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Multiple Dimensions And Correlates Of Fatigue In Individuals On Hemodialysis: A Quantitative Study

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MULTIPLE DIMENSIONS AND CORRELATES OF FATIGUE IN INDIVIDUALS ON HEMODIALYSIS: A QUANTITATIVE STUDY

by

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DISSERTATION

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Advisor Date

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DEDICATION

Dedicated to all the dreams, that make our existence worthy. To all the positive energies around me, that have preserved and believed in these dreams.

To God Almighty, who has bestowed his grace and wisdom on me. My greatest inspiration in my life, Mom, Dad and my brother, Beechan. Your prayers and struggle have brought me to this milestone. Thank you for believing in me and my dreams. To my late grandmother, whose memories and blessings provided me with willpower, strength at tough times.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: BACKGROUND AND SIGNIFICANCE

Background of the Study

Chronic Kidney Disease (CKD): Definition, Stages and Prevalence

CKD is a debilitating disease of the kidneys characterized by a gradual loss of kidney function ranging from months to years. The loss in kidney function is evident from reduction in the urine production rate from the kidneys, also known as glomerular filtration rate (GFR). CKD is classified to five stages based on GFR values and the albumin creatinine ratio. These five stages are shown in Table 1. The last stage of CKD, Stage G5 is also known as End Stage Renal Disease (ESRD).

Table 1

Stages of CKD

Stage of CKD	GFR (ml/minute/1.73m^2)
G1	≥ 90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	<15

Note. Adapted from Kidney Disease Statistics for the Unite States, 2016. GFR-Glomerular filtration rate, ml/minute/1.73m^2- milliliters per minute per 1.73 meters square.

Stage G5 CKD has a GFR of < 15 ml/minute/1.73m^2. While Stages G1 to G3 are mostly asymptomatic, Stages G4 and G5 are the most disturbing stages with innumerable symptoms and complications ("Kidney Disease Statistics for the United States," 2016). In Stage G5 CKD, the individual becomes dependent on various renal replacement therapies including hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation to sustain his/her life (Daugirdas, Blake, & Todd S., 2015).

CKD affects nearly 31 million people in the US and the most common causes of ESRD are diabetes and hypertension ("Kidney Disease Statistics for the United States," 2016). The prevalence of CKD is 15 percent and there are 726,331 cases of ESRD in the U.S. population ("Annual Data Report Highlights," 2018). CKD is the 9th leading cause of death in the US, and has a high incidence of premature death ("Kidney Disease Statistics for the United States," 2016).

Almost 63.1% of all patients with ESRD were receiving HD whereas 7% were treated with PD, and 29.6% had a kidney transplantation ("Annual Data Report Highlights," 2018). HD therapy involves filtration of blood across a membrane filter called dialyzer, and the individual is connected to a machine at a dialysis unit or at home. The blood is filtered across the membrane and various waste products from a person's blood shift to the other side of the dialyzer membrane where dialysate is present. These waste products include urea, creatinine, potassium and extra fluid that is accumulated in the blood. Individuals on HD must be dialyzed 2 to 3 times weekly to get rid of the waste products and fluids in their body (Daugirdas et al., 2015).

Fatigue in Stages G4 and G5 CKD

Multiple symptoms are reported by individuals suffering from CKD, particularly in the advanced stages. Almost 30 symptoms have been reported in individuals with CKD with the common ones including fatigue (81%), drowsiness (75%), pain (65%), pruritus (61%), and dry skin (57%) (Almutary, Bonner, & Douglas, 2016). Amongst these symptoms, fatigue is one of the most bothersome, distressing, troublesome and a major source of stress in the past studies conducted in individuals with advanced CKD (Almutary, Bonner, & Douglas, 2013; Biniaz, Tayybi, Nemati, Shermeh, & Ebadi, 2013; Horigan, Schneider, Docherty, & Barroso, 2013; Jhamb et al., 2013). The reported prevalence of fatigue ranges from 60-97% in individuals with Stage G5 CKD (Horigan, 2012), and 70-97% in Stage G4 and Stage G5 CKD (Bonner, Caltabiano, &

Berlund, 2013; Bossola, Vulpio, & Tazza, 2011). Almost 56% of individuals on HD reported suffering from severe fatigue (Bayumi, 2015).

Almost 94% of individuals on HD reported that they would accept more frequent HD if it would increase their energy, which indicates that fatigue is important to individuals on HD (Jhamb et al., 2013). In fact, the prevalence of fatigue in dialysis individuals is higher than the general population (Artom, Moss-Morris, Caskey, & Chilcot, 2014). Investigators found fatigue being cross loaded on five symptom clusters in Stage G5 CKD individuals that confirms the pervasive nature of fatigue (Almutary, Douglas, & Bonner, 2016).

Fatigue is a multidimensional and multifactorial concept with poor outcomes that encompasses an individual's personal, professional and social life (Ream & Richardson, 1996). Individuals with CKD describe fatigue as a subjective, unpleasant, distressing experience associated with generalized feelings of tiredness and exhaustion (Artom et al., 2014). Fatigue is multidimensional; various aspects such as physical, cognitive and affective components are involved. In 'physical fatigue' there is physical discomfort and the patient feels 'feeble, dizzy and tired' (Lee, Lin, Chaboyer, Chiang, & Hung, 2007) and is exhausted (Horigan et al., 2013). 'Affective fatigue' causes emotional reactions like 'feeling bad', 'being upset,' and 'cognitive fatigue' causes 'difficulty in paying attention' or 'difficulty in keeping eyes open' and 'difficult to concentrate' (Lee et al., 2007), 'difficulty in remembering names' and 'difficulty in participating in conversations' (Horigan et al., 2013). Among all the types of fatigue described above, individuals on HD in Taiwan reported 'affective fatigue' the most (Lee et al., 2007).

Other multidimensional aspects of fatigue include 'quality,' 'distress,' 'timing,' and 'severity.' Temporal patterns were studied using a qualitative approach in 14 individuals on HD over a 36-hour period from one HD session to the evening before the next session. Participants

reported continuous fatigue and a spike of fatigue after dialysis (Horigan & Barroso, 2016). Limited research is available on the 'quality' of symptom fatigue in individuals with CKD, in that fatigue has been described by different words such as 'feeling exhausted,' 'weak,' 'tired,' and having 'insufficient energy (Lee et al., 2007)'. The 'severity' of fatigue has been reported in various studies that used the Fatigue Severity Scale in individuals on HD, in that severe fatigue was reported in almost 56% of individuals on HD (Bayumi, 2015). Jhamb et al. (2013) reported profound levels of fatigue in 86 individuals with Stage G5 CKD. Patients after dialysis had severe fatigue that averaged 3.4 ± 1.2 (severity scale from 1 to 5, worst) in a study conducted on 85 patients on HD (Sklar, Riesenberg, Silber, Ahmed, & Ali, 1996). In terms of 'distress,' fatigue has been described as the most bothersome symptom by individuals on HD (Almutary et al., 2013; Macdonald, Fearn, Jibani, & Marcora, 2012).

Other than the physical, cognitive, and affective components, fatigue is reported to be severe, distressing and associated with reduced physical performance. A reduction in physical performance happens due to muscle fatigue. Various mechanisms such as oxidative stress (Modaresi, Nafar, & Sahraei, 2015; Scholze, Jankowski, Pedraza-Chaverri, & Evenepoel, 2016), mitochondrial dysfunction (Che, Yuan, Huang, & Zhang, 2014), or vascular changes in the capillaries that affect skeletal muscle function lead to fatigue (Adams, 2005). In 10 individuals on HD, peak oxygen consumption was reduced as measured by the cycle ergometer test indicating impaired exercise performance (Petersen et al., 2012). Another investigator reported low 6-minute walking distance across all age groups in 90 individuals on HD (Pajek et al., 2016). From these studies one can infer that in participants with HD, physical performance is reduced due to muscular fatigue and, perhaps, can be demonstrated through performance- based testing.

The literature available on epidemiology and factors associated with fatigue in CKD is surprisingly limited by a select population with focus on African-Americans, small sample size, inconsistencies in the correlates of fatigue, and flawed self-report fatigue measures (McCann & Boore, 2000; Williams, Crane, & Kring, 2007). These studies have been mostly conducted outside the US (Bossola, Luciani, & Tazza, 2009; Bossola et al., 2018, 2011, Bossola & Tazza, 2015, 2016; Letchmi et al., 2011; McCann & Boore, 2000). Fatigue is associated with negative outcomes such as increased cardiovascular risk, morbidity and premature death (Jhamb et al., 2009; Jhamb, Weisbord, Steel, & Unruh, 2008; Koyama et al., 2010; Sakkas & Karatzaferi, 2012). Fatigue hasn't been receiving much attention until recently, as it is considered an inherent part of the disease process and something that cannot be changed or is tenable to intervention (McCann & Boore, 2000). Under-recognition of fatigue could be also due to the invisible, insidious nature of fatigue (Horigan, 2012). In individuals on HD, fatigue remains an undertreated and under-recognized symptom despite the high prevalence and associated critical outcomes (Artom et al., 2014; McCann & Boore, 2000). There is a need to focus on more evidence about this negative symptom.

Fatigue Assessment in Individuals with HD

Various tools that have been used to assess fatigue in individuals with HD include unidimensional and multidimensional tools. Some of the unidimensional tools that have been repeatedly utilized are VAS-fatigue, the Fatigue Severity Scale, and the Short Form-36 (SF-36) vitality scale (Artom et al., 2014; Horigan, 2012). These unidimensional tools provide a single score in the end that measure one single aspect of fatigue such as severity or vitality. Surprisingly, most of the studies focusing on fatigue in CKD have used unidimensional tools for assessment (Bonner, Wellard, & Caltabiano, 2010; Bossola, Luciani, Giungi, & Tazza, 2010; Bossola & Tazza, 2015; Jhamb et al., 2009; Karadag, Kilic, & Metin, 2013; Williams et al., 2007). The SF-

36 vitality scale is a quality of life assessment tool that has been utilized in individuals on dialysis to assess their fatigue levels. For example, the large scale study 'Impact of Outcomes on Hemodialysis (HEMO)' study that was conducted in the US population used SF-36 to assess fatigue (Jhamb et al., 2009, 2011). However, SF-36 scale may not completely capture fatigue severity in the dialysis population (Jhamb et al., 2009). Also, SF-36 suffers from limitations such as the floor effect. Another frequently used measure of fatigue, VAS, is a single item measure that also suffers from floor and ceiling effects (Hawker, Mian, Kendzerska, & French, 2011). Floor effect happens when most of the reported scores lie on the lower level score of the instrument, whereas ceiling effect happens when most of the scores reported bunch together on the upper level score of the instrument. A psychometrically sound unidimensional tool will have a normal distribution of scores.

Among the list of multidimensional tools for fatigue assessment in individuals with HD, the Multidimensional Fatigue Inventory-20, the Functional Assessment of Chronic Illness Therapy-Fatigue, & the Piper Fatigue Scale (PFS) are some of the most commonly used in previous studies (Artom et al., 2014; Horigan, 2012). Multidimensional tools give separate scores for various subscales, and therefore, cover various aspects of fatigue in one tool such as physical, mental, general, or affective fatigue (Whitehead, 2009). Fatigue being a multidimensional construct requires multidimensional tools. However, few investigators have used multidimensional tools for fatigue assessment in individuals on HD (Biniaz et al., 2013; Karakan, Sezer, & Ozdemir, 2011; Letchmi et al., 2011; Liu, 2006; McCann & Boore, 2000). Therefore, more studies are required that use multidimensional tools for fatigue assessment in the same population.

Various tools used in individuals on dialysis, either unidimensional or multidimensional have another limitation, in that individuals have to answer questions based on their experiences in the past weeks to months. There is a possibility for participants to suffer from recall bias. Further, individuals on dialysis suffer from day to day and within the day (day of dialysis) variations in fatigue that an instrument with long recall periods cannot capture (Abdel-Kader et al., 2014). Therefore, fatigue in CKD requires tools that assess self-reported fatigue momentarily.

Performance-based tests may be a means of assessing fatigue in real time. A six- minute walk test gives a real time assessment of the individuals' momentary fatigue levels by measuring the distance walked by the individual. Some investigators have reported the use of six- minute walk test to measure physical performance in individuals on dialysis (Dziubek et al., 2016; Manfredini et al., 2017; Pajek et al., 2016). More studies are needed utilizing objective measures along with "gold standard" self-report measures to measure fatigue in dialysis.

Factors Influencing Fatigue in HD

There is limited research on fatigue and its associated factors in HD in the US population. Past studies have been conducted in Taiwan, Iran, Malaysia, Turkey, Ireland, India, Australia and Italy (Horigan, 2012). Every culture and geographical region is different, and therefore, the severity, quality and duration of fatigue and associated factors might be different in the US population from the other geographical regions. Myriad factors influence fatigue in individuals on HD including physiological, psychological, and situational.

Multiple physiological factors are known that cause fatigue in individuals on chronic HD treatment. One of the most common reasons for fatigue is sudden fluid shifts that happen during dialysis, causing 'post-dialysis fatigue.' Ultrafiltration, diffusion and osmosis are some of the processes that determine fluid shifts across the membrane (Horigan, 2012; Sklar et al., 1996). If

too much fluid is removed during dialysis or too much weight is gained after last dialysis treatment, fatigue can result. Another factor causing fatigue is anemia, which occurs due to insufficient production of erythropoietin by the kidneys in Stage G5 CKD (Zadrazil & Horak, 2015). Various other physiological factors that have been implicated in the pathogenesis of fatigue are uremia, protein energy malnutrition, levo-carnitine deficiency, chronic inflammation, dialysis inadequacy, presence of comorbidities such as hypertension, diabetes, cardiovascular disease, old age and sleep disorders (Jhamb et al., 2013; Joshwa & Campbell, 2017; Joshwa, Khakha, & Mahajan, 2012). However, equivocal relationships have been found between various physiological factors such as anemia and uremia with fatigue. More studies are required to explore the relationship of these variables with fatigue.

Some of the psychological factors that predict fatigue in individuals on HD and have been studied widely are depression and anxiety. Depression is thought to cause fatigue through inflammatory cytokines such as interleukin-6 in individuals on HD (Bossola, Di Stasio, Giungi, Rosa, & Tazza, 2015). A moderate relationship has been found in multiple investigations between depression and fatigue, with few investigators not finding any relationship between the two variables (Artom et al., 2014). Other psychological factors that are associated with fatigue are anxiety, suicide risk, stress and social support (Karadag et al., 2013; Letchmi et al., 2011).

Situational factors that are related to fatigue in individuals on HD include age, gender, race, educational status, and marital status. Among these factors, females (Liu, 2006), white race (Artom et al., 2014; Jhamb et al., 2009), unemployment status (Liu, 2006), and unmarried status have been found to be associated with increased fatigue in HD. Consistently, race has been associated with fatigue severity, but relationship with age, gender, marital status (Bayumi, 2015; McCann & Boore, 2000; O'Sullivan & McCarthy, 2007), educational status have been equivocal across

studies. More evidence is required to explore these relationships. Variability in the findings limits our ability to propose interventions for those who are at high risk of developing fatigue (Picariello, Moss-Morris, Macdougall, & Chilcot, 2017).

Given that the existing evidence on fatigue in individuals on dialysis have been limited by flawed unidimensional tools, lack of objective measures for fatigue assessment, underpowered samples, variable findings in terms of the correlates of fatigue; this study aims to examine the severity and trajectory pattern of fatigue and delineate various physiological and situational factors that influence fatigue severity in individuals with CKD Stage G5 on HD in a powered, ethnically diverse sample using multidimensional patient reports and performance measures. Studying the severity and trajectory patterns of fatigue will help in identifying the dynamics of fatigue that these individuals on HD go through. Knowledge of factors that predict fatigue may lead to identifying individuals on dialysis that are at high risk for fatigue. Potential findings from this study may lead to appropriate interventions to alleviate fatigue levels in participants on HD.

Significance of the Study

Number of demises occurring in Stage G5 CKD on dialysis therapy is very high, with cardiovascular deaths contributing to more than half of the deaths ("Kidney Disease Statistics for the United States," 2016). Fatigue has been linked with an increased risk of cardiovascular events, because there is a greater degree of underlying inflammation compared to healthy adults, which contributes to coronary artery disease and mortality (Aukrust et al., 2008). Premature death is known to occur in individuals with CKD having excessive fatigue and lower vitality scores (Jhamb et al., 2009). Besides these significant outcomes, fatigue also may have a negative effect on an individual's daily performance, activities, professional life, relationship with family and friends, sex life and course of treatment (Bonner et al., 2010). An individual with fatigue becomes

physically inactive and becomes more dependent (Jhamb et al., 2011). The capacity to engage in daily activity and exercise is reduced (Bonner et al., 2010). There is a considerable reduction in mental, physical, social and functional capacities further affecting quality of life (Jhamb et al., 2008).

Given that fatigue is associated with various negative health outcomes, such as increased cardiovascular morbidity, mortality, increased dependence on others and reduced physical activity, depression, and anxiety; there is a need to focus our research efforts onto this understudied symptom. There is limited research conducted on fatigue in individuals with Stage G5 CKD on HD in US.

This study aimed to examine the various dimensions of fatigue in the Michigan HD population and examine the various situational and physiological factors that are related to fatigue, and therefore would help in understanding the biological mechanisms that cause fatigue in individuals with Stage G5 CKD on HD. This aim is in alignment with one of the research priorities of the National Institute of Nursing Research (NINR) which proposes to understand the biologic basis behind symptoms like fatigue in various chronic illnesses. NINR proposed that a "better understanding of symptoms….will improve clinical management of illness and lead to more productive lives" ("Symptom Science | National Institute of Nursing Research," n.d.). Existing literature on various factors associated with fatigue suggests equivocal results and therefore, this study aimed to confirm or refute the findings from previous studies through a rigorous, multidimensional assessment with a powered sample. Variability in the findings on factors associated with fatigue limits our ability to propose interventions for individuals with Stage G5 CKD on HD. A predictive model of fatigue may be proposed from the results of this study data that will accurately identify individuals at risk for severe fatigue. Currently, there is no consistent

model to predict fatigue and management of fatigue relies primarily on treating anemia and increasing physical activity to alleviate fatigue (Picariello et al., 2017). Appropriate interventions directed towards high risk individuals with fatigue may help in improving quality of life and reducing morbid cardiovascular events in the CKD population.

This study is in alignment with the mission of the American Nurses Association ("About ANA |American Nurses Association," n.d.), in that it will contribute to improving the health of patients by achieving a greater quality of life in individuals with Stage G5 CKD on HD. This study utilized the Theory of Unpleasant Symptoms (TOUS) as the framework to generate various hypotheses based on the relevant past literature, and thereby, the results obtained from this study provided confirming evidence towards hypothesized relationships in the theory and eventually contributed towards the discipline of nursing.

Purpose of the Study

The purpose of this descriptive, correlational study was to examine the severity and trajectory pattern of fatigue and delineate various physiological and situational factors that influence fatigue severity in individuals with CKD Stage G5 on HD.

Specific Aims

Aim 1: Examine the severity and trajectory pattern of fatigue in individuals with Stage G5 CKD on HD.

Research Question 1a: How severe was the level of behavioral, cognitive and affective fatigue pre and post dialysis?

Research Question 1b: How frequently did the HD participants describe being fatigued?

Research Question 1c: Did the mean fatigue scores differ from U.S. and other chronic disease populations?

Research Question 1d: What was the trajectory of fatigue severity from the pre-dialysis to the post-dialysis period?

Research Question 1e: What was the impact of fatigue on the physical performance of HD participants pre and post dialysis?

Aim 2: Identify the extent to which select physiological factors such as anemia, dialysis adequacy, inter-dialytic weight gain, co-morbidities, and age influence fatigue severity in individuals with Stage G5 CKD on HD.

Hypothesis 2: There was no relationship between anemia, dialysis adequacy, co-morbidities, inter-dialytic weight gain and age with fatigue severity.

Aim 3: Identify the extent to which select situational factors such as living status, employment, gender, and race influence fatigue severity in individuals with Stage G5 CKD on HD.

Hypothesis 3: There was no significant difference in fatigue severity with respect to gender, race, employment, and living status.

CHAPTER 2: THEORETICAL FRAMEWORK AND SELECTION OF VARIABLES

Theory of Unpleasant Symptoms (TOUS)

The TOUS was used to guide the present study. According to Lenz & Pugh (2018), the TOUS was designed to improve understanding of a symptom in various contexts and provide information on designing new ways to prevent, ameliorate or manage unpleasant symptoms and their negative effects. The theory has three major concepts- the symptoms, influencing factors, and performance outcomes. The theory states that three interrelated categories of factors particularly, physiological, psychological, and situational factors influence a given symptom, the experience of that symptom and how an individual perceives a symptom. The 'symptom experience' affects the individual's performance, which encompasses cognitive, physical, and social functioning (see Figure 1) (Lenz & Pugh, 2018).

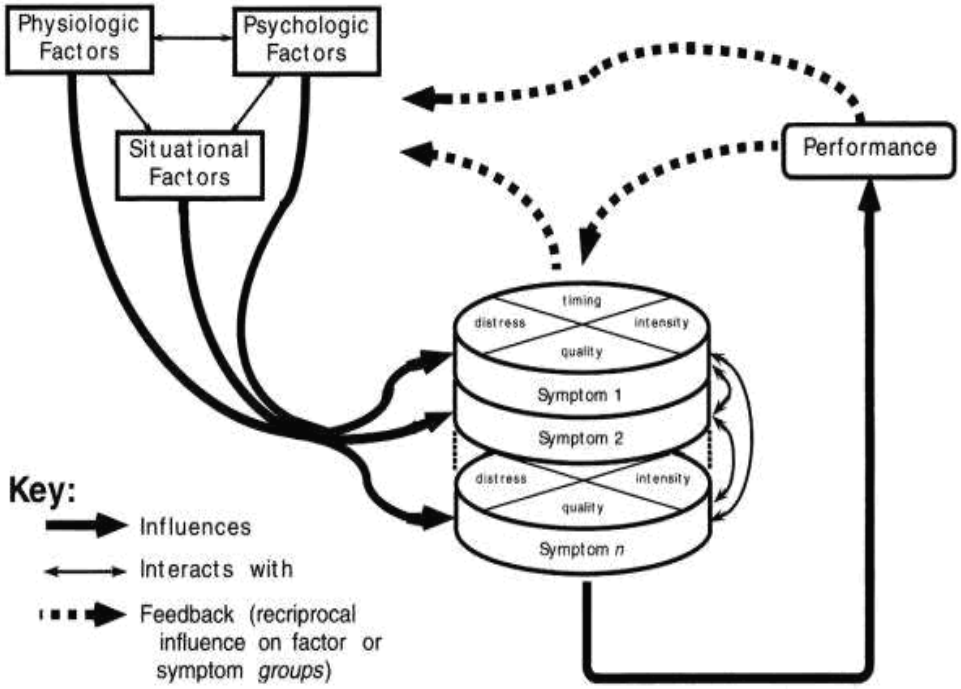


Figure 1. Theory of unpleasant symptoms (Lenz and Pugh, 2018)

Symptoms can be isolated or are clustered and are reported by the individual; sometimes objective signs are apparent. Symptoms are affected by various contextual factors (Lenz & Pugh, 2018). The rationale behind selecting this middle-range theory is that it focuses on symptom/symptoms, highlights multidimensionality, and delineates various factors that influence a given symptom, which was in alignment with the purpose of this proposed study. Symptoms are subjective and can be measured only through self-report although objective signs may be visible. Therefore, this study focused on a combination of subjective reports and objective performance measures to study fatigue. Also, the TOUS suggests that symptom is an unpleasant concept, and since fatigue is an unpleasant and distressing symptom, the TOUS seemed to be a perfect fit for this proposed study.

Propositions of Interest

The propositions from TOUS that are linking the concepts of interest are the following: (1) A symptom has multiple measurable dimensions including quality, distress, severity and timing as it

occurs. (2) Physiological factors, situational factors, and psychological factors influence a symptom and its dimensions.

Theoretical Constructs

The two major constructs that are of interest from TOUS for this study are symptoms and influencing factors.

Symptoms. According to Lenz & Pugh (2018), symptoms are defined as perceived indicators of change in normal functioning as experienced by individuals. Symptoms are conceptualized as having measurable dimensions such as quality, intensity/severity, distress and time as shown in Figure 1. 'Quality' is the nature of the symptom or the way it is manifested or experienced. 'Intensity' refers to the degree, strength, or severity of the symptom. 'Distress' is the degree to which the individual experiencing the symptom is bothered by it. The dimension of 'time' defines the frequency and duration of the symptom (Lenz & Pugh, 2018). The present study focused on fatigue as a symptom and measured various dimensions including intensity/severity and timing of fatigue experienced by the person. Severity of fatigue was the dependent variable in this study. The present study examined the level of sensory, cognitive and affective fatigue and has been added in Figure 2.

The TOUS states that symptoms can have observable signs along with subjective feelings (Lenz & Pugh, 2018). Therefore, this study utilized an objective measure to assess fatigue indirectly through reduced physical performance.

Influencing factors. Influencing factors are the factors that are relevant in producing a given symptom which includes physiological, situational and psychological factors.

Physiological factors. These factors include anatomical, physiological, genetic and treatment-related variables. For instance, the presence of structural anomalies, existence of

pathology, stage or duration of illness, inflammation due to infection and age are examples. Relevant physiological factors that were measured in this study follow.

Anemia. Anemia is caused due to reduced production of erythropoietin by the kidneys in CKD, and fatigue is a manifestation of anemia especially in HD. Anemia in CKD is diagnosed by serum hemoglobin values falling below 13 grams per deciliter (g/dL) in males and below 12 g/dL in females("Anemia in CKD | KDIGO," 2012). Various investigators have looked at the relationship between anemia and fatigue. In a longitudinal study conducted on 28 individuals in Australia suffering from Stages 3-5 CKD, low serum hemoglobin was moderately correlated with fatigue ($r = .39$, $p < .05$) (Bonner et al., 2013), with similar findings reported by a few investigators (Jhamb et al., 2013; Karakan et al., 2011; Williams et al., 2007). Contradictory findings have been reported by a majority of the investigators, in that they did not report a significant association between anemia and fatigue in individuals with CKD on HD (Bossola, Di Stasio, Antocicco, & Tazza, 2013; Bossola et al., 2009; Jhamb et al., 2009; Letchmi et al., 2011; Liu, 2006; McCann & Boore, 2000). These equivocal findings may be due to erythropoietin therapy and having homogenous levels of hemoglobin. Further exploration into the relationship between anemia and fatigue severity was done.

Co-morbidities. Co-morbidities refers to the disorders that an individual is suffering from at a time. A study conducted in individuals on hemodialysis reported that individuals with worse fatigue were more likely to have severe comorbidities (Jhamb et al., 2009). Another study reported a similar finding, with significantly positive correlations between post-dialysis fatigue and comorbidities ($r = .14$, $p = .031$) (Han & Kim, 2015). The present study explored relationship between pre-dialysis fatigue and post-dialysis fatigue with comorbidity scores.

