### Title
Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis




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# Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis[1–3]

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**ABSTRACT**

**Background:** Larger body size is associated with greater survival in maintenance hemodialysis (MHD) patients. It is not clear how lean body mass (LBM) and fat mass (FM) compare in their associations with survival across sex in these patients.

**Objective:** We examined the hypothesis that higher FM and LBM are associated with greater survival in MHD patents irrespective of sex.

**Design:** In 742 MHD patients, including 31% African Americans with a mean (±SD) age of 54 ± 15 y, we categorized men ($n$ = 391) and women ($n$ = 351) separately into 4 quartiles of near-infrared interactance–measured LBM and FM. Cox proportional hazards models estimated death hazard ratios (HRs) (and 95% CIs), and cubic spline models were used to examine associations with mortality over 5 y (2001–2006).

**Results:** After adjustment for case-mix and inflammatory markers, the highest quartiles of FM and LBM were associated with greater survival in women: HRs of 0.38 (95% CI: 0.20, 0.71) and 0.34 (95% CI: 0.17, 0.67), respectively (reference: first quartile). In men, the highest quartiles of FM and percentage FM (FM%) but not of LBM were associated with greater survival: HRs of 0.51 (95% CI: 0.27, 0.96), 0.45 (95% CI: 0.23, 0.88), and 1.17 (95% CI: 0.60, 2.27), respectively. Cubic spline analyses showed greater survival with higher FM% and higher "FM minus LBM percentiles" in both sexes, whereas a higher LBM was protective in women.

**Conclusions:** In MHD patients, higher FM in both sexes and higher LBM in women appear to be protective. The survival advantage of FM appears to be superior to that of LBM. Clinical trials to examine the outcomes of interventions that modify body composition in MHD patients are indicated. *Am J Clin Nutr* 2010;92:1060–70.

## INTRODUCTION

In persons with chronic kidney disease (CKD), studies that have examined the association between adiposity and outcomes have mostly focused on body mass index (BMI)—an imperfect measure of adiposity (1–3). BMI is not a good indicator of body composition, because it does not differentiate lean body mass (LBM) from fat mass (FM) (4). Body mass consists of FM and fat-free mass, including LBM. Women generally have less LBM and a greater proportion of FM than do men. LBM can serve as an indicator of muscle mass and somatic protein, whereas FM is more reflective of energy storage. Higher visceral FM may be associated with inflammation and adverse outcomes in both the general population (5) and in CKD patients (6), whereas higher muscle mass appears associated with better clinical outcomes, at least in the general population (7).

Comparisons of the mortality predictability of different body-composition compartments, including LBM and FM, have not been well studied in CKD patients, in whom a high BMI has been consistently shown to correlate with greater survival (8–11). To our knowledge, only a limited number of studies have examined the relative contributions of FM and LBM to clinical outcomes in CKD patients who undergo maintenance hemodialysis (MHD) (12, 13). Some of these studies have suggested that the protective effect of high BMI against mortality is related to higher FM (14–16). Ramkumar et al (17), however, suggested that the protective effect of BMI in the MHD population is mostly conferred to those patients with a higher LBM, and hence muscle mass, as determined indirectly on the basis of urine creatinine content. Huang et al (13) recently reported that low midarm muscle circumference (MAMC), a surrogate of LBM, and low triceps-skinfold thickness, an indicator of FM, were each associated with higher all-cause mortality in MHD patients. However, none of these studies compared these associations in men and women, separately. In the current study, we examined the association between LBM and FM, measured by near-infrared (NIR) interactance technology, with survival in a cohort of 742 MHD

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**TABLE 1**
Baseline demographic, clinical, and laboratory values in 742 maintenance hemodialysis patients at the start of the 5-y cohort study[1]

| | All ($n$ = 742) | Men ($n$ = 391) | Women ($n$ = 351) | $P$ value[2] |
|---|---|---|---|---|
| Age (y) | 54 ± 15[3] | 53 ± 15 | 55 ± 15 | 0.13 |
| Race (% African American) | 31 | 28 | 34 | 0.06 |
| Ethnicity (% Hispanic) | 52 | 54 | 49 | 0.17 |
| Primary insurance (% receiving Medicare) | 52 | 51 | 52 | 0.74 |
| Diabetes mellitus (%) | 53 | 51 | 56 | 0.19 |
| Marital status (% married) | 48 | 60 | 37 | <0.01 |
| Charlson comorbidity score | 1.9 ± 1.6 | 1.9 ± 1.6 | 1.8 ± 1.6 | 0.95 |
| BMI (kg/m$^2$) | 26.5 ± 5.8 | 25.3 ± 5.0 | 27.3 ± 6.4 | <0.01 |
| NIR interactance–measured body fat (%) | 26.4 ± 10.8 | 19.5 ± 18.1 | 34.1 ± 7.7 | <0.01 |
| NIR interactance–measured fat mass (kg) | 19.8 ± 11.5 | 15.3 ± 19.6 | 24.8 ± 11.4 | <0.01 |
| NIR interactance–measured LBM (kg) | 52.0 ± 10.9 | 58.6 ± 8.7 | 44.6 ± 8.0 | <0.01 |
| Triceps-skinfold thickness (mm) | 17.3 ± 9.5 | 12.9 ± 7.3 | 22.2 ± 9.9 | <0.01 |
| Biceps-skinfold thickness (mm) | 9.7 ± 7.8 | 7.3 ± 6.5 | 12.4 ± 8.2 | <0.01 |
| MAMC (cm) | 25.7 ± 4.3 | 26.3 ± 3.8 | 25.1 ± 4.8 | <0.01 |
| Dialysis vintage (mo) | 28 ± 26 | 27 ± 25 | 29 ± 26 | 0.95 |
| Dialysis dose, single pool (Kt/$V$) | 1.62 ± 0.30 | 1.53 ± 0.26 | 1.71 ± 0.31 | <0.01 |
| nPNA (kg/d) | 1.07 ± 0.22 | 1.09 ± 0.24 | 1.06 ± 0.22 | 0.10 |
| Serum albumin (mg/dL) | 3.90 ± 0.36 | 3.97 ± 0.37 | 3.82 ± 0.32 | <0.01 |
| Prealbumin (mg/dL) | 28.6 ± 9.5 | 29.6 ± 9.9 | 27.5 ± 9.0 | <0.01 |
| Creatinine (mg/dL) | 10.2 ± 3.2 | 10.9 ± 3.3 | 9.5 ± 2.9 | <0.01 |
| C-reactive protein (mg/L) | 5.6 ± 7.0 | 5.8 ± 7.7 | 5.4 ± 6.0 | <0.01 |
| IL-6 (pg/mL) | 11.7 ± 15.7 | 10.8 ± 12.2 | 11.8 ± 15.7 | <0.01 |
| TNF-α (pg/mL) | 8.6 ± 11.4 | 8.7 ± 12.4 | 8.5 ± 10.0 | <0.01 |

[1] NIR, near-infrared; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; LBM, lean body mass; MAMC, midarm muscle circumference; nPNA, total nitrogen appearance normalized to body weight; Kt/$V$, urea clearance over time.
[2] Independent-samples $t$ test for men compared with women.
[3] Mean ± SD (all such values).

patients. We hypothesized that larger FM and larger LBM are each associated with greater survival in MHD patents, irrespective of sex.

