Relationships between cystatin C- and creatinine-based eGFR in Japanese rural community-dwelling older adults with sarcopenia

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Abstract
Background Sarcopenia is prevalent in patients with chronic kidney disease (CKD). Sarcopenia is prevalent in patients with chronic kidney disease (CKD). The indices of physical function, such as grip power and gait speed, decreased according to the decline in estimated glomerular filtration rate (eGFR).

Methods We examined the relationships between cystatin C-based GFR (eGFRcys), and creatinine-based GFR (eGFRcre), and their ratio (eGFRcys/eGFRcre) and low skeletal muscle mass index (SMI) in community-dwelling older adults in Japan. This cross-sectional study included 286 men aged 73.3±6.2 years and 606 women aged 72.9±5.8 years from a rural area in Hyogo Prefecture, Japan. eGFRcys and eGFRcre were simultaneously measured, whereas low SMI based on the AWGS criteria was evaluated.

Results eGFRcys and the eGFRcys/eGFRcre were significantly correlated with grip power and gait speed. The eGFRcys/eGFRcre was also correlated with SMI. In the multivariate logistic regression analysis, when the eGFRcys/eGFRcre was added as a covariate to the basic model, it was significantly associated with low SMI, both in all subjects. Moreover, CKDcys with a low eGFRcys/eGFRcre ratio (<1.0) was associated with a higher risk of low SMI than CKDcys alone.

Conclusion In conclusion, CKDcys but not CKDcre is an independent risk factor of low SMI. In patients with CKDcys, lower eGFRcys/eGFRcre may be a practical screening marker of low SMI in community-dwelling older adults.

Background
Sarcopenia is a disease characterized by loss of skeletal muscle mass (SMM), and it is an important public health problem. The underlying mechanisms associated with the disorder include reduced physical function, underfeeding, loss of hormone production, and chronic inflammation.[1] Sarcopenia is common in patients with chronic kidney disease (CKD). The physical function, for example grip power and gait speed, decreased as the decline in estimated glomerular filtration rate (eGFR).[2]. Serum creatinine (Cr) is a common biomarker that reflects not only renal function, but also systemic muscle mass. Cystatin C (CysC) may be a more reliable biomarker that estimates glomerular filtration
rate (eGFR), and it is not influenced by gender, age, or muscle mass. CKD is defined as a reduced eGFR.

Recently, we reported the Cr/CysC ratio was correlated positively to muscle volume and physical function.[3] Another study has reported that the Cr/CysC ratio was associated with high risk of sarcopenia.[4] Sarcopenia is a major component of frailty in elderly individuals. In another study, a declined eGFR based on CysC (eGFRcys) was associated with a higher prevalence and incidence of frailty, whereas eGFR based on creatinine (eGFRcre) was not.[5] Another study has shown that eGFRcys but not eGFRcre was related to increased odds of frailty in a cohort of older people.[6] The Atherosclerosis Risk in Communities (ARIC) Study has shown that frail individuals had a high prevalence of declined kidney function, with large discrepancies when declined kidney function was classified by eGFRcys versus eGFRcre.[7] eGFRcys is related to a higher risk of sarcopenia than eGFRcre, because eGFRcys is not influenced by low muscle mass or quality. [8],[9] Recently, Kurajoh et al. have reported that a lower eGFRcys (CKDcys), but not a lower eGFRcre (CKDcre), was independently related to osteoporotic fracture in postmenopausal women. Furthermore, the eGFRcys/eGFRcre ratio was independently related to osteoporotic fracture in this study and was correlated to physical function. It is a clinically useful parameter for loss of muscle mass. [10]

Several studies have shown the correlation between sarcopenia and osteoporosis.[11, 12] and have suggested a significant correlation between bone and muscle as well as sarcopenia is and osteoporosis. Moreover, a prospective study has found that patients with osteoporosis are at increased risk of developing sarcopenia. [13]

We hypothesized that eGFRcys is superior to eGFRcre in evaluating muscle mass and physical function, and it is more associated with pre-sarcopenia and sarcopenia, which is characterized by a low SMI.

The eGFRcys/eGFRcre ratio may provide a clinically relevant measurement of muscle mass, whereas eGFRcre is identified by using not only renal function but also muscle mass, thus indicating that a lower eGFRcys/eGFRcre ratio is a clinically useful parameter for low SMI.[9] Hence, we examined the
relationships between eGFRcys and eGFRcre, as well as that between eGFRcys/eGFRcre ratio and low SMI in community-dwelling older adults in Japan.

