ORIGINAL ARTICLE

Relationship between sarcopenia and the serum creatinine/cystatin C ratio in Japanese rural community-dwelling older adults

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Abstract

Aims Sarcopenia, the age-related decline in skeletal muscle volume and function, is associated with negative clinical and socioeconomic outcomes in elderly people. Clinical biomarkers to diagnose sarcopenia that can be quantified in a reliable, and cost- effective manner, are needed. We investigated whether the creatinine (Cr) /cystatin C (CysC) ratio is correlated with muscle volume and physical function in Japanese community-dwelling elderly subjects.

Methods and results The present study included 213 men aged 73.2±6.2 years and 464 women aged 72.4±5.5 years from a rural area in the Hyogo prefecture of Japan. To evaluate whether the Cr/CysC ratio is correlated with sarcopenia criteria in elderly individuals without severe renal impairment, we excluded subjects with estimate glomerular filtration rate (eGFR) <45.

The prevalence of sarcopenia diagnosed according to the AWGS criteria was 2.8% in men and 3.4% in women. The Cr/CysC ratio correlated with skeletal mass index (r = 0.49, p <0.0001), skeletal muscle mass (r = 0.53, p <0.0001), grip power (r = 0.59, p <0.0001), knee extension muscle strength (r = 0.49, p <0.0001), normal gait speed (r = 0.18, p <0.0001), and maximal gait speed (r = 0.32, p <0.0001). A negative correlation between the Cr/CysC ratio and, body fat mass (r = -0.20, p <0.0001) and percentage of body fat mass (r = -0.39, p <0.0001) was observed. In a multiple regression analysis, Cr/CysC was also found to be significantly positively correlated with each component of the sarcopenia criteria.

Conclusions Even in elderly individuals without severe renal impairment, the Cr/CysC ratio was positively correlated with muscle volume and physical function and negatively correlated with body fat mass. Therefore, the Cr/CysC ratio might be a useful biomarker to predict sarcopenia.

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Introduction

One of the most recognized changes in body composition with senescence is the loss of skeletal muscle mass, a phenomenon that is known as sarcopenia. Sarcopenia is increasingly recognized as a correlate of aging and is associated with an increased likelihood of negative outcomes, including falls, fractures, frailty, and mortality. Sarcopenia is also associated with negative socioeconomic outcomes. According to the Asian Working Group for Sarcopenia (AWGS) criteria, bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DXA) have been recommended for the assessment of muscle mass.1) However, these tools are not easily applied in the daily clinical setting. Therefore, useful biomarkers that can be quantified in a

reliable, cost- effective manner are needed to guide the diagnosis and therapeutic strategies of pathological sarcopenia in routine clinical practice and clinical trials.

Recently, chronic kidney disease (CKD) has been found to be associated with the decline of physical function and increased frailty in elderly people. Indeed, physical function in patients with CKD decreased as the disease progressed according to stage .2) and CKD severity was associated with poor physical performance and frailty in a graded fashion. 3)

Serum creatinine (Cr) is a major biomarker that reflects not only renal function, but also total muscle mass. Cystatin C (CysC) may be a more sensitive biomarker to estimate glomerular filtration rate (eGFR) without being affected by sex, age, or muscle mass. CKD is characterized by a decline in eGFR. In a previous study, lower eGFR using CysC (eGFRcys) was found to be associated with a higher risk of prevalent and incident frailty, whereas eGFR using creatinine (eGFRcre) was not.4) It is reported that frailty is common among CKD patients and is associated with lower eGFRcys,5) and yet, another study reported that higher CysC, but not creatinine values, were associated with increased odds of a frailty status.6) Sarcopenia is a key component of frailty, and the prevalence of sarcopenia is reportedly higher in elderly individuals with even mildly reduced kidney function.7) According to the findings of Sharma et al., sarcopenia is highly prevalent among patients with CKD, however, they were unable to find a stronger association with low eGFRcys than with eGFRcre.8) In general, the association between these markers of kidney function and sarcopenia is not fully understood.

Recently, the correlation between muscle mass, physical function, and the Cr/CysC ratio was demonstrated in ICU patients.9) In the present study, we hypothesized that the Cr/CysC ratio would be associated with muscle mass and physical function in Japanese rural community-dwelling elderly subjects without severe renal dysfunction. We aimed to evaluate the usefulness of the Cr/CysC ratio as a diagnostic biomarker predicting the presence of sarcopenia.

Methods

This cross-sectional study was designated as the Frail Elderly in Sasayama-Tamba Area (FESTA) study. The study population, aged ≥65 years, was recruited from apparently healthy community-dwelling elderly people in the Sasayama-Tamba area, a rural area of the Hyogo prefecture in Japan, between 2015 and 2017. The study was approved by our institutional review board, and all subjects provided written informed consent.

Physical function assessment

Normal gait speed, maximal gait speed, handgrip power, and knee extension muscle strength as indices of physical function were measured. Knee extension strength (Nm) was measured in the dominant leg during isometric contraction of the knee extensor in the sitting position, with the knee position maintained at 60°, using a hand-held dynamometer (Sakai Medical. Co., Ltd, Tokyo, Japan). The hand-held dynamometer (HHD) was placed 25 cm distal to the knee joint.

