Prognostic value of computed tomography-derived skeletal muscle index and radiodensity in patients with gastric cancer after curative gastrectomy

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Abstract. The association of computed tomography (CT)-derived skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) with postoperative prognosis in patients with gastric cancer (GC) remains unknown. Therefore, the present study aimed to assess the association between SMI and SMD with 5-year overall survival (OS) and recurrence-free survival (RFS) in patients with GC. SMI and SMD were measured preoperatively in patients who underwent gastrectomy. Patients were categorized into Groups 1 (high SMI and SMD), 2 (high SMI or SMD) and 3 (low SMI and SMD). OS and RFS rates were assessed using Kaplan-Meier analysis and the log-rank test. Among 459 patients, OS and RFS rates were significantly lower in the low-SMD group than in the high-SMD group (OS, 83.4% vs. 88.8%, respectively; P=0.04 and RFS, 80.5% vs. 87.2%, respectively; P=0.02). OS and RFS rates were also significantly lower in Group 3 than in Groups 2 and 1 (P=0.006). Multivariate analysis revealed that a low SMI and SMD (Group 3) was a significant independent prognostic factor for OS [hazard ratio (HR), 2.32; 95% confidence interval (CI), 1.17-4.59; P=0.016] and RFS (HR, 2.28; 95% CI, 1.19-4.37; P=0.013). In summary, low SMI and SMD values may be useful postoperative prognostic indicators for patients with GC.

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Abbreviations: CT, computed tomography; SMI, skeletal muscle index; SMD, skeletal muscle radiodensity; GC, gastric cancer; OS, overall survival; RFS, recurrence-free survival; HU, Hounsfield units; HR, hazard ratios; CI, confidence interval; BMI, body mass index; PNI, Prognostic Nutritional Index

Key words: GC, SMI, SMD, CT, prognosis

Introduction

Gastric cancer (GC) is the third leading cause of cancer-related mortality worldwide, with a particularly high incidence in East Asia (men, 32.5%; women, 13.2%) (1). Despite recent advances in the diagnosis and treatment of GC, a poor prognosis for unresectable advanced GC and metastatic or recurrent GC persists (2,3).

Sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, has emerged as a novel prognostic factor of patients with cancer (4). The association of sarcopenia with a worse prognosis of GC has been reported across several types of cancers and treatment modalities (5,6). Common methods for assessing skeletal muscle index (SMI) and quality include dual-energy X-ray absorptiometry (7) and bioelectrical impedance analysis (8). Furthermore, novel methods using computed tomography (CT) to measure CT-derived SMI and skeletal muscle radiodensity (SMD) have been reported (9,10). Furthermore, several studies have highlighted SMI and SMD as prognostic indicators in patients with cancer (11,12). Thus, the combination of SMI and SMD may serve as a prognostic factor or indicate the risk of comorbidities by assessing total muscle mass and quality (13,14). However, the relationship between the combination of SMI and SMD and prognosis in patients with GC has not been fully investigated. Therefore, the present study aimed to determine the relationship between preoperative SMI and SMD and prognosis in patients with GC.

