Original Article

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Prognostic Significance of Preoperative CT-Determined Sarcopenia in Patients with Gastric Cancer Receiving Surgery

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Objective: Sarcopenia is a prognostic factor in the prediction of long-term outcomes of various cancers. This study investigates the impact of preoperative computed tomography (CT)-determined sarcopenia on gastric cancer patients who underwent curative-intent surgical resection.

Methods: This study retrospectively reviewed one hundred eighty-nine surgical patients with gastric adenocarcinoma at E-Da Hospital and E-Da Cancer Hospital from January 2008 to December 2017. The skeletal muscle index (SMI) and skeletal muscle density (SMD) were analyzed on the preoperative CT images. The sex-specific lowest quartile was the cut-off point for sarcopenia.

Results: SMI and SMD were evaluated as prognostic factors. In the Kaplan-Meier curve analysis, survival (log-rank test $p = 0.022$ for SMI and $p = 0.028$ for SMD) was significantly longer in nonsarcopenic than sarcopenic patients. Multivariate analysis demonstrated that hypoalbuminemia, disease stage, and SMD-sarcopenia showed significant negative prognostic impacts on overall survival. Meanwhile, SMI-sarcopenia, hypoalbuminemia, open total gastrectomy and high grade post-operative complications (i.e., Clavien-Dindo classification grade ≥ 3) were independent predictive factors for postoperative hospital stays longer than 14 days.

Conclusions: SMI-and SMD-sarcopenia correlated to poor survival rates in our patients. SMD-sarcopenia was an independent prognostic factor in the whole patient group. SMI-sarcopenia was a predictive factor for hospitalization longer than 14 days in all patients. There was no association either between sarcopenia and progression-free survival or between sarcopenia and severe postoperative complications.

Key words: sarcopenia, gastric cancer, skeletal muscle index, skeletal muscle density

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Introduction

Gastric cancer is the third most frequent cause of cancer-related death worldwide.[1] Surgical resection remains the essential curative treatment for gastric adenocarcinoma.[2] Sarcopenia, defined as a progressive loss of skeletal muscle mass and function, has a prevalence of 1% – 29% in community-dwelling populations.[3] Sarcopenia shares characteristics with other diseases associated with the risk of fall and fracture, including osteoporosis, frailty, and obesity.[4,5] Several studies have associated relatively low skeletal muscle mass with poor surgical outcomes, while others did not show this connection.[6-11] In a Japanese study, patients' skeletal muscle mass was assessed by anthropometric measurements of triceps skin fold and arm circumference, and sarcopenia was a significant negative prognostic factor in patients with gastric cancer who underwent curative resection.[12] However, the accuracy and reproducibility may be affected by calibration of the equipment, examiner, parameters used for predictive equation, and lack of standard criteria for defining sarcopenia in oncology study.[13]

Although dual energy X-ray absorptiometry (DXA) is ideal for the assessment of skeletal muscle mass in research and clinical practice because of its ability to distinguish fat, skeletal muscle, and bone,[14] DXA is currently not as popular as abdominal computed tomography (CT) for preoperative evaluation[15] because contrast medium enhancement CT scan is still the standard diagnostic modality for preoperative gastric cancer staging.[16] Besides, concomitant assessment of CT-based skeletal muscle mass and density before surgery could avoid additional costs and radiation exposure. A previous study reported a linear correlation between the CT-based cross-sectional skeletal muscle area from the third lumbar spine level and the DXA-detected skeletal muscle volume.[17] The mean value of the Hounsfield units in the area of interest, which represents skeletal muscle density (SMD), is closely related to muscle function.[18]

The aim of this study was to determine the impact of preoperative CT-determined sarcopenia on the overall survival, progression-free survival, postoperative complications, and length of hospitalization in patients who underwent radical gastrectomy for gastric cancer.

Materials and Methods

Study population and grouping

Approval from the institutional review board (EDAH IRB No. EMRP-107-089, approval date Aug 10, 2018) of E-Da Hospital was obtained. Information of all patients who underwent surgery of gastric adenocarcinoma between January 2008 and December 2017 at E-Da Hospital and E-Da Cancer Hospital from the registry database was retrospectively reviewed. Institutional review board waived the requirement for informed consent. The selection criteria included patients who had histologically proven gastric adenocarcinoma before surgery, underwent curative resection surgery, and had satisfactory quality abdominopelvic (AP) CT scans within 30 days before surgery. The exclusion criteria were patients who underwent gastric surgery with additional hepatectomy of more than two segments or Whipple procedures, those treated with endoscopic submucosal dissection, those with cancer of cardia that required additional thoracotomy or a thoracoscopic approach, those with acute perforation of gastric cancer who underwent emergency laparotomy, and those with CT scans of an insufficient image quality for skeletal muscle analysis.

