

Prevalence, Severity, and Importance of Physical and Emotional Symptoms in Chronic Hemodialysis Patients

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The prevalence, severity, and clinical significance of physical and emotional symptoms in patients who are on maintenance hemodialysis remain incompletely characterized. This study sought to assess symptoms and their relationship to quality of life and depression. The recently developed Dialysis Symptom Index was used to assess the presence and the severity of 30 symptoms. The Illness Effects Questionnaire and Beck Depression Inventory were used to evaluate quality of life and depression, respectively. Correlations among symptom burden, symptom severity, quality of life, and depression were assessed using Spearman correlation coefficient. A total of 162 patients from three dialysis units were enrolled. Mean age was 62 y, 48% were black, 62% were men, and 48% had diabetes. The median number of symptoms was 9.0 (interquartile range 6 to 13). Dry skin, fatigue, itching, and bone/joint pain each were reported by $\geq 50\%$ of patients. Seven additional symptoms were reported by $>33\%$ of patients. Sixteen individual symptoms were described as being more than "somewhat bothersome." Overall symptom burden and severity each were correlated directly with impaired quality of life and depression. In multivariable analyses adjusting for demographic and clinical variables including depression, associations between symptoms and quality of life remained robust. Physical and emotional symptoms are prevalent, can be severe, and are correlated directly with impaired quality of life and depression in maintenance hemodialysis patients. Incorporating a standard assessment of symptoms into the care provided to maintenance hemodialysis patients may provide a means to improve quality of life in this patient population.

J Am Soc Nephrol 16: 2487–2494, 2005. doi: 10.1681/ASN.2005020157

Physical and emotional symptoms are among the principal manifestations of chronic illness and play a central role in patients' experience with life-limiting disease. Studies of cancer and HIV populations have shown that symptom burden is substantial and has a strong inverse relationship with health-related quality of life (HRQoL) (1–8). It seems probable that a similar relationship exists in the chronic hemodialysis population. The rigors of thrice-weekly dialysis, metabolic derangements that are common in those with ESRD, and psychosocial and vocational impact of dialysis dependence likely contribute to the many symptoms that are known to

occur in patients who are on hemodialysis and to the decrements in HRQoL observed in this patient population (9–12). For example, fatigue that stems in part from the anemia of renal failure affects as many as 80% of hemodialysis patients and contributes to impaired HRQoL (13–15).

A relatively small number of studies have aimed to quantify and qualify symptom burden in maintenance hemodialysis patients (12,13,16–20). Most previous studies have not examined the broad constellation of symptoms that are known to affect this population and have used general HRQoL questionnaires or *ad hoc* instruments for this purpose, raising the issue of the validity of the assessment. When viewed collectively, the current literature paints an incomplete picture of the prevalence, severity, and clinical significance of symptoms in this patient population. An incomplete understanding of symptom burden by renal providers may lead in turn to the underassessment and undertreatment of bothersome symptoms in this chronically ill patient group.

Received February 10, 2005. Accepted May 8, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

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To address this apparent gap in our understanding of symptoms, we previously used structured qualitative and quantitative research techniques to develop an instrument designed specifically and solely to assess the presence and the severity of the most common and clinically significant physical and emotional symptoms in chronic hemodialysis patients (21). Our study describes the initial clinical application of this new symptom assessment index. The primary aims of this study were to characterize the prevalence and the severity of physical and emotional symptoms in patients who receive maintenance hemodialysis and to investigate their correlation with HRQoL and depression.

Materials and Methods

Patient Population/Demographics

Three dialysis units were selected for patient enrollment to help ensure the recruitment of a demographically diverse study population. These facilities included the VA Pittsburgh Healthcare System (VAPHS) dialysis unit and two nonprofit Dialysis Clinics Inc. units located in the greater Pittsburgh area. The Institutional Review Board of the VAPHS and National Office of Dialysis Clinics Inc. approved all study procedures.