## SUBJECTS AND METHODS

### Patient population

We studied MHD patients who participated in the National Institutes of Health–sponsored Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study (14, 18–20). The original patient cohort was derived from a pool of ≈1300 MHD outpatients in 8 DaVita Inc, chronic dialysis facilities in the South Bay Los Angeles area (*see* the NIED Study website at www.NIEDStudy.org for more details). Inclusion criteria were outpatients who had been undergoing MHD for ≥8 wk, were ≥18 y of age, and signed a local Institutional Review Board approved consent form. Patients with an anticipated life expectancy of <6 mo (eg, due to metastatic malignancy or advanced HIV/AIDS disease) were excluded. From 1 October 2001 through 31 December 2006, 893 MHD patients signed the informed consent form and underwent the periodic evaluations of the NIED Study.

For these analyses, data including baseline biochemical and anthropometrical measurements were available in 742 MHD patients. The medical chart of each MHD patient was thoroughly reviewed by a collaborating physician, and data pertaining to underlying kidney disease, cardiovascular history, and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index (ie, without the age and kidney disease components) was used to assess the severity of comorbidities

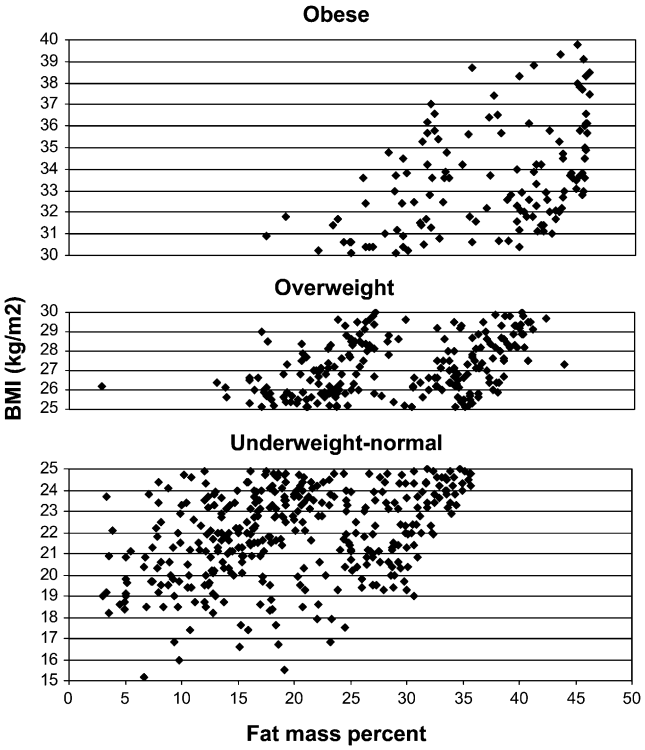


**FIGURE 1.** Misclassification of body fat by BMI, reflected by percentage total body fat estimated by near-infrared reactance in 742 maintenance hemodialysis patients across 3 different categories of BMI (in kg/m$^2$; <25, 25 to <30, and ≥30).

**TABLE 2**
Baseline demographic, clinical, and laboratory values in 391 male maintenance hemodialysis patients at the start of the 5-y cohort study, by lean body mass (LBM) quartile[1]

| | LBM quartile | | | | |
|---|---|---|---|---|---|
| Variables | 1 ($n$ = 100) | 2 ($n$ = 97) | 3 ($n$ = 98) | 4 ($n$ = 96) | $P$ for trend[2] |
| Age (y) | 54 ± 15[3] | 53 ± 15 | 53 ± 16 | 51 ± 13 | 0.07 |
| Race (% African American) | 9 | 14 | 31 | 57 | <0.01 |
| Ethnicity (% Hispanic) | 67 | 68 | 53 | 28 | <0.01 |
| Primary insurance (% receiving Medicare) | 47 | 42 | 54 | 60 | 0.06 |
| Diabetes mellitus (%) | 54 | 53 | 44 | 52 | 0.47 |
| Marital status (% married) | 59 | 59 | 63 | 47 | 0.18 |
| Charlson comorbidity score | 2.0 ± 1.5 | 1.8 ± 1.8 | 1.6 ± 1.5 | 2.0 ± 1.7 | 0.70 |
| BMI (kg/m$^2$) | 22.2 ± 3.1 | 23.6 ± 3.3 | 25.9 ± 4.1 | 29.7 ± 5.7 | <0.01 |
| Triceps-skinfold thickness (mm) | 10.7 ± 5.1 | 11.6 ± 5.5 | 12.3 ± 6.0 | 17.2 ± 10.6 | <0.01 |
| Biceps-skinfold thickness (mm) | 5.6 ± 3.8 | 6.1 ± 3.8 | 6.5 ± 4.0 | 10.8 ± 10.4 | <0.01 |
| MAMC (cm) | 23.7 ± 2.9 | 25.2 ± 3.0 | 26.7 ± 3.2 | 29.7 ± 3.1 | <0.01 |
| NIR interactance–measured body fat (%) | 17.1 ± 6.8 | 17.7 ± 6.3 | 19.6 ± 8.0 | 23.6 ± 9.4 | <0.01 |
| NIR interactance–measured fat mass (kg) | 10.4 ± 5.2 | 12.3 ± 5.3 | 15.7 ± 7.7 | 23.2 ± 12.8 | <0.01 |
| NIR interactance–measured LBM (kg) | 48.3 ± 3.4 | 55.1 ± 1.5 | 60.8 ± 1.9 | 70.6 ± 4.1 | <0.01 |
| Dialysis vintage (mo) | 25 ± 24 | 24 ± 23 | 24 ± 22 | 35 ± 28 | 0.01 |
| Dialysis dose, single pool (Kt/$V$) | 1.66 ± 0.28 | 1.55 ± 0.27 | 1.48 ± 0.20 | 1.44 ± 0.24 | <0.01 |
| nPNA (kg/d) | 1.13 ± 0.26 | 1.12 ± 0.23 | 1.08 ± 0.23 | 1.02 ± 0.23 | <0.01 |
| Serum albumin (mg/dL) | 3.96 ± 0.41 | 3.99 ± 0.38 | 4.00 ± 0.33 | 3.91 ± 0.32 | 0.20 |
| Prealbumin (mg/dL) | 28.9 ± 9.8 | 29.9 ± 10.9 | 29.7 ± 9.9 | 30.0 ± 9.0 | 0.65 |
| Creatinine (mg/dL) | 10.5 ± 3.2 | 10.5 ± 3.4 | 10.8 ± 3.2 | 11.9 ± 3.3 | <0.01 |
| C-reactive protein (mg/L) | 5.3 ± 5.5 | 5.2 ± 8.8 | 5.8 ± 6.1 | 6.7 ± 9.8 | 0.05 |
| IL-6 (pg/mL) | 11.4 ± 13.1 | 10.1 ± 9.9 | 9.2 ± 11.7 | 12.3 ± 13.5 | 0.49 |
| TNF-α (pg/mL) | 7.4 ± 5.9 | 8.7 ± 8.9 | 10.2 ± 17.2 | 8.7 ± 14.5 | 0.80 |

[1] NIR, near-infrared; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; MAMC, midarm muscle circumference; nPNA, total nitrogen appearance normalized to body weight; Kt/$V$, urea clearance over time.
[2] $P$ values for triceps- and biceps-skinfold thicknesses, dialysis dose (vintage), C-reactive protein, IL-6, and TNF-α are based on the logarithmic values of these measures (ANOVA).
[3] Mean ± SD (all such values).