Inter-dialytic weight gain (IDWG). IDWG is the difference in the weight between two consecutive dialysis sessions due to fluid and salt accumulation. The weight gained is calculated from pre-dialysis weight minus the post-dialysis weight of the previous HD session. Normally, a 70 kg individual should gain 2.4 kg between dialysis sessions (Daugirdas et al., 2015). A weak correlation of fatigue with IDWG ($r = .25$, $p < .05$) was reported in a group of 104 individuals on HD in Korea (Kim & Son, 2005). Higher IDWG are associated with higher fluid removals during a HD session and thereby higher ultrafiltration rate which might be contributing to greater fatigue levels. Exploration about the relationship between IDWG and fatigue severity was done.

Age. A weak, positive insignificant correlation was found between fatigue and age in an Irish study in 46 individuals on HD ($r = .20$, $p = .09$) (O'Sullivan & McCarthy, 2007). Older participants with CKD have significantly higher levels of fatigue than younger participants (Liu, 2006). Consistent findings have been reported on older participants tending to be more fatigued in participants on HD (Bossola et al., 2009; Kim & Son, 2005; Letchmi et al., 2011). One possible explanation is that older participants have more co-morbidities compared to younger participants, contributing to higher fatigue levels. Further exploration of age and fatigue severity was done in this study.

Dialysis adequacy. Dialysis adequacy is measured by various methods and calculation of Kt/V is one of them ("Hemodialysis Dose & Adequacy | NIDDK," 2014). A value of 1.2 or higher indicates adequate dialysis. Many investigators have not found an association between fatigue and inadequate dialysis (Bossola et al., 2018; Liu, 2006; Mollaoglu, 2009). An investigator in Iran found significant association ($p = .01$) between fatigue and dialysis adequacy in 43 patients on HD (Dadgari, Dadvar, & Eslam-Panah, 2015). Inadequate dialysis causes a higher circulation of uremic solutes in the blood and may cause fatigue in patients on HD. Investigators have found

association between uremia and fatigue levels in the past (Wang et al., 2016). Uremia might be acting as a mediator of the relationship between dialysis inadequacy and fatigue. Further exploration of relationship between dialysis adequacy and fatigue was done in this study.

Situational factors. According to TOUS, situational factors encompasses individual's social and physical environment. Examples are socio economic status, living status, temperature, light, pollution, and others (Lenz & Pugh, 2018). The situational factors in the present study included living status, employment status, race and gender; a review of which is provided below.

Living status. Living status means if the individual resides with anyone such as spouse, parents, relatives, or no-one. No significant difference between fatigue and being married versus not married (F (3, 41) = .50, p = .68) was found (O'Sullivan & McCarthy, 2007). Similar findings were reported by McCann & Boore (2000) and Bayumi (2015). The reason behind married individuals having lower fatigue levels could be due to the moral and psychological support provided by the spouse (Liu, 2006), however, none of the previous studies have found any relationship between marital status and fatigue. By convention, marital status has been studied frequently. The present study explored the relationship between fatigue severity and living status as living status may be a more relevant construct than marital status.

Employment. Unemployed individuals were more fatigued than their employed counterparts in Taiwan individuals on HD (Lee et al., 2007). Usually staying at home when unemployed might decrease physical activity and social support from colleagues, thereby increasing fatigue levels. Contrasting findings were reported by other investigators (McCann & Boore, 2000; O'Sullivan & McCarthy, 2007). The present study explored more about relationship between employment status and fatigue severity.

Gender. The majority of investigators have reported females being more fatigued than males, which could be due to females articulating their feelings more than males (O'Sullivan & McCarthy, 2007). Females were more fatigued than males in Taiwanese individuals on HD (Liu, 2006). Similar findings have been reported by other investigators (Kim & Son, 2005). Contradictory findings were reported by Bayumi (2015), in that men were more fatigued compared to women in participants receiving HD therapy. No significant difference in fatigue scores was observed between males and females in an Irish study on 39 individuals on HD (McCann & Boore, 2000). Further exploration was done on the relationship between gender and fatigue severity in this study.

Race. Among 36 African-American females on HD, 75% were reported to be fatigued (Williams et al., 2007). However, another investigator reported fatigue to be less prevalent in African-Americans and Asians compared to non-African-Americans (Artom et al., 2014). Similarly, African-American individuals on dialysis reported more energy than non-African-Americans (Jhamb et al., 2009). Caucasians take longer to recover from fatigue after dialysis sessions than African-Americans (Cardenas & Kutner, 1982). In fact, African Americans reported better psychological well-being and lower burden of disease in another study (Unruh et al., 2004). With CKD being more prevalent in African-Americans ("Kidney Disease Statistics for the United States," 2016), one would postulate that fatigue will be more prevalent in African-Americans. The paradoxical findings might be due to greater spiritual well-being in African-Americans (Tanyi & Werner, 2007). The present study explored relationship between fatigue severity and race.

Amongst the influencing factors proposed for this study, consistent relationships have been observed between race, age and fatigue severity. Other influencing factors in CKD that have shown

equivocal relationships with fatigue include anemia, living status, gender, and employment status. Variables such as IDWG have been examined only by a few studies and was explored in this study.

Theoretical Model

The conceptual model shown in Figure 2 summarizes TOUS and hypothesized relationships that are relevant to the present research study. The middle range theory concepts are shown along with the variables from literature review in fatigued individuals with CKD. Figure 3 illustrates the application of TOUS to the select variables chosen for this study. In addition, measures for the select variables are identified and are described in the next chapter.

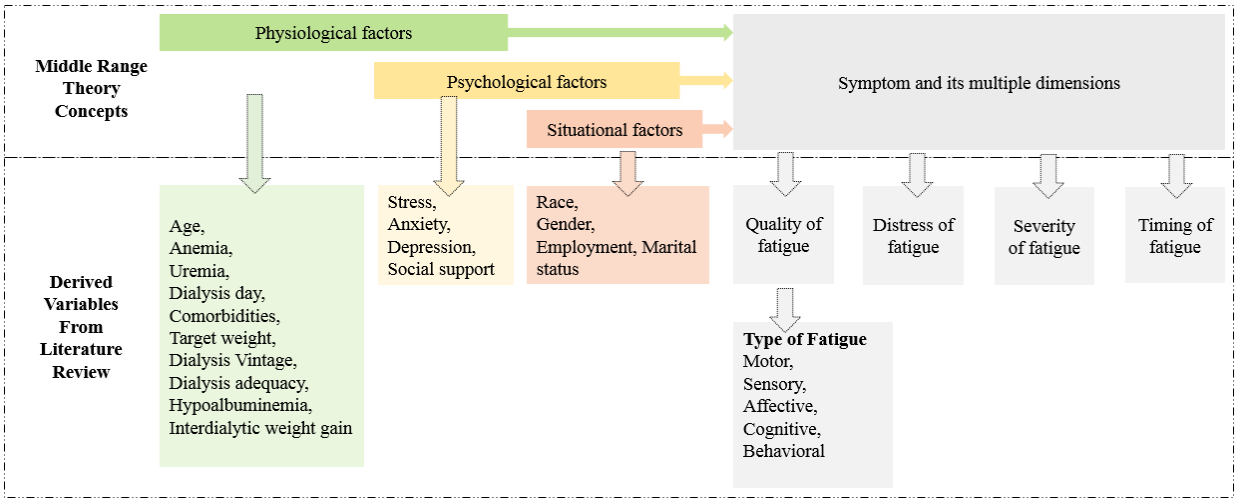
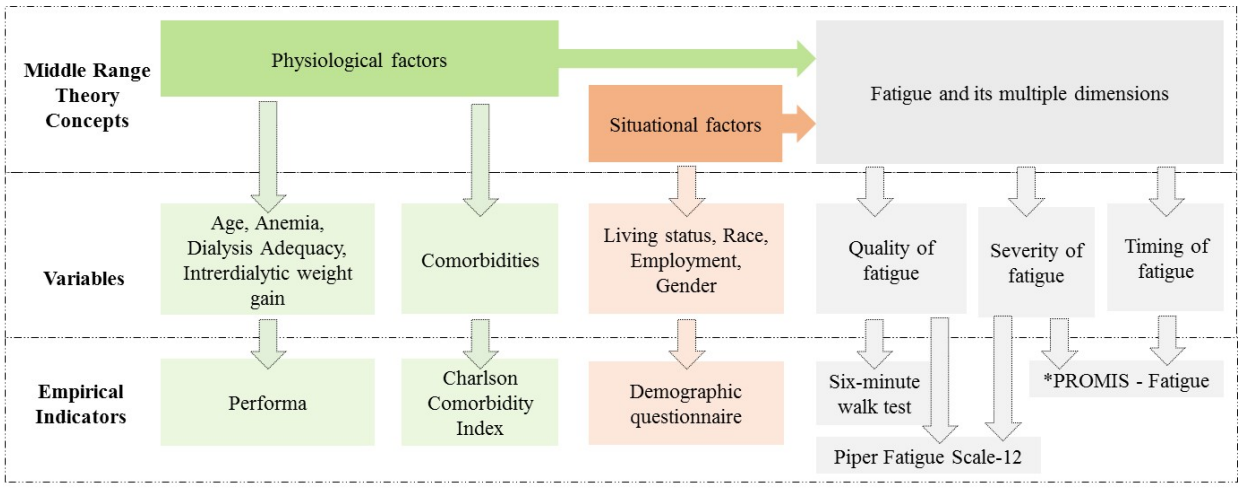


Figure 2. Conceptual theoretical model based on Theory of Unpleasant Symptoms



*PROMIS – Patient Reported Outcomes Measurement Information System

Figure 3. Substruction model showing relevant concepts, variables and empirical indicators

CHAPTER 3: METHODOLOGY

Purpose of the Study

The purpose of this descriptive, correlational study was to examine the severity and trajectory pattern of fatigue and delineate select physiological and situational factors that influenced fatigue severity in individuals with CKD Stage G5 on HD.

Specific Aims and Hypothesis

Aim 1: Examine severity and trajectory pattern of fatigue in individuals with Stage G5 CKD on HD.

Research Question 1a: How severe was the level of behavioral, cognitive and affective fatigue pre and post dialysis?

Research Question 1b: How frequently the HD participants described being fatigued?

Research Question 1c: Did the mean fatigue scores differ from U.S. and other chronic disease populations?

Research Question 1d: What was the trajectory of fatigue severity from the pre-dialysis to the post-dialysis period?

Research Question 1e: What was the impact of fatigue on the physical performance of HD participants pre and post dialysis?

Aim 2: Identify the extent to which select physiological factors such as anemia, dialysis adequacy, inter-dialytic weight gain, comorbidities, and age influence fatigue severity in individuals with Stage G5 CKD on HD.

Hypothesis 2: There was no relationship between anemia, inter-dialytic weight gain, dialysis adequacy, co-morbidities, and age with fatigue severity.

Aim 3: Identify the extent to which select situational factors such as living status, employment, gender, and race influence fatigue severity in individuals with Stage G5 CKD on HD.

Hypothesis 3: There was no significant difference in fatigue severity with respect to gender, and employment, race and living status.

Design

A quantitative, non-experimental, descriptive, correlational, before-after design was utilized in this study. A before-after design was considered because of the significant diurnal changes in fatigue severity levels and some of the associated factors, before and after dialysis. A pictorial representation of the research design is shown in Figure 4. The primary outcome measures were fatigue severity, whereas, the independent variables were anemia, IDWG, dialysis adequacy, age, comorbidities, living status, gender, employment status, and race.

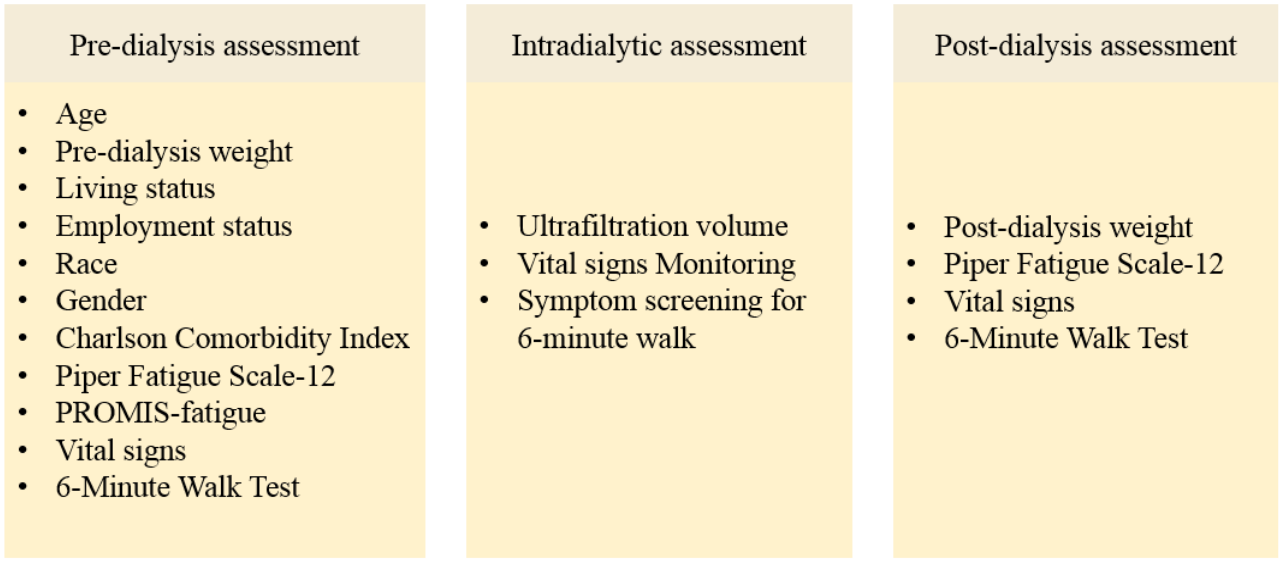


Figure 4. Non-experimental, before-after design

Sample

A non-probability, convenience sampling method was employed, since the study included only those patients who were visiting collaborating clinics, a description of which is provided in section 'Setting.' Individuals were screened according to the following inclusion/exclusion criteria.

Inclusion/ Exclusion Criteria

The inclusion criteria involved the following: (1) Participants who provided consent to participate and were between 18-89 years. (2) Participants who could understand/ converse in English language. (3) Participants with established diagnosis of CKD Stage G5 greater than 3 months and were on HD twice or thrice per week. (4) Participants who were conscious and alert enough to answer the questions according to Mini Cognitive assessment score (Appendix-A).

The exclusion criteria for 6-minute walk test included: (1) Participants who had mobility restrictions and relied on wheelchair for transportation purposes. (2) Participants who were unable to walk. (3) Participants who did not give a verbal approval or were not confident to walk. (4) Visual gait checks on the patient prior to walk showed instability to walk. (5) Participants with conditions such as unstable angina during the previous month, recent myocardial infarction in the previous month, resting heart rate of more than 120 per minute, & hypotension (Blood pressure< 90/50 mmHg) at time of 6MWT. (6) Patient reported about hypotensive signs like light headedness, nausea, vomiting and cramps. (7) Any episodes of intradialytic hypertension associated with an increase in systolic blood pressure >90 mmHg from pre-dialysis to post dialysis.

Setting

The target population was individuals diagnosed with CKD Stage G5 and were on HD twice or thrice a week. Our accessible population were individuals who were visiting the selective outpatient DaVita dialysis clinics in South East Michigan. Individuals who visited these dialysis clinics were primarily from Metro Detroit and Southeast Michigan. DaVita Health Care is a non-profit organization that has a chain of approximately 1500 dialysis clinics across the United States. The initial point of contact was the feasibility coordinator, who handled activities at the DaVita Clinical Research Center. This research center has a Protocol Review Committee that monitors research activities at DaVita across the U.S. After the Protocol Review Committee approved the study protocol, the PI reached out to the 3 DaVita dialysis clinics that participated in the study. Selection of these 3 clinics was based on feasibility and ethnic mix of population and a summary of the clinics is provided in Table 2. Permissions were obtained from the specific Regional Operational Director, Facility Administrator and Medical Directors of these clinics through emails and in-person meetings before beginning the project.

Table 2

Summary of Participating Sites

Facility	**Location**	**Distance from WSU* campus(miles)**	**Dialysis patients enrolled in clinic**
DaVita Health Care	Clinton Township	26	60
DaVita Health Care	Macomb	14.5	90
DaVita Health Care	Partridge Creek	28.1	40

*WSU: Wayne State University

Sample Size

The actual power depends on the specific statistical test used for a given sample size and estimated effect size. The apriori power analyses were run and findings are as follows. For research questions 1d & 1e, using paired samples test, a sample of 34 participants was required. This sample

size is based on a formulation of 80% power, a medium effect size of 0.5, and a significance of 0.05. For Hypothesis 2, using Pearson Correlation, 64 participants were required. This sample size is based on a formulation of 80% power, a medium effect size of 0.3, and a significance of 0.05. For Hypothesis 3, using Chi-square test, a sample of 110 participants was required. This sample size is based on a formulation of 80% power, a medium effect size of 0.3, and a significance of 0.05. To address all the hypotheses in this study, approximately 110 participants were required. Sample size calculations were performed using the G power 3 (Faul, Erdfelder, Buchner, & Lang, 2009). Based on the declination rates, we expected a 40% attrition rate and the total targeted sample size was increased to 150 participants.

Post-hoc power analyses were done to see if there was enough power in the study. For Chi-square, this study achieved 89% power with a moderate effect size with 86 participants. For multiple regression, with five predictors there was 77% power. For logistic regression, a power of 42% was achieved with an odds ratio of 1.5. For running t-tests, there was a power of 99% with moderate effect size. For independent t-tests, there was 95% power based on 86 participants in the study.

Recruitment Procedures and Screening

Permission from the Institutional Review Board of Wayne State University (Appendix-C) was obtained for ethical clearance in February 2018. A letter of support (Appendix-C) was obtained from DaVita Clinic Research Center and after the Protocol Review Committee approved the study in April 2018, the project began at the specific dialysis clinics in May 2018. The principal investigator (PI) reached out to the specific dialysis clinic Facility Administrators/Medical Directors and explained what was needed from the clinic staff. Data were collected from May 2018 to December 2018.

The staff were involved in screening the participants and completed Health Insurance Portability and Accountability Act of 1996 (HIPAA) form (Appendix-B) with the participants who were interested in the study. A waiver from IRB was requested to screen participants for eligibility before taking informed consent. Based on the inclusion criteria, participants were screened (Appendix-A) to look for eligibility by the dialysis clinic staff. If the patient was eligible, the dialysis clinic staff completed HIPAA form with the participants. The PI obtained informed consent (Appendix-B) from the participants who completed HIPAA from those who were interested in participating in Visit 1. A detailed description of the study was provided to the participant during the consent process. A mutually agreeable day of future dialysis was decided for interviewing the patient. Participants received 10-dollar gift cards after Visit 1 as a token of appreciation. Gift cards were from Walmart/Target/Meijer store.

On the day of interview (Visit 2), before dialysis was initiated, interview was conducted for 15 minutes to measure fatigue levels using self-report measures, demographic information (age, living status, employment status, gender and race) and information about comorbidities (Appendix-A). After the interview, participants were screened for the 6MWT (Appendix-A). Vital signs (Heart Rate, Blood Pressure) were measured by the PI. If the participant was eligible for 6MWT based on vital signs and walking history, the 6MWT was conducted. The 6MWT session took 15 minutes. Participants ineligible for 6MWT returned to the dialysis clinic for their dialysis session. Participants received 20-dollar gift cards after completing the pre-dialysis session.

On the same day of interview (Visit 2) after the dialysis session, there was a post-dialysis interview session. The post dialysis interview session included measurement of fatigue levels using self-report measures. Vital signs were measured by the PI to determine eligibility for the 6MWT. The 6MWT was repeated after the post-dialysis interview based on the same screening criteria

used pre-dialysis. Participants received 20-dollar gift cards after completing the post-dialysis session.

Weight was measured pre and post dialysis using the weighing scale installed in the specific dialysis clinics. Other necessary data (serum hemoglobin, recent dialysis adequacy and IDWG) were extracted from the medical records of the patient.

Various strategies were employed to advertise about the research study and encourage participation. DaVita specific flyers (Appendix-B) were distributed to the staff/nurses of specific dialysis clinics. Nurses and dialysis staff helped in spreading information about the study through word of mouth.

A few amendments were made in the study protocol and approved by the IRB in June, August 2018, and February 2019 regarding change in exclusion criteria, increase of enrollment number, deletion of key personnel, addition of key personnel and funding source. A continuation form was submitted to IRB in January 2019 to continue the study in case medical records need to be referred in the post enrollment and analyses period. The continuation was accepted by IRB in February 2019.

Instruments

This study included the following outcome measures derived from the TOUS.

Fatigue and Multiple Dimensions

This study measured quality, severity and timing of fatigue. The Piper Fatigue Scale-12 (PFS-12) (Appendix-A) was used to measure fatigue severity and quality. The Patient Reported Outcomes Measurement Information System-Computer Adaptive Test (PROMIS CAT) for Fatigue (Appendix-A) measured fatigue severity and timing of fatigue. The 6-minute walk test (6MWT) (Appendix-A) was used to measure quality of fatigue, specifically motor fatigue.

Piper fatigue scale. A description of Piper Fatigue Scale follows.

History. The Piper Fatigue Scale (PFS) was originally developed by Dr. Barbara Piper in 1989 to measure multidimensional aspects of fatigue in individuals suffering from cancer. PFS is a self-reported, multidimensional measurement scale that measures subjective perception of current levels of fatigue. The original version of PFS contained 40 items (Piper et al., 1998, 1989). However, due to various limitations observed in PFS such as comprehension difficulty with the response scale, lengthy questionnaire, respondent burden and being impractical for quick assessments (Reeve et al., 2012), the shorter versions of Piper Fatigue Scale has been released. The 12-item version, PFS-12 was used in this study.

Dimensions. The PFS-12 scale is composed of 12 numerically scaled items that measure four dimensions of fatigue using a simple rating from 0 to10 for each item. The four subjective dimensions are *behavioral/severity, affective meaning, sensory*, and *cognitive/mood*. The *behavioral/severity dimension* (three items) reflects the severity, distress of fatigue and changes in activities of daily living that could result from fatigue. The *affective meaning dimension* (three items) focuses on emotional meaning attributed to fatigue. The *sensory dimension* (three items) includes sensory symptoms of fatigue perceived physically such as feeling weak and tired. The *cognitive/mood dimension* (items items) includes perceptions of cognitive ability like difficulty with concentration/remembering ability (Clark, Ashford, Burt, Aycock, & Kimble, 2006).

Scoring. In order to calculate the subscale/dimension scores, the scores of all items within the particular subscale are added, and this sum is then divided by the number of items within the particular subscale. This calculation provides us with a mean subscale score for the participant from 0 to 10. Similarly, a total fatigue score can be obtained by adding the 4 subscale scores and dividing this sum by 4. A total score of 0 means ‘no’ fatigue, 1 to 3 means ‘mild’ fatigue, 4 to 6

means 'moderate' fatigue, and 7 to 10 means 'severe' fatigue. These cut off scores have been validated in a group of breast cancer survivors (Stover et al., 2013). Higher scores on the subscale and the total fatigue scale reflect severe fatigue.

Psychometrics. Excellent internal consistency of PFS-12 has been reported in a study with 799 women survivors from breast cancer. PFS-12 had a Cronbach's alpha of .92, along with the reliability for the PFS-12 subscales .89 (behavioral), .87 (cognitive/mood), .87 (affective), and .87 (sensory) (Reeve et al., 2012). Another investigator found a similar Cronbach's alpha reliability for the PFS-12 scale of .92 in 857 women survivors from breast cancer. Weak convergent validity was found between the PFS-12 and SF-36 physical function subscale ($r = -.374$, $p < .01$), and moderate validity with the SF-36 mental function subscale ($r = -.59$, $p < .01$) (Stover et al., 2013). A previous study that utilized PFS with 22 items in dialysis population did not report the validity in their findings (Karakan et al., 2011).

The Cronbach's alpha for the total scale in the current study was excellent, was .91 before dialysis and .94 after dialysis. For behavioral subscale alpha was .86 before dialysis, .92 after dialysis; affective subscale was .89 before dialysis, .93 after dialysis; sensory was .89 before dialysis, .91 after dialysis.; cognitive was .82 before dialysis and .79 after dialysis.

Rationale for using PFS-12. The PFS-12 is a multidimensional tool and measured specifically four aspects of fatigue that are reported in individuals on HD. Physical, cognitive and affective fatigue were reported in Taiwanese individuals on HD using a phenomenological approach (Lee et al., 2007). The *behavioral/severity* and *sensory subscale* of PFS-12 may be related to the physical aspects of fatigue in HD and *cognitive* and *affective subscale* of PFS-12 might be related to the psychological aspects of fatigue in individuals on HD.

Other multidimensional tools like the Multidimensional Fatigue Inventory-20 have been accused of not having an appropriate factor structure (Chilcot et al., 2017), and difficulty in comprehending the instrument (Artom et al., 2014). The Functional Assessment of Chronic Illness Therapy-fatigue is another tool that does not cover various aspects of fatigue such as *behavioral, sensory, affective* and *cognitive* domains (E. Smith, Lai, & Cella, 2010). Unidimensional tools like VAS, Fatigue Severity Scale only measure one aspect of fatigue and therefore, not appropriate for use in dialysis fatigue that has multiple dimensions (Whitehead, 2009). The revised and shorter version of PFS is preferred over the original version of PFS in the present study as it has 12 items compared to the 40 items in the original version, and therefore, there will be reduced respondent burden. Validity and reliability of PFS-12 has been shown to be acceptable in the past few studies (Reeve et al., 2012; Stover et al., 2013). To our knowledge, PFS-12 has not been utilized in the dialysis population before. Other versions of PFS, that has 22 items have been utilized in dialysis population (Karakan et al., 2011). The instrument is available free of cost and does not require any special training to administer.

The recall period of PFS-12 is of current or 24 hours which is better than a 1 week recall period of other tools like Functional Assessment of Chronic Illness Therapy fatigue, and Multidimensional Fatigue Inventory-20. Greater chances of error can happen in a 1 week recall method. The peak-end cognitive heuristic rule states that the most intense (peak) and final (end) moments of an experience has an influence on the judgements made by a person retrospectively. This influence can bias self-reports of somatic symptoms. Surprisingly, an investigator reported that peak and end experiences do not have a significant effect on daily recall of fatigue in individuals with rheumatic disorders (Schneider, Stone, Schwartz, & Broderick, 2011). In patients with osteoarthritis related low back pain, it was found that recalled overall daily pain is highly

concordant with the average of several momentary pain measurements carried out on the same day (Perrot et al., 2011). Therefore, it can be postulated that a 24-hour recall is concordant with a person's momentary symptom experience. The present study utilized PFS-12 which is a current or 24-hour recall tool that is postulated to adequately measure the momentary, daily variations of fatigue in the dialysis population.

PROMIS measures. The PROMIS measures were developed by National Institutes of Health (NIH) to assess a variety of outcomes and symptoms such as pain, fatigue, physical function, depression, anxiety and social function. PROMIS measures are standardized and rigorously tested in various populations ("PROMIS," n.d.).

