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Sleep Disorders and Kidney Transplant Outcomes: Findings From an 18-Year (1997-2015) Historical Cohort Study

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SLEEP DISORDERS AND KIDNEY TRANSPLANT OUTCOMES:

FINDINGS FROM AN 18-YEAR (1997-2015) HISTORICAL COHORT STUDY

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ABSTRACT

SLEEP DISORDERS AND KIDNEY TRANSPLANT OUTCOMES:
FINDINGS FROM AN 18-YEAR (1997-2015) HISTORICAL COHORT STUDY

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A historic cohort study of kidney transplant recipients with a failed graft was conducted to examine the associations between sleep disorders and kidney transplant outcomes. Adult kidney transplant recipients who were transplanted and failed or died with a functioning graft during the designated study time period (January 1, 1997 to September 1, 2015, inclusive) were included (n=299). The primary independent variables, any sleep disorder and any sleep-disordered breathing disorders, were defined through a diagnosis in a subject's medical record. Transplant outcomes included: death with a functioning graft, graft survival time, and patient survival time after graft failure.

Chi-square statistics were used to compare the proportion of death with a functioning graft between subjects with versus without any sleep disorder and to help inform the censoring approach for graft survival time. Kaplan Meier survival curves were used to examine the relationship of any sleep disorder to survival time. Cox regression models, examined the adjusted relationship of any sleep disorder to the outcomes, graft survival time and patient survival time after graft failure. Sub-analyses also examined associations between sleep-disordered breathing disorders and these outcomes.

The prevalence of any sleep disorder in this cohort was 20%, with the majority consisting of sleep apnea diagnoses, a sleep-disordered breathing disorder. Given a statistically significant ($p \leq 0.01$, adjusted model) sleep disorder by transplant-year heterogeneity, Cox regression models

were stratified by transplant-year for the graft survival outcome. Having a sleep disorder, namely, sleep apnea, was associated with a statistically significantly increased risk of graft failure or cardiovascular related death with a functioning graft among patients transplanted in 2009-2015 (adjusted HR=2.94, $p<0.05$). Sleep disorders, namely, sleep apnea, were not, however, associated with an increased risk of death with a functioning graft or an increased risk of death after graft failure.

In a single-center cohort of kidney transplant recipients with a failed graft, a sleep apnea diagnosis increased the risk of graft loss nearly three-fold among patients transplanted between 2009-2015. Further research is needed to better understand this relationship and whether prevention strategies, including treating sleep apnea, might increase longevity in kidney transplant patients.

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CHAPTER I

INTRODUCTION

End-stage renal disease (ESRD) is a chronic health condition that describes total and permanent kidney failure and is also known as stage five of chronic kidney disease (CKD) (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). There are approximately 26 million Americans diagnosed with CKD, and, of those individuals, more than 600,000 have progressed to stage five and are in renal failure (United States Renal Data System, 2016). ESRD is an irreversible condition, and once an individual progresses to this stage, medical intervention through dialysis or kidney transplantation is required for patient survival. Kidney transplantation is an intervention aimed at improving the health of ESRD patients as it allows patients to remain off of dialysis; thus, improving patient quality of life (Kovacs et al., 2011; Smith et al., 2008), increasing survival (Wolfe et al., 1999), and reducing health care costs (United States Renal Data System, 2013). Studies that attempt to identify modifiable risk factors related to improving health outcomes in kidney transplant recipients are needed at this time.

The purpose of this study was to examine the association between sleep disorders and kidney transplant outcomes of both graft survival and patient mortality, in a single-center study of patients with a failed kidney transplant. A rationale for this study includes the high prevalence rates of sleep disturbances which are reported across the spectrum of chronic kidney disease (CKD) (Burkhalter et al., 2011; De Santo, Bartiromo, Cesare, & Cirillo, 2008; Pierratos & Hanly, 2011; Teixeria do Santos & Moraes de Almondes, 2015; Williams, McCrae, Rodrigue, & Patton, 2016; Zhang et al., 2014). Additionally, the proposed study rationale is supported by the associations between adverse health outcomes and sleep disturbances throughout CKD and specifically, in kidney transplant patients (Benz, Pressman, Hovick, & Peterson, 2000; Jung, Lee,

Baek, Kim, & Lee, 2010; La Manna et al., 2011; Lee et al., 2015; Lindner et al., 2012; Molnar et al., 2010; Molnar et al., 2015; Szentkiralyi et al., 2011).

Background

Kidney transplantation is the preferred intervention for end-stage renal disease by both patients and providers (United States Renal Data System, 2016). Graft survival time, the length of time the transplanted kidney remains functioning after surgery, is an important outcome measure of transplant success. Transplant recipients are able to remain off of dialysis for the duration of time that their transplanted graft is functioning. However, when the transplant fails, patients must return to dialysis for continued survival, and if medically appropriate, patients may subsequently be evaluated for another transplant (Marcen & Teruel, 2008). National data have shown successful short-term outcomes of graft survival with averages of 1-year graft survival rates at 96% and 3-year graft survival rates at 88% (Matas et al., 2015). While data on long-term outcomes are reported less, as fewer studies have been conducted, the estimated national average for a kidney transplant graft half-life ranges from 8-12 years, meaning that 50% of transplant recipients maintain a functioning graft for approximately 8-12 years before the transplanted kidney fails (Hart et al., 2016; Lamb, Lodhi, & Meier-Kriesche, 2011).

Nationally reported mortality rates for kidney transplant recipients within three years post-transplant remain very low, meaning that patients have a high likelihood of survival post-transplant. Patient survival 1-year post transplant is reported at 97%, and patient survival 3-year post transplant is reported at 93% (Matas et al., 2015). Mortality in transplant recipients, while a separate outcome from graft survival, can also be closely related to graft survival. In some instances, patient mortality can impact graft survival, such as in cases where a patient dies with a functioning graft, reducing the longevity of the transplant. While mortality rates are low in the

first three years after a transplant, such rates increase as graft survival time increases, and death with a functioning graft has been identified as one of the major causes of graft failure for patients who have maintained their transplant for 10 or more years (Matas et al., 2008). In addition to death during the transplant course (death with a functioning graft), death after graft loss is another relevant outcome among kidney transplant recipients. Although transplantation is intended to increase patient survival (Wolfe et al., 1999) and improve quality of life in end-stage renal disease (ESRD) patients (Kovacs et al., 2011; Smith et al., 2008), kidney transplant recipients have an elevated death rate after graft loss, compared to ESRD patients who have remained on dialysis (Kaplan & Meier-Kriesche, 2002; McCaughan et al., 2014; Perl et al., 2012).

The focus on graft survival and mortality outcomes from kidney transplant centers has centered on improving short-term outcomes, as presently (as of April, 2017), transplant reimbursement and quality oversight from the Centers for Medicare and Medicaid Services are based on 1-year outcomes (Conditions of Participation for Hospitals, 2007). However, over the past twenty years, as improvements have been documented in graft survival and mortality outcomes at 1-year post-transplant (Matas et al., 2015) the focus on transplant research has begun to expand to other areas of need. For instance, there have been few improvements in long-term graft survival outcomes, and the rate of patient death with a functioning graft has actually worsened for 10-year outcomes (Matas et al., 2015). Moreover, there is limited research on the increased risk of patient mortality after graft loss. Improving long-term graft survival and patient survival outcomes in the kidney transplant population is an important issue related to national health care costs, health care policy, and patient quality of life (Lodhi & Meier-Kriesche, 2011; Mathis, 2015). Research has been identified as an essential part of better

understanding long-term outcomes in kidney transplantation (American Society of Transplantation, 2015), and studies that attempt to identify patient-related variables associated with graft survival and mortality are needed at this time.

Problem Statement

Exploring patient-centered risk factors in transplant recipients may be an important next step for transplant research aimed at improving long-term outcomes. Immunologic factors such as antigen matching and immunosuppressant medications have remained the focus of transplant research, as these variables are related to the risk of acute graft loss through cellular rejection (Mange, Cizman, Joffe, & Feldman, 2000; Pratschke, et al., 2016). However, over the past decades, as the improvement of immunosuppressant medications has lessened the risk of acute cellular rejection, research has identified that non-immunologic variables are also important mediators of graft survival (Mange et al., 2000). As patients now have a decreased risk of acute immunologic graft failure, a patient's medical comorbidities or lifestyle factors may be strongly associated with graft survival and mortality outcomes; thus, the importance of how such factors can relate to transplant outcomes merits further consideration. Sleep disturbances may be related to transplant outcomes, as sleep influences physiological processes in the body and may impact kidney functioning through both indirect and direct mechanisms.

Sleep and kidney functioning. Sleep is an essential aspect of quality of life among patients with end-stage renal disease (ESRD) (Eryilmaz, Ozdemir, Yurtman, Cilli, & Karman, 2005; Rodrigue et al., 2011). Moreover, sleep has documented biological influences on health, as sleep disturbances have been associated with increased inflammation (Irwin et al., 1996), hypertension (Bansil et al., 2011; Lavie, Herer, & Hoffstein, 2000; Sasaki et al., 2013), and diabetes (Reutrakul & Van Cauter, 2014). In turn, these problems can lead to endothelial

dysfunction and sympathetic activation, which have the potential to impact kidney functioning (Hanly & Ahmed, 2014; Nicholl et al., 2012; Ozok, Kanbay, Odabas, Covic, & Kanbay, 2014; Turek, Ricardo, & Lash, 2012). A possible direct relationship between sleep disturbances and renal failure has been proposed through the effect of hypoxia on the kidney (Hanly & Ahmed, 2014; Nicholl et al., 2012). Hypoxia refers to tissues lacking adequate oxygen through the blood, and occurs in patients with sleep-disordered breathing disorders. While the precise role that sleep disturbances play in kidney functioning remains unknown, the high prevalence of poor sleep quality (Burkhalter et al., 2011; Kachuee et al., 2007; Reilly-Spong, Park, & Gross, 2013; Silvas et al., 2012) and sleep disorders (Molnar et al., 2007a; Molnar et al., 2010; Szentkiralyi et al., 2011; Williams et al., 2016) among kidney transplant recipients calls for further exploration of the associations between sleep and kidney functioning, and a consideration of how sleep disturbances may impact transplant outcomes.

Poor sleep quality and kidney transplant patients. Poor sleep quality is common across the spectrum of chronic kidney disease (CKD) (Turek, Ricardo, & Lash, 2012), and remains prevalent among kidney transplant recipients. Rates of clinically significant poor sleep quality range from 38 to 62% in kidney transplant recipients (Burkhalter et al., 2011; Kachuee et al., 2007; Reilly-Spong et al., 2013; Silvas et al., 2012). While there is a noted high prevalence of sleep disorders across the stages of CKD (Hanley, 2014; Pierratos & Hanly, 2011), transplant patients, in particular, remain understudied among those with CKD (Merlino, Gigli, & Valente, 2008; Molnar, Novak, & Musci, 2009). High rates of poor sleep quality among transplant recipients (Burkhalter et al., 2011; Kachuee et al., 2007; Reilly-Spong et al., 2013; Silvas et al., 2012) may be indicative of a high rate of undiagnosed sleep disorders in this population

(Burkhalter et al., 2013). Therefore, the diagnosis and treatment of sleep disorders in kidney transplant recipients requires increased awareness (Merlino, Gigli, & Valente, 2008).

Sleep disorders and kidney transplant patients. The prevalence of sleep disorders in kidney transplant recipients is both an understudied and a complex topic. While post-transplant improvement of sleep disorders has been documented (Auckley, Schmidt-Nowara, & Brown, 1999; Beecroft, Zaltzman, Prasad, Meliton, & Hanly, 2008; Juardo-Gamez et al., 2008; Langevin et al., 1993; Winkelmann, Stautner, Samtleben, & Trankwalder, 2002), research shows that despite the potential for some improvement, that sleep disorders remain quite prevalent post-transplant (Molnar et al., 2007a; Molnar et al., 2010; Szentkiralyi et al., 2011; Williams et al., 2016). The primary sleep disorders studied among kidney transplant recipients are sleep-related movement disorders, insomnia, and sleep-disordered breathing disorders. Sleep-disordered breathing disorders, namely, obstructive sleep apnea, have the highest prevalence rate of sleep disorders in kidney transplant recipients, ranging from 25-45% of study samples, assessed through both self-report measures (Szentkiralyi et al., 2011) and polysomnography measures (Fornadi et al., 2012; Molnar et al., 2010).

While clear consensus on the prevalence of sleep disorders among transplant patients remains limited (as few studies with large samples exist), associations between sleep disorders and various aspects of patient health for kidney transplant patients have been documented. Both insomnia (Novaks et al., 2006) and sleep apnea (measured through self-report) (Molnar et al., 2007a) have been found to be associated with reduced quality of life and declining renal function among kidney transplant recipients. Restless leg syndrome is associated with an increased risk of mortality in kidney transplant patients (Molnar et al., 2007b). Two studies have previously explored the relationship between sleep apnea and kidney transplant graft survival, finding

conflicting results. Szentkiralyi and colleagues (2011) conducted a 66 month prospective cohort study and found that having a high risk of sleep apnea was an independent risk factor for graft failure in female kidney transplant patients. However, a study by Fornadi and colleagues (2014) found no significant relationship between sleep apnea and graft failure risk in their 75 month prospective cohort study. Sleep apnea was also not significantly associated with an increased all-cause mortality risk (Fornadi et al., 2014). Both studies (Fornadi et al., 2014; Szentkiralyi et al., 2011) examined small samples of patients who had experienced graft failure and both examined mid-range graft survival and mortality outcomes at approximately 5-6 years post-transplant.

Presently, the relationship between sleep disorders and transplant outcomes remains understudied, as few studies have been published (Fornadi et al., 2014; Szentkiralyi et al., 2011). More research is needed to further explore the associations between sleep disorders and kidney transplant graft survival and patient mortality. Moreover, studies that measure transplant outcomes beyond a 5-6 year post-transplant time period are needed.

Due to limited research, the inclusion of a theoretical framework can be a helpful addition when further conceptualizing the relationship between sleep and transplant outcomes.

Theoretical Framework: The Restoration Theory of Sleep

The Restoration Theory of Sleep (Adams & Oswald, 1977; Oswald, 1980) constitutes the theoretical foundation for this study, and it is one of several proposed functional theories of sleep. It proposes that sleep is essential for restoring physiological and brain functions within an individual, and further suggests that sleep disturbances play a vital role in adverse health outcomes through preventing the restorative functions that occur during sleep (Adams & Oswald, 1977; Oswald, 1980). The foundation for this theory was developed through research

identifying physiological processes associated with sleep and wake cycles, such as protein synthesis (Adams & Oswald, 1977), nocturnal secretion of growth hormones (Adams & Oswald, 1977; Oswald, 1980), and changes in metabolic rates (Oswald, 1980). The Restoration Theory of Sleep (Adams & Oswald, 1977; Oswald, 1980) has provided the basis for the study's development, and, in conjunction with the current literature, supports exploring the associations between sleep disturbances and kidney transplant outcomes of graft survival and mortality. It is proposed that kidney transplant patients who experience sleep disturbances will lack the restorative benefits of sleep, which will thus reduce their graft survival time and increase their risk of mortality.

Specific Aims

The primary aim of this study was to determine the association between any sleep disorder and graft survival time. Graft survival time was defined as graft failure or cardiovascular related death with a functioning graft. The proportion of patients who died with a functioning graft and the relationship of this to any sleep disorder was also evaluated. In addition, the study also explored whether sleep-disordered breathing disorders, in particular, were associated with graft survival time and death with a functioning graft. The secondary aim of the study was to examine whether having any sleep disorder was associated with a higher mortality hazard ratio after graft failure. It was also examined specifically, if having a sleep-disordered breathing disorder, versus not, was associated with a higher mortality hazard ratio after graft failure.

Overview of Methods

A historic cohort study of kidney transplant recipients with a failed graft was conducted to examine the association between sleep disorders and kidney transplant outcomes. The study

sample came from a single-center, the Sentara Norfolk General Transplant Center (SNGH), a Medicare certified transplant center in Southeastern Virginia. Inclusion criteria for the sample were as follows: adult SNGH kidney transplant recipients who were transplanted and experienced graft failure and/or died with a functioning graft during the timeframe of January 1, 1997 to September 1, 2015, inclusive. Criteria for exclusion were: SNGH kidney transplant recipients who received a previous kidney transplant or a multi-organ transplant, and recipients who experienced graft failure within the first 90 days of their transplant surgery. The main independent variable of interest in this study was sleep disorders (any sleep disorder and specifically, sleep-disordered breathing disorders). Sleep disorders were defined through a diagnosis in the patient's medical record that was documented prior to graft failure. Additional covariates were included in the study based on their relevance to the identified transplant outcomes and to the primary independent variables of interest, any sleep disorder and sleep-disordered breathing disorders. These covariates included: gender, race, age, body mass index, diabetes, hypertension, coronary artery disease, heart attack history, peripheral vascular disease, dyslipidemia, stroke history, end-stage renal disease etiology, education level, functional status, smoking history, tobacco pack-years, non-compliance with transplant medications, transplant type, human leukocyte antigen mismatch score, donor age, and year of transplant surgery.

Analytic approach. Descriptive statistics were used to describe the sample and to summarize prevalence rates of sleep disorders in the present sample. Chi-square and independent t-test analyses compared the covariates among two groups within the sample, patients with any sleep disorder and those without a sleep disorder. Chi-square statistics were also used to compare the proportion of death with a functioning graft in the any sleep disorder group to those without a sleep disorder. Kaplan Meier survival curves (Kaplan & Meier, 1958)

were used to examine the relationship of any sleep disorder to survival time. Further, the Cox regression (Cox, 1972) examined the adjusted relationship of any sleep disorder to the outcomes of graft survival time and patient survival time after graft failure. Separate regression analyses were used to test the study hypotheses with covariate adjustment. Sub-analyses involving sleep-disordered breathing disorders, were also run for each study outcome (death with a functioning graft, graft survival time, and patient survival time after graft failure).

Research Questions

This study explored the associations between sleep disorders and transplant outcomes, namely, the relationship between having any diagnosed sleep disorders and transplant outcomes, and also, the associations between sleep-disordered breathing disorders (a category of sleep disorders) and transplant outcomes. The study involved multivariate statistical analyses of historic cohort data from a single-transplant center to address the following research questions:

1a) Of kidney transplant recipients with graft failure, do those with any diagnosed sleep disorder, versus those without, have a higher proportion of death with a functioning graft?

1b) Of kidney transplant recipients with graft failure, do those with a diagnosed sleep-disordered breathing disorder, versus those without, have a higher proportion of death with a functioning graft?

2a) Of kidney transplant recipients with graft failure, do those with any diagnosed sleep disorder, versus those without, have a decreased graft survival time through graft failure or cardiovascular related death with a functioning graft?

2b) Of kidney transplant recipients with graft failure, do those with a diagnosed sleep-disordered breathing disorder, versus those without, have a decreased graft survival time through graft failure or cardiovascular related death with a functioning graft?

3a) Of kidney transplant recipients with graft failure, do those with any diagnosed sleep disorder, versus those without, have an increased mortality hazard ratio after graft failure?

3b) Of kidney transplant recipients with graft failure, do those with a diagnosed sleep-disordered breathing disorder, versus those without, have an increased mortality hazard ratio after graft failure?

CHAPTER II

LITERATURE REVIEW

Chapter II is a critical review of the literature relevant to the identified aims of this study. The chapter is organized into two sections. Section I reviews the literature on sleep disturbances across the spectrum of chronic kidney disease. It begins with a brief overview of chronic kidney disease and the sleep literature, followed by a focus on end-stage renal disease, presenting the sleep literature as it relates to both dialysis and transplant patients. Section I ends with the introduction of a theoretical framework that suggests a restorative benefit of sleep and presents an overview of the potential physiological mechanisms through which sleep disorders may relate to kidney functioning. Section II presents a brief summary of relevant literature pertaining to the dependent variables and study covariates.

Section I

Chronic Kidney Disease

Chronic kidney disease (CKD) is defined by structural or functional abnormalities of the kidney that result in a decreased level of kidney functioning for a period of at least three months (National Kidney Foundation, 2002). CKD is a significant public health problem worldwide, and, in the United States, it is estimated that CKD is more common than diabetes. National data based on NHANES reporting suggests that more than 14% of the United States adult population has CKD (United States Renal Data System, 2016).

There are five stages of chronic kidney disease (CKD), with stage five end-stage renal disease (ESRD) being the most severe (National Kidney Foundation, 2002). ESRD describes total and permanent kidney failure (National Institute of Diabetes and Digestive and Kidney Diseases, 2016) and is an irreversible condition. Once an individual progresses to stage five, the

treatment objective is disease management. Intervention outcomes are aimed at improving quality of life and increasing life expectancy, as patients who have progressed to ESRD have significantly higher rates of mortality than the general population (United States Renal Data System, 2016). Although CKD is a chronic and progressive disease that ultimately ends in renal failure, there are significant health implications throughout the disease's progression. Complications of CKD include cardiovascular events (Go, Chertow, Fan, McCulloch, & Hsu, 2004; Meisinger, Doring, & Lowel, 2006; Weiner et al., 2006), anemia (McClellan et al., 2004; Thomas, Kanso, & Sedor, 2009), and metabolic bone disease (Martin & Gonzalez, 2007; Thomas et al., 2009). Patients with CKD have higher infection risks (Naqvi & Collins, 2006), increased risk of strokes (Chen et al., 2012), and mortality (Astor, Hallan, Miller, Yeung, & Coresh, 2008; Go et al., 2004; Weiner, et al., 2006). Overall, individuals diagnosed with CKD (at any stage) have increased health care costs and reduced quality of life (United States Renal Data System, 2016).

Given the many complications associated with chronic kidney disease (CKD), research findings suggest that patients with CKD are more likely to die prior to progressing to stage five (Keith, Nichols, Gullion, Brown & Smith, 2004). However, due to the high prevalence of CKD, a significant number of patients with kidney disease progresses to kidney failure, and subsequently requires significant medical intervention, either through dialysis or kidney transplantation, to continue to live. In 2014, there were more than 600,000 Americans who had progressed to end-stage renal disease (ESRD) (United States Renal Data System, 2016). It is estimated that by the year 2030, more than 2 million individuals will require dialysis or a kidney transplant (Szczech & Lazar, 2004).

The development of chronic kidney disease (CKD) and the rate at which CKD progresses varies, and it is likely related to numerous factors. Progression of CKD is related to physiological factors such as glomerular hemodynamic factors, proteinuria, and hypertension (Yu, 2003). However, there are many other risk factors, such as age, race, gender, as well as lifestyle variables, such as smoking, obesity, and diet; that may relate to this progression. Progression of CKD can also be due to secondary factors that are unrelated to the initial disease (Metcalfe, 2007; Yu, 2003). Recent literature from 2012 and on identifies poor sleep quality and the presence of sleep disorders as possible non-traditional risk factors for both development and progression of kidney disease (Lee et al., 2015; Molnar et al., 2015; Sabbatini et al., 2008; Sakaguchi et al., 2013; Turek, Ricardo, & Lash, 2012). In light of these recent studies, further consideration should be given to the prevalence and impact of sleep disturbances, poor sleep quality, and sleep disorders across the spectrum of CKD.

Sleep Disturbances and Chronic Kidney Disease

Sleep quality is a complex clinical construct that often represents self-reported complaints about sleep (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Poor sleep quality can be a symptom of a sleep disorder, or a related consequence of medical and psychological disorders; it can also be a combination of these factors. Sleep quality is typically assessed via self-reported measures. While many measures exist, a widely used and well-validated questionnaire is the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Although few studies have specifically examined sleep quality in early stages of chronic kidney disease (CKD) (often focusing on end-stage renal disease patients), two studies using the PSQI found a prevalence range of approximately 50-80% of poor sleep quality in pre-dialysis CKD patients (Illiescu, Yeates, & Holland, 2004; Zhang et al. 2014). Kumar and colleagues (2010) also

measured self-reported sleep quality across a sample of 673 stage 3-5 CKD patients reporting the prevalence of poor sleep quality as 57%. These studies document that a high occurrence of self-reported sleep problems can occur even during early stages of CKD.

In addition to the high rates of self-reported poor sleep quality across samples of chronic kidney disease (CKD) patients, there is also an increased prevalence of sleep disorders in CKD patients. Sleep disorders can be classified according to the International Classification of Sleep Disorders (ICSD) Third Edition (American Academy of Sleep Medicine, 2014), a classification system that groups sleep disorders among six primary categories. There are three categories of sleep disorders based on the ICSD that are often explored across the spectrum of CKD, and they are, sleep-related breathing disorders, sleep-related movement disorders, and insomnia. As with sleep quality, the majority of the research literature on sleep disorders has focused on end-stage renal disease patients. However, some studies with pre-dialysis CKD patients have been reported.

In 2006, De Santo and colleagues measured the prevalence of sleep disorders in a sample of newly diagnosed CKD patients using the Sleep Disorders Questionnaire (SDQ), a 26-item self-report measure. The SDQ (Violani, Devoto, Lucidi, Lombardo, & Russo, 2004) was primarily created as a screening tool for insomnia and is based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria for insomnia (American Psychiatric Association, 2000). However, this measure also includes general questions about other sleep behaviors (snoring, lapses in breathing during sleep, daytime sleepiness, sleepwalking). Utilizing the SDQ, the prevalence rate of any sleep disturbance was reported in 80% of their CKD sample of approximately 50 patients. In 2008, De Santo and colleagues administered the SDQ to a larger sample of 124 newly diagnosed CKD patients, and they

included a chronically ill comparison group, matched on both age and gender. Individuals in the comparison group included those with a non-renal related chronic illness, 50 with hepatitis C, and 64 with heart failure. Prevalence rates of sleep disturbances as assessed by the SDQ in the comparison group were much lower, ranging from 25-30%, compared to 89% in the CKD group. This finding demonstrates a significantly higher prevalence of sleep complaints in patients with CKD. A study by Ahmad, Gupta, Gupta, and Dhyani (2013) reported a prevalence of insomnia of 40% (assessed through a clinical interview), and a 51% prevalence of obstructive sleep apnea (assessed through the STOP-bang) in a sample of CKD patients including 104 both pre-dialysis and end-stage renal disease patients.

Thus, overall, there is not a great deal of literature on the prevalence of sleep disorders in early stages of chronic kidney disease (CKD), and the use of objective measurement is lacking, yet, the studies that do exist highlight the pervasiveness of sleep complaints and sleep disorders in patients diagnosed with early stages of CKD. More recent studies from 2008 and on have expanded beyond prevalence research and have begun to explore the potential associations of sleep disturbances and CKD.

Sleep disturbances and progression of chronic kidney disease (CKD). In addition to determining the prevalence of sleep disturbances among patients with CKD, some studies have attempted to further elucidate whether sleep disturbances may serve as a possible risk factor for CKD development and progression to kidney failure (Kumar et al., 2010; Lee et al., 2015; Molnar et al., 2015; Sabbatini et al., 2008). Cross-sectional studies examining the relationship between sleep quality and kidney functioning have had conflicting results. In 2014, a study by Zhang et al. found that poor sleep quality was associated with poorer kidney functioning. After controlling for confounders, there was no direct relationship between poor sleep and decreased

kidney functioning. Kumar et al. (2010) compared mean sleep quality scores across three stages of CKD and did not find any significant differences in sleep quality across the CKD stages. Kurella, Luan, Lash, and Chertow (2005) studied both end-stage renal disease (ESRD) and CKD patients to examine the relationship between sleep quality and kidney functioning. When analyses were restricted to CKD pre-dialysis patients only, an association between reduced kidney functioning and poor sleep quality was found. However, this relationship was only present in non-African American patients, and it was weakened (yet remained significant) after adjustment for depression. In a more robust examination of the relationship between sleep quality and kidney functioning, Sabbatini and colleagues (2008) conducted a three year prospective cohort study with 78 pre-dialysis CKD patients. Researchers recorded the Pittsburgh Sleep Quality Index (PSQI) scores of the sample at baseline, and completed follow up measures two and three years after the initial baseline measurement. While higher PSQI scores (poor sleep quality) were associated with poorer kidney functioning (as measured through creatinine clearance), an independent relationship was not found after controlling for age.

Given the variability in the potential sources of the etiology of poor sleep quality, self-reported sleep quality may not be the ideal construct to directly examine the relationship between the progression of chronic kidney disease (CKD) and sleep disturbances. Nonetheless, it is important to consider that, while some previous studies have not found direct relationships between sleep quality and kidney functioning, these studies have found other clinical associations of interest (Kumar et al., 2010; Zhang et al., 2014). Zhang et al. (2014) reported that sleep quality was associated with cardiovascular damage in CKD patients, and Kumar et al. (2010) found that patients with poor sleep quality had a higher risk of mortality prior to reaching end-stage renal disease (ESRD). Even without demonstrating a direct relationship between sleep

quality and kidney functioning, these studies indicated that there are clinically significant associations between sleep quality and adverse health outcomes in CKD patients.

Other studies have gone beyond measures of sleep quality, and they have focused on sleep disorders, namely, sleep apnea, when evaluating the associations between sleep and chronic kidney disease (CKD) progression. Nicholl et al. (2012) studied approximately 250 patients diagnosed at various stages of CKD and compared the prevalence of sleep apnea across the sample. Patients were divided into three groups based on their kidney function, measured through their estimated glomerular filtration rate (eGFR) and were evaluated for sleep apnea by completing an overnight cardiopulmonary monitoring test. Findings revealed that the prevalence of sleep apnea increased as kidney functioning decreased. Of the patients in stages 1-2 (normal or mildly reduced kidney functioning), 27% were diagnosed with sleep apnea, of the patients in stages 3-4 (moderate to severely reduced kidney functioning), 41% were diagnosed with sleep apnea, and of those in stage 5 (kidney failure on dialysis), 57% were diagnosed with sleep apnea. Researchers also examined the prevalence of nocturnal hypoxia among these three groups and found that nocturnal hypoxia was higher in patients with late stage CKD (stages 3-4) and kidney failure (stage 5). Although this was a cross-sectional study relying on a home monitored sleep evaluation, the differences between the three groups of CKD patients merits consideration. Based on their findings, researchers suggested that not only does sleep apnea prevalence increase as eGFR decreases, but that the prevalence of nocturnal hypoxia could be a contributing factor to kidney function decline (Nicholl et al., 2012). In exploring another potential mechanism, Sakaguchi and colleagues (2013) found that moderate to severe nocturnal hypoxemia was associated with a three to fourfold faster decline in kidney functioning over the period of a year.

Although measurement of sleep disorders was not included in their study, nocturnal hypoxemia is often associated with sleep-disordered breathing in CKD patients (Hanly & Ahmed, 2014).

Through a retrospective population-based cohort study, researchers in Taiwan sought to determine whether sleep apnea was both an independent risk factor for the development of chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD) (Lee et al., 2015). Patients who were newly diagnosed with sleep apnea during an identified time frame and who did not have a diagnosis of CKD prior to that identified time frame were included in their sample (n=4,674). A comparison group of patients matched on age and gender (n=23,370) without sleep apnea were also included. During the identified 11-year study time frame, approximately 400 patients from the sample were diagnosed with CKD. Patients with diagnosed sleep apnea had a 1.9-fold increase in CKD incidence, and 2.2-fold increase of ESRD diagnoses, compared to patients without sleep apnea. These reported incidence rates reflect adjustment for covariates, which included known CKD risk factors, such as age, diabetes, hypertension and obesity.

In a similarly designed retrospective cohort study of US veterans, the relationship between sleep apnea and chronic kidney disease (CKD) progression was explored (Molnar et al., 2015). However, in this study, early stage CKD patients were only included if they did not have a diagnosis of obstructive sleep apnea during the inclusion time period from 2004-2006. The observed study time frame was from 2004-2013 and, on average, patients were followed for 8 years. During the study time frame, patients who were newly diagnosed with obstructive sleep apnea (OSA) were compared to those in the sample who did not have a diagnosis of OSA. Molnar and colleagues (2015) found that veterans with untreated OSA had an increased risk of mortality (OR 1.86), even after adjustment for comorbid conditions, age, and sociodemographic

variables. Moreover, researchers found that patients with untreated OSA had a significantly higher risk of rapid CKD progression (OR, 1.24-1.35 in fully adjusted model). In this large cohort of U.S. veterans, obstructive sleep apnea was associated with an increased all-cause mortality risk, and with a faster kidney function decline in a sample of CKD patients (Molnar et al., 2015). These studies by Lee et al. (2015) and Molnar et al. (2015) suggest an association between sleep apnea and risk of CKD development (Lee et al., 2015) and an accelerated progression to ESRD in patients with sleep apnea (Lee et al., 2015; Molnar et al., 2015).

