Sarcopenia as a leading risk factor for erosive esophagitis

Tae Jun Kim¹, Jeung Hui Pyo², Hyuk Lee¹, Seungho Ryu^{3,4,5}, Sun-Young Baek⁶, Kyunga Kim⁶, Yang Won Min¹, Byung-Hoon Min¹, Jun Haeng Lee¹, Hee Jung Son^{1,2}, Poong-Lyul Rhee¹ and Jae J Kim¹

¹Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

²Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

³Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

⁴Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

⁵Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Republic of Korea

⁶Statistics and Data Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence to: Hyuk Lee, email: leehyuk@skku.edu

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ABSTRACT

Backgrounds: Obesity is an established risk factor for erosive esophagitis. Yet, the associations of sarcopenia and obesity with erosive esophagitis remain unclear. We studied the associations of obesity, sarcopenia, and sarcopenic obesity with the risk of erosive esophagitis in a large number of asymptomatic men and women.

Materials and Methods: We conducted a cross-sectional study of 32,762 asymptomatic adults undergoing routine health check-ups including screening endoscopy, between August 2006 and December 2011. Sarcopenia was defined as an appendicular skeletal muscle mass (ASM) /body weight value beyond two standard deviations below the mean for healthy young adults. The ASM was estimated using bioelectrical impedance analysis.

Results: Participants were categorized into four groups according to their obesity and sarcopenic status: normal, obese, sarcopenic, and sarcopenic obese. In a multivariable model adjusted for age, sex, smoking status, alcohol intake, regular exercise, and metabolic variables, the risk of erosive esophagitis was higher in obese [adjusted odds ratio (aOR), 1.38; 95% confidence interval (CI), 1.26–1.52], sarcopenic (aOR, 2.20; 95% CI, 1.48–3.29), and sarcopenic obese participants (aOR, 1.68; 95% CI, 1.39–2.03) than in normal participants. Comparing sarcopenic and sarcopenic obese participants to obese participants, the ORs for erosive esophagitis were 1.59 (95% CI, 1.06–2.38) and 1.22 (95% CI, 1.02–1.47), respectively. In dose-response analyses, increasing sarcopenia severity showed a positive and graded relationship with overall, LA-B or higher grade, and LA-C erosive esophagitis.

Conclusions: Our findings suggest that sarcopenia, regardless of obesity status, is strongly and progressively associated with the risk of erosive esophagitis.

INTRODUCTION

Gastroesophageal reflux disease is a widespread gastrointestinal disorder that frequently occurs in primary care settings, imposing considerable burdens on global

health and economics [1]. Disease prevalence is 18.1–27.8% in North America, 8.8–25.9% in Europe, and 2.5–7.8% in East Asia, with rising rates worldwide [2]. Obesity is considered a significant contributing factor for a spectrum of reflux-related esophageal disorders ranging from

erosive esophagitis to Barrett's esophagus to esophageal adenocarcinoma [3, 4]. Although the exact mechanisms have not been fully identified, several studies have demonstrated that the pattern of body fat distribution may be more important than general adiposity for increasing the risk of erosive esophagitis [5, 6]. In addition to the increased intra-abdominal pressure caused by visceral adiposity, metabolically active visceral adipose tissue creates a pro-inflammatory and insulin-resistant condition [7–9]. Thus, the reflux-independent effect of adiposity on erosive esophagitis may contribute to the association, which cannot be solely explained by the mechanical effect of obesity.

Recent interest has focused on the age-related changes in body composition called sarcopenia. Sarcopenia is a pathological condition characterized by the progressive loss of muscle mass and increased amount of visceral fat, despite a relatively constant body weight [10]. Recent evidence shows that sarcopenia and sarcopenic obesity are associated with several cardiometabolic diseases, as well as with poor morbidity and mortality outcomes [11–17]. Reflux esophagitis (RE) and sarcopenia seem to have similar pathophysiologic backgrounds with regard to body composition and metabolic abnormalities. However, the effect of sarcopenia on erosive esophagitis has not been evaluated in a large population. Therefore, we examined the association between sarcopenia or sarcopenic obesity and the risk of erosive esophagitis. Furthermore, we evaluated whether sarcopenia or sarcopenic obesity is more likely to result in erosive esophagitis than is obesity in the absence of sarcopenia.

