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Original Article

Sleep apnea and kidney transplant outcomes: findings from a 20-year (1997–2017) historical cohort study

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ABSTRACT

Objective/background: A historic cohort single-center study of kidney transplant recipients with graft loss examined the associations between sleep apnea and two transplant outcomes, death with a functioning graft (DWFG), and graft survival time.

Patient/methods: Adult patients who received transplants and experienced graft failure or DWFG from January 1, 1997 to January 1, 2017 constituted the cohort (n = 322). Data for the study were obtained by merging two secondary data sources: the Organ Procurement and Transplantation Network (OPTN) database and the transplant center's medical records. A Cox regression modeled the association of diagnosed sleep apnea, stratified by year-of transplant surgery, with graft survival time. Using backward elimination, this model was adjusted for recipient age, race/ethnicity, gender, functional status, donor age, and antigen mismatch.

Results: No statistically significant differences were found for proportions of DWFG in those with, versus without, sleep apnea, informing our censoring approach. When examining graft survival time, the Cox regression model was stratified given a sleep apnea and year-of-transplant interaction ($p < 0.01$, adjusted model). For patients transplanted between 1997 and 2008, sleep apnea was statistically significantly associated with a decreased risk of graft failure or cardiovascular-related DWFG [adjusted Hazard Ratio (aHR) = 0.63, 95%CI, 0.42–0.94]. For patients transplanted between 2009 and 2017, sleep apnea statistically significantly increased the risk of graft failure or cardiovascular-related DWFG (aHR = 2.61, 95%CI, 1.13–6.00).

Conclusions: In a cohort of transplant recipients with graft loss, sleep apnea increased the risk of graft loss nearly three-fold among patients transplanted between 2009 and 2017. Similar DWFG proportions by sleep apnea presence indicate this risk is likely driven by renal failure, not mortality. Further research on whether treatment of sleep apnea can improve graft survival is warranted.

1. Introduction

Sleep-disordered breathing disorders (most commonly sleep apnea) are prevalent across the spectrum of chronic kidney disease (CKD) in pre-dialysis [1,2], dialysis [3], and transplant patients [4–6]. Sleep apnea is associated with CKD risk factors, such as obesity [7], hypertension [8], and diabetes [9,10]. Additionally, studies suggest a relationship between sleep apnea and kidney functioning [2,11–13], positing sleep apnea as a non-traditional risk factor for CKD. Cohort studies have documented an association of sleep apnea with an increased risk of CKD occurrence [11] and faster progression to end-stage renal disease [11,12].

Several studies have explored the prevalence and relationship of sleep apnea to survival and kidney functioning in patients with kidney disease prior to transplant [2,11–13]. However, few have examined these relationships post-transplant [4,6]. In both studies, sleep apnea was not found to be significantly associated with all-cause mortality [4,6]. However, Szentkiralyi and colleagues [6] found that sleep apnea was an independent risk factor for graft

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; DWFG, death with a functioning graft; EMR, electronic medical record; ESRD, end-stage renal disease; HLA, human leukocyte antigen.

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failure in female kidney transplant patients, while Fornadi and colleagues [4] did not find sleep apnea to be significantly associated with the rate of graft function decline. Furthermore, each of these studies [4,6] each examined a single-center sample of European patients over a 5–6 year post-transplant follow-up, limiting the number of graft failures that could be captured given the study time frames. Additional research, particularly over a longer time period, is needed to further explore the associations of sleep disorders with kidney transplant graft survival and mortality, particularly given conflicting results [4,6] with regard to graft failure.

We conducted a historic single-center cohort study of kidney transplant recipients with graft loss to examine the associations between diagnosed sleep apnea and transplant outcomes. The primary aim of the present study was to examine the associations between diagnosed sleep apnea and graft survival time. To investigate this aim, we first examined if sleep apnea was associated with an increased proportion of death with a functioning graft (DWFG), a leading cause of graft loss that can occur in up to 40% of transplant failures [14]. We hypothesized that a higher proportion of patients with diagnosed sleep apnea would experience DWFG, as patients with sleep apnea in non-transplant samples have been found to have an increased risk of mortality [15,16]. The proportion of DWFG in those with, versus without, diagnosed sleep apnea was also evaluated to inform the censoring designation for our primary outcome, graft survival. Our main hypothesis was that sleep apnea would be associated with shorter graft survival times. The present study extends prior research by examining the relationship between sleep apnea and kidney transplant outcomes over a 20-year follow-up in a historic cohort study of US end-stage renal disease patients with graft loss.