Methods
This cross-sectional study was called the Frail Elderly in Sasayama-Tamba Area (FESTA) study. The study population was composed of individuals aged ≥65 years. Healthy community-dwelling elderly individuals from the Sasayama-Tamba area, a rural area in Hyogo Prefecture, Japan, were recruited between 2015 and 2018. Physical function assessment, measurement of body composition and blood sample analysis were performed as described previously. [3]

Categorization of CKD
CKD was defined and classified according to the KDIGO criteria.[8] eGFRcre and eGFRcys were calculated using equations by the Japanese Society of Nephrology.[14, 15] Lower eGFRcre (CKDcre) is defined as an eGFRcre <60 mL/min/1.73 m2. Lower eGFRcys (CKDcys) is defined as an eGFRcys <60 mL/min/1.73 m2.

Diagnosis of sarcopenia
Sarcopenia was defined according to the criteria for the Asia Working Group for Sarcopenia (AWGS) (SMI of below 5.4 kg/m2 in women and below 7.0 kg/m2 in men).[16] Body composition was evaluated by bioimpedance analysis using an InBody 770® (InBody Japan Inc., Tokyo, Japan). The cutoff point for handgrip power was <26 kg for men and <18 kg for women. The handgrip power, the normal and maximal gait speed were evaluated as described previously. [3] The stage of sarcopenia was considered normal was if the participants had a normal SMI (≥7.0 kg/m2 in men; ≥5.7 kg/m2 in women). A low SMI was considered if the participants had a low SMI (<7.0 kg/m2 in men; <5.7 kg/m2 in women). The pre-sarcopenia stage was considered if the participants had a low SMI, normal handgrip strength (≥26 kg in men; ≥18 kg in women), and normal gait speed (≥0.8 m/sec). The sarcopenia stage was considered if the participants had a low SMI and low gait speed (<0.8 m/sec) or low handgrip strength (<26 kg in men; <18 kg in women).

Statistical analysis
The results were expressed as mean ± standard deviations (SD) or percentages. For intergroup
comparisons, the student’s t-test and one-way analysis of variance (ANOVA), followed by the Tukey-Krammer test were used for data analysis. Pearson’s product moment correlation coefficient was used to evaluate the associations between the eGFRcys/eGFRcre ratio and SMM, SMI, BFM, percentage of BFM, muscle strength (grip power, knee extension muscle strength), normal and maximal gait speed. Multivariate logistic regression analysis was performed to calculate the odds ratio and 95% confidence interval. Analysis of covariance (ANCOVA) was used to compare regression lines. For data analysis, the JMP 13.1 software was used. P-values < 0.05 were considered significant.

Results
The baseline characteristics, indices of body composition, and physical performance of the participants are shown in Table 1A. 286 men aged 65 to 94 years, and 606 women aged 65 to 91 years were included in this study. In women the BFM weight and BFM percentages (BFM %) were higher than in men. There were no differences in normal gait speed of all participants. However, SMM, and SMI, grip power, knee extension muscle strength and maximal gait speed were higher in men than in women (Table 1A). The average eGFRcre was 69.0 (men: 68.1, and women: 69.5). The average eGFRcys was 74.0 (men: 71.7, and women: 75.0).

Among the 892 participants, 54 (12 men and 42 women) had sarcopenia based on the AWGS criteria, whereas 233 (66 men and 167 women) had pre-sarcopenia (Table 1B). Other complications (diabetes, dyslipidemia, liver disease and heart disease) were more prevalent in men than women. In total, 219 (79 men and 140 women) had a lower eGFRcre (CKDcre), and 162 (66 men and 96 women) had a lower eGFRcys (CKDcys). In total, 308 (116 men and 192 women) had a low eGFRcys/eGFRcre ratio (<1.0). Among 162 participants with CKDcys, 102 (49 women and 53 men) had an eGFRcys/eGFRcre ratio <1.0.

