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The Effect of Sleep Disorder Diagnosis on Mortality in End-Stage Renal Disease Patients

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Featured Application: This retrospective evaluation of the association of sleep disorder diagnosis and mortality in end-stage renal disease (ESRD) patients emphasizes the importance of the diagnosis and treatment of sleep disorders in this population.

Abstract: Increased risk of all-cause mortality not accounted for by traditional cardiovascular risk factors has been linked to chronic kidney disease. This study tested the hypothesis that mortality may be greater in patients with end-stage renal disease (ESRD) and a sleep disorder diagnosis. The United States Renal Data System database was queried to determine the effect of sleep disorder diagnoses on mortality in ESRD patients enrolled between 2004 and 2015. Sleep disorders were identified using International Classification of Diseases-9 and -10 codes. Mortality risk associated with sleep disorders was examined using Cox proportional hazards (CPH) modeling. In the final CPH model, sleep disorder diagnoses were associated with decreased risk of mortality, with hazard ratios (and 95% confidence intervals) for insomnia, hypersomnolence, restless leg syndrome, and obstructive/central sleep apnea of 0.76 (0.75–0.76), 0.81 (0.78–0.84), 0.79 (0.77–0.80), and 0.82 (0.81–0.82), respectively. Black or other race and Hispanic ethnicity, and to a small extent, female sex and increasing Charlson comorbidity index, were also associated with decreased risk, whereas increasing age, hemodialysis (versus peritoneal dialysis) and catheter or graft access type were associated with increased risk. This study suggests that the diagnosis of a sleep disorder may be associated with improved survival in ESRD patients.

Keywords: humans; restless leg syndrome; kidney failure; chronic; sleep apnea; obstructive

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1. Introduction

Chronic kidney disease (CKD) is a leading cause of morbidity and mortality worldwide [1,2]. CKD also affects quality of life through symptoms of uremia, volume overload, and worsened fatigue. Changes in quality of life are especially evident once renal replacement therapy is initiated. CKD treatment is costly due to the expensive nature of renal replacement therapies including dialysis and transplant [2,3]. In the United States, annual Medicare spending on CKD and end-stage renal disease (ESRD) is more than USD 98 billion [4].

CKD has been linked to increased cardiovascular disease (CVD) risk and mortality as well as all-cause mortality [5]. Traditional cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia, and smoking do not completely explain this increased risk [6]. One hypothesized explanation for this discrepancy is that non-traditional risk factors, such as sleep disorders may increase mortality [5,7]. Compared to the general public, patients with CKD are reported to have a higher incidence of sleep disorders

including obstructive sleep apnea (OSA), insomnia, restless leg syndrome (RLS), and hypersomnia [8,9]. In fact, estimates of the prevalence of sleep disorders, based largely on questionnaires of patients on dialysis, range from 40 to 85% [10]; however, a recent study used actigraphy to monitor sleep in 64 dialysis patients versus matched healthy controls and also found a higher prevalence of poor quality sleep in the ESRD patients versus the controls (59% versus 13% in terms of sleep efficiency and 81% versus 34% for sleep fragmentation) [11]. Unfortunately, most ESRD patients with sleep difficulty receive no treatment [10].

OSA is common in patients with CKD and increases as kidney function declines [12,13]. OSA is characteristically associated with nocturnal hypoxemia which can lead to worsening the glomerular filtration rate (GFR) and accelerate the progression of CKD [14,15]. It is thought that through chronic, intermittent, nocturnal hypoxemia the decline in renal oxygenation can initiate and promote a fibrotic response [16,17]. While OSA contributes to the progression of CKD, there is also evidence that declining kidney function contributes to the pathogenesis of sleep disorders, such as OSA. Volume overload causes congestion of the upper airways which causes OSA due to swelling of the tissues [18]. Furthermore, accumulation of uremic toxins induces metabolic acidosis and hypocapnia and increases chemosensitivity to carbon dioxide, leading predominantly to central sleep apnea (CSA) [18]. Indeed, sleep apnea is estimated to occur in more than 50% of ESRD patients compared to 2–4% in the general population [13]. Uremia is also associated with restless leg syndrome (RLS) and affects between 12% and 57% of patients on dialysis [19,20]. RLS symptoms in dialysis are severe and have a negative impact on quality of life and are thought to increase the risk of mortality in this population [11]. Periodic limb movements during sleep induce rises in blood pressure, which may play a role in the pathogenesis of cardiovascular diseases [21].