Measurement of body composition

To evaluate muscle mass, the subjects were enrolled to bio-electrical impedance analysis (BIA) using the InBody770 (Biospace, Japan). Body fat mass (BFM) was also evaluated by using the InBody770. Skeletal mass index (SMI) was defined as muscle mass divided by height squared. Testing was performed in the morning.

Blood sample analysis

Non-fasting blood samples were obtained from all participants. Biochemical measures including serum levels of CysC, Cr, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, high- densitylipoprotein (HDL) cholesterol, γ-glutamyltransferase (γ-GTP), high -sensitive C-reactive protein (hs-CRP), and circulating blood cells were also estimated using standard procedures in Japan.

Categorization of CKD

CKD was defined and classified according to the KDIGO criteria.10) eGFR was determined using the revised equations derived from serum creatinine levels in Japan.11)

Diagnosis of sarcopenia

The diagnosis of sarcopenia and pre-sarcopenia was determined using the AWGS criteria.1) The SMI cutoff point was < 7.0 kg/m^2 for men and < 5.7 kg/m^2 for women using BIA. The cutoff point for handgrip power was <26 kg for males and <18 kg for females. Muscle performance was evaluated by calculating the walking speed over a distance of 10 m, with a speed of <0.8 m/s indicating low performance.

To measure normal and maximal gait speed, subjects were asked to walk straight ahead for 12 meters at their usual speed to measure the 10- meter walk time. The walking speed reached a steady speed within the first 2 meters. Gait speed (m/s) was calculated by dividing the distance covered (10 meters) by the 10-meter walk time (s).

The stage of sarcopenia was diagnosed as robust when the subjects had a normal SMI (≥7.0 kg/m^2 in males; ≥5.7 kg/m^2 in females). The pre-sarcopenia stage

was diagnosed when the subjects had a low SMI (<7.0 kg/m^2 in males; <5.7 kg/m^2 in females), normal handgrip strength (≥26 kg in males; ≥18 kg in females), and normal gait speed (≥0.8 m/sec). The sarcopenia stage was diagnosed when subjects had a low SMI and low gait speed (<0.8 m/sec) or low handgrip strength (<26 kg in males; <18 kg in females).

Statistical analysis

The results were expressed as a mean ± and standard deviations for continuous variables unless otherwise specified. Categorical variables were expressed as percentages. For intergroup comparisons, data were analyzed using the Student's t- test and one-way ANOVA, followed by the Tukey Krammer test. Spearman's correlation coefficient was used to assess the associations between the Cr/CysC ratio and skeletal muscle mass (SMM), SMI, BFM, percentage of BFM, grip power, knee extension muscle strength, normal gait speed, and maximal gait speed. Multivariate regression analysis was performed for each component of the AWGS criteria (SMI, grip power, and normal gait speed) as well as the individual parameters. JMP 13.1 software was used for data analysis. P-values < 0.05 were considered significant.

Results

The baseline characteristics, indices of body composition, and physical performance of the subjects are presented in Table 1A. In the muscles of chronic renal failure patients, the synthesis of muscle protein was suppressed and the degradation of muscle protein is increased. To reduce the influence of these uremic changes in the muscle, we excluded these subjects with low renal function (eGFRcr<45mL/min/1.73m^2). Ultimately, a total of 677 subjects (213 men and 464 women) remained.

The study included 213 men ranging from 65 to 94 years of age, and 464 women ranging from 65 to 91 years of age. The BFM weight and BFM percentages (BFM ％) were higher in women. While there was no difference in normal gait speed between men and women, maximal gait speed, grip power, knee extension muscle strength, SMM, and SMI were higher overall in men (Table 1A).

Among the 677 subjects, 22 (6 men and 16 women) were defined as having sarcopenia by the AWGS criteria, while 183 subjects (49 men, 134 women) were defined as having pre-sarcopenia (Table 1B).

Characteristics of each stage of sarcopenia (robust, pre-sarcopenia, and sarcopenia) are shown in Table 1C. The subjects in the sarcopenia and pre-sarcopenia stages subjects were older than those in the robust stage both among males and females. The height, body weight, and BMI decreased, as the stage of sarcopenia progressed in

both males and females. Among male subjects, normal and maximal gait speed did not change, but in females, they decreased in subjects in the sarcopenia stage. Muscle strength (grip power and knee extension muscle strength), skeletal muscle mass, and SMI decreased as the stage of sarcopenia progressed in both males and females. Body fat mass also decreased as the stage of sarcopenia progressed, however the percentage of BFM did not significantly change in each stage of sarcopenia.

The creatinine (Cr), cystatin C (CysC), and Cr/CysC levels in each stage of sarcopenia (robust, pre-sarcopenia and sarcopenia) are shown in Fig. 1, A-C (males) and Fig. 1D-F (females). Only Cr/CysC decreased in a consistent manner, as the stage of sarcopenia progressed. CysC levels were higher in the sarcopenia stage than in the robust stage in males, while whereas Cr levels did not show this trend.