The study population was divided into sarcopenic and non-sarcopenic groups according to the third lumbar dorsal skeletal muscle index (SMI, cm^2/m^2) and skeletal muscle density (SMD, HU) of the area of interest

computed from the CT images. Sarcopenia was defined as SMI and SMD values less than their respective sex-specific lowest quartiles, referred to as SMI-sarcopenia and SMD-sarcopenia, respectively.[19]

Image analysis and sarcopenia assessment

Abdominal CT scans were originally acquired for the purpose of preoperative staging. The median interval between the date of the CT scan and surgery was 12 (interquartile range, [IQR] = 5 – 20) days. The dorsal skeletal muscle group at the third lumbar spine level visualized on the abdominal CT scan was selected as the surrogate of patients' skeletal muscle mass. The dorsal muscle group area was defined as the bilateral psoas muscles, lumborum quadratus, and paraspinal muscles (Fig. 1). The skeletal muscle area on the CT scan was determined by averaging the areas obtained from the first two sections at the level of the third lumbar spine as CT sectioning proceeded caudally.

The CT images were analyzed using the open source software MATLAB (2018B, Mathworks, MA, USA), which permitted specific tissue demarcation with a Hounsfield unit interest threshold between -29 and +150 for skeletal muscles. The boundary of the skeletal muscle was manually outlined on the computer screen. The skeletal muscle area (cm^2) was measured by summing the tissue pixels and multiplying by the surface area of each pixel. All CT scans were analyzed by two well-trained independent PhD students of medical radiology science who were blinded to all clinical data. The area was normalized by dividing the body height (meter) squared to give the third lumbar dorsal skeletal muscle index (SMI, cm^2/m^2). The mean Hounsfield unit value of the above area of interest was used as a measurement of skeletal muscle density (SMD, HU).

Clinical data collection

Data on the patients' demographic and anthropometric characteristics [i.e., age, sex, body mass index (BMI), and body surface area (BSA)] as well as clinical features [i.e., hemoglobin concentration, serum albumin level, preoperative American Society of Anesthesiologists physical status (ASA-PS),[20] tumor stage, and comorbidities quantified with the updated Charlson comorbidity index (CCI)[21]] were collected and analyzed.

The surgical procedures were divided into four categories in order of increasing surgical invasiveness, namely, laparoscopic partial gastrectomy, laparoscopic total gastrectomy, open partial gastrectomy, and open total gastrectomy. Partial gastrectomy including distal

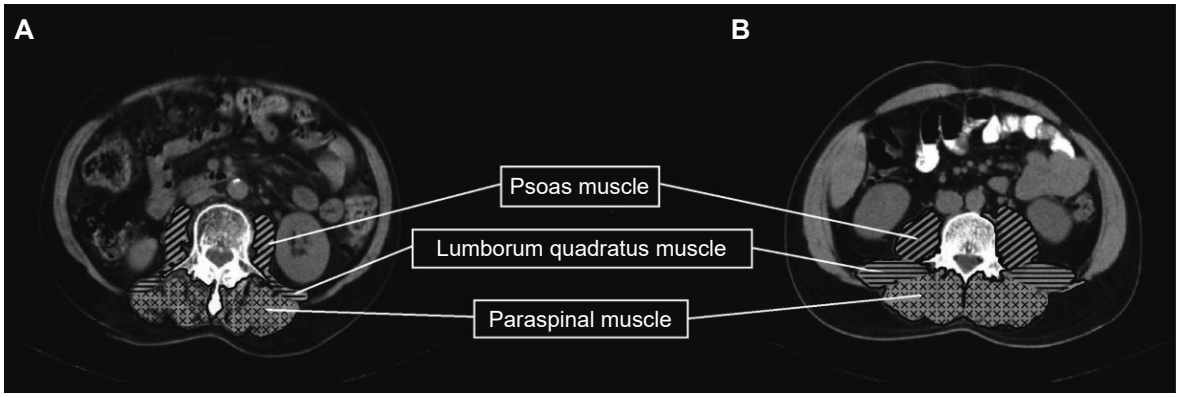

Fig. 1 Examples of the skeletal muscle index and skeletal muscle density at the level of the third lumbar spine. (A) Sarcopenic patient, 65 years old female, SMI = 6.19 cm^2/m^2, SMD = 28.32 HU. (B) Nonsarcopenic patient, 41 years old male, SMI = 10.18 cm^2/m^2, SMD = 50.98 HU.

and proximal gastrectomy and robot-assisted laparoscopic surgery was considered laparoscopic surgery. D2 lymphadenectomy was the standard surgical protocol in our clinical practice based on the Japanese gastric cancer treatment guidelines.[22] The procedures for reconstruction of gastrointestinal continuity consisted of Billroth I, Billroth II or Roux-en-Y gastrojejunostomy based on the surgeon's clinical decision.

