ratio (HR) with its 95% confidence interval (CI) was reported. Factors associated with overall survival were analyzed using Cox proportional hazards regression model. The multivariable-adjusted model was used for the analysis of overall survival and adjusted for sex, age, and potential factors with a significant *p*-value in the univariate analysis.

The nonlinearity of the effect of percent changes in SMI (Δ SMI %) to survival outcomes was assessed by restricted cubic splines (3 knots). To find the optimal cut-off value of Δ SMI% for classifying patients into good or poor survival benefit groups, the Maxstat (R package), a maximal chi-squared statistics method, was used. The patients were first divided into two groups according to the cut-off value of $SMI_{pre-NACR}$, namely, pre-NACR sarcopenia and pre-NACR non-sarcopenia groups. Similarly, the patients were also classified into two groups according to the cut-off value of $SMI_{post-NACR}$, namely, post-NACR sarcopenia and post-NACR non-sarcopenia groups. Second, on the basis of the results of restricted cubic splines (RCS) and maximal chi-squared statistics, we further classified the patients into four groups according to the quartile of Δ SMI%.

RESULTS

Patients' Characteristics

In total, 671 patients with locally advanced esophageal squamous cell cancer underwent neoadjuvant therapy followed by surgery. After screening, completed data of 367 patients were analyzed according to our inclusion and exclusion criteria (Supplementary Fig. 1). Clinical and pathological characteristics of included patients are summarized in Table 1. The majority of all patients were aged 62 years, were men (81.2%), had a normal BMI, and were clinically staged as cT3 (77.11%), cN1 (64.8%), or cIII (57.8%). In terms of neoadjuvant therapy regimen, most patients completed two cycles of paclitaxel-based platinum (94.2%), among whom 77.9% and 16.3% patients received TP and TC regimen, respectively. A total of 256 patients (69.8%) completed neoadjuvant radiation with a dose of 40–45 Gy. Postoperative complications classified as CD I–II and III–IV were reported in 26.2% and 7.1% of patients, respectively. Postoperative 30-day mortality was 3.0%. Pathological staging showed frequent ypT0 and ypN0 stages (40.3% and 67.0%, respectively), and staging I was the most frequent TNM stage (53.4%). The pCR rate was 34.6% in all patients. The microscopic radical resection rate (R0) was 98.2%. Tumor regression score of 0, 1, 2, 3 was found in 39.0%, 15.8%, 34.9%, and 10.4% of patients, respectively. There was a significant linear correlation between changes in weight and changes in SMI after NACR ($P = 0.003$, Supplementary Fig. 2), and the Δ weight increased with the Δ SMI (Supplementary Fig. 3).

Primary Outcomes

Effect of Sarcopenia on Survivorship

After a mean follow-up of 28 months [95% confidence interval (CI) 26–30 months], 107 (29.2%) patients died, and the 5-year cumulative OS rate was 58.0 % for all included patients. The clinicopathological characteristics of four groups (pre-NACR sarcopenia versus pre-NACR non-sarcopenia and post-NACR sarcopenia versus post-NACR non-sarcopenia) are summarized in Supplementary Table 1. The groups showed significant difference in sex ($P = 0.000$) and BMI ($P = 0.000$). On initial survival analysis, the 5-year cumulative OS rate was 56.6% in pre-NACR sarcopenia group and 59.0% in pre-NACR non-sarcopenia group, respectively (log-rank $P = 0.439$). Of note, patients in post-NACR sarcopenia group compared with those in post-NACR non-sarcopenia group showed poor survival benefit (5-yr cumulative OS 44.3% versus 64.6%; HR 1.67, 95% CI 1.05–2.43, $P = 0.016$). Similarly, significant difference also was found in the DFS (5-year cumulative DFS 43.9% versus 61.0%; HR 1.48, 95% CI 1.01–2.16, $P = 0.043$). The