2. Materials and methods

2.1. Study cohort

The historic cohort included adult kidney transplant recipients from a single center in Virginia who were transplanted and experienced graft loss (graft failure or DWFG) during the study period January 1, 1997 to January 1, 2017, inclusive. Excluded were recipients of a previous kidney transplant or a multi-organ transplant, patients documented as non-compliant with their immunosuppressant medications, and patients who experienced graft loss within 90 days of their transplant surgery. In sum, 322 subjects thus constituted the study cohort. The institutional review board approved the study prior to data abstraction and analysis.

2.2. Study variables

Sleep apnea diagnosis, the primary predictor, was defined using medical terminology and ICD-9/10 codes on the subject's medical record. A sleep apnea diagnosis was included only if documented pre-graft failure. Abstraction of sleep apnea diagnoses involved the review of medical history diagnosis codes, as well as utilization of a manual review process for all history and physical documentation, sleep medicine, pulmonary, and anesthesia notes. Covariates examined included recipient-related and donor-related variables. Recipient-related variables included gender, race/ethnicity, age, body mass index, diabetes, hypertension, coronary artery disease, myocardial infarction history, peripheral vascular disease, dyslipidemia, stroke history, end-stage renal disease etiology, educational level, functional status, and smoking history. Donor-related variables included donor type (living or deceased), human leukocyte antigen (HLA) mismatch, donor age, and year-of-transplant surgery. Due to the single-center setting, data on immunosuppressant medications were not included in analyses as covariates, since all patients followed the center's immunosuppressant protocol. The standard maintenance immunosuppressant therapy consisted of prednisone, either cyclosporine or tacrolimus, combined with mycophenolate or azathioprine.

Outcomes were DWFG and graft survival time. DWFG was operationalized as either: all-cause death with a functioning graft or cardiovascular (CVD)-related death with a functioning graft. Graft survival time referred to the duration the patient maintained a functioning kidney transplant, with end-of-survival time defined as graft failure or CVD-related DWFG. CVD-related deaths were included as end-of-survival time because CVD-related DWFG can be related to decreased functioning of the transplanted kidney [17–19]. Inclusion of CVD-related DWFG as an event (endpoint of graft survival time) recognizes the potential for competing risks in graft loss, an important consideration in transplant graft survival studies [17]. All deaths other than from CVD causes (eg, non-CVD deaths) were treated as censored observations for the graft survival outcome.

2.3. Data abstraction

Study data involved merging two sources: the Organ Procurement and Transplantation Network (OPTN) database and the transplant center's medical records. The use of these two data sets allowed for the incorporation of sleep data into the existing OPTN data set. Due to the merging of two data sources and the consequent use of identifying information, in order to obtain a waiver of consent and IRB approval, the study had to be limited to those patients who were transplanted and failed during the study time period. Given the richness of the OPTN data, most study variables were abstracted from the OPTN database, except for these medical record variables: sleep apnea, diabetes, hypertension, coronary artery disease, myocardial infarction history, peripheral vascular disease, dyslipidemia, stroke history, and smoking history. Medical record abstraction was completed by a research team member following a standardized process. Sleep apnea diagnoses and medical comorbidity diagnoses were only included in analyses if documented in medical records before or during the recipient's transplant (before graft failure). All other covariates were reported at transplant time.

For missing data, conditional means imputation was utilized to impute 47 missing values for body mass index (BMI). Seven subjects reporting a race/ethnicity other than African American or Caucasian were collapsed into the Caucasian and other category; the largest racial disparity found in transplant outcomes is between African Americans and other (Caucasians, Asians, Hispanics) according to a review by Gordon et al. [20].

2.4. Statistical analysis

Statistical analyses were performed using SAS™ Enterprise Guide software, version 6.1. Chi-square and independent *t*-test analyses compared study covariates according to sleep apnea presence.

2.4.1. Death with a functioning graft (DWFG)

To examine DWFG, a leading cause of graft loss among transplant recipients, first, the proportion of all-cause DWFG in those with, versus without, diagnosed sleep apnea was compared. Next, proportions of cardiovascular (CVD)-related and non-CVD-related deaths with a functioning graft by presence of sleep apnea were compared in subjects who died with a functioning graft; proportions were compared using chi-square statistics. These analyses informed the analytic approach, namely, whether deaths should be censored with respect to sleep apnea, our selected approach, or

whether a competing risks analysis should model sleep apnea's association with graft survival time.

