Original Article

Prognostic significance of preoperative skeletal muscle status in patients with gastric cancer after radical gastrectomy

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Background and Objectives: The association between skeletal muscle status and gastric cancer (GC) prognosis remains unclear. Here, we investigated the impact of the skeletal muscle index (SMI) on overall survival (OS) in GC patients after radical gastrectomy. **Methods and Study Design:** We divided 178 patients into four groups: adult men, adult women, elderly men and elderly women. The SMI, calculated using CT images, of patients was graded using cutoff values of group-specific tertiles. Age, body mass index, SMI grade, Charlson comorbidity index, surgical method (total vs distal gastrectomy), tumor stage, and histological type and differentiation were included in Cox regression models to assess the primary outcome parameter of OS. A new prognostic score for 3-year OS was established by combining the SMI grade and tumor stage, and receiver operating characteristic (ROC) curve analyses were used to determine its predictive reliability. **Results:** For groups with high, medium, and low SMI grades, the 3-year OS rates were 94.04, 79.08 and 59.09% and 86.09, 70.11 and 49.11% (p<0.001) in patients undergoing distal and total gastrectomy, respectively. In the multivariate analysis, low SMI (hazard ratio (HR) 1.82, 95% confidence interval (CI) 1.14-2.9), advanced stage (HR 2.89, 95% CI 1.43-5.83), and total gastrectomy (HR 1.69, 95% CI 0.95-3.01) were independent risk factors for OS (p<0.010). The areas under the ROC curves for the prognostic score were 0.77 (range 0.61-0.93) and 0.76 (range 0.65-0.86) in patients undergoing distal and total gastrectomy, respectively. **Conclusions:** The preoperative SMI was an independent prognostic factor for long-term survival in GC patients after radical gastrectomy.

Key Words: gastric cancer, skeletal muscle index, body composition, sarcopenia, overall survival

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer death worldwide.[1] Additionally, the Chinese population has the highest morbidity and mortality due to GC worldwide, and the 5-year overall survival (OS) rate of patients with advanced GC in China is less than 40%.[2,3] The prognoses of cancer patients are generally determined by both tumor factors and host-related factors. However, studies have mostly focused on tumor-related factors, and little is known about the importance of host-related factors and, more specifically, host body composition (BC). Skeletal muscle proteins are the body's preferential energy and amino acid substrates in response to disease-mediated stress and a malnourished state;[4] therefore, skeletal muscle is the most important nutritional component of BC.

In recent years, sarcopenia, a condition characterized by age-related loss of skeletal muscle mass and strength, has been accepted as a new nutritional problem world-

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wide and is considered a hierarchical standard in systematic treatment programs of hospitalized elderly cancer patients.[5,6] However, sarcopenia is not an appropriate definition of skeletal muscle wasting in certain diseases and under certain conditions, such as in adult patients.[7] Patients with GC are prone to malnutrition and often present with marked skeletal muscle wasting.[8] Therefore, more attention should be paid to detect the effect of skeletal muscle status on long-term survival in patients with GC. Although several studies have investigated the association between skeletal muscle status and the prognoses of patients with GC,[9-11] these previous studies have several limitations. First, patients who died due to postoperative complications over a short time period were included in the statistical analysis, and the implementation status of postoperative chemotherapy was not considered in these studies. Thus, the confounding effect of incomplete antitumor therapies on survival could not be ruled out. Second, more elderly patients and fewer young adult patients were recruited, and results stratified by sarcopenia in previous studies, in which the participants were mostly elderly (≥65 years), might not be widely applicable because the majority of patients with GC are younger than 65 years. Therefore, we need a more accurate indicator of muscle status that is associated with increased mortality risk across a wider age range of patients. The skeletal muscle index (SMI), calculated using abdominal CT images, is accepted as a gold standard for quantifying skeletal muscle status,[12] and the cutoff values of group-specific SMI could be used to distinguish skeletal muscle status in adult patients.

Thus, we conducted this study using cutoff values of group-specific tertiles of the SMI to detect an association between preoperative skeletal muscle status and long-term survival in both adult and elderly patients with GC after radical gastrectomy. To rule out the confounding effects of incomplete antitumor therapies on survival, we focused only on patients who had undergone surgery and received full-dose and full-course postoperative chemotherapy.