TABLE 1 Characteristics of all patients across different quartile groups

| Characteristics | All No. (%) | Quartile I (N = 93) | Quartile II (N = 92) | Quartile III (N = 92) | Quartile IV (N = 90) | P-value |
|--------------------------------------|----------------|---------------------|----------------------|-----------------------|----------------------|---------|
| Age, years | | | | | | 0.460 |
| Median | 62 | 62 | 63 | 62 | 63 | |
| IQR | 55–67 | 56–66 | 56–68 | 55–67 | 55–68 | |
| Sex | | | | | | 0.649 |
| Male | 298 (81.2) | 72 (77.4) | 76 (82.6) | 74 (80.4) | 76 (84.4) | |
| Female | 69 (18.8) | 21 (22.6) | 16 (17.4) | 18 (19.6) | 14 (15.6) | |
| Tumour location | | | | | | 0.738 |
| Upper | 36 (9.8) | 13 (14.0) | 10 (10.9) | 6 (6.5) | 7 (7.8) | |
| Middle | 220 (59.9) | 53 (57.0) | 54 (58.7) | 58 (63.0) | 55 (61.1) | |
| Lower | 111 (30.2) | 27 (29.0) | 28 (30.4) | 28 (30.4) | 28 (31.1) | |
| Weight, kg | | | | | | |
| Pre-NACR | 59.1 (9.43) | 57.9 (9.50) | 58.4 (10.02) | 60.3 (8.27) | 59.9 (9.79) | 0.174 |
| Post-NACR | 59.3 (9.51) | 59.1 (9.78) | 58.9 (9.65) | 59.9 (8.63) | 59.1 (10.05) | 0.905 |
| Δ Weight ^a | -0.12 (3.89) | -1.17 (3.37) | -0.56 (4.02) | 0.42 (3.91) | 0.85 (3.99) | 0.003 |
| BMI ^b , kg/m ² | | | | | | 0.092 |
| ≥ 25 | 61 (16.6) | 12 (12.9) | 16 (17.4) | 18 (19.6) | 15 (16.7) | |
| 18–24.9 | 282 (76.8) | 76 (81.7) | 72 (78.3) | 71 (77.2) | 63 (70.0) | |
| < 18 | 24 (6.5) | 5 (5.4) | 4 (4.3) | 3 (3.3) | 12 (13.3) | |
| Radiation doses | | | | | | 0.621 |
| 40–45 Gy | 256 (69.8) | 68 (73.1) | 65 (70.7) | 65 (70.7) | 58 (64.4) | |
| 45–50.4 Gy | 111 (30.2) | 25 (26.9) | 27 (29.3) | 27 (29.3) | 32 (35.6) | |
| Chemotherapy | | | | | | 0.922 |
| TP | 286 (77.9) | 69 (74.2) | 73 (79.3) | 71 (77.2) | 73 (81.1) | |
| TC | 60 (16.3) | 19 (20.4) | 14 (15.2) | 15 (16.3) | 12 (13.3) | |
| FP | 21 (5.7) | 5 (5.4) | 5 (5.4) | 6 (6.5) | 5 (5.6) | |
| cTNM stage | | | | | | 0.595 |
| II | 79 (21.5) | 21 (22.6) | 22 (23.9) | 23 (25.0) | 13 (14.4) | |
| III | 212 (57.8) | 54 (58.1) | 49 (53.3) | 53 (57.6) | 56 (62.2) | |
| IV | 76 (20.7) | 18 (19.4) | 21 (22.8) | 16 (17.4) | 21 (23.3) | |
| ypTNM stage | | | | | | 0.044 |
| I | 196 (53.4) | 53 (57.0) | 50 (54.3) | 54 (58.7) | 39 (43.3) | |
| II | 45 (12.3) | 11 (11.8) | 18 (19.6) | 9 (9.8) | 7 (7.8) | |
| III | 105 (28.6) | 24 (25.8) | 19 (20.7) | 26 (28.3) | 36 (40.0) | |
| IV | 21 (5.7) | 5 (5.4) | 5 (5.4) | 3 (3.3) | 8 (8.9) | |
| pCR | 127 (34.6) | 32 (34.4) | 30 (32.6) | 33 (35.9) | 32 (35.6) | 0.967 |
| TRS | | | | | | 0.463 |
| 0 | 143 (39.0) | 35 (37.6) | 34 (37.0) | 34 (37.0) | 40 (44.4) | |
| 1 | 58 (15.8) | 17 (18.3) | 14 (15.2) | 18 (19.6) | 9 (10.0) | |
| 2 | 128 (34.9) | 34 (36.6) | 32 (34.8) | 34 (37.0) | 28 (31.1) | |
| 3 | 38 (10.4) | 7 (7.5) | 12 (13.0) | 6 (6.5) | 13 (14.4) | |
| R0-resection | | | | | | 0.085 |
| Yes | 360 (98.1) | 93 (100) | 90 (97.8) | 91 (98.9) | 86 (95.6) | |
| No | 7 (1.9) | 0 | 2 (2.2) | 1 (1.1) | 4 (4.4) | |
| Lymph nodes | | | | | | 0.491 |
| Median | 21 | 21 | 19 | 21 | 20 | |
| IQR | 15–26 | 16–28 | 12–25 | 17–26 | 15–27 | |
| Lymph stations | | | | | | 0.075 |
| Median | 11 | 13 | 12 | 13 | 13 | |
| IQR | 9–11 | 11–17 | 10–15 | 10–15 | 11–14 | |

BMI body mass index, *NACR* neoadjuvant chemoradiotherapy, *TNM* tumor, node, metastasis, *IQR* interquartile range, *SCC* squamous cell cancer, *TP* cisplatin and paclitaxel, *TC* carboplatin and paclitaxel, *TRS* tumor regression score, *pCR* pathological complete response, *NA* not available

Table 1 (continued)

^a Δ Weight is calculated as (pre-NACR–post-NACR); values are mean (SD).