The relationship between sleep disorders and mortality has not been studied in ESRD patients. This study is a retrospective analysis of the United States Renal Data System (USRDS) database to determine whether there is worsened mortality in those with a sleep disorder diagnosis.

2. Materials and Methods

2.1. Population

ESRD subjects enrolled in the USRDS between 2004 and 2015 were eligible for inclusion.

2.2. Exclusions

Subjects with missing or unknown race, age, sex, ethnicity, access type or dialysis modality were excluded from the analysis. Subjects with no follow-up or who died at the time of entry into the USRDS were also excluded. The study sample size was 980,142 subjects.

2.3. Main Independent Variables

The main independent variables of interest were a diagnosis of a sleep disorder as grouped into broad categories of hypersomnolence disorders, insomnia disorders, RLS, or OSA/CSA disorders. Each diagnosis was identified using International Classification of Disease (ICD)-9 or ICD-10 codes from hospital, detailed, and physician/supplier claims and must have occurred after the start of dialysis. The codes used for the analysis are fully expanded in Supplemental Table S1.

2.4. Outcome Variabl

The main outcome of interest was mortality status determined using the date of death from the Centers for Medicare and Medicaid Services (CMS) 2746 Form—ESRD Death Notification. Time to death in years was determined from the date of first dialysis to death for those who died. Follow-up time for those who did not die was determined from the date of first dialysis to 31 December 2015. To the best of our knowledge, the only loss to

follow-up is through death, especially since patients with ESRD require continued dialysis to survive; we assume that the patients survive to the end of the study if there is no death date provided.

2.5. Demographic and Other Risk Factors

Demographic data including age at incident dialysis, race, sex, ethnicity, access type, and dialysis modality were determined from the patient data or CMS Form 2728—Medical Evidence Report Medicare Entitlement and or Patient Registration. Additionally, the Charlson comorbidity index (CCI) was assessed as a measure of additional co-morbidities, and all diagnoses included in the index were identified using ICD-9 or ICD-10 codes from hospital, detailed, and physician/supplier claims after the start of dialysis. The CCI includes the diagnoses of most of the traditional risk factors as well as of additional comorbidities that assess the overall health of the patient. Therefore, to include additional comorbidities and better control for health status, we elected to use CCI in examining mortality.

2.6. Statistical Analysis

All statistical analysis was performed using SAS 9.4, and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics including frequencies and percentages or means and standard deviations, where appropriate, on all variables overall, by each sleep diagnosis (hypersomnolence, insomnia, RLS, and OSA/CSA), and by mortality were determined.

To examine whether each sleep disorder diagnostic group (hypersomnolence, insomnia, RLS, or CSA/OSA) was a risk factor for mortality after controlling for demographic risk factors and the CCI, Cox proportional hazards (CPH) modeling was used. A Kaplan–Meier curve was determined, stratified by each sleep diagnosis along with the log–rank test for differences in survival. Due to the large sample size, the assumption of proportionality of the hazards was assessed using the log(−log(survival) plot, and this assumption was met for each sleep diagnosis. Each sleep disorder and each demographic or clinical covariate was first examined in a simple CPH model. Then, to build the final multivariable model for each sleep diagnosis on mortality controlling for demographic risk factors and the CCI, a backward model building strategy was used to arrive at the comprehensive final model. Starting with the full model, the most non-significant demographic or clinical risk factor was removed from the model. The Akaike's information criterion (AIC) and −Log likelihood (−2LL) test were used to determine whether the reduced model fit was as good as the previous model. A lower AIC and non-statistically significant −test indicated whether the reduced model was as good as the previous model. If the reduced model was not as good as the previous model, the variable was re-entered in the model and the next least significant variable was examined for removal. The final model included the sleep disorder, CCI, and any demographic risk factor that was statistically significant and/or needed in the model using the model building criteria. Adjusted hazard ratios (HR) and 95% confidence intervals are presented for the final model.

3. Results

Table 1 provides the descriptive statistics overall and by each sleep diagnosis. The prevalence of hypersomnolence was 0.5%, of insomnia was 6.9%, of RLS was 2.8%, and of OSA/CSA was 12.6%. Overall, subjects were 64.9 years old (SD = 14.3), 66% white and 28% black, 14% Hispanic, and 44% female. The majority had a catheter access type (82%) and were on hemodialysis (99.9%). The mean CCI was 7.0 (SD = 3.9).

Figure 1 shows the Kaplan–Meier survival curves for mortality by each sleep disorder diagnosis. For each sleep disorder diagnosis, the diagnosis was associated with better survival than no sleep disorder diagnosis, although the curves tended to superimpose at later time points.

