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Research Article

Comparison of Different Measures of Fat Mass and Their Association with Serum Cystatin C Levels

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Introduction. Cystatin C (CysC) is a glomerular filtration rate (GFR) marker affected by GFR and obesity. Because percentage body fat (%BF) distribution is affected by ethnicity, different measures of %BF may improve CysC prediction. This study aims to create multivariate models that predict serum CysC and determine which %BF metric gives the best prediction. *Methods*. Serum CysC was measured by nephelometric assay. We estimated %BF by considering weight, body mass index, waist-hip ratio, triceps skin fold, bioimpedance, and Deurenberg and Yap %BF equations. A base multivariate model for CysC was created with a %BF metric added in turn. The best model is considered by comparing P values, R^2, Akaike information criterion (AIC), and Bayesian information criterion (BIC). *Results*. There were 335 participants. Mean serum CysC and creatinine were 1.27 mg/L and 1.44 mg/dL, respectively. Variables for the base model were age, gender, ethnicity, creatinine, serum urea, c-reactive protein, log GFR, and serum albumin. %BF had a positive correlation with CysC. The best model for predicting CysC included bioimpedance-derived %BF ($P = 0.0011$), with the highest R^2 (0.917) and the lowest AIC and BIC (−371, −323). *Conclusion*. Obesity is associated with CysC, and the best predictive model for CysC includes bioimpedance-derived %BF.

1. Introduction

Cystatin C is an endogenous 13 kDa cysteine protease inhibitor filtered by the glomeruli and reabsorbed and catabolized by renal tubular cells. It is considered as an alternative marker of kidney function (glomerular filtration rate, GFR). It is thought to be superior to creatinine as a marker of kidney function because it is less affected by muscle mass and does not seem to be affected by age or gender [1–3]. However, it has been recognized that non-GFR factors also influence serum cystatin C levels. Stevens et al. examined this in chronic kidney disease (CKD) patients and found that, after adjusting for age, gender, sex, and GFR, serum cystatin C was significantly influenced by proteinuria, diabetes status, systolic blood pressure, weight, body mass index (BMI), white blood cell count, hemoglobin, and c-reactive protein [4].

Obesity has been shown to be associated with serum cystatin C levels in several studies [5, 6]. These studies indirectly used several metrics of obesity for analyzing the effects of body fat mass on serum cystatin C levels. Because percentage body fat (%BF) distribution may also be affected by ethnicity, different measures (or estimations) of %BF may improve the prediction of serum cystatin C levels [7, 8]. We hypothesize that direct measurement (or estimation) of body fat mass (%BF) improves the prediction of serum cystatin C levels in multivariate models.

Our study aims to (1) create multivariate models predicting serum cystatin C levels, using available data from

the Asian Kidney Disease Study and the Singapore Kidney Function Study [9, 10] that include variables with known associations from the study by Stevens et al. and (2) determine which metric of body fat (weight, BMI, triceps skin-fold, waist-hip ratio, multifrequency bioimpedance percentage body fat, %BF (calculated using the Deurenberg equation) [7], and %BF (calculated using the Yap equation) [8]) when included in a multivariate model results in the best prediction of serum cystatin C concentration.

2. Methods

2.1. Participants. We used data from the Singapore Kidney Function Study Phase 1 (SKFS1) and the Asian Kidney Disease Study (AKDS) [9, 10]. In SKFS1, 103 healthy volunteers were recruited. The inclusion criterion was nonpregnant adults (>21 years), and they were excluded if they had any of the following: inability to consent, physical conditions that render phlebotomy for blood samples difficult, inability to collect urine samples successfully, use of regular medications, hypertension, diabetes, possible kidney dysfunction (by urinalysis, or on renal imaging), and any condition that potentially interferes with the accuracy of the measurement of GFR. Volunteers were screened with urine dipsticks for hematuria, leukocyturia, proteinuria, and microalbuminuria. In AKDS, 232 patients with CKD were recruited (CKD stages 1 to 5: $n = 27$, 45, 99, 53, and 8, resp.). The inclusion criteria were nonpregnant adult (>21 years), serum creatinine with an estimated or measured GFR (MDRD, Cockroft-Gault [11], or creatinine clearance) of 10 mL/min to 90 mL/min, "stable CKD" defined as two sets of serum creatinine measured >60 days apart of less than 20% difference, and the definition of CKD that followed the clinical practice guidelines [12]. The exclusion criteria were the same as SKFS1.