2.4.2. Graft survival time

Kaplan Meier survival curves [21] displayed sleep apnea's relationship to graft survival time. Cox regression models [22] examined unadjusted and adjusted relationships of sleep apnea to graft survival time. In the multivariate modeling process, backward elimination was utilized to determine the final model, and, through this process, potential covariates that could be potential confounders with our main predictor of interest, sleep apnea, were examined. No confounding associations were found using a cut-off of a change in the parameter estimate of >15%. Due to the potential bias of any one covariate selection method, an automated best subset selection method was subsequently utilized to verify agreement between the selected covariates based on more than one covariate selection method. Variables non-statistically significantly ($p \leq 0.05$) related to the graft survival outcome were removed individually and in the following order: peripheral vascular disease, education level, dyslipidemia, donor type, body mass index, smoking history, coronary artery disease, heart attack history, end-stage renal disease etiology, and stroke history. All potential two-way interactions were also examined in the full model, with statistical significance assessed at $p \leq 0.05$. Final multivariate Cox regression models were adjusted for recipient age, race/ethnicity, gender, functional status (subjective nurse-reported Karnofsky score at transplant time), HLA mismatch, and donor age.

2.4.3. Secondary analyses

For a more comprehensive understanding of sleep apnea's relationship to graft loss with respect to death with a functioning graft (DWFG), adjusted hazard ratios were computed based on two additional censoring designations: (1) no censoring with end-of-graft survival time defined as all-cause graft loss (graft failure and return to dialysis or DWFG) and (2) censoring all deaths with a functioning graft (CVD-related and non-CVD-related), with end-of-graft survival time defined as graft failure and return to dialysis.

3. Results

3.1. Recipient characteristics

The study cohort consisted of a hypertensive (100%), predominantly African American (64%) end-stage renal disease patient population, aged 18–76 years at transplant time, with mean (SD) age 50 (12) years. Diagnosed sleep apnea prevalence was 19% ($n = 60$). Transplant recipients with, versus without, sleep apnea had a more recent transplant, higher prevalence of diabetes, higher BMI, and higher likelihood of limited functionality. Table 1 describes study cohort characteristics by sleep apnea diagnosis, the primary predictor.

3.2. Diagnosed sleep apnea and death with a functioning graft (DWFG)

The proportions of all-cause DWFG in those with, versus without, sleep apnea were virtually equivalent 47% ($n = 28$) versus 44% ($n = 115$), respectively, $p = 0.71$. Of patients who died with a functioning graft ($n = 143$), those with, versus without, sleep apnea had similar proportions of CVD-related DWFG 32% ($n = 9$) versus 25% ($n = 29$), respectively, $p = 0.46$. Given the lack of association between sleep apnea and increased DWFG occurrence, it was determined DWFG could be censored in survival analyses without significant concern for bias regarding sleep apnea.

3.3. Survival analysis: diagnosed sleep apnea and graft survival time

The end of graft survival time refers to graft failure and return to dialysis or CVD-related death with a functioning graft; all non-CVD deaths were censored. Given a significant interaction of sleep apnea and year-of-transplant (examined as a continuous variable) with respect to graft survival time ($p < 0.01$, adjusted model), analyses were stratified into two transplant periods: 1997–2008 and 2009–2017, based on subject matter expertise. Table 2 presents study cohort characteristics by these two periods specified a priori, before stratified analyses were conducted. Determination of these periods was based on transplant center-specific changes, particularly with regard to electronic medical records. Consideration was also given to advances in transplantation and allocation policy changes that could have occurred throughout the study period (1997–2017). A change in the transplant center's medical records in 2009 (ie, the adoption of an electronic medical record) was the main rationale for stratifying data into these two periods. Survival analysis results are based on 216 events with a 33% censoring rate. Year-of-transplant 1997–2008 included 193 events (31% censored), and year-of-transplant 2009–2017 included 23 events (45% censored).

Figs. 1 and 2 present stratified Kaplan Meier curves of graft survival time according to sleep apnea for two strata: year-of-transplant 1997–2008 and year-of-transplant 2009–2017. For those transplanted between 1997 and 2008, median graft survival time for those diagnosed with sleep apnea was longer than for those without (2827 days and 2343 days, respectively, $p = 0.29$). Conversely, for those transplanted 2009–2017, median graft survival time was shorter for those diagnosed with sleep apnea (960 days) versus those without (1834 days, $p = 0.10$). Neither difference was statistically significant using the Log–Rank test.

For this cohort with graft loss, one-year, three-year, and five-year graft survival rates for those with, versus without, diagnosed sleep apnea for the two transplant time periods are derived from Figs. 1 and 2. For 1997–2008 transplant recipients with graft loss, one-year, three-year, and five-year graft survival rates were similar or better for those with (94%, 88%, 72%), versus without (95%, 79%, 65%), sleep apnea. For 2009–2017 recipients with graft loss, those with sleep apnea had poorer one-year, three-year, and five-year graft survival rates (88%, 48%, 19%, respectively) versus those without sleep apnea (96%, 68%, 54%, respectively) (see Supplemental Table S1 for further information).