Correlations between the parameters of body composition based on BIA and the Cr/CysC ratio are shown in Fig. 2 (A, B) and Fig.3 (A, B). SMI and SMM exhibited a significant positive correlation with the Cr/CysC ratio .(Fig. 2A, Fig. 3A). The correlation coefficient (r) of men was higher than that of women in terms of both SMI and SMM (Fig. 2A, Fig. 3A). Conversely, body fat mass (BFM) and the percentage of BFM exhibited a significant negative correlation with Cr/CysC. The correlation coefficient (r) of females was higher than that of males in terms of both BFM and percentage of BFM. (Fig. 2B, Fig. 3)

Correlations between the parameters of physical performance and the Cr/CysC ratio are shown in Fig. 2 (C, D) and Fig. 3 (C, D). The Cr/CysC ratio exhibited a significant positive correlation with grip power, knee extension muscle strength, normal gait speed, and maximal gait speed. The Cr/CysC ratio exhibited a strong positive correlation with the muscle strength parameters (grip power: r= 0.59, p<0.0001, knee extension muscle strength: r= 0.49, p<0.0001)

Simple correlations between SMI and height, weight, BMI, and biochemical biomarkers are shown in Table 2. Among these explanatory variables, the correlation coefficients (r) of body size (height and weight) were the highest, meaning that body size is the most important factor to determine skeletal muscle mass. Among blood sample biomarkers, indices of anemia (RBC, hemoglobin and hematocrit) exhibited a mild positive correlation with SMI. These results support the previous report, wherein anemia was reported to be associated with lower muscle strength and physical performance.[12] In multiple regression analyses with adjustment of age, height, weight, and hemoglobin, Cr/CysC was found to be a significant and common positive correlating factor for SMI (Table 2B). In multiple regression analyses with the sexes separated, the Cr/CysC ratio was also found to be a significant positive correlating factor for SMI.

Simple correlations between grip power and

height, weight, BMI, and biochemical biomarkers are shown in Figure 3. The results were similar to those of SMI. In multiple regression analyses under the adjustment of age, height, weight, and hemoglobin, Cr/CysC was found to be a significant and common positive correlating factor for grip power (Figure 3).

Simple correlations between normal gait speed and height, weight, BMI, and biochemical biomarkers are shown in Table 4. Unlike the cases of SMI and grip power, weight did not exhibit a positive correlation with normal gait speed.

Among blood sample biomarkers, not only hemoglobin but also albumin exhibited a mild positive correlation with normal gait speed. It is already reported that low serum albumin is associated with physical function of elderly people.13) Thus, we chose albumin instead of weight as an explanatory variable for multiple regression analyses.

In multiple regression analyses with adjustment of age, height, albumin, and hemoglobin, Cr/CysC was found to be a significant and common positive correlating factor for normal gait speed (Table 4B).

Table 1

A. Clinical characteristics, body composition, and physical performance in the subjects

	Total (n=677)	Male (n=213)	Female(n=464)	p-vale
Age (year-old)	72.6.±5.7	73.2±6.2	72.4±5.5	0.1156
Height (cm)	155.4±8.0	163.7±5.6	151.5±5.6	<0.0001
Body weight (kg)	54.6±9.3	62.1±9.0	51.2±7.2	<0.0001
Body mass index	22.6±2.9	23.1±2.9	22.3±2.9	0.0003
Body fat mass (kg)	15.2±5.4	14.6±5.6	15.5±5.3	0.0350
Percentage of BFM (%)	27.6±7.7	23.0±6.7	29.8±7.2	<0.0001
Normal gait speed (m/s)	1.49±0.24	1.47±0.24	1.49±0.23	0.2380
Maximal gait speed (m/s)	1.91±0.31	1.98±0.31	1.89±0.31	0.0002
Grip power (kg)	27.3±7.2	35.2±5.9	23.8±4.2	<0.0001
Knee extension muscle strength (Nm)	353.1±120.0	457.2±122.5	305.4±83.0	<0.0001
Skeletal muscle mass(kg)	15.2±5.4	19.9±2.7	13.7±1.9	<0.0001
Skeletal Mass Index	6.41±0.93	7.40±0.72	5.95±0.60	<0.0001
eGFR (mL/min/1.73 m^2)	71.2±12.8	70.2±11.9	71.6±13.1	0.1810

Data are expressed as mean±SD or number (%).

Table 1

B. Number of sarcopenia and pre-sarcopenia by AWGS criteria.

	Total (n=677)	Male (n=213)	Female (n=464)
Robust	472(69.2)	158(74.2)	314(67.7)
Pre-sarcopenia	183(27.0)	49(23.0)	134(28.9)
Sarcopenia	22(3.2)	6(2.8)	16(3.4)

Data are expressed as number (%).

