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Association of abdominal adiposity with cardiovascular mortality in incident hemodialysis

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Abstract

Background: Risk of cardiovascular mortality is high among adults with end stage renal disease (ESRD) undergoing hemodialysis. Waist-to-hip ratio (WHR), a metric of abdominal adiposity, is a

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AUTHOR CONTRIBUTIONS

Research idea and study design: B.J., M.E., S.S., D.S., R.P., L.T., M.M.-D.; data acquisition: B.J., M.E., S.S., R.P.; data analysis/interpretation: J.F., R.P.; statistical analysis: J.F.; supervision/mentorship: R.P. 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.

STATEMENT OF ETHICS

The study protocol was approved by the Johns Hopkins University Institutional Review Board, MedStar Health Systems, and the medical director of each dialysis unit. Participants provided written informed consent.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

predictor of cardiovascular disease (CVD) and mortality in the general population; however, no studies have examined the association with CVD mortality, particularly sudden cardiac death (SCD), in incident hemodialysis.

Methods: Among 379 participants incident (< 6 months) to hemodialysis enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study, we evaluated associations between WHR and risk of CVD mortality, SCD, and non-CVD mortality in Cox proportional hazards regression models.

Results: At study enrollment, mean age was 55 years with 41% females, 73% African Americans, and 57% diabetics. Mean body mass index was 29.3 kg/m², and mean WHR was 0.95. During a median follow-up time of 2.5 years, there were 35 CVD deaths, 15 SCDs, and 48 non-CVD deaths. Every 0.1 increase in WHR was associated with higher risk (hazard ratio [95% confidence interval]) of CVD mortality (1.75 [1.06–2.86]) and SCD (2.45 [1.20–5.02]), but not non-CVD mortality (0.93 [0.59–1.45]), independently of demographics, BMI, comorbidities, inflammation, and traditional CVD risk factors.

Conclusions: WHR is significantly associated with CVD mortality including SCD, independently of other CVD risk factors in incident hemodialysis. This simple, easily-obtained bedside metric may be useful in dialysis patients for CVD risk stratification.

Keywords

Abdominal adiposity; waist-to-hip ratio; end stage renal disease; mortality; sudden cardiac death

INTRODUCTION

End stage renal disease (ESRD) patients receiving hemodialysis are at higher risk of cardiovascular disease (CVD) mortality than the general population. Forty-one percent of deaths in ESRD stem from CVD.[1] Sudden cardiac death (SCD), in particular, is the single most common cause of death among dialysis patients, accounting for approximately 29% of all deaths between 2012–2014.[1] Many investigated factors lack potential to identify dialysis patients at high-risk of CVD mortality and SCD or inform clinical decisions.[2–5] Simple, easily-measured clinical predictors of CVD mortality and SCD are needed.

Association of obesity with CVD mortality is well-established in the general population. In particular, both general and abdominal obesity are risk factors for SCD among community-dwelling individuals.[6, 7] In hemodialysis patients, however, general obesity is protective and results in reduced risk of all-cause and CVD mortality.[8–12] Although the mechanism by which this benefit is conferred remains under investigation, the greater nutritional reserve reflected in general obesity may protect patients from the risk associated with inflammation and wasting that accompany dialysis.[8–10] There is, however, evidence that all forms of obesity are not equally beneficial in dialysis and that the distribution of body fat plays a key role in determining mortality risk. Abdominal adiposity, as assessed by the waist-to-hip ratio (WHR), was associated with increased risk of all-cause and CVD mortality among 537 prevalent hemodialysis patients from Italy[11] and all-cause mortality in a small cohort of 22 peritoneal dialysis patients from a single center in Canada.[13] Survival bias in these prevalent dialysis patients remains an important limitation, which can be overcome with

studies of incident patients. No study has examined the association of WHR with either CVD mortality or SCD among incident hemodialysis patients.

Given the strong association of abdominal adiposity with CVD mortality in the general population, the importance of identifying modifiable risk factors of CVD mortality and SCD in ESRD, and the paucity of studies on abdominal adiposity and CVD, we sought to determine 1) whether abdominal adiposity, assessed using WHR, was associated with increased risk of CVD mortality, particularly SCD, in a large prospective cohort of adults initiating hemodialysis and 2) whether the association was modified by general obesity.