There is strong support suggesting relationships between sleep disturbances (Sabbatini et al., 2008) and sleep apnea (Lee et al., 2015; Molnar et al., 2015; Nicholl et al., 2012) to kidney functioning. Even when associations of kidney functioning and sleep disturbances have been attenuated after controlling for covariates (Kurella et al., 2005; Zhang et al., 2014), it is important to consider that the weakening of this association could be representative of a multifactorial casual pathway between sleep and kidney functioning, rather than the portrayal of non-association. If sleep disturbances, namely sleep apnea, are associated with kidney functioning and can hasten renal failure (Lee et al., 2015; Molnar et al., 2015), then consideration of sleep disturbances in patients who have progressed to renal failure are also important to examine.

End-Stage Renal Disease (ESRD) and Sleep

While research has identified that sleep disturbances are prevalent across all stages of chronic kidney disease (CKD) (Ahmad et al., 2013; De Santo et al., 2008; Pierratos & Hanly, 2011), historically, the focus of sleep research in the CKD population has centered on end-stage renal disease (ESRD) patients who are treated with dialysis (Teixeria do Santos & Moraes de Almondes, 2015). The diagnosis of ESRD or kidney failure, refers to both dialysis and

transplant patients. However, there are many physiological differences among these two groups of patients according to the medical intervention aimed to treat their kidney failure. Dialysis patients often have significant medical complications, due to both the kidney failure and dialysis treatment side effects; sleep disturbances can occur in relation to either kidney failure or dialysis side effects. It is this dynamic that has likely pushed the focus of sleep literature towards ESRD dialysis patients, given the wide range of opportunity for sleep disturbances.

Dialysis is a lifesaving medical intervention for end-stage renal disease (ESRD) patients that removes waste, fluid, and chemicals from an individual's system. Dialysis is utilized to prevent deaths from uremia, as there are many changes that physiologically take place when an individual's kidneys are non-functioning; such as the build-up of uremic toxins and extracellular fluid. Despite the necessity of dialysis for ESRD patients, the treatment can be associated with several complications such as: anxiety (Feroze et al., 2012), depression (Feroze et al., 2012), reduced quality of life (Elder et al., 2008), hypotension (Sulowicz & Radziszewski, 2006), and muscle cramping (Sulowicz & Radziszewski, 2006). Moreover, a frequently reported but often under-addressed aspects of patient health and quality of life among ESRD patients are the high prevalence rates of poor sleep quality (Abdelwhab, Kamel, & Noshey, 2010; Elder, et al., 2008; Illiescue, et al., 2003) and sleep disorders (Musci et al., 2004; Nicholl et al., 2012; Winkelman, Chertow, & Laxarus, 1996).

Sleep quality in dialysis patients. Self-reported sleep quality problems are present in approximately 50-80% of dialysis patients (Abdelwhab et al., 2010; Elder, et al., 2008; Illiescue, et al., 2003). In a literature review on end-stage renal disease (ESRD) and daytime sleepiness, Perl, Unruh, and Chan (2006) report an estimated prevalence of daytime sleepiness in 52-67% of dialysis patients. Sleep disturbances among dialysis patients have been associated with poor

health outcomes. Poor sleep quality has been associated with higher inflammatory markers (Abdelwhab et al., 2010; Chiu et al., 2009), poorer dialysis efficiency (Abdelwhab et al., 2010), higher body mass index (Elder et al., 2008), increased pain (Elder et al., 2008), and reduced quality of life (Abdelwhab et al., 2010; Elder et al., 2008; Illiescue, et al., 2003). In addition to high rates of poor sleep quality, dialysis patients have higher rates of sleep disorders than the general population (Musci et al., 2004; Nicholl et al., 2012; Unruh et al., 2006; Winkelman et al., 1996).

Sleep disorders in dialysis patients. Increased prevalence of sleep-disordered breathing disorders (Nicholl et al., 2012; Unruh et al., 2006), sleep-related movement disorders (Winkelman et al., 1996), and insomnia (Musci et al., 2004; Sabbatini et al., 2002) are commonly reported among end-stage renal disease (ESRD) dialysis patients. Unruh et al. (2006) found four-fold higher odds of having severe sleep-disordered breathing among hemodialysis patients, when compared to controls matched on age, gender, race, and body mass index. Nicholl et al. (2012) found a 57% prevalence of sleep apnea in dialysis patients. Restless leg syndrome (RLS), a sleep-related movement disorder, is also identified as a common disorder in ESRD dialysis patients (Winkelman et al., 1996). The reported prevalence of RLS in dialysis samples often ranges from 15-20% (Araujo et al., 2010; Musci et al., 2004; Winkelman et al., 1996). Insomnia symptoms have been self-reported in 45-50% of large samples of dialysis patients (Holley, Nespor, & Rault, 1992; Musci et al., 2004; Sabbatini et al., 2002). In a multi-center study of over 800 dialysis patients in Italy, 80% of the sample was identified as having a sleep disturbance, as assessed by a self-administered questionnaire (Merlino et al., 2006). Insomnia, restless leg syndrome, and obstructive sleep apnea were among the most prevalently reported sleep disorders (Merlino et al., 2006). High rates of sleep disorders have been reported in

dialysis samples through both self-report (Merlino et al., 2006; Musci et al., 2004; Sabbatini et al., 2002; Winkelman et al., 1996) and objective measurement (Nicholl et al., 2012; Unruh et al., 2006).

In addition to their increased prevalence in dialysis patients, sleep disorders have also been associated with adverse health outcomes in these patients. In dialysis patients, restless leg syndrome has been associated with increased inflammation (Higuchi et al., 2015) and increased risk of cardiovascular disease (Lindner et al., 2012). Both sleep-disordered breathing disorders and sleep-related movement disorders have been associated with mortality among end-stage renal disease (ESRD) dialysis patients. Tang and colleagues (2010) found that a baseline apnea-hypopnea index greater than 15 was an independent predictor of cardiovascular disease morbidity and all-cause mortality among their sample of 93 peritoneal dialysis patients. However, in a smaller study of 30 dialysis patients in Korea, periodic limb movement disorder (PLMD), rather than sleep-disordered breathing disorders, was an independent predictor of mortality (Jung et al., 2010). Benz and colleagues (2000) also conducted a 20 month prospective cohort study following 29 dialysis patients, and they found PLMD to be an independent predictor of mortality among this sample. La Manna and colleagues (2011) reported that dialysis patients with restless legs syndrome had increased rates of new cardiovascular events and mortality.

The high prevalence of sleep disturbances (Musci et al., 2004; Nicholl et al., 2012; Sabbatini et al., 2002; Unruh et al., 2006; Winkelman et al., 1996) and the association of sleep with adverse health outcomes in end-stage renal disease (ESRD) dialysis patients (Higuchi et al., 2015; La Manna et la., 2011; Lindner et al., 2012; Tang et al., 2010) suggests sleep as an important aspect of health among patients with kidney failure. Understanding the prevalence and associations of sleep problems in ESRD patients who have undergone kidney transplantation

remains important in the chronic kidney disease and kidney failure literature. Research examining sleep disturbances among kidney transplant patients may lead to an improvement in understanding the associations of sleep disturbances throughout the spectrum of chronic kidney disease. Furthermore, sleep disturbance may be a modifiable risk factor that could improve the overall quality of life and health of kidney transplant recipients.

Kidney Transplant Recipients and Sleep

Kidney transplant recipients are defined as individuals with end-stage renal disease (ESRD) who do not require dialysis, due to undergoing a kidney transplant surgery. While kidney transplantation is an intervention to treat ESRD, it is not a permanent curative intervention, and when the transplanted graft fails, patients require dialysis for continued survival. Successful transplantation often results in increased survival (Wolfe et al., 1999), improved quality of life (Kovacs et al., 2011), and reduced health care costs (United States Renal Data System, 2013) for ESRD patients. Kidney transplant management centers on two outcomes: 1) graft survival, the duration of time the transplanted kidney remains functioning, and 2) patient survival. Mortality in kidney transplant recipients may be the cause of a premature graft failure or can occur at a higher rate after graft failure (Kaplan & Meier-Kriesche, 2002; McCaughan et al., 2014; Perl et al., 2012). While quality of life is not often viewed as a clinical outcome of transplant success, it is an intended goal of the transplant, and, ultimately, has been found to be associated with morbidity and mortality in transplant patients (Chang, Winsett, Gaber, & Hathaway, 2004; Griva, Davenport, & Newman, 2013; Molnar-Varga et al., 2011).

Although transplantation improves quality of life in comparison to patients on dialysis (Alvares, Cesar, Acurcio, Andrade, & Cherchiglia, 2012; Rodrigue et al., 2011), reduced quality

of life remains after transplantation even with improved kidney functioning (Alvares et al., 2012; Molnar, Novak, & Musci, 2009; Smith et al., 2008). Sleep disturbances have been found to be associated with reduced quality of life in transplant patients (Molnar-Varga et al., 2011), as poor sleep has been associated with both the psychological (Kauchee et al., 2007) and physical (Kauchee et al., 2007; Rodrigue et al., 2011) components of quality of life measures. The relationship between reduced quality of life and poor health outcomes in kidney transplant patients may be due to the underlying presence of sleep disturbances (Molnar-Varga et al., 2011), which are known to impact various physiological aspects of an individual.

Sleep research may receive less attention in the transplant literature due to the restoration of kidney functioning, dialysis cessation, and the overall improvement in quality of life that can occur post-transplant (Kovacs et al., 2011; US Renal Data System, 2016). However, such improvements have not resulted in the absence of sleep complaints in transplant patients. More consideration must be given to how sleep disturbances can affect kidney transplant patients and transplant outcomes.

Sleep quality and kidney transplant patients. Poor sleep quality is self-reported among 38-62% of kidney transplant patients (Burkhalter et al., 2011; Kachuee et al., 2007; Reilly-Spong et al., 2013; Rodrigue et al., 2011; Silvas et al., 2012). Although this prevalence range is less than the reported occurrence of poor sleep quality in dialysis patients (Abdelwhab et al., 2010; Elder, et al., 2008; Illiescue, et al., 2003), poor sleep quality remains an area of clinical concern for transplant patients. Rodrigue et al. (2011) compared sleep quality in 100 pre-transplant (dialysis) patients to 100 post-transplant patients. Poor sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI), was indicated in 78% of the pre-transplant dialysis samples and 52% of the post-transplant sample. Sabbatini and colleagues (2005) compared the

mean PSQI scores of a control group with no diagnosed kidney problems, to dialysis patients, and kidney transplant patients. Researchers found that while dialysis patients had the worst sleep quality of the three groups (PSQI=8.52), that transplant patients' sleep quality (PSQI=6.46) was statistically significantly worse than that of the control group (PSQI=3.54). Despite these findings of some improvement in sleep quality post-transplant, a study by Liaveri and colleagues (2017) found that kidney transplant patients reported worse sleep quality (as measured through the Athens Insomnia Scale) compared to a group of dialysis patients. Additionally, a study by Silvas and colleagues (2012) found that rates of poor sleep quality 3-6 months post-transplant did not differ when measured again at 12-15 months post-transplant. Thus, while it seems that some improvements in sleep quality may occur post-transplant, sleep problems do not appear to completely resolve after transplant (Rodrigue et al., 2011; Sabbatini et al., 2005). Moreover, sleep quality does not seem to continue to improve several months following the transplant surgery (Silvas et al. 2012), as patients further adjust and experience restored kidney functioning.

The consequences of poor sleep quality are present in various aspects of patient health among kidney transplant patients. Sleep quality has been found to be an independent predictor for post-transplant fatigue (Chan et al., 2013, Rodrigue et al., 2011) and reduced physical and social functioning in transplant patients (Liaveri et al., 2017; Silvas et al., 2012). Poor sleep quality has also been correlated with increased pain (Liaveri et al., 2017; Reilly-Spong et al., 2013; Kachuee et al., 2007), anxiety (Noohi, Tavallaii, Bazzaz, Khoddami-Vishte, & Saadat, 2008; Kachuee et al., 2007), depression (Liaveri et al., 2017; Novaks et al. 2006), higher body mass index (Silva et al., 2012) and an increased number of medical comorbidities (Kachuee et al., 2007). Moreover, sleep quality has been associated with both mental (Kauchee et al., 2007) and physical (Kauchee et al., 2007; Rodrigue et al., 2011) aspects of quality of life measures in

kidney transplant recipients. Associations of sleep to quality of life measures are important, given that quality of life scores have been predictive of both graft failure (Griva et al., 2013) and mortality in kidney transplant patients (Griva et al., 2013, Molnar-Varga et al., 2011). Associations between sleep quality and various aspects of health in transplant patients merit the need for further exploration regarding how sleep quality and sleep disturbances could impact kidney transplant outcomes. Studies on sleep disorders have begun to further address this topic.

Sleep disorders and kidney transplant patients. Only recently have sleep disorders received increased attention in kidney transplant patients. In part, this diminished consideration may have been due to early case studies suggesting the improvement of sleep disorders post-transplant (Auckley et al., 1999; Langevin et al., 1993). While post-transplant improvement of sleep disorders has been documented (Auckley et al., 1999; Beecroft et al. 2008; Juardo-Gamez et al., 2008; Langevin et al., 1993; Winkelmann et al., 2002), sleep disorders remain quite prevalent in kidney transplant patients (Liaveri et al., 2017; Molnar et al., 2007a; Molnar et al., 2010; Szentkiralyi et al., 2011; Williams et al., 2016). The prevalence and impact of sleep disorders on kidney transplant recipients is presumably more complex than initially thought. The primary sleep disorders studied among kidney transplant recipients are sleep-related movement disorders, insomnia, and sleep-disordered breathing disorders.

Sleep-related movement disorders and kidney transplant patients. Sleep-related movement disorders are defined by stereotyped movements that disrupt sleep (American Academy of Sleep Medicine, 2014). Among transplant samples, restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) remain the focus. Sleep-related movement disorders, primarily, RLS, may improve post-transplant as this disorder can be related to uremic symptoms, such as anemia (Beecroft et al. 2008; Winkelmann et al., 2002). Winkelmann and

colleagues (2002) followed 11 patients with RLS, assessing RLS symptoms through a questionnaire at baseline (prior to transplant) and two times post-transplant. In all patients, RLS symptoms were no longer present less than one month post-transplant. However, researchers found that symptoms of RLS began to reappear throughout the course of the transplant, and readily reappeared after patients began to experience graft failure. Such findings of RLS improving post-transplant have been reinforced by other studies that report comparable prevalence rates for the general population and kidney transplant recipients (Molnar et al., 2005; Novaks et al., 2006). However, reports of comparable rates of RLS in kidney transplant recipients to general population (Molnar et al., 2005; Molnar et al., 2007b; Novaks et al., 2006) and reported resolution of RLS symptoms post-transplant (Winkelmann et al., 2002), have relied on self-report questionnaires which have not been validated in transplant samples. When objective measurements, such as polysomnography have been used, there remains a reported improvement of sleep-related movement disorders; however, such studies also report that some symptoms remain (Beecroft et al., 2008; Juardo-Gamez et al., 2008).

In 2008, Beecroft et al. reported findings from a study, which, to their knowledge was the first prospective cohort study using polysomnography sleep measurement both pre-transplant and post-transplant to examine periodic limb movements. In their sample, seven patients met criteria for periodic limb movement disorder prior to transplant. After transplant, all seven patients had statistically significant reductions in their periodic limb movement index (PLMI). Despite this improvement, PLMI remained elevated in three out of the seven patients, demonstrating that PLMI was reduced to the mild range in all patients, but PLMI remained at or above 15 for some patients, indicating a continued presence. A study by Jurado-Gamez et al. (2008) also relied on polysomnography assessment of their nine patients, again comparing polysomnography

measures both pre to post-transplant. In their small sample, PLMI statistically significantly decreased from 36 per hour, pre-transplant and to 24 per hour (post-transplant). These findings demonstrate an improvement of PLMD (from moderate to mild), yet a persistence of periodic limb movement disorder symptoms. William and colleagues (2015) compared a group (n=55) of pre-transplant patients on dialysis to a group of post-transplant patients using polysomnography measurement. The pre-transplant sample had a diagnosed prevalence rate of 32% for RLS, while the transplant sample had a reduced prevalence of 13%. Although the prevalence of RLS in the transplant sample was significantly lower in comparison to the dialysis sample, this remained higher than the prevalence of RLS in the general population. Overall, studies have found that RLS and PLMD improve post-transplant (Beecroft et al., 2008; Juardo-Gamez et al., 2008; Winkelmann et al., 2002) but not fully (Beecroft et al., 2008; Juardo-Gamez et al., 2008; Williams et al., 2016).

Insomnia and kidney transplant patients. Insomnia is defined as difficulty with sleep initiation, duration, or quality that occurs repeatedly and despite adequate opportunities for sleep (American Academy of Sleep Medicine, 2014). Insomnia is a prevalent problem in early stages of chronic kidney disease (CKD) (De Santo et al., 2008) and in dialysis patients (Holley, Nespor, & Rault, 1992; Musci et al., 2004; Sabbatini et al., 2012). However, there are few studies that evaluate its prevalence in kidney transplant patients. The highest reported prevalence of insomnia came from a study by Fornadi et al. (2012) using the Athens Insomnia Scale (Soldatos, Dikeos, & Paparrigopoulos, 2000) in a sample of 100 kidney transplant patients. In this transplant sample, 16% of patients met criteria for clinical insomnia (scoring 10 or higher). However, in a larger sample, Novaks et al. (2006) reported that the prevalence of insomnia in kidney transplant patients was similar to that of the general population. Novaks and colleagues

administered the Athens Insomnia Scale (Soldatos et al., 2000) in a sample of over 800 kidney transplant patients. They also compared these findings to a sample of dialysis patients, and to a gender-matched non-CKD group. Clinical insomnia rates were reported to be 8% among the transplant and the non-CKD group, and 15% in the dialysis group. However, researchers reported that rates of insomnia symptoms (insomnia complaints, but below clinical cut off scores) were higher among transplant patients than the general population. In this study, 83% of the dialysis group reported at least one insomnia symptom, while 70% of the transplant group and only 50% of the non-CKD group reported at least one insomnia symptom. Liaveri and colleagues (2017) also used the Athens Insomnia Scale (AIS) to measure insomnia symptoms among their sample of transplant patients, dialysis patients, and subjects with normal renal function. They found that the highest mean AIS scores were observed in transplant patients; however, the mean AIS scores for each group were below the clinical cut-off for insomnia. Williams et al. (2016) compared insomnia symptoms in a sample of pre and post-transplant patients (n=55). Using self-reported sleep diary calculations, 68% of insomnia symptoms were reported in pre-transplant dialysis patients, compared to 48% in post-transplant patients. Overall, few studies have explored the prevalence of insomnia in kidney transplant patients. While the prevalence of clinical insomnia is decreased in kidney transplant samples in comparison to dialysis samples, insomnia symptoms remain elevated post-transplant (Fornadi et al., 2012; Liaveri et al., 2017; Novaks et al., 2006; Williams et al., 2016).

Sleep-disordered breathing disorders and kidney transplant patients. Sleep-disordered breathing disorders refer to a wide range of ventilation abnormalities that can occur during sleep. Typically these disorders are divided into four categories: obstructive sleep apnea, central sleep apnea syndrome, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder

(American Academy of Sleep Medicine, 2014). Of these disorders, obstructive sleep apnea (OSA) and central sleep apnea (CSA) are commonly studied in kidney transplant samples, with obstructive sleep apnea being the most prevalently diagnosed (Molnar et al., 2010; Szentkiralyi et al., 2011).

Although a few case reports in the 1990s documented an improvement in sleep apnea post-kidney transplant (Auckley et al., 1999; Langevin et al., 1993), this has not been a widely supported phenomenon. Langevin et al. (1993) presented case reports on two patients; despite the reported improvement in the apnea-hypopnea index (AHI) from pre to post-transplant, both patients' AHI remained at five and above, denoting some remaining disease presence. Auckley et al. (1999) reported on a single patient whose severe sleep apnea improved post-transplant. However, this study relied on polysomnography diagnosis pre-transplant and on home oximetry monitoring post-transplant. Both case reports offer limited generalizability on this topic. In 2008, Juardo-Gamez and colleagues (2008) published a prospective cohort study (n=9) evaluating patients by polysomnography prior to transplant and three months post-transplant. In this sample, three patients were diagnosed with sleep apnea, and two out of the three patients improved post-transplant. Despite an improvement in AHI, researchers found that the improvement in sleep efficiency changes were not statistically significant. In a larger study, 18 patients (11 patients with sleep apnea), were followed longitudinally pre and post-transplant and were evaluated through polysomnography. After transplant, AHI and saturation of oxygen did not change significantly among the sample. Of the 11 patients with sleep apnea, three patients were considered responders with their AHI reducing by 50% (or to below 10), but not all improved (Beecroft, Zaltzman, Prasad, Meliton, & Hanly, 2007). Yet despite the possible post-transplant improvement of sleep apnea that has been documented through small samples, there is

a reported high prevalence of sleep apnea among kidney transplant recipients. Sleep apnea prevalence rates range from 25-45% in kidney transplant patients, assessed through both self-report measures (Szentkiralyi et al., 2011) and polysomnography diagnosis (Fornadi et al., 2012; Molnar et al., 2010). Such research indicates that despite some reported improvements, there remains an increased prevalence of sleep apnea in kidney transplant patients.

It has been suggested (Mallamaci et al., 2009) that transplant patients do not have an increased prevalence of sleep-disordered breathing disorders, contending that the relationship is confounded by body mass index (BMI). In a study of 163 transplant patients, sleep-disordered breathing was measured through a cardiorespiratory polygraph. Mallamaci et al. (2009) found no difference in the prevalence of sleep-disordered breathing disorders when comparing transplant samples to an age, gender, and BMI matched comparison group. While this finding is intriguing, it is important to note that several studies (Beecroft et al., 2007; Beecroft, Pierratos, & Hanly, 2009; Diaz de Atauri et al., 2003) have reported an atypical presentation of sleep-disordered breathing among kidney transplant samples. Studies have found that obesity is not a significant marker or correlate of sleep-disordered breathing in transplant patients (Beecroft et al., 2007; Beecroft et al., 2009; Diaz de Atauri et al., 2003) as it is in the general population (Young et al., 2002). To date, no other study has replicated the finding of Mallamaci et al. (2009), and, in general, the literature continues to suggest a high prevalence of sleep-disordered breathing disorders in kidney transplant patients irrespective of BMI.

Associations of sleep disorders to health outcomes in kidney transplant patients. The literature on the presence of sleep disturbances in kidney transplant recipients and whether sleep improves post-transplant, remains intriguing yet understudied. Some research studies report that sleep disorders improve post-transplant (Auckley et al., 1999; Langevin et al., 1993; Novaks

et al., 2006; Winkelmann et al., 2002), while other studies reveal that sleep problems remain prevalent after transplant (Liaveri et al., 2017; Molnar et al., 2010; Szentkiralyi et al., 2011; Williams et al., 2016). Studies have begun to document the association of sleep disorders with various aspects of kidney transplant patients' health. Kovacs et al. (2011) found that sleep disorders namely, restless leg syndrome, obstructive sleep apnea, and insomnia were associated with poorer quality of life post-transplant. Additionally, both insomnia (Novaks et al., 2006) and an assessed risk of sleep apnea (Molnar et al., 2007a) have been found to be associated with reduced quality of life and declining renal function among transplant recipients. The associations between sleep and quality of life are important to consider, given the strong predictive relationships between quality of life and clinical outcomes in kidney transplant recipients (Chang et al., 2004; Griva et al., 2013; Molnar-Varga et al., 2011).

Sleep disorders have also been associated with clinical measures of poor health in kidney transplant patients. Insomnia symptoms have been associated with higher inflammatory markers (increased IL-6) in transplant patients (Fornadi et al., 2012). Molnar et al. (2010) found that transplant patients with obstructive sleep apnea were at an increased risk for stroke incidence and coronary heart disease. In the study by Molnar et al. (2010), average overnight oxygen saturation was also inversely correlated with stroke and coronary heart disease risk. A study by Daabis and El-Gohary (2012) reported a correlation between the apnea hypopnea index (AHI) and kidney function (as measured through estimated glomerular filtration rate) in a sample of kidney transplant patients with sleep apnea. Molnar et al. (2007b) followed a cohort of over 800 kidney transplant recipients for four years after transplant. Although there were a small number of patients (n=38) within the cohort suspected to have restless leg syndrome (RLS) (based on the RLS questionnaire), patients with RLS, versus those without, had a two-fold increased risk of

mortality. RLS remained an independent predictor for mortality even after controlling for covariates; however, this study found no association between RLS and risk of graft failure (Molnar et al., 2007b). Although the relationship between sleep disorders and transplant outcomes remains understudied, two studies have applied a more in-depth approach to explore this (Fornadi et al., 2014; Szentkiralyi et al., 2011).

Szentkiralyi and colleagues (2011) conducted a 66 month longitudinal study to explore the relationship between obstructive sleep apnea (OSA) and graft failure in kidney transplant patients. In their sample of 823 kidney transplant patients, 28% (n=226) of patients were identified as being "high risk" for obstructive sleep apnea, as measured by the Berlin Questionnaire (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999). During the approximate five-year study time frame, 91 patients had a failed graft, and 138 patients died. A high risk of obstructive sleep apnea was found to be an independent risk factor for graft failure in female kidney transplant patients. A separate association between mortality and high risk for obstructive sleep apnea was found in males; however, this relationship was no longer significant after controlling for age. In contrast to the study by Szentkiralyi et al. (2011), a study by Fornadi and colleagues (2014) found no relationship between sleep apnea and graft failure or mortality. Fornadi and colleagues assessed 100 post-transplant patients for sleep apnea through polysomnography, and monitored graft functioning (eGFR) every six months over the time period of approximately six years. Of the 100 patients included in the study sample, 25 were diagnosed with obstructive sleep apnea. The rate of graft function decline was similar in both patients with obstructive sleep apnea and patients without sleep apnea. Additionally, there were no significant differences in the mortality rates of the sample based on the diagnosed presence of obstructive sleep apnea. While the prospective design of the study by Fornadi et al. (2014) is a significant strength, the lack of

association found in Fornadi et al. (2014) may have been due to the study being underpowered (as identified by Fornadi et al., 2014). In addition, Szentkiralyi et al. (2011) and Fornadi et al. (2014) measured graft failure and graft functioning at short-term and mid-range time periods (six years post-transplant). National averages for graft half-lives exceed eight years (Lamb et al., 2011); therefore, longer study time frames may be needed to observe the association of obstructive sleep apnea with graft outcomes and mortality in transplant patients. Despite this, both studies have addressed an interesting topic relevant to how sleep disorders may impact transplant patients, a topic often ignored in the chronic kidney disease literature. There are many proposed potential etiologies for sleep disturbance in kidney failure.

Possible Etiologies of Sleep Disturbances in Kidney Failure

Amidst the increased prevalence of sleep disturbances and their clinical consequences in end-stage renal disease (ESRD) patients both pre-transplant Higuchi et al., 2015; Kumar et al., 2010; La Manna et la., 2011; Lindner et al., 2012; Tang et al., 2010;Zhang et al., 2014) and post-transplant (Daabis & El-Gohary, 2012; Fornadi et al., 2012; Molnar et al., 2007b; Molnar et al., 2010), understanding the possible etiologies of sleep disturbances in patients with kidney failure remains important. Further consideration must be given to differing pathophysiologies of sleep disturbances that vary in healthy populations and then become increasingly complex among patients with kidney failure, consisting of both dialysis and transplant patients.

It is essential to consider that, while sleep disorders may be directly related to kidney failure, the overall increased prevalence of sleep disturbances in the end-stage renal disease (ESRD) population may in part be associated with the increased presence of additional medical comorbidities that accompany kidney failure, or may even be a consequence of dialysis. For instance, sleep apnea shares a common profile with other comorbidities common among ESRD

patients (obesity, hypertension, diabetes), and the increased prevalence of sleep apnea in this population could be due to these comorbidities. Restless leg syndrome is associated with anemia (Winkelmann et al., 2002) and extra cellular fluid (Perl et al., 2006), and, therefore, may be related to some of the medical consequences of kidney failure. The high prevalence of insomnia, in dialysis patients is also often associated with uremic symptoms, such as restless legs syndrome, and pruritus (Sabbatini et al., 2002), and it has been associated with psychological distress (Theofilou, 2013), which is common among dialysis patients (Feroze et al., 2012). In addition to comorbidities and treatment side effects, dialysis as an intervention (in and of itself) has the potential to impact sleep in various ways. For instance, the potential circadian impact of the time of treatment, increased body temperature, and the physiological impact of rapid fluid exchange are all mechanisms through which dialysis could impact sleep (Parker, Bliwise, Bailey, & Rye, 2005). The complexity of kidney failure, coupled with several potential medical comorbidities, the presence of dialysis, and the range of physiological underpinnings of different sleep disorders, makes uncovering the directionality of the relationship between sleep and ESRD a difficult feat.

While some variables that could impact sleep disorders in dialysis patients can change post-transplant, such as the cessation of dialysis and restoration of kidney functioning, new changes occur post-transplant that may also impact sleep. For instance, the addition of new medications (immunosuppressants) and their potential side effects and physiological influences can impact sleep. Furthermore, some medical conditions associated with end-stage renal disease (ESRD) (such as diabetes and hypertension) may not change post-transplant and could continue to influence sleep. Moreover, disturbances in fatigue and mood often remain prevalent post-transplant (Williams et al., 2016), which can in-turn continue to impact sleep in kidney transplant

recipients. Thus, there is the potential for both shared and different mechanisms when exploring how sleep relates to ESRD patients both on dialysis and those who have received transplants.

Presently, the relationship between sleep disturbances and transplant outcomes remains understudied, as few studies have been published (Fornadi et al., 2014; Szentkiralyi et al., 2011). However, given the increased prevalence of sleep disturbances across the spectrum of chronic kidney disease (CKD), and the identification of sleep disturbances as a risk factor for CKD development (Lee et al., 2015) and faster progression to end-stage renal disease (ESRD) (Lee et al., 2015; Molnar et al., 2015; Turek, Ricardo, & Lash, 2012), there is support for suggesting a relationship between sleep and kidney functioning (Abuyassin et al., 2015; Turek, Ricardo, & Lash, 2012). If a relationship between sleep and kidney functioning exists, then ESRD patients with sleep disturbances who have undergone kidney transplantation may be at increased risk for renal dysfunction post-transplant. Current literature supports the need for further exploring the role of sleep disturbances in the outcomes of kidney transplant recipients and, specifically, whether sleep disorders are associated with graft survival and mortality outcomes in transplant patients. The application of theory can provide an important contribution to the framing of this topic. Support for considering the role of sleep in kidney functioning comes from a theory that focuses on the restorative benefits of sleep.

Theoretical Foundation

The Restoration Theory of Sleep. The Restoration Theory of Sleep (Adams & Oswald, 1977; Oswald, 1980) represents the theoretical foundation for this study and is one of several proposed functional theories of sleep. It proposes that sleep is essential for restoring the physiological and brain functions within an individual (Adams & Oswald, 1977; Oswald, 1980). The basis for this theory further suggests that sleep disturbances play a vital role in adverse

health outcomes through preventing the restorative functions that occur during sleep. The theory began to take form in the 1970s and the 1980s and developed through studies identifying physiological processes associated with sleep and wake cycles from both animal and human models. At its inception, the theory contended that sleep was associated with physiological functions through tissue restoration (Adams & Oswald, 1977; Oswald, 1980), protein synthesis (Adams & Oswald, 1977), nocturnal secretion of growth hormones (Adams & Oswald, 1977; Oswald, 1980), and changes in metabolic rates (Oswald, 1980). The theory continues to evolve with the field of sleep medicine today, but it remains intact through the continued theorization that sleep plays a restorative role in brain and body functioning.

Sleep is a cyclical process that occurs throughout various stages. There are five stages of sleep (Loomis, Harvey, & Hobart, 1937), and these stages are divided into two types of sleep; rapid eye movement (REM) sleep and non-REM sleep (Dement & Kleitman, 1957). REM sleep has been considered restorative for the brain, and non-REM sleep is restorative for the body. Throughout the different stages of sleep, various physiological processes and changes occur, which further demonstrates the important restorative processes that occur throughout sleep cycles. Even in the early 1900s researchers uncovered the dipping of blood pressure that occurred within the first 1-2 hours of sleep (Kleitman, 1929). If these vital physiological processes and changes that take place during sleep cycles are disrupted through sleep disorders, the theory contends that individuals then lack the restorative benefits that are intended to occur during sleep (Adams & Oswald, 1977; Oswald, 1980).