PROMIS-fatigue. PROMIS fatigue measures mild to extreme sensations of tiredness and its impact on various aspects of life, including physical, social and mental activities. The instrument covers especially the experience of fatigue in terms of its intensity, duration and frequency in the past 7 days ("Patient-Reported Outcomes Measurement Systems- Fatigue," 2015). This proposed study utilized PROMIS CAT fatigue for measuring fatigue pre-dialysis.

PROMIS fatigue can be administered in short form and computer adaptive testing format to adults, children and parent proxies. Short forms are much shorter versions of this instrument, while the CAT format provides questions to the individual based on responses given. There are a total of 95 questions in the item bank, from which questions are retrieved.

In PROMIS CAT, the computer provides questions with medium trait level initially. The next item is administered according to the individual's previous response. The total time to administer the test is 3 to 5 minutes. The scores obtained from the individual responses are summed into a total also known as the 'raw score,' which is then converted to a T-score by the computer. In order to receive a fatigue score, an individual must respond to four to 12 items. The number of

items provided is response dependent and varies with every individual. The responses of the questions have five options ranging from 'not at all' to 'very much.' Questions that measure frequency have response options ranging from 'never' to 'always.' More questions administered to the individual decreases the chances of error in the scores obtained. A total score of 50 with a standard deviation of 10 is considered an average score. For fatigue, a score of 60 is 1 SD worse than average, and a score of 40 is 1 SD better than average. Therefore, higher scores obtained indicate more severe fatigue. The instrument is available free of cost from the Assessment Center on the National Institute of Health website, however, requires registration from the user ("Patient-Reported Outcomes Measurement Systems- Fatigue," 2015).

Psychometrics. Test-retest reliability was established in two studies. PROMIS CAT fatigue was administered to 100 individuals with osteoarthritis and 100 from the general population, with the retest administered after 7 days, in that desirable test-retest reliability coefficients were obtained ranging from .80 to .92 (Broderick, Schneider, Junghaenel, Schwartz, & Stone, 2013). Similarly, another study conducted on 177 individuals with rheumatoid arthritis found desirable test-retest reliability estimates of .88 with the retest being administered after 2 days (Bartlett et al., 2015).

Repeatedly, good to excellent internal consistency has been reported. Internal consistency of PROMIS CAT fatigue was found to be .98 in individuals with rheumatoid arthritis (Bartlett et al., 2015). The internal consistency of PROMIS CAT fatigue is excellent when scale score ranges from 30 to 90 ("Patient-Reported Outcomes Measurement Systems- Fatigue," 2015). Good internal consistency of .83 for PROMIS fatigue short form was reported in 60 individuals with sickle cell disease (Ameringer, Elswick Jr, & Smith, 2014). There are no studies that have utilized PROMIS-fatigue in HD population to our knowledge. A systematic review done by Ju et al (2018)

confirmed the same (Ju, Unruh, et al., 2018). In the current study, the Cronbach's alpha was excellent (α =.96) based on five items administered to the individual.

Concurrent validity of PROMIS CAT fatigue was found in correlating PROMIS CAT fatigue with Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (r = .76) with no p-value reported (Khanna et al., 2012). Correlation of PROMIS CAT fatigue with VAS-fatigue was .86 (p < .01) (Bartlett et al., 2015), with Fatigue Impact Scale was .86 in 133 individuals with multiple sclerosis (Senders, Hanes, Bourdette, Whitham, & Shinto, 2014).

All domains of PROMIS measures including fatigue were administered to 100 individuals with osteoarthritis and 100 from the general population, where mean scores on each domain in osteoarthritis sample exceeded those from the general population (p < .001) thus, establishing known group validity (Broderick et al., 2013).

Moderate discriminant validity of PROMIS CAT fatigue has been reported, in that the correlation of fatigue with differing constructs such as sleep, anxiety and depression being moderate to low. For example, correlation between PROMIS CAT fatigue and Center for Epidemiological Studies-Depression (depression scale) was .59, and with the Sleep Index scale was .49 in 143 individuals with scleroderma (Khanna et al., 2012). Similarly, moderate correlation of PROMIS CAT fatigue was reported with other differing constructs in PROMIS subscales, in that correlation with sleep subscale was .45, with depression subscale was .49 (Bartlett et al., 2015). Mild correlation of PROMIS fatigue with State Trait Anxiety Scale of .47 was found (Senders et al., 2014). All these correlations are in the moderate range from .30 to .50, suggesting that the discriminant validity is moderate.

Good convergence validity has been reported for PROMIS CAT fatigue, where it was significantly correlated with PROMIS fatigue short form ($r = .88$, $p < .001$) in 100 stable and 85 individuals with chronic obstructive pulmonary disease (Irwin et al., 2015).

PROMIS measures also uses a score metric where each individual question is linked to a presumed concept of fatigue, thereby increasing the validity of the instrument. The flexibility of PROMIS CAT to choose more informative questions offers more precision compared to a short form (Lai et al., 2011).

The PROMIS fatigue item bank was evaluated across various chronic conditions, in that significant improvement in fatigue was observed at follow-up (Cella et al., 2016). Adequate responsiveness was reported for PROMIS fatigue in 229 child parent dyads (Howell et al., 2016).

Advantage and rationale behind using PROMIS CAT fatigue. In this study PROMIS CAT fatigue is superior to various unidimensional tools like Fatigue Severity Scale, Visual Analog Scale-fatigue, Short Form-36 vitality subscale, Functional Assessment of Chronic Illness Therapy-fatigue as they measure one single aspect of fatigue. PROMIS CAT fatigue provides the option of studying various dimensions such as severity, duration and frequency of fatigue in one single tool. PROMIS measures are reliable and valid instruments, however, due to its novelty have not been used previously in the dialysis population. This study will be the first of its kind to use PROMIS-CAT for fatigue in the dialysis population. Tools such as the Functional Assessment of Chronic Illness Therapy- fatigue used in large scale studies with the dialysis individuals suffer from floor and ceiling effects (Acaster et al., 2015), whereas PROMIS measures have been demonstrated to have fewer floor and ceiling effects (Khanna et al., 2012).

The PROMIS CAT fatigue was preferred over PROMIS fatigue short forms as CAT is more precise than the PROMIS short form and therefore provides the option of having small

sample size in the study. The items in PROMIS CAT fatigue are adjusted according to the responses and therefore, is a personalized instrument for every participant. Also, the tool is available at no cost and once administered instantly provides the final scores after calibrating with the population norms ("Patient-Reported Outcomes Measurement Systems- Fatigue," 2015).

Six-minute walk test (6MWT). 6MWT measured motor fatigue in this study and informed 'quality' dimension of fatigue according to TOUS.

Rationale for selecting 6MWT. Due to various advantages of objective measures in general over self-report measures in terms of not having a recall bias and being more accurate (Polit & Beck, 2012), this study utilized an objective measure of fatigue. Various objective tools are available that measure fatigue, and one of the most direct way is through electromyography (EMG) that involves measuring electrical activity in a single muscle through insertion of needle electrodes into the skin. The cost of EMG equipment and the burden of using invasive electrodes in sick patients limits the use of EMG in the dialysis population.

Various factors affect skeletal muscles in dialysis individuals, causing muscle fatigue also known as motor fatigue, eventually that leads to reduced functional or exercise performance (Adams & Vaziri, 2006). Therefore, indirectly fatigue is visible in the task a person performs and can be measured through performance-based tests.

Various exercise-based tests have been related to muscle fatigue like treadmill/ bicycle ergometer testing. However, these tests are not considered safe in individuals with low exercise capacity. One of the golden standard method of measuring functional/exercise capacity is the cardiopulmonary exercise testing that also requires a treadmill. Various timed walking tests are also available such as 1-minute, 2-minute and 4-minute walk test which are shorter in duration, however, are considered not sensitive enough to measure functional capacity in an individual. A

longer duration walking test like a 12-minute walk test has been found to be too exhausting in individuals with respiratory and cardiac problems (Du, Newton, Salamonson, Carrieri-Kohlman, & Davidson, 2009; Venkatesh et al., 2011).

Measurement of functional performance is possible through a 6-minute walk test (6MWT). This study used 6MWT in HD individuals as superior to all the available objective measures to assess muscle fatigue. A 6MWT is considered safe and does not require much exertion like other exercise-based tests. A 6MWT is performed at a submaximal level of exertion, which is similar to the level of exertion at which one performs various activities of daily living (Pajek et al., 2016; Venkatesh et al., 2011). A 6MWT is more feasible, available at no cost and requires no special equipment such as EMG. Results obtained from a 6MWT are easy to interpret and does not require much training as needed for EMG wave interpretation. Also, a 6MWT has been found to be correlated with EMG manifestations of fatigue as measured by conduction velocity from vastus medialis and vastus lateralis muscle during an isometric knee extension in participants with chronic obstructive pulmonary disease (Boccia et al., 2015). In another study in multiple sclerosis participants, strong correlation was observed with short-form 36 physical function subscale (Goldman, Marrie, & Cohen, 2008). A detailed description of 6MWT follows.

According to the American Thoracic Society (2002), a 6MWT measures exercise tolerance also known as functional capacity in various chronic disorders and was developed by Balke in 1963. This test measures the distance an individual walks over 6 minutes on a flat surface. The participant is allowed to pace his walk and asked to walk as far as possible in 6 minutes in a marked hallway. This test has been applied in pediatric, adult healthy populations and across various diseases such as osteoarthritis, fibromyalgia, heart failure, chronic obstructive pulmonary disease and stroke ("ATS Statement," 2002).

Method and contraindications. The test was performed in a hallway of length ranging from 50 feet to 71 feet with cones placed at the beginning and end of the hallway. Ideally, the course must be 30 meters in length, however, an investigator found no significant effect of length course on the distance walked (Sciurba et al., 2003). Before the walk test was started, the participant sat on a chair for 6-8 minutes and his/her pulse and blood pressure were measured to see if it they were in normal limits. The participant was instructed to walk as quickly as possible, with breaks if participant needed them. Comfortable shoes, clothes, and walking aids can be used by the patient. Constant encouragement was provided frequently throughout the 6 minutes. Training was required for the researcher who administered the test. A total of 15 minutes was required to administer the test. The researcher performing the test is required to have Basic Life Support and Advanced Life Support Certification in case of any adverse event during the test (Enright, 2003).

Conditions such as unstable angina/recent myocardial infarction during the previous month, hypertension (>180/100 mmHg), and tachycardia of resting heart rate greater than 120 are considered contraindications as they are associated with a higher risk of cardiac arrhythmias during the 6MWT. The present study did not use hypertension as an exclusion criterion for participants as these individuals on dialysis are usually hypertensive on a daily basis and excluding them would result in losing a major cross-section of the dialysis population. This decision was taken under the discretion of the dialysis nephrologist, Medical Director, DaVita Clinton Township, Michigan. The 6MWT test should be stopped in case of any chest pain, shortness of breath, leg cramps, staggering, diaphoresis and pale appearance ("ATS Statement," 2002).

Scoring. The distance covered in meters or feet was measured over 6-minutes, with lower scores on the distance covered indicating worse function. The distance covered in healthy adults

has been reported to range from 400 to 700 meters (Venkatesh et al., 2011). This study measured 6-minute walk distance in meters.

A substantial meaningful change in 6MWT walking distance score varies by chronic condition. A minimal clinically important difference is the score that reflects changes and has been estimated to be 34.4-54 meters. Specifically, in individuals with chronic obstructive pulmonary disease, a substantial change has been estimated to be 54 meters (Rasekaba, Lee, Naughton, Williams, & Holland, 2009), 50 meters in geriatrics (Perera, Mody, Woodman, & Studenski, 2006), and 34.4 meters in stroke (Tang, Eng, & Rand, 2012).

Psychometrics. Excellent test-retest reliability of 6MWT has been reported in a series of studies involving various disorders, in that correlation coefficients ranged from .98 to .99 with a 30-minute rest in between (Skough, Broman, & Borg, 2013), .97 in cerebral palsy (Andersson, Asztalos, & Mattsson, 2006), .99 in knee osteoarthritis adults (Ateef, Kulandaivelan, & Tahseen, 2016), and .96 to .98 in stroke (Wevers, Kwakkel, & Van De Port, 2011). Excellent interrater reliability of 6MWT has been reported in 37 participants with spinal cord injury (r = .99) (Scivoletto et al., 2011), .97 in 22 participants with spinal cord injury (Van Hedel, Wirz, & Dietz, 2005).

Appropriate predictive validity of 6MWT was estimated by correlating 6MWT with peak oxygen consumption (VO_2) over time, in that moderate correlations were exhibited after 263 days ($r = .71$, $p < .001$) and after 381 days ($r = 0.74$, $p < .001$) in 113 patients with heart failure (Zugck et al., 2000). Another study demonstrated appropriate predictive validity of individuals with heart failure, in that a reduction in 6MWT walking distance predicted increased mortality in males and females (Steffen & Nelson, 2012).

Excellent concurrent validity was reported in individuals with Duchene's muscular dystrophy with timed function tests (McDonald et al., 2013), with 2-minute walk test, and with 12-minute walk test (r = .99) in individuals with stroke (Kosak & Smith, 2005).

Good discriminant validity of 6MWT was demonstrated by poor correlation with body mass index (r = -.07) (Harada, Chiu, & Stewart, 1999). The content of 6MWT was evaluated by 54 raters, and 37% of them reported 6MWT as valid (Jackson et al., 2008). The validity of 6MWT has not been previously reported in CKD Stage G5.

Rationale behind using self-report and objective measures of fatigue. Fatigue is self-reported by the individual through his subjective feelings. Being subjective, fatigue can be indirectly measured through various tools that asks participants about his feelings. This study utilized PFS-12 and PROMIS CAT fatigue as self-report tools to assess subjective fatigue. Other than self-report tools, fatigue can be observed through the performance of an individual in his daily activities. Reduced performance is observed in individuals on HD due to myriad reasons. This study utilized 6MWT to measure functional performance as an objective proxy measure of fatigue in individuals with HD. A combination of self-report and objective measures would provide more insight about an individuals' fatigue experience by contributing towards data triangulation.

Independent Variables (Appendix-A)

Anemia. Serum hemoglobin levels were recorded from the medical records of the individual. On a routine basis, serum hemoglobin values are checked from blood drawn every two weeks in individuals on HD. Before the person is initiated on dialysis, venipuncture is performed by the nurse and blood is sent to the laboratory for hemoglobin measurement. Anemia is diagnosed if the serum hemoglobin falls below 13 grams per deciliter (g/dL) in males and below 12 g/dL in females ("Anemia in CKD | KDIGO," 2012).

Dialysis adequacy. Dialysis adequacy was measured by Kt/V. K is dialyzer clearance, the rate at which blood passes through the dialyzer, t is for time and V is the volume of water a patient's body contains. The most recent Kt/V was obtained from the medical records of the patient. Since the blood test is done every month, we collected the blood records of the patient based on the month of interview with us. Patients with lower Kt/V have more health complications and a greater risk of death. A value of 1.2 and above is considered adequate dialysis ("Hemodialysis Dose & Adequacy | NIDDK," 2014).

Interdialytic weight gain. The amount of weight gained from the last dialysis session measured in pounds is considered as the interdialytic weight gain. The difference between last dialysis session weight and present pre-dialysis weight was determined from the medical records of the patient.

Age, living status, employment status, gender and race. Information about these variables were collected using self-administered questionnaire from the participant. The variable age was an open-ended question. Living status was categorized to living with spouse/ siblings/parents/multiple relatives/ alone, total number of people in the family, number of adults in the house, number of children in house, number of senior citizens in the house, living in own house versus rented house versus apartment versus condominiums versus assisted living versus shelter homes versus others. Employment status was categorized to working full time/part time/contingent, number of jobs, number of days per week, number of hours per day.

Comorbidities. Comorbidities refers to two or more disorders present in the same person. Comorbidities was measured by Charlson Comorbidity Index (CCI) (Appendix-A). CCI was developed by Mary Charlson in 1987 to predict mortality at 1 year due to specific disorders (Charlson, Pompei, Ales, & MacKenzie, 1987). CCI has been used in clinical research to predict

mortality, find confounding influence of comorbidities, and for self-report of comorbidities (De Groot, Beckerman, Lankhorst, & Bouter, 2003; Roffman, Buchanan, & Allison, 2016). There are 17 comorbidities, with 2 subcategories for diabetes and liver disease. Each comorbidity is assigned a weight or a score from 1 to 6. All the scores are added up to get a total CCI score. The severity of comorbidity was categorized into three grades: mild, with CCI scores of 1–2; moderate, with CCI scores of 3–4; and severe, with CCI scores ≥5. The higher the score, greater are the chances of early mortality (Charlson et al., 1987). This measure is available free of cost and requires minimal training. The CCI has proven to be a reliable and valid measure across various studies. In individuals on dialysis, the inter-rater reliability of CCI was found to be excellent (r = .93) (Bernardini, Callen, Fried, & Piraino, 2004). Concurrent validity of CCI was supported by high correlation of comorbidity with other indices such as ICED (Index of Coexistent Diseases) (r = .58, p = .0001) (Gabriel, Crowson, & O'Fallon, 1999). Predictive validity was supported by reports showing that survival time decreased when the CCI score rates went up using Kaplan-Meier curve analysis in individuals with diabetic nephropathy (Huang et al., 2014).

Data Analysis

Research Question 1a: How severe was the level of behavioral, cognitive and affective fatigue pre and post dialysis?

Descriptive statistics including measures of central tendency and standard deviation were used to describe the severity of behavioral, cognitive and affective fatigue.

Research Question 1b: How frequently did the HD participants describe being fatigued?

Descriptive statistics were used to describe the frequency.

Research Question 1c: Did the mean fatigue score differ from U.S. and other chronic disease populations?

Independent t-test was used to test significant differences in fatigue scores.

Research Question 1d: What was the trajectory of fatigue severity from pre-dialysis to post-dialysis period?

Dependent t-test were used to describe the trajectory of fatigue severity pre and post dialysis.

Research Question 1e: What was the impact of fatigue on physical performance of HD participants pre and post dialysis?

Dependent t-test were used to describe the impact of fatigue on physical performance.

Hypothesis 2: There was no relationship between anemia, uremia, inter-dialytic weight gain, comorbidities and age with fatigue severity.

Pearson's correlation test/Spearman's rank correlation was used to correlate physiological factors with fatigue severity.

Hypothesis 3: There will be no significant difference in fatigue severity with respect to gender, race, marital status and employment.

Chi square test was used to find significant difference in fatigue severity based on the select situational factors.

Human Participants Protections

This study recruited participants from 3 dialysis clinics in Southeast Michigan. Characteristics of the participants have been discussed in the inclusion/exclusion criteria section.

Sources of Materials

Information about the participants was collected from the medical records regarding the diagnosis, and other general health information. Questionnaires were used to collect information about their fatigue scores, & demographic information. The health information collected from the dialysis center were used for research purposes only. Coded ID numbers were used on all

questionnaires. Only the PI had access to participant identifiers. A master list with participant identifiers was prepared to keep track of the patients completing data collection as there were multiple encounters with the participants.

Potential Risks and Protections

There were no direct side effects associated with this study. However, there may have been chest pain, shortness of breath, leg cramps, staggering, diaphoresis and pale appearance while a 6MWT was being performed, in the event of which the test would have been stopped and necessary medical intervention would have been provided by the BLS certified nurses or personnel in the clinic. The hallway where 6MWT was done had easy access to crash cart and an automated external defibrillator in case of any serious adverse events. Measures were taken to exclude participants who were at high risk for adverse events. In addition, the PI undertook BLS certification.

Participation in this study may have increased a participant's awareness of various symptoms in CKD, which may cause anxiety. Basic education, counseling, and emotional support to relieve anxiety were available from the PI. The risk for serious psychological distress from participation in this research was expected to be minimal. However, referrals for psychological support would have been made to a counselling clinic; but the payment of these services would have been the responsibility of the participants.

A breach of confidentiality occurs if the signed consent form is not kept secure. Several safeguards to ensure privacy of data were undertaken. Coded ID numbers were used on the interview forms. All the instruments that were filled and completed were kept separately from the forms that were completed. No identifiers were kept except for the consent form. All paper records

were maintained in locked cabinet in a locked research office. In addition, published reports of results will not include participant identifiers.

Participants were advised that they can withdraw their clinical data from the study analysis at any time without penalty. Following completion of this study, the medical records and the interview forms will continue to be stored.

Potential Benefits of Research

There was no direct benefit for participants in this research. However, the findings may enable health care providers to improvise treatment for patients who present with a high risk for fatigue. Findings will provide researchers with a better understanding of the pathophysiologic mechanisms underlying fatigue in HD patients that may lead to development of interventions in the future.

Data and Safety Monitoring Plan

Study Monitoring

The dissertation committee members including 3 senior level researchers and a statistician along with the PI helped in monitoring the quality and standards of the research. A review was performed on a quarterly basis to determine attrition rates, documentation of any adverse events observed during fatigue assessment, and any missing data. This group kept an oversight of the study as well as considered factors external to the study when interpreting the data, such as scientific or therapeutic developments that may impact the safety of the participants or the ethics of the study. Any changes made in the protocol were reviewed by the advisor and information was sent to the IRB and the funding agency.

Security Procedures for Collection, Transfer and Storage of Electronic Data

Electronic data included data collection instrument excel sheets, data sheets, recruitment information. All the computers used for the purpose of storing research related data were password protected. A password was required to log into Windows and then log into specific software. Data was entered into the SPSS 22 software in a personal secured computer. Electronic copies of forms were stored on a secure server with firewalls. The system used 128-bit encryption (SSL certificate) to transfer data between the machines. This technology is the same as that used for online e-commerce applications to protect consumer information such as name, address, and credit card details. Also, the servers are scanned for viruses to detect attempts at unauthorized entry.

Security Procedures for Collection, Transfer and Storage of Paper Data

Paper files consisted of participant consents, completed participant assessment instruments. Double checking and spot checking was done during data entry. The data (hard copies of questionnaires) were stored in a safe place in a locked cabinet with the PI. All the paper copies of consent forms were kept separately from the completed study forms in the College of Nursing building.

Identification of Adverse Effects

Serious adverse events include death or any breach of confidentiality. In case of any adverse event that happened during the study would have been reported to the PI and the dissertation committee members within 24 hours. Subsequently the IRB would have been notified about the same. All the participants were provided with a telephone number to contact in case of any concerns. The necessary details of the adverse event would have been entered into the computer subsequently by the PI. The integrity of the study design was monitored as described

below, irrespective of the fact that the anticipation for any serious adverse event during the study is minimal.

Quality Assurance of the Data

A report was prepared regarding the key characteristics of the study participants, completeness and quality of data. The Dissertation Advisor was involved in checking the integrity of data storage, analyzing excessive number of "don't know" responses. Project meetings took place on a need basis. These meetings addressed concerns and gave project updates.

CHAPTER 4: RESULTS

The purpose of this descriptive correlational study was to examine the severity and trajectory pattern of fatigue and delineate various physiological and situational factors that may influence fatigue severity in individuals with CKD Stage G5 on HD. Figure 5 shows the details about the enrollment of participants. Altogether 93 participants consented, 86 people completed the interviews pre-dialysis.

A total of 27 individuals declined to participate of which 20 were not interested. From these 20 individuals who were not interested in participating, 12 were receiving dialysis from Macomb Kidney Center, six were from Clinton Township and two from Partridge Creek dialysis center. A higher volume of patients (approximately 90 patients) receive dialysis at Macomb compared to Partridge Creek (approximately 40 patients) and Clinton Township (approximately 60 patients), and a higher number of individuals (n = 12) were not interested to participate from Macomb compared to the other two. There were no significant differences between the participants who participated (n = 86) and those who declined (n = 20), based on gender (χ^2 = 1.94(1), p = .163). There were no significant differences between participants who participated (n = 86) and those dropped from the study (n = 7), based on gender (χ^2 = .003, p = .959).

The results from data analyses have been separated into 2 sections, Section 1, description of the sample and Section 2, results organized according to the specific aims, research questions and hypothesis.

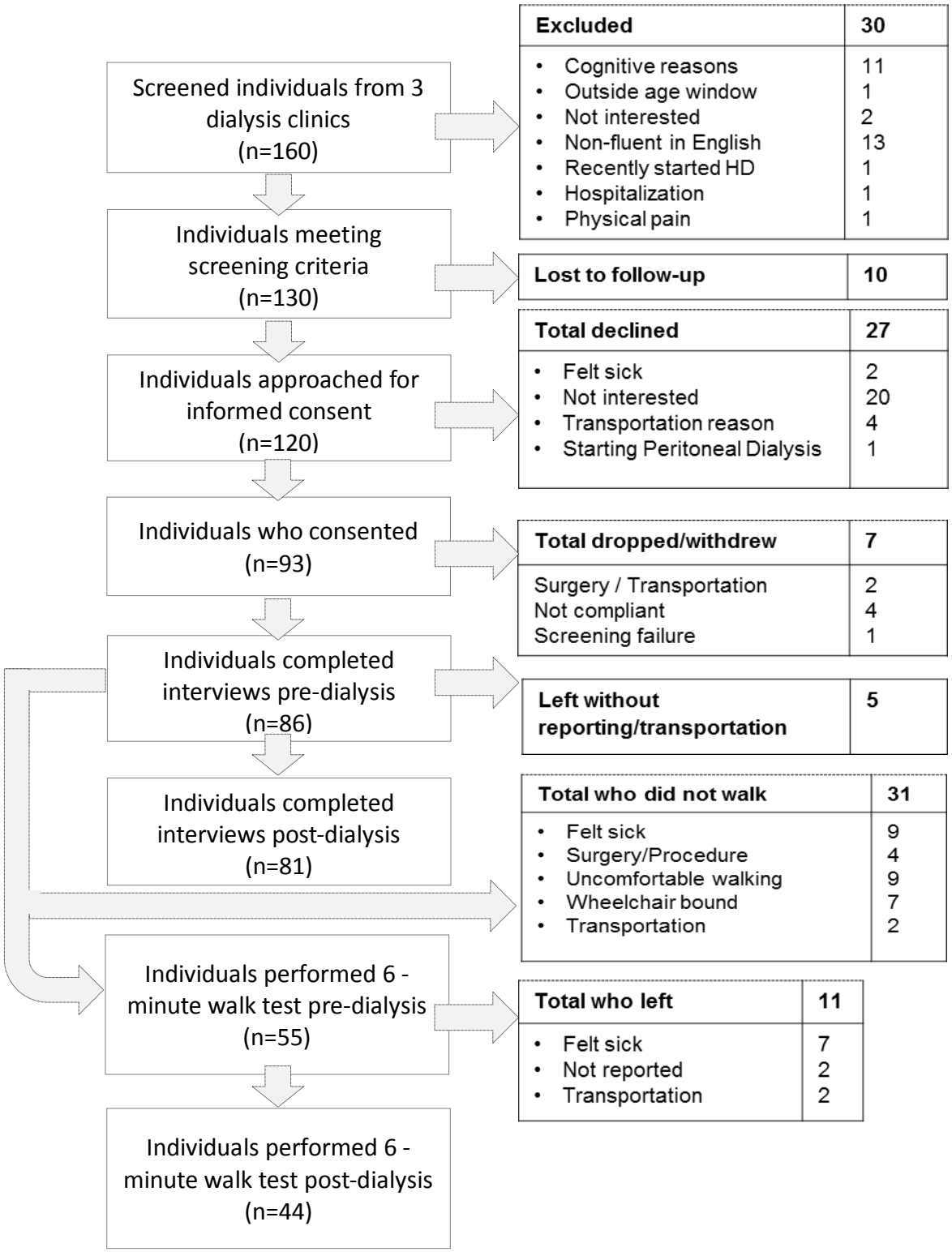


Figure 5. Enrollment of individuals: sampling process

Description of the Sample

Table 3 illustrates the frequency and percentages of demographic characteristics of the sample. Data were analyzed from a total of 86 participants who completed some measures in the study. The majority of the sample (90.7%, n = 78) were either African Americans (48.8%) or Caucasians (41.9%), with more males (n = 50) than females (n = 36). Most of the participants lived alone or with their spouses, while the remaining lived with their children, siblings, parents, and relatives. Most individuals owned their houses while others lived in an apartment, rented house, condo/townhome, and assisted living. Many of the individuals were not working or were retired.

