ORIGINAL

Novel formula using triceps skinfold thickness to revise the Cockcroft-Gault equation for estimating renal function in Japanese bedridden elderly patients

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Abstract : In recumbent elderly patients, creatinine clearance (eCCr) estimated by the Cockcroft-Gault (CG) equation may not necessarily reflect renal function. We aimed to develop a novel formula to revise the CG equation using anthropometric measurements in bedridden elderly patients and evaluate its clinical utility. The subjects included 77 bedridden Japanese patients aged $\geq$ 65, hospitalized at Naruto Yamakami Hospital. The actual CCr (mCCr) value was measured using the 24-hour urine collection method. Anthropometric data, such as skeletal muscle mass, body fat mass (BFM), and triceps skinfold thickness (TSF), were collected. We established a novel formula to estimate CCr(BFM) or CCr(TSF) by correcting the eCCr(Enz+0.2) value with BFM or TSF. The stage of classification of renal dysfunctions in patients with eGFR(BFM) or eGFR(TSF) was equivalent to the GFR(control) based on the mCCr. Notably, the novel equation for eCCr based on TSF (eCCr(TSF)), dubbed the "Naruto" formula, can be useful to evaluate renal function in bedridden elderly patients without expensive equipment or additional costs. In this study, mCCr was considered to be the true renal function of the patient, but whether and to what extent mCCr correlates with inulin clearance is unknown. J. Med. Invest. 65 : 195-202, August, 2018

Keywords : creatinine clearance, estimation of renal function, bedridden elderly patients, triceps skinfold thickness, "Naruto" formula

INTRODUCTION

When administering drug therapies to geriatric patients, it is important to design a treatment regimen that accounts for their decreased physical capacity and changes in physiological function that occur with age (1). As there is substantial individual variation with respect to age-related renal function deterioration, it is necessary to evaluate the renal function of each patient before issuing medication prescriptions.

Inulin clearance is considered to be the gold standard for measuring glomerular filtration rate (GFR), an index of renal function (2). However, measuring inulin clearance is labor-intensive and time-consuming, and, as such, this index is rarely used in routine clinical practice. In particular, it is difficult for certain patients, such as recumbent geriatric patients, to drink sufficient amounts of water and to produce frequent blood and urine samples after receiving inulin. Thus, the serum creatinine (SCr) value, an endogenous marker, often serves as a substitute indicator of renal function. One problem affecting the use of creatinine as an index is that SCr is influenced by factors other than renal function, such as sex, age, ethnicity, and nutritional status, since the quantity of creatinine produced by the body is proportional to muscle mass. Additionally, as creatinine is secreted in part by the renal tubules separately from glomerular filtration, the SCr value will not increase until renal function sufficiently decreases (3), and renal tubular

creatinine secretion is influenced by low albumin values (4, 5).

Meanwhile, serum cystatin C protein (CysC) concentration, which became a Japanese National Health Insurance adaptation in October 2005, is dependent on GFR (6), and is not readily influenced by factors, such as muscle mass, diet, or exercise habits. Additionally, endogenous production remains constant regardless of age or sex (7, 8). Therefore, CysC has been recognized as a marker of early-stage renal dysfunction that has high clinical utility (9, 10). SCr value measurements cannot accurately assess the extent of age-related decreases in renal function, but CysC levels increase with age (11) ; hence, this index can be used for such assessments (12, 13). However, there are several barriers to the use of this assay, including its higher cost compared with SCr measurement, the fact that only one CysC measurement per 3-month period is reimbursable under the Japanese National Health Insurance System, its ability to be influenced by medicines and thyroid dysfunction (14-16), and the observation that increases in CysC values peak in conjunction with end-stage renal failure due to its metabolism/excretion outside the kidney (17). For these reasons, CysC values have limited clinical application, and therefore adhering to the most suitable, situation-specific uses of either CysC or SCr values is essential when evaluating renal function.

Creatinine production is decreased in long-term recumbent patients and elderly people with poor nutritional status or low muscle mass. For this reason, diminished renal function is not necessarily reflected in SCr values. Creatinine clearance (CCr) calculated by renal function estimation formulas using the SCr value may result in overestimation. The SCr value is an excellent index of renal function that is simple, inexpensive, and reproducible, but is considered to be dependent on muscle mass. As the Cockcroft-Gault (CG) formula (18) and other such formulas (19-21) do not account

for muscle mass and degree of obesity, the use of estimated creatinine clearance (eCCr) values can be problematic with respect to geriatric patients since muscle mass decreases with age. As such, the purpose of this study was to collect data from bedridden elderly patients to investigate the relationship between eCCr values and various detailed body composition data, including muscle mass and body fat volume, and to establish a novel CCr estimation formula for use in recumbent geriatric patients. The performance of the new estimation formula was evaluated by comparing eCCr values calculated using the new formula to the measured CCr (mCCr) values based on a 24-hour urine collection method.

Next, the values of estimated glomerular filtration rates (eGFR) based on the CysC or various CCr values were compared in order to investigate which method is suitable to determine the renal function of bedridden patients. Horio *et al.* reported that the eGFR based on the CysC (eGFR$_{(CysC)}$) was compatible with the measured GFR using inulin renal clearance (22). Since the inulin clearance was not obtained in this study, we used eGFR$_{(CysC)}$ as an indicator of renal function and compared the GFR$_{(control)}$ value obtained from the mCCr value and other eGFR values, as calculated by CCr values based on the SCr.

