

[ORIGINAL ARTICLE]

The Association between Frailty and Abdominal Symptoms: A Hospital-based Cross-sectional Study

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Abstract:

Objective The association between frailty and abdominal symptoms has not been evaluated.

Methods We conducted a hospital-based, retrospective cross-sectional study of consecutive outpatients ≥ 65 years old at the Department of Gastroenterology, Juntendo Tokyo Koto Geriatric Medical Center from 2017 to 2019. Patients were included in the study if all of the following information was available from their medical records: patient's profile, the evaluation of osteoporosis, sarcopenia, frailty, nutritional status, findings of upper gastrointestinal endoscopy, and questionnaire results for abdominal symptoms [Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG) and Constipation Scoring System (CSS)]. We divided the subjects into frailty and non-frailty groups and investigated the risk factors for frailty.

Results Of the 313 eligible study subjects [134 men (42.8%) and 179 women (57.2%); mean age, 75.7 ± 6.0 years; mean body mass index, 22.8 ± 3.6 kg/m²], frailty was noted in 71 cases (22.7%). In a univariate analysis, an older age ($p < 0.001$), female gender ($p = 0.010$), successful eradication of *Helicobacter pylori* ($p = 0.049$), proton pump inhibitor (PPI) use ($p < 0.001$), laxative/prokinetics use ($p = 0.008$), sarcopenia ($p < 0.001$), osteoporosis ($p < 0.001$), hypozincemia ($p = 0.002$), hypoalbuminemia ($p < 0.001$), low lymphocytes ($p = 0.004$), a high CONUT score ($p < 0.001$), a high FSSG score ($p = 0.001$), and a high CSS score ($p < 0.001$) were significantly associated with frailty. A multivariate logistic regression analysis showed that an older age [odds ratio (OR) 1.16; 95% confidence interval (CI) 1.08-1.24, $p < 0.001$], PPI use (OR 2.42; 95% CI 1.18-4.98, $p = 0.016$), sarcopenia (OR 7.35; 95% CI 3.30-16.40, $p < 0.001$), hypozincemia (OR 0.96; 95% CI 0.92-0.99, $p = 0.027$), a high FSSG score (OR 1.08; 95% CI 1.01-1.16, $p = 0.021$), and a high CSS score (OR 1.13; 95% CI 1.03-1.23, $p = 0.007$) were significantly associated with frailty.

Conclusion Advanced age, PPI user, sarcopenia, hypozincemia, a high FSSG score, and high CSS score are associated with frailty.

Key words: frailty, frequency scale for the symptoms of gastroesophageal reflux disease (FSSG), constipation scoring system (CSS), sarcopenia, osteoporosis, hypozincemia

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Introduction

Over the last 50 years, the elderly population has grown rapidly in Japan, and the care of elderly patients has become a serious issue, with frailty attracting much attention as a

cause of heavy burden to families and society (1). Frailty is defined as a vulnerable state that places older adults at high risk for adverse health outcomes (2, 3). The morbidity and mortality rates of frail elderly patients are higher than those of non-frail elderly patients.

Malnutrition in elderly patients is indicated as a signifi-

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cant cause of frailty (4) and can be caused by various factors, such as gastrointestinal tract disorder (upper abdominal symptoms and constipation), psychological factors (depression and dementia), and physiological factors (taste disorder and appetite loss). Adebusoye et al. reported that constipation and oral problems were significantly associated with undernutrition in a cross-sectional study of older persons (5), so malnutrition and frailty may be caused by constipation and upper abdominal symptoms, such as heartburn, regurgitation, and epigastric discomfort. Taste disorder, depression, and appetite loss may be associated with the aging process; however, in later years, these symptoms may be related to hypozincemia (6-8). Zinc is involved in *in vivo* enzyme activation, and the physiological functions of zinc include roles in skin metabolism, the generative function, maintenance of taste, mental function, and immunity (9). However, the influence of abdominal symptoms on frailty in the Japanese population has not been clearly established.

