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ORIGINAL ARTICLE

Patterns and predictors of fatigue following living donor nephrectomy: Findings from the KDOC Study

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This study sought to identify the prevalence, pattern, and predictors of clinical fatigue in 193 living kidney donors (LKDs) and 20 healthy controls (HCs) assessed at predonation and 1, 6, 12, and 24 months postdonation. Relative to HCs, LKDs had significantly higher fatigue severity ($P = .01$), interference ($P = .03$), frequency ($P = .002$), and intensity ($P = .01$), and lower vitality ($P < .001$), at 1-month postdonation. Using published criteria, significantly more LKDs experienced clinical fatigue at 1 month postdonation, compared to HCs, on both the Fatigue Symptom Inventory (60% vs. 37%, $P < .001$) and SF-36 Vitality scale (67% vs. 16%, $P < .001$). No differences in fatigue scores or clinical prevalence were observed at other time points. Nearly half (47%) reported persistent clinical fatigue from 1 to 6 months postdonation. Multivariable analyses demonstrated that LKDs presenting for evaluation with a history of affective disorder and low vitality, those with clinical mood disturbance and anxiety about future kidney failure after donation, and those with less physical activity engagement were at highest risk for persistent clinical fatigue 6 months postdonation. Findings confirm inclusion of fatigue risk in existing OPTN informed consent requirements, have important clinical implications in the care of LKDs, and underscore the need for further scientific examination in this population.

KEYWORDS
allied health/nursing, clinical research/practice, donor nephrectomy, donors and donation, donors and donation: donor follow-up, donors and donation: living, health services and outcomes research, social sciences

Abbreviations: CDC, Centers for Disease Control; ERAS, Enhanced Recovery After Surgery; FSI, Fatigue Symptom Inventory; KDOC, Kidney Donor Outcomes Cohort; LKD, Living Kidney Donor; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; VT, vitality.

1 | INTRODUCTION

Fatigue is a common symptom following surgery. Its intensity and duration can prolong recovery, adversely impacting quality of life and delaying return to baseline functioning. Healthy adults undergoing laparoscopic donor nephrectomy are known to experience fatigue following donation, although most donors recover within a few months.[1-4] For some, however, fatigue persists for months, although it is unknown if fatigue levels differ substantially from non-donors.[5-10.]

Studies that examined fatigue following donor nephrectomy were mostly single-center cross-sectional studies and none were conducted in the United States.[1-12] In one prospective study of 105 living kidney donors (LKDs) in The Netherlands, Minnee et al[4] found that average fatigue scores worsened significantly from predonation to 1 month postdonation, but returned to predonation levels at 3, 6, and 12 months postdonation. In a multi-center study of 230 Dutch LKDs, Wirken et al[10] found higher fatigue levels at 6 and 12 months postdonation compared with predonation. Higher predonation fatigue, lower physical quality of life, younger age, and longer hospitalization predicted more fatigue at 6 months postdonation. In both studies, longitudinal changes in LKD fatigue were not compared with contemporaneous non-donors and no distinctions were made between normal and clinical fatigue.

Further prospective characterization of fatigue may help clinicians better inform potential LKDs of the short- and possibly longer-term nature of fatigue postdonation. Identifying adults at higher risk of persistent clinical fatigue may guide implementation of preventative interventions to mitigate this adverse outcome. In this study, we sought to identify the prevalence, pattern and predictors of clinical fatigue in a prospective, multi-center LKD cohort in the United States. Based on prior studies of LKDs[4,6,10-12] and non-donors,[13] we hypothesized that (A) clinical fatigue would peak at 1 month postdonation, with a return to baseline levels of fatigue for the majority of donors by 6 months postdonation, and (B) being female, younger age, higher mood distress, and less physically activity would be associated with persistent clinical fatigue postdonation.

2 | METHODS

2.1 | Kidney donor outcomes cohort (KDOC)

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), this study included a prospective observational cohort of LKDs at six centers in four Organ Procurement and Transplant Network (OPTN) regions: Massachusetts, Maine, and Rhode Island (Region 1); Arizona (Region 5); Iowa (Region 8); and New York (Region 9). LKDs and their transplant recipients were enrolled from September 2011 to November 2013. In addition, healthy controls (HCs) were enrolled if they completed donation evaluation but did not donate because (A) of anatomical issues on imaging, (B) the patient received a kidney from another donor, or (C) the patient was de-listed for reasons other than transplantation.

Each center used their existing evaluation processes and eligibility criteria in selecting donor candidates. LKDs and HCs were informed about the study following donation evaluation and approval by the evaluation team. After written informed consent, LKDs and HCs completed questionnaire assessments at predonation and at 1, 6, 12, and 24 months postdonation (or, for HCs, after study enrollment). Medical data were captured by on-site research personnel and transmitted electronically to the coordinating site. Participants received $20 for completion of each assessment. Institutional Review Boards at all centers approved the study, which was registered on ClinicalTrials.gov (NCT01427452).