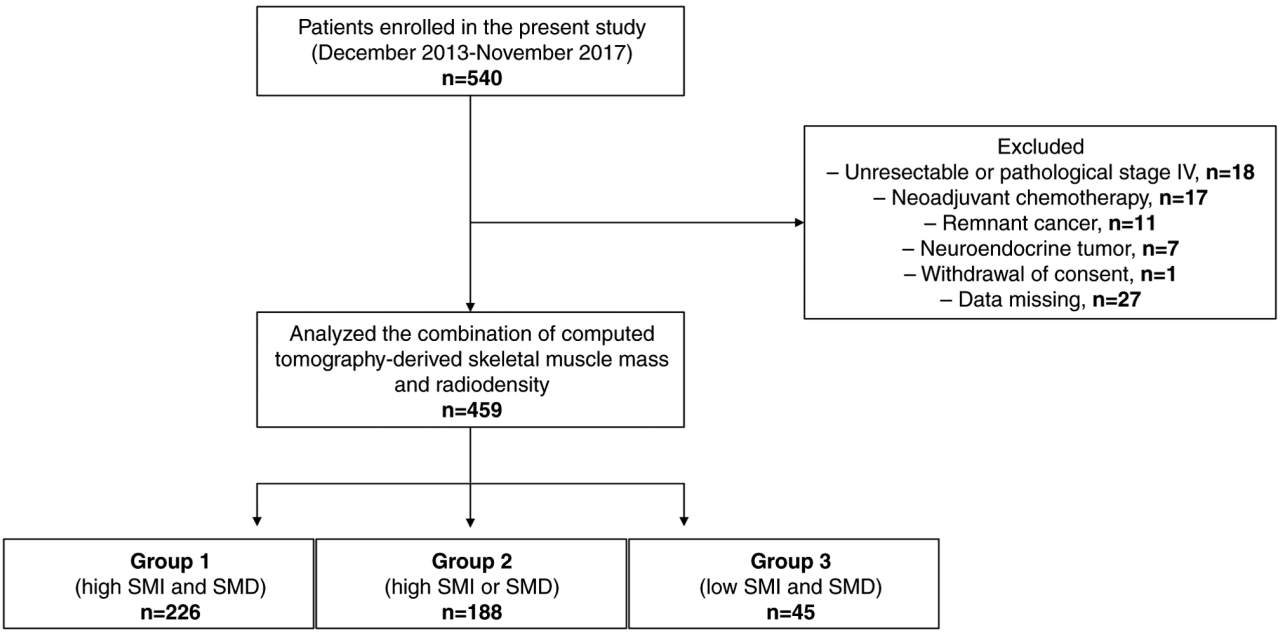

Figure 1. Flowchart of the patient selection process. SMI, skeletal muscle index; SMD, skeletal muscle density.

Materials and methods

Patients. In total, 540 patients with GC were enrolled in the present study at the Kanagawa Cancer Center (Yokohama, Japan) from December 2013 to November 2017. Eligibility criteria for patients were as follows: i) Age >20 years; ii) no history of cancer; iii) pathologically confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma; iv) no treatment before surgery; v) Eastern Cooperative Oncology Group performance status (15) of 0-2; vi) CT scans performed within 1 month before surgery; and vii) gastrectomy with R0 resection, ensuring complete removal of all cancerous tissue with no visible or microscopic residual tumor at the primary site. The exclusion criteria were as follows: i) Essential data were missing; ii) gastrectomy with R0 resection was not performed; iii) pathological assessment revealed neuroendocrine tumor involvement; and iv) consent was withdrawn. Of the 540 patients enrolled, 81 were excluded and 459 (300 men and 159 women) were included in the present study (Fig. 1). The median age was 68 years (range, 32-90 years).

The present study was approved by the Ethics Committee of Kanagawa Cancer Center (Yokohama, Japan; approval no. 25 Research-20). All patients provided informed consent, and this study adhered to the ethical guidelines outlined in the 1996 Declaration of Helsinki.

Image analysis. In accordance with previous studies (16,17), the SliceOmatic 5.0, Revision 9 graphics program (Tomovision) and ABACS (version 9; Voronoi Health Analytics Incorporated) were used to analyze skeletal muscle mass and radiodensity from preoperative CT images (Aquilion 64 CT Scanner; Canon Medical Systems Corporation). The threshold range was -29-150 Hounsfield units (HU) for skeletal muscle. The SMI was calculated based on patient height (m^2). The SMD was calculated as the average HU of all skeletal muscles at the level of L3.

Cutoff values for SMI and SMD. The SMI and SMD values demonstrate marked sex differences (18). Therefore, using receiver operating characteristic curve analysis of 5-year survival and mortality outcome data, sex-specific cutoff values were calculated. The cutoff values for SMI were 39.4 for men [area under the curve (AUC), 0.57; 95% confidence interval (CI), 0.47-0.66] and 31.9 for women (AUC, 0.56; 95% CI, 0.45-0.68; Fig. 2). The cut-off values for SMD were 36.3 for men (AUC, 0.63; 95% CI, 0.55-0.72) and 31.6 for women (AUC, 0.56; 95% CI, 0.43-0.69; Fig. 2). Based on these values, patients were categorized into the following groups based on high and low SMI and SMD: Group 1, high SMI and SMD; Group 2, high SMI or SMD; and Group 3, low SMI and SMD.

Statistical analysis. Continuous variables are presented as median ± standard deviation and were evaluated nonparametrically using the Kruskal-Wallis test and the Steel-Dwass test. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Correlation between SMI and SMD was analyzed using Spearman's rank correlation test. Kaplan-Meier analysis and the log-rank test were used to assess overall survival (OS) and relapse-free survival (RFS). Statistically significant variables ($P<0.05$) in the univariate analysis were included in multivariate regression analysis, with results reported as hazard ratios (HR) and 95% CIs. $P<0.05$ was considered to indicate a statistically significant difference. EZR (version 1.68, Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing), was used for all statistical analyses.

Results

Correlation between SMI and SMD. The results revealed a significant but weak positive correlation between SMI and SMD ($r=0.297$; $P<0.001$; Fig. 3).