The primary outcomes included overall survival (OS) and progression-free survival (PFS). The secondary outcomes were postoperative complications, length of hospitalization, and ICU stay after surgery. Overall survival was calculated from the date of diagnosis to death from any cause. Progression-free survival was the time between the date of diagnosis and detected disease progression or death. The postoperative complications were classified according to the Clavien-Dindo classification.[23]

Statistical analysis

Mean values are presented as the mean ± standard deviation (SD). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) v20.0 software (SPSS Inc., Chicago, IL, USA). Comparisons were made between subjects with and without sarcopenia. The significance of difference in categorical variables was determined using Pearson's $\chi 2$ test or Fisher's exact test where appropriate, while that of continuous variables was assessed with independent t-test and Mann-Whitney U test. Overall survival was evaluated by Kaplan-Meier survival analysis and the log-rank test. Univariate and multivariate Cox proportional hazard models were used to identify prognostic factors for survival. $P <$ 0.2 variable in univariate analysis was inserted into multivariate analysis in survival analysis. Univariate and multivariate logistic regression analyses were used to evaluate the risk factors for lengths of hospital stay longer than 14 days. Variables with a p-value of < 0.05 were included in the multivariate analysis. Two-sided p-values < 0.05 were considered statistically significant.

Results

Study population

In total, 232 patients with histologically proven gastric adenocarcinoma, who underwent curative intent resection surgery, were originally recruited. Of the 232 patients, 19 were excluded because of their surgical procedures, including four having gastric surgery with additional hepatectomy of more than two segments of the liver, three undergoing Whipple procedures, one treated with endoscopic submucosal dissection, ten with cancer of cardia requiring additional thoracotomy or a thoracoscopic approach, and one with acute perforation of gastric cancer receiving an emergency laparotomy. In addition, there were 24 patients whose CT scans were not of sufficient quality for skeletal muscle analysis. Eventually, 189 patients were eligible for the current study. The mean age of the patients was 67.21 ± 10.92 years (range, 34 – 93) with a slight male predominance (62.1%). Twenty-three patients (12.2%) were found to have local invasion to adjacent organs.

Skeletal muscle mass, density assessment and patient grouping

There was a significant difference in the mean SMI between men (9.18 ± 1.74 cm^2/m^2) and women (7.72 ± 1.38 cm^2/m^2) ($p < 0.001$). According to the value of the sex-specific lowest quartile, the patients were divided into SMI-sarcopenic (n = 47) and SMI-non-sarcopenic (n = 142) groups. The cut-off values of SMI-sarcopenia for males and females were 8.00 cm^2/m^2 and 6.84 cm^2/m^2, respectively. In terms of skeletal muscle density, there was a significant difference in the mean SMD between men (41.24 ± 5.37 HU) and women (37.02 ± 5.13 HU) ($p < 0.001$) (eTable 1 in

the Supplement). The cut-off values of SMD-sarcopenia for males and females were 38.06 HU and 33.29 HU, respectively, according to our stratification strategy (Fig. 1).

Demographic, anthropometric, and clinical parameters

The demographic and clinical characteristics of the two groups are shown in Table 1. Patients with SMI-sarcopenia had a lower body mass index (BMI) ($p < 0.001$), lower serum albumin level ($p = 0.001$) and lower hemoglobin concentration ($p = 0.023$) as well as more regional lymph node metastases ($p = 0.021$) than patients without SMI-sarcopenia. However, there were no significant differences in age, sex, body surface area (BSA), white blood cell count, tumor size, status of distant metastasis, clinical stage, adjuvant chemotherapy, CCI, ASA-PS score or type of surgery. In contrast, patients with SMD-sarcopenia were significantly younger ($p < 0.001$) and had a lower serum albumin level ($p < 0.001$) than patients without.

Post-operative outcomes

The median follow-up time was 41.2 months (IQR: 14.7 – 61.5 months) (95% CI: 36.46 – 45.94 months). Of the 70 (37.04%) non-survivors, 24 (51.06%) were SMI-sarcopenic. For all patients, the median OS was 76.38 months (95% CI: 68.19 – 84.56 months). Patients with SMI-sarcopenia had a significantly shorter OS than those without SMI-sarcopenia on Kaplan-Meier curve analysis (p for log-rank test: 0.022). Despite the trend of association between sarcopenia and a short progression-free survival (PFS), no statistically significant difference was noted (p for log-rank test: 0.058) (Fig. 2).

