



Prevalence and associated risk of advanced colorectal neoplasia in adults with sarcopenia

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Patients



First time
colonoscopy



Bioelectrical impedance
analysis (BIA)

10,676 Adults



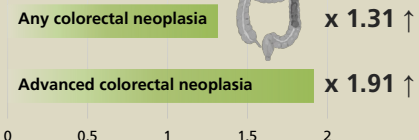
Normal
(10,093)



Sarcopenia
(583)

Results

Sarcopenia



Conclusion



Sarcopenia was a significant risk factor for colorectal neoplasia, especially for advanced colorectal neoplasia.

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Background/Aims: Although several studies have shown that sarcopenia is associated with poor outcomes in colorectal cancer patients, the impact of sarcopenia on the development of colorectal neoplasia remains unclear. We aimed to evaluate the prevalence and association of colorectal neoplasia, especially advanced colorectal neoplasia, in adults with sarcopenia.

Methods: We retrospectively analyzed the data for 10,676 adults who underwent first-time colonoscopy and bioelectrical impedance analysis (BIA) on the same day in a health screening program at a single center. Sarcopenia was diagnosed using established BIA-based criteria as adjusted appendicular skeletal muscle mass (ASM) divided by body mass index (BMI) (ASM/BMI), height (ASM/height²), or weight (ASM/weight). Prevalence of overall and advanced colorectal neoplasia and their association with sarcopenia, as established by the aforementioned diagnostic criteria, were evaluated.

Results: Among 10,676 subjects, 583 were diagnosed with sarcopenia using ASM/BMI. Subjects with sarcopenia had a higher prevalence of colorectal neoplasia than those without. In the multivariate analysis after adjusting for confounding factors, sarcopenia was an independent risk factor for any colorectal neoplasia (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.09 to 1.56) and advanced colorectal neoplasia (OR, 1.97; 95% CI, 1.27 to 3.06). The association between sarcopenia and advanced colorectal neoplasia remained significant for all sarcopenia measures including ASM/height² (OR, 2.19; 95% CI, 1.24 to 3.85) and ASM/weight (OR, 2.41; 95% CI, 1.54 to 3.77).

Conclusions: Prevalence of overall and advanced colorectal neoplasia was higher in subjects with sarcopenia than in those without. Sarcopenia was a significant risk factor for colorectal neoplasia, especially for advanced colorectal neoplasia.

Keywords: Sarcopenia; Colorectal neoplasms; Prevalence; Colonoscopy

INTRODUCTION

Colorectal cancer (CRC) is the fourth most commonly diagnosed malignancy and the second leading cause of cancer-related death worldwide [1]. The global burden of CRC has been increasing rapidly due to population growth, changes in demographics, and transition to more westernized lifestyles [2,3]. Since the majority of CRC cases develop from colorectal adenoma, the early detection and removal of colorectal adenoma has been considered the most effective strategy for reducing CRC incidence and related mortality [4]. In addition to genetic factors, the development of colorectal neoplasia is reportedly associated with environmental factors including physical activity, dietary habits, smoking, and alcoholic consumption [5,6]. Moreover, factors associated with the development of metabolic syndrome including obesity, dyslipidemia, impaired glucose tolerance, and insulin resistance have been reported as potential risk factors for colorectal neoplasia [7-10].

Recent studies have reported that sarcopenia, which is the loss of skeletal muscle mass and strength, may be one of the risk factors for poor outcomes in several chronic disorders [11-16]. This could be related to a prolonged catabolic state associated with immune dysfunction and systemic inflammatory response in the host [11,17,18]. Several studies have

also reported that sarcopenia is associated with metabolic syndrome, diabetes mellitus (DM), and non-alcoholic fatty liver disease, which are risk factors for colorectal neoplasia [14-16]. Although this suggests that colorectal neoplasia and sarcopenia may have similar pathophysiological mechanisms, studies on the association between the risk of colorectal neoplasia and sarcopenia are still lacking.