Table 3 presents unadjusted and adjusted hazard ratios for sleep apnea with respect to graft survival, according to year-of-transplant surgery time period strata. After adjustments for recipient age, race/ethnicity, gender, functional status, HLA mismatch, and donor age, patients with sleep apnea transplanted between years 2009–2017 had a statistically significantly ($p = 0.02$) increased risk of graft loss, while those transplanted between 1997 and 2008 had a statistically significantly ($p = 0.03$) decreased risk of graft loss.

3.4. Secondary analyses: additional censoring designations for graft survival

When graft survival time was defined as all-cause graft loss, adjusted hazard ratios for patients with, versus without, sleep apnea were 0.65 [95% confidence interval (CI): 0.46–0.90, $p = 0.01$] for 1997–2008 transplantees, and 1.60 (95% CI: 0.85–3.03, $p = 0.15$) for 2009–2017 transplantees. When graft survival time was defined as graft failure and return to dialysis, adjusted hazard ratios for patients with, versus without, sleep apnea were 0.60 (95% CI: 0.38–0.96, $p = 0.03$) for patients transplanted 1997–2008, and 3.73 (95% CI: 1.45–9.60, $p \leq 0.01$) for those transplanted 2009–2017.

Table 1
Transplant recipient characteristics according to diagnosed sleep apnea presence.

Recipient Characteristics (n = 322)	Diagnosed Sleep Apnea Presence (n = 60)	No Diagnosed Sleep Apnea (n = 262)	P-value
Recipient-Related Variables			
Age (mean ± SD) (years)	51 ± 13	50 ± 9	0.32
Gender			
Male (%)	67%	53%	0.06
Female (%)	33%	47%	
Education Level			
High school education or less (%)	37%	48%	0.11
Beyond high school (%)	58%	44%	
Unknown (%)	5%	8%	
Race/Ethnicity[a]			
African American (%)	67%	63%	0.67
Caucasian and other (%)	33%	37%	
ESRD Etiology[b]			
Hypertension (%)	33%	39%	0.42
Other (%)	67%	61%	
Lifestyle and Comorbidities			
Body mass index[c] (mean ± SD) (kg/m^2)	32 ± 5	27 ± 5	<0.001
Prevalence of smoking history[c] (%)	40%	44%	0.53
Prevalence of diabetes (%)	80%	58%	0.002
Prevalence of hypertension (%)	100%	100%	N/A
Prevalence of dyslipidemia (%)	82%	72%	0.13
Prevalence of peripheral vascular disease (%)	28%	22%	0.31
Prevalence of a stroke history (%)	18%	19%	0.95
Prevalence of a heart attack history (%)	5%	8%	0.42
Prevalence of coronary artery disease (%)	28%	22%	0.31
Functional Status (Karnofsky-derived measure)			
Full functional status, 100% (%)	30%	54%	0.001
Limited functional status, < 100% (%)	70%	46%	
Transplant-Related Variables			
Age of donor (mean ± SD) (years)	39 ± 15	38 ± 15	0.50
Deceased donor transplant (%)	57%	58%	0.85
Living donor transplant (%)	43%	42%	
HLA mismatch score (median) (0–6)	4	4	0.52
Year of Transplant 1997–2017 (mean ± SD)	2006 ± 3.7	2004 ± 3.9	<0.001
Year of Transplant Strata[d]			
1997–2008 (%)	73%	90%	0.001
2009–2017 (%)	27%	10%	

Abbreviations: ESRD, end-stage renal disease; N/A, not applicable; HLA, human leukocyte antigen.
[a] Caucasian and other: Seven subjects who reported a race/ethnicity other than African American or Caucasian were included in the Caucasian and Other category.
[b] ESRD etiology refers to the primary cause of renal failure and was dichotomized into Hypertension and Other (all other causes including a range of diagnoses [eg, diabetes, glomerulonephritis, polycystic kidney disease, lupus]).
[c] Analysis based on n = 321.
[d] Year of Transplant Strata refers to the time period (years) in which the transplant took place.

4. Discussion

In the present historical cohort study of predominately hypertensive African American transplant recipients with graft loss, diagnosed sleep apnea was associated with a 2.6-fold statistically significantly increased risk of graft failure or CVD-related death with a functioning graft among patients transplanted between years 2009–2017, inclusive. Few studies have examined the association between sleep apnea and kidney transplant graft survival. Our findings from the time period 2009–2017 bolster previous research that sleep apnea is associated with reduced kidney functioning both pre- [11,12] and post-transplant [6]. Szentkiralyi and colleagues [6] found that higher obstructive sleep apnea risk was an independent risk factor for graft failure in female kidney transplant patients [6]. Additionally, obstructive sleep apnea has been identified as a risk factor for chronic kidney disease (CKD) development, and, among those with CKD, associated with faster progression to kidney failure [4,6].

