Effects of Body Size and Body Composition on Survival in Hemodialysis Patients

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Abstract. It is unclear whether increased muscle mass or body fat confer the survival advantage in hemodialysis patients with high body-mass index (BMI). Twenty-four-hour urinary creatinine (UCr) excretion was used as a measure of muscle mass. The outcomes of hemodialysis patients with high BMI and normal or high muscle mass (inferred low body fat) and high BMI and low muscle mass (inferred high body fat) were studied to study the effects of body composition on outcomes. In 70,028 patients who initiated hemodialysis in the United States from January 1995 to December 1999 with measured creatinine clearances reported in the Medical Evidence form, all-cause and cardiovascular mortality were examined in Cox and parametric survival models. When compared with normal BMI (18.5 to 24.9 kg/m^2) group, patients with high BMI ($\geq$25 kg/m^2) had lower hazard of death (hazard ratio [HR], 0.85; $P < 0.001$). However, when compared with normal BMI patients with UCr >25th percentile (0.55 g/d), high BMI patients with UCr >0.55 g/d had lower hazard of all-cause (HR, 0.85; $P < 0.001$) and cardiovascular death (HR, 0.89; $P < 0.001$), and high BMI patients with UCr $\leq$0.55 g/d had higher hazard of all-cause death (HR, 1.14; $P < 0.001$) and cardiovascular death (HR, 1.19; $P < 0.001$). Both BMI and body composition are strong predictors of death. The protective effect conferred by high BMI is limited to those patients with normal or high muscle mass. High BMI patients with inferred high body fat have increased and not decreased mortality.

Cardiac disease is the primary cause of morbidity and mortality in the dialysis population. In contrast to the general population, higher body-mass index (BMI) is associated with better outcomes in dialysis patients (1–8). This has been suggested as a risk factor paradox or reverse epidemiology for cardiovascular disease in uremic patients (9–11). Because BMI does not differentiate between muscle mass and adipose tissue, the proper interpretation of the findings of prior studies might be that the effects of obesity on outcomes in dialysis patients are unknown. Radiologic imaging techniques such as dual-energy x-ray absorptiometry could be used to determine muscle mass and adipose tissue content, but these techniques are expensive.

We propose that because high BMI might result from either increased fat or muscle, high BMI patients with low muscle mass could be inferred to have high body fat. Thus, the outcomes of high BMI and normal or high muscle mass (low body fat) patients and high BMI and low muscle mass (high body fat) patients could be compared against patients with normal BMI to examine the effects of body composition on outcomes. In this study, BMI in conjunction with 24-h urinary creatinine (UCr) excretion (a measure of muscle mass) at initiation of dialysis in incident dialysis patients was used to estimate body composition and to examine the effects of estimated body composition on all-cause and cardiovascular mortality.

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Materials and Methods

Study Population

The Medical Evidence (Form 2728) form is the mandatory form gathered by the Centers for Medicare and Medicaid on patients who initiate chronic maintenance dialysis in the United States. Patients with creatinine clearances and serum creatinine reported in the Form 2728 from January 1, 1995, to December 31, 1999, were studied. Of these, patients with duplicate entries, previous renal replacement therapies, age <18 yr, and incomplete follow-up information were excluded. In addition, patients with missing data for serum albumin, height, and weight were excluded.

Data Assembly

The Form 2728 data on demographics (age, gender, and race), cause of end-stage renal disease (ESRD; diabetes or other), insurance status (Medicare or non-Medicare), comorbid conditions (coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, malignancy, AIDS, chronic lung disease), smoking, height, weight, and functional ability were used in this analysis (12). Medical Evidence form data for serum creatinine, serum albumin, and 24-h creatinine clearance were also used.

BMI (kg/m^2) was calculated from height and weight. Total daily UCr was calculated from serum creatinine level and reported 24-h creatinine clearance and considered indicative of creatinine production and muscle mass. Patients with BMI between 18.5 and 24.9 kg/m^2 were considered normal as per the National Heart, Lung, and Blood Institute (NHLBI) consensus statement (13). Patients with BMI

≥25 kg/m^2 were classified as high BMI group (13). High BMI group was further subclassified by the 25th percentile of UCr to identify patients with low muscle mass and high body fat within the high BMI group. Similarly, normal BMI group was further subclassified by the 25th percentile of UCr to identify patients with low muscle mass.