METHODS

Study population and design

A retrospective analysis of 178 patients with GC who underwent radical gastrectomy at Peking University Shenzhen Hospital (Shenzhen, China) from January 2013 to June 2018 was conducted. The enrolled patients met the following inclusion criteria: 1) age ≥18 years; 2) an American Society of Anesthesiologists (ASA) score ≤3; 3) confirmed stage II-III disease by postoperative pathology; 4) no antitumor therapy before surgery; 5) presence of complete case data before and after surgery, including surgical records, postoperative chemotherapy records, and follow-up files; 6) availability of abdominal CT images (no more than 1 month before surgery); and 7) follow-up for no less than 6 months. The exclusion criteria were 1) emergency surgery, palliative surgery or combined organ resection; 2) postoperative confirmation of pathological stage I or IV disease; 3) reoperation and hospital stay longer than 1 month due to severe short-term (within 30 days after surgery) postoperative complications such as intestinal fistula, bleeding, abdominal infection, among other factors; 4) incomplete postoperative chemotherapy: any dose or course change in chemotherapy due to severe complications or other reasons, delay in first course of chemotherapy by more than 2 weeks after surgery, no postoperative chemotherapy in our hospital, or incomplete data files; 5) death within 6 months after surgery due to severe complications or other reasons; and 6) lack of available CT image or preoperative CT image acquired more than 1 month before surgery.

Clinical data

Data collected from inpatient and outpatient records included demographic data [age, gender, height, weight, body mass index (BMI), and comorbidities], tumor-specific data (tumor differentiation, location, size, and TNM stage), surgery data [surgical methods, anastomotic methods, number of lymph nodes retrieved, number of metastatic lymph nodes, and severe postoperative complications (within 30 days after surgery)], postoperative chemotherapy data (doses, courses and severe complications), and survival data.

The stage of tumor, type of surgical resection and extent of lymph node dissection were determined according to the Japanese GC treatment guidelines. Postoperative complications were assessed using the Clavien–Dindo classification, with severe complications defined as grade III or above. Comorbidities were assessed using the Charlson comorbidity index (CCI).

Measurement of skeletal muscle status

CT is the gold standard for quantifying skeletal muscle mass, and the single-slice CT cross-sectional area at L3 is employed in many studies as a reliable method to evaluate BC.[12] Images were analyzed with a Volume Analyzer SYNAPSE VINCENT (Fujifilm, Tokyo, Japan), which enabled the demarcation of specific tissues using Hounsfield units (HUs). Skeletal muscle was identified and quantified by HU thresholds of -29 to 150. The following HU thresholds were used for adipose tissues: -190 to -30 for subcutaneous and intramuscular adipose tissue and -150 to -50 for visceral adipose tissue. Tissue boundaries were manually corrected if necessary. Tissue cross-sectional areas (cm^2) of both skeletal muscle and fat tissue were automatically calculated by summing tissue pixels and multiplying by the pixel surface area. Skeletal muscle area was subsequently normalized for stature (m^2) and reported as the lumbar SMI (cm^2/m^2).[12] The ratio of the fat tissue area (cm^2) to skeletal muscle area (cm^2) (F/M) was also calculated.

Although the SMI has been shown to correlate well with whole-body muscle mass, there is no consensus on the cutoff values delineating low and high SMI. Evidence indicates that SMI data should be stratified by gender and age. Thus, our patients were divided by age [adults (18-64 years) and elderly (≥65 years)] and by gender to form 4 groups: adult men, adult women, elderly men, and elderly women. We used group-specific tertiles to determine the SMI. For adult men (n=78), the low, medium and high SMI cutoffs were ≤47.30, 47.31-52.96, and ≥52.97 cm^2/m^2, respectively; for adult women (n=44), the cutoffs were ≤37.28, 37.29-47.75, and (≥47.76 cm^2/m^2, respectively; for elderly men (n=41), the cutoffs were ≤41.65, 41.66-47.74, and ≥47.75 cm^2/m^2, respectively; and for elderly women (n=17), the cutoffs were ≤32.59, 32.60-42.75, and (≥42.76 cm^2/m^2, respectively. However, for elderly patients, the following defined sarcopenia criteria, which were obtained from a large retrospective study in the Chinese population, was used: SMI ≤40.8 cm^2/m^2 for men and ≤34.9 cm^2/m^2 for women.[9]

Follow-up

All patients were followed up via inpatient medical visits and telephone interviews. Mortality data, including the time and cause of death, were acquired for all patients. OS was defined as the interval between the date of surgery and the date of death. The accurate time of tumor recurrence should be confirmed by imaging and pathological data; however, in this study, some patients lacked available postoperative imaging data to ascertain accurate time of tumor recurrence during the follow-up. Thus, to avoid the impact of recall bias, recurrence-free survival (RFS) was not included in the statistical evaluation.

