Establishment of muscle mass-based indications for the cystatin C test in renal function evaluation

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Directed by Professor Jeong-Ho Kim

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June 2022

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ABSTRACT

Establishment of muscle mass-based indications for the cystatin C test in renal function evaluation

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Introduction: The aim of this study is to suggest indications for the use of the cystatin C test based on muscle mass in an effort to avoid using the creatinine test, which may overestimate the estimated glomerular filtration rate (eGFR) in case of low muscle mass, to obtain an accurate eGFR for precise renal function evaluation.

Methods: This study is a cross-sectional analysis of 138 (males, 57; females, 81) Koreans aged 40-95 years (mean and standard deviation [SD], 66.4 ± 13.6 for males; 67.1 ± 12.1 for females), including inpatients (n = 66) and health-check subjects (n = 72). We determined eGFRcys (derived from Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI], 2012 version, based on cystatin C measurement) as the reference value. eGFRcr (derived from CKD-EPI, 2009 version, based on creatinine measurement) was compared to eGFRcys. To avoid interference with cystatin C, subjects with chronic inflammation (C-reactive protein, > 8 mg/dL), insulin resistance, obesity (body mass index ≥ 30 kg/m^2), thyroid dysfunction, and

regular steroid intake were excluded. We determined the skeletal muscle mass index (SMI) to be a suitable surrogate for muscle mass. SMI is derived from appendicular lean muscle mass, measured by bioelectrical impedance analysis (BIA), and adjusted by height squared (SMI_h), body weight (SMI_w), or body mass index (SMI_BMI). Various anthropometric measurements were performed, including calf circumference (CC). We also calculated estimated lean body mass (LBM) by the James, Boer, or Yu formulas as muscle mass parameters. The correlations between SMI_h and serum creatinine were retrospectively analyzed using additional data from 1,956 people who participated in the National Health and Nutrition Examination Survey, and 6,094 people who visited the Severance Health Promotion Center. We also calculated eGFR %difference between eGFRcr and eGFRcys, and defined the cases of detection of hidden renal impairment (DHRI) as eGFRcr $\geq$ 60 mL/min/1.73 m^2 and eGFRcys < 60 mL/min/1.73 m^2. We also derived cut-off values based on muscle mass through threshold curves to determine which subjects should use the cystatin C test; diagnostic utility was assessed using receiver operating characteristic (ROC) curves. We analyzed the correlation among various parameters related or affected to muscle mass, such as SMI_h, CC, eGFR %difference and creatinine, using Pearson's correlation coefficient (*r*). The association of age, sex, and SMI with the assigned eGFR category was determined via logistic regression analysis.

Results: We confirmed significant correlation between serum creatinine levels and SMI_h (*r*, 0.344 for male, 0.348 for female) in both sexes. We also confirmed significant negative correlation between eGFR %difference and SMI_h (*r*, -0.592 for male, -0.484 for female) or CC (*r*, -0.646 for male, -0.351 for female). Diagnostic utility was assessed via ROC curves based on good correlations between creatinine

and SMI_h, CC, or various LBM formulas. We found that SMI_h could be a significant parameter indicating that to be taken the cystatin C test, rather than creatinine test in renal function evaluation, as the cut-off values of 7.3 kg/m^2 for male and 5.7 kg/m^2 for female by logistic regression analysis at a fixed sensitivity of 100%. These cut-off values were similar to those of the 2019 Asian Working Group for Sarcopenia. We also suggested 31.5 cm or below for males (P value = 0.0081) and 29.6 cm or below for females (P value = 0.0111) as cut-off values of CC as indications for the use of the cystatin C test with 100% fixed sensitivity by the logistic regression test. Although the specificity was reduced compared to those of SMI_h and CC, we also presented the cut-off values of various estimated LBM at a fixed sensitivity of 85% as follows (49.4 kg for males and 37.2 kg for females with the James formula; 50.5 kg for males and 38.5 kg for females with the Boer formula; and 49.2 kg for males and 32.7 kg for females with the Yu formula).

Conclusion: We suggest the muscle mass-based criteria relating to SMI_h, CC, or some estimated LBM formulas that would indicate the use of cystatin C rather than creatinine to evaluate renal function test.

Key words: estimated glomerular filtration rate (eGFR), creatinine, cystatin C, muscle mass, bioelectrical impedance analysis, calf circumference, kidney function test

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I. INTRODUCTION

Accurate prediction of renal function is important in the diagnosis and treatment of renal disease, determination of the appropriate time for initiating renal replacement therapy, drug dosage adjustment, and nephrotoxic contrast agent use[1]. Although serum creatinine is the most commonly used marker of renal function, its interpretation is hampered by various affecting factors, such as age, sex, muscle mass, and dietary protein intake [2,3]. Muscle mass is known as a major contributing factor, and creatinine levels could stay within the reference interval despite significant kidney damage in patients with low muscle mass. Frailty, sarcopenia, and

malnutrition often occur concomitantly in hospitalized older adults[4]. One week of bed rest was reported to reduce skeletal muscle mass substantially; as such, inpatients are at a higher risk of sarcopenia[5]. Consequently, serum creatinine is not a good indicator when analyzing the elderly or patients who are expected to have a reduced muscle mass[6,7].

Cystatin C, a low molecular weight protein of 13.4 kDa, is produced at a constant rate in all nucleated cells, freely filtered in the glomerulus, and metabolized in the proximal tubule, meeting the criteria for a renal endogenous marker[8]. Unlike that of serum creatinine, the rate of production of cystatin C is not related to muscle mass and is therefore not affected by non-glomerular filtration rate (GFR) determinants such as age, sex, and race[7]. The independence of cystatin C values from muscle mass is an important advantage for early detection of kidney damage[8,9]. In many studies of adults and children, cystatin C-based estimated GFR (eGFR) predicted GFR more accurately than did serum creatinine[9-11].

Despite the known advantages of cystatin C, it remains far from established as a marker in routine clinical practice. Cystatin C could also be affected by other factors, such as chronic inflammation, obesity, diabetes, smoking, and thyroid dysfunction, among others[11]. Cystatin C test is more expensive than the creatinine test, its standardization is in progress and there are unresolved problems relating to its use, such as uncertainty about insurance coverage of cystatin C and creatinine test simultaneously.

Moreover, for measuring muscle mass, evaluation methods, such as magnetic resonance imaging (MRI) and dual-energy x-ray absorption (DXA) measurement have been introduced and evaluated for muscle mass measurement[12]. However, expensive imaging devices that run radiation exposure risk are not commonly

employed in routine clinical practice. Bioelectrical impedance analysis (BIA) has been an inexpensive, safe, and easily performed test without radiation hazard for muscle mass assessment. In addition, since the development of a model appropriate for measurement in supine patients, such as the S10 (InBody, Seoul, Korea)[13], it has become possible to measure bed-ridden patients who cannot stand up for the duration of measurement using BIAs. In addition, methods such as reanalyzing image data of computed tomography (CT)[14,15] or anthropometric analysis can be used.

The elderly and inpatients would continue to be the main target of health care. Because the elderly and patients with severe chronic disease requiring long-term hospitalization would have reduced muscle mass, serum creatinine may underestimate the extent of renal failure in this population. This would lead to under-recognition of renal impairment and thus delayed or suboptimal care. Although it is widely known that creatinine is affected by muscle mass, there are only a few studies that objectively evaluate muscle mass criteria and their effect on creatinine levels. To accurately evaluate renal function, it is necessary to select the most representative test according to patients' conditions; one of the major criteria that affect this decision is muscle mass. In this study, we determined objective muscle mass using various methods, such as BIA, deep learning CT image analysis, and anthropometric measurement, and proposed the most clinically feasible methods for measuring muscle mass. Several prediction formulas of lean body muscle mass based on height and weight have been developed for drug dosing[16-20], but have not been applied to eGFR evaluation; we also evaluated these formulas. Additionally, we analyzed the correlation between muscle mass and creatinine or eGFR, and tried to suggest criteria for selecting an appropriate test, to maximize detection of renal impairment. The aim of this study is to determine the clinical senarios and objective criteria regarding cases

wherein not to use the creatinine-based estimated glomerular filtration rate (eGFRcr), which may overestimate eGFR in the case of low muscle mass and to suggest cystatin C indication using muscle mass-based parameters for the desirable estimation of GFR.

II. MATERIALS AND METHOD

1. Abbreviations

GFR	glomerular filtration rate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFRcr	estimated glomerular filtration rate derived from CKD-EPI_2009 based on creatinine measurement
eGFRcys	estimated glomerular filtration rate derived from CKD-EPI_2012 based on cystatin C measurement
eGFRcr+cys	estimated glomerular filtration rate derived from CKD-EPI_2012 based on both creatinine and cystatin C measurement
ALM	appendicular lean muscle mass
SMI	skeletal muscle mass index
SMI_h	skeletal muscle mass index adjusted by height squared
SMI_w	skeletal muscle mass index adjusted by (body) weight
SMI_BMI	skeletal muscle mass index adjusted by Body Mass Index
DHRI	detection of hidden renal impairment
BIA	bioelectrical impedance analysis
DXA	dual-energy x-ray absorptiometry
CT	computed tomography
TAMA	total abdominal muscle mass area derived from CT image data
BW	body weight
Ht	height
BMI	body mass index
MAC	mid-arm circumference

MAMC	mid-arm muscle circumference
CC	calf circumference
HGS	handgrip strength
LBM	lean body mass

2. Subjects

A. Cross-sectional analysis of inpatient and health-check examinees

In this study, Korean inpatients and health-check subjects over the age of 40 admitted to Yongin Severance Hospital, a 500-bed capacity secondary care hospital, were recruited for cross-sectional analysis from July, 2021 to November, 2021. To avoid interference with cystatin C levels, subjects with chronic inflammation (C-reactive protein, CRP> 8 mg/dL), diabetes, obesity (body weight/height^2, BMI≥30), thyroid dysfunction, and steroid use (glucocorticoids) were excluded. In addition, to exclude factors that possibly interfere with BIA, patients with an implanted pacemaker and patients with amputation, ascites, edema, and skin damage to the wrist or ankle were excluded. Finally, 138 adults (male, 57; female, 81) were eligible for enrollment in this study. All enrolled patients were evaluated for BIA (BWA2.0, InBody, Seoul, Korea), anthropometric measurements, serum creatinine levels, and cystatin C levels. We obtained written informed consent from all participants, and the study was reviewed and approved by the institutional review board of the Yongin Severance Hospital, Yongin-si, Korea (IRB No. 9-2021-0095).

B. Retrospective analysis of Korean National Health and Nutrition

Examination Survey (KNHANES) subjects

We retrospectively analyzed the correlation between skeletal muscle mass index adjusted for height squared (SMI_h, appendicular lean muscle mass per height squared) by DXA and serum creatinine using data of 1,956 subjects over the age of 30 from KNHANES in 2011, when standardized creatinine levels and DXA examination data were available[21,22].

C. Heath-check subjects as another retrospective analysis

Correlation analysis between SMI_h and serum creatinine was performed in 6,094 patients who visited the health promotion center for 21 months from March, 2020 to November, 2021, and underwent creatinine tests and testing using another BIA model, Accuniq BC720 (SELVAS healthcare, Daejeon, Korea).

3. Measurement and Assessment

A. Creatinine and Cystatin C

Creatinine and cystatin C were measured in serum samples. Creatinine was measured using the enzymatic method (Roche Creatinine Plus ver.2 assay), which is standardized against the Isotope Dilution-Mass Spectrometry method. Cystatin C was measured using the immunoturbidimetric method (Tina-quant Cystatin C Gen. 2, Roche), which is standardized and traceable against ERM-DA471/IFCC reference material. Both values were measured using the Roche cobas 8000 c702 (Roche Diagnostics, Mannheim, Germany).

B. Anthropometric analysis

Anthropometric analysis of mid-arm circumference (MAC), mid-arm muscle circumference (MAMC), and calf circumference (CC) were performed on inpatients. MAMC was calculated using the following formula: MAMC (cm) = MAC (cm) − 0.314 × triceps skinfold thickness (mm). MAC and CC were measured to the nearest 0.1 cm with a non-elastic tape measure. Triceps skinfold thickness was the average of two measurements taken by the same researcher using a Dynatron skinfold caliper (Dynatronics Corporation, Salt Lake City, Utah, USA) on the mid arm area. CC was also measured twice, and the average recorded. MAMC and CC were measured only for inpatients. Hand grip strength (HGS) was measured with both hands three times for both inpatients and health-check subjects using the Jamar plus hand dynamometer (Performance Health, Warrenville, IL, USA). We chose the maximum-value HGS.

C. Bioelectrical impedance analysis

BIA is a non-invasive tool that measures impedance by sending a weak electric current through the body and estimates body composition through differences in the conductance of various tissues due to differences in the biological properties of the media in question, such as fat, water, bone mass, lean body mass, and muscle. Electrodes are placed at eight tactile points on the body to achieve multi-segment frequency analysis. Two different types of multi-frequency BIA devices were used in this study: InBody BWA2.0 (InBody, Seoul, Korea) for inpatients or health-check subjects, and Accuniq BC720 (SELVAS Healthcare Inc., Daejeon, South Korea) for health-check subjects only.

The Accuniq BC720 model can measure in a standing position using six different

frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 550 kHz, and 1 MHz). This model was used for measuring the body composition of the subjects who visited the health promotion center for a health checkup. The patients stood in the anatomical position, with arms outstretched about 30° away from the body, during the measurement.

InBody BWA2.0 is a multi-frequency BIA device that can perform measurement on supine subjects. It uses eight different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, 1 MHz, 2 MHz, and 3 MHz). Supine subjects were asked to hold their limbs slightly away from their bodies, and measurements were performed according to the manufacturer's instructions. Over 270 items, including appendicular lean muscle mass (ALM) and skeletal muscle mass index (SMI_h), were calculated from the InBody software.

D. Computed tomography-based volumetric analysis

Among our study subjects, those who underwent abdominal CT scan due to other clinical purposes (n = 20) were evaluated for the total abdominal muscle mass area (TAMA); the values were then compared to SMI_h by BIA. To reduce the bias of muscle mass measurement at different time points—for example, inpatients who have been at bed rest for longer periods of time would have progressively less muscle mass—the CT scans that were analyzed were limited to those performed on patients with BIA, serum creatinine, and cystatin C data obtained within 5 days for inpatients, and within 7 days for health-check subjects. Abdominal CT scans were performed using 256-slice multi-detector CT scanner (Philips Healthcare, Amsterdam, The Netherlands). Pre-contrast or contrast CT dicom files were uploaded to commercially available segmentation software (MEDIP Deep Catch v1.1.4.4918, MEDICALIP Co. Ltd., Seoul, South Korea). This software analyzes automatically segmented CT

images into a volumetric mask of seven body compartments (skin, bone, muscle, visceral fat, subcutaneous fat, internal organs with vessels, and spinal cord) through a deep learning algorithm, and then calculates targeted area at the corresponding level. We used the L3 spine level of CT scan images to measure TAMA, which was shown to have the highest correlation with whole-body skeletal muscle mass in a previous study[23,24].

E. Formulas and definitions

eGFR estimated according to eGFRcr (derived from CKD-EPI_2009 based on creatinine measurement)[25] and that estimated according to eGFRcys (derived from CKD-EPI_2012 based on Cystatin C measurement)[26] were compared. Based on the fact that cystatin C is independent of muscle mass, we hypothesized that the discrepancy between creatinine and cystatin C-based GFR could be representative of muscle mass. A discordance between eGFRcr and eGFRcys was calculated as eGFR %difference, which was defined as follows: (eGFRcr / eGFRcys – 1) × 100 (%). We defined the patients with the detection of hidden renal impairment (DHRI) by eGFRcr as those with values of eGFRcr $\geq$ 60 mL/min/1.73 m^2 and eGFRcys < 60 mL/min/1.73 m^2. The scenario behind DHRI is when creatinine-based eGFR is within the reference interval due to the insufficient muscle mass, while cystatin C-based eGFR shows renal impairment. We also derived cut-off values using DHRI to determine which subjects should undergo cystatin C testing rather than creatinine testing for renal function assessment, based on muscle mass. ALM was the sum of muscle mass for four limbs. Skeletal muscle mass indices (SMIs) were calculated as follows: SMI_h was calculated as ALM per height squared (ALM/Ht^2), SMI_w was calculated as ALM per body weight (ALM/BW), and SMI_BMI was calculated as

ALM per BMI (ALM/BMI). We also compared the lean body muscle mass (LBM) formulas presented in previous studies[16-20] with SMI_h and evaluated whether these equations could be an alternative for SMI measurements. The formulas used are as follow

(1) James formula[17,18]:

LBM (men) = 1.1 × BW - 128 × $(BW/Ht)^2$

LBM (women) = 1.07 × BW - 148 × $(BW/Ht)^2$

where weight is in kg, height is in cm, and LBM is in kg

(2) Boer formula[19]:

LBM (men) = 0.407 × BW + 0.267 × Ht - 19.2

LBM (women) = 0.252 × BW + 0.473 × Ht - 48.3

where weight is in kg, height is in cm, and LBM is in kg

(3) Yu formula[20]:

LBM = 22.932326 + 0.684668 × BW -1.137156 × BMI -0.009213 × age + 9.940015 (if male)

where weight is in kg, BMI is in kg/m^2, and LBM is in kg

F. Statistical analyses

The Pearson correlation coefficient (r) and/or Spearman's correlation coefficient (r_s) were used to determine the correlation between parameters according to the distribution normality. The association of each parameter, such as age, sex, and SMI, with creatinine level was determined via logistic regression for DHRI. The level of

significance was defined as P value < 0.05. For the total population and subgroups by sex, receiver operating characteristic (ROC) curves were constructed from DHRI and parameters for muscle mass to obtain the optimal cut-off value, which showed fixed 100% sensitivity and best specificity to conservatively detect hidden renal impairment. Statistical analysis was performed with Analyse-it version 5.92 for Microsoft Excel (Analyse-it Software Ltd, Leeds, UK).