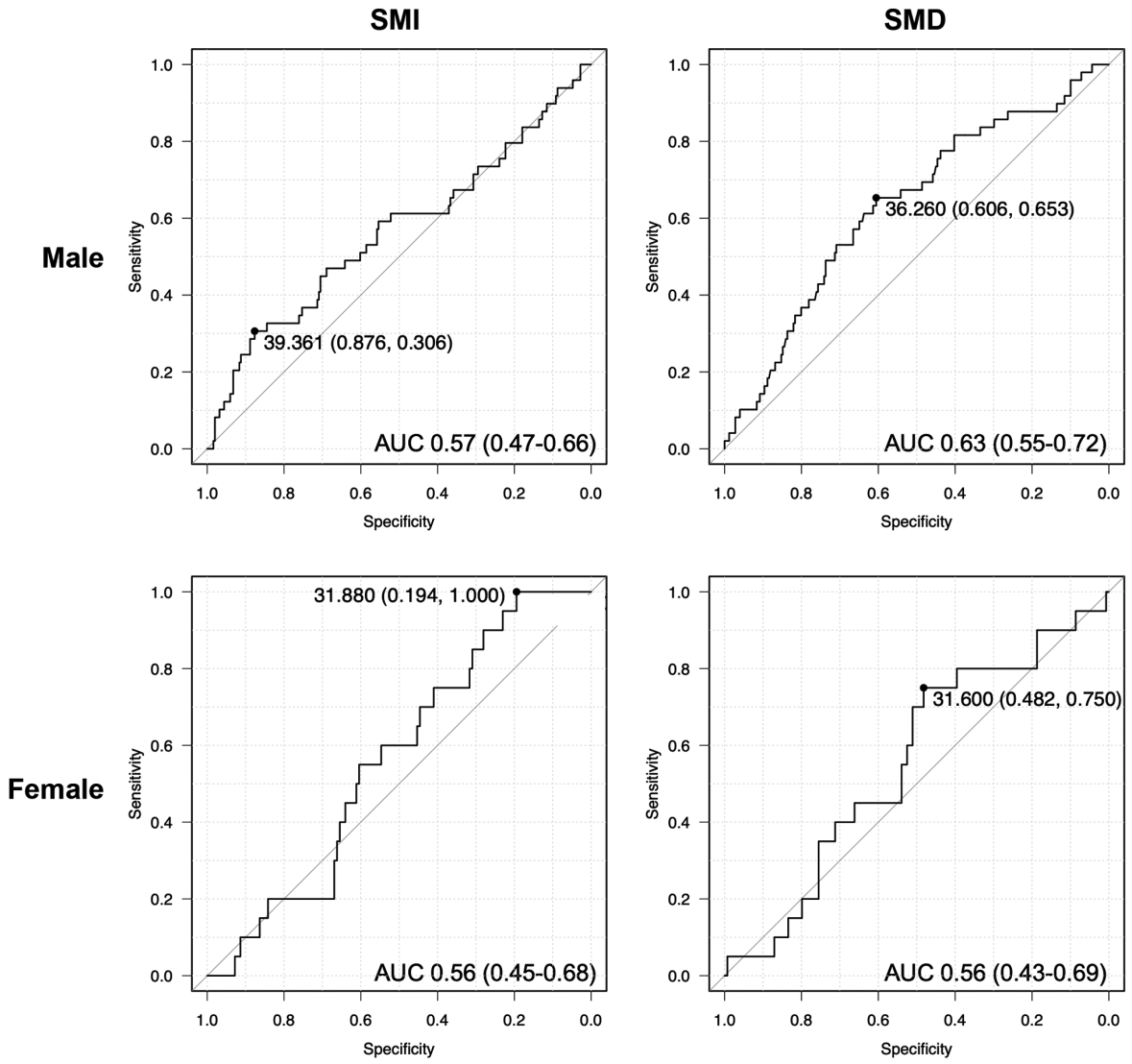

Figure 2. Receiver operating characteristic curve analysis defining the cutoff value for survival prediction using SMI and SMD. SMI, skeletal muscle index; SMD, skeletal muscle density.