Statistical analysis

Statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate the normality of distribution of variables. Data are expressed as the mean value (± standard deviation) or median (interquartile range) depending on the normality of distribution of variables. The characteristics of different variables in each group were compared among groups using ANOVA or the Kruskal-Wallis test depending on the normality of distribution of variables. Chi square tests were used for categorical variables. Survival curves were estimated using the Kaplan-Meier method and analyzed using the log-rank test. Univariate Cox proportional hazards models of all potential baseline predictors were constructed to compute hazard ratios (HRs) with their 95% confidence intervals (CIs). We established a multivariate Cox proportional hazards model containing gender (men vs women), age, BMI, SMI grade, CCI, ASA score, surgical method (total vs distal gastrectomy and open vs laparoscopic operation), histological differentiation, and tumor stage to compute HRs. Backward stepwise elimination with a threshold of $p = 0.10$ was used to select variables for the final model. Analyses of receiver operating characteristic (ROC) curves were used to observe differences in predictive reliability between prognostic scores based on tumor stage alone or both SMI grade and tumor stage. $p \le 0.05$ was considered significant in all statistical analyses except the multivariate Cox proportional hazards model.

RESULTS

General characteristics

A total of 508 patients with stage II or III GC underwent radical gastrectomy in our department during the study period. Finally, 178 subjects met the inclusion criteria and were included in the statistical analysis for this study. A total of 110 subjects underwent distal gastrectomy, and the remaining 68 underwent total gastrectomy. There were significant differences in survival between the distal and total gastrectomy groups; however, the clinical and demographic data, including age, BMI, SMI grade, tumor stage, ASA score, CCI, surgical methods (open vs laparoscopic operation) and histological differentiation, did not differ significantly between the two groups (p>0.05). The anastomotic methods greatly differed depending on the surgical methods. Billroth I and II reconstruction were used in subjects who underwent distal gastrectomy, and Roux-en-Y reconstruction was primarily performed in subjects who underwent total gastrectomy. The demographic and clinical characteristics of the included subjects are listed in Table 1.

Clinicopathologic features according to the SMI classification

Patients with advanced tumor stage and patients who were older had a lower SMI. Sarcopenia was present in 32.75% (n=19) of all elderly patients, 26.83% (n=11) in elderly men and 47.05% (n=8) in elderly women. F/M values were 1.52±0.81, 1.77±0.73, 1.62±0.61 and 2.34±0.70 in adult men, adult women, elderly men and elderly women, respectively. Thus, F/M values in male patients were significantly lower than those in female patients, and the F/M values in adult women were signifi-

Table 1. Demographic and clinical characteristics of patients stratified by surgical methods (distal gastrectomy and total gastrectomy)

Variable	Distal gastrectomy	Total gastrectomy	*p* value
Age, mean (SD), year	55.97±13.29	58.44±11.76	0.277†
Gender, (n), men/women	75/35	44/24	0.869§
BMI, mean (SD), kg/m^2	22.03 ± 3.02	21.72 ± 2.63	0.475†
Tumor stage, (n), II/III	34/76	22/44	0.622§
CCI, median (IQR), score	4 (3/5)	4 (2/5)	0.892‡
ASA, median (IQR), score	1 (1/2)	2 (1/2)	0.332‡
SMI grade, (n), low/medium/high	39/37/34	21/22/25	0.699§
Surgical method, (n), Laparoscopic/Open operation	70/40	37/31	0.270§
Anastomotic method, (n), Billroth I and II/Roux-en-Y reconstruction	102/8	0/68	NA
Pathology grade, (n), W/M/L	54/36/20	29/22/17	0.235§

BMI: body mass index; CCI: Charlson comorbidity index; ASA: American Society of Anesthesiologists score; SMI: skeletal muscle index; SMI grades (low/medium/high): SMI graded by cutoff values of group-specific tertiles for adult men: adult women: elderly men and elderly women; W: well differentiated; M: moderately differentiated; L: poorly differentiated. NA Differences among anastomotic methods were not calculated, since anastomotic methods mainly depend on surgical methods.
†ANOVA; ‡Kruskal-Wallis test; §Chi square test.

cantly lower than those in elderly women. These results reflect gender- and age-related BC differences. Unexpectedly, the SMI levels in patients undergoing total gastrectomy were slightly higher than patients undergoing distal gastrectomy in our study, although there was no statistically significant difference. The SMI levels were 49.21±9.29 and 39.65±8.03 cm^2/m^2 in male and female patients who underwent distal gastrectomy and 47.83±6.19 and 38.17±5.25 cm^2/m^2 in the male and female patients who underwent total gastrectomy, respectively.