In the present study, we carried out a hospital-based retrospective cross-sectional analysis to clarify the association between frailty and abdominal symptoms in elderly outpatients.

Materials and Methods

Study design

Between April 2017 and December 2019, we conducted a hospital-based, retrospective cross-sectional study of consecutive outpatients ≥ 65 years old at the Department of Gastroenterology, Juntendo Tokyo Koto Geriatric Medical Center. Subjects were included if all of the following information was available from their medical records:

- 1) Patient profile [age, gender, body mass index (BMI)];
- 2) *Helicobacter pylori* infection status (negative, positive, or negative after eradication);
- 3) Internal medicine therapeutic agent use [proton pump inhibitor (PPI), aspirin, laxative/prokinetics];
- 4) Presence of osteoporosis, sarcopenia, and frailty;
- 5) Nutritional status [serum zinc, albumin, cholesterol, lymphocyte, CONTrolling NUTritional status (CONUT) score];
- 6) Findings of upper gastrointestinal endoscopy [reflux esophagitis (RE), hiatal hernia (HH), and endoscopic gastric mucosal atrophy score (EGAS)]; and
- 7) Response to questionnaires on abdominal symptoms [Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG), Constipation Scoring System (CSS), and Bristol Stool Form Scale (BSFS)].

The collection of patient profile data, serum zinc levels, medications, questionnaires, upper gastrointestinal endoscopy, and findings concerning osteoporosis, sarcopenia, and frailty were performed at the same time.

Exclusion criteria

Patients who were unable to walk due to severe osteoar-

thritis or neuromuscular disease, immobile patients, patients presenting with delirium tremens, and patients with a history of acute cerebrovascular, gastrointestinal, renal, coronary, hepatic, and respiratory events were excluded from this study.

We also excluded subjects with certain comorbidities and those using drugs that affect osteoporosis. We excluded patients who were currently being or had been previously treated with glucocorticoids, hormone replacement therapy, thyroid/parathyroid drugs, psychotropic drugs, anticonvulsants, selective estrogen receptor modulators (SERMs), vitamin D, calcium, zinc agent, and bisphosphonates. We also performed a colonoscopy (or barium enema) and chest, abdomen, and pelvic computerized tomography for all subjects within one year and excluded patients found to have the following conditions: gastrectomy, inflammatory bowel disease (IBD), malignant disease (gastric, esophageal, colon, lung, pancreatic, liver, bile duct, gallbladder, breast, uterine, ovarian, prostate, and bladder cancer, as well as malignant lymphoma, leukemia, and multiple myeloma), type 1 diabetes mellitus, hypo/hyper-thyroidism, hypo/hyper-parathyroid disorder, and mental illness.

Subjects were also excluded if they met any of the following criteria that affect sarcopenia: severe cardiac, pulmonary, or musculoskeletal disorders; severe neurologic disorders, such as Parkinson's disease and stroke; and subjects in Japan's long-term care service.

Assessments

The BMI was calculated as the body weight divided by the body height in meters squared (kg/m^2). *H. pylori* infection status was assessed by the ^{13}C -urea breath test (UBT) and/or presence of serum antibodies to *H. pylori*. We defined a positive result for any of these tests as positive for *H. pylori* infection. We defined a successful eradication result by the UBT as negative findings for *H. pylori* infection at 4 to 8 weeks after *H. pylori* eradication therapy.

Patients who used any of the five types of PPIs (rabeprazole, omeprazole, lansoprazole, esomeprazole, or vonoprazan) daily for more 8 weeks were defined as PPI users. We defined patients taking the usual dose of aspirin or PPI as users of that specific therapy.

Definition of sarcopenia

We defined sarcopenia using the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia, which assesses the presence of both a low muscle function (low physical performance or low muscle strength) and low muscle mass (10).

