Fatigue in Nondialysis Chronic Kidney Disease: Correlates and Association with Kidney Outcomes

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Keywords

Fatigue · Chronic kidney disease · Mortality · Hospitalization · Outcomes

Abstract

Background: Fatigue, although common and associated with outcomes in dialysis-dependent chronic kidney disease (CKD), has not been studied in nondialysis chronic kidney disease (CKD-ND) patients. **Methods:** In this longitudinal cohort of 266 outpatients with CKD-ND stages 2–5, we measured self-reported fatigue on 3 scales—Quick Inventory of Depression Symptomatology-Self Report (QIDS-SR₁₆), Beck Depression Inventory-I (BDI-I), and short form 12 health survey (SF-12) questionnaires and evaluated the prespecified composite of progression to dialysis initiation, death, or hospitalization after 12 months. Logistic and linear regression assessed characteristics associated with fatigue. Survival analysis measured associations of fatigue with outcomes. **Results:** Mean age was 64.4 ± 12.0 years, and mean estimated glomerular filtration rate (eGFR) was 31.6 ± 16.7 mL/

min/1.73 m². Fatigue was common, with 69.2% reporting fatigue on QIDS-SR₁₆ and 77.7% on BDI-I. Unemployment, comorbidities, use of antidepressant medications, and lower hemoglobin correlated with fatigue. There were 126 outcome events. Participants that reported any versus no fatigue on QIDS-SR₁₆ were more likely to reach the composite, hazard ratio (HR) 1.70 (95% CI 1.11–2.59), which persisted after adjusting for demographics, comorbidities, substance abuse, hemoglobin, albumin, eGFR, and calcium-phosphorus product, HR 1.63 (1.05–2.55). Fatigue severity by the SF-12 was also associated with outcomes independent of demographics, comorbidities, and substance abuse, HR per unit increase 1.18 (1.03–1.35). No association was observed with fatigue on the BDI-I. **Conclusion:** Fatigue affected about 2/3 of CKD-ND patients and associated with unemployment, comorbidities, antidepressant medication use, and anemia. Fatigue measured by the QIDS-SR₁₆ and SF-12 independently predicted outcomes in CKD patients. Eliciting the presence of fatigue may be a clinically significant prognostic assessment in CKD patients.

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Introduction

Fatigue is a common clinical manifestation in patients with chronic diseases including dialysis-dependent chronic kidney disease (CKD-D), congestive heart failure, rheumatologic diseases, and recipients of hematopoietic stem cell transplant [1–6]. In patients with CKD-D, fatigue impairs health-related quality of life [6] and is associated with mortality [7–9]. Several complex clinical factors, some of which may be modifiable, correlate with fatigue in patients with CKD-D, including higher burden of medical comorbidities, sedentary lifestyle, obesity, hypoalbuminemia, and use of sleeping medications [4, 8–10]. Fatigue can be easily measured using self-reported patient questionnaires, such as the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR₁₆) scale [11–13], the Beck Depression Inventory-I (BDI-I) [13, 14], or the 12-Item short form 12 health survey (SF-12) scale [15]. However, one limitation of prior studies of fatigue in CKD-D patients is the use of several different self-report scales across studies, so it is not known which one of these scales most reliably determines the presence of clinically relevant fatigue [16]. It has been proposed that a fatigue measure that is simple, short, and focused on the severity of the impact of fatigue on life participation may facilitate consistency of measurements across future studies to inform clinical decision-making about CKD-D patients [16].

In addition, data on the prevalence of fatigue symptoms and related clinical factors are scarce in patients with nondialysis CKD (CKD-ND) [4, 10], a stage of disease at which earlier intervention may affect long-term outcomes. Importantly, no prospective studies have evaluated the association of fatigue with outcomes in this patient population. Addressing these knowledge gaps in patients with CKD-ND could assist clinicians in early identification of fatigue in kidney disease patients, as well as consideration of interventions aimed at ameliorating fatigue-associated factors that may improve both hard and patient-centered outcomes at an earlier stage in disease.

The purpose of this study was to investigate (1) the prevalence of self-reported fatigue symptoms; (2) clinical factors associated with fatigue; and (3) whether fatigue was independently associated with adverse outcomes in patients with CKD-ND. We hypothesized that even prior to the development of CKD-D, fatigue measured on 3 different scales would be common in patients with CKD-ND and independently associated with worse outcomes.