When examining one-year, three-year, and five-year graft survival rates for recipients who were transplanted and failed between the years 2009–2017, those with, versus without, diagnosed sleep apnea had poorer graft survival, by 8%, 20%, and 35%, respectively. The 35% lower survival rate at the five-year mark in those diagnosed with sleep apnea suggests longer time frames should be considered when studying the relationship between sleep apnea and graft survival.

Among recipients who were transplanted and failed between the years 1997–2008, diagnosed sleep apnea was associated with a statistically significantly decreased risk of graft failure or CVD-related death with a functioning graft. For recipients who were transplanted and failed between 1997 and 2008, the three-year and five-year graft survival rates were thus improved by 9% and 7%, respectively, for those with, versus without, sleep apnea. To our knowledge, no other published studies have reported an association between sleep apnea and increased graft survival as found presently for transplant recipients between 1997 and 2008 with, versus without, sleep apnea.

The difference in findings for the two transplant periods warrants discussion. Consideration was given to the significant sleep apnea and year-of-transplant interaction with regard to graft survival time. In 2009, the transplant center implemented an electronic medical record (EMR), which may have resulted in an

Table 2
Transplant recipient characteristics according to transplant time period.

Recipient Characteristics (n = 322)	Year of Transplant 1997–2008 (n = 280)	Year of Transplant 2009–2017 (n = 42)	P-value
Recipient-Related Variables			
Age (mean ± SD) (years)	50 ± 13	53 ± 10	0.11
Gender			
Male (%)	54%	67%	0.13
Female (%)	46%	33%	
Education Level			
High school education or less (%)	45%	45%	0.11
Beyond high school (%)	46%	55%	
Unknown (%)	9%	0%	
Race/Ethnicity[a]			
African American (%)	61%	83%	0.01
Caucasian and other (%)	39%	17%	
ESRD Etiology[b]			
Hypertension (%)	38%	36%	0.76
Other (%)	62%	64%	
Lifestyle and Comorbidities			
Body mass index[c] (mean ± SD) (kg/m^2)	28 ± 5	32 ± 7	0.002
Prevalence of smoking history[c] (%)	43%	45%	0.82
Prevalence of diabetes (%)	61%	71%	0.18
Prevalence of hypertension (%)	100%	100%	N/A
Prevalence of dyslipidemia (%)	73%	79%	0.46
Prevalence of peripheral vascular disease (%)	10%	5%	0.30
Prevalence of a stroke history (%)	18%	24%	0.36
Prevalence of a heart attack history (%)	8%	7%	0.93
Prevalence of coronary artery disease	20%	45%	<0.001
Prevalence of diagnosed sleep apnea (%)	16%	38%	0.001
Functional Status (Karnofsky-derived measure)			
Full functional status, 100% (%)	56%	5%	<0.001
Limited functional status, < 100% (%)	44%	95%	
Transplant-Related Variables			
Age of donor (mean ± SD) (years)	40 ± 15	39 ± 14	0.63
Deceased donor transplant (%)	54%	81%	0.001
Living donor transplant (%)	46%	19%	
HLA mismatch score (median) (0–6)	4	5	<0.001

Abbreviations: ESRD, end-stage renal disease; HLA, human leukocyte antigen; N/A, not applicable
[a] Caucasian and Other: Seven subjects who reported a race/ethnicity other than African American or Caucasian were included in the Caucasian and Other category.
[b] ESRD etiology refers to the primary cause of renal failure and was dichotomized into Hypertension and Other (all other causes including a range of diagnoses [eg, diabetes, glomerulonephritis, polycystic kidney disease, lupus]).
[c] Analysis based on n = 321.

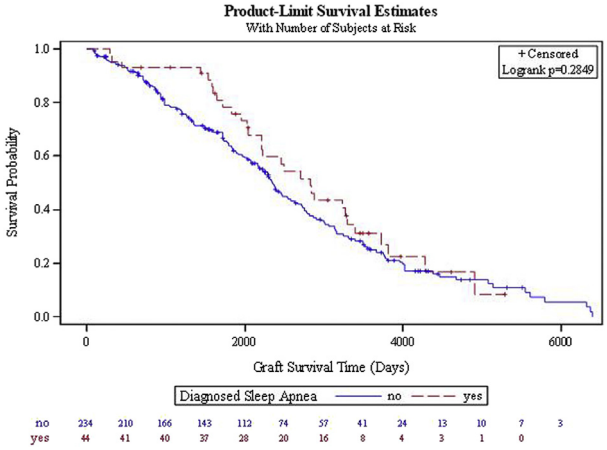

Fig. 1. Kaplan Meier survival curves for year of transplant 1997–2008: Graft survival time by sleep apnea diagnosis.