MATERIALS AND METHODS

Study design and population

Abdominal adiposity was measured in an incident (< 6 months) hemodialysis cohort enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study.[14] Briefly, 568 participants were recruited from 27 dialysis units in Baltimore, MD, from November 2008 to August 2012. Participants who attended the baseline clinic visit for physical examination (N=379) were eligible for the present study. The study protocol was approved by the Johns Hopkins University Institutional Review Board, MedStar Health Systems, and the medical director of each dialysis unit. Participants provided written informed consent.

Abdominal adiposity

Abdominal adiposity at study enrollment was assessed using the validated WHR metric. WHR was calculated as the ratio of measured waist circumference (cm) to hip circumference (cm). High WHR was defined as WHR x sex-specific sample median (females=0.92, males=0.98).

Characteristics

At study enrollment, socio-demographic characteristics (age, sex, and race), smoking status, alcohol use, and medical history were collected through standardized questionnaires. BMI was calculated as the ratio of self-reported dry weight (kg) to height (m) squared at enrollment. General obesity was defined as BMI ≥ 30 kg/m². Comorbidities were assessed by medical chart review and adjudicated by the PACE Endpoint Committee, and classified using the Charlson Comorbidity Index. Systolic blood pressure was measured with participants in a seated position on a non-dialysis day. Measures of serum albumin, serum creatinine, single pool Kt/V, and relative weight loss during dialysis sessions were examined as 90-day averages from dialysis initiation. Serum C-reactive protein (CRP), triglyceride, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol concentrations were measured from fasting blood samples obtained at study enrollment. Non-HDL cholesterol concentration was calculated by subtracting HDL cholesterol from the total cholesterol concentration. High-sensitivity CRP was measured using an enzyme-linked immunosorbent assay at the Laboratory for Clinical Biochemical Research at the University of Vermont, with an intra-assay coefficient of variation of 7.3%. Lipid profile, also measured

at the University of Vermont, was obtained using a Roche Integra Analyzer with intra-assay coefficients of variation of 2.0% (HDL), 2.8% (LDL), and 5.1% (triglycerides).

Outcomes

Participants were followed until July 31, 2014 (n=161), death (n=83), transplant (n=40), transfer to peritoneal dialysis (n=14), transfer to long-term hospitalization (n=15), or loss to follow-up (n=66). Mortality was ascertained using reports from dialysis units confirmed with Centers for Medicare and Medicaid Services Form 2746. Cause of death was established using an adjudication protocol adapted from the HEMO study.[15] Two independent reviewers adjudicated all cases and discrepancies were resolved by a third reviewer. SCD was defined as a sudden pulseless condition (collapse or syncope), presumed to arise from arrhythmia, occurring out of the hospital or in the emergency room in an otherwise stable individual. An unwitnessed death was classified as SCD if there was evidence that the patient was in stable condition 24 hours preceding the event or at the last dialysis session. CVD death was defined as death arising from arrhythmia, ischemic CVD, ischemic cerebrovascular disease, or SCD.

Statistical Analyses

Participant characteristics were summarized using means and standard deviations for normally distributed data, medians and interquartile ranges for skewed data, and frequencies and proportions for categorical data. Characteristics were compared by WHR category using Student's t-test, the Mann-Whitney U test, or the χ^2 test.

Unadjusted cumulative incidence of mortality curves were computed to estimate the probability of CVD mortality, SCD, and non-CVD mortality, accounting for competing risks using the methods of Fine and Gray.[16] Non-CVD mortality was treated as a competing event for CVD-mortality and non-SCD mortality was treated as a competing event for SCD. The associations between WHR and CVD mortality, SCD, and non-CVD mortality were evaluated using cause-specific Cox proportional hazards regression. A forward model building approach was employed in which initial variable selection was conducted on the basis of known risk factors for abdominal adiposity and mortality in ESRD, P-values from univariate analyses, and changes in effect size. We separately examined non-linear relationships between WHR and CVD mortality, SCD, and non-CVD mortality by including restricted cubic splines with knots at the 10th, 50th, and 90th quantiles in fully-adjusted models.