Analysis of survival difference for the patients

The median follow-up was 31 months (range 9-66 months). During the follow-up, 52 (29.2%) patients died. The estimated 1-, 3- and 5-year survival rates were 98.01, 70.04 and 39.10% among all patients, 98.02, 64.07, and 38.10% in patients who underwent total gastrectomy, and 97.02, 73.05, and 41.13% in patients who underwent distal gastrectomy, respectively. As the median follow-up was 31 months, we chose the 3-year OS rate for further analysis and found a significant difference among patients classified by the SMI. The 3-year OS rates in patients who underwent distal gastrectomy stratified by high, medium, and low SMI grades were 94.04, 79.08 and 59.09%, respectively ($p<0.001$); in patients who underwent total gastrectomy, the corresponding rates were 86.09, 70.11 and 49.11%, respectively ($p<0.001$) (Figure 1a, b).

Analysis of prognostic factors for the patients

Univariate analysis showed that in the whole cohort, low SMI, advanced tumor stage, high CCI, total gastrectomy (vs distal gastrectomy), and Roux-en-Y reconstruction (vs Billroth I and II reconstruction) were significantly related to poor OS rates ($p<0.05$), while open operation (vs laparoscopic operation), ASA scores and histology (pathological type and differentiation) were not associated with OS rates. Multivariate analysis showed that low SMI (HR 1.82, 95% CI 1.14-2.90, $p=0.012$), advanced stage (HR 2.89, 95% CI 1.43-5.83, $p=0.003$) and total gastrectomy (HR 1.69, 95% CI 0.95-3.01, $p=0.076$) were independent risk factors related to poor OS rates (Table 2).

OS according to a new prognostic score

Distal gastrectomy and total gastrectomy are markedly different, and the long-term survival of patients who un-