Various tools, with different criteria even for the same tool, are utilized for measuring muscle mass in studies. Among these, the bioelectrical impedance analysis (BIA), using a non-invasive body composition analyzer, is a convenient and cost-effective tool for the evaluation of lean body mass. Recent studies have also reported its use for the assessment of skeletal muscle mass and a conclusive diagnosis of sarcopenia [19,20]. We aimed to investigate the association between sarcopenia, as indicated by three currently accepted diagnostic criteria, and the risk of colorectal neoplasia, especially advanced neoplasia, in a large sample of asymptomatic, average-risk population.

METHODS

Study subjects and design

We reviewed the clinical data of 11,642 adults (≥ 18 years)

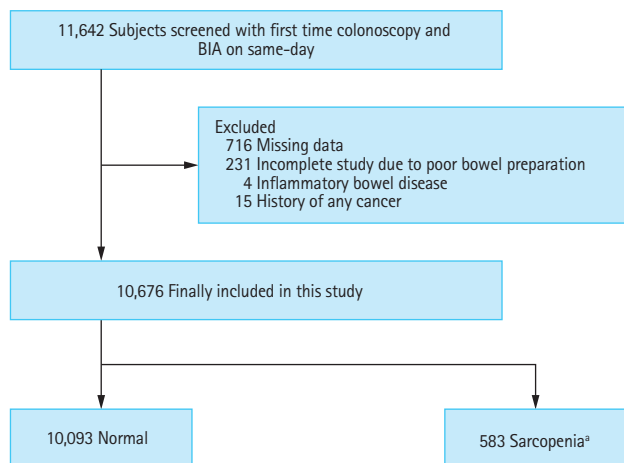


Figure 1. Flow diagram for the selection of study subjects. BIA, bioelectrical impedance analysis. ^aWhen sarcopenia was defined using body mass index-adjusted appendicular skeletal muscular mass model, one of the three established BIA-based diagnostic criteria in defining sarcopenia.

who underwent their first colonoscopy screening and BIA on the same day during a health screening program at Yeungnam University Medical Center from June 2009 to June 2017. Subjects were excluded if they met any of the following criteria: missing data (n = 716); incomplete colonoscopy due to poor bowel preparation (n = 231); inflammatory bowel disease such as Crohn’s disease and ulcerative colitis (n = 4); and previous history of any type of cancer (n = 15). Finally, 10,676 subjects were included in this analysis and divided into two groups according to the presence of sarcopenia, based on three diagnostic criteria (Fig. 1). We first investigated the difference in the prevalence of colorectal neoplasia stratified according to the presence of sarcopenia. Next, we evaluated the association between sarcopenia and the risk of colorectal neoplasia after adjusting for potential confounding factors. Furthermore, our analysis included the risk of advanced colorectal neoplasia and multiple colorectal neoplasia. This study was approved by the Institutional Review Board of Yeungnam University Medical Center, and the requirement of consent was waived due to its retrospective study design (YUMC-2020-08-021).

Clinical data and laboratory evaluations

During the health screening program, the height, weight, waist circumference, and blood pressure (BP) of the subjects

were measured by trained nurses. Data on smoking status, alcohol consumption, personal medical history, and medication use were collected using a self-administered questionnaire. The subject’s smoking status was categorized as never, former, or current smoker. Alcohol consumption was calculated using the number of drinks consumed multiplied by the frequency, and ≥ 210 g/week for men and ≥ 140 g/week for women were defined as excessive drinking.

A blood sample was collected in the morning after at least 10 hours of fasting. This was analyzed by trained staff in the hospital’s clinical laboratory for parameters including complete blood count, blood chemistry, glucose level, and lipid profile. Body mass index (BMI) was calculated by dividing the weight (kg) by the height squared (m²), and obesity was defined as a BMI ≥ 25 kg/m², according to the criteria for the Asia-Pacific region. Visceral obesity was defined based on waist circumference (≥ 90 cm in men and ≥ 80 cm in women based on ethnicity-specific values). Hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or a history of disease/medication use. DM was defined as a fasting glucose level ≥ 126 mg/dL or glycated hemoglobin level $\geq 6.5\%$ or a history of disease/medication use. Hyperlipidemia was defined as a serum triglyceride level ≥ 150 mg/dL or serum cholesterol level ≥ 200 mg/dL or a history of disease/medication use. Metabolic syndrome was defined in accordance with the International Diabetes Federation criteria as central (visceral) obesity plus any two of the following four factors: increased triglyceride level (≥ 150 mg/dL) or specific treatment for this lipid abnormality; reduced high-density lipoprotein cholesterol level (< 40 mg/dL in men and < 50 mg/dL in women) or receiving specific treatment for this lipid abnormality; systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension; and an increased fasting plasma glucose level (≥ 100 mg/dL) or a previous diagnosis of type 2 DM.

