

1 **Differential association of frailty with cognitive decline and sarcopenia in**
2 **community-dwelling older adults**

3
4 ***Running Title: Frailty with cognitive decline and sarcopenia***

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1 **Abstract:**

2 **Objectives:** Frailty in older adults is a serious problem due to various adverse health outcomes in
3 many countries with aging populations, such as Japan. The purpose of this study was to determine
4 whether frailty and pre-frailty are associated with cognitive decline and sarcopenia in
5 community-dwelling older adults.

6 **Design:** This is a cross-sectional study.

7 **Setting:** Japan.

8 **Participants:** The participants were 273 Japanese community-dwelling older women aged 65
9 years and older.

10 **Measurements:** We used the frailty criteria developed by the Cardiovascular Health Study to
11 define physical frailty. We divided the cohort into non-frail, pre-frail, and frail according to frailty
12 scores. Cognitive decline and memory decline were defined by using the Mini-Mental State
13 Examination and Scenery Picture Memory Test, respectively. Sarcopenia was defined according to
14 the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia.

15 **Results:** In the multivariate logistic regression analysis by using non-frail participants as the
16 reference, pre-frail elderly individuals were significantly more likely to have sarcopenia than
17 non-frail elderly individuals (odds ratio [OR]: 2.77, 95% confidence interval [CI]: 1.05–9.26), but not
18 cognitive decline or memory decline. Frail elderly individuals were significantly more likely to have
19 cognitive decline (OR: 5.76, 95% CI: 1.20–27.6), memory decline (OR: 5.53, 95% CI: 1.64–18.7)
20 and sarcopenia (OR: 19.1, 95% CI: 3.73–98.0) than non-frail elderly individuals.

21 **Conclusions:** Sarcopenia was associated with pre-frailty and frailty, while cognitive decline was

1 associated only with frailty.

1 **Highlights**

2 • We studied the association of physical frailty with cognitive decline and sarcopenia.

3 • We focused on the level of frailty in community-dwelling older adults.

4 • Frailty, but not pre-frailty, was associated with cognitive and memory decline.

5 • Both frailty and pre-frailty were associated with sarcopenia.

6

1 Introduction

2 Frailty in older adults is a serious concern in countries with aging populations, such as Japan. In
3 general, frailty is defined as a vulnerable state that places older adults at high risk for adverse
4 health outcomes, such as falls, hospitalization, and mortality ^{1,2}. Using the frailty criteria developed
5 by the Cardiovascular Health Study (CHS), the overall prevalence of frailty in community-dwelling
6 adults aged 65 or older in the United States has been found to range from 7% to 12%, and was
7 greater in women than in men ¹. In Japanese, the prevalence of frailty in community-dwelling adults
8 aged 65 or older was 11.3%, and it increased with aging ³. Frail older adults are considered to have
9 a substantially increased risk of disability, dependency, and need for long-term care insurance.

10 Therefore, prevention and early detection of frailty is important for addressing age-related health
11 care issues.

12 The causes of frailty are not clearly defined, but it has been suggested that age-related physical
13 changes are the main causes of frailty ⁴. Sarcopenia, defined as progressive loss of skeletal muscle
14 mass, strength, and physical function, is regarded as a key component of physical frailty ^{5,6}. The
15 Interventions on Frailty Working Group assessed various methods for screening, recruiting,
16 evaluating, and retaining frail elderly individuals in clinical trials ⁷. They reported that most
17 researchers focused on the following domains when identifying physical frailty: mobility, such as
18 lower-extremity performance and gait abnormalities; muscle weakness; poor exercise tolerance;
19 unstable balance; and factors related to body composition, such as weight loss, malnutrition, and
20 muscle loss ⁷. Age-dependent loss of skeletal muscle mass is a multifactorial process; contributing
21 factors include physical inactivity, malnutrition, oxidative stress, changes in endocrine function, and

1 increases in inflammatory cytokines.⁵ Thus, the domains of frailty overlap with the factors related to
2 sarcopenia, and both frailty and sarcopenia mutually result in adverse health outcomes^{5,6}.

3 Of note, some definitions of frailty include cognitive function and dementia^{4,8}. Several
4 cross-sectional studies have reported an association between physical frailty and cognitive function
5^{1,7,9,10}. In addition, longitudinal studies have revealed that a higher level of physical frailty is
6 associated with increased risk of incident Alzheimer's disease (AD)¹¹ and mild cognitive impairment
7 (MCI)¹². It has been indicated that frailty is associated with AD pathology¹³ and its biological
8 mechanisms¹⁴. However, not all dementia patients become frail; therefore, the association
9 between frailty and cognitive impairment warrants further study.