Materials and Methods

Study Design, Setting, and Participants

This is a prospective cohort study of consecutively recruited outpatients with CKD-ND. Institutional Review Board approval was obtained in accordance with the ethical standards. CKD-ND patients were approached consecutively during routine clinic visits at the Dallas Veterans Affairs Medical Center. Prior to enrollment, written informed consent was obtained. Inclusion criteria were stages 2–5 CKD-ND and the ability to participate in informed consent. CKD-ND was defined as either estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or eGFR 60–89 with another marker of kidney disease, such as albuminuria, proteinuria, hematuria, or abnormal pathology on kidney imaging or biopsy, present for at least 3 months prior to enrollment. Stage 2 CKD-ND was defined eGFR 60–89 with another marker of kidney disease; stage 3, eGFR 30–59; stage 4, eGFR 15–29; and stage 5, eGFR <15 [17]. Patients on chronic peritoneal dialysis or hemodialysis and kidney transplant recipients were excluded.

Clinical Covariates

Demographic and clinical data were obtained from electronic health records (EHR) and patient interviews. We defined comorbidities as follows: (1) *Diabetes mellitus* as use of insulin or oral hypoglycemic medication or documentation of diabetes mellitus in the EHR; (2) *cardiovascular disease* as presence of coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease; (3) *major depressive disorder (MDD)*, ascertained in all patients at baseline using the Mini International Neuropsychiatric Interview [18]; and (4) *drug and alcohol abuse* as current or past abuse of drug and/or alcohol, either self-reported or documented in the EHR. The number of medical comorbidities other than diabetes or cardiovascular disease (hypertension, lung disease, liver disease, cancer, and human immunodeficiency virus infection) was also recorded. Baseline laboratory data were noted at enrollment. Calcium × phosphorus product was calculated as the product of serum calcium and phosphorus concentrations (reported as mg²/dL²). The 4-variable *Modification of Diet in Renal Disease Study* formula was used to calculate the eGFR [19]. Baseline medications, including antidepressants, beta-blockers, and erythropoietin-stimulating agents (ESA), were recorded.

Assessment of Fatigue

The QIDS-SR₁₆, BDI-I, and SF-12 questionnaires were given out by trained research personnel, blinded to the EHR, to all participants to fill out at enrollment. The QIDS-SR₁₆ has 16 items based on the 9 symptom domains of MDD, with a score range of 0–27, and takes 5–10 min to complete [11–13]. The BDI-I has 21 items with a score ranging from 0 to 63. Higher scores indicate more severe symptoms on both. These scales were previously validated by our group and others against a Diagnostic and Statistical Manual of Mental Disorders IV-based structured psychiatric interview in CKD-ND patients [13, 14]. On the QIDS-SR₁₆ and the BDI-I, fatigue symptoms are self-reported on a Likert scale of 0 (no fatigue) to 3 (severe fatigue; online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000500668). The SF-12 is a shortened version derived from the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) to represent the Physical and Mental Component Summary in the general US population [15]. The SF-12 has fewer items, takes less time

to complete, and was shown to give similar predictions of mortality as the SF-36 in CKD-D patients [20]. The SF-12 Vitality Scale (item 10) was used to ascertain fatigue, with a Likert score range of 1–6, and higher scores representing more fatigue (online suppl. Fig. 1).

Outcome Measures

The prespecified endpoint was a composite of (1) progression to ESRD (defined as initiation of chronic hemodialysis, peritoneal dialysis, or kidney transplantation), (2) all-cause death, or (3) hospitalization. All patients were followed prospectively for 12 months after assessment of fatigue symptoms. Outcomes were adjudicated independently by 2 members of the research team blinded to fatigue scores and depression diagnosis. Each outcome was confirmed by reviewing the EHR and direct participant contact.

Statistical Analysis

Baseline variables were reported. Fatigue symptoms on QIDS-SR₁₆ and BDI-I were converted to binary variables by collapsing the score of 0 (i.e., no symptoms) versus 1, 2, or 3 (presence of any symptoms) given we did not consider it advisable to treat a variable with only 4 levels as continuous and presence/absence of symptoms is the most clinically meaningful division. The fatigue item on the SF-12 scale was used as a continuous variable.

Univariate logistic regression models were constructed to investigate the association of clinical covariates with the fatigue items on the QIDS-SR₁₆ and BDI-I scales. Univariate linear regression models were constructed to investigate the association of covariates with the fatigue item reported on SF-12 scale. Chi-square tests compared outcomes between participants with *any* versus *no* fatigue symptoms reported on the QIDS-SR₁₆ and BDI-I scales. Multivariable Cox Proportional hazards models were constructed to investigate the independent associations of fatigue on each of the 3 scales with the composite endpoint. Kaplan-Meier curves estimated time to the first event, which was compared between groups using the Log-rank test. Censorship took place at first event, last follow-up, or 12 months if the participant was alive and not hospitalized or initiated on dialysis. Four participants had missing dates for the first event and were excluded from survival analyses.