Table 1. Descriptive statistics overall and by hypersomnolence, insomnia, RLS, and OCA/CSA among all ESRD patients in the USRDS from 2004 to 2015.

Variable		Overall	Hypersomnolence		Insomnia		RLS		OSA/CSA	
			Dx N = 4, 561 (0.5%)	**No Dx N = 975,581 (99.5%)**	**Dx N = 67,812 (6.9%)**	**No Dx N = 912,330 (93.1%)**	**Dx N = 27,261 (2.8%)**	**No Dx N = 952,881 (97.2%)**	**Dx N = 123,220 (12.6%)**	**No Dx N = 856,922 (87.4%)**
Person Years Follow-Up—mean (SD)			2.3 (2.0)	2.7 (2.4)	2.1 (20)	2.6 (2.4)	2.2 (1.9)	2.7 (2.4)	1.6 (1.8)	2.6 (2.4)
Age—mean (SD)		64.9 (14.3)	61.1 (13.5)	64.9 (14.3)	63.5 (14.4)	65 (14.3)	63.4 (13.8)	64.9 (14.4)	62.6 (12.6)	65.2 (14.5)
Race—n (%)	Black	277,164 (28.3)	1383 (30.3)	275,781 (28.3)	17,192 (25.4)	259,972 (28.5)	3679 (13.5)	273,485 (28.7)	34,087 (27.7)	243,077 (28.4)
	Other	53,772 (5.5)	123 (2.7)	53,649 (5.5)	3128 (4.6)	50,644 (5.6)	958 (3.5)	52,814 (5.5)	3804 (3.1)	49,968 (5.8)
	White	649,206 (66.2)	3055 (67.0)	646,151 (66.2)	47,492 (70.0.)	601,714 (66.0)	22,624 (83.0)	626,582 (65.8)	85,329 (69.3)	563,877 (65.8)
Sex—n (%)	Female	427,690 (43.6)	2045 (44.8)	425,645 (43.6)	31,842 (47.0)	395,848 (43.4)	14,275 (52.4)	413,415 (43.4)	50,140 (40.7)	377,550 (44.1)
	Male	552,452 (56.4)	2516 (55.2)	549,936 (56.4)	35,970 (53.0)	516,482 (56.6)	12,986 (47.6)	539,466 (56.6)	73,080 (59.3)	479,372 (55.9)
Ethnicity—n (%)	Hispanic	141,527 (14.4)	468 (10.3)	141,059 (14.5)	9560 (14.1)	131,967 (14.5)	2496 (9.2)	139,031 (14.6)	12,939 (10.5)	128,588 (15.0)
	Non-Hispanic	838,615 (85.6)	4093 (89.7)	834,522 (85.5)	58,252 (85.9)	780,363 (85.5)	24,765 (90.8)	813,850 (85.4)	110,281 (89.5)	728,334 (85.0)
Access Type—n (%)	Catheter	803,615 (82.0)	3547 (77.8)	800,068 (82.0.)	54,869 (80.9)	748,746 (82.1)	21,044 (77.2)	782,571 (82.1)	98,986 (80.3)	704,629 (82.2)
	Graft	32,785 (3.3)	183 (4.0)	32,602 (3.3)	2607 (3.8)	30,178 (3.3)	1025 (3.8)	31,760 (3.3)	4145 (3.4)	28,640 (3.3)
	AVF	143,742 (14.7)	831 (18.2)	142,911 (14.7)	10,336 (15.2)	133,406 (14.6)	5192 (19.1)	138,550 (14.5)	20,089 (16.3)	123,653 (14.4)
Dialysis Modality—n (%)	Hemodia-lysis	979,124 (99.9)	4553 (99.8)	974,571 (99.9)	67,714 (99.9)	911,410 (99.9)	27,219 (99.9)	951,905 (99.9)	123,069 (99.9)	856,055 (99.9)
	Peritoneal	1018 (0.1)	NR *	NR *	98 (0.1)	920 (0.1)	42 (0.2)	976 (0.1)	151 (0.1)	867 (0.1)
CCI—mean (SD)		7.0 (3.9)	9.5 (2.8)	7.0 (3.9)	9.5 (2.9)	6.8 (3.9)	9.2 (2.7)	7.0 (3.9)	9.2 (2.7)	6.7 (3.9)

* NR = not reported; according to USRDS regulations, values of <11 must be suppressed.