III. RESULTS

1. Study population and baseline characteristics

A. Inpatients and health-check examinee in cross-sectional analysis

A total of 138 inpatients and health-check examinees were enrolled in this cross-sectional analysis. The basic characteristics of the study population were classified according to sex (57 males, 81 females) and purpose of visit (inpatients 66, health-check 72), and the baseline characteristics are presented in Table 1. SMI_h and handgrip strength values showed significant differences between sex groups and according to age, while eGFRcr and eGFRcys values did not show significant differences. Conversely, in the comparison between the inpatient and the health-check group, were shown significant difference in age, eGFRcys, SMI_h, and handgrip strength, while eGFRcr did not.

Table 1. Baseline characteristics of the enrolled study population

Characteristics	Enrolled inpatients and health-check examinees (n=138)					
	Sex			Visiting purpose		
	Male	Female	P value**	Inpatients	Health-check	P value**
Number of subjects, n	57	81		66	72	
Age, year	66.4 (13.6)*	67.1 (12.1)	0.7400	73.5 (10.4)	60.8 (11.6)	< 0.0001
Age range, year	40~93	41~95	-	41~95	40~83	-
BMI, kg/m^2	23.38 (2.95)	23.14 (2.90)	0.6340	22.86 (3.06)	23.59 (2.74)	0.1410
BMI range	15.00~29.49	16.27~29.80	-	15.00~29.80	16.27~29.49	-
†eGFRcr, mL/min/1.73 m^2	89.2 (11.8)	90.8 (12.7)	0.4511	88.1 (12.0)	92.0 (12.4)	0.0651
‡eGFRcys, mL/min/1.73 m^2	80.8 (16.7)	82.2 (16.6)	0.6296	74.6 (16.8)	88.0 (13.6)	< 0.0001
SMI_h by BIA, kg/m^2	7.40 (1.11)	5.86 (0.73)	< 0.0001	6.08 (1.17)	6.88 (1.06)	< 0.0001
MAMC, cm	-	-	-	18.8 (3.0)	-	-
CC, cm	-	-	-	30.6 (3.35)	-	-
Handgrip strength, kg	34.7 (10.0)	20.9 (5.8)	< 0.0001	23.2 (9.4)	29.2 (10.3)	0.0029

*Mean (standard deviation), all such values
** Student's t-test
†Estimated by the CKD-EPI creatinine equation, 2009 version (Reference #25)

‡Estimated by the CKD-EPI cystatin C equation, 2012 version (Reference #26)
¶Abbreviations: SMI_h, skeletal muscle mass index adjusted by height squared; eGFR, estimated glomerular filtration rate; BMI, body mass index, (weight/height squared, kg/m^2); BIA, bioelectrical impedance analysis; MAMC, mid arm muscle circumference; CC, calf circumference

B. Retrospective analysis of KNHANES and health-check examinee populations

We reviewed 1,956 KNHANES participants (809 males and 1,147 females) and 6,094 Yongin Severance Health Promotion Center examinees (3,223 males and 2,871 females) enrolled in this retrospective study. Table S1 shows the basic characteristics of participants and method for determination of muscle mass.

Table S1. Baseline characteristics of the retrospective study population

Characteristics		Retrospective analysis (n)	
		KNHANES	Health Promotion Center
Study period		2011	Mar 2020 to Nov 2021
Age, year			
	Median	53	53
	Range	30-80	30-90
Age group distribution, year			
	30-40	449	994
	40-49	373	1,537
	50-59	445	1,742
	60-69	391	1,271
	70-79	258	461
	80-89	40	88
	90-99	0	1
Sex			
	Male	809	3,223
	Female	1,147	2,871
BIA	Accuniq BC720		6,094
DXA	Hologic	1,956	

¶Abbreviations: KNHANES, the Korea National Health and Nutrition Examination Survey; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry

2. Correlation between SMI and creatinine

We confirmed a significant correlation between SMI_h and serum creatinine levels among both sexes (r = 0.344 [95% confidence interval (CI) 0.091 to 0.555]; P value, 0.0089 for male and r = 0.348 [95% CI, 0.141 to 0.527]; P value, 0.0014 for female) (Figure 1 (B) and (C), respectively) in our cross-sectional data (composed by inpatients and health-check subjects), when only subjects with eGFR were included (CKD-EPI by Cr) $\geq$ 60 ml/min/1.73 m^2. The results of the retrospective examinations of the health promotion center (using Accuniq BC720) and KNHANES (using DXA) data, both of which were collected from relatively healthy subjects, also showed a significant positive correlation between SMI_h and creatinine, but when only subjects with eGFR were included (CKD-EPI by Cr) $\geq$ 60 ml/min/1.73 m^2 (Figure 1 (D)-(I)). In these two retrospective study groups, the r value was relatively lower in the analysis results according to each sex (Figure 1 (E), (F), (H), (I); r = 0.147, 0.111, 0.263, 0.128, respectively), compared to the same in the cross-sectional study results (Figure 1 (B) and (C); r = 0.344, r = 0.348, respectively).

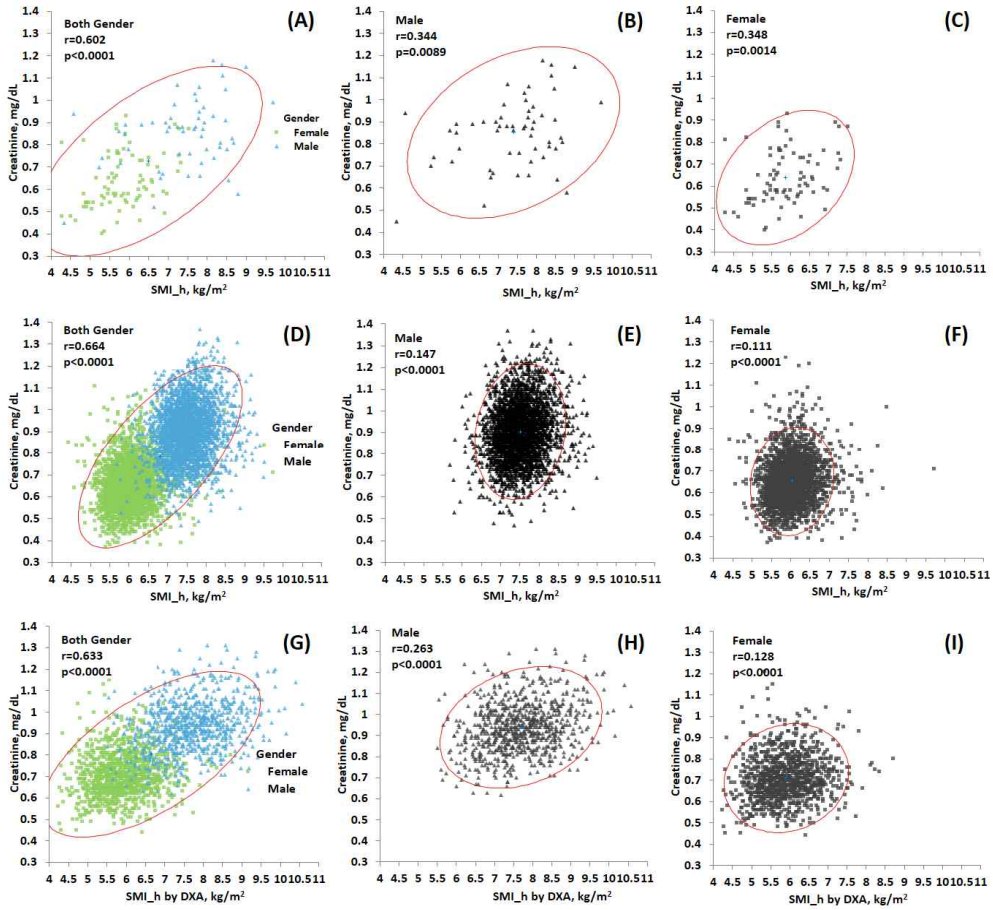


Figure 1. Pearson's correlation analysis for serum creatinine and SMI_h. Correlation analysis results between serum creatinine and SMI_h (by BIA InBody BWA2.0 model) in both sexes (A), males (B) and females (C) among inpatients and health-check examinees. Correlation analysis results between serum creatinine and SMI_h (by BIA Accuniq BC 720 model) in both sexes (D), males (E), and females (F) in health promotion center examinees.
Correlation analysis results between serum creatinine and SMI_h (by DXA Discovery QDR 4500 W fan-beam densitometers model) in both sexes (G), males (H), and females (I) in KNHANES participants.
¶Abbreviations: SMI_h, skeletal muscle mass index adjusted by height squared; BIA, bioelectrical impedance analysis; KNHANES, the Korea National Health and Nutrition Examination Survey; DXA, dual-energy X-ray absorptiometry

We obtained the following equation and fit model for serum creatinine (Figure 2). SMI_h and sex could explain 44.1% of the serum creatinine levels by multiple regression analysis (r^2 adjusted = 0.441).

Serum Creatinine = 0.3329 + 0.0521 SMI_h + 0.1337 Sex

(P value <0.0001; males = 1, females = 0)

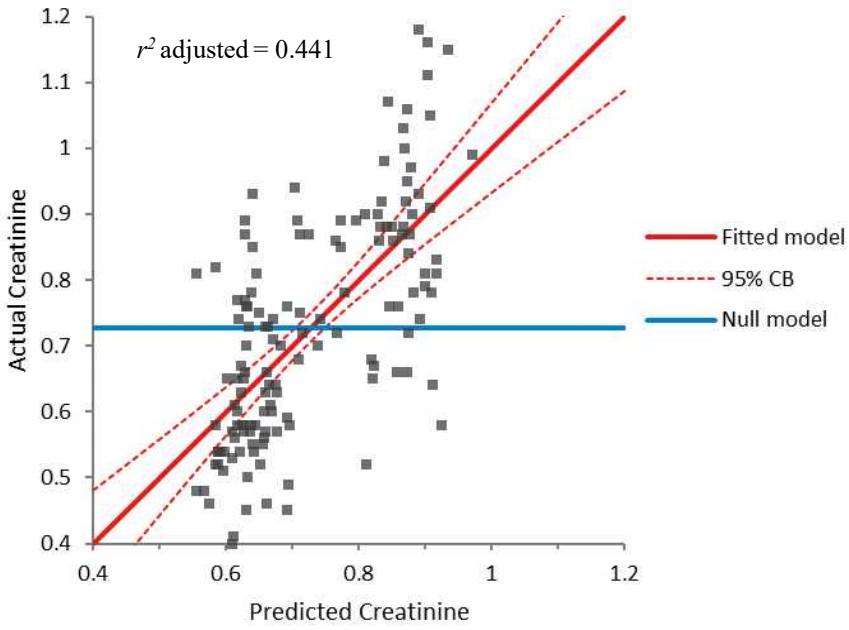


Figure 2. Fitted model between actual and predicted serum creatinine values by multiple regression analysis for creatinine, SMI_h, and sex. The null hypothesis was rejected, with a P value <0.0001 by the F-test.
¶Abbreviations: SMI_h, skeletal muscle mass index adjusted by height squared; CB, confidence bounds

Although multiple regression analysis had also been performed with other independent parameters other than SMI_h and sex, the explanatory power was not significantly increased. We also found significant correlations using various SMI and estimated LBM formulas as in Table 2 (P value < 0.0001 for all correlations).

Table 2. Correlation matrix of creatinine, various skeletal muscle mass index parameters, and estimated lean body mass formulas (n = 138)

	SMI_h	SMI_BMI	SMI_w	LBM James formula	LBM Boer formula	LBM Yu formula	Serum Creatinine	
SMI_h	-	0.776	0.727	0.886	0.853	0.833	0.602	Pearson's r
	-	0.755	0.728	0.865	0.828	0.810	0.589	Spearman's rs
SMI_BMI	0.776	-	0.950	0.805	0.858	0.872	0.539	
	0.755	-	0.957	0.785	0.855	0.857	0.531	
SMI_w	0.727	0.950	-	0.638	0.699	0.740	0.494	
	0.728	0.957	-	0.649	0.723	0.737	0.512	
LBM James formula	0.886	0.805	0.638	-	0.987	0.963	0.610	
	0.865	0.785	0.649	-	0.982	0.967	0.597	
LBM Boer formula	0.853	0.858	0.699	0.987	-	0.980	0.602	
	0.828	0.855	0.723	0.982	-	0.992	0.588	
LBM Yu formula	0.833	0.872	0.740	0.963	0.980	-	0.632	
	0.810	0.857	0.737	0.967	0.992	-	0.599	
Serum Creatinine	0.602	0.539	0.494	0.610	0.602	0.632	-	
	0.589	0.531	0.512	0.597	0.588	0.599	-	

¶Abbreviations: SMI_h, Skeletal muscle mass index adjusted by height squared; SMI_w, Skeletal muscle mass index adjusted by body weight; SMI_BMI, Skeletal muscle mass index adjusted by body mass index; LBM, lean body mass; LBM James formula (References 17 and 18), LBM Boer formula (Reference 19), LBM Yu formula (Reference 20)

3. Correlation between SMI_h and eGFR %difference

There were significant negative correlations between SMI_h and eGFR %differences (r = -0.592 [95% CI -0.739 to -0.392] for males and r = -0.484 [95% CI- 0.635 to -0.297] for females; P value <0.0001 for both sexes) (Figure 3).

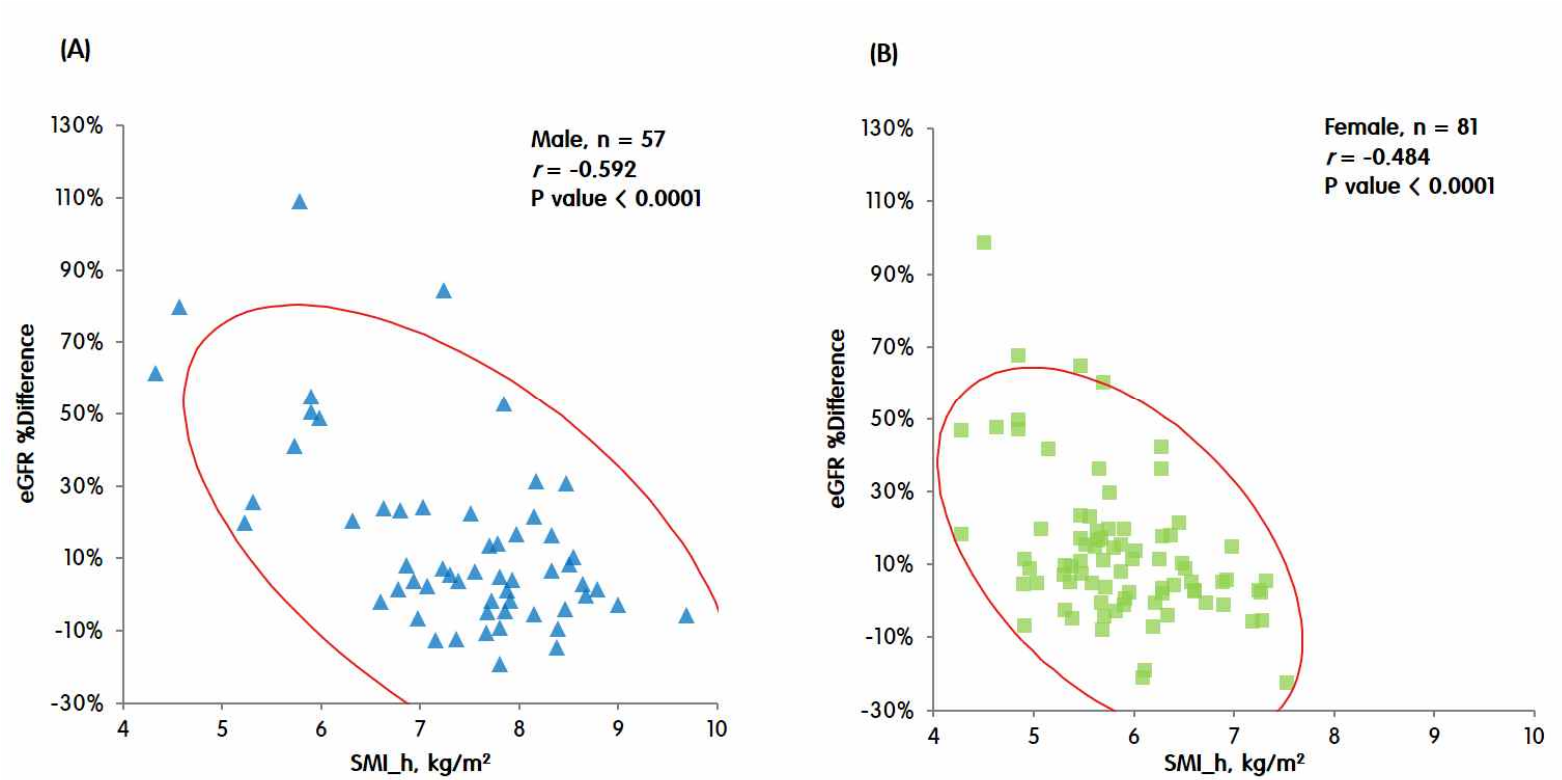


Figure 3. Pearson's correlation analysis for eGFR %difference and SMI_h (by BIA InBody BWA2.0 model) in male (A) and female (B) cross-sectional study participants (inpatients and health-check examinee).
¶Abbreviations: eGFR, estimated glomerular filtration rate; SMI_h, skeletal muscle mass index adjusted by height squared; BIA, bioelectrical impedance analysis

SMI_h could explain 15.3% of eGFR% difference by multiple regression analysis (r^2 adjusted = 0.153). When the sex parameter was added for the same analysis, explanatory power was increased to 28.6%, and the equation was as follows (Figure 4):

eGFR %Difference = 0.9426 - 0.1378 × SMI_h + 0.2236 × Sex

(P value < 0.0001; males = 1, females = 0)