Covariates were included in the models only if clinically relevant and significantly associated with the composite, with a retention *p* value <0.05. If data were missing for included covariates, complete case analysis was used. All statistical tests were 2-sided, conducted at the nominal significance level of 0.05 and reported using *p* values and/or 95% CIs. Statistical analyses were performed using SAS 9.3 (SAS, Inc., Cary, NC, USA) software.

Results

Participant Characteristics

Among the 266 participants, mean age was 64 ± 12 years (range 25–89 years), and 2 were women. One hundred and fifty participants (56.4%) were white, 99 (37.2%) were African American, and 17 (6.4%) were of other races. Diabetes mellitus was present in 55.8% and hypertension in 97.0% (Table 1). Mean eGFR was

31.6 ± 16.7 mL/min/1.73 m². The proportion with stages 2, 3, 4, and 5 CKD-ND were 6.4% (*n* = 17), 38.0% (*n* = 101), 41.0% (*n* = 109), and 14.6% (*n* = 39), respectively (Table 1). A total of 56 participants (21.1%) had a diagnosis of MDD and 53 (19.9%) were on antidepressant medications. Of the 53 participants taking antidepressant medications, 28 (52.8%) had current MDD. Proportions using beta blockers and ESA were 68.3 and 19.2%, respectively. The mean SF-12 fatigue score was 4.4 ± 1.5 (Table 1). Of the 266 participants with a completed QIDS-SR₁₆, 69.2% reported any fatigue symptoms and 10.9% reported *severe* fatigue symptoms (i.e., a score of 3), whereas of the 265 participants who completed the BDI-I, 77.7% reported *any* fatigue symptoms and 5.3% reported *severe* fatigue symptoms (Table 1; Fig. 1a). Participants reported more severe fatigue on the SF-12, with a median score of 5 (corresponding to having a lot of energy a little of the time), and milder symptoms on the QIDS-SR₁₆ and the BDI-I, with the most common response of 1 (corresponding to getting tired more easily; Fig. 1b).

Factors Associated with Fatigue

Age and race were not associated with fatigue on any of the 3 scales (Table 2). Unemployed status was associated with fatigue on all 3 scales, such that participants that were employed were less likely to report *any* fatigue symptoms compared to those that were unemployed, OR 0.41 (95% CI 0.22–0.77) on the QIDS-SR₁₆ and 0.47 (0.24–0.91) on the BDI-I (Table 2). Employed individuals also reported less severe fatigue on the SF-12, β regression coefficient -0.68 (95% CI -1.15 to -0.22 ; Table 2). Increase in the number of comorbid medical conditions was associated with the presence of fatigue on the BDI-I, OR 1.33 (95% CI 1.08–1.63), and increased severity of fatigue as measured by the SF-12, β regression coefficient 0.24 (95% CI 0.12–0.36; Table 2). The presence of MDD was associated with fatigue on the BDI-I and the SF-12, but because all participants with MDD identified fatigue on the QIDS-SR₁₆, an OR could not be calculated for this association (Table 2). Use of antidepressant medications was associated with fatigue on the QIDS-SR₁₆, OR 4.34 (95% CI 1.78–10.62), the BDI-I, OR 2.54 (95% CI 1.03–6.28), and the SF-12, β regression coefficient 0.64 (95% CI 0.19–1.10; Table 2). Finally, each 1 g/dL decrease in hemoglobin concentration was associated with fatigue on the BDI-I, OR 1.19 (95% CI 1.03–1.39), and a 13% increase in fatigue severity on the SF-12 scale, β regression coefficient 0.13 (95% CI 0.04–0.22; Table 2).

Table 1. Baseline characteristics of the study cohort

Variable	n = 266	Variable	n = 266
Demographic variables		Measures of fatigue, n (%)	
Age, years, mean (SD)	64.4 (12.0)	QIDS-SR ₁₆	
Race, n (%)		Fatigue score ≥1	184 (69.2)
White	150 (56.4)	Fatigue score 0	82 (30.8)
Black	99 (37.2)	Fatigue score 1	106 (39.9)
Other	17 (6.4)	Fatigue score 2	49 (18.4)
Employed, n (%)	51 (19.3)	Fatigue score 3	29 (10.9)
Clinical variables, n (%)		BDI-I	
CKD		Fatigue score ≥1	206 (77.7)
Stage 2	17 (6.4)	Fatigue score 0	59 (22.2)
Stage 3	101 (38.0)	Fatigue score 1	153 (57.5)
Stage 4	109 (41.0)	Fatigue score 2	39 (14.7)
Stage 5	39 (14.6)	Fatigue score 3	14 (5.3)
Diabetes mellitus	148 (55.9)	SF-12 vitality score, mean (SD)	4.4 (1.5) ³
Hypertension	258 (97.0)	Median (IQR)	5 (3–6)
Cardiovascular disease ¹	167 (63.0)		
Number of other comorbid illnesses ²			
Mean (SD)	1.6 (0.7)		
Median (IQR)	1 (1–2)		
History of drug or alcohol abuse	78 (29.6)		
Depression by MINI	56 (21.1)		
Medications, n (%)			
Beta blockers	181 (68.3)		
Erythropoietin-stimulating agent use	51 (19.2)		
Use of antidepressant medication	53 (19.9)		
Laboratory values, mean (SD)			
Hemoglobin, g/dL	12.5 (2.0)		
Calcium-phosphorus-product, mg ² /dL ²	36.6 (8.8)		
Albumin, g/dL	4.0 (0.5)		
Creatinine, mg/dL	3.2 (2.4)		
Blood urea nitrogen, mg/dL	42.2 (20.5)		
Estimated GFR, mL/min/1.73 m ²	31.6 (16.7)		