In the present study, we considered subjects ≥ 65 years old as having sarcopenia if they had a low skeletal muscle mass with either a low handgrip strength or slow gait speed. The handgrip strength, gait speed, and muscle mass were measured as follows: The handgrip strength was measured using a handgrip dynamometer (Toei Light, Soka, Japan). Both hands were tested, and the larger value was noted as the

maximum muscle strength. A low grip strength was established according to the sex-specific cut-off for the maximum muscle strength of the subject according to the Asian Working Group for Sarcopenia (AWGS) criteria (<26 kg for men; <18 kg for women). The gait speed was manually assessed using a stopwatch. A slow gait speed was defined as ≤ 0.8 m/s according to the AWGS criteria. Regional fat and lean mass were measured by whole-body dual X-ray absorptiometry (DXA; Prodigy Advance, GE Healthcare, Madison, USA). Subjects were positioned for whole-body scans in accordance with the manufacturer's protocol. The whole-body fat mass and lean mass were divided into several regions, such as the arms, legs, and trunk. The appendicular lean mass was estimated as the sum of the lean mass of the two upper limbs and two lower limbs. The skeletal muscle mass index (SMI) was calculated as the appendicular lean mass divided by the square of the height (kg/m^2). A low appendicular skeletal muscle mass was defined as an SMI of <7.0 kg/m^2 for men and <5.4 kg/m^2 for women

Definition of osteoporosis

The percent of young adult mean (YAM) and T-score were determined based on DXA of the lumbar spine (L2-L4) and total hip. DXA was performed using a Prodigy Advance (GE Healthcare). We investigated the presence of fragility fractures in the chest and lumbar spine by lateral vertebral X-rays. The diagnosis of osteoporosis was made in accordance with the Japanese diagnostic criteria established by the Japanese Society for Bone and Mineral Research (11). Osteoporosis was defined as a lumbar spine and total hip BMD $<70\%$ of the YAM, even in subjects without any prevalent fragility fracture. Osteoporosis was also defined as the presence of fragility fractures in any bone in a person with a BMD $<80\%$ of the YAM.

The assessment of frailty

The diagnosis of frailty was made by applying the Japanese version of the Cardiovascular Health Study (J-CHS) criteria (12), which were adapted from the original CHS criteria. The criteria include unintentional weight loss, fatigue, inactivity, low grip strength, and slow gait speed.

Unintentional weight loss was defined as a decrease in the body weight of >2 kg in the past 6 months without any particular cause. Fatigue was defined as self-reported exhaustion and was assessed using the following question: "In the past two weeks, have you felt tired without a reason?" The activity level was evaluated using the following questions: "Do you engage in moderate levels of physical exercise or sports in an effort to maintain health?" and "Do you engage in low levels of physical exercise in an effort to maintain health?" If a subject answered "No" to both of these questions, then we considered their physical activity to be low. A low grip strength and slow gait speed were defined as mentioned above. In the present study, subjects with impairment in three or more of the five criteria were categorized into the frailty group, while those with fewer than three criteria were

categorized into the non-frailty group.

Nutritional status

In this study, the CONUT score (between 0 and 12) was used to evaluate the objective nutritional status. This score evaluated the following three parameters: serum albumin level, total cholesterol level, and total lymphocyte count (13). The serum albumin level indicates the protein reserves, the serum total cholesterol level indicates caloric depletion, and the total lymphocyte count indicates immune system impairment due to malnutrition. The CONUT score is based on the following: albumin (≥ 3.5 g/dL, 0 points; 3.00-3.49 g/dL, 2 points; 2.50-2.99 g/dL, 4 points; <2.50 g/dL, 6 points), total cholesterol (≥ 180 mg/dL, 0 points; 140-179 mg/dL, 1 point; 100-139 mg/dL, 2 points; <100 mg/dL, 3 points), and total lymphocyte count ($\geq 1,600/\mu\text{L}$, 0 points; 1,200-1,599/ μL , 1 point; 800-1,199/ μL , 2 points; $<800/\mu\text{L}$, 3 points). Venous blood samples for serum preparation were obtained in the early morning after 12 hours of fasting from all subjects, and serum concentrations of albumin (g/dL), total lymphocyte, total cholesterol (mg/dL), and zinc ($\mu\text{g}/\text{dL}$) were measured.