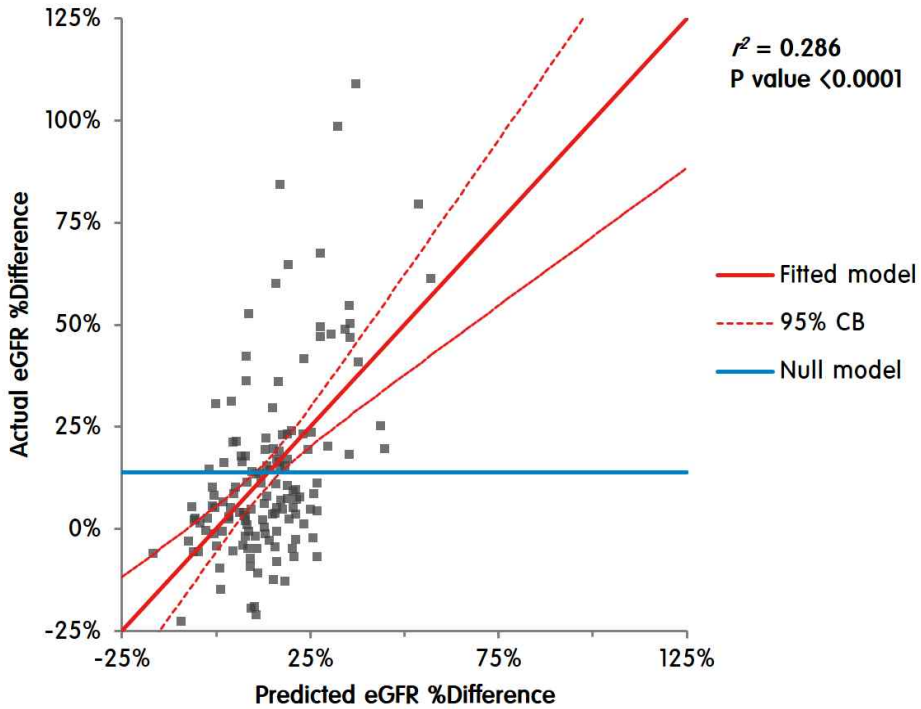


Figure 4. Fitted model between actual and predicted eGFR %difference of multiple regression analysis for eGFR %difference, SMI_h and sex. The null hypothesis was rejected, with a P value <0.0001 by the F-test.
¶Abbreviations: eGFR, estimated glomerular filtration rate; SMI_h, skeletal muscle mass index adjusted by height squared; CB, confidence bounds

4. Other parameters correlated with SMI or eGFR %differences

We analyzed the correlation between SMI_h and other related parameters, such as MAMC, CC, handgrip strength, TAMA, and BMI. Significant positive correlation with SMI_h was shown for CC (r = 0.902 [95% CI, 0.795 to 0.955]; P value <0.0001 for males and r = 0.687 [95% CI, 0.475 to 0.824]; P value <0.0001 for females) (Figure S1 (A) for males and (B) for females). TAMA also showed a significant positive correlation with SMI_h (n = 20; Spearman's rank correlation coefficient, r_s, 0.859; P value <0.0001, Figure S2). Another significant correlation with SMI was found in BMI (r = 0.660 [95% CI, 0.483 to 0.786]; P value <0.0001 for males and r = 0.571 [95% CI, 0.402 to 0.702]; P value <0.0001 for females) (Figure S3). We could also find significant correlation between SMI_h and other parameters, such as MAMC (r = 0.608 [95% CI, 0.297 to 0.803]; P value = 0.0008 for males and r = 0.412 [95% CI, 0.111 to 0.644]; P value = 0.0092 for females) (Figure S4 (A) for males and (B) for females) and the handgrip strength test results (r = 0.662 [95% CI, 0.445 to 0.806]; P value <0.0001 for males and r = 0.554 [95% CI, 0.352 to 0.707]; P value <0.0001 for females) (Figure S5 (A) for male and (B) for female) in both sexes.

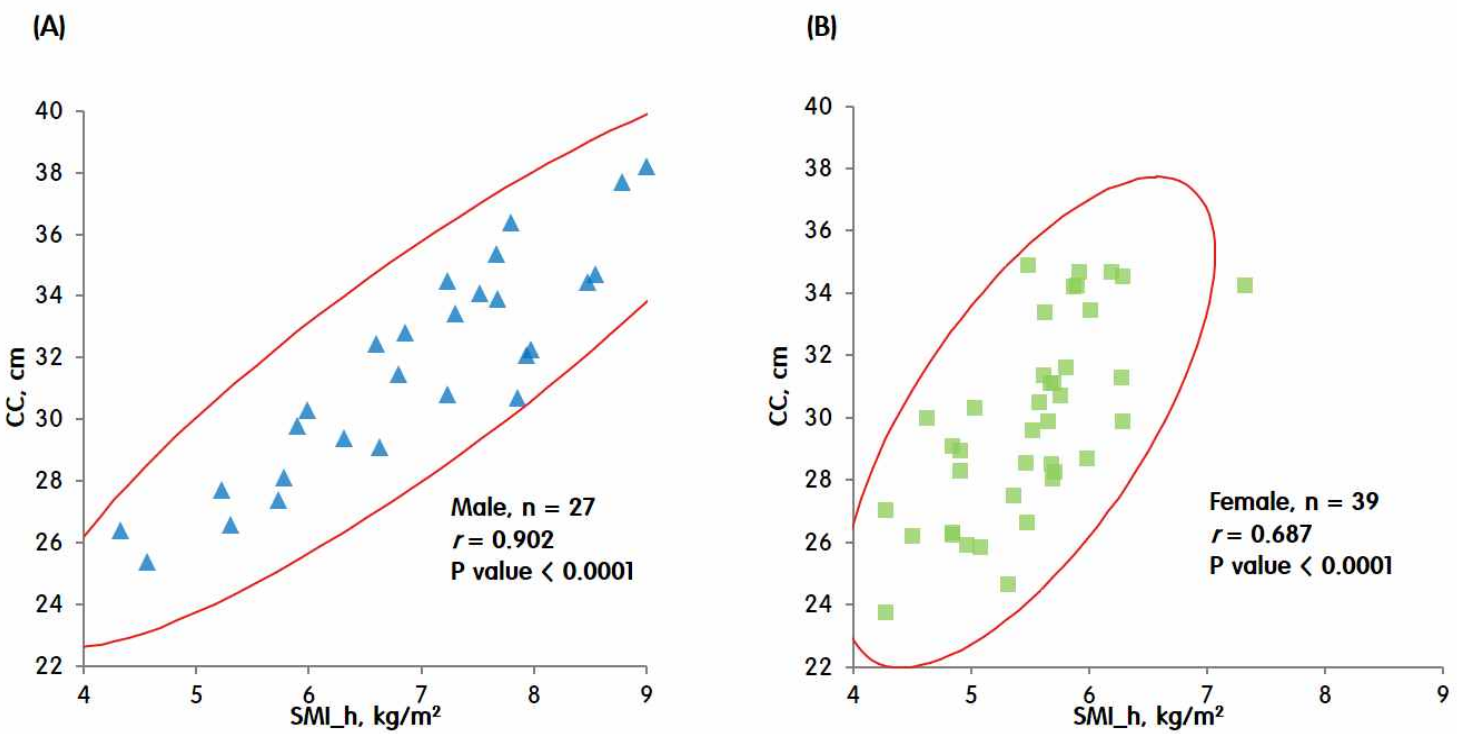


Figure S1. Scatter plot for correlation between CC and SMI_h (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: CC, calf circumference; SMI_h, skeletal muscle mass index adjusted by height squared; *r*, coefficient of correlation

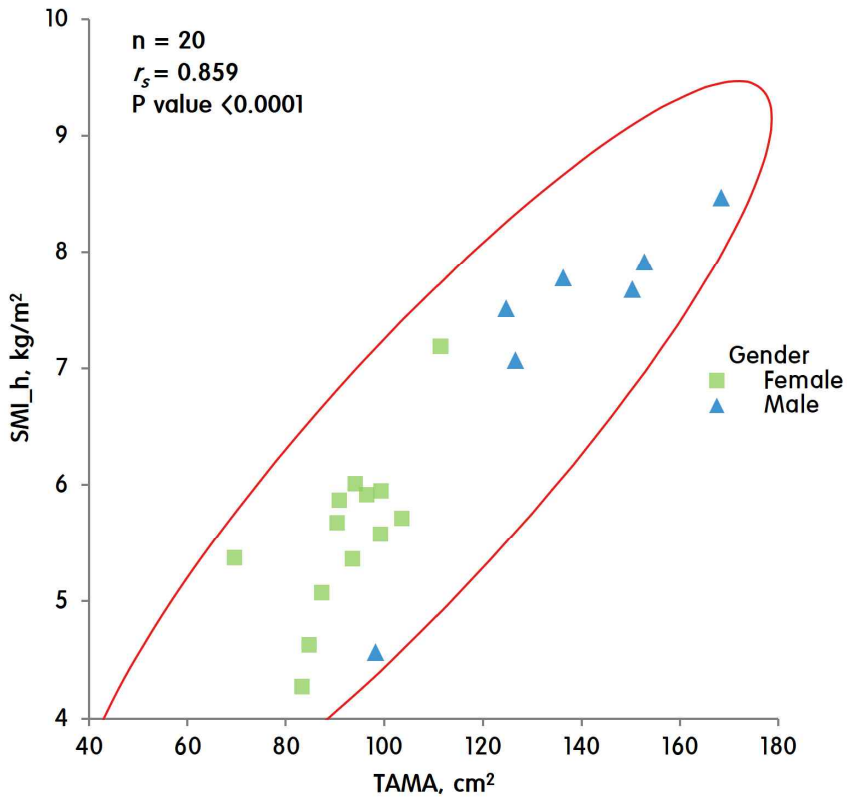


Figure S2. Scatter plot for correlation between TAMA and SMI_h.
¶Abbreviations: r_s, the coefficient of Spearman's rank correlation; SMI_h, skeletal muscle mass index adjusted by height squared; TAMA, total abdominal muscle area of abdominal computed tomography L3 level

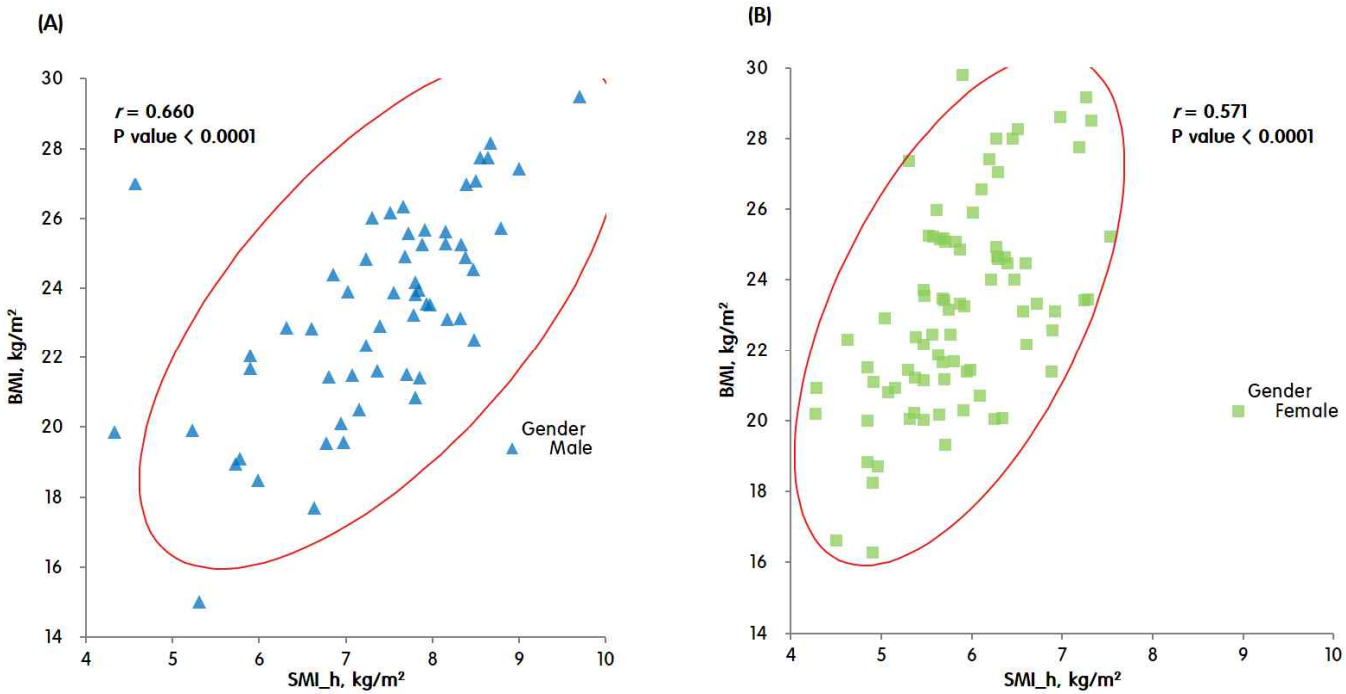


Figure S3. Scatter plot for correlation between BMI and SMI_h (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: BMI, body mass index; SMI_h, skeletal muscle mass index adjusted by height squared; *r*, coefficient of correlation

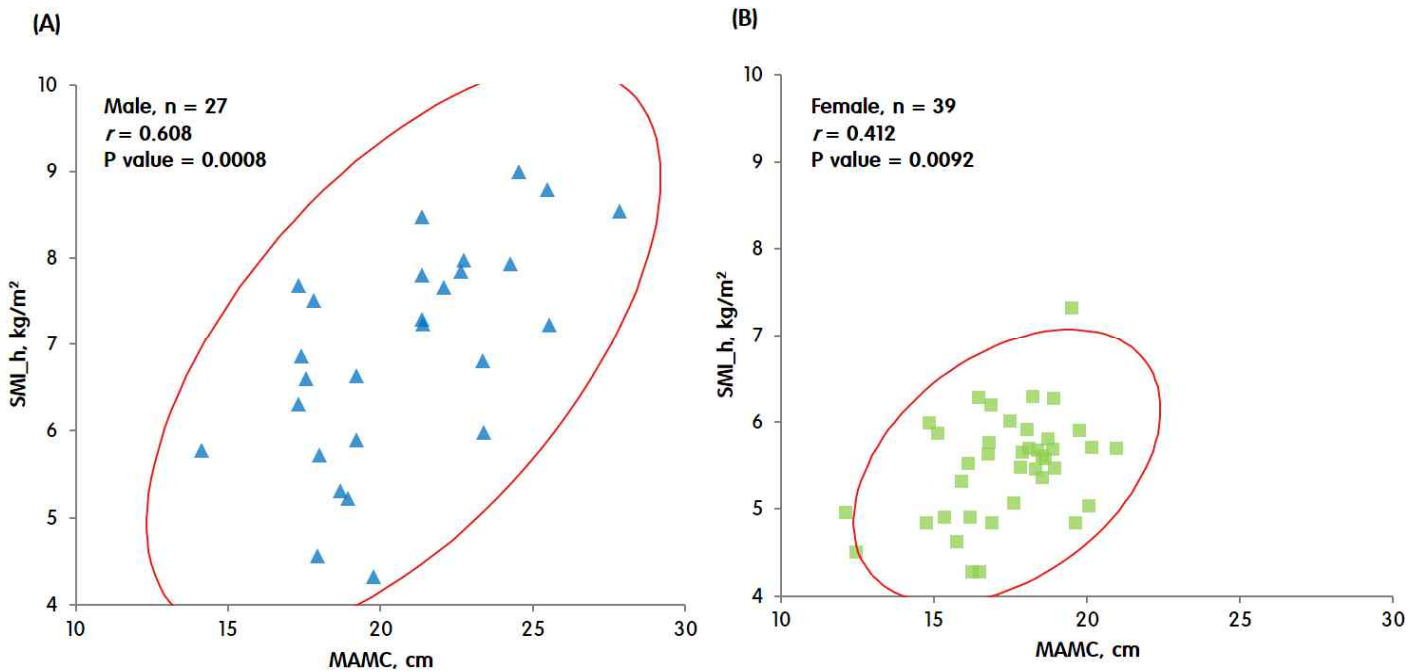


Figure S4. Scatter plot for correlation between MAMC and SMI_h (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: MAMC, mid arm muscle circumference; SMI_h, skeletal muscle mass index adjusted by height squared; *r*, coefficient of correlation

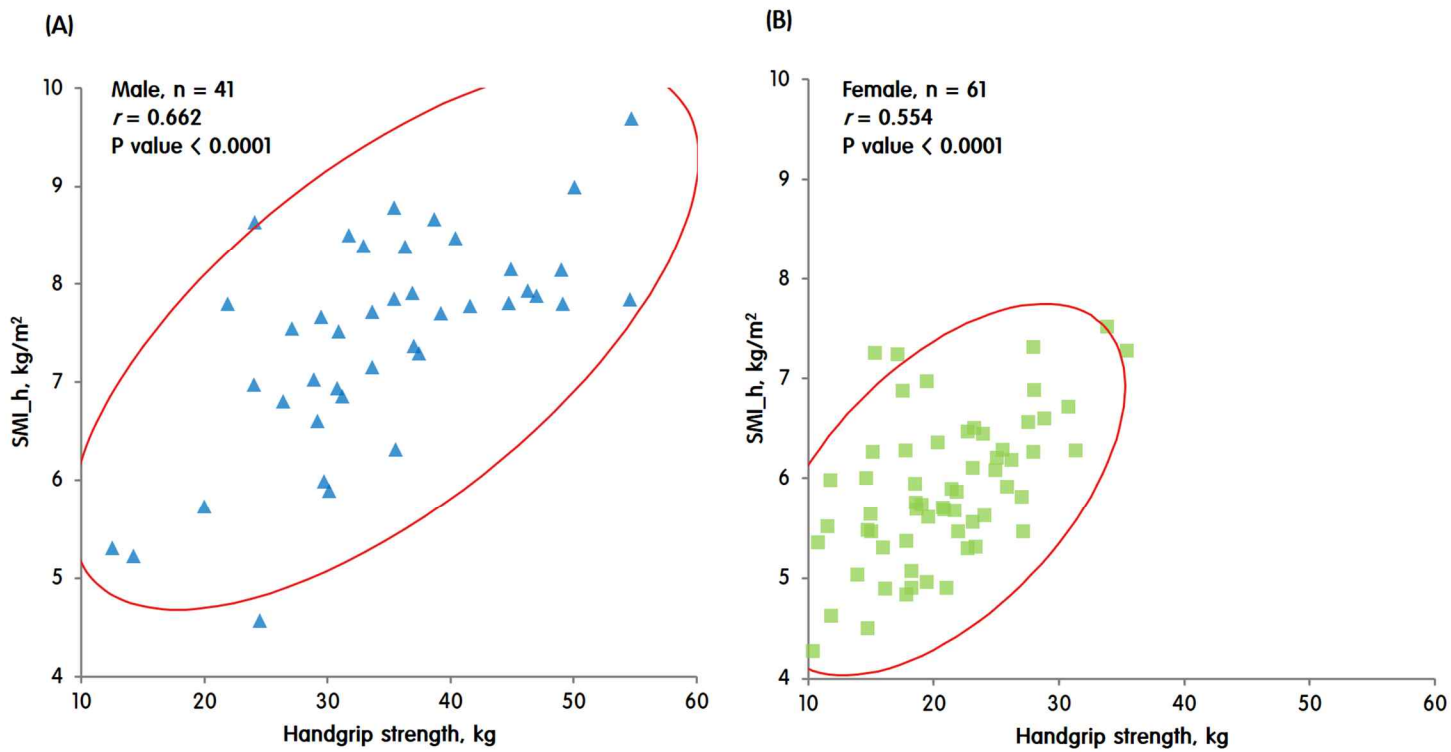


Figure S5. Scatter plot for correlation between maximum values of handgrip strength and SMI_h (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: SMI_h, skeletal muscle mass index adjusted by height squared; *r*, Pearson correlation coefficient

CC and eGFR %differences showed significant negative correlation (r = -0.646 [95% CI -0.824 to -0.353]; P value = 0.0003 for males, and r = -0.351 [95% CI - 0.600 to -0.040] for females; P value = 0.0285) (Figure S6). TAMA also showed a significant negative correlation with eGFR %differences (r_s, -0.629; P value = 0.0030), as we hypothesized (Figure S7).

