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Original Article

TO STUDY THE QOL DEPRESSION AND SYMPTOMS IN BOTH CKD AND ESKD

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Abstract:
End-stage kidney disease is also called end-stage renal disease (ESRD). The kidneys of people with ESRD function below 10 percent of their normal ability, which may mean they are barely functioning or not functioning at all. The study was conducted to know the physical and psychological well-being in patients with advanced chronic kidney disease (CKD) and To compare symptoms, depression, and quality of life in patients with ESRD and those with CKD. To assess the impact of demographic and clinical variables on group differences in symptoms, depression, and QOL, we used linear regression, logistic regression, or the Wilcoxon-Mann-Whitney rank sum test, as appropriate. Variables included in these analyses were those that demonstrated statistically significant differences between the study groups in univariate analyses. We report differences in the eight subscales of the SF-36 as well as the PCS and MCS scores. We assessed correlations in each patient group among overall symptom burden, overall symptom severity, depression, and physical and mental well-being as measured by the PCS and MCS using Spearman's correlation coefficient, and evaluated the internal consistency reliability of the DSI using Cronbach's coefficient alpha. In conclusion, we found that patients with ESRD on maintenance dialysis and those with advanced CKD experience a similar overall burden of physical and emotional symptoms and depression and comparably low QOL. Given the substantial and well-recognized decrements in the physical and psychosocial well-being of patients with ESRD receiving chronic renal replacement therapy, our findings suggest that significant attention should be paid to these health-related domains in the large and growing number of patients who suffer from advanced CKD.

1. INTRODUCTION

Chronic kidney disease (CKD), also known as chronic renal disease, is progressive loss in kidney function over a period of months or years. The symptoms of worsening kidney function are not specific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a bloodline relative with CKD. This disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia, pericarditis or renal osteodystrophy (the latter included in the novel term CKD-MBD).[1][2] CKD is a long-term form of kidney disease; thus, it is differentiated from acute kidney disease (acute kidney injury) in that the reduction in kidney function must be present for over 3 months. CKD is an internationally recognized public health problem affecting 5–10% of the world population.[3][4]

Chronic kidney disease is identified by a blood test for creatinine, which is a breakdown product of muscle metabolism. Higher levels of creatinine indicate a lower glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products. Creatinine levels may be normal in the early stages of CKD, and the

condition is discovered if urinalysis (testing of a urine sample) shows the kidney is allowing the loss of protein or red blood cells into the urine. To fully investigate the underlying cause of kidney damage, various forms of medical imaging, blood tests, and sometimes a kidney biopsy (removing a small sample of kidney tissue) are employed to find out if a reversible cause for the kidney malfunction is present.[1]

Previous professional guidelines classified the severity of CKD in five stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is often called end-stage kidney disease, end-stage renal disease, or end-stage kidney failure, and is largely synonymous with the now outdated terms chronic renal failure or chronic kidney failure; and usually means the patient requires renal replacement therapy, which may involve a form of dialysis, but ideally constitutes a kidney transplant. Recent international guidelines reclassified CKD based on cause, glomerular filtration rate category (G1,G2,G3a,G3b,G4 and G5), and albuminuria category (A1,A2,A3).[5]

Screening of at-risk people is important because treatments exist that delay the progression of CKD.[6] If an underlying cause of CKD, such as vasculitis, or obstructive nephropathy (blockage to the drainage system of the kidneys) is found, it may be treated directly to slow the damage. In more advanced stages, treatments may be required for anemia and kidney bone disease

The aim of the study is to know the physical and psychological well-being in patients with advanced chronic kidney disease (CKD).

MATERIALS AND METHODS:

Study Setting and Design

As part of a larger, prospective cohort study of sleep, memory, and QOL in patients with advanced CKD and subjects undergoing chronic peritoneal dialysis or thrice-weekly in-center hemodialysis, we conducted a subanalysis of patients' symptoms, depression, and QOL. This study was approved by the Institutional Review Board, and all participants provided informed consent.

Between April 2016 and March 2017, patients with ESRD on maintenance dialysis and individuals with a history of stage 4 or 5 CKD receiving care at local dialysis units. Exclusion criteria included age <18 yr or >90 yr, not residing at home, active malignancy, active infection (pneumonia), active coronary artery disease (*e.g.*, unstable angina, myocardial infarction) within the last 6 mo, advanced cirrhosis, advanced dementia, active alcohol abuse, active treatment for sleep apnea, refractory psychiatric disease, or an unsafe home environment. Patients without exclusions were approached at the time of their routine CKD clinic visit, dialysis clinic visit, or initial visit to the kidney transplantation clinic and signed informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki.