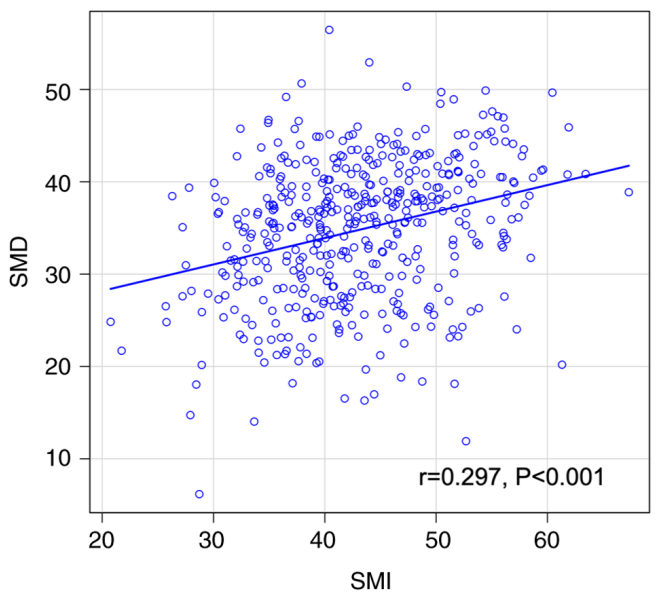

Figure 3. Scatter plot of the correlation between SMI and SMD. SMI, skeletal muscle index; SMD, skeletal muscle density.

OS and RFS based on SMI and SMD after gastrectomy. OS rates were notably lower in the low-SMI group than in the high-SMI group; however, the difference was not significant (79.1% vs. 87.8%, respectively; P=0.06; Fig. 4A). However, OS rates were significantly lower in the low-SMD group than in the high-SMD group (83.4% vs. 88.8%, respectively; P=0.04; Fig. 4B). There was no significant difference in RFS rates between the high- and low-SMI groups (77.8% vs. 85.5%, respectively; P=0.11; Fig. 5A). However, RFS rates were significantly lower in the low-SMD group than in the high-SMD group (80.5% vs. 87.2%, respectively; P=0.02; Fig. 5B).

Combined analysis of SMI and SMD. Both OS and RFS rates were significantly lower in Group 3 compared with Groups 2 and 1 (OS, 72.3% vs. 86.9% vs. 88.7%, respectively; P=0.006; Fig. 6A and RFS, 70.2% vs. 84.3% vs. 87.0%, respectively; P=0.006; Fig. 6B).

Comparison of the association between clinicopathologic factors and SMI and SMD between groups. Table I presents the clinicopathologic factors and SMI and SMD between groups.

Table I. Association between clinicopathological factors and the combination of computed tomography-derived skeletal muscle index and radiodensity.

Variable	Group 1 (n=226)	Group 2 (n=188)	Group 3 (n=45)	P-value
Age				<0.001
<65 years	100 (44.2)	33 (17.6)	7 (15.6)	
≥65 years	126 (55.8)	155 (82.4)	38 (84.4)	
Sex				0.527
Male	149 (65.9)	125 (66.5)	26 (57.8)	
Female	77 (34.1)	63 (33.5)	19 (42.2)	
BMI				<0.001
<18.5 kg/m^2	24 (10.6)	12 (6.4)	11 (24.4)	
≤18.5, <25.0 kg/m^2	159 (70.4)	119 (63.3)	33 (73.3)	
≥25 kg/m^2	43 (19.0)	57 (30.3)	1 (2.2)	
Pre Alb, median (SD)	4.2 (0.3)	4.0 (0.4)[a]	4.0 (0.4)[a]	<0.001
Pre PNI, median (SD)	50.5 (4.7)	48.7 (5.0)[a]	47.3 (4.8)[a]	<0.001
Pre NLR, median (SD)	2.0 (1.2)	2.0 (1.8)	2.3 (1.6)	0.067
Pre CRP, median (SD)	0.06 (0.16)	0.09 (0.21)[a]	0.10 (0.37)	0.006
Total gastrectomy				0.177
No	180 (79.6)	135 (71.8)	34 (75.6)	
Yes	46 (20.4)	53 (28.2)	11 (24.4)	
Tumor size				0.032
≤30 mm	125 (55.3)	84 (44.7)	28 (62.2)	
>30 mm	101 (44.7)	104 (55.3)	17 (37.8)	
Histological type				<0.001
Well moderate	93 (41.2)	113 (60.1)	20 (44.4)	
Poorly	133 (58.8)	75 (39.9)	25 (55.6)	
Lymphatic invasion				0.340
No	163 (72.1)	124 (66.0)	33 (73.3)	
Yes	63 (27.9)	64 (34.0)	12 (26.7)	
Venous invasion				0.340
No	140 (61.9)	108 (57.4)	23 (51.1)	
Yes	86 (38.1)	80 (42.6)	22 (48.9)	
pStage				0.874
I	158 (69.9)	128 (68.1)	30 (66.7)	
II/III	68 (30.1)	60 (31.9)	15 (33.3)	
Surgical complications				0.430
No	195 (86.3)	153 (81.8)	38 (86.4)	
Yes	31 (13.7)	34 (18.2)	6 (13.6)	

[a]Steel-Dwass test: P<0.05 (reference: Group 1). Pre Alb, preoperative albumin; BMI, body mass index; pre NLR, preoperative neutrophil-lymphocyte ratio; pre PNI, preoperative prognostic nutritional index; pre CRP, preoperative C-reactive protein; pStage, pathological stage; SD, standard deviation.