2.2 | Fatigue assessment

2.2.1 | Fatigue Symptom Inventory

The 14-item Fatigue Symptom Inventory (FSI) measures fatigue severity (four items: 1 = not at all fatigued to 10 = as fatigued as I could be), frequency (number of days in past week felt fatigued, 0 to 7), intensity (extent of each day felt fatigued, 1 = none of the day to 10 = entire day), and perceived interference with general activity level, concentration, relationships, life enjoyment, and mood (7 items: 1 = no interference to 10 = extreme interference).[14] One additional item assesses the daily fatigue pattern (not at all fatigued, worse in morning, worse in afternoon, worse in evening, no consistent daily pattern). A composite fatigue severity score is calculated by averaging the four severity items, with a higher score indicating more fatigue. A total fatigue interference score is obtained by summing the seven interference items, with a higher score indicating more fatigue interference. The FSI has been used with medical patients, with strong evidence of convergent, divergent, and construct validity.[15] Internal consistencies of severity and disruptiveness items across all assessment points were acceptable (Cronbach's alpha: 0.84 to 0.90 for severity, 0.90 to 0.95 for interference). A clinical cut-off score has not been identified for LKDs; however, Goedendorp et al[16] found that a two-item composite index was most robust as a screening tool for clinical fatigue in women with breast cancer. Using their criteria, ratings for the following two items were summed: “Rate your level of fatigue on the day you felt most fatigued in the past week” and “Rate how much in the past week fatigue interfered with your normal work activity (includes both work outside the home and housework)” (range 0-20), with a score ≥8 considered clinically significant.

2.2.2 | SF-36 Vitality scale

The SF-36 Health Survey[17] is a widely used and validated measure of health-related quality of life. The four-item vitality (VT) scale measures energy and fatigue, asking respondents how much time in the past 4 weeks they felt full of pep, energetic, worn out, and tired (5-point scale ranging from all of the time to none of the time).

Standardized scale scores range from 0 to 100, with lower scores indicating more fatigue. Internal consistencies across all LKD assessments were acceptable (Cronbach's alpha: 0.87 to 0.91). VT scores <50 and ≤45 both have been used to identify clinically meaningful fatigue.[5,16,18] The more stringent VT score (≤45) was used to represent clinical fatigue in this study, as it was used by de Groot et al[5] in their study of LKDs and likely increases the robustness of our findings.

2.3 | Possible predonation predictors of persistent clinical fatigue

Persistent clinical fatigue was operationalized as having clinical fatigue on at least one fatigue measures (FSI, SF-36 VT) at both 1- and 6-month assessments.

2.3.1 | Sociodemographic characteristics

Age, sex, race/ethnicity, education, marital status, employment, health insurance, household income, and donor-recipient relationship were examined.

2.3.2 | Predonation clinical characteristics

Predonation clinical variables included: body mass index (BMI), systolic and diastolic pressures, smoking, substance abuse, mood disturbance, fear of kidney failure, fatigue severity (FSI), vitality (SF-36), and physical activity. Smoking was self-reported as any cigarette smoking in the past year (yes/no). Mood disturbance was assessed by summing 10 anxiety, depression, and anger adjectives from the Profile of Mood States[19] (POMS; Cronbach's $\alpha = 0.83$), with higher score indicating more mood disturbance. A total score >10 indicates possible mood disturbance.[19,20] Fear of kidney failure was assessed using the Fear of Kidney Failure questionnaire[21] (FKF; Cronbach's $\alpha = 0.91$), with higher scores indicating more anxiety and worry about kidney injury/failure postdonation. A score >10 suggests a clinically meaningful anxiety about future kidney-related health.[21] Physical activity was self-reported as amount of time engaged in moderate-intensity and vigorous-intensity physical activity in a typical week, as well as number of days in a typical week engaged in muscle-strengthening activity. Participants were classified as meeting or not meeting national and international recommendations[22,23] that adults engage in a weekly minimum of 150 minutes of moderate-intensity activity, 75 minutes of vigorous-intensity activity, or an equivalent combination of moderate- and vigorous-intensity activity, and at least 2 days weekly of muscle-strengthening activity.

2.3.3 | Surgical and postsurgery recovery variables

Operative time (minutes), kidney removed (right/left), surgical complications (yes/no), re-operation (yes/no), hospitalization duration (hours), re-hospitalization (yes/no), systolic and diastolic pressures, kidney function at 1 and 6 months, any clinical mood disturbance or any fear of kidney failure within 6 months postdonation, total minutes of physical activity per week at 1 and 6 months postdonation assessment, and time (days) between donation and return to work were examined. To assess kidney function, serum creatinine was used to calculate renal clearance with the Cockcroft-Gault equation[24] at baseline and at 1 and 6 months postdonation. Only serum creatinine values obtained ±30 days of the postdonation fatigue assessments were used. We used the percent change in renal clearance from baseline to the 6-month assessment in examining its relationship to persistent clinical fatigue.