We assessed patients' demographic characteristics and abstracted serologic variables from the medical record including the most recent hemoglobin and serum calcium, phosphorous, albumin, and creatinine. For patients with a history of stage 4 or 5 CKD, we used the most recent serum creatinine and 4-variable Modification of Diet in Renal Disease study equation to calculate their estimated GFR (eGFR). Some patients initially identified in the screening phase as having a history of stage 4 CKD demonstrated an eGFR that was consistent with advanced stage 3 CKD. These individuals were included in our study (21). We also assessed patients' functional status using the Karnofsky Performance Status Scale and Lawton Instrumental Activities of Daily Living Scale (22,23). Lower scores on the Karnofsky scale and higher scores on the Lawton scale indicate greater functionality. As the parent study involved the assessment of sleep quality in patients' homes, all enrolled patients self-administered the study surveys at the time of this home visit.

Assessment of Symptoms, Depression, and Quality of Life

We used the 30-item Dialysis Symptom Index (DSI) to assess the presence and severity of physical and emotional symptoms. To complete the DSI, patients were asked to report which of 30 individual symptoms had been present over the past 7 d. We considered missing responses, which were present in fewer than 4% of any of the individual symptoms to indicate that the symptom was not present. For symptoms that were present, the patient was asked to describe the severity of the symptom on a 5-point Likert scale ranging from "not at all bothersome" to "very bothersome." For missing responses on symptom severity, which were also present in fewer than 4% of responses, we confirmed that the symptom was reported as not present and assigned a severity score of zero. An overall symptom burden score ranging from 0 to 30 was generated by summing the number of symptoms reported as being present. In addition, an overall symptom-severity score ranging from 0 to 150 was generated by summing the severity of symptoms, assigning a score of zero for symptoms that were not present. Past studies confirmed the test-retest reliability and content and construct validity of the DSI in patients on hemodialysis (12,24).

We used the PHQ-9 to assess the presence and severity of depression. This 9-item tool assesses the frequency with which patients experience depressive thoughts or feelings over the prior 2 wk. The severity of depressive disorder is considered moderate for scores ranging from 10 to 14, moderately severe for scores of 15 to 19, and severe for scores of 20 to 27. The PHQ-9 has been used to assess depression in patients with ESRD and those with CKD (25–27). In patients on hemodialysis, scores >9 are 92% sensitive and specific for a diagnosis of depressive disorder (25).

We used the Medical Outcomes Study Short Form-36 (SF-36) to assess QOL. The SF-36 contains eight subscales (physical function, role limitations-physical, bodily pain, vitality, general health perceptions, role limitations-emotional, social function, and mental health) and two component summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Higher scores indicate better QOL. The SF-36 has been used extensively in patients with kidney disease and has sound psychometric characteristics in this patient population (28–30).

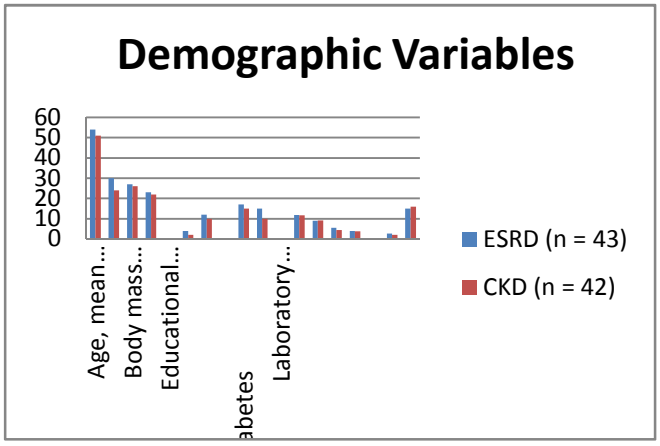
Statistical Analyses

For our analyses, we considered hemodialysis and peritoneal dialysis patients collectively as one group (herein referred to as the ESRD group). These patients were compared with those with advanced CKD (CKD group). Differences between the groups in demographic characteristics, clinical variables, the prevalence and severity of individual symptoms, overall symptom burden and overall symptom severity, depression, and QOL were assessed using *t* test or Mann-Whitney tests for continuous variables, and the χ^2 statistic or Fisher's exac*t* test for categorical variables. To assess the impact of demographic and clinical variables on group differences in symptoms, depression, and QOL, we used linear regression, logistic regression, or the Wilcoxon-Mann-Whitney rank sum test, as appropriate. Variables included in these analyses were those that demonstrated statistically significant differences between the study groups in univariate analyses. We report differences in the eight subscales of the SF-36 as well as the PCS and MCS scores. We assessed correlations in each patient group among overall symptom burden, overall symptom severity, depression, and physical and mental well-b