Similarly, patients with SMD-sarcopenia had a significantly shorter OS (p for log-rank test = 0.028) than those without, but no significant difference was found in PFS between the two groups (p for log-rank test = 0.054) (Fig. 3). The detailed one-, three-, and five-year overall survival rates and the progression-free survival rates are shown in eTable 2 in the Supplement.

In terms of secondary postoperative outcomes, significantly more patients in the SMI-sarcopenia group had post-surgery hospital stays greater than 14 days than in the SMI-nonsarcopenia group. For severe post-operative complications (defined as Clavien-Dindo classification > 3) and length of ICU stay, there were no significant differences between the two groups regardless of the definition of sarcopenia (i.e., SMI or SMD) (Table 2). Among ten patients who had severe post-operative complications, five experienced intestinal anastomosis leakage, one had grade III hepatic encephalopathy, and four suffered from cerebrovascular accident with neurological sequelae.

Predictors of overall survival and length of hospital stay

Univariate analysis demonstrated significant negative associations of SMI-sarcopenia, SMD-sarcopenia, advanced disease stage, hypoalbuminemia (serum albumin < 3.5 g/dL), anemia (male Hb < 13 g/dL, female Hb < 12 g/dL), a low BMI (≤ 18.5 kg/m^2) and a CCI score ≥ 3 with overall survival. In multivariate Cox regression analysis, hypoalbuminemia (HR: 2.65, 95% CI: [1.36 – 5.16], $p = 0.004$), disease stage (stage I: reference, stage II, HR: 4.89, 95% CI: [1.97 – 12.15], $p = 0.001$, stage III + VI, HR: 5.18, 95% CI: [2.14 – 12.57], $p < 0.001$) and SMD-sarcopenia (HR:1.75, 95% CI: [1.02 – 3.01], $p = 0.04$) showed significant negative prognostic impacts on overall survival (Table 3).

In our series, 35 (18.5%) patients stayed in hospital for more than 14 days after surgery. Univariate analysis identified SMI-sarcopenia, a BMI ≤ 18.5 kg/m^2, hypoalbuminemia and open total gastrectomy as significant risk factors for a postoperative hospital stay longer than 14 days, while multivariate regression

Table 1. Demographic and clinical characteristics of the patients.

	All (n = 189)	SMI-sarcopenia (n = 47)	SMI-non-sarcopenia (n = 142)	*p*-value	SMD-sarcopenia (n = 47)	SMD-non-sarcopenia (n = 142)	*p*-value
Age, years[†]	67.21 (10.92)	69.7 (10.23)	66.37 (11.04)	0.069	74.51 (8.01)	64.77 (10.68)	< 0.001[§]
Gender[*]							
Male	117 (62)	29 (61.7)	88 (62.0)	0.973	29 (61.7)	88 (62.0)	0.973
Female	72 (38)	18 (38.3)	54 (38.0)		18 (38.3)	54 (38.0)	
BMI, kg/m^{2}[†]	23.71 (3.64)	21.87 (3.63)	24.32 (3.45)	< 0.001[§]	23.88 (3.70)	23.65 (3.64)	0.712
BSA, m^{2}[†]	1.66 (0.18)	1.63 (0.16)	1.67 (0.18)	0.224	1.66 (0.200)	1.66 (0.169)	0.936
Albumin, g/dL[†]	3.99 (0.35)	3.84 (0.39)	4.04 (0.32)	0.001[§]	3.80 (0.38)	4.05 (0.32)	< 0.001[§]
Hemoglobin, g/dL[†]	11.66 (2.69)	10.89 (2.47)	11.91 (2.71)	0.023[§]	11.13 (2.79)	11.83 (2.64)	0.118
White blood count, 103/μL[†]	6.73 (2.55)	6.31 (1.72)	6.87 (2.76)	0.186	6.70 (2.63)	6.74 (2.53)	0.92
Tumor Stage[*]							
T1	49 (25.9)	10 (21.3)	39 (27.5)	0.814	9 (19.1)	40 (28.2)	0.346
T2	29 (15.3)	7 (14.9)	22 (15.5)		9 (19.1)	20 (14.1)	
T3	45 (23.8)	13 (27.7)	32 (22.5)		9 (19.1)	36 (25.4)	
T4	66 (34.9)	17 (36.2)	49 (34.5)		20 (42.6)	46 (32.4)	
Lymph node status[*]							
N0	117 (61.9)	22 (46.8)	95 (66.9)	0.018[§]	30 (63.8)	87 (61.3)	0.622
N1	36 (19.0)	9 (19.1)	27 (19.0)		8 (17.0)	28 (19.7)	
N2	32 (19.0)	14 (39.8)	18 (12.7)		7 (14.9)	25 (17.0)	
N3	4 (2.1)	2 (4.3)	2 (1.4)		2 (4.3)	2 (1.4)	
Metastasis[*]							
M0	166 (87.8)	39 (83.0)	127 (89.4)	0.240	42 (89.4)	124 (87.3)	0.711
M1	23 (12.2)	8 (17.0)	15 (10.6)		5 (10.6)	18 (12.7)	
Adjuvant chemotherapy[*]							
Yes	75 (39.7)	21 (44.7)	54 (38.0)	0.419	21 (44.7)	54 (38.0)	0.419
No	114 (60.3)	26 (55.3)	88 (62.0)		26 (55.3)	88 (62.0)	
Clinical stage (AJCC, 8th edition)[*]							
Stage I	58 (30.7)	9 (19.1)	49 (34.5)	0.181	14 (29.8)	44 (31.0)	0.403
Stage II	45 (23.8)	14 (29.8)	31 (21.8)		10 (21.3)	35 (24.6)	
Stage III	63 (33.3)	16 (34.0)	4 (33.1)		14 (29.8)	49 (34.5)	
Stage IV	23 (12.2)	8 (17.0)	15 (10.6)		9 (19.1)	14 (9.9)	
CCI score[†]	0.99 (1.91)	1.13 (2.08)	0.94 (1.86)	0.569	1.28 (2.15)	0.89 (1.83)	0.184
ASA-PS score[*]							
I	5 (2.6)	0	5 (3.5)	0.051	0	5 (3.5%)	0.022[§]
II	124 (65.6)	26 (55.3)	98 (69.0)		25 (53.2)	99 (69.7)	
III	60 (31.7)	21 (44.7)	39 (27.5)		22 (46.8)	38 (26.8)	
Type of gastrectomy[*]							
Scope, partial	28 (14.8)	8 (17.0)	20 (14.1)	0.730	5 (10.6)	23 (16.2)	0.479
Open, partial	132 (69.8)	34 (72.3)	98 (69.0)		37 (78.7)	95 (66.9)	
Scope, total	8 (4.2)	1 (2.1)	7 (4.9)		1 (21.0)	7 (4.9)	
Open, total	21 (11.1)	4 (8.5)	17 (12.0)		4 (8.5)	17 (12.0)	