Colonoscopy procedure and colorectal neoplasia

Colonoscopies were performed by five faculties from the gastroenterology department in Yeungnam University Medical Center, each with at least 5 years of experience after board certification for gastrointestinal endoscopy. This procedure was done using a conventional colonoscope (CV-160 Evis EXTRA and CV-180 Evis EXTRA II, Olympus, Tokyo,

Japan) after bowel preparation. All specimens of colorectal neoplasia were histologically assessed by two experienced board-certified pathologists. We investigated the following in the medical record: (1) complete colonoscopy examination; (2) status of bowel preparation; (3) size, location, and number of colorectal neoplasia; and (4) histopathology of colorectal neoplasia. Overall colorectal neoplasia was defined as cancer or any adenoma (tubular, tubulovillous, villous, and serrated adenoma), and advanced colorectal neoplasia was defined as cancer or advanced adenoma. Advanced adenoma was defined as an adenoma with a diameter ≥ 10 mm, high grade dysplasia, or $> 25\%$ villous component. Multiple colorectal neoplasia was defined as the presence of more than three colorectal neoplasia.

Measurement of appendicular skeletal muscle mass and definition of sarcopenia

BIA was performed to measure the appendicular skeletal muscle mass (ASM) using Inbody 720 (Biospace, Seoul, Korea), a non-invasive body composition analyzer, by well-trained staff on the same day as the colonoscopy procedure. ASM was calculated as the sum of lean muscle mass in the bilateral upper and lower extremities. In this study, sarcopenia was defined using the following three formulas, all of which have been previously reported as validated measures of sarcopenia. (1) BMI-adjusted ASM was defined as ASM divided by BMI (ASM/BMI); as suggested by the Foundation for the National Institutes of Health, sarcopenia was defined in terms of ASM/BMI using cutoffs of < 0.789 for men and < 0.512 for women [21]. (2) Height-adjusted ASM was defined as ASM divided by height in meters squared (ASM/height², kg/m²); as suggested by the Consensus Report of the Asian Working Group for Sarcopenia, sarcopenia was defined in terms of ASM/height² using cutoffs of < 6.75 kg/m² for men and < 5.07 kg/m² for women, which are more than two standard deviations for sex-specific values in young healthy adults [22]. (3) Weight-adjusted ASM was defined as ASM divided by body weight (ASM/weight, %); sarcopenia was defined in terms of ASM/weight with cutoffs of $< 29.1\%$ for men and $< 23.0\%$ for women, which are more than two standard deviations for sex-specific values in young healthy adults, according to the national health examination in Korea [23].

Statistical analysis

Continuous and categorical variables were expressed as

mean \pm standard deviation and number (%), respectively. The characteristics of the study subjects were analyzed based on sarcopenia status using the Student's *t* test for continuous variables and the chi-square test for categorical variables. The association between sarcopenia and colorectal neoplasia was assessed using logistic regression analysis. Three models with increasing levels of adjustment to account for potential confounding factors were used to determine risk factors for any colorectal neoplasm, advanced neoplasm, and multiple polyps. Model 1 was adjusted for age and sex. Model 2 was further adjusted for current smoking status, excessive alcohol intake, obesity, and visceral obesity. Model 3 was additionally adjusted for hypertension, DM, dyslipidemia, and metabolic syndrome. The odds ratio was considered to be statistically significant if the 95% confidence interval did not include 1.0. Statistical analysis was performed using SPSS version 25.0 (IBM Co., Armonk, NY, USA), and the level of statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics of study subjects