Follow-up duration, mortality, and transplantation data were obtained from the United States Renal Data System treatment history, claims, and patients files. Patients were tracked until loss to follow-up, transplantation, death, or the administrative censor date of December 31, 1999. All-cause and cardiovascular deaths were the outcomes of interest.

Statistical Analyses

Baseline characteristics of high and normal BMI groups and patients with UCr ≤25th percentile and >25th percentile within high BMI group were tested using a χ^2 test, one-way ANOVA, or Kruskal-Wallis rank-sum test.

All-cause and cardiovascular mortality of high BMI group was examined in relation to the normal BMI group adjusted for age, gender, race, Medicare insurance, comorbid conditions listed in Table 1, functional status, and serum albumin. To further examine the effects of body composition on outcomes, normal BMI and UCr >25th percentile group was used as the referent group, and the outcomes of other BMI and UCr groups were examined in multivariable models with covariate adjustment as above. Subgroup analyses by gender and race were also performed.

To examine the linearity in the association between mortality and BMI, separate multivariable models were fit for each BMI group using BMI as a continuous variable. In these analyses, high BMI (≥25 kg/m^2) patients were further classified as per the NHLBI guidelines as overweight (25.0 to 29.9 kg/m^2) and obese (≥ 30 kg/m^2).

The analysis of scaled Schoenfeld residuals indicated that BMI groups exhibited nonproportional hazard as described in prior studies (1); however, results of Cox and parametric proportional-odds models (14) were similar. Furthermore, because violations of proportionality assumption by BMI and body composition groups were not severe by graphical assessments, only the results of Cox models are reported.

Results

There were 70,028 patients who met the inclusion criteria. The mean age of the study population was 64.8 ± 14.2 yr, 48.1% were men, 66.6% were white, and 25.6% were African American. Diabetes was the cause of ESRD in 45.5%. The mean BMI was 26.4 ± 5.7 and 24-h UCr excretion was 0.8 ± 0.4 g/d. There were 29,962 all-cause deaths (42.8%) and

Table 1. Baseline patient characteristics by body mass index (BMI) groups (N = 70,028)[a]

Characteristic	Normal BMI (n = 34,046)	High BMI (n = 35,982)
Age, mean ± SD (yr)	66 ± 15.0	64 ± 13.3
Male gender, *n* (%)	18,106 (53)	15,582 (43)
Race, *n* (%)		
white	23,231 (68)	23,431 (65)
African American	7891 (23)	10,033 (28)
other	2924 (9)	2518 (7)
Medicare insurance, *n* (%)	22,043 (65)	21,179 (59)
Comorbid condition, *n* (%)		
diabetes as cause of renal failure	13,057 (38)	18,795 (52)
coronary artery disease	11,727 (34)	11,630 (32)
cerebrovascular accident	4123 (12)	3677 (10)
peripheral vascular disease	6783 (20)	6385 (18)
heart failure[b]	13,962 (41)	14,976 (42)
lung disease	3412 (10)	2713 (8)
cancer	2084 (6)	1713 (5)
current smoker	2334 (7)	1691 (5)
Functional status, *n* (%)		
requires assistance to transfer[b]	626 (2)	610 (2)
requires assistance to ambulate[b]	1819 (5)	1850 (5)
Nutritional parameters		
BMI, mean ± SD (kg/m^2)	22.0 ± 1.8	30.5 ± 4.9
weight (kg)	62.2 ± 9.2	82.9 ± 14.6
24-h urine creatinine (g/dl)	0.76 ± 0.35	0.86 ± 0.39
Serum albumin, mean ± SD (g/dl)	3.1 ± 0.7	3.2 ± 0.6
Outcome		
all-cause death	16,285 (48)	13,677 (38)
cardiovascular death	8388 (25)	7413 (21)

[a] Normal BMI, 18.5 ≤ BMI ≤ 24.9 kg/m^2; high BMI, ≥25.0 kg/m^2.
[b] Differences between groups were not significant ($P \geq 0.05$). For all other comparisons, $P < 0.05$.