Table 2 provides the descriptive statistics by mortality as well as the simple and final CPH model results. As shown, in the final model, diagnosis of any of the sleep disturbances (hypersomnolence, insomnia, RLS, and OSA/CSA) was all associated with protection from mortality, with adjusted hazard ratios of 0.81, 0.76, 0.70, and 0.82, respectively. Demographic variables associated with a decreased risk of mortality included black or other race compared to white and Hispanic ethnicity; there was a slight, but likely not clinically important protection detected in those of female sex or increasing CCI. Several factors were associated with increased risk of mortality, including increased age, hemodialysis compared to peritoneal dialysis, and catheter or graft access compared to an arteriovenous fistula (AVF).

Figure 2 illustrates the forest plot of the results of the final CPH multivariable model indicating the relative risk of each of the sleep diagnoses, demographic risk factors, and CCI on mortality. The final CPH model showed that a diagnosis of hypersomnolence, insomnia, RLS, or OSA/CSA was associated with a decreased risk of death after controlling for ethnicity, age, race, sex, access type, dialysis modality, and CCI. Increasing age, catheter access type, graft access type, and hemodialysis were associated with increased risk of mortality, while black or other race or Hispanic ethnicity. Female sex and increased CCI were associated with a slightly decreased risk of mortality in the final model.