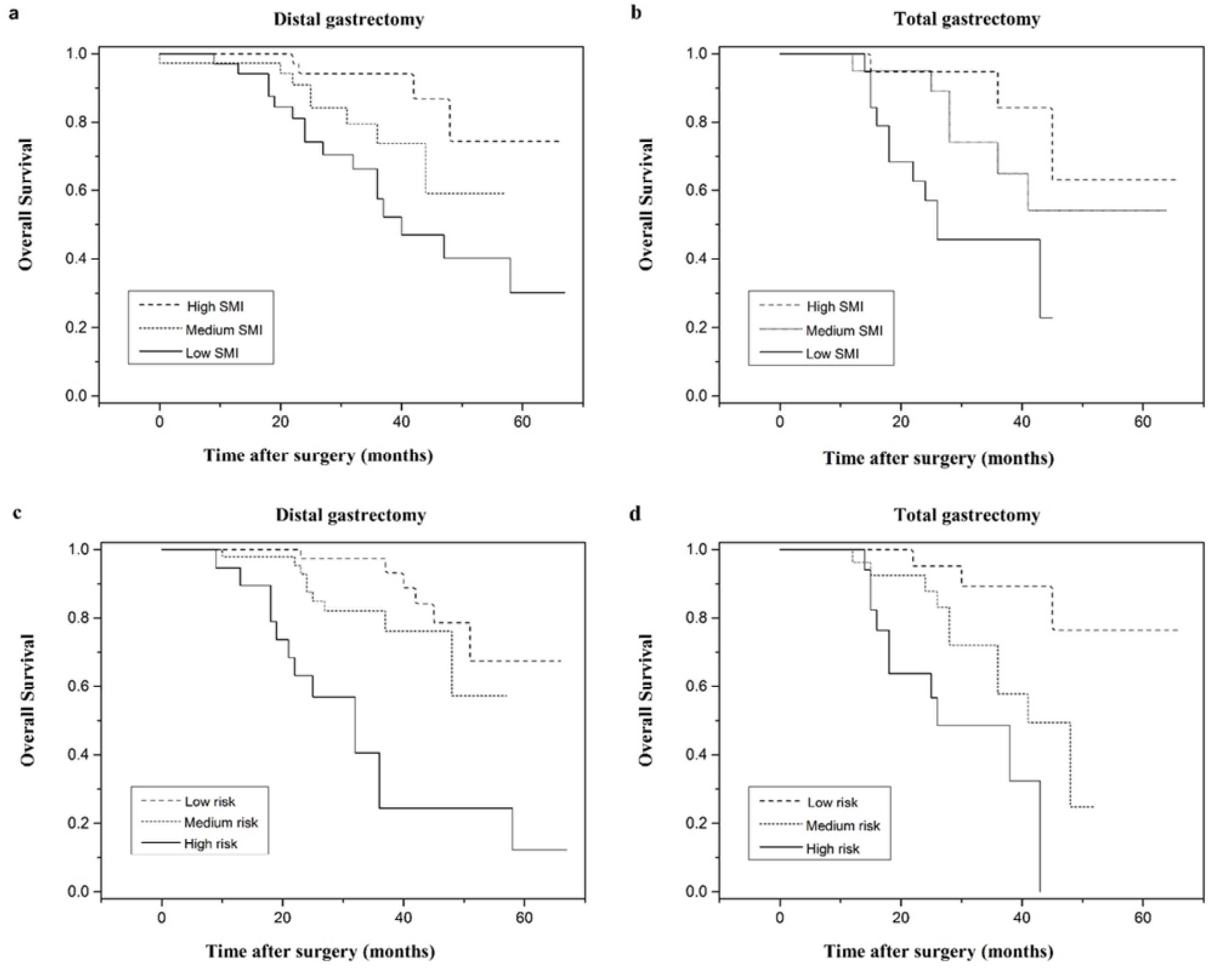

Figure 1. Three-year overall survival among patients undergoing distal and total gastrectomy. a and b, Three-year OS among patients undergoing distal and total gastrectomy stratified by SMI grades (low/medium/high): SMI graded by cutoff values of group-specific tertiles for adult men, adult women, elderly men and elderly women; c and d, Three-year OS among patients undergoing distal and total gastrectomy stratified by a new prognostic risk score based on a combination of SMI grades and tumor stages: high SMI (0 point), medium SMI (1 point), low SMI (2 points), stage IIA (1 point), IIB (2 points), IIIA (3 points), IIIB (4 points), and IIIC (5 points), and low, medium and high risk was classified by 1-3 points, 4-5 points, and 6-7 points, respectively. $p<0.001$ (log-rank test).

Table 2. Univariate and multivariate analyses of factors associated with 3-year overall survival

	Univariate analysis				Multivariate analysis			
Variable	HR	95% CI		p value	HR	95% CI		p value
Gender, (n), (men/women)	1.31	0.71	2.42	0.390		——		
Age, years (<65/≥65)	1.49	0.84	2.63	0.172		——		
Tumor stage, (n), (II/III)	2.69	1.34	5.40	0.005†	2.89	1.43	5.83	0.003‡
BMI, kg/m^2								
≤18.5	Reference							
18.5–24	0.75	0.27	1.12	0.099		——		
>25	0.58	0.08	0.92	0.034†				
CCI, score, (≤ 4/≥ 5)	1.17	0.95	1.44	0.031†		——		
Surgical method, (n)								
Laparoscopic/Open operation	0.97	0.55	1.71	0.908		——		
Total/Distal gastrectomy	1.49	0.86	2.59	0.045†	1.69	0.95	3.01	0.076‡
Anastomotic method, (n), Billroth I and II/Roux-en-Y	1.51	1.09	2.10	0.013†		NA		
SMI grade, (n)								
High	Reference							
Medium	3.08	0.98	9.74	0.045†	1.82	1.14	2.9	0.012‡
Low	4.39	1.74	11.3	0.036†				
Pathology grade, (n)								
Poorly differentiated	Reference							
Moderately differentiated	0.90	0.43	1.87	0.776		——		
Well differentiated	0.47	0.13	1.43	0.163				
ASA, score, (1/≥ 2)	1.53	0.89	2.62	0.124		——		

HR: hazard ratio; CI: confidence interval; BMI: body mass index; CCI: Charlson comorbidity index; ASA: American Society of Anesthesiologists score; SMI: skeletal muscle index; SMI grades (low/medium/high): SMI graded by cutoff values of group-specific tertiles for adult men: adult women: elderly men and elderly women; A multivariate Cox proportional hazards model was built: including gender (men vs women): age: BMI: SMI grades (low: medium and high): CCI: ASA score: surgical methods (total gastrectomy vs distal gastrectomy and open vs laparoscopic operation): histological differentiation (well: moderate and poor): and tumor stage. NA Anastomotic methods were not included in the multivariate analysis to prevent confusion caused by the inclusion of highly correlated variables: since anastomotic methods mainly depend on surgical methods.
†Univariate Cox proportional hazards model analysis ($p<0.05$).
‡Multivariate Cox proportional hazards model ($p<0.10$).
— Variates that had no statistical significance in the multivariate analysis.

derwent total gastrectomy was shorter than that of patients who underwent distal gastrectomy. Thus, patients who underwent distal gastrectomy and total gastrectomy were evaluated separately in the analysis of survival curves and ROC curves. A new prognostic score for OS was established by combining the SMI grade and tumor stage, which were independent risk factors in the multivariate analysis, as follows: SMI grade: high (0 point), medium SMI (1 point), and low SMI (2 points); tumor stage: IIA (1 point), IIB (2 points), IIIA (3 points), IIIB (4 points), and IIIC (5 points). Using this scoring system, patients were divided into low- (1-3 points), medium- (4-5 points), and high-risk (6-7 points) groups.