The lymph node status was analyzed by the Fisher exact test.

ASA: American Society of Anesthesiologists; BMI: body mass index; SMI: skeletal muscle index; SMD: skeletal muscle density; BSA: body surface area; CCI: Charlson comorbidity index; AJCC: American Joint Committee on Cancer.

[*] Values are number of patients and percent unless indicated otherwise.

[†] Values are mean (standard deviation).

[§] Statistically significant.

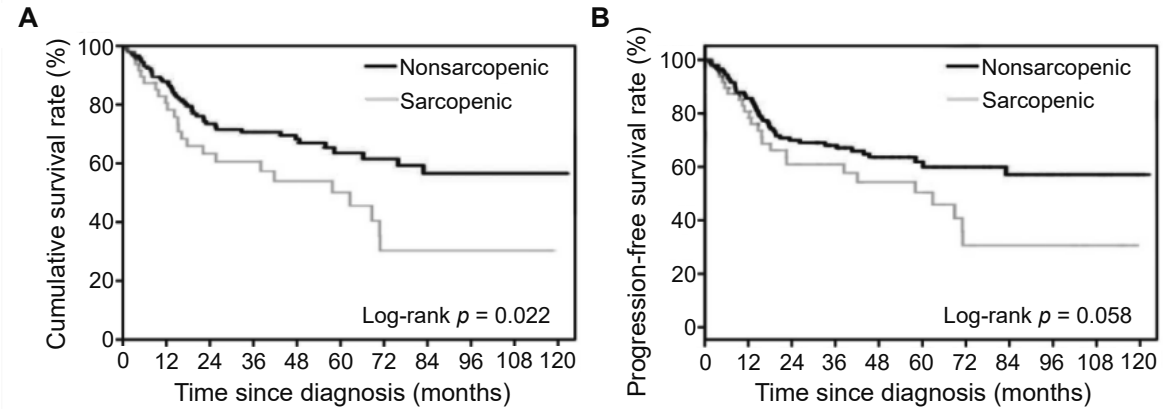

Fig. 2 Kaplan-Meier survival curves for (A) overall survival and (B) progression-free survival in patients with and without SMI-sarcopenia.