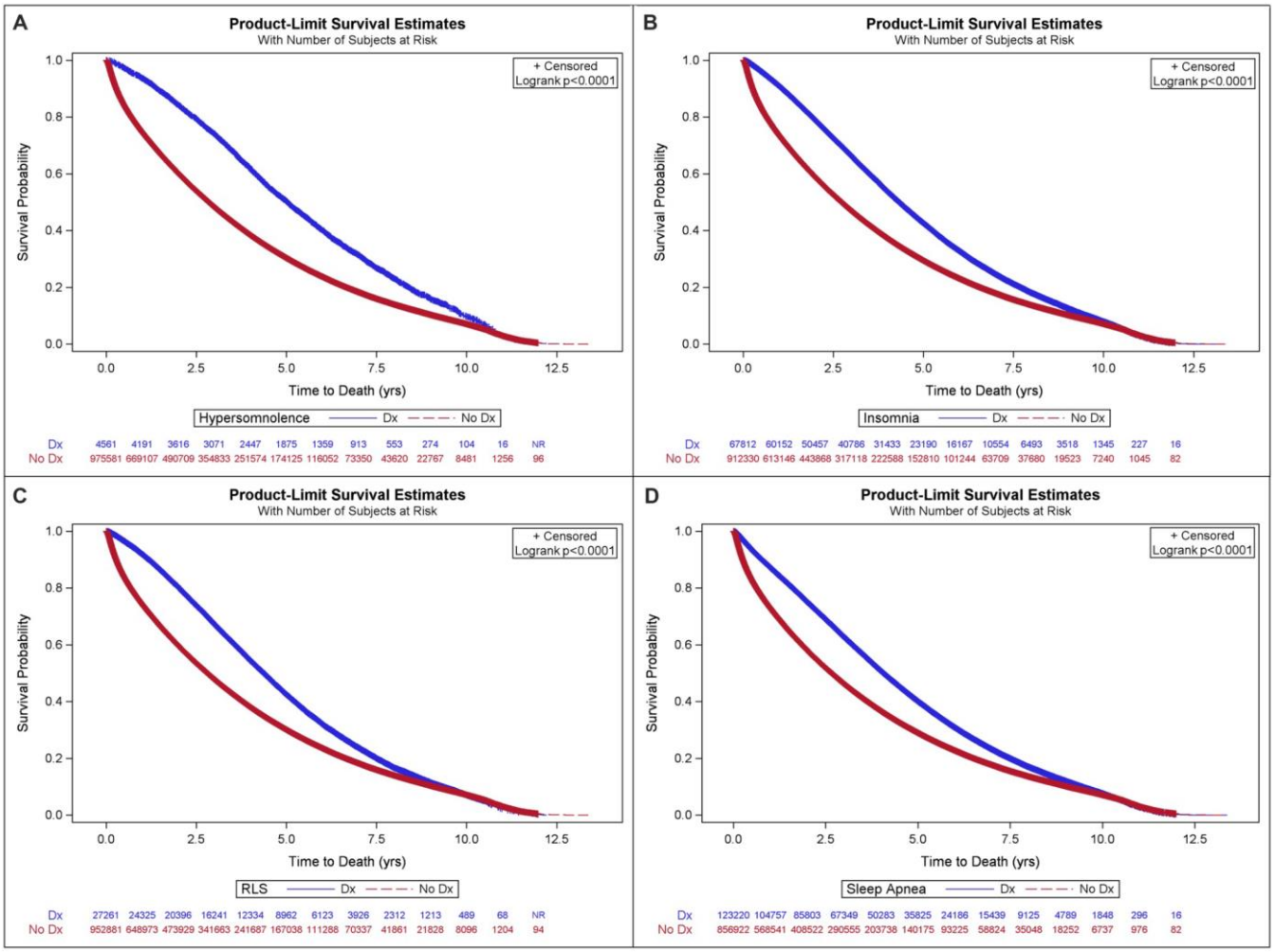

Figure 1. Kaplan–Meier survival curves for each sleep disorder diagnosis. Blue curves represent those with the diagnosis (Dx) of (**A**) hypersomnolence, (**B**) insomnia, (**C**) restless leg syndrome (RLS), and (**D**) sleep apnea. NR = not reported; according to USRDS regulations, values of <11 must be suppressed.

Table 2. Descriptive statistics by mortality status and simple and final CPH models on mortality.

Variable	Level	Mortality		Simple CPH		Final CPH	
		Died N = 671,568 (68.5%)	**Alive N = 308,574 (31.5%)**	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
Time to Death/ Follow-Up—mean (SD)		2.4 (2.3)	3.4 (2.7)				
Hypersomnolence—n (%)	Diagnosis	3225 (70.7)	1336 (29.3)	0.64 (0.61–0.65)	<0.0001	0.81 (0.78–0.84)	<0.0001
	No Diagnosis	668,343 (68.5)	307,238 (31.5)	1.00		1.00	
Insomnia—n (%)	Diagnosis	50,691 (74.8)	17,121 (25.3)	0.71 (0.81–0.72)	<0.0001	0.76 (0.75–0.76)	<0.0001
	No Diagnosis	620,877 (68.1)	291,453 (32)	1.00		1.00	
RLS—n (%)	Diagnosis	20,015 (73.4)	7246 (26.6)	0.73 (0.73–0.74)	<0.0001	0.79 (0.77–0.80)	<0.0001
	No Diagnosis	651,553 (68.4)	301,328 (31.6)	1.00		1.00	
OSA/CSA—n (%)	Diagnosis	87,877 (71.3)	35,343 (28.7)	0.74 (0.73–0.74)	<0.0001	0.82 (0.81–0.82)	<0.0001
	No Diagnosis	583,691 (68.1)	273,231 (31.9)	1.00		1.00	
Age—mean (SD)		67.9 (13.3)	58.3 (14.3)	1.03 (0.1034–1.034)	<0.0001	1.032 (1.032–1.032)	<0.0001
Race—n (%)	Black	167,741 (60.5)	109,423 (39.5)	0.67 (0.66–0.67)	<0.0001	0.73 (0.72–0.73)	<0.0001
	Other	31,452 (58.5)	22,320 (41.5)	0.67 (0.66–0.68)		0.65 (0.64–0.66)	
	White	472,375 (72.8)	176,831 (27.2)	1.00		1.00	
Sex—n (%)	Female	295,485 (69.1)	132,205 (30.9)	0.99 (0.98–0.99)	0.0005	0.96 (0.95–0.96)	<0.0001
	Male	376,083 (68.1)	176,369 (31.9)	1.00		1.00	
Ethnicity—n (%)	Hispanic	82,676 (58.4)	58,851 (41.6)	0.72 (0.71–0.72)	<0.0001	0.68 (0.67–0.68)	<0.0001
	Non-Hispanic	588,892 (70.2)	249,723 (29.8)	1.00		1.00	
Access Type – n (%)	Catheter	562,837 (70.0)	240,778 (30.0)	1.37 (1.36–1.38)	<0.0001	1.51 (1.50–1.52)	<0.0001
	Graft	22,785 (69.5)	10,000 (30.5)	1.16 (1.14–1.17)		1.20 (1.18–1.22)	
	AVF	85,946 (59.8)	57,796 (40.2)	1.00		1.00	
Dialysis Modality—n (%)	Hemodialysis	670,986 (68.5)	308,138 (31.5)	1.57 (1.45–1.71)	<0.0001	1.49 (1.37–1.61)	<0.0001
	Peritoneal	582 (57.2)	436 (42.8)	1.00		1.00	
CCI—mean (SD)		7.7 (3.8)	5.4 (3.7)	1.008 (1.008–1.009)	<0.0001	0.990 (0.989–0.991)	<0.0001

