Impact of Misclassification of Obesity by Body Mass Index on Mortality in Patients With CKD

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Introduction: Unlike the general population, a higher body mass index (BMI) is associated with greater survival among patients with chronic kidney disease (CKD). This "obesity paradox" may be due to limitations of BMI as a measure of adiposity in CKD. Both BMI and body fat percentage (BF%) are used to classify obesity, but outcomes may vary. Therefore, we investigated the 2 different cutoffs for diagnosing obesity (BMI $\geq$28 kg/m^2 or BF% >25% for men and >35% for women) and the impact on all-cause mortality in CKD.

Methods: A total of 326 patients with non–dialysis-dependent CKD were prospectively followed for a median of 4.9 years (range 2.9–5.3). BF% and lean body mass were determined using the Body Composition Monitor, a novel multifrequency bioimpedance spectroscopy device. Covariates included age, gender, diabetes, cardiovascular disease, estimated glomerular filtration rate, proteinuria, and high-sensitivity C-reactive protein.

Results: Per the BMI definition, 27.9% of patients were obese. However, 48.8% of patients were obese according to the BF% definition. A BMI $\geq$28 kg/m^2 had a moderately high specificity of 83.2% but a low sensitivity of 39.6% for detecting BF%-defined obesity. In the fully adjusted models containing both BMI and BF%, obesity defined by BMI was associated with a significantly lower risk of death (hazard ratio [HR]: 0.23; 95% CI: 0.07–0.71; $P = 0.011$), whereas the result was reversed when obesity was defined by BF% (HR: 2.75; 95% CI: 1.28–5.89; $P = 0.009$). When patients were classified into 4 distinct groups based on both the BMI and BF% cutoffs for obesity, a considerable proportion of patients (29.4%) had excess body fat in the context of a normal BMI. These patients were more likely to have lower lean body mass (i.e., sarcopenic obesity) and had higher mortality compared with patients with obesity defined by both BMI and BF% (HR: 5.11; 95% CI: 1.43–18.26; $P = 0.012$).

Conclusion: Diagnostic discordance between BMI and BF% may partly explain the obesity paradox. Proper diagnosis of obesity in patients with CKD is required for both risk prediction and treatment.

O besity is a major public health problem, with increasing prevalence worldwide.[1,2] Obesity is associated with higher risk of type 2 diabetes mellitus, cardiovascular disease (CVD), dyslipidemia, cancer, and a shortened life expectancy in the general population.[3–5] Furthermore, obesity increases the risk of chronic kidney disease (CKD) and its progression.[6] Meanwhile, CKD is also increasingly recognized as a global health burden.[7,8] Thus, early detection and prevention of obesity in at-risk populations is extremely important. According to the World Health Organization (WHO), obesity is defined as the degree of fat storage associated with clearly elevated health risks.[9] A body fat percentage (BF%) that is >25% for men and >35% for women is conventionally proposed for obesity diagnosis.[10,11] Because the direct measurement of fat is difficult in clinical practice, body mass index, or BMI, is used instead as a screening tool for obesity.

In contrast to the general population, obesity is inversely associated with better survival among patients with CKD, a phenomenon commonly referred

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to as the "obesity paradox."[12–15] Few studies, however, have attempted to explain why this paradox exists. Because BMI does not acknowledge the muscle wasting commonly seen in patients with CKD,[16] it may misclassify patients with CKD with sarcopenic obesity as normal when their BF% would classify them as obese. Thus, the imperfection of BMI as a measure of adiposity may confound the relationship between BMI and mortality risk in CKD.

WHO defines obesity as a BMI of 30 kg/m^2 or higher. However, at the same BMI, people of Asian ancestry might have higher BF% and greater risk of developing metabolic diseases than people of European ancestry.[17] A BMI of 28 kg/m^2 has been shown to identify risk factors with a specificity of approximately 90% and is recommended as the cutoff point for obesity in Chinese adults.[18] Both BMI and BF% are used to classify obesity, but outcomes may vary. Therefore, in this prospective cohort study, we sought to characterize the degree of misclassification of obesity according to BMI $\geq$28 kg/m^2 using BF% as a reference among patients with stage 3 to 5 CKD who were not yet on dialysis. We further explored the impact of using different metrics to define obesity on mortality risk.