In exploratory analyses, we investigated whether the magnitude of the association between baseline WHR and CVD or non-CVD mortality differs at short versus longer follow-up times. Analyses were repeated within two time windows: 1) within the first year of dialysis initiation and 2) after the first year of follow-up conditional of having survived the first year. [17] The small number of events precluded an analogous analysis for SCD.

Effect modification between WHR and CVD mortality was assessed with interaction terms between WHR and age, sex, race, and BMI in separate adjusted models. Stratified analyses were performed to assess modification by general obesity status. Final results are presented only for minimally adjusted models due to the small number of deaths per stratum.

We tested whether the results were similar following adjustment for 1) medication use, 2) individual comorbidities (diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, and chronic pulmonary disease), 3) smoking status, 4) cause of ESRD, 5) dialysis access type, and 6) dialysis adequacy.

The proportional hazards assumption was verified using scaled Schoenfeld residuals, and the linearity assumption of continuous variables was assessed using plots of Martingale residuals versus fitted values. Multicollinearity was assessed by measuring variance inflation factors. All missing covariate data were imputed using the multiple imputation by chained equations method with 20 imputations and 20 iterations.[18] Imputed variables include smoking status (0.3%), BMI (0.3%), CRP (3%), albumin (0.8%), LDL-cholesterol (4%), HDL-cholesterol (3%), triglycerides (3%), and lipid-lowering medication use (9%). Statistical analyses were performed in R version 3.4.1.

RESULTS

Participant characteristics at study enrollment

Among 379 adults initiating hemodialysis, mean age was 55 ± 13 years, and most were younger than 65 years (77%). The majority were male, African American, and had a history of smoking (Table 1). The most common primary cause of ESRD was diabetic nephropathy. Median dialysis vintage at study enrollment was 3.5 months (IQR: 2.6, 4.9). All participants had a history of hypertension, and congestive heart failure and coronary artery disease were also highly prevalent. Mean WHR was 0.98 ± 0.08 for men and 0.92 ± 0.07 for women; the corresponding medians were 0.98 (IQR: 0.92–1.02) and 0.92 (IQR: 0.87–0.96). WHR and BMI were weakly correlated ($r=0.21$).

Compared to participants below the median WHR by sex, those above the median WHR had higher BMI with 49% having a BMI ≥ 30 kg/m². Diabetic nephropathy was the most common cause of ESRD among those above the median WHR, whereas hypertension was the most common cause of ESRD among those below the median WHR. Additionally, those above the median WHR were more likely to have diabetes and use lipid-lowering medication at study entry. Median serum CRP and triglyceride concentrations were higher in those above the median WHR. In contrast, median HDL cholesterol was lower among those above the median WHR.

WHR and mortality

During 938 person-years, there were 83 deaths from all causes, 48 non-CVD deaths (incidence rate: 52.2, 95% CI: 37.7–67.9 per 1000 person-years), and 35 CVD deaths (incidence rate: 37.3, 95% CI: 26.0–51.9 per 1000 person-years), including 15 SCD (incidence rate: 16.0, 95% CI: 9.0–26.4 per 1000 person-years) (Figure 1). Median follow-up time was 2.5 years (IQR: 1.4–3.5).

Each 0.1 increase in WHR was associated with 1.73-fold increased risk of CVD mortality (95% CI: 1.03–2.90) independent of demographics, BMI, and the Charlson Comorbidity Index (Table 2). WHR remained associated with CVD mortality after further adjustment for CRP, albumin, and non-HDL cholesterol concentrations (0.1 increase, HR: 1.75, 95% CI:

1.06–2.86). Similarly, WHR was significantly associated with increased risk of SCD (0.1 increase, HR: 2.45, 95% CI: 1.20–5.02) after adjusting for demographic characteristics, BMI, the Charlson Comorbidity Index, CRP, albumin, and non-HDL cholesterol concentrations. There was no evidence of nonlinear associations of WHR with CVD mortality or SCD (both $P_{\text{non-linearity}} > 0.3$). WHR was not associated with non-CVD mortality. There was no evidence that the association between WHR and CVD mortality, SCD, or non-CVD mortality differed by race (all $P_{\text{interaction}} > 0.5$).