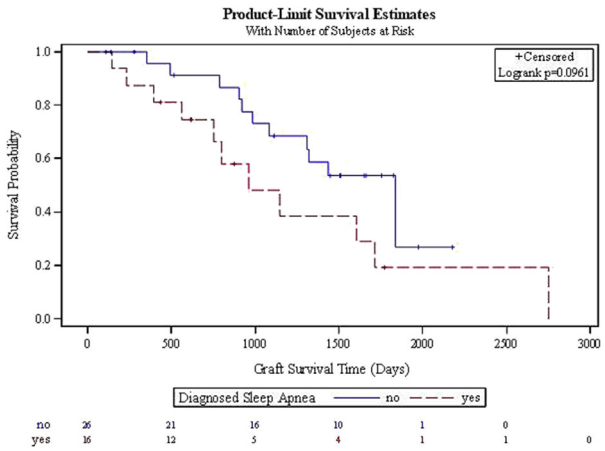

Fig. 2. Kaplan Meier survival curves for year of transplant 2009–2017: Graft survival time by sleep apnea diagnosis.

increased abstraction of diagnosed sleep apnea cases from the 2009–2017 year-of-transplant period. The abstraction source used before 2009 was a database consisting primarily of history and physicals from transplant nephrologists rather than an EMR with documentation from other medical providers. One possible explanation for decreased graft failure risk for sleep apnea patients transplanted 1997–2008 is a potential misclassification of patients without sleep apnea as having sleep apnea, perhaps due to decreased sleep apnea diagnoses from 1997–2008. Variable nephrologist documentation of sleep apnea may have impacted

Table 3
Unadjusted and adjusted hazard ratios for graft failure or cardiovascular-related death with a functioning graft with respect to sleep apnea stratified by year of kidney transplant strata.

Sleep Apnea by Year of Kidney Transplant	Unadjusted			Adjusted		
	HR	HR CI	P- value	aHR[a]	aHR CI	P-value
Year of Transplant 1997–2008						
Diagnosed sleep apnea (n = 44)	0.81	0.55–1.20	0.29	0.63	0.42–0.94	0.03
No diagnosed sleep apnea (n = 234)	1.00	Referent		1.00	Referent	
Year of Transplant 2009–2017						
Diagnosed sleep apnea (n = 16)	2.03	0.87–4.74	0.10	2.61	1.13–6.00	0.02
No diagnosed sleep apnea (n = 26)	1.00	Referent		1.00	Referent	

Abbreviations: HR, hazard ratio; CI, 95% confidence interval; aHR, adjusted hazard ratio.
[a] Adjusted for recipient age, race/ethnicity, gender, functional status, HLA mismatch, and donor age.

sleep apnea information reported in transplant history and physicals (1997–2008) vis-à-vis the full EMR (2009–2017). Underascertainment of sleep apnea is possible given its lower prevalence in 1997–2008 (16%) versus 2009–2017 (38%). The higher prevalence of sleep apnea diagnoses abstracted for 2009–2017 may indicate the EMR as a better abstraction source, or reflect increased awareness and diagnosis of sleep apnea in recent years. Although it is difficult to quantify how the increased diagnosis of sleep apnea could have affected our findings, an analysis of two US national surveys using data from outpatient physician offices from 1993 to 2010 found that the diagnosis of sleep apnea increased 14.6-fold from 1993 to 2010 [23], indicating a substantive change in the prevalence of sleep apnea diagnosed throughout a period similar to our study time frame.

Furthermore, 1997–2008 and 2009–2017 represent two different periods with regard to graft survival time given the study design and overall advances in transplantation. They reflect different durations regarding graft survival time (opportunity to fail) as the study cohort only included subjects with graft failure or who died with a functioning graft between 1997 and 2017. Thus, patients transplanted between 1997–2008 may have had a longer opportunity to fail; their median graft survival time was 2387 days vis-à-vis 1435 days for those transplanted 2009–2017. While earlier data (1997–2008) may be more precise given the longer follow-up, this is counterbalanced by later data (2009–2017) having greater validity. Although the period 2009–2017 only captured patients with early or mid-range graft loss and relied on a smaller patient sample, this time frame represents a more modern transplant era and reflects increased stability regarding transplant outcomes, with decreased risk of acute rejection the most notable change in the past 20 years of transplantation. Such improvements have remained relatively stable since 2008 [24]. Moreover, in addition to the risk of acute graft loss stabilizing, characteristics of transplant recipients have changed throughout the present 20-year study period. Patients once considered too high risk for transplant are presently more routinely transplanted and increased survival on dialysis, which has contributed to increases in transplant wait-times [25], has likely also contributed to the rise in kidney transplants among older adults and patients with increased comorbidities. From 1997 to 2014, the number of deceased donor transplants increased among those aged 65 years and older [25]. An analysis of the US kidney transplant registry has also shown that the prevalence of obesity among kidney transplant recipients has nearly doubled when comparing patients transplanted from 1987 to 2008 to 2009–2013 [26]. Moreover, the increasing prevalence of obesity in these transplant recipients has been associated with increased rates of coronary artery disease (CAD) and diabetes [26]. These differences in patient characteristics during a time period similar to our strata designations for transplant year reinforce the relevant changes in transplantation procedures during our study time period. Ultimately, both periods have different strengths and limitations regarding our study design.