15,801 cardiovascular deaths (22.6%) over 105,042 patient-years of follow-up.

Table 1 depicts the baseline clinical characteristics and outcomes for each BMI group. Compared with the normal BMI group, the high BMI group had higher prevalence of diabetes ($P < .001$) but lower prevalence of coronary artery disease ($P < .001$), cerebrovascular disease ($P < .001$), and peripheral vascular disease ($P < .001$) (Table 1). As reported in previous studies, the high BMI group had lower risk of death (HR, 0.85; 95% CI, 0.83 to 0.87) compared with the normal BMI group in a multivariable Cox model not adjusted for UCr but adjusted for other factors such as demographics, comorbidity, functional status, serum albumin, and dialysis modality (multivariable model not shown).

High BMI patients with low UCr (inferred high body fat) had increased baseline prevalence of atherosclerotic conditions and heart failure compared with high BMI patients with high UCr (inferred low body fat) (Table 2). In a multivariable Cox model, compared with the normal BMI group with UCr >0.55 g/d, high BMI patients with inferred low body fat had 15% lower hazard of all-cause and 11% lower hazard of cardiovascular death (Table 3). In contrast, the high BMI patients with inferred high body fat had 14% higher risk of all-cause and 19% higher risk of cardiovascular death (Table 3). Thus, the survival advantage of high BMI was confined to those with normal or high muscle mass. The results were consistently similar in subgroup analyses by gender and race (data not reported). Kaplan-Meier survival curves by BMI and body composition groups of all-cause and cardiovascular deaths are represented in Figures 1 and 2.

In multivariable models, a 5-kg/m^2 increase in BMI in the entire cohort was associated with a 5% lower hazard of death adjusted for 24-h UCr and other factors (Table 4), similar to the earlier finding of decreased hazard of death with high BMI adjusted for predialysis serum creatinine (2). However, a 5-kg/m^2 increase in BMI was associated with significantly lower hazard of death (13%, $P < 0.001$) among normal BMI patients, nonsignificant lower hazard of death (6%, $P = 0.10$) in overweight patients, and significantly higher hazard of death (4%, $P = 0.02$) in obese patients. In contrast, the associations of higher UCr with lower all-cause and cardiovascular mortality were consistent across the BMI groups.

Table 2. Baseline patient characteristics within high body-mass index (BMI) group by muscle mass ($n = 35,982$)[a]

Characteristic	High BMI (≥ 25 kg/m^2)	
	UCr >0.55 g/d ($n = 28,413$)	UCr ≤0.55 g/d ($n = 7569$)
Age, mean ± SD (yr)	62.7 ± 13.4	66.6 ± 12.6
Male gender, *n* (%)	13,315 (47)	2,267 (30)
Race, *n* (%)		
white	18,063 (64)	5368 (71)
African American	8327 (29)	1706 (23)
other	2023 (7)	495 (7)
Medicare insurance, *n* (%)	16,149 (57)	5031 (66)
Comorbid condition		
diabetes as cause of renal failure,[b] *n* (%)	14,785 (52)	4010 (53)
coronary artery disease, *n* (%)	8840 (31)	2790 (37)
cerebrovascular accident, *n* (%)	2799 (10)	878 (12)
peripheral vascular disease, *n* (%)	4855 (17)	1530 (20)
heart failure, *n* (%)	11,305 (40)	3671 (49)
lung disease, *n* (%)	2052 (7)	661 (9)
cancer,[b] *n* (%)	1345 (5)	368 (5)
current smoker, *n* (%)	1305 (5)	286 (4)
Functional status, *n* (%)		
requires assistance to transfer	381 (1)	229 (3)
requires assistance to ambulate	1212 (4)	628 (8)
Nutritional parameters		
BMI, mean ± SD (kg/m^2)	30.5 ± 4.9	30.3 ± 4.9
24-h urine creatinine (g/d)	0.98 ± 0.35	0.41 ± 0.10
serum albumin, mean ± SD (g/dl)	3.2 ± 0.6	3.0 ± 0.7
Outcome		
all-cause death	9961 (35)	3716 (49)
cardiovascular death	5408 (19)	2005 (26)

[a] UCr, urinary creatinine.
[b] Differences between groups were not significant ($P \geq 0.05$). For all other comparisons, $P < 0.05$.