Finally, we evaluated the patients' conditions based on the Japanese Society of Nephrology chronic kidney disease (CKD) severity classification using various GFR values, and evaluated our new estimation formula in Japanese bedridden elderly patients.

METHODS

Study population

We studied 77 recumbent patients aged 65 or older who were hospitalized at Naruto Yamakami Hospital between August 2014 and July 2016. Patients with missing limbs and those undergoing treatment for infection were excluded. Since elderly people often have multiple chronic diseases and take multiple drug combinations, no exclusion criteria related to current diseases or concomitant medications were established.

Assessment of renal function
1. Measurement of renal function

In this study, mCCr was based on the 24-hour urine collection method (2) to accurately evaluate the patients' renal functions. To ensure precise urine collection, an indwelling bladder catheter was inserted into all patients. To ensure the reliability of the urine collection, the excretion of urinary creatinine (UCr) in one day was checked (23). Urine collection was initiated at a designated time and then continued until the same time on the following day. Total urine volume (mL/day) was measured after mixing the samples thoroughly, and a portion of the urine collected was used to determine the UCr concentration (mg/dL). SCr (mg/dL) was measured in the morning before patients took meals, and mCCr (mL/min) was calculated based on the following formula :

mCCr = (UCr × total urine volume) / (SCr × 1440)

Where, total urine volume is in mL.

2. Estimation of renal function

The CG equation (18) was used to calculate eCCr. The SCr value used in the CG formula was determined colorimetrically using the Jaffé rate assay. Therefore, it was necessary to convert the enzymatic SCr value (SCr$_{(Enz)}$), which was measured using the creatinase-sarcosine oxidase-peroxidase method (24, 25), to a value approximating the SCr value determined using the colorimetric Jaffé assay, before applying the value to the CG formula. The eCCr$_{(Enz+0.2)}$ was calculated using the Jaffé assay-equivalent SCr value. SCr$_{(Enz+0.2)}$, obtained by adding 0.2 mg/dL to the SCr$_{(Enz)}$ value, according to the method proposed by Horio and Orita (26).

With the CG equation, eCCr$_{(Enz)}$ and eCCr$_{(Enz+0.2)}$ values were estimated using formulas (A) and (B) below, respectively.

eCCr$_{(Enz)}$ = ((140-Age) × Weight) / (72 × SCr$_{(Enz)}$) × 0.85 (in women)   ···(A)

eCCr$_{(Enz+0.2)}$ = ((140-Age) × Weight) / (72 × (SCr$_{(Enz)}$ + 0.2)) × 0.85 (in women)   ···(B)

Where, eCCr$_{(Enz)}$ and eCCr$_{(Enz+0.2)}$ are in mL/min, age is in years, and weight is in kg.

3. Development of a novel estimation formula

Multiple linear regression analysis was performed using mCCr values as dependent variables, and eCCr$_{(Enz+0.2)}$ values, serum albumin values, triceps skinfold thickness (TSF), arm muscle area (AMA), skeletal muscle mass (SMM), hemoglobin values, and body fat mass (BFM) as independent variables. Multicollinearity was confirmed not to occur between independent variables based on variance inflation factor (VIF) values. Parameters having substantial impact on the dependent variable (mCCr) based on the absolute value of the standard partial regression coefficient (β) were selected and new estimation formulas (C) and (D) were created in the results.

SCr and UCr values were determined using the enzymatic method with an Aqua Auto-Kainos CRE-II reagent (Kainos Co., Tokyo, Japan). CysC values were measured using the gold colloid colorimetric method with the Nescoat GC Cystatin C Kit (Alfresa Pharma, Osaka, Japan). Several types of automatic analyzers were used as measurement devices (AU5800 (Beckman Coulter, Tokyo, Japan) ; JCA-BM 9130, JCA-BM 8030 (JEOL Ltd., Tokyo, Japan)).

Physical measurement method

The bioelectrical impedance method is a technique for measuring body composition by determining a resistance value (impedance) that is created by the body from the application of a weak and harmless electrical current of approximately 1 mA. The In Body S20 (INBODY JAPAN CORPORATION, Tokyo, Japan) body composition analyzer was used to measure physical metrics, such as the SMM and BFM. A total of 8 touch type electrodes were measured : 1 electrode on each of the thumb and middle fingers on the left and right hands (4 points) and 1 electrode on the inner and outer temporal surfaces of the left and right heels (4 points). Electrode measurements were taken with patients lying supine on a bed.

TSF and arm circumference (AC) measurements were obtained at the level of the midpoint between the acromion and olecranon processes in the non-dominant and non-paralyzed arm. AC (cm) and TSF (mm) were measured using the insertape and adipometer (Abbott Japan Co., Ltd., Tokyo, Japan), and the average of three readings in a single place was used. AMA (cm²) was calculated based on the following formula (27) :

AMA = (AC - 3.14 × TSF)^2 / (4 × 3.14)

GFR (mL/min/1.73 m²) Estimation Formulas

CCr (mL/min) was converted to GFR (mL/min/1.73m²) using the following GFR estimation formula. A body surface area (BSA) correction was performed using the DuBois formula (28), as follows :

BSA = 0.007184 × Height$^{0.725}$ × Weight$^{0.425}$

Where, BSA is in m², height is in cm, and weight is in kg.

Japanese GFR estimation formula using serum CysC (2, 22) :

eGFR$_{(CysC)}$ = (104 × CysC$^{-1.019}$ × 0.996^{Age} × 0.929 (in women) -8   ···Equation 1

Where, CysC is in mg/L.