2.4 | Statistical analysis

Cohort characteristics, fatigue outcomes and predictor variables were summarized using descriptive statistics (frequency counts with percentages for categorical variables, means with standard deviations for continuous variables). LKD characteristics were compared to the 12 799 United States adults who donated a kidney during study enrollment using Fisher's exact and chi-squared tests.[25] The *t*-tests for continuous variables and chi-squared or Fisher's exact tests for categorical variables were calculated to examine LKD and HC differences on sociodemographic characteristics and fatigue measures at all time points. The *t*-tests were calculated to examine differences between LKDs and HCs on FSI severity, interference, frequency, and intensity, and on the SF-36 VT. The percentage of LKDs and HCs who met clinical fatigue criteria on the FSI and SF36 VT scale at each time point was calculated and compared using Fisher's exact test.

Next, we used unadjusted logistic regression models to examine the relationship between LKD sociodemographic, clinical, and surgical characteristics and persistent clinical fatigue. Only LKDs who completed the predonation assessment and the 1- and 6-month assessments were included in the model. To assess for multicollinearity, we examined the variance inflation factor (>5 indicating multicollinearity) and the correlation coefficients among predictor variables ($r > 0.80$ indicating multicollinearity). Variables with $P < .10$ in the univariate screen were included in the multivariable regression model. Finally, we examined the prevalence of LKDs with persistent clinical fatigue through the 12- and 24-month assessments, ie, clinical fatigue, as defined above, at all postdonation time points. For all analyses, a P value <.05 was considered statistical significant. All data were managed in REDCap and statistical analyses were conducted using SPSS (Chicago, IL).

3 | RESULTS

3.1 | KDOC characteristics

The 193 LKDs who completed donation and 20 HCs enrolled in KDOC were the focus of analysis. Participation rates for LKDs and HCs were 84% and 83%, respectively. Table 1 summarizes sociodemographic, predonation clinical, and surgical characteristics. There were no significant differences between LKDs and HCs on any baseline characteristics. Donor sociodemographic characteristics

TABLE 1 Sociodemographic, predonation clinical, and surgical characteristics of the KDOC living kidney donors and healthy controls

Characteristic	Donors (n = 193)	Controls (n = 20)	*P* value
Sociodemographic			
Age, y, mean (SD)	42.6 (11.8)	41.1 (15.0)	.60
Sex, female, n (%)	122 (63)	12 (60)	.78
Race, White, non-Hispanic, n (%)	147 (76)	14 (70)	.54
Education, college or professional degree, n (%)	98 (51)	10 (50)	.95
Marital status, married/partnered, n (%)	99 (51)	11 (55)	.75
Work status, employed, n (%)	152 (79)	15 (75)	.70
Health insurance, yes, n (%)	172 (89)	18 (90)	.90
Household income, ≥$50 000, n (%)	123 (64)	10 (50)	.23
Relationship to recipient/donor, n (%)			.07
Biological	111 (58)	7 (35)	
Spouse	32 (17)	3 (15)	
Unrelated	50 (26)	10 (50)	
Predonation clinical			
Body mass index, mean (SD)	27.1 (3.8)	27.1 (3.2)	1.00
Systolic blood pressure, mean (SD)	123.6 (12.6)	119.5 (11.0)	.16
Diastolic blood pressure, mean (SD)	77.5 (8.9)	73.6 (8.7)	.06
Renal clearance[a], mean (SD)	118.5 (30.2)	—	—
Smoking history in past year, yes, n (%)	30 (16)	4 (20)	.60
History of mood disorder, yes, n (%)	46 (24)	1 (5)	.05
History of substance abuse (remission), yes, n (%)	11 (6)	3 (15)	.11
SF-36 physical health component, mean (SD)	57.2 (4.9)	56.2 (4.6)	.38
SF-36 mental health component, mean (SD)	54.3 (6.5)	53.2 (10.7)	.47
Physical activity in typical week			
Moderate intensity, yes, n (%)	156 (81)	14 (70)	.15
Moderate intensity, min, mean (SD)	222.1 (214.9)	281.1 (358.9)	.28
Vigorous intensity, yes, n (%)	99 (51)	11 (55)	.75
Vigorous intensity, min, mean (SD)	88.5 (128.6)	146.8 (180.2)	.07
Muscle strengthening, days, mean (SD)	2.0 (1.9)	2.4 (1.9)	.37
Meets national and international physical activity guidelines, yes, n (%)	84 (44)	8 (40)	.76
Surgical			
Operative time, min, mean (SD)	182.7 (59.0)	—	
Kidney removed, left, n (%)	175 (91)	—	
Surgical complication, yes, n (%)	50 (26)	—	
Re-operation, yes, n (%)	4 (2)	—	
Hospital duration, h, mean (SD)	73.6 (23.4)	—	
Re-hospitalization, yes, n (%)	8 (4)	—	

Abbreviations: KDOC, Kidney Donor Outcomes Cohort; SD, standard deviation.
[a]Calculated using Cockcroft-Gault equation.

were comparable to the population of US LKDs, although the KDOC sample included more college educated donors (51% vs 41%, $P = .01$).[25]

Most donors completed fatigue assessments predonation (n = 189, 98%) and 1 (n = 177, 92%), 6 (n = 161, 83%), 12 (n = 156, 81%), and 24 (n = 163, 85%) months postdonation. On average, predonation assessments were completed 6.3 days prior to surgery. Most (n = 182, 94%) completed the predonation assessment and at least one postdonation assessment, and 138 (72%) completed fatigue assessments at all postdonation time points. Older donors were more likely than younger donors to have completed ≥1 postdonation assessment (43.0 years vs. 31.6 years, $P = .01$).