The low-, medium-, and high-risk groups had 66 (37.1%), 76 (42.7%), and 36 (20.2%) patients, respectively. For the low-, medium-, and high-risk groups, the 3-year OS rates were 89.05, 60.27, and 45.03% in patients who underwent total gastrectomy and 97.02, 81.53, and 47.21% in patients who underwent distal gastrectomy, respectively ($p<0.001$) (Figure 1c, d).

In the ROC analyses, the areas under the curve (AUCs) for the 3-year OS rates predicted by the new prognostic score and the score based on tumor stage were 0.77 (range 0.61-0.93) and 0.71 (range 0.53-0.90) in patients who underwent distal gastrectomy and 0.76 (range 0.65-0.86) and 0.68 (range 0.57-0.75) in patients who underwent total gastrectomy, respectively. Thus, the new prognostic score has a better predictive ability than the score based on tumor stage alone (Figure 2).

DISCUSSION

Our results showed that the preoperative SMI was an equally important an independent prognostic factor as tumor stage for long-term survival in patients with GC after radical gastrectomy. The long-term survival of patients varies with differences in preoperative skeletal muscle status and therapy stress, regardless of whether skeletal muscle wasting is worse than sarcopenia.

Several studies have confirmed that preoperative sarcopenia is an independent prognostic factor for long-term survival in patients with GC.[9-11] However, more elderly patients and fewer young adult patients were recruited in those studies, and some of the studies were limited to elderly patients (≥65 years) because sarcopenia was used to evaluate skeletal muscle status. Thus, the results of those studies may not be widely applicable because the majority of patients with GC are younger than 65 years. Although sarcopenia is used worldwide in assessing skeletal muscle status, it is not an appropriate definition of skeletal muscle status in certain diseases and under certain conditions, such as in adult patients, because sarcopenia is defined as progressive physiological skeletal muscle loss or atrophy associated with aging.[7] Skeletal muscle wasting may be driven by numerous factors, including age, inflammation, chronic disease, malnutrition, and malignancy.[17] Therefore, to evaluate the relationship between skeletal muscle status and long-term survival across a wider age range in GC patients, we chose group-specific tertiles of SMI instead of sarcopenia in the pre-