Of the 10,676 subjects enrolled in this study, 583 (5.5%), 297 (2.8%) and 685 (6.4%) subjects had sarcopenia defined by the BMI-adjusted, height-adjusted, and weight-adjusted ASM models, respectively. Of these subjects with sarcopenia, 35 subjects met all three BIA-based criteria, 358 subjects met two of three BIA-based criteria, and 744 subjects met only one BIA-based criterion. The baseline characteristics of the subjects according to sarcopenia defined using the three BIA-based diagnostic criteria are shown in Table 1. Subjects with sarcopenia defined using the BMI-adjusted ASM model were older (56.3 ± 10.8 vs. 48.7 ± 10.3 , $p < 0.001$), predominantly male (79.2% vs. 62.0%, $p < 0.001$), and had a higher BMI (26.9 ± 3.6 vs. 24.0 ± 2.9 , $p < 0.001$) and waist circumference (92.1 ± 9.9 vs. 85.6 ± 8.4 , $p < 0.001$) than those without sarcopenia. The prevalence of hypertension (46.7% vs. 23.9%, $p < 0.001$), DM (18.4% vs. 4.7%, $p < 0.001$), dyslipidemia (68.3% vs. 60.4%, $p < 0.001$), and metabolic syndrome (35.7% vs. 18.5%, $p < 0.001$) was higher in subjects with sarcopenia defined using the BMI-adjusted ASM model than in those without sarcopenia. Subjects with sarcopenia defined using weight adjusted ASM model had a similar tendency. However, BMI

Table 1. Baseline characteristics according to sarcopenia defined using the three bioelectrical impedance analysis-based diagnostic criteria