3.2 | Fatigue outcomes: Donors vs. controls

With the exception of the 1-month postdonation assessment, LKDs and HCs did not differ significantly from each other on fatigue outcomes ($P > .05$) (Table 2). One month after donation, LKDs reported significantly more fatigue severity ($P = .01$), interference ($P = .03$), frequency ($P = .002$), and intensity ($P = .01$) on the FSI and significantly less vitality (ie, more fatigue) on the SF-36 VT scale ($P < .001$) than HCs. Compared to HCs, a higher proportion of LKDs were classified as having clinical fatigue at 1 month postdonation on both the FSI (37% vs. 60%, $P = .04$) and SF-36 VT scale (16% vs. 67%, $P < .001$) (Figures 1 and 2, respectively).

3.3 | Persistent clinical fatigue

Of the 155 donors who completed 1 and 6 month postdonation assessments, 50 (32%) had persistent clinical fatigue, ie, clinical fatigue at both time points following surgery. The daily pattern of clinical fatigue for these LKDs was described as worse in the morning (n = 7, 14%), afternoon (n = 12, 24%), evening (n = 15, 30%), or as having no consistent daily pattern (n = 16, 32%). In multivariable analysis, mood disorder history, lower SF-36 VT score at predonation, clinical mood disturbance and clinical fear of kidney failure postdonation, and fewer minutes per week (on average) of total physical activity (moderate + vigorous-intensity exercise) at 6 months postdonation were significantly associated with persistent clinical fatigue postdonation (Table 3).

Of the 50 LKDs with persistent clinical fatigue at 6 months postdonation, 19 (38%) reported fatigue resolution by the 12-month assessment, 26 (52%) reported continued clinical fatigue at 12 months, and 5 (10%) did not complete the assessment. Compared to those with clinical fatigue resolution, LKDs with persistent clinical fatigue at 12 months postdonation were more likely to report clinical mood disturbance (37% vs. 88%, $P = .001$) and less likely to engage in any vigorous physical activity (73% vs. 43%, $P = .04$) at the 12-month assessment. There were no other statistically significant differences between those with continued clinical fatigue vs. clinical fatigue resolution a year after donation. Finally, of the 26 LKDs who reported persistent clinical fatigue at 1, 6, and 12 months postdonation, 24 (92%) continued to report clinical fatigue at 24 months postdonation. Considering the entire KDOC sample (n = 193), 26 (13%) and 24 (12%) LKDs reported persistent clinical fatigue through the 12 and 24 month postdonation assessment, respectively.

4 | DISCUSSION

Fatigue following surgery, including donor nephrectomy, is common and clinically expected.[1-4] Potential causes of fatigue include many pre-, peri-, and postoperative factors, including nutritional status, exercise capacity, anesthesia exposure and duration, anemia secondary to blood loss, nutritional recovery, hydration, sleep disruption, and medications. It is not surprising, therefore, that the prevalence of clinical fatigue at 1 month postdonation was much

TABLE 2 Fatigue outcomes for LKD and HC at each assessment time point

Psychosocial outcome	Predonation		1 month postdonation		6 months postdonation		12 months postdonation		24 months postdonation	
	LKD (n = 189)	HC (n = 19)	LKD (n = 177)	HC (n = 19)	LKD (n = 161)	HC (n = 18)	LKD (n = 156)	HC (n = 17)	LKD (n = 163)	HC (n = 15)
Fatigue Symptom Inventory (FSI)[b]										
Severity, mean (SD)	2.8 (1.5)	2.8 (1.4)	3.9[a] (1.8)	2.8[a] (1.4)	2.9 (1.8)	2.6 (1.3)	2.9 (1.9)	3.0 (1.4)	2.9 (1.7)	2.9 (1.3)
Interference, mean (SD)	11.1 (6.4)	13.5 (11.7)	20.2[a] (12.0)	13.4[a] (11.6)	13.7 (10.9)	13.5 (10.5)	13.0 (10.1)	13.6 (11.0)	13.3 (9.5)	14.3 (12.5)
Frequency, days, mean (SD)	1.8 (1.8)	2.2 (1.8)	4.1[a] (2.5)	2.2[a] (2.1)	2.4 (2.1)	2.3 (1.9)	2.2 (2.1)	2.4 (1.8)	2.3 (2.1)	2.3 (2.5)
Intensity, mean (SD)	2.4 (1.4)	2.3 (1.6)	3.8[a] (2.1)	2.5[a] (1.6)	2.9 (2.1)	2.3 (1.0)	2.9 (2.0)	2.9 (2.1)	2.7 (1.8)	2.5 (1.7)
SF-36 Vitality[3]	57.8 (7.8)	56.3 (9.4)	43.9[a] (10.5)	55.5[a] (9.2)	54.7 (9.6)	57.6 (8.2)	55.6 (9.6)	56.3 (7.8)	55.6 (9.4)	55.7 (8.7)

Abbreviations: HC, healthy controls; LKD, living kidney donors.