2.2. Laboratory Tests. GFR was determined by 3-sample plasma clearance of an intravenous bolus of ^{99m}Tc-DPTA [13], calculated by the slope-intercept method, normalized to body surface area, with the result corrected using the Brochner-Mortensen equation [14]. Body surface area is calculated using the du Bois equation [15].

Serum cystatin C was measured by particle-enhanced immunonephelometry on the BN Prospec platform (Dade Behring) in 2009 and standardized by using adjustment equation SyC = 1.12 × cysC [16]. Serum creatinine was measured by an enzymatic method and calibrated with materials traceable to standardized creatinine (Siemens Advia). All participants performed a 24-hour urine collection, GFR measurement, anthropometric measurement (height, weight, blood pressure, waist-hip circumference, triceps skin-fold, and bioimpedance), and serum assays (albumin, creatinine, urea, C-reactive protein, and cystatin C).

We chose variables based on the findings of Stevens et al. [4]. These included measures of muscle mass and body size (age, sex, ethnicity, height, weight, body mass index, urine creatinine, tricep skin fold, waist-hip circumference, and bioimpedance), cardiovascular disease risk factors (hypertension, diabetes, systolic blood pressure, and diastolic blood pressure), cardiovascular diseases (coronary artery disease and cerebrovascular disease), measures of inflammation (albumin and C-reactive protein), urine analysis (24 hr urine total protein, phosphate, and urea nitrogen), and other variables such as phosphate binder use.

2.3. Fat Measurement. Body mass index was calculated as mass/height × height. Waist-hip ratio (WHR) is the ratio of the waist circumference to the circumference of the hips [17]. Triceps skin fold is measured at the triceps site using calipers. Bioelectrical impedance was measured with Bodystat Quadscan 4000 [18].

The Deurenberg equation predicts %BF from BMI, age, and sex and was developed from a Caucasian population [7]: $\%BF = 1.20 \times BMI + 0.23 \times age - 10.8 \times sex - 5.4$.

The Yap equation predicts %BF from BMI, age, sex, and ethnicity and was derived from a population comprising Chinese, Malay, and Indian [8]: $\%BF = 1.04 \times BMI - 10.9 \times sex + 0.1 \times age + 2.0 \times E_1 + 1.5 \times E_2 + 5.7$. The dummy variables for ethnicity were E_1 and E_2. For Chinese $E_1 = 0$ and $E_2 = 1$, for Malays E_1 and $E_2 = 0$, and for Indian $E_1 = 1$ and $E_2 = 1$.

3. Statistical Analysis

Variables with nonnormal distribution are natural log-transformed where appropriate. The initial multivariate model (base) is created with step-wise backward elimination without including the body fat metrics, using a P value of <0.20 for keeping the variable. The variables considered were age, gender, GFR, diabetes status, c-reactive protein, proteinuria, urine urea nitrogen, serum albumin, serum creatinine, serum urea nitrogen, and urine phosphate. The best significant multivariate base model is then used to further build models that included the metrics of body fat in turn. These models are compared using body fat metric (factor) P values, R^2, Akaike information criterion (AIC), and Bayesian information criterion (BIC). The best model is characterized by having the highest R^2 and lowest AIC and BIC values. Since R^2 always will increase with an increasing number of predictor variables in a model, the best model is selected using the AIC and BIC criterion which penalizes models for having large number of predictor variables. AIC favors more complex models and might overfit, while BIC may select a parsimonious model and underfit.

4. Results

4.1. Clinical Characteristics. We recruited 335 participants with a mean age of 53.5 ± 15.1 years and GFR of 67 ± 33 mL/min per 1.73 m^2 (Table 1). There were 129 Chinese, 79 Indian, 99 Malay, and 28 others, and 51% were men. Mean serum concentrations of cystatin C and creatinine were 1.27 ± 0.66 mg/L and 1.44 ± 0.97 mg/dL, respectively. The mean ± SD for weight, BMI, bioimpedance, and waist-hip ratio were 68.9 ± 15.1 kg, 26.8 ± 5.21 kg/m^2, 34.1 ± 9.53, and 0.89 ± 0.07, respectively.

4.2. Variables Selected. The initial multivariate model is created with step-wise backward elimination, with insignificant

Table 1: Patient characteristics (n = 335).