^bBMI is assessed after neoadjuvant chemoradiotherapy; values are mean (SD)

survival curves using Kaplan–Meier estimate are shown in Fig. 1.

Effect of the Changes of SMI during NACR on Survivorship

According to the results of restricted cubic splines, the association of Δ SMI% with OS and DFS was non-linear ($P = 0.047$, $P = 0.001$, respectively) (Fig. 2). Moreover, the percent changes in SMI during NACR showed a strong U-shaped association with cancer progression. Notably, additional SMI loss after NACR was associated with an increased risk of death (HR 1.93 per SD, 95% CI 1.21–3.09, $P = 0.006$) and cancer progression (HR 2.01 per SD, 95% CI 1.31–3.09, $P = 0.001$). Of note, the one-sample Kolmogorov–Smirnov (K-S) tests verified that the distribution of Δ SMI% was normal ($P = 0.000$). The optimal cut-off point of Δ SMI was 0.12 using Maxstat method (Fig. 3B). On the basis of these novel findings, we further classified patients

into four groups according to Δ SMI% quartile. The clinicopathological characteristics of the four groups are listed in Table 1. On initial survival analysis, the 5-year cumulative OS and DFS rates were, respectively, 65.0% in quartile I, 66.1% in quartile II, 69.1% in quartile III, and 40.2% in quartile IV (log-rank $P = 0.009$), and 57.1% in quartile I, 66.0% in quartile II, 67.3% in quartile III, and 38.1% in quartile IV (log-rank $P = 0.002$) (Fig. 3C, D). Patients in the quartile IV group compared with those in the quartile II or III groups had a higher risk of death (HR 1.96, 95% CI 1.14–3.35 or HR 2.14, 95% CI 1.26–3.59, respectively) and were associated with higher probability of recurrence (HR 2.03, 95% CI 1.24–3.30 or HR 2.18, 95% CI 1.35–3.51, respectively). In addition, on multivariable analysis of OS, quartile IV was the independent prognostic factor (HR 1.76, 95% CI 1.03–2.99, $P = 0.039$) and significant difference was also found on DFS analysis (HR 1.75, 95% CI 1.07–2.87, P