Table 1

C. Characteristics of each stage of sarcopenia (robust, pre-sarcopenia and sarcopenia)

	Male			Female		
	Robust (n=158)	Pre-sarcopenia (n=49)	Sarcopenia (n=6)	Robust (n=314)	Pre-sarcopenia (n=134)	Sarcopenia (n=16)
Age (year-old)	72.3±5.4	75.0±7.2†	80.5±8.2*	72.1±5.5	72.9±5.2	75.9±6.6†
Height (cm)	164.9±5.0	160.1±6.0†	159.9±4.9	152.5±5.3	150.3±5.3*	143.2±6.1* #
Body weight (kg)	65.2±7.8	53.4±5.0*	51.3±9.9*	53.9±6.3	45.7±5.0*	43.1±6.1*
Body mass index	24.0±2.7	20.8±1.9*	20.1±3.9*	23.2±2.6	20.3±2.3*	21.1±3.4*
Normal gait speed (m/s)	1.49±0.24	1.43±0.24	1.34±0.09	1.51±0.23	1.49±0.22	1.26±0.30* #
Maximal gait speed (m/s)	2.01±0.31	1.89±0.32	1.87±0.07	1.90±0.30	1.88±0.29	1.54±0.37* #
Grip power (kg)	36.8±5.6	31.4±3.2*	23.1±1.7*#	24.6±4.0	22.7±3.3*	15.2±2.4*#
Knee extension muscle strength(Nm)	481.8±118.3	394.0±109.2*	325.1±56.8*	321.7±81.3	279.6±72.0*	202.6±77.5*#
Skeletal muscle mass (kg)	21.0±2.1	16.9±1.7*	15.9±1.8*	14.6±1.5	12.1±1.2*	10.3±1.5*#
Skeletal Mass Index: SMI	7.71±0.53	6.56±0.35*	6.20±0.59*	6.27±0.42	5.34±0.28*	4.99±0.43*
Body fat mass (kg)	15.4±5.7	12.2±4.2*	11.9±6.9	16.6±5.2	13.3±4.6*	12.9±5.3†
Percentage of BFM (%)	23.2±6.6	22.5±6.8	22.0±8.2	30.2±6.9	28.7±7.7	29.1±8.7

Data are expressed as mean±SD. P values were calculated using ANOVA. *:$p<0.01$ vs Robust, †:$p<0.05$ vs Robust, #:$p<0.01$ vs Pre-sarcopenia
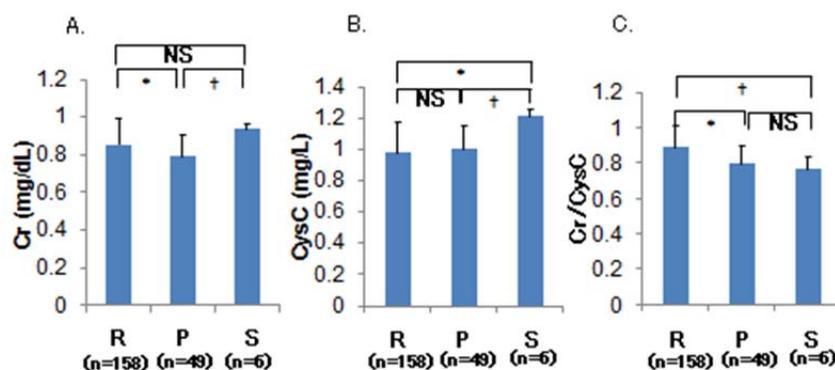
Fig. 1

Creatinine (Cr), cystatin C (CysC) and Cr/CysC levels in robust (R), pre-sarcopenia (P) and sarcopenia (S).

A: Cr in males, B: CysC in males, C: Cr/CysC in males

D: Cr in females, E: CysC in females, F: Cr/CysC in females

P values were calculated using ANOVA.

*: $p<0.01$, † : $p<0.05$, NS: not significantly different
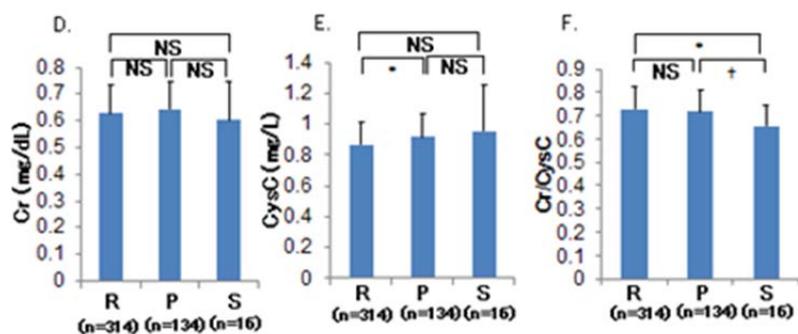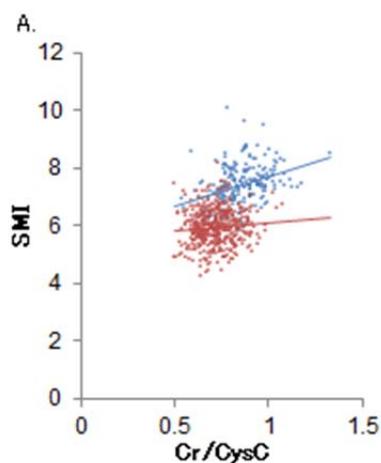

Fig 1

Fig. 2 A, B

The Pearson's simple correlations between parameters of body composition by BIA and Cr/CysC.
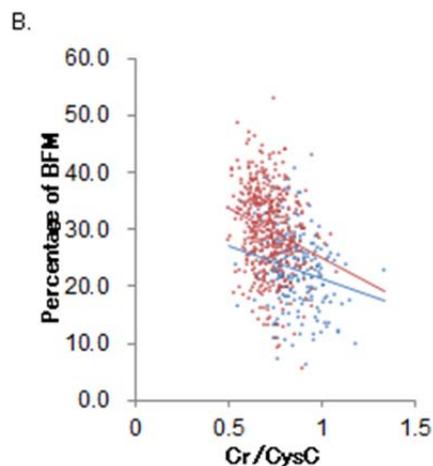
A: SMI, B: Percentage of BFM

Blue dots: male. Red dots: female. BIA: bio-electrical impedance analysis, Cre: creatinine, CysC: cystatin C. SMI: skeletal mass index, BFM: body fat mass

Fig.2

A.

	total	male	female
r	0.49	0.34	0.08
p	<0.0001	<0.0001	0.0767

B.