Variable	Statistic*
Age (years)	53.5 ± 15.1
Men (n, %)	171 (51.0)
Chinese	129 (38.5)
Indian	79 (23.6)
Malay	99 (29.6)
Others	28 (8.4)
Diabetes (n, %)	119 (35.5)
Hypertension (n, %)	192 (57.3)
Coronary artery disease (n, %)	54 (16.1)
Cerebrovascular disease (n, %)	10 (3.0)
Systolic BP (SBP, mmHg)	128 ± 22
Diastolic BP (DBP, mmHg)	71 ± 10
Height (m)	1.60 ± 0.09
Weight (kg)	68.9 ± 15.1
Body Mass Index (BMI; kg/m^2)	26.8 ± 5.21
Triceps skin-fold thickness (TSF, cm)	2.61 ± 1.04
Measured GFR (mL/min per 1.73 m^2)	67 ± 33
Serum creatinine (mg/dL)	1.44 ± 0.972
Serum cystatin C (mg/L)	1.27 ± 0.66
Serum albumin (g/L)	42.3 ± 3.1
Serum C-reactive protein (mg/L)	5.0 (5.0-5.0)
Serum urea (mmol/L)	6.0 (4.0–10.6)
24-hr urine total protein (g/day)	0.14 (0.08–0.39)
24-hr urine phosphate (mmol/day)	14.6 ± 7.78
24-hr urine urea nitrogen (g/day)	6.77 ± 2.91
Phosphate binders use (n, %)	214 (16)
Percentage body fat (Bioimpedance)	34.1 ± 9.53
Waist-hip ratio	0.89 ± 0.07

*Data is reported as mean ± SD, or median (25%–75%), or frequency (%).

variables being eliminated. The variables selected (Table 2) for the best base predictive model of cystatin C were age (r = 0.00236, P = 0.0007), gender (r = −0.0260, P = 0.0141), ethnicity (P = 0.0045), creatinine (r = 0.371, P < 0.0001), serum urea (r = 0.121, P = 0.0001), c-reactive protein (r = 0.04700, 0.0033), Log GFR (r = −0.230, P < 0.0001), and serum albumin (r = −0.00922, P = 0.0007). Serum creatinine had the strongest association with cystatin C (r = 0.371, P < 0.0001). The best base predictive model without any fat metrics had a R^2 of 0.905 and AIC and BIC of −335 and −290, respectively.

4.3. Best Fat Metric. Adding different fat metrics in turn (Table 3) into the base predictive model, we determined that measurement of body fat with the bioimpedance method gave the best prediction model for serum cystatin C. The model with bioimpedance-determined %BF had the highest R^2 (0.917) and the lowest AIC and BIC (−371 and −323, resp.; factor P = 0.0011). Waist-hip ratio had the strongest association with cystatin C, with r = 0.307 and SE = 0.134, but a prediction model containing WHR performed poorer (R^2 = 0.916, AIC = −366, BIC = −318; factor P = 0.023).

Table 2: Factors selected for the best predictive base model for cystatin C.

Factors	Estimate	Standard error	P value
Intercept	1.05	0.217	<0.0001
Age	0.00236	0.000692	0.0007
Men	−0.0260	0.0106	0.0141
Ethnicity	—	—	0.0045
Chinese	−0.0388	0.0133	0.0037
Indian	0.00828	0.0152	0.586
Malay	0.0306	0.0141	0.0301
Others	−0.0001	0.022	0.9954
Log creatinine	0.371	0.0468	<0.0001
Log serum urea	0.121	0.0313	0.0001
Log CRP	0.04700	0.0159	0.0033
Log GFR	−0.230	0.0391	<0.0001
Serum albumin	−0.00922	0.00271	0.0007

The prediction models containing weight and triceps skin fold also performed poorer than the base model; BIC = −287 (factor P = 0.071), and BIC = −288 (factor P = 0.048), respectively.

5. Discussion

Serum cystatin C is considered as an alternative marker of kidney function (glomerular filtration rate, GFR) and is used in GFR prediction equations and the accuracy of GFR estimation may be affected by other factors [19]. Obesity and body fat percentage are associated with increased serum cystatin C levels [5]. Our study shows that all fat metrics exhibited a positive correlation with serum cystatin C, which is similar to previous reports [5, 6]. We also show that adding a measurement or estimation of %BF (except weight) into a predictive model for serum cystatin C improves the performance of prediction. Of all significant predictors, triceps skin fold marginally improved the performance of prediction, but using %BF by bioimpedance analysis as a predictor gave the best performing model. The bioimpedance method may be more accurate in quantifying %BF compared to BMI, especially in a population of multiple Asian ethnicities [20–23]. Waist-hip ratio is the second best fat metric for cystatin C prediction. This is consistent with other reports, which suggests that WHR is a better indicator of body fat than BMI [24]. A possible reason is that unlike BMI, WHR considers the distribution of abdominal body fat, which more accurately reflects %BF. In addition, BMI is unable to differentiate between someone with high muscle mass and someone with excess adipose tissue [25]. The prediction models containing %BF calculated with the Deurenberg equation or Yap equation performed similarly to a model using BMI. The Deurenberg equation for %BF estimation takes into account BMI, age, and sex, while the Yap equation also includes ethnicity categories consistent with our study population. Although we should expect a more accurate %BF assessment when using the Yap equation, we did not find improved prediction of serum cystatin C.