Table 4 illustrates the summary measures of demographic characteristics of the sample. The age of the sample ranged from 24 to 89 years, with a mean of 61.71 years (SD = 13.81, Mdn = 63.5). Majority (n = 53) of the individuals were less than 65 years of age, whereas lesser number (n = 33) belonged to age group greater than 65 years. Based on race who were less than 65 years, 31 (36%) were African Americans, 22 (25.6%) were non-African Americans. Beyond 65 years of age, 11 (22.8%) were African Americans and 22 (25.6%) were non-African Americans. There was a significant difference in racial categories based on the two age groups, as evidenced by Chi-square test ($\chi 2$ = 5.15(1), p = .023). There were four people in the household on an average, with two adults in the house. On an average, participants worked one day in a week.

In terms of the site where participants were getting dialyzed, 44 individuals were from Clinton Township, 23 from Macomb, and 19 from Partridge Creek. Based on age groups, 25 individuals (56.8%) were less than 65 years, whereas 19 (43.2%) were greater than 65 years of age at Clinton Township. At Macomb Kidney Center, there were 14 (60.9%) individuals lesser than 65 years compared to 9 individuals (39.1%) who were beyond 65 years of age. At Partridge Creek, 14 individuals (73.7%) were less than 65 years, whereas 5 people (26.3%) were beyond 65 years.

However, no significant differences were observed between these 3 sites, in terms on age groups (χ^2 = 1.60(2), p = .448). There were no significant differences noted between the three sites, in terms of race (χ^2 = 0.50(2), p = .779) and living status, (χ^2 = 1.77(2), p = .411).

Table 3

Frequency and Percentage of Demographic Characteristics (N=86)

Variables	Frequency	Percentage
Race		
Asian	1	1.2
African American	42	48.8
Caucasian	36	41.9
Hispanic/Latino	2	2.3
Other	5	5.8
Gender		
Male	50	58.1
Female	36	41.9
Employment		
Fulltime	5	5.8
Part-time	5	5.8
Contingent	2	2.3
Not working	74	86.0
Number of jobs		
None	74	86.0
One job	12	14.0
Living status		
Spouse	21	24.4
Siblings	3	3.5
Parents	4	4.7
Multiple relatives	4	4.7
Alone	25	29.1
Children/son/daughter	14	16.3
Spouse and kids	8	9.3
Spouse and siblings	3	3.5
Friends	4	4.7
Living status		
Own house	38	44.2
Rented house	10	11.6
Apartment	20	23.3
Condominium	9	10.5
Assisted living	2	2.3
Others	6	7.0
Townhome	1	1.2
Age		
More than 65 years	33	38.3
Less than 65 years	53	61.6

Table 4

Summary Measures of Demographic Characteristics

Variables	N	Range	Minimum	Maximum	Mean	SD
Age (years)	86	65	24	89	61.71	13.85
No. of people in the family	86	16	0	16	4.27	2.99
No. of adults in the house	86	6	0	6	1.78	1.47
No. of children < 18 years in the house	86	6	0	6	0.44	1.01
No. of senior citizens in the house	86	2	0	2	0.56	0.76
No. of days working per week	86	7	0	7	0.56	1.58
No. of hours working per day	86	12	0	12	1.03	2.90

Note. SD=Standard Deviation, N=Number of subjects

Table 5 shows the summary measures of physiological data collected in the study. The dialysis adequacy scores were adequate (>1.2) on average. The post-dialysis target weight of the individuals ranged from 53.5 kilograms to 162 kilograms, with an average of 90.8 kgs (*SD* = 26.46). Individuals were anemic, both males and females on an average. A person with anemic kidney disease on hemodialysis is recommended erythropoietin injection intravenously at low dose if hemoglobin is below 10 gms/dL ("Anemia in Chronic Kidney Disease | NIDDK," 2014). The patients were on dialysis treatment for 3 and 1/2 hours on an average.

Among the individuals who completed 6-minute walk test, pre-dialysis and post-dialysis systolic blood pressure was high on an average, while diastolic blood pressure was mildly elevated. As shown in Table 6, the majority of the participants had arteriovenous fistula as their vascular access for dialysis treatment.

Table 5

Summary Measures of Physiological Data

Variables	n	Minimum	Maximum	Mean	SD
Dialysis adequacy (Kt/V)	85	0.98	2.03	1.48	0.21
Serum hemoglobin					
Male	49	7.60	14.50	10.53	1.17
Female	36	7.10	13.30	10.41	1.22
Dialysis duration	86	150.00	300.00	216.62	25.68
IDWG	84	-2.30	6.10	2.15	1.50
Target weight	86	53.50	162.00	90.8	26.45
Pre-dialysis parameters					
Weight	86	52.60	165.20	91.74	26.53
SBP pre-walk	55	108.00	234.00	149.22	29.30
DBP pre-walk	55	54.00	157.00	84.76	18.26
Pre-walk HR	55	50.00	112.00	76.38	12.44
Post-walk HR	52	59.00	130.00	88.06	18.21
Post-dialysis parameters					
Weight	86	52.20	162.10	89.84	25.78
SBP pre-walk	48	94.00	205.00	144.42	25.27
DBP pre-walk	48	54.00	125.00	82.48	15.94
Pre-walk HR	48	50.00	114.00	79.98	15.40
HR post walk	44	61.00	123.00	88.27	16.05

Note. Weight in kilograms, hemoglobin in grams per deciliters, blood pressure in mm/Hg, Duration is in minutes, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, HR= Heart Rate in beats per minute, IDWG=Inter-dialytic weight gain, SD=Standard Deviation.

Table 6

Frequency and Percentage of Physiological Data (N=86)

Variables	Categories	Frequency	Percentage
Vascular	Arteriovenous fistula	61	70.9
access	Arteriovenous graft	20	23.3
	Catheter-femoral/subclavian	5	5.8
Comorbidity	Moderate	11	12.8
	Severe	75	87.2

Analyses according to Specific Aims and Research Questions

Specific Aim 1: To describe the severity and trajectory pattern of fatigue severity in individuals on HD.

Research Question 1a: How severe was the level of sensory, behavioral, cognitive and affective fatigue before and after dialysis?

In the Piper Fatigue Scale, there are four subscales namely, behavioral, affective, sensory and cognitive. Each individual subscale score is obtained by adding the 3 specific item scores belonging to that subscale. Since each item has a score from 0 to 10, the total scores for the subscales can range from 0 to 30. Severe fatigue ranges from 21 to 30 based on PFS subscale scores. In this study, the scores from each subscale items were added up to get a total score for each subscale. Table 7 illustrates the summary measures of the subscales in the pre-dialysis and post-dialysis period. Moderate affective fatigue was the highest type reported in the pre-dialysis period, while moderate affective and moderate sensory types were reported in the post-dialysis period. Mild cognitive fatigue was reported during pre-dialysis and post-dialysis period. There

were significant differences between various types of fatigue subscales pre and post-dialysis, a detail of which is provided later in Table 12.

Table 7

Summary Measures of Fatigue Types Based on Piper Fatigue Scale

Variables	Pre-dialysis				Post-dialysis			
	N	Mean	SD	Maximum	N	Mean	SD	Maximum
Behavioral fatigue	86	13.79	8.66	30	81	13.86	9.55	30
Affective fatigue	86	15.24	9.07	30	81	14.27	9.60	30
Sensory fatigue	86	11.32	8.64	30	81	14.31	9.28	30
Cognitive fatigue	86	6.29	5.98	26	81	7.86	6.57	28

Note. The minimum score was 0 for all the subscales. SD= Standard Deviation, N= Sample

The total score from each PFS subscale ranges from 0 to 30. Based on original PFS-12 scoring, the subscale score ranges between 1 to 3 in 'mild' fatigue, 4-6 in 'moderate' fatigue and 7 to10 in 'severe' fatigue. When multiplied by 3 items based on number of items in each subscale, these scores range from 3 to 9, 12 to 18, and 21 to 30, in 'mild', 'moderate' and 'severe' fatigue respectively. Clearly, some of the scores are not accounted for such as 1, 2, 10, 11, 19, 20 are not part of the range. That's why, a new categorization was done to account for the scores that lie in between. Please note that we have reclassified the categories of PFS from those previously established (Reeve et al., 2012). In this study, the score obtained from individual PFS subscales was categorized to 4 groups, namely, no fatigue with score of 0, mild fatigue with score from 1 to 10, moderate fatigue for a score of 11 to 20, and severe fatigue for a score of 21 to 30. Results shown in Table 8 were obtained using same process. Table 8 shows the frequencies of various types of fatigue and fatigue severity in the pre-dialysis and post-dialysis period. From the subjects who reported affective and behavioral fatigue, majority of the people were in the 'moderate'

category. From those who reported sensory and cognitive fatigue, a majority were in the 'mild' category. A total of 81 people completed the PFS post-dialysis. Most reported only severe affective fatigue (n = 26), mild sensory (n = 27), mild cognitive (n = 39) and mild behavioral fatigue (n = 29). Few patients reported no sensory fatigue (n = 5) & no behavioral fatigue (n = 6). Based on proportions, a total of 90% people reported affective fatigue, 85% had sensory fatigue, 75% had cognitive fatigue and 89% had behavioral fatigue pre-dialysis. In the post-dialysis period, 85% had affective fatigue, 94% had sensory fatigue, 82% had cognitive fatigue and 93% had behavioral fatigue.

Table 8

Frequency of Fatigue Types & Severity Based on Piper Fatigue Scale

Severity	Affective fatigue		Sensory fatigue		Cognitive fatigue		Behavioral fatigue	
of fatigue	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Pre-Dialysis								
None	9	10.5	13	15.1	21	24.4	10	11.6
Mild	16	18.6	34	39.5	48	55.8	22	25.6
Moderate	34	39.5	21	24.4	14	16.3	33	38.4
Severe	27	31.4	18	20.9	3	3.5	21	24.4
Total	86	100.0	86	100.0	86	100.0	86	100.0
Post-Dialysis								
None	12	14.8	5	6.2	15	18.5	6	7.4
Mild	22	27.2	27	33.3	39	48.1	29	35.8
Moderate	21	25.9	26	32.1	23	28.4	24	29.6
Severe	26	32.1	23	28.4	4	4.9	22	27.2
Total	81	100.0	81	100.0	81	100.0	81	100.0

Research Question 1b. How frequently did the participants on HD describe being fatigued?

Table 9 presents the frequency of responses pre-dialysis based on the PROMIS question 'In the past 7 days, how often did you have to push yourself to get things done because of your fatigue?' PROMIS-CAT for fatigue was administered pre-dialysis. A majority of the patients said that they had suffered from fatigue 'sometimes' in the past 7 days. Nearly 70% (n = 61) patients said that they had fatigue 'often' and 'sometimes' in the past 7 days. Only 9% participants reported fatigue was present 'always' in the past 7 days.

Table 9

Frequency of Fatigue based on PROMIS Questionnaire

Responses	Frequency	Percent
Never	9	10
Rarely	8	9
Sometimes	38	44
Often	23	27
Always	8	9
Total	86	100

Research Question 1c. Did the mean fatigue score differ from U.S. and other chronic disease populations?

A mean score of 50 with a standard deviation of 10 has been reported for most PROMIS instruments when administered to the U.S. general population. The mean severity of fatigue based on PROMIS was higher and significantly different from the average population of the U.S. (t = 5.96 (85), $p < .001$).

A comparison of various fatigue scores in different disease populations (Broderick et al., 2013; Cella et al., 2016) based on the PROMIS fatigue questionnaire is provided in Table 10. The mean pre-dialysis fatigue scores in this study were significantly higher than individuals with cancer ($p < .001$), and rheumatoid arthritis ($p = .037$). The mean fatigue score in this study was significantly lower than in individuals with congestive heart failure ($p = .004$), COPD exacerbation ($p = .000$), and major depressive disorder ($p < .001$) (Cella et al., 2016).

Based on this study findings, a moderate significant correlation was obtained between PROMIS score and PFS total fatigue score pre-dialysis ($r = .58$, $p = .000$). A significant weak to moderate correlation was obtained between PROMIS fatigue scores and all pre-dialysis PFS subscales, affective ($r = .45$, $p = .000$), behavioral ($r = .56$, $p = .000$), sensory ($r = .46$, $p = .000$), and cognitive ($r = .322$, $p = .000$). These findings inform convergent validity of PFS-12.

Table 10

Fatigue Score Based on PROMIS in this Study & Other Populations

PROMIS fatigue version	Disease	n	Mean	Standard Deviation	t-score(d.f.)	p-value
CAT	Osteoarthritis	100	56.2	7.8	-.29(85)	.765
CAT	CHF	60	58.8	10.4	-2.92(85)	**.004**
CAT	COPD exacerbation	46	62.9	8.3	-7.06(85)	**<.001**
CAT	COPD stable	79	56.1	8.6	-.19(85)	.843
CAT	Back pain	218	56.7	9.4	-.8(85)	.423
CAT	MDD	196	61.3	8.3	-5.45(85)	**<.001**
SF	Cancer	310	52	7.6	3.94(85)	**<.001**
SF	RA	521	53.8	8.8	2.12(85)	**.037**
CAT	**Chronic dialysis[a]**	86	55.9	9.18	5.96 (85)	**<.001**

Note. Information adapted from (Broderick et al., 2013; Cella et al., 2016), CAT= Computer Administered Format, SF= Short Form, COPD= Chronic Obstructive Pulmonary Disorder, MDD= Major Depressive Disorder, RA= Rheumatoid Arthritis, d.f.=degrees of freedom, [a]Current study.
Bold indicates p-value is significant

Research Question 1d: What was the trajectory of fatigue severity from the pre-dialysis to the post-dialysis period?

Table 11 shows the frequency of fatigue severity based on PFS before and after dialysis. Based on original PFS-12 scoring, the total scale score ranges between 1 to 3 in 'mild' fatigue, 4-6 in 'moderate' fatigue and 7 to10 in 'severe' fatigue. When multiplied by 12 items based on number of items in the scale, these scores range from 12 to 36, 48 to 72, and 84 to 120, in 'mild', 'moderate' and 'severe' fatigue respectively. Clearly, some of the total scale scores are not

accounted for such as 1-11, 37-47, 73-83 are not part of the range. That's why, a new categorization was done to account for the scores that lie in between. The category cut-off points were rounded to closest 10s'. The new category cut-off points adopted were 0 to 10 for "no fatigue", "mild" for score of 11 to 40, "moderate" for a score of 41 to 80, and "severe" for a score of 81 to 120. As shown in Table 11, most individuals reported moderate fatigue pre-dialysis which was significantly different than the number of individuals who reported none, mild, moderate or severe fatigue, based on chi square test for difference in proportions. After dialysis, most individuals reported moderate fatigue with no significant difference in fatigue levels.

Also, Table 11 shows the prevalence of patients who reported being fatigued versus not fatigued. Almost 90.7% ($n = 78$) of the patients were fatigued pre-dialysis whereas 84.6% ($n = 69$) of the patients were fatigued post-dialysis. However, please note that the number of patients increased in the "severe fatigue" category from 10.5% to 24.1% respectively. The proportion increase in 'severe fatigue' category was not significant from pre-dialysis to post-dialysis period based on McNemar's test ($p = .289$).

Table 11

Fatigue Severity Based on Piper Fatigue Scale Pre-dialysis & Post-dialysis

Severity of fatigue	Pre-dialysis fatigue[a]		Post-dialysis fatigue[b]	
	Frequency	Percent	Frequency	Percent
None	8	9.3	12	14.8
Mild	27	31.4	23	28.4
Moderate	42	48.8	26	32.1
Severe	9	10.5	20	24.1
Total	86	100.0	81	100.0

Note. [a]$\chi^2 = 36.7$, d.f.= 3*, [b]$\chi^2 = 5.37$, d.f.= 3
*p-value is significant

Based on the total raw score from adding the scores from 12 items of PFS, mean scores were obtained. As shown in Table 13, the mean scores of fatigue increased after dialysis. Despite the mean fatigue scores being higher post-dialysis, results from dependent/ paired t-tests found no statistical difference in total fatigue scores pre-dialysis and post-dialysis. In terms of different types of fatigue based on PFS, no significant differences were obtained in pre-dialysis versus post-dialysis behavioral fatigue (t (80) = -.19, p = .843) and pre-dialysis versus post-dialysis affective fatigue (t (80) = -.87, p = .386). A significant increase was noted in pre-dialysis sensory fatigue (M = 10.95, SD = 8.62) versus post-dialysis sensory fatigue (M = 14.30, SD = 9.28), based on dependent t-tests (t (80) = -3.06, p = .003). A significant increase (t (80) = -2.60, p = .011) in cognitive fatigue was noted pre versus post-dialysis as shown in Table 12.

Table 12

Comparison of Mean Fatigue Scores Before & After dialysis Based on PFS

Variables	n	Mean	Standard deviation	t-score (d.f.)	p-value
Pre-D total fatigue	81	45.74	25.80	-1.48 (80)	.144
Post-D total fatigue	81	50.30	31.62		
Pre-D behavioral fatigue	81	13.68	8.77	-0.19 (80)	.843
Post-D behavioral fatigue	81	13.86	9.55		
Pre-D affective fatigue	81	15.16	9.15	-0.87 (80)	.386
Post-D affective fatigue	81	14.27	9.60		
Pre-D sensory fatigue	81	10.95	8.62	-3.06 (80)	**.003**
Post-D sensory fatigue	81	14.30	9.28		
Pre-D cognitive fatigue	81	5.95	5.84	-2.60 (80)	**.011**
Post-D cognitive fatigue	81	7.86	6.57		

Note. d.f.=degrees of freedom, n=number of subjects, t=t-test, D=dialysis
Bold=p-values are significant at .05 level.

Research Question 1e: What was the impact of fatigue on physical performance of HD participants pre and post-dialysis?

The three dialysis sites where walk tests happened had different course lengths due to limited space availability. The course length was 50 feet in two of the sites, whereas 71 feet in the third site. As seen in Table 13, based on dependent *t*-tests results, individuals walked significantly further during the 6-minute walk test before dialysis compared to post-dialysis.

In terms of the patients' vital signs, systolic blood pressure ($t(47) = 1.86$, $p = .069$) and diastolic blood pressure ($t(47) = 1.29$, $p = .203$) did not differ before and after dialysis. No

significant difference was observed in heart rate {$t(41) = 0.41$, $p = .679$}before walk pre-dialysis versus post-dialysis. A significant difference between heart rate pre walk and post walk done pre-dialysis {$t(51) = -5.52$, $p = .000$}, oxygen saturation pre-walk and post-walk post-dialysis{$t(51) = 5.18$, $p = .000$}. A significant difference was noted in oxygen saturation pre-walk and post-walk post dialysis {$t(41) = 3.96$, $p = .000$}, heart rate pre-walk and post-walk post dialysis {$t(43) = -3.55$, $p = .001$}.

Table 13

Comparison of Mean 6MWD Before & After dialysis (n=44)

Variables	Mean	Standard deviation	t-score (d.f.)	p-value
Pre-dialysis 6MWD	290.22	90.22	2.45(43)	**.018***
Post-dialysis 6MWD	273.96	89.54		

Note. 6MWD=6-minute walk distance, d.f.-degrees of freedom.
*p-value is significant at .05 level.

Adding all the 12 items in PFS gives the total raw score. Participants who got a total raw score in PFS of 0 to 10 were recoded to a category of 'no fatigue' and those who got a raw score of 11 to 120 were recoded to a category of 'fatigue present.' Independent sample t-test was done to compare the mean 6MWD (6-minute walk distance) covered between these reclassified groups. Individuals who reported 'no fatigue' walked further compared to individuals who reported some level of fatigue (i.e. 'fatigue present'). However, no significant difference was observed before or after dialysis as shown in Table 14 and Table 15.

Table 14

Summary Measures of 6MWT Based on PFS Pre-dialysis (n=55)

Fatigue severity	n	Mean of distance walked (meters)	Standard Deviation	*t*-score (d.f.)	*p*-value
No fatigue	4	316.04	151.96	.83 (53)	.408
Fatigue present	51	276.75	85.65		

Note. d.f.=degrees of freedom, n=number of subjects, *t*=Dependent t-test

Table 15

Summary Measures of 6MWT Based on PFS Post-dialysis (n=44)

Fatigue severity	n	Mean of distance walked (meters)	Standard Deviation	*t*-score (d.f.)	*p*-value
Fatigue absent	6	291.84	112.11	.52 (42)	.605
Fatigue present	38	271.13	86.95		

Note. d.f.=degrees of freedom, n=number of subjects, *t*=Dependent t-test

A correlation was obtained between total raw score derived from PFS and 6MWD. A weak but non-significant relationship was observed between fatigue score and distance walked pre-dialysis (r = -.08, p = .567). A statistically significant inverse relationship was observed between fatigue score and distance walked in 6 minutes post-dialysis (r = -.32, p = .034).

The mean pre-dialysis 6MWD covered was significantly lower {t = -23.89 (54), p < .001} in this study (279.61±90.45 meters, n = 55) when compared to overall mean walk distance of healthy subjects from seven different countries (571±90 meters, n = 444) (Casanova et al., 2011). The mean pre-dialysis 6MWD covered was significantly lower {t = -3.14 (54), p = .003} in this study (279.61±90.45 meters, n = 55) as compared to subjects with heart failure (318±106 meters, n = 64).

The 6MWD in pre-dialysis period did not correlate with PFS-12 total pre-dialysis (r = -.07, p = .56), however, 6MWD in post-dialysis period significantly correlated, weakly with PFS-12 total post-dialysis (r = -.32, p = .03).

Specific Aim 2: Identify the extent to which selected physiological factors such as anemia, dialysis adequacy, inter-dialytic weight gain, co-morbidities and age influence fatigue severity in individuals with Stage G5 CKD on HD.

Hemoglobin and Fatigue Severity

The correlation between hemoglobin values and fatigue severity scores was negative in the pre-dialysis period and the p-value was statistically significant. The higher the hemoglobin, the lower the fatigue scores (r = - .24, p = .027). There was a weak, negative, non-significant relation between hemoglobin values and fatigue scores in the post-dialysis period (r = -.13, p = .250). A weak, inverse significant correlation was obtained between hemoglobin and pre-dialysis sensory fatigue (r = -.25, p = .020). A non-significant relation was observed with the other subscales of PFS pre-dialysis and hemoglobin, i.e. behavioral fatigue (r = -.12, p = .265), affective fatigue (r = -.20, p = .061), and cognitive fatigue (r = -.18, p = .095).

Dialysis Adequacy and Fatigue Severity

Dialysis adequacy was measured using recent Kt/V value from the medical records of the individual. A pre and post -dialysis urea blood sample is withdrawn every month in order to calculate the same. Since this value is assessed every month, this study used the Kt/V values from the same month patient was interviewed with us. The correlation between dialysis adequacy and pre-dialysis fatigue severity score was negative (r = -.21, p = .058) in the pre-dialysis period, and was trending towards statistical significance.

Interdialytic Weight Gain and Fatigue Severity

Table 16 summarizes summary measures of interdialytic weight gain according to fatigue severity in the pre-dialysis period. Based on dependent *t*-tests, there was no statistically significant difference between the mean interdialytic weight gains and fatigue severity. As seen in Table 17, the means of interdialytic weight gain were not statistically different according to fatigue severity post-dialysis.

Table 16

Interdialytic Weight Gain Based on PFS Pre-dialysis (n=85)

Fatigue severity	n	Mean of interdialytic weight gain (kgs)	Standard Deviation	*t*-score (d.f.)	*p*-value
No fatigue	7	1.95	.64	-.34	.734
Fatigue present	78	2.16	1.55	(83)	

Note. One patient record was missing in the dataset, that's why number of subjects has one patient less compared to previous pre-dialysis data, d.f.=degrees of freedom, t=dependent t-tests

Table 17

Interdialytic Weight Gain Based on PFS Post-dialysis (n=80)

Fatigue severity	n	Mean of interdialytic weight gain (kgs)	Standard Deviation	*t*-score (d.f.)	*p*-value
No fatigue	11	2.34	1.19	.42	.676
Fatigue present	69	2.13	1.56	(78)	

Note. One patient record was missing in the dataset, that's why number of subjects has one patient less compared to previous post-dialysis data, d.f.=degrees of freedom, t=dependent t-tests

Comorbidity and Fatigue Severity

A total from all the items on the Charlson Comorbidity Index (CCI) was computed. Pearson's correlation value was obtained between the CCI total and the total pre-dialysis PFS score. No significant correlation was found between comorbidity scores and fatigue scores pre-dialysis (r = .02, p = .791) and post-dialysis (r = .06, p = .581). The correlation between the PROMIS fatigue score and comorbidity score was statistically significant (r = .21, p = .05), but was weak in strength. The higher the comorbidities, the higher the fatigue score.

Age and Fatigue Severity

There was a significant but weak inverse correlation between age and fatigue scores pre-dialysis (r = -.26, p = .017) and post-dialysis (r = -.23, p = .034). Younger age was associated with a higher fatigue score or vice versa. Based on independent t-tests, no significant difference in pre-dialysis fatigue severity {$t(84)$ = .09, p = .922} and post-dialysis fatigue severity {$t(79)$ = .98, p = .328} was observed between individuals who were less than 65 years and greater than 65 years of age.