METHODS

Study Design and Participants

This is a prospective cohort study. The study design and patients were previously described.[19] Briefly, 395 prevalent patients with nondialysis CKD (defined as estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2 calculated according to the Modification of Diet in Renal Disease formula) seen in the nephrology outpatient clinics of Taipei Tzu Chi Hospital, Taiwan, were assessed for eligibility for inclusion between September 2011 and December 2012. All participants provided informed consent. Patients were excluded if they had a malignancy, liver cirrhosis, or an acute cardiovascular (CV) event within the 3 months before screening for inclusion. We also excluded patients with a cardiac pacemaker or metallic implant and patients who were amputees or pregnant. For each participant, a thorough medical history was obtained, and the corresponding medical chart was reviewed at the time of screening. CVD was defined by coronary artery disease, as documented by coronary angiography or a history of myocardial infarction, class III to IV congestive heart failure, or stroke. The presence of diabetes mellitus was based on the current or past use of insulin and/or oral hypoglycemic agents. Hypertension was defined as either a blood pressure $\geq$140/90 mm Hg or by current treatment with antihypertensive agents. The patients were followed up every 3 months. All participants

received a comprehensive CKD education program, including dietary salt and protein restriction, strict blood pressure and glycemic control, and avoidance of nephrotoxin exposure. The number of participants during the study period determined the sample size. The study complied with the Declaration of Helsinki and was approved by the institutional review board of Taipei Tzu Chi Hospital (99-IRB-016-XD).

Outcomes

The primary outcome was death from any cause. Patients were censored at the time of their last contact or end of follow-up in March 2017.

Measurements

All blood samples were drawn after patients had fasted overnight. The albumin level was determined using a bromocresol purple assay. Proteinuria, expressed as the urine protein creatinine ratio, was estimated using the first morning void. The plasma levels of interleukin-6, tumor necrosis factor-α, leptin, and adiponectin were measured using commercially available enzyme-linked immunosorbent assay kits based on the manufacturer's instructions (R&D Systems, Minneapolis, MN). Arterial stiffness was assessed by measuring the brachial-ankle pulse wave velocity using a VP-1000 analyzer (Colin Corporation, Komaki, Japan).[20]

Body Mass Index

The body weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) of each participant were measured using an auto-anthropometer (Seca, Hamburg, Germany) by trained staff. BMI was calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m^2). The Working Group on Obesity in China criteria for obesity based on BMI were used to classify patients as obese (BMI $\geq$28 kg/m^2).[18]

Body Composition

Body composition was assessed using a portable whole-body bioimpedance spectroscopy device, the Body Composition Monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany). The BCM has been commonly used for determining body composition in patients with dialysis-dependent CKD, and its accuracy has been validated against gold standard reference methods such as dual energy X-ray absorptiometry (DEXA).[21] Almost all output parameters among Taiwanese healthy controls fit into the same reference ranges set by Fresenius Medical Care.[19] Electrodes were positioned on the hand and foot on the nondominant side of the body while the patient was in a supine position. Input variables included the body height, body weight, age, and gender of the patient. The BCM measures body composition by analyzing the electrical responses at 50 different frequencies from 5 to

1000 kHz. Body fat mass and lean mass were derived from the impedance data and expressed as the BF% (fat mass divided by body weight) and lean tissue index (lean tissue mass/height^2), respectively.[22] The WHO recommendation for BF% classifies men as obese when body fat (BF) >25% and women as obese when BF >35%.[9] BMI (obese vs. nonobese) was compared with BF% (obese vs. nonobese) to determine the percent agreement between the 2 definitions.

Statistical Analyses

All variables were expressed as frequencies and percentages for categorical data and as the means ± SDs or medians and interquartile ranges for continuous data with or without a normal distribution, respectively. The baseline characteristics were compared using a χ^2 test for categorical variables. Student t test and 1-way analysis of variance were used for comparison of continuous variables with a normal distribution as appropriate. The Mann-Whitney U test and Kruskal-Wallis test were used for comparing continuous variables without a normal distribution, as appropriate. Cox proportional hazards modeling was used to estimate the hazard ratios (HRs) of all-cause mortality associated with obesity or not according to the BMI or BF% definition. Model 1 was adjusted for age and gender, and Model 2 was further adjusted for diabetes mellitus, CVD, eGFR, urine protein creatinine ratio, high-sensitivity C-reactive protein, and BMI or BF%. Variance inflation factors were less than 3 when BMI and BF% were simultaneously included, indicating absence of significant multicollinearity. Because the mortality events were relatively low, we avoided overfitting the model by selecting 8 clinically relevant variables for the adjustments. The proportional hazards assumption was inspected by using log-log survival curves. A 2-tailed P value less than 0.05 was considered statistically significant. The association of the BF% and BMI with mortality, adjusted for the aforementioned confounding variables, was further demonstrated by restricted cubic spline models using STATA version 14 (STATACorp, College Station, TX). All other statistical analyses were performed using the computer software Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

