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Sarcopenia Obesity Definitions by Body Composition and Mortality in the Hemodialysis Patients

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Abstract

Objective—Sarcopenic obesity (SO), a combination of low muscle mass and high fat mass, is considered as risk factor for mortality in general population. It is unclear if SO affects mortality in maintenance hemodialysis (MHD) patients. In this study, we aimed to determine whether body composition as assessed by currently available SO definitions are related to all-cause mortality in MHD subjects. We also examined the impact of applying different definitions on the prevalence of SO in our MHD database.

Design—Retrospective analysis

Subjects and Settings—Adult patients on MHD for at least 3 months with no acute illness studied in the clinical research center between 2003 and 2011.

Intervention—Assessment of body composition was performed using dual energy x-ray absorptiometry (DEXA). SO (Appendicular Skeletal Mass (ASM): arm lean mass + leg lean mass and fat mass) was defined according to Baumgartner definition, Janssen Criteria 1 and Janssen Criteria 2.

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Main Outcome Measure—All-cause mortality and prevalence of SO. Patient deaths were ascertained from medical records and United States social security death index.

Results—Of 122 participants, 62% were male; mean age was 46 (interquartile range [IQR] 40, 54) in men and 50 (44, 61) in women. Prevalence of SO ranged from 12% to 62% in men and 2% to 74% in female according to different definitions. SO prevalence was lowest using the Baumgartner criteria (all: 8%, men 12%, women: 2%), and highest according to the Janssen Criteria 2 (all: 57%, men 46%, women 74%). There were 45 deaths during a median follow-up period of 44 (20, 76) months. SO by any definition was not statistically significantly associated with mortality during follow up.

Conclusions—The current SO definitions are not applicable to predict increased risk of death in MHD patients. We found high degree of variation in the rates of SO when using different definitions. Future studies should focus on establishing MHD population-specific thresholds of muscle mass and adiposity for accurate prognostication.

Introduction

Low muscle mass, also termed as sarcopenia, is common in maintenance hemodialysis (MHD) patients and contributes to increased morbidity and mortality (1–3). In addition, sarcopenic MHD patients exhibit reduced physical functioning and are at an increased risk of hospitalization (4–6). Over the past decade, with increasing prevalence of obesity, researchers have started to focus on potential interplay of muscle and fat mass and its association with mortality (12–14). In fact, the term “sarcopenia obesity (SO)” has been coined to describe the concurrence presence of lower muscle mass and higher fat mass in an individual. Several SO definitions developed in healthy young or elderly populations have been studied extensively, especially regarding their association with clinical outcomes (15, 16). However, the applicability of these current definitions to predict mortality in MHD subjects has yet to be fully investigated (17, 18). While obesity is known to be an independent risk factor for cardiovascular disease and mortality in the general population (19, 20), this may not be true in MHD patients where presence of excessive fat mass seems to be protective and obese MHD patients have more favorable clinical prognosis (21, 22).

In this study, we hypothesized that the currently proposed SO definitions based on low muscle and high fat mass can predict increased all-cause mortality in MHD subjects. We also determined the impact of using different SO definitions on prevalence estimates.

Methods

This is a retrospective study conducted at large, tertiary care university hospital. The Institutional Review Board committee at the Vanderbilt University Medical Center (VUMC) approved each study that the data was collected from. Written informed consent was obtained from each participant.

Study Population

In this study, 122 MHD patients were enrolled who had formerly participated in a variety of metabolic studies at the VUMC between 2003 and 2011, and who had data available on

body composition. All eligible patients were aged 18 years or older and were on MHD therapy for more than 3 months. Pregnant women and patients with clinical signs of overt infection, vasculitis or liver disease, and those who hospitalized within 1 month prior to enrollment into the studies were excluded from the analysis. We recorded demographic, comorbidities, anthropometric, clinical, dialysis vintage and laboratory data at the time of study enrollment.