The application of the Restoration Theory of Sleep (Adams & Oswald, 1977; Oswald, 1980) has provided the basis for the present study's development, and, in conjunction with the current literature, supports the exploration of assessing the associations of sleep disturbances and

kidney transplant outcomes. Although the precise relationship between sleep and kidney functioning remains unknown, research in the field and the application of the Restoration Theory of Sleep (Adams & Oswald, 1977; Oswald, 1980) enables the identification of a functional and important relationship between sleep and kidney functioning that may be disrupted through sleep disturbances. It is proposed that kidney transplant patients who experience sleep disturbances will lack the restorative benefits of sleep, which will shorten the longevity of their kidney transplant graft survival and increase the incidence of mortality.

Potential Mechanisms of Sleep and Kidney Functioning

Indirect mediators of sleep and kidney functioning. There are several proposed mechanisms through which declining kidney function could be accelerated by the presence of sleep disturbances. Turek and colleagues (2012) suggest that poor sleep quality and/or sleep disorders exacerbate the severity of three risk factors associated with renal failure: hypertension, diabetes, and obesity (through inflammation). In turn, these risk factors influence increased sympathetic activation and endothelial dysfunction, two physiological mechanisms through which sleep can impact kidney functioning (Hanly, 2014; Nicholl et al., 2012; Ozok et al., 2014; Turek et al., 2012).

Hypertension. Hypertension remains a leading cause of kidney failure in the United States (United States Renal Data System, 2016). Hypertension can impact renal functioning through damaged blood vessels that occur in the kidney. Although studies identifying a causal relationship between sleep and hypertension are unclear, several studies offer support for an association between hypertension and sleep disturbances. A study using NHANES data from 2005 to 2008 reported an association between an increased risk of hypertension among adults with a sleep disorder, who also reported short sleep (OR 2.3) (Bansil, Kuklina, Merritt, & Yoon,

2011). A review (Palagini et al., 2013) of sleep deprivation studies summarized that both total and partial sleep deprivation has been associated with increased blood pressure. Decreased slow wave sleep, has been associated with morning hypertension (Sasaki et al., 2013). Moreover, there is a documented relationship between sleep apnea and blood pressure dipping, which typically occurs overnight, and is associated with difficult to treat hypertension. Sleep-disordered breathing severity has been associated with non-dipping systolic pressure (Hla et al., 2008), and poor sleep quality has also been associated with non-dipping of both systolic and diastolic blood pressure (Huang et al., 2011).

Diabetes. Diabetes is another leading cause of kidney failure in the United States (United States Renal Data System, 2016) and has been associated with sleep (Kendzerska, Gershon, Hawker, Tomlinson, & Leung, 2014; Nagayoshi et al., 2016; Reutrakul & Van Cauter, 2014). Diabetes is a pro-inflammatory state that can increase the risk of vascular diseases. Sleep restriction and short sleep duration are both associated with increased abnormal glucose metabolism and literature reviews have documented the long-standing relationship between sleep disturbances and diabetes (Reutrakul & Van Cauter, 2014). Studies have specifically found associations between sleep apnea and an increased risk of type II diabetes (Kendzerska et al., 2014; Nagayoshi et al., 2016). Both diabetes and hypertension commonly co-occur in patients. The conditions also share a physiological pathway with inflammation, all of which (individually and combined) can impact kidney functioning.

Inflammation. Inflammation is associated with sleep, as research in other patient populations has linked sleep quality and sleep disorders to immune functioning (Bryant, Trinder & Curtis, 2004; Chiu et al., 2009; Irwin et al., 1996). It has been suggested that several genes, which regulate the quantity of sleep an individual receives, are also involved in regulating the

immune system (Bryant et al., 2004). Irwin and colleagues (1996) found that partial sleep deprivation reduced natural killer cells in individuals, and they also found that, with a recovery night of sleep, natural killer cell levels returned to base values. End-stage renal disease patients with sleep disturbances have been found to have increased inflammation (Chiu et al., 2009). The relationship of sleep to inflammation is difficult to measure among transplant patients due to immunosuppressant medications, but inflammation is common in chronic kidney disease and dialysis patients. Moreover, inflammation has been associated with renal failure (Dahle et al., 2011), as inflammatory cytokines associated with oxidative stress can promote tissue damage of the kidney, which can accelerate progression to kidney failure (Gupta et al., 2013; Xu et al., 2015). The occurrence of hypertension, diabetes, and inflammation are all distinct but shared pathways that can lead to more significant health damage when uncontrolled.

Direct associations between sleep and kidney functioning. Much of the literature on sleep and kidney functioning has focused on sleep-related breathing disorders which are considered the most prevalent sleep disorders in transplant patients. Several theories have been proposed that sleep apnea can accelerate renal failure. A possible direct relationship between sleep apnea and renal failure has been proposed through the effect of hypoxia on the kidney (Hanly, 2014; Nicholl et al., 2012). Hypoxia refers to tissues lacking adequate oxygen through the blood. In an animal model study, a mouse kidney was used to examine the renal response to hypoxia. Hypoxia resulted in decreased renal function (measured through estimated glomerular filtration rate) (Galat, Robinson, & Rhodes, 1988). A study by Ahmed and colleagues (2011) examined the effects of nocturnal hypoxia on kidney functioning. In their sample of 858 patients, 374 patients had nocturnal hypoxia. It was found that patients with nocturnal hypoxia developed a three-fold risk of accelerated kidney loss, even after controlling for age, body mass

index, diabetes, and heart failure. In a review of the molecular impact of the kidney, Haase (2013) identified that the kidney is particularly susceptible to hypoxic injury due to "its complex transport functions within a relatively narrow range of pO2" (Haase, 2013, pp. 537).

Another potential direct mechanism through which sleep apnea may impact renal function is through proteinuria. Proteinuria is the presence of abnormal amounts of protein in urine, and can often reflect a kidney filtration problem which reduces renal function. While there is research refuting the relationship between sleep apnea and proteinuria (Mello et al., 2004), an association between proteinuria and sleep apnea in patients with chronic kidney disease has been reported (Chan et al., 2015).

The implications of the associations between sleep and kidney functioning are vast, and involve several proposed mechanisms. The relationship between sleep and kidney functioning throughout all stages of chronic kidney disease further highlights the significance of this relationship. If sleep relates to kidney functioning, then sleep disorders in kidney transplant recipients could very likely impact the clinical outcomes of the newly transplanted kidney, impacting both the longevity of the transplanted graft and patient survival.

Section II

Section I summarized the chronic kidney disease and transplant literature in relation to the main independent variable of the present study, sleep disorders. Section II presents a brief review of the literature pertaining to the dependent variables, and to additional covariates included in this study. The purpose of this section is to present the relevant literature providing an overview of the determined dependent variables, which include graft survival time and mortality (death with a functioning graft and patient survival time after graft failure). Subsequently, a summary of the relevant research literature pertaining to each covariate and its

association with transplant outcomes are presented, if known. In addition, a brief summary of any known research on the relationship between each covariate and sleep disorders, the primary predictor, are also presented.

Dependent Variables

Graft survival. Graft survival refers to the length of time the transplanted kidney remains functioning after surgery. Graft survival time is the main transplant outcome of interest for both patients and providers because transplant recipients are able to remain off of dialysis for the duration of time that the transplanted graft remains functioning. National graft survival data have shown successful short-term outcomes with averages of 1-year graft survival rates at 96% and 3-year graft survival rates at 88% (Matas et al., 2015). Data on long-term outcomes are less often reported, as fewer studies have been conducted. However, the estimated national average for a kidney transplant graft half-life ranges from 8-12 years (Hart et al., 2017; Lamb et al., 2011), meaning that 50% of transplant recipients maintain a functioning graft for approximately 8-12 years before the transplanted kidney fails.

Mortality. Mortality in transplant recipients, while a separate outcome from graft survival, can be closely related to graft survival. Patient mortality can impact graft survival outcomes registered in cases where a patient dies with a functioning graft, reducing the longevity of the transplant. Nationally reported mortality rates for kidney transplant recipients within the first three years post-transplant remain very low, with patient survival 1-year post-transplant reported at 97% and patient survival 3-year post-transplant reported at 93% (Matas et al., 2015). However, mortality rates increase as graft survival time increases, and death with a functioning graft has been identified as a primary cause of graft failure for patients who had maintained their transplant for 10 or more years (Matas et al., 2008).

Additionally, mortality rates for end stage renal disease patients (ESRD) increase after graft loss. Although a long-term goal of transplant is to increase the survival of patients compared to those remaining on dialysis (Wolfe et al., 1999), kidney transplant recipients have an elevated death rate after graft loss, compared to patients who have remained on dialysis (Kaplan & Meier-Kriesche, 2002; McCaughan et al., 2014; Perl et al., 2012). Mortality rates up to two years after graft failure are reported at approximately 25%, indicating an increased risk of death for patients who have experienced graft loss, compared to those ESRD patients who have remained on dialysis (Gill, Abichandani, Kausz, & Pereira, 2002; Rao et al., 2007).

Study Covariates

In addition to examining the primary predictor, sleep disorders, additional study covariates that might be related to the dependent variables (graft survival and mortality) and/or to sleep disorders were considered. For each covariate its association with transplant outcomes are presented, if known. In addition, a brief summary of any known research on the relationship between each covariate and sleep disorders, the primary predictor, are presented.

Gender of the recipient. Past studies have found that male kidney transplant recipients have shorter graft survival time compared to females (Chen et al., 2013; Meier-Kriesche et al., 2001). While the exact cause of this gender disparity is unknown, a literature review of gender and transplantation has suggested that longer graft survival times for females may be related to hormonal differences and the relation of this to the immune system (Sanfey, 2005). Occurrence of death with a functioning graft does not differ by gender (Meier-Kriesche et al., 2001).

In the general population, males have a higher prevalence of sleep apnea compared to females (Dancy et al., 2003). However, in a gender comparison of sleep apnea among kidney transplant recipients, Musci and colleagues (2004) found no associations between gender and

sleep apnea. Other sleep disorders, such as restless leg syndrome (Manconi et al., 2012) and insomnia (Lind, Aggen, Kirkpatrick, Kendler, & Amstadter, 2015; Zhang & Wing, 2006) are both found to be more prevalent among women in the general population.

Race of the recipient. African American transplant recipients have poorer graft survival outcomes compared to Caucasian, Hispanic, and Asian transplant recipients (Gordon, Ladner, Caicdeo, & Franklin, 2010; Keith, Cantarovich, Paraskevas, & Tchervenkov, 2006; Meier-Kreische et al., 2001). A cohort study of approximately 80,000 veterans found that, within a sample of patients with a universal access to health care, African Americans had a higher risk of graft failure (Chakkera et al., 2005), suggesting that differences in transplant outcomes related to race may not be a health disparity issue. A systematic review summarizing racial disparities in kidney transplantation, identified a difference in immunologic risk factors in different ethnicities, proposing immunology risks as the reason for racial differences in graft survival (Gordon et al., 2010). Regarding mortality outcomes, such as death with a functioning graft, research has found that African Americans have a lower risk of death with a functioning graft compared to Caucasian transplant recipients (Ojo et al., 2000).

A high prevalence of undiagnosed sleep apnea among minority populations has been identified (Chen et al., 2015). Additionally, African Americans are more likely to report long or short sleep durations (Krueger & Friedman, 2009). A systematic review on sleep and race suggested that racial disparities in sleep health may contribute to the higher proportion of cardiovascular disease among minority populations (Kingsbury, Buxton & Emmons, 2013).

Age of the recipient. Younger patients have a higher risk of graft failure (Keith et al., 2006). This may be related to an increased prevalence of non-adherence with immunosuppressant medications among younger patients (Brahm, Manfro, Mello, Cioato, &

Goncalves, 2012), which can greatly impact graft survival times. Risk of death with a functioning graft is seven times higher in recipients over age 65 compared to adults ages 18-29 (Ojo et al., 2000). In addition, older patients have an increased risk of death after graft failure (McCaughan et al., 2014).

Sleep architecture changes throughout the lifespan, and sleep disorders and sleep disturbances are more frequently reported among older adults (Vitiello, 1997). Factors that influence the prevalence of sleep disorders within the context of age are likely vast and multifactorial; however, a review of the research suggests that in-part, increased sleep disturbances among older adults may be related to comorbid medical and psychiatric conditions and medications used to treat such conditions (Roepke & Ancoli-Israel, 2010).

Body mass index. A recent meta-analysis reported that patients with a higher body mass index (BMI) have been found to be at increased risk of graft failure and mortality post kidney transplant (Lafranca et al., 2015). However, other studies have contradicted such findings, by reporting no difference in patient survival or graft survival time related to BMI in kidney transplant recipients (Khwaja & El-Nahas, 2012; Krishnan et al., 2015). BMI listing criteria are common among transplant centers, meaning that centers may only medically clear patients for a transplant surgery if their BMI is within a certain range. Such listing criteria are important to consider and may affect research findings. Meier-Kriesche, Arndorfer, and Kaplan (2002) identified that extreme lows and extreme highs of BMI are the significant risk areas for transplant outcomes. A BMI greater than 40 kg/m^2 is considered to pose increased risks to transplant outcomes (Khwaja & El-Nahas, 2012); however, a BMI less than 40 kg/m^2 is often required in order to be transplanted at many centers, and thus, it may be difficult to assess the true relationship between BMI and transplant outcomes.

Past studies have found that poor sleep quality is associated with higher BMI in transplant patients (Silvas et al. 2012). BMI is also associated with a higher risk of sleep apnea in the general population (Young et al., 2002). However, two past studies have proposed that BMI may not be associated with sleep apnea in kidney transplant patients (Beecroft et al., 2007; Diaz de Atauri et al., 2003), indicating a potentially different relationship between BMI and sleep apnea among kidney transplant recipients.

Medical comorbidities. The literature on medical comorbidities and transplant outcomes vary. While research has found that patients with increased comorbidities do not have shorter graft survival time (Grosso et al., 2012), studies have also reported an increased risk of death with a functioning graft, and increased risk of mortality after graft loss in transplant patients with increased medical comorbidities (Grosso et al., 2012; Wu et al., 2005). Research on comorbidity and transplant outcomes have included both measures of comorbidity scores and individual measurements of common comorbid conditions that may be relevant to transplant outcomes. In the present study, the following comorbid conditions were measured individually: hypertension, diabetes, stroke history, heart attack history, peripheral vascular disease, coronary artery disease, and dyslipidemia. The rationale for including these comorbid conditions can be found earlier in Section I (potential mechanisms of sleep and kidney functioning).

The relationship between sleep disorders and medical comorbidities can vary and can be specific to each comorbidity being measured. However, in a past study of kidney transplant recipients, it was found that patients with diagnosed sleep apnea did not have higher comorbidity scores, as measured through the Charlson Comorbidity Index, compared to those transplant patients without diagnosed sleep apnea (Molnar et al., 2010).

End-stage renal disease etiology. There are many diagnoses that can cause end-stage renal disease (ESRD); however, in the United States, uncontrolled hypertension and diabetes are leading causes of ESRD (United States Renal Data System, 2016). Other causes, such as genetic disorders, autoimmune diseases, and nephrotic syndrome can also lead to renal failure (United States Renal Data System, 2016). Few studies have examined each specific cause of ESRD and compared transplant outcomes; however, recent national findings from the Scientific Registry of Transplant Recipients report that patients whose ESRD was caused by diabetes and hypertension have poorer graft survival outcomes, compared to patients with other etiologies (Hart et al., 2016). Additionally, a single-center study found that transplant patients diagnosed with an autoimmune disease, lupus, had poorer graft survival rates compared to non-lupus diagnosed ESRD patients (Lionaki et al., 2008). This study reported similar patient survival rates among the lupus and non-lupus diagnosed group of ESRD patients (Lionaki et al., 2008). Despite limited research, ESRD etiology may be associated with comorbidities or disease presence that may influence the newly transplanted kidney.

Only one study was found regarding end-stage renal disease (ESRD) etiology and its relation to sleep disorders. Patients with a hypertensive ESRD etiology had worse sleep quality scores than patients whose ESRD was due to other causes (Ameli et al., 2007). However, there does not to our knowledge appear to be further research on whether ESRD etiology may differ in the presence of a sleep disorder.

Education level. Few studies have examined education level as a predictor of kidney transplant graft survival. In the literature, education level can sometimes serve as a proxy for socioeconomic status (SES), but it is important to consider that education level may also reflect access to care, or even health literacy in samples. Of the studies that do exist, there is a reported

increased risk of graft failure in patients with less education (Gordon et al., 2010; Schaeffner, Mehta, & Wikelmayer, 2008). There is no known relationship between mortality and education level in a sample of kidney transplant recipients (Schaeffener et al., 2008).

Research suggests an association between low SES and an increased risk of sleep disturbances (Mezick et al., 2008; Patel, Grandner, Xie, Branas, & Gooneratne, 2010). In a prospective cohort study, lower education levels were associated with an increased risk of self-reported short sleep duration (Stamatakis, Kaplan, & Roberts, 2007).

Functional status. Functional status refers to an individual's ability to manage activities of daily living and their degree of dependence on others. Patients with no functional limitations report a better health-related quality of life post-transplant (Rebollo et al., 2000). Although few studies have explored functional status as a potential predictor of graft failure, Garonzik-Wang and colleagues (2012) reported that patients with limited functionality (as they defined frailty) were more likely to have delayed graft functioning, which has been associated with poorer transplant outcomes (Yarlagadda, Coca, Formica, Poggio, & Parikh, 2008). In a large national sample of US kidney transplant recipients, pre-transplant functional status was found to be an independent predictor of patient survival post-transplant (Reese et al., 2015).

Past research indicates a relationship between sleep disturbances and functional status. Both poor sleep quality (Chasens, Sereika, Burke, Strollo, & Korytkowski, 2014) and sleep-disordered breathing disorders (Spira et al., 2014) have been found to be independent predictors of decreased functional status in patients with diabetes (Chasens et al., 2014) and older females (Spira et al., 2014).

Non-compliance with transplant medications. A meta-analysis of 36 studies reported that the odds of graft failure increased seven-fold when patients were non-adherent with

transplant immunosuppressant medications (Butler, Roderick, Mullee, Mason, & Peveler, 2004). Obtaining a clear hazard ratio of non-compliance and its relation to graft failure is difficult due to patient variation in the severity of non-compliance and variation in the time period that the non-adherence to transplant medications occurred. However, such findings demonstrates the widely supported significance of compliance with transplant medications post-transplant. A recent study by Brahm and colleagues (2012) also reported that non-compliance with transplant medications was associated with poorer kidney function. Research addressing transplant medication non-compliance and sleep disorders could not be found, to our knowledge.

Smoking history and pack-years. Smoking is a cardiovascular risk factor, and past research reports a relationship between smoking and transplant outcomes. Nourbala, Nemati, Rostami, and Einollahi, (2011) presented a systematic review on the impact of cigarette smoking of kidney transplant recipients on graft survival and patient survival. Smoking history was associated with a higher risk of graft failure and patient mortality. A study by Cosio and colleagues (1999) reported that smoking was associated with a higher risk of death with a functioning graft.

Patients who smoke are more likely to report sleep disturbances (Phillips & Danner, 1995); moreover, smoking is a risk factor for sleep-disordered breathing (Wetter, Young, Bidwell, Badr, & Palta, 1994). The relationship between smoking and sleep disorders was also considered in the present study.

Donor type. Kidney transplantation includes the use of both living donor kidneys and deceased donor kidneys. Living donor transplants typically result in longer graft survival time compared to deceased donor transplants (Cecka, 2001; Wang, Skeans, & Israni, 2016). Living donor recipients tend to have fewer postoperative complications and readmissions, which may

also be related to long-term graft survival (Guimaraes, Araujo, Santos, Nunes, & Casal, 2015). Research addressing transplant donor type and sleep disorders could not be found, to our knowledge.

Human Leukocyte Antigen (HLA) mismatch. HLA mismatch is an immunology measure referring to the degree of antigen mismatch between the donor and recipient. Such markers identify what cells belong to the recipient's body and better HLA matching increases the chance of engraftment, which refers to when donated cells from the transplanted organ start to make new blood cells in the recipient (Nguyen, Williams, Wong, & Lim, 2013). HLA antibodies play a role in the immune response in accepting a newly transplanted kidney. Research supports that HLA matching can impact graft survival outcomes, as patients with a poorer antigen match have a higher risk of graft loss (Pirsch et al., 1996; Zhou & Cecka, 1993). Research addressing HLA matching and sleep disorders could not be found, to our knowledge.

Donor age. The relationship between donor age and transplant outcomes vary. Donor age was not found to be predictive of long-term graft survival in a study by Pirsch et al. (1992). However, a systematic review identified donor age as a powerful predictor in long-term graft survival (Schratzberger & Mayer 2003). Research addressing transplant donor age and sleep disorders could not be found, to our knowledge.

Year of transplant surgery. The year of transplant time frame in this study spans from 1997 to 2015. Consideration was given to documented changes or advances in the field of transplant that may be associated to transplant outcomes. The most notable change over the past twenty years in the field of kidney transplant has been improvements in immunosuppressant medication which has led to improvements in graft survival. In 1997, Prograf, an immunosuppressant medication gained FDA approval for kidney transplant (Bowman &

Brennan, 2008), and shortly after this approval, transplant centers throughout the United States started to use this medication. Since the approval and use of Prograf, there have been decreases in acute rejection (Knoll, 2008). National transplant data reports that the occurrence of rejection during the first year post-transplant has steadily improved since the use of Prograf (in the 1990s), but that these improvements have remained relatively stable since 2008 (Hart et al., 2016). Findings from the national database, the Scientific Registry of Transplant Recipients, also report a steady increase in graft half-lives and patient survival over the past twenty years (Matas et al., 2014). Such findings indicate that transplant graft survival outcomes and patient survival have improved throughout the study time period.

Consideration in the present study was also given to the potential advances in the sleep field that may have taken place during the transplant time frame (1997-2015). Thus, a variable, year of transplant was included. Although sleep disorders, namely, sleep apnea have gained more widespread medical attention in the 1980s (Punjabi, 2008), increased awareness and diagnosis of sleep apnea and all sleep disorders have likely steadily increased over the past 20 years, although this is difficult to quantify.

Summary

The present study examined associations between sleep disorders and transplant outcomes, while considering key covariates that might be potential confounders and/or adjustment variables or might modify the relationship of sleep disorders to the identified dependent variables. Section I of this review summarized the literature on sleep disturbances across the spectrum of chronic kidney disease, specifically, the sleep literature among kidney transplant patients. Thus, it summarized the rationale and basis for the study development. Section II provided an overview of the relevant literature pertaining to the dependent variables,

main independent variable (sleep disorders), and other covariates. The additional covariates were included in the study due to their potential association with transplant outcomes and/or sleep disorders.

CHAPTER III

METHODOLOGY

The overall goal of the present study was to examine associations between sleep disorders and transplant outcomes; namely, death with a functioning graft, graft survival and patient survival after graft failure. This chapter addresses following: the study setting, research design, data sources, protection of human subjects, data abstraction procedures, the operationalization of study variables, and hypotheses. Following the presentation of study hypotheses, the statistical analysis plan and analytic approach for each hypothesis is further described.

Study Setting

Data from this study came from a sample of patients who were transplanted at the Sentara Norfolk General Hospital (SNGH) Kidney Transplant Center, in Norfolk, Virginia. SNGH is a Medicare certified kidney transplant center. All patients transplanted at SNGH follow an immunosuppressant dosing protocol and a standardized post-transplant plan of care, with regards to the frequency of clinic visits and measures of laboratory monitoring of kidney functioning post-transplant. Patients transplanted at SNGH are followed at least monthly for the first year after their transplant, then are evaluated annually for the duration of their functioning transplant. Once a transplanted kidney fails, patients are no longer followed at the SNGH transplant center.

Study Design and Data Selection

The study design is a historic cohort study that utilizes data from Sentara Norfolk General Hospital (SNGH) adult kidney transplant patients who have a failed kidney transplant graft and/or died with a functioning graft. Data for the study involved merging two secondary sources, namely, a national transplant registry maintained by the United Network for Organ

Sharing (UNOS) and the medical records maintained by the transplant center (SNGH) from which the sample is selected. The study time frame was determined by the availability of data from both sources. Although the national registry of transplant outcomes (UNOS) has been in place since 1988, access to medical record data from the SNGH transplant center was only available back to 1997. Therefore, the study time frame was determined to be January 1, 1997 to September 1, 2015, inclusive.

Inclusion criteria for the sample were as follows: adult SNGH kidney transplant recipients who have been transplanted and experienced graft failure and/or death with a functioning graft during the time frame of January 1, 1997 to September 1, 2015, inclusive. Criteria for exclusion were: SNGH kidney transplant recipients who had received a previous kidney transplant or a multi-organ transplant, and patients who experienced graft failure within 90 days of their transplant surgery. Data were not obtained on those subjects who had a previous kidney transplant or a multi-organ transplant. However, data were originally obtained regarding all others with graft failure, including subjects who experienced graft failure within 90 days of their transplant. Graft failure within 90 days of a transplant occurs in less than 3% of US kidney transplants (Matas et al., 2015) and is considered a rare occurrence often related to surgical complications or complications from the donor kidney, and thus informed the exclusion of 40 subjects. There were 367 subjects that satisfied all inclusion criteria.

Data Sources

The United Network for Organ Sharing (UNOS) is a private, non-profit organization, which manages the United States' organ transplant system. UNOS was formed in 1984 after the National Organ Transplant Act (NOTA; P.L. 98-507); however, it was not until 1988 that the organization began collecting regulated data on all organ transplants performed nationwide.

Since 1988, UNOS has maintained a database consisting of both donor and recipient information for each organ transplant performed in the United States at all Medicare certified transplant centers. All study variables requested from UNOS are outlined in the UNOS data collection tool (Appendix A).

Medical records from the Sentara Norfolk General Transplant Center (SNGH) were the second data source for this study. The SNGH data collection tool (Appendix B) outlines the variables and information that were abstracted from the SNGH medical record. The SNGH medical record has two sources, EPIC™ and Voyager™. EPIC is an electronic health software that is utilized by the SNGH hospital system. The SNGH transplant center began using EPIC software in 2009 as an electronic medical record. Medical record data prior to 2009 was found in an additional abstraction source, the Voyager database. Voyager is a Technicon Data System utilized by the SNGH hospital system that dates back to 1986. Although the Voyager system dates back to 1986, the range of information that has been uploaded into this database varies and data on transplant patients was not recorded in Voyager until 1997. Thus, the availability of the SNGH medical record data informed the designated study time frame.

Protection of Human Subjects and Ethical Considerations

This study received ethical approval from the Eastern Virginia Medical School Institutional Review Board (identifier 15-09-WC-0198). Secondary approval was received from the Old Dominion University Institutional Review Board (identifier 826031). Additionally, the Sentara Research Compliance Department approved this study. A waiver of subject consent and a waiver of subject protected health information were approved through all previously mentioned ethical review parties. The sample consisted only of data from patients with failed grafts or patients who died with a functioning graft, and this inclusion criteria was related to the protection

of human subjects. Patients with failed grafts or those who died with a functioning graft were no longer being followed at the Sentara Norfolk General Hospital (SNGH) kidney transplant center during the time of data collection; therefore, any research on such patients, our study sample, would have no impact on the care received.

Data Abstraction Procedures

After receiving approval from the identified Institutional Review Boards, a data request was submitted to the United Network for Organ Sharing database (UNOS) for all variables outlined in the UNOS data collection tool (Appendix A). Two subject identifiers listed in the UNOS data collection tool (name and date of birth) served as the linking mechanism between UNOS data and the Sentara Norfolk General Hospital (SNGH) medical record. Upon receipt of UNOS data, variables from the SNGH data collection tool (Appendix B) were then abstracted from the SNGH medical record. A systematic approach was followed when abstracting variables from the SNGH medical record. First, the medical history section of the subject's chart was reviewed for variable abstraction. Then, all history and physical notes in the subject's medical record were reviewed to verify medical history abstractions and date of diagnoses. In addition, every pulmonary and anesthesia note in the subject's medical record was specifically reviewed to further search for the documentation of any diagnosed sleep disorder that may not have been recorded in the subject's medical history. Whether any variable abstracted from the SNGH medical record occurred prior to transplant, during the transplant time, or after graft failure was recorded. Abstraction from the SNGH medical record was completed by one member of the research team who followed a uniform process.

Only diagnosed sleep disorders, medical comorbidity diagnoses, and smoking history information reported prior to transplant and/or during the subject's transplant time period were

considered in data analyses. For example, if a patient had a sleep disorder that was noted in their medical record after their graft failed, this sleep disorder was not considered in the analysis. The only exception to this was the documentation of the variable relating to smoking history as assessed by packs per year (tobacco pack-years); this was notated in the medical history section of the medical record and often did not include a diagnosis timeframe. Therefore, the calculation of a subject's smoking history pre-transplant or prior to graft failure could not be ascertained. Upon completion of abstraction, data collected from UNOS and the data abstracted from the SNGH medical record were aggregated into one database. All potential identifying information was removed from the data set.

Operational Definitions of Study Variables

Study variables outlined in the data collection tools (Appendices A and B) consist of independent variables and dependent variables. Dependent variables, the identified transplant outcomes, were defined from the transplant literature and through consultation with transplant nephrologists. The primary independent variables, any sleep disorder and sleep-disordered breathing disorders, were selected based on review of the literature and were operationally defined according to The International Classification of Sleep Disorders, Third Edition (American Academy of Sleep Medicine, 2014). Additional study covariates were selected in consideration of the transplant literature and sleep literature, the operational definitions for these variables are summarized in Table 1.

Dependent Variables. *Death with a functioning graft* refers to graft failure due to the subject's death, as opposed to graft failure resulting in return to dialysis. Determination of graft failure due to death was reported by variables maintained in the United Network for Organ

Sharing (UNOS) database. Any subject whose date of death was documented as the same date of graft failure was classified as "death with a functioning graft."

Graft survival time or duration of the transplant refers to the length of time the patient maintained a functioning kidney transplant. The endpoint of graft survival time in this study was defined as graft failure or cardiovascular (CVD) related death with a functioning graft. Data on graft survival time was reported by variables recorded in the UNOS database. Graft survival time was calculated by subtracting the date of the subject's graft failure from the date of their transplant. Graft survival time was reported in days.

Survival time after graft failure refers to survival time after a subject's transplant graft failure. Data on mortality after graft failure was reported by variables maintained in the UNOS database and through the most recent contact with subjects recorded in the Sentara Norfolk General (SNGH) medical record. Subjects that died with a functioning graft had a survival time after graft failure of 0; therefore, these subjects were excluded from analyses. Survival time after graft failure was reported in days.

Primary Independent Variables. *Any sleep disorder* is defined as any diagnosed sleep disorder documented in the subject's medical record, as classified by The International Classification of Sleep Disorders, Third Edition (American Academy of Sleep Medicine, 2014). Sleep disorder classifications include six major categories: insomnia, sleep-related breathing disorders, sleep-related movement disorders, central disorders of hypersomnolence, circadian rhythm disorders, and parasomnias. Documentation of diagnosed sleep disorders occurred through the assignment of medical terminology and ICD-10 codes located in the subject's medical history section of their Sentara Norfolk General Hospital medical record, or through medical notations in their records. When the date of any sleep disorder diagnosis could not be

ascertained, the date of the first medical record notation reporting the diagnosed sleep disorder was recorded. Only sleep disorders reported in the medical record pre-transplant and/or during the transplant time frame were included in analyses. Diagnosed sleep disorders documented after graft failure were not included in the analyses.

Sleep-disordered breathing disorders are a classification of sleep disorders which refer to a wide range of ventilation abnormalities that can occur during sleep. Typically, these disorders are divided into four sub-categories: obstructive sleep apnea, central sleep apnea syndrome, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder (American Academy of Sleep Medicine, 2014). Of these disorders, obstructive sleep apnea (OSA) and central sleep apnea (CSA) are commonly studied in kidney transplant samples; with obstructive sleep apnea being the most prevalently diagnosed (Molnar et al., 2009; Molnar et al., 2010; Szentkiralyi et al., 2011). Documentation of diagnosed sleep-disordered breathing disorders occurred through the assignment of medical terminology and ICD-10 codes located in the subject's medical history section of their Sentara Norfolk General Hospital medical record, or through medical notations in their records. Only sleep-disordered breathing disorders reported in the medical record pre-transplant and/or during the transplant time frame were included in analyses. Diagnosed sleep-disordered breathing disorders documented after graft failure were not included in the analyses.