Table 3. Multivariable Cox regression models of all-cause death and cardiovascular death ($N = 70,028$)[a]

Characteristic	All-Cause Death		Cardiovascular Death	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Body composition group				
normal BMI and UCr >0.55 g/d	Reference		Reference	
high BMI and UCr >0.55 g/d	0.85	0.83 to 0.87	0.89	0.86 to 0.93
high BMI and UCr ≤0.55 g/d	1.14	1.10 to 1.18	1.19	1.13 to 1.26
normal BMI and UCr ≤.55 g/d	1.24	1.20 to 1.29	1.28	1.22 to 1.34
Age (per 10 yr older)	1.34	1.33 to 1.36	1.33	1.31 to 1.36
Male gender	1.09	1.06 to 1.11	1.11	1.07 to 1.14
Race				
African American *versus* white	0.82	0.79 to 0.84	0.81	0.77 to 0.84
other *versus* white	0.80	0.76 to 0.83	0.81	0.76 to 0.86
Medicare insurance	1.14	1.10 to 1.17	1.19	1.14 to 1.25
Diabetes as cause of renal failure	1.05	1.02 to 1.07	1.12	1.08 to 1.15
Coronary artery disease	1.14	1.1.1 to 1.17	1.28	1.23 to 1.32
Heart failure	1.23	1.20 to 1.26	1.37	1.32 to 1.42
Cerebrovascular accident	1.13	1.09 to 1.17	1.12	1.08 to 1.15
Peripheral vascular disease	1.11	1.08 to 1.14	1.16	1.11 to 1.20
Lung disease	1.17	1.13 to 1.22	1.11	1.06 to 1.17
AIDS	2.75	2.40 to 3.15	1.54	1.18 to 2.00
Current smoker	1.05	1.00 to 1.11	0.97	0.90 to 1.05
Cancer	1.31	1.26 to 1.37	0.98	0.91 to 1.05
Requires assistance to transfer	1.34	1.23 to 1.45	1.23	1.10 to 1.38
Requires assistance to ambulate	1.40	1.33 to 1.47	1.38	1.29 to 1.48
Serum albumin (per 1.0 g/dl higher)	0.78	0.76 to 0.79	0.84	0.82 to 0.86

[a] BMI, body-mass index; UCr, urinary creatinine. Normal BMI indicates 18.5 to 24.9 kg/m^2; high BMI, ≥25 kg/m^2.

Discussion

Cardiovascular disease is the leading cause of death in patients undergoing maintenance hemodialysis and accounts for nearly half of deaths. The US ESRD population is anticipated to double in the next decade, mostly as a result of the increasing incidence of ESRD in the elderly and in patients with diabetes. Because the elderly and patients with diabetes are at high risk of cardiovascular disease, the morbidity and mortality associated with cardiovascular disease in the ESRD population will remain high. Therefore, understanding the risk factors for cardiovascular disease in ESRD is of paramount importance.

In a cross-sectional analysis of the HEMO Study, the prevalence of cardiovascular disease in dialysis patients far exceeded that in the general population and could not be readily explained by conventional cardiovascular risk factors (15). Dialysis patients have a tenfold increased risk of cardiovascular death compared with the general population, adjusted for age, gender, race, and diabetes (16). In a longitudinal analysis of 8600 patients who underwent cardiac catheterization, Beddhu *et al.* (17) showed that even moderate renal failure was associated with increased risk of subsequent myocardial infarction and death independent of underlying angiographic evidence of coronary disease, the choice of therapy for coronary disease, and other clinical characteristics. These studies support the hypothesis that uremia *per se* is an atherogenic milieu.