(21, 22). The 742 MHD patients were followed for up to 63 mo, ie, until 31 December 2006.

### Anthropometric measures

Body weight assessment and anthropometric measurements were performed while patients were undergoing a hemodialysis treatment or within 5–20 min after termination of the treatment. Biceps-skinfold and triceps-skinfold thicknesses were measured with a conventional skinfold caliper by using standard techniques as previously described (23, 24). MAMC was calculated as indicated below (25):

$$\text{MAMC (cm)} = \text{midarm circumference (cm)} - \pi \times \text{triceps (cm)} \quad (1)$$

### Near-infrared interactance

To estimate percentage body fat and fat-free body mass in the main cohort, NIR interactance technology was used at baseline at the same time as the anthropometric measurements. A commercial NIR sensor with a CV of 0.5% for total body fat measurements (portable model 6100; Futrex, Gaithersburg, MD; www.futrex.com) was used. NIR measurements were performed by placing a Futrex sensor on the nonvascular access upper arm for several seconds and entering the required data (date of birth, sex, weight, and height) from each patient. NIR accuracy was validated previously (26, 27), including in our own studies (18, 28, 29).

### Laboratory tests

Predialysis blood samples and postdialysis serum urea nitrogen were obtained on a midweek day, which coincided chronologically with the drawing of quarterly blood samples in the DaVita clinics. The single-pool Kt/$V$ (urea clearance over time) was used to represent the weekly dialysis dose. Except as indicated below, all laboratory measurements were performed by DaVita Laboratories (Deland, FL) by using automated methods. For repeated measures (such as weekly or monthly blood tests), an average of all laboratory values taken during the first 3 mo of the 5-y period were used.

In addition, serum high-sensitivity C-reactive protein (CRP) was measured with a turbidometric immunoassay in which a serum sample is mixed with latex beads coated with anti-human CRP antibodies to form an insoluble aggregate (WPCI, Osaka, Japan; normal range: <3.0 mg/L) (19, 30). Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured with immunoassay kits based on a solid-phase sandwich enzyme-linked immunosorbent assay by using recombinant human IL-6 and TNF-α (R&D Systems, Minneapolis, MN; normal range: <9.9 pg/mL for IL-6 and <4.7 pg/mL for TNF-α) (31, 32). CRP and the

**TABLE 3**
Baseline demographic, clinical, and laboratory values in 391 male maintenance hemodialysis patients at the start of the 5-y cohort study, by fat mass (FM) quartile[1]

| | FM quartiles | | | | |
|---|---|---|---|---|---|
| | 1 ($n$ = 102) | 2 ($n$ = 94) | 3 ($n$ = 100) | 4 ($n$ = 95) | $P$ for trend[2] |
| Age (y) | 56 ± 16[3] | 55 ± 15 | 55 ± 14 | 51 ± 14 | <0.01 |
| Race (% African American) | 14 | 25 | 42 | 57 | 0.77 |
| Ethnicity (% Hispanic) | 67 | 61 | 42 | 53 | 0.59 |
| Primary insurance (% receiving Medicare) | 42 | 53 | 55 | 60 | 0.02 |
| Diabetes mellitus (%) | 49 | 57 | 56 | 59 | <0.01 |
| Marital status (% married) | 41 | 44 | 36 | 26 | <0.01 |
| Charlson comorbidity score | 1.8 ± 1.5 | 1.6 ± 1.5 | 2.0 ± 1.6 | 2.0 ± 1.7 | <0.01 |
| BMI (kg/m$^2$) | 22.1 ± 4.0 | 25.1 ± 3.5 | 28.7 ± 4.1 | 34.0 ± 6.6 | <0.01 |
| Triceps-skinfold thickness (mm) | 16.1 ± 6.0 | 19.9 ± 7.7 | 23.7 ± 9.0 | 29.9 ± 10.7 | <0.01 |
| Biceps-skinfold thickness (mm) | 8.8 ± 5.0 | 10.3 ± 5.7 | 12.2 ± 6.4 | 18.6 ± 10.9 | <0.01 |
| MAMC (cm) | 21.9 ± 3.0 | 24.3 ± 4.4 | 26.1 ± 3.7 | 25.9 ± 5.0 | <0.01 |
| NIR interactance–measured body fat (%) | 28.9 ± 6.6 | 32.3 ± 6.4 | 36.4 ± 7.0 | 39.3 ± 6.6 | <0.01 |
| NIR interactance–measured FM (kg) | 6.0 ± 2.0 | 11.2 ± 1.4 | 16.2 ± 1.8 | 28.5 ± 9.3 | <0.01 |
| NIR interactance–measured LBM (kg) | 53.9 ± 7.9 | 56.6 ± 7.1 | 58.9 ± 6.5 | 65.3 ± 8.7 | <0.01 |
| Dialysis vintage (mo) | 29.0 ± 30.1 | 26.5 ± 23.1 | 31.5 ± 29.9 | 29.9 ± 25.9 | 0.87 |
| Dialysis dose, single pool (Kt/$V$) | 1.9 ± 0.3 | 1.8 ± 0.3 | 1.6 ± 0.3 | 1.6 ± 0.2 | 0.02 |
| nPNA (kg/d) | 1.11 ± 0.24 | 1.06 ± 0.19 | 1.03 ± 0.22 | 1.01 ± 0.21 | 0.58 |
| Serum albumin (mg/dL) | 3.82 ± 0.34 | 3.82 ± 0.34 | 3.86 ± 0.33 | 3.80 ± 0.26 | 0.04 |
| Prealbumin (mg/dL) | 26.9 ± 9.0 | 26.9 ± 8.5 | 29.2 ± 9.2 | 27.5 ± 9.1 | 0.83 |
| Creatinine (mg/dL) | 8.4 ± 2.4 | 9.4 ± 2.6 | 9.4 ± 2.9 | 10.6 ± 3.2 | <0.01 |
| C-reactive protein (mg/L) | 4.4 ± 4.9 | 4.4 ± 4.8 | 6.3 ± 6.6 | 6.8 ± 7.1 | <0.01 |
| IL-6 (pg/mL) | 11.5 ± 14.3 | 9.1 ± 8.4 | 12.8 ± 12.5 | 12.6 ± 17.2 | 0.02 |
| TNF-α (pg/mL) | 9.0 ± 7.7 | 8.4 ± 7.2 | 8.9 ± 13.7 | 9.7 ± 11.2 | 0.92 |

[1] NIR, near-infrared; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; LBM, lean body mass; MAMC, midarm muscle circumference; nPNA, total nitrogen appearance normalized to body weight; Kt/$V$, urea clearance over time.
[2] $P$ values for triceps- and biceps-skinfold thicknesses, dialysis dose (vintage), C-reactive protein, IL-6, and TNF-α are based on the logarithmic values of these measures (ANOVA).
[3] Mean ± SD (all such values).

cytokines were measured in the General Clinical Research Center Laboratories of the Harbor–UCLA Medical Center. Plasma total homocysteine concentrations were measured by HPLC in the Harbor–UCLA Clinical Laboratories. Serum prealbumin was measured by using immunoprecipitin analysis (33).