RESULTS

Baseline characteristics of the study participants

Among the 32,762 participants (mean age, 50.1 $\pm$ 8.6 years), the prevalence of erosive esophagitis was 7.6% (n = 2,493). According to the Los Angeles (LA) classification of erosive esophagitis, the prevalence of erosive esophagitis was 6.3% (n = 2,063) of LA-A, 1.2% (n = 408) of LA-B, and 0.07% (n = 22) of LA-C. There were no cases of LA grade D erosive esophagitis in this study of asymptomatic participants. The baseline characteristics of the participants are shown in Table 1 organized according to their obesity and sarcopenic status (normal, obese, sarcopenic, and sarcopenic obese groups), with significant differences observed among groups. The sarcopenic groups (sarcopenic obese and sarcopenic) were older, more likely to be male and not exercise regularly, had higher systolic blood pressures, had higher triglyceride, fasting glucose, and high sensitivity C-reactive protein (hsCRP) levels, and had lower ASM/weight, ASM/body mass index (BMI), and high density lipoprotein cholesterol (HDL-C) values; higher proportions of current smokers and modest alcohol consumers were also present in these groups than in the non-sarcopenic groups (normal and obese). Participants in

the obese groups (obese and sarcopenic obesity) had higher proportions of current smokers, modest alcohol consumers, and had higher BMI and waist circumference values than did the non-obese groups (normal and sarcopenic).

Risk of erosive esophagitis according to obesity and sarcopenia status

Among the 32,762 participants, the prevalences of erosive esophagitis in the four groups was 6.0% (normal), 11.1% (obese), 15.2% (sarcopenic), and 14.8% (sarcopenic obese) (Figure 1). Participants in the sarcopenic, and sarcopenic obese groups had higher prevalence of each grade of erosive esophagitis as well as overall erosive esophagitis (P < 0.001). Table 2 shows the risks of erosive esophagitis, based on obesity and sarcopenia status. Compared with the normal group, the obese, sarcopenic, and sarcopenic obese groups were more highly associated with erosive esophagitis. These associations were attenuated, but persisted, after adjusting for potential confounding factors and metabolic risk factors. In addition, the sarcopenic (non-obese) and sarcopenic obese groups were at higher risk of erosive esophagitis than were participants in the obese, non-sarcopenic group (Table 3). These associations persisted after adjusting for potential confounders and metabolic parameters. In the multivariable analysis, male sex, current smoking, modest alcohol intake (> 10 g/day), and metabolic risk factors (e.g., systolic blood pressure, fasting blood glucose level, and triglyceride level) were independent risk factors for erosive esophagitis (data not shown).

Risk of erosive esophagitis by grading according to sarcopenia status

Table 4 shows the dose-response relationship between sarcopenia and erosive esophagitis. In models adjusted for age, sex, waist circumference, smoking status, alcohol intake, and exercise, adjusted ORs (95% CIs) for overall erosive esophagitis comparing class I sarcopenia and class II sarcopenia with normal participants were 1.19 (1.08–1.32) and 1.51 (1.26–1.81), respectively. In the dose-response analyses, increasing sarcopenia severity also showed a positive and graded dose-response relationship with erosive esophagitis LA-B or higher grade and LA-C. Further, the adjusted OR associated with a 1% decrease when ASM/weight was introduced as a continuous variable in regression models was 1.04 (1.01–1.06) for overall erosive esophagitis. The adjusted ORs for LA-B or higher grade and LA-C were 1.07 (1.01–1.13) and 1.30 (1.10–1.55), respectively.