[a]Indicates statistically significant difference ($P < .05$) between LKD and HC

[b]Fatigue Symptom Inventory (FSI): Severity (average of 4 items, 1 = not at all fatigued to 10 = as fatigued as you could be, range 1 to 10), Interference (sum total of 7 items, 1 = no interference to 10 = extreme interference, total range 7 to 70), Frequency (# days in past week felt fatigued, range 0 to 7), Intensity (how much of day, on average, felt fatigued, 1 = none of the day to 10 = the entire day, range 1 to 10).

[c]SF-26 Vitality scale: 4 items, standardized score range 0 to 100, lower score = more fatigue.

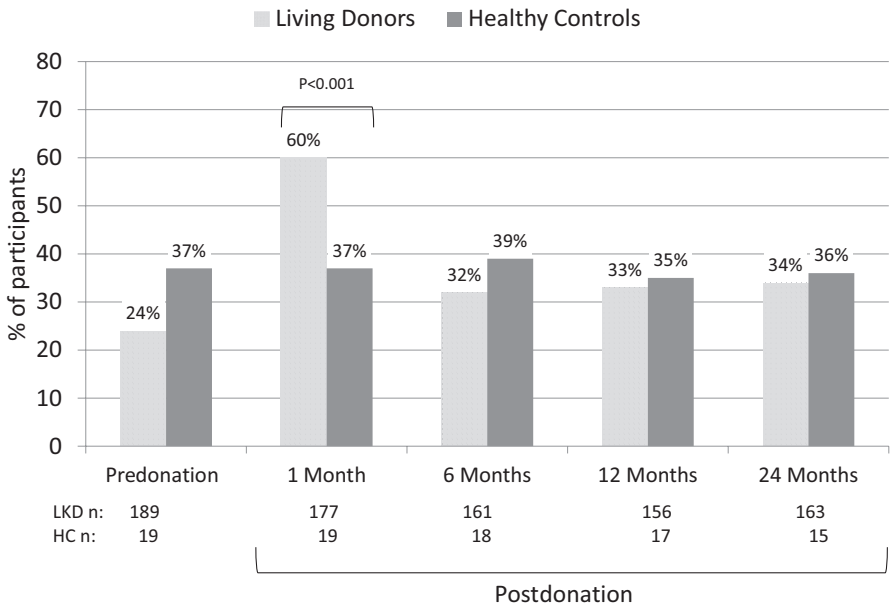

FIGURE 1 Percentage of living donors and healthy controls at each assessment time point meeting Fatigue Symptom Inventory (FSI) criteria for clinical fatigue

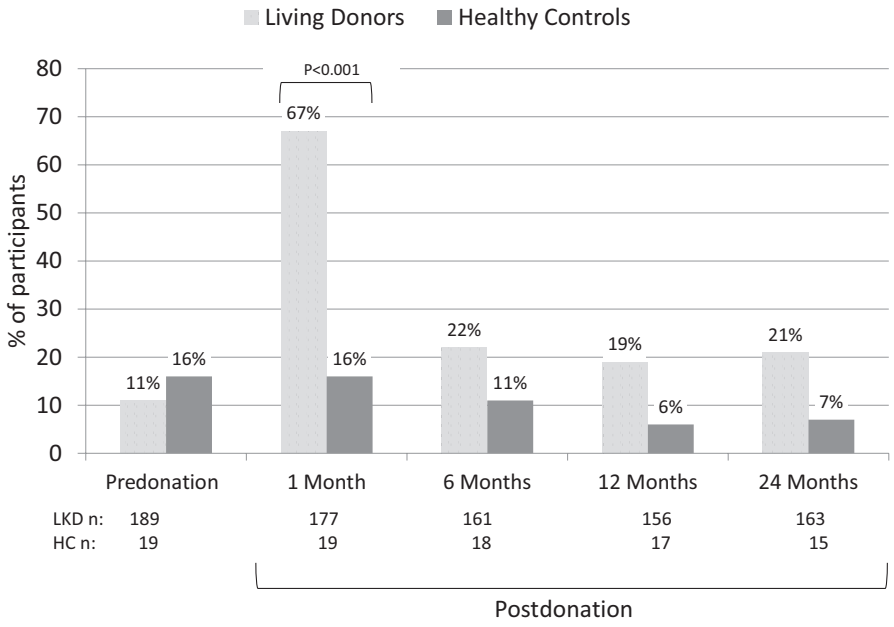

FIGURE 2 Percentage of living donors and healthy controls at each assessment time point meeting SF-36 Vitality scale criteria for clinical fatigue

higher for LKDs than for non-donors. Clinical fatigue in LKDs was manifested by higher fatigue severity, more days and more time feeling fatigued, and fatigue's interference with other aspects of daily life. This finding is consistent with our clinical experience and prior research,[2-4,8] and it confirms the OPTN requirement that potential LKDs be informed of the risk of clinical fatigue. Importantly, most LKDs reported resolution of clinical fatigue by the 6-month assessment. Unfortunately, the timing of assessments did not allow us to determine precisely how long clinical fatigue lasted until its resolution, although the prevalence of clinical fatigue in LKDs did not differ significantly from non-donors beyond the 1-month assessment. Studies are needed to assess the natural progression of clinical fatigue after donation, which would provide potential LKDs and clinicians with more granular information about its duration.