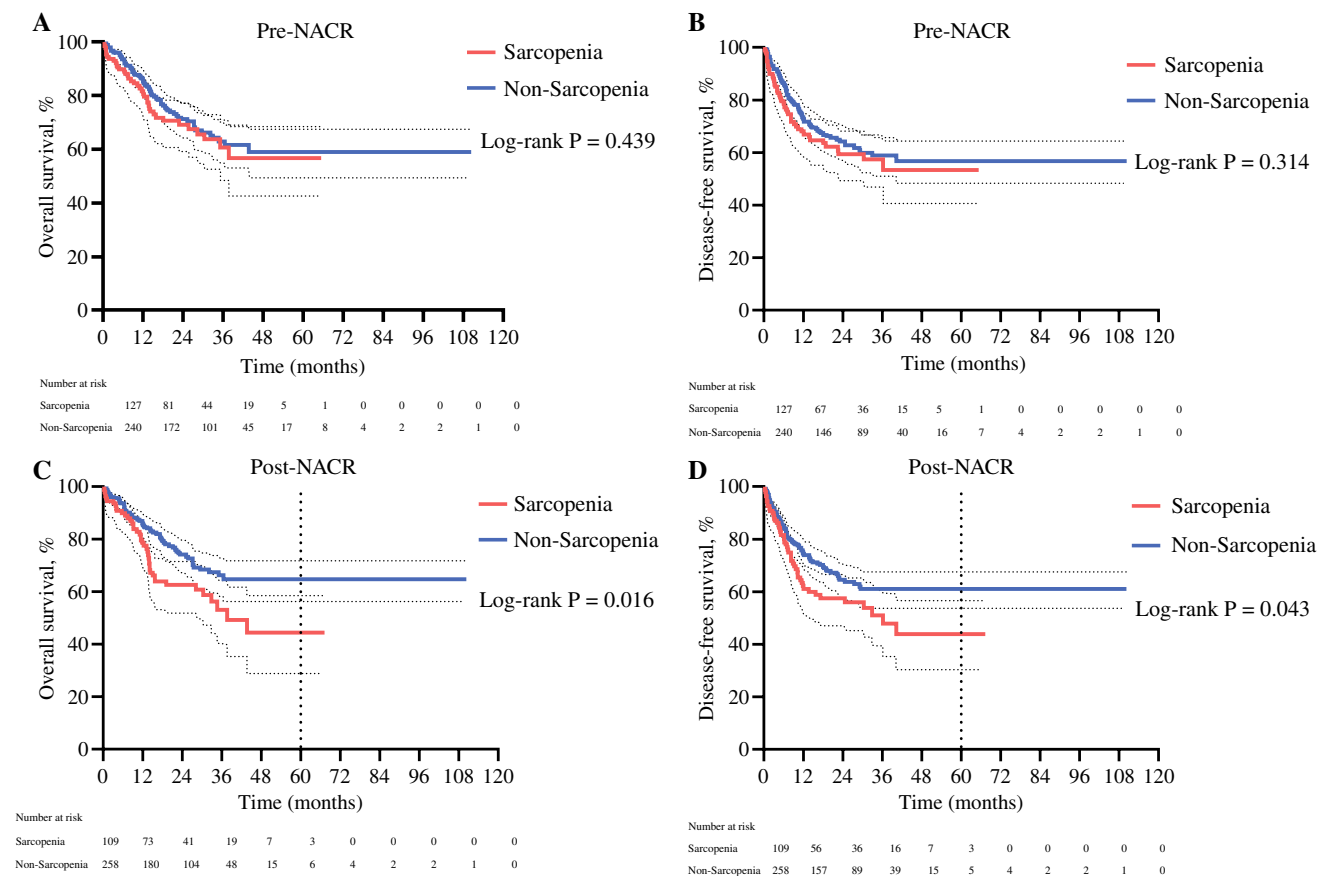


FIG. 1 Overall survival (A) and disease-free survival (B) between pre-NACR sarcopenia versus pre-NACR non-sarcopenia; overall survival (C) and disease-free survival (D) between post-NACR sarcopenia versus post-NACR non-sarcopenia

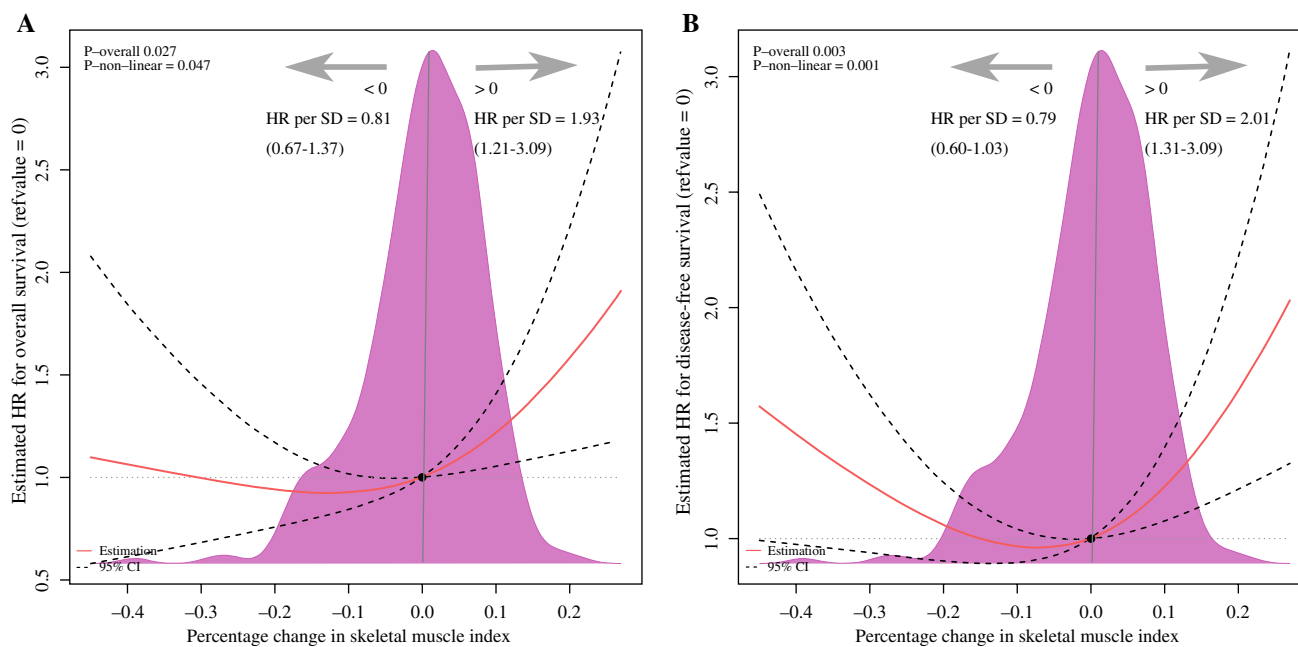


FIG. 2 Nonlinearity of the effect of percent changes in skeletal muscle index (SMI) to overall survival (A) and disease-free survival (B) was assessed by restricted cubic splines

= 0.025) (Table 2). Namely, patients suffering intense loss of SMI greater than 12% showed poor survival and disease progression during NACR.