The characteristics of each stage of sarcopenia (normal, pre-sarcopenia, and sarcopenia) are presented in Table 2A. Among both male and female participants, those who are in the low SMI stages (sarcopenia and pre-sarcopenia) were older than those who are in the normal stage. Height, body weight, and BMI decreased, as the stage of sarcopenia progressed in all participants. Among male participants, there were no differences in normal and maximal gait speed. However, they decreased
in the sarcopenia stage in females. Muscle strength (grip power and knee extension muscle strength), muscle volume (SMM and SMI) decreased as the stage of sarcopenia progressed in all participants. BFM weight also decreased as the stage of sarcopenia progressed. However, the percentage of BFM did not significantly change even if the stage of sarcopenia progressed.

eGFRcys but not eGFRcre decreased, as the stage of sarcopenia progressed in both men and women. The eGFRcys/eGFRcre ratio also decreased as the stage of sarcopenia progressed in both men and women.

The correlations between eGFRcre, eGFRcys, and eGFRcys/eGFRcre ratio and the parameters of body composition based on BIA (SMI, SMM, body fat mass, and percentage of body fat mass) and muscle strength parameters (grip power, knee extension muscle strength, normal gait speed, and maximal gait speed) are shown in Table 2B.

eGFRcre was not significantly correlated to muscle volume and strength parameters. On the contrary, eGFRcys was positively correlated to SMM in men and was negatively correlated to body fat mass and percentage of body fat mass. The eGFRcys/eGFRcre ratio was significantly correlated to SMI, SMM, and muscle strength parameters and was exhibited a negatively correlation with to body fat mass and percentage of body fat mass.

A previous study on patients with CKDcys (eGFRcys <60 mL/min/1.73m2) has shown that the eGFRcys and eGFRcys/eGFRcre ratio, but not eGFRcre, was significantly lower in the group with osteoporotic fracture.[10] We suspected that the same phenomenon occurs in the case of sarcopenia and pre-sarcopenia. The subjects with CKDcys eGFRcys/eGFRcre ratio but not eGFRcys and eGFRcre were lower in the group with sarcopenia and pre-sarcopenia. In participants without CKDcys, eGFRcys, eGFRcre, and eGFRcys/eGFRcre ratio did not significantly differ from those with and without sarcopenia and pre-sarcopenia, both in men and women (Tables 3A and 3B). The percentage of patients with sarcopenia and pre-sarcopenia was significantly higher in the group with an eGFRcys/eGFRcre ratio <1.0 than those with a ratio ≥1.0 both in men and women (Tables 3C and 3D). The relationship between eGFRcre and eGFRcys was not significantly different between the non-CKDcys participants with and without sarcopenia and pre-sarcopenia. The relationship between
eGFRcre and eGFRcys in all participants with and without a low SMI (sarcopenia and pre-sarcopenia) is shown in Figs. 1A and 1B. The regression line significantly shifted to the right in male participants with a low SMI in males. Although the shift of the regression line was not obvious in women, a significant difference was observed between the two female groups using the ANCOVA (p = 0.0165). The relationship between eGFRcre and eGFRcys in participants both who developed CKDcys with and without a low SMI (sarcopenia and pre-sarcopenia) is shown in Figs. 1C and 1D. The regression line was shifted to the right in participants with a low SMI both in men and women. This trend indicated in the subjects with low SMI, that eGFRcys is likely to be higher than eGFRcre (eGFRcys/eGFRcre ratio <1.0) in participants with a low SMI than in participants with CKDcys. A multivariate logistic regression analysis was performed to examine whether eGFRcys, eGFRcre, and eGFRcys/eGFRcre ratio were independently associated with low SMI. In both men and women, when eGFRcre was added as a covariate to the basic model, eGFRcre was not significantly associated with a low SMI. eGFRcys was significantly associated with a low SMI only in women. However, when the GFRcys/eGFRcre ratio was added as a covariate to the basic model, a significant association was observed between the GFRcys/eGFRcre ratio and low SMI both in men and women (Tables 4A and 4B). Multivariate logistic regression analysis was performed adjusted for complications (hypertension, diabetes, dyslipidemia, liver disease and heart disease) to examine whether CKDcys and CKDcre were independently associated with low SMI. The combination of CKDcys and an eGFRcys/eGFRcre ratio<1.0 was independently associated with low SMI, both in men and women (Tables 4C and 4D).

