

Symptom Burden, Depression, and Quality of Life in Chronic and End-Stage Kidney Disease

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Background and objectives: While many patients with end-stage renal disease (ESRD) have impaired physical and psychologic well-being, less is known about these health domains in patients with advanced chronic kidney disease (CKD). The authors sought to compare symptoms, depression, and quality of life in patients with ESRD and those with CKD.

Design, setting, participants, & measurements: Patients with ESRD and subjects with advanced CKD were enrolled. Patients' symptoms, depression, and quality of life were assessed using the Dialysis Symptom Index (DSI), Patient Health Questionnaire-9 (PHQ-9), and Short Form 36 (SF-36), respectively, and these health domains were compared between patient groups.

Results: Ninety patients with ESRD and 87 with CKD were enrolled. There were no differences in the overall number of symptoms or in the total DSI symptom-severity score. Median scores on the PHQ-9 were similar, as was the proportion of patients with PHQ-9 scores >9. SF-36 Physical Component Summary scores were comparable, as were SF-36 Mental Component Summary scores.

Conclusions: The burden of symptoms, prevalence of depression, and low quality of life are comparable in patients with ESRD and advanced CKD. Given the widely recognized impairments in these domains in ESRD, findings of this study underscore the substantial decrements in the physical and psychologic well-being of patients with CKD.

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Patients with end-stage renal disease (ESRD) receiving maintenance dialysis suffer from a multitude of physical and emotional symptoms, exhibit a particularly high prevalence of depression, and experience substantial impairments in quality of life (QOL) (1–11). Symptoms including fatigue, pain, muscle cramps, difficulty with sleep, and sexual dysfunction affect half or more of patients receiving chronic dialysis (12–15). Moreover, as many as 25% of patients suffer from depression, which in longitudinal analysis has been associated with an increased risk of death (16–18). This high burden of symptoms and depression likely contributes to the marked impairments in QOL in this population (19).

While there is little doubt that patients dependent on maintenance dialysis experience reduced physical and psychologic well-being, considerably less is known about these health-related domains in patients with advanced chronic kidney disease (CKD) who do not require chronic renal replacement therapy. Understanding the degree to which symptoms, depression, and impaired QOL affect patients with advanced CKD is important for two reasons. First, while ESRD affects approximately 500,000 patients in the United States, CKD is

present in as many as 20 million Americans and this number is likely to increase with the growing burden of diabetes mellitus and hypertension (20). Understanding the degree to which symptoms and depression affect this large and growing population may help facilitate the implementation of symptom-alleviating therapies that favorably impact QOL. Second, characterizing the burden of symptoms and depression and impairments in QOL in those not yet dependent on renal replacement therapy will improve patient and provider understanding of how such health-related domains may change when advanced CKD progresses to ESRD. We undertook the current study to compare symptom burden, depression, and QOL in patients with ESRD receiving chronic dialysis and patients with advanced CKD not dependent on dialysis.

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 University of Pittsburgh Institutional Review Board, and all participants provided informed consent.

Between April 2004 and November 2006, patients with ESRD on maintenance dialysis and individuals with a history of stage 4 or 5 CKD receiving care at local dialysis units or outpatient nephrology clinics in Pittsburgh, PA, and/or the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh were preliminarily screened. Exclusion criteria included age <18 yr or >90 yr, not residing at home, active

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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 exact 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-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. 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).

Results

Patient Characteristics

A total of 249 patients were screened for study participation, and 185 met eligibility criteria. Of these, eight did not complete the study surveys, resulting in a patient population of 177. Ninety patients (51%) had ESRD; 70 (78%) on hemodialysis and 20 (22%) on peritoneal dialysis. This cohort included all ESRD patients from the larger cohort study as of November 2006. Eighty-seven patients (49%) had CKD. Patients with ESRD were more likely to be African American, 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 (Table 1).

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 de-

Table 1. Patient characteristics

Demographic Variables	ESRD (n = 90)	CKD (n = 87)	P value
Age, mean (SD), y	54 ± 15	51 ± 15	0.2
Men % (n)	57 (51)	66 (57)	0.3
African American % (n)	41 (37)	20 (17)	0.002
Body mass index, mean (SD), kg/m ²	27 ± 5	26 ± 15	0.4
Married (%)	61 (53)	58 (52)	0.7
Educational status			
Less than 9 th grade % (n)	11 (10)	5 (4)	0.1
High school graduate % (n)	31 (28)	28 (24)	0.6
Comorbid conditions			
Diabetes	35 (39)	31 (36)	0.6
Cardiovascular disease	32 (36)	21 (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

^aADL, activities of daily living.

creased 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 3).

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 (Figure 1).

Eleven patients, four in the ESRD group and seven in the CKD group, did not complete the SF-36 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-36 subscales (Figure 2). 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 attenu-

ated 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-36 (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.

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 (2,3,5,7,8,11,12,16,31,32). 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