The results revealed that patients in Group 3 were significantly older (P<0.001), had a significantly lower body mass index (BMI; P<0.001), significantly lower preoperative albumin levels (P<0.001), significantly lower preoperative Prognostic Nutritional Index (PNI) values (P<0.001), and significantly worse histological type (P<0.001) than those in Groups 1 and 2.

Univariate and multivariate analysis of OS and RFS. Multivariate analyses for OS demonstrated that PNI <40 [Hazard Ratio (HR), 2.22; 95% CI, 1.03-4.76; P=0.041], pStage II-III (HR, 2.56; 95% CI, 1.35-4.84; P=0.004) and low SMI and SMD (Group 3; HR, 2.32; 95% CI, 1.17-4.59; P=0.016) were independent prognostic factors (Table II). Multivariate analyses for RFS demonstrated that PNI <40 (HR, 2.63; 95% CI, 1.27-5.56; P=0.010), lymphatic invasion (HR, 2.01; 95% CI, 1.20-3.39; P=0.009), pStage II-III (HR, 2.40; 95% CI, 1.33-4.33; P=0.004) and low SMI and SMD (Group 3; HR, 2.28; 95% CI, 1.19-4.37; P=0.013) were independent prognostic factors (Table III).

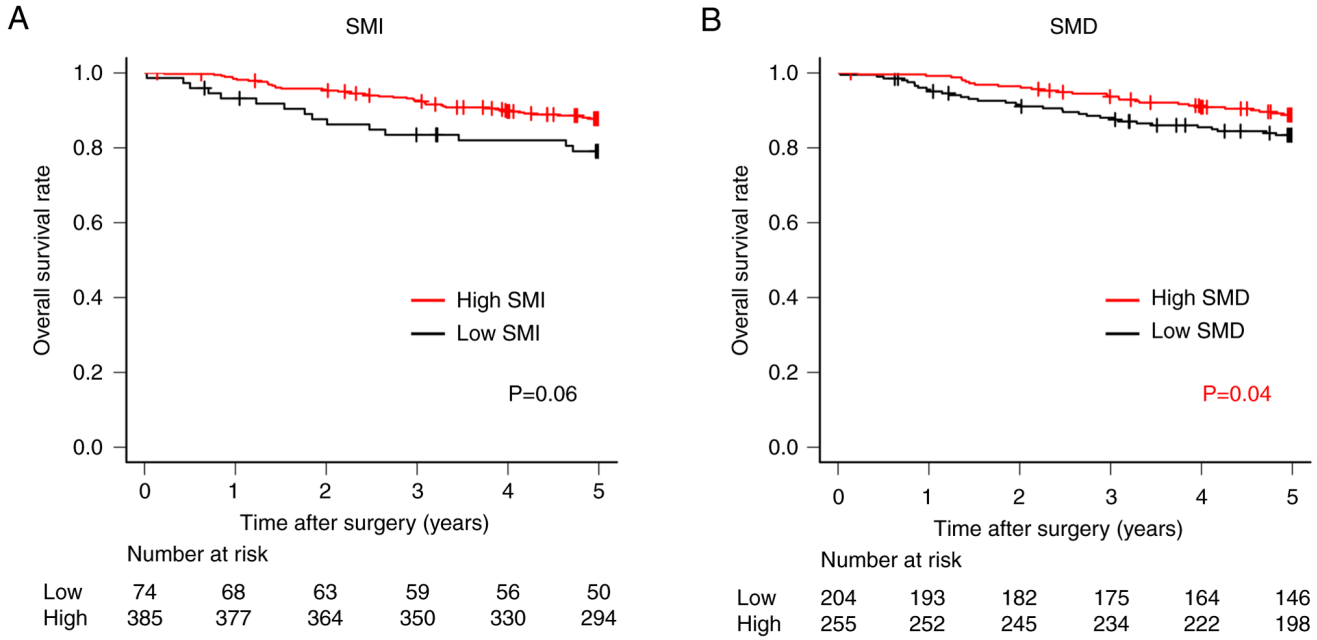

Figure 4. Kaplan-Meier plot demonstrating overall survival according to (A) SMI and (B) SMD. The OS of the low-SMD group was significantly poorer compared with that of the high-SMD group. SMI, skeletal muscle index; SMD, skeletal muscle density.