Conversion factors for units: serum creatinine in mg/dL to mol/L, $\times 88.4$; serum urea nitrogen in mg/dL to mmol/L, $\times 0.357$.

¹ Cardiovascular disease refers to the presence of coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease.

² Other comorbid illnesses refers to the number of medical comorbidities other than diabetes or cardiovascular disease (hypertension, lung disease, liver disease, cancer, and human immunodeficiency virus infection).

³ The score on the SF-12 Vitality Scale ranges from 1 to 6 on a Likert scale, with a higher score representing less vitality and more fatigue. A score of 4 on the SF-12 Vitality Scale represents having “a lot of energy some of the time” and a score of 5 represents having “a lot of energy a little of the time.”

CKD, chronic kidney disease; GFR, glomerular filtration rate; MINI, Mini International Neuropsychiatric Interview; IQR, interquartile range; BDI-I, Beck Depression Inventory-I; SF-12, short form 12 health survey; QIDS-SR₁₆, Quick Inventory of Depression Symptomatology-Self Report.

Association of Fatigue with Outcomes

There were 126 composite events, including 37 dialysis initiations, 18 deaths, and 115 hospitalizations. The number of composite outcome events in participants with stages 2, 3, 4, and 5 CKD was 2 (11.8%), 42 (41.6%), 48 (44.0%), and 34 (87.2%), respectively. A higher proportion of participants who reported *any* versus *no* fatigue on the QIDS-SR₁₆ experienced the composite outcome during the follow-up (53 vs. 34%, $p = 0.004$). Such a difference did not reach statistical significance when using the BDI-I scale to ascertain the presence of fatigue (50 vs. 37%, $p = 0.09$). Event-free mean (SE) survival time to death, ESRD, or first hospitalization was shorter for those that reported any fatigue on the QIDS-SR₁₆ at 242.6 (9.7) days than in those that reported no fatigue at 291.0 (13) days, log-rank p value = 0.01 (Fig. 1c).

Participants who reported any fatigue compared to those who reported no fatigue on the QIDS-SR₁₆ were at an increased hazard of the composite outcome, hazard ratio (HR) 1.70 (95% CI 1.11–2.59). This association remained significant even after controlling for demographic variables (age, race, employment status), number of medical comorbidities and current or past drug use, laboratory data (hemoglobin, serum albumin, eGFR, and serum calcium phosphorous product), and beta blocker use, HR 1.62 (95% CI 1.03–2.54; Table 3). However, the association became nonsignificant after adjusting for antidepressant use or MDD. No significant association was observed between the composite outcome and fatigue reported on the BDI-I, even in the unadjusted model, HR 1.49 (95% CI 0.93–2.38; Table 3).

Fig. 1. Prevalence and severity of fatigue and associations with outcomes. **a** Proportion of participants self-reporting scores of 0, 1, 2, or 3 on the QIDS-SR₁₆ and the BDI-I. Higher scores indicate more severe fatigue. **b** Median (interquartile range) SF-12 score on a scale of 1–6, with higher scores indicating more severe fatigue. **c** Kaplan-Meier curve showing time to composite outcome of all-cause hospitalization, dialysis initiation, or death in participants with any versus no fatigue on the QIDS-SR₁₆. QIDS-SR₁₆, Quick Inventory of Depression Symptomatology-Self Report scale; SF-12, short-form 12 health survey; BDI-I, Beck Depression Inventory; IQR, interquartile range.

In the unadjusted model, there was a 22% increase in the hazard of the composite event per one-unit increase in the vitality item on the SF-12 scale, HR 1.22 (95% CI 1.07–1.39; Table 3). The association of the SF-12 vitality score with the composite outcome remained significant after controlling for demographics, comorbidities, and history of drug or alcohol use, HR 1.18 (95% CI 1.03–1.35; Table 3). However, this association was no longer significant when adjusted for laboratory values, beta blocker use, antidepressant use, or MDD (Table 3).