Formula to estimate GFR$_{(control)}$ from mCCr values (2, 19)

GFR$_{(control)}$ = 0.715 × mCCr × 1.73/BSA   ···Equation 2

Japanese GFR estimation formula using $SCr_{(Enz)}$ values (2, 19)

$$eGFR_{(creat)} = 194 \times Scr_{(Enz)}{}^{-1.094} \times Age^{-0.287} \times 0.739 \text{ (in women)}$$

$\cdots$ Equation 3

Estimation formula using $eCCr_{(Enz)}$ values (2, 19) calculated by the CG formula with $SCr_{(Enz)}$ values (18)

$$eGFR_{(CG)} = 0.789 \times eCCr_{(Enz)} \times 1.73/BSA \qquad \cdots \text{Equation 4}$$

Novel estimation formula using $eCCr_{(Enz+0.2)}$ values corrected using TSF $(eCCr_{(TSF)})$

$$eGFR_{(TSF)} = 0.789 \times eCCr_{(TSF)} \times 1.73/BSA \qquad \cdots \text{Equation 5}$$

Novel estimation formula using $eCCr_{(Enz+0.2)}$ values corrected using BFM $(eCCr_{(BFM)})$

$$eGFR_{(BFM)} = 0.789 \times eCCr_{(BFM)} \times 1.73/BSA \qquad \cdots \text{Equation 6}$$

Statistical analysis

The minimum required sample size was calculated a priori to be 31 patients, using A-priori Sample Size Calculator for Multiple Regression software version 4.0 (29), based on an $\alpha = 0.05$, power of 80%, and a large effect size (0.35) with 2 predictors.

The results are expressed as the mean $\pm$ standard deviation (mean $\pm$ SD). The intercept and slope of the regression equation of eCCr(y) and mCCr(x) and the coefficient of determination R^2 were used to evaluate the predicted performance.

A Bland-Altman analysis (30) was performed to assess the degree of agreement between the mCCr and eCCr values. The average of the differences between the eCCr and mCCr values was taken as bias or systemic error and the standard deviation (SD) of the differences was taken as an index of precision. The average value $\pm$ 2 SD was taken as the 95% limits of agreement (LOA). The proximity of the average of the differences between the eCCr and mCCr values from zero was considered to be highly consistent. The accuracy of the eCCr values obtained was defined as the percentage of patients for which errors between the mCCr and eCCr values were within $\pm$ 30%.

A one-way analysis of variance (ANOVA) was conducted using GFR (mL/min/1.73 m^2) values calculated by a different method as the dependent variable and the calculation method as the group variable, and multiple comparisons tests were conducted for all pairs. Patients' GFR (mL/min/1.73 m^2) values calculated by each

method were also classified by disease stage based on the Japanese Society of Nephrology CKD severity classification (2), as follows : G1 (GFR $\geq$90, normal), G2 (GFR 60-89, normal to mild deterioration), G3a (GFR 45-59, mild to moderate deterioration), G3b (GFR 30-44, moderate to pronounced deterioration), G4 (GFR 15-29, pronounced deterioration) and G5 (GFR $<$ 15, end-stage renal failure). The degree of agreement was compared using Pearson's x^2 test.

A p-value of $<$ 0.05 was considered to be statistically significant. Statistical analyses were performed using the JMP 11.0 software (SAS Institute, Cary, NC, USA).

RESULTS

The backgrounds of the 77 subjects (34 men, 43 women) targeted by this study are shown in Table 1. The measured mean SMM was 17.18 $\pm$ 2.98 kg in men and 12.14 $\pm$ 2.32 kg in women (p $<$ 0.0001), with a statistically significant difference between the male and female patients. The mean SCr value was 0.89 $\pm$ 0.44 mg/dL in men and 0.70 $\pm$ 0.45 mg/dL in women. Male patients tended to have slightly higher SCr values, although this difference was not significant (p = 0.06). No differences between the sexes were observed with respect to the other measurement items.

A simple linear regression analysis using mCCr values as the dependent variable and eCCr values as the independent variable resulted in (a) $eCCr_{(Enz)}$ values calculated using $SCr_{(Enz)}$ values (R^2 = 0.74), or (b) $eCCR_{(Enz+0.2)}$ values calculated using $SCr_{(Enz+0.2)}$ values (R^2 = 0.72). Significant positive correlations were observed between the mCCr and both $eCCr_{(Enz)}$ and $eCCr_{(Enz+0.2)}$ values (p $<$ 0.0001) (Figures 1 [a] and [b]). A favorable linear regression equation (y = 1.07x + 1.00, R^2 = 0.72, p $<$ 0.0001) was obtained in Figure 1 (b) when the $SCr_{(Enz+0.2)}$ values were used to estimate eCCr. Figures 2 (a) and (b) show the Bland-Altman plot in which the average of the mCCr and eCCr values are plotted on the x-axis and the difference between the mCCr and eCCr values are plotted on the y-axis. When the $SCr_{(Enz)}$ values were used in method (a), the average difference was 11.6 mL/min and the standard deviation was 15.3 mL/min (Table 2). In contrast, the average difference was smaller (- 3.57 $\pm$ 11.1 mL/min) in method (b) when the $SCr_{(Enz+0.2)}$ values were used (Table 2). Thus, the $eCCr_{(Enz+0.2)}$ values