Additional Covariates. Identified covariates can be organized into two categories: recipient-related variables and transplant-related variables. Recipient variables refer to data about the transplant recipient and include: gender, race, age, body mass index (BMI), diabetes, hypertension, coronary artery disease, heart attack history, peripheral vascular disease, dyslipidemia, stroke history, end-stage renal disease etiology, education level, functional status,

smoking history, tobacco pack-years, and non-compliance with transplant medications. Transplant variables refer to data about the kidney donor or transplant surgery and include: transplant type, human leukocyte antigen (HLA) mismatch, donor age, and year of transplant surgery. Table 1 provides a summary of covariates, including the variable measurement scale, the data source from which they were obtained, and operational definitions.

Table 1.
Description and Operational Definitions of Study Covariates

Variable	Measurement Scale	Data Source	Operational Definition
Transplant Recipient Variables			
Gender	Categorical	UNOS	Male or female
Race	Categorical	UNOS	African American or Caucasian
Age	Continuous	UNOS	Age at the time of transplant (years)
Body Mass Index (BMI)	Continuous	UNOS	BMI at the time of transplant (kg/m^2)
Diabetes	Categorical	SNGH	Diagnosed diabetes documented prior to transplant or prior to graft failure (yes or no)
Hypertension	Categorical	SNGH	Diagnosed hypertension documented prior to transplant or prior to graft failure (yes or no)

Table 1. (continued)

Variable	Measurement Scale	Data Source	Operational Definition
Coronary Artery Disease	Categorical	SNGH	Diagnosed coronary artery disease documented prior to transplant or prior to graft failure (yes or no)
Heart Attack History	Categorical	SNGH	Diagnosed heart attack history documented prior to transplant or prior to graft failure (yes or no)
Peripheral Vascular Disease	Categorical	SNGH	Diagnosed peripheral vascular disease documented prior to transplant or prior to graft failure (yes or no)
Dyslipidemia	Categorical	SNGH	Diagnosed dyslipidemia documented prior to transplant or prior to graft failure (yes or no)
Stroke History	Categorical	SNGH	Diagnosed stroke history documented prior to transplant or prior to graft failure (yes or no)
End-Stage Renal Disease Etiology	Categorical	UNOS	Reported cause of end-stage renal disease (hypertensive nephrosclerosis or other diagnosis)
Education Level	Categorical	UNOS	Highest level of education completed at the time of transplant (high school or below, beyond high school, or unknown)
Functional Status	Categorical	UNOS	Karnofsky scale measure (nurse reported) of patient functional status at the time of transplant, full functionality (100%) or limited functionality (<100%)
Non-compliance	Categorical	SNGH	Documented non-compliance with transplant medications during the time of transplant (yes or no).
Smoking History	Categorical	SNGH	Smoking history documented prior to transplant or prior to graft failure (yes or no)

Table 1. (continued)

Variable	Measurement Scale	Data Source	Operational Definition
Tobacco Pack-Years	Continuous	SNGH	Most recent documentation of tobacco pack-years (years)
Transplant-Related Variables			
Donor Type	Categorical	UNOS	Type of kidney donation (living donor or deceased donor)
HLA Mismatch	Ordinal	UNOS	Scale of an immunology match between transplant recipient with donor kidney. The degree of the match is measured on a 0-6 scale, with a 0 mismatch designating a perfect match
Age of Donor	Continuous	UNOS	Age of kidney donor at the time of donation (years)
Year of Transplant Surgery	Continuous	UNOS	Calendar year when recipient was transplanted (1997-2015)

Abbreviations: UNOS, United Network for Organ Sharing; SNGH, Sentara Norfolk General Hospital; HLA mismatch, human leukocyte antigen mismatch

Missing Data

Missing data were addressed after data abstraction had been completed. The variable, body mass index (BMI), had missing data due to lapsed time periods in which this variable was not maintained by the United Network for Organ Sharing (UNOS) database. A conditional means imputation was utilized to impute the 47 missing BMI values. The imputation was informed by two variables, sleep apnea diagnosis and functional status (Karnofsky score measure of a patient's functional status at the time of transplant), and it was performed by a statistical

consultant. There were 24 missing cases of the variable education level. An imputation was not considered appropriate for education level; therefore, the decision was made to create a third category designated as "unknown". The method of creating a category for missing or unknown data is recommended by Klein, Rizzo, Zhang, and Keiding (2001), and it is considered an appropriate method to address missing data in a survival analysis. Tobacco pack-years, a variable abstracted from the SNGH medical record, had 48 cases of missing data. After abstraction, pack-years was considered a limited variable due to the large amount of missing data and limited ability to verify pack-years prior to graft failure; therefore, the categorical variable, smoking history, was used instead of pack-years in multivariate models.

The variable, recipient race, did not have any missing data; however, there were six subjects in the sample with a reported race other than African American and Caucasian. Due to this small number, creating a third category for race was considered uninformative. Therefore, these six subjects were collapsed into the category Caucasian. According to the research literature, the largest racial disparity in transplant outcomes found has been between African Americans and other races (Caucasians, Asians, and Hispanics) (Gordon et al., 2010); thus, the above approach was considered appropriate.

Hypotheses

Study hypotheses corresponded to three identified dependent variables: death with a functioning graft, graft survival time, and patient survival time after graft failure. Six hypotheses were tested, including a main hypothesis and sub-hypothesis for each dependent variable. Hypothesis 1 examined the outcome death with a functioning graft, and it helped to inform the analytic approach for hypothesis 2, which examined graft survival time.

Hypothesis 1: Death with a functioning graft. Hypothesis 1a: Of patients with graft failure, patients with any diagnosed sleep disorder have a statistically significantly higher proportion of graft failure due to death (compared to graft failure and return to dialysis) than patients without any diagnosed sleep disorder. Sub-hypothesis 1b: Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have a statistically significantly higher proportion of graft failure due to death (compared to graft failure and return to dialysis) than patients without a diagnosed sleep-disordered breathing diagnosis.

Hypothesis 2: Graft survival time. Hypothesis 2a: Of patients with graft failure, patients with any diagnosed sleep disorder have statistically significantly shorter graft survival times than patients without any diagnosed sleep disorder, even after adjustment for potential confounders. Sub-hypothesis 2b: Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have statistically significantly shorter graft survival times than patients without a diagnosed sleep-disordered breathing disorder, even after adjustment for potential confounders.

Hypothesis 3: Patient survival time after graft failure. Hypothesis 3a: Of patients with graft failure, patients with any diagnosed sleep disorder have a statistically significantly higher total death hazard after graft failure than patients without any diagnosed sleep disorder, even after adjustment for potential confounders. Sub-hypothesis 3b: Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have a statistically significantly higher total death hazard after graft failure than patients without a diagnosed sleep-disordered breathing disorder, even after adjustment for potential confounders.

Data Analysis

Data was analyzed using SAS™ Enterprise Guide software, version 6.1. Descriptive statistics were used to describe the sample and to summarize prevalence rates of sleep disorders in the sample. Chi-square and independent t-test analyses compared the covariates among two groups within the sample, patients with any sleep disorder and those without any sleep disorder. Chi-square statistics were also used to test hypothesis 1, comparing the proportion of death with a functioning graft in those with any sleep disorder (or a sleep-disordered breathing disorder) to those without any sleep disorder. Separate survival analyses including Kaplan Meier survival curves (Kaplan & Meier, 1958) and the Cox regression (Cox, 1972) were used to test hypothesis 2 (graft survival time) and hypothesis 3 (patient survival after graft failure). The goal of survival analysis is to estimate and interpret survival and hazard functions from time-to-event data (Hosmer, Lemeshow, & May, 2008). The utilization of survival curves allows for a comparison between two groups. Further, the use of the Cox regression allows for the exploration of the relationship between a predictor variable and a survival outcome, while controlling for possible covariates. Statistical significance was met for all analyses if the two-tailed p value was $\leq .05$. A general overview of the analysis plan is summarized below. Subsequently, a more in-depth discussion of the each hypothesis and the analysis approach for each hypothesis is further outlined.

Censoring. Survival analyses allow for the inclusion of censored data. Censoring occurs when survival time becomes unknown for a subject. Censoring may be the result of a patient being lost-to follow up, or a death from causes unrelated to a study hypothesis (competing risk), or the event not occurring during a designated study time frame (administrative censoring). Censoring resulting from any of these events is referred to as right censored data. Censored data

may also be left censored, representing when true survival time is less than the observed survival time (Allison, 2010). Censored survival times underestimate the true time to a designated event and the consideration of whether censoring in a study is informative is necessary to address (Allison, 2010). Informative censoring occurs when censored observations are related to the research hypothesis (or a specific variable) and thus have the potential to lead to significant biases in findings (Allison, 2010). Right censoring approaches are further defined in the analytic approach for hypotheses 2 and 3. The censoring definitions and consideration of informative censoring are addressed further in the section outlining analysis plans for individual hypotheses.

Survival curves. Survival curves plot the probability that an individual survives longer than a specified time, and can be graphed as a curve or step-function. Survival curves are often useful for preliminary analyses of survival data (Allison, 2010). The Kaplan Meier method was used to estimate survivor functions (Kaplan & Meier, 1958). This method was used to examine the relationship of sleep disorders to survival time, by comparing the survival time of those with any sleep disorder to those without a sleep disorder. In order to statistically compare the differences between two survival curves, the Log-Rank test was used. Alternatives to the Log-Rank test exist; however, such methods involve weighted tests at different points in survival times (Wilcoxon, Tarone-West, and Flemington-Harrington) and did not offer additional benefits with regards to the hypotheses being tested in this study.

Cox regression. The Cox regression (Cox, 1972) was used to examine univariate and multivariate relationships of predictors to the dependent variables in hypothesis 2 (graft survival time), and hypothesis 3 (patient survival after graft failure). The Cox regression is a semi-parametric regression technique that can be used to model time-to-event data. The Cox Proportional Hazards Model (Cox PH) is the basic foundation for the Cox regression. The Cox

PH is a survival analysis model that assumes a proportional hazard, meaning the assumption that hazard ratios of variables are constant over time. The basic mathematical foundation of the Cox PH model could be described as follows:

$$h(t)= h_0(t) \exp \{b_1x_1 + b_2x_2 + \ldots + b_{group}x_{group})$$

h(t) represents the baseline hazard function, X represents the predictor variables, and b represents the regression coefficients. The regression coefficients present the relative effect of every predictor variable on the survivor function. As the value of the predictor increases, the hazard of event occurrence increases. Any violations of the proportional hazards assumption call for the consideration of utilizing extensions of the Cox PH Model, namely, the stratified Cox Model, or the extended Cox Model. The decision to use an extension of the Cox PH Model comes from an iterative process of model building and testing model assumptions.

There are three primary assumptions for the Cox model: 1) proportional hazards assumption, 2) linearity assumption, and 3) additivity assumption. The proportional hazards assumption refers to the assumption that the effect of a predictor variable is constant across all values of time, meaning that the hazard ratio of a variable does not vary with time. The linearity assumption refers to continuous variables, when a single analytic unit is used, addressing that the shape of the relationship between continuous predictor variables and the log of the hazard should be a straight line. The assumption of additivity addresses that joint effects of the predictors should equal the sum of their individual effects (multiplicative interaction). When the latter assumption is not met, an interaction term can be added to the regression model.

Power. A power estimation was not computed in order to inform sample size as the sample size was limited by a designated retrospective study time frame. In a survival analysis, power considerations are related to the number of events in a sample, rather than the number of

subjects (Bradburn, Clark, Love, & Altman, 2003; Hosmer et al., 2008). Vittinghoff and McCulloch (2007) reported that, while 10 events per covariate have been considered the rule of thumb in regression models for adequate power and model stability, similar model stability and adequate power can be achieved with 5-9 events per covariate. Consideration was given to the number of events per covariate, and the limitations of this approach are reported in the discussion section. Moreover, confidence intervals were also reported for hazard ratios to garner information on power estimates and model stability (Hosmer et al., 2008)

Preliminary Findings and Statistical Methods for Hypotheses

Prior to the description of the analysis approach for each hypothesis, a brief summary of preliminary analyses are presented. Preliminary analyses yielded findings that informed inclusion and exclusion changes prior to testing hypotheses. After preliminary findings are reported, the analytic approach for each hypothesis is further described. All results of hypothesis testing are provided in Chapter IV.

Preliminary findings. Preliminary analyses identified an interaction between any sleep disorder and non-compliance with transplant medications (Figures 1 and 2). Despite similar proportions of the number of non-compliant patients in those with any sleep disorder (13%) compared to those without any sleep disorder (14%), χ^2=.062, df=1, p=.803; a difference was detected among the survival times between patients with any sleep disorder and those without, based on the level of non-compliance (yes or no). A graphical analysis of Kaplan Meier curves revealed that, among the sample of compliant patients (Figure 1), graft survival times were similar for those with, versus without, any sleep disorder (n=299). However, in the subset of non-compliant patients (Figure 2), those with any sleep disorder had better survival compared to

those without any sleep disorder (n=68). Figures 1 and 2 indicate there was an interaction between non-compliance with transplant medications and any sleep disorder.

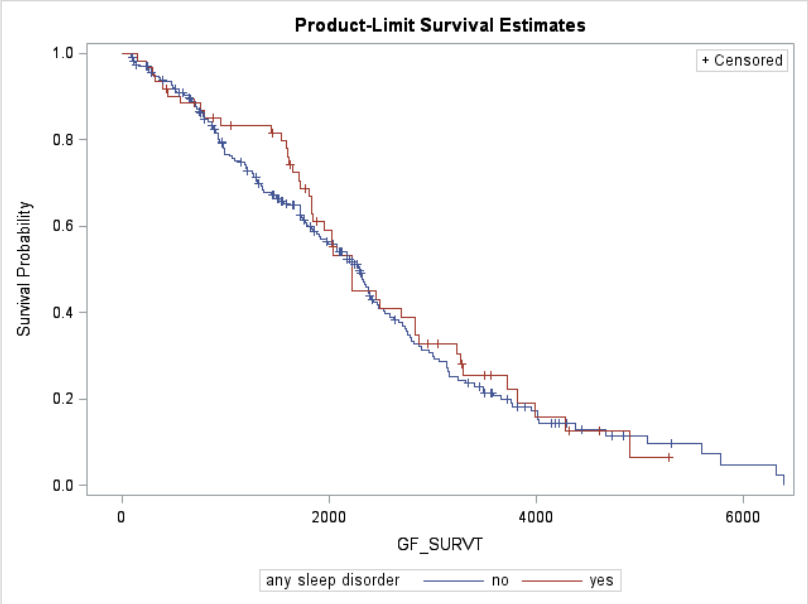

Figure 1. Graft Survival Time for Compliant Patients with and without Any Sleep Disorder

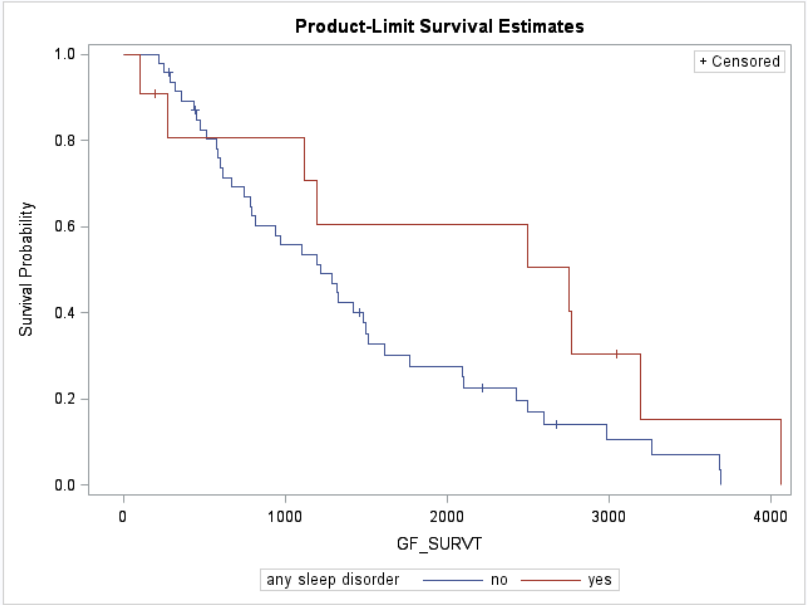

Figure 2. Graft Survival Time for Non-Compliant Patients with and without Any Sleep Disorder

After consideration of this interaction, it was determined that there was not a large enough sample of non-compliant patients (n=68) to conduct stratified analyses and that non-compliant patients should be excluded from analyses. In addition, non-compliance is a known cause of early graft failure (Butler et al., 2004), and it had been included in the study as a control variable. Thus, the decision to exclude non-compliant patients from all analyses was made prior to hypothesis testing. Sixty-eight non-compliant subjects were removed from all analyses. Analyses for descriptive statistics and all hypothesis testing was thus carried out on the remaining 299 (of 367) subjects.

Hypothesis 1 Approach: Chi-Square Test Comparing Proportions

Hypothesis 1a: Of patients with graft failure, patients with any diagnosed sleep disorder have a statistically significantly higher proportion of graft failure due to death (compared to graft failure and return to dialysis) than patients without any diagnosed sleep disorder.

Analytic approach. The approach for hypothesis 1a involved using Chi-square statistics to compare the proportion of death with a functioning graft in subjects with any sleep disorder and those without a sleep disorder. Two considerations were given to death with a functioning graft. First a chi-square test was used to compare the proportion of all-cause death with a functioning graft among the group of subjects with any sleep disorder and those without a sleep disorder. Then, using only subjects who died with a functioning graft, a comparison of the proportions for non-cardiovascular related death with a functioning graft, and cardiovascular (CVD) related death with a functioning graft among the any sleep disorder and non-sleep disorder group was made. This determination was made because CVD related death with a functioning graft has been found to be the most common cause of death in kidney transplant patients and may be related to end-stage renal disease (Jardine, Gaston, Fellstrom, & Holdaas,

2011; Ojo et al., 2000). In addition, sleep disturbances are often associated with a higher risk of CVD (Hoevenaar-Blom, Spijkerman, Kromhout, van den Berg, & Vershuren, 2011; Somers et al., 2008). Thus, comparing the proportion of CVD related death among those with and without sleep disorders was considered relevant in a sample of kidney transplant recipients.

Additionally, comparing the proportion of death with a functioning graft among subjects with any sleep disorder and those without any sleep disorder was also meant to inform the analytic approach for hypothesis 2, which involved examining the association between sleep disorders and graft survival time. In kidney transplant recipients, a subject's end of graft survival time can occur through one of two ways: 1) death with a functioning graft or 2) graft failure while the subject is still living (thereby resulting in the return to dialysis). Determining whether to consider death with a functioning graft as an endpoint of graft survival time or as a censored observation (a competing risk) was necessary in order to test hypothesis 2. In the transplant literature, there is no determined consensus on how to define the end of graft survival time. However, clearly defining events and censored observations is important in every survival analysis (Hosmer et al., 2008). Additionally, when determining censoring approaches, an important assumption in a survival analysis is that censoring is independent or non-informative; if this assumption is violated, this can introduce bias into the results of the Kaplan Meier estimator and the Cox regression (Allison, 2010; Hosmer et al., 2008). In our study, comparing the proportion of death with a functioning graft in subjects with any sleep disorder and those without a sleep disorder, was necessary to inform whether censoring death with a functioning graft could be considered informative censoring. If subjects with any sleep disorder have a statistically significant higher proportion of death with a functioning graft compared to those without any sleep disorder, then censoring death with a functioning graft may bias survival

outcomes. In that instance, death with a functioning graft should not be censored, and a competing risks model should be considered.

Sub-hypothesis 1b. Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have a statistically significantly higher proportion of graft failure due to death (compared to graft failure and return to dialysis) than patients without a diagnosed sleep-disordered breathing disorder.

Analytic approach. Sub-hypothesis 1b followed the same analysis plan outlined for hypothesis 1a. However, the independent variable was patients with a sleep-disordered breathing disorder, instead of any sleep disorder.

Hypothesis 2 Approach: Survival Analysis

Hypothesis 2a: Of patients with graft failure, patients with any diagnosed sleep disorder have statistically significantly shorter graft survival times than patients without any diagnosed sleep disorder, even after adjustment for potential confounders.

Analytic approach. Hypothesis 2a was evaluated through a process of calculating Kaplan Meier survival curves, which examined univariate analyses of covariates to graft survival time, followed by a multivariate stratified Cox regression model. The Cox model, stratified by year of transplant surgery, examined the association between any sleep disorder and graft survival time while controlling for key covariates.

Censoring. The subject selection criteria in this study involved only patients with a failed graft or those who died with a functioning graft. Therefore, the only consideration for censoring involved subjects who died with a functioning graft, thereby resulting in the designation of graft failure.

As stated previously, hypothesis 1 was meant to help inform the censoring decision for the graft survival time outcome. After comparing the proportion of death with a functioning graft (both all-cause death and a comparison of cardiovascular (CVD) related death and non-CVD related death), neither all-cause death nor specifically CVD related death with a functioning graft was associated with any sleep disorder. Thus, death with a functioning graft could be considered in the censoring determination.

Consideration was then given as to whether excluding all-cause death with a functioning graft or if only excluding non-cardiovascular (CVD) related death with a functioning graft would be more appropriate. Kidney transplant recipients are at increased risk for CVD related mortality compared to the general population, due to the overlap of disease etiologies in end-stage renal disease. Moreover, CVD related death with a functioning graft may also be related to the decreased functioning of the transplanted kidney (Holme et al., 2013; Jardine et al., 2011; Meier-Kriesche, Balgia, & Kaplan, 2003). Therefore, in defining the censoring approach, rather than censoring all-cause death with a functioning graft, a decision was made to censor only non-CVD related deaths with a functioning graft. The inclusion of CVD related death with a functioning graft as event (endpoint of graft survival time) acknowledges the potential for competing risks in graft failure, an important consideration in transplant graft survival studies (Holme et al., 2013). Graft survival time was operationally defined as graft loss and return to dialysis or CVD related death with a functioning graft.

After defining the censoring approach (non-cardiovascular death with a functioning graft), consideration was also given to whether any of the identified study covariates may be associated with censoring. Although this was previously addressed for the primary independent variable, any sleep disorder, in hypothesis 1, analyses were also conducted to assess covariate

associations regarding the chosen censoring approach. This was examined by comparing the proportion censoring among the levels of categorical variables, and comparing the means of continuous variables for censored observations. This information is summarized in Appendix C. Four covariates were identified as being associated with the censoring approach: recipient age, diabetes, tobacco pack-years, and stroke history, and will be further addressed in the multivariate modeling process.

Survival curves. Kaplan Meier curves were computed to compare survival time between subjects with any sleep disorder versus those without any sleep disorder. The Log-Rank test was used to summarize the difference in survival curves. Univariate analyses between the independent variable and all identified covariates to graft survival time were computed. Univariate analyses describe the association between one predictor variable to survival time without taking into account the impact of any other variables (Bradburn et al., 2003). The following variables were included in the univariate analyses: any sleep disorder, age, education level, race, gender, body mass index, smoking history, tobacco pack-years, functionality, diabetes, dyslipidemia, coronary artery disease, heart attack, peripheral vascular disease, stroke history, heart attack history, donor age, donor type, human leukocyte antigen mismatch, end-stage renal disease etiology, and year of transplant surgery.

Stratification. Prior to starting the covariate selection process in the multivariate model, two-way interactions were assessed for all study covariates at the $p \leq .05$ level. A statistically significant interaction was found between transplant year and any sleep disorder ($p=.002$). The decision to run a Cox Model, stratified by year of transplant surgery, was determined based on the interaction between year of transplant surgery, and the variable, any sleep disorder. In addition, the variable, year of transplant surgery, violated the proportional hazards assumption of

the Cox model (Appendix D). Thus, in addition to recognizing the heterogeneity between two time periods, the stratification of this variable amends this proportional hazards violation. Strata for this variable included two periods of transplant surgery, 1997-2008 and 2009-2015.

Designation of year of transplant strata was determined through subject matter expertise. Consideration was given to any relevant changes in the transplant field or specifically at the Sentara Norfolk General Hospital (SNGH) transplant center that may have occurred throughout the study time frame (1997-2015). Advances in surgical techniques, immunosuppressant medications, and changes in the allocation policy were considered. No known national surgical advances or relevant changes in the organ allocation policy were noted during the study time period; however, two center specific considerations were given when determining strata. First, a notable change in the quality of the transplant center's medical records was noted. In 2009, the SNGH transplant center began using an electronic medical record, and because some study variables were abstracted from the two sources of records, this was determined relevant to the study; and thus, informed the strata designation. The second change that was given consideration in strata designation was the use of the medication, Prograf, which began in 2000 at the SNGH center. Prograf is considered to be a stronger immunosuppressant medication compared to those medications of the past, and since the approval of Prograf in the United States, there have been decreases in acute rejection (Knoll, 2008). Given the improvement in graft survival associated with Prograf, initially this change was accounted for in the stratification through the creation of three strata: 1997-2000, 2001-2008, and 2009-2015. However, there were no noted survival differences between the Pre-Prograf era (1997-2000) and Post-Prograf era (2001-2008), likely this was due to the short time frame involved in the study prior to the use of Prograf. Therefore, the decision was made to collapse the strata 1997-2000 and 2001-2008.

Thus, the final strata remained 1997-2008 and 2009-2015. After making a decision to stratify analyses, Kaplan Meier curves were recomputed for each strata.

Cox regression. In the multivariate modeling process, backward elimination was utilized as the covariate selection method to develop a final model. Variables that were not significant ($p \leq .05$) and did not have a confounding effect on the main variable of interest, any sleep disorder, were removed individually until none of the remaining variables in the model met the specified significance level for removal ($p \leq .05$). Variables were removed from the model in the following order: body mass index, education level, coronary artery disease, heart attack history, peripheral vascular disease, smoking history, donor type, diabetes, end-stage renal disease etiology, dyslipidemia and donor age.

Prior to selecting a final model, consideration was given to the potential for informative censoring and how this may bias the study findings (Appendix C). The variable, stroke history, remained statistically significant in the final model predicting better graft survival. However, due to a statistically significant higher proportion of censoring in subjects with a stroke history ($\chi^2=7.7065$, df=1, $p \leq .01$), the decision to remove the variable stroke history from the multivariate model was made. There was no significant interaction between stroke and any sleep disorder with regard to the outcome. Collinearity was also assessed prior to accepting a final model (Appendix E). There was a high correlation between the variable race and human leukocyte antigen (HLA) mismatch. The variable HLA mismatch was selected to remain in the final model based on the literature citing that racial differences in kidney transplant graft survival may be related to immunology differences among different ethnicities (Chakkera et al., 2005; Gordon et al., 2010). In consideration of the literature, HLA mismatch is a more representative

measure of immunology. Thus, the variable, HLA mismatch, remained in the final model and race was removed.

After the completion of the covariate selection process, the final variables remaining in the model were: any sleep disorder, year of transplant surgery, recipient age at the time of transplant, functional status, human leukocyte antigen mismatch, and gender. Due to the potential bias of any one covariate selection method (Burnham & Anderson, 2002), the best subset covariate selection method was also utilized to verify agreement between the selected covariates based on more than one covariate selection method. Best subset selection in SAS, is an automated covariate selection method that is based on an algorithm developed by Furnival and Wilson (1974) that compares many combination of variables and selects the best subset of models according to goodness-of-fit criteria. A best subset regression was computed in SAS and presented the ten best subsets. The group of covariates that were determined through the backward elimination process were also presented in the list of potential models determined through the best subset covariate selection process.

Prior to acceptance of the final model, model assumptions were assessed. The proportional hazards assumption was first assessed graphically through transformed cumulative martingale residuals. However, because graphical analyses can be somewhat subjective, an interaction with time was also computed for all variables in the final model. The linearity assumption was assessed through graphs of functional form for continuous variables. Additivity was previously assessed by evaluating interaction terms among predictors prior to development of a final model.

Sub-hypothesis 2b. Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have statistically significantly shorter graft survival times than

patients without a diagnosed sleep-disordered breathing disorder, even after adjustment for potential confounders.

Analytic approach. Sub-hypothesis 2b followed the same analysis plan outlined for hypothesis 2a. However, the independent variable was patients with a sleep-disordered breathing disorder, instead of any sleep disorder.

Hypothesis 3 Approach: Survival Analysis

Hypothesis 3a: Of those with graft failure, patients with any diagnosed sleep disorder have a statistically significantly higher total death hazard after graft failure than patients without any diagnosed sleep disorder, even after adjustment for potential confounders.

Analytic approach. Hypothesis 3 was evaluated through the following: examination of a Kaplan Meier survival curve, univariate analyses of covariates to patient survival time after graft failure, and a multivariate Cox Regression model to test the association between any sleep disorder and patient survival time after graft failure. Survival time after graft failure signified that only patients who experienced graft failure and continued to live were included in this model. Thus, subjects who died with a functioning graft were not included in analyses.

Censoring. Any subjects lost to follow-up or subjects who were still living at the end of the designated study time frame (September 1, 2015) were censored. Consideration of informative censoring was given as to whether subjects lost to follow-up may be different than those not lost to follow-up. Patients were likely to maintain follow-up records if they were re-transplanted at the SNGH transplant center and receiving care for a subsequent transplant or if they received any type of medical care from the hospital system (Sentara) which relies on a shared medical record among all Sentara facilities. Although re-transplanted patients may indicate a healthier sub-group of the population (compared to those patients who may not have

been medically cleared for a second transplant), due to the added ability to capture follow-up time through use of a Sentara facility, and, given the widespread presence of Sentara healthcare systems in the Virginia area, there was a high likelihood that patients may follow at a Sentara facility for their non-transplant care. Thus, while the potential bias of the censoring approach could not entirely be ascertained, it was thought that the defined censoring mechanism was likely random (non-informative), indicating no concern for bias.

Survival curves. Kaplan Meier curves were computed comparing patient survival time between those with any sleep disorder and those without a sleep disorder. The Log-Rank test was used to compare differences between the two curves. Univariate measures of predictors to patient survival time were computed. Several study covariates outlined in Table 1 were not included in hypothesis 3 due to their lack of relevance to the outcome of patient survival after graft failure. This was determined through subject matter expertise and previous research (Gill et al., 2002). Transplant related variables including donor type, human leukocyte antigen mismatch, and age of donor, were removed because they are not related to patient survival after graft failure. Thus, the full subset of variables modeled included: any sleep disorder, age, education level, race, gender, body mass index, smoking history, pack-years, functionality, diabetes, coronary artery disease, peripheral vascular disease, stroke history, heart attack history, end-stage renal disease etiology, and year of transplant surgery.

Cox regression. Prior to starting the covariate selection process in the multivariate model, assessment for statistically significant two way interactions were computed between all study covariates at the $p \leq .05$ level. A highly significant and clinically relevant interaction between recipient age and functional status ($p=.003$) was found, and the interaction term was included in the covariate selection process. An interaction term between year of transplant surgery period

and any sleep disorder was not significant (p=.994), but it could not be assessed due to the small number of events in 2009-2015. Thus, the Cox regression was not stratified by year of transplant surgery. Year of transplant surgery was included in the model (at the start of the backward elimination process) in order to obtain its main effect.

Backward elimination was utilized as the covariate selection method. Variables that were not significant ($p \leq .05$) and did not have a confounding effect on the main variable of interest, any sleep disorder, were removed individually until none of the remaining variables in the model met the specified significance level for removal. Variables were removed from the model in the following order: education level, body mass index, smoking history, year of transplant surgery, heart attack history, diabetes, race, coronary artery disease, gender, stroke history, and peripheral vascular disease. The variable, dyslipidemia, remained significant throughout the covariate selection process, but it was excluded in the final multivariate model after further insight from transplant nephrologists on the limitations of this variable in its abstraction as a dichotomous variable (yes or no) without treatment considerations. After the completion of the covariate selection process, the final variables remaining in the model were: any sleep disorder, recipient age, functional status, and end stage renal disease etiology. Due to the potential bias of any one covariate selection method (Burnham & Anderson, 2002), the best subset covariate selection method was also utilized to verify agreement between the selected covariates based on more than one covariate selection methods. A best subset regression was computed in SAS and presented the ten best subsets of variables according to a goodness-of-fit criteria. The group of covariates that were determined through the backward elimination process were also presented in the list of potential models determined through the best subset covariate selection process.

Prior to accepting a final model, model assumptions were assessed. The proportional hazards assumption was assessed graphically through transformed cumulative martingale residuals and through computing an interaction with time for each variable in included in the final model. The linearity assumption was assessed through graphs of functional form for continuous variables. Additivity was previously assessed by looking for interaction terms among predictors prior to development of a final model, which in included the age and functional status interaction. Functional status refers to the subjects reported functional status at the time of transplant.