The study cohort comprised 326 patients (224 men and 102 women; mean age 66 ± 13 years) with moderate to severe CKD (mean eGFR 29 ± 15 ml/min per 1.73 m^2). In this population, 45.4% were diabetic ($n = 148$), and 23.6% had CVD ($n = 77$). BMI-defined obesity was present in 27.9% of patients ($n = 91$),

whereas BF%-defined obesity was present in 48.8% of patients ($n = 159$). The baseline study participant characteristics stratified by different obesity definitions are shown in Tables 1 and 2. The subgroup of patients with BMI- or BF%-defined obesity was compared with the corresponding subgroup without obesity. Overall, obese patients (according to BMI or BF%) were more likely to have diabetes mellitus and higher leptin levels. Nevertheless, the subgroup of patients with BMI-defined obesity was younger; had lower brachial-ankle pulse wave velocity; higher eGFR, blood sugar, and triglycerides; and had a higher lean tissue index (Table 1). In contrast, the subgroup of patients with BF%-defined obesity was older, had higher brachial-ankle pulse wave velocity, and had a lower lean tissue index (Table 2). In addition, more (albeit not significant) BF%-defined obese patients had a history of CVD (28.3% vs. 19.2%; $P = 0.052$) compared with BF%-defined nonobese patients, although there was no difference with respect to CV risk factors (e.g., sex, smoking, hypertension, blood sugar, and dyslipidemia) between groups.

Table 1. Characteristics of the patient group stratified according to BMI-defined obesity (BMI ≥28 kg/m^2)

Characteristics	BMI-defined obesity Yes, $n = 91$	BMI-defined obesity No, $n = 235$	P
Body composition			
BMI (kg/m^2)	30.8 ± 3.2	24.0 ± 2.5	<0.001
BF (%)	31.3 ± 8.0	25.7 ± 9.6	<0.001
LTI (kg/m^2)	16.6 ± 3.1	14.7 ± 3.1	<0.001
Demographics			
Age (yr)	61.2 ± 13.8	67.6 ± 12.7	<0.001
Male sex, n (%)	66 (72.5)	158 (67.2)	0.355
Smoking history, n (%)	19 (20.9)	48 (20.4)	0.928
DM, n (%)	58 (63.7)	90 (38.3)	<0.001
CVD, n (%)	23 (25.3)	54 (23.0)	0.662
Statin, n (%)	37 (40.7)	49 (20.9)	<0.001
RAASI, n (%)	66 (72.5)	130 (55.3)	0.004
Clinical parameters			
Systolic BP (mm Hg)	140.1 ± 17.5	136.7 ± 17.0	0.105
baPWV (m/s)	15.3 ± 3.5	16.2 ± 2.8	0.020
eGFR (ml/min per 1.73 m^2)	32.4 ± 14.7	27.5 ± 14.5	0.007
UPCR (g/g)	0.94 (0.33–3.36)	0.86 (0.31–2.11)	0.286
Albumin (g/dl)	3.6 ± 0.4	3.6 ± 0.4	0.878
Fasting glucose (mg/dl)	133 ± 48	116 ± 38	0.001
Total cholesterol (mg/dl)	175 ± 42	174 ± 40	0.846
Triglycerides (mg/dl)	199 ± 156	150 ± 90	<0.001
hs-CRP (mg/l)	5.3 (1.9–11.2)	3.4 (1.1–9.6)	0.060
IL-6 (pg/ml)	3.56 (2.06–5.05)	3.50 (2.07–6.42)	0.885
TNF-α (pg/ml)	6.22 (4.18–8.81)	6.95 (4.77–9.69)	0.104
Leptin (ng/ml)	17.16 (8.52–32.69)	8.04 (3.48–14.25)	<0.001
Adiponectin (μg/ml)	4.27 (2.63–8.96)	5.79 (3.06–9.22)	0.190

baPWV, brachial-ankle pulse wave velocity; BF, body fat; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LTI, lean tissue index; RAASI, renin-angiotensin-aldosterone system inhibitor; TNF-α, tumor necrosis factor-α; UPCR, urine protein creatinine ratio.

Table 2. Characteristics of patient group stratified according to BF%-defined obesity (BF% >25% for men and >35% for women)