Body Composition Data

Assessment of body composition was performed by Dual Energy X-Ray Absorptiometry (DEXA), which offers a rapid, non-invasive three-compartment evaluation that quantifies fat mass, lean body mass, and bone mineral content with minimal radiation exposure. All DEXA measurements were done on a non-dialysis day using a Lunar Prodigy iDEXA machine, v.11.40.004 (software versions 2003 to 2011, General Electric, Madison, WI). Appendicular skeletal mass (ASM) was defined as the sum of total lean mass of the both arms and legs divided by the square of the height or weight. SO was defined based on three research definitions: Baumgartner (ASM/Ht^2 + % FM: Men <7.26 kg/m^2 & >27%FM and Women <5.45 kg/m^2 & >38%FM); Janssen Criteria 1 (ASM/Ht^2 + % FM: (CLASS 1 Men 8.51–10.75 kg/m^2 & >27%FM and Women 5.76–6.75 kg/m^2 & >38%FM) and (CLASS 2 Men <8.5 kg/m^2 & >27%FM and Women <5.75 kg/m^2 & >38%FM)) and Janssen Criteria 2: (ASM/Wt + % FM: Men <29.9%SMM & >27%FM) (Table 1) (15, 16, 23, 24). We have chosen these definitions as they were most commonly used in epidemiological research and has defined threshold cut-offs for muscle and fat mass. We excluded definitions which were derived from fewer than 50 participants. SO definitions were further applied to our MHD database to determine comparisons of prevalence estimates.

Outcome variable

The primary outcome was all-cause mortality. Patient deaths were determined from VUMC medical records. Deaths at outside hospitals were screened from United States social security death index. Subjects were censored if they received kidney transplantation, or no survival data were available.

Statistical Analysis

Continuous variables were expressed as the mean (SD) or median and IQR and analyzed by unpaired *t* test or the Wilcoxon Rank-Sum test, as appropriate. Categorical variables are expressed as absolute (n) and relative (%) frequency and analyzed by Chi-square test or Fisher's exact test. Correlation analysis was performed by Spearman correlation coefficient. Kaplan-Meier survival curves with log-rank test are presented to compare mortality by SO definition status (yes or no). Cox-proportional hazard model was used to predict mortality adjusting for age, gender and SO definitions. Statistical analysis was performed using SPSS software Version 21.0 (SPSS Inc., Chicago, IL, USA) and R 3.3.0 (R Core Team, Vienna, Austria).

Results

Study cohort characteristics

Clinical, demographic and body composition characteristics at baseline are summarized in Table 2 and Table 3. Of 122 participants, 62% were male and 38% female. The median (IQR) age was 46 (40, 54) years in men and 50 (44, 61) years in women. The study subjects were predominantly African-American (76%), and 34% (n=42) were diabetic. The median duration of dialysis was 31 (10, 68) months.

The mean arm lean mass (7.1 vs 4.6 kg), leg lean mass (18.1 vs 14.6 kg) and ASM/Ht^2 (8.4 vs 7.4) were higher in men. In contrast, fat mass percentage (43.2 vs 30.0) and BMI (33.6 vs 28.4 kg/m^2) were higher in women.

Prevalence of SO based on differing definitions

Applying the three definitions (Table 2), the prevalence of SO ranged from 12% to 62% for men and 2% to 74% for female. SO prevalence was lowest using the Baumgartner criteria (all: 8%, men 12%, women: 2%), intermediate for Janssen criteria 1 (combined class 1 and class 2: all 48%, men 62%, women 24%) and highest according to the Janssen criteria 2 (all: 57%, men 46%, women 74%). Prevalence of the SO was higher in men than women for Janssen criteria 1 (62% vs 24%). Whereas, women were more often diagnosed to have SO by using Janssen criteria 2 (74% vs 46%).

SO Status at Baseline and Mortality Outcome

There were 37% (n=45) deaths during a median follow-up period of 44 (20, 76) months. Figure 1 shows the raw data mapping of SO criteria's and mortality stratified by gender. Kaplan-Meier curves according to the presence of SO was not statistically associated with mortality during follow up (all log rank test P value >0.05) for all 3 definitions (Figure 2). On Cox proportional hazard multivariate analysis, SO definitions were not found to predict increased mortality after adjustment for age and gender (Table 4). Further adjustment for c-reactive protein (CRP) did not change the association appreciably (data not shown). Also, according to other body composition categories: non-sarcopenia obese patients had best survival; whereas, sarcopenia non-obese had the worse survival (log rank p=0.002) (Figure 3).