To better understand sleep apnea's relationship to graft survival, and to inform the censoring approaches for our cohort, we examined whether diagnosed sleep apnea was related to an increased proportion of death with a functioning graft (DWFG). Similar to previous studies [4,6], we found no association between sleep apnea and increased DWFG occurrence. While studies of non-transplant samples have reported increased mortality risk among patients with moderate to severe sleep apnea [15,16,27], a study of kidney transplant recipients found no relationship between sleep apnea and increased mortality risk, even in those with moderate to severe sleep apnea [4]. Therefore, it is worth considering that there may not be a relationship between sleep apnea and increased mortality risk in kidney transplant recipients, who have an increased risk of cardiovascular disease (CVD) post-transplant regardless of sleep apnea presence or absence [28,29]. Given the already high CVD prevalence among end-stage renal disease patients, sleep apnea may thus not pose an additive mortality risk. The lack of association between sleep apnea and an increased DWFG proportion provided support for including DWFG as censored observations without concern additional bias would be introduced when examining the association of sleep apnea with graft survival.

Secondary analyses using different censoring determinations of graft survival were elucidating, particularly as our cohort included only those with failed grafts. In 1997–2008, inclusive, patients with diagnosed sleep apnea had a significantly decreased risk of graft loss (by 35–40%) for both censoring designations: all-cause graft loss, and graft failure and return to dialysis. For patients transplanted 2009–2017, the risk of graft loss according to sleep apnea diagnosis changed greatly depending on the censoring designation. When all-cause graft loss was the outcome, patients with sleep apnea transplanted between 2009 and 2017 had a 60% increased risk of graft loss versus those without, though not statistically significant. However, when all deaths were censored, risk of graft failure for patients with, versus without, sleep apnea transplanted 2009–2017 was statistically significant ($p \leq 0.01$) and increased nearly four-fold. The increased risk of graft loss for patients with sleep apnea when all deaths were censored as well as the similar proportions of death with a functioning graft in those with and without sleep apnea (no statistically significant differences) suggest that the association between sleep apnea and graft loss was likely due to kidney failure, not mortality. Consideration should be given to the role sleep apnea may play in kidney functioning.

Sleep apnea is associated with kidney disease risk factors such as hypertension, diabetes, obesity, inflammation [2,30–32], all of which may reduce kidney functioning post-transplant. Additionally, the relationship between hypoxia, a consequence of sleep apnea, and kidney functioning warrants consideration. Hypoxia can

directly affect kidneys' organ function [33]. It is associated with sympathetic nervous system hyperactivity [34], a physiological state that can damage kidney function through various pathways, including increased sensitivity to norepinephrine, hypertension, and proteinuria [35,36]. Sleep apnea thus poses many health risks that may, directly or indirectly, relate to reduced kidney functioning. Our findings from the 2009–2017 transplant period align with previous research identifying sleep apnea's association with reduced kidney functioning [2,11–13].

Limitations potentially affecting study findings were considered. Causal inferences cannot be drawn from a single observational study. Findings from our single-center study are solely generalizable to similar populations, namely a predominantly African American sample of patients who were transplanted and failed during our study time period (1997–2017), and to similar transplant centers. However, despite more limited external validity, these data offered uniformity: transplanted patients followed the same pre-transplant evaluations and post-transplant standardized care plan, thus increasing the study's internal validity. Sleep apnea diagnoses were based on medical record documentation. This review process was extensive and involved the review of every history and physical, sleep medicine, pulmonary and anesthesia notes recorded in the medical record prior to the recipient's graft loss, undiagnosed sleep disorders may have been present. Moreover, one of our study's strengths is that study data involved merging two sources: the OPTN database and the transplant center's medical records. Merging two data sources led to identifying information which resulted in the necessary exclusion of patients with a functioning graft in order for the study to be approved by the institutional IRB with a waiver of consent. However, this merging enabled us to examine sleep apnea and, thus, its association with transplant outcomes.