Characteristics	BF%-defined obesity		
	Yes, *n* = 159	No, *n* = 167	*P*
Body composition			
BMI (kg/m^2)	27.5 ± 4.1	24.4 ± 3.4	<0.001
BF (%)	33.7 ± 6.3	21.1 ± 7.8	<0.001
LTI (kg/m^2)	13.9 ± 3.0	16.5 ± 2.9	<0.001
Demographics			
Age (yr)	68.8 ± 13.2	62.9 ± 12.9	<0.001
Male sex, *n* (%)	114 (71.7)	110 (65.9)	0.256
Smoking history, *n* (%)	31 (19.5)	36 (21.6)	0.645
DM, *n* (%)	87 (54.7)	61 (36.5)	0.001
CVD, *n* (%)	45 (28.3)	32 (19.2)	0.052
Statin, *n* (%)	49 (30.8)	37 (22.2)	0.076
RAASI, *n* (%)	100 (62.9)	96 (57.5)	0.319
Clinical parameters			
Systolic BP (mm Hg)	137.5 ± 17.2	137.7 ± 17.2	0.925
baPWV (m/s)	16.3 ± 3.2	15.6 ± 2.8	0.029
eGFR (ml/min per 1.73 m^2)	28.8 ± 14.5	28.9 ± 15.0	0.961
UPCR (g/g)	0.84 (0.30–2.01)	0.94 (0.32–3.15)	0.379
Albumin (g/dl)	3.6 ± 0.4	3.6 ± 0.5	0.570
Fasting glucose (mg/dl)	122 ± 38	119 ± 45	0.527
Total cholesterol (mg/dl)	172 ± 37	177 ± 44	0.298
Triglycerides (mg/dl)	168 ± 114	159 ± 115	0.506
hs-CRP (mg/l)	5.1 (1.7–10.6)	3.1 (1.1–8.9)	0.008
IL-6 (pg/ml)	3.81 (2.29–6.90)	3.25 (1.84–5.36)	0.051
TNF-α (pg/ml)	7.35 (4.97–9.92)	6.41 (4.56–8.97)	0.141
Leptin (ng/ml)	12.98 (7.54–25.03)	6.35 (2.66–12.27)	<0.001
Adiponectin (μg/ml)	4.44 (2.63–7.97)	6.89 (3.50–10.48)	0.001

baPWV, brachial-ankle pulse wave velocity; BF, body fat; BF%, body fat percentage; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LTI, lean tissue index; RAASI, renin-angiotensin-aldosterone system inhibitor; TNF-α, tumor necrosis factor-α; UPCR, urine protein creatinine ratio.

Diagnostic Performance of BMI

The relation between BMI and BF% is shown in Figure 1a. It is worth noting that patients with considerably different BMIs may have nearly identical BF%. A BMI ≥28 kg/m^2 had a moderately high specificity of 83.2% but a low sensitivity of 39.6% for detecting BF%-defined obesity. That is, regarding specificity, approximately 9% of all patients (8% of men and 11% of women) were incorrectly classified as obese using the BMI cutoff of 28 kg/m^2 and BF% as the gold standard for diagnosis (Table 3; Figure 1b and c, Quadrant II). Sensitivity was even worse. Approximately 29% of all patients (29% of men and 30% of women) had false-negative results when BMI was used (Table 3; Figure 1b and c, Quadrant IV).

Obesity and All-Cause Mortality

During a median follow-up time of 4.9 years, 40 patients reached the primary outcome. CV death occurred in 17 patients, whereas 23 deaths were due to non-CV causes. The most common causes of non-CV death included infection (*n* = 7), cancer (*n* = 4), and gastrointestinal bleeding (*n* = 4). Table 4 shows the

results of the multivariable Cox proportional hazard analyses for mortality in patients with BMI- or BF%-defined obesity, compared with the corresponding reference nonobese patients. In the fully adjusted models containing both BMI and BF%, obese patients according to BMI were associated with a significantly lower risk of death from any cause (HR: 0.23; 95% confidence interval: 0.07–0.71; *P* = 0.011). In contrast, obese patients according to BF% were associated with a significantly higher risk of mortality (HR: 2.75; 95% confidence interval: 1.28–5.89; *P* = 0.009).

Classification According to Both BMI and BF%

We further grouped the patients based on both the BMI and BF% cutoffs for obesity: group I (patients with BMI ≥28 kg/m^2 and BF% >25% for men or >35% for women), group II (patients with BMI ≥28 kg/m^2 and BF% ≤25% for men or ≤35% for women), group III (patients with BMI <28 kg/m^2 and BF% ≤25% for men or ≤35% for women), and group IV (patients with BMI <28 kg/m^2 and BF% >25% for men or >35% for women). The baseline characteristics of the 4 BMI/BF% combinations are presented in Table 5. The 4 groups significantly differed in body composition, age, number with diabetes, brachial-ankle pulse wave velocity, eGFR, fasting glucose, triglycerides, high-sensitivity C-reactive protein, and tumor necrosis factor-α. Moreover, patients in group IV were the oldest and had the lowest lean tissue index compared with the other 3 groups. The results of the multivariable Cox proportional hazard analyses of the 4 groups for mortality with group I as the reference are shown in Table 6. The HR was significantly greater for the group IV patients even after multivariable adjustment (HR: 5.11; 95% confidence interval: 1.43–18.26; *P* = 0.012).