Subgroup analyses of erosive esophagitis risk by obesity and sarcopenia status

To evaluate the consistency of the effect of obesity and sarcopenia status on erosive esophagitis, we

Table 1: Baseline characteristics of study participants according to obesity and sarcopenia status

	Normal (n = 22,810)	Obese (n = 8,533)	Sarcopenic (n = 311)	Sarcopenic obese (n = 1,108)	P value
Age (years)	49.6 ± 8.3	51.1 ± 6.8	54.9 ± 7.8	53.0 ± 7.7	< 0.001
Male (%)	49.7	70.5	73.0	81.6	< 0.001
BMI (kg/m ²)	22.5 ± 2.2	26.5 ± 2.2	25.4 ± 2.0	29.6 ± 3.1	< 0.001
Waist circumference (cm)	78.9 ± 6.5	92.9 ± 4.6	84.2 ± 4.2	98.9 ± 7.4	< 0.001
ASM (kg)	19.2 ± 4.1	22.9 ± 4.4	17.1 ± 3.4	21.9 ± 4.4	< 0.001
ASM/weight (%)	31 ± 3	30 ± 3	27 ± 3	27 ± 3	< 0.001
ASM/BMI (m ²)	1.41 ± 0.57	1.13 ± 0.32	0.82 ± 0.19	0.77 ± 0.16	< 0.001
Body fat percentage (%)	24.4 ± 6.1	28.3 ± 5.8	33.6 ± 5.2	35.7 ± 5.2	< 0.001
Current smoking (%)	19.7	27.5	18.5	29.0	< 0.001
Modest alcohol intake (%)	12.7	21.6	14.6	24.1	< 0.001
Regular exercise (%)	29.9	25.6	26.9	22.7	< 0.001
SBP (mmHg)	116 (106–127)	123 (113–134)	126 (113–137)	127 (117–139)	< 0.001
Triglycerides (mg/dl)	89 (65–128)	117 (85–162)	115 (84–160)	134 (99–191)	< 0.001
HDL-C (mg/dl)	55 (46–66)	50 (44–61)	47 (41–56)	46 (39–55)	< 0.001
Fasting glucose (mg/dl)	90 (84–97)	94 (88–103)	94 (87–104)	97 (90–109)	< 0.001
hsCRP (mg/dl)	0.04 (0.03–0.08)	0.07 (0.04–0.15)	0.08 (0.04–0.16)	0.12 (0.06–0.24)	< 0.001

Values are expressed as means ± standard deviation, percentages, or median (interquartile range).

BMI, body mass index; ASM, appendicular skeletal muscle mass; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol.

performed subgroup analyses of factors affecting the risk of erosive esophagitis (Table 5). The pre-specified subgroup analysis did not show heterogeneity of the risk of erosive esophagitis from obesity and sarcopenia status, or significant interactions with age (< 60 vs. ≥ 60 years), sex (women vs. men), smoking status (non-current vs. current smokers), alcohol intake (mild vs. modest), or regular exercise (no vs. yes).

DISCUSSION

In this large, cross-sectional study of asymptomatic men and women undergoing upper gastrointestinal tract endoscopies, we found that sarcopenic obese individuals were at higher risk of erosive esophagitis than obese individuals without sarcopenia. Our results also showed that non-obese sarcopenic individuals are at an increased risk of erosive esophagitis compared to obese individuals without sarcopenia. These associations persisted after adjusting for potential confounders and metabolic risk factors, and remained evident across all evaluated subgroups. Thus, our findings indicate that sarcopenia, regardless of the presence of central obesity, is associated with a greater risk of erosive esophagitis than is central obesity in the absence of sarcopenia.

To our knowledge, this is the first large scale study investigating obesity/sarcopenia and the risk of erosive esophagitis. Sarcopenia has become an important concept for understanding the impact of aging on health outcomes.

This condition is not only a physiological symptom of aging, but there is growing evidence that low muscle mass is a condition associated with a number of disorders [11–17]. Sarcopenia is common in elderly populations and contributes to functional limitations, disabilities, and frailty [18, 19]. Furthermore, several previous studies have found an association with increased risk for several disorders, such as cardiovascular disease, metabolic syndrome, and morbidity or mortality, in individuals with sarcopenia [11–17].