Discussion

In this study, we found that current SO criteria are of limited utility in predicting all-cause mortality in prevalent MHD patients. In fact, the contrary was true and the patients who did not meet the criteria for SO phenotype had worse survival. We also found large differences in SO prevalence rates when using different definitions. These findings indicate the need to develop appropriate cutoff values of muscle and fat mass for predicting mortality in MHD patients.

Our findings are in contrast with a previous published report where SO was associated with presence of systemic inflammation and increased mortality in ESRD population (17). In a sample of 328 HD patients, Honda *et al.* showed that protein-energy wasting was common in

overweight dialysis patient and is associated with high fat and low muscle mass and increased risk of mortality (17). The possible reasoning for this association was attributed to increased pro-inflammatory mediators and oxidative stress observed in obese dialysis patients. However, in our study, we found no association between SO definitions and increased risk of mortality after adjusting for CRP. One of the explanations for our results is that the different ratios for lean to fat mass may have different outcomes and not captured by pre-defined dichotomous values of SO definitions. This is supported by study of body composition and survival by Marcelli *et al.*, where patients with both lean muscle and fat mass within 10^{th}–90^{th} percentile of health population was associated with best survival (18). Whereas, patient with low muscle and low fat indices was associated with poor outcomes. We have also demonstrated similar findings suggesting that sarcopenic non-obese patient had highest mortality (Figure 3).

Our study results have significant clinical and research implications. When we aimed to examine the prevalence of SO in our HD database, we observed lack of consensus and wide variation in prevalence among different diagnostic definitions. The SO definitions used for this analysis were the ones recognized as useful in both research and clinical practice. This result is important as differences in SO ascertainment may affect designing effective nutritional interventions. Several factors may explain wide variability in prevalence estimates including use of different cut-offs for defining sarcopenia between studies, differences in methodology (DEXA or bioimpedance) and diagnostic approach (-2SD, residuals, quantiles) and lack of agreement over using ASM/Wt or ASM/Ht^2. We believe that the current working definitions of SO need further refining and must incorporate muscle strength and quality to determine sarcopenia in ESRD patients who represent a different mortality risk profile in terms of their nutrition status. Development of a maintenance dialysis population-specific SO definition, preferably using longitudinal measurements of body composition and function along with the establishment of cut-off related to meaningful long-term outcomes is necessary in ESRD patients. A more appropriately defined SO criteria would also help clinicians identify high-risk patients, inform clinical decisions, and facilitate patient counseling. Clinicians can evaluate baseline risk and thus implement preventive and therapeutic strategies, e.g., exercise, diet and anti-inflammatory approaches.

Our study has several strengths including the long follow-up period (median followup of 44 months) and the use of precise and direct measurement of body composition by DEXA. There are also limitations to our study. First, the relatively small sample size of our MHD database precludes our ability to perform detailed analysis and detect significant associations between body composition indices and mortality. Observational nature of our study would not allow inferring causality. Thirdly, the participants in our study were selected from metabolic studies, thus increasing the potential for selection bias. Fourth, body composition measurements were obtained at baseline. It is possible that patients' body composition may have changed during follow-up. Finally, a majority proportion of our study subjects were African-American that may limit generalizability to other races/ethnicity.

In conclusion, our data question the utility of current SO definitions to identify high-risk MHD patients. Development of new SO criteria will help target high-risk patients for surveillance and enable clinicians and researchers to evaluate novel diagnostic, preventive,

and therapeutic modalities to mitigate the devastating consequences of low muscle mass and fat mass.

Practical Application

The present study indicates that SO defined by current definitions do not seem to predict mortality in MHD patients. Prevalence of SO vary widely with different SO diagnostic criteria's. Future confirmatory studies are warranted to validate our results.

