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Authors
Kerns, Eric S
Kim, Esther D
Meoni, Lucy A
et al.

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Obstructive Sleep Apnea Increases Sudden Cardiac Death in Incident Hemodialysis Patients

Eric S. Kerns[a], **Esther D. Kim**[b,c], **Lucy A. Meoni**[d,e,f], **Stephen M. Sozio**[d,e], **Bernard G. Jaar**[b,d,e,g], **Michelle M. Estrella**[h,i], **Rulan S. Parekh**[b,c,d,j], and **Ghada Bourjeily**[k]

[a]Department of Medicine, Division of Nephrology, Lahey Hospital and Medical Center, Burlington, MA, USA

[b]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[c]Hospital for Sick Children, Toronto, ON, Canada

[d]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[e]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, MD, USA

[f]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[g]Nephrology Center of Maryland, Baltimore, MD, USA

[h]University of California San Francisco, Kidney Health Research Collaborative, San Francisco, CA, USA

[i]San Francisco VA Health Care System, San Francisco, CA, USA

[j]Department of Pediatrics and Medicine, School of Medicine, University of Toronto, Toronto, ON, Canada

[k]Department of Medicine, Divisions of Pulmonary, Critical Care and Sleep Medicine, and Obstetric Medicine, The Miriam Hospital and Alpert Medical School of Brown University, Providence, RI, USA

Abstract

Background: Mortality in end-stage renal disease (ESRD) occurs predominantly from cardiovascular disease (CVD) and sudden cardiac death (SCD). Obstructive sleep apnea (OSA) is characterized by periodic airflow limitation associated with sleep arousal and oxygen desaturation and is prevalent in patients with ESRD. Whether OSA increases the risk for SCD, cardiovascular and all-cause mortality among hemodi alysis patients remains unknown.

Rulan S. Parekh, MD Professor of Pediatrics and Medicine, Department of Pediatrics and Medicine Hospital for Sick Children and University Health Network and University of Toronto 555 University Ave., Toronto, ON M5G 1X8 (Canada), Rulan.Parekh@sickkids.ca.

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Methods: In a prospective cohort of 558 incident hemodialysis patients, we examined the association of OSA with all-cause mortality, cardiovascular mortality, and SCD using Cox proportional hazards models controlling for traditional CVD risk factors.

Results: Sixty-six incident hemodialysis patients (12%) had OSA. Mean age (56 years) and percentage of males (56%) were identical in OSA and no-OSA groups. Fewer African Americans had OSA than non-African Americans (9 vs. 18%, respectively). Participants with OSA had higher body-mass index, Charlson comorbidity score, and left ventricular mass index and greater prevalence of diabetes and coronary artery disease. During 1,080 person-years of follow-up, 104 deaths occurred, 29% of which were cardiovascular. OSA was associated with a higher risk of all-cause mortality (HR 1.90 [95% CI 1.04–3.46]) and cardiovascular mortality (HR 3.62 [95% CI 1.36–9.66]) after adjusting for demographics and body-mass index. OSA was associated with a higher risk of SCD after adjusting for demographics (HR 3.28 [95% CI 1.12–9.57]) and multiple cardiovascular risk factors.

Conclusions: Incident hemodialysis patients with OSA are at increased risk of all-cause and cardiovascular mortality and SCD. Future studies should assess the impact of screening for OSA and OSA-targeted interventions on mortality in ESRD.

Keywords

Hemodialysis; Obstructive sleep apnea; Sudden cardiac death; Cardiovascular death; Cardiovascular disease

Introduction

Mortality in end-stage renal disease (ESRD) patients undergoing dialysis approaches 20% per year, and the leading cause of mortality is cardiovascular disease (CVD). Sudden cardiac death (SCD) and arrhythmias account for as many as 60% of cardiovascular mortality [1–3] and 30% of all deaths [4, 5]. The reason for the high incidence of SCD in the ESRD population is multifactorial, likely related to cardiac conduction abnormalities from left ventricular hypertrophy, atherosclerotic coronary artery disease, abnormal myocardial ultrastructure, and electrolyte imbalances. While processes specific to ESRD and the dialysis procedure such as electrolyte and fluid shifts and chronic inflammation may play a role in increased CVD mortality [6], factors outside of dialysis may also be important.