10 Frailty is associated with sarcopenia and cognitive decline. Furthermore, frailty has been
11 considered to include other aspects, such as psychosocial issues and comorbidities¹⁵. However, it
12 is unclear whether the associations between frailty and cognitive decline as well as between frailty
13 and sarcopenia are different according to the level of frailty. Therefore, the purpose of this study
14 was to determine whether frailty and pre-frailty are associated with cognitive decline and
15 sarcopenia in community-dwelling older adults.

1 **Methods**

2 ***Participants***

3 Participants for this study were recruited through the local press; 273 Japanese women aged 65
4 years and older (mean age 73.0 ± 5.4 years) responded. We included community-dwelling older
5 adults who were independent in activities of daily living (ADLs). Participants were interviewed and
6 excluded if they met any of the following criteria: severe cardiac, pulmonary, or musculoskeletal
7 disorders; severe neurological disorders, such as Parkinson disease and stroke; and participation
8 in Japan's long-term care service. The following data were collected from each participant: age,
9 height, weight, and number of medications being consumed.

10 Written informed consent was obtained from each participant in accordance with the guidelines
11 approved by the Kyoto University Graduate School of Medicine and the Declaration of Human
12 Rights, Helsinki, 1975. The study protocol was approved by the ethical committee of the Kyoto
13 University Graduate School of Medicine.

15 ***Assessment of frailty***

16 We measured physical frailty domains determined in a previous study³. As in that study, we
17 considered the frailty phenotype to be characterized by limitations in the following five domains by
18 using frailty criteria developed by the CHS¹: slowness, weakness, exhaustion, low activity, and
19 shrinking. To measure slowness, each participant's 10-m normal walking speed (m/s) was
20 calculated, and a slow walk was defined as <1.0 m/s. To measure weakness, low grip strength was
21 established according to a sex-specific cutoff of the average grip strength in each arm (women:

1 <17 kg). Exhaustion was assessed via self-report by using the Geriatric Depression Scale ¹⁶ -i.e.,
2 exhaustion was defined as a negative (“no”) answer to the question “do you feel full of energy?” We
3 evaluated the role of physical activity by asking the following questions about time spent engaged
4 in sports and exercise: (1) “Do you engage in moderate levels of physical exercise or sports aimed
5 at health?” and (2) “Do you engage in low levels of physical exercise aimed at health?” If a
6 participant answered “no” to both of these questions, then we considered their physical activity to
7 be low. Shrinking was established according to self-reports of weight loss in response to the
8 following question: “In the past 2 years, have you lost more than 5% of your body weight
9 irrespective of intent to lose weight?” If a participant answered “yes” to this question, then we
10 considered them to have shrunk. We calculated the number of affected domains and classified
11 participants as follows: pre-frailty = 1 or 2, frailty ≥ 3 ¹.

13 ***Measurement of cognitive function***

14 Participants’ cognitive function was measured by using two neuropsychological tests: the
15 Mini-Mental State Examination (MMSE) ¹⁷ and the Scenery Picture Memory Test (SPMT) ¹⁸.

16 Global cognitive function was assessed by using the MMSE, a standard test in cognitive aging
17 research to assess mental status. The MMSE tests five areas of cognitive function: orientation,
18 registration, attention and calculation, recall, and language. It has 11 questions and a possible
19 maximum score of 30. We divided the participants into a normal or a cognitive decline group based
20 on a cut-off of 23/24 as the MMSE score ¹⁹.

21 The SPMT is a simple memory test that assesses visual memory combined with verbal

1 responses. This test uses a line drawing of a living room in a house with 23 objects commonly
2 observed in daily life on an A4 piece of paper. The examinee is instructed to look at the picture for 1
3 minute and remember the items. After this encoding period, participants are distracted by
4 completing a brief digits forward test. Participants are then asked to recall the objects in the picture
5 without a time limitation. The recall usually takes approximately 2 minutes. The number of items
6 recalled is the score for the SPMT. We divided the participants into a normal or memory decline
7 group based on a cut-off of 9/10 as the SPMT score¹⁸.