Discussion

CKD is considered as a risk factor of several aging-related diseases, including cardiovascular diseases (CVDs), metabolic syndrome, frailty, and sarcopenia. Previous studies have reported that CKDcys was more associated with life prognosis and physical function than CKDcre. In octogenarians, CKDcys was associated with increased odds of CVDs.[17] The Cardiovascular Health Study has shown that elder individuals with CKDcys had a higher risk of heart failure and mortality.[18] Recently, a significant relationship was observed between the risk for CVD and sarcopenia, because of the increased circulating markers of oxidative stress in sarcopenia.[19] In the Framingham Offspring Study,
participants with CKDcys had greater gait speed declines than those with CKDcre. The participants with CKDcys also had greater odds of mobility disability than those with CKDcre.[20]

The present study first showed that, the eGFRcys/eGFRcre ratio was significantly positive correlated to skeletal mass index, SMM, and muscle strength parameters and was negatively correlated to body fat mass and percentage of body fat mass. (Table 2B). The eGFR/eGFRcre ratio may provide a clinically relevant measurement of muscle mass, based on the assumption that eGFRcre is determined using not only renal function but also muscle mass.[9] A multivariate logistic regression analysis showed that the eGFRcys/eGFRcre ratio was independently associated with low SMI (Tables 4A and 4B).

In the participants with CKDcys, the eGFRcys/eGFRcre ratio was lower in the group with sarcopenia and pre-sarcopenia. In the participants without CKDcys, the eGFRcys/eGFRcre ratio did not significantly differ than that of those with and without sarcopenia and pre-sarcopenia both in men and women (Tables 3A and 3B). In addition, the percentage of patients with sarcopenia and pre-sarcopenia was significantly higher in the group with an eGFRcys/eGFRcre ratio <1.0 than in the group with a ratio ≥1.0 both in men and women (Tables 3C and 3D). The combination of CKDcys and an eGFRcys/eGFRcre ratio <1.0 was significantly associated with low SMI both in men and women (Tables 4C and 4D). This result suggested that participants with both CKDcys and an eGFRcys/eGFRcre ratio <1.0 were significantly at increased risk of sarcopenia. In Figs. 1C and 1D, the relationship between eGFRcre and eGFRcys in participants who developed CKDcys with and without low SMI is shown. The regression line significantly shifted to the right in participants with low SMI in both men and women. This trend indicated that eGFRcys is likely to be lower than eGFRcre (an eGFRcys/eGFRcre ratio <1.0) in participants with low SMI. This tendency may explain the association between low eGFRcys/eGFRcre ratio <1.0 and low SMI.

This study first showed that the eGFR/eGFRcre ratio may be a clinically useful parameter for reduced muscle mass, and the combination of CKDcys and an eGFRcys/eGFRcre ratio <1.0 is useful in evaluating the risk of low SMI.

The release of creatine from the muscle is the major determinant of serum Cr levels, due to its
conversion to Cr in the circulation. Serum Cr level should be lower, and eGFRcre must be higher as muscle volume in affected patients lowers based on renal function.[8]

CysC is a cysteine protease inhibitor that is constantly produced by all nucleated cells. Thus, it is unaffected by muscles mass [8, 9], and the eGFRcys value has a lower level of bias. As mentioned in the previous study, CysC may be influenced by mild chronic inflammation and oxidative stress. Thus, eGFRcys may be affected more sensitively by mild inflammatory and oxidative changes in presarcopenia and sarcopenia than eGFRcre.

In Japan, CysC is widely available in daily clinical settings. Moreover, in numerous institutions, both eGFRcre and eGFRcys are calculated automatically by the center clinical inspection section. The combination of CKDcys and an eGFRcys/eGFRcre ratio <1.0 can be evaluated easily in several institutions.

This study has limitations that must be considered. First, this is a cross-sectional nature of the study. Therefore, any cause-and-effect relationships cannot be evaluated. In addition, a prospective study must be conducted to assess better for any causal associations between CKD and sarcopenia. Second, most of this study participants voluntarily participated in our study. Thus, the study participants may be healthier, and they might have lower rates of sarcopenia than those in the general population. Therefore, there may be inconsistency between our results and previous reports. Third, we did not measure urinary protein. Therefore, the association between CKD and sarcopenia that was modified by the presence of subclinical kidney disease was not examined. Finally, there were only a little participants with sarcopenia were included in the study, which obviously limits the reliability and applicability of this study.