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent partial or complete upper airway obstruction during sleep with hypoxia and sleep disruption. Airflow limitation, intermittent hypoxemia, and sleep fragmentation are associated with autonomic nervous system activation [7], oxidative stress [8], enhanced inflammatory profile, and endothelial dysfunction [9, 10], potentially leading to cardiovascular morbidity and mortality. In observational cross-sectional and longitudinal studies in the general population, OSA has been linked to hypertension [11–13], prolonged QRS duration [14], nocturnal arrhythmias [15], CVD [16], and SCD [17].

The prevalence of OSA increases with worsening severity of chronic kidney disease (CKD), and it may be up to ten-fold greater in dialysis patients than the general population [18–20]. This observation has led researchers to postulate a bidirectional relationship between OSA

and CKD [21], whereby conditions common to CKD, such as metabolic acidosis, volume overload, and uremia, predispose to abnormal breathing during sleep. On the other hand, consequences of OSA, such as nocturnal hypoxia, renin-angiotensin activation, and hypertension, may also lead to CKD progression [21–23].

Due to the high prevalence of OSA in ESRD, several investigators have explored associations between ESRD, OSA, and cardiovascular morbidity and mortality [24–27]. These studies used different definitions of sleep-disordered breathing and varying cardiovascular outcomes and were limited by small sample sizes and study designs. On the other hand, data stemming from large datasets lack the ability to review records or perform a firsthand determination of the cause of death. As a result, there is a need for large-scale, longitudinal studies investigating OSA as a risk factor for all-cause and cardiovascular mortality in dialysis patients. In this study, we aimed to determine the prevalence of OSA confirmed by medical record review in a large cohort of incident hemodialysis patients and to establish whether a diagnosis of OSA at the time of dialysis initiation was associated with an increased risk of mortality. We hypothesized that patients who were starting hemodialysis with OSA would be at significantly higher risk of all-cause and cardiovascular mortality and SCD.

Materials and Methods

Study Design and Data Collection

Data were analyzed from the Predictors of Arrhythmic and Cardiovascular risk in ESRD (PACE) study. The construction of the PACE cohort has been described previously [3]. PACE enrolled individuals if they started in-center hemodialysis within the preceding 6 months. Participants were recruited from 25 freestanding outpatient dialysis centers around Baltimore, MD. Incident hemodialysis was defined as regular outpatient dialysis 3 times per week for less than 6 months. Participants were included if they were on incident hemodialysis, were 18 years or older, English speaking, and able to tolerate imaging procedures and an electrocardiogram (ECG). Participants were excluded if they had (1) cancer diagnosis other than non-melanoma skin cancer; (2) were on home hemodialysis or peritoneal dialysis, hospice care, or lived in a skilled nursing home facility or prison; (3) had a permanent pacemaker or an automatic implantable cardioverter defibrillator; (4) pregnant or nursing; (5) or had health conditions that impacted study participation. After informed consent, detailed questionnaires on sociodemographic information were obtained. During a baseline visit, physical examination, waist to hip ratio, and cardiac testing including 3 resting blood pressure measurement using an oscillometry machine, standard 12-lead electrocardiogram, two-dimensional echocardiography occurred at the Johns Hopkins Institute for Clinical and Translational Research. Participants were then followed for up to 48 months by phone call that occurred on a bi-annual basis and an annual visit on a nondialysis day. The protocol was approved by the Johns Hopkins School of Medicine and MedStar Institutional Review Boards.

Detailed questionnaires reviewed substance use, medical history, family history, and physical activity. In order to gather past medical history for study participants – including coronary artery disease, hypertension, diabetes, and OSA status – 2 nephrologists reviewed

all clinical medical records available in the year prior to dialysis initiation. These included outpatient and inpatient notes of nephrologists, general physicians, internists, problem lists, laboratories, and test results. Participants were deemed to have OSA if there was mention of OSAS in (1) the problem list, the past medical history, or any consultation note done 1 year prior to dialysis initiation, or (2) the primary care notes in the year prior to starting dialysis. A sleep study confirmation was not uniformly available. If there was a discrepancy in findings, there was a 3rd physician who reviewed to reconcile any differences. Participants underwent height, weight, and body mass index (BMI) measurement. If measured height was missing, then self-reported height was used to calculate BMI. Physical activity (kcal/week) was measured based on 16 different activities using the Minnesota Leisure Time Activity questionnaire. Weekly pre- and post-dialysis weights, average intradialytic weight (IDW) change, and measures of dialysis adequacy (monthly Kt/V and urea reduction ratio) were collected through the link established with dialysis provider electronic data.