Variable	BMI adjusted ASM model			Height adjusted ASM model			Weight adjusted ASM model		
	Normal (n = 10,093)	Sarcopenia (n = 583)	p value	Normal (n = 10,379)	Sarcopenia (n = 297)	p value	Normal (n = 9,991)	Sarcopenia (n = 685)	p value
Age, yr	48.7 ± 10.3	56.3 ± 10.8	< 0.001	49.0 ± 10.4	54.1 ± 12.0	< 0.001	49.0 ± 10.3	51.9 ± 12.4	< 0.001
≥ 50 years	4,863 (48.2)	431 (73.9)	< 0.001	5,097 (49.1)	197 (66.3)	< 0.001	4,887 (48.9)	407 (59.4)	< 0.001
Male sex	6,253 (62.0)	462 (79.2)	< 0.001	6,493 (62.6)	222 (74.7)	< 0.001	6,181 (61.9)	534 (78.8)	< 0.001
Height, cm	166.4 ± 8.3	158.8 ± 7.0	< 0.001	166.1 ± 8.5	162.6 ± 7.2	< 0.001	166.2 ± 8.4	164.1 ± 9.1	0.210
Weight, kg	66.8 ± 11.7	68.2 ± 12.2	0.004	67.3 ± 11.6	52.5 ± 6.9	0.004	66.1 ± 11.2	77.7 ± 14.3	< 0.001
BMI, kg/m ²	24.0 ± 2.9	26.9 ± 3.6	< 0.001	24.3 ± 3.0	19.9 ± 2.2	< 0.001	23.8 ± 2.8	28.6 ± 3.4	< 0.001
Obesity	3,510 (34.8)	395 (67.8)	< 0.001	3,900 (37.6)	5 (1.7)	< 0.001	3,313 (33.2)	592 (86.4)	< 0.001
Waist circumference, cm	85.6 ± 8.4	92.1 ± 9.9	< 0.001	86.2 ± 8.5	77.0 ± 7.4	< 0.001	85.0 ± 7.8	98.9 ± 9.7	< 0.001
Visceral obesity	4,470 (44.3)	351 (60.2)	< 0.001	4,806 (46.3)	15 (5.1)	< 0.001	4,214 (42.2)	607 (88.6)	< 0.001
ASM, kg	20.6 ± 4.6	18.5 ± 3.6	< 0.001	20.6 ± 4.5	16.2 ± 3.0	< 0.001	20.4 ± 4.5	20.8 ± 4.8	0.331
Current smoking	1,073 (10.6)	62 (10.6)	0.998	1,089 (10.5)	46 (15.5)	0.006	1,053 (10.5)	603 (12.0)	0.240
Excessive alcohol intake	604 (6.0)	40 (6.9)	0.387	624 (6.0)	20 (6.7)	0.606	592 (5.9)	52 (7.6)	0.076
Hypertension	2,411 (23.9)	272 (46.7)	< 0.001	2,602 (25.1)	81 (27.3)	0.388	2,351 (23.5)	332 (48.5)	< 0.001
Anti-hypertensive medication	682 (6.8)	87 (14.9)	< 0.001	745 (7.2)	24 (8.1)	0.553	667 (6.7)	102 (14.9)	< 0.001
Diabetes mellitus	892 (8.8)	107 (18.4)	< 0.001	957 (9.2)	42 (14.1)	0.004	879 (8.8)	120 (17.5)	< 0.001
Fasting glucose, mg/dL	93.7 ± 20.8	100.5 ± 24.1	< 0.001	94.11 ± 20.9	93.8 ± 26.6	< 0.001	93.6 ± 20.5	102.1 ± 27.1	< 0.001
HbA1c, %	5.7 ± 0.8	6.0 ± 0.9	< 0.001	5.7 ± 0.8	5.8 ± 1.1	< 0.001	5.7 ± 0.8	6.0 ± 1.0	< 0.001
Anti-diabetic medication	278 (2.8)	26 (4.5)	0.016	288 (2.8)	16 (5.4)	0.008	275 (2.8)	29 (4.2)	0.024
Dyslipidemia	6,099 (60.4)	398 (68.3)	< 0.001	6,332 (61.0)	165 (55.6)	0.058	6,000 (60.1)	497 (72.6)	< 0.001
Total cholesterol, mg/dL	204.4 ± 38.2	207.5 ± 40.9	0.075	204.6 ± 38.3	201.4 ± 40.0	0.476	204.2 ± 38.2	210.1 ± 39.8	0.696
Triglycerides, mg/dL	114.4 ± 83.7	143.4 ± 95.6	< 0.001	116.3 ± 85.0	103.5 ± 72.2	0.013	113.1 ± 82.5	157.2 ± 102.8	< 0.001
HDL-C, mg/dL	56.9 ± 15.2	51.6 ± 12.5	< 0.001	56.4 ± 15.1	61.1 ± 15.5	0.205	57.0 ± 15.2	50.7 ± 12.4	< 0.001
Anti-dyslipidemic medication	82 (0.8)	7 (1.2)	0.341	89 (0.9)	0	0.182	79 (0.8)	10 (1.5)	0.062
Metabolic syndrome	1,864 (18.5)	208 (35.7)	< 0.001	2,061 (19.9)	11 (3.7)	< 0.001	1,708 (17.1)	364 (53.1)	< 0.001

Values are presented as mean ± standard deviation or number (%).

BMI, body mass index; ASM, appendicular skeletal muscular mass; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol.

Table 2. The prevalence of colorectal neoplasia according to sarcopenia

Variable	BMI adjusted ASM model			Height adjusted ASM model			Weight adjusted ASM model		
	Normal (n = 10,093)	Sarcopenia (n = 583)	p value	Normal (n = 10,397)	Sarcopenia (n = 279)	p value	Normal (n = 9,991)	Sarcopenia (n = 685)	p value
Any colorectal neoplasia	2,808 (27.8)	246 (42.2)	< 0.001	2,949 (28.4)	105 (35.4)	0.009	2,792 (27.9)	262 (38.2)	< 0.001
Advanced colorectal neoplasia	164 (1.6)	25 (4.3)	< 0.001	175 (1.7)	14 (4.7)	< 0.001	162 (1.6)	27 (3.9)	< 0.001
Advanced adenoma	151 (1.5)	25 (4.3)	< 0.001	162 (1.6)	14 (4.7)	< 0.001	149 (1.5)	27 (3.9)	< 0.001
≥ 10 mm	114 (1.1)	18 (3.1)	< 0.001	120 (1.2)	12 (4.0)	< 0.001	110 (1.1)	22 (3.2)	< 0.001
≥ 25% villous component	44 (0.4)	7 (1.2)	0.020	48 (0.5)	3 (1.0)	0.169	43 (0.4)	8 (1.2)	0.015
High grade dysplasia	21 (0.2)	5 (0.9)	0.012	25 (0.2)	1 (0.3)	0.520	22 (0.2)	4 (0.6)	0.082
Adenocarcinoma	17 (0.2)	2 (0.3)	0.278	17 (0.2)	2 (0.7)	0.097	17 (0.2)	2 (0.3)	0.347
Serrated adenoma	74 (0.7)	4 (0.7)	1.000	77 (0.7)	1 (0.3)	0.727	70 (0.7)	8 (1.2)	0.165
Multiple (≥ 3) colorectal neoplasia	458 (4.5)	59 (10.1)	< 0.001	488 (4.7)	29 (9.8)	< 0.001	453 (4.5)	64 (9.3)	< 0.001