Secondary Outcomes

Effect of Sarcopenia on Postoperative Outcomes

In the groups defined as sarcopenia and non-sarcopenia before NACR, no significant differences were found in terms of postoperative complication (Supplementary Table 2). These negative results notwithstanding, several meaningful results were found in the groups defined by post-NACR SMI. Patients in the post-NACR sarcopenia group had a higher rate of pneumonia, classified as CD grades 3–5 (11.0% versus 5.0%, $P = 0.038$), and respiratory failure and readmission ICU (8.3% versus 1.9%, $P = 0.010$). In total, all severe postoperative complication (CD grades 3–5) rates were 11.9% in post-NACR sarcopenia group and 5.0% in post-NACR non-sarcopenia group ($P = 0.019$). Summarily, patients with sarcopenia were associated with worse short-term surgical outcomes, notwithstanding, this result was only proven by evidence on post-NACR body composition.

Effect of the Changes of SMI during NACR on Postoperative Outcomes

The rates of postoperative complications classified as CD grades 1–2 were 28.0% in quartile I, 30.4% in quartile II, 22.8% in quartile III, and 23.3% in quartile IV ($P = 0.588$). The more severe postoperative (CD grades 3–5) were 9.7%

in quartile I, 2.2% in quartile II, 5.4% in quartile III, and 11.1% in quartile IV ($P = 0.075$). The anastomotic leakage rate in quartile I or IV groups was nearly twice as high as other groups ($P = 0.133$). The median postoperative length of stay was 11 days, similar in all four groups ($P = 0.246$). In terms of 30-day mortality rates, no significant difference was found in the four groups ($P = 0.799$) (Supplementary Table 3).

DISCUSSION

This study summarized the role of sarcopenia through neoadjuvant chemoradiotherapy of locally advanced esophageal cancer, and in short-term and long-term outcomes, providing novel results suggesting that sarcopenia and changes in SMI should be evaluated as potential risk markers. Sarcopenia diagnosed after NACR was associated with high risk of death and disease progression, high incidence of postoperative complications, and adverse oncological outcomes. Moreover, additional SMI loss per 9.0% after NACR increased the risk of death and disease progression nearly onefold. Patients suffering SMI decline more than 12% after NACR had a disadvantage of disease-free survival and short-term outcomes.

Many studies and meta-analyses had evaluated the effect of sarcopenia on the short-term and long-term outcomes for patients with esophageal cancer.^{7–13,25–28} This welcome progress notwithstanding, these results were contradictory. Three studies concluded that patients with sarcopenia had no