Sensitivity Analyses

We performed a sensitivity analysis using the American Society of Bariatric Physicians definition of obesity (BF >25% in men and >32% in women) as the reference to test the robustness of our main results.[23] We found that characterizing BF% according to the American Society of Bariatric Physicians categories did not appear to affect BF% predictability for the primary outcome. Furthermore, a fully adjusted cubic spline model was used to test the mortality predictability of BMI or BF% as a continuous variable. Although high BMI is associated with decreased overall mortality in this cohort (Figure 2a), a J-shaped relationship between BF% and mortality was observed, with a value of approximately 10% representing the lowest risk and a trend toward an increased risk in patients with BF% higher than 10% (Figure 2b).
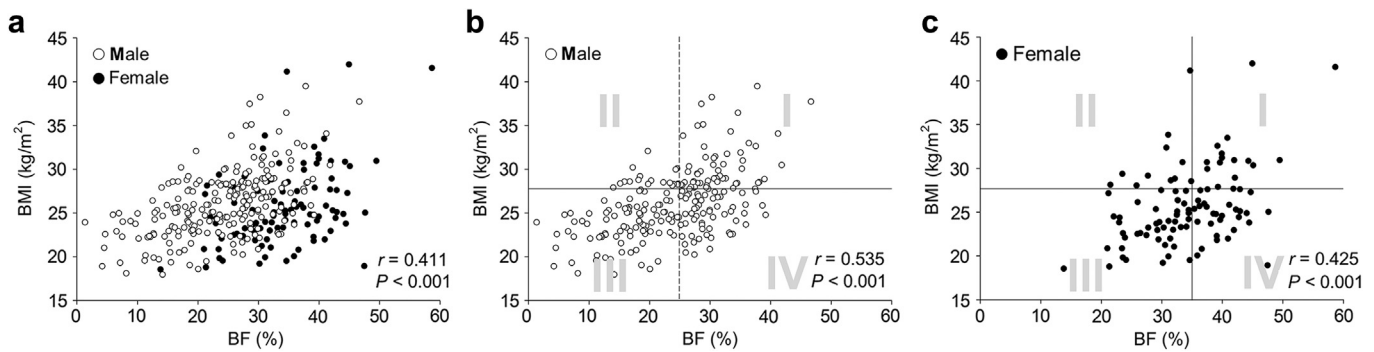
Figure 1. Relationship of BMI versus BF% among patients with overall non–dialysis-dependent CKD (a), men (b), and women (c). The horizontal line represents the cutoff for BMI-defined obesity and the vertical line represents the cutoffs for BF%-defined obesity. Patients who are above the horizontal line are obese according to the Working Group on Obesity in China criteria (BMI ≥28 kg/m^2). Patients who fall in quadrants I and IV are obese according to the World Health Organization criteria (BF >25% for men and >35% for women). Quadrant IV demonstrates CKD patients misclassified as "nonobese" by BMI yet "obese" by BF%. BF%, body fat percentage; BMI, body mass index; CKD, chronic kidney disease.

DISCUSSION

In this study of patients with non–dialysis-dependent CKD, we examined associations among BMI, BF%, and all-cause mortality. We found that both the prevalence and profile of BMI- or BF%-defined obesity were quite different. Compared with the corresponding patients without obesity, patients with BMI-defined obesity were younger and had more lean body mass, whereas patients with BF%-defined obesity were older and had less lean body mass. When both BMI and BF% were included in the same fully adjusted model, high BMI was protective, whereas high BF% was associated with increased all-cause mortality. Our findings suggest the importance of using direct measures of adiposity instead of BMI for assessing mortality risk in patients with CKD.

BMI has been used widely as a proxy for adiposity in epidemiological studies and clinical practice because of its simplicity. However, BMI is unable to distinguish between lean body mass and fat mass. In the adult general population from the Third National Health and Nutrition Examination Survey, a BMI cutoff of ≥30 kg/m^2 had high specificity but missed more than half of the people who had an excess of body fat.[24] Several studies also have

shown the good specificity but poor sensitivity of BMI toward detecting BF%-defined obesity among patients with coronary heart disease,[25,26] congestive heart failure,[27] and cancer.[28] These results suggest that BMI may be an inappropriate surrogate for adiposity, and this limitation may help to explain the unexpectedly better survival of obese patients.