9 ***Definition of sarcopenia***

10 We defined sarcopenia by using the diagnostic algorithm recommended by the Asian Working
11 Group for Sarcopenia (AWGS), which assesses the presence of both low muscle function (low
12 physical performance or low muscle strength) and low muscle mass²⁰. A bioelectrical impedance
13 data acquisition system (Inbody 430; Biospace Co, Ltd, Seoul, Korea) was used to perform
14 bioelectrical impedance analysis²¹. This system uses electrical current at multiple frequencies (5,
15 50, 250, 500, and 1000 kHz) to directly measure the amount of extracellular and intracellular water.
16 Participants stood on two metallic electrodes and held metallic grip electrodes. Using segmental
17 body composition, appendicular skeletal muscle mass was determined and used for further
18 analysis. Skeletal muscle mass index (SMI) was calculated by dividing muscle mass by height
19 squared in meters (kg/m^2). This index has been used in several epidemiological studies^{22, 23}. If a
20 participant had both low muscle function (slow walking speed, ≤ 0.8 m/s; low grip strength for
21 women, ≤ 18 kg) and low SMI (low muscle mass for women, ≤ 5.7 kg/m^2), then they were defined as

1 having sarcopenia ²⁰.

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3 ***Statistical analysis***

4 Prior to the analysis, we classified participants into the following three groups according to their
5 frailty score: non-frailty, pre-frailty, and frailty. Differences in the demographic variables, MMSE,
6 SPMT, and SMI among the three groups were examined by using the analysis of variance (ANOVA).
7 When a significant effect was found, differences were determined with the Tukey-Kramer post-hoc
8 test. Differences in the prevalence of cognitive decline, memory decline, and sarcopenia among the
9 three groups were evaluated by using the chi-square test. In addition, multivariate logistic
10 regression analyses, adjusted for age, BMI, and medications, were performed to determine
11 whether physical frailty was associated with cognitive decline, memory decline, or sarcopenia. For
12 this analysis, cognitive decline, memory decline, and sarcopenia were dependent variables, while
13 the three frailty groups (dummy coded with non-frailty group as the reference group) were
14 independent variable. Subsequent multivariate logistic regression analyses were performed to
15 determine the independent association between each level of frailty and the risk of cognitive
16 decline or sarcopenia. In these subsequent analyses (adjusted for age and medications), the frailty
17 groups were the dependent variables, and cognitive decline and sarcopenia were independent
18 variables. Odds ratios (ORs) with 95% confidence intervals (CI) were presented. Statistical
19 analyses were carried out by using SPSS Statistics for Windows, version 20.0 (SPSS Inc. Chicago,
20 IL, USA), with a significance threshold of 0.05.

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1 **Results**

2 Demographic data for participants stratified by frailty group are shown in Table 1. There were 89
3 participants (32.6%) in the non-frailty group, 155 participants (56.8%) in the pre-frailty group, and
4 29 participants (10.6%) in the frailty group. ANOVA showed that there were significant differences in
5 age, walking speed, and grip strength among the three groups (Table 1). In the chi-square test,
6 there were significant differences in the prevalence of cognitive decline, memory decline, and
7 sarcopenia (Table 1). In addition, the frailty group had significantly lower MMSE ($F = 6.78$, $p =$
8 0.001 , Figure 1a) and SPMT ($F = 18.5$, $p < 0.001$, Figure 1b) than the non-frailty and pre-frailty
9 groups, and lower SMI ($F = 5.17$, $p = 0.006$, Figure 1c) than the non-frailty group.

10 Eighteen participants (6.6%) had cognitive decline, 20 participants (7.3%) had memory decline,
11 and 23 participants (8.4%) had sarcopenia. In the multivariate logistic regression analysis after
12 adjustment for age, BMI, and medications, by using non-frailty group as the reference, the
13 pre-frailty group was significantly more likely to have sarcopenia (OR: 2.77, 95% CI: 1.05–9.26,
14 $p = 0.044$), but not cognitive decline or memory decline (Table 2). The frailty group was significantly
15 more likely to have cognitive decline (OR: 5.76, 95% CI: 1.20–27.6, $p = 0.029$), memory decline
16 (OR: 5.53, 95% CI: 1.64–18.7, $p = 0.006$), and sarcopenia (OR: 19.1, 95% CI: 3.73–98.0,
17 $p < 0.001$) (Table 2).

18 In the logistic regression analysis in which the frailty groups were the dependent variables and
19 cognitive decline and sarcopenia were independent variables, cognitive decline was independently
20 only associated with a frailty score of ≥ 3 (OR: 3.73, 95% CI: 1.23–11.4, $p = 0.020$), while
21 sarcopenia was independently associated with both pre-frailty (score ≥ 1 ; OR: 5.33, 95% CI:

1 1.22–23.3, $p = 0.026$) and frailty (score ≥ 3 ; OR: 13.1, 95% CI: 4.98–34.2, $p < 0.001$). These
2 associations remained significant after adjustment for age and medications (Table 3).

