Title

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Journal

Nephrology Dialysis Transplantation, 34(2)

ISSN

0931-0509

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Publication Date

2019-02-01

DOI

10.1093/ndt/gfy124

Peer reviewed

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Received: 18.10.2017; Editorial decision: 20.2.2018

ORIGINAL ARTICLE

Nephrol Dial Transplant (2019) 34: 346–354
doi: 10.1093/ndt/gfy124
Advance Access publication 4 June 2018

Frailty, body composition and the risk of mortality in incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study

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ABSTRACT

Background. Frail obese community-dwelling older adults are at increased mortality risk. Among hemodialysis (HD) patients, frailty is common and associated with increased mortality risk; however, in dialysis, obesity is associated with decreased mortality risk. Whether the frail–obese phenotype is associated with increased mortality risk among HD patients remains unclear.

Methods. This study included 370 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study. We measured frailty using the Fried phenotype, general obesity [body mass index (BMI) $\geq$30 kg/m^2] and abdominal obesity [waist:hip ratio (WHR) $\geq$median WHR] and estimated their associations with mortality.

Results. The mean age was 55 years, with 42% female, 73% African American, 57% diabetic and 52% frail. Frail HD patients had higher mean BMI (frail = 30.3 kg/m^2, non-frail = 28.3 kg/m^2; P = 0.02) and similar WHR (P = 0.8). Twenty-two percent were frail with general obesity and 27% were frail with abdominal obesity. Frailty was associated with 1.66-fold increased mortality risk [95% confidence interval (CI) 1.03–2.67]. BMI was associated with a decreased mortality risk [25.0–29.9 kg/m^2 hazard ratio (HR) 0.53 (95% CI 0.31–0.93); $\geq$30 kg/m^2 HR 0.34 (95% CI 0.19–0.62)]. Frailty was associated with elevated mortality risk among HD patients with general [HR 3.77 (95% CI 1.10–12.92)] and abdominal obesity [HR 2.38 (95% CI 1.17–4.82)]. Frailty was not associated with mortality among HD patients without general or abdominal obesity.

Conclusions. In adults initiating HD, frailty was associated with elevated mortality risk, even among the obese. Frail–obese HD patients may be a high-risk, often-overlooked population, as obesity is assumed to be protective. Measurement of frailty and obesity may facilitate risk stratification.

Keywords: body composition, end-stage renal disease, frailty, hemodialysis, mortality

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Frailty is a syndrome characterized by decreased physiological reserve and consequent susceptibility to stressors and adverse outcomes [1]. The frail phenotype was initially identified in community-dwelling older adults but has since been identified as common in chronic disease populations of all ages [2, 3]. Although frailty is typically viewed as a wasting disorder, it may in fact capture sarcopenic obesity, a condition characterized by low muscle mass in conjunction with high adiposity [4]. Studies of community-dwelling older adults have identified associations between frailty and sarcopenic obesity [5, 6]. A clinically relevant frail–obese phenotype, assessed using body mass index (BMI) as a measure of general obesity, has been proposed [7]. Indeed, in community-dwelling older adults, those who were frail and had general obesity were at higher risk for mortality than the nonobese frail [8].

Frailty is highly prevalent in end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) and results in increased mortality risk [9, 10]. Frailty is associated with not only decreased muscle mass but also increased fat mass in HD patients [11]. In contrast to frailty, general obesity is associated with decreased risk of mortality in this population [12, 13]. The distribution of body fat also contributes to the risk of mortality in HD patients [14], and unlike general obesity, abdominal obesity has been associated with an increased risk of mortality [15]. Therefore it is likely that there is a synergistic effect of obesity and frailty on mortality risk. Yet, it is unclear whether classifying the frail–obese phenotype using either general or abdominal obesity among HD patients identifies a subset of obese patients at increased risk for mortality.

The goals of this study were to estimate the prevalence of the frail–obese phenotype in a prospective cohort of incident HD patients; separately quantify the association of frailty, general obesity (assessed using BMI) and abdominal obesity [assessed with the waist:hip ratio (WHR)] with the risk of all-cause mortality in this cohort; and quantify the association of frailty and mortality among HD patients with general obesity and among those with abdominal obesity.

MATERIALS AND METHODS

Study design and population

Frailty was measured in 370 incident HD (<6 months) patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study, as described in detail elsewhere [16]. Patients were recruited from 27 dialysis units in the Baltimore, MD, USA metropolitan area from November 2008 to August 2012. Inclusion criteria included ≥18 years of age and the ability to speak English. Exclusion criteria included patients in hospice, nursing facilities or prison; persons with a cancer diagnosis other than nonmelanoma skin cancer; persons with a pacemaker or an automatic implantable cardioverter defibrillator and pregnant or nursing women. All participants provided written informed consent and the study protocol was approved by the Johns Hopkins School of Medicine Institutional Review Board, MedStar Health Systems and by the medical director of each dialysis unit.