We found a significant negative correlation between eGFR %difference and BMI for males (r = -0.272 [95% CI -0.497 to -0.012], P value = 0.0407, Figure S8 (A)), but not for females (r = -0.207 [95% CI -0.407 to -0.012], P value = 0.0633, Figure S8 (B)). Another significant negative correlation was shown between eGFR %difference and MAMC only for males (n = 27; r = -0.421 [95% CI -0.691 to 0.049], P value = 0.0286, Figure S9 (A)) and not for females (n = 39; r = -0.263 [95% CI -0.534 to 0.057], P value = 0.1054, Figure S9 (B)). Similarly, a significant negative correlation was found between eGFR %difference and the handgrip strength test results, only for females (r = -0.402 [95% CI -0.594 to -0.167]; n = 61, P value = 0.0013, Figure S10 (B)) but not for males (r = -0.254 [95% CI -0.521 to 0.058], n = 41, P value = 0.1088, Figure S10 (A)).

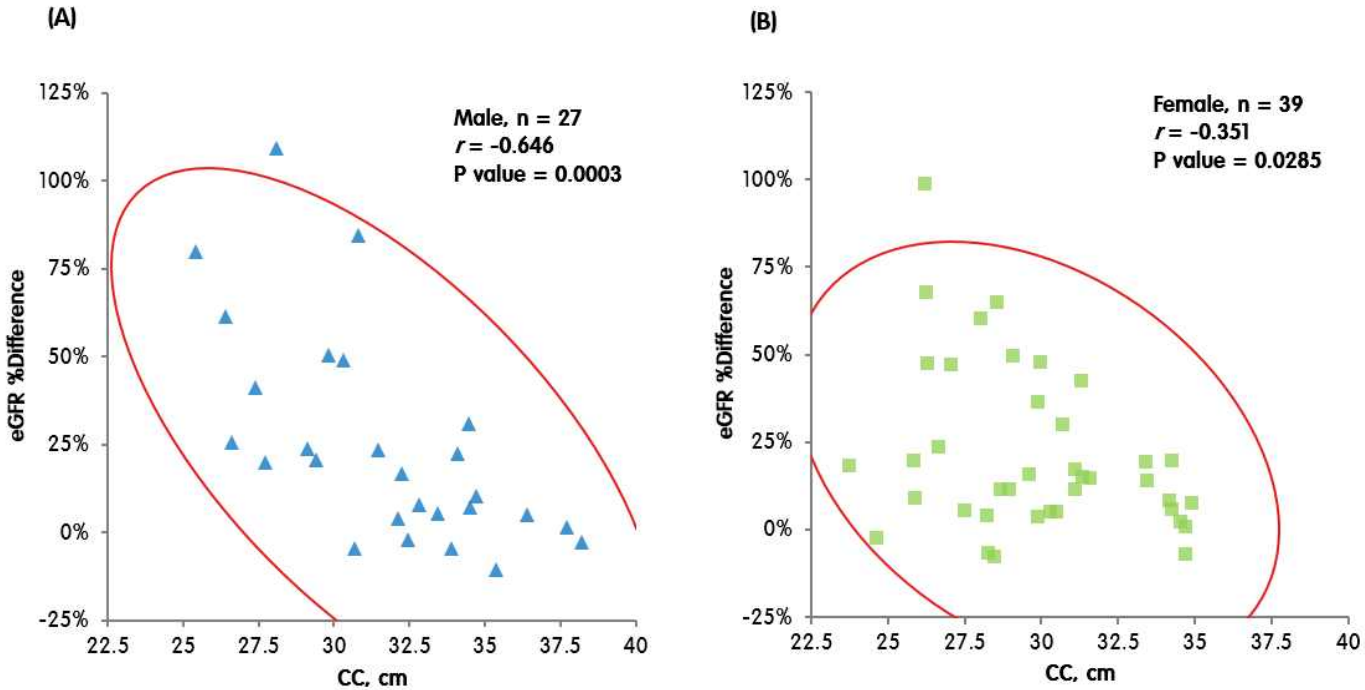


Figure S6. Scatter plot for correlation between CC and eGFR %difference (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: CC, calf circumference; *r*, coefficient of correlation; eGFR, estimated glomerular filtration rate

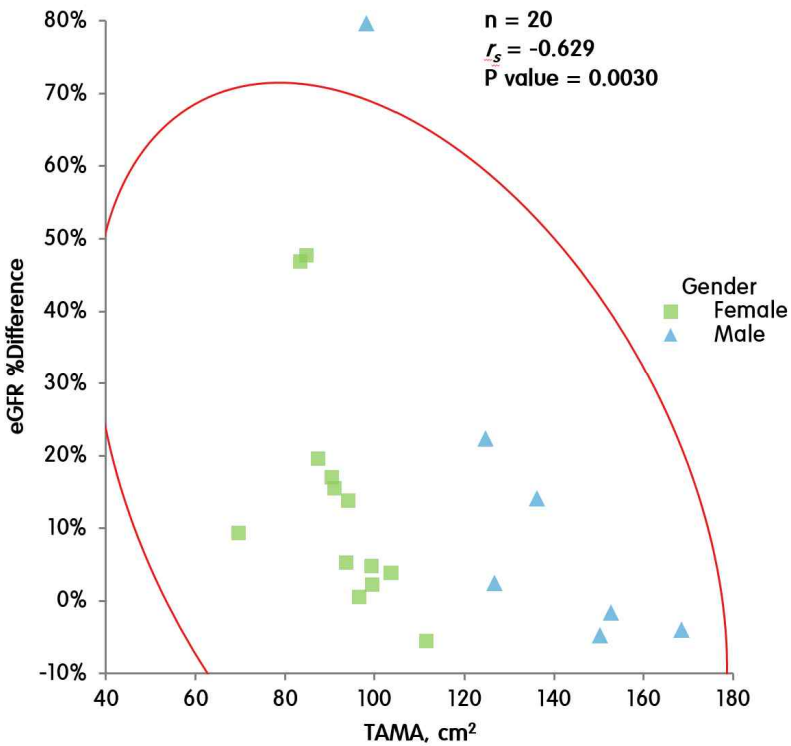


Figure S7. Scatter plot for correlation between TAMA and eGFR %difference.
¶Abbreviations: r_s, coefficient of Spearman's rank correlation; TAMA, total abdominal muscle area of abdominal computed tomography L3 level; eGFR, estimated glomerular filtration rate

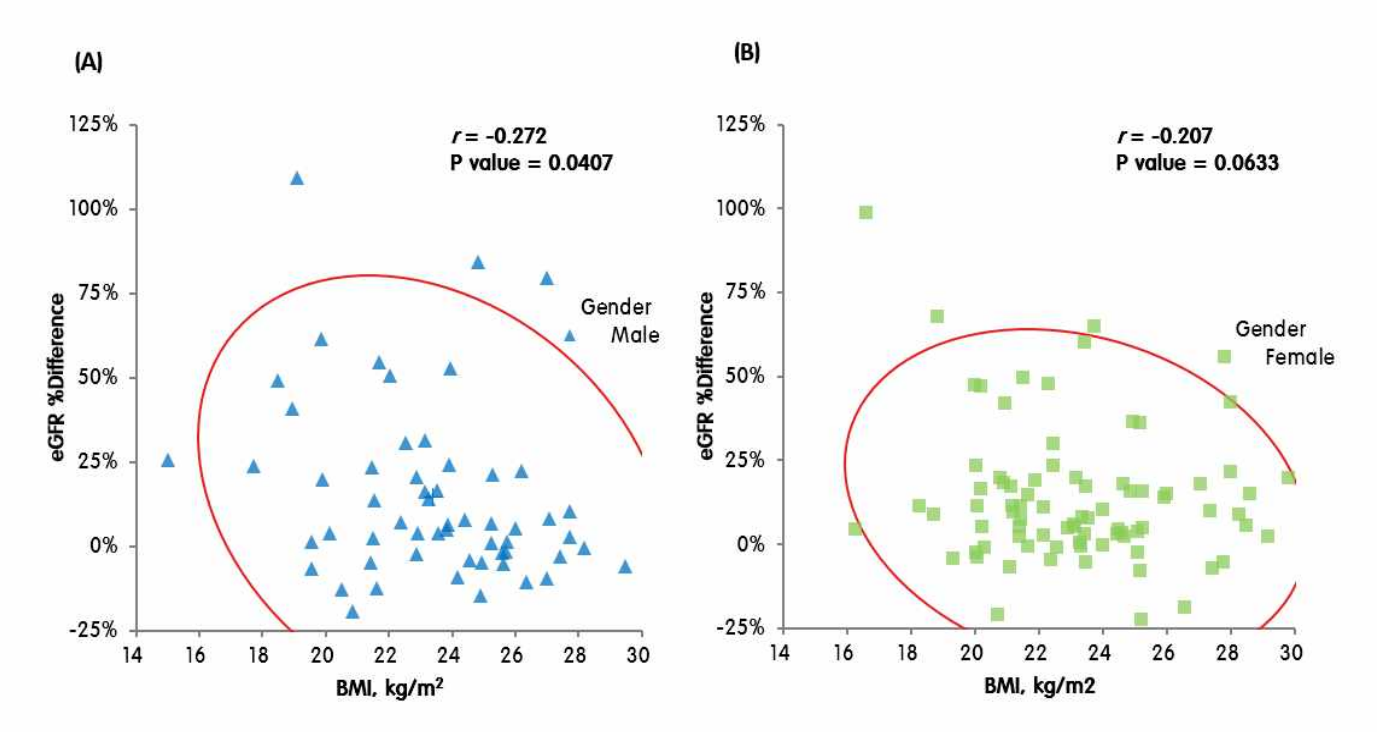


Figure S8. Scatter plot for correlation between BMI and eGFR %difference (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: BMI, body mass index; *r*, coefficient of correlation; eGFR, estimated glomerular filtration rate

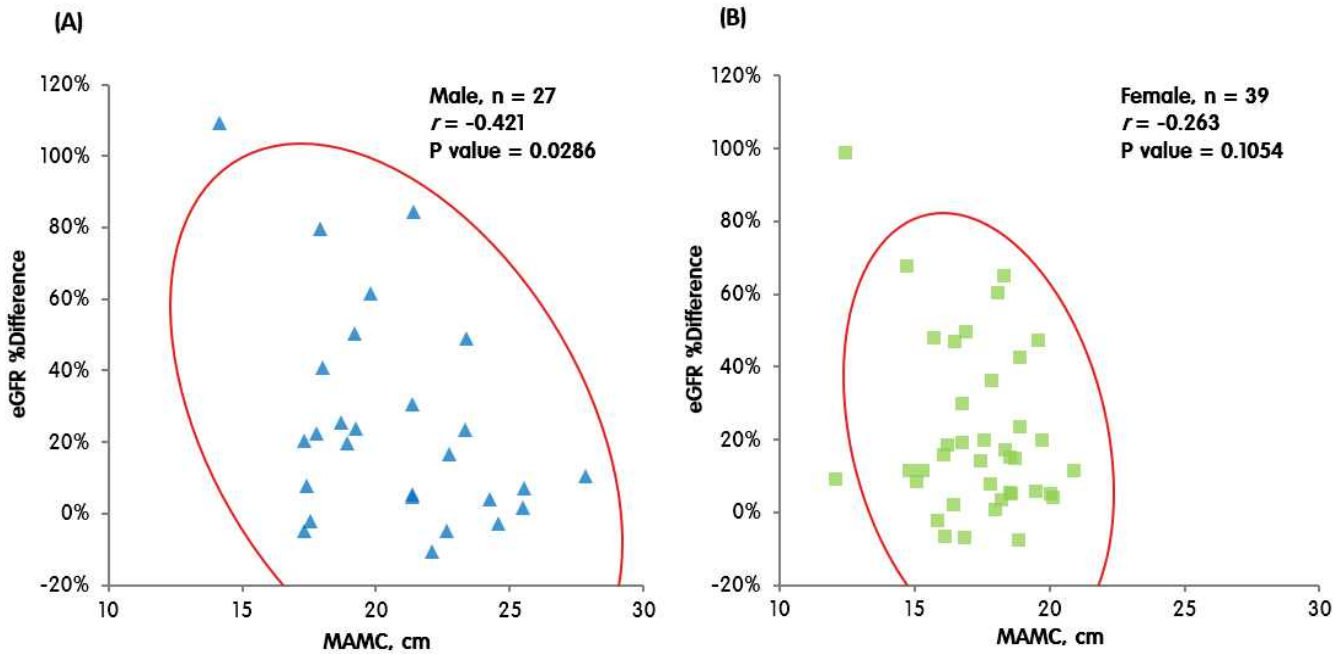


Figure S9. Scatter plot for correlation between MAMC and eGFR %difference (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: MAMC, mid arm muscle circumference; *r*, coefficient of correlation; eGFR, estimated glomerular filtration rate

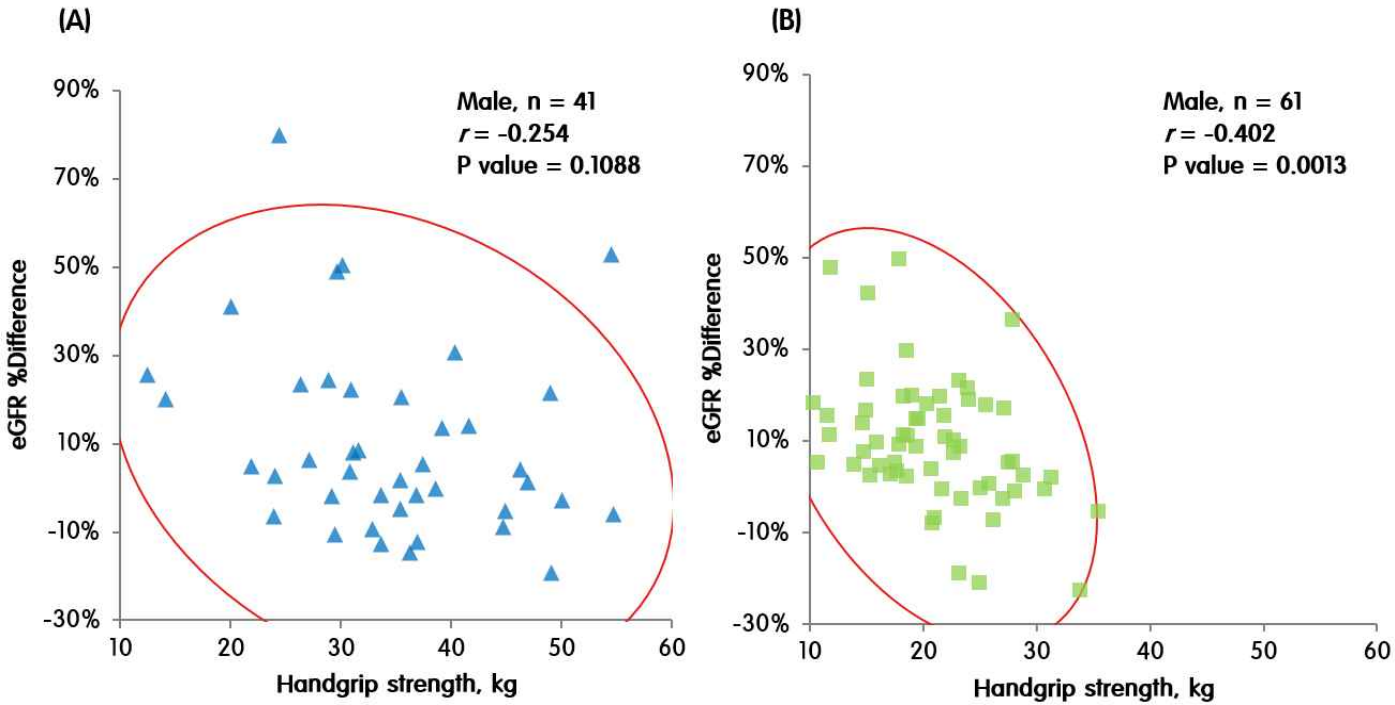


Figure S10. Scatter plot for correlation between handgrip strength and eGFR %difference (A) for males and (B) for females. Pearson's correlation was used.
¶Abbreviations: *r*, coefficient of correlation; eGFR, estimated glomerular filtration rate

5. Comparison between the inpatient and health-check groups

Upon comparison between the inpatient and health-check groups, a significantly lower SMI_h and significantly higher eGFR %difference were detected in the inpatient group (Figure 5).