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1 **Discussion**

2 The results of this study showed that frailty (defined as frailty score ≥ 3) was associated with
3 cognitive decline, memory decline, and sarcopenia, and that pre-frailty (frailty score = 1 or 2) was
4 associated with only sarcopenia. It is a new and interesting finding that there were differences in
5 the association between physical frailty and cognitive decline, memory decline, and sarcopenia
6 according to level of frailty.

7 In this study, we showed that frailty, but not pre-frailty, was associated with cognitive decline and
8 memory decline. Our results also showed that frailty and pre-frailty were associated with
9 sarcopenia, in contrast to cognitive and memory decline. In Japanese, multicenter,
10 population-based studies, the prevalence of dementia was not high among those aged
11 65–74 years (less than 10%), but was higher among those aged 75 years and older ²⁴. The
12 prevalence of sarcopenia exhibited the same tendency, with the prevalence rising among those
13 aged 75 years and older ^{25, 26}. Thus, older adults (particularly those 75 and older) are prone to both
14 cognitive impairment and sarcopenia. However, low physical performance, low physical strength,
15 and the decrease of muscle mass, which overlap with both sarcopenia and frailty, can be found
16 from middle age ²⁷⁻²⁹. Thus, as shown in the results of this study, it is possible that sarcopenia is
17 associated with frailty at an earlier stage than is cognitive impairment, and that sarcopenia is
18 affected more by frailty than is cognitive impairment.

19 A recent study investigated the association of physical frailty and pre-frailty with dementia and
20 cognitive impairment ³⁰. In that study, physically frail older adults were over four times more likely to
21 have AD, and eight times more likely to have cognitive impairment than robust older adults were.

1 Pre-frail older adults showed an increased risk for dementia in the aforementioned study, but some
2 estimates were not statistically significant in the fully adjusted models ³⁰. The results of that study
3 were consistent with our study. Previous studies indicated that frailty is associated with AD
4 pathology ¹³ and biological mechanisms ¹⁴, such as diffuse neuritic plaques, oxidative stress, and
5 inflammation. It is also possible that frailty and AD share common lifestyle risk factors, such as
6 physical inactivity and smoking, that lead to their pathophysiology, which contributes
7 simultaneously to physical frailty and AD ¹³. On the other hand, it has been indicated that
8 comorbidities caused by cognitive impairment were also associated with frailty in AD or MCI
9 patients ³¹. Thus, it is likely that these associations interact with one another, leaving the causal
10 association between physical frailty and cognitive decline unclear. Further studies are required to
11 understand these associations.

12 Definitions of frailty and sarcopenia overlap, and sarcopenia is considered one of the core
13 symptoms of physical frailty ^{5, 6}. The causal mechanisms underlying sarcopenia can be oxidative
14 stress, dysregulation of inflammatory cytokines and hormones, malnutrition, physical inactivity, and
15 muscle apoptosis, all of which have been hypothesized to contribute to frailty through interactive
16 pathways ^{32, 33}. Recently, the definition of sarcopenia has been the coexistence of low muscle mass
17 and low physical performance ^{5, 20, 34}, which are contained in frailty domains. Thus, the association
18 of sarcopenia with even pre-frailty seems reasonable. Overlapping intervention strategies (e.g.,
19 nutritional supplementation and exercise) may be required to prevent both frailty and sarcopenia.

20 During recent years, the definition of frailty has been changing. Frailty has been considered to
21 include other aspects, for instance social aspects and comorbidities ¹⁵. In addition to these aspects,

1 poor cognition needs to be included in the definition of frailty, as shown in previous studies ^{4, 8} and
2 by this study. Furthermore, this study indicated that poor cognition was associated with frailty, and
3 that sarcopenia was associated even with pre-frailty. The results indicate that we need to
4 understand the consecutive mechanism as well as the association of pre-frailty and frailty with
5 cognitive decline, sarcopenia, and other adverse health outcomes. Interventions may need to be
6 tailored to the level of frailty to effectively prevent various functional declines. Future studies should
7 investigate these intervention strategies.