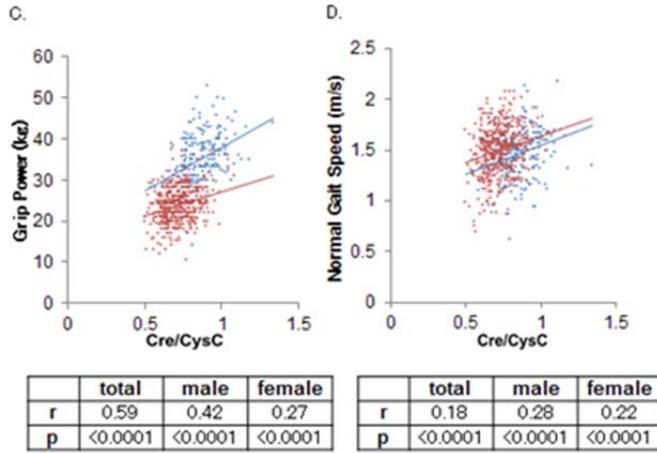|	total	male	female
r	−0.39	−0.20	−0.23
p	<0.0001	<0.0001	<0.0001

Fig. 2 C, D

The Pearson's simple correlations between parameters of physical performance and Cr/CysC.

C: Grip power, D: Normal gait speed

Blue dots: male. Red dots: female. Cr: creatinine, CysC: cystatin C.

C.

	total	male	female
r	0.59	0.42	0.27
p	<0.0001	<0.0001	<0.0001

D.

|	total	male	female
r	0.18	0.28	0.22
p	<0.0001	<0.0001	<0.0001

Figure 3 A, B

The Pearson's simple correlations between parameters of body composition by BIA and Cr/CysC.

A: Skeletal muscle mass, B: Body fat mass

Blue dots: male. Red dots: female. BIA: bio-electrical impedance analysis, Cre: creatinine, CysC: cystatin C.

A.

	total	male	female
r	0.53	0.27	0.14
p	<0.0001	<0.0001	<0.0001

B.

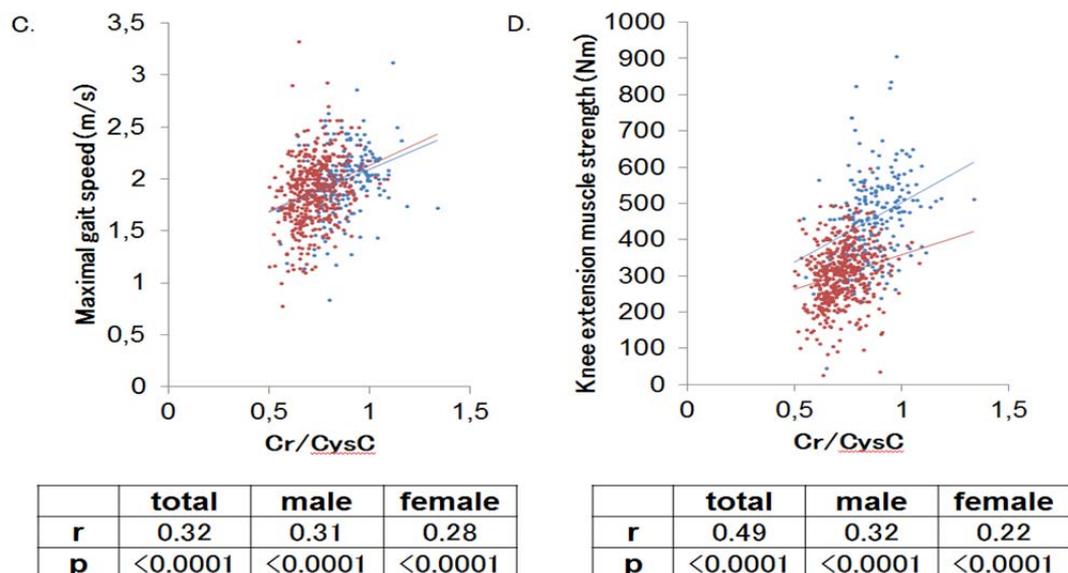|	total	male	female
r	−0.20	−0.13	−0.22
p	<0.0001	0.0524	<0.0001
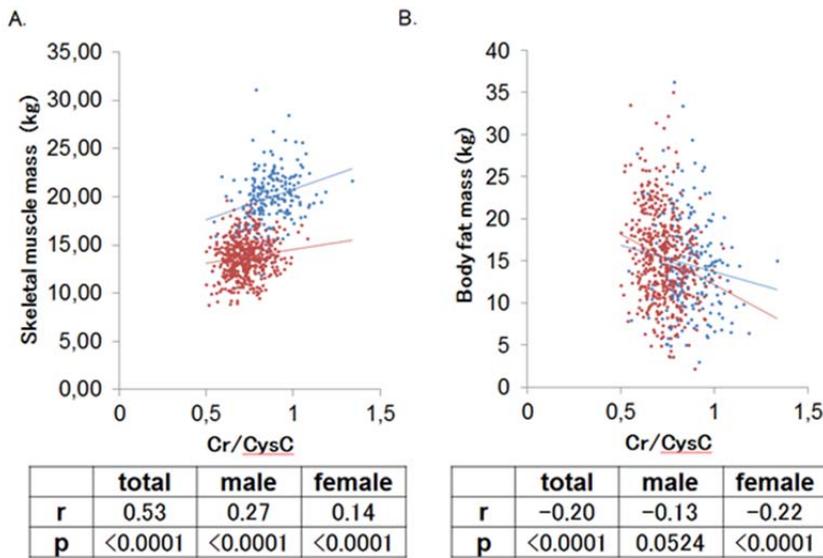
Figure 3 C, D