Conclusions
In conclusion, CKDcys but not CKDcre is an independent risk factor of reduced SMI. In patients with CKDcys, a lower eGFRcys/eGFRcre ratio may be a practical screening marker of reduced SMI in rural community-dwelling older adults. Further studies are needed to evaluate the diagnostic value of eGFRcys/eGFRcre ratio for estimating sarcopenia. The prognostic value of eGFRcys/eGFRcre ratio for predicting clinical outcomes in older adults also warrants further study.
Abbreviations
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Cr: creatinine; CysC: cystatin C; BMI: Body mass index; CI: Confidence interval; FESTA: Frail Elderly in Sasayama-Tamba Area; KDIGO: Kidney Disease Improving Global Outcome; AWGS: Asian Working Group for Sarcopenia; BIA: bioelectrical impedance analysis; SMM: skeletal muscle mass; SMI: skeletal muscle mass index; BFM: body fat mass; CVDs: cardiovascular diseases

Declarations

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Availability of data and material
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
Concept and study design: H. R. K. and K. N. S.
Data collection and analyses: H. R.K, S.T, T.K, Y.W, K.T, Y.O, K.N, M.I, K. N.S, M.A, H.M, H.S, Y.H, H. S.K, S.S, K. N. S.

Original draft: H. R. K. and K. N. S.

Ethics approval and consent to participate
The study was approved by our institutional review board, and written informed consent was obtained
from the participants. The Research Ethics Committee of Hyogo College of Hyogo approved the study protocol. All methods in this study were in accordance with relevant regulations and guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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**Tables**

**Table 1**

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

|                      | total (n=892) | male (n=286) | female (n=606) | p   |
|----------------------|--------------|--------------|----------------|-----|
| Age (year-old)       | 73.2±5.9     | 73.7±6.2     | 72.9±5.8       | 0.02t|
| Height (cm)          | 155.4±8.2    | 164.0±5.9    | 151.3±5.6      | <0.00|
| Body weight (kg)     | 54.9±9.4     | 62.6±9.1     | 51.3±7.0       | <0.00|
| Body mass index      | 22.7±2.9     | 23.2±2.9     | 22.4±2.9       | <0.00|
| Skeletal muscle mass (kg) | 15.7±3.7   | 19.9±2.7     | 13.6±1.9       | <0.00|
| Skeletal Mass Index  | 6.40±0.92    | 7.38±0.69    | 5.94±0.59      | <0.00|
| Body fat mass (kg)   | 15.5±5.4     | 14.9±5.7     | 15.7±5.2       | 0.01t|
| Percentage of BFM (%)| 28.0±7.6     | 23.3±6.6     | 30.2±7.1       | <0.00|
| Grip power (kg)      | 27.1±7.4     | 35.0±6.2     | 23.3±4.3       | <0.00|
| Knee extension muscle strength (Nm) | 348.7±119.1 | 449.9±121.9 | 300.9±82.1 | <0.00|
| Normal gait speed (m/s) | 1.47±0.24  | 1.45±0.24    | 1.48±0.24      | 0.11t|
| Maximal gait speed (m/s) | 1.90±0.31  | 1.96±0.33    | 1.87±0.30      | <0.00|
| eGFRcre (mL/min/1.73 m²) | 69.0±13.9  | 68.1±13.7    | 69.5±14.0      | 0.18t|
| eGFRcys (mL/min/1.73 m²) | 74.0±15.6  | 71.7±15.9    | 75.0±15.4      | 0.00t|
| eGFRcys/eGFRcre       | 1.08±0.17    | 1.06±0.17    | 1.09±0.16      | 0.00t|

B. Prevalence of robust, sarcopenia and pre-sarcopenia by AWGS criteria, other complications (hypertension, diabetes, dyslipidemia, liver disease and heart disease), CKDcre, CKDcys,
### eGFRcys/eGFRcre<1.0 and CKDcys and eGFRcys/eGFRcre<1.0