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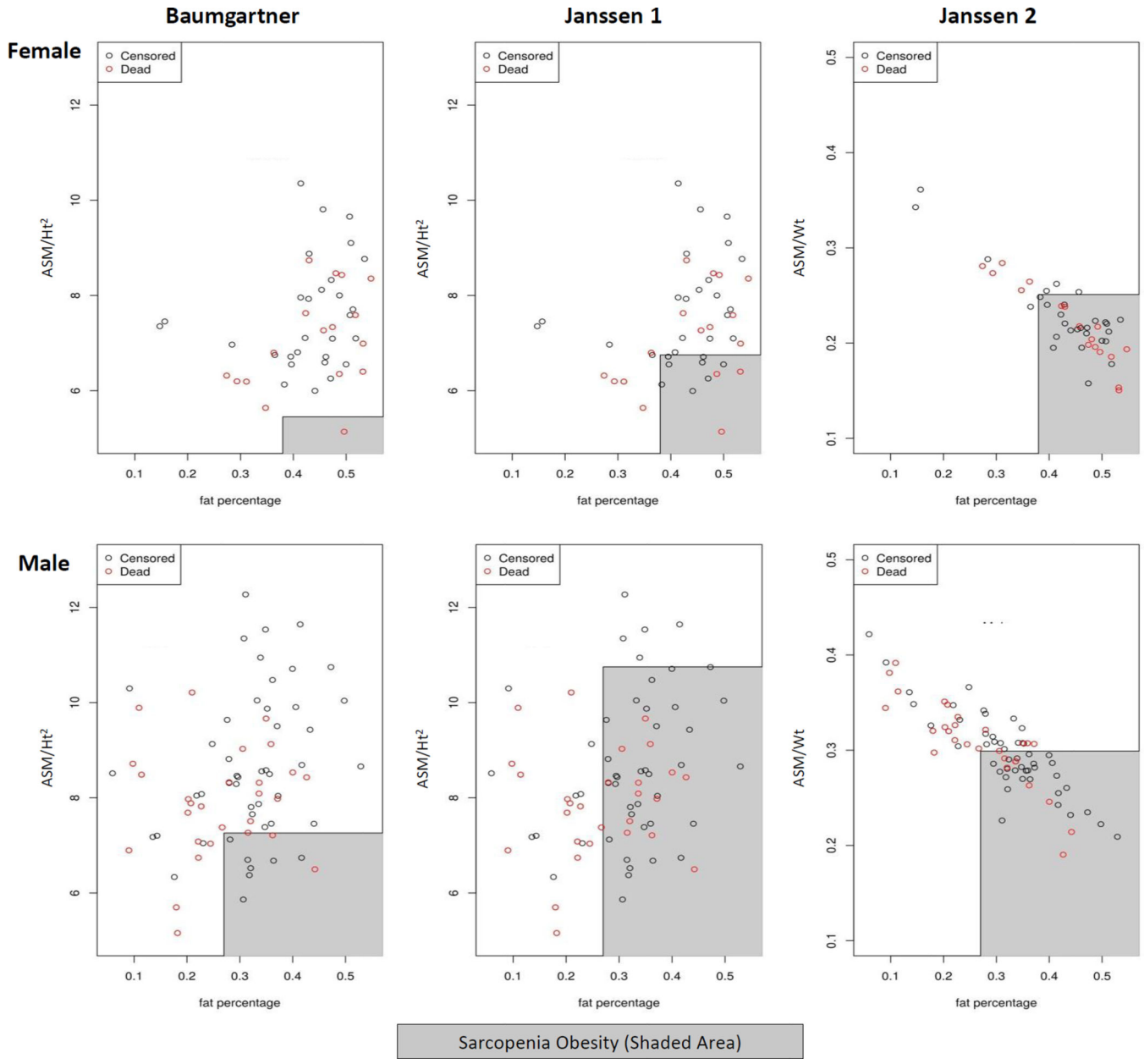

Figure 1.