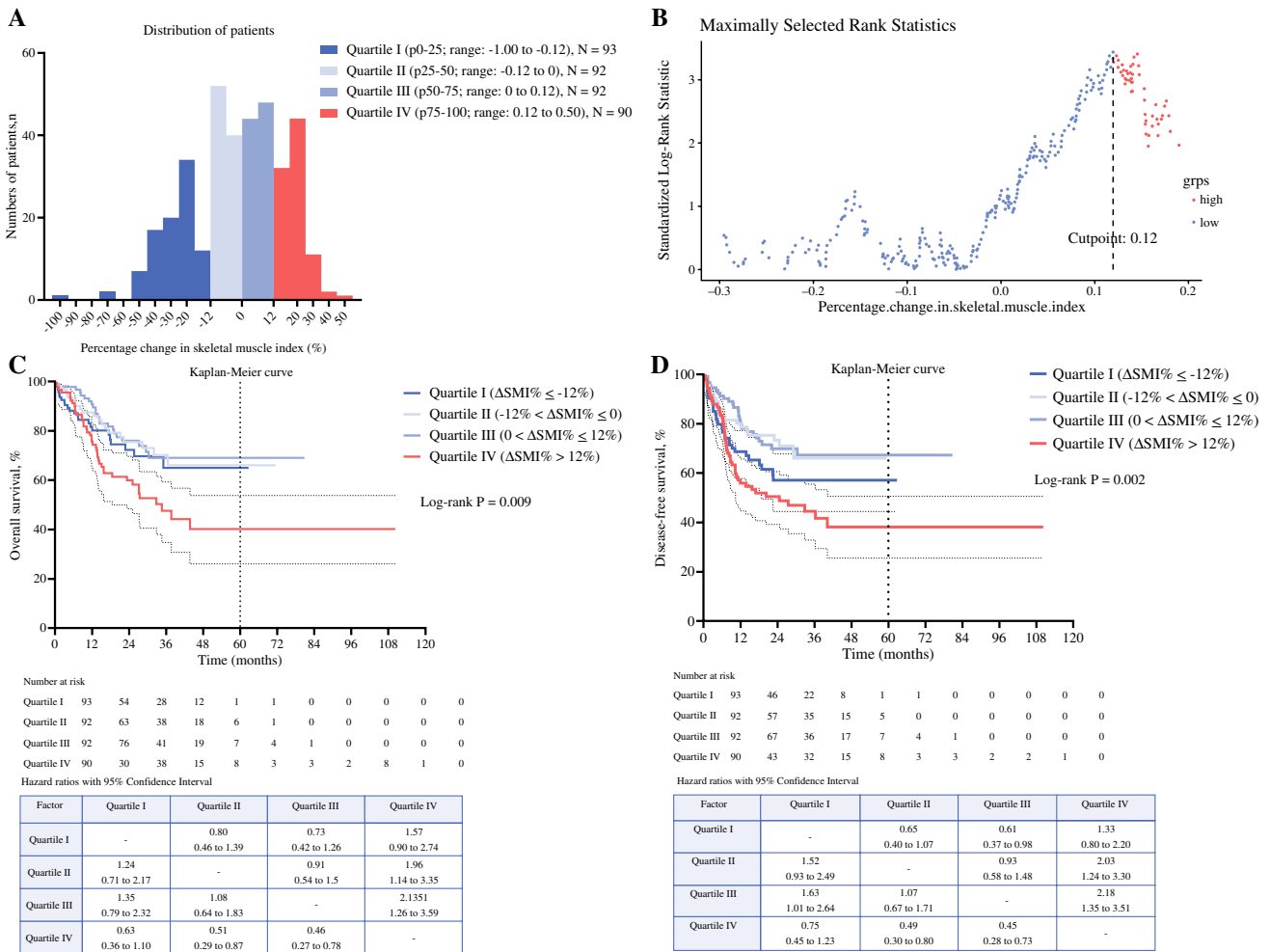


FIG. 3 (A) Distribution of patients with different percent changes in skeletal muscle index; (B) optimal cut-off point for overall survival by using receiver operating characteristic (ROC) curve; (C) overall

survival across different groups of percent changes in SMI ($\Delta\text{SMI}\%$); (D) disease-free survival across different groups of percent changes in SMI ($\Delta\text{SMI}\%$)

impact on overall survival.^{9,25,28} There are many methods to assess SMI, including CT images at L3, dual energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA). It is very simple to diagnosis sarcopenia through routine CT images, however, the cut-off values of SMI at L3 are reported differently. For patients with locally advanced esophageal cancer receiving NACR followed by surgery, it is more important to examine changes in SMI instead of SMI at presentation. As reported in previous studies, SMI loss was associated with poor survival.¹³⁻¹⁸ Kamitani et al. reported that SMI loss greater than 12% was significantly associated with poor survival.¹⁶ Similarly with our study, we found a meaningful cut-off point of 12% for the changes in SMI. Additionally, our results also demonstrated that the probability of death and disease progression was increased along with a significant SMI decline. Additionally, Yoon et al. reported that patients with SMI loss greater than 10% had poor overall survival and recurrence-free survival.¹⁴

The mechanism of sarcopenia with cancer still remains unclear. Inflammatory, oxidative stress, mitochondrial function disorders, and so on were associated with sarcopenia.^{29,30} Many inflammation-induced signal pathways can lead to unintentional skeletal muscle loss, which is mediated by several known factors such as interleukin-6 (IL-6), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and tumor necrosis factor (TNF).³¹ Mitochondrial function disorders also plays an important role in sarcopenia, which can also be induced by anti-cancer drugs such as doxorubicin and paclitaxel.³² In this context, NACR itself can change skeletal muscle status and the body composition of patients with esophageal cancers. Chemotherapeutic drugs such as cisplatin can cause skeletal muscle decline through Akt pathway, and patients with sarcopenia in esophageal cancer suffered a higher rate of dose-limiting chemotoxicity.³³⁻³⁵

TABLE 2 Univariable and multivariable logistic regression model of risk factors for overall survival and disease-free survival