A total of 100 patients were screened for study participation, and 93 met eligibility criteria. Of these, eight did not complete the study surveys, resulting in a patient population of 85. 43 patients (51%) had ESRD; 33 (78%) on hemodialysis and 10 (22%) on peritoneal dialysis. This cohort included all ESRD patients from the larger cohort study as of November 2017. 42 patients (49%) had CKD. Patients with ESRD, have a higher serum phosphorous concentration, and have higher scores on the Karnofsky index and lower scores on the Activities of Daily Living Scale, indicating poorer functional status.

TABLES: 01. **Patient Characteristics**

Demographic Variables	**ESRD (*n* = 43)**	**CKD (*n* = 42)**	***P* value**
Age, mean (SD), y	54 ± 15	51 ± 15	0.2
Men % (n)	30 (51)	24 (57)	0.3
Body mass index, mean (SD), kg/m^2	27 ± 5	26 ± 15	0.4
Married (%)	23 (53)	22(52)	0.7
Educational status			
Less than 9 th grade % (n)	4 (10)	2 (4)	0.1
High school graduate % (n)	12 (28)	10 (24)	0.6
Comorbid conditions			
Diabetes	17 (39)	15(36)	0.6
Cardiovascular disease	15 (36)	10 (24)	0.07
Laboratory variables			
Hemoglobin, mean (SD) g/dl	11.9 (1.6)	11.7 (1.5)	0.5
Serum calcium, mean (SD) mg/dl	9.0 (1.0)	9.1 (0.6)	0.5
Serum phosphorous, mean (SD) mg/dl	5.5 (1.6)	4.5 (1.2)	<0.001
Serum albumin, mean (SD) g/dl	3.9 (0.5)	3.8 (0.6)	0.1
Functional status			
Karnofsky score, mean (SD)	2.75 ± 1.3	2.1 ± 1.1	0.001
ADL, median (IQR)a	15 (13, 16)	16 (14.5, 16)	0.008



Symptoms, Depression, and Quality of Life

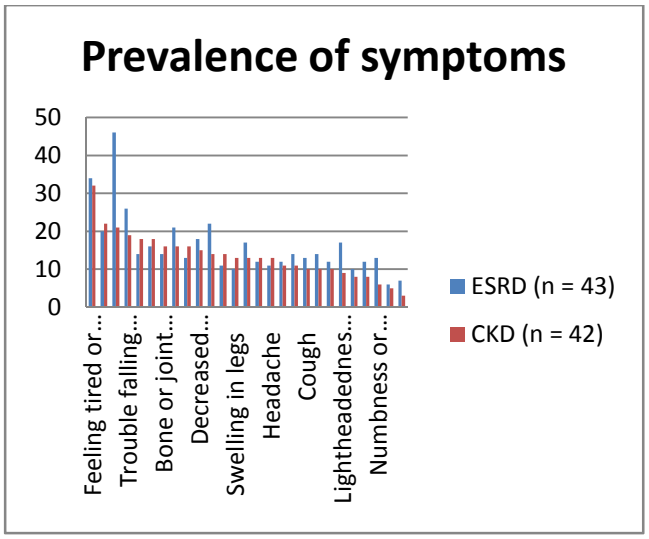
There was no difference in the mean overall number of symptoms in patients with ESRD compared with those with CKD (11.2 ± 6.4 *versus* 10.2 ± 5.6, *P* = 0.3). Patients with ESRD were more likely to report difficulty falling asleep (60% *versus* 44%, *P* = 0.04), dry mouth (50% *versus* 34%, *P* = 0.05), and lightheadedness/dizziness (39% *versus* 23%, *P* = 0.02). However, none of these differences met the level of statistical significance after Bonferroni correction (Table 2). The median overall symptom-severity score was not different in patients with ESRD compared with CKD (20.5 *versus* 15, *P* = 0.2). The median severity of itching was greater in patients with ESRD compared with CKD (2.0 *versus* 1.0, *P* = 0.001). Patients with ESRD also reported higher median severity scores for decreased interest in sex (3.0 *versus* 2.0, *P* = 0.009) and difficulty becoming sexually aroused (3.0 *versus* 2.0, *P* = 0.004), although these differences did not reach the level of statistical significance after Bonferroni correction. There was a trend toward more severe swelling in the legs among CKD patients compared with patients with ESRD (2.5 *versus* 1.0, *P* = 0.08), although this difference was also not statistically significant