Nonetheless, these studies should not be interpreted as conventional cardiovascular risk factors are unimportant in patients with renal failure. The BMI paradox in dialysis patients is one of the often-quoted reasons that the conventional cardiovascular risk factors do not apply to ESRD patients. Leavey *et al.* (1) examined the United States Renal Data System Case Mix Adequacy special study and found that the effect of a high BMI on mortality risk in hemodialysis patients to be opposite that reported for healthy adults. In another study of 1346 hemodialysis patients, compared with normal-weight patients (BMI 20 to 27.5 kg/m^2), the 1-yr survival was significantly better in overweight patients (BMI >27.5 kg/m^2) and worse in underweight patients (BMI <20 kg/m^2) (4). Kopple *et al.* and others have found consistently similar results in several other studies (2,5–6,18–20). These data have raised the question whether obesity confers a survival advantage in dialysis patients: in this patient population, is it good to be fat? (21).

In this study, longitudinal analyses confirmed that high BMI was associated with lower risk of all-cause and cardiovascular death as reported in earlier studies. Nonetheless, BMI does not differentiate between fat and muscle. We used creatinine production as a marker of muscle mass and differentiated between

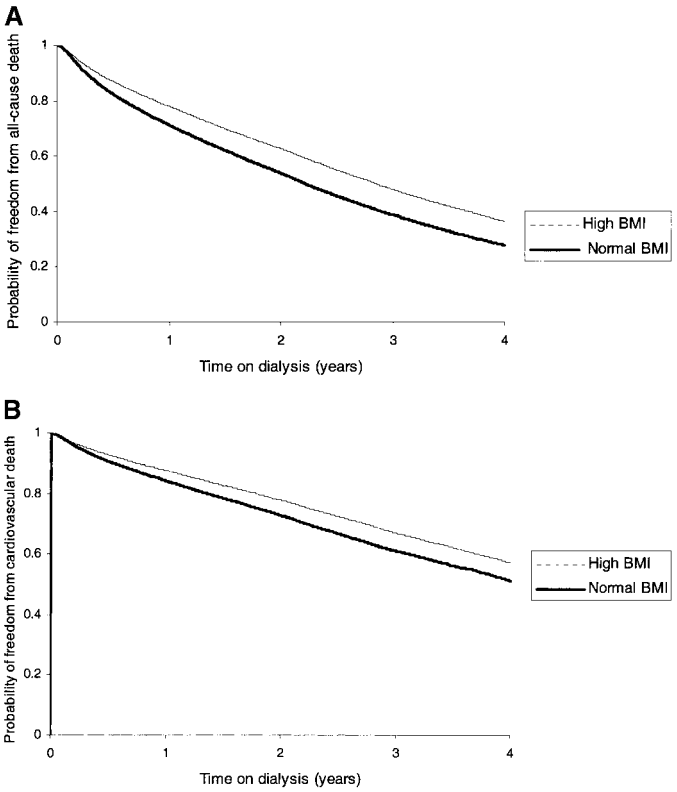

Figure 1. Kaplan-Meier curves for (a) all-cause death and (b) cardiovascular death by normal (18.5 to 24.9 kg/m^2) and high ($\geq$ 25 kg/m^2) body-mass index (BMI) groups.