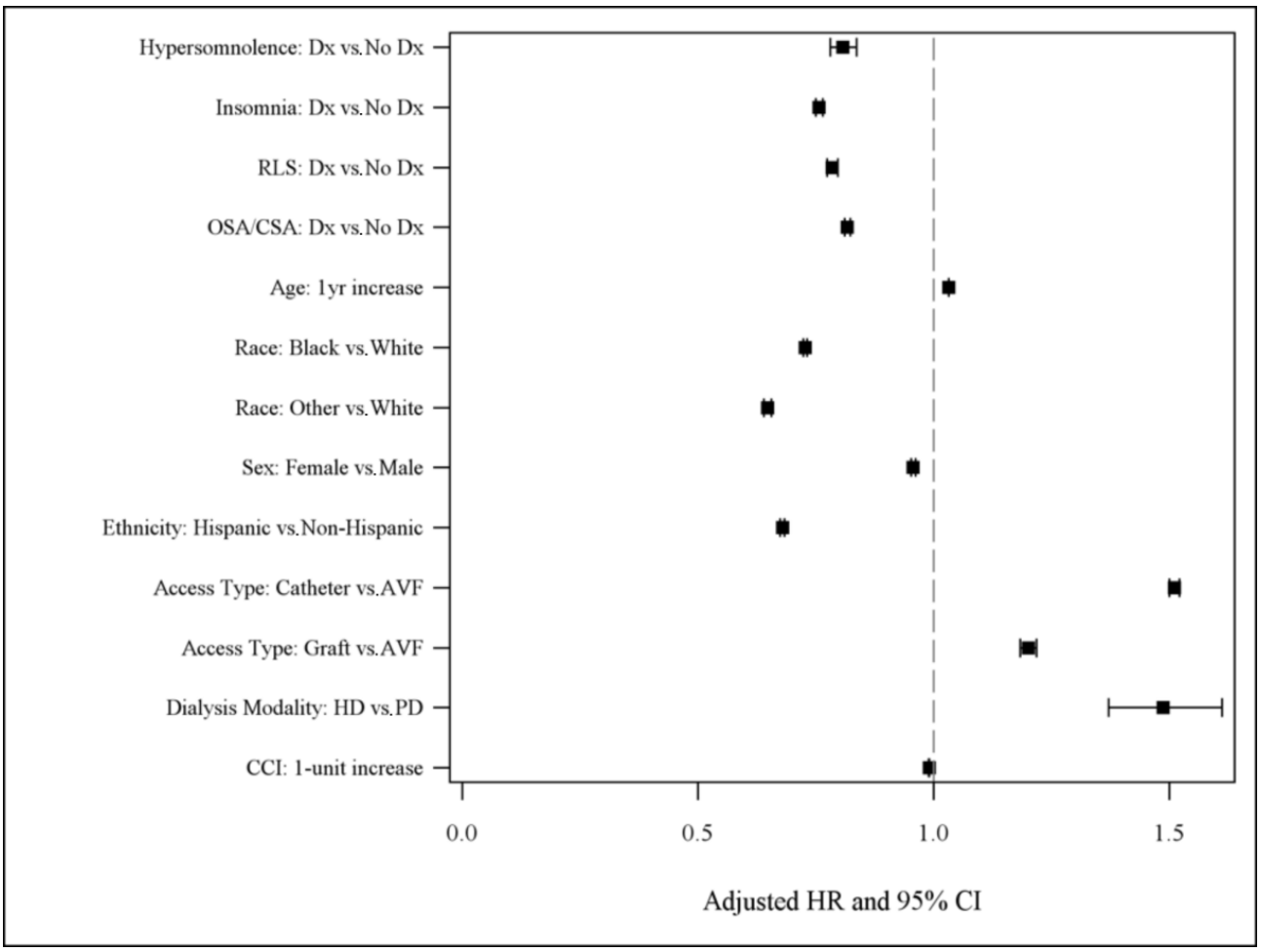

Figure 2. Forest plot showing the relative risk of mortality associated with various demographic parameters, CCI, and each sleep disorder diagnosis. Error bars indicate the 95% confidence interval.

4. Discussion

There is a high prevalence of sleep disorders in patients with ESRD [8,9,22], and specific sleep disorders, such as OSA lead to progression of CKD and increased complications [14,15]. The relationship between sleep disorders and mortality has not been studied in ESRD patients. This study was a retrospective analysis of the USRDS database to examine the relationship between the diagnosis of the disorders of hypersomnolence, insomnia, RLS, or OSA/CSA and mortality in ESRD patients while controlling for various demographic variabilities and overall health (as assessed by the CCI).