Upper gastrointestinal endoscopy findings

Regarding the results of upper gastrointestinal endoscopy, HH was defined as an apparent separation of the esophago-gastric junction and diaphragm impression by >2 cm. Patients with RE were defined as those who had results indicating RE of grade A, B, C, or D according to the Los Angeles Classification system (14). Grade A is defined as ≥ 1 mucosal breaks confined to the mucosal folds, each no longer than 5 mm. Grade B is defined as ≥ 1 mucosal break >5 mm long confined to the mucosal folds but not continuous between the tops of 2 mucosal folds. Grade C is defined as ≥ 1 mucosal break continuous between the tops of ≥ 2 mucosal folds but not circumferential. Grade D is defined as a circumferential mucosal break. Endoscopic gastric mucosal atrophy was classified as C-0 (normal), C-1, C-2, C-3, O-1, O-2, or O-3 using the Kimura-Takemoto classification system (15), which identifies the location of the endoscopic atrophic border. Overall, the EGAS was defined as 0 for C-0 type, 1 for C-1 type, 2 for C-2 type, 3 for C-3 type, 4 for O-1 type, 5 for O-2 type, and 6 for O-3 type. The mean EGAS was calculated.

Questionnaires concerning abdominal symptoms

The FSSG, which is a self-administered questionnaire developed by Kusano et al. (16), has been validated for the assessment of upper abdominal symptoms, such as gastroesophageal reflux disease (GERD), in clinical trial settings. The FSSG comprises 12 items. Each response is assigned a score for the frequency of each symptom, as follows: 0, never; 1, occasionally; 2, sometimes; 3, often; and 4, always. The FSSG score was calculated as the total number of points accumulated from the FSSG questionnaire.

The CSS, which is a self-administered questionnaire, has

Table 1. Clinical Characteristics of Study Patients (n=313).

Patient profile	
Age (years)	75.7 (±6.0)**
Gender	
Male	134 (42.8)*
Female	179 (57.2)*
BMI (kg/m ²)	22.8 (±3.6)**
<i>Helicobacter pylori</i> infection status	
<i>Helicobacter pylori</i> infection	
negative	168 (53.7)*
positive	69 (22.0)*
successful eradication	76 (24.3)*
Internal medicine therapeutic agents	
Proton pump inhibitor (PPI)	
non-user	195 (62.3)*
user	118 (37.7)*
Aspirin	
non-user	284 (90.7)*
user	29 (9.3)*
Laxative/Prokinetics	
non-user	243 (77.6)*
user	70 (22.4)*
Comorbidity	
Sarcopenia	
no	241 (77.0)*
yes	72 (23.0)*
Osteoporosis	
no	188 (60.1)*
yes	125 (39.9)*
Frailty	
no	242 (77.3)*
yes	71 (22.7)*
Nutritional status	
Zinc (µg/dL)	73.2 (±11.5)**
Albumin (g/dL)	4.2 (±0.3)**
Cholesterol (mg/dL)	203 (±36)**
Lymphocyte (counts/µL)	1,845 (±611)**
CONUT score	0.9 (±1.1)**
Upper GI Findings	
Reflux esophagitis (RE)	
no	288 (92.0)*
yes	25 (8.0)*
Hiatal hernia (HH)	
no	148 (47.3)*
yes	165 (52.7)*
Endoscopic gastric mucosal atrophy score (EGAS)	2.6 (±2.0)**
Questionnaire	
FSSG	4.9 (±5.6)**
CSS	4.0 (±4.2)**
BSFS	4.0 (±1.0)**

* Number (%), ** Median (±SD). FSSG: Frequency Scale for Symptoms of Gastroesophageal Reflux Disease, CSS: Constipation Scoring System, BSFS: Bristol Stool Form Scale

been validated for the assessment of constipation in clinical trial settings (17). The CSS comprises 8 items describing the following symptoms of constipation: frequency of bowel movements, painful evacuation, incomplete evacuation, abdominal pain, length of time per attempt, assistance for evacuation, unsuccessful attempts at evacuation per 24 hours, and duration of constipation. The score for each item ranges from 0-4 with the exception of “assistance for evacuation,” which is 0-2. Consequently, the overall score for CSS ranges from 0 to 30, with a higher score indicating worse constipation symptoms.