Table 1.   Patient characteristics

	Men (Mean $\pm$ SD)	Women (Mean $\pm$ SD)	(Mean $\pm$ SD)	All (minimum - median - maximum)
Number	34	43	77	
Age (years)	82.9 $\pm$ 5.75	83.8 $\pm$ 9.47	83.4 $\pm$ 0.81	(65 - 85 - 98)
BMI (kg/m^2)	18.8 $\pm$ 2.99	19.9 $\pm$ 3.62	19.4 $\pm$ 3.38	(10.3 - 19.6 - 27.0)
Alb (g/dL)	2.85 $\pm$ 0.57	2.96 $\pm$ 0.47	2.91 $\pm$ 0.52	(1.9 - 2.9 - 4.4)
SCr (mg/dL)	0.89 $\pm$ 0.44[a]	0.70 $\pm$ 0.45[a]	0.78 $\pm$ 0.45	(0.17 - 0.65 - 2.26)
BUN (mg/dL)	22.4 $\pm$ 10.5	23.6 $\pm$ 15.3	23.0 $\pm$ 13.3	(4.3 - 20.9 - 74.1)
CysC (mg/L)	1.86 $\pm$ 0.67	1.80 $\pm$ 0.77	1.82 $\pm$ 0.72	(0.61 - 1.67 - 4.24)
mCCr (mL/min)	46.84 $\pm$ 21.87	39.77 $\pm$ 19.71	42.89 $\pm$ 20.86	(6.67 - 42.42 - 97.99)
eCCr$_{(Enz)}$ (mL/min)	55.10 $\pm$ 24.93	54.07 $\pm$ 32.13	54.52 $\pm$ 28.99	(10.45 - 50.64 - 169.58)
TSF (mm)	6.77 $\pm$ 4.44	7.86 $\pm$ 4.93	7.40 $\pm$ 4.73	(1.0 - 6.0 - 23.0)
BFM (kg)	17.21 $\pm$ 7.18	18.12 $\pm$ 5.44	17.74 $\pm$ 6.19	(6.5 - 18.4 - 38.0)
AMA (cm^2)	32.11 $\pm$ 8.56	29.85 $\pm$ 7.86	30.81 $\pm$ 8.19	(6.1 - 29.9 - 51.7)
SMM (kg)	17.18 $\pm$ 2.98*	12.14 $\pm$ 2.32*	14.29 $\pm$ 3.61	(6.1 - 13.8 - 23.9)

BMI : Body mass index ; Alb : Serum albumin ; SCr : Serum creatinine ; BUN : Blood urea nitrogen ; CysC : serum cystatin C ; mCCr : measured creatinine clearance ; eCCr$_{(Enz)}$: creatinine clearance estimated using the Cockcroft-Gault formula ; TSF : triceps skinfold thickness ; BFM : body fat mass ; AMA : arm muscle area ; SMM : skeletal muscle mass ;
Data are expressed as mean $\pm$ standard deviation (SD). [a] p = 0.06, *p $<$ 0.0001

calculated with $SCr_{(Enz+0.2)}$ in method (b) were used for the subsequent analyses.
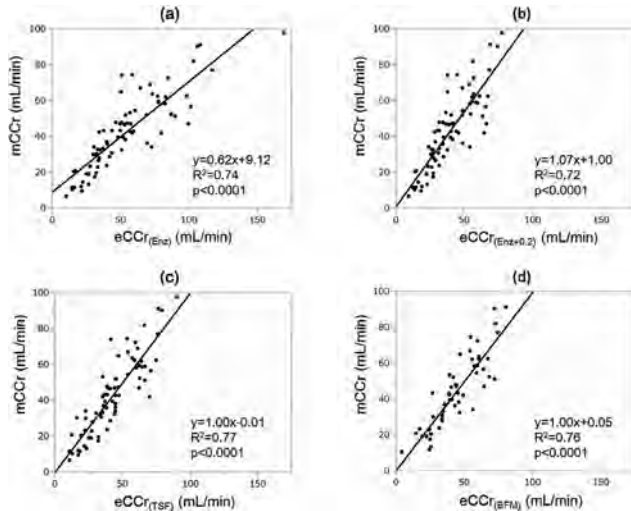

Figure 1. Correlation between mCCr and eCCr values obtained by different methods.
(a) $eCCr_{(Enz)}$ was calculated using the $SCr_{(Enz)}$ value determined by the enzymatic method ; (b) $eCCr_{(Enz+0.2)}$ was calculated using the $SCr_{(Enz+0.2)}$ value obtained by adding 0.2 mg/dL to the $SCr_{(Enz)}$ value ; (c) $eCCr_{(TSF)}$ was corrected $eCCr_{(Enz+0.2)}$ with triceps skinfold thickness (TSF) ; (d) $eCCr_{(BFM)}$ was corrected $eCCr_{(Enz+0.2)}$ with body fat mass (BFM). Solid lines represent the line of identity.
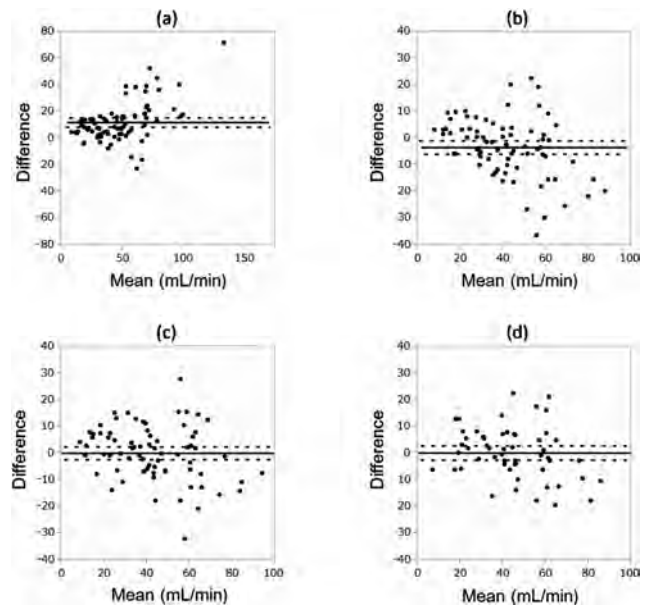