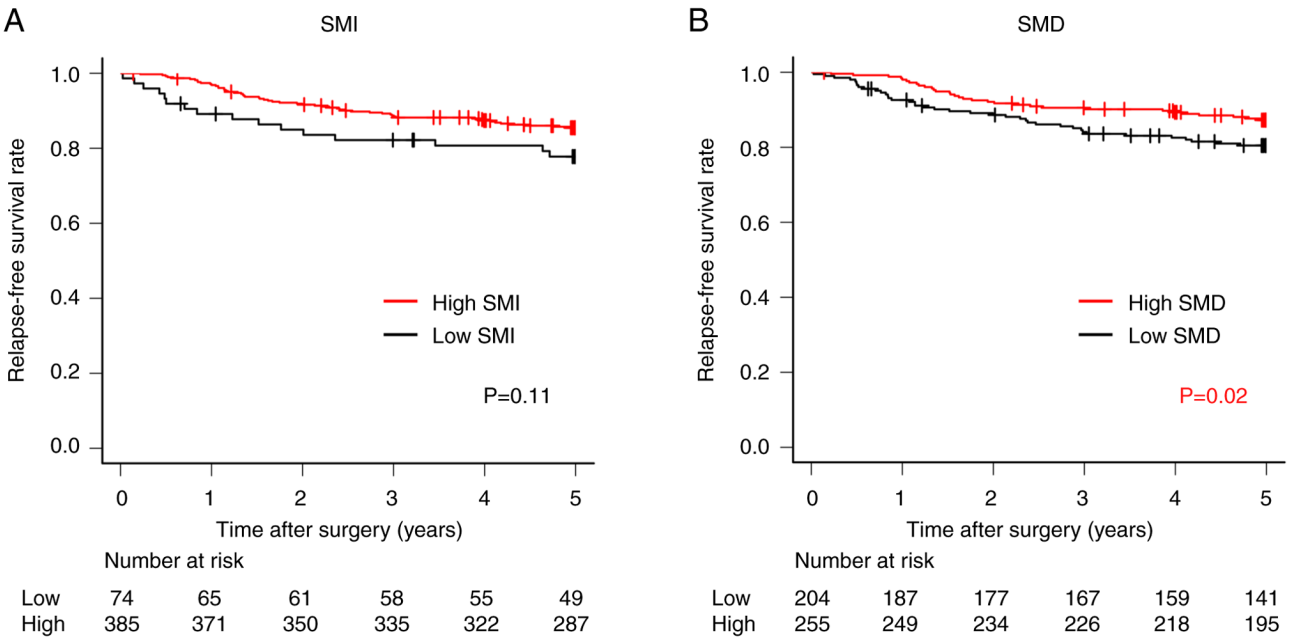

Figure 5. Kaplan-Meier plot demonstrating relapse-free survival according to (A) SMI and (B) SMD. The RFS of the low-SMD group was significantly poorer compared with that of the high-SMD group. SMI, skeletal muscle index; SMD, skeletal muscle density.

Comparison of causes of death between groups of SMI and SMD. Group 3 had significantly more intercurrent disease death than Groups 2 and 1 (P=0.002; Table IV).

Discussion

The purpose of the present study was to assess the clinical impact of preoperative SMI and SMD on long-term survival outcomes of patients with GC. SMI and SMD were quantified using CT and their impact on 5-year OS and 5-year RFS was evaluated. The findings revealed that patients in Group 3 (low SMI and SMD group) had significantly lower 5-year OS and RFS rates than those in Group 2 (high SMI or SMD group) and Group 1 (high SMI and SMD group). Additionally, the combination of low SMI and low SMD was identified as an independent predictor of lower 5-year OS and RFS rates.

The significance of assessing the combination of SMI and SMD lies in the ability of these parameters to provide a more comprehensive assessment of sarcopenia in patients with cancer, where SMI and SMD reflect muscle mass and muscle function, respectively (4,19-21). Sarcopenia is associated with

Table II. Univariate and multivariate analyses of clinicopathological factors and the combination of computed tomography-derived skeletal muscle index and radiodensity for overall survival.