The misclassification of obesity according to the use of BMI or BF% also was seen among patients with CKD with or without dialysis. A discordance in obesity according to BMI and BF% was found across eGFR categories in the adult National Health and Nutrition Examination Survey 1999–2004 participants, in whom DEXA was performed.[29] Underestimation of obesity by BMI compared with BF% by DEXA progressively increased with declining eGFR (P for trend <0.001) and was highly likely among obese participants with sarcopenia (97.7% misclassified as nonobese by BMI). In a recent study, Agarwal et al.[30] showed that the prevalence of obesity among patients with non–dialysis-dependent CKD increased from 65%, as defined by BMI, to 90% when applying the gold standard of BF%. Misclassification of obese patients defined by BF% as nonobese according to BMI was also observed in both patients with incident and prevalent dialysis-dependent CKD from Sweden.[31] From their findings, 25% of patients with non–dialysis-dependent and 55% of dialysis-dependent CKD were obese in the context of a normal BMI.[30,31] These patients with so-called "subclinical obesity" were characterized because they had low lean body masses. The findings of our longitudinal follow-up study provide strong support for the view that this misclassification would introduce bias into studies that estimate the effects of obesity on health outcomes in CKD.

Muscle wasting, commonly seen in patients with CKD, might interfere with the diagnostic performance of BMI to identify obesity. Sarcopenia, defined by loss

Table 3. Discordant classification of obesity according to BMI and BF% in patients with CKD

Patient group	Male n = 224	Female n = 102	Total n = 326
Concordant, n (%)			
Group I: BMI obese, BF% obese	49 (22)	14 (14)	63 (19)
Group III: BMI nonobese, BF% nonobese	93 (41)	46 (45)	139 (43)
Discordant, n (%)			
Group II: BMI obese, BF% nonobese	17 (8)	11 (11)	28 (9)
Group IV: BMI nonobese, BF% obese	65 (29)	31 (30)	96 (29)

BF%, body fat percentage; BMI, body mass index.
Group I: patients with BMI ≥28 kg/m^2 and BF% >25% for men or >35% for women.
Group II: patients with BMI ≥28 kg/m^2 and BF% ≤25% for men or ≤35% for women.
Group III: patients with BMI <28 kg/m^2 and BF% ≤25% for men or ≤35% for women.
Group IV: patients with BMI <28 kg/m^2 and BF% >25% for men or >35% for women.

Table 4. Multivariable Cox proportional hazards analysis for the relative risk of all-cause mortality calculated for obesity or not defined by BMI ($\geq$28 kg/m^2) or BF% (>25% for men or >35% for women)

	Unadjusted		Model 1		Model 2	
Characteristics	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
BMI-defined						
Nonobese	1		1		1	
Obese	0.26 (0.09–0.74)	0.012	0.32 (0.11–0.92)	0.034	0.23 (0.07–0.71)	0.011
BF%-defined						
Nonobese	1		1		1	
Obese	1.93 (1.01–3.71)	0.047	1.55 (0.79–3.02)	0.20	2.75 (1.28–5.89)	0.009

BF%, body fat percentage; BMI, body mass index; CI, confidence interval; HR, hazard ratio.
Model 1 is adjusted for age and sex. Model 2 is adjusted for the Model 1 variables and for diabetes mellitus, cardiovascular disease, estimated glomerular filtration rate, urine protein creatinine ratio, high-sensitivity C-reactive protein, and BMI or BF%.

of both muscle mass and muscle function (strength or performance),[32] is prevalent among patients with all stages of CKD. Foley *et al.*[33] found increasing prevalence of sarcopenia with lower eGFR in adult participants in the Third National Health and Nutrition Examination Survey who underwent bioimpedance studies. Among patients with end-stage renal disease on dialysis, recent studies have reported that the prevalence of sarcopenia or muscle wasting ranged from 20.0% to 42.5%,[34–36] which is significantly

higher than in the healthy population. Many explanations for the obesity paradox in CKD have been proposed.[37] Recently, we have shown that increasing BMI may more closely reflect higher lean body mass that is associated with better survival in patients with CKD.[38] Because the high prevalence of muscle wasting may have an impact on mortality among patients with CKD, we hypothesized that the misclassification of patients with excess BF as nonobese by BMI may potentially explain the obesity paradox in CKD because

Table 5. Characteristics of the patient group defined using the combination of BMI- and BF%-defined obesity