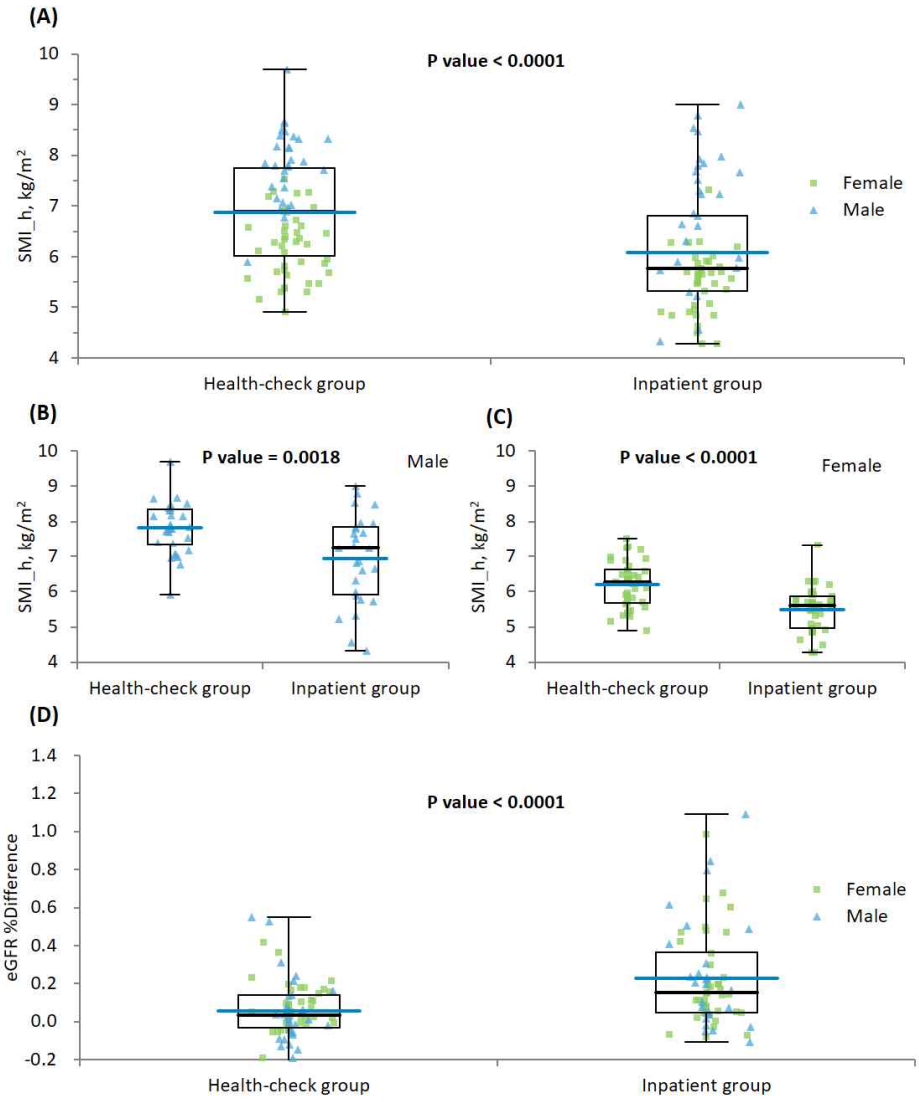
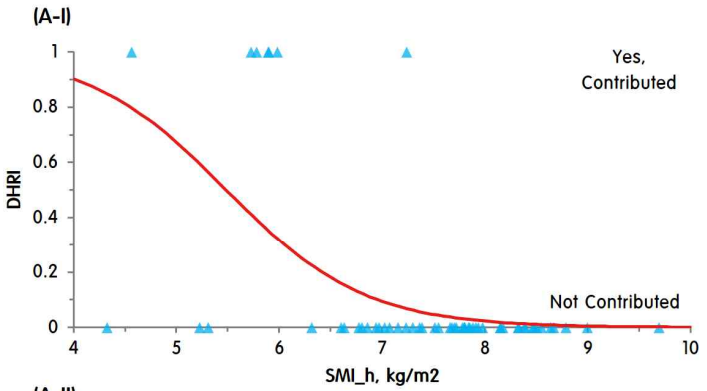
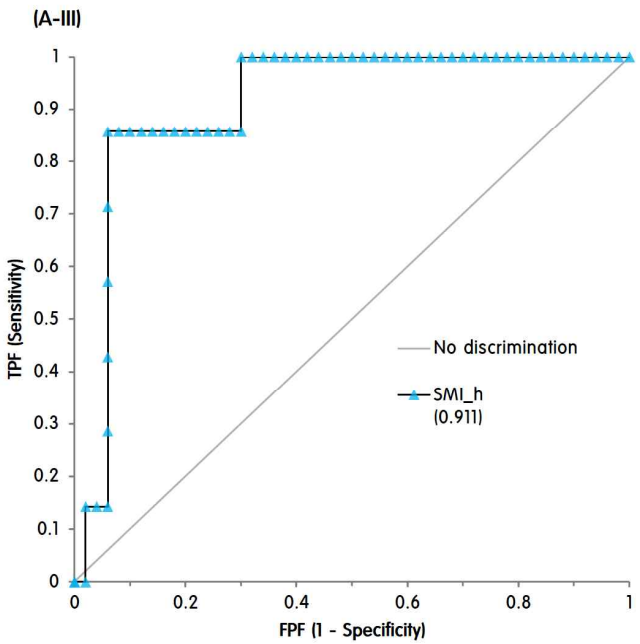


Figure 5. Comparison of SMI_h and eGFR %differences in the inpatient and health-check groups. A significant decrease in SMI_h in both sexes (A), in males (B), and in females (C) was confirmed in the inpatient group compared to that in the health-check group by Student's t test. A significant increase for eGFR % difference was confirmed in the inpatient group compared to that in the health-check group by Student's t-test (D).
¶Abbreviations: eGFR, estimated glomerular filtration rate; SMI_h, skeletal muscle mass index adjusted by height squared

6. Establishment of cut-off values to guide for the cystatin C test

We performed logistic regression analysis accounting for SMI_h and DHRI to determine cut-off values that would indicate a recommendation for cystatin C rather than creatinine testing for renal function evaluation (Figure 6 (A) for males and (B) for females; (I) logistic regression, (II) decision threshold with 100% fixed sensitivity, and (III) ROC). We determined the cut-off values for having a cystatin C test rather than a creatinine test for renal function evaluation to be an SMI_h value of 7.3 kg/m^2 for males (P value <0.0001) and 5.7 kg/m^2 for females (P value <0.0001). We also performed logistic regression analysis between SMI_h and other anthropometric parameters, but the results were not significant except for those of CC. Thus, we determined a CC value of 31.5 cm for males (P value = 0.0081) and 29.6 cm for females (P value = 0.0111) as cutoff values indicating a preferential cystatin C test (Figure 7 (A) for males and (B) for females; (I) logistic regression, (II) decision threshold, and (III) ROC).





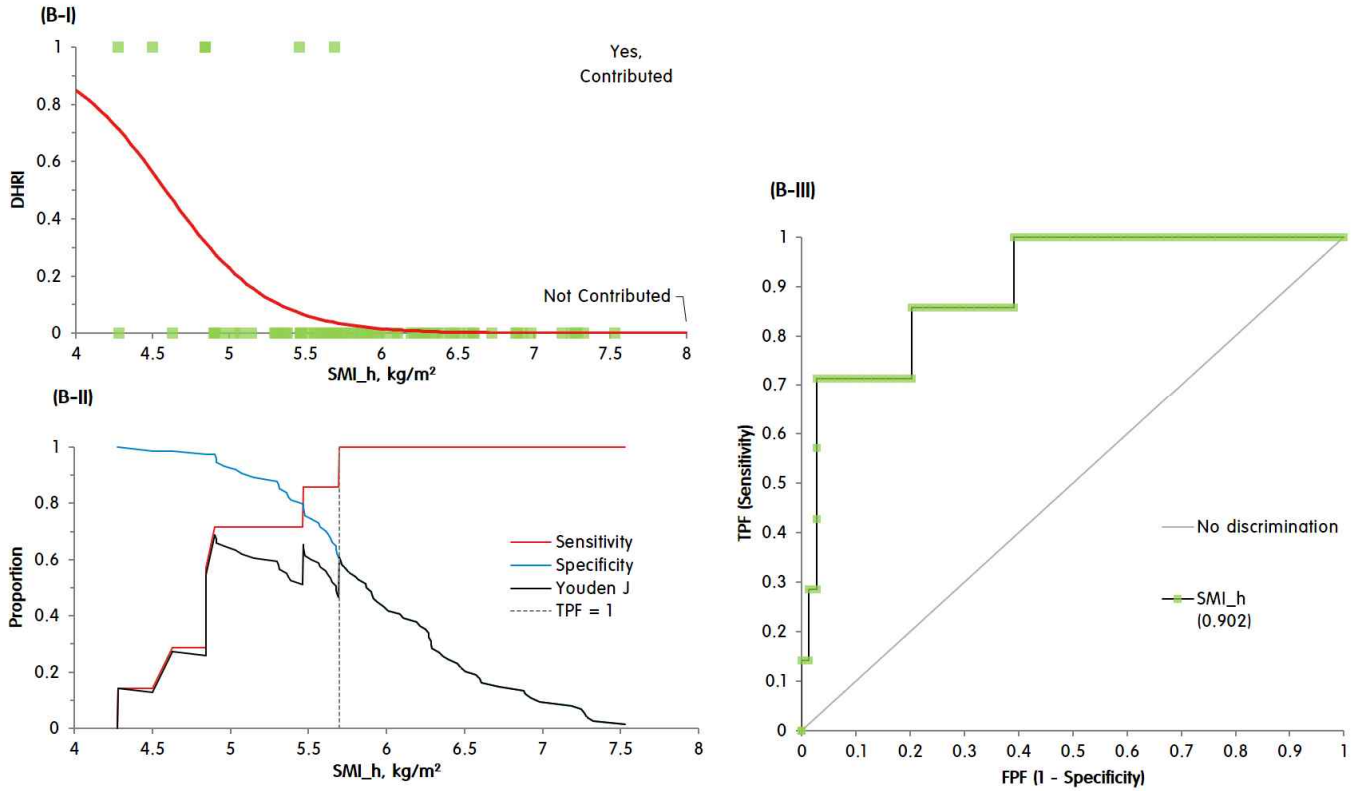
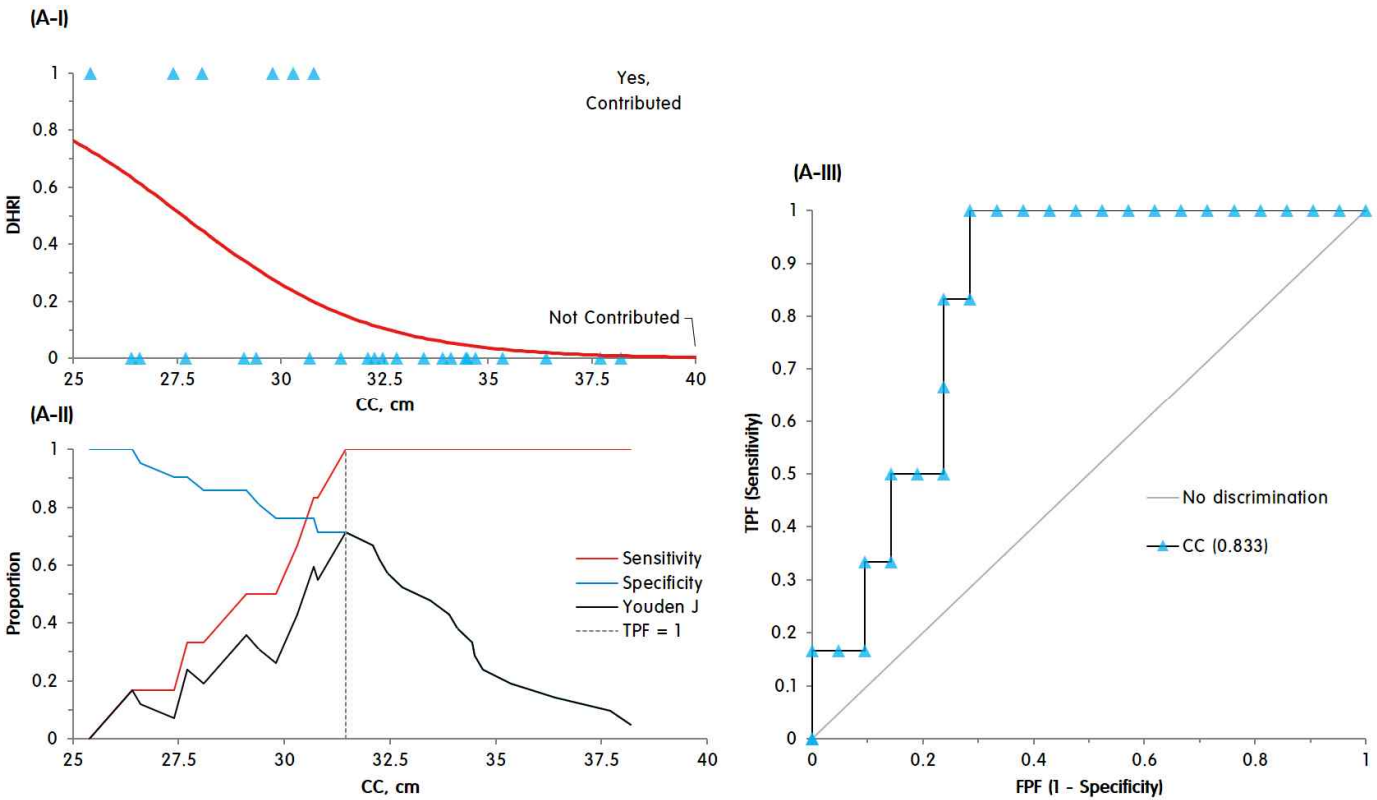


Figure 6. Cut-off value determination by SMI_h for the cystatin C test vs creatinine test for renal function evaluation. Cut-off values were 7.3 kg/m^2 for males (P value <0.0001) (A) and 5.7 kg/m^2 for females (P value <0.0001) (B). (I) Logistic regression, (II) Decision threshold, (III) Receiver operating characteristic (ROC). ROC curves showed fixed 100% sensitivity and best specificity (70% for males and 61% for females). DHRI: hidden renal impairment case defined as eGFRcr ≥ 60

mL/min/1.73 m^2 and eGFRcys < 60 mL/min/1.73 m^2. In the graphs above, DHRI is indicated as 1 and non-DHRI is indicated as 0.

¶Abbreviations: eGFR, estimated glomerular filtration rate; SMI_h, skeletal muscle mass index adjusted by height squared; DHRI, detection of hidden renal impairment; TPF, true positive fraction; FPF, False positive fraction



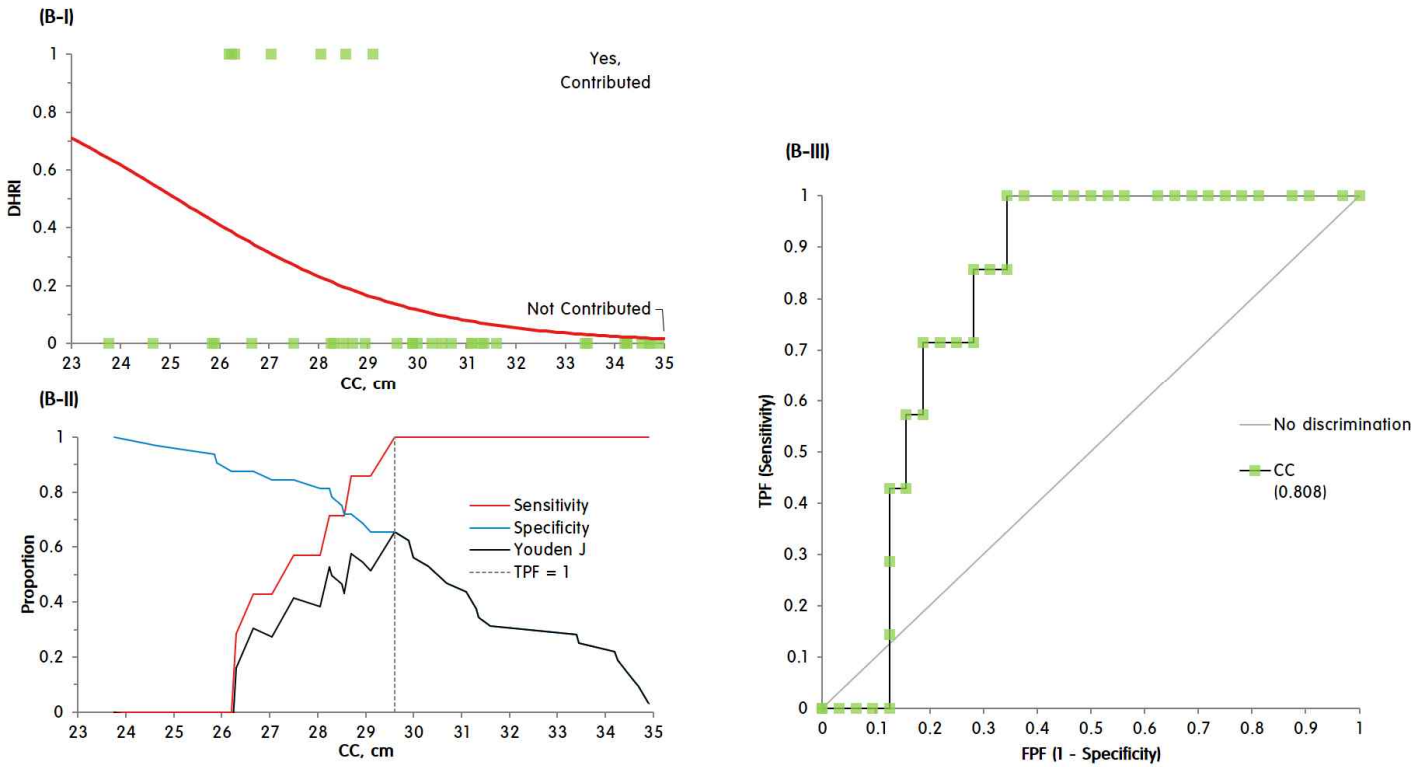


Figure 7. Cut-off value determination by calf circumference for the cystatin C test vs creatinine test for renal function evaluation. The cut-off values were 31.5 cm for males (P value = 0.0081) (A) and 29.6 cm for females (P value = 0.0111) (B). (I) Logistic regression, (II) Decision threshold, (III Receiver operating characteristic (ROC). ROC curves showed fixed 100% sensitivity and best specificity (71% for males and 66% for females). DHRI: hidden renal impairment case defined as

eGFRcr ≥ 60 mL/min/1.73 m^2 and eGFRcys < 60 mL/min/1.73 m^2. In the graph above, DHRI is indicated as 1 and non-DHRI is indicated as 0.