Outcomes

The main outcomes were all-cause mortality, cardiovascular mortality, and SCD. SCD was defined as a sudden collapse that was presumed to be due to an arrhythmia occurring out of the hospital or in an emergency room in an otherwise stable individual. In the case of an unwitnessed event, the patient had to have been seen in a stable condition within the preceding 24 h or during a dialysis session. Events that occurred during a hospitalization or hospice care were not classified as SCD. Cardiovascular mortality was the composite of SCD and death caused by arrhythmias, cardiac arrest, ischemic CVD, and ischemic cerebrovascular disease either inside or outside of the hospital.

Through regular contact with the dialysis units, study investigators were informed at the time of a participant's death. Once notified, investigators obtained the Centers for Medicare and Medicaid Services (CMS) Death Notification Form 2746 and interviewed the next of kin to determine when the participant was last seen prior to death, and whether any symptoms preceded the event. Hospitalization and emergency room records were obtained when available. All data were reviewed by 2 trained physician abstractors, and the final determination of cause of death was conducted by the chair of the PACE study endpoint committee [3].

Statistical Analysis

Baseline demographic and clinical characteristics were compared using parametric and nonparametric tests. Normally distributed continuous variables were described using mean ± SD and compared across groups using the Student *t* test; non-normally distributed variables were described using median (interquartile range [IQR]) and compared using the Wilcoxon rank-sum test. Categorical variables were compared across groups using the chi-square test. A p value <0.05 was considered statistically significant. Risk of all-cause mortality, CVD mortality, and SCD by OSA were graphically assessed using the Kaplan-Meier product limit method and compared using log-rank tests, which would account for loss of participants over time. The associations of OSA with all-cause mortality, CVD mortality, and SCD were assessed using multivariable cox proportional hazard models. Multivariable models included demographics (age, sex, and ethnicity), Charlson comorbidity index (a risk score that

incorporates multiple comorbid conditions, including diabetes and coronary disease), BMI, history of atrial fibrillation, left ventricular mass index, Kt/V, and IDW change. Due to the limited number of SCD events, we presented parsimonious models. Variables with missing values were imputed using the multiple imputations by chained equations method [28]. Covariates with missing values in the analysis were Charlson comorbidity index (1%), BMI (1%), left ventricular mass index (32%), Kt/V (9%), and IDW change (5%). The proportional hazards assumption was checked using the Schoenfeld residuals. For all analyses, a two-tailed p value of <0.05 was considered significant. All analyses were performed using STATA 14.0 (College Station, TX, USA).

Results

Study Population

Five hundred sixty-eight incident HD patients consented to participate, of whom 558 were eligible for baseline and survival analyses. Ten patients had incomplete medical records to assess for OSA diagnosis and were excluded.

Of the 558 participants at time of dialysis initiation, 66 patients (12%) were identified as having OSA by chart review. Table 1 illustrates the demographics, cardiovascular comorbidities, and dialysis-specific measures among study participants, by OSA status. Median age and sex were similar in the OSA and no OSA groups. African Americans were less likely to have a diagnosis of OSA than non-African Americans. Patients with OSA had a higher median BMI (37 kg/m^2 [IQR 31–42] vs. 27 kg/m^2 [IQR 24–32]). In addition, patients with OSA had a higher median Charlson comorbidity index (6 [(IQR 5–7] vs. 5 [IQR 4–7]), higher prevalence of diabetes (76 vs. 56%), hypercholesterolemia (84 vs. 63%), coronary artery disease (47 vs. 34%), and atrial fibrillation (38 vs. 25%) respectively (all p values <0.05).

There was no difference in hypertension or corrected QT (QTc) prolongation between OSA and no OSA groups. Patients with OSA had a higher left ventricular mass index (76 g/m^2 [IQR 59–93] vs. 61 g/m^2 [IQR 50–79]), while patients with OSA had similar ejection fractions to those without OSA (64 and 66%, OSA and no OSA groups respectively).