8 There were several limitations to this study. First, the cross-sectional design prevented us from
9 establishing causal associations between frailty and cognitive decline or sarcopenia. Second, the
10 findings in this study should be considered preliminary owing to the relatively small sample size,
11 which may introduce some error of inference, reduce the power of analysis, and limit generalization.
12 Third, the design of this study was not a population sampling, and participants in this study were
13 independent in ADLs. This may lead to an underestimation of the prevalence of frailty, cognitive
14 decline, and sarcopenia, as the participants were relatively healthy elderly persons.

15 In conclusion, our results indicate that there were differences in the association between physical
16 frailty and cognitive decline, memory decline, and sarcopenia according to the level of frailty.
17 Cognitive decline and memory decline were associated with frailty. Sarcopenia was associated with
18 pre-frailty and frailty. Further studies are required to understand these associations including
19 biological mechanisms.

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4

5 **Conflict of Interest:** The authors declare no conflicts of interest.

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Table 1. Demographic differences according to frailty scores

	Total (n = 273)	Frailty level			<i>p</i> for trend	<i>Post-hoc</i>
		Non-frailty (n = 89)	Pre-frailty (n = 155)	Frailty (n = 29)		
Age (y)	73.0 ± 5.4	73.1 ± 4.6	72.3 ± 5.6	76.6 ± 5.1	<0.001 [†]	a, b
BMI (kg/m ²)	22.5 ± 3.2	22.2 ± 3.0	22.7 ± 3.3	21.9 ± 3.8	0.291	–
Medications	2.32 ± 2.24	2.18 ± 2.35	2.23 ± 2.10	3.27 ± 2.55	0.072	–
Walking speed (m/s)	1.40 ± 0.20	1.43 ± 0.18	1.41 ± 0.20	1.21 ± 0.20	<0.001 [†]	a, b
Grip strength (kg)	22.4 ± 4.0	23.4 ± 3.4	22.6 ± 3.8	18.3 ± 4.1	<0.001 [†]	a, b
Cognitive decline (n)	18 (6.56%)	4 (4.49%)	9 (5.81%)	5 (17.2%)	0.047*	
Memory decline (n)	20 (7.33%)	6 (6.74%)	4 (2.58%)	10 (34.5%)	<0.001 [†]	
Sarcopenia (n)	22 (8.06%)	2 (2.25%)	9 (5.81%)	11 (37.9%)	<0.001 [†]	

BMI = body mass index

Non-frailty was defined as frailty score of 0, pre-frailty was score 1 or 2, frailty was score 3 or greater.

Cognitive decline was defined as the cut-off of MMSE score (23/24).

Memory decline was defined as the cut-off of SPMT score (9/10).

Sarcopenia was defined by using the AWGS-recommended diagnostic algorithm.

*: $p < 0.05$, †: $p < 0.01$

a, significant difference between frailty and non-frailty ($p < 0.01$)

b, significant difference between score frailty and pre-frailty ($p < 0.01$)

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Table 2. Relationship between the level of frailty and cognitive decline, memory decline, and sarcopenia

Frailty level	Cognitive decline		Memory decline		Sarcopenia	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Non-frailty	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Pre-frailty	1.79 (0.47–6.84)	0.394	0.37 (0.10–1.36)	0.134	2.77 (1.05–9.26)	0.044*
Frailty	5.76 (1.20–27.6)	0.029*	5.53 (1.64–18.7)	0.006†	19.1 (3.73–98.0)	<0.001†

The analyses for cognitive decline and memory decline were adjusted for age, BMI, and medications.

The analysis for sarcopenia was adjusted for age and medications.