Regression of Physiological Factors on Fatigue Severity

Multiple regression was done on the total raw scores obtained from PFS during the pre-dialysis period. The independent variables were interdialytic weight gain (IDWG), hemoglobin, dialysis adequacy (Kt/V), age and CCI scores. Findings from multiple regression are shown in Table 18. The multiple regression coefficient, R indicates a moderate level of prediction. Adjusted R-square signifies the percentage of variance explained by the model. Based on adjusted R-square, about 16.7% of variance in total scores of fatigue severity is predicted by the physiological factors. The physiological factors significantly predicted pre-dialysis fatigue severity, F = 4.28 (5,77), p = .002. Among these physiological factors, hemoglobin, dialysis adequacy, and age significantly contributed to the model. Adding 'age*race' (p = .322) and 'race' (p = .358) to the model did not show any significance, which means that there was no interaction between age and race. Please note that these findings are not reported in Table 18. The equation to predict fatigue severity before dialysis is the following:

Predicted pre-dialysis fatigue severity = 200.63 – 2.23 (IDWG) – 6.77 (Hb) – 31.75 (Kt/V) – 0.52 (Age) + 0.22 (CCI)

Table 18

Regression: Influence of Physiological Factors on PFS Pre-dialysis (n=83)

Predictors	B values	S.E. B.	Beta	t-value	p-value
Constant	200.63	36.29		5.53	<.001
IDWG	-2.23	1.78	-0.13	-1.25	.216
Hemoglobin (Hb)	-6.77	2.18	-0.32	-3.10	.003**
Dialysis adequacy (Kt/V)	-31.75	12.37	-0.27	-2.57	.012*
Age	-0.52	0.19	-0.29	-2.71	.008**
Comorbidity (CCI)	0.22	1.22	0.02	0.18	.855
R^2			0.22		
ΔR^2			0.16		
F			4.28**		

Note. IDWG=Interdialytic Weight Gain, B=unstandardized coefficients, SE B=standard error of unstandardized coefficients, R2=Multiple regression coefficient, Δ R2=Adjusted R2

* p value is significant at .05 level

** p value is significant at .01 level

Table 19 shows the findings from multiple regression that was done on total raw scores obtained from PFS post-dialysis. The physiological variables were the independent variables. Only 4% of variance in total scores of fatigue severity was predicted by physiological factors post-dialysis. Age was contributing significantly to the model, $p = .029$. However, the model was not statistically significant, $F = 1.732(5,74)$, $p = .138$. The equation to predict fatigue post-dialysis is:

Predicted post-dialysis fatigue severity=153.51- 0.50 (IDWG) – 4.02 (Hb) -20.91 (Kt/V) -0.57 (Age) +0.97 (CCI)

Table 19

Regression: Influence of Physiological Factors on PFS Post-dialysis (n=80)

Predictors	B values	S.E. B.	Beta	t-value	p-value
Constant	153.51	48.32		3.17	.002
IDWG	-0.50	2.39	-0.24	-0.21	.837
Hemoglobin (Hb)	-4.02	2.88	0.15	-1.39	.169
Dialysis adequacy (Kt/V)	-20.91	16.72	-0.14	-1.25	.215
Age	-0.57	0.25	-0.25	-2.22	.029*
Comorbidity (CCI)	0.97	1.62	0.06	0.59	.552
R^2			0.10		
ΔR^2			0.04		
F			1.73		

Note. IDWG=Interdialytic Weight Gain, B=unstandardized coefficients, SE B=standard error of unstandardized coefficients, R^2=Multiple regression coefficient, ΔR^2=Adjusted R^2
* p value is significant at .05 level.

Specific Aim 3: Identify the extent to which select situational factors such as living status, employment, gender, and race influence fatigue severity in individuals with Stage G5 CKD on HD.

The variable 'race' was recoded to two categories, 'African Americans' and 'Non-African Americans'; 'living status' to 'living alone' versus 'living with someone', employment status to 'working' and 'not working.' The total scores from adding 12 items on PFS are put into four categories, namely, "no fatigue" with a score of 0 to 10, "mild fatigue" for a score of 11 to 40, "moderate fatigue" for a score of 41 to 80, "severe fatigue" for a score of 81 to 120.

Living Status and Fatigue Severity

As seen in Table 20, living status and fatigue severity are significantly associated (p = .003). As shown in Figure 6, more people living with someone were moderately fatigued compared to people who lived alone. All the patients who lived alone reported fatigue.

Table 20

Association between Living Status and Fatigue Severity in Pre-dialysis Period (N=86)

Living status	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Living with someone	8 (9.3%)	13 (15.1%)	35 (40.7%)	5 (5.8%)
Living alone	0	14(16.3%)	7 (8.1%)	4 (4.7%)

Note. $\chi^2 = 14.24$, d.f.= 3, p = .003*
*p-value is significant

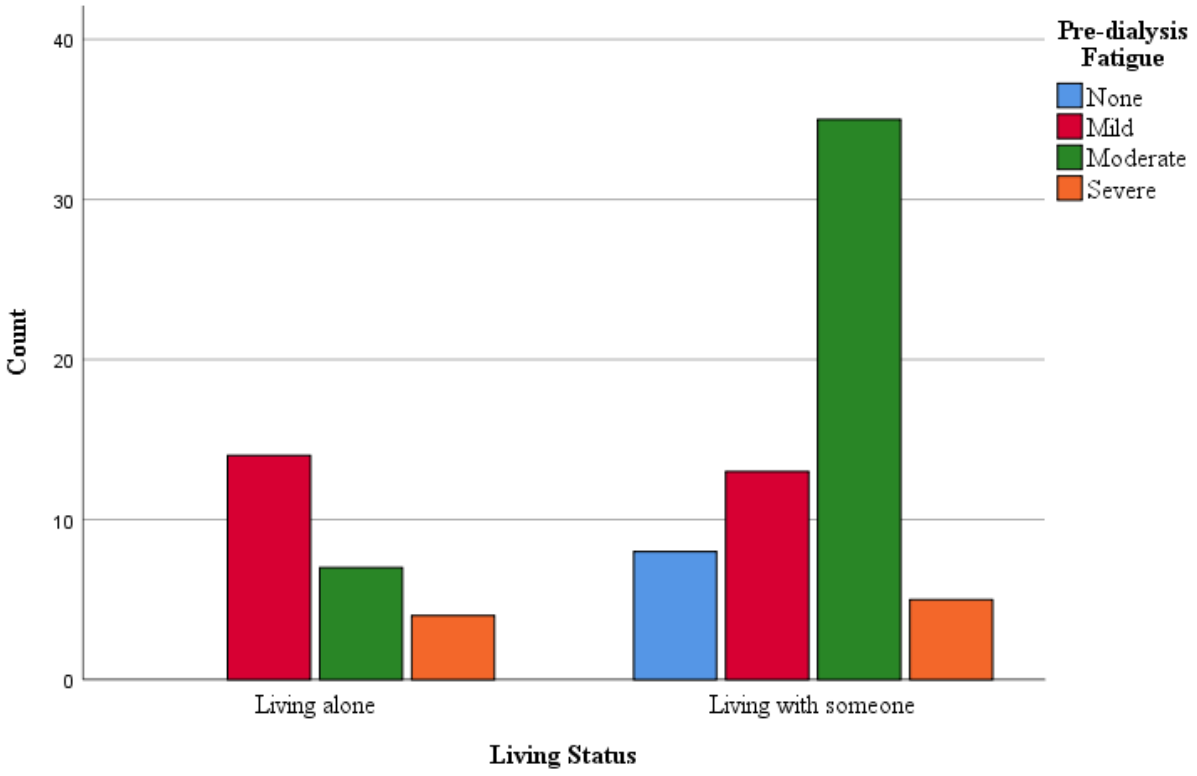


Figure 6. Bar chart: living status by fatigue severity in pre-dialysis

Table 21 and Figure 7 shows the association between living status and fatigue severity in the post-dialysis period, and the Chi- square value was not significant at .05 level. People who lived alone reported similar fatigue severity compared to people who lived with someone post-dialysis.

Table 21

Association between Living Status and Fatigue Severity in Post-dialysis Period (n=81)

Living status	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Living with someone	10(12.3%)	15(18.5%)	19(23.5%)	13(16%)
Living alone	2(2.5%)	8(9.9%)	7(8.6%)	7(8.6%)

Note. $\chi^2 = 1.62(3)$, $p = .653$

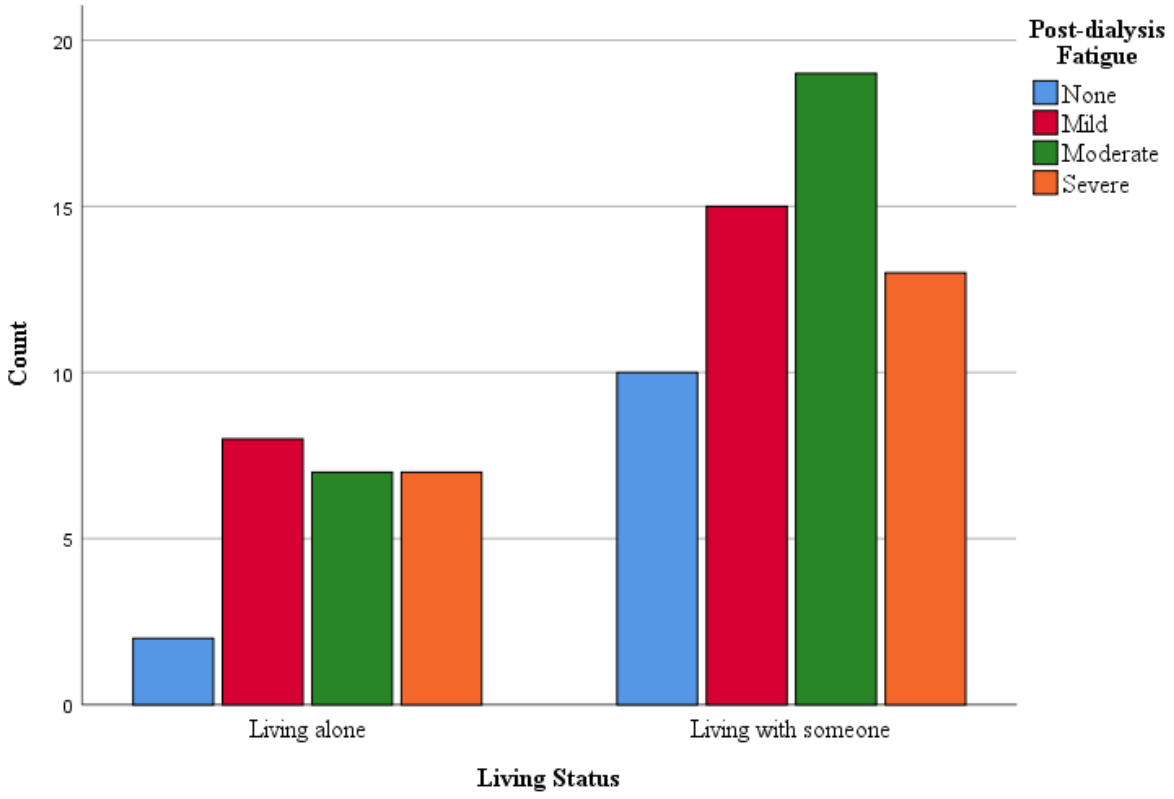


Figure 7. Bar chart: living status by fatigue severity in post-dialysis

Employment Status and Fatigue Severity

As seen in Table 22 and Figure 8, the association between employment status and fatigue severity in pre-dialysis period was not statistically significant, however, the p-value was trending towards significance. People who were 'not working' reported similar fatigue severity compared to people who were working 'pre-dialysis'.

Table 22

Association Between Employment and Fatigue Severity Pre-dialysis (N=86)

Employment	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Not working	7(8.1%)	26(30.2%)	32(37.2%)	9(10.5%)
Working	1(1.2%)	1(1.2%)	10(11.6%)	0

Note. χ^2=7.23(3), p = .065

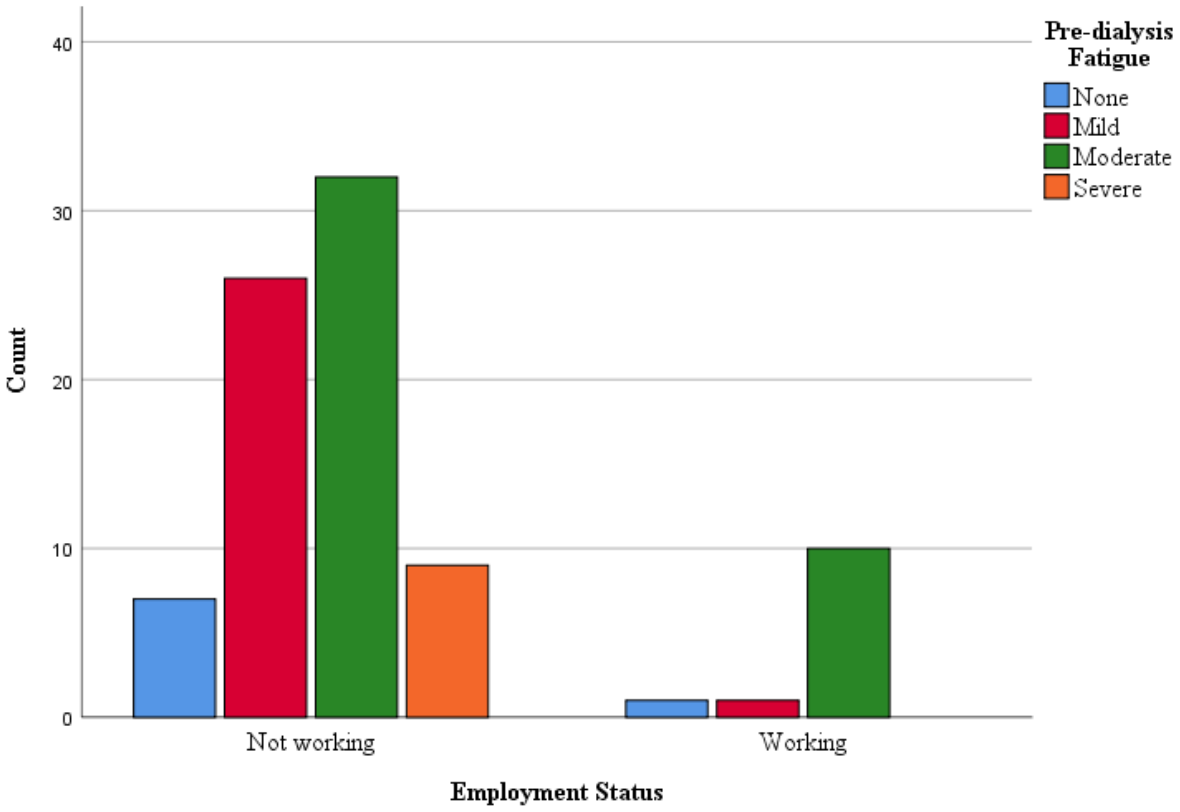


Figure 8. Bar chart: employment status by fatigue severity pre-dialysis

As seen in Table 23 and Figure 9, association between employment status and fatigue severity in post-dialysis period was not statistically significant. People who were 'not working' reported similar fatigue severity compared to people who were working post-dialysis. All people who were 'working' reported fatigue in the post-dialysis period, however, not significant.

Table 23

Association between Employment and Fatigue Severity Post-dialysis (N=81)

Employment	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Not working	12(14.8%)	20(24.7%)	21(25.9%)	17(21%)
Working	0	3(3.7%)	5(6.2%)	3(3.7%)

Note. χ^2=2.63(3), p = .452

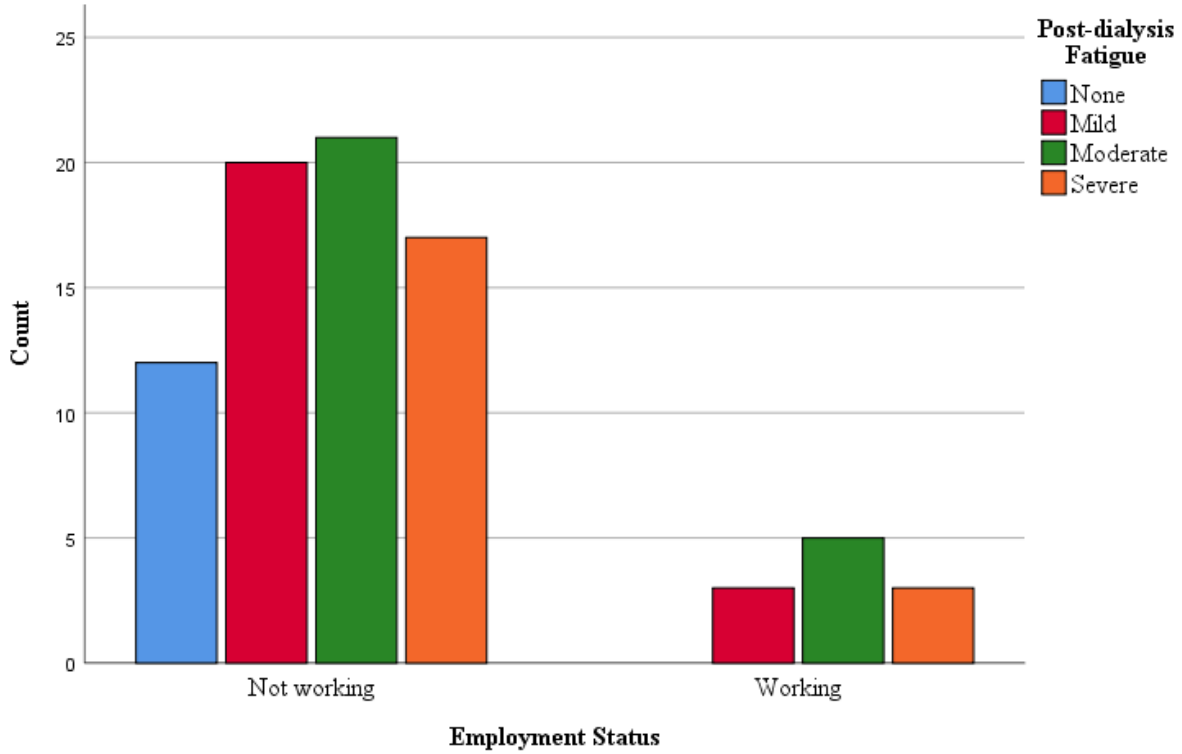


Figure 9. Bar chart: employment status by fatigue severity in post-dialysis period

Gender and Fatigue Severity

Table 24 and Figure 10 presents the association between gender and fatigue severity in the pre-dialysis period, and the chi-square value was not statistically significant. Males and females reported similar fatigue severity in pre-dialysis period.

Table 24

Association between Gender and Fatigue Severity Pre-dialysis (N=86)

Gender	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Male	7(8.1%)	15(17.4%)	23(26.7%)	5(5.8%)
Female	1(1.2%)	12(14%)	19(22.1%)	4(4.7%)

Note. $\chi^2 = 3.12(3)$, $p = .372$

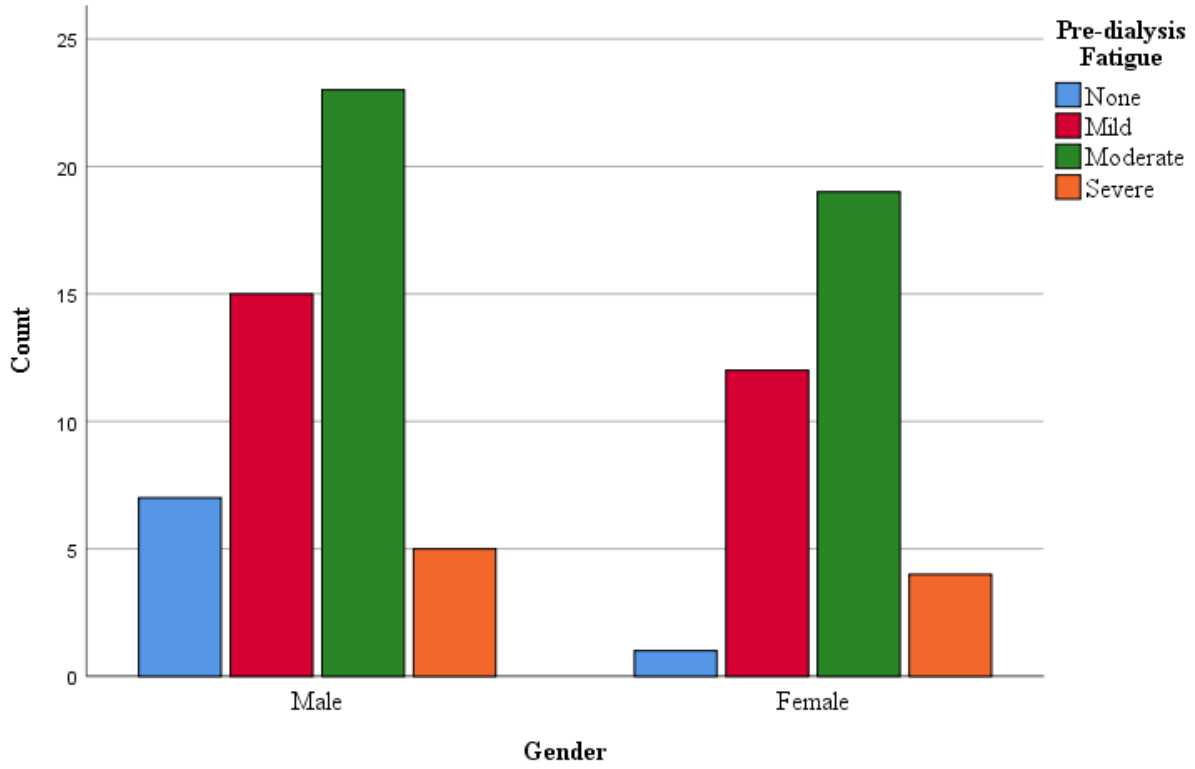


Figure 10. Bar chart: gender by fatigue severity in pre-dialysis period

Table 25 and Figure 11 presents the association between gender and fatigue severity in the post-dialysis period, and the Chi-square value was not significant at .05 level. Males and females reported similar fatigue severity in post-dialysis period.

Table 25

Association between Gender and Fatigue Severity Post-dialysis (N=81)

Gender	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
Male	9(11.1%)	13(16%)	15(18.5%)	9(11.1%)
Female	3(3.7%)	10(12.3%)	11(13.6%)	11(13.6%)

Note. χ^2=2.76(3), p = .429

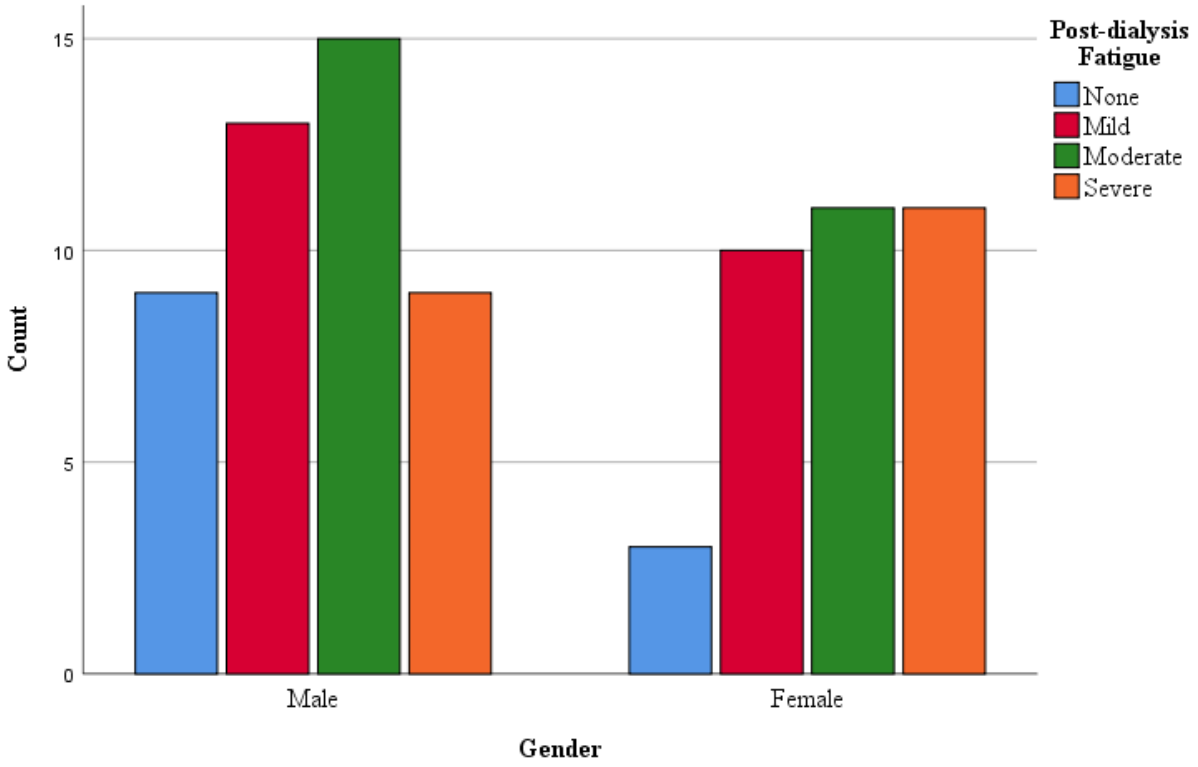


Figure 11. Bar chart: gender by fatigue severity in post-dialysis period

Race and Fatigue Severity

As seen in Table 26 and Figure 12, the association between race and fatigue severity is not statistically significant in the pre-dialysis period. African Americans and non-African Americans reported similar fatigue severity.

Table 26

Association between Race and Fatigue Severity Pre-dialysis (N=86)

Race	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
AA	4(4.7%)	13(15.1%)	21(24.4%)	4(4.7%)
Non-AA	4(4.7%)	14(16.3%)	21(24.4%)	5(5.8%)

Note. $\chi^2 = .1(3)$, $p = .992$, AA=African Americans

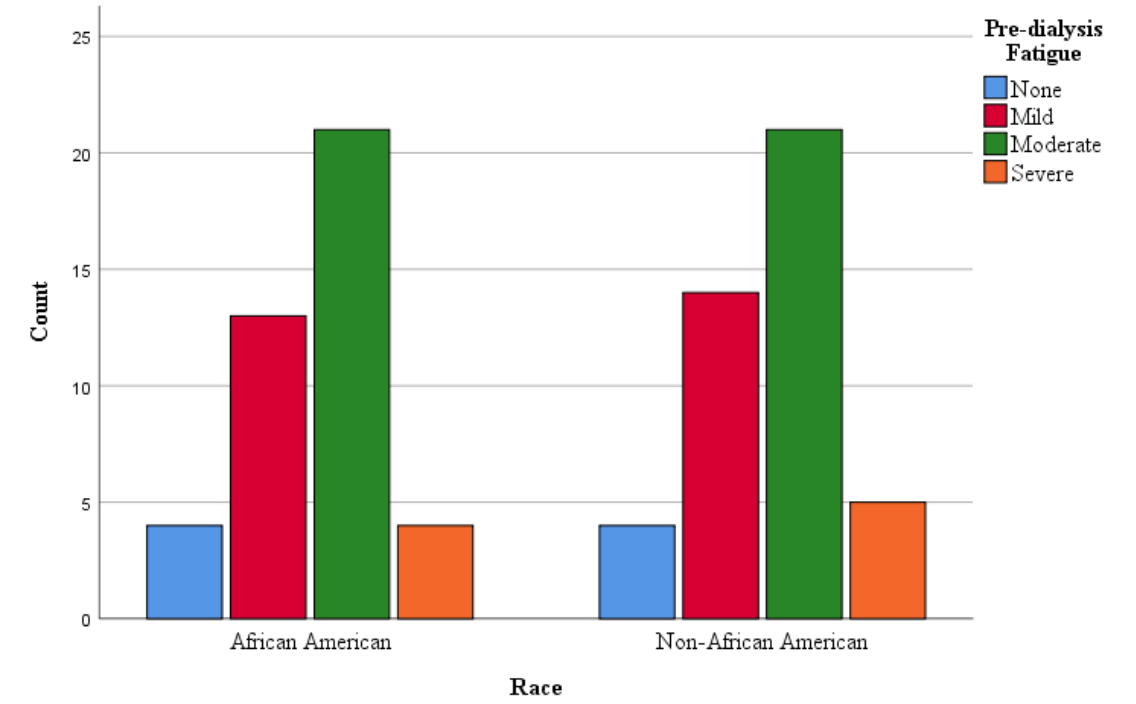


Figure 12. Bar chart: race by fatigue severity in pre-dialysis period

Table 27 and Figure 13 presents the association between race and fatigue severity in the post-dialysis period, and the chi-square was not statistically significant at .05 level. African Americans and Non-African Americans reported similar fatigue severity in the post-dialysis period.