Previous evidence has shown a significant association between RE and obesity, especially central obesity [20–22]. Although the precise mechanisms that link central obesity and RE are not yet fully elucidated, multiple mechanisms have been implicated to account for this association. Central obesity, which is typically measured in terms of waist circumference, waist-hip ratio, or visceral adiposity, seems to be a more important predictor of RE than is general obesity [23]. This may be due to the mechanical effect of the increased pressure gradient caused by visceral adiposity inducing RE in individuals with central obesity [8, 24]. The important changes in body composition associated with RE, including a decline in skeletal muscle and an increase in body fat, especially abdominal visceral fat, are noticed in individuals with sarcopenia [14, 25–27]. In our study, participants with sarcopenia had higher body fat percentages than did participants without sarcopenia. Thus, increased body fat, especially abdominal adiposity,

Table 2: The risk of erosive esophagitis according to sarcopenic obesity groups

	Sarcopenic obesity groups				P value
	Normal OR	Obese OR (95% CI)	Sarcopenic OR (95% CI)	Sarcopenic obese OR (95% CI)	
Crude Model	1.00 (reference)	1.95 (1.79–2.12)	2.80 (1.92–4.09)	2.72 (2.29–3.24)	< 0.001
Model 1	1.00 (reference)	1.53 (1.40–1.67)	2.23 (1.51–3.29)	1.93 (1.61–2.30)	< 0.001
Model 2	1.00 (reference)	1.46 (1.12–1.33)	2.33 (1.57–3.46)	1.82 (1.51–2.18)	< 0.001
Model 3	1.00 (reference)	1.38 (1.26–1.52)	2.20 (1.48–3.29)	1.68 (1.39–2.03)	< 0.001

Model 1 adjusted for age and sex, Model. 2 adjusted for age, sex, smoking status, alcohol intake, and regular exercise. Model. 3 adjusted for systolic blood pressure, triglycerides, HDL-cholesterol, and fasting glucose in addition to the factors included in model, 2. OR, odds ratio; CI, confidence intervals.

might contribute to RE through a mechanical effect in sarcopenic patients. In addition, skeletal muscle is a primary tissue for insulin-mediated glucose disposal; therefore, the low skeletal muscle mass in patients with sarcopenia reduces insulin-mediated glucose uptake and, subsequently, induces insulin resistance [28, 29]. Moreover, a recent study, using data from the National Health and Nutrition Examination Survey III, showed that sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia [30]. Additionally, the sarcopenia-associated loss of skeletal muscle mass and gain of visceral adiposity were positively associated with blood pressure, triglyceride levels, hyperglycemia, and a number of other metabolic syndrome components [14, 28, 29]. Strong evidence also supports the association of metabolic syndrome with RE [31, 32]. Our study also revealed that metabolic components, such as

systolic blood pressure, fasting blood glucose levels, and triglyceride levels, were independent risk factors for erosive esophagitis. Further, individuals with sarcopenia had higher systolic blood pressures, and higher fasting blood glucose and triglyceride levels, than did those without sarcopenia.

Sarcopenia-induced chronic inflammation is another potential RE mechanism. Recently, esophageal inflammation involving a cytokine-mediated pathway, rather than reflux, has been proposed as a mechanism underlying the pathogenesis of RE [33]. Further, age-related, chronic, low-grade inflammation is recognized as an important causative factor for sarcopenia [34], and cross-sectional and longitudinal studies support the association between inflammation and sarcopenia [34]. Adipocytokines, such as tumor necrosis factor- α and interleukin-6, are mainly involved in sarcopenia-

Figure 1: The prevalence of erosive esophagitis by Los Angeles classification according to sarcopenia and obesity status.

Table 3: The risk of erosive esophagitis for sarcopenic and sarcopenic obese group comparing to obese group

	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Obese	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Sarcopenic	1.46 (0.99–2.15)	0.05	1.59 (1.07–2.37)	0.02	1.59 (1.06–2.38)	0.02
Sarcopenic obese	1.26 (1.05–1.51)	0.01	1.24 (1.03–1.50)	0.03	1.22 (1.01–1.47)	0.04

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, smoking status, alcohol intake, and regular exercise. Model 3 adjusted for systolic blood pressure, triglycerides, HDL-cholesterol, and fasting glucose in addition to the factors included in model 2. OR, odds ratio; CI, confidence intervals.

associated inflammation [34]. However, further research is needed to understand the underlying mechanisms of insulin resistance, inflammation, and metabolic syndrome associated with sarcopenia and their roles in RE.