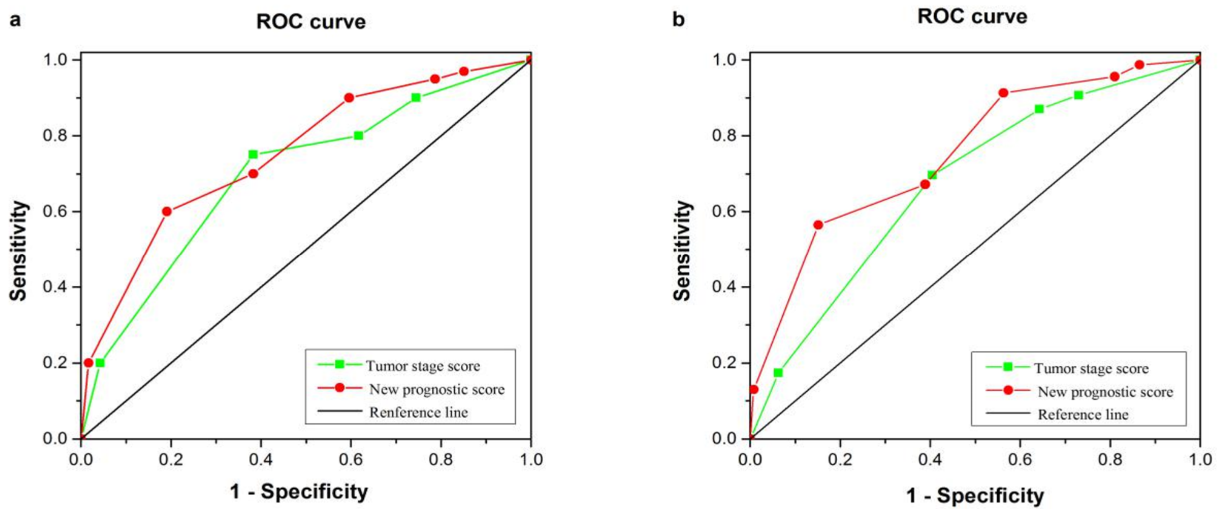

Figure 2. Area under the receiver operating characteristic (ROC) curve demonstrating better predictive value of the new prognostic score than of a score with tumor stage alone for 3-year survival. Tumor stage was quantified as follows: IIA (1 point), IIB (2 points), IIIA (3 points), IIIB (4 points), and IIIC (5 points); the new prognostic score was established by combining stages and skeletal muscle status index (SMI) grades (low/medium/high), stratified by the cutoff values of group-specific tertiles for adult men, adult women, elderly men and elderly women: high SMI (0 point), medium SMI (1 points), low SMI (2 points), stage IIA (1 point), IIB (2 points), IIIA (3 points), IIIB (4 point), and IIIC (5 points). a, patients who underwent distal gastrectomy; b, patients who underwent total gastrectomy. $p<0.001$ (ROC curve analysis).

sent study and observed similar results.

Notably, the effect of differences in the SMI on prognoses appears to differ with surgical method, age and gender. This effect is particularly prominent among the total gastrectomy, adult and male groups. GC is categorized into upper-, middle-, or lower-third cancer according to the location of the main tumor. Although the pathologic features are similar, the required surgical procedures differ widely according to the location of the gastric tumor. Patients with middle or lower GC usually undergo distal gastrectomy, whereas total gastrectomy is often required in patients with upper GC. The extent of surgical stress and interference of intestinal function after total gastrectomy are considered to be more serious than those after distal gastrectomy, and this may exacerbate muscle wasting and the impact of SMI differences on long-term outcomes.[18] In our study, the prognoses of patients who underwent total gastrectomy were worse and the differences in survival were more significant than those of patients who underwent distal gastrectomy. Notably, our results revealed that the SMI in patients who underwent total gastrectomy was slightly higher than that in patients who underwent distal gastrectomy. Generally, patients with upper GC have an earlier and higher incidence of malnutrition than patients with middle or lower GC due to the early onset of obstructive symptoms; nevertheless, upper GC patients might also visit doctors' offices earlier, leading to a shorter course of disease and lower wasting of skeletal muscle. Thus, these patients may have better skeletal muscle status before surgery than patients who undergo distal gastrectomy. These results suggest that the relationship between skeletal muscle status and disease prognosis is associated with specific disease and therapy stress, and that a higher initial SMI does not definitively lead to a better prognosis.

Although elderly patients generally have worse prognoses than adult patients, the differences in survival in adults were more significant in our study. Sarcopenia is common in elderly patients. In patients with GC, a high prevalence of sarcopenia is expected and has been described to be as high as 57% in elderly patients (≥65 years) before surgery.[19] This may contribute to the smaller differences in survival in elderly patients. There are two studies in which the participants were older and had a higher incidence of sarcopenia, even though there were no associations between sarcopenia and prognoses.[19,20] The elderly patients in our study had a lower incidence of sarcopenia (32.75%) than the patients in those studies. Nevertheless, adult patients have a higher SMI and thus have a wider range of SMI than elderly patients, which might contribute to greater differences in survival.[21]

The prognoses of women were significantly worse than those of men in the present study. The F/M rates were significantly higher in women than in men. In situations such as malignancy, inactivity, and aging, the loss of muscle mass may be associated with preserved or even increased body fat content. Consequently, patients could have marked skeletal muscle loss despite having a normal weight. Due to the lack of appropriate screening tools and diagnostic criteria, the occult skeletal muscle loss in those patients is frequently overlooked, and approximately 20% of well-nourished hospitalized patients diagnosed by routinely used nutrition assessment tools were found to have sarcopenia.[22] In our study, the rate of sarcopenia in elderly women (47.05%) was significantly higher than that in elderly men (26.83%), although there was no significant difference in their BMIs. Thus, women were more likely to be classified as well-nourished than men with thinner body types. As a result, skeletal muscle wasting in these patients could be even worse during the progression of disease and treatment due to untimely nutritional intervention, which might ultimately contribute to a worse prognosis.[23]