With respect to dialysis-specific measures, patients with OSA had significantly lower dialysis adequacy as compared to those without OSA (Kt/V 1.6 ± 0.4 vs. 1.8 ± 0.3) and they had higher IDW change (2.4 kg ± 0.9 vs. 2.1 kg ± 0.8). Dialysis adherence – assessed by the number of sessions missed per month – was similar between the 2 groups, with the majority of patients missing less than a session per month.

Mortality Outcomes

Participants were followed until end of the study (n = 138), death (n = 104), transplant (n = 52), recovery of renal function (n = 3), transfer to peritoneal dialysis (n = 25), transfer to long-term hospitalization (n = 21), or loss to follow-up (n = 215). Participants were censored in the survival analyses (n = 215), due to moving away (n = 24), withdrawal of consent (n = 33), non-compliance (n = 99), no longer meeting eligibility (n = 22), and inability to reach (n = 37).

Participants who did not complete the study were less likely to be African American. As compared to participants who were retained until death or end of study, those who did not complete the study did not significantly differ by age, sex, dialysis adequacy, dialysis adherence, or any of the baseline cardiovascular risk profiles listed in Table 1 (data not shown).

During a mean follow-up period of 23.2 months (1,080 person-years), 104 deaths occurred, of which 30 were due to cardiovascular deaths and 16 due to SCD. The median time to death from dialysis initiation was 17 months (IQR 10–23); 2 deaths (2%) occurred within the first 90 days of dialysis initiation. Figure 1 depicts unadjusted Kaplan-Meier plots. Though cumulative event probability appears to be higher for all-cause mortality and cardiovascular mortality in the group with OSA, this difference did not reach statistical significance. Cumulative event probability showed higher probability of SCD in patients with OSA compared to those without OSA.

Cox regression analyses showed an unadjusted increased risk of SCD (HR 3.27, 95% CI 1.14–9.42) associated with OSA diagnosis. The association of a diagnosis of OSA with all-cause mortality (HR 1.32, 95% CI 0.77–2.24) and cardiovascular mortality (HR 1.52, 95% CI 0.67–3.43) did not reach statistical significance in the unadjusted model.

In adjusted models, OSA was significantly associated with higher risk of SCD in all models (Table 2, Models 2–10) which included demographics, comorbidity index, BMI, atrial fibrillation, left ventricular mass index, Kt/V and IDW change. The inclusion of physical activity in the model did not significantly change the associations. OSA emerged as a risk factor for all-cause and cardiovascular mortality after adjustment for BMI and other demographics (Table 2, Model 4).

To better understand the role of BMI in the association of OSA with all-cause mortality, we performed a stratified analysis by BMI (low/normal BMI versus overweight/obese BMI). OSA, compared to no OSA, was associated with an increased risk of all-cause mortality in the low/normal BMI group (HR 13.00, 95% CI 1.69–100.26) but not in the overweight/obese BMI group (HR 1.69, 95% CI 0.94–3.06), $p = 0.06$. In addition, stratified analyses using BMI as the exposure variable and normal/low BMI as the referent showed a decreased risk of all-cause mortality and cardiovascular mortality associated with overweight/obese BMI. This reduction in risk in the overweight/obesity group persisted after adjusting for age, sex, ethnicity, and OSA. The risk reduction for SCD in the obesity/overweight group was only significant once OSA status was introduced into the model (Table 3).

Discussion

In this large prospective cohort of incident hemodialysis patients, 12% of participants had prevalent OSA. Over a median follow-up period of 2 years, those with OSA were at a 3 fold higher risk of SCD, a risk that persisted after controlling for known cardiovascular risk factors, BMI, and comorbidities such as hypertension and diabetes. After controlling for BMI, OSA diagnosis was associated with an increased risk of CVD and all-cause mortality, as well as SCD. This is the largest study to follow incident hemodialysis patients with

preexisting OSA for these specific cardiovascular endpoints. While central sleep apnea is also known to occur in patients with ESRD [29], our study focused on OSA and its associated outcomes.