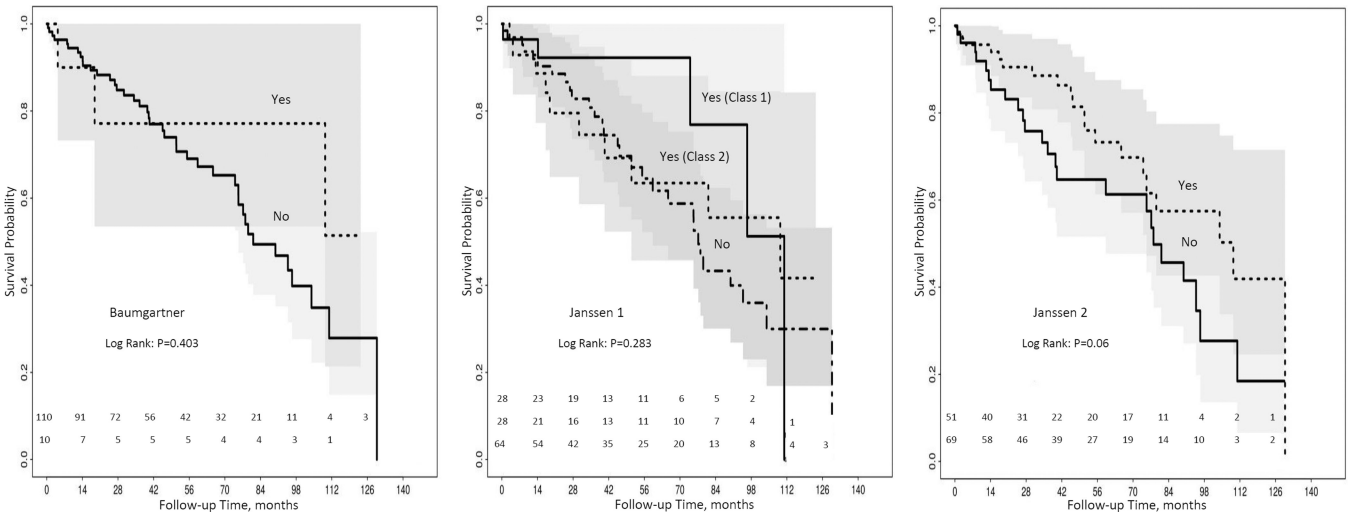

Figure 2.