TABLE :02. Prevalence of symptoms

Symptom	**ESRD (*n* = 43)**	**CKD (*n* = 42)**	P valueb
Feeling tired or lack of energy	34 (79)	32 (78)	1
Dry skin	20 (47)	22(53)	0.5
Itching	46 (51)	21(51)	0.4
Trouble falling asleep	26 (60)	19 (44)	0.04
Feeling sad	14 (33)	18 (43)	0.2
Feeling irritable	16(37)	18(43)	0.5
Bone or joint pain	14 (33)	16(39)	0.4
Muscle cramps	21 (50)	16 (38)	0.1
Feeling anxious	13 (31)	16(38)	0.3
Decreased interest in sex	18 (43)	15 (36)	0.4
Dry mouth	22 (50)	14 (34)	0.05
Constipation	11 (26)	14 (33)	0.3
Swelling in legs	10 (24)	13(32)	0.3
Restless legs	17 (39)	13(32)	0.4
Feeling nervous	12 (29)	13(31)	0.9
Headache	11 (26)	13 (30)	0.6
Diarrhea	12 (28)	11(25)	0.7
Decreased appetite	14 (32)	11(25)	0.3

Cough	13 (31)	10 (24)	0.3
Muscle soreness	14 (33)	10 (24)	0.2
Nausea	12 (27)	10 (24)	0.7
Lightheadedness or dizziness	17(39)	9(23)	0.02
Shortness of breath	10 (23)	8 (22)	0.9
Difficulty concentrating	12 (28)	8 (22)	0.4
Numbness or tingling in feet	13 (30)	6 (21)	0.2
Vomiting	6(13)	5 (11)	0.8
Chest pain	3 (8)	3(8)	1

Lightheadedness or dizziness	1	1	0.5
Feeling anxious	2	2	0.5
Nausea	2	1	0.2
Headache	1	1	0.3
Restless legs or difficulty keeping legs still	2	1	0.1
Feeling irritable	1	2	0.01
Constipation	2	1	0.7
Difficulty concentrating	2	1	0.3
Vomiting	3	1.5	0.2
Feeling nervous	2	1	0.5
Chest pain	2	2	0.6



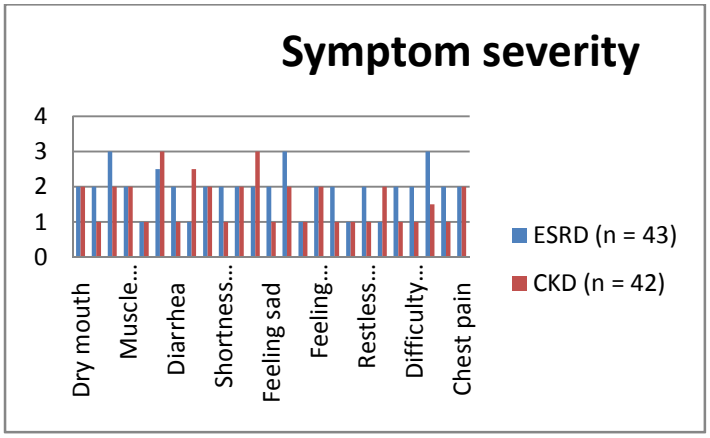


TABLE:03. Symptom severity

Symptom	**ESRD (*n* = 43)**	**CKD (*n* = 42)**	P valueb
Dry mouth	2	2	0.2
Itching	2	1	0.001
Trouble falling asleep	3	2	0.4
Muscle cramps	2	2	0.1
Cough	1	1	0.6
Bone or joint pain	2.5	3	0.7
Diarrhea	2	1	0.04
Swelling in legs	1	2.5	0.08
Muscle soreness	2	2	0.1
Shortness of breath	2	1	0.3
Decreased appetite	2	2	0.7
Numbness or tingling in feet	2	3	0.3
Feeling sad	2	1	0.6
Decreased interest in sex	3	2	0.009

The median PHQ-9 score in patients with ESRD was similar to that of patients with CKD (5.0 *versus* 4.0, *P* = 0.95). The proportion of patients with PHQ-9 scores >9 was similar in patients with ESRD and CKD (15.5% *versus* 15%, respectively, *P* = 0.9). There were no differences in the proportion of patients with moderate, moderately severe, and severe depressive disorder.