This study highlights clinical characteristics of patients diagnosed with sleep disorders and ESRD. Our data show that amongst patients with ESRD, 0.5% were diagnosed with hypersomnolence, 6.9% were diagnosed with insomnia, 2.8% were diagnosed with RLS, and 12.6% were diagnosed with OSA/CSA. This is similar to the prevalence of these conditions in the general population except for OSA/CSA, which exhibited an increased prevalence in patients with ESRD compared to what has been found in studies of the general population [23]. This contrasts with several studies that showed patients with CKD have higher rates of all sleep disorders than the general population [8,24,25]. Unfortunately, despite their high prevalence, many sleep disorders often go undiagnosed, and less than 20% of patients with insomnia are properly diagnosed and treated [23]. This number is even smaller for hypersomnolence and RLS [23]. Studies have also shown a high prevalence of sleep disorders amongst minorities [26–28]. To investigate this disparity, a

future prospective study could objectively measure sleep in this population to determine whether there are disparities in diagnosing sleep disorders in minority ESRD patients. Our study suggests that certain sleep disorders may be underdiagnosed in this population, especially amongst minorities.

Previous studies also showed an association between sleep disorders and increased overall mortality in patients with CKD [29,30]. However, there have been other studies that produced conflicting results, especially in patients with ESRD on hemodialysis. Argekar et al. [31], found that despite the presence of a strong association between sleep apnea and mortality in the general population, a similar association could not be demonstrated in ESRD patients with a high prevalence of this condition. Their study found that a high probability of sleep apnea at baseline did not predict total or cardiovascular mortality [31]. These results are of interest to our study since despite the multifactorial mechanisms that could produce an association between sleep disorders and increased mortality in patients with ESRD, our final CPH model showed that a diagnosis of hypersomnolence, insomnia, RLS, or OSA/CSA was associated with a decreased risk of death after controlling for sex, age, race, ethnicity, access type, dialysis modality, and CCI. The odds ratios in these cases take into account the person years at risk. In Figure 1, patients with sleep disorders show improved survival early in their disease history, although both those with and those without a diagnosis of sleep disorders eventually die. Therefore, when results are corrected for the length of time that the patient has lived with a certain diagnosis, sleep disorders become protective. Catheter access type, increasing age, graft access type, and hemodialysis were associated with increased risk of mortality. Black race, other race, and Hispanic ethnicity, were correlated with decreased risk of mortality, and female sex and increasing CCI with a slightly decreased risk, in the final model. With large datasets, such as the USRDS, occasionally there are values, particularly for continuous variables, that are statistically significant but not biologically relevant. In the case of CCI, a change in the adjusted odds ratio of ~0.01 (i.e., aHR = 0.990 with a 95% CI of 0.989–0.991) is likely not particularly clinically important.

Two of the leading causes of mortality in patients with ESRD on dialysis are cardiovascular disease and infection [32]. Sleep disorders are associated with adverse effects on blood pressure control, cardiac remodeling, and immune function, which would lead one to anticipate higher mortality rates in this population [15,33]. One possible explanation for this finding is that patients with sleep disorders and ESRD are seeing medical professionals more often due to their dialysis. This could lead to earlier detection of complications in order that their problems are promptly worked up and treated. Additionally, OSA causes progression of CKD through a decline in renal oxygenation that can initiate and promote a fibrotic response [16,17]. This could explain the "wearing off" of the protective effect of a sleep diagnosis at the 10-year mark. Sleep disorders are tightly linked with cardiac complications, such as hypertension that can worsen renal disease and increase mortality. Our study indicates that diagnosing sleep disorders may impart a survival advantage in patients with ESRD, although this study did not monitor the treatment of sleep disorders after diagnosis. The American College of Physicians recommends cognitive behavioral therapy for insomnia as a line first treatment and pharmacological intervention (benzodiazepines and non-benzodiazepine receptor agonists) as an adjunct or for secondary treatment of insomnia [10]. For treatment of sleep apnea in ESRD patients, conservative non-pharmacologic, such as weight loss and avoidance of some exacerbating medicines have shown limited success, but nasal continuous positive airway pressure (C-PAP) shows efficacy. Better uremic control with nocturnal hemodialysis or renal transplantation may also improve sleep apnea. RLS is associated with iron deficiency and anemia in order that high-dose iron-dextran and erythropoietin have been shown to improve the disorder. Dopamine agonists and precursors may also provide relief [13].