Stool consistency and shape were assessed by the BSFS (18), which classifies stool into seven categories: 1, nut-like; 2, lumpy sausage; 3, sausage with cracks; 4, smooth snake; 5, soft blobs; 6, fluffy pieces; and 7, watery.

Ethics

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The Juntendo Tokyo Koto Geriatric Medical Center Ethics Committee approved the study and the study protocol. With regard to the informed consent of participants, the Juntendo Tokyo Koto Geriatric Medical Center Ethics Committee determined that this study was exempt from the need to obtain patient consent. According to the decision of the Juntendo Tokyo Koto Geriatric Medical Center Ethics Committee, we notified the study subjects about our study contents on the homepage of our hospital and guaranteed them the opportunity to refuse participation.

Statistical analyses

We classified the subjects into frailty and non-frailty groups and investigated the risk factors for frailty between the two groups by univariate and multivariate analyses. The age, BMI, zinc and cholesterol levels, lymphocyte count, CONUT score, EGAS, FSSG, CSS, and BSFS were presented as the mean±standard deviation. Univariate analyses were performed using a χ^2 test and Student's *t*-test. No cut-off for age was used for patients ≥65 years old. All age data were used in the multivariate analysis. Independent variables with a *p* value of less than 0.20 in the univariate analysis were included in the multivariate logistic regression analysis. The multivariate logistic regression analysis of the risk factors for frailty was performed using a backward selection method (likelihood ratio). The odds ratio (OR) and 95% confidence intervals (CIs) were also used to identify the presence and strength of any associations. All statistical analyses were performed using the SPSS version 19 software program (IBM Corporation, Armonk, USA). *P*<0.05 was considered to indicate a statistically significant difference.

Table 2. Association between the Likelihood of Frailty in Univariate Analysis.

Covariates	Non-Frailty Group 242 subjects (77.3%)*	Frailty Group 71 subjects (22.7%)*	p value
Patient profile			
Age (years)	74.4 (\pm 5.7)**	80.0 (\pm 5.0)**	<0.001
Gender			
Male	113 (46.7)*	21 (29.6)*	
Female	129 (53.3)*	50 (70.4)*	0.010
BMI (kg/m ²)	23.0 (\pm 3.6)**	22.0 (\pm 3.3)**	0.050
<i>Helicobacter pylori</i> infection status			
<i>Helicobacter pylori</i> infection			
negative	125 (51.6)*	43 (60.6)*	
positive	52 (21.5)*	17 (23.9)*	0.661
successful eradication	65 (26.9)*	11 (15.5)*	0.049
Internal medicine therapeutic agents			
Proton pump inhibitor (PPI)			
non-user	164 (67.8)*	31 (43.7)*	
user	78 (32.2)*	40 (56.3)*	<0.001
Aspirin			
non-user	222 (91.7)*	62 (87.3)*	
user	20 (8.3)*	9 (12.7)*	0.260
Laxative/Prokinetics			
non-user	196 (81.0)*	47 (66.2)*	
user	46 (19.0)*	24 (33.8)*	0.008
Comorbidity			
Sarcopenia			
no	211 (87.2)*	30 (42.3)*	
yes	31 (12.8)*	41 (57.7)*	<0.001
Osteoporosis			
no	163 (67.4)*	25 (35.2)*	
yes	79 (32.6)*	46 (64.8)*	<0.001
Nutritional status			
Zinc (μ g/dL)	74.3 (\pm 11.9)**	69.6 (\pm 9.6)**	0.002
Albumin (g/dL)	4.2 (\pm 0.3)**	4.0 (\pm 0.4)**	<0.001
Cholesterol (mg/dL)	205 (\pm 34)**	199 (\pm 41)**	0.272
Lymphocyte (counts/ μ L)	1,898 (\pm 610)**	1,662 (\pm 584)**	0.004
CONUT score	0.7 (\pm 1.0)**	1.3 (\pm 1.4)**	<0.001
Upper GI Findings			
Reflux esophagitis (RE)			
no	222 (91.3)*	67 (94.4)*	
yes	21 (8.7)*	4 (5.6)*	0.405
Hiatal hernia (HH)			
no	121 (50.0)*	27 (38.0)*	
yes	121 (50.0)*	44 (62.0)*	0.076
Endoscopic gastric mucosal atrophy score (EGAS)	2.5 (\pm 2.0)**	2.9 (\pm 2.1)**	0.164
Questionnaire			
FSSG	4.3 (\pm 5.0)**	6.7 (\pm 7.0)**	0.001
CSS	3.4 (\pm 3.4)**	6.2 (\pm 5.6)**	<0.001
BSFS	4.0 (\pm 1.0)**	4.0 (\pm 1.3)**	0.903