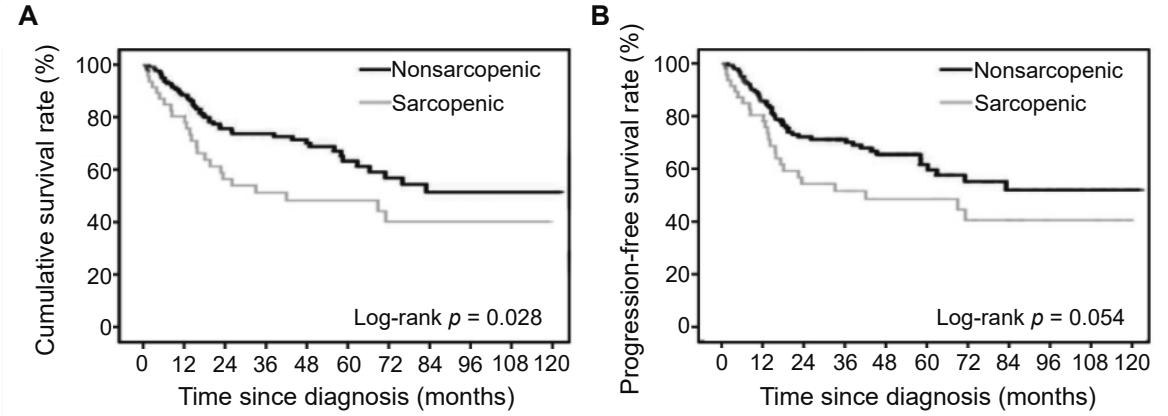

Fig. 3 Kaplan-Meier survival curves for (A) overall survival and (B) progression-free survival in patients with and without SMD-sarcopenia.

Table 2. Secondary outcomes of patients with gastric cancer following surgical treatment.

		SMI-sarcopenia			SMD-sarcopenia		
Classification of Surgical Complications*	Total	SMI-sarcopenia	SMI-non-sarcopenia	*p*-value	SMD-sarcopenia	SMD-non-sarcopenia	*p*-value
≥ Grade III	10 (32.2)	2 (18.2)	8 (40)	0.262	3 (33.3)	7 (46.6)	1
< Grade III	21 (67.8)	9 (81.8)	12 (60)		6 (66.6)	15 (53.4)	
Length of stay							
Inpatient days†	11.81 (5.39)	12.68 (5.49)	11.53 (5.34)	0.204	12.23 (5.18)	11.68 (5.47)	0.540
≥ 14 days*	45 (23.8)	19 (40.4)	26 (18.3)	0.002§	13 (27.6)	32 (22.5)	0.475
< 14 days*	144 (76.2)	26 (59.6)	116 (81.7)		34 (72.4)	110 (77.5)	
Postoperative care in the ICU							
ICU care*	33 (17.5)	10 (21.3)	23 (16.2)	0.427	12 (25.5)	21 (14.8)	0.093
Length of ICU stay, days†	2.64 (3.25)	2.7 (3.02)	2.61 (3.41)	0.94	3.58 (4.56)	2.10 (2.14)	0.211

Classification of Surgical Complications evaluated by Clavien-Dindo classification.
Length of ICU stay was analyzed by the Mann-Whitney U test, and the classification of the surgical complications was analyzed by the Fisher exact test.
* Values are number of patients and percent unless indicated otherwise.
† Values are mean (standard deviation).
§ Statistically significant.

Table 3. Univariate and multivariate Cox regression analysis of the factors associated with overall survival for all patients.

	Univariate Analysis		Multivariate Analysis	
Factors	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.01 (0.98 – 1.03)	0.559		
Sex				
Female (ref)	1			
Male	0.97 (0.59 – 1.57)	0.888		
BMI				
> 18.5 kg/m^2 (ref)	1			
≤ 18.5 kg/m^2	2.07 (1.11 – 3.85)	0.022[§]	0.84 (0.40 – 1.77)	0.645
SMI-sarcopenia				
No (ref)	1			
Yes	1.77 (1.08 – 2.89)	0.024[§]	1.15 (0.65 – 2.04)	0.64
SMD-sarcopenia				
No (ref)	1			
Yes	1.73 (1.05 – 2.83)	0.03[§]	1.75 (1.02 – 3.01)	0.04[§]
Stage				
I (ref)	1			
II	1.98 (0.833 – 4.70)	0.122[#]	4.89 (1.97 – 12.15)	0.001[§]
III + IV	6.97 (3.40 – 14.32)	< 0.001[§]	13.236 (4.06 – 43.15)	< 0.001[§]
Albumin				
≥ 3.5 g/dL (ref)	1			
< 3.5 g/dL	4.81 (2.70 – 8.57)	< 0.001[§]	2.56 (1.28 – 5.12)	0.008[§]
White blood count				
≥ 4 × 103/μL (ref)	1			
< 4 × 103/μL	1.42 (0.61 – 3.29)	0.411		
Hemoglobin				
Male ≥ 13 g/dL Female ≥ 12 g/dL (ref)	1			
Male < 13 g/dL Female < 12 g/dL	2.48 (1.49 – 4.15)	0.001[§]	1.31 (0.73 – 2.36)	0.373
Type of gastrectomy				
Scope, partial (ref)	1			
Scope, total	1.87 (0.36 – 9.65)	0.456		
Open, partial	1.74 (0.69 – 4.39)	0.238		
Open, total	2.71 (0.94 – 7.82)	0.065[#]	1.51 (0.46 – 4.88)	0.495
Postoperative complica-tions				
Grade I + II (ref)	1			
≥ Grade III	1.72 (0.69 – 4.29)	0.247		
ASA grade				
I (ref)	1			
II	1.02 (0.25 – 4.24)	0.977		
III	1.41 (0.34 – 5.93)	0.640		
Postoperative care in the ICU				
No (ref)	1			
Yes	1.81 (1.00 – 3.28)	0.051[#]	1.79 (0.92 – 3.51)	0.87
Adjuvant chemotherapy				
No (ref)	1			
Yes	2.21 (1.37 – 3.56)	0.001[§]	0.89 (0.49 – 1.60)	0.70