Patient Recruitment and Data Collection

All patients who were receiving thrice-weekly, in-center hemodialysis at the participating dialysis units were approached for enrollment between January and April 2003. For patients who expressed willingness to participate, informed consent was obtained and the CLOX test, a clock drawing task of executive function, was applied to help ensure that patients' cognitive functioning was adequate to understand the nature and the details of the study (22,23). For each patient who gave consent and passed the CLOX test, a trained research assistant administered the study surveys verbally during a routine weekday dialysis session. Interviews lasted approximately 30 min. Basic demographic and clinical data including age, race, gender, marital status, diabetic status, duration of dialysis therapy, history of kidney transplant, educational level, and site of residence were collected from the patient at the time of the patient interview. Medical record reviews were not performed.

Survey Instruments

Symptoms. We used the Dialysis Symptom Index (DSI) to assess physical and emotional symptoms and their severity (21). The DSI contains 30 items, each of which targets a specific physical or emotional symptom. Enrolled patients were asked to report the presence (yes/no) of each symptom at any time during the previous 7 d. Using a five-point Likert scale (1 = "not at all bothersome" to 5 = "bothers very much"), the severity of each symptom that was reported as being present was assessed by asking patients to rate the degree to which the symptom was bothersome. The steps that previously were used to develop the DSI confirm that the index has good test-retest reliability (mean κ 0.52 \pm 0.17) and content validity in the hemodialysis population (21).

HRQoL. To evaluate patients' HRQoL, we used the Illness Effects Questionnaire (IEQ) (11,24,25). The IEQ is a 20-item scale that was designed to assess the degree to which patients' illness interferes with their sense of well-being, referred to as level of distress. Higher scores reflect a more significant level of distress and hence lower HRQoL. Scores >97 indicate extreme distress, 71 to 97 indicate moderate distress, 44 to 70 indicate average distress, and 17 to 43 indicate mild

distress (26). Depression, lower levels of perceived social support, impaired HRQoL measured by other quality-of-life instruments, and mortality all are correlated with higher IEQ scores, supporting its validity in the hemodialysis population (10,11,26–28). The reliability of the questionnaire also has been established (10,27–29). We chose the IEQ because of its sound psychometric properties, relationship with important outcomes in dialysis patients, and ease of administration. Moreover, because one of our primary aims was to assess the correlation between symptoms and HRQoL, we chose the IEQ, which contains only a minimal number of items on specific symptoms, to avoid confounding this assessment.

Depression. We used the Beck Depression Inventory (BDI) to assess the presence and the degree of depression. The BDI is a 21-item, patient-rated scale that has been used extensively in the dialysis population (30–32). Higher scores correlate with more severe depression. Depression was defined as a BDI score of >15, which corresponds to moderate to severe depression. The BDI has been used in several studies of patients with ESRD and has been shown to correlate highly with diagnostic criteria of depression, quality of life, functional status, severity of illness, and mortality over time (27,28,32,33).

Statistical Analyses

We report the overall symptom burden, which represents the total number of symptoms described by each patient. To generate an overall symptom severity score for each patient, we summed the individual severity scores for all of the symptoms that were reported on the DSI. Symptoms that were not reported as being present were assigned a severity score of zero. Thus, the minimum possible overall severity score was zero when none of the 30 symptoms were reported, and the maximum potential overall severity score was 150 when all 30 symptoms were reported and rated as "bothers very much" (Likert-scale severity score of 5). Scores on the IEQ and the BDI were generated by summing the responses to individual items, as is standard practice for these measures. With the skewed distributions observed for the scores on the DSI, IEQ, and BDI, results are expressed as the median \pm interquartile range (IQR). Unadjusted correlations among overall symptom burden, overall symptom severity, HRQoL, and depression were assessed using Spearman correlation coefficient. Similar methods were used to examine associations between the severity of individual symptoms and HRQoL and depression.