Values are presented as number (%).
 BMI, body mass index; ASM, appendicular skeletal muscular mass.

and waist circumference values and the prevalence of metabolic syndrome were lower in subjects with sarcopenia defined using the height-adjusted ASM model than in those without sarcopenia.

Prevalence of colorectal neoplasia stratified by sarcopenia

During the study period, 3,054 (28.6%) subjects were found to have colorectal neoplasia during their first-time colonoscopy. The prevalence of colorectal neoplasia according to sarcopenia based on different diagnostic criteria are shown in Table 2. Subjects with sarcopenia, irrespective of diagnostic criteria, had a significantly higher prevalence of any colorectal neoplasia than the subjects without sarcopenia. The prevalence of advanced colorectal neoplasia and multiple colorectal neoplasia was also significantly higher in subjects with sarcopenia, irrespective of diagnostic criteria, than in those without sarcopenia. However, among subjects with advanced colorectal neoplasia, there was a significant difference in the prevalence of advanced adenoma when subjects were stratified according to the presence of sarcopenia. However, no such difference could be seen for adenocarcinoma.

Association between sarcopenia and risk of colorectal neoplasia

Table 3 shows the association between sarcopenia, as defined by each of the three formulas, and colorectal neoplasia including advanced colorectal neoplasia and multiple colorectal neoplasia after stepwise adjustment for potential confounders and metabolic parameters. Sarcopenia defined using BMI or weight adjusted ASM was associated with a significantly higher risk of any colorectal neoplasia. However, sarcopenia defined using height adjusted ASM was not significantly associated with the risk of overall colorectal neoplasia. For advanced colorectal neoplasia, sarcopenia defined using any of the ASM measures was associated with a higher risk of advanced colorectal neoplasia, and the magnitude of the association was stronger than that with any colorectal neoplasia. These results were consistent even after stepwise adjustment for several confounding factors, and a similar trend was seen for multiple colorectal neoplasia.

Table 3. Risk of colorectal neoplasia, advanced colorectal neoplasia, and multiple colorectal neoplasia according to sarcopenia

	Any colorectal neoplasia		Advanced colorectal neoplasia		Multiple colorectal neoplasia	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
BMI-adjusted ASM^a						
Unadjusted	1.89 (1.60–2.25)	< 0.001	2.71 (1.77–4.17)	< 0.001	2.37 (1.78–3.15)	< 0.001
Model 1	1.38 (1.15–1.64)	< 0.001	2.02 (1.30–3.12)	0.002	1.58 (1.18–2.11)	0.002
Model 2	1.34 (1.12–1.60)	0.001	2.04 (1.32–3.16)	0.001	1.52 (1.13–2.03)	0.005
Model 3	1.31 (1.09–1.56)	0.003	1.97 (1.27–3.06)	0.002	1.49 (1.11–1.99)	0.008
Height-adjusted ASM^a						
Unadjusted	1.38 (1.08–1.76)	0.009	2.89 (1.65–5.04)	< 0.001	2.20 (1.48–3.25)	< 0.001
Model 1	1.08 (0.84–1.38)	0.570	2.28 (1.30–4.00)	0.004	1.57 (1.05–2.35)	0.028
Model 2	1.17 (0.91–1.51)	0.218	2.22 (1.26–3.90)	0.006	1.80 (1.19–2.71)	0.005
Model 3	1.16 (0.90–1.50)	0.254	2.19 (1.24–3.85)	0.007	1.77 (1.17–2.67)	0.007
Weight-adjusted ASM^a						
Unadjusted	1.60 (1.36–1.87)	< 0.001	2.49 (1.64–3.77)	< 0.001	2.17 (1.65–2.85)	< 0.001
Model 1	1.34 (1.14–1.58)	0.001	2.12 (1.40–3.22)	< 0.001	1.77 (1.34–2.34)	< 0.001
Model 2	1.25 (1.06–1.49)	0.009	2.48 (1.59–3.89)	< 0.001	1.60 (1.19–2.14)	0.002
Model 3	1.21 (1.02–1.43)	0.029	2.41 (1.54–3.77)	< 0.001	1.58 (1.18–2.11)	0.002