Charlson comorbidity index				
1 (ref)	1			
≥ 3	5.60 (3.20 – 9.18)	< 0.001[§]	2.15 (0.96 – 4.81)	0.062

HR (95% CI): Hazards ratio (95% confidence intervals).
ASA: American Society of Anesthesiologists; BMI: body mass index; SMI: skeletal muscle index; SMD: skeletal muscle density; BSA: body surface area; CCI: Charlson comorbidity index.
[§] Statistically significant.
[#] $p < 0.2$ variable in univariate analysis was inserted into multivariate analysis.

10.13], $p = 0.045$), open total gastrectomy (OR: 16.51, 95% CI: [3.14 – 86.84], $p = 0.001$) and high grade post-operative complications (i.e., Clavien-Dindo classification grade ≥ 3) (OR: 13.02, 95% CI: [2.50 – 68.89], $p = 0.002$) were independent predictive factors for postoperative hospital stays longer than 14 days (Table 4).

Discussion

The association of CT-determined SMI-sarcopenia with short- and long-term outcomes of gastric cancer following surgical treatments remains controversial.[11,24,25] This study is the first to concomitantly investigate the associations of skeletal muscle index and skeletal muscle density determined by abdominal CT scan with the postoperative outcomes of patients with gastric cancers. We found that both preoperative SMI-sarcopenia and SMD-sarcopenia were significantly associated with poor overall survival but not progression-free survival on Kaplan-Meier analysis. In multivariate analysis, hypoalbuminemia and disease stage and SMD-sarcopenia were shown to be independent prognostic factors for worse overall survival for the whole patient group. According to the above results, we recommend the routine determination of CT-based SMI and SMD before surgery in patients undergoing gastrectomy for cancer.

Regarding the short-term postoperative outcomes in the present study, SMI-sarcopenia, hypoalbuminemia, open total gastrectomy, and high grade post-operative complications were of significance in predicting a hospital stay longer than 14 day after surgery. However, we found no significant association of SMI- or SMD-sarcopenia with postoperative complications and length of ICU stay.

The popularity of CT in analyzing body composition is attributed to its unique radiation attenuation patterns for different tissues. Mourtzakis and colleagues first described a linear correlation between the cross-sectional skeletal muscle area on contrast-enhanced abdominal CT at the third lumbar spine level with the DXA-detected skeletal muscle volume.[17] CT scan of the abdomen is the standard preoperative staging modality for gastric cancer and could provide information about body composition without imposing additional costs or radiation exposure. Therefore, CT-determined skeletal muscle index is widely used as a surrogate of skeletal muscle mass. However, no consensus was reached regarding the methodology of measuring CT-determined sarcopenia. The spinal level for scanning, choice of skeletal muscle group for assessment,[26-28] and the stratification strategy for defining sarcopenia[24] varied in different studies, causing a lack of universally accepted guidelines on the use of CT for defining sarcopenia. The present study adopted sex-specific lowest quartile of the skeletal muscle index in a patient series as the cut-off value for determining sarcopenia. This stratification strategy has been commonly used in studies of sarcopenia related to various malignancies.[19,26,29,30]

Previous research revealed that a low muscle mass is associated with prolonged hospitalization.[31,32] This finding was supported by other studies showing the importance of ambu-

lating early and maintaining chest hygiene in regaining intestinal peristalsis and avoiding postoperative complications during the recovery period after major abdominal surgery.[33] The results of this study demonstrated that a low SMI per se would prolong postoperative hospitalization in patients undergoing gastrectomy for gastric cancer.