Frailty

Frailty was measured at study enrollment and operationalized using the Fried phenotype [1], a definition previously validated in both older adults [1, 17, 18] and ESRD populations [9, 19, 20]. This phenotype is characterized by five domains, namely, shrinkage, low physical activity, exhaustion, weakness and slowed gait speed [1]. Shrinkage was defined as unintentional weight loss >4.5 kg (10 lb) dry weight in the previous year and low physical activity was operationalized as kJ/week below a sex-specific cutoff [1]. Exhaustion was defined as reporting 'moderate amount of the time' or 'most of the time' to two items from the Center for Epidemiological Studies - Depression scale: 'I felt that everything I did was an effort' and 'I could not get going.' Weakness was defined as grip strength below a cutoff that differed by sex and BMI [1]. Slowed gait speed was defined as time to walk 4.6 m (15 feet) below a cutoff by sex and height [1]. Participants with three or more of the domains were categorized as frail.

General and abdominal adiposity

Anthropometric measures were collected at study entry. BMI, used to assess general adiposity, was calculated as the ratio of self-reported dry weight (in kg) to height (in m) squared. General obesity was defined as BMI ≥30 kg/m^2. WHR, a proxy for abdominal adiposity, was calculated as the ratio of waist circumference (in cm) to hip circumference (in cm). Abdominal obesity was defined as WHR ≥ sex-specific sample median (females 0.92, males 0.98).

Frail–obese phenotype

The frail–obese phenotype was defined as the presence of both frailty and obesity. The phenotype was evaluated separately for general (frail–general obese phenotype) and abdominal obesity (frail–abdominal obese phenotype).

Other participant characteristics

Sociodemographic characteristics (age, sex and race), smoking status, alcohol use and medical history were collected at study enrollment. Comorbidities, assessed by medical chart review, were adjudicated by the PACE Endpoint Committee and classified using the Charlson Comorbidity Index (CCI), which summarizes and weights a range of comorbidities based on 1-year mortality risk. The presence of comorbidity was defined as a CCI score ≥5. Systolic blood pressure was measured on a non-HD day with participants in a seated position. HD laboratory measures of serum albumin, serum creatinine and single-pool Kt/V (K = dialyzer clearance, t = time, V = volume of water) were collected as previously described and the value for each of these measures reflected the average from HD initiation to 90 days after

the start of HD [16]. C-reactive protein (CRP), triglyceride and cholesterol concentrations were measured at the baseline visit.

Outcomes

Participants were followed until the end of the study ($n = 170$), death ($n = 81$), transplant ($n = 40$), transfer to peritoneal dialysis ($n = 14$), transfer to long-term hospitalization ($n = 13$) or loss to follow-up ($n = 52$). All-cause mortality was ascertained using reports from dialysis units confirmed with Centers for Medicare and Medicaid Services Form 2746.

Statistical analyses

Characteristics of the study population were summarized using means and standard deviations (SDs), medians and interquartile ranges (IQRs) or frequencies and percentages and were compared by frailty status using Student's *t*-test or the chi-squared test. Multivariable logistic regression estimated the association of BMI and WHR with frailty, adjusting for age, sex, race, CCI and serum albumin.

Unadjusted Kaplan–Meier survival curves were computed to evaluate the cumulative incidence of mortality among frail and nonfrail participants. The association between frailty at HD initiation and all-cause mortality was estimated using adjusted Cox proportional hazards regression. Potential confounders were identified a priori based on previous studies of frailty in ESRD patients and all factors predictive of mortality and associated with frailty in univariate analyses were included. The final model was adjusted for age, sex, race, CCI and serum albumin. An analogous approach was taken to investigate the associations between WHR and all-cause mortality and BMI and all-causemortality. To assess the independent association of frailty, WHR and BMI with mortality, these variables were simultaneously incorporated into a Cox proportional hazards model.

Heterogeneity of effect was assessed by including a multiplicative interaction term between frailty and WHR and frailty and BMI in separate adjusted models. Stratified analyses were performed to estimate the association of frailty with all-cause mortality by BMI category ($<30\ kg/m^2$ versus $\geq 30\ kg/m^2$) and by WHR (<sex-specific median versus ≥sex-specific median). For these stratified models, the potential covariates included all variables used in unadjusted models as well as those factors that differed between either the general obese and the non-general obese or the abdominal obese and non-abdominal obese.

In a secondary analysis, the frailty score was rescaled according to sample tertiles of the individual components of the Fried phenotype, as previously done in community-dwelling older adults [21]. This frailty score was treated as an ordinal variable ranging from 0 to 10. We examined the association of this rescaled frailty score and mortality using a multivariable Cox proportional hazards model adjusting for age, sex, race, CCI, BMI and serum albumin.