Discussion

We report 3 new and compelling findings: (1) Fatigue was common in patients with CKD-ND, with about 70% of patients reporting symptoms of fatigue; (2) unemployment, number of comorbid medical conditions, antidepressant medication use, and decreased hemoglobin concentration were associated with fatigue, as measured by at least 2 of the 3 scales; and (3) self-reported fatigue was independently associated with progression to ESRD,

Table 2. Variables associated with fatigue reported on QIDS-SR₁₆, BDI-I, and SF-12 scales in univariate models

Variable	QIDS-SR ₁₆ OR (95% CI) ¹	BDI-I OR (95% CI) ¹	SF-12 regression coefficient (95% CI) ²
Age, years	1.01 (0.99 to 1.03)	1.01 (0.98 to 1.03)	0 (−0.02 to 0.01)
White vs. non-white	1.26 (0.75 to 2.13)	1.02 (0.57 to 1.82)	−0.05 (−0.42 to 0.33)
Employed	0.41 (0.22 to 0.77)	0.47 (0.24 to 0.91)	−0.68 (−1.15 to −0.22)
CKD-ND stages 2–3 vs. 4–5	1.49 (0.88 to 2.52)	1.41 (0.79 to 2.53)	0.14 (−0.24 to 0.51)
Diabetes mellitus	1.31 (0.78 to 2.21)	1.53 (0.86 to 2.74)	0.49 (0.12 to 0.86)
Cardiovascular disease ³	1.36 (0.79 to 2.32)	1.59 (0.89 to 2.87)	0.31 (−0.07 to 0.69)
Number of comorbidities ⁴	1.13 (0.95 to 1.35)	1.33 (1.08 to 1.63)	0.24 (0.12 to 0.36)
MDD ⁵	N/A	20.60 (2.79 to 152.37)	1.19 (0.76 to 1.62)
Alcohol or drug abuse ⁶	1.42 (0.78 to 2.56)	1.83 (0.91 to 3.68)	0.63 (0.22 to 1.04)
Beta blocker	1.49 (0.86 to 2.58)	1.70 (0.93 to 3.10)	0.43 (0.03 to 0.83)
Erythropoietin-stimulating agent	1.09 (0.56 to 2.12)	1.38 (0.63 to 3.03)	0.17 (−0.31 to 0.64)
Antidepressant medication	4.34 (1.78 to 10.62)	2.54 (1.03 to 6.28)	0.64 (0.19 to 1.10)
Hemoglobin, per unit decrease	1.09 (0.95 to 1.24)	1.19 (1.03 to 1.39)	0.13 (0.04 to 0.22)
Calcium-phosphorus-product	1.01 (0.98 to 1.04)	1.03 (1.00 to 1.07)	0.02 (0 to 0.04)
Serum albumin, per unit decrease	1.61 (0.89 to 2.93)	1.61 (0.82 to 3.16)	0.41 (0.01 to 0.81)
eGFR, per unit decrease	1.01 (1.00 to 1.03)	1.01 (1.00 to 1.03)	0.01 (0 to 0.02)

¹ Reported as any versus no fatigue on the QIDS-SR₁₆ or BDI-I.

² Reported per unit increase in fatigue symptom severity on the SF-12.

³ Cardiovascular disease refers to the presence of coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral vascular disease.

⁴ Other comorbid illnesses refers to the number of medical comorbidities other than diabetes or cardiovascular disease (hypertension, lung disease, liver disease, cancer, and human immunodeficiency virus infection).

⁵ Unable to calculate an OR for the QIDS-SR₁₆ as 100% of participants with MDD had fatigue on this metric.

⁶ Defined as current or past abuse of drug and/or alcohol, either self-reported or documented in the EHR.

CKD-ND, nondialysis chronic kidney disease; eGFR, estimated glomerular filtration rate; MDD, major depressive disorder; QIDS-SR₁₆, Quick Inventory of Depression Symptomatology Self-Report; BDI-I, Beck Depression Inventory-I; SF-12, short-form 12 health survey; EHR, electronic health records.

death, or hospital admission at 1 year in patients with CKD-ND.