The results of this study and prior reports [24–27] demonstrate that OSA is associated with an increased risk of cardiovascular morbidity and mortality among dialysis patients. Previous research showed that nocturnal hypoxia conferred an increased risk of cardiovascular events and all-cause mortality in prevalent hemodialysis patients [24, 26, 27]. In incident peritoneal dialysis patients, a diagnosis of sleep apnea by polysomnography (measuring both obstructive and central apneic events) was associated with an increased risk of all-cause mortality and cardiovascular events [25]. On the other hand, a recently published report provides contradictory information [30]. The investigators studied 184,217 Medicare recipients older than 67 years of age who were initiating dialysis and found that a diagnosis of sleep-disordered breathing as determined by the international classification of disease, ninth version (ICD-9) was associated with a slightly lower risk of death, myocardial infarction, and ischemic stroke. The discrepancies in these findings as compared to our results can be explained by multiple factors. The Medicare population was on average about a decade older than the PACE study population and was comprised mainly of Whites, whereas our population was about 70% African American. In addition, the definition of the exposure (sleep apnea, not otherwise specified, by ICD-9 code) as well as the selected outcomes (death, myocardial infarction, ischemic stroke, and atrial fibrillation) differed from those of our study. Additionally, administrative codes are known to have the disadvantage of low sensitivity and specificity, leading to misclassification [31] which may have underestimated cardiovascular outcomes in the Medicare population. In addition, overweight/obesity may play a role in the discrepancies as obesity may be a confounding factor in the associations of OSA with CVD in general, and some of the previous studies did not accurately ascertain BMI or the diagnosis of overweight and obesity. Interestingly, patients with sleep-disordered breathing by ICD-9 had a significantly higher BMI, and in the outcomes models that were adjusted for BMI, sleep-disordered breathing diagnosis was associated with an increased risk of death and atrial fibrillation [30]. In the analysis that examines BMI as an exposure in our study, BMI plays a protective role against cardiovascular mortality and hence appears to be a negative confounder of the associations. The protective effect of BMI on SCD was only evident once the model was adjusted for OSA. These findings, combined with others [32], suggest that BMI plays a protective role against adverse cardiovascular events in patients with ESRD and its impact on cardiovascular mortality is opposite that of OSA, and the presence of OSA may counteract the protective effect of an elevated BMI.

Our study demonstrated that patients with OSA have a higher IDW change and lower dialysis adequacy despite similar dialysis adherence. Considering that previous studies have shown that rostral fluid movement from the lower extremities during sleep impacts the upper airway size [33], patency [34], pharyngeal resistance [35], and obstructive events [36], and that ultrafiltration improves sleep apnea severity [37], our data support the potential role of nocturnal fluid shifts in the pathogenesis of sleep apnea. Yet, IDW change and dialysis adequacy did not modify the risk of SCD, CVD, or all-cause mortality, suggesting that

mechanisms other than nocturnal fluid shifts are responsible for the association with mortality.

It is possible that cyclical hypoxemia and re-oxygenation and enhanced sympathetic activation related to airflow limitation and repetitive arousals – phenomena seen in OSA but not in obesity without OSA – may contribute to endothelial dysfunction and oxidative stress leading to cardiovascular morbidity [8–10]. In addition, sympathetic activation as seen in OSA may play a role in SCD. The increased arrythmogenicity associated with OSA [38] may be related to intrathoracic pressure swings, higher sympathetic tone, and left ventricular remodeling [39]. Specifically, apneic episodes have been associated with a prolongation in QT intervals due to an increased parasympathetic tone with an abrupt shortening in this interval post apnea due to the predominance of sympathetic drive and parasympathetic withdrawal [40]. Though our study found no significant difference in QTc intervals between patients with and without OSA, the intervals were measured only during the daytime.

Continuous positive airway pressure (CPAP) is the first-line treatment for OSA and has been shown to improve blood pressure [41–43] and decrease the risk of recurrence of atrial fibrillation [44, 45]. The link between OSA and renal disease, however, is a relatively new concept and data on the impact of CPAP on cardiovascular and kidney outcomes are lacking. There are no data to date that examine the role of CPAP on hypertension or cardiovascular outcomes in patients with ESRD. Given the complexity of the pathogenesis of hypertension and CVD in ESRD, it would be difficult to extrapolate conclusions from data obtained from non-ESRD trials.