In this regard, our study may be less comparable to other studies as the present cohort covered 20 years, and examined a predominantly African-American sample. However, our single-center study extends the previous research based on two previous studies of predominately Caucasian European transplant recipients at a single-center in Hungary [4,6]. Sleep apnea severity and treatment information were not available (treatment may affect sleep apnea's relationship to graft survival). However, given the high rate of non-adherence to continuous positive airway pressure (CPAP) treatment of sleep apnea [37,38], it cannot be assumed that every individual diagnosed with sleep apnea was treated. Adherence to CPAP treatment has remained consistently low throughout a 20-year time period (1994–2015) [37], a period overlapping with most of our study time frame.

The functional status measure in our study was assessed on a 0–100% Karnofsky scale based on nurse assessment of the patient's physical presentation at the time of transplant. Functional status scores were not determined by factoring in the patient's estimated glomerular filtration rate and/or medical comorbidities at the time of transplant. To account for limitations such as potentially low inter-reliability between nurses for this score, the measure was categorized as 100% or <100%. Another potential limitation is that our dataset did not include information on all variables which could be potential confounders or effect modifiers for sleep apnea's relationship to graft survival. While we were unable to examine variables such as dialysis vintage, pulmonary hypertension, and cold ischemia time, a wide range of potential confounders/adjustment variables (eg, chronic illnesses) were in our dataset and could be examined.

Findings from the 2009–2017 transplant period were based on 23 events, approximately 4 events per covariate in the adjusted model. While a smaller number of events can increase the risk of model instability and overestimate hazard ratios [39], there is support for statistically significant findings based on analyzing 5 to 9 events per covariate [40]. This limitation is acknowledged in presenting both unadjusted and adjusted models, as well as confidence intervals for each hazard ratio. Furthermore, we assessed for outliers and influential observations and did not find any observation(s) fitting these criteria to be the cause of statistical significance in the model. The two outliers retained in the 2009–2017 cohort model were patients with sleep apnea with longer graft survival, further suggesting our estimate was likely conservative and that the association could not be attributed to outliers.

While the 2009–2017 analysis may have decreased precision [39], it may have increased validity due to the more recent transplant time period and access to an electronic medical record for data abstraction. Additionally, our sample was limited to subjects who experienced graft loss and did not include those transplanted and still surviving. Graft survival outcomes reported in this study may not be representative of the survival outcomes of the overall center. However, they reflect the study cohort consisting of recipients who were transplanted and failed or died with a functioning graft during the study time period of 1997–2017. Excluding surviving transplant patients did not systematically exclude all long-term survival times, given our long study period of 20 years, a strength of our study design. Furthermore, although the study was focused on individuals whose grafts failed, a potential limitation which may have resulted in selection bias, this bias is likely to be the same in both those with and those without sleep apnea which would result in compensating bias [41], and thus a valid comparison between these groups. Careful consideration was also given to censoring designations, established a priori, as this study investigated a cohort of patients with graft failure or death with a functioning graft. By estimating the hazard ratios for each possible censoring designation available including all-cause graft loss, and graft failure only and return to dialysis, the data available were considered to the fullest extent possible.

5. Conclusions

Several studies have documented a high prevalence of sleep apnea among kidney transplant recipients, ranging from 25% to 45% of study samples [4,6]. In light of this high prevalence, our findings from 2009 to 2017 and previous research [6] identifying an increased risk of graft loss related to sleep apnea suggest the need to raise awareness of sleep apnea's potential role in transplant outcomes. While further research is warranted to understand the impact of CPAP therapy on transplant outcomes, awareness and management of sleep apnea among medically complex transplant patients requires recognition by all involved in treatment. In non-transplant samples, sleep apnea treatment through CPAP has resulted in identified improvements in hypertension control [42–44] and blood glucose control [45], both of which are important in post-transplant management. Short-term CPAP use has also been shown to increase renal plasma flow [46]. Improvement in kidney function was reported after four weeks of CPAP use [47]. Such findings show promise in the use of CPAP in renal patients [46,47] though further work on CPAP's efficacy on transplant outcomes is needed. Additionally, whether the reduction of body mass index could improve sleep apnea in transplant patients also may merit further study.

Sleep apnea is an increasing public health concern [48,49] and may pose significant risks to renal patients. Understanding the role of sleep disturbances in adverse health outcomes extends beyond the sleep medicine professional. Awareness and understanding of the significance of sleep apnea and associated risks, including its relationship to transplant outcomes, could be useful for patients, clinicians, and public health professionals to improve health outcomes in the population.

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Conflict of interest

All authors declare that they have no financial support, no conflicts of interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.014.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.05.014.

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