|                          | total (n=892) | male (n=286) | female (n=606) | p       |
|--------------------------|---------------|--------------|----------------|---------|
| Normal                   | 605(67.8)     | 208(72.7)    | 397(65.5)      | 0.4971  |
| Low SMI                  |               |              |                |         |
| Pre-sarcopenia           | 233(26.1)     | 66(23.0)     | 167(27.6)      | 0.2641  |
| Sarcopenia               | 54(6.1)       | 12(4.2)      | 42(6.9)        | <0.0001 |
| Hypertension             | 398(44.6)     | 142(49.7)    | 256(42.2)      | 0.7873  |
| Diabetes                 | 104(11.7)     | 53(18.5)     | 51(8.4)        | <0.0001 |
| Dyslipidemia             | 191(21.4)     | 49(17.1)     | 142(23.4)      | 0.0252  |
| Liver disease            | 37(4.1)       | 17(5.9)      | 20(3.3)        | <0.0001 |
| CKDcre (eGFRcre<60)      | 219(24.6)     | 79(27.6)     | 140(23.1)      | 0.2300  |
| CKDcys (eGFRcys<60)      | 162(18.2)     | 66(23.1)     | 96(15.8)       | 0.0038  |
| eGFRcys/eGFRcre<1.0      | 308(34.5)     | 116(40.6)    | 192(31.7)      | 0.2724  |
| CKDcys and eGFRcys/eGFRcre<1.0 | 102(11.4) | 49(17.1) | 53(8.7) | <0.0001 |

Data are expressed as number (%). Cre: creatinine, CysC: cystatin C. Data are expressed as mean ±SD.

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Table 2

A. Characteristics of each stage of sarcopenia (robust, pre-sarcopenia and sarcopenia)
### Data

| Age (year-old)  | Male | Pre-sarcopenia | Sarcopenia | Normal |
|-----------------|------|----------------|------------|--------|
| (n=208)         | 72.9±5.6 | 75.8±7.1* | 77.8±7.5* | 72.3±5.7 |
| Height (cm)     | 165.4±5.1 | 160.8±6.1* | 157.9±6.1† | 152.4±5.1 |
| Body weight (kg)| 65.9±7.9 | 54.3±4.4* | 50.0±8.2* | 54.3±6.1 |
| Body mass index | 24.1±2.7 | 21.0±1.9* | 20.0±3.0* | 23.4±2.6 |
| Skeletal muscle mass (kg)| 21.1±2.1 | 17.2±1.7* | 15.3±1.9* | 14.6±1.5 |
| Skeletal Mass Index | 7.69±0.50 | 6.63±0.30* | 6.12±0.52*# | 6.27±0.42* |
| Body fat mass (kg)| 15.8±5.8 | 12.2±4.0* | 11.3±5.5 | 17.0±5.2 |
| Percentage of BFM (%) | 23.6±6.6 | 22.4±6.4 | 21.8±7.0 | 30.8±6.8 |
| Grip power (kg) | 36.7±5.9 | 32.0±3.6* | 23.3±1.7*# | 24.4±4.1 |
| Knee extension muscle strength (Nm) | 476.6±115.8 | 392.8±107.7* | 301.8±85.7* | 316.1±81.0 |
| Normal gait speed (m/s) | 1.48±0.24 | 1.40±0.21* | 1.28±0.24 | 1.49±0.23 |
| Maximal gait speed (m/s) | 1.99±0.32 | 1.88±0.32* | 1.78±0.29 | 1.89±0.30 |
| eGFRcre (mL/min/1.73 m²) | 67.5±14.1 | 70.9±12.6† | 65.0±11.1 | 69.6±14.1 |
| eGFRcys (mL/min/1.73 m²) | 72.9±16.0 | 69.5±14.8 | 62.8±14.9 | 75.9±15.3 |
| eGFRcys/eGFRcre | 1.09±0.17 | 0.98±0.15* | 0.96±0.11† | 1.10±0.17 |

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

### B. Correlations between eGFRcre, eGFRcys and eGFRcys/eGFRcre and the parameters of body composition based on BIA and muscle strength parameters.

|               | male (n=286)  |             |             |     |               |     |     |     | fema (n=606) |             |             |     |               |
|---------------|----------------|--------------|--------------|-----|----------------|-----|-----|-----|----------------|--------------|--------------|-----|----------------|
|               | eGFRcre | eGFRcys | eGFRcys/eGFRcre | eGFRcre |                  |     |     |     | eGFRcre |                  |     |     |
|               | r     | p       | r     | p       | r     | p       | r     | p       | r     | p       | r     | p       |
| Skeletal Mass Index | -0.11 | 0.0662 | 0.12 | 0.0493 | 0.31 | <0.0001 | -0.01 | 0.7962 | 0.05 |
| Skeletal muscle mass | -0.07 | 0.2197 | 0.11 | 0.0576 | 0.27 | <0.0001 | 0.03 | 0.4651 | 0.14 |
| Body fat mass | -0.16 | 0.0701 | -0.26 | <0.0001 | -0.12 | 0.0070 | -0.02 | 0.6613 | -0.17 |
| Percentage of BFM | -0.15 | 0.0131 | -0.30 | <0.0001 | -0.23 | 0.0007 | 0.02 | 0.5839 | -0.18 |
| Grip power | -0.08 | 0.1963 | 0.24 | <0.0001 | 0.44 | <0.0001 | 0.05 | 0.2467 | 0.21 |
| Knee extension muscle strength | 0.05 | 0.4084 | 0.27 | <0.0001 | 0.33 | <0.0001 | 0.05 | 0.1968 | 0.20 |
| Normal gait speed | 0.12 | 0.0389 | 0.25 | 0.0003 | 0.20 | 0.0008 | 0.11 | 0.0081 | 0.22 |
| Maximal gait speed | 0.13 | 0.0315 | 0.29 | <0.0001 | 0.25 | <0.0001 | 0.08 | 0.0392 | 0.26 |
Table 3