*: $p < 0.05$, †: $p < 0.01$

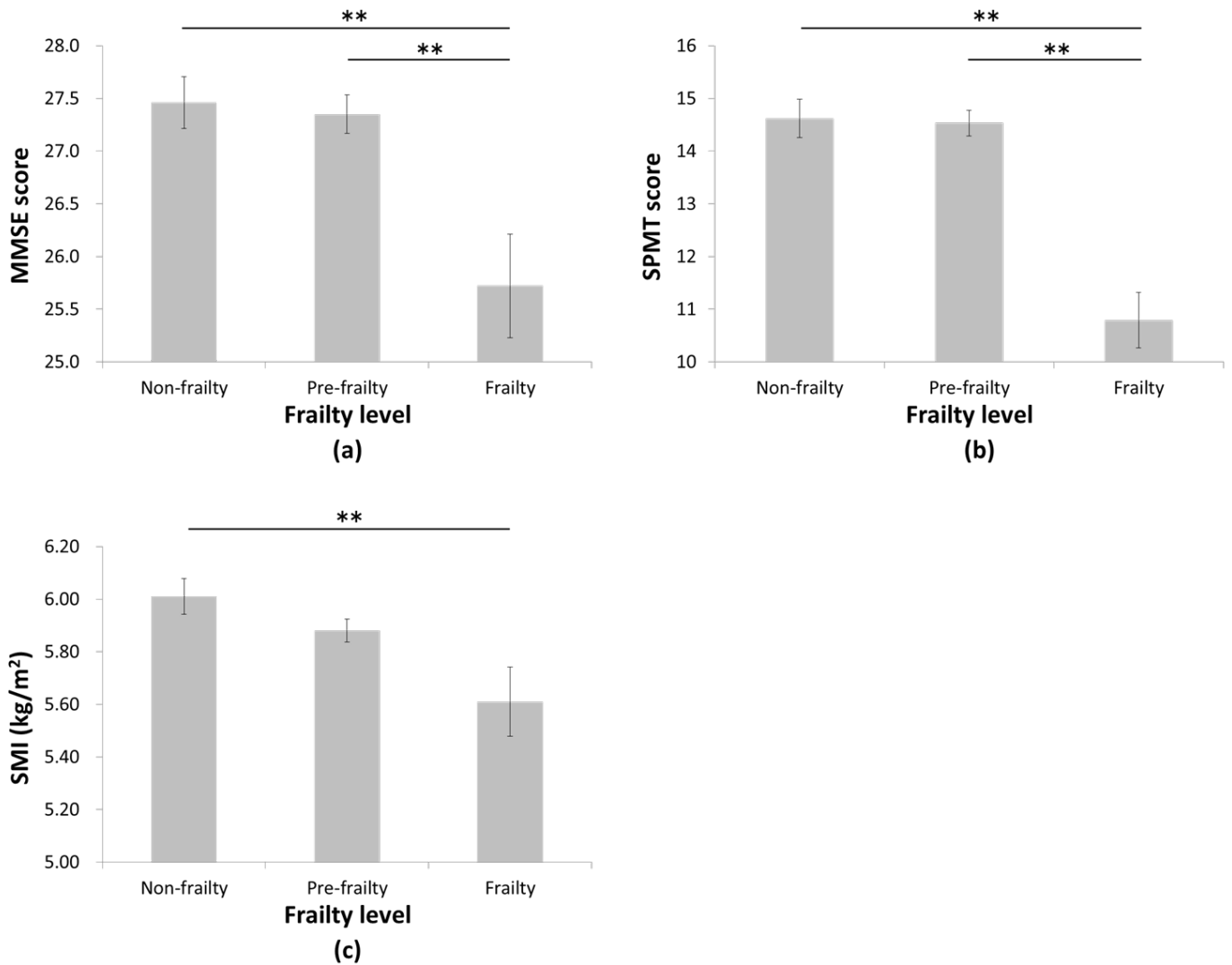
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Table 3. Independent relationship between each level of frailty and cognitive decline or sarcopenia

Domains	Univariate analysis						Multivariate analysis										
	Frailty score ≤ 1			Frailty score ≤ 2			Frailty score ≤ 1			Frailty score ≤ 2			Frailty score ≤ 3				
	OR (95% CI)	p		OR (95% CI)	p		OR (95% CI)	p		OR (95% CI)	p		OR (95% CI)	p			
Cognitive decline	1.76 (0.56–5.51)	0.331		1.43 (0.54–3.84)	0.473		3.73 (1.23–11.4)	0.020*		2.48 (0.68–9.07)	0.168		1.63 (0.56–4.72)	0.371		4.61 (1.27–16.8)	0.020*
Sarcopenia	5.33 (1.22–23.3)	0.026*		9.07 (3.22–25.5)	<0.001**		13.1 (4.98–34.2)	<0.001**		5.47 (1.21–24.6)	0.027*		8.75 (3.00–25.5)	<0.001**		10.0 (3.40–29.6)	<0.001**

Note:
The multivariate analyses were adjusted for age and medications.
*: p < 0.05, **: p < 0.01



2

3 Figure 1. Comparison of the MMSE, SPMT, and SMI between the groups according to the level of
4 frailty.

5 (a) There were significant differences in the MMSE scores between the three groups ($F = 6.78$,
6 $p = 0.001$).

7 (b) There were significant differences in the SPMT scores between the three groups ($F = 18.5$,
8 $p < 0.001$).

9 (c) There were significant differences in the SMI between the three groups ($F = 5.17$, $p = 0.006$).

10 *: $p < 0.05$, **: $p < 0.01$