* Number (%), ** Median (\pm SD). FSSG: Frequency Scale for Symptoms of Gastroesophageal Reflux Disease, CSS: Constipation Scoring System, BSFS: Bristol Stool Form Scale

Table 3. Association between the Likelihood of Frailty in Multivariate Logistic Regression Analysis.

Covariates	Multivariate***		
	Standardized coefficient	OR (95% CI)	p value
Patient profile			
Age (years)	0.146	1.16 (1.08-1.24)	<0.001
Gender			
Male		1.00 (reference)	
Female	0.818	2.27 (0.96-5.33)	0.061
BMI (kg/m ²)	0.056	1.06 (0.94-1.19)	0.346
<i>Helicobacter pylori</i> infection status			
<i>Helicobacter pylori</i> infection			
negative		1.00 (reference)	
positive	-0.329	0.72 (0.30-1.76)	0.470
successful eradication	0.088	1.09 (0.37-3.20)	0.872
Internal medicine therapeutic agents			
Proton pump inhibitor (PPI)			
non-user		1.00 (reference)	
user	0.884	2.42 (1.18-4.98)	0.016
Laxative/Prokinetics			
non-user		1.00 (reference)	
user	-0.407	0.67 (0.28-1.59)	0.360
Comorbidity			
Sarcopenia			
no		1.00 (reference)	
yes	1.995	7.35 (3.30-16.40)	<0.001
Osteoporosis			
no		1.00 (reference)	
yes	0.781	2.18 (0.99-4.84)	0.055
Nutritional status			
Zinc (µg/dL)	-0.042	0.96 (0.92-0.99)	0.027
Albumin (g/dL)	-0.202	0.82 (0.24-2.78)	0.747
Lymphocyte (counts/µL)	0.000	1.00 (0.99-1.00)	0.920
CONUT score	0.258	1.30 (0.98-1.71)	0.071
Upper GI Findings			
Hiatal hernia (HH)			
no		1.00 (reference)	
yes	0.756	2.13 (0.99-4.59)	0.053
Endoscopic gastric mucosal atrophy score (EGAS)	0.155	1.17 (0.97-1.40)	0.096
Questionnaire			
FSSG	0.078	1.08 (1.01-1.16)	0.021
CSS	0.120	1.13 (1.03-1.23)	0.007

* Number (%), ** Median (±SD). FSSG: Frequency Scale for Symptoms of Gastroesophageal Reflux Disease, CSS: Constipation Scoring System

Results

Clinical characteristics of study patients

The clinical characteristics of the 313 eligible study subjects [134 men (42.8%) and 179 women (57.2%); mean age, 75.7±6.0 years; mean body mass index, 22.8±3.6 kg/m²] are summarized in Table 1. Among PPI users, esomeprazole, ra-

beprazole, lansoprazole, omeprazole, and vonoprazan were taken by 41, 27, 24, 6, and 20 patients, respectively.

The results of the univariate analysis are shown in Table 2. Between the frailty and non-frailty groups, significant differences were observed in the age, gender, successful eradication of *H. pylori*, PPI usage, laxative/prokinetics usage, and presence of sarcopenia and osteoporosis. In addition, significant differences were observed in the zinc and albumin levels, lymphocyte counts, and the CONUT, FSSG,

and CSS scores.