Several limitations need to be a considered when interpreting the results of our study. First, the cross-sectional design of this study makes it impossible to determine any causality for the association. Second, although BIA is a convenient and safe method for assessing skeletal muscle mass index, it is not the gold standard method; the gold standards remain dual-energy X-ray absorptiometry, computed tomography, and magnetic resonance. However, several studies have validated the use of BIA, compared with either absorptiometry or magnetic resonance; these studies reported BIA to provide an accurate estimate of skeletal muscle mass index [35–38]. Another limitation of BIA is that it cannot provide information on muscle quality, such as gait speed or grip strength; such characterizations describe sarcopenia in a functional way, not solely on the basis of muscle mass. Third, inter-observer variations in the endoscopic diagnoses of erosive esophagitis were not evaluated. However, experienced board-certified gastroenterologists performed the endoscopies, and erosive esophagitis was clearly defined; the same classification system was used for all of the participants. Finally, this study focused on healthy participants who underwent routine health check-ups; thus, our findings may not generalize to other populations.

This study also has several strengths. First, its large sample size and the adjustment for potential confounding factors of erosive esophagitis allowed us to minimize temporal bias. Additional strengths include the use of high-quality, standardized anthropometric measurements; the incorporation of an epidemiological questionnaire regarding lifestyle factors, and the inclusion of various laboratory studies.

In conclusion, this study showed that sarcopenia is associated with an increased risk of erosive esophagitis, regardless of the presence of central obesity. Furthermore, sarcopenia without central obesity and sarcopenic obesity also demonstrated increased risk of erosive esophagitis, compared with obesity in the absence of sarcopenia. The risk of erosive esophagitis appears to have been mediated

by metabolic risk factors. Further longitudinal studies are needed to confirm our findings and to elucidate the causal relationship between sarcopenia and erosive esophagitis.

MATERIALS AND METHODS

Study population

We conducted a retrospective, cross-sectional study of healthy men and women, who underwent a routine health check-up that included endoscopy. The participants underwent their health check-up at the Center for Health Promotion, Samsung Medical Center, Seoul, South Korea, between August 2006 and December 2011. We screened consecutive participants who underwent esophagogastroduodenoscopy (EGD) during the study period. Since our objective was to evaluate the association between obesity/sarcopenic status and RE, we included participants who underwent both EGD and anthropometric measurements, including waist circumference, body weight, and appendicular skeletal muscle mass (ASM) (*n* = 37,815). We excluded participants meeting any of the following exclusion criteria: gastric cancer (*n* = 124), esophageal cancer (*n* = 25), history of other malignancy (*n* = 772), Barrett’s esophagitis (*n* = 37), or previous gastric surgery (*n* = 322). We also excluded participants missing data on important covariates: incomplete endoscopic report (*n* = 649), alcohol consumption (*n* = 1,164), smoking history (*n* = 1,487), exercise (*n* = 1,083), lipid profiles (*n* = 327), fasting blood glucose levels (*n* = 1), or systolic blood pressure (*n* = 7). Finally, 32,762 asymptomatic participants who underwent screening EGD and anthropometric measurements were included in this study (Supplementary Figure 1). This study was approved by the Samsung Medical Center Institutional Review Board and was conducted in accordance with the Declaration of Helsinki and current legal regulations in Korea. Institutional Review Board approval was obtained, but did not require specific informed consent because the study used only de-identified data collected for clinical purposes as part of the health screening. However, informed consent was obtained from all subjects for their examinations during the health check-up.

Table 4: The risk of erosive esophagitis by LA classification according to sarcopenia status

	Multivariable-adjusted OR (95% CI)		
	≥ LA-A	≥ LA-B	≥ LA-C
Cut-off values for sarcopenia			
Normal	1.00 (reference)	1.00 (reference)	1.00 (reference)
Class I sarcopenia ^a	1.19 (1.08–1.32)	1.59 (1.29–1.96)	2.60 (0.97–6.99)
Class II sarcopenia ^b	1.51 (1.26–1.81)	1.74 (1.42–2.13)	4.93 (1.24–19.57)
<i>P</i> for trend	< 0.001	0.004	0.046
Per 1% decrease in ASM/weight	1.04 (1.01–1.06)	1.07 (1.01–1.13)	1.30 (1.10–1.55)

Multivariable model was adjusted for age, sex, waist circumference, smoking status, alcohol intake, and regular exercise.