Figure 2. Bland-Altman plots showing the differences between mCCr and eCCr values obtained by the different methods.
(a) $eCCr_{(Enz)}$ was calculated using the $SCr_{(Enz)}$ values determined by the enzymatic method ; (b) $eCCr_{(Enz+0.2)}$ was calculated using the $SCr_{(Enz+0.2)}$ value obtained by adding 0.2 mg/dL to the $SCr_{(Enz)}$ value ; (c) $eCCr_{(TSF)}$ was corrected $eCCr_{(Enz+0.2)}$ with triceps skinfold thickness (TSF) ; (d) $eCCr_{(BFM)}$ was corrected $eCCr_{(Enz+0.2)}$ with body fat mass (BFM). The solid line indicates the mean difference, and the dashed lines depict the upper and lower 95% limits of agreement.

Next, a multiple regression analysis was performed using the mCCr values as the dependent variable and the $eCCr_{(Enz+0.2)}$ values, serum albumin values, TSFs, AMAs, SMM, hemoglobin values, and BFMs as the independent variables. The multiple linear regression indicated that the mCCr values were positively correlated with the $eCCr_{(Enz+0.2)}$ and serum albumin values and negatively correlated with the BFMs and TSFs (Table 3). The statistically significant independent variables, for which the absolute values of the standard partial regression coefficients (β) were relatively large (β> 0.2), were selected after confirming that there were

no instances of multicollinearity with enough low VIF values (VIF< 2.0 in Table 3). Under these conditions in the multiple regression analysis, $eCCr_{(Enz+0.2)}$ (β= 0.98), TSF (β= -0.24), and BFM (β= -0.25) were selected as the independent variables to predict the CCr values. Since both TSF and BFM measurements are indices of body fat volume, a CCr estimation formula (C) or (D) using $eCCr_{(Enz+0.2)}$ values and either TSF or BFM was built with high performance.

$$eCCr_{(TSF)} = 5.75 + 1.11 \times eCCr_{(Enz+0.2)} -0.93 \times TSF \qquad \cdots(C)$$
$$n = 73, R^2 = 0.768, s = 10.4, F = 116.0$$
$$eCCr_{(BFM)} = 16.5 + 1.14 \times eCCr_{(Enz+0.2)} -1.08 \times BFM \qquad \cdots(D)$$
$$n = 54, R^2 = 0.761, s = 9.89, F = 81.3$$

Where, eCCr is in mL/min, TSF is in mm and BFM is in kg.

Table 2. Mean difference between mCCr and eCCr values and accuracy of the eCCr measurement in the Bland-Altman analysis

Equations	Mean of difference ± SD (mL/min)	95% limits of agreement (mL/min)	Accuracy within 30% (%)
$eCCr_{(Enz)}$	11.6 ± 15.3	8.16 - 15.1	71.4
$eCCr_{(Enz+0.2)}$	-3.57 ± 11.1	-6.08 - -1.05	70.1
$eCCr_{(TSF)}$	-0.087 ± 10.2	-2.47 - 2.30	75.3
$eCCr_{(BFM)}$	0.015 ± 9.7	-2.63 - 2.66	77.8

mCCr, measured creatinine clearance ; eCCr, estimated creatinine clearance.
$eCCr_{(Enz)} = [(140 - Age) \times Weight]/[72 \times SCr_{(Enz)}] \times 0.85$ (if women)
$eCCr_{(Enz+0.2)} = [(140 - Age) \times Weight]/[72 \times (SCr_{(Enz)}+0.2)] \times 0.85$ (if women)
$eCCr_{(TSF)} = 5.75 + 1.11 \times eCCr_{(Enz+0.2)} - 0.93 \times TSF$
$eCCr_{(BFM)} = 16.5 + 1.14 \times eCCr_{(Enz+0.2)} - 1.08 \times BFM$
Where, eCCr is in mL/min, age is in years, weight is in kg, SCr is in mg/dL, TSF is in mm, and BFM is in kg.
In the Bland-Altman analysis, the accuracy of the eCCr measurement was defined as the percentage of patients with eCCr values within ± 30% of the mCCr values. Data are expressed as mean ± standard deviation (SD).

Table 3.   Relationship between mCCr and various factors : multiple regression analysis

Independent variables	Partial correlation coefficient (β)	95% CI	VIF	p-value
eCCr (Enz + 0.2)	0.98	1.00 - 1.39	1.58	<0.0001
BFM	-0.25	-1.4 - -0.28	1.77	0.0041
TSF	-0.24	-1.7 - -0.32	1.69	0.0052
Alb	0.15	0.05 - 13.7	1.39	0.048
AMA	-0.077	-0.62 - 0.23	1.8	0.37
Hb	0.057	-1.51 - 3.06	1.77	0.50
SMM	0.054	-0.55 - 1.14	1.45	0.48

CI : confidence interval ; VIF : variance inflation factor ; eCCr(Enz+0.2) : creatinine clearance estimated using the Cockcroft-Gault formula with SCr to which we added 0.2 mg/dL to the enzymatically measured value ; BFM : body fat mass ; TSF : triceps skinfold thickness ; Alb : serum albumin ; AMA : arm muscle area ; Hb : hemoglobin value ; SMM : skeletal muscle mass.