The pathophysiology and clinical implications of SMI- and SMD-sarcopenia are still obscure. A decrease in CT-derived SMI, which represents the skeletal muscle mass

Table 4. Univariate and multivariate logistic regression analyses for risk factors of lengths of stay longer than 14 days.

	Univariate Analysis		Multivariate Analysis	
Factors	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.02 (0.99 – 1.06)	0.173		
Sex				
Female (ref)	1			
Male	1.49 (0.73 – 3.05)	0.271		
BMI				
> 18.5 (ref)	1			
≤ 18.5	3.24 (1.17 – 9.00)	0.024§	1.31 (0.38 – 4.45)	0.671
SMI-sarcopenia				
No (ref)	1			
Yes	3.03 (1.47 – 6.23)	0.003§	3.79 (1.56 – 9.21)	0.003§
SMD-sarcopenia				
No (ref)	1			
Yes	1.31 (0.62 – 2.78)	0.475		
Stage				
I (ref)	1			
II	1.55 (0.59 – 4.07)	0.370		
III + IV	1.86 (0.81 – 4.25)	0.143		
Albumin				
≥ 3.5 g/dL (ref)	1			
< 3.5 g/dL	5.50 (2.05 – 14.73)	0.001§	3.25 (1.03 – 10.13)	0.045§
White blood count				
≥ 4 × 103/μL (ref)	1			
< 4 × 103/μL	0.31 (0.04 – 2.45)	0.263		
Hemoglobin				
Male ≥ 13 g/dL Female ≥ 12 g/dL (ref)	1			
Male < 13 g/dL Female < 12 g/dL	1.62 (0.81 – 3.24)	0.171		
Type of gastrectomy				
Scope, partial	1			
Scope, total	2.78 (0.38 – 20.500)	0.316	4.69 (0.51 – 43.60)	0.174
Open, partial	2.35 (0.66 – 8.33)	0.187	2.56 (0.63 – 10.13)	0.191
Open, total	9.17 (2.10 – 39.96)	0.003§	16.51 (3.14 – 86.84)	0.001§
Postoperative complica-tions				
Grade I + II (ref)	1			
≥ Grade III	8.66 (2.14 – 35.08)	0.002§	13.2 (2.50 – 67.89)	0.002§
Charlson Comorbidity Index				
< 3 (ref)	1			
≥ 3	1.62 (0.65 – 4.040)	0.305		

OR (95% CI): Odds ratio (95% confidence intervals).
BMI: body mass index; SMI: skeletal muscle index; SMD: skeletal muscle density; BSA: body surface area; CCI: Charlson comorbidity index.
§ Statistically significant.

(quantity), is due to a decrease in size and number of type II muscle fibers leading to a reduction in muscle strength.[34] SMD represents the degree of adipose tissue infiltration into skeletal muscle (quality).[35] These two distinct molecular mechanisms might occur concomitantly or alone in the process of aging or illness and contribute to impaired muscle strength and physical performance.

Individual skeletal muscle density can vary greatly. Muscle with lower SMD has increased fat production and infiltration (also known as myosteatosis).[36] A study demonstrated that CT-determined low SMD is an important prognosticator of survival in patients who received chemotherapy for metastatic gastric cancer.[37] Another study focusing on perihilar cholangiocarcinoma showed that skeletal muscle density played a more important role in predicting prognosis compared to that of skeletal muscle mass.[38] In concert with these findings, two other studies demonstrated that CT-determined low SMD was an independent prognostic factor for treatment response and outcomes in patients with lymphoma receiving immunochemotherapy.[28,39] Our study is the first to reveal that CT-determined SMD-sarcopenia is an independent prognostic factor for overall survival patients with gastric cancer receiving curative-intent surgery. The literature review and findings of our present study support SMD-sarcopenia as a better prognostic indicator than SMI-sarcopenia in both solid and hematological cancers. Further research is needed to elucidate the exact mechanisms of these clinical findings.

Significant limitations of this study included the relatively small sample size that precluded a strong conclusion to be drawn, as well as its retrospective cross-sectional nature that did not provide information on the associations between serial postoperative changes in the parameters and prognosis. Large-scale cohort studies are warranted to validate the findings.

In conclusion, SMD- and SMI-sarcopenia were significantly related to overall survival in patients with gastric cancer who underwent curative-intent surgery. In addition, SMD-sarcopenia was an independent negative predictor for these patients. Furthermore, SMI-sarcopenia was an independent predictor of the length of postoperative hospitalization. Our study provided essential evidence that skeletal muscle composition disclosed by CT scan is of essential prognostic significance for patients receiving gastric cancer surgery. Further prospective studies are warranted to validate the findings.

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Supplementary Material

eTable 1: Mean SMI and SMD values classified by gender.

eTable 2: Primary outcomes of patients with gastric cancer who underwent surgical treatment.

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