^aParticipants with class I sarcopenia were those with weight-adjusted skeletal muscle mass index between one and two standard deviations below the sex-specific values measured in young healthy adults.

^bParticipants with class II sarcopenia were those with weight-adjusted skeletal muscle mass index more than two standard deviations below the sex-specific values measured in young healthy adults. LA, Los Angeles; OR, odds ratio; CI, confidence intervals; ASM, appendicular skeletal muscle mass.

Data collection

The comprehensive health-screening program included anthropometric measurements, endoscopy, serum biochemical measurements, and completion of an epidemiological questionnaire regarding smoking habits, alcohol consumption, physical activity, personal medical history, and family history of cancer [39]. Smoking status was categorized as never, former, or current smoker. Alcohol consumption status was categorized as either mild (≤ 10 g/day) or modest (> 10 g/day). Regular exercise was defined as exercising ≥ 3 times/week at a moderate intensity. The participants' weights and heights were measured while wearing light clothing and bare feet. Weight and height were determined to the nearest 0.1 kg and 0.1 cm, respectively; the body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2). Waist circumference was measured in a horizontal plane at the midpoint between the inferior margin of the last rib and the superior iliac crest. Blood pressure was measured, using an automated blood pressure monitor (Dinamap PRO 100; GE Healthcare, Milwaukee, WI), while the participant was in the seated position after > 5 minutes of quiet rest.

After a ≥ 12 -h fast, blood samples were collected in the morning and analyzed in the hospital's clinical laboratory. Serum glucose levels were measured using the hexokinase/glucose-6-phosphate dehydrogenase method and an autoanalyzer (7600 Modular Dp-110, Hitachi, Tokyo, Japan). Serum levels of glucose, total cholesterol, triglycerides, and high-density lipoprotein-cholesterol (HDL-C) were measured using enzymatic colorimetric and liquid-selective detergent methods in the same type of autoanalyzer.

Definitions of obesity and sarcopenia

To estimate the ASM, bioelectrical impedance analysis (BIA) was performed using an Inbody 720 (Biospace, Seoul, Korea), which is a convenient and cost-effective tool for

assessing impedance in various body segments, including the four limbs and trunk [38]. ASM was calculated as the sum of the lean muscle mass of the bilateral upper and lower limbs. The skeletal muscle mass index, a validated measure of sarcopenia, was calculated as: the skeletal muscle mass index (%) = ASM (kg)/body weight (kg) $\times 100$ [36]. Sarcopenia was defined as a skeletal muscle mass index more than two standard deviations below the sex-specific values measured in young healthy adults, according to national health examinations in Korea (skeletal muscle mass index < 29.1 in males and < 23.0 in females) [40].

Obesity was defined as central obesity (waist circumference ≥ 90 cm in men and ≥ 85 cm in women) according to the Korean Society for the Study of Obesity [41]. Study participants were classified into four groups based on sarcopenia and obesity status: non-sarcopenic and non-obese (normal) group; sarcopenic and non-obese (sarcopenic) group; non-sarcopenic and obese (obese) group; and sarcopenic and obese (sarcopenic obese) group.

Esophagogastroduodenoscopy

Thirty-four experienced board-certified gastroenterologists performed each endoscopy using a gastroscope (Olympus GIF-Q260; Olympus Medical Systems, Tokyo, Japan). All endoscopists completed a gastroenterology fellowship. Median year of graduation from medical school of the 34 gastroenterologists is 1997 (range, 1989–2003). The primary endpoint was the presence of erosive esophagitis noted during EGD. Erosive esophagitis was defined as the presence of definite mucosal breaks (erosions) and was classified according to the Los Angeles classification system [42].