For LKDs whose early postoperative clinical fatigue persisted for at least 6 months, their fatigue was more severe and more debilitating than so-called "normal" fatigue experienced by nondonors or other LKDs. Their fatigue interfered more with general activity, work inside and outside the home, concentration ability, relationships, mood, and general enjoyment of life. Notably, most of these LKDs did not have clinical fatigue prior to donation. While one-third of LKDs with clinical fatigue at 6 months reported complete resolution by the 1-year assessment, we were surprised to find a small LKD cohort (n = 24, 12%) with persistent clinical fatigue lasting 24 months postdonation. Others have found that fatigue is present in former LKDs several years after donation,[5-7,9,27] but this is the first study reporting on the prevalence of persistent *clinical* fatigue up to 2 years postdonation. While we cannot say that donation caused

TABLE 3 Multivariable predictors of persistent clinical fatigue 6 months postdonation

Variables	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Predonation variables				
History of affective disorder, yes	2.96 (1.38, 6.36)	.005	2.36 (1.05, 5.34)	.04
Fear of kidney failure, yes	4.19 (1.65, 10.42)	.002	2.22 (0.74, 6.64)	.15
FSI	1.62 (1.26, 2.08)	<.001	1.14 (0.83, 1.56)	.43
Vitality (SF-36)	0.90 (0.85, 0.95)	<.001	0.93 (0.87, 0.99)	.03
Postdonation variables				
Mood disturbance	4.33 (1.95, 9.62)	<.001	2.65 (1.04, 6.73)	.04
Fear of kidney failure	3.34 (1.59, 7.01)	.001	2.20 (1.03, 5.22)	.04
Total minutes of physical activity per week, on average, 6 month	0.80 (0.73, 0.85)	<.001	0.93 (0.82, 0.98)	.02

Abbreviations: CI, confidence interval; FSI, Fatigue Severity Index; OR, odds ratio.

long-term clinical fatigue, it is a clinical outcome that warrants inclusion in ongoing LKD surveillance efforts.[26]

We found that LKDs with a history of affective disorder and those with elevated distress after donation are at risk for persistent clinical fatigue postdonation, a finding that is consistent with prior studies of LKDs and other patient populations.[5,27-29] It is important to emphasize the bidirectional nature of this relationship, particularly postdonation. Anxiety about future kidney failure, for instance, may contribute to some LKDs being more hypervigilant about even subtle variations in energy or fatigue. Heightened anxiety may also lead to avoidance of physical activity, sleep dysregulation, and emotional exhaustion, which collectively may exacerbate symptoms of fatigue. Additionally, LKDs who engaged in less physical activity were more likely to experience persistent clinical fatigue. Minimal physical activity and time spent in sedentary behaviors impacts fatigue levels in other surgical patients.[29-31] Surgery followed by physical Inactivity may lead to physical deconditioning, which makes daily activities more challenging and increases the likelihood of persistent clinical fatigue.

Interestingly, sociodemographic, surgical, and medical variables we examined were not significant predictors of persistent clinical fatigue. We hypothesized that women would report more fatigue than men following donation based on prior findings,[6,11,12] but this was not supported. It is likely that factors other than biological sex are more critical to developing clinical fatigue, including those that we did not assess (eg, caregiving demands). Schachtner and Reinke[32] showed that fatigue may be more prominent for those who undergo left-sided nephrectomy, perhaps secondary to transection of adrenal vessels resulting in latent adrenal insufficiency. However, as noted by Burn et al,[33] while there appears to be a transiently reduced adrenocortical responsiveness in left-sided donor nephrectomy, functioning returns to baseline after 28 days. In our study, fatigue did not vary significantly based on which kidney was removed. Also, hospital length of stay, number of complications, and renal clearance were not associated with fatigue. De Groot et al[5] also found that renal clearance was not associated with quality of life or fatigue following donation. It is possible that a more dramatic decline in renal function is necessary to impact fatigue, particularly since change in renal clearance due to surgery is likely qualitatively different than a progressive decline and still provides ample function for healthy living.

Based on our findings, potential LKDs should be informed about the high likelihood of clinical fatigue 1 month following surgery and that this fatigue is likely to interfere with many daily activities during the recovery period. However, they should also be reassured that clinical fatigue typically resolves between 1 and 6 months postdonation and that its prevalence does not differ from that of non-donors in the long term. LKDs with known mood disturbance or anxiety about future kidney health should be informed that they are at a higher risk for more persistent clinical fatigue lasting 6 months or longer, as are those engaged in minimal or no physical activity. During postdonation follow-up visits, LKDs should be screened for fatigue and to determine any adverse impact on daily activities. Both the FSI two-item composite we used to identify clinical fatigue and the SF-36 VT scale are brief, validated measures that appear to be sensitive to change over time.[34] If clinical fatigue is present on either measure, LKDs should be counseled about undergoing further evaluation and possible treatment. Physical activity, psychosocial, mind-body, and pharmacological treatments may be effective in attenuating clinical fatigue.[35,36] Also, Enhanced Recovery After Surgery (ERAS) interventions offer potential to reduce pain and fatigue after surgery and facilitating return to activities sooner in surgical patients.[37,38] ERAS protocols vary considerably but generally are a multidisciplinary and patient-centered approach designed to reduce a patient's stress response to surgery, maximize their physiologic function, and facilitate a quicker recovery and return to normal activities. This approach