Model 1: adjusted for age and sex; Model 2: further adjusted for current smoking, excessive alcohol intake, obesity (BMI ≥ 25 kg/m²), and visceral obesity; Model 3: further adjusted for hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome.

OR, odds ratio; CI, confidence interval; BMI, body mass index; ASM, appendicular skeletal muscular mass.

^aASM/BMI of < 0.789 for men, < 0.512 for women; ASM/height² of < 6.75 for men, < 5.07 for women; and ASM/weight of < 29.1 for men, < 23.0 for women were considered as sarcopenia.

DISCUSSION

In this large-scale, cross-sectional retrospective study, we found a significant association between the presence of sarcopenia and the risk of colorectal neoplasia in asymptomatic adults who had undergone first-time colonoscopy. Even after adjusting for demographic characteristics and currently reported metabolic risk factors for colorectal neoplasia, our study showed that sarcopenia is a significant independent risk factor for colorectal neoplasia. Furthermore, sarcopenia was more strongly associated with advanced colorectal neoplasia and multiple colorectal neoplasia than with overall colorectal neoplasia.

Previous studies have found that sarcopenia is associated with an increased risk of several chronic disorders such as cardiovascular disease, obstructive pulmonary disease, metabolic syndrome, DM, and non-alcoholic fatty liver disease [13-16,24]. Additionally, the relationship between sar-

copenia and CRC has been previously reported. According to these studies, sarcopenia is associated with poor clinical outcomes and surgical advanced events in CRC patients, which may be related to a prolonged catabolic state associated with immune dysfunction and systemic inflammatory responses [11,17,18]. However, there have been limited studies on the relationship between sarcopenia and the development of colorectal neoplasia. Only three studies have reported that sarcopenia is a risk factor for colorectal neoplasia; all studies used the established BIA-based diagnostic criteria for sarcopenia. Among these, two studies defined sarcopenia using ASM adjusting by body weight [25,26], whereas one defined it as a value below the lower limit or < 90% of the standard [27]. Although dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT) are currently considered as gold standard methods for measuring of the skeletal muscle mass, radiation exposure may be a drawback in actual clinical settings.

BIA, a non-invasive body composition analyzer, is a convenient, safe, and cost-effective tool for measuring skeletal muscle mass, and several studies have validated its clinical usefulness and accuracy when compared with either DEXA or CT [28-30]. However, the cutoff value of the skeletal muscle mass index for a conclusive diagnosis of sarcopenia using BIA varies from study to study. Therefore, to compensate for this shortcoming, various formulas for defining sarcopenia using BIA, such as BMI-adjusted ASM model, height-adjusted ASM model, and body weight-adjusted ASM model, were used in the analysis.

In our study, sarcopenia defined by the BMI or weight-adjusted ASM model showed a significant association with the risk of colorectal neoplasia, but sarcopenia defined by the height-adjusted ASM model did not. However, sarcopenia defined using any of the ASM models showed a significant association with the risk of advanced colorectal neoplasia and multiple colorectal neoplasia, and the magnitude of the association was stronger than that with any colorectal neoplasia. In other words, sarcopenia may be associated with the risk of any colorectal neoplasia but is more strongly associated with the risk of advanced colorectal neoplasia and multiple colorectal neoplasia. The insignificant association between sarcopenia defined by the height-adjusted ASM model and any colorectal neoplasia might be due to the patient sample. In our study, the height-adjusted ASM model was used for a relatively small number of sarcopenia subjects (297 subjects) compared to the other models (583 subjects in the BMI-adjusted ASM model and 685 subjects in the weight-adjusted ASM model). In addition, contrary to previous reports, patients for whom sarcopenia was defined by the height-adjusted ASM model had lower obesity, lower visceral obesity, and lower incidence of metabolic syndrome than normal subjects. This may have contributed to the difference in the strength of association mentioned earlier. Further studies with a larger number of patients for the height-adjusted ASM model are required.