### Statistical methods

We estimated death hazard ratios (HRs) across increasing levels (quartiles and percentiles) of LBM and FM by using Cox proportional hazards models at 4 adjustment levels: *1*) no adjustment for covariates; *2*) adjustment for age and sex; *3*) adjustment for case-mix variables, including age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance (Medicare compared with others), marital status, modified Charlson comorbidity score, dialysis dose (Kt/$V$), and residual renal function; and *4*) adjustment for case-mix and 3 inflammatory markers (serum CRP, IL-6, and TNF-α). Restricted cubic spline graphs were used as exploratory data analysis strategies to illustrate systematic relations between survival and the body-composition measures: LBM, FM, FM%, and FM percentiles minus LBM percentiles. This method also served to examine nonlinear associations as continuous mortality predictors as an alternative to linearity assumptions. Descriptive statistics are presented as means ± SDs or medians; hazard ratios are reported with 95% CIs. A $P$ value <0.05 or a 95% CI that did not span 1.0 was considered statistically significant. Statistical analyses were carried out with the statistical software program Stata version 10.0 (Stata Corporation, College Station, TX).

## RESULTS

Relevant demographic and clinical characteristics of the 742 patients including 391 men and 351 women characterized according to sex are shown in **Table 1**. The mean (±SD) ages of the men and women were 53 ± 15 and 54 ± 15 y, respectively. The proportion of blacks, Hispanics, and patients with diabetes were 28%, 54%, and 51% for men and 34%, 49%, and 56% for women, respectively. The distribution of percentage FM (FM%) across 3 main categories of BMI (in kg/m$^2$; <25, 25 to <30, and ≥30) is shown in **Figure 1**, which suggests the misclassification of body composition.

The characteristics of men and women across quartiles of LBM and FM at baseline are shown in **Tables 2–5**. Women with a higher LBM were younger. The proportion of blacks with a higher LBM was higher, whereas the proportion of Hispanics was lower in both sexes. Both the men and women with a greater LBM also had higher BMI, triceps- and biceps-skinfold thicknesses, MAMC, FM%, and serum creatinine concentrations than did the men and women with a lower LBM. Men and women with a higher FM were younger and older, respectively. Both men and women with a higher FM had higher BMI, triceps- and

**TABLE 4**
Baseline demographic, clinical, and laboratory values in 351 maintenance hemodialysis women at the start of the 5-y cohort study according to their lean body mass (LBM) quartiles[1]

| | LBM quartiles | | | | |
|---|---|---|---|---|---|
| Variables | 1 ($n$ = 91) | 2 ($n$ = 96) | 3 ($n$ = 78) | 4 ($n$ = 86) | $P$ for trend[2] |
| Age (y) | 56 ± 16[3] | 55 ± 15 | 55 ± 14 | 51 ± 14 | 0.02 |
| Race (% African American) | 14 | 25 | 42 | 57 | <0.01 |
| Ethnicity (% Hispanic) | 67 | 61 | 42 | 23 | <0.01 |
| Primary insurance (% receiving Medicare) | 42 | 53 | 55 | 60 | 0.06 |
| Diabetes mellitus (%) | 49 | 57 | 56 | 59 | 0.22 |
| Marital status (% married) | 41 | 44 | 36 | 26 | 0.04 |
| Charlson comorbidity score | 1.8 ± 1.5 | 1.6 ± 1.5 | 2.0 ± 1.6 | 2.0 ± 1.7 | 0.30 |
| BMI (kg/m$^2$) | 22.1 ± 4.0 | 25.1 ± 3.5 | 28.7 ± 4.1 | 34.0 ± 6.7 | <0.01 |
| Triceps-skinfold thickness (mm) | 16.1 ± 6.0 | 19.9 ± 7.7 | 23.7 ± 9.0 | 29.9 ± 10.7 | <0.01 |
| Biceps-skinfold thickness (mm) | 8.8 ± 5.0 | 10.3 ± 5.7 | 12.2 ± 6.4 | 18.6 ± 10.9 | <0.01 |
| MAMC (cm) | 21.9 ± 3.0 | 24.3 ± 4.4 | 26.1 ± 3.7 | 28.6 ± 5.0 | <0.01 |
| NIR interactance–measured body fat (%) | 28.9 ± 6.6 | 32.5 ± 6.4 | 36.4 ± 7.0 | 39.3 ± 6.6 | <0.01 |
| NIR interactance–measured fat mass (kg) | 15.2 ± 5.0 | 20.7 ± 5.9 | 27.5 ± 7.9 | 37.2 ± 11.5 | <0.01 |
| NIR interactance–measured LBM (kg) | 35.7 ± 3.5 | 41.9 ± 1.5 | 46.5 ± 1.4 | 55.3 ± 6.0 | <0.01 |
| Dialysis vintage (mo) | 29 ± 30 | 26 ± 33 | 31 ± 30 | 30 ± 26 | 0.30 |
| Dialysis dose, single pool (Kt/$V$) | 1.86 ± 0.35 | 1.76 ± 0.28 | 1.65 ± 0.32 | 1.55 ± 0.23 | <0.01 |
| nPNA (kg/d) | 1.11 ± 0.24 | 1.06 ± 0.19 | 1.04 ± 0.22 | 1.01 ± 0.21 | <0.01 |
| Serum albumin (mg/dL) | 3.82 ± 0.34 | 3.83 ± 0.34 | 3.86 ± 0.33 | 3.80 ± 0.26 | 0.47 |
| Prealbumin (mg/dL) | 26.9 ± 9.0 | 26.9 ± 8.5 | 29.2 ± 9.2 | 27.5 ± 9.1 | 0.32 |
| Creatinine (mg/dL) | 8.5 ± 2.4 | 9.4 ± 2.6 | 9.4 ± 2.9 | 10.6 ± 3.2 | <0.01 |
| C-reactive protein (mg/L) | 4.4 ± 4.9 | 4.4 ± 4.8 | 6.3 ± 6.6 | 6.8 ± 7.1 | <0.01 |
| IL-6 (pg/mL) | 11.5 ± 14.4 | 10.8 ± 18.1 | 12.8 ± 12.5 | 12.6 ± 17.2 | 0.32 |
| TNF- α (pg/mL) | 7.2 ± 7.6 | 8.4 ± 7.2 | 8.9 ± 13.7 | 9.7 ± 11.2 | 0.24 |

[1] NIR, near-infrared; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; MAMC, midarm muscle circumference; nPNA, total nitrogen appearance normalized to body weight; Kt/$V$, urea clearance over time.

[2] $P$ values for triceps- and biceps-skinfold thicknesses, dialysis dose (vintage), C-reactive protein, IL-6, and TNF-α are based on the logarithmic values of these measures (ANOVA).

[3] Mean ± SD (all such values).

biceps-skinfold thicknesses, and MAMC than did those with a lower FM, and a greater proportion of men and women with a higher FM had diabetes.

Over the 5 y of the cohort, 213 (29%) patients died. Because sex had a significant interaction with the association between survival and body composition ($P < 0.001$), particularly LBM, the analyses were also performed separately in men and women. The hazard ratios of death across quartiles of LBM, FM, and FM % in men and women are shown in **Tables 6–11**. In men, the lowest quartile of FM was associated with a significantly increased risk of death [hazard ratio (95% CI)] in unadjusted and adjusted models. Higher FM% in men was associated with greater survival in the unadjusted [0.95 (0.54, 1.67)], age- and sex-adjusted [0.47 (0.25, 0.82)], case mix–adjusted [0.43 (0.23, 0.80)], and case mix plus inflammation–adjusted [0.45 (0.23, 0.88)] models. In women, both LBM and FM were protective after adjustment for case mix and inflammation. The HR of death for the highest quartile of LBM was 0.34 (0.17, 0.67) after adjustment for case mix and inflammation. The HRs of death for the highest quartiles of FM and FM% were 0.38 (0.20, 0.71) and 0.57 (0.32, 1.03), respectively, in comparison with the first quartiles after adjustment for case mix and inflammation.