As additional sensitivity analyses, we evaluated the cumulative incidence of mortality among frail and nonfrail participants from the date of dialysis initiation; in these analyses participants did not enter the risk set until the date of study entry (delayed entry). We also tested whether the results were similar when we modeled BMI as a continuous variable and dichotomized at $\geq 30\ kg/m^2$ or we adjusted for additional factors including age and dialysis vintage at study enrollment. We also examined nonlinear relationships between BMI and mortality by including restricted cubic splines with knots at the 10th, 50th and 90th quantiles in the fully adjusted models. Furthermore, we tested an interaction between frailty and BMI as a spline in adjusted models. Finally, additional stratified analyses were performed to estimate the association of frailty with all-cause mortality by BMI category ($<23\ kg/m^2$ versus $\geq 23\ kg/m^2$ and $<20\ kg/m^2$ versus $\geq 20\ kg/m^2$).

The proportional hazards assumption for all models was verified with plots of Schoenfeld residuals versus time and the linearity assumption of continuous variables was assessed by visual inspection of plots of Martingale residuals versus fitted values. Missing covariate data were imputed using multiple imputations by chained equations [22]. The imputed variables with missing data were BMI (0.3%), CRP (3.5%), serum albumin (0.8%), low-density lipoprotein (LDL) cholesterol (4.3%), high-density lipoprotein (HDL) cholesterol (3.5%), triglycerides (3.5%), serum creatinine (5.1%) and single-pool Kt/V (7.6%). All statistical analyses were performed in R version 3.4.0 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Among the 370 participants, mean age 54.9 ± 13.1 years, 42% were female, 73% were African American and 52% were frail (Table 1). The mean CCI score was 5.2 ± 2.2 and the three most common comorbidities were diabetes (57%), congestive heart failure (42%) and coronary artery disease (37%). The most common primary cause of ESRD was diabetic nephropathy (34%). The median dialysis vintage at study enrollment was 3.4 months (IQR 2.6–4.9). The mean serum albumin concentration was 3.55 ± 0.48 g/dL and the median CRP concentration was 5.86 μg/mL (IQR 2.33–14.9).

The mean BMI was $29.3 \pm 7.9\ kg/m^2$ and 38% had general obesity. The mean WHR was 0.95 ± 0.08 and 50% had abdominal obesity (Table 1). Twenty-four percent had both general obesity and abdominal obesity and 37% had neither general obesity nor abdominal obesity (Table 2). The prevalence of general obesity ($P = 0.9$) and abdominal obesity ($P = 0.1$) was similar among African Americans as compared with non-African Americans. The distributions of BMI and WHR did not differ greatly between male and female participants (Supplementary data, Figure S1).

Among incident HD participants, the most prevalent frailty domain was slowed gait speed (62%) (Supplementary data, Table S1). As compared with participants without general obesity, those with general obesity were more likely to have slowed gait speed (general obese 71%, non-general obese 57%; $P = 0.02$) but no such difference was present between those with and without abdominal obesity. There were no differences in the prevalence of other frailty domains by general or abdominal obesity.

Participant characteristics by frailty status

Frail participants were older [frail 57.2 years (SD 13.5), nonfrail 52.3 years (SD 12.1); $P < 0.001$] and more likely to

Table 1. Baseline demographic and clinical participant characteristics among adults initiating HD ($N = 370$)