Sub-hypothesis 3b. Of those with graft failure, patients with a diagnosed sleep-disordered breathing disorder have a statistically significantly higher total death hazard after graft failure than patients without a diagnosed sleep-disordered breathing disorder, even after adjustment for potential confounders.

Analytic approach. Sub-hypothesis 3b followed the same analysis plan outlined for hypothesis 3a. However, the independent variable was patients with a sleep-disordered breathing disorder, instead of any sleep disorder.

CHAPTER IV

RESULTS

This chapter begins with a summary of descriptive statistics and group comparisons between patients with any sleep disorder and those without any sleep disorder. Following descriptive summaries, the results of the evaluation of each main hypothesis (1a-3a) related to any sleep disorder are presented. The results for sub-hypotheses (1b-3b) related to sleep-disordered breathing disorders were very similar to findings for the main hypotheses (related to any sleep disorder), due to sleep-disordered breathing disorders accounting for 85% of the sleep disorders in the present cohort. Thus, it is likely that sleep-disordered breathing disorders were driving the findings of the main hypotheses (any sleep disorder).

The results of the main hypotheses (any sleep disorder) are presented and summarized. Following the presentation of results for all main hypotheses, the results for the sub-hypotheses (sleep-disordered breathing disorders) are presented.

Descriptive Statistics

At the outset of the study, 367 subjects satisfied inclusion criteria. However, as previously addressed in Figures 1 and 2, after removing non-compliant patients from the cohort, the final cohort consisted of 299 subjects. Tables 2 and 3 summarize the descriptive data of the study sample, consisting of patients compliant with their immunosuppressant medications, who were transplanted and experienced graft failure and/or died with a functioning graft during the designated study time frame (January 1, 1997 to September 1, 2015, inclusive). The study sample consisted of a hypertensive (100%) and predominantly African American end-stage renal disease patient population (64%). Subjects ranged in age from 18-76 years at the time of transplant, and the mean age reported at the time of transplant was approximately 50 years. Of the sample, 20% had a diagnosed sleep disorder that was documented prior to graft failure.

Table 2.
Descriptive Statistics for Categorical Variables in the Sample

Variable	Frequency	n	Percentage
Sleep Disorders			
Any Sleep Disorder	61	299	20%
No Sleep Disorder	238	299	80%
Transplant Recipient Variables			
Female	132	299	44%
Male	167	299	56%
African American	190	299	64%
Caucasian	104	299	36%
Education Level (high school or below)	139	299	46.5%
Education Level (beyond high school)	136	299	45.5%
Education Level (unknown)	24	299	8%
ESRD Etiology (hypertensive)	114	299	38%
ESRD Etiology (other)	185	299	62%
Smoking History (yes)	131	298	44%
Functional Status (full)	153	299	51%
Hypertension (yes)	299	299	100%
Diabetes (yes)	183	299	61%
Dyslipidemia (yes)	222	299	75%
Coronary Artery Disease (yes)	69	299	23%
Stroke History (yes)	57	299	19%
Peripheral Vascular Disease (yes)	29	299	9.7%
Heart Attack History (yes)	21	299	7%
Transplant Variables			
Deceased Donor Transplant	173	299	58%
Living Donor Transplant	126	299	42%

Abbreviations: ESRD, end-stage renal disease

Table 3.
Descriptive Statistics for Continuous Variables in the Sample

Variable	n	Mean (range)
Age of Recipient (years)	299	49.78 (18-76)
Age of Donor (years)	299	39.72 (2-73)
Tobacco Pack-Years (years)	251	7.02 (0-96)
BMI (kg/m^2)	299	28.36 (16.27-54.01)
HLA Mismatch Score (0-6)	299	3.54 (0-6)

Abbreviations: BMI, body mass index; HLA, human leukocyte antigen

Table 4 summarizes the prevalence of all abstracted diagnosed sleep disorders, categorized by type of sleep disorder diagnosis. Three classifications of sleep disorders were abstracted from the medical record: insomnia, periodic limb movement disorders, and sleep apnea (a classification of a sleep-disordered breathing disorder). The total number of subjects with any sleep disorder in the sample (n=61) is less than the sum of the sleep disorders in Table 4 due to some patients having co-occurring sleep disorders, often sleep apnea and insomnia. Of those subjects with a diagnosed sleep disorder, 52 out of 61 subjects were diagnosed with sleep apnea (85%). Given the high prevalence of sleep apnea among those with diagnosed sleep disorders, the sub-hypotheses related to sleep-disordered breathing disorders (sleep apnea) yielded similar findings to the hypotheses related to any sleep disorders.

Table 4.
Frequency of Diagnosed Sleep Disorders in the Sample (n=299)

Sleep Disorder	Frequency	n	Percentage
Any Sleep Disorder	61	299	20%
Sleep Apnea	52	299	17%
Insomnia	8	299	3%
Periodic Limb Movement Disorders	5	299	2%

Summary Statistics for Group Differences

A chi-square test was used to compare categorical variables to determine whether differences existed between patients with any sleep disorder and patients without any sleep disorder. An independent t-test was used to compare group differences among continuous variables. Table 5 is a summary of group differences between categorical variables, and Table 6 is a summary of group differences between continuous variables. Tables 5 and 6 identify that

patients with any sleep disorder had a statistically significant higher prevalence of diabetes, a higher body mass index, and were more likely to have limited functionality (as reported on a Karnofsky scale) relative to those without any sleep disorder. The variable, year of transplant surgery also differed among those with and without any sleep disorder, indicating that subjects with any sleep disorder, versus those without any sleep disorder were more likely to have had a more recent transplant.

Table 5.
Any Sleep Disorder versus No Sleep Disorder by Categorical Variables

	Any Sleep Disorder (n=61)	**No Sleep Disorder** (n=238)	χ^2	**DF**	**P-Value**
Gender Male *(versus female)*	64% (39)	54% (128)	2.030	1	.154
Race African American *(versus Caucasian)*	62% (38)	67% (152)	.466	1	.494
Education high school or below (*versus beyond high school, or unknown)*	41% (25)	48% (114)	2.672	2	.262
Smoking History yes (*versus no*)	45% (28)	44% (103)	.117	1	.731
Diabetes Yes *(versus no)*	77% (47)	57% (136)	8.103	1	.004*
Hypertension yes *(versus no)*	100% (61)	100% (238)		1	NA
Dyslipidemia yes *(versus no)*	82% (50)	72% (172)	2.389	1	.122
Peripheral Vascular Disease yes *(versus no)*	13% (8)	8% (21)	1.021	1	.312

Table 5. (continued)

	Any Sleep Disorder (n=61)	**No Sleep Disorder** (n=238)	**χ^2**	**DF**	**P-Value**
Coronary Artery Disease yes *(versus no)*	25% (15)	23% (54)	.099	1	.753
Stroke History yes *(versus no)*	18% (11)	19% (46)	.053	1	.818
Heart Attack History yes *(versus no)*	7% (4)	7% (17)	.023	1	.873
Donor Type deceased donor *(versus living donor)*	51% (31)	60% (142)	1.558	1	.212
Functional Status full *(versus limited)*	36% (22)	55% (131)	6.998	1	.008*
ESRD Etiology hypertensive *(versus other)*	34% (21)	39% (93)	.445	1	.504
Year of Transplant Strata 1997-2008 *(versus 2009-2015)*	82% (50)	91% (216)	3.820	1	.051*

Abbreviations: ESRD, end-stage renal disease
* Significant at the $p \leq .05$ level

Table 6.

Any Sleep Disorder versus No Sleep Disorder by Continuous Variables

	Any Sleep Disorder (n=61)	**No Sleep Disorder (n=238)**	**t**	**DF**	**P-Value**
	Mean	**Mean**			
Body Mass Index (kg/m^2)	31.39	27.59	5.08	297	.000*
HLA Mismatch (0-6)	3.59	3.53	.22	297	.828
Recipient Age (years)	50.74	49.54	.67	297	.501
Donor Age (years)	38.87	39.93	.49	297	.625
Pack-years (tobacco)	8.09	6.73	.06	249	.551
Year of Transplant	2005	2003	3.51	297	.001*

Abbreviations: HLA mismatch, human leukocyte antigen mismatch
* Significant at the $p \leq .05$ level

Results of Hypothesis 1a: Death with a Functioning Graft

Hypothesis 1a: Of patients with graft failure, patients with any diagnosed sleep disorder have a statistically significantly higher proportion of graft failure due to death (compared to graft failure and return to dialysis) than patients without any diagnosed sleep disorder.

Results of hypothesis 1a are summarized in Table 7. The prevalence rates of subjects who experienced death with a functioning graft in the any sleep disorder group and the non-sleep disorder group were found to be virtually the same (44% vs 45%, respectively, p=.94). Patients with any sleep disorder had a higher proportion of cardiovascular (CVD) related death with a functioning graft (37%) compared to those without any sleep disorder (25%), but this difference was not found to be statistically significant (p=.19).

Table 7.
Proportions of Death with a Functioning Graft in Patients with Any Sleep Disorder Compared to Patients without Any Sleep Disorder

Death with a Functioning Graft	**Any Sleep Disorder** (n=61)	**No Sleep Disorder** (n=237)	**Chi-Square**	**DF**	**P-value**
All-Cause Death	44% (27/61)	45% (106/237)	.004	1	.945
	Any Sleep Disorder (n=27)	**No Sleep Disorder** (n=106)			
CVD Related Death	37% (10/27)	25% (26/106)	1.706	1	.192
Non-CVD Related Death	63% (17/27)	75% (80/106)			

Abbreviations: CVD, cardiovascular disease

Results of Hypothesis 2a: Graft Survival Time

Hypothesis 2a: Of patients with graft failure, patients with any diagnosed sleep disorder have statistically significantly shorter graft survival times than patients without any diagnosed sleep disorder, even after adjustment for potential confounders.

Hypothesis 2 tested the relationship between any sleep disorder and graft survival time, which was operationally defined as graft failure or cardiovascular (CVD) related death with a functioning graft. Univariate analyses and bivariate Kaplan Meier curves are presented prior the multivariate stratified Cox regression. Although 299 patients were included in the final sample, data on graft survival time was available for 297 patients. Univariate and multivariate models consisted of 297 patients as the sample size to examine hypothesis 2. As previously outlined, subjects were considered censored if they experienced non-CVD related death with a functioning graft.

Table 8 is a summary of the univariate hazard ratio of each predictor variable to the dependent variable, graft survival time. The univariate analyses are considered preliminary analyses for a multivariate Cox Regression; therefore, its results are not stratified. The sample size, parameter estimate, hazard ratio, 95% confidence intervals for each hazard ratio, and statistical significance are reported. Approximately 32% of the subjects were censored when evaluating hypothesis 2. At the univariate level, statistically significant variables ($p \leq .05$) associated with graft survival time were: age of recipient, race, gender, dyslipidemia, HLA, and year of transplant surgery. A hazard ratio greater than 1 indicates a higher risk of the hazard of graft failure or cardiovascular (CVD) related death with a functioning graft, identifying shorter graft survival times. A hazard ratio less than 1 identifies variables that are associated with longer graft survival times. Moreover, it is important to consider that some variables with a hazard ratio

less than 1, predicting better survival, may be biased by informative censoring if such variable was also associated with non-CVD related death with a functioning graft (Appendix D). For instance, the univariate hazard ratios presented for diabetes, increased number of pack-years, smoking history, stroke history, diagnosed coronary artery disease, diagnosed peripheral vascular disease, heart attack history, and recipients who are older all predict longer graft survival time. However, all of these variables were associated with higher rates of censoring (non-CVD related death with a functioning graft), as presented in Appendix D.

Table 8.
Univariate Analysis of Each Predictor Variable to Graft Failure or Cardiovascular Related Death with a Functioning Graft (All Non-Cardiovascular Related Deaths are Censored)

Covariates	N	Parameter Estimate	HR	HR CI	P-value
Any Sleep Disorder					
Yes (n=61)	297	-0.071	.93	.66-1.29	.679
No (n=236)			1.00	Referent	
Sleep Apnea					
Yes (n=52)	297	-0.052	.95	.65-1.34	.776
No (n=245)			1.00	Referent	
Age of recipient at time of transplant					
Years (n=297)	297	-0.015	.99	.98-1.00	.010*
Education Level					
High school or below (n=139)	297	-0.113	.89	.67-1.20	.449
Beyond high school (n=135) or unknown (n=23)			1.00	Referent	
Race					
African American (n=189)	297	0.481	1.62	1.21-2.19	.002*
Caucasian (n=108)			1.00	Referent	
Gender					
Male (n=167)	297	0.340	1.41	1.06-1.87	.019*
Female (n=130)			1.00	Referent	

Table 8. (continued)

Covariates	N	Parameter Estimate	HR	HR CI	P-value
Body Mass Index					
Kg/m^2 (n=297)	297	0.025	1.03	1.00-1.05	.077
Smoking History					
Yes (n=131)	296	-0.175	.84	.63-1.11	.224
No (n=165)			1.00	Referent	
Tobacco Pack-Years					
Years (n=249)	249	-0.013	.99	.98-1.00	.010*
Functional Status					
Full (n=151)	297	-0.525	.59	.44-.79	.000*
Limited (n=146)			1.00	Referent	
Diabetes					
Yes (n=181)	297	-0.229	.80	.60-1.06	.112
No (n=116)			1.00	Referent	
Dyslipidemia					
Yes (n=220)	297	-0.526	.59	.43-.82	.001*
No (n=77)			1.00	Referent	
Coronary Artery Disease					
Yes (n=68)	297	-0.292	.75	.52-1.04	.093
No (n=229)			1.00	Referent	
Heart Attack History					
Yes (n=21)	297	-0.378	.69	.37-1.16	.191
No (n=276)			1.00	Referent	
Peripheral Vascular Disease					
Yes (n=29)	297	-0.442	.64	.38-1.03	.083
No (n=268)			1.00	Referent	
Stroke History					
Yes (n=55)	297	-0.406	.67	.44-.97	.044*
No (n=242)			1.00	Referent	
Donor Type					
Living (n=125)	297	-0.136	.87	.66-1.16	.344
Deceased (n=172)			1.00	Referent	

Table 8. (continued)

Covariates	N	Parameter Estimate	HR	HR CI	P-value
Human Leukocyte Antigen Mismatch					
0-6 (n=297)	297	0.158	1.17	1.08-1.28	.000*
Age of donor at the time of transplant				.	
Years (n=297)	297	-0.003	1.00	99-1.01	.590
ESRD Etiology					
Hypertensive (n=113)	297	0.129	1.14	.85-1.51	.374
Other (n=184)			1.00	Referent	
Year of Transplant Surgery					
Years 1997-2015 (n=297)	297	0.165	1.17	1.13-1.24	.000*
Year of Transplant Surgery Strata					
1997-2008 (n=264)	297	-0.894	.41	.25-.70	.001*
2009-2015 (n=33)			1.00	Referent	

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; HR CI, hazard ratio 95% confidence interval
* Significant at the $p \leq .05$ level

Kaplan Meier curves. After univariate analyses were run, Kaplan Meier curves were computed. For the entire follow-up period, the survival curves indicated no statistically significant difference in graft survival time between those with any sleep disorder versus those without (Log-Rank=.17, p=.679). Next, stratification according to two periods for the year of transplant was conducted as follows: Year of Transplant 1997-2008 and Year of Transplant 2009-2015.

Year of Transplant 1997-2008 contained 264 subjects (88.3% of the total sample). The prevalence of any sleep disorder in 1997-2008 was 19%. Table 9 summarizes the total number of censored data and events by sleep disorder category (presence or absence), for Year of Transplant Surgery 1997-2008.

Table 9.
Proportions of Censored Observations for Graft Survival Time According to the Presence and Absence of Any Sleep Disorder for Year of Transplant Surgery 1997-2008

Any Sleep Disorder	Total	Events	Censored	% Censored
Presence	50	36	14	28%
Absence	214	147	67	31%
Total	264	183	81	31%

Figure 3 displays Kaplan Meier curves for Year of Transplant 1997-2008, comparing subjects with any sleep disorder to those without any sleep disorder with regard to graft survival time. Median graft survival times for the group of subjects with any sleep disorder was longer than that for those without a sleep disorder (2,457 days and 2,313 days, respectively). However, this difference was not statistically significant (Log-Rank=1.19, p=.275).

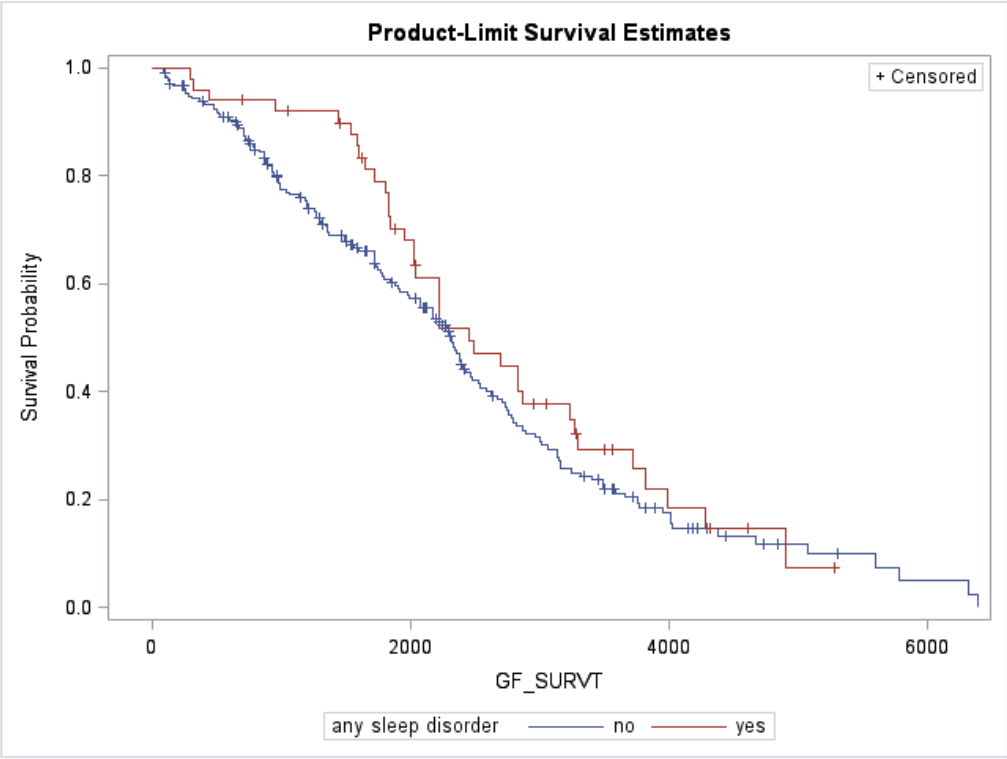

Figure 3. Kaplan Meier Survival Curves for Year of Transplant 1997-2008: Graft Survival Time by Presence and Absence of Any Sleep Disorder

Table 10 summarizes the total number of censored data and events by sleep disorder category (presence or absence), for year of transplant 2009-2015. Data from 33 subjects were analyzed for this stratum. The prevalence of any sleep disorder for those transplanted between 2009-2015 was 33%. The total rate of censoring was higher for those transplanted in 2009-2015 (45%) compared to 1997-2008 (31%), indicating that subjects in 2009-2015 had a higher proportion of death with a functioning graft from non-CVD related causes compared to subjects transplanted in 1997-2008.

Table 10.
Proportions of Censored Observations for Graft Survival Time According to the Presence and Absence of Any Sleep Disorder for Year of Transplant Surgery 2009-2015

Any Sleep Disorder	Total	Events	Censored	% Censored
Presence	11	8	3	27%
Absence	22	10	12	55%
Total	33	18	15	45%

Figure 4 displays Kaplan Meier curves for Year of Transplant 2009-2015, comparing subjects with any sleep disorder to those without a sleep disorder. Median graft survival times for the group of subjects with any sleep disorder was 800 days and that for subjects without any sleep disorder was 1,834 days, indicating that patients with any sleep disorder had shorter graft survival times. This difference in graft survival time between the two groups was statistically significant (Log-Rank=3.82, p=.051).

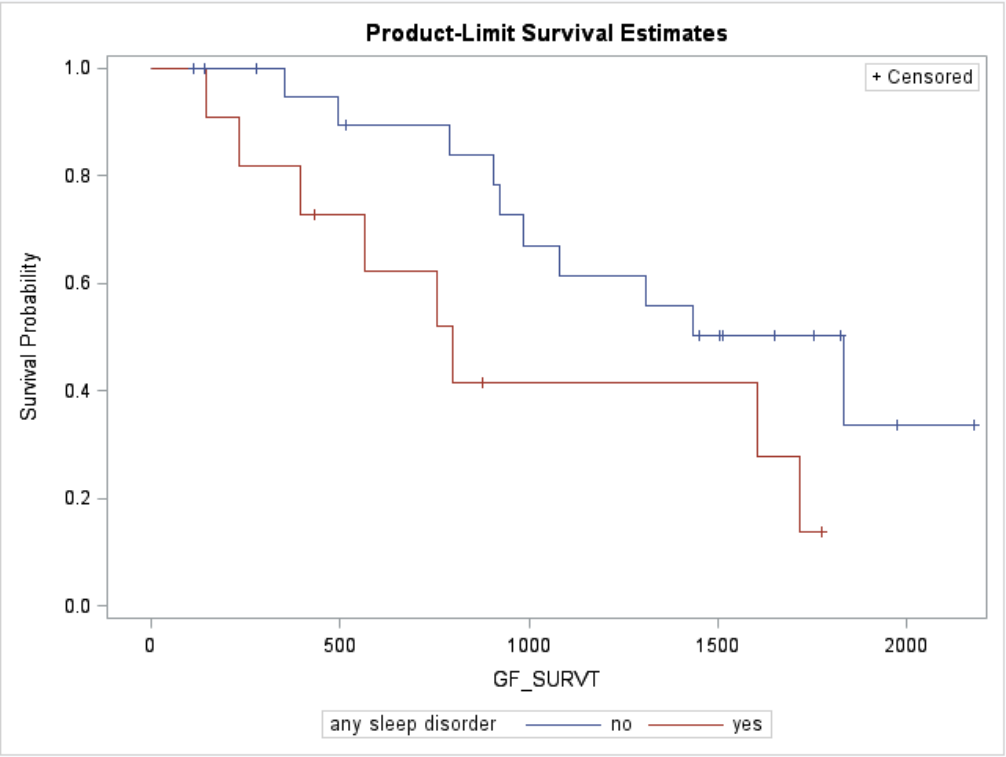

Figure 4. Kaplan Meier Survival Curves for Year of Transplant 2009-2015: Graft Survival Time by Presence and Absence of Any Sleep Disorder

Summary of Kaplan Meier curves. For patients transplanted in 1997-2008 (Figure 3), any sleep disorder was associated with longer graft survival versus no sleep disorder; however, this difference was not statistically significant (Log-Rank=1.19, p=.275). For patients transplanted in 2009-2015 (Figure 4), any sleep disorder was statistically signficantly (Log-Rank=3.82, p=.051) associated with shorter graft survival times relative to no sleep disorder.

Stratified univariate results of any sleep disorder. After computation of stratified Kaplan Meier curves, a stratified univariate analysis of any sleep disorder to graft survival time was computed to estimate the unadjusted hazard ratio of any sleep disorder with graft failure or cardiovascular related death with a functioning graft prior to multivariate testing. Table 11 presents that stratified univariate analysis of any sleep disorder and graft survival time.

Table 11.
Univariate (Unadjusted) Analysis: Association of Any Sleep Disorder with Graft Failure or Cardiovascular Related Death with a Functioning Graft (All Non-Cardiovascular Related Deaths Censored) According to Year of Transplant

Any Sleep Disorder/Year of Transplant	N	Parameter Estimate	HR	HR CI	p-value
Year of Transplant 1997-2008					
Any Sleep Disorder (n=50)	264	-0.204	.82	.57-1.18	.276
No Sleep Disorder (n=214)			1.00	Referent	
Year of Transplant 2009-2015					
Any Sleep Disorder (n=11)	33	0.923	2.53	.97-6.64	.059
No Sleep Disorder (n=22)			1.00	Referent	

Abbreviations: HR, hazard ratio; HR CI, hazard ratio 95% confidence interval
N refers to the sample size for each strata
The hazard ratio refers to the comparison of any sleep disorder versus no sleep disorder

Multivariate results for hypothesis 2a. A multivariate Cox regression was used to estimate the adjusted hazard ratios for the association of any sleep disorder, versus no sleep disorder, with the risk of graft failure or cardiovascular (CVD) related death with a functioning graft, after adjustment of key covariates. Backward elimination was used as the covariate selection process, resulting in the final model presented in Table 12a. Parameter estimates, hazard ratios, 95% confidence intervals, and significance levels are presented for each variable that remained in the final model. Table 12a presents the results of multivariate Cox regression with the statistically significant interaction term ($p \leq .01$) between any sleep disorder and year of transplant strata. The final model is presented below (Table 12a) and reflects an iterative process of model building and verification of model assumptions (Appendix F).

Table 12a.
Results of the Multivariate Cox Regression Model: Interaction of Any Sleep Disorder and Year of Transplant on the Risk of Graft Failure or Cardiovascular Related Death with a Functioning Graft

Predictor	**Parameter Estimate**	**HR**	**HR CI**	**p-value**
Recipient age at time of transplant Years (n=297)	-0.019	.98	.97-.99	.002*
HLA mismatch 0-6 (n=297)	0.149	1.16	1.07-1.27	.001*
Gender				
Male (n=167)	0.371	1.45	1.09-1.94	.011*
Female (n=130)		1.00	Referent	
Functional Status				
Full (n=151)	-0.553	.58	.42-.78	.000*
Limited (n=146)		1.00	Referent	
Year of Transplant Surgery[a]				
1997- 2008 (n=264)				.667
2009-2015 (n=33)				
Any Sleep Disorder[a]				
Yes (n=61)				.0341
No (n=236)				
Any Sleep Disorder*Year of Transplant Interaction Term	1.370			.010*

Abbreviations: HR, hazard ratio; HR CI, hazard ratio 95% confidence interval, HLA, human leukocyte antigen mismatch
Each variable is simultaneously and reciprocally adjusted for all the other variables in the model
a: Main effects of hazard ratios are not reported in the multivariate model and cannot be interpreted in this table given the interaction term, see Table 12b
* Significant at the $p \leq .05$ level

The interaction between any sleep disorder and year of transplant surgery strata was statistically significant with full adjustments ($p \leq .01$). The strata specific adjusted hazard ratios for graft failure or cardiovascular related death with a functioning graft are reported in Table 12b, they are from the same model as presented in Table 12a.

Table 12b.
Adjusted Hazard Ratios for Graft Failure or Cardiovascular Related Death with a Functioning Graft with respect to Any Sleep Disorder Stratified by Year of Transplant

Predictor	N	Parameter Estimate	aHR	HR CI	p-value
Year of Transplant 1997-2008					
Any Sleep Disorder(n=50)	264	-0.316	.73	.50-1.06	.099
No Sleep Disorder (n=214)			1.00	Referent	
Year of Transplant 2009-2015					
Any Sleep Disorder (n=11)	33	1.072	2.92	1.11-7.69	.030*
No Sleep Disorder (n=22)			1.00	Referent	

Abbreviations: aHR, adjusted hazard ratio; HR CI, hazard ratio 95% confidence interval
N refers to the sample size for each strata
For each stratum, the adjusted hazard ratio refers to the comparison of any sleep disorder versus no sleep disorder, adjusted for all other variables in the final model (recipient age, HLA mismatch, functional status, gender)
*Significant at the $p \leq .05$ level

Summary of results for hypothesis 2a: graft failure or cardiovascular related death with a functioning graft. The final model for graft survival time included recipient age, HLA mismatch, gender, functional status, and any sleep disorder. Each hazard ratio presented in Table 12a represents the adjusted hazard ratio for each variable, while controlling for all other variables in the model. Table 12b presents the adjusted hazard ratio for any sleep disorder, versus no sleep disorder, stratified by year of transplant, while adjusting for all variables

included in the final multivariate model presented in Table 12a (recipient age, human leukocyte antigen mismatch, gender, and functional status).

For patients transplanted in 1997-2008, any sleep disorder, was associated with a decreased (albeit non-statistically significantly) risk of graft failure or cardiovascular related death with a functioning graft (adjusted Hazard Ratio (HR) = 0.73, 95% CI, 0.50-1.06) relative to no sleep disorder. However, for patients transplanted in 2009-2015, any sleep disorder was strongly and statistically significantly (p=.03) associated with increased risk of graft failure or cardiovascular related death with a functioning graft (adjusted HR = 2.92, 95% CI, 1.11-7.69), relative to no sleep disorder. Thus, the risk of graft failure or risk of cardiovascular related death with a functioning graft for patients with any sleep disorder transplanted in 2009-2015 was nearly three times the rate of patients without a sleep disorder transplanted in 2009-2015. For the more recent time period of transplant (2009-2015), the null hypothesis was thus rejected for hypothesis 2a.

Results of Hypothesis 3a: Patient Survival after Graft Failure

Hypothesis 3a: Of patients with graft failure, patients with any diagnosed sleep disorder have a statistically significantly higher death hazard after graft failure than patients without any diagnosed sleep disorder, even after adjustment for potential confounders.

Hypothesis 3 was tested regarding the relationship between any sleep disorder and patient survival time after graft failure. Patients who died with a functioning graft (n=133) were not included in the analysis of hypothesis 3, as they did not have any survival time beyond their graft failure. Thus, 164 patients were analyzed to examine patient survival time after graft failure. Patients lost to follow-up or those still living at the end of the study time frame were censored. Approximately two-thirds of the sample were censored in the examination of hypothesis 3

(n=104), indicating a high rate of censoring which can underestimate true survival times. Median patient survival time after graft failure was 3,249 days in the sample.

Table 13 presents the univariate analyses of predictor variables to patient survival time after graft failure. The sample size, parameter estimate, hazard ratio, 95% confidence intervals for hazard ratios, and the significance level are in reported in the table. Several variables that were included in the model testing hypothesis 2 were not included in the model testing hypothesis 3 due to their lack of relevance. Specifically, transplant-related variables such as: donor type, human leukocyte antigen mismatch, and age of donor were removed because they were not related to patient survival after graft failure, and, therefore, univariate analyses are not reported for these variables in Table 13.

At the univariate level, statistically significant ($p \leq .05$) variables associated with patient survival time after graft failure were: age of recipient, coronary artery disease, diabetes, and peripheral vascular disease. A hazard ratio greater than 1 indicates a higher risk of patient death after graft failure, identifying shorter patient survival times. A hazard ratio less than 1 identifies variables that are associated with increased patient survival times.

Table 13.
Univariate (Unadjusted) Analysis of the Association of Each Predictor Variable to Survival after Graft Failure with Censoring of Patients Lost to Follow-Up (N=164)

Covariates	N	Parameter Estimate	HR	HR CI	P-value
Any Sleep Disorder					
Yes (n=34)	164	0.361	1.44	.72-2.65	.272
No (n=130)			1.00	Referent	
Sleep Apnea					
Yes (n=38)	164	0.342	1.41	.67-2.60	.331
No (n=136)			1.00	Referent	

Table 13. (continued)

Covariates	N	Parameter Estimate	HR	HR CI	P-value
Age of recipient at time of transplant					
Years (n=164)	164	0.049	1.05	1.03-1.08	.000*
Body Mass Index					
Kg/m^2 (n=164)	164	0.013	1.01	.96-1.06	.611
Education Level					
High school or below (n=75)	164	0.280	1.32	.77-2.31	.317
Beyond high school (n=77) or unknown (n=12)			1.00	Referent	
Race					
African American (n=113)	164	-0.435	.65	.38-1.15	.126
Caucasian (n=51)			1.00	Referent	
Gender					
Male (n=88)	164	-0.235	.791	.47-1.32	.368
Female (n=76)			1.00	Referent	
Smoking History					
Yes (n=65)	164	0.155	1.17	.69-1.96	.560
No (n=99)			1.00	Referent	
Tobacco Pack-Years					
Years (n=144)	144	0.007	1.01	.98-1.03	.568
Functional Status					
Full (n=91)	164	-0.325	.72	.43-1.23	.224
Limited (n=73)			1.00	Referent	
Diabetes					
Yes (n=87)	164	0.752	2.12	1.25-3.67	.006*
No (n=7)			1.00	Referent	
Dyslipidemia					
Yes (n=117)	164	-0.062	.94	.55-1.67	.826
No (n=47)			1.00	Referent	

Table 13. (continued)

Covariates	N	Parameter Estimate	HR	HR CI	P-value
Coronary Artery Disease					
Yes (n=28)	164	0.819	2.27	1.19-4.06	.008*
No (n=136)			1.00	Referent	
Heart Attack History					
Yes (n=6)	164	0.544	1.72	.42-4.68	.360
No (n=158)			1.00	Referent	
Peripheral Vascular Disease					
Yes (n= 10)	164	1.198	3.31	1.36-6.93	.004*
No (n=154)			1.00	Referent	
Stroke History					
Yes (n=16)	164	0.784	2.19	.96-4.39	.041*
No (n=148)			1.00	Referent	
ESRD Etiology					
Hypertensive (n=63)	164	-0.480	.62	.35-1.06	.089
Other (n=101)			1.00	Referent	
Year of Transplant Surgery					
Years (n=164)	164	-0.015	.99	.92-1.06	.699
Year of Transplant Surgery Strata					
1997-2008 (n=151)	164	-0.519	1.68	.52-10.29	.473
2009-2015 (n=13)			1.00	Referent	

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; HR CI, hazard ratio 95% confidence interval
* Significant at the $p \leq .05$ level

Kaplan Meier Curves. After univariate analyses were run, Kaplan Meier curves were computed comparing patient survival time after graft failure according to the presence of any sleep disorder. Table 14 summarizes the total number of events and censored observations by sleep disorder category (presence or absence). Figure 5 presents Kaplan Meier curves. Median patient survival time after graft failure for patients with any sleep disorder was much shorter

(2,421 days) than that for those without a sleep disorder (3,249 days). Despite this large difference in median patient survival time, the survival curves were not statistically significantly different (Log-Rank=1.22, p=.270).