After these analyses, we performed multivariable linear regression to assess the associations of overall symptom burden and overall symptom severity with HRQoL and depression adjusting for baseline demographic and clinical covariates. IEQ and BDI scores were log-transformed for these regression analyses to meet the assumption of normality. The results are expressed as effect sizes (described as β coefficients), which represent the observed effect of 1 SD change in these variables on the log of IEQ and BDI scores. To investigate further the effect of depression on the relationship between symptoms and quality of life, we evaluated whether there was an interaction between symptom burden and depression on the log of IEQ. As this interaction term was found to be significant, we stratified patients by depression and performed similar multivariable analyses.

The Mann-Whitney *U* test was used to compare overall symptom burden, overall symptom severity, and individual symptom severity by gender, race, diabetic status, and history of renal transplant and to evaluate the relationships between the prevalence of individual symptoms and HRQoL and depression. χ^2 analyses were used to examine unadjusted differences in the prevalence of individual symptoms by gender, race, diabetic status, and history of renal transplant using the Bonferroni correction for multiple comparisons and a $P = 0.001$ for

these analyses. A two-sided $P < 0.05$ was considered statistically significant for all other analyses.

Finally, a principal components factor analysis with varimax rotation was performed on symptoms that were reported on the DSI to ascertain whether there were underlying groups of symptoms that appeared together in patients. All statistical analyses were completed using the NCSS 2001 statistical package.

Results

Study Population

A total of 220 patients were approached for participation. A total of 162 (74%) enrolled, and all completed the study questionnaires. The 26% of patients who were not enrolled were composed almost entirely of patients who elected not to participate. Reasons for refusal to participate were not elicited. Of the 162 enrolled patients, 21 (13%) were from the VAPHS dialysis unit and 141 (87%) were from the Dialysis Clinic Inc. units. A summary of patient demographics is presented in Table 1.

DSI, IEQ, and BDI Results

The median number of symptoms was 9.0 (IQR 6 to 13; Figure 1). As shown in Table 2, four symptoms were reported by at least 50% of patients, including dry skin (72%), feeling tired or lack of energy (69%), itching (54%), and bone/joint pain (50%). Mean severity scores for individual symptoms that were reported as being present were highest for bone or joint pain (3.6), chest pain (3.6), vomiting (3.5), difficulty becoming sexually aroused (3.4), and muscle cramps (3.3). The median overall symptom severity score for all 162 participants was 25.0 (IQR 14 to 42; Figure 2). The factor analysis failed to converge, indicating that, at least in this cohort of patients, there does not seem to be a consistent set(s) of symptoms that appear as a group.

The median score on the IEQ was 47 (IQR 29 to 68). Thirteen percent of patients had minimal distress, 29% had mild distress, 36% reported average distress, 14% described moderate distress, and 8% experienced extreme distress. The median BDI score was 10 (IQR 5 to 16). Overall, 25.9% of patients experienced moderate to severe depression.

Table 1. Demographic and clinical characteristics of study patients

No. of patients	162
Black (%)	48
White (%)	51
Asian (%)	1
Male (%)	62
Mean age (yr)	61.9
Diabetic (%)	48
Previous renal transplant (%)	9.9
Mean duration of dialysis (yr)	4 ± 4.1
Marital status (% married)	59
Education (% high school or less)	56
Residence (% living independently)	91

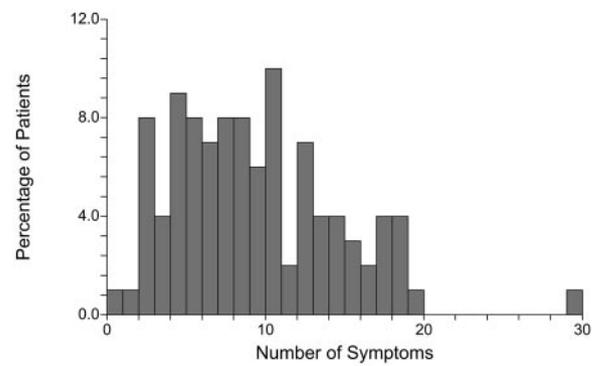


Figure 1. Overall burden of symptoms. The width of each bar represents one symptom.