	Group I	Group II	Group III	Group IV	
Characteristics	n = 63	n = 28	n = 139	n = 96	P
Body composition					
BMI (kg/m^2)	31.3 ± 3.3	29.7 ± 2.7	23.3 ± 2.4	24.9 ± 2.2	<0.001
BF (%)	34.3 ± 6.8	24.3 ± 5.9	20.4 ± 7.9	33.2 ± 6.0	<0.001
LTI (kg/m^2)	15.7 ± 2.9	18.7 ± 2.6	16.1 ± 2.8	12.8 ± 2.4	<0.001
Demographics					
Age (yr)	63.1 ± 13.7	56.7 ± 13.1	64.2 ± 12.5	72.5 ± 11.4	<0.001
Male sex, n (%)	49 (77.8)	17 (60.7)	93 (66.9)	65 (67.7)	0.321
Smoking history, n (%)	14 (22.2)	5 (17.9)	31 (22.3)	17 (17.7)	0.809
DM, n (%)	43 (68.3)	15 (53.6)	46 (33.1)	44 (45.8)	<0.001
CVD, n (%)	18 (28.6)	5 (17.9)	27 (19.4)	27 (28.1)	0.283
Clinical parameters					
Systolic BP (mm Hg)	139.8 ± 18.2	140.9 ± 16.0	137.1 ± 17.4	136.1 ± 16.4	0.407
baPWV (m/s)	15.6 ± 3.8	14.8 ± 2.8	15.8 ± 2.8	16.9 ± 2.7	0.003
eGFR (ml/min per 1.73 m^2)	32.5 ± 15.6	32.1 ± 12.8	28.2 ± 15.3	26.3 ± 13.2	0.039
UPCR (g/g)	0.82 (0.33–2.45)	2.27 (0.29–5.17)	0.91 (0.32–2.25)	0.84 (0.30–1.81)	0.404
Albumin (g/dl)	3.6 ± 0.4	3.5 ± 0.5	3.6 ± 0.5	3.6 ± 0.4	0.641
Fasting glucose (mg/dl)	130 ± 46	140 ± 51	115 ± 42	117 ± 31	0.005
Total cholesterol (mg/dl)	170 ± 35	187 ± 54	175 ± 41	174 ± 38	0.372
Triglycerides (mg/dl)	189 ± 145	222 ± 180	147 ± 93	154 ± 85	0.003
hs-CRP (mg/l)	5.4 (2.2–12.6)	3.9 (1.9–8.9)	3.0 (1.0–8.9)	4.5 (1.7–10.6)	0.034
IL-6 (pg/ml)	3.55 (1.97–5.10)	3.77 (2.10–5.08)	3.21 (1.73–5.74)	3.91 (2.33–8.36)	0.126
TNF-α (pg/ml)	6.22 (3.93–8.81)	6.07 (4.59–8.91)	6.53 (4.54–8.97)	7.79 (5.55–10.22)	0.028
Leptin (ng/ml)	20.5 (9.7–38.6)	12.6 (7.5–23.8)	5.8 (2.6–12.3)	11.2 (6.1–17.6)	<0.001
Adiponectin (μg/ml)	4.67 (2.72–9.38)	3.95 (2.34–8.47)	6.04 (2.89–9.25)	5.73 (3.26–8.82)	0.531

baPWV, brachial-ankle pulse wave velocity; BF, body fat; BF%, body fat percentage; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LTI, lean tissue index; TNF-α, tumor necrosis factor α; UPCR, urine protein creatinine ratio.
Group I: patients with BMI $\geq$28 kg/m^2 and BF% >25% for men or >35% for women.
Group II: patients with BMI $\geq$28 kg/m^2 and BF% $\leq$25% for men or $\leq$35% for women.
Group III: patients with BMI <28 kg/m^2 and BF% $\leq$25% for men or $\leq$35% for women.
Group IV: patients with BMI <28 kg/m^2 and BF% >25% for men or >35% for women.

Table 6. Multivariable Cox proportional hazards analysis for the relative risk of all-cause mortality calculated for patient groups defined using the combination of BMI and BF%.

Patient group	Unadjusted		Model 1		Model 2	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Group I	1		1		1	
Group II	0.89 (0.09–8.53)	0.917	1.04 (0.11–10.19)	0.975	0.86 (0.09–8.70)	0.901
Group III	2.19 (0.62–7.69)	0.223	2.15 (0.61–7.58)	0.234	2.47 (0.68–9.01)	0.170
Group IV	6.06 (1.81–20.30)	0.003	4.61 (1.36–15.71)	0.014	5.11 (1.43–18.26)	0.012