The observed prevalence of sleep disorders that we detected in this study is lower than what has been found in other studies of CKD [30], and it would seem that many ESRD patients with sleep disorders are not being diagnosed. Presumably, if patients with

these sleep disorders are not diagnosed, their sleep disorders are not treated. Therefore, diagnosis and subsequent treatment of sleep disorders could impart a survival advantage by slowing the effects of sleep disorders on kidney function.

The observed results appear to be similar to what is known as "the obesity paradox", where obese patients with cardiovascular disease appear to have better survival compared with CVD patients of normal weight [34]. This is an example of collider bias (or selection bias), which may explain the unexpected results in this study. A collider is a common effect of the exposure and the outcome. In this case, ESRD may be a collider, with sleep disorders (particularly OSA) as the exposure. OSA may worsen CKD, leading to progression to ESRD. Additionally, there are unmeasured confounders (such as BMI, socioeconomic status, among others) that may cause or worsen ESRD, and are associated with increased risk of death. In this case, selection of study participants with ESRD represents conditioning on a variable that acts as a collider between OSA (or other sleep disorders) and unmeasured confounders.

There are significant limitations to the observed findings in this study as this was a retrospective analysis of the USRDS database, which consists of procedural and diagnostic codes from billing CMS claims in an ESRD population limited to the United States. Interpretation of these data assumes accuracy of the ICD-9 and ICD-10 codes used by both hospitals and physicians while caring for patients enrolled in the database. The absence of a diagnosis code does not rule out the presence of a sleep disorder. Another limitation is that obesity is an important common risk factor for sleep apnea and CKD. ESRD may lead to weight loss, which in turn, can improve OSA. Therefore, it is possible that ESRD patients tend to have mild OSA, which could explain some of the unexpected results. This could have been added to the model using BMI. However, we only have the baseline value at initiation of dialysis, which may be many years before other outcomes and clinical risk factors are diagnosed; therefore, we elected not to control for baseline BMI. In addition, it is possible that patients without these codes may be sicker with more serious health issues, which may explain their worse survival in the first few years of follow-up. Furthermore, we are not able to clinically confirm the diagnoses present in the database by an independent review of diagnostic testing, such as a sleep test, which is another limitation. Some of the codes used in the various sleep clusters are more general than others and the ability of each cluster to remain distinct may be limited by this finding. Finally, it is possible that the patients without a sleep disorder diagnosis may not have had sufficient time to receive this diagnosis since they died more quickly, and controlling for the number of visits might have enhanced the analysis. However, it seems unlikely that this would change the results. The frequency of dialysis visits during which the database variables are collected greatly outnumbers other types of outpatient visits. Therefore, while this is a potential limitation, we feel that overall the diagnosis of a sleep disorder as protective is valid, as it indicates that the patients are receiving enhanced physician scrutiny and/or receiving treatment of diagnosed conditions. This is further supported by the lower prevalence of these disorders that were detected in our study versus questionnaire-based studies of CKD and ESRD. Additionally, a time to event, Cox proportional hazards model analysis was performed. Individuals who had no follow-up were excluded from this sample, which should aid in diminishing bias due to any potential differences in number of visits. A Kaplan–Meier analysis was performed for descriptive purposes. However, the reduced risk is also seen in these Kaplan–Meier plots, with those with the sleep disorder showing better survival than those without the sleep disorder (Figure 1), suggesting the validity of the results. However, given the size and statistical power of the USRDS database, these limitations are not felt to significantly affect the results observed.

5. Conclusions

Chronic kidney disease (CKD) has been linked to increased mortality that is not completely explained by traditional cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia, and smoking, suggesting the possibility that non-traditional risk factors,

such as sleep disorders may be involved. Whereas most studies show an association between sleep disorders and increased mortality in ESRD, there have been conflicting results obtained in patients with CKD [25,26]. Our final CPH model showed that a diagnosis of hypersomnolence, insomnia, RLS, or OSA/CSA was associated with a decreased risk of death after controlling for other confounding variables, and Kaplan–Meier curves indicated increased survival with these disorders. One possible explanation for this finding is that patients with sleep disorders and ESRD are diagnosed and treated or are more frequently in contact with medical professionals. Increased physician vigilance could possibly lead to earlier detection of complications in order that any issues are promptly detected, diagnosed, and treated.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app13095354/s1, Table S1: ICD-9 and ICD-10 codes used during the analysis.

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