Correlations of Symptoms, HRQoL, and Depression

Increased overall symptom burden and overall symptom severity each were independently associated with higher IEQ score ($r = 0.60$ and 0.61 , respectively; $P < 0.00001$) and with BDI-rated depressive affect ($r = 0.62$ and $r = 0.64$, respectively; $P < 0.00001$). Both symptom burden and severity were associated with log of IEQ score adjusting for depression. After these analyses were stratified by depression, both symptom burden and severity remained highly associated with log of IEQ score, with greater effect sizes observed in patients without depression. These results along with the associations of patient variables with log of IEQ score are displayed in Table 3. In the multivariable model, the R^2 values for symptom burden and depression were 0.05 and 0.12, respectively.

Significant and independent associations were found between 21 individual symptoms and higher IEQ scores, the strongest of which were for nausea, feeling tired or lack of energy, worrying, feeling irritable, and feeling sad ($P < 0.0001$). Nineteen symptoms were also independently associated with BDI-rated depressive affect ($P < 0.01$). Among the four most commonly reported symptoms, bone/joint pain and feeling tired or lack of energy had statistically significant associations with both increased IEQ score and BDI-rated depressive affect. The median number of symptoms was notably higher in patients with BDI-rated depression than those without (13 versus eight; $P < 0.0001$) as was median overall symptom severity score (42 versus 22; $P < 0.0001$).

Ethnic, Gender, and Clinical Differences

No differences were observed in overall symptom burden between white and black patients (median number of symptoms 9.0 versus 8.5; $P = 0.74$). White patients seemed to report trouble staying asleep more frequently than did black patients ($\chi^2 = 6.8$, $P = 0.01$), whereas cough and decreased appetite were more commonly described among black patients ($\chi^2 = 4.5$, $P = 0.03$, and $\chi^2 = 5.3$, $P < 0.02$), although these differences failed to meet statistical significance. Although overall symptom severity scores did not differ significantly by racial group (median severity 24 in whites versus 25 in blacks; $P = 0.94$), there was a trend for black patients to report greater difficulty

Table 2. Prevalence and severity of individual symptoms

Symptom	Prevalence (%) ^a	Mean Severity ^b
Constipation	21	2.85
Nausea	26	3.16
Vomiting	11	3.5
Diarrhea	17	3.21
Decreased appetite	29	2.52
Muscle cramps	43	3.31
Swelling in legs	26	2.25
Shortness of breath	19	2.90
Lightheadedness or dizziness	31	2.98
Restless legs or difficulty keeping legs still	29	2.79
Numbness or tingling in feet	36	2.64
Feeling tired or lack of energy	69	3.12
Cough	29	2.60
Dry mouth	49	2.97
Bone or joint pain	50	3.61
Chest pain	10	3.63
Headache	19	3.03
Muscle soreness	28	3.14
Difficulty concentrating	14	2.77
Dry skin	72	2.81
Itching	54	3.24
Worrying	28	3.09
Feeling nervous	19	2.90
Trouble falling asleep	44	3.35
Trouble staying asleep	43	3.10
Feeling irritable	23	2.81
Feeling sad	20	2.97
Feeling anxious	31	3.04
Decreased interest in sex	36	3.12
Difficulty becoming sexually aroused	34	3.44

^aPercentage of patients who reported the symptom.

^bBased on the five-point Likert scale: 1 = “not at all bothersome” to 5 = “bothers very much.”

in becoming sexually aroused (median severity 3.0 *versus* 2.0; $P = 0.002$).

There was a trend toward greater overall symptom burden in women (median number of symptoms 10.5 *versus* 8.0; $P = 0.07$). Overall symptom severity was greater in women (median severity 29 *versus* 23; $P = 0.01$), and there was a trend toward more severe numbness or tingling in feet in women (median severity 2.0 *versus* 1.0; $P = 0.01$), even after controlling for diabetes.