The cubic spline Cox models for LBM in men and women, adjusted for case mix and inflammatory markers, are shown in **Figure 2**. Higher LBM was associated with greater survival in women but not in men. Similarly adjusted cubic spline survival graphs for FM% in men and women are shown in **Figure 3**. Higher FM% was associated with greater survival in all subjects. However, sex-specific analyses confirmed a more linear association in women but a reverse J-shaped pattern in men.

To compare the survival predictability of excess FM relative to LBM in each patient, we ranked MHD patients according to their absolute FM (in kg) and assigned a percentile score to each patient within each sex group, ie, a number between 0 (lowest FM) and 100 (highest FM). We created similar percentile scores for LBM. The difference between the 2 percentile scores (FM percentile minus LBM percentile) in each patients yielded a number between –100 (indicating patients with lowest FM and highest LBM) and +100 (indicating patients with highest FM and lowest LBM). The cubic spline Cox models for FM minus LBM percentiles, after adjustment for case mix and inflammatory markers, are shown in **Figure 4**. A relatively linear trend toward greater survival is observed with higher excess fat relative to lean mass.

## DISCUSSION

We examined and compared the sex-specific mortality predictability of LBM and FM, assessed by the NIR interactance technique, in a large and contemporary cohort of 742 Californian MHD patients, who were followed for up to 5 y. We found that higher FM and LBM were associated with greater survival in

**TABLE 5**
Baseline demographic, clinical, and laboratory values in 351 maintenance hemodialysis women at the start of the 5-y cohort study according to their fat mass (FM) quartiles[1]

| | FM quartiles | | | | |
|---|---|---|---|---|---|
| | 1 ($n$ = 89) | 2 ($n$ = 96) | 3 ($n$ = 80) | 4 ($n$ = 86) | $P$ for trend[2] |
| Age (y) | 50 ± 18[3] | 57 ± 15 | 56 ± 14 | 56 ± 11 | 0.05 |
| Race (% African American) | 30 | 21 | 37 | 49 | <0.01 |
| Ethnicity (% Hispanic) | 57 | 59 | 49 | 30 | <0.01 |
| Primary insurance (% receiving Medicare) | 43 | 52 | 58 | 59 | 0.06 |
| Diabetes mellitus (%) | 39 | 62 | 50 | 70 | <0.01 |
| Marital status (% married) | 35 | 44 | 37 | 30 | 0.35 |
| Charlson comorbidity score | 1.5 ± 1.7 | 1.9 ± 1.4 | 1.7 ± 1.6 | 2.3 ± 1.5 | <0.01 |
| BMI (kg/m$^2$) | 20.5 ± 2.4 | 24.9 ± 2.0 | 28.6 ± 2.2 | 35.9 ± 5.1 | <0.01 |
| Triceps-skinfold thickness (mm) | 14.7 ± 6.1 | 19.2 ± 5.6 | 24.6 ± 8.1 | 31.0 ± 10.6 | <0.01 |
| Biceps-skinfold thickness (mm) | 7.9 ± 5.1 | 9.6 ± 5.4 | 13.1 ± 5.8 | 19.3 ± 10.3 | <0.01 |
| MAMC (cm) | 21.6 ± 4.1 | 23.7 ± 2.8 | 26.4 ± 3.4 | 29.2 ± 4.6 | <0.01 |
| NIR interactance–measured body fat (%) | 24.6 ± 5.1 | 32.2 ± 2.8 | 37.1 ± 2.8 | 43.3 ± 2.7 | <0.01 |
| NIR interactance–measured FM (kg) | 12.4 ± 3.1 | 19.9 ± 2.0 | 27.0 ± 2.3 | 41.0 ± 7.7 | <0.01 |
| NIR interactance–measured LBM (kg) | 37.9 ± 4.8 | 41.8 ± 5.4 | 45.9 ± 4.8 | 53.3 ± 7.4 | <0.01 |
| Dialysis vintage (mo) | 32 ± 31 | 25 ± 24 | 33 ± 26 | 27 ± 26 | 0.77 |
| Dialysis dose, single pool (Kt/$V$) | 1.8 ± 0.3 | 1.8 ± 0.3 | 1.7 ± 0.2 | 1.5 ± 0.3 | <0.01 |
| nPNA (kg/d) | 1.10 ± 0.22 | 1.06 ± 0.22 | 1.05 ± 0.20 | 1.02 ± 0.22 | 0.02 |
| Serum albumin (mg/dL) | 3.85 ± 0.36 | 3.80 ± 0.33 | 3.86 ± 0.31 | 3.79 ± 0.26 | 0.33 |
| Prealbumin (mg/dL) | 27.5 ± 19.1 | 26.9 ± 7.9 | 28.5 ± 9.0 | 27.4 ± 9.0 | 0.56 |
| Creatinine (mg/dL) | 9.4 ± 2.8 | 9.0 ± 2.6 | 10.1 ± 2.8 | 9.5 ± 3.2 | 0.33 |
| C-reactive protein (mg/L) | 3.8 ± 4.8 | 4.9 ± 5.3 | 5.9 ± 5.7 | 7.1 ± 7.3 | <0.01 |
| IL-6 (pg/mL) | 9.0 ± 11.2 | 12.1 ± 14.0 | 10.5 ± 8.7 | 13.9 ± 17.6 | 0.01 |
| TNF-α (pg/mL) | 7.1 ± 5.1 | 8.7 ± 8.9 | 8.7 ± 11.7 | 9.7 ± 13.2 | 0.61 |

[1] NIR, near-infrared; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; LBM, lean body mass; MAMC, midarm muscle circumference; nPNA, total nitrogen appearance normalized to body weight; Kt/$V$, urea clearance over time.
[2] $P$ values for triceps- and biceps-skinfold thicknesses, dialysis dose (vintage), C-reactive protein, IL-6, and TNF-α are based on the logarithmic values of these measures (ANOVA).
[3] Mean ± SD (all such values).

women, whereas only high FM, and not LBM, was associated with greater survival in men. The excess FM relative to LBM was linearly associated with greater survival in all subjects. Our findings may have major clinical and public health implications, especially because they suggest that FM is superior to LBM in conferring survival advantages of large body size to MHD patients, whereas larger LBM appears associated with greater survival in women but not in men.

Both LBM and FM are measures of nutritional status; however, LBM is a rather reliable indicator of muscle mass and somatic protein mass, whereas FM is more of a reflection of energy storage. It should be emphasized that LBM also includes almost all body water, and volume expanded or edematous persons could therefore have a large LBM because of excess body water and not because of increased muscle or protein mass. Nonetheless, efforts are virtually always made successfully to prevent edema fluid from occurring in MHD patients. A study that compared maintenance dialysis patients with healthy persons (34) found that MHD patients had a lower LBM across both men and women. Another study (35) also found that FM and LBM were significantly lower in dialysis patients than in the general population.