BF, body fat; BMI, body mass index; CI, confidence interval; HR, hazard ratio.
Model 1 is adjusted for age and sex. Model 2 is adjusted for the Model 1 variables and for diabetes mellitus, cardiovascular disease, estimated glomerular filtration rate, urine protein creatinine ratio, and high-sensitivity C-reactive protein.
Group I: patients with BMI ≥28 kg/m^2 and BF% >25% for male or >35% for female.
Group II: patients with BMI ≥28 kg/m^2 and BF% ≤25% for male or ≤35% for female.
Group III: patients with BMI <28 kg/m^2 and BF% ≤25% for male or ≤35% for female.
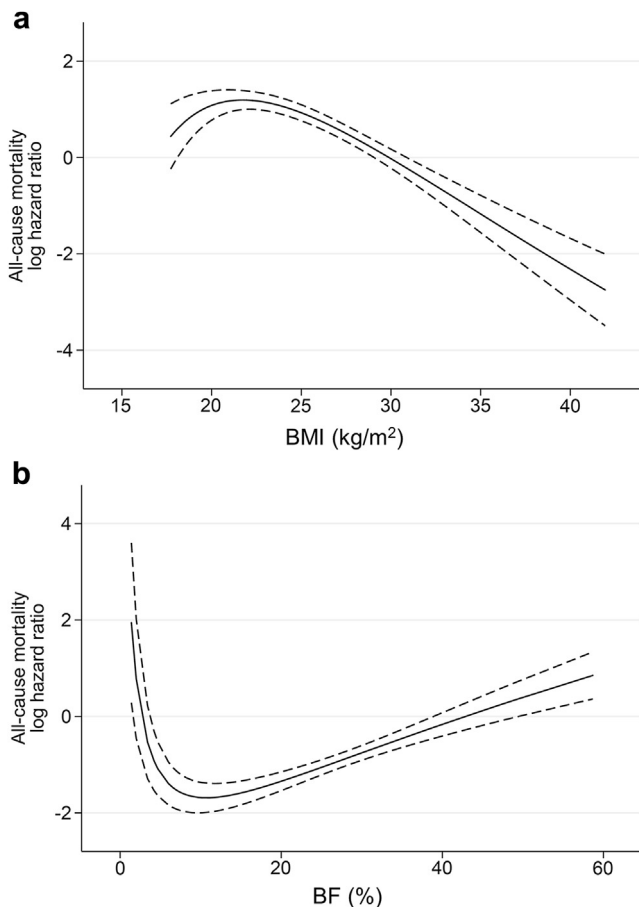Group IV: patients with BMI <28 kg/m^2 and BF% >25% for male or >35% for female.

these "misclassified" patients had normal or low BMIs due to decreased lean body mass, which was associated with increased mortality.

An observational cohort study of 54,420 participants aged 40 years and older who were referred for bone

Figure 2. Relationship of adjusted log hazard ratio of all-cause mortality with BMI (a) or BF% (b). The solid line is the restricted cubic spline fit, and the dotted lines are the 95% confidence intervals. Spline models contain 3 degrees of freedom. Models are adjusted for age, gender, diabetes, cardiovascular disease, estimated glomerular filtration rate, urine protein creatinine ratio, high-sensitivity C-reactive protein, and BF% (for BMI) or BMI (for BF%). BF%, body fat percentage; BMI, body mass index.

mineral density testing showed that low BMI and high BF% by DEXA were independently associated with increased mortality.[39] In our study, obesity defined by BMI was associated with a decreased risk of death, but the relationship was reversed when obesity was defined by BF%. Moreover, when we classified the patients into 4 subgroups according to both BMI- and BF%-defined obesity cutoffs, a considerable proportion of patients (29.4%) had excess BF but a normal or low BMI. These patients with "subclinical obesity" had the worst survival among the 4 subgroups. These findings might help clarify the counterintuitive association between higher BMI and lower mortality among patients with CKD.

Some limitations of our study should be acknowledged. First, BMI and BF% were measured only once at baseline. Observed associations between a baseline body composition and long-term outcomes might be susceptible to time-varying biases and reverse causation.[40] Second, although the definition of BF >25% in men and >35% in women proposed by WHO was used as the gold standard to determine the diagnostic performance of BMI in the present study, there is still no consensus on the most appropriate BF% ranges. However, analyzing BF% according to the American Society of Bariatric Physicians rather than the WHO categories did not appear to affect our results. In addition, HR for death in the fully adjusted cubic spline model increased progressively with increasing BF% >10%. Third, whereas DEXA is one of the most widely accepted methods used to directly assess body composition, we measured the BF% using the BCM. Recently, Lim *et al.*[21] showed that the BCM yielded accurate estimates of the total BF mass when validated against DEXA in Taiwanese patients with end-stage renal disease on maintenance hemodialysis. Hence, the BCM correlated well with DEXA and may provide a more accessible tool for early diagnosis of obesity in patients with CKD. Fourth, dietary and physical activity details of the study participants were not

assessed. Further studies should be carried out to identify whether these factors may modify the observed associations. Finally, racial differences may have some influence on body composition and its association with outcomes, so the results of this study should be extrapolated with caution.

In conclusion, BMI is an indirect and imperfect measure of adiposity. The diagnostic discrepancy between BMI and BF% for obesity diagnoses among patients with non–dialysis-dependent CKD may help explain the obesity paradox, because a considerable number of patients with sarcopenic obesity will be misclassified into the normal adiposity group when BMI is used. Our findings underscore the importance of a proper diagnosis of obesity for both risk prediction and therapy in CKD.

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