Eleven patients, four in the ESRD group and seven in the CKD group, did not complete the SF-12 and were not included in the QOL analyses. Patients with ESRD had lower physical function scores than those with CKD, with no differences noted in any of the other SF-12 subscale. However, overall physical well-being as measured by the PCS was comparable (36.6 ± 10.3 in ESRD *versus* 39.3 ± 10.5 in CKD, *P* = 0.1), as was overall mental well-being as measured by MCS (44.6 ± 7.8 in ESRD *versus* 44 ± 7.3 in

CKD, $P = 0.6$). There were no associations of stage of CKD or type of dialysis with symptoms, depression, or QOL scores.in regression analysis, we examined the attenuating or intensifying effects of race, phosphorous concentration, cardiovascular disease, Karnofsky score, and Activities of Daily Living Scale score on differences in symptoms, depression, and QOL between the study groups. Phosphorous concentration attenuated the nonstatistically significant difference in the severity of "decreased interest in sex," while functional status as measured by the Activities of Daily Living Scale attenuated the nonstatistically significant difference in the severity of the symptom "difficulty becoming sexually aroused." Adjusting for functional status as measured by the Karnofsky scale rendered the difference in the severity of itching between the groups nonstatistically significant. Adjustment for these demographic and clinical variables did not unmask differences in overall symptom burden, overall symptom severity, PHQ-9 scores, or QOL scores and did not attenuate the modest difference in the physical function subscale of the SF-12 (data not shown).

Correlations of Symptoms, Depression, and Quality of Life

Total symptom burden and total symptom severity were correlated with depression in both patient groups, with PCS scores in patients with ESRD and with MCS scores in patients with CKD. Depression was strongly correlated with MCS scores in both groups (Table 4). The Cronbach's coefficient alpha for the DSI in patients with ESRD was 0.86, and was 0.82 in patients with CKD.

TABLE 04: Correlations of symptoms, depression, and quality of life.

	PHQ-9		PCS		MCS	
	ESRD	CKD	ESRD	CKD	ESRD	CKD
Total symptom burden	0.49b	0.54	−0.47b	−0.21	−0.26c	−0.38c
Total symptom severity	0.58b	0.53b	−0.44b	−0.31c	−0.23	−0.41c
PHQ-9	-	-	−0.21	−0.19	−0.51b	−0.51b

[a]Data denote correlation coefficient (r).
[b]$P < 0.001$.
[c]$P < 0.05$.

eing as measured by the PCS and MCS using Spearman's correlation coefficient, and evaluated the internal consistency reliability of the DSI using Cronbach's coefficient alpha. We applied the Bonferroni correction for the analyses of differences in the prevalence and severity of individual symptoms on the DSI given the multiple comparisons. For these analyses, a two-sided p-value of <0.002 was considered to represent statistical significance. For all other analyses, a two-sided p-value <0.05 was applied. All analyses were performed using STATA version 8 (College Station, TX).

DISCUSSION:

Past studies demonstrated that patients receiving maintenance dialysis experience a multitude of physical and emotional symptoms, a particularly high prevalence of depression, and significant impairments in QOL. The findings of the present study suggest that patients with advanced CKD who are not dependent on chronic renal replacement therapy experience a comparable overall burden of symptoms and depression and low QOL. These novel findings have a series of important clinical implications for patients and providers.

Despite research demonstrating the impaired physical and psychosocial well-being of patients with ESRD, the clinical, treatment, and/or patient-related factors that cause symptoms, depression, and impaired QOL in this patient population remain incompletely understood. While the physical rigors of dialysis therapy and emotional, social, and vocational impact of this chronic treatment would seem to be likely mediators, the findings of this study suggest that this may not be so. A significant loss without an absence of

kidney function may be sufficient for patients to develop symptoms, depression, and impaired QOL. Determining whether this relates to metabolic derangements, retained uremic toxins, comorbid medical conditions, anxiety about the presence of CKD and potential future need for renal replacement therapy, or other factors, is important to facilitate the implementation of appropriate treatment.