Table 14.
Proportions of Censored Observations for Patient Survival Time after Graft Failure According to the Presence and Absence of Any Sleep Disorder (N=164)

Any Sleep Disorder	Total	Events	Censored	% Censored
Presence	34	12	22	65%
Absence	130	48	82	63%
Total	164	60	104	63%

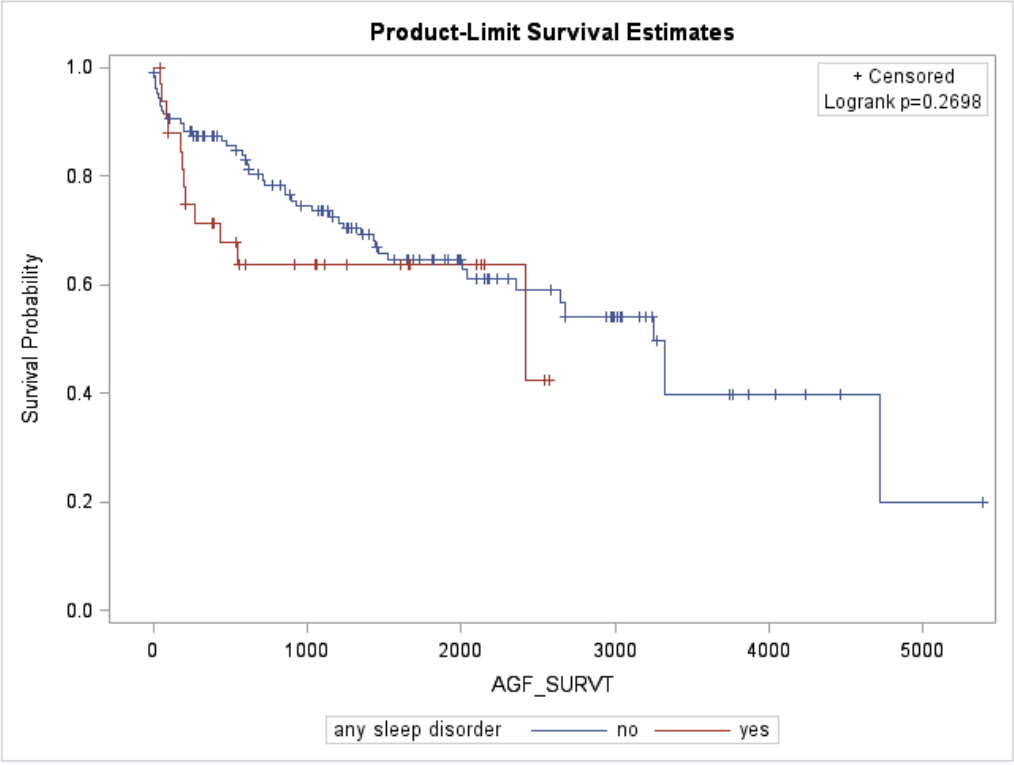

Figure 5. Kaplan Meier Survival Curves for Patient Survival Time after Graft Failure by Presence and Absence of Any Sleep Disorder

Multivariate results for hypothesis 3a. A multivariate Cox regression was used to estimate the hazard ratios for the associations of predictor variables with the risk of patient death after graft failure. Of patients transplanted between 2009-2015, there were no events for any sleep disorder. Thus, this model could not be stratified by year of transplant as we did not find a statistically significant interaction between the variable, year of transplant surgery examined with 2 strata and any sleep disorder (p=.994). The period of transplant surgery (continuously) was included in the backward elimination selection process along with other variables. The final model is presented below and reflects an iterative process of model building and verification of model assumptions (Appendix G).

Table 15.
Results of the Multivariate Cox Regression Model: Association of Any Sleep Disorder with Patient Survival Time after Graft Failure

Predictor	Parameter Estimate	HR	HR CI	P-value
Any Sleep Disorder				
Yes (n=34)	0.032	1.03	.51-1.95	.922
No (n=130)		1.00	Referent	
ESRD Etiology				
Hypertensive (n=63)	-.0567	.57	.31-.99	.051*
Other (n=101)		1.00	Referent	
Recipient Age at Time of Transplant[a]				
Years (n=164)				.000*
Functional Status[a]				
Full (n=91)				.013*
Limited (n=73)				
Age*Functional Status Interaction Term	-0.076			.006*

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; HR CI, hazard ratio 95% confidence interval
Each variable is simultaneously and reciprocally adjusted for all the other variables in the model.
a: Main effects of hazard ratios are not reported in the multivariate model and cannot be interpreted in this table given the interaction term, but will be addressed in the summary section below.
* Significant at the $p \leq .05$ level

Summary of multivariate results for hypothesis 3a. The final model included an end-stage renal disease (ESRD) etiology, any sleep disorder, and an interaction between recipient age and functional status. Each hazard ratio presented in Table 15 represents the adjusted hazard ratio for each variable, while controlling for all other variables in the model. Patients with any sleep disorder had an increase (3%) in the risk of death after graft failure compared to those without a sleep disorder, but this difference was not statistically significant (HR=1.03, 95% CI=.51-1.95, p=.925).

The statistically significant interaction between recipient age and functional status, signified that the risk of death increased as patients with limited functionality aged. Of those with a limited functional status, as age increased the risk of death after graft failure increased by 11% (HR=1.11, 95% CI=1.06-1.12). Of those with no functional limitations (full functional status), as age increased the risk of death after graft failure also remained elevated (HR=1.03, 95% CI=1.00-1.06), but this risk of death in those with a full functional status was lower compared to those with a limited functional status. Figure 6 displays the interaction between recipient age and functional status.

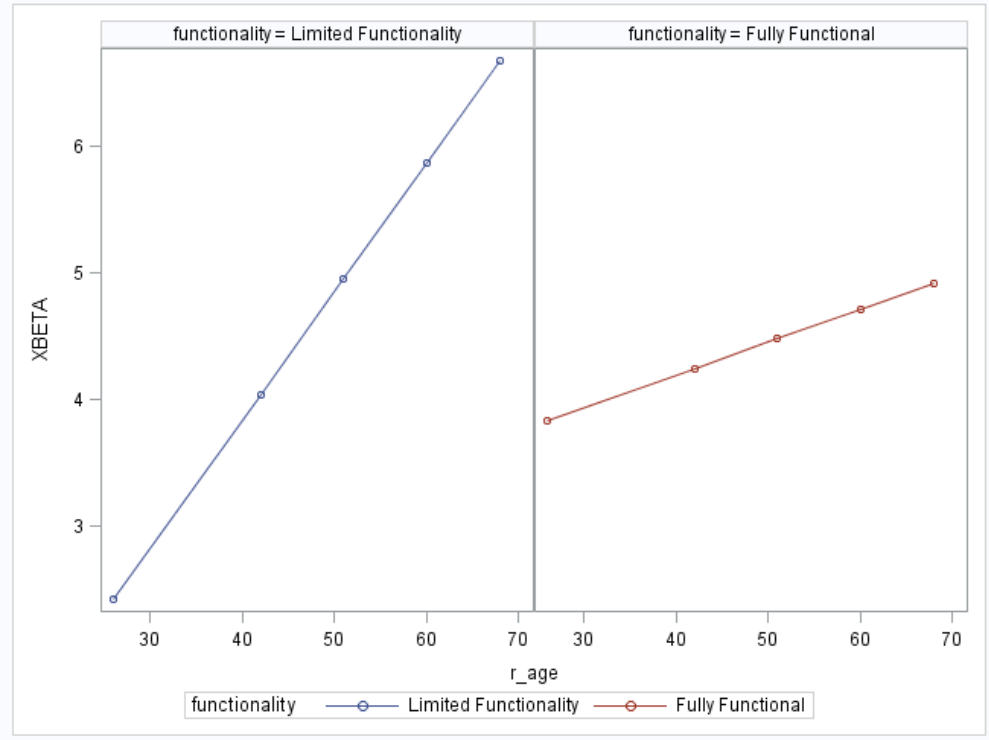

Fig 6: Age and Functional Status Interaction with Regard to Death after Graft Loss

Results of Sub-Hypotheses 1b-3b: Associations of Sleep-Disordered Breathing Disorders to Transplant Outcomes.

The study sub-hypotheses 1b-3b involved examining associations between sleep-disordered breathing disorders (a subset of any sleep disorder) and transplant outcomes. Each sub-hypothesis is stated below, followed by the results. All of the diagnosed sleep-disordered breathing disorders abstracted were classified as sleep apnea (as previously summarized in Table 4), and, thus, for the presentation of the sub-hypothesis results (Tables 16-22 and Figures 7-9), sleep-disordered breathing disorders are henceforth referred to as sleep apnea.

Results of Sub-Hypothesis 1b: Death with a Functioning Graft

Hypothesis 1b: Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have a statistically significantly higher proportion of graft failure due to death (compared to graft failure and return to dialysis) than patients without a diagnosed sleep-disordered breathing diagnosis.

Results of hypothesis 1b are summarized in Table 16. The prevalence rates of subjects who experienced death with a functioning graft in those with sleep apnea and those without sleep apnea were found to be virtually the same (46% vs 44%, respectively, p=.81). Patients with sleep apnea had a higher proportion of cardiovascular related death with a functioning graft (38%) compared to those without sleep apnea (25%), but this difference was not found to be statistically significant (p=.20).

Table 16.
Proportions of Death with a Functioning Graft in Patients with Sleep Apnea Compared to Patients without Sleep Apnea

	Sleep Apnea (n=52)	**No Sleep Apnea** (n=246)	**Chi-Square**	**DF**	**P-value**
All-Cause Death	46% (24/52)	44% (109/246)	.006	1	.808
	Sleep Apnea (n=24)	**No Sleep Apnea** (n=109)	**Chi-Square**	**DF**	**P-value**
CVD Related Death	38% (9/24)	25% (27/109)	1.615	1	.204
Non-CVD Related Death	62% (15/24)	75% (82/109)			

Abbreviations: CVD, cardiovascular disease

Results of Sub- Hypothesis 2b: Graft Survival Time

Hypothesis 2b: Of patients with graft failure, patients with a diagnosed sleep-disordered breathing disorder have statistically significantly shorter graft survival times than patients without a diagnosed sleep-disordered breathing disorder, even after adjustment for potential confounders.

Kaplan Meier Curves. For the entire follow-up period (1997-2015), the Kaplan Meier curves indicated no statistically significant difference in graft survival time between those with sleep apnea versus those without (p=.776). Next, stratification according to two periods for the year of transplant was conducted as follows: Year of Transplant 1997-2008 and Year of Transplant 2009-2015. Table 17 summarizes the total number of censored data and events for Year of Transplant Surgery 1997-2008 by sleep apnea category (presence or absence).

Table 17.
Proportions of Censored Observations for Graft Survival Time According to the Presence and Absence of Sleep Apnea for Year of Transplant Surgery 1997-2008

Sleep Apnea	Total	Events	Censored	% Censored
Presence	41	29	12	29%
Absence	223	154	69	31%
Total	264	183	81	31%

Figure 7 displays Kaplan Meier curves for year of transplant 1997-2008, comparing subjects with sleep apnea to those without sleep apnea. Median graft survival times for the group of subjects with sleep apnea was longer than that for those without sleep apnea (2,699 days and 2,303 days, respectively). However, this difference (Figure 7) was not statistically significant (Log-Rank=.08, p=.277).

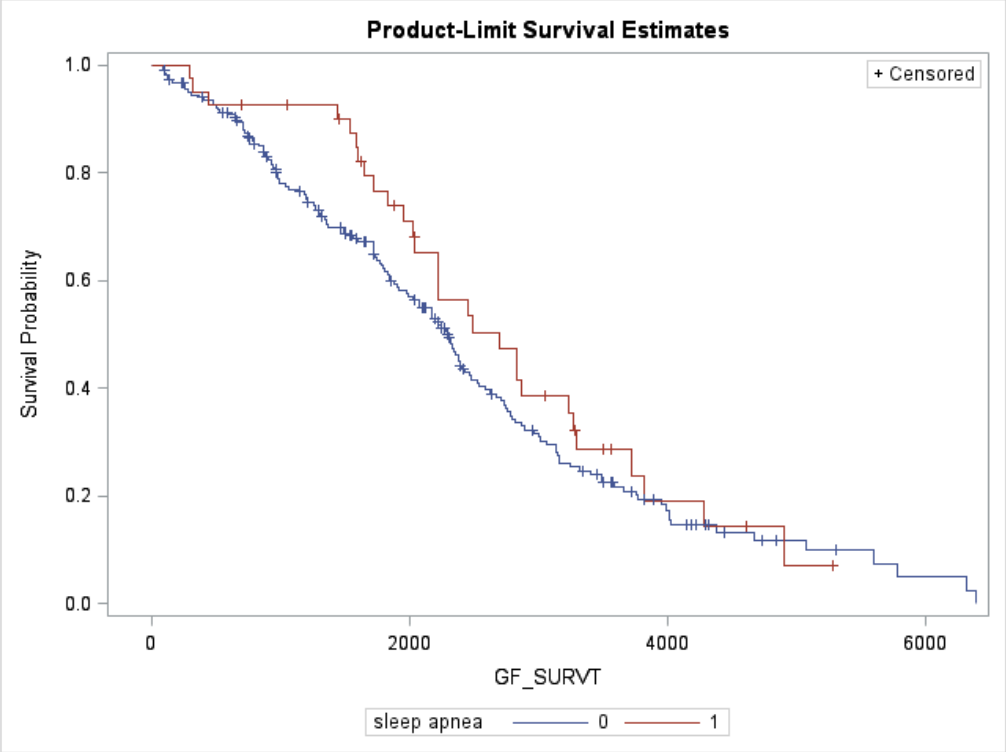

Figure 7. Kaplan Meier Survival Curves for Year of Transplant 1997-2008: Graft Survival Time by Presence and Absence of Sleep Apnea

Table 18 summarizes the total number of censored data and events for year of transplant 2009-2015 by sleep apnea category. Data from 33 subjects were analyzed for this stratum.

Table 18.
Proportions of Censored Observations for Graft Survival Time According to the Presence and Absence of Sleep Apnea for Year of Transplant Surgery 2009-2015

Sleep Apnea	Total	Events	Censored	% Censored
Presence	11	8	3	27%
Absence	22	10	12	55%
Total	33	18	15	45%

Figure 8 displays Kaplan Meier curves for year of transplant 2009-2015, comparing subjects with sleep apnea to those without sleep apnea. Median graft survival times for the group of subjects with sleep apnea was shorter than that for those without sleep apnea (800 days and 1,834 days, respectively). This difference in graft survival time between the two groups (Figure 8) was statistically significant (Log-Rank=3.82, p=. 051)

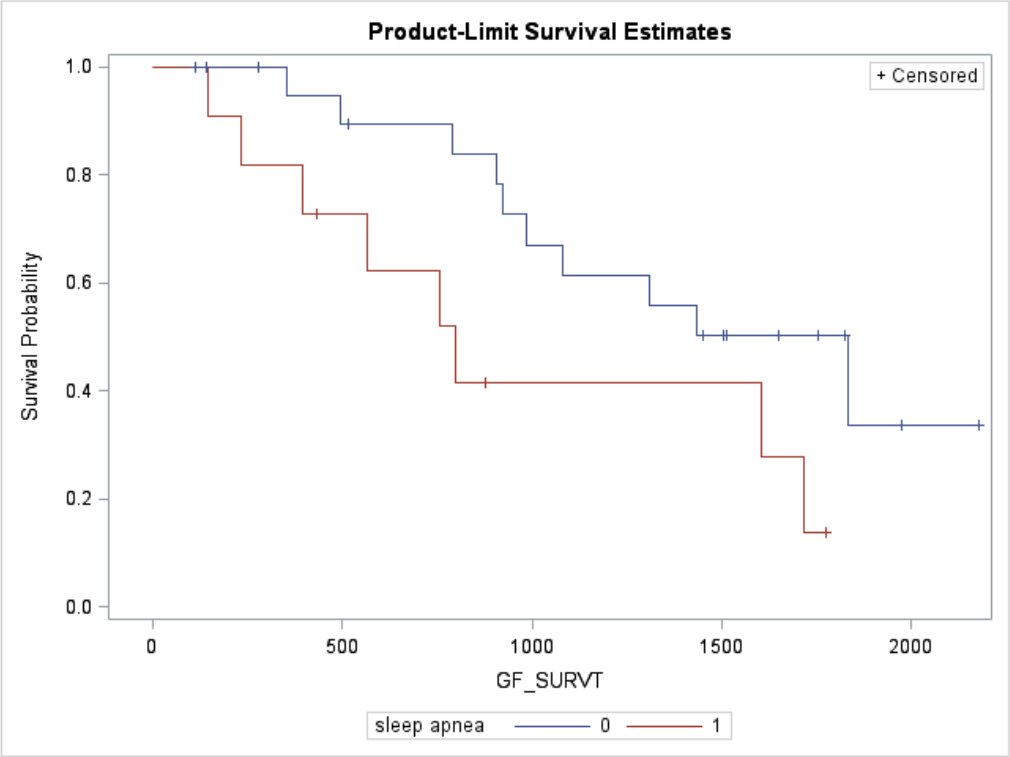

Figure 8. Kaplan Meier Survival Curves for Year of Transplant 2009-2015: Graft Survival Time by Presence and Absence of Sleep Apnea

Stratified univariate results of sleep apnea. After computation of stratified Kaplan Meier curves, a stratified univariate analysis of sleep apnea to graft survival time was computed to estimate the unadjusted hazard ratio of sleep apnea with graft failure or cardiovascular related death with a functioning graft, prior to multivariate testing. Table 19 presents that stratified univariate analysis of sleep apnea and graft survival time.

Table 19.
Univariate (Unadjusted) Analysis: Association of Sleep Apnea with Graft Failure or Cardiovascular Related Death with a Functioning Graft (All Non-Cardiovascular Deaths Censored) According to Year of Transplant

Sleep Apnea/Year of Transplant	N	Parameter Estimate	HR	HR CI	p-value
Year of Transplant 1997-2008					
Sleep Apnea (n=41)	264	-0.220	.80	.54-1.19	.278
No Sleep Apnea (n=224)			1.00	Referent	
Year of Transplant 2009-2015					
Sleep Apnea (n=11)	33	0.929	2.53	.97-6.64	.059
No Sleep Apnea (n=22)			1.00	Referent	

Abbreviations: HR, hazard ratio; HR CI, hazard ratio 95% confidence interval
N refers to the sample size for each strata
The hazard ratio refers to the comparison of any sleep disorder versus no sleep disorder

Multivariate results for hypothesis 2b. A multivariate Cox regression was used to estimate the adjusted hazard ratios for the association of sleep apnea with the risk of graft failure or cardiovascular (CVD) related death with a functioning graft, after adjustment of key covariates. Backward elimination was used as the covariate selection process, resulting in the final model presented in Table 20a. Parameter estimates, hazard ratios, 95% confidence intervals and significance levels are presented for each variable that remained in the final model. Table 20a presents the results of multivariate Cox regression with the statistically significant interaction term ($p \leq .01$) between sleep apnea and year of transplant strata.

Table 20a.
Results of the Multivariate Cox Regression Model: Interaction of Sleep Apnea and Year of Transplant on the Risk of Graft Failure or Cardiovascular Related Death with a Functioning Graft

Predictor	Parameter Estimate	HR	HR CI	p-value
Recipient age at time of transplant Years (n=297)	-0.019	.98	.97-.99	.001*
HLA Mismatch 0-6 (n=297)	0.148	1.6	1.07-1.26	.001*
Gender				
Male (n=167)	0.406	1.50	1.13-2.01	.006*
Female (n=130)		1.00	Referent	
Functional Status				
Full (n=151)	-0.551	.57	.42-.78	.000*
Limited (n=146)		1.00	Referent	
Year of Transplant Surgery[a]				
1997-2008 (n=264)				.680
2009-2015 (n=33)				
Sleep Apnea[a]				
Yes (n=52)				.052
No (n=245)				
Sleep Apnea*Year of Transplant Interaction Term	1.476			.006*

Abbreviations: HR, hazard ratio; HR CI, hazard ratio 95% confidence interval, HLA, human leukocyte antigen mismatch
Each Variable is simultaneously and reciprocally adjusted for all the other variables in the model
a: Main effects of hazard ratios are not reported in the multivariate model and cannot be interpreted in this table given the interaction term, see Table 20b.
* Significant at the $p \leq .05$ level

The interaction between sleep apnea and year of transplant surgery strata was statistically significant with adjustments ($p \leq .01$). The strata specific adjusted hazard ratios for graft failure or cardiovascular related death with a functioning graft are reported in Table 20b. These are from the same model as presented in Table 20a.

Table 20b.
Adjusted Hazard Ratios for Graft Failure or Cardiovascular Related Death with a Functioning Graft with respect to Sleep Apnea Stratified by Year of Transplant

Predictor	**N**	**Parameter Estimate**	**aHR**	**HR CI**	**p-value**
Year of Transplant 1997-2008					
Sleep Apnea (n=41)	264	-0.396	.67	.45-1.01	.058
No Sleep Apnea (n=223)			1.00	Referent	
Year of Transplant 2009-2015					
Sleep Apnea (n=11)	33	1.080	2.94	1.12-7.75	.029*
No Sleep Apnea (n=22)			1.00	Referent	

Abbreviations: aHR, adjusted hazard ratio; HR CI, hazard ratio 95% confidence interval
N refers to the sample size for each strata
For each stratum, the adjusted hazard ratio refers to the comparison of sleep apnea versus no sleep apnea, adjusted for all other variables in the final model (recipient age, HLA mismatch, functional status, gender)
*Significant at the $p \leq .05$ level

Summary of results for hypothesis 2b: graft failure or cardiovascular related death with a functioning graft. The final model for graft survival time included recipient age, human leukocyte antigen (HLA) mismatch, gender, functional status, and sleep apnea. Each hazard ratio presented in Table 20a represents the adjusted hazard ratio for each variable, while controlling for all other variables in the model. Table 20b presents the adjusted hazard ratio for

sleep apnea, versus no sleep apnea, stratified by year of transplant, while adjusting for all variables included in final multivariate model presented in Table 20a (recipient age, HLA mismatch, gender, and functional status).

For patients transplanted in 1997-2008, sleep apnea was associated with a decreased (albeit non-statistically significantly) risk of graft failure or cardiovascular related death with a functioning graft (adjusted Hazard Ratio (HR) = 0.67, 95% CI, 0.45-1.01) relative to no sleep apnea. However, for patients transplanted in 2009-2015, sleep apnea was strongly and statistically significantly (p=.03) associated with increased risk of graft failure or cardiovascular related death with a functioning graft (adjusted HR = 2.94, 95% CI, 1.12-7.76), relative to no sleep apnea. For the more recent time period of transplant (2009-2015), the null hypothesis was thus rejected for hypothesis 2b.

Results of Sub-Hypothesis 3b: Patient Survival after Graft Failure

Hypothesis 3b: Of those with graft failure, patients with a diagnosed sleep-disordered breathing disorder have a statistically significantly higher death hazard after graft failure than patients without a diagnosed sleep-disordered breathing disorder, even after adjustment for potential confounders.

Kaplan Meier Curves. Kaplan Meier curves were computed comparing patient survival time after graft failure according to the presence of sleep apnea. Table 21 summarizes the total number of events and censored observations by sleep apnea category (presence or absence). Figure 9 presents Kaplan Meier curves. Median patient survival time after graft failure for patients with sleep apnea was much shorter (2,421 days) than that for those without a sleep apnea (3,249 days). Despite this large difference in median patient survival time, the survival curves were not statistically significantly different (Log-Rank=.95; p=.330) (Figure 9).

Table 21.
Proportions of Censored Observations for Patient Survival Time after Graft Failure According to the Presence and Absence of Sleep Apnea (N=164)

Sleep Apnea	Total	Events	Censored	% Censored
Presence	28	10	18	64%
Absence	136	50	86	63%
Total	164	60	104	63%

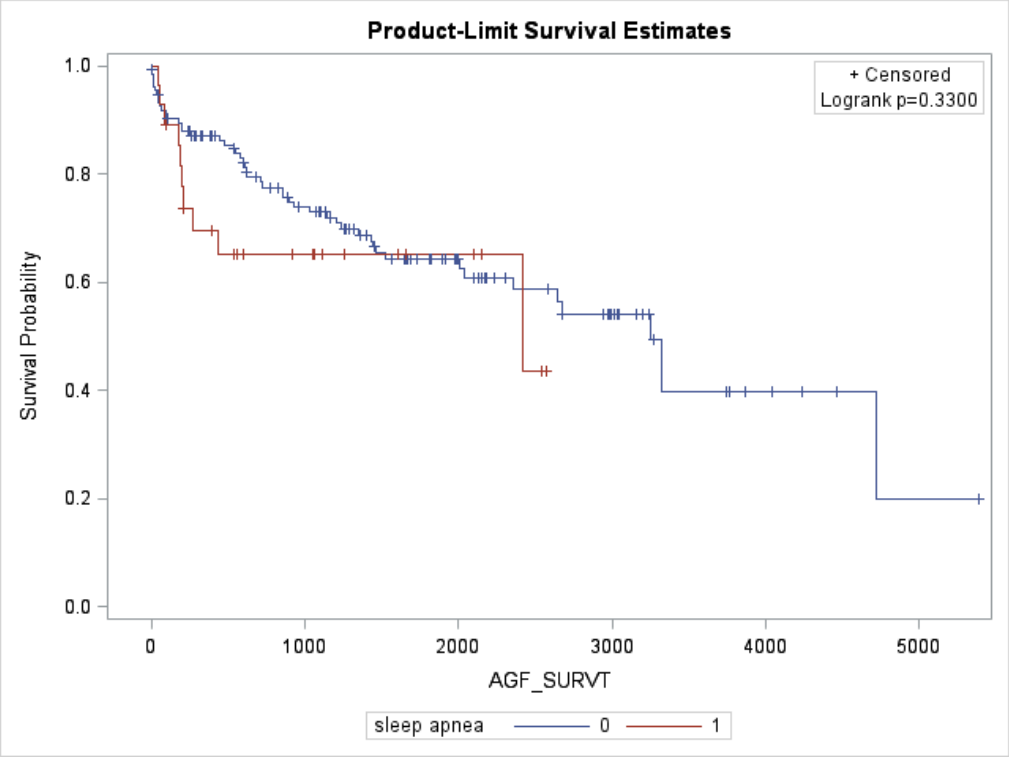

Fig 9: Kaplan Meier Survival Curves for Patient Survival Time after Graft Failure by Presence and Absence of Sleep Apnea

Multivariate results for hypothesis 3b. A multivariate Cox regression was used to estimate the hazard ratios for the associations of predictor variables with the risk of patient death after graft failure. Of patients transplanted between 2009-2015, there were no events for subjects with sleep apnea diagnoses. Thus, this model could not be stratified by year of transplant. As we

did not find a statistically significant interaction between year of transplant surgery (2009-2015 and 1998-2008) and sleep apnea (p=.986), the period of transplant surgery (continuous variable) was included in the backward elimination selection process along with other variables. The final model is presented below and reflects an iterative process of model building and verification of model assumptions.

Table 22.
Results of the Multivariate Cox Regression Model: Association of Sleep Apnea with Patient Survival Time after Graft Failure

Predictor	**Parameter Estimate**	**HR**	**HR CI**	**p-value**
Sleep Apnea				
Yes (n=34)	0.052	1.05	.49-2.05	.886
No (n=130)		1.00	Referent	
ESRD Etiology				
Hypertensive (n=63)	-.0567	.57	.32-.99	.051*
Other (n=101)		1.00	Referent	
Recipient Age at Time of Transplant[a]				
Years (n=164)				.000*
Functional Status[a]				
Full (n=91)				.013*
Limited (n=73)				
Age*Functional Status Interaction Term	-0.076			.005*

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; HR CI, hazard ratio 95% confidence interval
Each variable is simultaneously and reciprocally adjusted for all the other variables in the model.
a: Main effects of hazard ratios are not reported in the multivariate model and cannot be interpreted in this table given the interaction term.
* Significant at the $p \leq .05$ level

Summary of multivariate results for hypothesis 3b. The final model included a recipient age and functional status interaction, end-stage renal disease (ESRD) etiology, and sleep apnea. Each hazard ratio presented in Table 22 represents the adjusted hazard ratio for each variable, while controlling for all other variables in the model. Patients with sleep apnea had an increase (5%) in the risk of death after graft failure compared to those without sleep apnea, but this difference was not statistically significant (HR=1.05, 95% CI=.49-2.05, p=.886).

CHAPTER V

DISCUSSION AND CONCLUSIONS

The primary purpose of this historic cohort study was to investigate the associations between sleep disorders and clinical transplant outcomes in a sample of kidney transplant recipients with a failed graft. This chapter presents a discussion of the results organized by each hypothesis. Results of hypothesis testing are summarized and interpreted in relation to the primary independent variables, any sleep disorder (main predictor for the main hypotheses) and sleep-disordered breathing disorders (main predictor for the sub-hypotheses). While both the main hypotheses and sub-hypotheses are presented, the focus of this discussion centers on the associations between sleep-disordered breathing disorders, namely, sleep apnea, to transplant outcomes. Sleep apnea will be discussed as 85% of the sleep disorders in our sample consisted of sleep apnea diagnoses, a type of a sleep-disordered breathing disorder, and of those with sleep-disordered breathing disorders, 100% had sleep apnea.

Following the discussion of the results pertaining to sleep apnea, for the hypotheses that involve multivariate modeling, a brief discussion of additional study covariates and their relationship to the transplant outcomes are presented. Then, study limitations and health policy implications of the study are addressed. The chapter concludes with the presentation of future research topics and with concluding remarks.

Discussion of Hypothesis 1: Death with a Functioning Graft

Death with a functioning graft is the leading cause of graft loss in patients who have maintained a transplant for 10 or more years (Matas et al., 2008). Identifying modifiable risk factors associated with death with a functioning graft is a relevant topic in the transplant field and may help improve long-term patient outcomes. It was hypothesized that patients with any

sleep disorder would have a statistically significantly higher proportion of death with a functioning graft compared to those without a sleep disorder. The sub-hypothesis posited that patients with a sleep-disordered breathing disorder (sleep apnea) would have a higher proportion of death with a functioning graft compared to those without a sleep-disordered breathing disorder. For both any sleep disorder and sleep apnea, there were no statistically significant differences found for the proportion of death with a functioning graft based on the diagnosis of any sleep disorder or, specifically, sleep apnea. Of patients with any sleep disorder, 44% died with a functioning graft, which was similar to those without a sleep disorder (45%). The proportion of death with a functioning graft in patients with sleep apnea was 46%, and 44% in those patients without sleep apnea.