¶Abbreviations: eGFR, estimated glomerular filtration rate; DHRI, detection of hidden renal impairment; CC, calf circumference; TPF, true positive fraction; FPF, False positive fraction

Correlation analysis was performed between the estimated LBM formulas, which were not directly measured values in this study, and various SMIs. All LBM equations showed significant positive correlations with SMI_h and significant negative correlations with eGFR %difference (Table 3).

We plotted a decision threshold for the estimated LBM formulas to determine the appropriate cut-off values for choosing the cystatin C test (Figure 8 for males and Figure 9 for females, (A) for the James formula, (B) for the Boer formula, and (C) for the Yu formula). The cut-off values for males were 49.4 kg in the James formula (A), 50.5 kg in the Boer formula (B), and 49.2 kg in the Yu formula (C). The cut-off values for females were 37.2 kg for the James formula (A), 38.5 kg for the Boer formula (B), and 32.7 kg for the Yu formula (C). The cut-off values were constructed from DHRI and parameters for muscle mass with fixed 85% sensitivity and best specificity (80% for the James formula (A), 76% for the Boer formula (B), and 72% for the Yu formula (C) in male, and 72% for the James formula (A), 58% for the Boer formula (B), 59% for the Yu formula (C) in female). If 100% fixed sensitivity was applied, the specificity is markedly reduced (32% for James formula (D), 34% for Boer formula (E), and 34% for Yu formula (F) in male, and 23% for James formula (D), 23% for Boer formula (E), and 26% for Yu formula (F) in female).

Table 3. Correlation matrix† of eGFR% difference with various skeletal muscle mass index parameters and estimated lean body mass formulas

	eGFR %Difference	SMI_h	SMI_BMI	SMI_w	LBM James formula	LBM Boer formula	LBM Yu formula	
eGFR %Difference	-	-0.592	-0.423	-0.466	-0.390	-0.390	-0.387	Pearson's r
	-	-0.447	-0.283	-0.296	-0.332	-0.327	-0.301	Spearman's rs
SMI_h	-0.484	-	0.631	0.553	0.841	0.832	0.812	
	-0.431	-	0.464	0.362	0.855	0.837	0.807	
SMI_BMI	-0.268	0.520	-	0.908	0.553	0.607	0.679	
	-0.332	0.467	-	0.890	0.452	0.488	0.559	
SMI_w	-0.305	0.462	0.895	-	0.264	0.314	0.386	
	-0.357	0.405	0.884	-	0.162	0.187	0.247	
LBM James formula	-0.275	0.727	0.581	0.238	-	0.995	0.978	
	-0.231	0.709	0.491	0.155	-	0.996	0.979	
LBM Boer formula	-0.228	0.634	0.735	0.394	0.963	-	0.992	
	-0.245	0.612	0.686	0.338	0.946	-	0.988	
LBM Yu formula	-0.239	0.654	0.726	0.388	0.969	0.997	-	
	-0.246	0.628	0.678	0.336	0.953	0.998	-	

†Matrix consist of upper triangle for males (n = 57) and lower triangle for females (n=81)
¶Abbreviations: SMI_h, Skeletal muscle mass index adjusted by height square; SMI_w, Skeletal muscle mass index adjusted by body weight; SMI_BMI, Skeletal muscle mass index adjusted by body mass index; LBM, lean body mass; eGFR, estimated glomerular filtration rate; eGFR %Difference was defined as (eGFRcr / eGFRcys – 1) × 100 (%); LBM James formula (Reference 15), LBM Boer formula (Reference 17), and LBM Yu formula (Reference 18)

Table 4. Correlation results of between estimated lean body mass formulas and eGFR %difference or skeletal muscle mass index adjusted by height squared for females.

Pair	Pearson's r	95% CI	P value
eGFR %Difference, LBM James formula	-0.275	-0.465 to -0.060	0.0130
eGFR %Difference, LBM Boer formula	-0.228	-0.425 to -0.010	0.0410
eGFR %Difference, LBM Yu formula	-0.239	-0.435 to -0.022	0.0310
SMI_h, LBM James formula	0.727	0.605 to 0.816	<0.0001
SMI_h, LBM Boer formula	0.634	0.482 to 0.749	<0.0001
SMI_h, LBM Yu formula	0.654	0.508 to 0.763	<0.0001

¶Abbreviations: SMI_h, Skeletal muscle mass index adjusted by height squared; SMI_w, Skeletal muscle mass index adjusted by body weight; SMI_BMI, Skeletal muscle mass index adjusted by body mass index; LBM, lean body mass; eGFR, estimated glomerular filtration rate; eGFR %Difference was defined as (eGFRcr / eGFRcys – 1) × 100 (%); LBM James formula (Reference 17,18), LBM Boer formula (Reference 19), LBM Yu formula (Reference 20)

Table 5. Correlation results of between estimated lean body mass formulas and eGFR %difference or skeletal muscle mass index adjusted by height squared for males.

Pair	Pearson's r	95% CI	P value
eGFR %Difference, LBM James formula	-0.390	-0.591 to -0.144	0.0027
eGFR %Difference, LBM Boer formula	-0.390	-0.591 to -0.144	0.0027
eGFR %Difference, LBM Yu formula	-0.397	-0.588 to -0.141	0.0029
SMI_h, LBM James formula	0.841	0.743 to 0.904	<0.0001
SMI_h, LBM Boer formula	0.832	0.730 to 0.898	<0.0001
SMI_h, LBM Yu formula	0.812	0.699 to 0.885	<0.0001

¶Abbreviations: SMI_h, Skeletal muscle mass index adjusted by height squared; SMI_w, Skeletal muscle mass index adjusted by body weight; SMI_BMI, Skeletal muscle mass index adjusted by body mass index; LBM, lean body mass; eGFR, estimated glomerular filtration rate; eGFR %Difference was defined as (eGFRcr / eGFRcys – 1) × 100 (%); LBM James formula (Reference 17,18), LBM Boer formula (Reference 19), LBM Yu formula (Reference 20)

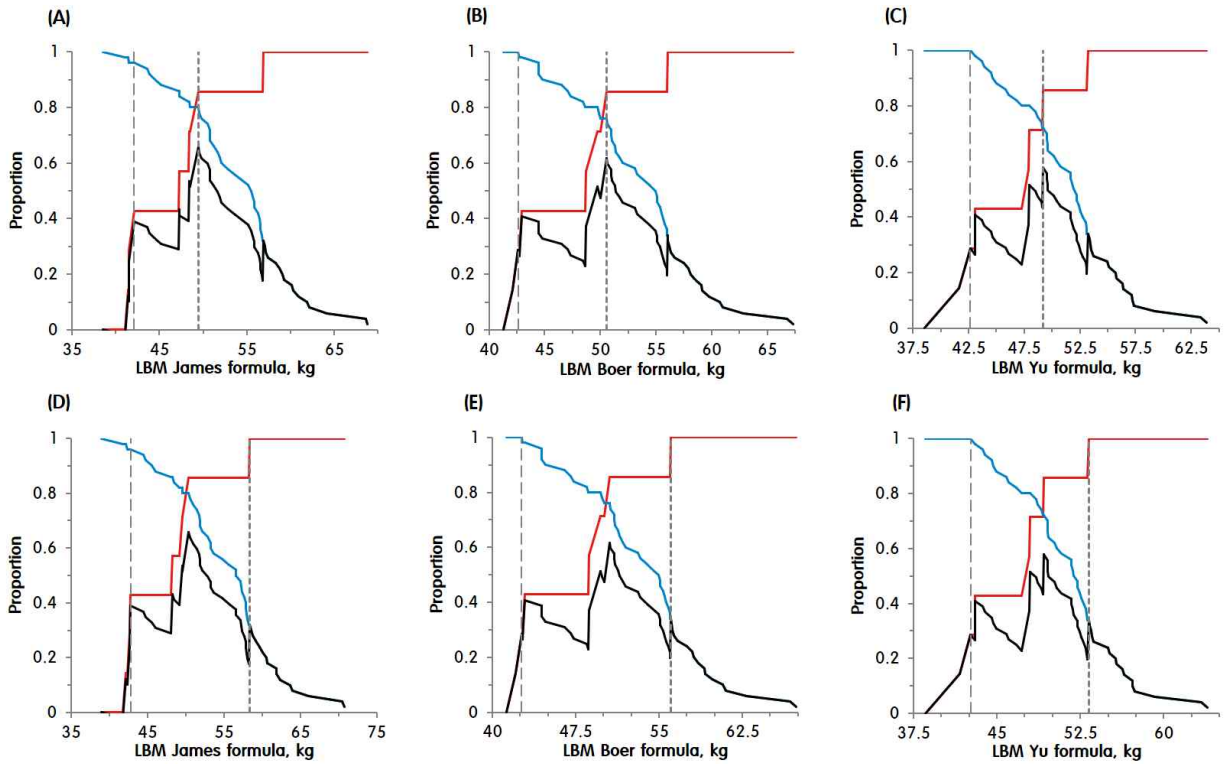


Figure 8. Decision threshold curves for the estimated lean body mass (LBM) formulas to determine cut-off values for choosing a cystatin C test rather than a creatinine test as a renal function test in males (n = 57).
The cut-off values were 49.4 kg for the James formula (A), 50.5 kg for the Boer formula (B), and 49.2 kg for the Yu formula (C). The cut-off values were constructed with fixed 85% sensitivity and best specificity (80% for the James formula (A), 76% for the Boer formula (B), and 72% for the Yu formula (C)). If 100% fixed sensitivity is applied, the specificity is markedly reduced (32% for the James formula (D), 34% for the Boer formula (E), and 34% for the Yu formula (F)).

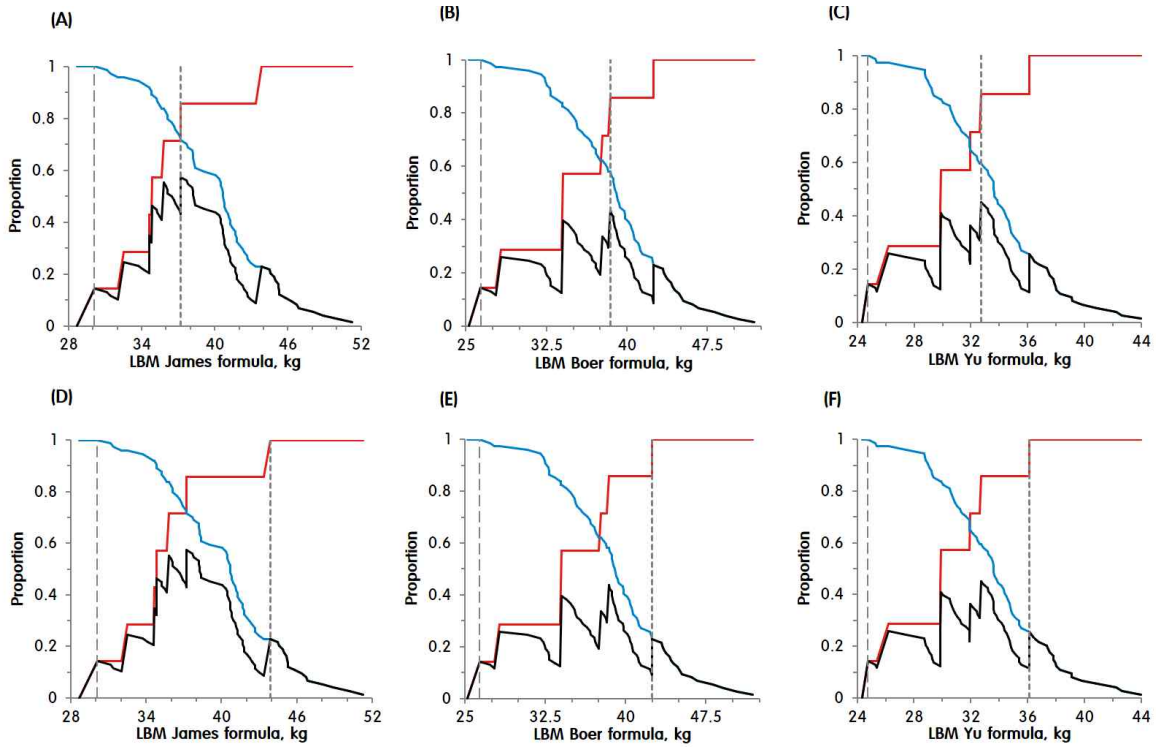
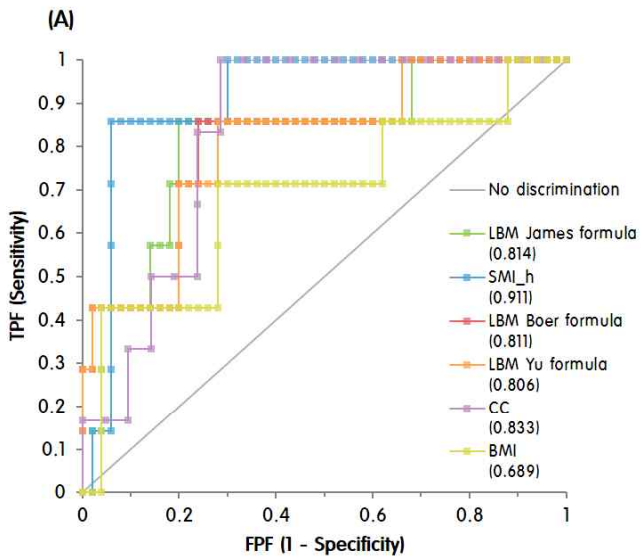
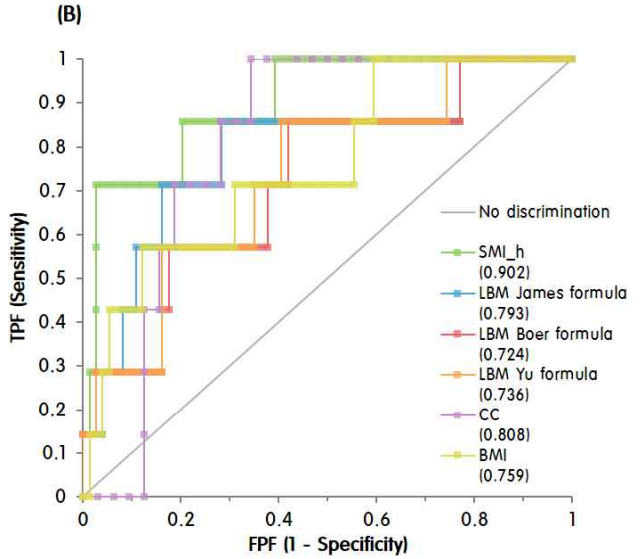


Figure 9. Decision threshold curves for the estimated lean body mass (LBM) formulas to determine cut-off values for choosing a cystatin C test rather than a creatinine test as a renal function test in females (n = 81).
The cut-off values were 37.2 kg for the James formula (A), 38.5 kg for the Boer formula (B), and 32.7 kg for the Yu formula (C). The cut-off values were constructed with fixed 85% sensitivity and best specificity (72% for the James formula (A), 58% for the Boer formula (B), and 59% for the Yu formula (C)). If 100% fixed sensitivity is applied, the specificity is markedly reduced (23% for the James formula (D), 23% for the Boer formula (E), and 26% for the Yu formula (F)).

Figure 10 shows the ROC curves and P values of AUCs of SMI_h, CC, and three kinds of LBM formulas all at once, showing that the AUC of CC was 0.833 for males and 0.808 for females, that of James formula was 0.814 for males and 0.793 for females, that of Boer formula was 0.811 for males and 0.724 for females, and that of Yu formula was 0.806 for males and 0.736 for females. AUC of SMI_h was 0.911 (95% CI, 0.819 to 1.004; P value <0.0001) for males and 0.902 (95% CI, 0.787 to 1.016; P value <0.0001) for females, showing that SMI_h has the largest AUC among those of CC, or LBM James formula, Boer formula, or Yu formula in both sexes.



	AUC	95% CI		P value
SMI_h	0.911	0.819	to 1.004	<0.0001
LBM James formula	0.814	0.633	to 0.996	0.0007
LBM Boer formula	0.811	0.629	to 0.994	0.0008
LBM Yu formula	0.806	0.622	to 0.989	0.0011
CC	0.833	0.680	to 0.987	<0.0001
BMI	0.689	0.438	to 0.939	0.1407



	AUC	95% CI		P value
SMI_h	0.902	0.787	to 1.016	<0.0001
LBM James formula	0.793	0.591	to 0.996	0.0045
LBM Boer formula	0.724	0.516	to 0.932	0.0350
LBM Yu formula	0.736	0.535	to 0.936	0.0216
CC	0.808	0.673	to 0.943	<0.0001
BMI	0.759	0.567	to 0.951	0.0083

Figure 10. ROC curves of SMI_h, CC, and three kinds of estimated LBM formula in males (A) and females (B).
¶Abbreviations: ROC, receiver operating characteristic curve; AUC, area under the curve; SMI_h, skeletal muscle mass index adjusted by height squared; CC, calf circumference; LBM, lean body mass; BMI, body mass index; CI, confidence interval

Table 6 shows analysis results for the statistical difference between the AUC of SMI_h and those of other method representing muscle mass. There was no significant difference between the AUCs of SMI_h and other parameters in males. The AUCs of SMI_h and those of Boer and Yu formula were shown as significantly different in females.