In a simple linear regression analysis, the coefficients of determination between the dependent variable (i.e., the mCCr values) and the independent variables (i.e., eCCr$_{(TSF)}$ and eCCr$_{(BFM)}$) were 0.767 and 0.761, respectively. Both the eCCr$_{(TSF)}$ and eCCr$_{(BFM)}$ values demonstrated a significantly positive correlation with the mCCr values ($p < 0.0001$) (Figures 1 (c) and (d)).

A Bland-Altman plot of the mCCr values and either the eCCr$_{(TSF)}$ or the eCCr$_{(BFM)}$ values is shown in Figures 2 (c) and (d). The analysis results are summarized in Table 2. The average difference between the eCCr$_{(TSF)}$ values was 0.087 mL/min, with a SD of 10.2 mL/min. For the eCCr$_{(BFM)}$ values, the average difference was 0.015 mL/min and the SD was 9.70 mL/min, both of which were smaller than those of the eCCr$_{(Enz)}$ or the eCCr$_{(Enz+0.2)}$ values. The accuracy of the eCCr values was defined as the percentage of patients for which the degree of error between their corresponding mCCr and eCCr values fell within ± 30%, and the 4 groups were compared relatively. As a result, the accuracy of the eCCr$_{(BFM)}$ values was the highest at 77.8%, followed by the eCCr$_{(TSF)}$ values at 75.3%. Compared to these, the accuracy of eCCr$_{(Enz)}$ and eCCr$_{(Enz+0.2)}$ were lower at 71.4% and 70.1%, respectively (Table 2).

Next, using the obtained CCr (mL/min) values, the estimated GFR (mL/min/1.73 m²) value for each patient was calculated based on the GFR estimation formulas described above (Equation 1 through Equation 6). Box-and-whisker plots of the distribution of GFR (mL/min/1.73 m²) values in the 6 eGFR groups are shown in Figure 3. A one-way ANOVA was performed with the GFR estimation method as a group variable and the derived GFR values as dependent variables. Significant differences were observed between the groups. Further, to determine which groups exhibited differences, a nonparametric, multiple comparison test was performed using the Steel-Dwass method. As a result, no significant difference was observed between the eGFR$_{(CysC)}$ group and the GFR$_{(control)}$ group. The mean value of eGFR$_{(creat)}$ group was significantly higher than those of all other groups ($p < 0.05$). No significant differences were observed between the GFR$_{(control)}$ and the eGFR$_{(TSF)}$ groups, the GFR$_{(control)}$ and the eGFR$_{(BFM)}$ groups, or the eGFR$_{(TSF)}$ and the eGFR$_{(BFM)}$ groups (Figure 3).

Furthermore, each patient's degree of renal dysfunction was classified by stage based on the Japanese Society of Nephrology CKD severity classification, and the degrees of coincidence were compared using Pearson's x^2 test based on the derived GFR values (mL/min/1.73 m²). The results are described in Figure 4. When the eGFR$_{(CysC)}$ value was used to evaluate the patient's renal function, it was shown that only 6 (7.9%) patients had normal or nearly normal renal functions, while 71 patients (92.1%) exhibited a degree of renal failure. In detail, 2 (2.6%), 4 (5.3%), 11 (14.5%), 30 (39.5%), 24 (31.6%), and 5 (6.6%) patients were classified as having CKD stages G1, G2, G3a, G3b, G4, and G5, respectively. Using the
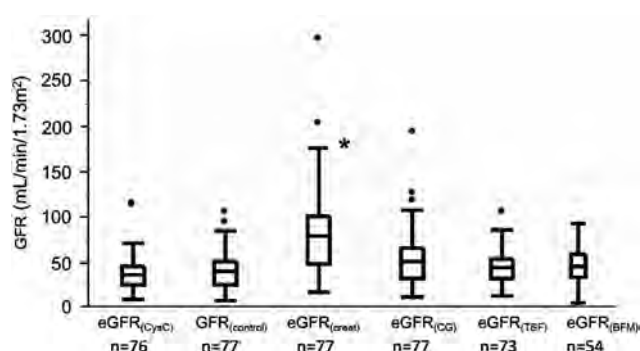

Figure 3.   Box-and-whisker plots of GFR$_{(control)}$ and eGFR values obtained by different methods.

The equations to estimate GFR values were described in the methods. eGFR$_{(CysC)}$, based on the Japanese estimation formula using CysC ; GFR$_{(control)}$, based on the mCCr value ; eGFR$_{(creat)}$, based on the Japanese GFR estimation formula ; eGFR$_{(CG)}$, based on eCCr$_{(Enz)}$ estimated by the Cockcroft-Gault formula with enzymatic SCr ; eGFR$_{(TSF)}$, based on eCCr$_{(TSF)}$; eGFR$_{(BFM)}$, based on eCCr$_{(BFM)}$. The box-and-whisker plots represent the medians and interquartile ranges. Medians are indicated by the lines inside the boxes. Boxes indicate the interquartile range. Whiskers indicate the maximum and minimum values. Data were analyzed using one-way ANOVA followed by the Steel-Dwass test. A significant difference ($p < 0.05$) was observed between the eGFR$_{(creat)}$ group and all other groups. No significant differences were observed between the other groups.