Although increased prevalence of fatigue has been recognized in multiple chronic diseases including CKD-D [1–3, 21], data are scarce in CKD-ND samples with earlier stages of CKD before frank uremic symptoms begin to manifest. Several studies have shown that approximately 70% of hemodialysis and peritoneal dialysis patients report fatigue [2, 22, 23]. One study showed a prevalence of 82.0% in CKD stage 5 patients who either declined or were not offered dialysis, compared to 67.8% in those receiving dialysis [24]. Another study assessed several symptoms in 55 patients with stages 4–5 CKD-ND who had a mean age of 85 years and were being managed conservatively without dialysis. While fatigue was not specifically ascertained, the study did report a prevalence of weakness in 61–85%, drowsiness in 35–63%, difficulty sleeping in 24–50%, and depression in 21–47% of participants using a modified ver-

sion of the Patient Outcome Scale-symptom module [25]. There is wide variability in the scales used to assess fatigue and other symptoms between these studies. This makes it difficult to compare results across studies and challenging to determine which scales might be the most useful for clinical assessment of fatigue in patients with kidney disease. Our results reinforce this concept by demonstrating variability in the degree of fatigue severity reported on each of the 3 self-report scales used, even when the scales were administered to the same patients at the same time point.

Our study consisted of 85% individuals with CKD-ND stages 2–4, at a stage of kidney disease where uremic symptoms are, generally, not yet manifested [26]. Importantly, we ascertained fatigue using 3 different validated self-report scales, one of which accounts for the severity of symptoms. Interestingly, even in this cohort with earlier stages of CKD-ND, we showed that fatigue is prevalent in 69.2% of patients by the QIDS-SR₁₆ and

Table 3. Association of self-reported fatigue with primary outcome

Predictor	Model ¹	HR (95% CI)	<i>p</i> value
Fatigue on QIDS-SR ₁₆ ²	Unadjusted	1.70 (1.11–2.59)	0.01
	+Demographics	1.68 (1.10–2.58)	0.02
	+Comorbidities/drug abuse	1.74 (1.13–2.68)	0.01
	+Labs	1.63 (1.05–2.55)	0.03
	+Beta blocker use	1.62 (1.03–2.54)	0.04
	+Beta blocker and antidepressant use	1.56 (0.99–2.47)	0.06
	+Beta blocker use and MDD	1.35 (0.84–2.19)	0.22
Fatigue on BDI-I ²	Unadjusted	1.49 (0.93–2.38)	0.10
	+Demographics	1.42 (0.88–2.29)	0.15
	+Comorbidities/drug abuse	1.27 (0.79–2.06)	0.32
	+Labs	1.07 (0.65–1.77)	0.78
	+Beta blocker use	1.03 (0.62–1.72)	0.90
	+Beta blocker and antidepressant use	0.99 (0.59–1.66)	0.98
	+Beta blocker use and MDD	0.88 (0.52–1.50)	0.65
Fatigue on SF-12 ³	Unadjusted	1.22 (1.07–1.39)	0.002
	+Demographics	1.23 (1.07–1.41)	0.003
	+Comorbidities/drug abuse	1.18 (1.03–1.35)	0.02
	+Labs	1.11 (0.96–1.28)	0.15
	+Beta blocker use	1.11 (0.97–1.28)	0.14
	+Beta blocker and antidepressant use	1.10 (0.96–1.27)	0.17
	+Beta blocker use and MDD	1.06 (0.92–1.23)	0.41

¹ Models: demographics includes age, race, employed; comorbidities/drug abuse includes total number of comorbidities and alcohol or drug abuse; labs include serum hemoglobin concentration, serum albumin, estimated glomerular filtration rate calculated by the 4-variable modification of diet in renal diseases formula, and serum calcium-phosphorus-product.

² HRs expressed for presence of any fatigue versus no fatigue.

³ HRs expressed per 1-unit increase in SF-12 Vitality scale. The score on this item ranges from 1 to 6 on a Likert scale, with a higher score representing less vitality and more fatigue.

HR, hazard ratio; QIDS-SR₁₆, Quick Inventory of Depression Symptomatology Self-Report; MDD, major depressive disorder; BDI-I, Beck Depression Inventory-I; SF-12, short-form 12 health survey.

77.7% by the BDI-I, which is comparable to the prevalence seen in ESRD samples [2, 22, 23]. This contradicts conventional wisdom among nephrologists that those with CKD-ND, particularly at earlier stages before the incidence of uremia, have lower symptom burden than those who require maintenance dialysis. We are the first to demonstrate the markedly elevated prevalence of fatigue in a sample including individuals with CKD-ND stages 2–3 (which comprised approximately half of the sample), even prior to the development of advanced CKD-ND when uremic symptoms are expected to develop. Importantly, investigation of clinical characteristics associated with the presence of fatigue at earlier CKD stages may lead to identification of potentially modifiable risk factors.