Table 27

Test of Association between Race and Fatigue Severity Post-dialysis (N=81)

Race	No fatigue	Mild fatigue	Moderate fatigue	Severe fatigue
AA	6(7.4%)	12(14.8%)	10(12.3%)	12(14.8%)
Non-AA	6(7.4%)	11(13.6%)	16(19.8%)	8(9.9%)

Note. $\chi^2 = 2.21(3)$, $p = .529$, AA: African Americans

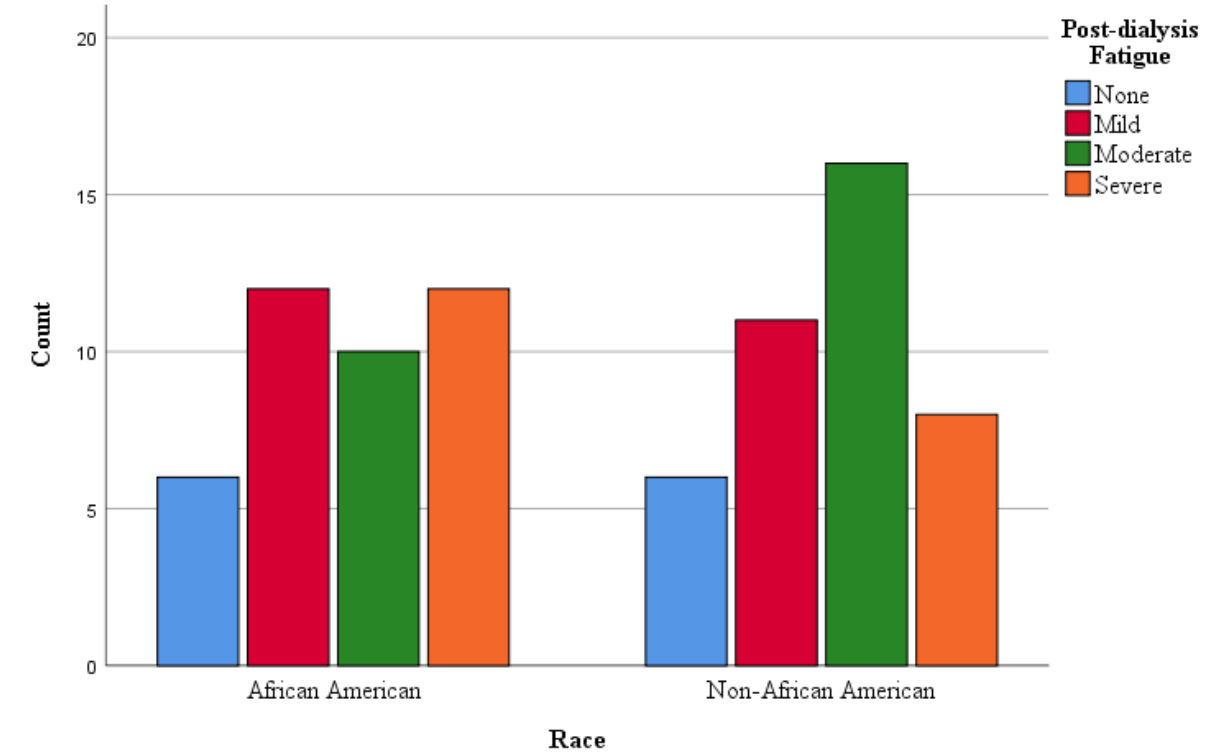


Figure 13. Bar chart: race by fatigue severity in post-dialysis period

Regression of Situational Factors on Fatigue Severity

The variables 'race' was recoded to two categories, 'African Americans' and 'Non-African Americans'; 'living status' to 'living alone' versus 'living with someone', employment status to 'working' and 'not working.' The dependent variable, fatigue severity was recoded to two categories, 'fatigue absent' and 'fatigue present.' A logistic regression was done to study the

influence of situational factors such as race, gender, living status and employment status on fatigue severity (dependent variable). Table 28 presents findings from logistic regression in the pre-dialysis period. The logistic regression model was statistically significant, $\chi^2 = 10.77(4)$, $p = .029$. None of the independent variables such as race, gender, living status and employment status added significantly to the model, however, gender was trending towards significance. Males were 7.31 times more likely to be fatigued severely compared to females, pre-dialysis.

Table 28

Regression: Influence of Situational Factors on Fatigue Severity Pre-Dialysis

Factors	B values	B (Exp)	Significance
Race	.44	1.55	.582
Living status	-19.6	0	.998
Employment status	.56	1.75	.628
Gender	2	7.31	.073
R^2		.255	

Note. $\chi^2 = 10.77(4)$, $p = .029$

A logistic regression was done to study the influence of situational factors such as race, gender, living status and employment status on fatigue severity (dependent variable). Table 29 presents findings from logistic regression in the post-dialysis period. The logistic regression model was not statistically significant, $\chi^2 = 8.84(4)$, $p = .065$, but was trending. None of the independent variables such as race, gender, living status and employment status added significantly to the model, however, gender was trending. Males were 3.36 times more likely to be fatigued severely than females in the post-dialysis period. Please note the odds ratios or B(Exp) have reduced from pre-dialysis to the post-dialysis period.

Table 29

Regression: Influence of Situational Factors on Fatigue Severity Post-Dialysis

Factors	B values	B (Exp)	Significance
Race	.06	1.07	.924
Living status	-1.2	.3	.157
Employment status	20.04	-	.999
Gender	1.21	3.36	.097
R^2		.182	

Note. $\chi^2 = 8.84(4)$, $p = .065$

Summary

Almost 90% reported fatigue pre-dialysis, and 85% reported fatigue post-dialysis. Based on different types of fatigue, a total of 90% people reported affective fatigue, 85% had sensory fatigue, 75% had cognitive fatigue and 89% had behavioral fatigue pre-dialysis. In the post-dialysis period, 85% had affective fatigue, 94% had sensory fatigue, 82% had cognitive fatigue and 93% had behavioral fatigue.

Based on the levels of fatigue as categorized by PFS-12, 31.4% were mildly fatigued pre-dialysis, 28.4% were mildly fatigued post-dialysis. Almost 50% were moderately fatigued pre-dialysis, 32% fatigued post-dialysis. And severely fatigued were 10% pre-dialysis, whereas 24% were severely fatigued post-dialysis.

Based on the frequency of fatigue as defined by PROMIS-fatigue, 44% were fatigued 'sometimes' in the past 7 days, and 36% were fatigued 'often' and 'always' in the past 7 days. The fatigue severity was higher than the general U.S. population based on PROMIS-fatigue. The fatigue severity in the current study was higher than patients with cancer and rheumatoid arthritis, and was lower than patients with heart failure, depression and COPD exacerbation.

Based on the 6MWT, patients walked significantly less post-dialysis than they did pre-dialysis. Based on PFS-12, the mean fatigue scores increased from pre-dialysis to post-dialysis period, however, was not statistically significant.

Among the influencing factors, many physiological factors were associated with fatigue severity. Age was correlated weakly to fatigue severity pre-dialysis and post-dialysis. Hemoglobin values and dialysis adequacy were correlated with fatigue severity in the pre-dialysis period. Comorbidities were associated with PROMIS fatigue. From multiple regression, age, dialysis adequacy and hemoglobin significantly predicted fatigue severity pre-dialysis. After dialysis, only age significantly predicted fatigue severity.

Among the situational factors, more people living with someone reported fatigue compared to people who were living alone. From findings of the regression analyses, none of the situational variables predicted fatigue severity pre-dialysis or post-dialysis. However, gender was trending towards significance. Males were more likely to be fatigued severely compared to females before and after dialysis.

CHAPTER 5: DISCUSSION

The purpose of this study was to examine the severity and trajectory pattern of fatigue and delineate various physiological and situational factors that may influence fatigue severity in individuals with CKD Stage G5 on HD. The discussion is according to the aims and research questions.

This study was done in subjects on hemodialysis treatment. The chronic and frequent nature of the treatment makes these patients unique, as they come for HD treatment every 2-3 days per week in an outpatient dialysis clinic. Due to this frequency of visits, the follow-up and availability of subjects becomes very easy as a researcher. And the volume of patients seen by a dialysis clinic remains stable for a long period of time, since dialysis is a chronic treatment most of the times.

This study was conducted in multiple DaVita dialysis sites. DaVita has a chain of dialysis clinics with supported infrastructure and guidelines for conducting research, that makes 'gaining entry' into the clinic easier. There were no significant differences in the subject population in terms of age, gender and race. However, there were a few differences between the three sites, such as, volume of patients being dialyzed at a clinic, volume of patients interested in participating in the study, and course length that was used for the 6-minute walk test.

This is the first study to report 6MWT results on a dialysis day, before and after dialysis. Studies conducted in the past have utilized 6MWT to measure physical performance or on a non-dialysis day. And therefore, a real-time assessment of physical fatigue before and after dialysis has been done for the first time.

This study had 55 individuals who performed 6MWT before dialysis and 44 walked after dialysis. Most patients who gave approval to walk were walking daily either to do chores or for

work. Most patients were interested or motivated to do the walk test. There were subjects who had stigma attached to the word "walk" and thought of it as a stress test or physical exertion test. On explaining further, they agreed. Some individuals were reluctant to walk due to reasons such as work and transportation. Some individuals walked before dialysis, however, could not walk post-dialysis due to feeling sick, pain in legs, feeling dizzy, cramping and tiredness. There were a few individuals who walked with prosthetic device, tracheostomy, and walkers.

PROMIS-CAT fatigue was used for the first time in dialysis individuals in this study, and therefore, is a significant contribution to the body of evidence. The measure was easy to administer, the user requires a registration with the Red Cap software. Patients were able to understand the questions, and more questions were administered to the individuals by the computer in case patients did not answer appropriately. The computer itself picks questions from the PROMIS item bank based on the responses given. However, the number of questions administered varied person to person which makes analysis difficult. A T-score in the end determines the intensity or severity of fatigue. The other dimensions such as frequency and duration are measured through individual questions in the questionnaire, however, the multidimensionality does not get reflected in the end on analysis, and researcher has to search for questions that could be answering a specific dimension for analysis purposes. More clarity is needed in this area of PROMIS-CAT fatigue measure.

The PFS-12 was administered to individuals before and after dialysis to measure their current levels of fatigue for the first time in this study. To our knowledge, previous study that has utilized PFS used a longer version of the questionnaire with 22-27 items and was administered post-dialysis only. PFS-12 had excellent reliability in this study and measured various subtypes of fatigue. We also found a significant inverse weak correlation of PFS-12 with 6-minute walk

distance post-dialysis. Therefore, PFS-12 could be an excellent measure of examining physical fatigue as well.

Aim 1: Examine severity and trajectory pattern of fatigue in individuals with Stage G5 CKD on HD.

Research Question 1a: How severe was the level of sensory, behavioral, cognitive and affective fatigue before and after dialysis?

In this study, participants reported moderate severity of affective, sensory and behavioral fatigue, and mild cognitive fatigue. A significant difference was noted before and after dialysis, in terms of cognitive and sensory fatigue, whereas no significant difference was seen in behavioral and affective fatigue pre and post-dialysis.

Among the various types of fatigue subscales according to Piper Fatigue Scale, moderate 'affective fatigue' scores were reported before and after dialysis session in this study. Almost 90% patients had affective fatigue pre-dialysis and 85% had affective fatigue post-dialysis. A previous investigator who did a qualitative study in patients on HD reported 'affective fatigue' as an overarching subtheme in the findings (Lee et al., 2007). However, a before and after dialysis assessment of fatigue was missing in that study. Thus, our findings confirm findings from Lee (2007), and add to the evidence of 'affective fatigue' being present in the pre-dialysis period.

The present study found moderate 'sensory fatigue' scores with a significant increase in scores post-dialysis compared to pre-dialysis period. Almost 85% had sensory fatigue pre-dialysis and 94% had sensory fatigue post-dialysis. The 'sensory fatigue' subscale in PFS is similar to 'physical fatigue' described in qualitative studies by Horrigan (2013) and Lee (2007). During dialysis, there are fluid shifts and other exchanges of small molecules and ions that happen and cause physical symptoms. There is a decline in energy and strength (Horigan et al., 2013). Some

patients described after dialysis, 'it felt as if life was taken from me' (Lee et al., 2007). Karakan (2011) did a quantitative study that has reported 'sensory fatigue' in HD subjects after dialysis treatment. Sensory PFS scores were 21% mild, 37% moderate, and 42% severe in that study (Karakan et al., 2011). Post-dialysis sensory fatigue was 33.3% mild, 32.1% moderate and 28.4% severe in our study. Presence of sensory fatigue pre-dialysis has not been studied in the past, and this study is the first to report the same.

This study found mild 'cognitive fatigue' in pre and post-dialysis sessions, with a significant increase in cognitive fatigue after dialysis. Almost 75% reported cognitive fatigue pre-dialysis and 82% had cognitive fatigue post-dialysis. No other studies have done a comparison of cognitive fatigue pre and post-dialysis. Lee (2007) described 'cognitive fatigue' as an important domain in her qualitative study on 14 patients on HD and is a decline in cognitive function. Patients had intentional isolation, regretted lost cognition and tried to cope with cognitive fatigue. Horrigan (2013) mentioned 'mental fatigue' as an overarching subtheme in individuals on dialysis. Patients in that study had difficulty in remembering names and details they knew for a long time. A low 'mental fatigue' score was reported in another quantitative study (Biniaz et al., 2013). Both 'mental fatigue' and 'cognitive fatigue' seem to be overlapping in features and needs further investigation. A weak non-significant correlation was observed between hemoglobin and cognitive fatigue in this study, that was trending towards significance. Anemia could be a causative factor for cognitive fatigue or cognitive impairment (Patel, Dasgupta, Tadros, & Baharani, 2016), as evidenced by Karakan et al (2011). Some theories suggest 'dialysis disequilibrium' that leads to cerebral edema, and causes reduction in cognitive function (Patel et al., 2016). Cognitive fatigue happens due to low serum glucose, high serum urea and C-reactive protein levels, that leads to cerebral disintegration and cognitive dysfunction eventually (Karakan et al., 2011). Investigators have

shown an increase in C-reactive protein levels in 454 individuals on HD with reduced cognitive function (Watanabe et al., 2016). This study did not examine serum markers and is an area for further investigation.

Research Question 1b: How frequently did the HD participants describe being fatigued?

This study utilized PROMIS-CAT fatigue in dialysis population for the first time. In response to the PROMIS question 'how often did you have to push yourself to get things done because of your fatigue in the past seven days?', almost 70% (n = 61) patients said that they had fatigue 'often' or 'sometimes' in the past seven days. These responses indicate that participants are frequently fatigued. There are no previous studies that have reported data on frequency of fatigue in dialysis population to our knowledge. Dialysis treatment happened 2-3 times in a week, and this study shows that patients are fatigued before and after dialysis. These findings support qualitative data from Horigan and Barroso (2016), in which the combination of continuous fatigue and acute fatigue after dialysis creates a vicious circle of fatigue. Thus, patients are never 'fatigue-free' in a week. Before they recover from the past dialysis treatment, it's time for another dialysis treatment (Horigan & Barroso, 2016).

Research Question 1c: Did the mean fatigue score differ from US and other chronic disease populations?

The mean fatigue score was higher and was significantly different from the average population of U.S., and was significantly higher than individuals with cancer, and rheumatoid arthritis (Cella et al., 2016). The mean fatigue score in this study was significantly lower than individuals with congestive heart failure, COPD exacerbation, and major depressive disorder (Cella et al., 2016).

The current study had higher mean fatigue scores compared to patients with congestive heart failure (Cella et al., 2016). Cytokines are responsible for fatigue, cognitive fatigue and depression (Karshikoff, Sundelin, & Lasselin, 2017; Lasselin & Capuron, 2014). Levels of cytokines such as C-Reactive Protein are much higher in patients on dialysis and range from 5 to 50 ng/ml, whereas in cardiovascular disease, the levels are much lower and range between 1 to 3 ng/ml (Kovesdy, Joel, & Zadeh, 2017). Based on this finding, one would expect higher fatigue scores in dialysis patients. However, contrasting findings found in this study could be due to majority of the subjects were from a younger age group and subjects living with someone.

In cancer, cytokines lead to cytokine-induced sickness behavior, however, an investigator found that these cytokines are related to physical fatigue and not mental fatigue (de Raaf et al., 2012). The current study found both types of fatigue, physical and cognitive in patients on dialysis. Perhaps, the higher fatigue scores in this study are reflective of both types of fatigue present in the dialysis population. No studies have compared different qualities of fatigue present in cancer, and therefore to draw a necessary hypothesis is difficult.

Research Question 1d: What was the trajectory of fatigue severity from the pre-dialysis to the post-dialysis period?

In terms of prevalence, nearly all of the patients (90.7%) in this sample were fatigued pre-dialysis whereas a lesser number, but still a majority of the patients (84.6%) were fatigued post-dialysis. The intensity increased in the 'severe fatigue' category from 10.5% to 24.1%. However, no significant difference was observed pre versus post-dialysis. These findings are similar to Biniaz and colleagues (2013) who reported that all the patients on HD, with a mean age of 61 years (*SD* = 12.61 years), complained of fatigue. However, a description of comorbidities is missing in the study. Other investigators have reported a lower prevalence of fatigue in HD. Zyga and

colleagues (2015) reported prevalence of fatigue to be 62%, with a mean age of 56 years (Zyga et al., 2015). Another investigator reported 65% fatigue in patients on HD post-dialysis (Karakan et al., 2011). However, Karakan and colleagues did not include subjects who had co-morbidities, and the median age of subjects in that study was 55 years compared to the mean age of 61 years (*Mdn* = 63.5 years) in the current study. In this study, majority of the subjects (n = 53) were less than 65 years of age, with no significant difference in fatigue severity between individuals less than and greater than 65 years of age. Our study found an inverse relation between fatigue severity levels and age. Therefore, it can be postulated that the high prevalence of fatigue in the current study could be due to patients with higher comorbidities. Based on Charlson Comorbidity Index, 87% patients had severe comorbidities in this study.

In this study, most individuals had 'moderate fatigue' pre-dialysis. These findings are similar to Horigan & Barroso (2016) who reported temporal patterns of fatigue after dialysis. In that study, participants had continuous fatigue even after long hours of rest and sleep. Some participants who had 'continuous fatigue' never returned to a baseline but continued to have fatigue until the next day when they get started for another hemodialysis session (Horigan & Barroso, 2016). The same continuous fatigue extends to next day and is captured by pre-dialysis questionnaire in this study. No other studies have reported pre-dialysis fatigue and needs further investigation.

Post-dialysis, most individuals reported moderate fatigue in this study. Letchmi (2011) found 54% of the patients with high level of fatigue and 45.6% experienced a low level of fatigue. They used Multidimensional Fatigue Inventory that classified subjects to 2 categories of fatigue (Letchmi et al., 2011). In this study, Piper Fatigue Scale was used that classified subjects to 3 categories, and therefore, the variable findings might be due to different types of fatigue

instruments used. The findings are contrasting with another investigator findings that utilized Piper Fatigue Scale and had 43% patients reporting severe fatigue post-dialysis (Karakan et al., 2011).

The mean scores of fatigue increased after dialysis, however, there was no statistical difference between the mean scores in this study. Interestingly, this is the only study that reports a comparison of fatigue score before and after dialysis. Only 1 previous study compared 'non-dialysis' and 'dialysis day' fatigue scores, in that there was increased fatigue severity on 'dialysis day' and an increase in fatigue intensity later in evening compared to morning or afternoon time (Abdel-Kader et al., 2014). Our study confirms these findings that fatigue gets worse later in the day after dialysis. Other investigators have reported post-dialysis fatigue scores or non-dialysis day fatigue scores (Horigan & Barroso, 2016; Karakan et al., 2011; Picariello, Moss-Morris, Macdougall, & Chilcot, 2018). Some investigators do not specifically report the timing of questionnaire administration in relation to timing of hemodialysis session (Zyga et al., 2015). This study reiterates the importance of diurnal variations of fatigue in the dialysis population.

Research Question 1e: What was the impact of fatigue on the physical performance of HD participants pre and post dialysis?

The current study examined motor fatigue using 6MWT and for the first-time patients performed walk test pre-dialysis and post-dialysis. No falls were reported during the walk in the study. Most patients completed walk test. Some patients had to lean on the wall to get their balance back, and some could not complete the walk due to feeling dizzy, breathlessness, pain in legs, back pain. Some individuals took breaks to rest during the walk and finished the walk at 6 minutes.

In this study, individuals walked significantly further during 6-minute walk test before dialysis compared to post-dialysis. On an average, patients walked 290 meters before dialysis and 273 meters after dialysis. Two studies were found that examined 6MWT results on patients on HD

and found that patients walked much further than those in the current study. However, the other studies did the walk test on non-dialysis days. Results from those studies indicated that patients walked 400-600 meters (Pajek et al., 2016)and 387.89 meters (Dziubek et al., 2016).

Only one other study was found that conducted the walk test on dialysis day. Results from that study, 310 meters (Manfredini et al., 2017), are similar to results from the current study. The current study had subjects do walk-test 10 minutes before and after they were initiated and terminated on dialysis respectively. The present study adds to the evidence of ranges walked during 6MWT on a dialysis day. A 6MWD of 300 or less indicates a poor prognosis ("ATS Statement," 2002). Since the distance walked before and after dialysis is less than 300 meters in this study, this finding suggests that the sample in our study had a poor prognosis. However, a future study with walk test performed on dialysis and non-dialysis day might provide more information about prognosis in this population.

Individuals who reported 'no fatigue' walked further compared to individuals who reported 'fatigue present.' However, no significant difference was observed before and after dialysis based on subjective fatigue levels. The number of patients with 'no fatigue' was small; 8 pre-dialysis and 12 post-dialysis. No previous studies have compared 6-minute walk distance (6MWD) with subjective fatigue levels. In this study, a significant correlation was obtained between total raw score derived from PFS and 6MWD post-dialysis, but the relationship was not significant pre-dialysis. The correlation between 6-minute walk and subjective fatigue could be due to the 'physical fatigue' described as 'feelings of being washed out and lifelessness' presenting in the post-dialysis period. Since there was no correlation between pre-dialysis PFS and 6MWD, it could be stated that the pre-dialysis fatigue may not have physical symptoms compared to the post-dialysis session.

The mean 6MWD covered was significantly lower in this study when compared to healthy subjects from seven different countries (Casanova et al., 2011). This finding signifies that subjects on dialysis have significantly reduced physical functional ability (Roshanravan et al., 2013; Torino et al., 2014). A review by Kosmadakis and colleagues (2010) suggested decline of physical activity by 3.4% every month after initiation of dialysis in patients. There is a catabolic state associated with hemodialysis leading to protein catabolism and degradation, and skeletal muscles start getting wasted away. The transport of amino acids to the muscle to generate force does not happen appropriately. Mitochondria, the power house of a cell are not able to metabolize energy the same way as before. Furthermore, the release of inflammatory markers such as IL-6 lead to a muscle wasting and affect physical function (Kosmadakis et al., 2010).

Aim 2: Identify the extent to which select physiological factors such as anemia, dialysis adequacy, inter-dialytic weight gain, co-morbidities, and age influence fatigue severity in individuals with Stage G5 CKD on HD.

In this study, the correlation between hemoglobin values and fatigue scores was weak and inverse in the pre-dialysis period and was statistically significant, which means that the higher hemoglobin levels were associated with lower fatigue scores. Among the physiological factors, hemoglobin was a significant predictor of fatigue severity pre-dialysis. Please note that the hemoglobin values were not done on the same day when interviews and fatigue assessment was done. The dialysis clinic performed hemoglobin checks every two weeks routinely, and in this current study we collected information about hemoglobin values from the medical records of the patient.

The relationship between hemoglobin values and fatigue scores in the post-dialysis period was not statistically significant. Most of the previous studies have reported similar findings. These

studies did not find a statistical correlation between total fatigue scores and anemia (Biniaz et al., 2013; Bossola et al., 2018; Chilcot et al., 2016). However, Karakan (2011) found that sensory fatigue was correlated with hemoglobin levels (Karakan et al., 2011). Weak and lack of relationship could be due to the erythropoietin therapy treatment that patients on dialysis are usually on to achieve a target hemoglobin level. Homogeneity of treated hemoglobin values may be leading to a weak relationship.

The correlation between dialysis adequacy and fatigue severity score was not significant in the pre or post-dialysis period, however, was trending towards statistical significance. Dialysis adequacy was a significant predictor of fatigue pre-dialysis. In a study by Bossola and colleagues (2018), post-dialysis fatigue was not associated with dialysis adequacy indicator, Kt/V. The present study did not see a relationship, which could be due to all patients being treated to achieve adequate Kt/V according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Also, in the present study, fatigue assessment was done on a different day than the day set for laboratory blood collection. It could be interesting to see if these relationships would be significant if laboratory analyses were done on the same day of interview. This is an area for further exploration. This study had insufficient funding to offset laboratory costs.

In this study, there was no statistically significant difference between the mean interdialytic weight gains and fatigue severity. Our findings are similar to Bossola and colleagues (2018), who did not find an association between interdialytic weight gain and post-dialysis fatigue.

No correlation was found between comorbidity scores and fatigue pre and post-dialysis. But, based on the PROMIS questionnaire, the correlation between pre-dialysis fatigue score and comorbidity score was statistically significant, which means that higher the comorbidities, the higher the intensity of fatigue. Contrasting findings have been reported by some investigators, in

that post dialysis fatigue was not associated with comorbidity (Bossola et al., 2018; Chilcot et al., 2016). However, Wang and colleagues (2016) reported a significant association between comorbidity and fatigue scores. Patients who have severe comorbidities might be requiring more frequent hospital visits and hospitalizations, that might be causing financial and emotional stress to the individual impacting fatigue severity.

There was a significant but weak and inverse correlation between age and fatigue severity scores pre and post-dialysis in this study. Age was a significant predictor of fatigue severity before and after dialysis. Younger age was associated with higher fatigue scores. This is an interesting finding as most investigators have reported higher fatigue levels in older age groups (Karakan et al., 2011). The physiological changes that occur in elderly people causes them to be more fatigued compared to younger patients (Zyga et al., 2015).Some investigators have reported no association between age and fatigue (Jhamb et al., 2009; Zyga et al., 2015). In the present study, no interaction was reported between age and race. However, the current study had 36% people who were African Americans and were less than 65 years of age. Perhaps, young patients probably had some racial differences that led to greater fatigue levels.