The Pearson's simple correlations between parameters of physical performance and Cr/CysC.

C: Maximal gait speed, D: Knee extension muscle strength (Nm)

Blue dots: male. Red dots: female. Cre: creatinine, CysC: cystatin C.

	total	male	female
r	0.32	0.31	0.28
p	<0.0001	<0.0001	<0.0001

	total	male	female
r	0.49	0.32	0.22
p	<0.0001	<0.0001	<0.0001

Table 2

A. Correlations between SMI and body size (height and weight) and biomarkers.

	All		male		Female	
	r	p-value	r	p-value	r	p-value
Age	-0.11	0.0031	-0.31	<0.0001	-0.18	<0.0001
Height	0.67	<0.0001	0.37	<0.0001	0.31	<0.0001
Weight	0.83	<0.0001	0.79	<0.0001	0.74	<0.0001
BMI	0.55	<0.0001	0.71	<0.0001	0.63	<0.0001
Cr/CysC	0.49	<0.0001	0.34	<0.0001	0.08	0.0767
Cr	0.52	<0.0001	0.19	0.0044	0.03	0.5908
CysC	0.17	<0.0001	-0.05	0.4785	-0.08	0.0736
WBC	-0.02	0.6863	0.03	0.7075	-0.02	0.6308
RBC	0.25	<0.0001	0.16	0.0217	0.07	0.1115
Hemoglobin	0.35	<0.0001	0.14	0.0355	0.05	0.2980
Hematocrit	0.30	<0.0001	0.11	0.1135	0.04	0.3686
Platelet	-0.12	0.0021	-0.02	0.7753	0.002	0.9695
Total protein	0.01	0.7388	0.12	0.0925	-0.09	0.0465
Albumin	0.05	0.1847	0.21	0.0022	-0.03	0.5186
Total cholesterol	-0.14	0.0003	-0.004	0.9543	-0.05	0.3164

HDL-cholesterol	-0.18	<0.0001	0.03	0.6666	-0.09	0.0495
Triglycelyde	0.18	<0.0001	0.16	0.0231	0.05	0.2629
AST	0.10	0.0106	-0.07	0.3448	-0.02	0.6422
ALT	0.17	<0.0001	0.10	0.1314	0.16	0.1674
γ-GTP	0.13	0.0004	-0.08	0.2241	-0.04	0.3900
log hsCRP	0.10	0.0091	-0.004	0.9590	-0.002	0.9691

Table 2

B.   Multiple regression analysis of SMI and individual parameters

	All		Male		Female	
	β	p-value	β	p-value	β	p-value
Age	0.04	0.0503	-0.12	0.0061	-0.04	0.1805
Height	0.12	<0.0001	-0.04	0.3349	-0.04	0.2719
Weight	0.70	<0.0001	0.79	<0.0001	0.79	<0.0001
Cr/CysC	0.26	<0.0001	0.23	<0.0001	0.18	<0.0001
Hemoglobin	-0.02	0.3369	-0.10	0.0170	-0.11	0.0004

BMI: body mass index; WBC: white blood cells; RBC: red blood cells; HDL: high density lipoprotein; AST: aspartate transaminase; alanine transaminase; γ-GTP: γ-glutamyltransferase; hsCRP: high sensitive C-reactive protein; Cr: creatinine; CysC: cystatin C.β: standard partial regression coefficient