Table 6. Comparison results between AUCs for SMI_h, CC, and three kinds of estimated LBM formulas (A) for males and (B) for females.

(A)

Contrast	Difference	95% CI		P value
SMI_h - LBM Yu formula	0.106	-0.021	to 0.232	0.1010
SMI_h - LBM Boer formula	0.100	-0.023	to 0.223	0.1106
SMI_h - LBM James formula	0.097	-0.016	to 0.210	0.0920
SMI_h - CC	0.078	-0.030	to 0.186	0.1563

(B)

Contrast	Difference	95% CI		P value
SMI_h - LBM Boer formula	0.178	0.009	to 0.346	0.0391
SMI_h - LBM Yu formula	0.166	0.004	to 0.328	0.0447
SMI_h - LBM James formula	0.108	-0.028	to 0.245	0.1204
SMI_h - CC	0.094	-0.063	to 0.250	0.2424

Comparison analysis was performed by Z statistics, Rejection criteria of the null hypothesis (inequality) was use at the 5% significance level.
¶Abbreviations: CI, confidence interval; SMI_h, skeletal muscle mass index adjusted by height squared; CC, calf circumference; LBM, lean body mass

We suggested each cutoff of various parameters, such as SMI_h by BIA, CC at the fixed sensitivity of 100%, and estimated LBM James, Boer, and Yu formulas at the fixed sensitivity of 85%, as shown in Table 7.

Table 7. Cut-off values for testing cystatin C in renal function evaluation.

Parameter	Threshold* for males	Threshold* for females	References
SMI_h by BIA†	7.3 kg/m^2	5.7 kg/m^2	
CC†	31.5 cm	29.6 cm	
Estimated LBM James formula‡	49.4 kg	37.2 kg	(17,18)
Estimated LBM Boer formula‡	50.5 kg	38.5 kg	(19)
Estimated LBM Yu formula‡	49.2 kg	32.7 kg	(20)

*Cystatin C test should be added for all subjects below this threshold.
†At the fixed sensitivity of 100%
‡At the fixed sensitivity of 85%
¶Abbreviations: SMI_h, Skeletal muscle mass index adjusted by height squared; BIA, bioelectric impedance analysis; CC, calf circumference; LBM, lean body mass

As shown in Table 8, we hypothesize that cystatin C, in addition to creatinine, is required to detect hidden renal impairment in 31% to 45% of the hospitalized patient population due to low muscle mass based on SMI_h or various estimated LBM formulas.

Table 8. Proportion of the patients with cystatin C or creatinine test requirement among the study subjects according to the various parameters.

Parameter	Proportion of patients requiring cystatin C tests	Proportion of patients in whom creatinine tests are sufficient	References
SMI_h by BIA*	43%	57%	
CC*	45%	55%	
Estimated LBM James formula†	31%	69%	(17,18)
Estimated LBM Boer formula†	41%	59%	(19)
Estimated LBM Yu formula†	41%	59%	(20)

*At the fixed sensitivity of 100%
†At the fixed sensitivity of 85%
¶Abbreviations: SMI_h, Skeletal muscle mass index adjusted by height squared; CC, calf circumference; BIA, bioelectric impedance analysis; LBM, lean body mass

7. Supplementary issues

A. Correlation analysis between cystatin C and SMI_h

In the correlation analysis between SMI_h and cystatin C, there was no significant correlation when both sexes were analyzed together (Figure 11 (A)). When both sexes were analyzed separately, a significant negative correlation was found in both males and females (Figure 11 (B) and (C)). However, when only subjects with normal renal function (eGFRcys >60 ml/min/1.73 m^2) were evaluated, no significant correlations between SMI_h and cystatin C were obtained (D-F).

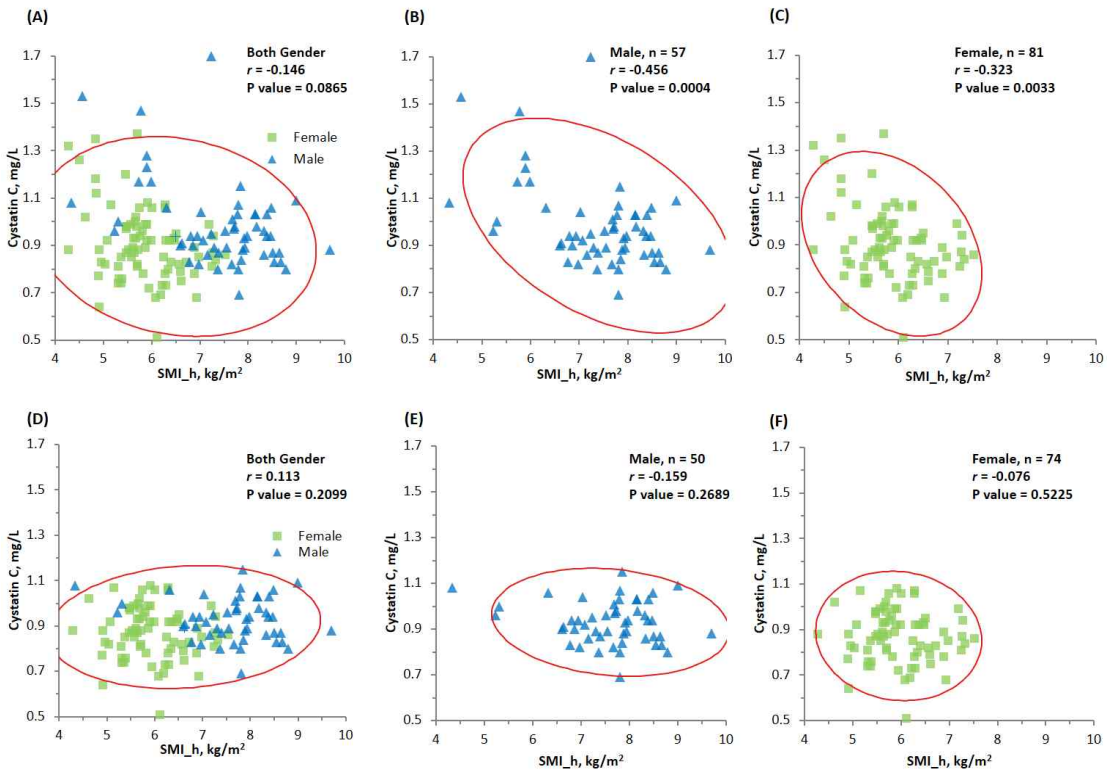


Figure 11. Scatter plot for correlation between SMI_h and cystatin C. Correlation analysis for both sexes (A), for males (B), and for females (C) regardless of the eGFRcys value. Correlation analysis for both sexes (D), for males (E), and for females (F) between SMI_h and cystatin C only in subjects with normal renal function (eGFRcys > 60 ml/min/1.73 m^2).
¶Abbreviations: SMI_h, skeletal muscle mass index adjusted by height squared; *r*, coefficient of correlation; eGFR, estimated glomerular filtration rate

B. Three kinds of adjusted indices for muscle mass

We compared three kinds of adjustment indices for muscle mass in 138 cross-sectional study subjects, summarized in Table 2. Each muscle mass index was calculated using ALM per height squared (SMI_h), body mass index (SMI_BMI), or body weight (SMI_w). Based on SMI_h, the coefficients of correlation with SMI_BMI were 0.631 (95% CI, 0.443-0.765; P value <0.0001) for males and 0.520 (95% CI, 0.341-0.663; P value <0.0001) for females. The coefficients of correlation between SMI_h and SMI_w were 0.553 (95% CI, 0.341-0.711; P value <0.0001) for males and 0.462 (95% CI, 0.271-0.618; P value <0.0001) for females. The correlation coefficients between SMI_BMI and SMI_w were 0.908 (95% CI, 0.848-0.945; P value <0.0001) for males and 0.895 (95% CI, 0.842-0.932; P value <0.0001) for females.

The correlation coefficients between each index and eGFR %difference all displayed significant negative correlations. The coefficients of correlation between eGFR %difference and SMI_h were -0.592 (95% CI, -0.739 to -0.392; P value <0.0001) for males and -0.484 (95% CI, -0.635 to -0.297; P value <0.0001) for females. The coefficients of correlation between eGFR %difference and SMI_BMI were -0.423 (95% CI, -0.616 to -0.183; P value = 0.0010) for males and -0.268 (95% CI, -0.459 to -0.052; P value = 0.0157) for females. The correlation coefficients between eGFR %difference and SMI_w were -0.466 (95% CI, -0.648 to -0.234; P value = 0.0003) for males and -0.305 (95% CI, -0.491 to -0.093; P value = 0.0056) for females.

Correlation analysis between serum creatinine level and various SMI indices that only showed significant positive correlation in SMI_h in both sexes. The coefficients of correlation between serum creatinine and SMI_h were 0.344 (95% CI, 0.091 to 0.555;

P value = 0.0089) for males and 0.348 (95% CI, 0.141 to 0.527; P value = 0.0014) for females. The coefficients of correlation between creatinine and SMI_BMI were 0.161 (95% CI, -0.104 to 0.405; P value = 0.2317) for males and 0.171 (95% CI, -0.049 to 0.375; P value = 0.1275) for females. The correlation coefficients between creatinine and SMI_w were 0.077 (95% CI, -0.187 to 0.331; P value = 0.5676) for males and 0.182 (95% CI, -0.038 to 0.385; P value = 0.1038) for females.

C. Comparison of SMI results of two BIA instruments

The correlation between the two models of BIA for the SMI_h results was analyzed in 86 health-check subjects who had undergone evaluation with both BIA models, InBody BWA2.0 and Accuniq BC720. The coefficient of correlation between the results obtained by the two models was 0.940 (95% CI, 0.910 to 0.961, P value <0.0001, Figure S11). Regression analysis shows an equation as follows, and coefficient of determination (r^2) was 0.884. The threshold in question might require separate evaluation, as some bias may be present.

[SMI_h by Accuniq BC720] = 0.4419 + 0.9093 x [SMI_h by InBody BWA2.0]

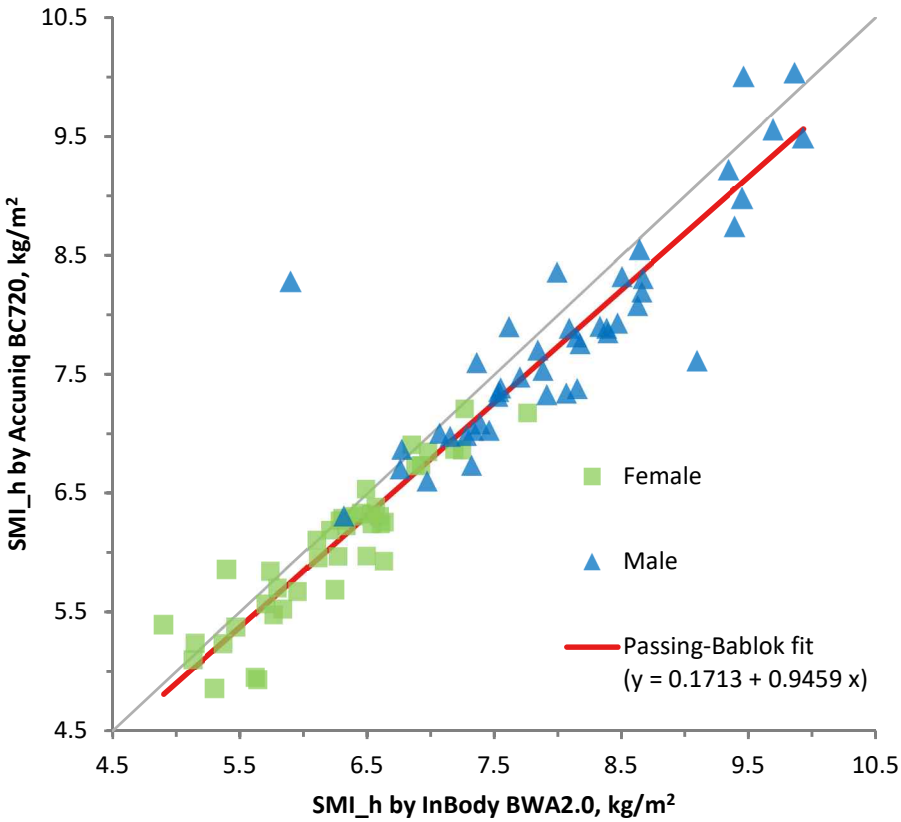


Figure S11. Linear regression analysis between SMI_h by BWA2.0 and SMI_h by Accuniq BC720. The null hypothesis was rejected with a P value <0.0001 by the F-test.
¶Abbreviations: SMI_h, skeletal muscle mass index adjusted by height squared; *r*, coefficient of correlation

D. Optimal eGFR equations according to muscle mass

We compared the results calculated with the eGFRcr formula and those of the formula based on both creatinine and cystatin C CKD-EPI eGFR (eGFRcr+cys), to those of the eGFRcys formula. Patients were categorized into the sarcopenia and non-sarcopenia groups based on the obtained cut-off values (7.3 kg/m^2 for males and 5.7 kg/m^2 for females) for SMI_h in the present study. The percentages falling within ±30%, ±20%, and ±10% of the eGFRcys results were defined as P30, P20, and P10, respectively (Table S2).

Table S2. Proportion of P30, P20, and P10 of eGFRcr or eGFRcr+cys based on eGFRcys according to the presence of sarcopenia by SMI_h measured by BIA.

	eGFRcr			eGFRcr+cys		
	P30	P20	P10	P30	P20	P10
Non-sarcopenia	93.60%	85.90%	59.00%	100.00%	97.40%	82.10%
Sarcopenia	70.00%	58.30%	36.70%	90.00%	73.30%	41.70%

¶Abbreviations: eGFRcr, creatinine-based CKD-EPI eGFR; eGFRcr+cys, creatinine and cystatin C-based CKD-EPI eGFR, SMI_h, skeletal muscle mass index adjusted by height squared; eGFR, estimated glomerular filtration rate
†Non-sarcopenia and sarcopenia group classification was based on the obtained cut-off values (7.3 kg/m^2 for male and 5.7 kg/m^2 for female) for SMI_h from present study.
‡The percentages falling within ±30%, ±20% and ±10% to the eGFRcys results were defined as P30, P20, and P10, respectively.

IV. DISCUSSION

GFR is a parameter necessary for the clinician's ability to detect and monitor impaired renal function, determine initiation of renal replacement therapy, decide optimum renal-clearance drug dosages, and implement nephrotoxic contrast agents[1]. Direct GFR measurement, however, is time-consuming and expensive, frequently requires urine and/or blood collection and isotope use, and is routinely available in only a few medical centers[9]. Therefore, a number of GFR prediction equations, using endogenous biomarkers such as creatinine and cystatin C, have been developed[27].

Although serum creatinine is widely used as an indicator of GFR, it is not a sensitive indicator, as the GFR may need to decrease by >50% before serum creatinine is outside the broad reference interval[28]. Creatinine is also affected by various interferences such as sex, age, muscle mass, and dietary protein intake, among other factors.[2,3,29] Among these interfering factors, muscle mass is known to affect creatinine level markedly[9]. Formulas for creatinine-based eGFR take sex, age, and weight into account as surrogates for muscle mass, because direct muscle mass measurement is clinically difficult[30,31]. Nevertheless, as these eGFR formulas still had unsolved fundamental problems relating to creatinine, such as having a wide reference interval for normal levels of creatinine, displaying results with reduced sensitivity, and not taking muscle mass into account, eGFRcr could be within the reference interval even with impaired renal function in individuals with low muscle mass.

Many studies that have examined the effect of creatinine according to muscle mass reported a clinically significant difference between inferred and actual renal function; they also suggested the use of cystatin C as appropriate[6,7,9,32]. However, information

about measuring muscle mass and assessing the degree of impact this factor has on eGFR is lacking. Based on these concerns, in our study, objective muscle mass measurements such as BIA, CT image analysis with deep learning algorithm, and anthropometric analysis were performed, and the effect of muscle mass on creatinine and creatinine-based eGFR was analyzed. In addition, based on the measured muscle mass, a criterion for performing the cystatin C test instead of the creatinine test was derived.

Since it is difficult to directly measure muscle mass, there have been attempts at analyzing the correlation using LBM as an index representing muscle mass. As Swaminathan et al. described, the proportion of contribution of lean body mass (LBM) by DXA for the serum creatinine is small and correction of serum creatinine according to LBM is unlikely to improve the utility of this measurement[28]. However, in our study, a significant correlation between SMI_h and serum creatinine was noted in both sexes (*r*, 0.344, P value = 0.0089 for male; *r*, 0.348, P value = 0.0014 for female), and a significant positive correlation was also observed between various LBM formulas and creatinine (Table 6). Additionally, the correlation between the eGFR %difference and SMI_h was confirmed to have a significant negative correlation (Figure 3).

Conversely, in the comparison between hospitalized patients and health-check subjects, there was no significant difference between eGFRcr values, while eGFRcys showed a significant difference, as shown in Table 1. Likewise, a significantly larger increase in eGFR %difference values in the inpatient group compared to that in the health-check group could be interpreted in a similar context; these results are probably because the former group includes elderly patients and patients with sarcopenia (Figure 6). These results imply that eGFRcr could miss impaired renal

function due to low muscle mass, as reported in previous studies[6,9], and would be an explanation for why the results of ours study are different from those of Swaminathan et al.'s study, which had been conducted on healthy subjects[28]. According to our study results, if renal function is evaluated in subjects whose eGFRcr is not impaired, especially in hospitalized patients, muscle mass evaluation would be necessary to determine the presence of sarcopenia. Furthermore, if there is sarcopenia, it would be preferable to perform a cystatin C test rather than a creatinine test to obtain an appropriate renal function result.