Our study and others' support a role for screening incident hemodialysis patients for OSA; it remains important, also, to assess the impact of CPAP on cardiovascular outcomes and survival in this population. Though markers of SCD have been identified and some, such as the expression of mRNA in white blood cell potassium channels [46], have been shown to be altered in patients with OSA and positively impacted by CPAP therapy, such markers would need to be validated in the ESRD population.

Strengths of our study include the large sample size, the prospective design, and the careful adjudication of cardiovascular mortality and SCD by multiple physician study investigators. The results need to be interpreted in the context of certain limitations. The PACE cohort was comprised predominantly of younger patients and included a larger proportion of African Americans than other large ESRD cohorts; however, PACE participants had a similar proportion of diabetics with a similar BMI to United States Renal Data System and Comprehensive Dialysis Study cohorts, which are representative of the US dialysis population. In addition, OSA in the PACE cohort was ascertained by chart review rather than polysomnography. While obtaining information from the Centers for Medicare and Medicaid Services Form 2728 in incident dialysis patients has the disadvantage of lack of sensitivity compared to nurse abstraction ranging between 0.36 and 0.83 for various comorbidities [47], our study employed chart abstraction by 2 physician investigators. Due to lack of consistent polysomnography data, a dose-response relationship between the severity of sleep apnea and the outcomes of interest could not be ascertained. The actual OSA prevalence is likely higher in this cohort and under-diagnosis could have been

impacted by access to care, prevalence of symptoms, and functional status. Hence, the underestimation of the exposure was most likely non-differential and would have biased associations towards the null. The lower prevalence of OSA between our study population and other ESRD populations [25, 27] or the general population [48, 49] can be explained by a number of factors such as the lack of standardized screening across the cohort, studying an incident population compared to a prevalent hemodialysis population, and screening with nocturnal oximetry that may be complicated by lack of specificity [50] and may be dependent on OSA severity with specificity having been reported to be as low as 31% [51]. Furthermore, our study was limited by the lack of data regarding CPAP therapy. It is possible that the OSA group has been treated and was potentially compliant with CPAP – though patients with multiple comorbidities have low compliance in general. In this case, the comparison between the 2 groups would have been assessing a group of potentially treated and untreated OSA with a group consisting of undiagnosed OSA and non-OSA patients, potentially biasing our results toward the null. While it is true that many patients were lost to follow-up during the study period, those who did not complete the study did not significantly differ by age, sex, dialysis adequacy or dialysis adherence, and had similar baseline cardiovascular risk profiles. Finally, this was an observational study and the OSA population clearly had more comorbid disease than the non-OSA population. Though we adjusted for multiple cardiovascular risk factors in the analysis, the results cannot be used to determine causality between OSA and mortality, and one must consider the role of residual confounding when interpreting the associations.

Conclusions

OSA is a significant risk factor for mortality in incident dialysis patients. Ascertainment of OSA should be included in routine clinical evaluation to monitor those at high risk and should be regarded as a cardiovascular risk equivalent. Future studies should assess the impact of OSA screening and OSA-targeted interventions on cardiovascular outcomes in ESRD patients.