Aim 3: Identify the extent to which select situational factors such as living status, employment, gender, and race influence fatigue severity in individuals with Stage G5 CKD on HD.

Pre-dialysis people who 'lived with someone' had more fatigue compared to people who 'lived alone.' However, post-dialysis fatigue was similar in both the groups. Perhaps, people who 'lived with someone' are burdened with care of their spouse and children, and this perception might be impacting their fatigue levels.

In terms of employment, people who were 'not working' reported similar fatigue severity compared to people who were 'working.' However, in this study there were more people who were 'retired.' Perhaps, a study with more subjects who are 'working' may yield a significant association between the two variables. Contrasting findings were reported by Karakan (2011), in that fatigue score was correlated with employment status (Karakan et al., 2011). Biniaz and colleagues (2013) reported that employed patients were less fatigued than unemployed, or retired patients. Employed patients have more physical activity, adequate social relations and may get support from colleagues and friends (Biniaz et al., 2013).

According to Chi-square analysis, males and females reported similar fatigue severity in pre and post-dialysis period. In the current study, 26.7% males reported moderate fatigue compared to 22% females who were moderately fatigued pre-dialysis. Post-dialysis 18.5% males were moderately fatigued, and 13.6% females were moderately fatigued. However, the Chi-square was not significant. On performing a logistic regression to study the influence of situational factors on fatigue severity, none of the situational factors were significant predictors. However, gender was trending towards significance. Males were more likely to be fatigued severely compared to females in the pre-dialysis and post-dialysis period. Some investigators have denied any relationship between fatigue and gender (Biniaz et al., 2013; Zyga et al., 2015) whereas some have found significant relationship. Most report that women report being more fatigued than men. It has been suggested that this may be because women express their feelings/illnesses whereas men see illness as a loss of power (Artom et al., 2014; Zyga et al., 2015). Therefore, fatigue is underreported by men in many cultures (Biniaz et al., 2013). Perhaps, the culture in U.S. population is different than other cultures and could be moderating the relationship between fatigue and gender.

In terms of race, African Americans and non-African Americans reported similar fatigue severity. Jhamb and colleagues (2009) reported that African Americans had higher energy levels compared to non-African Americans. Perhaps, African Americans on dialysis are spiritually stronger and may not perceive their illness as a burden (Jhamb et al., 2009). However, the current study could not illustrate a relationship between race and fatigue.

Conformation of Findings with Theoretical Framework

This study has confirmed and refuted some of the relationships from theory of unpleasant symptoms (Lenz & Pugh, 2018). The two constructs that were studied are: Symptoms and influencing factors. Findings from the current study have been organized into the following sections.

Symptoms

Fatigue, as a single symptom was examined in patients on chronic dialysis. This study supports the proposition from TOUS that a 'symptom has various dimensions.' This study examined the types of fatigue, severity of different fatigue types, overall severity and frequency of fatigue. Based on PROMIS-fatigue, participants had higher fatigue levels compared to the general U.S. population, patients with cancer and rheumatoid arthritis (Broderick et al., 2013; Cella et al., 2016). Nearly all of the patients were fatigued pre-dialysis whereas most of the patients were fatigued post-dialysis. The proportion of patients in the severely fatigued category increased from 10% to 24%. Tiredness was reported by 77% of patients on hemodialysis in a study by Jablonski (2007) who used TOUS as a framework (Jablonski, 2007). In the current study with regard to the frequency of fatigue, most patients said they were fatigued 'sometimes' and 'often' in the past 1 week. Jablonski (2007) reported similar findings in relation to the frequency of fatigue, in that

muscle weakness was the most 'frequently occurring' symptom and was present 'most' of the days.

Different sub-types of fatigue exist such as sensory, affective, behavioral, cognitive and motor fatigue. These different types describe the quality of fatigue consistent with TOUS. Most patients on dialysis suffered from 'affective fatigue' before and after dialysis, and 'sensory fatigue' was more frequent post-dialysis. Very few patients complained of cognitive fatigue. Motor fatigue causes reduced physical function, and patients walked less far after dialysis than they did pre-dialysis.

Influencing Factors

Factors are classified to physiological and situational factors that influence fatigue and its dimensions.

Physiological factors. Four from the five physiological factors were associated with fatigue severity pre-dialysis, whereas one physiological factor was associated with fatigue severity post-dialysis. Age was correlated weakly to fatigue severity pre and post-dialysis. Age, dialysis adequacy, and hemoglobin predicted fatigue severity pre-dialysis significantly. After dialysis, age predicted fatigue severity significantly. Hemoglobin values and dialysis adequacy were correlated with fatigue severity in the pre-dialysis period. Comorbidities were associated with PROMIS fatigue pre-dialysis. In summary, our study supports the proposition from TOUS that 'influencing factors affect a particular symptom and its dimension' in pre-dialysis, not in the post-dialysis period. Mc Cann and Boore (2000) did not find any significant association between physiological factors such as hemoglobin, dialysis adequacy, other laboratory tests, gender with fatigue severity in 39 subjects on HD. The subjects however, in that study differed as they had all subjects below 65 years of age. In that study, an interaction was noted between physiological and situational

factors (McCann & Boore, 2000). The current study did not find an interaction between physiological factor, age and situational factor, race. The other major difference to be noted is that there was no real-time fatigue measurement in that study, and patients were given questionnaires to be filled at home irrespective to the timing of dialysis. Such a measurement could have recall bias unlike the current study where we used real-time methods to study fatigue. Almutary and colleagues (2017) noted that age and comorbidities were important predictors of 'symptom experience' as a part of the structural equation model in patients on dialysis.

Situational factors. Among the situational factors, more people living with someone reported fatigue pre-dialysis compared to people who were living alone based on Chi-square analysis. Gender, race, living status and employment were not associated with fatigue pre and post dialysis based on logistic regression. To summarize, our study did not support TOUS propositions as confirmed by McCann and Boore (2000). In that study, they did not find association between situational factors such as marital status, employment status, years on dialysis and fatigue presence. The influencing factor, gender was dropped from the structural equation model in another study done on 423 subjects on HD (Almutary, Douglas, & Bonner, 2017). Thus, it could be stated that situational factors do not play an important role in influencing fatigue severity. To be noted, most studies in the past have collected information about marital status, and the current study examined 'living status' for the first time in dialysis subjects. Also, we did not have a powered sample for doing a logistic regression in this study.

From the findings of our study, TOUS was able to describe dimensions of symptom 'fatigue.' TOUS provided minimal confirmation in terms of predicting fatigue symptom dimensions. However, other studies have noticed an important role of 'psychological factors' in predicting fatigue in dialysis (Almutary et al., 2017; McCann & Boore, 2000). The current study

did not examine 'psychological factors' and therefore, a final comment on the predictive ability of TOUS is not possible at this time. Also, a future study with enough power may be helpful in commenting on the predictive ability of TOUS.

Clinical Implications

Clinical Practice

This study found a high prevalence of fatigued individuals pre-dialysis and post-dialysis. Assessment of fatigue is important and must be taught to nurses, doctors and families caring for individuals with CKD and HD. Subjective questionnaires such as PFS are a great way to assess fatigue. At the same time, the 6MWT is a safe, and effective way to assess and trend physical or motor fatigue.

This study found high fatigue levels in individuals less than 65 years of age who lived with someone. This signifies people who live with someone need to be assessed for fatigue severity. Social support could be provided to individuals on HD who are burdened with care of spouses and families. Caregivers and family members can be instructed not to burden the patient on fatigue days. 'Psychosocial counselling' interventions that counsels a patient regarding energy distribution, improving physical activity, sleep hygiene practices can be helpful in reducing their fatigue levels (Ju, Strippoli, et al., 2018; Van Der Borg, Schipper, & Abma, 2016).

Physiological factors play a role in increasing fatigue levels. Especially, individuals with anemia and inadequate dialysis who need to be identified and treated accordingly. Patients with anemia can be treated with erythropoietin injections whereas for inadequate dialysis patients may be considered for dialysis with a higher dialysate flow rate (Cha & Min, 2016). Some investigators suggest lowering the dialysate temperatures also called cold dialysis to improve post-dialysis fatigue (Sajadi, Gholami, Hekmatpour, Soltani, & Haghverdi, 2016), however this intervention

needs further exploration (Azar, 2009). Sajadi and colleagues (2016) reported a significant 31% reduction in fatigue in a group of patients on HD who were cold dialyzed. Nocturnal (Bugeja et al., 2009) or daily dialysis (Jaber et al., 2010; Ray, 2010) may have effect on post-dialysis fatigue.

Patients on HD were moderately fatigued before and after dialysis, with an increase in fatigue post-dialysis. Taking rest for few hours before patient comes in for a dialysis session and after session concludes could be a testable strategy. Some clinicians advise patients to keep a diary of activities that require most energy, and accordingly prioritizing those activities that are less energy demanding around the dialysis treatment may be helpful in managing fatigue (Goudsmit, Nijs, Jason, & Wallman, 2012). Strategies can be discussed with participants on how to cope with fatigue periods. Brochures and self-help groups based on fatigue assessment could be helpful in patients with high risk for developing fatigue, which is nearly all patients on HD (Mohamed, 2014).

Improving levels of physical activity (Sheshadri, Kittiskulnam, & Johansen, 2018), complimentary therapies such as tai-chi (Zhang Y et al., 2013), acupressure (Sabouhi, Kalani, Valiani, Mortazavi, & Bemanian, 2013), foot reflexology could be considered for patients with high fatigue levels (Unal & Balci Akpinar, 2016). Cognitive behavior therapy is another treatment being tested in dialysis population and involves modification of distorted thoughts, emotions and behavior. This therapy may help in reducing fatigue levels (Picariello, Moss-Morris, Macdougall, Norton, et al., 2018).

Medications such as levocarnitine, human growth hormone and serum albumin infusion may help in reducing fatigue in dialysis population through various mechanisms. However, these medications needs further investigation (Jhamb et al., 2008; Ju, Strippoli, et al., 2018).

Clinical Education

Based on the findings that there is a high prevalence of fatigue, it is imperative to educate nurses about fatigue in patients on dialysis. Information can be incorporated from this study in undergraduate and graduate level curricula. Nurses can be taught through continuing education or primary education on topics such as measures for fatigue assessment, influencing factors of fatigue, and use of the 6-minute walk test in fatigue assessment. Educational programs could include strategies for alleviating fatigue, and the impact of fatigue on health. Content addressing impact of fatigue on health and quality of life must be included to create awareness among nurses about the importance of fatigue assessment and alleviation in dialysis population. It is not only important to educate nurses and staff, but also to provide education to patients and families.

Research Implications

Measures need to be identified that study multidimensional aspects of fatigue. Existing measures of fatigue are limited by their unidimensionality and scarcity of validating studies. More research is needed to validate existing multidimensional measures for assessment of fatigue in individuals on HD. Objective measures such as the 6-minute walk test is an excellent measure to assess physical fatigue. More research is required to validate the use of 6-minute walk in dialysis population. A 6MWT conducted on dialysis versus non-dialysis day can provide information about physical fatigue on non-treatment days. A 6MWT conducted four times a day on a treatment as well as non-treatment day may be also helpful in getting real-time data about a person's physical fatigue levels.

More studies on different patterns of fatigue such as continuous fatigue and acute fatigue, in dialysis are needed that utilize real-time methods such as 6-minute walk test, and ecological momentary assessment. Following a patient after dialysis and through the non-dialysis day until

the person goes for the next dialysis session could open new findings about fatigue and factors that influence it.

The current study had more retired individuals compared to individuals who were working. Most of the working individuals were not interested in the study as they had to rush for work after dialysis finishes and could not wait for study purposes. A working sample may have different findings on fatigue and could be studied further in a larger group of patients. Utilizing phone-based applications for fatigue assessment might be another strategy for this group of people. However, in that case other factors such as literacy level must be considered while using phone-based application in this population.

This study showed some of the physiological factors predicting fatigue levels. There are more clinical parameters that this study could not include due to modest funding and grant timelines. Studies finding relationship with other physiological factors like albumin, C-reactive protein, and sleep problems are needed.

This study did not study psychological factors such as depression, anxiety and social support. Psychological factors may significantly predict fatigue in dialysis and requires further exploration.

Since patients suffer from cognitive, behavioral and affective fatigue, psychological interventions like Cognitive Behavior Therapy may be a helpful intervention in patients suffering from fatigue in dialysis. More research is needed in this regard.

The majority of the subjects in this study were retired and had severe comorbidities. The 6-minute walk test could be studied in a type of dialysis population who are employed and has fewer co-morbidities.

Strengths of the Study

This study has used the PROMIS measures for fatigue assessment using computer administration method in Redcap software, thereby contributing towards NIH goal of using this measure across various diseases. We utilized this measure in a dialysis population that consisted of retired individuals, who are not usually considered computer-savvy.

The current study utilized PFS-12, a modified version of PFS for the first time in dialysis population. Studies that have utilized PFS in dialysis administered the measure after dialysis (Karakan et al., 2011). Our study measured fatigue before and after dialysis.

This study had 6-minute walk test conducted in the pre and post-dialysis sessions, which provides a real-time assessment of fatigue as opposed to other studies that have performed 6-minute walk test on a non-dialysis day or have measured physical performance.

This study reports the reliability of PROMIS-CAT fatigue and PFS-12; that conforms the robustness of these measures and has a potential to be used in future studies for assessment of fatigue.

This study has findings from multi-sites with real time assessment of fatigue before and after dialysis, that increases the generalizability of the findings. Almost all studies on fatigue have utilized self-report measures in the past. This study uses a combination of self-report and objective measures like 6-minute walk test that increases the validity of our findings. This study has an ethnically-diverse powered sample and findings may be attributable to bigger population with diversity.

Limitations of the Study

Convenience sampling was used and therefore, the findings may not be generalizable to a bigger population. We could not collect data from individuals who were dropped or declined from

the study to examine significant differences of subjects based on age, weight gain, and race. More subjects could be enrolled with greater funding and hiring research assistants from a bigger team that the present study could not achieve. The laboratory collection was not done on the same day of interview and walk test due to modest funding. Laboratory collection on the same day may have resulted in achieving significant findings with physiological factors.

We had a higher consent declination rate from one of the sites, which could be due to the principal investigator (who obtained consent) being seen an 'outsider' by many of the patients. The consent rates may be higher if a site personnel obtains informed consent from the subjects. Some of the findings from regression did not achieve significance due to inadequate sample size in the study based on the post-hoc power analysis. A future study with enough power may be helpful.

Summary

Fatigue is a ubiquitous symptom in majority of the chronic diseases, and currently one of the research priorities in NINR. This study examined fatigue in 86 patients on chronic dialysis from various dialysis centers in Michigan. The multiple dimensions of fatigue were examined using multidimensional subjective measures such as Piper Fatigue Scale and PROMIS-fatigue, along with one objective measure, the six-minute walk test. Some of these measures have never been utilized in the dialysis population. Nearly all the patients had fatigue, with most patients suffering from affective fatigue pre and post dialysis; and sensory fatigue post-dialysis. This study examined various physiological and situational factors that influenced fatigue severity in this dialysis population. Among these factors, dialysis adequacy, age, hemoglobin, comorbidity and living status were associated with fatigue severity. Thus, this study has advanced knowledge about the prevalence and dimensions of fatigue, and the underlying factors that influence fatigue in

dialysis population. A better understanding of symptoms such as fatigue may eventually help in better management of chronic kidney disease and contribute to a better quality of life in this population.

APPENDIX A MEASURES

Screening tool

Criteria	Yes, document reading/reason	No, document reading/reason
Consent given		
18 years old to 87 years old		
HD twice/thrice per week		
Mini cognitive assessment score <3		
Criteria for 6 minute walk (pre-dialysis)		
Rely on wheelchair for transportation		
Any mobility restrictions/ are unable to walk		
Pt states discomfort during walks usually or do not give verbal approval to walk		
Heart conditions such as unstable angina, myocardial infarction in the previous month,		
Hypotension (Blood pressure< 90/50 mmHg) prior to walk		
Heart Rate >120/minute prior to walk		
SpO2<90% prior to walk		
Criteria for 6 minute walk (post-dialysis)		
Rely on wheelchair for transportation		
Any mobility restrictions/ are unable to walk		
Pt states discomfort during walks usually or do not give verbal approval to walk		
Hypotension (Blood pressure< 90/50 mmHg)		
Any episodes of intradialytic hypertension with increase in systolic blood pressure >90 mmHg from pre to post dialysis.		
SpO2 <90%		
Heart Rate >120/minute		
Patient reported symptoms of intradialytic hypotension like light headedness, nausea, vomiting during dialysis		

Mini Cognitive assessment test

Step 1: Three word registration: Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are –Banana, Sunrise, Chair. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2.

Step 2: Clock drawing: Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11." Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three word recall: Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers.

Selection criteria: Not met_____ Met _____

Performa

Patient ID#_____

Please answer the following questions.

Age .	_____
Living status	a. Living with spouse/ siblings/parents/multiple relatives/ alone b. Living in own house/ rented house/ apartment/ condominiums/ assisted living /shelter homes/ others. c. Number of people in the family_____ d. Number of adults in the house_____ e. Number of children in house_____ f. Number of senior citizens in the house_____
Race	a. Asian b. African American c. Caucasian d. Hispanic/Latino e. Middle East f. Other_____
Gender	a. Male b. Female c. Other_____
Employment status	a. Working full time/part time/contingent b. Number of jobs_____ c. Number of days/ week_____ d. Number of hours per day_____ e. Unemployed
Physiological information (collected from medical records)	a. Blood Urea _____(g/dL) b. Blood Creatinine _____(g/dL) c. Blood Hemoglobin recent_____(g/dL) d. Weight gain since last dialysis_____(kg) e. Ultrafiltration rate_____(ml/hr) f. Ultrafiltration volume_____(ml) g. Vascular Access _____ h. Pre dialysis weight_____(kg), post dialysis weight_____(kg) i. Recent Kt/V_____

Charlson Comorbidity Index
Chart review version

Components of classical Charlson Comorbidity Index[1]

1. Has the patient had a myocardial infarction? (MI)
   ___ No
   ___ Yes

Criteria: Myocardial infarction includes patients with one or more definite or probable myocardial infarction. These patients should have been hospitalized for chest pain or an equivalent clinical event and have had electrocardiographic and/ or enzyme changes. Patients with electrocardiographic changes alone who have no clinical history are not designated as having had an infarction.

2. Has the patient been hospitalized or treated for heart failure? (CHF)
   ___ No
   ___ Yes

Criteria: Congestive heart failure includes patients who have had exertional or paroxysmal nocturnal dyspnea and who have responded symptomatically (or on physical examination) to digitalis, diuretics, or afterload reducing agents. It does not include patients who are on one of those medications but who have had no response and no evidence of improvement of physical signs with treatment.

3. Does the patient have peripheral vascular disease? (PVD)
   ___ No
   ___ Yes

Criteria: Peripheral vascular includes patients with intermittent claudication or those who had a bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with a treated or untreated thoracic or abdominal aneurysm (6 cm or more).

4. Has the patient had a CVA or transient ischemic disease? (CVA)
   ___ No
   ___ Yes

Criteria: Cerebrovascular disease includes patients with a history of a cerebrovascular accident with minor or no residua, and patients who have had transient ischemic attacks. If the CVA resulted in hemiplegia, code only hemiplegia.

[1] Charlson, ME, Ales, KA, Pompei, P, MacKenzie, CR. A new method of classification of prognostic comorbidity for longitudinal studies: development and validation. J Chron Disease, 1987, 40(5): 373–383

5. Does the patient have hemiplegia? (PLEGIA)
   ___ No
   ___ Yes

Criteria: This includes patients with a hemiplegia or paraplegia, whether it occurred as a result of a cerebrovascular accident or other condition.

6. Does the patient have asthma, chronic lung disease, chronic bronchitis or emphysema? (COPD)
   ___ No
   ___ Yes

Criteria: Pulmonary disease includes patients with asthma, chronic bronchitis, emphysema, and other chronic lung disease who have ongoing symptoms such as dyspnea or cough, with mild or moderate activity. This includes patients who are dyspneic with slight activity, with or without treatment and those who are dyspneic with moderate activity despite treatment, as well as patients who are dyspneic at rest, despite treatment, those who require constant oxygen, those with CO_2 retention and those with a baseline PO_2 below 50 torr.

7. Does the patient have diabetes that requires treatment? (DM)
   ___ No
   ___ Yes

Criteria: Diabetes includes all patients with diabetes treated with insulin or oral hypoglycemic, but not diet alone. Diabetes during pregnancy alone is not counted.

7a. Does the patient have end organ damage from diabetes? (DMENDORGAN)
   ___ No
   ___ Yes

Criteria: This includes patients with retinopathy, neuropathy, or nephropathy attributable to diabetes.

8. Does the patient have moderate or severe renal disease? (RENAL)
   ___ No
   ___ Yes

Criteria: Moderate renal insufficiency includes patients with a serum creatinine >3 mg/dl. Severe renal disease includes patients on dialysis, those who had a transplant, and those with uremia.

9. Does the patient have a chronic liver disease? (MILDLIVER)
___ No
___ Yes

Criteria: Mild liver disease consists of chronic hepatitis (B or C) or cirrhosis without portal hypertension.

9a. Does the patient have moderate to severe liver disease? (SEVERELIVER)
___ No
___ Yes

Criteria: Moderate liver disease consists of cirrhosis with portal hypertension, but without bleeding. Severe liver disease consists of patients with ascites, chronic jaundice, portal hypertension or a history of variceal bleeding or those who have had liver transplant.

10. Has the patient had gastric or peptic ulcers? (ULCER)
___ No
___ Yes

Criteria: Peptic ulcer disease includes patients who have required treatment for ulcer disease, including those who have bled from ulcers.

11. Has the patient had cancer (other than basal cell skin cancer)? (CANCER)
___ No
___ Yes
If yes, which:
___ Lymphoma?
___ Leukemia?
___ Solid tumor (which?)_____

Criteria: Lymphoma includes patients with Hodgkins, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, and other lymphomas. Leukemia includes patients with acute and chronic myelogenous leukemia, acute and chronic lymphocylic leukemia, and polycythemia vera. Solid tumor consists of patients with solid tumors without documented metastases, including breast, colon, lung, prostate, and a variety of other tumors.

11a. Has the patient had a metastatic solid tumor? (METASTASES)
___ Breast
___ Colon
___ Prostate
___ Lung
___ Melanoma
___ Other _____

Criteria: Metastatic cancer includes patients with metastatic solid tumors, including breast, lung, colon and other tumors

12. Does the patient have Alzheimer's, dementia from any etiology or any serious cognitive impairment? (DEMENTIA)
___ No
___ Yes

Criteria: Dementia includes patients with moderate to severe chronic cognitive deficit resulting in impaired function from any cause

13. Does the patient have any rheumatic or connective tissue disease? (RHEUMATIC)
___ No
___ Yes

Criteria: Rheumatologic disease includes patients with systemic lupus erythematous, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyositis, polymyalgia rheumatica, vasculitis, sarcoidosis, Sjogrens syndrome or any other systemicvasculitis

14. Does the patient have HIV or AIDS? (HIV)
___ No
___ Yes

Criteria: Acquired immune deficiency syndrome includes patients with definite or probable AIDS, i.e. AIDS related complex, and those who are HIV positive and asymptomatic.

Additional components of Charlson Comorbidity Index adapted to predict cost[2]

15. Does the patient have hypertension? (HBP)
___ No
___ Yes

Criteria: Hypertension includes patients who have systolic pressures >140 mm Hg and/ or diastolic pressures >90 mm Hg if without diabetes or renal disease, as well as controlled hypertensives, or patients with diabetes or renal disease who have systolic pressures >140 mm Hg or diastolic pressures >80 mm Hg.

[2] Charlson, ME, Charlson RE, Briggs, W. Hollenberg, J. Can disease management target patients most likely to generate high costs? The impact of comorbidity. J Gen Intern Med. 2007; 22(4): 464-469

16. Has the patient had decubitus ulcers, peripheral skin ulcers or repeated episodes of cellulitis? (SKINULCER)
___ No
___ Yes

Criteria: Partial thickness loss of skin over legs or back with open ulcers or two or more episodes of cellulitis requiring treatment with antibiotics, regardless of etiology.

17. Does the patient have depression? (DEPRESSION)
___ No
___ Yes

Criteria: Patients who are currently receiving treatment for depression, whether pharmacologic or psychotherapy, or cognitive behavioral therapy, or notes indicating that the patient has probable or definite depression.

18. Is the patient on warfarin or coumadin? (WARFARIN)
___ No
___ Yes

Conditions that are not assigned weights

- Angina includes patients with chronic exertional angina, those who had coronary artery bypass graft, and those initially admitted with unstable angina.
- Arrhythmia includes patients with chronic atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring chronic treatment.
- Valvular disease includes patients with hemodynamically significant aortic stenosis and/or insufficiency, those with significant mitral stenosis and/or insufficiency, and those with prosthetic aortic or mitral valves, asymmetric septal hypertrophy requiring treatment, or tricuspid insufficiency.
- Other neurologic conditions includes patients with Parkinson's disease, uncontrolled seizures, or syncope without an identified cause or treatment.
- Other endocrine includes patients with hypopituitarism, adrenal insufficiency, and recurrent acidosis.
- Inflammatory bowel disease includes patients with ulcerative colitis or regional enteritis.
- Gastrointestinal bleeding includes those who have had bleeding requiring transfusions from causes other than ulcer disease.
- Coagulopathy includes patients with a circulating anticoagulant, or other coagulopathy.

Tool 3

Six minute walk test

Patient ID# _____
Date: _____
Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters
Weight: _____ lbs, _____kg Blood pressure: _____ / _____
Medications taken before the test (dose and time): _____
Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____
SpO2 before the walk test_____
Before beginning read the following to the patient

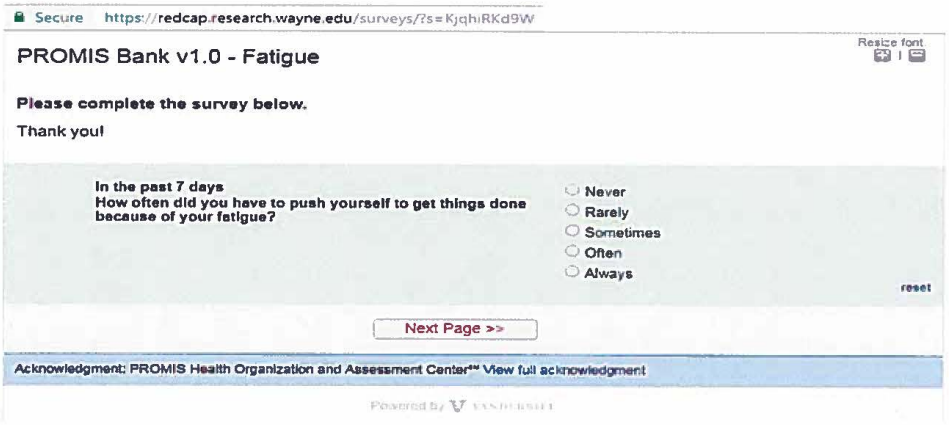
"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."
Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly. "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE
for 6 minutes, but don't run or jog. Start now, or whenever you are ready."