| Hazard ratio (95% CI) | Univariable model | <i>P</i> -value | Multivariable model | <i>P</i> -value |
|---|-------------------|-----------------|---------------------|-----------------|
| Overall survival | | | | |
| Sex (reference: female) | | | | |
| Male | 2.06 (1.15–3.68) | 0.015 | 1.35 (0.74–2.47) | 0.325 |
| Age (reference: age < 63) | | | | |
| Age ≥ 62 | 1.07 (0.73–1.57) | 0.717 | | |
| BMI (reference: 18 ≤ BMI < 25) | | | | |
| BMI < 18 | 2.09 (1.14–3.84) | 0.017 | 1.50 (0.78–2.88) | 0.218 |
| BMI ≥ 25 | 0.54 (0.29–1.02) | 0.056 | 0.66 (0.35–1.26) | 0.208 |
| cTNM (reference: cTNM II) | | | | |
| cTNM IV | 1.50 (0.83–2.70) | 0.176 | | |
| cTNM III | 1.19 (0.71–2.00) | 0.503 | | |
| Tumor location (reference: upper) | | | | |
| Lower | 1.02 (0.52–2.01) | 0.955 | | |
| Middle | 0.97 (0.51–1.85) | 0.932 | | |
| Neoadjuvant chemotherapy regimen (reference: TP) | | | | |
| TC | 0.83 (0.38–1.80) | 0.640 | | |
| FP | 1.14 (0.48–2.70) | 0.761 | | |
| Neoadjuvant radiation doses (reference: 40–45 Gy) | | | | |
| > 45 Gy | 1.29 (0.85–1.94) | 0.231 | | |
| ypTNM (reference: ypTNM I) | | | | |
| ypTNM IV | 14.2 (7.62–26.44) | 0.000 | 13.06 (5.68–30.03) | 0.000 |
| ypTNM III | 4.18 (2.60–6.75) | 0.000 | 3.67 (1.82–7.40) | 0.000 |
| ypTNM II | 2.77 (1.48–5.16) | 0.001 | 2.44 (1.06–5.61) | 0.000 |
| TRS (reference: 0/1) | | | | |
| TRS2/3 | 2.53 (1.70–3.76) | 0.000 | 1.21 (0.72–2.05) | 0.468 |
| pCR (reference: pCR) | | | | |
| Non-pCR | 3.01 (1.81–5.00) | 0.000 | 1.21 (0.53–2.75) | 0.656 |
| ΔSMI (reference: quartile III) | | | | |
| Quartile IV | 2.14 (1.26–3.59) | 0.004 | 1.76 (1.03–2.99) | 0.039 |
| Quartile II | 1.08 (0.64–1.83) | 0.779 | 1.52 (0.84–2.76) | 0.164 |
| Quartile I | 1.35 (0.79–2.32) | 0.305 | 1.08 (0.59–1.98) | 0.787 |
| Disease-free survival | | | | |
| Sex (reference: female) | | | | |
| Male | 1.62 (0.99–2.63) | 0.053 | 1.13 (0.68–1.188) | 0.633 |
| Age (reference: age < 63) | | | | |
| Age ≥ 62 | 1.05 (0.744–1.47) | 0.790 | | |
| BMI (reference: 18 ≤ BMI < 25) | | | | |
| BMI < 18 | 2.39 (1.39–4.12) | 0.002 | 1.88 (1.05–3.33) | 0.031 |
| BMI ≥ 25 | 0.73 (0.44–1.22) | 0.230 | 0.87 (0.52–1.47) | 0.602 |
| cTNM (reference: cTNM II) | | | | |
| cTNM IV | 1.58 (0.91–2.75) | 0.107 | | |
| cTNM III | 1.44 (0.89–2.34) | 0.132 | | |
| Neoadjuvant chemotherapy regimen (reference: TP) | | | | |
| TC | 1.26 (0.81–1.96) | 0.295 | | |
| FP | 1.06 (0.51–2.19) | 0.860 | | |
| Neoadjuvant radiation doses (reference: 40–45 Gy) | | | | |
| > 45 Gy | 1.01 (0.70–1.45) | 0.947 | | |
| Tumor location (reference: upper) | | | | |
| Lower | 1.06 (0.56–1.98) | 0.857 | | |
| Middle | 0.99 (0.55–1.79) | 0.985 | | |

Table 2 (continued)

| | Hazard ratio (95% CI) | Univariable model | <i>P</i> -value | Multivariable model | <i>P</i> -value |
|---|-----------------------|-------------------|-----------------|---------------------|-----------------|
| ypTNM (reference: ypTNM I) | | | | | |
| ypTNM IV | | 9.34 (5.26–16.61) | 0.000 | 9.52 (4.56–19.87) | 0.000 |
| ypTNM III | | 3.31 (2.21–4.97) | 0.000 | 3.03 (1.68–5.48) | 0.000 |
| ypTNM II | | 2.05 (1.17–3.58) | 0.011 | 1.83 (0.88–3.78) | 0.103 |
| TRS (reference: 0/1) | | | | | |
| TRS 2/3 | | 2.28 (1.60–3.24) | 0.000 | 1.47 (0.90–2.03) | 0.123 |
| pCR (reference: pCR) | | | | | |
| Non-pCR | | 2.24 (1.47–3.41) | 0.000 | 1.45 (0.73–2.90) | 0.289 |
| Δ SMI% (reference: quartile III) | | | | | |
| Quartile IV | | 2.18 (1.35–3.53) | 0.001 | 1.75 (1.07–2.87) | 0.025 |
| Quartile II | | 1.07 (0.67–1.71) | 0.794 | 1.09 (0.63–1.91) | 0.745 |
| Quartile I | | 1.63 (1.01–2.64) | 0.058 | 1.67 (1.00–2.81) | 0.049 |