Time-stratified association of WHR and mortality

During follow-up, 14 CVD deaths occurred in the first year and 21 CVD deaths thereafter. In a fully-adjusted Cox model, every 0.1 increase in WHR was associated with 2.48-fold increased risk of CVD mortality (95% CI: 1.15–5.33) within the first year of follow-up (Table 3). WHR was not associated with longer-term mortality risk (> 1 year follow-up). During the study, 17 non-CVD deaths occurred in the first year and 31 non-CVD deaths thereafter. WHR was not associated with non-CVD mortality in either of the follow-up time windows. The proportional hazards assumption was not formally violated ($P=0.1$).

WHR, general obesity, and mortality

There were 11 CVD deaths among those with general obesity and 24 CVD deaths among those without general obesity. Among participants with general obesity, there was no evidence of association between WHR and CVD mortality (0.1 increase, HR: 1.26, 95% CI: 0.54–2.82; Table 3). In contrast, every 0.1 increase in WHR was associated with 1.91-fold increased CVD mortality risk among participants without general obesity (95% CI: 1.03–3.57). The risk of CVD mortality associated with WHR, however, was not statistically different between those with and without general obesity ($P_{\text{interaction}}=0.2$). There was no evidence of association of WHR with non-CVD mortality among participants with or without general obesity (Table 3).

Sensitivity Analyses

The associations of WHR with CVD mortality and SCD were similar when adjusted for 1) lipid-lowering medication use, 2) individual comorbidities instead of the the Charlson Comorbidity Index, 3) smoking status, 4) cause of ESRD, and 5) dialysis access type and adequacy.

DISCUSSION

In a prospective cohort of adults with ESRD, abdominal adiposity, as assessed by WHR at the time of hemodialysis initiation, was linearly associated with increased risk of CVD mortality and SCD independently of demographics, comorbidities, markers of inflammation, and traditional cardiovascular risk factors. Each 0.1 increase in WHR was associated with 1.75-fold increased risk of CVD mortality and 2.45-fold increased risk of SCD.

Our results suggest that clinical risk stratification of incident hemodialysis patients may benefit from incorporating a measure of abdominal adiposity to help identify those patients at highest risk of CVD mortality, in particular SCD. The allocation of resources to more

mortality or SCD in the present study of hemodialysis patients. This finding could suggest that factors other than inflammation may play a dominant role or that CRP is not the correct inflammatory marker to assess inflammation from abdominal adiposity. Furthermore, the influence of abdominal adiposity on risk of CVD mortality was greater in the first year of follow-up than at later times, a finding that appears to contrast the progressive nature of inflammatory stress observed in the general population.

In addition to influencing atherosclerotic disease, abdominal adiposity may also influence arrhythmogenicity, which is important in SCD development. General and abdominal obesity have been associated with increased intramyocardial fat,[32–34] which can lead to left ventricular hypertrophy, diastolic dysfunction, electrocardiographic abnormalities, and increased arrhythmogenicity.[32] Intraarterial fat, which can elicit a paracrine effect via the release of proinflammatory and profibrotic cytokines,[35] was associated with increased risk of atrial fibrillation,[36, 37] which may in turn progress to terminal arrhythmia. Although several electrocardiographic factors have been identified as predictors of CVD mortality and SCD in this population,[2, 4, 5] few easily-obtained anthropometric measures are available to function in this capacity. Moreover, abdominal adiposity may be a modifiable risk factor that provides a means to actively decrease risk of CVD mortality, particularly SCD, in hemodialysis.

Strengths of this study include the prospective nature of this well-characterized cohort, inclusion of adults of all ages, adjudication of comorbidities and cause of death, and use of a standardized protocol to measure WHR. In this cohort, the WHR distribution was similar to those of general,[6, 38] and CKD populations.[39] In comparison to the 2012–2014 U.S. incident hemodialysis population, our study population featured greater proportions of African Americans (73% vs. 27%) and younger adults (77% vs. 49% below 65 years), but similar proportions of females and primary diagnoses of diabetic nephropathy.[1] The cohort contained a large proportion of African American participants from urban areas, a population often under-represented in clinical studies. Although 66 (17%) participants were lost to follow-up, they did not differ from those who completed the study by general or abdominal obesity, or any other clinical factors. 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 non-dialysis day was only 0.6 kg. Another limitation of the study is that other measures of body composition, such as bioelectrical impedance analysis, were not available. Also, electrolyte fluxes over the course of the dialysis session which contribute to SCD were not available for this study. Finally, this study also had limited statistical power: although we were adequately powered to detect independent associations, we may not have had sufficient power to detect significant interactions with obesity.