Increasing numbers of observational studies indicate a consistent association between high BMI and greater survival in

**TABLE 6**
Death hazard ratios (and 95% CIs) of 5-y mortality according to lean body mass (LBM) quartiles in 391 male maintenance hemodialysis patients

| | LBM quartiles | | | | |
|---|---|---|---|---|---|
| Variables | 1 ($n$ = 100) | 2 ($n$ = 97) | 3 ($n$ = 98) | 4 ($n$ = 96) | $P$ for trend[1] |
| Unadjusted | 1.00 | 0.76 (0.41, 1.40) | 1.44 (0.81, 2.55) | 1.28 (0.72, 2.26) | 0.14 |
| Adjusted for age and sex | 1.00 | 0.81 (0.44, 1.52) | 1.54 (0.85, 2.79) | 1.58 (0.89, 2.91) | 0.05 |
| Adjusted for case mix[2] | 1.00 | 0.70 (0.37, 1.32) | 1.65 (0.90, 3.02) | 1.26 (0.66, 2.38) | 0.15 |
| Adjusted for case mix + inflammation[3] | 1.00 | 0.63 (0.32, 1.24) | 1.85 (0.94, 3.49) | 1.17 (0.60, 2.27) | 0.15 |

[1] Derived by using a Cox proportional hazards model.
[2] Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ ( urea clearance over time)], and residual urine.
[3] Inflammatory markers: C-reactive protein, interleukin-6, and tumor necrosis factor-α.

**TABLE 7**
Death hazard ratios (and 95% CIs) of 5-y mortality according to fat mass (FM) quartiles in 391 male maintenance hemodialysis patients

| | FM quartiles | | | | |
|---|---|---|---|---|---|
| | 1 ($n$ = 102) | 2 ($n$ = 94) | 3 ($n$ = 100) | 4 ($n$ = 95) | $P$ for trend[1] |
| Unadjusted | 1.00 | 0.87 (0.43, 1.61) | 1.38 (0.80, 2.40) | 1.15 (0.66, 2.02) | 0.35 |
| Adjusted for age and sex | 1.00 | 0.52 (0.28, 0.97)[2] | 0.58 (0.32, 1.06) | 0.65 (0.36, 1.17) | 0.29 |
| Adjusted for case mix[3] | 1.00 | 0.37 (0.19, 0.72)[2] | 0.51 (0.28, 0.93)[2] | 0.51 (0.28, 0.94)[2] | 0.17 |
| Adjusted for case mix + inflammation[4] | 1.00 | 0.33 (0.15, 0.69)[2] | 0.50 (0.26, 0.97)[2] | 0.51 (0.27, 0.96)[2] | 0.22 |

[1] Derived by using a Cox proportional hazards model.
[2] $P < 0.05$.
[3] Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ ( urea clearance over time)], and residual urine.
[4] Inflammatory markers: C-reactive protein, interleukin-6, and tumor necrosis factor-α.

**TABLE 8**
Death hazard ratios (and 95% CIs) of 5-y mortality according to percentage fat mass (FM%) in 391 male maintenance hemodialysis patients

| | FM% quartiles | | | | |
|---|---|---|---|---|---|
| | 1 ($n$ = 98) | 2 ($n$ = 98) | 3 ($n$ = 99) | 4 ($n$ = 96) | $P$ for trend[1] |
| Unadjusted | 1.00 | 0.67 (0.36, 1.25) | 1.13 (0.66, 1.93) | 0.95 (0.54, 1.67) | 0.73 |
| Adjusted for age and sex | 1.00 | 0.41 (0.22, 0.76)[2] | 0.47 (0.26, 0.85)[2] | 0.47 (0.25, 0.82)[2] | 0.04 |
| Adjusted for case mix[3] | 1.00 | 0.36 (0.18, 0.69)[2] | 0.50 (0.27, 0.91)[2] | 0.43 (0.23, 0.80)[2] | 0.04 |
| Adjusted for case mix + inflammation[4] | 1.00 | 0.42 (0.20, 0.88)[2] | 0.51 (0.26, 0.99)[2] | 0.45 (0.23, 0.88)[2] | 0.06 |

[1] Derived by using a Cox proportional hazards model.
[2] $P < 0.05$.
[3] Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ ( urea clearance over time)], and residual urine.
[4] Inflammatory markers: C-reactive protein, interleukin-6, and tumor necrosis factor-α.

**TABLE 9**
Death hazard ratios (and 95% CIs) of 5-y mortality according to lean body mass (LBM) in 351 female maintenance hemodialysis patients

| | LBM quartiles | | | | |
|---|---|---|---|---|---|
| Variables | 1 ($n$ = 91) | 2 ($n$ = 96) | 3 ($n$ = 78) | 4 ($n$ = 86) | $P$ for trend[1] |
| Unadjusted | 1.00 | 0.55 (0.33, 0.91)[2] | 0.94 (0.58, 1.52) | 0.77 (0.47, 1.25) | 0.67 |
| Adjusted for age and sex | 1.00 | 0.51 (0.30, 0.85)[2] | 0.85 (0.51, 1.42) | 0.69 (0.40, 1.21) | 0.44 |
| Adjusted for case mix[3] | 1.00 | 0.47 (0.27, 0.79)[2] | 0.70 (0.41, 1.20) | 0.49 (0.26, 0.90)[2] | 0.07 |
| Adjusted for case mix + inflammation[4] | 1.00 | 0.48 (0.28, 0.83)[2] | 0.60 (0.34, 1.08) | 0.34 (0.17, 0.67)[2] | <0.01 |

[1] Derived by using a Cox proportional hazards model.
[2] $P < 0.05$.
[3] Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ ( urea clearance over time)], and residual urine.
[4] Inflammatory markers: C-reactive protein, interleukin-6, and tumor necrosis factor-α.

MHD patients (8–11, 36, 37). It is not clear which body compartment is more strongly related to survival. The protective effect of large body size may be associated with higher adipose tissue and fat reserves (12, 14–16). This so-called "obesity paradox" (38) or "reverse epidemiology" (38) is intriguing, because adipose tissue, especially visceral fat, has pro-inflammatory properties (39). In our study, BMI appeared to misclassify body composition in MHD patients, as shown in Figure 1. We found that higher absolute FM and higher FM% were associated with greater survival in both sexes. These findings are somewhat similar to some previous studies, although they did not examine the role of sex (14–16, 30). In our study, the protective effect of FM was somewhat independent of sex. There are several potential reasons why lower FM is linked to higher mortality in MHD patients. These factors include its role as a nutritional reserve during biological hardship, such as during a chronic disease state, including CKD, because patients with less body fat may have more difficulty coping with the catabolic stress of the chronic disease in general and dialysis treatment in particular (14). Even though fat tissue is related to inflammation in the general population (40), in dialysis patients it may be associated with relatively more antiinflammatory cytokines, such as adiponectin, than pro-inflammatory cytokines (41). Several studies have found no difference in inflammatory markers (IL-6, TNF-α, and CRP) in individuals with different proportions of body fat (12, 14, 42).