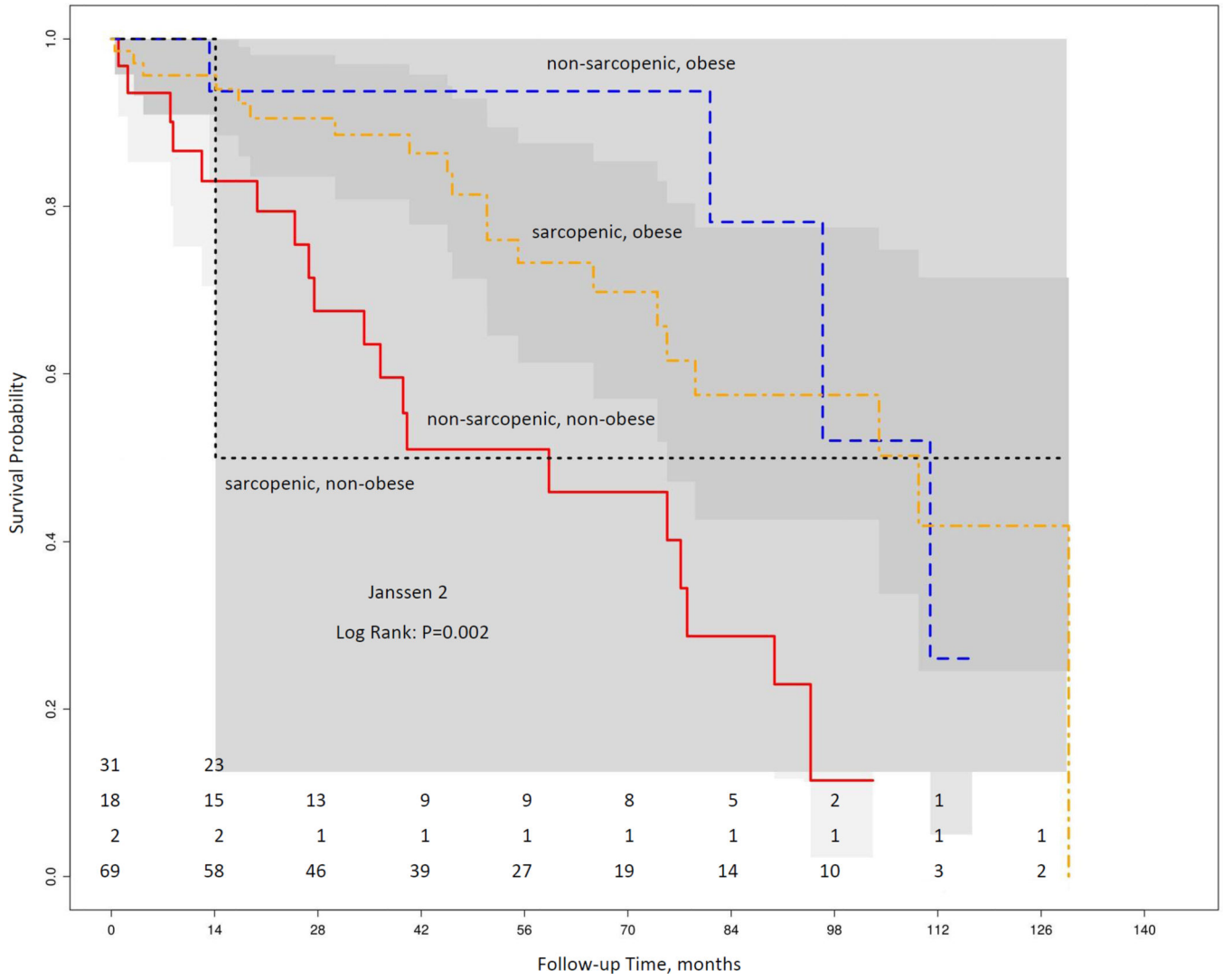

Figure 3.

Table 1

Definition of Sarcopenic Obesity Criteria's

BAUMGARTNER CRITERIA	ASM/Ht^2 and % FM	Men <7.26 kg/m^2 & >27%FM Women <5.45 kg/m^2 & >38%FM
JANSSEN CRITERIA (1)	ASM/Ht^2 and % FM	CLASS 1 Men 8.51–10.75 kg/m^2 & >27%FM Women 5.76–6.75 kg/m^2 & >38%FM CLASS 2 Men <8.5 kg/m^2 & >27%FM Women <5.75 kg/m^2 & >38%FM
JANSSEN CRITERIA (2)	ASM/Wt and % FM	Men <29.9% & >27%FM Women <25.1% & >38%FM