In summary, abdominal adiposity was strongly associated with increased risk of CVD mortality, especially SCD, in incident hemodialysis patients. This association was independent of many confounders, specifically inflammatory and traditional CVD risk factors. Furthermore, the association between abdominal adiposity and CVD mortality was greatest in the first year on dialysis and among those without general obesity. The utility of the waist-to-hip ratio is further highlighted by its simplicity and the ease with which it can

be obtained and aid in risk stratification of dialysis patients. Our results advocate for further studies of timely interventions that treat abdominal adiposity to mitigate CVD mortality among dialysis patients.

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Figure 1. Competing risk survival curves for cardiovascular disease (CVD) mortality, sudden cardiac death (SCD), non-CVD mortality, and all-cause mortality among incident hemodialysis patients (N=379).

Table 1.

PACE participant characteristics at study enrollment overall and by waist-to-hip ratio category

Characteristic	Mean $\pm$ SD, median (IQR), or frequency (%)			P-value
	Overall (N=379)	Below median WHR (N=189)	Above median WHR (N=190)	
Age, years	55 $\pm$ 13	55 $\pm$ 14	54 $\pm$ 13	0.4
Female sex	156 (41)	78 (41)	78 (41)	0.9
Black race	277 (73)	146 (77)	131 (68)	0.09
High school education or higher	233 (62)	111 (59)	112 (65)	0.3
Smoking status				0.6
Current smoker	114 (30)	56 (30)	48 (25)	
Former smoker	128 (34)	64 (34)	64 (34)	
Never smoker	146 (39)	69 (37)	77 (41)	
Current or former drinker	304 (81)	153 (82)	151 (80)	0.7
BMI, kg/m ²	29.3 $\pm$ 7.9	27.3 $\pm$ 7.8	31.2 $\pm$ 7.5	<0.001
Obese (BMI $\geq$ 30 kg/m ²)	141 (37)	48 (26)	93 (49)	<0.001
Cause ESRD				<0.001
Glomerulonephritis	52 (14)	28 (15)	24 (13)	
Hypertension	100 (26)	60 (32)	40 (21)	
Diabetes	131 (35)	46 (24)	85 (45)	
Other	59 (16)	38 (20)	21 (11)	
Unknown	37 (10)	17 (9)	20 (11)	
Comorbidities				
Coronary artery disease	141 (37)	62 (33)	79 (42)	0.09
Congestive heart failure	157 (41)	73 (39)	84 (44)	0.3
Cerebrovascular disease	86 (23)	44 (23)	42 (22)	0.9
Peripheral vascular disease	74 (20)	35 (19)	39 (21)	0.7
Hypertension	379 (100)	189 (100)	190 (100)	0.9
Diabetes	216 (57)	84 (44)	132 (69)	<0.001
History of cancer	31 (8)	24 (13)	7 (4)	0.003
Chronic pulmonary disease	87 (23)	37 (20)	50 (26)	0.2
Charlson comorbidity index	5.2 $\pm$ 2.2	5.1 $\pm$ 2.3	5.3 $\pm$ 2.1	0.4
Systolic blood pressure, mm Hg	137 $\pm$ 25	138 $\pm$ 25	136 $\pm$ 26	0.5
C-reactive protein, μ g/ml	5.9 (2.3, 15.0)	5.1 (1.9, 11.4)	6.5 (2.6, 17.1)	0.05
Serum albumin, g/dl	3.6 $\pm$ 0.5	3.5 $\pm$ 0.5	3.6 $\pm$ 0.4	0.6
LDL cholesterol, mg/dl	83 (61, 108)	89 (62, 117)	81 (61, 103)	0.1
HDL cholesterol, mg/dl	49 (39, 63)	55 (44, 68)	45 (36, 56)	<0.001
Serum triglycerides, mg/dl	118 (87, 164)	109 (82, 137)	133 (96, 186)	<0.001
Serum creatinine, mg/dl	6.3 (5.3, 7.9)	6.4 (5.2, 7.9)	6.3 (5.3, 7.9)	0.9
Single pool Kt/V	1.4 (1.3, 1.6)	1.5 (1.3, 1.6)	1.4 (1.2, 1.6)	0.07
Weight loss during dialysis (%)	-2.49 $\pm$ 0.96	-2.63 $\pm$ 1.00	-2.36 $\pm$ 0.90	0.008
Vascular access				0.6