Skeletal muscle is receiving attention from the medical community, not only as the tissue related to mobility, but also as a secondary secretory organ, with endocrine functions influencing several systems and preserving health[33,34]. Popular muscle mass assessment tools include body imaging techniques (e.g., MRI, CT, and DXA, ultrasonography), BIA, anthropometric parameters (e.g., CC and MAMC), and biochemical markers (total or partial body potassium, serum and urinary creatinine, and deuterated creatine dilution method)[35]. However, despite the fact that other methods such as MRI, CT, and DXA, which have been previously introduced as methods to measure muscle mass, use precise imaging technology, these modalities are expensive, may entail radiation exposure, and require patient transport. These methods are limited in term of feasibility.

Practicality, accuracy, and cost are important factors for choosing any method in clinical practice. In this study, we tried to find a practical method that could be used easily by clinicians when they actually suspect kidney disease or test creatinine or cystatin C for kidney function evaluation. BIA is an appropriate method of measuring muscle mass for our purposes. MacDonald et al. mentioned that ALM by BIA provides a clinically obtainable and valid method to predict muscle mass in patients

with CKD; the improvement of GFR_{inulin} estimation upon using ALM by BIA has also been reported[36]. The correlation of BIA and other muscle mass measurement methods, such as DXA, has been studied extensively in measuring muscle mass[37-40]. BIA models that could be viable to patients in the supine position has been developed recently; it seems to be appropriate for critically ill patients or inpatients who have difficulty in standing or ambulation[39,41,42]. Additionally, our study showed that measuring CC would also be a good alternative for the assessment of sarcopenia. We could not find a significant threshold for MAMC or HGS for cystatin C test indication, probably because the number of subjects in which these parameters were analyzed was limited (MAMC [n = 66; male, 27; female, 39] or HGS [n = 102; male, 41; female, 61]). It is not always easy to measure MAMC or HGS accurately for inpatients, due to various reasons.

Abdominal CT muscle mass are expected to be another choice for sarcopenia evaluation to indicate cystatin C test requirement. Among inpatients, there would be patients who perform abdominal CT scans because of other medical needs. In this study, the correlation between the TAMA calculation results by recycling CT scan data and the SMI levels were analyzed, and a significant positive correlation between SMI and TAMA was found (Figure S2; Spearman's rank correlation coefficient, r_s = 0.859; P value <0.0001). Additionally, a significant negative correlation between eGFR %difference and TAMA (Figure S7; Spearman's rank correlation coefficient, r_s = -0.629; P value = 0.030) was noted. We suggested that TAMA could be used for sarcopenia evaluation and could indicate a need for cystatin C levels to detect possible hidden renal impairment, although we could not provide optimum cutoff values for TAMA due to the small numbers of study subjects. This method might be worth implementing because it utilizes existing data and is a simple method using image

analysis software, especially for patients in bed-ridden condition.

The %difference between eGFRcr and eGFRcys showed a significant negative correlation with SMI_h, as expected. Unlike other anthropometric parameters, CC showed a significant correlation with eGFR %difference. We used these two variables to determine the cut-off for DHRI. DHRI imply that subjects with normal eGFRcr due to low muscle mass. We suggest that, if individuals have a muscle mass lower than the suggested cut-off, the cystatin C test is recommended rather than, or in combination with, creatinine test.

We found that SMI_h or CC can be a significant parameter to indicate the need for testing for cystatin C levels. The sarcopenic cutoffs we obtained (SMI < 7.3 kg/m^2 for male, <5.7 kg/m^2 for female by BIA), were similar to those reported by the Asian Working Group for Sarcopenia 2019[34] and could be good indicators for the need for cystatin C instead of creatinine testing for renal function evaluation. Low CC (<31.5 cm for males, <29.6 cm for females) would be an alternative parameter to indicate cystatin C preference for possible sarcopenia. The CC cutoffs we obtained to indicate the requirement for cystatin C testing were much lower than those of the AWGS 2019 (<34 cm in males and <33 cm in females) [34] or another Korean study (<35 cm in males and <33 cm in females) [43]. Why our CC cutoff is much lower than the usual sarcopenia cutoff is unclear, especially in light of 100% sensitivity cutoff rather than Youden' J index; we hypothesize that creatinine values are probably more strongly affected by lower calf muscle mass decrease. A further study may be required to elucidate these differences. The appropriate use of cystatin C, based on actual usable cut-off for surrogates of muscle mass, may result in more adequate management through the accurate assessment of renal function for a wide range of patients. In our study, we found that a cystatin C test may be required in addition to creatinine levels to detect

hidden renal impairment in 31% to 45% of inpatients, due to low muscle mass detected by SMI_h or various other LBM formula estimations (Table 8).

If it is not feasible to measure muscle mass, estimated LBM formulas might be alternative parameters (Table 2), although accurate body weight and height measurement for each patient is absolutely required. Therefore, the disadvantage of LBM formulas would present itself in the case of critically ill patients, in whom healthcare workers would have difficulty accurately measuring weight and height[44], especially if the patients are bed-ridden or have difficulty in ambulation.

The various estimated LBM formulas evaluated in this study showed a significant positive correlation with the various SMI formulas (Table 2; P value <0.0001 for all), and showed a significant negative correlation with the eGFR %difference (Table 3; P value = 0.0129 for James formula, 0.0410 for Boer formula, and 0.0313 for Yu formula). We tried to discover the diagnostic utility through the ROC curve based on the good correlation between estimated LBM formulas and SMI_h. Each estimated LBM showed adequate AUCs in terms of SMI_h; the statistical difference between them was not significant in men (Figure 10 and Table 6). Although all three kinds of LBM formulas showed unexpected high correlation with skeletal muscle mass directly measured by BIA in this study, we could not easily extrapolate and corroborate these parameters for muscle mass evaluation. Muscle mass measurement would be more desirable, because estimated LBM shows severely low specificity (range, 34%–23%) at 100% fixed sensitivity, as shown in the threshold curves (Figure 8 and Figure 9). Therefore, the cut-off value of LBM was constructed with a sensitivity fixed at 85% to increase specificity. Conversely, specificities for SMI_h and CC were maintained at a range approximately 71%–60%. Similar to estimated LBM, the specificity of BMI was also low (range, 40%–24%), which might be

attributed to the exceptional cases such as relatively abundant fat, sparse muscle, or presence of edema, although we excluded obese patients whose BMI exceeded 30 kg/m^2.

Unlike serum creatinine, the serum cystatin C level remains almost constant. It is generally accepted that cystatin C is produced at a constant rate in almost all nucleated cells. The advantage of using cystatin C as a GFR marker is that it is less affected by age, sex, weight, and muscle mass than serum creatinine. The risk of using creatinine alone and the superiority of cystatin C in renal function evaluation for populations with relatively lower muscle masses, such as the elderly, children, or women, has been agreed upon in many previous studies[6,7,9]. In our supplementary analysis, we analyzed the correlation between cystatin C and SMI_h. Cystatin C was confirmed as having no correlation when both sexes were analyzed together (Figure 11 (A)). Interestingly, when each sex was analyzed separately, a significant negative correlation was found in males and females in our cross-sectional study group (Figure 11 (B-C)). However, the correlation between SMI_h and cystatin C were not significant if only subjects with eGFRcys > 60 ml/min/1.73 m^2 were analyzed in the male and female groups (Figure 11 (E-F)). There have been studies on the prevalence of sarcopenia in chronic kidney disease and its association with frailty and prognosis[45-47]. More detailed studies are required to determine whether the association between sarcopenia and chronic kidney disease is significant, even in the case of early renal impairment.

In our study, patients with overt chronic renal disease were not included, Moreover, correlation analysis between serum creatinine level and various SMI indices only showed significant positive correlation in SMI_h, in both sexes. Han et al. described that height-adjusted muscle mass is recommended for the detection of sarcopenia

because it has a closer correlation with grip strength and muscle function[48].

When we set eGFRcys as a reference, we found that P30 of eGFRcr was significantly decreased from 93.6% in the non-sarcopenic group to 70.0% in the sarcopenic group as in Table S2. If we use the eGFRcr+cys as recommended by Inker et al. [26], P30 showed values above 80% for both the non-sarcopenic and sarcopenic groups, 100% and 90%, respectively. Although it is not appropriate to obtain eGFR by a single marker, namely, creatinine, in the sarcopenic group, creatinine is still applicable as a good single marker in the non-sarcopenic group (Table S2).

Although Inker et al. recently suggested a new race-free equation[49], Korean populations showed positive bias when using this race-free equation (personal communication); we still use the older eGFRcr (CKD-EPI) equation, which showed valid and minimal bias for Korean populations based on the studies which use measured GFR by ^{51}Cr-EDTA[50,51]. When standardized creatinine and cystatin C determination were used, ethnicity coefficients were reported not to improve the accuracy of eGFR in a multi-ethnic Asian population[52,53]. Most Korean doctors do not use ethnicity coefficients for eGFRcr (CKD-EPI)due to the preceding reasons.

Our study has several strengths, as follows. Although creatinine and eGFRcr are not suitable for assessing kidney dysfunction in patients with low muscle mass, there have been no objective criteria for when creatinine levels are not valid or when cystatin C test is required. To the best of our knowledge, this is the first study to provide an objective muscle mass criterion for testing cystatin C. Considering the missed or delayed diagnosis of renal impairment in the population of patients with low muscle mass, our suggested criteria for obtaining cystatin C levels instead of creatinine levels might be helpful. In addition, unlike MRI, CT, and DXA, our suggested methods for muscle mass measurement are valuable in that they could be

applied to relevant clinical practice, as it could relieve the pressure of time and space. However, there are several limitations to this cross-sectional study, as follows. Firstly, we could not use exogenous markers that directly measured GFR (mGFR), such as, inulin, iothalamate, iohexol, chromium-51 labeled ethylenediamine tetraacetic acid (^{51}Cr-EDTA), or technetium-99m labeled diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) in plasma or urine[54]. Thus, we were unable to determine the actual true bias of the eGFRcr values in this study compared to that of the mGFR. However, we tried to detect differences in eGFRcr due to muscle mass, using eGFRcys as a reference among the subjects, excluding those with factors affecting the measurement of cystatin C. We calculated the accuracy, P30, P20, or P10 of $eGFR_{Cr}$ and $eGFR_{Cr\text{-}Cys}$, in relation to eGFRcys in Table S2. Because of the limitations of both creatinine and cystatin C, we agree that assessment of kidney function beyond creatinine and cystatin C using mGFR would reduce misclassification and would be an important milestone in the establishment of more accurate and expanding personalized medicine in nephrology practice[55]. However, using mGFR is not viable in actual clinical setting of most Korean hospitals. Secondly, we determined muscle mass with multi-frequency BIA rather than DXA, which is currently considered to be a reference method for the evaluation of muscle mass[56]. However, some prediction equations have been suggested to rectify the inaccuracy of multi-frequency BIA[37,39,40], which generally shows good agreement with DXA[38,57] and can be used for muscle mass evaluation. BIA also has its own limitations. Clinical uses of BIA in subjects at extremes of BMI ranges and in subjects with abnormal hydration is not recommended[58,59], and we cannot extrapolate our results to obese subjects[60]. BIA is also contraindicated, or should be performed with great caution, in patients with implanted pacemakers[13]. Thirdly, various models of multi-frequency BIA from

different manufacturers have not been standardized. The correlation coefficient of SMI_h between with both InBody BWA2.0 and Accuniq BC720, 0.940 (n = 86, P value <0.0001, Figure S11), was encouraging; however, there was some bias between two instruments (SMI_h by Accuniq BC720 = 0.4419 + 0.9093 x SMI_h by InBody BWA2.0). There have been some reports of slightly different prediction equations according to the type of multi-frequency BIA, but we hypothesize that the differences are small[41,42]. Fourthly, there might be deviations attributed to SMI was obtained using other methods or tools. Finally, we could not enroll a larger population, and could not obtain enough power to discern clear differences between various parameters.

In this study, the criteria for selecting the cystatin C test rather than the creatinine test were presented according to the objective muscle mass. We also introduced applicable methods of measuring muscle mass that could apply to the relevant clinical practice. Because renal function test results are widely used in clinical practice and are considered fundamental data that factors in critical clinical decisions, effort should be expended to optimize renal function tests for proper patient management. Further investigation may be necessary for validation of low muscle mass cutoffs and their clinical impact.

V. CONCLUSION

In this study, the criteria for using cystatin C levels in replacement of, or in combination with, creatinine levels were presented according to the objective muscle mass or estimated LBM. We also introduced applicable methods of measuring muscle mass that could be relevant and viable in clinical practice. Because renal function test results are widely used in clinical practice and result in data fundamental for critical clinical decisions, optimizing these tests and discerning their precise clinical utility is required for proper patient management. Further research may be necessary to validate our presented low muscle mass cutoffs and their clinical impact.

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ABSTRACT(IN KOREAN)

신기능 평가에서 시스타틴 C 에 대한 근육량 기반 적응증 확립

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임 지 숙

서론: 본 연구의 목적은 적절한 사구체여과율을 구하기 위하여 낮은 근육량 환자에서 추정 사구체여과율(estimated glomerular filtration rate, eGFR)이 과대평가 될 수 있는 크레아티닌 검사 대신, 시스타틴 C 검사를 수행할 근육량 기반 지표의 적응증을 제안하는 것이다.

방법: 본 연구는 입원환자(n = 66)와 건강검진 대상자(n = 72)를 포함하여 40~95세(평균 및 표준편차, 남성 66.4 ± 13.6, 여성 67.1 ± 12.1) 한국인 138명(남성 57명 및 여성 81명)을 대상으로 횡단면

연구를 하였다. 사구체여과율을 직접 측정하지는 않았지만 eGFRcys (2012년 버전의 cystatin C 기반 CKD-EPI 식을 사용)를 참고 값으로 정하고, eGFRcys와 eGFRcr (2009년 버전의 크레아티닌 기반 CKD-EPI 식을 사용)을 비교하였다. Cystatin C에 대한 간섭 요인을 배제하기 위하여 만성 염증(C- reactive protein, CRP > 8 mg/dL), 인슐린 저항성, 비만 (체질량지수, BMI ≥ 30 kg/m^2), 갑상선 기능 이상, 스테로이드 복용 중인 피험자를 제외하였다. 골격근 질량지수(skeletal muscle mass index, SMI)는 생체전기 임피던스 분석(bioelectrical impedance analysis, BIA)에 의해 사지 골격근 질량(appendicular skeletal muscle mass, ALM)으로부터 구하였고, 신장의 제곱, 체중, 또는 체질량지수로 보정하여 각각 SMI_h, SMI_w, 및 SMI_BMI를 산출하였다. 또한, 종아리 근육 둘레(calf circumference, CC)를 측정하였고, James, Boer, 또는 Yu의 공식에 의해 근육량 매개변수로 추정된 제지방량(eLBM)을 계산하였다. 추가적으로, 국민건강영양조사에 참가한 1,956명과 건강검진을 위해 용인세브란스병원 건강증진센터를 찾은 6,094명을 대상으로 SMI_h와 혈청 크레아티닌의 상관관계를 후향적으로 분석했다. 우리는 eGFRcys에 대한 eGFRcr의 eGFR %차이를 계산하였고, 숨겨진 신장 손상(detection of hidden renal impairment, DHRI)을 eGFRcr ≥ 60 mL/min/1.73 m^2 및 eGFRcys < 60 mL/min/1.73 m^{2}로 정의하였다.

시스타틴 C 검사를 할 대상을 결정하기 위해 임계점 결정 곡선을 통해 근육량을 기반으로 한 판정기준치 값을 도출하고, ROC 곡선을 사용하여 진단적 유용성을 평가하였다. 통계적 분석은 피어슨의 상관 계수(*r*)를 사용하였고, 로지스틱 회귀 분석을 통해 관련 추정사구체여과율의 범주와 연령, 성별 및 골격근 질량의 연관성을 분석하였다.

결과: 우리는 남녀 모두에서 SMI_h와 혈청 크레아티닌 값 사이의 유의한 양의 상관 관계를 확인하였다(*r*, 남성의 경우 0.344, 여성의 경우 0.348). 우리는 SMI_h와 CC 사이의 유의한 양의 상관성 (*r*, 남성 0.902, 여성 0.687)을 확인했으며, 반면 eGFR %차이와 SMI_h (*r*, 남성 -0.592, 여성 -0.484) 또는 CC (*r*, 남성 -0.646, 여성 -0.351)와 사이에서는 유의한 음의 상관관계를 확인하였다. 진단적 유용성은 크레아티닌과 SMI_h, CC 또는 다양한 LBM 공식 간의 우수한 상관성을 기반으로 하는 ROC 곡선을 통해 평가되었다. SMI_h의 판정기준치로 로지스틱 회귀 분석에 의해 남성의 경우 7.3 kg/m^2 (P 값 <0.0001), 여성의 경우 5.7 kg/m^2 (P 값 <0.0001)으로 결정하였고, 이는 신기능 평가 시 크레아티닌 검사보다는 시스타틴 C 검사를 받아야 하는 경우를 나타내는 유의한 매개변수임을 확인하였다. 추가적으로, 우리는 로지스틱 회귀 분석을 통해 남성의 경우 31.5

cm 이하(P 값 = 0.0081), 여성의 경우 29.6 cm 이하(P 값 <0.0111)를 시스타틴 C 검사를 권고하는 종아리근육둘레의 판정기준치로 제안하였다. 비록, SMI_h 및 CC에 비해 특이도의 감소를 보이긴 했지만, 다양한 LBM 식들의 판정기준치 값도 추가적으로 제시하였다(James 공식에서 남성 49.4 kg, 여성 37.2 kg; Boer 공식에서는 남성 50.5 kg, 여성 38.5 kg; Yu 공식에서는 남성 49.2 kg, 여성 32.7 kg).

결론: 우리는 본 연구에서 SMI_h, CC 또는 일부 LBM 공식을 통해 객관적 근육량의 측정을 기반으로, 크레아티닌 검사 보다는 시스타틴 C 검사를 시행할 필요가 있는 경우에 대한 기준을 제시하였다.

핵심되는 말: 추정사구체여과율, 크레아티닌, 시스타틴 C, 근육량, 생체전기 임피던스 분석, 종아리 근육 둘레, 신장 기능 검사