Appendicular Skeletal Mass (ASM) = Arm Lean Mass + Leg Lean Mass; FM= fat mass

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Table 2

Patient characteristics by Sarcopenia Obesity Definitions

	Total	Baumgartner Criteria		Jansen Criteria 1			Jansen Criteria 2	
		NO	YES	NO	Yes		NO	YES
					Class 1	Class 2		
Total Subjects, N	122	112	10	64	29	29	53	69
Age (years)	48±13	48±13	49±18	49±13	45±13	49±13	46±13	50±13
Gender, n (%)								
Male	76 (62)	67 (60)	9 (90)	29 (45)	19 (66)	28 (97)	41 (77)	35 (51)
Female	46 (38)	45 (40)	1 (10)	35 (55)	10 (34)	1 (3)	12 (23)	34 (49)
Dialysis Vintage (months)	31 (10–68)	31 (9–67)	42 (17–66)	21(8–56)	32 (39–52)	51 (42–58)	47 (39–55)	50 (42–60)
Follow-up Duration (months)	44 (20–76)	44 (20–73)	41 (13–103)	44(24–77)	38 (17–66)	48 (18–81)	31 (14–68)	30 (9–64)
Ethnicity, n (%)								
Non-Hispanics	116 (95)	107 (96)	9 (90)	0(0)	25 (86)	27 (93)	51 (96)	65 (94)
Hispanic	6 (5)	5 (4)	1 (1)	64(100)	4 (14)	2 (7)	2 (4)	4 (6)
Race, n (%)								
African American	93 (76)	90 (80)	3 (30)	55(86)	23 (79)	15 (52)	44 (83)	49 (71)
Caucasian	25 (20)	21 (19)	4 (40)	9(14)	5 (17)	11 (38)	8 (15)	17 (25)
Diabetes, n (%)	42 (34)	40 (36)	2 (20)	25(39)	10 (34)	7 (24)	11 (21)	31 (45)
CAD, n (%)	35 (31)	32 (31)	3 (30)	22(38)	5 (19)	8 (29)	14 (28)	21 (33)
Etiology of ESRD, n (%)								
DM	22 (18)	21 (19)	1 (10)	31 (20)	6 (21)	3 (10)	5 (9)	17 (25)
HTN	57 (47)	55 (49)	2 (20)	29 (45)	15 (52)	13 (45)	32 (60)	25 (36)
GN	17 (14)	14 (12)	3 (30)	10 (16)	3 (10)	4 (14)	9 (17)	8 (12)
PCKD	4 (3)	3 (3)	1 (10)	2 (3)	0 (0)	2 (7)	1 (2)	3 (4)
Others	9 (7)	7 (6)	2 (20)	3 (5)	2 (7)	4 (14)	3 (6)	6 (9)

	Total	Baumgartner Criteria		Jansen Criteria 1			Jansen Criteria 2	
		NO	YES	NO	Yes		NO	YES
					Class 1	Class 2		
Total death, n (%)	45 (37)	42 (38)	3 (30)	29 (45)	6 (21)	10 (34)	25 (47)	20 (29)

Continuous variables are expressed as mean ± SD or median (inter-quartile range) and categorical variables as n (%)

Abbreviations: DM= diabetes mellitus; HTN= hypertension; GN= glomerulonephritis; PCKD= polycystic kidney disease; CAD = coronary artery disease

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Table 3

Body Composition, nutritional and inflammatory markers by Sarcopenia Obesity Definitions