eGFRcys, eGFRcre and eGFRcys/eGFRcre ratio and robust, pre-sarcopenia and sarcopenia in subjects with and without CKD cys.

A. male

|                  | With CKDcys | Without CKDcys |
|------------------|-------------|----------------|
|                  | Normal (n=43) | Pre-sarcopenia (n=16) | Sarcopenia (n=7) | Normal (n=165) | Pre-sarcopenia (n=50) |
| eGFRcre          | 51.9±8.8     | 59.7±12.8†     | 57.5±4.0       | 71.5±12.2     | 74.5±10.3           |
| eGFRcys          | 50.1±7.8     | 49.7±9.0       | 52.9±4.9       | 78.8±11.9     | 75.9±9.7            |
| eGFRcys/eGFRcre  | 0.97±0.12    | 0.84±0.11*     | 0.92±0.06      | 1.12±0.17     | 1.03±0.13           |

†: p<0.05 vs Robust, *: p<0.01 vs Robust

B. female

|                  | With CKDcys | Without CKDcys |
|------------------|-------------|----------------|
|                  | Normal (n=57) | Pre-sarcopenia (n=25) | Sarcopenia (n=14) | Normal (n=340) | Pre-sarcopenia (n=142) |
| eGFRcre          | 50.4±8.9     | 53.1±9.2       | 53.9±10.4      | 72.7±12.1     | 72.7±12.1           |
| eGFRcys          | 51.4±7.6     | 51.2±6.9       | 49.2±9.3       | 80.0±12.1     | 78.8±11.3           |
| eGFRcys/eGFRcre  | 1.03±0.13    | 0.97±0.11      | 0.92±0.14†     | 1.10±0.17     | 1.10±0.15           |

†: p<0.05 vs Robust

Pre-sarcopenia, sarcopenia and eGFRcys/eGFRcre ratio in subjects with and without CKDcys.

C. male

| CKDcys | eGFRcys/eGFRcre | Low SMI (SMI<7.0) | Normal |
|--------|-----------------|-------------------|--------|
|        |                 | Sarcopenia | Pre-sarcopenia | total |                 |
| (+)    |                 |            |              |       |                 |
| <1.0   | 6(12.2)         | 16(32.7)   | 22(44.9)     | 27(55.1)|                 |
| ≥1.0   | 15(5.9)         | 0(0)       | 15(5.9)      | 16(94.1)|                 |
| total  | 7(10.6)         | 16(24.2)   | 23(34.8)     | 43(65.2)|                 |
| (-)    |                 |            |              |       |                 |
| <1.0   | 2(3.0)          | 23(34.3)   | 25(37.3)     | 42(62.7)|                 |
| ≥1.0   | 3(2.0)          | 27(17.6)   | 30(19.6)     | 123(80.4)|                 |
| total  | 5(2.3)          | 50(22.7)   | 55(25.0)     | 165(75.0)|                 |

D. female
Table 4

Multivariate logistic regression analysis of associated with sarcopenia and pre-sarcopenia in males (A), in females (B)

Model 1 included age, BMI, hemoglobin and albumin as covariates. In other models, eGFRcre (model 2), eGFRcys (model 3) and eGFRcys/eGFRcre ratio (model 4) were added to model 1.

eGFR: estimated glomerular filtration rate, cr: creatinine, cys: cystatin C, OR: odds ratio, CI: confidence interval