Characteristic	Mean $\pm$ SD, median (IQR), or frequency (%)			P-value
	Overall (N=379)	Below median WHR (N=189)	Above median WHR (N=190)	
Arteriovenous fistula	114 (30)	55 (29)	59 (31)	
Arteriovenous graft	15 (4)	6 (3)	9 (5)	
Venous catheter	249 (66)	128 (68)	121 (64)	
Medications				
β -blocker	244 (70)	123 (70)	121 (70)	0.9
ACE inhibitor	116 (33)	58 (33)	58 (34)	0.9
Angiotensin receptor blocker	42 (12)	16 (9)	26 (15)	0.1
Calcium channel blocker	208 (60)	111 (63)	97 (56)	0.2
Total number of antihypertensive medications	3 (2, 3)	3 (2, 3.5)	2 (2, 3)	0.7
Lipid-lowering	179 (51)	75 (43)	104 (60)	0.002

NB: IQR: interquartile range, BMI: body mass index, WHR: waist-to-hip ratio, ESRD: end stage renal disease, LDL: low density lipoprotein, HDL: high density lipoprotein

Table 2.

Association of waist-to-hip ratio with cardiovascular disease mortality, sudden cardiac death, and non-cardiovascular disease mortality among incident hemodialysis patients (N=379)

	Per 0.1 increase in WHR	
	HR (95% CI)	P-Value
CVD Mortality		
Unadjusted model	1.35 (0.88, 2.07)	0.17
Model 1 ^a	1.79 (1.07, 2.99)	0.03
Model 2 ^b	1.73 (1.03, 2.90)	0.04
Model 3 ^c	1.75 (1.06, 2.86)	0.03
SCD		
Unadjusted	2.07 (1.09, 3.94)	0.03
Model 1 ^a	2.62 (1.25, 5.51)	0.01
Model 2 ^b	2.58 (1.22, 5.44)	0.01
Model 3 ^c	2.45 (1.20, 5.02)	0.01
Non-CVD Mortality		
Unadjusted model	0.72 (0.49, 1.05)	0.09
Model 1 ^a	0.88 (0.56, 1.39)	0.6
Model 2 ^b	0.86 (0.54, 1.35)	0.7
Model 3 ^c	0.93 (0.59, 1.45)	0.7

NB: WHR: waist-to-hip ratio, CVD: cardiovascular disease, SCD: sudden cardiac death

^aModel adjusted for age, sex, race, and BMI

^bModel adjusted for age, sex, race, BMI, Charlson Comorbidity Index

^cModel adjusted for age, sex, race, BMI, Charlson Comorbidity Index, CRP, albumin, non-HDL cholesterol

Table 3.

Stratified associations of waist-to-hip ratio with cardiovascular disease, and non-cardiovascular disease mortality among incident hemodialysis patients (N=379)

	Per 0.1 increase in WHR			
	CVD mortality		Non-CVD mortality	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
<i>Stratification by follow-up time</i>				
1 year mortality [†]	2.48 (1.15, 5.33)	0.02	0.93 (0.45, 1.91)	0.8
> 1 year mortality [†]	1.38 (0.74, 2.58)	0.3	0.91 (0.51, 1.63)	0.8
<i>Stratification by BMI category</i>				
30 kg/m ² ^{††}	1.23 (0.54, 2.82)	0.5	1.15 (0.44, 2.98)	0.8
< 30 kg/m ² ^{††}	1.91 (1.03, 3.57)	0.04	0.86 (0.50, 1.49)	0.6

[†]Model adjusted for age, sex, race, BMI, Charlson Comorbidity index, and serum albumin

^{††}Model adjusted for age, sex, race, Charlson Comorbidity index, and serum albumin