commonly includes pre-surgery patient education, behavioral risk reduction (eg, smoking cessation), and carbohydrate-rich beverages, goal-directed fluid management, limited use of drains, multidisciplinary opioid sparing pain management, and early oral nutrition and mobilization postoperatively. Early studies of ERAS in the context of living donation are promising, although fatigue has not yet been integrated into outcomes assessment and follow-up has been short-term.[3,39-41]

There are several notable limitations to the study. The KDOC study was designed to assess multiple patient-reported outcomes, thus leading us to compromise some granularity in data collection. For instance, there are other measures of fatigue (eg, Multidimensional Fatigue Inventory; Checklist Individual Strength) that we did not use, thus preventing us from directly comparing our findings with those of others.[4,5,10] Also, the FSI and SF-36 VT yielded two different estimates of clinical fatigue prevalence, which may be due to the different time parameters patients are asked to consider when responding to questions (1 week for FSI vs. 4 weeks for SF-36 VT). Also, the FSI clinical cut-off score, which has been validated with cancer patients (primarily women), may be too low for LKDs, thus resulting in a higher proportion of LKDs in the clinical range, compared to the SF-36 VT scale. Inferences about nephrectomy causing persistent clinical fatigue cannot be made, as there may be other factors contributing to both its onset and duration (eg, genetic, biological, nutritional, psychosocial). Additionally, it is not known whether fatigue following donor nephrectomy is any worse (prevalence, severity, duration) than fatigue following other abdominal surgeries. Finally, as we have noted elsewhere,[20] comparisons between LKDs and healthy non-donors should be considered in light of the very small HC sample size in our study. These limitations notwithstanding, findings confirm inclusion of fatigue risk in OPTN informed consent requirements, have important clinical implications in the care of LKDs, and underscore the need for further scientific examination in this population.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Kok NF, Alwayn IP, Tran KT, Hop WC, Weimar W, Ijzermans JN. Psychosocial and physical impairment after mini-incision open and laparoscopic donor nephrectomy: a prospective study. *Transplantation*. 2006;82:1291-1297.
2. Bergman S, Feldman LS, Mayo NE, et al. Measuring surgical recovery: the study of laparoscopic live donor nephrectomy. *Am J Transplant*. 2005;5:2489-2495.
3. Mansour AM, El-Nahas AR, Ali-El-Dein B, et al. Enhanced recovery open vs laparoscopic left donor nephrectomy: a randomized controlled trial. *Urology*. 2017;110:98-103.
4. Minnee RC, Bemelman WA, Polle SW, et al. Older living kidney donors: surgical outcome and quality of life. *Transplantation*. 2008;86:251-256.
5. de Groot IB. Stiggelbout AM, van der Boog PJ, Baranski AG, Marang-van de Mheen PJ; PARTNER-Study Group. Reduced quality of life in living kidney donors: association with fatigue, societal participation and pre-donation variables. *Transpl Int*. 2012;25:967-975.
6. Meyer K, Wahl AK, Bjørk IT, Wisløff T, Hartmann A, Andersen MH. Long-term, self-reported health outcomes in kidney donors. *BMC Nephrol*. 2016;17:8.
7. Gross CR, Messersmith EE, Hong BA, et al.; RELIVE Study Group. Health-related quality of life in kidney donors from the last five decades: results from the RELIVE study. *Am J Transplant*. 2013;13:2924-2934.
8. Dols LF, Ijzermans JN, Wentink N, et al. Long-term follow-up of a randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy. *Am J Transplant*. 2010;10:2481-2487.
9. Janki S, Klop KW, Dooper IM, Weimar W, Ijzermans JN, Kok NF. More than a decade after live donor nephrectomy: a prospective cohort study. *Transpl Int*. 2015;28:1268-1275.
10. Wirken L, van Middendorp H, Hooghof CW, et al. Psychosocial consequences of living kidney donation: a prospective multicentre study on health-related quality of life, donor-recipient relationships and regret. *Nephrol Dial Transplant*. 2019;34:1045-1055.
11. Sommerer C, Estelmann S, Metzendorf NG, Leuschner M, Zeier M. Gender disparity in health-related quality of life and fatigue after living renal donation. *BMC Nephrol*. 2018;27(19):377.
12. Meyer KB, Hartmann A, Mjøen G, Andersen MH. Relationships between clinical, self-reported, and donation specific outcomes: a prospective follow-up study 10 years after kidney donation. *Ann Transplant*. 2017;22:148-155.
13. Engberg I, Segerstedt J, Waller G, Wennberg P, Eliasson M. Fatigue in the general population- associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014. *BMC Public Health*. 2017;17:654.
14. Hann D, Jacobsen P, Martin S, et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. *Qual Life Res*. 1998;7:301-310.