A. male

| Variables       | model 1          |           |           |           |           |           |           |           |           |           |           |
|-----------------|------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|                 | OR               | 95% CI    | p         | OR        | 95% CI    | p         | OR        | 95% CI    | p         | OR        | 95% CI    |
| Age(per 1year)  | 1.110            | 1.049-1.180 | 0.0002    | 1.115     | 1.051-1.182 | 0.0002    | 1.085     | 1.018-1.157 | 0.0102    |
| BMI (per 1kg/m2)| 0.492            | 0.404-0.599 | <0.0001   | 0.496     | 0.406-0.605 | <0.0001   | 0.387     | 0.388-0.584 | <0.0001   |
| Hb(per 1g/dL)   | 1.274            | 0.981-1.654 | 0.0655    | 1.263     | 0.970-1.644 | 0.0787    | 1.284     | 0.988-1.670 | 0.0594    |
| Alb (per 1mg/dL)| 0.905            | 0.258-3.183 | 0.8770    | 0.892     | 0.253-3.140 | 0.8585    | 1.121     | 0.384-4.138 | 0.8634    |
| eGFRcre (per 10mL/min/1.73m2) | | | | | | | | | 1.054 | 0.816-1.361 | 0.6885 |
| eGFRcys (per 10mL/min/1.73m2) | | | | | | | | | | 0.781 | 0.605-1.007 | 0.0532 |
| eGFRcys/eGFRcre (per 0.1) | | | | | | | | | | |  |
B. female

| Variables | model 1 | | model 2 | | model 3 | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | p | OR | 95%CI | p | OR | 95%CI | p |
| Age (per 1 year) | 1.101 | 1.061-1.142 | <0.0001 | 1.103 | 1.061-1.147 | <0.0001 | 1.069 | 1.025-1.115 | 0.0015 |
| BMI (per 1 kg/m2) | 0.596 | 0.541-0.657 | <0.0001 | 0.597 | 0.541-0.658 | <0.0001 | 0.581 | 0.525-0.642 | <0.0001 |
| Hb (per 1 g/dL) | 1.196 | 0.980-1.461 | 0.0766 | 1.196 | 0.979-1.460 | 0.0772 | 1.204 | 0.982-1.475 | 0.0715 |
| Alb (per 1 mg/dL) | 1.308 | 0.607-2.817 | 0.4932 | 1.319 | 0.612-2.846 | 0.4796 | 1.389 | 0.637-3.029 | 0.4087 |
| eGFRcre (per 10 mL/min/1.73 m2) | | | | 1.029 | 0.881-1.202 | 0.7164 |
| eGFRcys (per 10 mL/min/1.73 m2) | | | | | | |
| eGFRcys/eGFRcre < 1.0 | | | | | | |
| CKDcre, CKDcys and eGFRcys/eGFRcre < 1.0 | | | | | | |

Multivariate logistic regression analysis of complications (hypertension, diabetes, dyslipidemia, liver disease and heart disease), CKDcre, CKDcys and eGFRcys/eGFRcre < 1.0 associated with sarcopenia and pre-sarcopenia in males (C), in females (D)

C. male

| Variables | OR | 95%CI | 
|---|---|---|
| CKDcre | 0.689 | 0.368-1.292 |
| CKDcys | 1.828 | 0.983-3.399 |
| eGFRcys/eGFRcre < 1.0 | 3.514 | 2.001-6.170 |
| CKDcys and eGFRcys/eGFRcre < 1.0 | 3.007 | 1.547-5.847 |

D. female

| Variables | OR | 95%CI | 
|---|---|---|
| CKDcre | 1.126 | 0.752-1.686 |
| CKDcys | 1.468 | 0.932-2.311 |
| eGFRcys/eGFRcre < 1.0 | 1.289 | 0.896-1.855 |
| CKDcys and eGFRcys/eGFRcre < 1.0 | 2.282 | 1.281-4.064 |

Figures
A, B Relationship between eGFRcre and eGFRcys in all patients with or without low SMI in males (A), in females (B) Analysis of covariance (ANCOVA) indicated that the regression line was significantly different between those with and without low SMI. eGFR: estimated glomerular filtration rate, cre: creatinine, cys: cystatin C

C, D Relationship between eGFRcre and eGFRcys in CKDcys patients with or without low SMI in males (C), in females (D) Analysis of covariance (ANCOVA) indicated that the regression line was significantly different between those with and without low SMI. eGFR: estimated glomerular filtration rate, cre: creatinine, cys: cystatin C