Sleep apnea and death with a functioning graft. A relationship between sleep apnea and death with a functioning graft was proposed due to research identifying an increased risk of mortality among patients with sleep apnea, in non-transplant samples (Lavie, 2007; Marshall, Wong, Cullen, Knuiman, & Grunstein, 2014; Young et al., 2008). In the present study, there are two considerations that may explain the lack of association between sleep apnea and death with a functioning graft. First, the lack of association may be explained by the inability to assess the severity of sleep apnea and to account for this in analyses. Past research reporting the associations between sleep apnea and mortality identifies such relationships in patients with severe (Young et al., 2008), and moderate to severe sleep apnea (Marshall et al., 2014). Specifically, in a sample of end-stage renal disease patients on dialysis, Tang and colleagues (2010) found that moderate to severe sleep apnea was an independent predictor of mortality. These findings offer some support for the importance of considering severity when examining the relationship between sleep apnea and mortality. In the present study, we were unable to

examine the relationship between moderate to severe sleep apnea and death with a functioning graft due to the unavailability of data on sleep apnea severity.

Second, the lack of association between sleep apnea and death with a functioning graft may be due to an absence of a relationship between sleep apnea and increased risk of mortality in kidney transplant recipients. Although research has identified a relationship between sleep apnea and increased risk of mortality in patients with end-stage renal disease (ESRD) (Tang et al., 2010), past studies among transplant recipients have found no relationship between sleep apnea and death with a functioning graft (Fornadi et al., 2014; Szentkiralyi et al., 2011), even when assessing this relationship in patients with moderate to severe sleep apnea (Fornadi et al., 2014). It is important to consider that sleep apnea may not increase the risk of mortality in ESRD patients, who are already at increased risk for cardiovascular disease. A systematic review of the sleep apnea and mortality research cited conflicting evidence as to whether the presence of sleep apnea in patients with existing cardiovascular disease increased mortality risk, beyond the risk of the cardiovascular disease itself (Lavie, 2007). Kidney transplant recipients have an increased occurrence of cardiovascular disease, which may be related to their renal failure, and further, cardiovascular disease is common in (ESRD) patients with sleep apnea and those without sleep apnea (Weiner et al., 2006). Thus, the presence of sleep apnea may not pose an additive risk of mortality in kidney transplant recipients given the existing high prevalence of cardiovascular disease among ESRD patients.

Relationship of death with a functioning graft to hypothesis 2 (graft survival time). Comparing the proportion of death with a functioning graft in subjects with sleep apnea and those without sleep apnea was also intended to help inform the analytic approach for examining the relationship between sleep apnea and graft survival time (hypothesis 2b). In the transplant

literature, death with a functioning graft can be considered the end of graft survival time for a subject, or it can be considered a competing risk of graft loss. Understanding the association between death with a functioning graft and sleep apnea was important to determine whether deaths could be censored or whether a competing risks model should be used when examining the association between sleep apnea and graft survival time. In finding that sleep apnea was not associated with death with a functioning graft, we determined that death with a functioning graft could be treated as a censored observation for the graft survival time outcome (hypothesis 2b) without significant concern for bias. Had we found a statistically significant higher proportion of subjects with sleep apnea who experienced death with a functioning graft, then censoring this outcome (death with a functioning graft) could have led to considerable bias in the analysis.

Although there was no statistically significant association between sleep apnea and death with a functioning graft (either all-cause or cardiovascular related death), it was determined that only non-cardiovascular (CVD) related deaths would be treated as censored observations. CVD related deaths were retained in the analysis as "events" (end of graft survival time), because CVD related deaths may be related to the decreased function of the transplanted kidney (Jardine et al., 2011; Meier-Kriesche et al., 2003). In doing so, we attempted to account for a competing risk in our analysis, but one that could be related to the graft failure of the transplanted kidney.

Discussion of Hypothesis 2: Graft Survival Time

Graft survival time is a measure of transplant longevity, and it is the primary measure of transplant success for both patients and providers. In our study, graft survival time was operationally defined as graft failure or cardiovascular (CVD) related death with a functioning graft. It was hypothesized that patients with, versus without, any sleep disorder would have a higher hazard of graft failure or CVD related death with a functioning graft. The sub-hypothesis

posited that patients with a sleep-disordered breathing disorder, versus without, would have a higher hazard of graft failure or CVD related death with a functioning graft. The null hypothesis was rejected for both the main and sub-hypotheses related to the findings that patients with any sleep disorder transplanted in 2009-2015 (adjusted HR=2.92, p=.030) had nearly a three-fold increased risk of graft failure or CVD related death with a functioning graft, compared to those without a sleep disorder, in a model adjusted for recipient age, HLA mismatch, functional status, and gender. Findings yielded similar results for the sub-hypothesis, as patients with sleep apnea transplanted in 2009-2015 had a similar hazard of graft loss (adjusted HR= 2.94, p=.029), demonstrating a statistically significant increased risk of graft failure or CVD related death with a functioning graft. Prior to the discussion of the results, stratification is addressed.

Stratification. When interpreting results, consideration was given to the statistically significant interaction between sleep apnea and year of transplant time period and how the relationship of sleep apnea and graft survival time varied by the two year of transplant strata. Patients transplanted in 1997-2008 with sleep apnea, versus without, had a decreased risk of graft failure or cardiovascular (CVD) related death with a functioning graft, although this was not statistically significant. Patients transplanted during 2009-2015 with sleep apnea, versus without, had a statistically significant increased risk of graft failure or CVD related death with a functioning graft in adjusted models.

Designation of year of transplant strata was determined through subject matter expertise. Consideration was given to center-specific changes, transplant advances, and allocation policy changes that could have occurred throughout the study time period (1997-2015). After consideration of several factors that could inform the strata designation for the variable, year of transplant surgery, a change in the quality of the transplant center's medical records relevant to

the study was determined to inform how the year of transplant time periods would be designated. In 2009, the transplant center implemented an electronic medical record (EMR) which served as a more robust source for data abstraction compared to the previous source (Voyager) and resulted in an increased abstraction of diagnosed sleep disorders in the 2009-2015 strata. This data source change also had the potential to impact the patients transplanted in 1997-2008, as patients who were transplanted earlier eventually had a more robust medical record source from which to abstract a diagnosed sleep disorder if they survived until 2009. That may in part be why patients with sleep apnea had increased graft survival times in 1997-2008, as we were more likely to find sleep apnea diagnoses through the electronic medical record, which became available in 2009.

The prevalence of sleep apnea and how this differed among the two year of transplant time periods (1997-2008 and 2009-2015) merits consideration. In 1997-2008, the prevalence of sleep apnea was 16%. In 2009-2015, the prevalence of sleep apnea was 33%. The higher prevalence of sleep disorders abstracted in 2009-2015 with the presence of the electronic medical record (EMR) may be representative of the EMR as a better abstraction source, or it may reflect an increased awareness and diagnosis of sleep apnea in the recent years. Additionally, the lower prevalence of sleep apnea in 1997-2008 may reflect a higher prevalence of undiagnosed (or unrecorded) sleep apnea in the sample, which could have impacted study outcomes for that time period.

Lastly, it is important to consider that the two strata (1997-2008 and 2009-2015) represent two different time periods with the regards to graft survival time, both due to the study design and overall advances in transplantation. First, these two time periods reflect different durations with regards to graft survival time (opportunity to fail) because the study cohort only

included those subjects with graft failure or those who died with a functioning graft during the time period of 1997-2015. Thus, patients transplanted in 1997-2008 had a longer opportunity to fail during the study time period, which resulted in this time period having longer median survival times due to being able to capture longer survival times. The time period of 2009-2015 only captured patients with early or mid-range graft loss, but it represents a more modern era of transplant. National transplant data reports that the occurrence of rejection during the first year post-transplant has steadily decreased since the 1990s but that these improvements have remained relatively stable since 2008 (Hart et al., 2016). Thus, the 2009-2015 time period is more reflective of the current rates of acute rejection (which have stabilized), while the acute rejection rates during the time period of 1997-2008 were likely higher and varied throughout that time period.

In summary, although the findings from the year of transplant time period 2009-2015 involve a much smaller sample, this time period reflects a more reliable medical record source (which is relevant to this study's design), and the time period also reflects a more stable time period with regards to transplant outcomes. Specifically, improvement in the decreased risk of acute rejection has been the most notable outcome change (nationally) that has taken place in the past twenty years of transplant (Hart et al., 2016). Furthermore, as this improvement has remained relatively stable since 2008 (Hart et al., 2016), this further supports the significance of the associations found between sleep apnea and graft survival time in the 2009-2015 year of transplant time period.

Sleep apnea and graft survival time. Patients with sleep apnea who were transplanted in 2009-2015 had a higher hazard of graft failure or cardiovascular (CVD) related death with a functioning graft compared to those without sleep apnea. Two studies have explored the

association of sleep apnea to graft survival time and found conflicting results. Szentkiralyi and colleagues (2011) found that having a high risk of sleep apnea (measured through the Berlin Questionnaire) was an independent risk factor for graft failure in female kidney transplant patients. However, a study by Fornadi and colleagues (2014) using polysomnography measurement found no relationship between sleep apnea and graft failure risk. Both studies relied on small samples of patients who had experienced graft failure, each consisting of less than 100 patients with graft failure and involved a predominantly Caucasian sample of transplant patients from Budapest, Hungary (Fornadi et al., 2014; Szentkiralyi et al., 2011). The present study attempts to expand upon this past literature, and it is the first study, to our knowledge, that examines the association between sleep apnea and graft survival time in a US transplant sample. Our study time frame involved an 18-year period; however, we only found an increased risk for graft loss, with respect to sleep apnea, for the 2009-2015 time period which reflects early to mid-range graft loss. Additionally, the sample of patients in our study differed from other samples (Fornadi et al., 2014; Szentkiralyi et al., 2011) involving a hypertensive sample of kidney transplant recipients with a failed graft, consisting of predominately African American patients in Southeastern Virginia.

Potential Mechanisms. There are several potential mechanisms that may underlie the relationship between sleep apnea and kidney functioning post-transplant. A possible direct relationship between sleep apnea and renal failure has been proposed through the effect of hypoxia on the kidney (Hanly & Ahmed, 2014; Nicholl et al., 2012). In a sample of over 300 patients, nocturnal hypoxia was associated with accelerated loss of renal function, even after adjustment for relevant covariates that may impact renal loss, such as age, body mass index, diabetes, and heart failure (Ahmed et al., 2011). Another potential mechanism through which

sleep apnea may impact kidney functioning is through proteinuria. Proteinuria is the presence of abnormal amounts of protein in urine, and it can often reflect a kidney filtration problem. The presence of proteinuria after a kidney transplant is associated with reduced graft survival time (Amer & Cosio, 2009; Amer et al., 2007; Halimi et al., 2005), and an association has been found between proteinuria and sleep apnea in patients with chronic kidney disease (Chan et al., 2015).

Indirect mechanisms linking sleep apnea to kidney functioning may also occur through hypertension, diabetes, and obesity (inflammation) (Hanly & Ahmed, 2014; Ozok et al., 2014; Nicholl et al., 2012; Turek, Ricardo, & Lash, 2012). There is a relationship between sleep apnea and difficult to control hypertension (Hla et al., 2008; Huang et al., 2011), increased risk of type II diabetes (Kendzerska et al., 2014; Nagayoshi et al., 2016), and obesity (Young et al., 2002). Our findings also suggest such associations. As our entire sample was hypertensive, an association between sleep apnea and hypertension could not be evaluated in our study. However, patients with sleep apnea in our sample were found to have a statistically significantly higher prevalence of diabetes and a higher body mass index than patients without sleep apnea. Hypertension, diabetes, and inflammation are all known risk factors for renal failure (Turek, Ricardo, & Lash, 2012), and they can impact the graft survival of a newly transplanted kidney.

Given the many potential direct or indirect and interrelated mechanisms through which sleep apnea may relate to kidney functioning, it is probably more realistic to consider this relationship in the context of a multifactorial causal pathway. For instance, not only can hypoxia directly impact the organ function of the kidneys (Abuyassin et al., 2015), but also, hypoxia can be associated with hyperactivity of the sympathetic nervous system (Narkiewicz &Somers, 1997). Increased sympathetic activation results in a physiological state that can damage kidney function through various pathways, such as increased sensitivity to norepinephrine and resistant

hypertension (Adeseun & Ross, 2010; Schalich et al., 2009). Thus, there is support that increased sympathetic activation may be a primary pathway through which hypoxia from sleep-disordered breathing can lead to kidney failure (Schalich et al., 2009).

Additional covariates and graft survival time. In the final multivariate model, four additional covariates remained statistically significantly associated with graft survival time, and included: recipient age, human leukocyte antigen (HLA) mismatch, gender, and functional status. These variables were identified as key covariates and remained in the multivariate model for adjustment. However, the significance and direction of these covariates in the present study are similar to the findings of other US kidney transplant studies, including multi-center studies and larger population based cohort studies. These findings are briefly summarized below.

In the present study, younger patients had a slightly higher risk of graft failure or cardiovascular (CVD) related death with a functioning graft. Although age was associated with censoring, which may have led to an overestimation of survival times for older patients, previous research has also reported a higher risk of graft loss in younger patients (Keith et al., 2006). This may be due to the increased prevalence of immunosuppressant non-compliance in younger patients (Brahm et al., 2012), which remains a significant cause of early graft loss. HLA mismatch was also associated with graft survival, indicating a higher risk of graft loss with poorer antigen matches between the donor and recipient, a finding that is also supported in the transplant literature (Pirsch et al., 1996; Zhou & Cecka, 1993). Additionally, we found that males had approximately a 50% higher risk of graft failure or CVD related death with a functioning graft, compared to females, a finding that has been reflected in larger transplant studies (Chen et al., 2013; Meier-Kriesche et al., 2001; Nyberg, Blohme, & Norden, 1997). Lastly, patients with limited functional status at the time of transplant (<100% Karnofsky score),

compared to those identified as having full functionality, had a statistically significantly increased risk of graft failure or CVD related death with a functioning graft. In previous research, reduced functionality has been associated with delayed graft function (Garonzik-Wang, 2012), a risk factor in graft loss (Yarlagadda et al., 2008).

Although race was not included in the final model due to collinearity between race and HLA mismatch, race remained statistically significantly associated with graft failure or cardiovascular (CVD) related death with a functioning graft at the univariate (HR=1.62, p=.002) and multivariate levels (adjusted HR=1.53, p=.013). Such findings suggest that African Americans had a 53% higher risk of graft failure or CVD related death with a functioning graft than Caucasians even after adjustments. This finding is consistent with past literature (Chakkera et al., 2005; Meier-Kreische et al., 2001), including data from a large nationally representative sample of US transplant recipients (n=73,477) (Meier-Kreische et al., 2001).

Discussion of Hypothesis 3: Patient Survival Time after Graft Failure

Patient survival time after graft failure is a relevant, yet understudied, phenomenon in the transplant literature. Compared to end-stage renal disease (ESRD) patients who have remained on dialysis, ESRD transplant patients have an increased risk of death after graft failure during the three years following their graft loss (Kaplan & Meier-Kriesche, 2002; McCaughan et al., 2014; Perl et al., 2012). Although transplantation is intended to increase ESRD patient survival (Wolfe et al., 1999) and improve quality of life (Kovacs et al., 2011; Smith et al., 2008), the long-term impact of immunosuppression and the health implications of a second progressive period of chronic kidney disease may be factors that increase mortality risk after graft loss (McCaughan et al., 2014). It was hypothesized that patients with any sleep disorder would have a higher hazard of mortality after graft failure compared to those without a sleep disorder. The sub-hypothesis

proposed patients with a sleep-disordered breathing disorder would have a higher hazard of mortality after graft failure compared to those without a sleep-disordered breathing disorder. No statistically significant differences in patient survival time after graft failure based on the presence of any sleep disorder, or, specifically, sleep apnea, were found. Sleep apnea was not statistically significantly associated with an increased risk of death after graft loss in our sample (HR=1.05, p=.887). Median patient survival time after graft failure for patients with sleep apnea was much shorter (2,421 days) than the median survival time for those without sleep apnea (3,249 days). However, the lack of statistical significance of the relationship between sleep apnea and patient survival time after graft loss may have been impacted by the high rate of censoring (64%) for this outcome. Additionally, despite a known interaction between sleep apnea and year of transplant, we were unable to stratify sleep apnea in the Cox regression analysis by year of transplant due to there being too few events in the 2009-2015 strata. This may have also impacted our findings.

Sleep apnea and patient survival time after graft failure. To our knowledge, this was the first study to examine the relationship between sleep disorders, particularly, sleep apnea, and patient survival time after graft failure. It was hypothesized that patients with sleep apnea would have an increased risk of death post graft failure. Possible mechanisms (while beyond the scope of this study) might include the associations between sleep apnea and increased inflammation (Calvin, Albuquerque, Lopez-Jimenez, & Somers, 2009), and the associations between moderate to severe sleep apnea and an increased risk of mortality in non-transplant samples (Lavie, 2007; Marshall et al., 2014; Young et al., 2008).

In addition to the sample limitations that may have impacted our findings (high rate of censoring and inability to stratify analyses), as addressed previously, the inability to measure

severity of sleep apnea may have impacted our findings and could be a potential limitation of the present study. Furthermore, it remains important to consider that sleep apnea may not increase the risk of mortality in an end-stage renal disease (ESRD) sample with a high prevalence of cardiovascular disease (Lavie, 2007). Fornadi and colleagues (2014) examined the relationship of patient death after graft loss (although this outcome was grouped with death with a functioning graft), and they found no relationship between moderate to severe sleep apnea and mortality risk after graft loss (Fornadi et al., 2014).

Additional covariates and patient survival time after graft failure. In the final multivariate model, three additional covariates remained statistically significantly associated with patient survival time after graft failure, and included end-stage renal disease (ESRD) etiology, recipient age, and functional status. Patients whose ESRD etiology was hypertensive nephersclerorsis had a decreased risk of death after graft loss compared to other ESRD etiologies. Patients whose ESRD is caused by hypertension may have less comorbidities or serious health conditions than other diseases that can contribute to ESRD, such as lupus, an autoimmune disease, or diabetes, a disease that can often cause many additional health complications. Increased recipient age and decreased functional status were independently associated with a higher risk of mortality after graft failure. Furthermore, there was a statistically significant interaction between these two variables, which signified that the risk of death after graft failure increased as patients with limited functionality aged.

Generally, there has been limited research identifying variables that are associated with patient survival time after graft failure, and findings from this study can hopefully contribute to the transplant literature. Other research has identified recipient age, diabetes, and cardiovascular disease as variables associated with an increased risk of death post graft failure (McCaughan et

al., 2014). A study by McCaughan et al. (2014) also found that re-transplantation is a primary factor in increased likelihood of survival after graft failure. Re-transplantation was not analyzed in the present study, thus, due to the lack of assessment of this variable, the inability to control for re-transplantation may have impacted our findings.

Summary for the Discussion of Results (Hypotheses 1-3)

Results of hypothesis testing suggested that sleep disorders, namely, sleep apnea, were not associated with mortality outcomes in our sample of kidney transplant recipients with a failed graft. The lack of an association between sleep apnea and death with a functioning graft and risk of patient mortality after graft failure might be explained through one of two primary considerations. First, there may be a relationship between sleep apnea and mortality outcomes in kidney transplant recipients, but the relationship may only exist between patients with moderate to severe sleep apnea, and we were unable to test these associations in this study as we lacked severity data. Second, there may not be a relationship between sleep disorders and mortality in a kidney transplant sample that has an existing increased prevalence of cardiovascular disease which may be related to end-stage renal disease. Thus, the presence of sleep apnea may not pose an additive risk of mortality in a sample of patients with existing cardiovascular disease.

Although no relationship was found between sleep apnea and increased proportion of death with a functioning graft (hypothesis 1b), the results of hypothesis 1b can also provide further insight into the interpretation of the results for the graft survival time outcome (hypothesis 2b). In our study, the end of graft survival time was defined as graft failure and return to dialysis or cardiovascular (CVD) related death with a functioning graft (which could also be related to renal dysfunction) (Jardine et al., 2011; Meier-Kriesche et al., 2003). In other words, we examined graft survival time without the end of survival time being driven by all-

cause mortality (specifically, non-CVD related mortality). This is an important distinction when interpreting the graft survival findings because the relationship between sleep apnea and graft survival time could involve different mechanisms through which sleep apnea relates to graft loss due to all-cause mortality or graft loss due to renal dysfunction (the failure of the transplanted kidney).

A relationship was found between sleep apnea, and an increased risk of graft failure or cardiovascular related death with a functioning graft among patients transplanted in 2009-2015. Within the context of this finding, the lack of association between sleep apnea and death with a functioning graft may indicate that sleep apnea may be a factor in reducing graft survival time through impacting the renal function of the transplanted kidney, rather than due an increased risk of death with a functioning graft in kidney transplant recipients. Previous research has identified sleep apnea as a risk factor for renal dysfunction through chronic kidney disease development (Lee et al., 2015) and faster progression to kidney failure (Lee et al., 2015; Molnar et al., 2015); therefore, it is not unfounded to consider that sleep apnea may also accelerate kidney failure post-transplant. Thus, a better understanding of sleep apnea and how it can relate to kidney functioning is important. While there are several potential mechanisms through which sleep apnea could impact kidney functioning, there is strong support for a multifactorial casual pathway that may begin through the impact of hypoxia both directly on the kidney and then indirectly through the pathway of increased sympathetic activation (Abuyassin et al., 2015; Adeseun & Ross, 2010; Schalich et al., 2009). Further understanding of these mechanisms and whether treatment of sleep apnea can improve renal function (or slow the rate of progression to kidney failure) may help to improve transplant outcomes. Our findings regarding the association between sleep apnea and increased risk of graft loss are relevant to the chronic kidney disease

literature, but also, specifically, to the kidney transplant literature. Such findings merit further consideration of sleep disorders, and specifically sleep apnea, among transplant nephrologists. In addition to the relevance of the present study to the transplant literature, our findings also contribute to the literature characterizing the growing public health concern regarding sleep apnea in the United States.

The estimated prevalence of sleep apnea in the US varies based on age and gender but ranges approximately from 3-10% in those aged 30-49 years old, and 9-17% in those aged 50-70 years old. These prevalence rates reflect a substantial increase of sleep apnea over the last two decades (Peppard et al., 2013). Among the general population, sleep apnea is associated with a reported increase in health service utilization (Kao, Lee, Lin, Tsai & Chung, 2015; Kapur et al., 2002), an increased risk of cardiovascular disease (Shahar et al., 2001) and an increased risk of mortality (Lavie, 2007; Marshall et al., 2014; Young et al., 2008). As the incidence of sleep apnea continues to increase, more research is needed to examine the potential associations between sleep apnea and adverse health outcomes. In our sample of kidney transplant recipients, a statistically significant association between sleep apnea diagnosis and shorter graft survival time was found in patients transplanted in 2009-2015. This finding further highlights the pervasive and negative health risks of sleep apnea.

Limitations

It is important to consider the findings of this study within the context of its limitations, and causal associations cannot be ascertained from a single observational study. First, the data for the primary independent variable (sleep disorders) were limited to sleep disorders that were documented in the subjects' medical records. Therefore, results may be impacted by undiagnosed sleep disorders or sleep disorders that were diagnosed but not reported in the

medical record. While the prevalence of sleep apnea in the general population is estimated to range from 3-17% based on age and gender considerations (Peppard et al., 2013), there is literature to support a higher prevalence of sleep apnea among patients with end-stage renal disease (ESRD) (Hanly, 2004; Unruh et al., 2006). Furthermore, the estimated prevalence of sleep apnea among transplant samples has been reported to range from 25-45% (Fornadi et al., 2012; Molnar et al., 2010; Szentkiralyi et al., 2011). The prevalence of sleep apnea in our cohort was 17%, which is lower than the estimated prevalence in other kidney transplant samples and may indicate that some subjects who were classified as not having sleep apnea in our study may have had sleep apnea that was undiagnosed or that this diagnosis was not reported in their medical record.

In addition to the potential for undiagnosed sleep disorders to affect study results, there was insufficient information provided in the medical records on the severity or treatment of the diagnosed sleep disorders that were included in analyses. Often, the literature summarizing associations between sleep apnea and adverse health outcomes are centered on moderate to severe apnea (Marshall et al., 2014; Young et al., 2008), and such severity information may have been relevant to transplant outcomes. Additionally, the inability to assess whether patients with diagnosed sleep disorders, specifically sleep apnea, were receiving treatment was a limitation. Patients examined in this study may have been treated for sleep apnea, and this may have impacted the relationship of sleep apnea to graft survival time. It could be informative to compare transplant outcomes among patients treated with continuous positive airway pressure (CPAP) therapy versus those who were not. Patients treated with CPAP may have had better graft survival outcomes. Other unknown variables, such as patient compliance with comorbid conditions that are known to relate to kidney function and/or patient survival (ie diabetes

management), and a subject's overall access to care, are examples of variables that are relevant to the study outcomes but that could not be assessed in our study as they were not available in the data. Additionally, re-transplantation is a known variable related to patient survival time after graft loss (McCaughan et al., 2014), and this variable was not examined in our study.

The Sentara Norfolk General Hospital (SNGH) medical record consisted of two different sources throughout the 1997-2015 study time frame. Thus, another limitation of the study is related to the change of the data abstraction source that occurred for medical records after 2009. Data was available from 1997-2008 through Voyager, a digital storage system for past history and physicals and physicians' records. In 2009, Epic, an electronic medical record came into use at the SNGH transplant center. The data stored in Epic involves a more robust source than the data found in Voyager, and this primarily impacted the abstraction of diagnosed sleep disorders, as the abstraction of sleep disorders involved a multi-pronged approach. Sleep disorders were not only abstracted from a subject's medical history, but they also were abstracted from pulmonary and anesthesia notes. Moreover, it was not uncommon to find sleep disorders diagnoses reported in pulmonary notes when that same sleep disorder was not listed in a subject's medical history, thus supporting the consideration that a more robust abstraction source influenced the abstraction of sleep disorders.

Limitations of the sampling approach are also important to consider. This study was limited to a sample of patients with graft failure or those who died with a functioning graft. Patients who were transplanted and still surviving were excluded. Such exclusion resulted in a sample that is not fully representative of kidney transplant recipients at the Sentara Norfolk General Transplant Center who were transplanted during the study time frame (January 1, 1997 to September 1, 2015, inclusive). The exclusion of censored subjects can introduce bias into a

study. However, given the 18-year study time frame, the exclusion of patients who were still surviving did not systematically exclude all long-term survival times, and that is a strength of the study time frame, despite only having a sample of subjects with a failed graft or those who died with a functioning graft.

Additionally, this study utilizes data from one transplant center during an approximate 18-year time frame; therefore, findings can only be carefully generalized to graft failure populations admitted to similar hospitals and with the same characteristics as this study sample. However, despite limitations of a single-center sample, utilizing data from one transplant center did offer some uniformity in the patients' characteristics, thus increasing internal validity. Patients transplanted at the Sentara Norfolk General Hospital transplant center follow the same pre-transplant evaluations and follow a standardized post-transplant plan of care, including a standard immunosuppressant dosing protocol, thus highlighting a benefit of single-center sampling.

Lastly, power and analysis limitations should be considered when interpreting results. For analyses related to graft survival time (hypothesis 2), the findings from 2009-2015 were based on an analysis of 18 events. Relying on a stratum with a small number of events can result in model instability for multivariate models, which can overestimate hazard ratios and confidence intervals (Hosmer et al., 2008). Less conservative views of model stability recommend at least 5-9 events per covariate (Vittinghoff & McCulloch, 2007). When examining graft survival time (hypothesis 2), we had 4 events per covariate in the 2009-2015 strata, which is less than the number of recommended events. However, a univariate analysis stratified by year of transplant surgery that examined the association of any sleep disorder and of sleep apnea with graft survival time was computed and yielded similar hazard ratios and significance values

compared to the multivariate model. The similar hazard ratios and significance values at the univariate level prior to the addition of other predictor variables may offer some support in considering that the significant relationship between sleep disorder and graft survival time was not over inflated by model instability in the 2009-2015 strata.

In the analysis of hypothesis 3, related to examining patient survival time after graft failure, due to the lack of events in 2009-2015, the method of stratification by year of transplant could not be utilized, and this may have impacted findings. Additionally, the high prevalence of censoring (64%) that was present in patient survival time after graft failure may have also led to biased findings in underestimating the variance in survival times (Hosmer et al., 2008).

Health Policy Implications

Despite the identified limitations, valuable information can be garnered from this study, and findings can hopefully contribute to the transplant literature. Health policy implications related to this study merit consideration at the transplant center-specific level. Given the association found between sleep apnea diagnosis and an increased risk of graft failure or cardiovascular related death with a functioning graft in patients transplanted in 2009-2015, an increased awareness of sleep disorders is important. Recommendations were made to the Sentara Norfolk General Hospital (SNGH) Transplant Center to consider screening patients for sleep apnea as part of the pre-transplant medical evaluation. Screening for sleep apnea involves a low cost and limited time investment and can easily be incorporated into the SNGH pre-transplant medical evaluation. The STOP-Bang (Chung et al., 2008) and the Berlin questionnaire (Netzer et al., 1999) are examples of self-report measures that assess the risk of obstructive sleep apnea. Each measure can be completed in less than five minutes, and patients who are identified as high risk for obstructive sleep apnea can then be referred for a sleep study

for further evaluation. This process could be incorporated into the SNGH pre-transplant evaluation policy, which would standardize it across the center.

Consideration of national policy recommendations based on the findings of this study would require further research, due to the single-center nature of this study. However, our study follows the recommendation of the American Society of Transplantation which has called for research on modifiable patient risk factors that may relate to long-term graft survival (American Society of Transplantation, 2015). Our findings suggest further consideration and evaluation of a novel patient risk factor, sleep disorders. Additional transplant research on sleep disorders, namely, sleep apnea, and how treatment of such may impact transplant outcomes are needed.

Future Research

The findings from this study highlight several questions that remain unanswered and present opportunities for future research. Three main considerations for future research are addressed. First, additional studies exploring the association between sleep disorders with graft survival and patient survival are needed. The estimated prevalence of sleep apnea in kidney transplant samples ranges from 25-45% (Fornadi et al., 2012; Molnar et al., 2010; Szentkiralyi et al., 2011), highlighting the potential significance of this disorder in kidney transplant recipients. A better understanding of sleep apnea and its associations to transplant outcomes is important. Multi-center studies are encouraged to further examine whether sleep disorders are associated with transplant outcomes amongst robust patient characteristics. Future research could include polysomnographic measurement of sleep disorders, as a limitation of this study involved reliance on medical record diagnoses. Additionally, polysomnographic measurement would provide the ability to classify the severity of sleep apnea through the apnea–hypopnea index.

In addition to better understanding relationships between sleep apnea and transplant outcomes, studies that examine the impact of continuous positive airway pressure (CPAP) treatment in transplant outcomes also merit consideration. Given the association between sleep apnea and risk of graft failure in this study and previous research (Szentkiralyi et al., 2011), further studies are needed to determine whether treatment of sleep apnea improves graft survival outcomes. An indirect relationship between CPAP use and improvement of kidney functioning may be supported through past studies identifying improvements in hypertension control (Chin et al., 2006; Gottlieb et al., 2014; Lozano et al., 2010) and blood glucose control (Babu, Herdegen, Fogelfeld, Shott, & Mazzone, 2005) after CPAP use. Hypertension and diabetes control are both important factors in post-transplant management. A potential direct relationship supporting CPAP therapy in transplant patients may be seen through the association between CPAP use and decreased proteinuria (Chaudhary, Sklar, Chaudhary, Kolbeck, & Speir, 1988). Moreover, two studies have explored the potential implications of CPAP use on kidney functioning. Short-term CPAP use in patients with obstructive sleep apnea has been shown to increase renal plasma flow, and reduce the filtration fraction, suggesting that CPAP use may be able to prevent renal dysfunction (Kinebuchi et al., 2014). A study by Nicholl and colleagues (2014) reported improvement in kidney function after four weeks of CPAP use. If sleep apnea remains a factor associated with increased risk of graft failure, then research comparing the renal function of treated and untreated patients with sleep apnea will be needed.

Lastly, as this study follows the recommendations of the American Society of Transplantation identifying the need for more research on modifiable patient predictors of long-term graft loss (American Society of Transplantation, 2015), transplant centers may consider using the design of this study as a potential model for future transplant research. Combining data

from a national transplant registry with the transplant center's medical record data can be an important method in studying novel risk factors that may be related to transplant outcomes beyond the variables that are collected by the United Network for Organ Sharing (UNOS) database.