Results of a multivariate logistic regression analysis

Models were adjusted for the age, gender, BMI, *H. pylori* infection status, PPI use, laxative/prokinetics use, presence of sarcopenia or osteoporosis, zinc or albumin levels, lymphocyte count, CONUT score, HH presence, EGAS, FSSG, and CSS. The multivariate logistic regression analysis showed that an older age (OR 1.16; 95% CI 1.08-1.24, $p < 0.001$), PPI use (OR 2.42; 95% CI 1.18-4.98, $p = 0.016$), sarcopenia (OR 7.35; 95% CI 3.30-16.40, $p < 0.001$), hypozincemia (OR 0.96; 95% CI 0.92-0.99, $p = 0.027$), a high FSSG score (OR 1.08; 95% CI 1.01-1.16, $p = 0.021$), and a high CSS score (OR 1.13; 95% CI 1.03-1.23, $p = 0.007$) were significantly associated with frailty (Table 3).

Discussion

In this study, we identified the following factors as being associated with frailty: advanced age, PPI use, sarcopenia, hypozincemia, and high FSSG and CSS scores in our multivariate logistic regression analysis. This is the first report of an association between frailty and abdominal symptoms evaluated by FSSG and CSS in Japan.

Our study showed that the CSS score, which has been validated for the assessment of constipation, was higher in the frailty group than in the non-frailty group in a multivariate analysis. Malnutrition in elderly patients has been shown to be a significant cause of frailty (4). In a systematic review of risk factors for malnutrition in older adults, frailty and constipation were significant risk factors for malnutrition (19). Matsushita et al. reported that, in the logistic regression model for the prevalence of prefrailty, chronic constipation was a significant and independent determinant, and they suggested that autonomic failure is associated with prefrailty among older individuals (20). According to a study that investigated the frailty status of inpatients >65 years old in Shanghai, constipation is a risk factor of frailty, and it was recommended to include frailty as an indicator in the existing assessment to rate the disease and develop a disease observation plan (21).

In the present study, the FSSG score, which has been validated for the assessment of upper abdominal symptoms such as heartburn, regurgitation and epigastric discomfort, was greater in the frailty group than in the non-frailty group in a multivariate analysis. Recently, Imagama et al., in a prospective longitudinal study, reported that lumbar kyphotic change, aggravation of spinal inclination, decreased back muscle strength, and sarcopenia were significant risk factors for the new development of GERD. They suggested that an increase in intra-abdominal pressure caused by lumbar kyphosis might induce a decreased lower esophageal sphincter (LES) pressure and HH, thereby leading to GERD (22). In our study, osteoporosis and sarcopenia were associated with frailty in a univariate analysis, so GERD symptom generation due to osteoporosis and sarcopenia may be related to

the onset of frailty. Cardin et al. reported that being bedridden was an independent risk factor for esophagitis, that esophagitis exacerbates frailty in hospitalized elderly people, and that its identification may be helpful in these patients (23). Therefore, the management of GERD symptoms may be important for the prevention of frailty.

PPI was also associated with frailty in a multivariate analysis. Long-term proton pump inhibitor therapy has been associated with an increased rate of fracture; however, there does not seem to be a clear association between PPI use and bone mineral density measurements as assessed by DXA (24). In our study, the FSSG score was higher in the frailty group than in the non-frailty group. Since subjects with frailty have stronger GERD symptoms than those without frailty, there may have been more subjects using PPIs in the frailty group than in the non-frailty group. In summary, elderly patients who use PPI for upper abdominal symptoms and those with chronic constipation may be prone to hypoalimentation, which is a cause of frailty.