Prior studies have identified multiple factors associated with the presence of fatigue in CKD-D patients, in-

cluding non-black race, medical comorbidities, diabetes, low serum albumin, use of sleep medication, urban living, unemployed status, low education level, low hemoglobin, anorexia, physical inactivity, depression, and chronic inflammation [2, 8, 9, 23, 27]. One study investigating a combined sample of CKD-ND and hemodialysis patients determined that a history of cardiovascular disease, low albumin, depressive symptoms, poor sleep quality, daytime sleepiness, and restless leg syndrome were all associated with fatigue after adjusting for age, sex, race, dialysis status, and use of antidepressants or benzodiazepines [4]. In peritoneal dialysis patients, there are fewer studies, which identify anemia and dialysis adequacy as possible correlates of fatigue [28, 29]. This broad and complex array of factors associated with fatigue can be in part attributed to the various scales used in the studies, and partially due to the relatively multifactorial nature of fatigue,

insofar as it could be a general manifestation of many other medical and psychological conditions.

Similarly, in our study, the factors associated with fatigue differed by which scale was used. The most parsimonious was the QIDS-SR₁₆, which was associated only with unemployment and baseline antidepressant medication use. Fatigue identified by the BDI-I was associated with more factors, including those seen with the QIDS-SR₁₆ as well as increasing number of medical comorbidities and decreasing hemoglobin level. Finally, increasing severity of fatigue measured by the SF-12 was associated with all factors observed using the BDI-I, in addition to serum albumin, diabetes, drug abuse, and beta blocker use. Recognizing that associated factors differ based on which scale was used to measure fatigue highlights the complexity of measuring fatigue for research or clinical purposes and reinforces the difficulty in comparison of prior studies that used different measurement scales. However, the 4 factors that were associated with fatigue measured by at least 2 of the scales in our study (unemployment, baseline antidepressant medication use, number of medical comorbidities, and lower hemoglobin) have also been previously identified in CKD-D samples [4, 8, 9, 27, 29–31]. It is unclear whether unemployment begets fatigue or whether fatigue leads to an inability to work. Depression and medical comorbidities have been previously associated with fatigue in hemodialysis samples, but it remains unclear whether treatment of depression and other medical illnesses improve fatigue [2, 8, 32]. Fatigue may be a common symptom reported in depression of chronic disease. Associations between hemoglobin level and fatigue have been demonstrated in other studies, and interestingly, in one study of palliative care patients with anemia and CKD-ND stage 5 who declined to initiate dialysis, treatment with ESA increased hemoglobin levels and decreased fatigue symptoms after 3–6 months [33]. Even though the TREAT study did not reveal a clinically relevant improvement in health-care quality of life in CKD-ND patients treated with ESA versus placebo [34], these results suggest that anemia may be a potential modifiable risk factor for managing fatigue in CKD-ND patients, although the optimal hemoglobin level for symptom reduction in this population remains to be determined.

Finally, we explored the associations of fatigue with a clinically relevant composite outcome of progression to ESRD, death, or all-cause hospitalization. This is the first study, to our knowledge, to report that the presence of fatigue is independently associated with these important

clinical outcomes in patients with CKD-ND. Using a national registry of nursing home residents, Kurella et al. [35] evaluated 7 clinical signs and symptoms – dependence in activities of daily living, cognitive function, edema, dyspnea, nutritional problems, vomiting, and body size – and reported that each additional sign or symptom was associated with a higher odds for earlier dialysis initiation (OR 1.16 per symptom; 95% CI 1.06–1.28). Our findings become imperative as fatigue is the most common physical symptom reported by kidney disease patients, shown to be present in 74% of those with CKD-D [6]. Prior studies have explored associations of fatigue with clinical outcomes in patients with other chronic conditions. For example, in heart failure patients, fatigue was associated with cardiovascular death or hospitalization for heart failure [21]. In hemodialysis patients, fatigue was associated with all-cause death [7, 9, 36], the composite of first cardiac hospitalization or cardiac death [8], and cardiovascular events [37]. It was previously unknown whether fatigue is associated with these outcomes or renal outcomes in CKD-ND patients. Our study extends these findings to patients with CKD-ND and indicates that the presence of fatigue may represent more severe underlying chronic illness or unfavorable health status and may be a harbinger of future adverse events. As such, eliciting the presence of fatigue by validated tools such as the QIDS-SR₁₆ may be a relevant and important part of prognostic assessment for CKD-ND patients. In addition, such symptoms should be addressed using best available evidence for treatment, until more data become available regarding whether symptom management in patients with CKD-ND will improve quality of life or survival.