Our findings have important implications for patients with CKD. Patients with advanced CKD may be unfamiliar with how chronic renal replacement therapy will impact their physical and psychosocial well-being. The need for chronic dialysis results in a significant change in lifestyle for many patients. Based on our findings, it seems plausible that many individuals with CKD may not experience a substantial change in physical and/or psychosocial well-being at the time of this transition. If confirmed in longitudinal studies, patients and providers will be able to use this knowledge to make more informed decisions on whether and when to initiate chronic renal replacement therapy.

Approximately 500,000 patients in the United States receive chronic renal replacement therapy, most of whom are treated with hemodialysis (33). Prior studies demonstrate that bothersome symptoms and depression are commonly undertreated in this population (13,34,35). It is currently unknown whether similar undertreatment of symptoms exists in patients with CKD. Recent analyses suggest that as many as 20 million Americans have moderate to advanced CKD (20). Analogous to patients with ESRD, the care of those with advanced CKD is focused in large part on the treatment of anemia, bone disease, electrolyte disturbances, and hypertension. Nonetheless, awareness among renal providers of the high burden of symptoms and depression in the large group of patients with CKD is essential for the implementation of appropriate symptom-alleviating and antidepressive therapies. Studies assessing renal and primary provider awareness and treatment of symptoms and depression in this patient group are warranted, as are efforts to examine whether the implementation of treatment translates into improvements in QOL.

It should be noted that depression has been linked with impaired QOL and increased mortality in patients receiving hemodialysis, and may be associated with mortality in CKD as well (18,36). Confirming that depression is associated with adverse outcomes including death in patients with CKD is essential, as are efforts to determine whether pharmacologic and/or nonpharmacologic therapy for depression can attenuate such adverse effects in the broad spectrum of patients with renal disease.

While the SF-36 and PHQ-9 have been used previously in patients with CKD, the DSI has not been tested in this patient group. We found moderate correlation between the DSI and PHQ-9, PCS, and MCS scores. Moreover, the DSI demonstrated strong internal consistency reliability in patients with CKD. These findings suggest that with additional examination of its psychometric characteristics, this questionnaire could be used on a broad basis to assess symptoms in patients with CKD.

It is important to note that patients with ESRD were somewhat more likely to report sleep-related symptoms, muscle cramps, dry mouth, and lightheadedness. Although these differences did not meet the level of statistical significance after adjustment for multiple comparisons, there is biologic plausibility to such differences that warrants future study. Similarly, patients with ESRD reported lower scores on the physical function subscale of the SF-36. Although this did not translate into differences in PCS scores, this finding sheds preliminary light on subdomains of QOL that may vary between these two populations.

There are limitations to this study. First, our patient population was relatively small, which may decrease the generalizability of our findings. Second, we excluded patients with severe comorbidities and those not residing at home. These are exclusion criteria that may have disproportionately affected those with ESRD and rendered our dialysis cohort healthier than dialysis

patients in general. However, it should be noted that the general demographic characteristics of our ESRD cohort were similar to the US ESRD population, while our CKD cohort comprised a larger number of men compared with the overall population of patients with CKD (33). Future studies should compare these health-related domains in a much larger and broader sample of ESRD and CKD patients, including those with serious comorbid illness. Third, the assessment of symptoms in patients on hemodialysis was conducted in patients' homes, rather than during dialysis sessions. It is possible that patients on hemodialysis experience more symptoms at the time of their treatment than in the confines of their home. However, the DSI ascertains symptoms over the past week, making it likely that patients would integrate both dialysis and nondialysis experiences in their responses. Lastly, the cross-sectional nature of our study precluded an assessment of the evolution of symptoms across the spectrum of CKD stages and did not permit us to evaluate the associations of symptoms, depression, and impaired QOL with serious adverse patient outcomes.

CONCLUSION:

In conclusion, we found that patients with ESRD on maintenance dialysis and those with advanced CKD experience a similar overall burden of physical and emotional symptoms and depression and comparably low QOL. Given the substantial and well-recognized decrements in the physical and psychosocial well-being of patients with ESRD receiving chronic renal replacement therapy, our findings suggest that significant attention should be paid to these health-related domains in the large and growing number of patients who suffer from advanced CKD.

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