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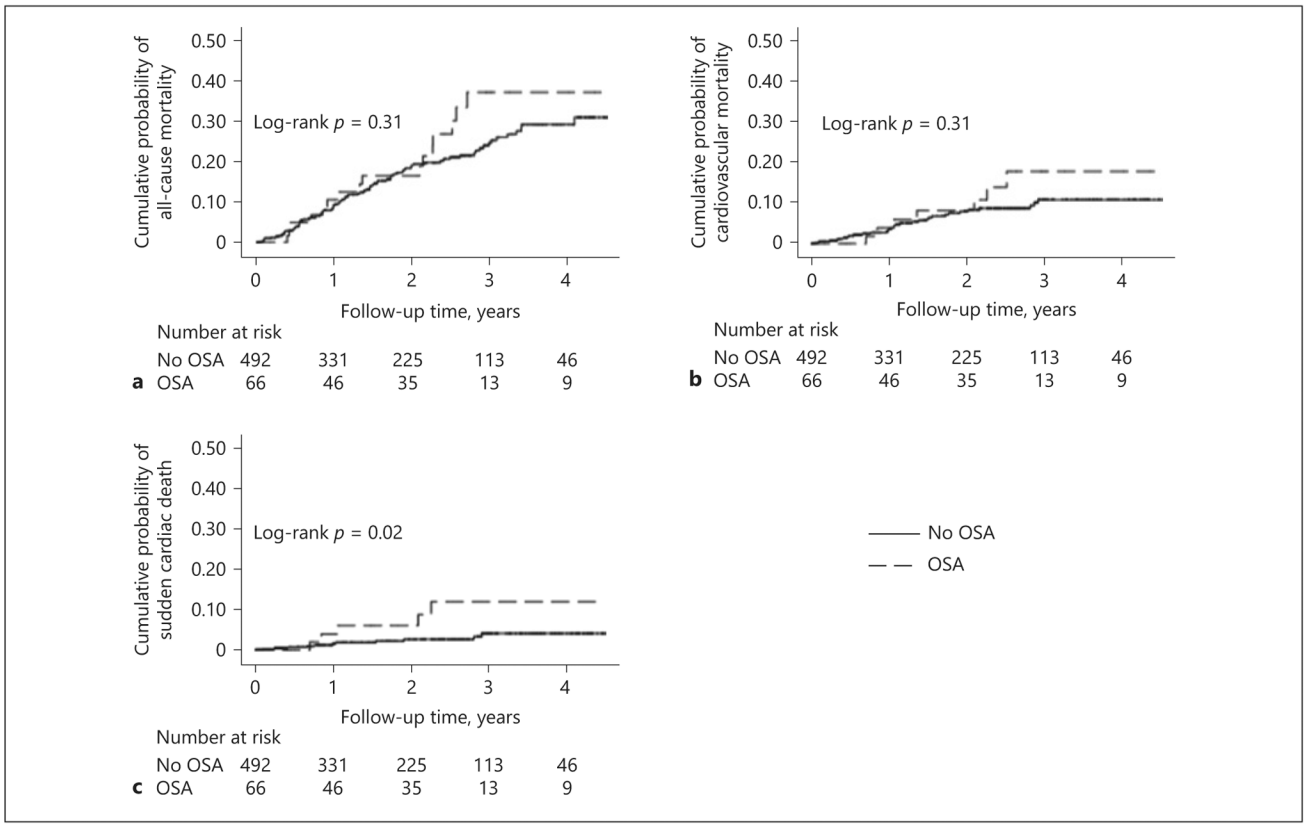

Fig. 1.

Unadjusted Kaplan-Meier plots for (**a**) all-cause mortality, (**b**) cardiovascular mortality, and (**c**) sudden cardiac death (SCD) by obstructive sleep apnea status at dialysis initiation.

Table 1.

Baseline characteristics for patients with OSA, and those without OSA, as ascertained by chart review in the PACE study

Variables	Mean ± SD, median(IQR), frequency (%)		*p* value*
	OSA (*n* = 66)	no OSA (*n* = 492)	
Demographics			
Age, years	59±12	56±14	0.12
Gender			
Male	37 (56)	275 (56)	0.98
Female	29 (44)	217 (44)	
Race			
African American	35 (53)	350 (71)	0.003
Non-African American	31 (47)	142 (29)	
WHR	0.95 (0.08)	0.98 (0.07)	0.02
Physical activity#, kcal/week	6.2 (1.3)	6.1 (1.4)	0.59
CVD risk factors			
BMI, kg/m^2	37 (31–42)†	27 (24–32)†	<0.001
Hypertension	66 (100)	489 (99)	0.53
Hypercholesterolemia	54 (84)†	308 (63)†	0.001
Diabetes	50 (76)	276 (56)	0.002
Coronary artery disease	31 (47)	167 (34)	0.04
History of atrial fibrillation	25 (38)	125 (25)	0.03
Charlson comorbidity index	6 (5–7)†	5 (4–7)†	0.02
QTc prolongation	21 (53)†	150 (47)†	0.51
Left ventricular mass index, g/m^2	76 (59–93)†	61 (50–79)†	0.001
Left ventricular ejection fraction, %	64±12†	66±12†	0.41
Dialysis adequacy/volume measurements			
spKt/V	1.6±0.4†	1.8±0.3†	<0.001
URR	65.2±6.3†	69.0±7.0†	<0.001