**TABLE 10**
Death hazard ratios (and 95% CIs) of 5-y mortality according to fat mass (FM) quartiles in 351 female maintenance hemodialysis patients

| | FM quartiles | | | | |
|---|---|---|---|---|---|
| | 1 ($n$ = 89) | 2 ($n$ = 96) | 3 ($n$ = 80) | 4 ($n$ = 86) | $P$ for trend[1] |
| Unadjusted | 1.00 | 0.71 (0.43, 1.17) | 0.84 (0.50, 1.40) | 0.96 (0.58, 1.57) | 0.96 |
| Adjusted for age and sex | 1.00 | 0.56 (0.33, 0.92)[2] | 0.61 (0.36, 1.02) | 0.72 (0.43, 1.19) | 0.29 |
| Adjusted for case mix[3] | 1.00 | 0.50 (0.29, 0.87)[2] | 0.57 (0.32, 0.97)[2] | 0.55 (0.31, 0.98)[2] | 0.09 |
| Adjusted for case mix + inflammation[4] | 1.00 | 0.45 (0.26, 0.78)[2] | 0.45 (0.25, 0.80)[2] | 0.38 (0.20, 0.71)[2] | <0.01 |

[1] Derived by using a Cox proportional hazards model.
[2] $P < 0.05$.
[3] Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ ( urea clearance over time)], and residual urine.
[4] Inflammatory markers: C-reactive protein, interleukin-6, and tumor necrosis factor-α.

Some recent studies (43) have suggested that higher LBM, but not FM, is associated with greater survival in CKD patients. We found that higher LBM conferred survival advantages in women but not in men. Several reasons explain why low LBM or muscle mass might be associated with worse survival in at least 1 of the 2 sexes: Similarly to patients with a low FM, patients with a low LBM may have suboptimal nutritional status with inadequate diet (30, 44). Reduced muscle mass is observed more commonly in patients with higher levels of inflammation (30, 42). Honda et al (42) found a higher prevalence of inflammation (CRP > 10 mg/L) in MHD patients with a low LBM. Uremic toxins may be diluted in the muscle mass compartment, which may render these toxins less effective, especially because higher muscle mass is correlated with higher total body water (45). Higher muscle mass likely enables more effective physical activity and exercise training (46), which can improve arterial stiffness in MHD patients (47). Arterial stiffness per se is an independent predictor of cardiovascular disease and death in MHD patients (48, 49). Although a recent study (47) failed to detect a beneficial metabolic effect of exercise in a small number of MHD patients, exercise may improve insulin resistance, which another independent predictor of mortality in MHD patients (50). Nevertheless, when we compared the competing association of FM compared with LBM with longevity, FM appeared to have sex-robust and superior survival benefit compared with LBM, as shown in Figure 4 on the basis of a percentile difference analysis.

Some limitations should be considered when our findings are interpreted. First, there was selection bias during enrollment. However, because mortality in our cohort was less than that in the base population, it might be argued that selection bias was in a direction that would lead to bias toward the null; therefore, without this bias, our results may have been even stronger. Second, there was a lack of information regarding dialysis access, dialysis membrane, and other known or unknown confounders. Third, as in any observational study, we could not account for unmeasured or residual confounding. Fourth, we used the NIR interactance technique to measure body composition, whereas dual-energy X-ray absorptiometry (DXA) is often considered the gold standard; however, although LBM in dialysis patients may be affected by water and fat measurement appears to be more robust, NIR measurement is more independent of the fluid status in dialysis patients compared with DXA (29). NIR was previously shown to be a reliable and reproducible technique in many studies (26, 27), including in our own studies (18, 28, 29). By using DXA as the reference standard, we showed that percentage body fat measured by NIR interactance corresponded closely with that measured with DXA (28). Another limitation of our study was that data were obtained at baseline; hence, adjustment for potential changes over time was not accounted for.

An important strength of our study was the long follow-up period, ie, up to 63 mo. Other strengths include the comprehensive laboratory evaluations, the direct measurement of LBM and FM with NIR interactance technology, and the detailed evaluation of the clinical and comorbid states of the patients by study physicians. Our cohort has been extensively characterized for markers of inflammation and nutritional status. Finally, participants were selected randomly without having prior knowledge of their inflammatory status.

**TABLE 11**
Death hazard ratios (and 95% CIs) of 5-y mortality according to percentage fat mass (FM%) quartiles in 351 female maintenance hemodialysis patients

| | FM% quartiles | | | | |
|---|---|---|---|---|---|
| | 1 ($n$ = 88) | 2 ($n$ = 88) | 3 ($n$ = 89) | 4 ($n$ = 86) | $P$ for trend[1] |
| Unadjusted | 1.00 | 1.13 (0.68, 1.87) | 0.85 (0.50, 1.43) | 1.28 (0.78, 2.11) | 0.56 |
| Adjusted for age and sex | 1.00 | 0.77 (0.45, 1.30) | 0.58 (0.34, 1.00)[2] | 0.87 (0.52, 1.44) | 0.46 |
| Adjusted for case mix[3] | 1.00 | 0.78 (0.45, 1.33) | 0.61 (0.35, 1.07) | 0.85 (0.50, 1.44) | 0.43 |
| Adjusted for case mix + inflammation[4] | 1.00 | 0.59 (0.34, 1.04) | 0.53 (0.29, 0.95)[2] | 0.57 (0.32, 1.03) | 0.07 |

[1] Derived by using a Cox proportional hazards model.
[2] $P < 0.05$.
[3] Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ ( urea clearance over time)], and residual urine.
[4] Inflammatory markers: C-reactive protein, interleukin-6, and tumor necrosis factor-α.

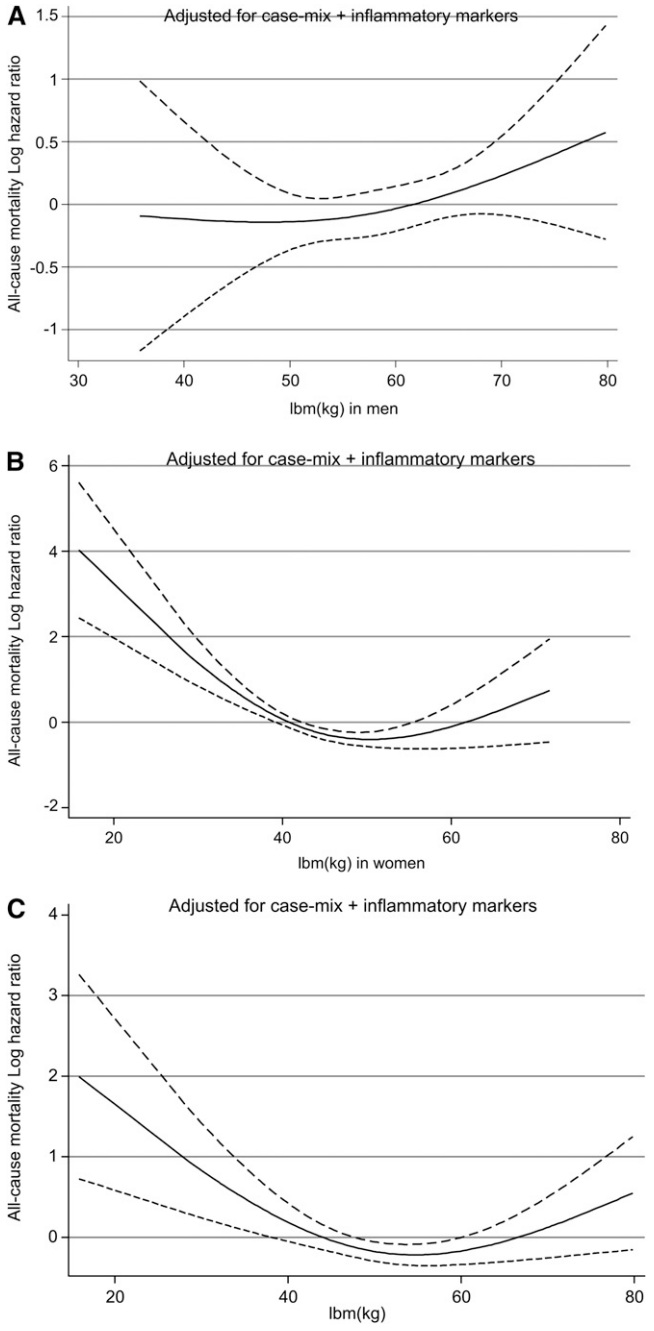


**FIGURE 2.** Cubic spline models of the Cox proportional regression analyses reflecting case-mix– and inflammation-adjusted mortality-predictability (with 95% CIs) according to lean body mass (lbm) in men (A) and women (B) separately and in both sexes combined (C) over 5 y in 742 maintenance hemodialysis patients (351 women and 391 men). Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/*V* (urea clearance over time)], residual urine, and inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor-α). Spline models are shown with 2 df. Note that the scales of the *y* axes have different ranges across the 3 panels.