Table 3

A.   Correlations between grip power and body size (height and weight) and biomarkers.

	All		male		Female	
	r	p-value	r	p-value	r	p-value
Age	-0.19	<0.0001	-0.38	<0.0001	-0.33	<0.0001
Height	0.71	<0.0001	0.35	<0.0001	0.43	<0.0001
Weight	0.59	<0.0001	0.40	<0.0001	0.26	<0.0001
BMI	0.19	<0.0001	0.27	<0.0001	0.04	<0.0001
Cr/CysC	0.59	<0.0001	0.42	<0.0001	0.27	<0.0001
Cr	0.51	<0.0001	0.05	0.4316	0.04	0.3536
CysC	0.07	0.0807	-0.26	0.0001	-0.22	<0.0001
WBC	-0.002	0.9576	0.05	0.4264	-0.01	0.8309
RBC	0.27	<0.0001	0.15	0.0278	0.13	0.0063
Hemoglobin	0.38	<0.0001	0.13	0.0615	0.11	0.0212
Hematocrit	0.33	<0.0001	0.10	0.1308	0.11	0.0149
Platelet	-0.11	0.0039	-0.003	0.9633	0.02	0.7149
Total protein	0.03	0.3763	0.02	0.7186	0.02	0.6850
Albumin	0.10	0.007	0.15	0.0280	0.13	0.0046
Total cholesterol	-0.02	0.5591	0.10	0.1286	0.19	<0.0001

HDL-cholesterol	-0.12	0.0024	0.01	0.8395	0.08	0.0717
Triglycelyde	0.18	<0.0001	0.16	0.0222	0.05	0.2676
AST	0.08	0.0271	-0.11	0.1253	-0.03	0.4704
ALT	0.12	0.0015	-0.02	0.7600	0.01	0.7612
γ-GTP	0.18	<0.0001	-0.006	0.9364	0.03	0.5756
log hsCRP	0.05	0.2293	-0.07	0.2871	-0.10	0.0346

Table 3

B. Multiple regression analysis of grip power and individual parameters

	All		Male		Female	
	β	p-value	β	p-value	β	p-value
Age	-0.001	0.6532	-0.19	0.0025	-0.15	0.0012
Height	0.40	<0.0001	0.16	0.0106	0.28	<0.0001
Weight	0.22	<0.0001	0.26	0.0001	0.15	0.0011
Cr/CysC	0.33	<0.0001	0.32	<0.0001	0.20	<0.0001
Hemoglobin	0.07	0.0080	-0.02	0.7202	0.02	0.6648

BMI: body mass index; WBC: white blood cells; RBC: red blood cells; HDL: high density lipoprotein; AST: aspartate transaminase; alanine transaminase; γ-GTP: γ-glutamyltransferase; hsCRP: high sensitive C-reactive protein; Cr: creatinine; CysC: cystatin C; β : standard partial regression coefficient

Table 4

A. Correlations between normal gait speed and body size (height and weight) and biomarkers.

	All		male		Female	
	r	p-value	r	p-value	r	p-value
Age	-0.23	<0.0001	-0.13	0.0503	-0.27	<0.0001
Height	0.13	0.0005	0.15	0.0288	0.28	<0.0001
Weight	0.02	0.5870	0.08	0.2300	0.04	0.4079
BMI	-0.08	0.0277	0.02	0.8036	-0.13	0.0069
Cr/CysC	0.18	<0.0001	0.28	<0.0001	0.22	<0.0001
Cr	-0.04	0.3298	-0.01	0.8414	-0.02	0.6503
CysC	-0.27	<0.0001	-0.28	<0.0001	-0.27	<0.0001
WBC	-0.02	0.6569	0.03	0.6414	-0.04	0.3737
RBC	0.09	0.0160	0.11	0.1196	0.11	0.0201
Hemoglobin	0.09	0.0224	0.14	0.0379	0.10	0.0270
Hematocrit	0.09	0.0156	0.14	0.0467	0.11	0.0231
Platelet	-0.008	0.8256	0.05	0.5011	-0.04	0.3655
Total protein	0.05	0.1994	0.08	0.2234	0.03	0.4869
Albumin	0.13	0.0005	0.19	0.0064	0.11	0.0174
Total cholesterol	0.11	0.004	0.03	0.6651	0.14	0.0022

HDL-cholesterol	0.14	0.0004	0.02	0.8171	0.19	<0.0001
Triglycelyde	-0.03	0.4487	-0.02	0.7516	-0.03	0.5630
AST	-0.04	0.3575	-0.03	0.6636	-0.03	0.5128
ALT	0.03	0.4129	0.08	0.2365	0.02	0.7313
γ-GTP	-0.04	0.3572	-0.07	0.3209	0.03	0.5055
log hsCRP	-0.0003	0.9406	-0.01	0.8798	0.01	0.8274

Table 4

B. Multiple regression analysis of normal gait speed and individual parameters

	All		Male		Female	
	β	p-value	β	p-value	β	p-value
Age	-0.18	<0.0001	0.03	0.7161	-0.15	0.0019
Height	0.05	0.2329	0.13	0.0588	0.19	<0.0001
Cr/CysC	0.11	0.0112	0.26	0.0004	0.15	0.0015
Hemoglobin	-0.004	0.9223	0.11	0.1230	0.05	0.2555
Albumin	0.04	0.3033	0.04	0.5785	-0.01	0.8334

BMI: body mass index; WBC: white blood cells; RBC: red blood cells; HDL: high density lipoprotein; AST: aspartate transaminase; alanine transaminase; γ-GTP: γ-glutamyltransferase; hsCRP: high sensitive C-reactive protein; Cr: creatinine; CysC: cystatin C; β : standard partial regression coefficient.

Discussion

In the present study, the Cr/CysC ratio was positively correlated with muscle volume and physical function and negatively correlated with BFM, even in elderly subjects without severe renal impairment. This suggests the usefulness of the measurement of the Cr/CysC ratio as a diagnostic biomarker in the daily clinical setting.