Characteristic	Overall ($n = 370$)	Frail ($n = 193$)	Nonfrail ($n = 177$)	P-value
Age (years)	54.9 ± 13.1	57.2 ± 13.5	52.3 ± 12.1	< 0.001
Female	155 (42)	82 (42)	73 (41)	0.9
African American	270 (73)	138 (72)	132 (75)	0.6
High school education or higher	227 (62)	114 (59)	113 (64)	0.4
Current or former smoker	226 (61)	110 (57)	116 (66)	0.1
Current or former drinker	29 (81)	151 (79)	145 (83)	0.4
BMI (kg/m^2)	29.3 ± 7.9	30.3 ± 8.3	28.3 ± 7.4	0.02
Obese (BMI ≥ $30 kg/m^2$)	139 (38)	83 (43)	56 (32)	0.03
WHR	0.95 ± 0.08	0.95 ± 0.08	0.95 ± 0.08	0.8
Primary cause of ESRD				0.8
Glomerulonephritis	52 (14)	26 (13)	26 (15)	
Hypertension	98 (26)	47 (24)	51 (29)	
Diabetes	126 (34)	71 (37)	55 (31)	
Other	57 (15)	29 (15)	28 (16)	
Unknown	37 (10)	20 (10)	17 (10)	
Comorbidities				
Coronary artery disease	137 (37)	78 (40)	59 (33)	0.2
Congestive heart failure	155 (42)	92 (48)	63 (36)	0.03
Cerebrovascular disease	83 (22)	49 (25)	34 (19)	0.2
Peripheral vascular disease	72 (19)	45 (23)	27 (15)	0.07
Hypertension	370 (100)	193 (100)	177 (100)	0.9
Diabetes	211 (57)	120 (62)	91 (51)	0.05
History of cancer	30 (8)	21 (11)	9 (5)	0.06
Chronic pulmonary disease	85 (23)	51 (26)	34 (19)	0.1
CCI	5.2 ± 2.2	5.3 ± 2.1	5.0 ± 2.2	0.2
Systolic blood pressure (mm Hg)	136.9 ± 25.4	139.1 ± 26.8	134.5 ± 23.7	0.09
CRP (μg/mL)	5.86 (2.33–14.9)	6.24 (2.43–17.4)	5.39 (2.32–10.3)	0.1
Serum albumin (g/dL)	3.55 ± 0.48	3.50 ± 0.45	3.60 ± 0.50	0.03
LDL cholesterol (g/dL)	83.4 (61.3–108.3)	81.1 (60.6–115.8)	85.0 (62.8–105.1)	0.9
HDL cholesterol (g/dL)	50.0 (40.0–63.0)	48.0 (39.0–59.0)	53.0 (42.0–66.3)	0.05
Serum triglycerides (mg/dL)	118.0 (86.5–163.0)	118.0 (91.0–161.5)	124.0 (84.0–166.3)	0.4
Serum creatinine (mg/dL)	6.35 (5.28–7.91)	6.22 (5.09–7.81)	6.52 (5.41–8.01)	0.1
Single-pool Kt/V	1.25 (1.25–1.60)	1.43 (1.24–1.60)	1.43 (1.26–1.61)	0.2

Data are presented as mean ± SD, median (IQR) or n (%).
WHR, waist-to-hip ratio, BMI, body mass index, ESRD, end stage renal disease, CCI, Charlson comorbidity index, LDL, low density lipoprotein, HDL, high density lipoprotein.

have congestive heart failure (frail 48%, nonfrail 36%; P = 0.03) and diabetes (frail 62%, nonfrail 51%; P = 0.05). Overall, however, CCI did not differ between frail and nonfrail participants. The median dialysis vintage at study enrollment did not differ between frail and nonfrail participants [frail 3.5 months (IQR 2.7–5.3), nonfrail 3.3 months (IQR 2.4–4.7); P = 0.3]. Frail participants had lower serum albumin concentration [frail 3.50 g/dL (SD 0.45), nonfrail 3.60 g/dL (SD 0.50); P = 0.03] and lower median HDL cholesterol levels [frail 48.0 mg/dL (IQR 39.0–59.0), nonfrail 53.0 mg/dL (IQR 42.0–66.3); P = 0.05]. Of note, CRP concentration did not differ between frail and nonfrail participants.

There were no significant differences in characteristics, including age and prevalence of diabetes, between either frail and nonfrail participants with general obesity or frail and nonfrail participants with abdominal obesity (Supplementary data, Table S2).

General obesity and frailty

Among adults initiating HD, 22% had the frail–general obese phenotype. The prevalence of the frail–general obese phenotype did not vary significantly by race, with 23% of African Americans and 22% of non-African Americans, exhibiting this phenotype (P > 0.9). Notably, 65% of those with the frail–general obese phenotype had comorbidity and 35% did not (Figure 1A). Frail participants had a higher mean BMI [frail 30.3 kg/m^2 (SD 8.3), nonfrail 28.3 kg/m^2 (SD 7.4); P = 0.02] (Supplementary data, Figure S2) and were more likely to have general obesity (frail 43%, nonfrail 32%; P = 0.03). As compared with BMI < 25 kg/m^2, BMI ≥ 30 kg/m^2 was associated with a 2.34-fold increased odds of being frail [95% confidence interval (CI) 1.36–4.04; P = 0.002] and a BMI of

Table 2. Distribution of general obesity by abdominal obesity among adults initiating HD ($N = 370$)

General obesity	Abdominal obesity		Total
	Above median WHR	Below median WHR	
BMI ≥ $30 kg/m^2$	90	49	139
BMI < $30 kg/m^2$	95	136	231
Total	185	185	370

WHR, waist-to-hip ratio, BMI, body mass index.