Statistical analysis

Continuous variables are reported as means $\pm$ standard deviations, while categorical variables are

Table 5: The risk of erosive esophagitis by sarcopenic obesity groups in clinically-relevant subgroups

Subgroup	Sarcopenic obesity groups				P for interaction
	Normal	Obese	Sarcopenic	Sarcopenic obese	
Age					0.25
< 60 years (n = 27,957)	reference	1.52 (1.33–1.82)	2.77 (1.80–4.27)	1.91 (1.46–2.55)	
≥ 60 years (n = 4,805)	reference	1.33 (1.14–1.72)	2.03 (1.10–4.55)	1.48 (1.17–2.16)	
Sex					0.69
Women (n = 14,373)	reference	1.45 (1.10–1.91)	1.73 (1.18–6.52)	2.45 (1.27–4.74)	
Men (n = 18,389)	reference	1.46 (1.32–1.60)	2.32 (1.54–3.51)	1.74 (1.44–2.11)	
Current Smoking					0.5
No (n = 25,584)	reference	1.43 (1.27–1.61)	2.11 (1.32–3.38)	1.94 (1.54–2.44)	
Yes (n = 7,178)	reference	1.51 (1.31–1.74)	2.65 (1.28–5.51)	1.56 (1.15–2.12)	
Alcohol intake					0.96
Mild (n = 27,736)	reference	1.47 (1.31–1.63)	2.20 (1.41–3.44)	1.83 (1.47–2.28)	
Modest (n = 5,026)	reference	1.46 (1.23–1.74)	2.61 (1.10–6.16)	1.70 (1.21–2.39)	
Regular exercise					0.06
No (23,395)	reference	1.47 (1.32–1.64)	2.84 (1.84–4.38)	1.96 (1.60–2.41)	
Yes (9,367)	reference	1.44 (1.21–1.71)	2.14 (1.21–4.72)	1.44 (1.13–1.92)	

Estimated from logistic regression models adjusted for age, sex, smoking status, alcohol intake, regular exercise, and metabolic variables

presented as percentages. Continuous variables were compared between groups using one-way ANOVA; categorical variables were compared using the Chi-squared test. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for erosive esophagitis in the sarcopenic obese, sarcopenic, and obese groups using the normal group as the reference group. To evaluate whether sarcopenia imparts a greater risk for the development of erosive esophagitis than obesity, we estimated adjusted ORs in the sarcopenic obese and sarcopenic groups, using the obese group as the reference group. We used three models, with increasing levels of adjustment, to account for potential confounders. Model 1 was adjusted for age (/year) and sex. Model 2 was further adjusted for smoking status (never/past vs. current smoker), alcoholic intake (mild vs. modest), and regular exercise (yes vs. no). Model 3 was further adjusted for metabolic variables, including systolic blood pressure, triglyceride level, HDL-C level, and fasting glucose level, to account for the possible mediation of the association between sarcopenia and erosive esophagitis by these metabolic risk factors.

We conducted two additional types of dose-response analyses. First, we conducted the multivariable analysis based on the severity categories of sarcopenia, and estimated adjusted ORs with 95% CIs for erosive esophagitis comparing categories with the normal category. We categorized the sarcopenia into 3 groups according to severity: normal, class I sarcopenia, and class II sarcopenia. Subjects with class I sarcopenia were

those with weight-adjusted skeletal muscle mass index between one and two standard deviations below the sex-specific values measured in young healthy adults. Subjects with class II sarcopenia were those with weight-adjusted skeletal muscle mass index more than two standard deviations below the sex-specific values measured in young healthy adults. To evaluate the linear trends of risk, we used a continuous variable with the category number and tested its statistical significance in the regression models. Second, we estimated the adjusted ORs with 95% CIs associated with weight-adjusted skeletal muscle mass index decrease of 1% using ASM/weight as a continuous variable in the logistic regression model.

We conducted subgroup analyses to identify interactions between obesity/sarcopenic status and clinically relevant groups, defined by age (< 60 years vs. ≥ 60 years), sex (women vs. men), smoking status (non-current vs. current smokers), alcohol intake (mild vs. modest), and regular exercise (no vs. yes). Subgroup interactions were tested using likelihood ratio tests and comparing models with and without multiplicative interaction terms. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC); a *P*-value < 0.05 was considered statistically significant.

Abbreviations

RE, Reflux esophagitis; EGD, esophagogastroduodenoscopy; OR, odds ratios; CI, confidence interval; HDL-C, high-density lipoprotein-

cholesterol; BIA, Bioelectrical impedance analysis; ASM, appendicular skeletal muscle mass.

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CONFLICTS OF INTEREST

The authors declare no any conflicts of interest in this work.

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