15. Donovan KA, Jacobsen PB. The Fatigue Symptom Inventory: a systematic review of its psychometric properties. *Support Care Cancer*. 2010;19:169-185.
16. Goedendorp MM, Jacobsen PB, Andrykowski MA. Fatigue screening in breast cancer patients: identifying likely cases of cancer-related fatigue. *Psychooncology*. 2016;25:275-281.
17. Ware JE, Kosinki M, Dewey JE. *How to score version 2 of the SF-36® health survey (standard & acute forms)*. Lincoln, RI: QualityMetric; 2000.
18. Donovan KA, Jacobsen PB, Small BJ, Munster PN, Andrykowski MA. Identifying clinically meaningful fatigue with the fatigue symptom inventory. *J Pain Symptom Manage*. 2008;36:480-487.
19. McNair D, Lorr M, Droppelman L. *Manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service; 1981.
20. Rodrigue JR, Schold JD, Morrissey P, et al.; KDOC Study Group. Mood, body image, fear of kidney failure, life satisfaction, and decisional stability following living kidney donation: findings from the KDOC study. *Am J Transplant*. 2018;18:1397-1407.
21. Rodrigue JR, Fleishman A, Vishnevsky T, et al. Development and validation of a questionnaire to assess fear of kidney failure following living donation. *Transpl Int*. 2014;27:570-575.
22. U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans*, 2nd edn. Washington, DC: U.S. Department of Health and Human Services; 2018.
23. World Health Organization. Global Recommendations on Physical Activity for Health; 2011. https://www.who.int/dietphysicalactivity/physical-activity-recommendations-18-64years.pdf?ua=1. Accessed October 8, 2018.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
25. Rodrigue JR, Schold JD, Morrissey P, et al. Direct and indirect costs following living kidney donation: findings from the KDOC study. *Am J Transplant*. 2016;16:869-876.
26. Kasiske BL, Asrani SK, Dew MA, et al. The Living Donor Collective: a scientific registry for living donors. *Am J Transplant*. 2017;17:3040-3048.
27. Sommerer C, Feuerstein D, Dikow R, et al. Psychosocial and physical outcome following kidney donation-a retrospective analysis. *Transpl Int*. 2015;28:416-428.
28. Pollmann I, Gueler F, Mikuteit M, et al. Adaptive personality traits and psychosocial correlates among living kidney donors. *Front Psychiatry*. 2017;8:210.
29. Bower JE. Cancer-related fatigue–mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11:597-609.
30. Brandenbarg D, Korsten JHWM, Berger MY, Berendsen AJ. The effect of physical activity on fatigue among survivors of colorectal cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2018;26:393-403.
31. Ellingson LD, Kuffel AE, Vack NJ, Cook DB. Active and sedentary behaviors influence feelings of energy and fatigue in women. *Med Sci Sports Exerc*. 2014;46:192-200.
32. Schachtner T, Reinke P. Left-Sided Donor Nephrectomy Predisposes Living Kidney Donors to Latent Adrenal Insufficiency with Symptoms of Fatigue and Inferior Quality of Life. Chicago, IL: ATC; 2017. https://atcmeetingabstracts.com/abstract/left-sided-donor-nephrectomy-predisposes-living-kidney-donors-to-latent-adrenal-insufficiency-with-symptoms-of-fatigue-and-inferior-quality-of-life/. Accessed November 5, 2018.
33. Burn F, Schirpenbach C, Bidlingmaier M, et al. Left-sided living kidney donation leads to transiently reduced adrenocortical responsiveness. *Am J Transplant*. 2017;17:1879-1884.
34. Brown LF, Kroenke K, Theobald DE, Wu J. Comparison of SF-36 vitality scale and Fatigue Symptom Inventory in assessing cancer-related fatigue. *Support Care Cancer*. 2011;19:1255-1259.
35. Mohandas H, Jaganathan SK, Mani MP, Ayyar M, Rohini Thevi GV. Cancer-related fatigue treatment: an overview. *J Cancer Res Ther*. 2017;13:916-929.
36. Mustian KM, Alfano CM, Heckler C, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol*. 2017;3:961-968.
37. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg*. 2017;152:292-298.
38. Li D, Jensen CC. Patient satisfaction and quality of life with enhanced recovery protocols. *Clin Colon Rectal Surg*. 2019;32:138-144.
39. Campsen J, Call T, Allen CM, et al. Prospective, double-blind, randomized clinical trial comparing an ERAS pathway with ketorolac and pregabalin versus standard of care plus placebo during live donor nephrectomy for kidney transplant. *Am J Transplant*. 2018;19:1777-1781.
40. Rege A, Leraas H, Vikraman D, et al. Could the use of an enhanced recovery protocol in laparoscopic donor nephrectomy be an incentive for live kidney donation? *Cureus*. 2016;8:e889.
41. Waits SA, Hilliard P, Sheetz KH, Sung RS, Englesbe MJ. Building the case for enhanced recovery protocols in living kidney donors. *Transplantation*. 2015;99:405-408.

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