Table 2. Prevalence of symptoms^a

Symptom	ESRD (n = 90)	CKD (n = 87)	P value ^b
Feeling tired or lack of energy	71 (79)	68 (78)	1.0
Worrying	42 (47)	52 (59)	0.1
Dry skin	42 (47)	46 (53)	0.5
Itching	46 (51)	38 (44)	0.4
Trouble staying asleep	50 (56)	38 (44)	0.1
Trouble falling asleep	54 (60)	38 (44)	0.04
Feeling sad	30 (33)	37 (43)	0.2
Feeling irritable	33 (37)	37 (43)	0.5
Difficulty becoming sexually aroused	42 (47)	35 (40)	0.5
Bone or joint pain	30 (33)	34 (39)	0.4
Muscle cramps	45 (50)	33 (38)	0.1
Feeling anxious	28 (31)	33 (38)	0.3
Decreased interest in sex	39 (43)	31 (36)	0.4
Dry mouth	45 (50)	30 (34)	0.05
Constipation	23 (26)	30 (33)	0.3
Swelling in legs	22 (24)	28 (32)	0.3
Restless legs	35 (39)	28 (32)	0.4
Feeling nervous	26 (29)	27 (31)	0.9
Headache	23 (26)	26 (30)	0.6
Diarrhea	25 (28)	22 (25)	0.7
Decreased appetite	29 (32)	22 (25)	0.3
Cough	28 (31)	21 (24)	0.3
Muscle soreness	30 (33)	21 (24)	0.2
Nausea	24 (27)	21 (24)	0.7
Lightheadedness or dizziness	35 (39)	20 (23)	0.02
Shortness of breath	21 (23)	19 (22)	0.9
Difficulty concentrating	25 (28)	19 (22)	0.4
Numbness or tingling in feet	27 (30)	18 (21)	0.2
Vomiting	12 (13)	10 (11)	0.8
Chest pain	7 (8)	7 (8)	1.0

^aData reported as n (%).

^bAll P values are pre-Bonferroni correction.

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

Table 3. Symptom severity^a

Symptom	ESRD (n = 90)	CKD (n = 87)	P value
Feeling tired or lack of energy	2.0	2.0	0.9
Dry skin	2.0	2.0	0.03
Dry mouth	2.0	2.0	0.2
Itching	2.0	1.0	0.001
Trouble staying asleep	2.0	2.0	0.3
Trouble falling asleep	3.0	2.0	0.4
Muscle cramps	2.0	2.0	0.1
Cough	1.0	1.0	0.6
Bone or joint pain	2.5	3.0	0.7
Diarrhea	2.0	1.0	0.04
Swelling in legs	1.0	2.5	0.08
Worrying	2.0	2.0	0.7
Muscle soreness	2.0	2.0	0.1
Shortness of breath	2.0	1.0	0.3
Difficulty becoming sex aroused	3.0	2.0	0.004
Decreased appetite	2.0	2.0	0.7
Numbness or tingling in feet	2.0	3.0	0.3
Feeling sad	2.0	1.0	0.6
Decreased interest in sex	3.0	2.0	0.009
Lightheadedness or dizziness	1.0	1.0	0.5
Feeling anxious	2.0	2.0	0.5
Nausea	2.0	1.0	0.2
Headache	1.0	1.0	0.3
Restless legs or difficulty keeping legs still	2.0	1.0	0.1
Feeling irritable	1.0	2.0	0.01
Constipation	2.0	1.0	0.7
Difficulty concentrating	2.0	1.0	0.3
Vomiting	3.0	1.5	0.2
Feeling nervous	2.0	1.0	0.5
Chest pain	2.0	2.0	0.6

^aData denote median severity.

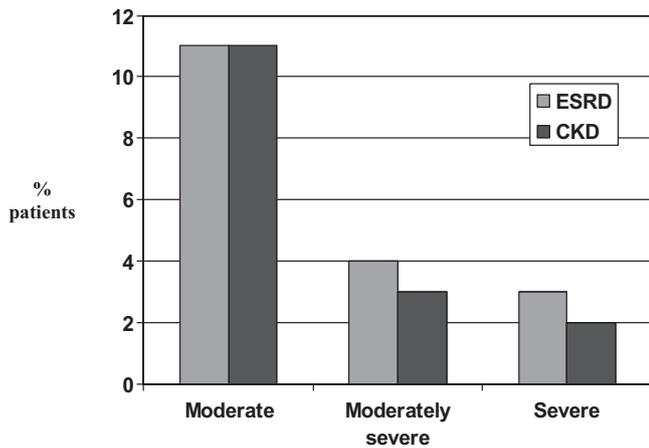
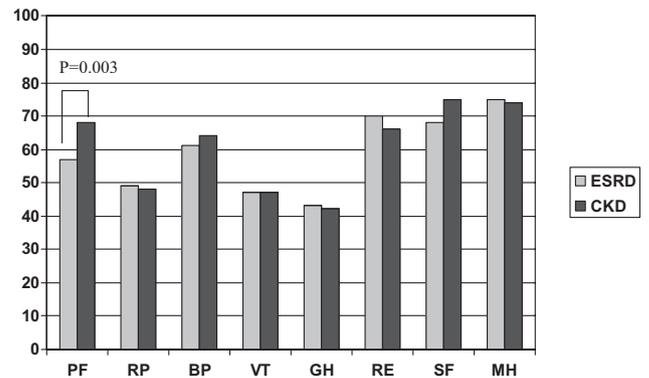


Figure 1. Severity of depressive disorder.^{ab} ^abased on PHQ-9 scores: moderate = 10–14; moderately severe = 15–19; severe = 20–27 ^b p-value = 1.0 for each comparison.



* data presented as mean scores; PF = physical function; RP = role limitations-physical; BP = bodily pain; VT = vitality; GH = general health; RE = role limitations emotional; SF = social function; MH = mental health
[†] differences did not meet the level of statistical significance unless otherwise specified

Figure 2. Quality of life sub-scale scores.^{ab} ^adata presented as mean scores; PF, physical function; RP, role limitations-physical; BP, bodily pain; VT, vitality; GH, general health; RE, role limitations emotional; SF, function; MH, mental health ^bdifferences did not meet the level of statistical significance unless otherwise specified.

Table 4. Correlations of symptoms, depression, and quality of life^a

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

^aData denote correlation coefficient (*r*).

^b*P* < 0.001.

^c*P* < 0.05.

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.

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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Disclosures

None.

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