	Univariate			Multivariate		
Factor	HR	95% CI	P-value	HR	95% CI	P-value
Age						
≥65 years	1			1		
≥65 years	2.05	1.12-3.74	0.020	1.76	0.93-3.33	0.080
Sex						
Male	1					
Female	0.77	0.46-1.30	0.325			
BMI						
<18.5 kg/m^2	1					
≤18.5, <25.0 kg/m^2	0.68	0.33-1.39	0.287			
≥25 kg/m^2	0.87	0.39-1.94	0.733			
PNI						
≥40	1			1		
<40	4.35	2.04-9.09	<0.001	2.22	1.03-4.76	0.041
Total gastrectomy						
No	1			1		
Yes	2.17	1.34-3.52	0.002	1.65	0.99-2.75	0.052
Tumor size						
≤30 mm	1			1		
>30 mm	1.97	1.21-3.22	0.007	0.93	0.52-1.63	0.790
Histological type						
Well/moderate	1					
Poorly	1.16	0.72-1.86	0.548			
Lymphatic invasion						
No	1			1		
Yes	3.39	2.10-5.46	<0.001	1.72	0.99-2.99	0.054
Venous invasion						
No	1			1		
Yes	3.92	2.33-6.60	<0.001	1.75	0.94-3.25	0.075
pStage						
I	1			1		
II-III	4.66	2.84-7.66	<0.001	2.56	1.35-4.84	0.004
Surgical complications						
No	1					
Yes	0.76	0.37-1.53	0.435			
Combination of SMI and SMD						
Group 1	1			1		
Group 2	1.24	0.73-2.09	0.426	0.90	0.52-1.56	0.700
Group 3	2.80	1.45-5.41	0.002	2.32	1.17-4.59	0.016

BMI, body mass index; CI, confidence interval; HR, hazard ratio; pStage, pathological stage; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.

poor prognosis (22,23) and a high risk of cancer (24-27). Although the association between low SMI and poor prognosis in patients with GC is well known (24,25), the clinical significance of low SMD has been inadequately explored, despite studies linking it with a poor prognosis (26,27). Furthermore, the combined evaluation of SMI and SMD has demonstrated prognostic significance in patients with colorectal cancer (28). Low SMI is a recognized hallmark of sarcopenia (11), whereas low SMD indicates adiposity and muscle fibrosis, signifying reduced muscle quality and function (29,30). Decreased

Table III. Univariate and multivariate analyses of clinicopathological factors and the combination of computed tomography-derived skeletal muscle index and radiodensity for relapse free survival.

	Univariate			Multivariate		
Factor	HR	95% CI	P-value	HR	95% CI	P-value
Age						
<65 years	1			1		
≥65 years	1.85	1.07-3.20	0.028	1.50	0.84-2.70	0.170
Sex						
Male	1					
Female	0.83	0.52-1.35	0.453			
BMI						
<18.5 kg/m^2	1					
≤18.5-25.0 kg/m^2	0.66	0.34-1.31	0.239			
≥25 kg/m^2	0.94	0.45-1.99	0.877			
PNI						
≥40	1			1		
<40	4.55	2.27-9.09	<0.001	2.63	1.27-5.56	0.010
Total gastrectomy						
No	1			1		
Yes	1.93	1.22-3.06	0.005	1.50	0.93-2.42	0.097
Tumor size						
≤30 mm	1			1		
>30 mm	2.06	1.30-3.27	0.002	1.03	0.60-1.75	0.920
Histological type						
Well/moderate	1					
Poorly	1.19	0.77-1.86	0.434			
Lymphatic invasion						
No	1			1		
Yes	3.45	2.21-5.39	<0.001	2.01	1.20-3.39	0.009
Venous invasion						
No	1			1		
Yes	2.94	1.85-4.66	<0.001	1.25	0.71-2.19	0.430
pStage						
I	1			1		
II-III	4.21	2.67-6.64	<0.001	2.40	1.33-4.33	0.004
Surgical complications						
No	1					
Yes	0.92	0.50-1.71	0.801			
Combination of SMI and SMD						
Group 1	1			1		
Group 2	1.26	0.77-2.05	0.352	0.91	0.55-1.52	0.720
Group 3	2.68	1.43-5.03	0.002	2.28	1.19-4.37	0.013

BMI, body mass index; CI, confidence interval; HR, hazard ratio; pStage, pathological stage; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.

muscle quality and function are caused by aging (31), inflammation (30,32) and malnutrition (33), all of which are poor prognostic indicators in patients with cancer (34,35). Furthermore, the combined evaluation of SMI and SMD allows for the detection of patients with a poor prognosis preoperatively. The findings of the present study indicate that patients with low SMI and SMD are often older, have a lower BMI and exhibit lower PNI values. Although these patients are more likely to die from other causes, perioperative rehabilitation (36), enhanced nutritional support (36) and proactive

Table IV. Association between the cause of death and the combination of computed tomography-derived skeletal muscle mass and radiodensity.