Conclusions

The present study examined the associations between sleep disorders and three relevant transplant outcomes: death with a functioning graft, graft survival time, and patient survival time after graft failure. Sleep apnea, which comprised 85% of all diagnosed sleep disorders in this sample, was statistically significantly associated with an increased risk of graft failure or cardiovascular related death with a functioning graft among patients transplanted in 2009-2015, while being associated with a decreased, albeit not statistically significant, risk for those transplanted in 1997-2008. Sleep apnea statistically significantly increased the risk of graft loss nearly three-fold among patients transplanted in 2009-2015.

This study supports previous research which found an association between sleep apnea and increased risk of graft failure in female kidney transplant recipients (Szentkiralyi et al., 2011). Study findings also identify the need for new research on sleep apnea and transplant outcomes and suggest the importance of investigating whether treatment of sleep apnea can improve transplant outcomes. While research is needed on the impact of continuous positive airway pressure (CPAP) therapy on transplant outcomes, awareness and management of sleep apnea among the medically complex transplant patient is important and requires keen awareness among all treating providers. Screening for sleep apnea in transplant evaluations, where patients undergo comprehensive medical evaluations, may be an important next step for transplant nephrologists.

This study, to our knowledge, is the first to examine sleep disorders and transplant outcomes in a sample of US transplant patients with a failed graft over an 18-year time period. The study's methodology, analytic approach, and identified limitations may help to inform future studies of this nature. Further consideration of sleep disorders and of their associations to patient outcomes and quality of life remains a significant area with several future research opportunities. Sleep disorders, specifically, sleep apnea, are prevalent throughout the spectrum of chronic kidney disease, and remain prevalent post-transplant. Understanding the role of sleep disturbances in adverse health outcomes extends beyond the sleep medicine professional. Awareness of the significance of sleep disorders and how they can impact transplant outcomes is needed among all types of medical providers, patients, and public health professionals to help improve patient outcomes in the population.

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LIST OF APPENDICES

APPENDIX A

1. Name	_____	
2. Date of Birth	_____ (month/day/year)	
3. Date of Transplant	_____ (month/day/year)	
4. Race/ethnicity	□ African American □ Asian □ Caucasian	□ Hispanic or Latino □ Other: _____
5. BMI at the Time of Transplant	___ In kg/m^2	
6. Gender	□ Male □ Female	
7. Date of Graft Failure	_____ (month/day/year)	
8. Graft Failure Outcome	□ Graft Failure □ Patient Death	
9. Donor Type	□ Deceased Donor □ Living Donor	
10. HLA Mismatch	0-6	
11. ESRD Etiology	□ Hypertension □ Hypertension & Diabetes □ Polycystic Kidney	□ Lupus □ Glomerulonephritis □ Other_____
12. Cause of Patient Death	_____	
13. Date of Recipient Death (if applicable)	_____ (month/day/year)	
14. Age of Donor at Time of Transplant	___ years	
15. Age of Recipient at Time of Transplant	___ years	
16. Year of Transplant Surgery	_____	
17. Graft Survival Time	_____ days	
18. Education Level (at the time of transplant)	_____ (highest grade level completed)	
19. Karnofsky Score (at the time of transplant)	_____ (0-100)	
20. Non-compliance with immunosuppressant medications	□ Yes □ No	

APPENDIX B

21. Diagnosed sleep disorder	□ yes$_1$ □ no$_2$
22. Sleep disorder	___ (name, ICD-9/10 code, and treatment comments)
23. Date of sleep disorder diagnosis (if documented)	___ (month/year)
24. Hypertension	□ documented pre-transplant □ documented post-transplant
25. Diabetes	□ documented pre-transplant □ documented post-transplant
26. Hyperlipidemia/Dyslipidemia	□ documented pre-transplant □ documented post-transplant
27. Stroke	□ documented pre-transplant □ documented post-transplant
28. Myocardial Infarction	□ documented pre-transplant □ documented post-transplant
29. Coronary Artery Disease	□ documented pre-transplant □ documented post-transplant
30. Peripheral Vascular Disease	□ documented pre-transplant □ documented post-transplant
31. Immunosuppressant Medications (check all that apply)	□ Prednisone □ Prograf □ Myfortic □ Imuran □ Cellcept □ Sandimmune □ Rappamune □ Neoral □ Gengraf
32. Smoking history	___ (pack-years)
33. Non-compliance with transplant medications	□ yes □ no

APPENDIX C

Table 23 presents the Chi-square statistic and significance values comparing the proportion of censoring in all categorical study variables. Diabetes and stroke history were found to have a statistically significant difference ($p \leq 0.05$) in censoring among the categories. It was found that patients with diabetes and patients with a history of a stroke were more likely to be censored (non-cardiovascular related death with a functioning graft).

Table 23.
Comparing Censoring (Non-Cardiovascular Related Death with a Functioning Graft) in Categorical Predictors

Variable	Proportion Censored	DF	Chi-Square	P-value
Sleep Disorder		1		
YES (61)	28% (17/61)		.7656	.3816
NO (237)	34% (80/237)			
Gender		1		
Male (167)	32% (53/167)		.1146	.7350
Female (131)	34% (44/131)			
Race		1		
Caucasian (108)	37% (40/108)		1.5531	.2127
African American (109)	30% (57/190)			
Smoking History		1		
Yes (131)	37% (48/131)		1.6892	.1937
No (166)	30% (49/166)			
Diabetes		1		
Yes (182)	37% (68/182)		4.9317	.0264*
No (116)	25% (29/116)			
Dyslipidemia		1		
Yes (221)	34% (74/221)		.3397	.5600
No (77)	30% (23/77)			
Coronary Artery Disease		1		
Yes (69)	39% (27/69)		1.7708	.1833
No (229)	31% (70/229)			

Table 23. (continued)

Variable	Proportion Censored	DF	Chi-Square	P-value
Stroke History		1		
Yes (56)	48% (27/56)		7.7065	.0055*
No (242)	29% (70/242)			
Heart Attack History		1		
Yes (21)	38% (8/21)		.3164	.5738
No (277)	32% (89/277)			
Donor Type		1		
Living Donor (125)	34% (42/125)		.1081	.7424
Deceased Donor (173)	32% (55/173)			
Functional Status		1		
Full (152)	31% (47/152)		.3751	.5402
Limited (146)	34% (50/146)			
ESRD Etiology		1		
Hypertension (113)	30% (34/113)		.5025	.4784
Other (185)	34% (63/185)			
Education Level		2		
Unknown (24)	33% (8/24)		4.1060	.1283
High School or Below (139)	38% (53/139)			
Beyond High School (135)	27% (36/135)			
Peripheral Vascular Disease		1		
Yes (29)	41% (12/29)		1.1406	.2855
No (269)	32% (85/269)			

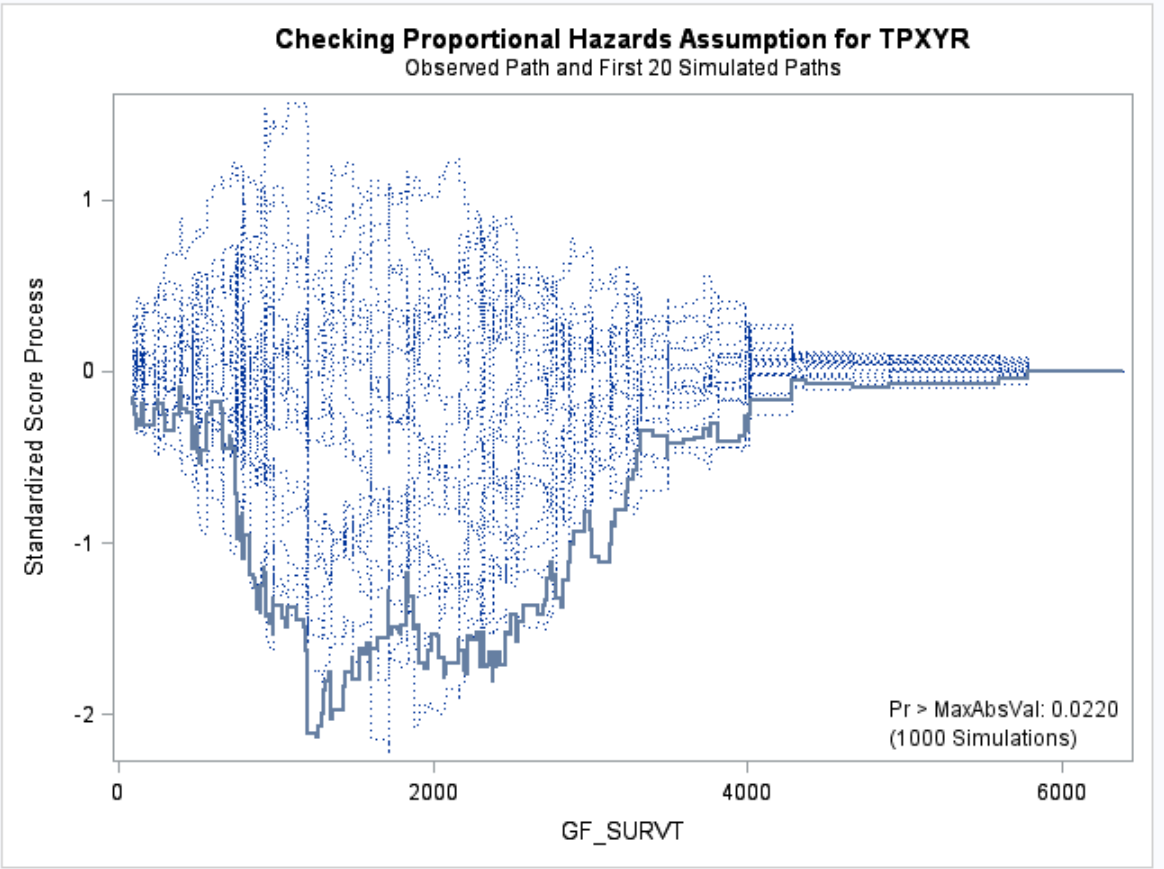
Table 24 presents the t-score statistic and significance value (both one and two tailed) comparing the proportion of censoring in all continuous study variables. The variables tobacco pack-years and recipient age were associated with censoring. Older patients were more likely to be censored (one-tailed significance, $p<.001$). Patients with increased tobacco pack-years were more likely to be censored (one-tailed significance, $p<.04$). One-tailed significance was presented because the comparison involved a directional difference as opposed to a general group difference.

Table 24.
Comparing Censoring (Non-Cardiovascular Related Death with a Functioning Graft) in Continuous Predictors

Variable	**Mean Censored**	**Mean Event**	**t-score**	**DF**	**p-value (two tailed)**	**p-value (one tailed)**
Pack Years	9.7	5.8	1.76	124	.0810	.0405*
Recipient Age	55	47	5.82	229	<.0001*	<.0001*
Body Mass Index	28.21	28.44	.34	296	.7320	.366
HLA Mismatch	3.33	3.64	1.53	296	.1263	.0634
Donor Age	41	39	.97	296	.3308	.1654
Year of Transplant Surgery	2004	2003.6	.68	296	.4961	.2481

APPENDIX D

The outputs below present the violation of the proportional hazards assumption for the variable year of transplant surgery. Both the graphical analysis (p=.0220) and the calculation of the interaction with time (p=.0011) indicate a violation of the proportional hazards assumption.



Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
sleep	1	1	-0.32186	0.17532	3.3705	0.0664	0.725	sleep 1
R_AGE		1	-0.02322	0.00589	15.5304	<.0001	0.977	
R_GENDER	Male	1	0.26272	0.14709	3.1903	0.0741	1.300	R_GENDER Male
Functionality	1	1	0.04687	0.18793	0.0622	0.8031	1.048	Functionality 1
TPXYR		1	0.05690	0.04622	1.5156	0.2183	.	
HLA		1	0.07008	0.04428	2.5053	0.1135	1.073	
T*TPXYR		1	0.0000761	0.0000233	10.6421	0.0011	.	T * TPXYR

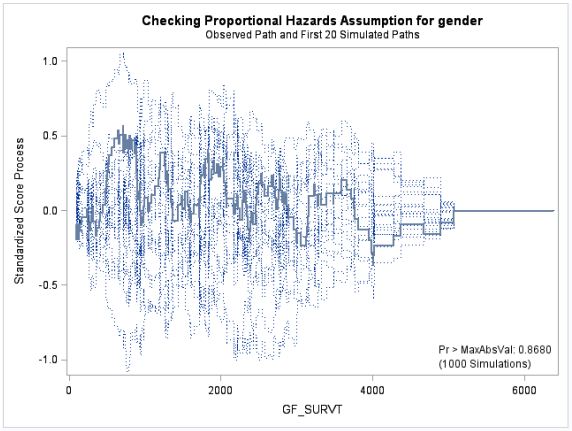
APPENDIX E

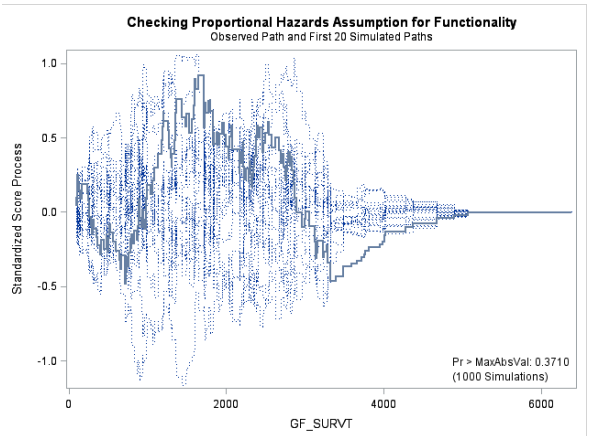
Prior to multivariate modeling, a test for collinearity was conducted using a variable reduction method in SAS, PROC VARCLUS (SAS Institute Inc, 2011). PROC VAR CLUS divides a set of study variables into hierarchical clusters. The program begins with a single cluster, then runs several iterations splitting clusters into correlated variables. Below is the SAS output of the final iteration, identifying three clusters of correlated variables. Cluster 1 identifies a correlation between the variable year of transplant surgery and functionality status. A decision regarding this correlation was not needed due to the stratification of year of transplant surgery. Cluster 2 indicated a high correlation between diabetes and recipient age. However, diabetes was not a significant predictor of graft survival time at the univariate or multivariate level, therefore, no determination was needed. Cluster 3 indicated a high correlation between the variables, race and HLA. Both race and HLA were significant predictors in the univariate and multivariate analyses; therefore a determination was needed regarding what variable to retain in the final model. The variable HLA mismatch was selected based on the literature indicating that African Americans have poorer graft survival outcomes than other races, but that this may be more reflective of immunology variables (Gordon et al., 2010). Because the variable HLA mismatch is a measure of donor and recipient antigen match, and is representative of an immunology measure, the determination was made to retain the variable HLA mismatch (and remove race) from the final multivariate model.

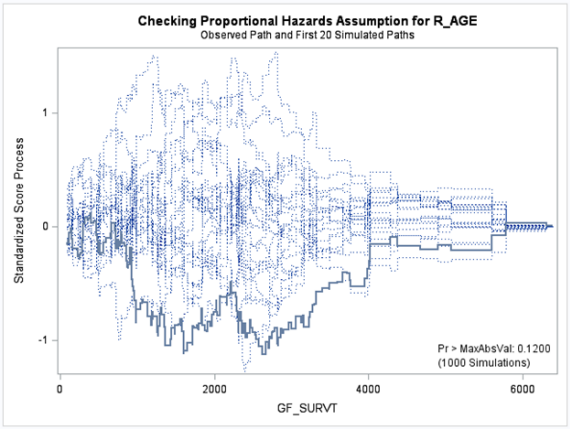
14 Clusters		R-squared with		
Cluster	Variable	Own Cluster	Next Closest	1-R**2 Ratio
Cluster 1	TPXYR	0.8313	0.0791	0.1832
	Functionality	0.8313	0.1025	0.1880
Cluster 2	diabetes	0.6501	0.0398	0.3644
	R_AGE	0.6501	0.0752	0.3784
Cluster 3	race	0.6546	0.0485	0.3630
	HLA	0.6546	0.0298	0.3560
Cluster 4	D_AGE	1.0000	0.0105	0.0000
Cluster 5	H_attack	1.0000	0.0828	0.0000
Cluster 6	Body_Mass_Index	1.0000	0.1088	0.0000
Cluster 7	gender	1.0000	0.0418	0.0000
Cluster 8	smoke	1.0000	0.0418	0.0000
Cluster 9	diagnosis	1.0000	0.0337	0.0000
Cluster 10	PVD	1.0000	0.0448	0.0000
Cluster 11	donorn	1.0000	0.0407	0.0000
Cluster 12	Stroke	1.0000	0.0503	0.0000
Cluster 13	sleep	1.0000	0.0796	0.0000
Cluster 14	CAD	1.0000	0.0828	0.0000

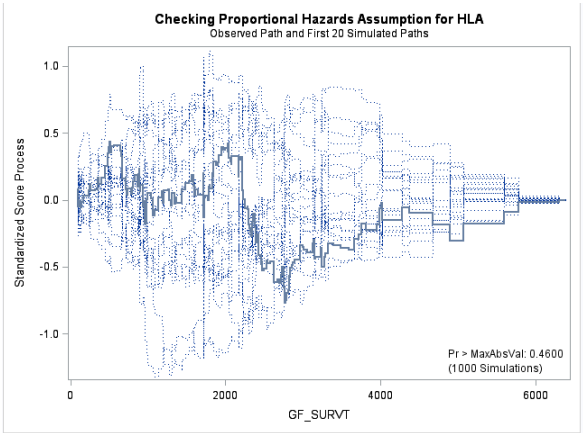
APPENDIX F

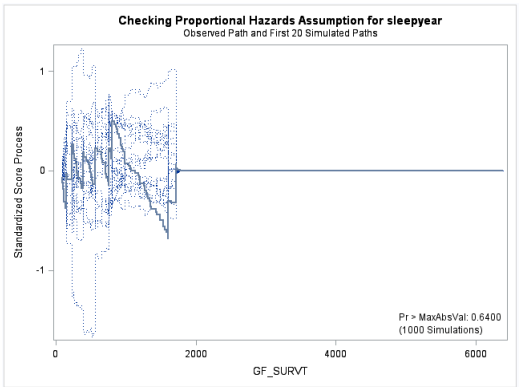
Appendix F presents the verification of model assumptions for hypothesis 2 (graft survival time). The figures below are a graphical measure of proportional hazard assumptions. For each covariate included in the final model the graphical assessment of the proportional hazards assumption reported a p ≥.05, thus indicating no violation of the proportional hazards assumption for gender, functionality, recipient age, HLA, and the interaction between any diagnosed sleep disorder and year of transplant surgery.



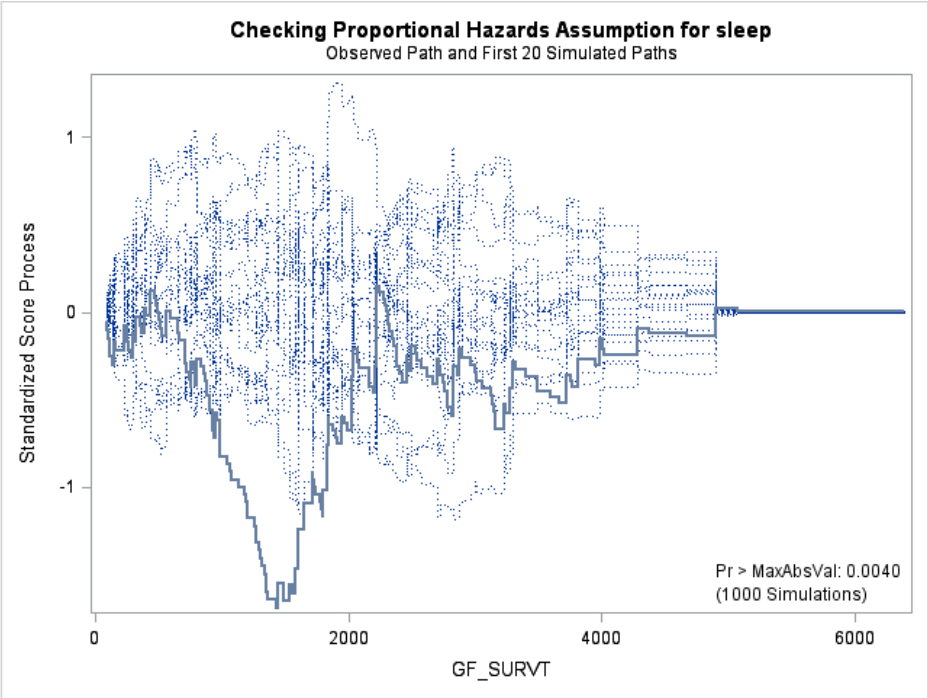








Regarding the variable any diagnosed sleep disrder the graphical measurement of the proportional hazards assumption indicted a potential violation (p=.0040). However, as graphical measurements can sometimes be biased an interaction between the variable any diagnosed sleep disorder and time (graft survival time) was computed.



This table below is a SAS output of the assessment of the proportional hazards assumption by computing an interaction with time for the variable any diagnosed sleep disorder (p=.3473). The lack of significance of this interaction indicates no violation of the proportional hazards assumption.

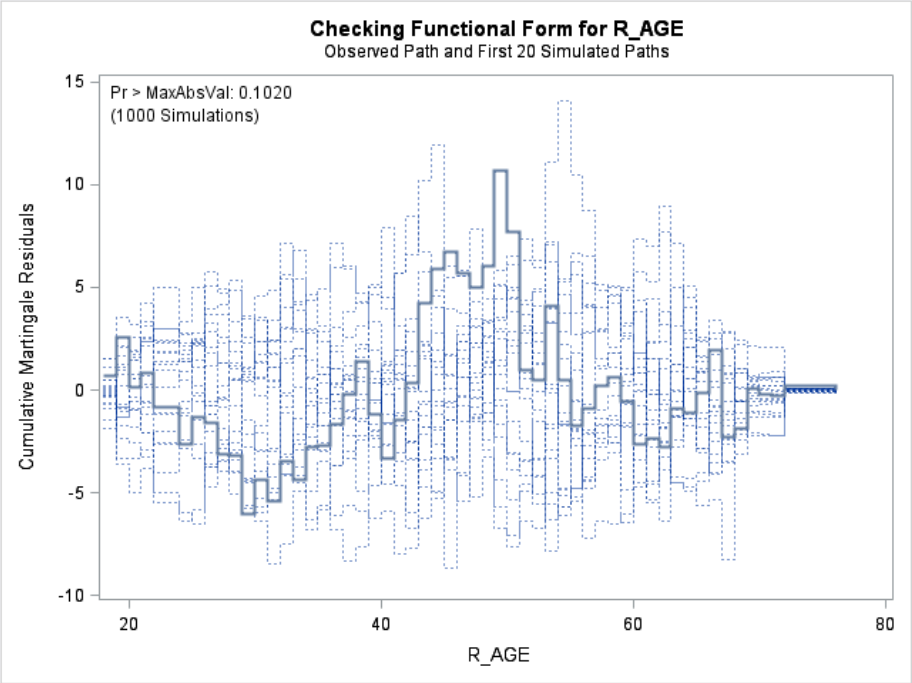
Assessing PH using Interactions with Time

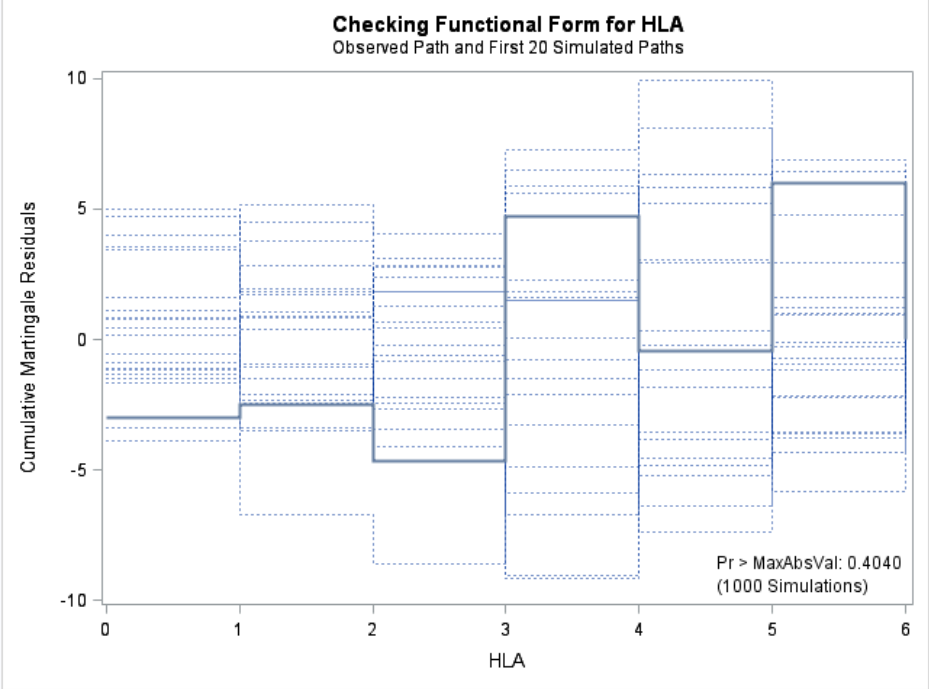
The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
sleep	1	1	-0.45681	0.35429	1.6625	0.1973	.	sleep 1
R_AGE		1	-0.01888	0.00582	10.5123	0.0012	0.981	
R_GENDER	Male	1	0.33840	0.14613	5.3628	0.0206	1.403	R_GENDER Male
Functionality	1	1	-0.59908	0.15134	15.6704	<.0001	0.549	Functionality 1
HLA		1	0.15421	0.04305	12.8338	0.0003	1.167	
T*sleep	1	1	0.0001481	0.0001576	0.8834	0.3473	.	sleep 1 * T

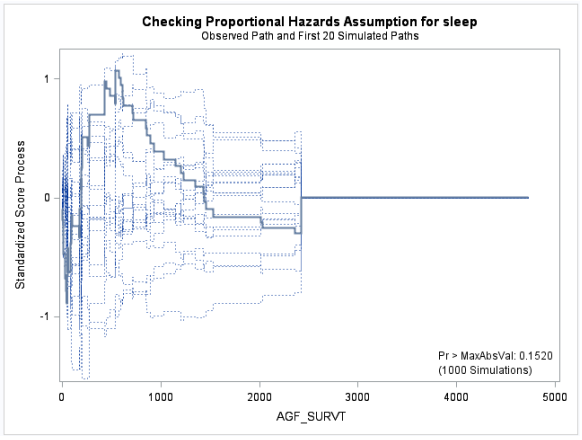
The linearity assumption was assessed through a measure of functional form for all continuous variables in final Cox model. The functional form of recipient age, and HLA both indicate no violations of linearity, which is presented in the figures below.

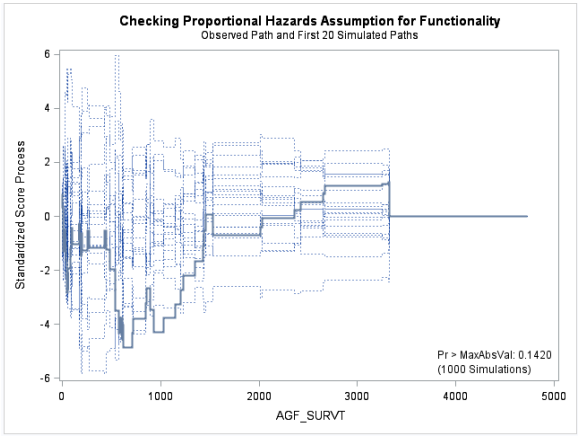


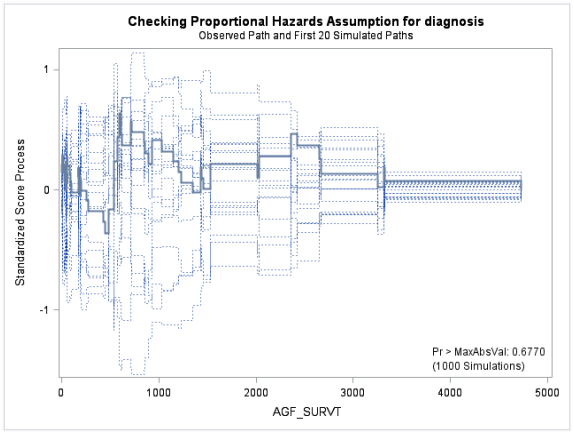


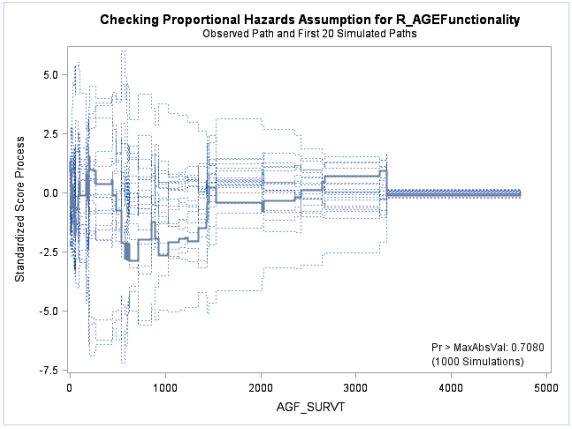
APPENDIX G

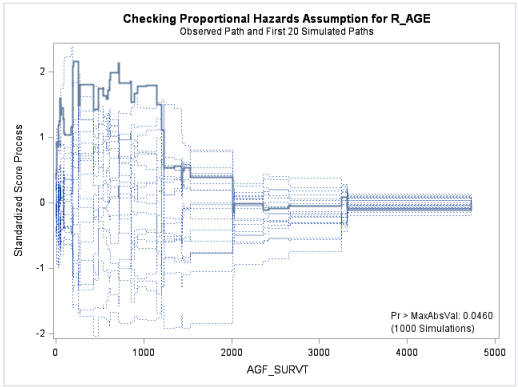
Appendix G presents the verification of model assumptions for hypothesis 3 (patient survival after graft failure. The figures below are a graphical measure of proportional hazard assumptions. For each variable included in the final model the graphical assessment of the proportional hazards assumption reported $p \geq .05$, thus indicating no violation of the proportional hazards assumption for any diagnosed sleep disorder, functionality, recipient age, ESRD etiology, and the age by functionality interaction



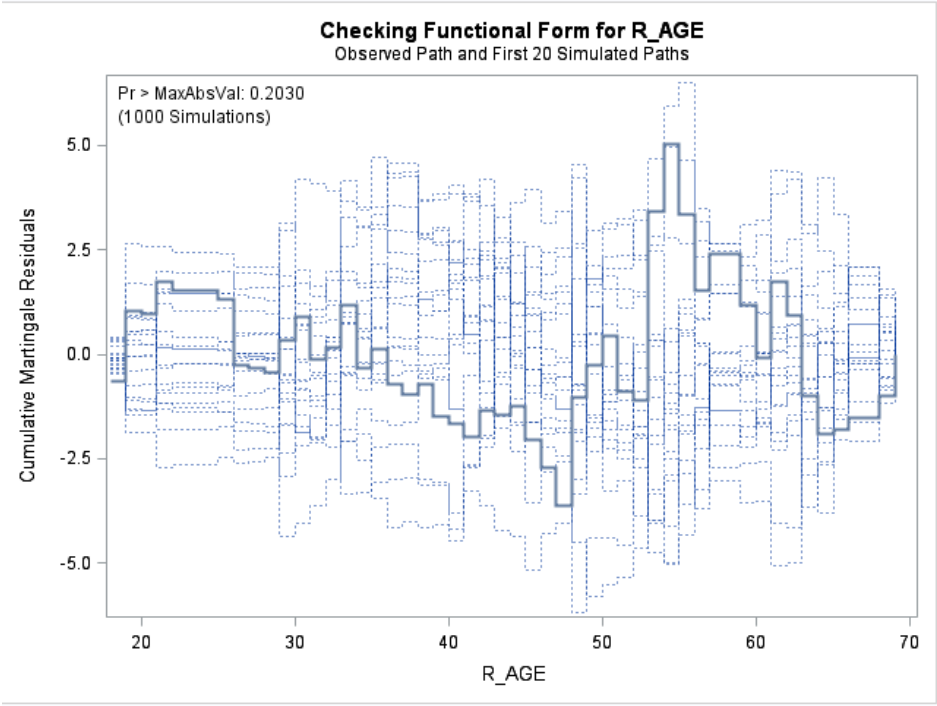








The linearity assumption was assessed through a measure of functional form for all continuous variables in final Cox model. The functional form of recipient age indicated no violation of linearity, which is presented in the figure below.



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Lubas M., De Leo G., Grief Group Facilitators' Attitudes Toward Online Grief Support Groups: Exploring Barriers and Opportunities, *Death Studies,* 38, 517-521. 2014

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