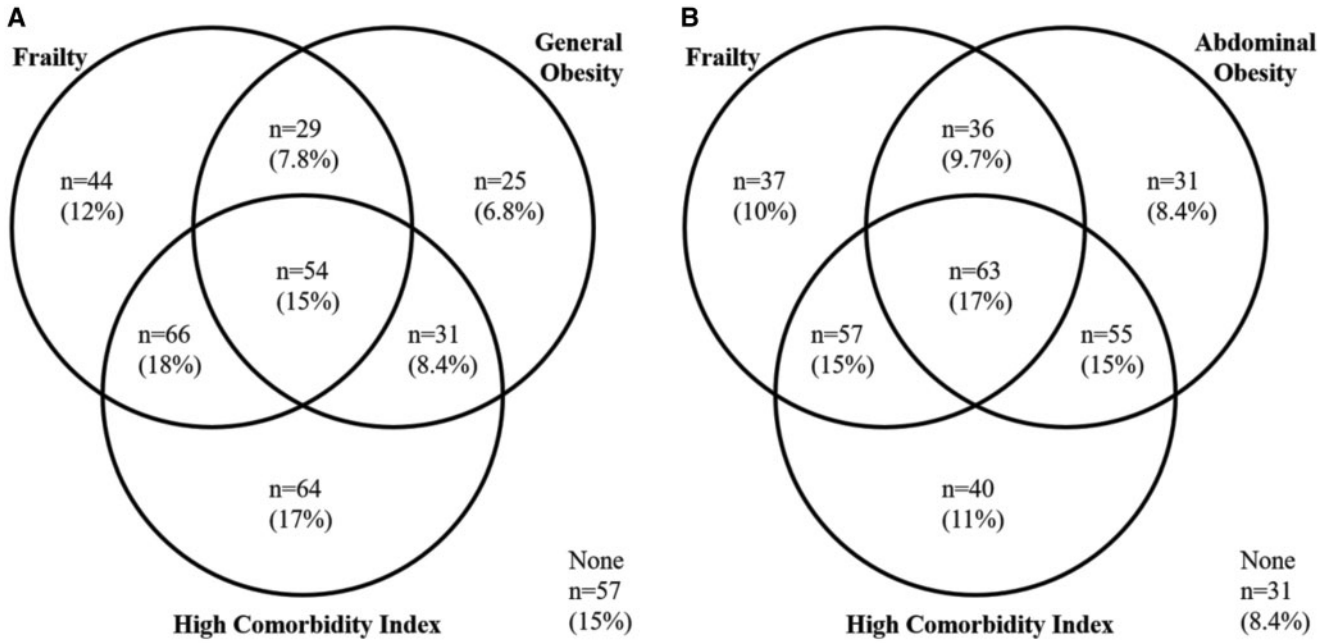

FIGURE 1: Venn diagram displaying the overlap of frailty, **(A)** general obesity, measured by BMI, or **(B)** abdominal obesity, measured by WHR, and comorbidity among adults initiating HD ($n = 370$). Frailty defined as three or more of the Fried criteria. Obesity was defined as BMI $\geq$30 kg/m^2 or above-median WHR. High comorbidity index was defined as a CCI score $\geq$5.

25–29.99 kg/m^2 was not statistically associated with higher odds of being frail [odds ratio (OR) 1.62 (95% CI 0.94–2.82); P = 0.08] after adjusting for age, sex, race, WHR, CCI and serum albumin ($P_{trend} = 0.001$).

Abdominal obesity and frailty

Among adults initiating HD, 27% had the frail–abdominal obese phenotype. The prevalence of the frail–abdominal obese phenotype did not vary significantly by race, with 25% of African Americans and 31% of non-African Americans exhibiting this phenotype (P = 0.3). Notably, 64% of those with the frail–abdominal obese phenotype had comorbidity and 36% did not (Figure 1B). Mean WHR did not differ by frailty status (P = 0.8) (Supplementary data, Figure S2) nor did the proportion of participants with abdominal obesity (frail 51%, nonfrail 51%; P = 0.7). The lack of association between WHR and frailty status persisted in adjusted analyses [0.1 WHR increase; OR 0.90 (95% CI 0.66–1.21)].

Frailty and mortality

A total of 915.3 person-years of follow-up were accrued during this study with 81 deaths. The median follow-up time was 2.48 years (IQR 1.37–3.51). The crude incidence rates of all-cause mortality were 88.5 per 1000 person-years (95% CI 70.3–110.0) overall, 109.8 per 1000 person-years (95% CI 81.7–144.4) among frail individuals and 66.5 per 1000 person-years (95% CI 44.9–95.0) among nonfrail individuals.

The unadjusted cumulative incidence of all-cause mortality was higher among frail participants (P = 0.03) (Figure 2). Frail individuals had a 1.66-fold increased risk of mortality (95% CI 1.03–2.67) independent of age, sex, race, BMI, WHR, CCI and serum albumin (Table 3). There was no evidence that the association between frailty and mortality differed by race ($P_{interaction} = 0.7$).