Table 3: Comparison of predictive models of cystatin C with different metrics of body fat.

Base model* + body fat measurement	Factor			Model			
	Estimate	Standard error	*P* value	R^2	*P* value	AIC	BIC
No body fat measurement	—	—	—	0.905	<0.0001	−335	−290
Weight (kg)	0.00107	0.00059	0.071	0.906	<0.0001	−336	−287
Body mass index (kg/m^2)	0.00447	0.00160	0.0056	0.907	<0.0001	−340	−292
Triceps skin-fold (cm)	0.0167	0.00842	0.048	0.906	<0.0001	−336	−288
Waist-hip ratio	0.307	0.134	0.023	0.916	<0.0001	−366	−318
Bioimpedance %BF	0.00496	0.00151	0.0011	0.917	<0.0001	−371	−323
Yap %BF	0.00430	0.00154	0.0056	0.907	<0.0001	−340	−292
Deurenberg %BF	0.00373	0.00134	0.0056	0.907	<0.0001	−340	−292

*The models include the significant variables age, gender, ethnicity, Log creatinine, Log serum urea, Log c-reactive protein, Log GFR, and serum albumin.
%BF: percentage body fat.

CKD is a risk factor for mortality and the interactions of %BF with cystatin C and estimated GFR may be important in clarifying the sometimes conflicting outcomes noted with adiposity (as determined by various measures). There is evidence that body mass index (BMI) cut-off values should not be applied to different patient populations [8, 26]. Many populations should not be classified as obese based on their BMI alone [27–29]. Direct measurements of %BF would reduce misclassifications and be a better tool for preobesity and obesity diagnosis [30–32]. Waist circumference or WHR is a proxy measure for body fat distribution when investigating health risks [32]. Waist circumference reflects abdominal or intra-abdominal fat, and hip circumference reflects other aspects of body composition in the gluteofemoral region (muscle mass, bone, and fat mass). The importance of WHR lies in the different physical and metabolic characteristics of these two regions, and therefore the diverse clinical outcomes in patients with a gynoid (low WHR, lower body obesity) or android (high WHR, upper body obesity) body morphology [29, 32].

The other variables used in our base prediction model for cystatin C are creatinine, serum urea, c-reactive protein, albumin, and glomerular filtration rate. These variables are consistent with previous reports [4]. C-reactive protein, a marker of inflammation, is associated with higher levels of serum cystatin C [33]. Recruitment of inflammatory cells leads to an increased production of cystatin C by adipocytes [34, 35]. Serum cystatin C concentrations increase when the glomerular filtration rate decrease, as cystatin C is freely filtered at the glomerulus and is not secreted by the renal tubules [36].

The strengths of this study include the fairly large study population with participants from two studies recruited and assessed using the same protocols, calibrated serum cystatin C and creatinine assays, and reference GFR measurements. The recruitment of participants was strategized to ensure a cohort of both healthy and CKD patients over a range of GFR and with participants representative of gender and ethnicity. The limitations of this study include the lack of a reference method of body fat percentage measurement (such as magnetic resonance imaging or dual-energy x-ray absorptiometry) or having participants with recent illness that reduces percentage body fat. The accuracy of bioimpedance is also affected by ethnicity, and the %BF estimation obtained through the Bodystat Quadscan in our study may not have adequately adjusted for ethnicity [37]. This is a cross-sectional study and a future longitudinal study is required to ascertain the impact of changes in %BF on serum cystatin C in progressive CKD and possible interactions with other biochemical factors.

In summary, metrics of body fat are associated with serum cystatin C, and bioimpedance-determined percentage body fat is the best predictor in a multivariate model of factors predicting serum cystatin C.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Boon Wee Teo and Evan J. C. Lee conceived and supervised the study. Qi Chun Toh and Hui Xu recruited and prepared the database. Boon Wee Teo, Jonathan J. H. Soon, Jialiang Li, and Evan J. C. Lee analyzed the data. Jonathan J. H. Soon and Boon Wee Teo prepared the initial draft. All authors reviewed and edited the paper.

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