Although the role of sarcopenia in the development of colorectal neoplasia has not been fully elucidated yet, several observational and experimental studies have suggested a putative mechanism to explain such an association. These studies also indicate that sarcopenia and colorectal neoplasia may have common risk factors. Several studies have reported that sarcopenia is associated with decreased physical inactivity and the accumulation of visceral fat [31,32], both of which are associated with the development of colorec-

tal neoplasia [33,34]. Decreased physical activity leads to an abnormal accumulation of visceral fat, which activates inflammatory pathways. Metabolically active visceral adipose tissue produces proinflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and IL-8, which play a key role in angiogenesis, promotion of cellular proliferation, and inhibition of apoptosis during the development of colorectal neoplasia [35-37]. These conditions are also observed when there are changes in the body composition associated with sarcopenia, including decreased skeletal muscle mass and increased visceral fat [38]. Beyer et al. [39] reported that age-related chronic low-grade inflammation is an important causative factor for sarcopenia, and sarcopenia associated inflammation is mediated by adipocytokines such as TNF- α and IL-6. In addition, a reduction in skeletal muscle mass lowers the insulin-mediated glucose uptake in myocytes, and in turn, induces insulin resistance [16,40]. Furthermore, insulin resistance elevates the insulin-like growth factor, which may promote the development of colorectal neoplasia through proliferative and anti-apoptotic effects [41]. Recently, metabolic syndrome has been reported to be an important risk factor for the development of colorectal neoplasia. Additionally, high BP, hyperglycemia, and dyslipidemia, which contribute to metabolic syndrome, are also associated with sarcopenia [16,40,42]. The interaction between these factors may consist of a complex vicious cycle, and multiple mechanisms have been implicated in the association between sarcopenia and colorectal neoplasia.

Our study has certain limitations. First, because of the cross-sectional design of this study, any causality between sarcopenia and colorectal neoplasia could not be inferred. Second, the study subjects that participated in the health screening program at a single center could not be representative of the general population. Third, there was a lack of data on physical activity, a factor associated with both sarcopenia and colorectal neoplasia in this study. Fourth, although BIA is a convenient and cost-effective tool for assessing the skeletal muscle mass index, it is not the gold standard for sarcopenia diagnosis. Another limitation is that sarcopenia includes not only lowered skeletal muscle mass but also reduced muscle functions such as gait speed and grip strength. However, BIA does not provide information about the latter. Therefore, further study is needed to analyze the association between sarcopenia and colorectal neoplasia, wherein muscle function is included as a parameter. Nevertheless, this study is meaningful as it confirms the

association between sarcopenia, irrespective of diagnostic criteria, and colorectal neoplasia with a relatively large number of subjects who underwent first-time colonoscopies. In addition, the temporal bias was minimized by stepwise adjustment for potential confounding factors for colorectal neoplasia.

In conclusion, sarcopenia was a significant risk factor for any colorectal neoplasia independent of traditional risk factors. Furthermore, the presence of sarcopenia was more significantly associated with the risk of advanced colorectal neoplasia and multiple colorectal neoplasia than with the risk of any colorectal neoplasia. However, longitudinal studies are needed to elucidate the exact causal relationship between sarcopenia and colorectal neoplasia.

KEY MESSAGE

1. In this large-scale, cross-sectional retrospective study showed that sarcopenia was a significant risk factor for colorectal neoplasia independent of traditional risk factors.
2. Sarcopenia was more strongly associated with advanced colorectal neoplasia and multiple colorectal neoplasia than with overall colorectal neoplasia.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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