In our multivariate analysis, *H. pylori* infection was not associated with frailty; however, EGAS tended to be related to frailty ($p = 0.096$). Vitale et al. reported that several observations demonstrated a correlation between *H. pylori* and the malabsorption of essential nutrients such as iron and some vitamins. The main mechanism related to the malabsorption of such components is the modified intragastric pH (hypo-achlorhydria) which occurs due to *H. pylori* infection. (25). Therefore, malnutrition and frailty may be caused by the intragastric pH being modified due to gastric mucosal atrophy. Among several important components reflecting the degree of frailty, chronic undernutrition and malnutrition are key determinants of disability and death. Simple risk scoring algorithms, such as the CONUT score, have been proposed as useful screening tools for the assessment of the nutritional status.

Regarding the nutritional status, in the present study, the serum zinc and albumin levels and the CONUT score were lower in the frailty group than in the non-frailty group in our univariate analysis. Frailty may develop under conditions of deficiency in various nutrients, including calcium, zinc, albumin, and protein, which is associated with the onset of osteoporosis and sarcopenia. Hypozincemia is related to appetite loss (6), depression (7), and taste abnormality (8), and these symptoms are risk factors for hypoalimentation. Semba et al. reported that frail women had lower serum concentrations of zinc at baseline than women who were not frail (26). Grieger et al. reported that higher levels of depression were associated with lower serum zinc levels in a cross-sectional study using the Geriatric Depression Scale (GDS) (27). Doi et al. reported that the GDS score was related to the new incidence of frailty (28). When depression, appetite loss, and taste abnormality in frail patients is treated with zinc administration, it may lead to the improvement of frailty.

In our multivariate analysis, an advanced age was shown to be a risk factor for frailty ($p < 0.001$), while a female gen-

der ($p=0.061$) tended to be related to frailty, which is similar to the findings of previous reports. Collard et al. and Kojima et al. reported that, in a systematic review, frailty increased with age, and women had higher rates of frailty than men (29, 30).

In the present study, the prevalence rates for sarcopenia, osteoporosis, and frailty were 23.0% (72/313), 39.9% (125/313), and 22.7% (71/313), respectively. Reijnierse et al. reviewed the prevalence rates from 3 definitions of sarcopenia (the European Working Group on Sarcopenia in Older People, International Working Group on Sarcopenia and the definition by Janssen) and 2 definitions of frailty (the Fried frailty phenotype and the definition of Rockwood) and reported that the prevalence rates for sarcopenia varied between 17% and 22%, while those for frailty varied between 29% and 33% in a clinically relevant population of geriatric outpatients (31). In the present study, the prevalence rates for sarcopenia and osteoporosis in the frailty group were 50.0% (31/62) and 66.1% (41/62), respectively.

In our multivariate analysis, our results showed that sarcopenia was strongly associated with frailty ($p<0.001$), while osteoporosis ($p=0.055$) tended to be related to frailty, and these results are similar to those of previous reports. Nishiguchi et al. reported that frail elderly individuals were significantly more likely to have sarcopenia than non-frail elderly individuals among community-dwelling older adults (32). Calado et al. reported that, in non-frail, pre-frail, and frail subjects, the prevalence rates for osteoporosis were 16.4%, 21.5%, and 42.9%, respectively, in an elderly urban population (33).

Several limitations associated with the present study warrant mention. First, the single-center hospital-based retrospective cross-sectional design prevented us from establishing causal associations between abdominal symptoms and frailty. Second, we did not investigate abdominal symptoms related to the pancreas, liver, or biliary tract or the education level, marital status, or medications aside from PPI, aspirin, and laxative/prokinetics. In addition, the findings in this study should be considered preliminary owing to the relatively small sample size. Therefore, it might be possible that the present data are not generalizable to all community-dwelling older people.

In conclusion, our study showed that advanced age, PPI user, sarcopenia, hypozincemia, a high FSSG score, and a high CSS score were associated with frailty in our multivariate logistic regression model. Further studies will be required to clarify these associations, including their biological mechanisms. We suggest that frailty be screened positively for elderly patients, and risk factors should be identified, such as sarcopenia, hypozincemia, and upper abdominal symptoms and constipation, as early as possible.

The authors state that they have no Conflict of Interest (COI).

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