	Total	Baumgartner Criteria		Jansen Criteria 1			Jansen Criteria 2	
		NO	Yes	NO	Yes		NO	Yes
					Class 1	Class 2		
BMI (kg/m^2)	30.4±7.6	30.8±7.7	25±3	30.7±9	32.8±5.4	27.2±4.3	25.5±5.1	34.1±7.0
BSA (m^2)	2.0±0.3	2.01±0.3	1.87±0.16	1.95±0.3	2.0±0.3	1.98±0.2	1.89±0.22	2.1±0.3
Arm Lean (g)	6183±1847	6270±1858	5210±1097	5853±1772	6817±2336	6276±1241	6761±1736	5738±1817
Leg Lean (g)	16806±4177	17060±4233	13957±1956	16554±4283	17985±5020	16181±2636	17226±3873	16483±4397
Total Fat mass, %	35±12	35±12	36±7	33±14	40±7	35±5	25±9	42±7
ASM/Ht^2 (kg/m^2)	8.0±1.4	8.13±1.42	6.5±0.7	8.1±1.5	8.42±1.6	7.5±0.9	8.0±1.5	8.0±1.4
ASM/Weight	0.3±.06	0.3±0.06	0.3±.04	0.3±.06	0.3±.05	0.3±.03	0.3±.04	0.2±.04
6 min Walk, m	1385±403 (50/122)	1372±379 (44/112)	1478±588 (6/10)	1291±381 (44/64)	1474±345 (13/29)	1484±487 (13/29)	1467±398 (25/53)	1303±399 (25/69)
BF BIA	28(20–47) (66/122)	29(21–48) (60/112)	22(16–25) (6/10)	30(16–51) (50/64)	39(24–45) (18/29)	24(21–26) (15/29)	21(16–30) (31/53)	41(25–49) (35/69)
Insulin (μU/ml)	13(8–20) (83/122)	13(7–20) (75/112)	14 (11–20) (8/10)	12.3(7–19) (53/64)	16(12–26) (17/29)	13(7–20) (19/29)	8(6–13) (40/53)	17(12–24) (43/69)
Leptin (ng/mL)	15(6–65) (77/122)	20(6–67) (70/112)	9 (6–13) (7/10)	9(3–69) (50/64)	50(18–70) (21/29)	9(7–21) (17/29)	5(2–9) (34/53)	53(18–77) (43/69)
CRP (mg/dL)	7 (3–15) (97/122)	7 (3–15) (89/112)	11 (4–24) (8/10)	4(2–14) (59/64)	10 (6–15) (21/29)	9 (4–19) (21/29)	4 (3–15) (46/53)	9 (5–17) (51/69)
Resistin (ng/ml)	5.4± 3.8 (100/122)	5.5±3.8 (92/112)	4.5±3.0 (8/10)	5.8±4.2 (59/64)	5.1±2.4 (22/29)	4.9±3.8 (21/29)	5.2± 4.0 (45/53)	5.6±3.6 (55/69)
Albumin (g/dL)	3.9± 0.5 (96/122)	3.9±0.5 (88/112)	3.7±0.5 (8/10)	3.9±0.4 (59/64)	3.9± 0.7 (21/29)	3.9± 0.4 (21/29)	3.9± 0.4 (45/53)	3.8± 0.5 (51/69)
Pre-albumin (mg/dL)	35.6± 9.5 (83/122)	35.5±9.6 (78/112)	36.1±8.8 (5/10)	34.5±9.4 (57/64)	37.6± 9.6 (16/29)	36.2± 9.7 (15/29)	34.9± 10.2 (41/53)	36.2± 8.9 (42/69)
Creatinine (mg/dl)	9± 3 (97/122)	9±3 (89/112)	8.4±2.6 (8/10)	8.8±3.1 (59/64)	9.1± 2.8 (21/29)	8.9±2.8 (21/29)	9.7± 3.2 (46/53)	8.2± 2.6 (51/69)
IL-6 (pg/mL)	9 (4–15) (58/122)	9 (5–15) (55/112)	3 (3–28) (3/10)	7(4–14) (45/64)	13(6–18) (13/29)	6 (2–11) (13/29)	5 (2–13) (25/53)	9 (6–15) (33/69)

Continuous variables are expressed as mean ± SD or median (inter-quartile range) and categorical variables as n (%)

Abbreviations: IL-6 = interleukin-6; CRP= C - reactive protein; ASM= appendicular skeletal mass; BSA = body surface area; BMI= body mass index; BIA= bioelectric impedance; m= meter; g= gram

Table 4

Cox proportional hazards model evaluating the effect of Sarcopenia obesity definitions and covariates on mortality

Variable	Hazard ratio	95% Confidence Interval		p-value
		Lower limit	Upper limit	
Age (per year)	3.54	2.18	5.72	<.0001
Gender (female)	0.28	0.08	0.95	0.03
Baumgartner Criteria	0.48	0.25	0.94	0.04

Variable	Hazard ratio	95% Confidence Interval		p-value
		Lower limit	Upper limit	
Age (per year)	3.19	1.99	5.10	<.0001
Gender (female)	0.38	0.18	0.78	<0.01
Jansen Criteria Class 1	0.41	0.15	1.10	0.07
Jansen Criteria Class 2	0.48	0.22	1.04	0.07

Variable	Hazard ratio	95% Confidence Interval		p-value
		Lower limit	Upper limit	
Age (per year)	3.53	2.18	5.72	<.0001
Gender (female)	0.75	0.37	1.52	0.42
Jansen Criteria 2	0.36	0.18	0.74	<0.01

Data adjusted for age, gender and sarcopenia obesity definitions