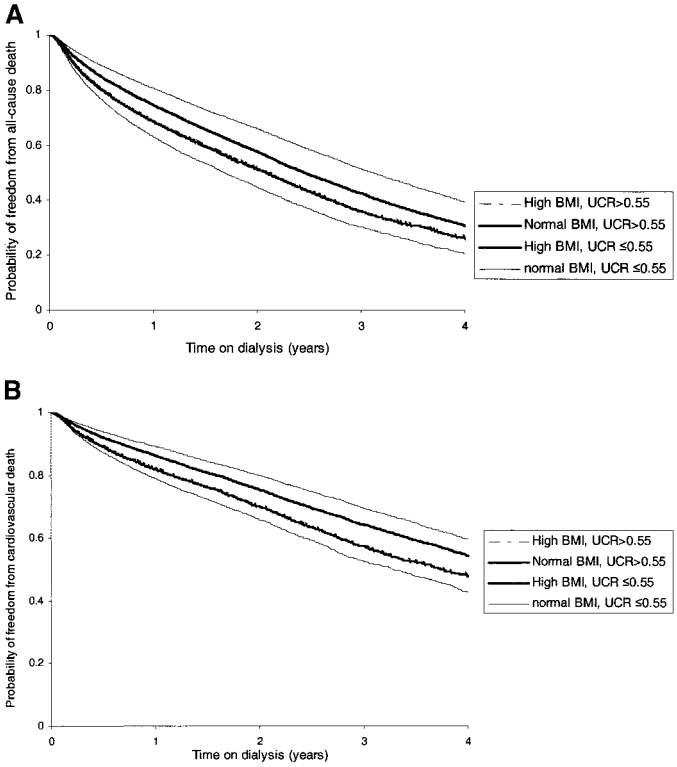

Figure 2. Kaplan-Meier curves for (a) all-cause death and (b) cardiovascular death by body composition groups. Body-mass index (BMI) is categorized as normal (18.5 to 24.9 kg/m^2) and high ($\geq$25 kg/m^2). UCr, 24-h urine creatinine (g/d).

body fat and muscle mass. At baseline, high BMI patients with inferred high body fat had higher prevalence of atherosclerotic conditions such as coronary, cerebral, and peripheral vascular diseases (Table 2). The survival advantage conferred by high BMI compared with normal BMI patients was limited to those with normal or high muscle mass (low body fat), and those high BMI patients with inferred high body fat had increased risk of death (Table 3). These data suggest that obesity is associated with increased prevalence of atherosclerotic conditions at initiation of dialysis and long-term risk of all-cause and cardiovascular death in dialysis patients. Thus, the traditional risk factors for cardiovascular disease such as obesity might be relevant in the ESRD population.

Our data also show that body size is a predictor of death. Within both low and high UCr groups, patients with higher BMI had better survival (Figure 2). However, as noted in Table 4, the association of BMI with hazard of death was not the same within normal, overweight, and obese groups. Therefore, these data do not support a consistent inverse relationship between BMI and mortality. These results are also supported by a recent observation of a J-shaped association of BMI with mortality by Lowrie *et al.* (22).

There are several issues regarding the reliability of 24-h UCr. First, it has been suggested that as much as two-thirds of total daily creatinine excretion can occur by extrarenal excretion in patients with advanced renal failure (23). In a study by Nielsen *et al.* (24), in 30 predialysis patients with creatinine clearances $<$ 30 ml/min, lean body mass (LBM) estimated from 24-h UCr corrected for extrarenal creatinine excretion and LBM measured by dual-energy x-ray absorptiometry were 44.8 and 47.8 kg, respectively ($P < .001$). Thus, 24-h UCr was not an accurate quantitative measure of muscle mass. However, analysis of a scatter plot of estimated and measured LBM in predialysis patients revealed that the higher the estimated LBM, the higher the measured LBM was, indicating that 24-h UCr was a qualitative measure of muscle mass. The authors concluded, "In predialysis patients creatinine recovery is inaccurate in estimating the lean body mass, but might be a precise estimate of muscle mass and, in this respect, an important tool in the evaluation of nutritional status." We would also suggest that recalibration in patients with advanced renal failure of the formula that was used in the Nielsen study to calculate muscle mass from 24-h UCr might result in more accurate quantification of muscle mass from 24-h UCr in advanced renal failure.

Second, sicker patients might not have accurately collected 24-h urine. However, as shown in our earlier study, patients in the lowest compared with the highest 24-h UCr quartile had lower measured serum creatinine at initiation of dialysis (25). Inability to collect adequate 24-h UCr in sicker patients should not result in lower measured serum creatinine. On the other hand, loss of muscle mass in sicker patients with consequent lower creatinine production would result in lower measured serum creatinine and 24-h UCr. Third, a temporary lower meat intake due to intercurrent illnesses at the time of 24-h urinary

Table 4. Multivariable Cox regression models of all-cause death and cardiovascular death with body-mass index (BMI) and urinary creatinine (UCr) as continuous variables in the entire cohort and in BMI subgroups[a]