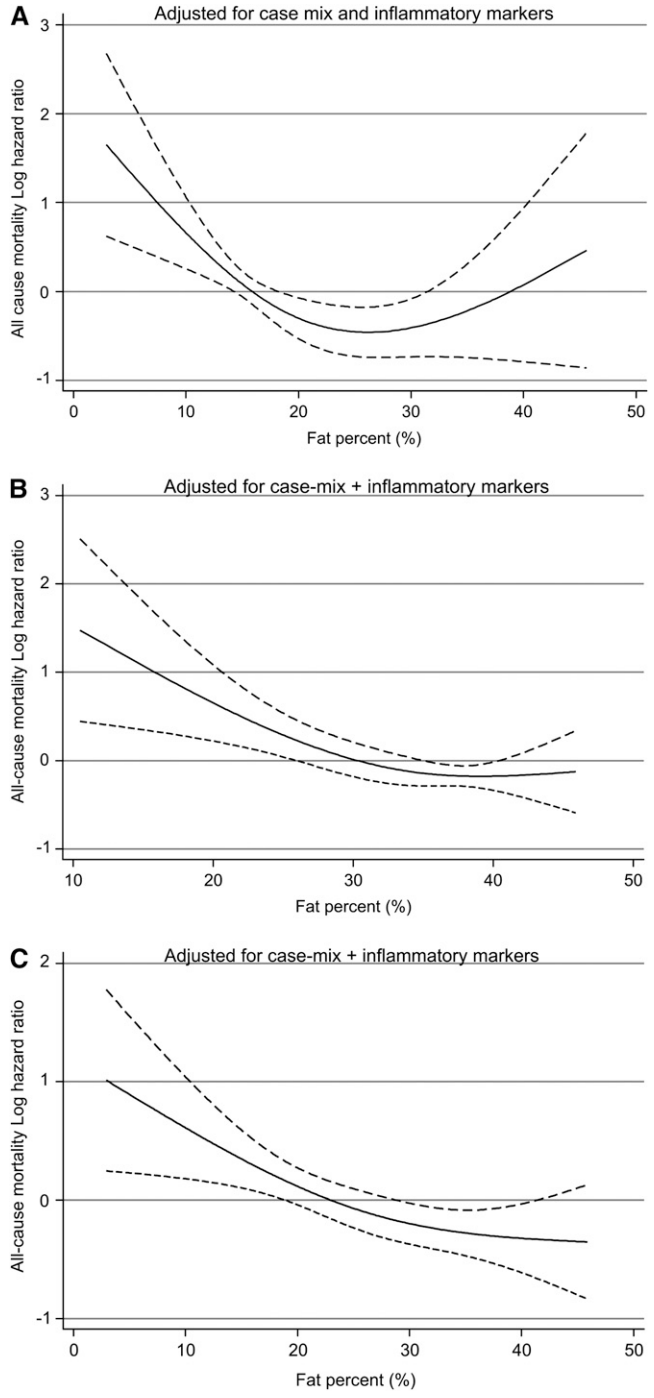


**FIGURE 3.** Cubic spline models of the Cox proportional regression analyses reflecting case-mix– and inflammation-adjusted mortality predictability (with 95% CIs) according to the fat mass in men (A) and women (B) separately and in both sexes combined (C) over 5 y in 742 maintenance hemodialysis patients (351 women and 391 men). Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/*V* (urea clearance over time)], residual urine, and inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor-α). Spline models are shown with 2 df. Note that the scales of the *y* axes have different ranges across the 3 panels.

In conclusion, in MHD patients higher FM in men and women and higher LBM in women are associated with greater survival. Patients with higher excess fat relative to lean mass have a lower death risk. These findings may have important clinical and public health implications, especially because the current practice of medicine has a heavy bias on the undifferentiated advice for obese persons to lose weight (16, 51), whereas in maintenance dialysis patients and other populations with chronic disease states

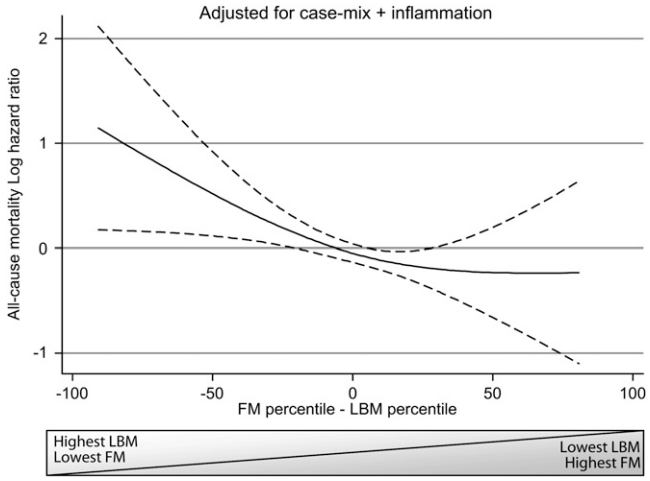


**FIGURE 4.** Cubic spline models of the Cox proportional regression analyses reflecting case-mix– and inflammation-adjusted mortality predictability (with 95% CIs) according to differences between the sex-specific ranked percentiles of fat mass (FM) and lean body mass (LBM) over 5 y ($n$ = 742). Case-mix variables included age, sex, race-ethnicity, diabetes mellitus, dialysis vintage, insurance, marital status, modified Charlson comorbidity score, dialysis dose [Kt/$V$ (urea clearance over time)], residual urine, and inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor-$\alpha$). Spline models are shown with 2 df.

an obesity paradox prevails. Many dialysis patients are aggressively encouraged to lose weight as a prerequisite to be listed on and to remain on kidney transplant waiting lists, a practice that was recently questioned (16). Clinical trials to examine interventions that may increase FM and LBM in high-risk dialysis patients are indicated.

The authors' responsibilities were as follows—NN: conducted and analyzed the study data and wrote, reviewed, and approved the manuscript; CPK, RD, YK, UD, RB, AO, AL, DB, and JDK: analyzed and interpreted the data and reviewed, amended, and approved the manuscript; and KK-Z (Principal Investigator of the grants): designed, conducted, and analyzed the NIED study and wrote the manuscript. KKZ and JDK have received honoraria, consultation fees, or grant funds from Abbott Nutrition (manufacturer of Nepro and Supplena) and NovoNordisk (manufacturer of Human Growth Hormone). No conflicts of interest were declared by the other authors.

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