Frailty, general obesity and mortality

A BMI $\geq$30 kg/m^2 was independently associated with a 0.34-times decreased risk of mortality (95% CI 0.19–0.62) and a BMI of 25–29.99 kg/m^2 was associated with a 0.53-times decreased risk of mortality (95% CI 0.31–0.93) as compared with a BMI $<$25 kg/m^2 (Table 3). The association of BMI and mortality was qualitatively similar among frail and nonfrail participants; there was no evidence of effect modification by frailty status ($P_{interaction} = 0.3$; Supplementary data, Table S4). Among participants with general obesity, those who were frail had a 3.77-fold increased risk of all-cause mortality (95% CI 1.10–12.92) independent of race, CCI and serum albumin. This association was robust to further adjustment for factors that were significantly different between participants with and without general obesity, including sex, smoking status, dialysis adequacy and serum CRP, HDL cholesterol and triglyceride concentrations [frail versus nonfrail, hazard ratio (HR) 3.74 (95% CI 1.07–13.05)]. There was no evidence of association between frailty and mortality among participants without general obesity [HR 1.23 (95% CI 0.74–2.07)]. The risk of mortality associated with frailty, however, was not statistically different between those with and without general obesity ($P_{interaction} = 0.3$).

Frailty, abdominal obesity and mortality

WHR was not associated with all-cause mortality in unadjusted or fully adjusted Cox models (Table 3). Among HD patients with abdominal obesity, those who were frail had a 2.38-fold increased risk of all-cause mortality (95% CI 1.17–4.82) independent of race, BMI, CCI and serum albumin. This

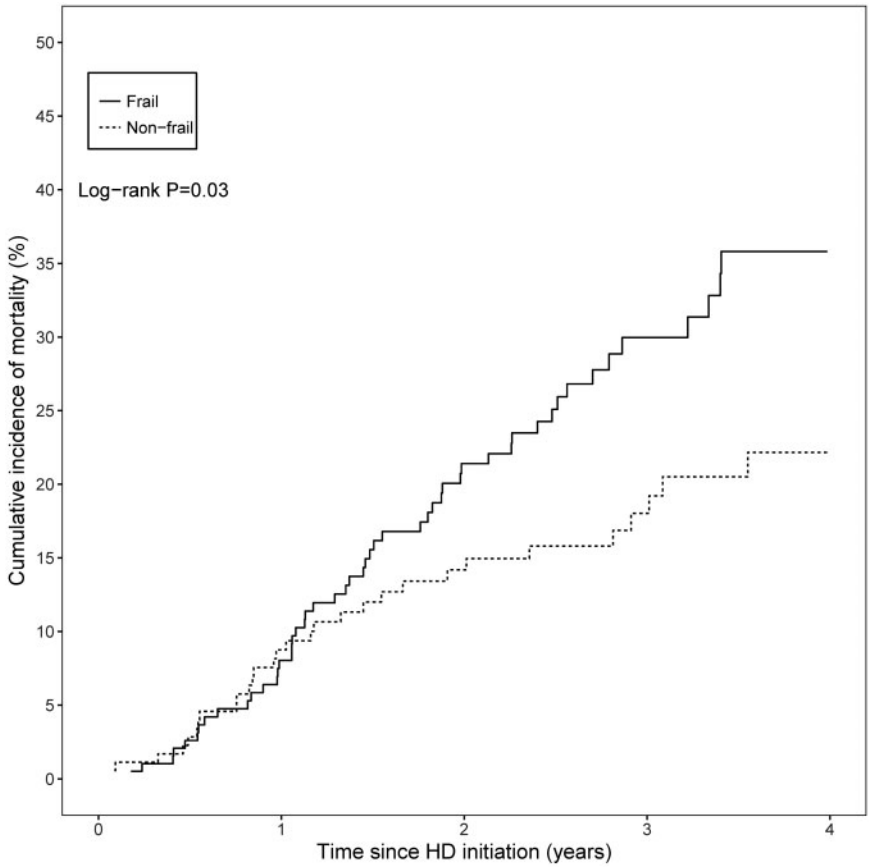

FIGURE 2: Cumulative incidence of all-cause mortality among frail and nonfrail incident HD patients ($n = 370$).

Table 3. Independent associations of baseline frailty, BMI and WHR with all-cause mortality among adults initiating HD ($n = 370$)

	Independent association	
Model	HR (95% CI)	P-value
Overall[a]		
Frail versus nonfrail	1.66 (1.03–2.67)	0.04
WHR, per 0.1 increase	1.01 (1.01–1.02)	0.4
BMI versus 25 kg/m^2		
25–29.99 kg/m^2	0.53 (0.31–0.93)	0.02
≥30 kg/m^2	0.34 (0.19–0.62)	<0.001
Among BMI <30 kg/m^2[b]		
Frail versus nonfrail	1.23 (0.74–2.07)	0.4
Among BMI ≥30 kg/m^2[b]		
Frail versus nonfrail	3.77 (1.10–12.92)	0.04
Below median WHR[c]		
Frail versus nonfrail	1.21 (0.65–2.25)	0.6
Above median WHR[c]		
Frail versus nonfrail	2.38 (1.17–4.82)	0.02