BMI body mass index, *TNM* tumor, node, metastasis, *TP* cisplatin and paclitaxel, *TC* carboplatin and paclitaxel, *TRS* tumor regression score, *pCR* pathological complete response, *SMI* skeletal muscle index

Moreover, many researchers not only investigated the body composition at certain times, but also systematically examined the changes in SMI and sarcopenia during neoadjuvant therapy. Generally, numbers of studies demonstrated that the rates of sarcopenia increased and SMI mostly decreased from neoadjuvant therapy to surgery.^{13–18} To date, the influence of neoadjuvant therapy on nutrition status remains unclear, and many potential factors may affect it, such as efficacy of neoadjuvant therapy, use of corticosteroids, adverse treatment-related events, and individual differences during neoadjuvant therapy, and these may contribute to body composition changes either increasing or declining. Thus, the meaning of Δ SMI% may differ between patients with and without pre-NACR sarcopenia. As shown in Supplementary Fig. 4, 71.7% patients in the pre-NACR sarcopenia group show an increased SMI. Hence, it was better to use changes in SMI to predict long-term survival outcomes. Different from previous studies, our results showed patients suffering SMI loss only accounted for half of included patients, and the sarcopenia rate did not show a significant increase. Moreover, patients with a SMI increase of more than 12% were associated with poor disease-free survival in our analysis compared with those with a SMI decrease of less than 12%. These novel results demonstrated that it was better to maintain skeletal muscle during neoadjuvant therapy. According to a report of the International Sarcopenia Initiative, exercise (resistance training, combined exercise/physical activity) and nutrition (protein supplements, essential amino acid supplementation) interventions were the main treatment strategies to enhance muscle mass and function in patients with sarcopenia.³⁶ Nutritional intervention played an important role in the treatment of sarcopenia, and a randomized controlled trial (RCT) proved that home enteral nutrition and preoperative nutritional support was safe and feasible for patients' recovery after esophagectomy.³⁷ On

the basis of our results, when patients had sarcopenia after neoadjuvant therapy or show a SMI loss of more than 12%, it was suggested that specific interventions should be incorporated into clinical management, for example, providing them with essential amino acid and protein through oral feeding or intravenous infusion peri- and preoperatively might be advantageous to decreasing the rates of postoperative complications and thus benefit survival outcomes.

In the present study, pathological factors across different quartile groups showed significantly different. High SMI loss (Δ SMI% > 12%) was associated with higher risk of a tumor with ypTNM III. In addition, differences in TRS and R0 resection were observed in patients with post-NACR sarcopenia, and they had a lower rate of TRS 0/1 and a higher rate of non-R0 resection compared with those with non-sarcopenia. Consistent with previous studies, patients with major SMI loss or sarcopenia had poor oncological outcomes. In terms of postoperative complications, all severe complications and pneumonia (CD grades 3–5) occurred frequently in patients with post-NACR sarcopenia. These results were consistent with our newly published meta-analysis.³⁸

The main strength of this study was that it included the largest numbers of patients with esophageal cancer who received NACR followed by surgery at present. Further, we could divide the patients into four groups according to cut-off point, and compare survival and postoperative outcomes between different ranges of the changes in SMI.

Several inherent caveats of our study should be acknowledged. First, since this is a retrospective analysis based on our non-randomized controlled cohort, we cannot exclude potential selection bias. Second, owing to our retrospective study design, several inflammation indicators such as CRP, IL-1, IL-6, PCT, and TNF- α could not be investigated. Third, patients' individual characteristics, such as the use of glucocorticoids, capacity for eating, and external nutrition

support during neoadjuvant chemoradiotherapy, could not be collected and analyzed. Finally, since there is no gold standard for the cut-off value of L3-SMI to diagnosis sarcopenia, this study used the value proposed by a relatively large unhealthy population-based study, which was used widely in many studies. This optimal cut-off value based on high-quality research notwithstanding, future studies are warranted to find the optimal cut-off value of L3-SMI for defining sarcopenia in accordance with Asian individuals.

In conclusion, post-neoadjuvant chemoradiotherapy sarcopenia is a significant factor for overall survival, disease-free survival, oncological outcomes, and postoperative complications in this study. Patients with sarcopenia have worse survival and adverse short-term outcomes. Moreover, greater loss in skeletal muscle index is associated with increased risks of death and disease progression during neoadjuvant chemoradiotherapy, with maximum impact noted with SMI loss greater than 12%.

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