Despite the high prognostic and predictive value of skeletal muscle status for long-term survival in cancer patients, the mechanism remains unclear. However, the main reasons might be as follows. First, skeletal muscle is the most important nutritional component used to fight against the stress of disease and antitumor therapy because skeletal muscle proteins are the body's preferential source of energy and amino acid substrates, especially for inflammatory and immune cells, in response to disease stress and a malnourished state.[4] Thus, continuous skeletal muscle wasting, based on a poor preoperative skeletal muscle status, might affect the patient's rehabilitation and prognoses during further disease progression and treatment, even if it does not affect the current treatment. Second, increasing levels of proinflammatory and procachectic factors, such as insulin-like growth factor-1, nuclear factor-kappa B, and tumor necrosis factor α, in patients with tumors may stimulate a host inflammatory response and trigger both tumor progression and muscle wasting. Thus, a low SMI may reflect the increased metabolic activity of a more aggressive tumor biology, leading to both muscle wasting and tumor progression and cause negative outcomes.[24,25] Another reason is that cancer is a potentially recurrent disease, and skeletal muscle wasting is a continuous problem in cancer patients. In the long run, a low preoperative SMI will inevitably lead to a higher risk and earlier emergence of cachexia, which would ultimately cause earlier death.[26]

Sarcopenia has been considered an independent prognostic indicator of poor outcomes in cancer patients for several years,[4,5,27] and many studies suggest screening patients for sarcopenia in clinical practice.[28,29] However, our results further demonstrated that in both adult and elderly patients, there were significant differences in OS between patients with medium and high SMI grades. This finding suggests that the long-term survival of patients varies with differences in preoperative skeletal muscle status, even if it is not worse than sarcopenia. Therefore, patients' skeletal muscle status must be identified earlier than the potential progression to sarcopenia and to provide appropriate management to improve long-term patient survival. For this reason, a new cancer management strategy, named 'prehabilitation', has been proposed. Prehabilitation refers to the importance of the simultaneous determination of a patient's baseline skeletal muscle status and tumor stage at the time of disease diagnosis to facilitate targeted interventions.[30]

Before surgery, CT is routinely performed in patients with GC. Therefore, we can use a preoperative CT scan to simultaneously determine the tumor stage and skeletal muscle status. In addition, the present study showed that a new scoring system combining SMI grades obtained via CT and tumor stages has a better discriminatory capacity for predicting the 3-year OS than tumor stage alone. Thus, we hope that the results of this study will shift more attention toward the crucial effect of skeletal muscle status on long-term survival.

The present study has several advantages. First, our study provides more specific and stronger evidence regarding the association between preoperative muscle status and long-term survival than previous studies because we excluded patients with confounding factors associated with technical details and incomplete antitumor therapy, such as patients who died within 6 months after surgery due to serve postoperative complications or patients did not complete postoperative chemotherapy. Second, we found that the long-term survival of patients with GC varies with differences in therapy stress. Thus, our results remind researchers that the relationship between skeletal muscle status and long-term survival should be specified by the combined consideration of disease and treatment factors rather than the general estimation of skeletal muscle status alone. Third, our results show that poorer skeletal muscle status was associated with shorter OS, regardless of whether it was worse than sarcopenia. Thus, we should detect patients' skeletal muscle status and implement appropriate management earlier than the progression to sarcopenia. This study also had some limitations. First, some studies have indicated that poorer preoperative skeletal muscle status is associated with shorter RFS. However, our study did not analyze the association of skeletal muscle status with RFS and subsequent relationship between RFS and OS due to the lack of imaging data confirming the exact recurrence time in some patients. Nevertheless, the relationship between preoperative skeletal muscle status and OS found in this study is still worthy of attention. Second, this was a single-center retrospective study. Future studies are needed to determine the predictive value of preoperative skeletal muscle status assessment in GC patients and to clarify the beneficial effects of earlier management indicated by CT-defined skeletal muscle status, especially for patients undergoing total gastrectomy.

Conclusions

In conclusion, our study shows that the long-term survival of patients with GC after radical gastrectomy varies with differences in preoperative skeletal muscle status and therapy stress. Thus, the relationship between skeletal muscle status and prognosis should be specified by assessing both disease and treatment stress, rather than just generally estimating skeletal muscle status alone. Furthermore, poorer skeletal muscle status can cause shorter OS, even if the skeletal muscle status is not worse than sarcopenia. According to the results of this study, we hope that investigators will pay more attention to the crucial effect of skeletal muscle status on long-term survival, make more efforts to detect patients' skeletal muscle status at the same time as tumor diagnosis, and implement appropriate management earlier than the potential progression to sarcopenia to improve long-term patient survival.

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AUTHOR DISCLOSURES

The authors declare that they have no conflicts of interest. We acknowledge financial support from SZSM201612051.

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