Model	All-Cause Death		Cardiovascular Death	
	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
All patients (n = 70,028)				
each 5 kg/m^2 increase in BMI	0.95 (0.93 to 0.96)	<0.001	0.95 (0.94 to 0.97)	<0.001
each g/d increase in UCr	0.68 (0.65 to 0.70)	<0.001	0.67 (0.64 to 0.71)	<0.001
18.5 ≤BMI <25 (n = 34,046)				
each 5 kg/m^2 increase in BMI	0.87 (0.83 to 0.91)	<0.001	0.91 (0.85 to 0.96)	0.001
each g/d increase in UCr	0.70 (0.66 to 0.74)	<0.001	0.68 (0.63 to 0.73)	<0.001
25 ≤BMI <30 (n = 20,598)				
each 5 kg/m^2 increase in BMI	0.94 (0.87 to 1.01)	0.097	0.90 to 0.81 to 1.00)	0.055
each g/d increase in UCr	0.68 (0.63 to 0.73)	<0.001	0.67 (0.61 to 0.74)	<0.001
BMI ≥30 (n = 15,384)				
each 5 kg/m^2 increase in BMI	1.04 (1.01 to 1.07)	0.021	1.02 (0.98 to 1.07)	0.317
each g/d increase in UCr	0.67 (0.62 to 0.73)	<0.001	0.69 (0.62 to 0.78)	<0.001

[a] Each model adjusted for age, gender, race, Medicare insurance, comorbid condition, functional status, and serum albumin levels.

collection but without actual loss of muscle mass would result in falsely low UCr, but one would not expect temporary lower meat intake at the time of 24-h urine collection to influence outcomes for 4 yr, as evident from the Kaplan-Meier plots.

Fourth, our earlier data suggested that 24-h UCr excretion strongly correlated with malnutrition (25). These findings in incident dialysis patients were similar to the earlier findings by Ohkawa *et al.* (26) that malnutrition strongly correlated with thigh muscle mass quantified by computed tomography and creatinine production (determined from the sum of creatinine present in the spent dialysate and estimated metabolic degradation) in anuric hemodialysis patients. Therefore, even in patients with advanced renal failure, 24-h UCr excretion is likely a reliable qualitative measure of muscle mass and creatinine generation.

Finally, the possibility that the creatinine clearances reported in Form 2728 were not actually measured but calculated from Cockcroft-Gault or Modification of Diet in Renal Diseases (MDRD) equations needs to be considered. Our earlier analysis of mortality and the estimated GFR at initiation of dialysis showed divergent results for GFR estimated from MDRD or Cockcroft-Gault equations compared with those creatinine clearances reported in Form 2728 (27). These results would not be divergent if the creatinine clearances reported in Form 2728 were actually calculated from Cockcroft-Gault or MDRD equations.

There are several limitations to our study. First, as shown earlier, less than a third of patients initiated on dialysis had creatinine clearances reported (25). These patients were older, and they had more comorbidity and worse functional and nutritional status compared with those without reported creatinine clearances. However, the anticipated doubling of the US ESRD population over the next decade will primarily be the result of older patients with significant comorbidity. Therefore, the results of this study should be generalizable to a large proportion of the rapidly growing segment of the US ESRD population. Second, we acknowledge the lack of direct measurement of body fat in our study. Third, it could be argued that the excess of weight in high BMI patients with low muscle mass was not the result of fat but the result of increased water retention reflecting worse cardiac status. The difference in average weight between high and normal BMI groups (20.7 kg) was more than 50% of the estimated total body water of the normal BMI group (average total body weight, 62.2 kg). Therefore, it is unlikely that this magnitude of excess body weight was explained by water retention. Fourth, the limitations of this study include that of all observational studies that rely on existing databases.

In summary, we conclude that both body size and body composition are strong predictors of death in dialysis patients. Compared with normal BMI patients with normal or high muscle mass, the survival advantage conferred by high BMI in dialysis patients is limited to those with normal or high muscle mass. Furthermore, patients with high BMI and low muscle mass (inferred high body fat) have increased all-cause and cardiovascular mortality. Therefore, conventional cardiovascular risk factors might be relevant in the ESRD population, and further studies are warranted.

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