We showed that the associations of fatigue with outcomes again varied by the measurement scale used to ascertain fatigue. Fatigue identified by the QIDS-SR₁₆ was independently associated with the primary outcome when adjusting for demographic factors, comorbidities, drug abuse, laboratory values, and beta blocker use. The association became nonsignificant when adjusting for baseline antidepressant medication use or the presence of MDD. Of note, as previously reported, only 50% of individuals with MDD in this cohort were prescribed antidepressant medications at baseline, so such treatment should not be considered a proxy for the presence of depression [38]. This finding could be explained by collinearity between depression and fatigue in patients with CKD-ND, due either to a direct effect of depression on symptoms of fatigue or a common underlying pathway such as elevated systemic inflammation [39]. The QIDS-

SR₁₆ identified fatigue in a lower proportion of the sample than the other measures, but may be more selective for identifying individuals at future risk for poor outcomes. The BDI-I, which was positive for fatigue in almost 80% of participants, was not associated with the primary outcome in unadjusted or adjusted models. It is possible that the BDI-I, which was the most sensitive of the measures used for fatigue identification, was unable to discriminate those at risk for adverse outcomes. Severity of fatigue measured by the SF-12 was associated with outcomes independent of comorbidities, employment status, and drug abuse, but this was accounted for by laboratory values and the use of beta blockers or antidepressants. While the gradations of symptoms may be clinically useful, the independent association disappeared when adjusting for commonly clinically indicated laboratory values and medications, so it may not add to usual clinical care for predicting outcomes. Ultimately, the QIDS-SR₁₆ may be the most clinically useful measure of fatigue in this patient population given its discriminative ability to predict outcomes in CKD-ND patients.

Several limitations of this study merit discussion. It has been shown in multiple studies of hemodialysis patients that older age is associated with fatigue [2, 10], so our sample weighted toward older patients may have overestimated fatigue presence in CKD-ND patients. Female sex has also been associated with fatigue [10], with women most frequently reporting fatigue and bone/joint pain as severe symptoms in one study of CKD-ND patients with an incident eGFR ≤ 20 mL/min/1.73 m² [40]. We were unable to evaluate sex-based differences in our study comprised predominantly of men. However, it is notable that we demonstrated that fatigue also affects a large proportion of men with CKD-ND. In addition, the higher percentage of participants in our sample with diabetes mellitus is more representative of the US CKD-ND population [41] than previous studies investigating fatigue [42, 43]. Larger studies that include more women may be needed to confirm the independent association found between fatigue on the QIDS-SR₁₆ and outcomes in CKD-ND patients. We were unable to assess associations of fatigue with other important clinical factors such as chronic pain in our analysis. We measured fatigue using individual items from depression questionnaires that have not been validated for independent use to quantify fatigue. However, because the fatigue items on the QIDS-SR₁₆ and the SF-12 were associated with outcomes, they could still be considered as simple and clinically relevant assessments.

Finally, although models were adjusted for baseline demographic, clinical, and laboratory variables, repeated measures of fatigue symptoms over time were not included.

In conclusion, fatigue was highly prevalent in CKD-ND patients when measured by the QIDS-SR₁₆, the BDI-I, or the SF-12. Factors associated with fatigue measured by at least 2 of these scales included unemployment, antidepressant use, number of medical comorbidities, and hemoglobin level. Of the 3 scales, the QIDS-SR₁₆ is likely the most clinically useful as it predicted the occurrence of clinically important outcomes even after controlling for risk factors associated with poor outcomes in this patient population. Future studies are needed to confirm our findings regarding the fatigue component of the QIDS-SR₁₆. Identifying and validating a universal measure of fatigue in patients with CKD-ND that can be easily administered, has face validity, and predicts both hard and patient-centered outcomes is imperative both for clinical decision-making and as a target measure for future interventional trials.

Statement of Ethics

All participants provided written informed consent to participate in this study. The study protocol was approved by the Institutional Review Board at the VA North Texas Health Care System, and the study was conducted in accordance with ethical standards.

Disclosure Statement

A.J.R. has received consulting fees from Akili, Brain Resource Inc., Compass Inc., Curbstone Consultant LLC., Emmes Corp., Johnson and Johnson (Janssen), Liva-Nova, Mind Linc, Sunovion, Taj Medical; speaking fees from Liva-Nova; and royalties from Guilford Press and the University of Texas Southwestern Medical Center, Dallas, TX, USA (for the Inventory of Depressive Symptoms and its derivatives). He is also named co-inventor on 2 patents: US Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS; and US Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S. Dr. Trivedi has served as an advisor or consultant to the following organizations: Allergan Sales LLC, Alkermes, Arcadia Pharmaceuticals Inc., AstraZeneca, Axon Advisors, Bristol-Myers Squibb Company, Eli Lilly and Company, Evotec, Johnson and Johnson, Lundbeck, MedAvante, Merck, MSI Methylation Sciences Inc., Nestle Health Science-PamLab Inc., Naurex, Neuronetics, One

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Author Contributions

S.S.H., N.J., and M.H.T.: research idea and study design. S.S.H.: data acquisition. S.S.H., N.J., and L.P.G.: data analysis/interpretation. T.C. and A.T.M.: statistical analysis. S.S.H., A.J.R., and M.H.T.: supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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