GFR$_{(control)}$ values derived from the mCCr values based on the 24-hour urine collection method, there were 2 (2.6%), 8 (10.4%), 19 (24.7%), 22 (28.6%), 18 (23.4%), and 8 (10.4%) patients classified as having CKD stages G1, G2, G3a, G3b, G4, and G5, respectively. It was shown that the patterns of CKD severity classification were not significantly different between the eGFR$_{(CysC)}$ and GFR$_{(control)}$ groups. Therefore, the CKD severity patterns of the other 4 eGFR groups, which were calculated with eCCr values based on the SCr, were compared with those of the GFR$_{(control)}$ group. When evaluating with the eGFR$_{(creat)}$ value recommended by the Japanese Society of Nephrology CKD Guide (2), more than 60% of patients were classified as having G1 (37.7%) and G2 (26.0%), whereas, many patients were classified as normal or nearly normal regardless of their poor renal function. In contrast, the data in the GFR$_{(control)}$ group showed that 13% of patients were classified as having both G1 and G2 stages, thereby accounting for approximately 20% of the eGFR$_{(creat)}$ patient group. In the eGFR$_{(CG)}$ group, the proportion of patients classified within the normal range was also relatively higher that the proportion in the GFR$_{(control)}$ group, as the proportion of G1 and G2 among

patients was 11.7% and 19.5%, respectively. Meanwhile, no significant difference in CKD classification patterns in the GFR(control) group was observed in either the eGFR(TSF) group (p=0.640) or the eGFR(BFM) group (p=0.406), based upon the new GFR estimation formula developed in this study.
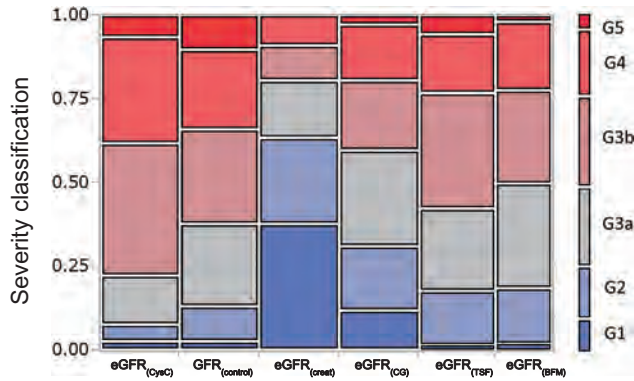

Figure 4. Contingency analysis of chronic kidney disease severity by GFR value.
The GFR values were estimated by the equations described in the methods. GFR stages : descriptions and range (mL/min/1.73 m²) were according to the Japanese Society of Nephrology CKD severity classification as follows, G1 : GFR ≥90, G2 : GFR60~89, G3a : GFR45~59, G3b : GFR30~44, G4 : GFR15~29, G5 : GFR<15. To enhance the interpretability of the results, a Pearson Chi square analysis was used. Mosaic plots shows that the eGFR(TSF) or eCCr(BFM) groups were most similar to the classification patterns observed for the GFR(control) group.

DISCUSSION

When administering drug therapy, overestimation of renal function leads to adverse drug events, while underestimation can lead to improper timing of administration. Therefore, accurate renal function assessment is essential for ensuring safe and efficacious drug therapy. Normally, SCr values are used as an index of renal function. However, renal function assessments based on SCr values have low reliability, particularly in geriatric patients. Since systemic SMM decreases with age, the accuracy of estimation formulas based on SCr values and parameters related to muscle mass could potentially be improved with respect to geriatric patients. Therefore, in this study, we attempted to develop a novel CCr estimation formula to correct the CG formula using physical measurement data for use in elderly bedridden patients first, and then evaluated the clinical utility of the formula.

The In Body S20 apparatus was used during this study to accurately measure SMM and BFM. However, due to the high cost of the In Body S20, only a limited number of medical institutions and facilities make use of this system, and using the system in routine clinical practice or in elder care facilities is difficult. Furthermore, even with simple body composition meters/adipometers, their use can be difficult in bedridden patients because of the need to step onto the measurement platform or grasp the electrode. Thus, instead of measuring SMM and BFM with special equipment, we considered substituting physical measurement indices, such as the AMA and TSF, which are routinely measured by clinical nutritionists to assess the nutritional status of geriatric patients.

In this study, we demonstrated that BMF or TSF, markers of body fat volume, were useful in correcting the estimation of renal function in elderly patients. A potential reason for these observa-

tions may be the fact that this study included bedridden geriatric patients, who tend to exhibit reduced physical activity in conjunction with aging, often suffer from additional conditions, and usually have an altered nutritional status. Elderly people are often in a qualitatively obese state (increased proportion of adipose tissue) as muscle mass decreases while body fat mass increases with age (31). We can infer that these factors likely have a multifaceted impact on bedridden geriatric patients. Furthermore, the results of this study are consistent with the results of reports on body fat and renal function deterioration (32-35).

According to the results of the present study, it was found that the patients' renal function can be assessed most accurately using our new eCCr(BFM) estimation formula based on the CG formula that was corrected using SCr(Enz+0.2) values and BFM (Table 2). The eCCr(TSF) values calculated using TSF also had a high degree of agreement with the mCCr similar to the eCCr(BFM) values (Table 2). Generally, in the case of drugs that are excreted from the kidney, the method of drug administration should be changed according to the CCr value of individual patients, as stated in the package insert. Therefore, the eCCr(BFM) and eCCr(TSF) values may be useful for the prescriber to adjust the drug dosage.