After the first minute, say: "You are doing well. You have 5 minutes to go."
When 4 minutes remaining, say: "Keep up the good work. You have 4 minutes to go."
When 3 minutes remaining, say: "You are doing well. You are halfway done."
When 2 minutes remaining, say: "Keep up the good work. You have only 2 minutes left."
When only 1 minute remaining, say: "You are doing well. You have only 1 minute to go."
When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
When the timer rings (or buzzes), say this: "Stop!" Do not use other words of encouragement (or body language to speed up).
Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.
6MWT worksheet and report:
Lap counter: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Baseline End of Test
Time ___:___ ___:___ Heart Rate _____ _____
Stopped or paused before 6 minutes? No Yes, reason: _____
Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain
SpO2 if taking oxygen_____%
Number of laps: ____ (_60 meters) _ final partial lap: _____ meters _
Total distance walked in 6 minutes: _____ meters
Any desaturation during the walk _____
Predicted distance: _____ meters Percent predicted: _____%
Tech comments:

Tool 4

PROMIS Fatigue is a compute adaptive test and will be administered through a secure REDcap account. Following is a snapshot of a sample question. The next question appears only after a response is given by the subject to the first question. In the end, a T-score is generated by the computer.



Subject ID # _____

Tool 5
Piper Fatigue Scale-12

Directions: People can experience a sense of unusual or excessive tiredness whenever they might become ill or receive treatment for their illness. This unusual sense of tiredness is not usually relieved by a good night's sleep or by rest. Some call this symptom "fatigue" to distinguish it from the usual sense of tiredness.

For each of the following questions, please indicate the number that best describes your current fatigue (now or for today) on a "0-10" scale with "0" indicating "none" and "10" indicating "a great deal". If you are not experiencing fatigue, please select "0" for your responses. Thank you very much!

1. My fatigue interferes with my ability to do work or school activities:

0 1 2 3 4 5 6 7 8 9 10
None **A great deal**

2. My fatigue interferes with my performing the activities I enjoy doing:

0 1 2 3 4 5 6 7 8 9 10
None **A great deal**

3. I describe my fatigue as being:

0 1 2 3 4 5 6 7 8 9 10
Mild **Severe**

4. I describe my fatigue as being:

0 1 2 3 4 5 6 7 8 9 10
Pleasant **Unpleasant**

5. I describe my fatigue as being:

0 1 2 3 4 5 6 7 8 9 10
Positive **Negative**

Subject ID #_____

6. I describe my fatigue as being:

0 1 2 3 4 5 6 7 8 9 10

Normal **Abnormal**

7. Currently I am feeling:

0 1 2 3 4 5 6 7 8 9 10

Strong **Weak**

8. Currently I am feeling:

0 1 2 3 4 5 6 7 8 9 10

Awake **Sleepy**

9. Currently I am feeling:

0 1 2 3 4 5 6 7 8 9 10

Refreshed **Tired**

10. Currently I am feeling:

0 1 2 3 4 5 6 7 8 9 10

Patient **Impatient**

11. Currently I am feeling:

0 1 2 3 4 5 6 7 8 9 10

Able to concentrate **Unable to concentrate**

12. Currently I am feeling:

0 1 2 3 4 5 6 7 8 9 10

Able to think clearly **Unable to think clearly**

APPENDIX B HIPAA, CONSENT FORM AND FLYERS

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. We must obtain your written authorization before we may use or disclose your protected health information for the research purposes described below. This form may add to the information in the consent form you have already signed. You will receive a signed and dated copy of this authorization form for your records.

Introduction

This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. Before deciding whether to participate in the study, you may take home an unsigned copy of this authorization form to think about, or discuss with family or friends.

In this authorization form, "you" always refers to the study subject. If you are a legally authorized representative, please remember that "you" refers to the study subject.

This study includes a number of researchers, businesses and government agencies. They may use your health information and share it with others. We want you to know who may use this information and how they may use it.

We also want to tell you about your rights before you agree to take part in the study.

What information may be used and given to others?

If you choose to be in this study, personal information about you and your health will be reviewed, created and shared with others. This may include information that might identify you, including the following types of information:

- Demographic information, including, but not limited to, your name, address, telephone number, Social Security number, health plan number, etc.
- Information from your medical records that may be relevant to the study, such as medical history, results of physical examinations, diagnoses, treatments, laboratory values, etc.
- Research records, including, but not limited to, information obtained from the procedures used to find out whether you are eligible to take part in this study, your response to any study treatments you receive, physical examinations, laboratory test results, x-rays, other tests and procedures that may be performed, etc.
- Records about phone calls made as part of this research

- Records about your study visits
- Records about any study drug or placebo that you received

Do I have to give my permission for certain sensitive information to be released?
Yes, the following information will only be released if you give your specific permission by putting your initials on the line(s).
____ I agree to the release of information pertaining to drug and alcohol abuse, diagnosis or treatment.
____ I agree to the release of HIV/AIDS testing information.
____ I agree to the release of Sickle Cell Anemia testing information.
____ I agree to the release of genetic testing information.
____ I agree to the release of information pertaining to mental health diagnosis or treatment.

Who may use and give out information about you?
Information about you may be used and given to others by the study doctor, the study doctor's staff, the clinical laboratories used for the study, other health care providers who have treated you, and DaVita HealthCare Partners Inc. ("DaVita") and any of its subsidiaries and their professional and administrative staff. They may also use the research information until all the research ends and all required study monitoring is over.

Who might receive this information?
Your information may be given to the study doctor, the study doctor's staff, the clinical laboratories used for the study, and the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor.

Information about you and your health, which might identify you, may also be given to:

- Doctors and healthcare professionals taking part in the study
- DaVita and its subsidiaries, and persons working for or with them
- The U.S. Food and Drug Administration (FDA)
- U.S. Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Government agencies that must receive reports about certain diseases
- An Institutional Review Board (IRB). An Institutional Review Board is a group of people who perform independent reviews of research as required by regulations.

Why will this information be used and/or given to others?
Information about you and your health, that might identify you, may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. The sponsor may also reanalyze the results at a later date, combine them with the results of other studies and use the information to develop medical products. People from the sponsor and its consultants will be visiting the research site. They will review how the study is being conducted. They may review your information to see if it is accurate and complete. DaVita professional and administrative staff will assist the research doctors with certain administrative aspects related to the study.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by an IRB to review the research as required by regulations.

Photographs may be taken of side effects on your body, such as if you develop a rash during the study. A photograph of you and a copy of your picture ID may also be collected to verify who you are and your date of birth. All photographs/videos will be property of DaVita Clinical Research and will be kept confidential as described in this authorization. In addition, the research facilities may be equipped with electronic surveillance (video cameras) and your activities may be monitored.

If you are moved to a different hospital or clinic prior to the end of your participation in this clinical study, your signature on this document gives your study doctor permission to ask for copies of your medical records from the new hospital or clinic which will be reviewed by those listed above.

What if I decide not to give permission to use and give out my health information?
By signing this authorization form, you are giving permission to use and give out the health information listed above for the purposes described above. You have a right to refuse to sign this authorization. Refusing to sign this authorization will not affect your health care outside of the study, the payment of your health care,

and your health care benefits. However, if you refuse to sign this authorization, you will not be able to participate in this research study.

May I review or copy the information obtained from me or created about me as it relates to this study?
If you decide to be in this study and sign this authorization form, you will not be allowed to look at or copy your health information related to this research study until after the research is completed.

Is there a fee for a copy of my medical records?
Yes, copies of medical records are subject to reproduction fees in accordance with federal and state regulations of the state in which the healthcare is provided. You may contact the Medical Records Department for an estimate of the fees or go to http://www.lamblawoffice.com/medical-records-copying-charges.html for copy charges by state.

How long will it take to receive my records?
DaVita complies with state and federal release time requirements. DaVita utilizes both hardcopy (paper) and electronic patient information. Hard copy records may need to be retrieved from long-term storage.

Is my health information protected after it has been given to others?
If you authorize the use and disclosure of your information, there is a risk that the information disclosed pursuant to this authorization may be re-disclosed by the recipient of your information.

Does my permission expire?
This permission to release your Personal Health Information expires when the research ends and all required study monitoring is over.

This permission to release your Personal Health Information expires in 20 years or when the research ends and all required study monitoring is over or until you revoke your permission whichever is earlier. If you are in Maine or Maryland your authorization/permission will remain in effect for one (1) year. If you are in Montana your authorization/permission will remain in effect for six (6) months or the day you revoke your permission.

May I withdraw or revoke (cancel) my permission?
You have the right to revoke this authorization in writing at any time. When you withdraw your permission, no new health information, which might identify you,

will be gathered after that date. Information that has already been gathered may still be used and given to others for use in the study. This would be done if it were necessary for the research to be reliable.

You can revoke this authorization by sending written notice to DaVita Clinical Research, 825 South 8th Street, Suite 300, Minneapolis, MN 55404, Attn: Research Director. If you withdraw your permission, you will not be able to continue being in this study.

Authorization:
I have been given the information about the use and disclosure of my health information for this research study.

I authorize the use and disclosure of my health information as described in this authorization.

AUTHORIZATION SIGNATURE:

_____
Subject Name (Please Print)

_____ _____
Subject Signature Date

If the Study Subject is a minor or has a legal representative, I represent that I am the parent/legal guardian/legal representative of the Study Subject named above and I am not prohibited by Court Order from releasing access to the requested information.

_____
Name of Subject's Parent/Legal Guardian/Legal Representative
(Please Print)

_____ _____
Signature of Parent/Legal Guardian/Legal Representative Date

_____

Description of the Representative's Authority to Sign for the Study Subject

Behavioral Research Informed Consent
Title of Study: Fatigue in Chronic Kidney Disease-Hemodialysis

Principal Investigator (PI): Bincy Joshwa
College of Nursing, Wayne State University
248-495-3496

Funding Source: American Nephrology Nurses Association

Purpose
You are being asked to be in a research study of fatigue in patients on hemodialysis because you have Chronic Kidney Disease and are on Hemodialysis. This study is being conducted at various dialysis centers around Detroit. The estimated number of study participants to be enrolled at is about 150. **Please read this form and ask any questions you may have before agreeing to be in the study.** Some people on dialysis say that they feel very tired (fatigued). In this research study, we will examine the level and pattern of your fatigue and will compare two different ways to measure fatigue: your answers to questions on a questionnaire and a six-minute walk test. You also will be asked about other reasons that you may feel tired such as anemia, weight gain between dialysis sessions, age and living situation.

Study Procedures
If you agree to take part in this research study, you will be asked to answer a few questions about how tired you feel and to walk for six minutes in a hallway. As a part of this study, there will be two (2) clinic visits and these visits will last approximately 1-1¼ hours. The two visits will take place during your regularly scheduled dialysis clinic appointments.
At visit 1, there will be session 1 which will take approximately 20 – 30 minutes, you will have the following procedures:

- Review this document with a member of the study team so you understand the details of the study, including the risks and benefits, and have a chance to ask questions. Sign this document if you are willing to participate. This can be done either before or after your dialysis treatment.
- If you decide to participate, we will schedule a mutually agreeable date and time for visit 2.

At visit 2, you will have 2 sessions. Session 2 and session 3 will last approximately 45 minutes before and after you complete your dialysis treatment, you will have the following procedures:

- Answer questions about how tired you are feeling and about your age, health, other diseases you suffer from and living situation.
- The following information will be collected from your clinic medical records: levels of hemoglobin, urea and creatinine before and after dialysis, indicators that measure dialysis adequacy, weight and other illnesses you suffer from.
- Blood pressure and pulse will be checked before the six-minute walk. If your health is stable, only then six-minute walk be performed.
- If you suffer from recent heart problems, use a wheelchair, or feel uncomfortable to walk, the six-minute walk will not be performed.
- Six-minute walk test: You will be asked to walk in the hallway for six minutes as fast as you can. The total distance you walk in these six minutes will be calculated by an observer. You can rest on a chair whenever you want. The test will end at the end of six

minutes or when you indicate that you do not wish to continue. The six-minute walk test will be done twice: before and again after your dialysis treatment.

Benefits
The information obtained from this study may benefit other people now or in the future.

Risks
While you are in the study, you may be at risk for the following side effects:

- Likely: As a result of the six-minute walk you may experience physical problems (e.g., shortness of breath and/or leg cramps) for a short time. This usually goes away after a few minutes of rest.
- Less Likely: There may be physical risks such as staggering, dizziness, increased sweating and a pale appearance during the six-minute walk.
- Rare but serious: There may be a rare possibility of physical risks such as falls, chest pain/discomfort, blood pressure disturbances, and death. Social risks, such as breach of confidentiality during the study, may also occur.

There may also be risks involved from taking part in this study that are not known to researchers at this time.

Study Costs
Participation in this study will be of no cost to you. We do not expect there to be any additional costs to you if you participate in this study. Items related to the routine medical care that you would receive even if you did not participate in this study will be billed to you or your insurance company.

Compensation
For taking part in this research study, you will be paid for your time and inconvenience. You will receive a $10 gift card after session 1 if you agree to participate in this study. If you complete session 2 you will be awarded with a 20 dollar gift card. You will receive another $20 gift card after you finish the session 3. If you do not finish the study, you will be paid only for the part that you completed.

Research Related Injuries
In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Care for such will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation, or free medical care is offered by Wayne State University or Dialysis clinic. If you think that you have suffered a research related injury, contact the PI right away at 248-495-3496.

Confidentiality
All information collected about you during the course of this study will be kept confidential to the extent permitted by law. You will be identified in the research records by a code name or number. Information that identifies you personally will not be released without your written permission. However, the study sponsor, the Institutional Review Board (IRB) at Wayne State University, or federal agencies with appropriate regulatory oversight [e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.) may review your records.

When the results of this research are published or discussed in conferences, no information will be included that would reveal your identity.

Voluntary Participation/Withdrawal

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you decide to take part in the study you can later change your mind and withdraw from the study. You are free to only answer questions that you want to answer. You are free to withdraw from participation in this study at any time. Your decisions will not change any present or future relationship with Wayne State University or its affiliates, or other services you are entitled to receive. The PI may stop your participation in this study without your consent. The PI will make the decision and let you know if it is not possible for you to continue. The decision that is made is to protect your health and safety, or because you did not follow the instructions to take part in the study

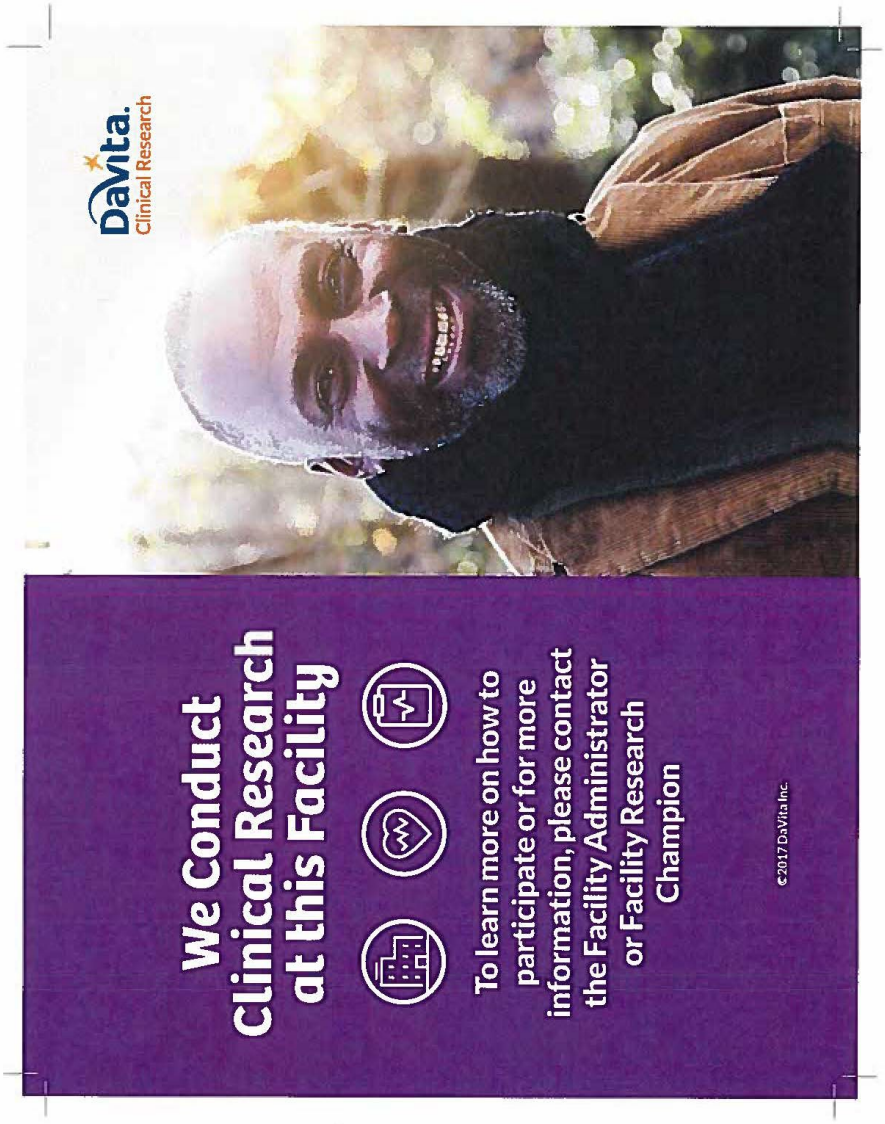
Questions

If you have any questions about this study now or in the future, you may contact Bincy Joshwa or one of her research team members at the following phone number (248) 495-3496. If you have questions or concerns about your rights as a research participant, the Chair of the Institutional Review Board can be contacted at (313) 577-1628. If you are unable to contact the research staff, or if you want to talk to someone other than the research staff, you may also call the Wayne State Research Subject Advocate at (313) 577-1628 to discuss problems, obtain information, or offer input.

Consent to Participate in a Research Study

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

Signature of participant	Date
Printed name of participant	Time
Signature of witness	Date
Printed of witness	Time
Signature of person obtaining consent	Date
Printed name of person obtaining consent	Time



APPROVAL PERIOD

MAR 22 2018 FEB 28 2019

WAYNE STATE UNIVERSITY
INSTITUTIONAL REVIEW BOARD

QUORUM REVIEW
APPROVED
JAN 08 2018
INSTITUTIONAL
REVIEW BOARD

APPENDIX C APPROVAL LETTERS

DaVita Clinical Research

Minneapolis Office
825 South Eighth Street
Suite 300
Minneapolis, MN. 55404
(612) 852-7000 phone
(612) 852-3241 fax

Bincy Joshwa, PhD Candidate
Wayne State University College of Nursing
Detroit, MI 48202

February 9, 2018

Bincy Joshwa

Re: Letter of Support – "Fatigue in Chronic Kidney Disease-Hemodialysis"

Dear Bincy,

This letter acknowledges support by DaVita Clinical Research (DCR) for the above-referenced study. We look forward to supporting you and your research team on this study in which we hope you will be able to recruit from approximately *130* of our patients from *4 facilities*.

This letter does not serve as official study approval from DaVita Clinical Research. Only at the time when you receive official study approval terms, which includes but is not limited to IRB approval, are you allowed to begin executing your proposed research project within the DaVita network.

Our clinical research team will assist you in completing the necessary DaVita paperwork required for research studies in the DaVita facility and obtaining the official study approvals.

We look forward to collaborating with you on this project.

Sincerely,

DocuSigned by:
Brian Wood
B75F99DC57CF4A5...

Brian Wood
Director, Clinical Operations (DCR)
DaVita Clinical Research

Please note this letter does not serve as official study approval from DaVita Clinical Research. Only at the time when you receive official study approval terms are you allowed to begin executing your proposed research project within the DaVita network.

WAYNE STATE UNIVERSITY

IRB Administration Office
87 East Canfield, Second Floor
Detroit, Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
http://irb.wayne.edu

NOTICE OF FULL BOARD APPROVAL

To: Bincy Joshwa
Family, Comm Mental Health
5557 Cass Ave., Cohn Building

From: Lawrence R. Crane, M.D. or designee LCrane / UB
Chairman, Medical Institutional Review Board (M1)

Date: March 22, 2018

RE: IRB #: 030218M1F
Protocol Title: Fatigue in Chronic Kidney Disease-Hemodialysis
Funding Source: Sponsor: American Nephrology Nurses Association
Protocol #: 1802001223

Expiration Date: February 28, 2019

Risk Level / Category: Research involving greater than minimal risk but presenting the prospect of direct benefit to the subject

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The above-referenced protocol and items listed below (if applicable) were **APPROVED** following *Full Board Review* by the Wayne State University Institutional Review Board (M1) for the period of 03/22/2018 through 02/28/2019. This approval does not replace any departmental or other approvals that may be required.

- Protocol and revised Protocol Summary Form (revisions received in IRB Administration Office 03/19/2018)
- A waiver of consent and waiver of written documentation of consent has been granted to screen for eligible participants according to 45CFR46.116(d) and 45CFR46.117(c). This waiver satisfies: 1) risk is no more than minimal, 2) the waiver does not adversely affect the rights and welfare of research participants, 3) the research could not be practicably carried out without the waiver, and 4) the participant will be given information.
- Note to PI: WSU is not the privacy board for DaVita facilities, therefore HIPAA Waiver does not apply.
- Behavioral Research Informed Consent (revision dated 03/19/2018)
- Authorization to Use and Disclose Information for Research Purposes
- Flyers (4)
- Data Collection Tools: (I) Screening Tool, (II) Mini Cognitive Assessment Test, (III) Performa, (IV) Six Minute Walk Test,(V) Tool 4, (VI) Piper Fatigue Scale-12, and (VII) Charlson Comorbidity Index

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- Federal regulations require that all research be reviewed at least annually. You *may* receive a *"Continuation Renewal Reminder"* approximately two months prior to the expiration date; however, it is the Principal Investigator's responsibility to obtain review and continued approval ***before*** the expiration date. Data collected during a period of lapsed approval is unapproved research and can *never* be reported or published as research data.
- All changes or amendments to the above-referenced protocol require review and approval by the IRB **BEFORE** implementation.
- Adverse Reactions/Unexpected Events (AR/UE) must be submitted on the appropriate form within the timeframe specified in the IRB Administration Office Policy (http://www.irb.wayne.edu/policies-human-research.php).

NOTE:

1. Upon notification of an impending regulatory site visit, hold notification, and/or external audit the IRB Administration Office must be contacted immediately.
2. Forms should be downloaded from the IRB website at **each** use.

Notify the IRB of any changes to the funding status of the above-referenced protocol.

WAYNE STATE UNIVERSITY

IRB Administration Office
87 East Canfield, Second Floor
Detroit, Michigan 48201
Phone: (313) 577-1628
FAX: (313) 993-7122
http://irb.wayne.edu

NOTICE OF EXPEDITED AMENDMENT APPROVAL

To: Bincy Joshwa
Family, Comm Mental Health
5557 Cass Ave., Cohn Building

From: For Lawrence R. Crane, M.D. or designee K. Schwartz IRB
Chairperson, Medical Institutional Review Board (M1)

Date: July 24, 2018

RE:

IRB #:	030218M1F
Protocol Title:	Fatigue in Chronic Kidney Disease-Hemodialysis
Funding Source:	Sponsor: American Nephrology Nurses Association
Protocol #:	1802001223
Expiration Date:	February 28, 2019
Risk Level / Category:	Research involving greater than minimal risk but presenting the prospect of direct benefit to the subject

The above-referenced protocol amendment, as itemized below, was reviewed by the Chairperson/designee of the Wayne State University Institutional Review Board (M1) and is APPROVED effective immediately.

- Protocol (version 2)- Protocol modified to reflect accrual, enrollment criteria, and data collection method changes. Changes include increasing the accrual number from 130 to 150 participants, change of exclusion criteria that was rigid to a more lineant one and addition of a few variables in the performa.
- Consent Form (revision dated 07/18/2018)- Consent forms modified to reflect an increase in accrual to 150 participants, and updated enrollment criteria.
- Receipt of revised screening tool, and revised performa form.
- Other- Electronic Data Storage- The electronic data will be stored in SPSS software on a computer protected by passwords owned by the PI due to feasibility aspects.

Notify the IRB of any changes to the funding status of the above-referenced protocol.

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ABSTRACT

MULTIPLE DIMENSIONS AND CORRELATES OF FATIGUE IN INDIVIDUALS ON HEMODIALYSIS: A QUANTITATIVE STUDY

by

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Major: Nursing

Degree: Doctor of Philosophy

Background: Fatigue is present in individuals on Hemodialysis (HD). Evidence on fatigue in HD are limited by focus on unidimensional aspect of fatigue, flawed unidimensional tools, lack of objective measures, and variability in the correlates of fatigue. **Purpose:** To examine severity and trajectory pattern of fatigue; delineate influencing physiological and situational factors pre-dialysis and post-dialysis. **Theoretical Framework:** The Theory of Unpleasant Symptoms was used to guide the study. **Methodology:** A descriptive, correlational, before-after design was utilized. Measures were Piper Fatigue Scale (PFS)-12, Patient Reported Outcomes Measurement Information Systems (PROMIS)-Fatigue, Charlson Comorbidity Index and six-minute walk test (6MWT). Adults, cognitively intact patients on HD were included; patients with limited mobility, heart issues and abnormal vital signs were excluded for the 6MWT. **Results:** Sample was 86 participants, 24-89 years old, 58.1% males, and 51.1% non-whites. In terms of prevalence, 90% of the patients were fatigued pre-dialysis whereas 85% of the patients were fatigued post-dialysis. Most individuals were moderately fatigued pre-dialysis and most were mildly and moderately fatigued post-dialysis. The mean scores of fatigue based on PFS-12 increased after dialysis, however, no statistical difference was observed. In terms of quality of fatigue, high 'affective

fatigue' mean scores were reported before and after dialysis session. An increase in sensory and cognitive fatigue was observed from pre-dialysis to the post-dialysis period. In terms of frequency,70% patients said that they had fatigue 'often' or 'sometimes' in the past 7 days. The mean PROMIS fatigue score was significantly higher than average U.S. population. Individuals walked significantly further during 6-minute walk test pre-dialysis than post-dialysis, that indicates patients are physically fatigued. Fatigue was severe in individuals with low hemoglobin values, inadequate dialysis, comorbidities, young age group and individuals who lived with someone. **Conclusion:** Prevalence of fatigue is higher in dialysis than general population, and fatigue escalates after dialysis. Therapies that can target sensory, cognitive and physical fatigue may be helpful in alleviation of fatigue in these patients. A better understanding of fatigue will eventually help in better management of chronic kidney disease and contribute to a better quality of life in this population.

AUTOBIOGRAPHICAL STATEMENT

Bincy Joshwa is a symptom scientist whose research focuses on fatigue. She has completed her bachelor's in nursing and master's in nephrology nursing from All India Institute of Medical Sciences, India. Her education in nephrology nursing initiated her interest in individuals with kidney failure and dialysis. Findings from her first study on patients on dialysis found a high prevalence of multiple symptoms such as sleep, fatigue and depression. Her doctoral dissertation study focused on fatigue specifically, its multiple dimensions and correlates. She received various fellowships, awards and research grants in her program of study. She has taught various levels of graduate nurses and brings expertise from her clinical background working as a nurse with medical-surgical and dialysis patients.