[a]Independent associations of frailty, BMI and WHR adjusted for age, sex, race, CCI and albumin.
[b]Models adjusted for race, CCI and albumin.
[c]Models adjusted for race, CCI, BMI and albumin.
HR, hazard ratio, WHR, waist-to-hip ratio, BMI, body mass index, CCI, Charlson comorbidity index.

association was robust to further adjustment for sex, smoking status, dialysis adequacy and serum CRP, HDL cholesterol and triglyceride concentrations [frail versus nonfrail, HR 2.52 (95% CI 1.23–5.18)]. There was no evidence of an association between frailty and mortality among participants without abdominal obesity [HR 1.21 (95% CI 0.65–2.25)]. The risk of mortality associated with frailty, however, was not statistically different between those with and without abdominal obesity ($P_{interaction} = 0.9$).

Sensitivity analyses

In an adjusted Cox model, a 1-point increase in the rescaled frailty score was associated with 1.24-fold increased mortality risk (95% CI 1.09–1.41) independent of age, sex, race, BMI, WHR, CCI and serum albumin.

The unadjusted cumulative incidence of all-cause mortality remained higher among frail individuals when the Kaplan–Meier estimate was adjusted for delayed entry ($P = 0.02$). The association of frailty and mortality was robust to the functional form of BMI used. In addition, there was no evidence of non-linearity in the association of BMI with risk of mortality ($P = 0.2$). Furthermore, an interaction between frailty and BMI as a spline was not significant ($P = 0.06$). The association of frailty and mortality was also robust to further adjustment for dialysis vintage at study enrollment [frail versus nonfrail, HR 1.65 (95% CI 1.02–2.65)]. Among general obese individuals, the adjustment for age [frail versus nonfrail, HR 3.76 (95% CI 1.08–13.0)] and dialysis vintage [frail versus nonfrail, HR 3.85 (95% CI 1.10, 13.4)] did not change inferences on the association between frailty and mortality. Similarly, among individuals with abdominal obesity, the association of frailty and mortality was

robust to further adjustment for age [frail versus nonfrail, HR 2.38 (95% CI 1.17–4.84)] and dialysis vintage [frail versus nonfrail, HR 2.49 (95% CI 1.21–5.11)]. The association between frailty and mortality was similar in magnitude among individuals with BMI $<23\,kg/m^2$ and $\geq 23\,kg/m^2$ and among individuals with BMI $<20\,kg/m^2$ and $\geq 20\,kg/m^2$ (data not shown).

DISCUSSION

In this prospective cohort study of adults who have recently initiated HD, the prevalence of the frail–general obese phenotype was 22% and that of the frail–abdominal obese phenotype was 27%. General obesity was associated with 66% lower risk of mortality, whereas abdominal obesity was not associated with mortality. Frailty was associated with 1.7-fold increased risk of mortality among HD patients overall and, by obesity status, frailty had a 3.8-fold greater risk of mortality among those with general obesity and a 2.4-fold greater risk of mortality among those with abdominal obesity.

General obesity is commonly described as lowering the risk of mortality despite a higher BMI in dialysis patients. Repeated confirmation of this observation led to the formulation of the so-called 'obesity paradox' [14, 23, 24]. A recent meta-analysis of four studies including 81 423 HD participants reported that those with elevated adiposity (BMI $>25\,kg/m^2$) had 0.67-fold odds of mortality [25]. Our data confirm the association of general obesity with decreased risk of mortality in incident HD patients. The association of abdominal obesity with all-cause mortality in the HD population, however, remains relatively unexplored. Our finding that abdominal obesity was not associated with mortality contrasts with a previous study in which abdominal obesity was associated with an increased risk of all-cause mortality among 537 prevalent HD patients [15]. This difference may arise from survival bias introduced into the previous study by including prevalent HD patients.

Frailty is prevalent in ESRD patients of all ages [2, 9, 10, 26–28]. Previous studies have found that frailty is associated with an increased risk of mortality among ESRD patients [29], incident HD patients [10] and prevalent HD patients [9]. Frailty is also associated with falls [19], hospitalization [9, 29] and cognitive dysfunction [30]. Our present results confirm that frailty is associated with an increased risk of mortality in incident HD patients.

The frail–general obese phenotype has previously been identified in community-dwelling elderly [7], where the frail–general obese have a 3.89-fold increased risk of mortality as compared with the nonfrail nonobese [8]. Moreover, in ESRD patients, protein energy wasting was associated with an increased mortality risk in both overweight and nonoverweight patients [31]. Here we extend these findings to HD patients where the frail–obese phenotype can be identified using either general or abdominal obesity. Frail–general obese HD patients had a 3.8-fold increased risk of mortality and the corresponding fold increase among frail–abdominal obese HD patients was 2.4. Our findings suggest that physicians may not be reassured by obesity when managing HD patients, as sarcopenia may still ensue with increasing frailty, potentially resulting in increased morbidity and mortality.