As shown in Figure 3, the multiple comparisons test revealed no significant differences between the GFR(control) group and the eGFR(TSF) or eGFR(BFM) groups, and no difference was observed between the eGFR(TSF) group and the eGFR(BFM) group. Therefore, it is clear that substituting the anthropometrical TSF values is sufficiently feasible in cases where BFM cannot be measured using the bioelectrical impedance method from bedridden patients. In addition, it was also suggested that high TSF values were not reflective of edema due to renal dysfunction in these patients.

The severity of patients' kidney dysfunction has traditionally been classified using the Japanese Society of Nephrology CKD severity classification (2). It has been reported that the measured GFR value, which is based on inulin, and the eGFR(CysC) value are similar (22). In eGFR(CysC), which uses values that are similar in nature to that obtained by measuring inulin, 92% of patients were classified as having CKD stage G3 or higher, exhibiting a moderate or more severe reduction in renal function. Since there was no difference in classification pattern in the GFR(control) group when using the mCCr and the eGFR(CysC) group, which used values that are similar in nature to that obtained by measuring inulin, we compared other methods to the GFR(control) value, which we considered the control group. In so doing, we found that using eGFR(creat), which is usually used for CKD severity classification, resulted in 60% of patients being classified as having stage G1 to G2. Since eGFR(creat) is clearly different from the classification pattern determined using other methods, we determined that eGFR(creat) is not suitable for elderly people. Furthermore, when compared to GFR(control), eGFR(CG) resulted in more patients being considered normal. It was revealed that the eGFR(creat) and the eGFR(CG) groups did not reflect the actual renal function of patients. Consequently, making these values an indicator of renal dysfunction might lead delaying the timing of treatment and suboptimal results with regular dosages for patients. Meanwhile, the eGFR(TSF) and eGFR(BFM) groups showed the classification pattern closest to the GFR(control) group derived from mCCr (Figure 4). Furthermore, no difference was found in the classification patterns of eGFR(CysC), GFR(control), and eGFR(TSF). Therefore, when mCCr or CysC cannot be measured, eCCr(TSF) values calculated using TSF can be an alternative method of renal function evaluation in bedridden elderly patients.

Based on these results, we named this new TSF-based estimation formula the "Naruto" formula, which is named after our hospital.

$$eCCr_{(Naruto)} = 5.75 + 1.11 \times eCCr_{(Enz+0.2)} -0.93 \times TSF$$
$$= 5.75 + 1.11 \times [(140 - Age) \times Weight] / [72 \times (SCr_{(Enz)} + 0.2)] \times 0.85 \text{ (in women) } -0.93 \times TSF$$

$$eGFR_{(Naruto)} = 0.789 \times eCCr_{(Naruto)} \times 1.73 / BSA$$

Where, eCCr is in mL/min, Age is in year, Weight is in kg, SCr is in mg/dL, TSF is in mm, eGFR is in mL/min/1.73 m², and BSA is in m².

Because the Naruto formula utilizes clinical laboratory values and routine nutrition management metrics in bedridden geriatric patients, $eCCr_{(Naruto)}$ values can be calculated easily without additional costs or the utilization of specialized resources. The $eGFR_{(Naruto)}$ values that derive from $eCCr_{(Naruto)}$ values have been demonstrated to correlate with CKD severity classification corresponding to $GFR_{(control)}$ values when evaluating patients' renal functions. These observations indicate that renal function determinations using the Naruto formula in bedridden geriatric patients is extremely useful from the perspective of drug therapy optimization. We expect that this formula will be utilized in clinical practice.

Limitations of this study include the fact that results were obtained from a single elder care facility, and the fact that the patients' concomitant medications and prior medical histories were not considered in our assessment. In this study, mCCr was considered to be the true renal function of the patient. There is a large difference between mCCr value and inulin clearance value, and correction is reportedly necessary (19, 26, 36). However, no correction method has been established for elderly people or elderly people with sarcopenia (37). Furthermore, the difference between the mCCr value and the inulin clearance value increases in accordance with renal function deterioration (19, 26, 38). Furthermore, since the SCr value is included in the mCCr formula, a bedridden elderly patient with a low SCr value may possibly result in the overestimation of mCCr itself. Since the SCr value is also used for the new estimation formula, the problem of using the SCr value has not been resolved. In cases of low SCr value, it is unclear the extent to which mCCr correlates with inulin clearance. Accordingly, further verification of our results based on data obtained from additional patients and facilities is necessary.

CONCLUSION

In the present study, we developed a novel equation to update the CG equation, called the "Naruto" formula, for estimating the CCr when evaluating the renal function of Japanese bedridden elderly patients. In using $eCCr_{(Naruto)}$ values corrected by the anthropometrical TSF value, we were able to derive the $eGFR_{(Naruto)}$ values, which sufficiently correlated with the CKD severity classification pattern corresponding to the real GFR. The Naruto formula can be clinically useful for managing drug therapies of geriatric patients by determining their renal functions without the use of expensive equipment and avoiding incurring additional medical expenses. Notably, as the SCr value is included in the mCCr formula, a bedridden elderly patient with a low SCr value may possibly suffer from the overestimation of the mCCr itself. Since the SCr value is also used for the new estimation formula, we have not resolved the concern of using the SCr value.

CONFLICT OF INTERESTS DISCLOSURE

The authors declare no financial conflicts of interest.

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None

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