Event	Group 1 (n=226)	Group 2 (n=188)	Group 3 (n=45)	P-value
Gastric cancer-specific death	18 (8.0)	14 (7.4)	4 (8.9)	0.945
Intercurrent disease death	11 (4.9)	15 (8.0)	9 (20.0)	0.002

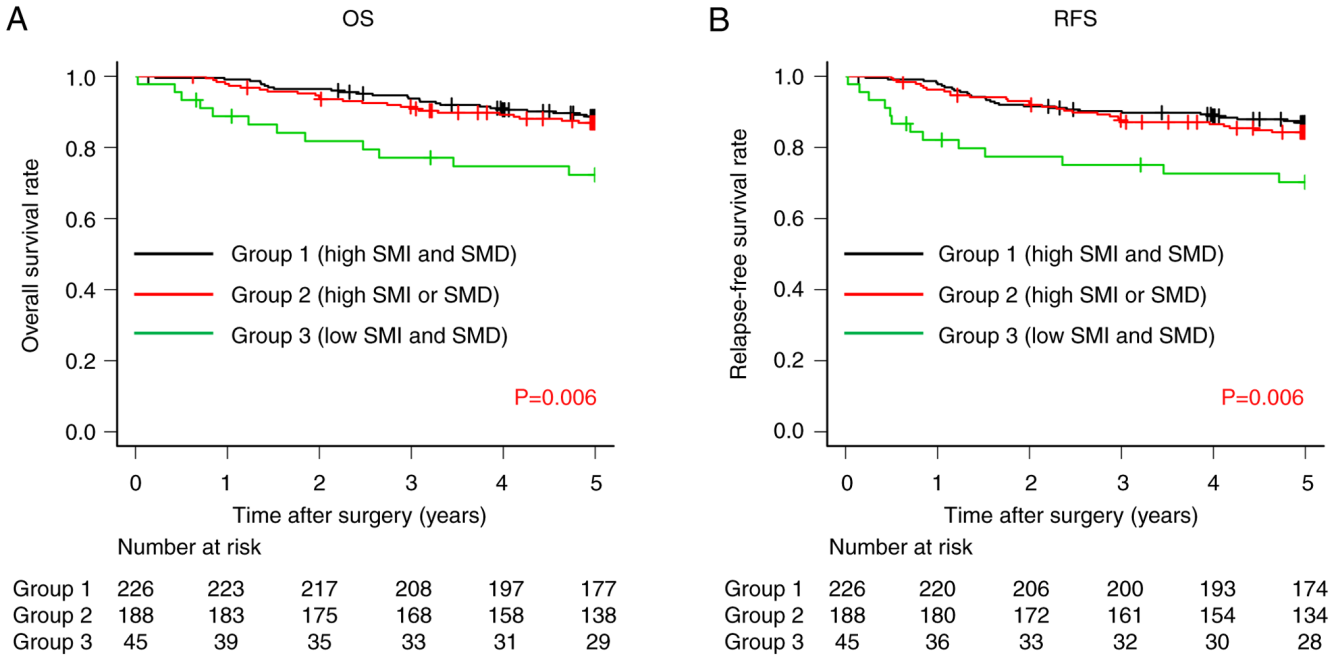

Figure 6. Kaplan-Meier plot demonstrating (A) OS and (B) RFS based on the combined assessment of SMI and SMD. The OS and RFS of Group 3 were significantly poorer compared with Group 2 and Group 1. OS, overall survival; RFS, recurrence-free survival; SMI, skeletal muscle index; SMD, skeletal muscle density.

management of comorbidities (37) have shown promise in improving prognosis.

Nonetheless, the present study had certain limitations. First, it was a single-center retrospective study with a limited sample size. Thus, further validation through a multicenter study is required. Moreover, although SMI and SMD have been reported as prognostic factors of patients with cancer (13,14), there is no consensus on how to determine cutoff values; thus, this requires further investigation.

In conclusion, the results of the present study indicate the potential of the combined evaluation of preoperative SMI and SMD as a significant prognostic indicator after gastrectomy in patients with GC. Incorporating this index into preoperative screening and implementing interventions such as intensified nutritional support and comorbidity management based on it may offer opportunities to enhance patient outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

IH and TOs had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analysis. IH and TOs confirm the authenticity of all the raw data. IH, KK, YM, SN, TK, TA, TH, TYa, TS, TOg, HC, TYo, NY, YR, AS and TOs conceptualized and designed the study. IH, KK, YM, SN, TK, TA, TH, TYa, TS, TOg, HC, TYo, NY, YR, AS and TOs collected the data and performed the literature search. IH and TOs prepared the draft manuscript and figures. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Kanagawa Cancer Center (Yokohama, Japan; approval no. 25 Research-20). Written informed consent was obtained from all patients in the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declared that they have no competing interests.

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