A recent study showed that sarcopenia was more prevalent in the advanced stages of CKD in patients who were not yet on dialysis (34.5% in stages 2 and 3A; 65.5% in stages 3B, 4, and 5).14) Since the aim of this study was the establishment of a novel biomarker for screening sarcopenia in people without severe renal impairment, subjects with low renal function (CKD stages 3B, 4, and 5; eGFR<45) were excluded.

Although many studies have investigated the prevalence of sarcopenia, the results have been inconsistent. Han et al. previously reported a sarcopenia prevalence of 7% in the general population, which reached 14.8% when individuals aged over 60 were included.15) A recent meta-analysis showed that the overall estimates of sarcopenia prevalence were 10% (95% CI: 8-12%) in men and 10% (95% CI: 8-13%) in women.16) Wang et al. reported that among Chinese community-dwelling people, the prevalence of

AWGS-defined sarcopenia was 12.5% in women and 8.2% in men, with a total prevalence of 10.4%.17) In this study, the rates of sarcopenia prevalence were 2.8% in men and 3.4% in women, which are low compared to those in previous reports. Our findings indicate that elderly people in the Sasayama-Tamba area are very healthy overall, with only a few people experiencing physical dysfunction.

Increased levels of inflammatory cytokines such as IL-6 and TNF-α, as well as hsCRP, have been found to be associated with sarcopenia in the general population and in patients with end stage renal disease (ESRD).18) However, the specificity of these inflammatory parameters as a diagnostic biomarker is not high, since they are easily affected by the co-morbidities associated with acute and/or chronic inflammation.

The Cr/CysC ratio was found to be a good predictor of the toxicity of chemotherapy in a small cohort of patients with non-small cell lung cancer.19) In another study, the Cr/CysC ratio was found to be associated with the severity of muscle loss in a cohort of patients with amyotrophic lateral sclerosis.20) Inactivity, inflammation, age-related factors, anorexia, and changes in skeletal muscle and fat mass can induce sarcopenic obesity and sarcopenia.21) The Cr/CysC ratio is a novel approach for estimating muscle health.9)

In this study, CysC increased in subjects in the pre-sarcopenia and sarcopenia stages compared with

those in the robust (Fig 1) stage, and in some cases, CysC exhibited a negative correlation with muscle mass and strength. In contrast, Cr exhibited a positive correlation with SMI and grip power. (Table 2, Table 3). However, this tendency of CysC or Cr alone was inconsistent. Even in the sexes- separated analysis, the Cr/CysC ratio was found to be a significant positive correlating factor for SMI, grip power and gait speed. This tendency of the Cr/CysC ratio is more consistent than that of CysC or Cr alone, and the Cr/CysC ratio may be more useful for estimating muscle mass, muscle strength and physical function.

Recent findings suggest that CysC is regulated at both the transcriptional and post- transcriptional levels. CysC is directly linked to many pathologic processes through various mechanisms, one of which is inflammation. Previous studies have suggested that sarcopenia is an inflammatory state that is driven by proinflammatory cytokines.[22],[23] The influence of inflammatory cytokines on the production of CysC was documented almost 30 years ago.[24] Different roles and/or regulatory mechanisms of CysC might exist in different cell types and tissues. Another mechanism linked to CysC is oxidative stress. Oxidative stress has been repeatedly reported to upregulate CysC expression in the neurological and cardiovascular systems.[25],[26]

Aging is associated with significant changes in structure and function of the kidney, even in the absence of age-related comorbidities. Cr/CysC may reflect not only chronic inflammation, but also subclinical and potential renal injury.

Sarcopenia is characterized by changes in body composition, such as an increase in visceral fat and reduced muscle mass. A graded association between higher BMI and elevated CysC has been previously reported.[27]-[29] Moreover, CysC gene expression and secretion from adipose tissue increased in obese individuals, and increased production of CysC was attributed to enlarged adipose tissue in an in vitro study.[30] Even in the context of slight changes in body composition, CysC may be influenced by mild chronic inflammation and oxidative stress. Our study suggests that CysC may be a useful sensor to predict changes in body composition in the early stage of sarcopenia.

This study has several limitations. First, the cross-sectional nature of the study made it impossible to assess any cause-and-effect relationships. Further, prospective research is warranted to better assess any causal associations between kidney function and sarcopenia. Second, most of our study subjects voluntarily participated in the FESTA study. Therefore, it is probable that the study subjects were relatively healthy and showed lower rates of frailty and sarcopenia than those occurring in the general population. Thus, there is the potential for inconsistency between our results and those of previous studies. Third, we did not perform measurements of urinary protein, and therefore, did not examine whether the association between kidney function and sarcopenia was modified by the presence of subclinical nephropathy. Last, there were only a few subjects with overt sarcopenia. This obviously limits the reliability and applicability of the proposed test.

In conclusion, even in subjects without severe renal impairment, the Cr/CysC ratio positively correlated with muscle volume and physical function and negatively correlated with BFM. Thus, the Cr/CysC ratio may be a useful biomarker in the early stage of sarcopenia.

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Conflicts of interest

There are no conflicts of interest.

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