Variables	Mean ± SD, median(IQR), frequency (%)		*p* value*
	OSA (*n* = 66)	no OSA (*n* = 492)	
IDW change, kg	2.4±0.9†	2.1±0.8†	0.01
IDW change/body weight	0.026 (0.011)	0.022 (0.008)	0.004
Dialysis adherence (HD sessions missed per month)			
0 sessions per month	56 (85)†	435 (88)†	0.4
1 session per month	10 (15)†	57 (12)†	

*p value by t test for normally distributed data; Wilcoxon ranksum test for non-normal data; chi-square test for categorical data.

†Missing data for some patients.

#Physical activity data were log transformed.

OSA, obstructive sleep apnea; PACE, predictors of arrhythmic and cardiovascular risk in ESRD; IQR, interquartile range; WHR, waist to hip ratio; CVD, cardiovascular disease; BMI, body mass index; URR, urea reduction ratio; HD, hemodialysis; IDW, intradialytic weight.

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Table 2.

Association of OSA status with all-cause mortality, cardiovascular mortality, and sudden cardiac death with no OSA as the referent group

Model	Covariates	All-cause mortality		CVD mortality		Sudden cardiac death	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
1	Unadjusted	1.32 (0.77–2.24)	0.31	1.52 (0.67–3.43)	0.32	3.27 (1.14–9.42)	0.03
2	Adjusted by age, gender, ethnicity	1.27 (o.74–2.18)	0.38	1.50 (0.66–3.42)	0.33	3.28 (1.12–9.57)	0.03
3	Model 2 + Charlson comorbidity index	1.10 (o.64–1.89)	0.74	1.38 (0.60–3.18)	0.45	3.00 (1.01–8.86)	0.047
4	Model 2 + BMI †	1.90 (1.04–3.46)	0.04	3.62 (1.36–9.66)	0.01	12.12 (2.70–54.40)	0.001
5	Model 2 + history of atrial fibrillation	1.30 (0.75–2.23)	0.35	1.46 (0.64–3.35)	0.37	3.40 (1.15–10.05)	0.03
6	Model 2 + left ventricular mass index	1.25 (0.72–2.14)	0.43	1.56 (0.67–3.60)	0.3	3.95 (1.31–11.90)	0.01
7	Model 2 + Kt/V	1.60 (0.92–2.80)	0.1	1.93 (0.82–4.57)	0.13	3.42 (1.09–10.74)	0.04
8	Model 2 + IDW change	1.23 (0.72–2.12)	0.45	1.40 (0.61–3.22)	0.43	3.31 (1.10–9.94)	0.03
9	Model 2 + IDW change/body weight	1.41 (0.82–2.44)	0.21	1.90 (0.81–4.45)	0.14	3.77 (1.24–11.48)	0.02
10	Model 2 + waist-to-hip ratio	1.27 (0.74–2.18)	0.39	1.44 (0.63–3.29)	0.39	3.40 (1.15–10.0)	0.03

† Body mass index is a continuous variable.

OSA, obstructive sleep apnea; CVD, cardiovascular disease; HR, hazard ratio; BMI, body mass index; IDW, intradialytic weight.

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Table 3.

Association of overweight/obese BMI (BMI >25) with all-cause mortality, cardiovascular mortality, and sudden cardiac death with normal/underweight BMI (BMI ≤25) as the referent group

Model	Covariates	All-cause mortality		CVD mortality		Sudden cardiac death	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
1	Unadjusted	0.56 (0.38–0.83)	0.004	0.46 (0.25–0.85)	0.01	0.46 (0.17–1.22)	0.12
2	Adjusted by age, gender, ethnicity	0.55 (0.37–0.82)	0.003	0.45 (0.24–0.83)	0.01	0.46 (0.17–1.25)	0.13
3	Model 2 + OSA	0.49 (0.32–0.74)	0.001	0.36 (0.18–0.72)	0.004	0.22 (0.06–0.81)	0.02

CVD, cardiovascular disease; HR hazard ratio.

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