The cohort demographics differ from those of the US HD population in that the cohort was 73% African American participants and from urban areas; this population is often underrepresented in clinical studies. We noted that the prevalence of the frail–general obese and frail–abdominal obese phenotypes did not differ by race. Furthermore, the association between frailty, body composition and mortality did not differ by race. Thus, although this cohort comprised 73% African Americans, the lack of a differential association between frailty, body composition and mortality by race suggests that the impact of the frail–obese phenotype does not differ by race and this allows us to generalize the results of our study to the US HD population.

Strengths of this study include the prospective nature of the cohort and the inclusion of adults of all ages who have recently initiated HD. This is a well-characterized cohort with adjudicated comorbidities at baseline. Frailty was measured using a validated and objective instrument. Another limitation of our study was the absence of a measure of fluid status at study enrollment. Although body composition at dialysis initiation may be affected by fluid overload, we do not expect fluid overload to greatly affect our results because the median dialysis vintage at study enrollment was 3.4 months. Our use of self-reported dry weight reflects another limitation, because it is not always an accurate measure of dry weight. In this cohort, however, the mean difference between self-reported dry weight and measured weight on the nondialysis day was only 0.6 kg. Furthermore, although BMI is commonly used to reflect obesity, its validity as a measure of excess adiposity has been questioned [32], which is one of the reasons that we considered multiple measures of adiposity. Moreover, frailty and body composition were measured at study enrollment only, thus we were unable to examine longitudinal changes in body composition and progression of frailty. Although 52 (14%) participants were lost to follow-up, these participants did not differ from those who completed the study by general obesity, abdominal obesity, frailty status or any other clinical factors. Finally, although we had adequate statistical power to detect independent associations, we may not have had sufficient power to detect interactions in the analyses of effect modification.

In summary, we have identified the frail–general obese phenotype in 22% of a cohort of incident HD patients and the frail–abdominal obese phenotype in 27%. This phenotype was associated with a 3.8-fold (general obesity) or 2.4-fold (abdominal obesity) increased risk of mortality. Our results suggest that the protective effect generally ascribed to obesity in HD patients may not be consistent across all members of this population and that the frail–obese comprise a subgroup at high risk of mortality. Previous work has highlighted that clinicians are less likely to identify frailty in obese HD patients [33], possibly because obesity is generally viewed as a protective factor. Frail–obese HD patients are therefore not only at high risk of mortality but may also be an overlooked population, and identification of this phenotype could play an important role in clinical risk stratification.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

We thank the participants who volunteered their time and effort. We also thank the nephrologists and staff of the DaVita and MedStar dialysis units in the Baltimore area, in particular, Mid-Atlantic Nephrology Associates and the Nephrology Center of Maryland, who all contributed actively to the PACE study. We thank Lucy Meoni for her longstanding contributions to the PACE study. We thank the PACE study Endpoint Committee: Bernard G. Jaar, MD, MPH (Chair); Michelle M. Estrella, MD, MHS; Stephen M. Sozio, MD, MHS, MEHP; Rulan S. Parekh, MD, MS; N'Dama Bamba, MD; Wei Tsai, MD, MS, MPH; Geetha Duvuru, MD; Julia Scialla, MD, MHS; Teresa K. Chen, MD, MHS; Jose Manuel Monroy Trujillo, MD; Frances-LLena Capili, MD; Ijaz Anwar, MD; Lili Zhang, MD; Manisha Ghimire, MD; Raghotham Narayanaswamy, MD; Ramya Ravindran, MD; Svetlana Chembrovich, MD; and Stefan Hemmings, MD.

FUNDING

This study was supported by the National Institutes of Health [R01AG042504, K24DK101828 (principle investigator D.S.) and R01AG055781 (principle investigator M.A.M-D.). M.A.M-D. was also supported by the Johns Hopkins University Claude D. Pepper Older Americans Independence Center (P30AG021334) and the National Institute on Aging (K01AG043501). The PACE study was supported by National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK072367 (principle investigator R.S.P.).

AUTHORS' CONTRIBUTIONS

B.G.J., M.M.E., S.M.S., D.L.S., R.S.P. and M.A.M-D. were responsible for the research idea and study design. B.G.J., M.M.E., S.M.S. and R.S.P were responsible for the data acquisition. J.F. and M.A.M-D. performed the data analysis/interpretation. J.F. performed the statistical analysis. R.S.P. and M.A.M-D. provided supervision/mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

R.S.P. reports grants from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease and the Canadian Institutes of Health Research during the conduct of the study.

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Received: 21.12.2017; Editorial decision: 28.3.2018