No differences were observed in the overall burden or overall severity of symptoms between patients with and without diabetes (median number of symptoms 9.0 *versus* 9.0, $P = 0.26$; median severity 23 *versus* 27, $P = 0.38$). Patients with a previous failed renal transplant did not report greater overall symptom burden (median number of symptoms 10.0 *versus* 9.0; $P = 0.6$)

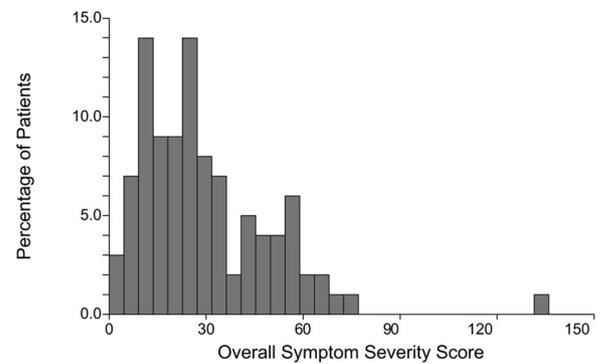


Figure 2. Overall symptom severity scores. The width of each bar represents five points.

or a higher level of overall symptom severity (median severity 26.5 *versus* 24.5; $P = 0.4$). *Post hoc* analyses failed to reveal any associations between older age and symptom burden or severity or between previous time on dialysis and symptom burden or severity ($P > 0.10$).

Discussion

This study demonstrated that physical and emotional symptoms are prevalent and can be severe in patients who receive maintenance hemodialysis. Our patients reported an average of nine symptoms, which is comparable to the number of symptoms seen in AIDS and cancer populations when symptom assessment instruments similar in content and length to the DSI have been used in these patient groups (2,8). Consistent with the results of previous studies in dialysis patients, feeling tired/lack of energy and itching were among the most frequently reported symptoms in our population (13,17). However, several symptoms that have not been described as comprehensively in previous investigations were reported commonly in this study, including bone/joint pain, which was present in half of our study patients, and numbness or tingling in feet, trouble sleeping, decreased sexual desire and arousal, and dry mouth, which all were seen in more than one third of our patients.

Several symptoms were described as being severe. Mean severity scores for 16 individual symptoms corresponded to a severity rating of more than “somewhat bothersome.” Many of the most prevalent symptoms were also among the most severe. Pain, difficulty with sleep, and difficulty with sex are known to occur in those with ESRD, yet the pervasiveness and the severity of such symptoms are particularly noteworthy (12,34–36). Kimmel *et al.* (12) demonstrated that among hemodialysis patients who described the presence of symptoms on the McGill Quality of Life Scale, nearly 50% reported experiencing pain. Our results reinforce this finding and demonstrate that pain can be severe. Moreover, when symptoms that represent various manifestations of pain such as muscle cramps, numbness, muscle soreness, headache, and chest pain are considered collectively, >85% of our patients experienced at least one form of pain. Unfortunately, our study did not evaluate provider assessment or treatment of symptoms. However, a recent study by Davison (37) found not only that pain was

Table 3. Multivariable models of overall symptom burden and severity with log of IEQ score^a

Variable	Overall β	β for Patients with Depression	β for Patients without Depression
Model 1: Overall symptom burden			
symptom burden	0.2 ^b	0.15 ^c	0.2 ^b
age	−0.09	−0.03	−0.12
gender	−0.001	−0.03	−0.1
diabetes	0.11	−0.15	0.2
BDI depression	0.34 ^b	—	—
race	−0.16	0.02	−0.2
transplant	0.27	0.16	0.24
educational level	0.05	0.07	0.06
Model 2: Overall symptom severity			
symptom severity	0.15 ^c	0.19 ^c	0.2 ^c
age	−0.07	−0.1	−0.12
gender	−0.01	−0.12	−0.1
diabetes	0.12	−0.21	0.2
BDI depression	0.34 ^b	—	—
race	−0.17	−0.21	−0.2
transplant	0.27	0.23	0.24
educational level	0.05	0.07	0.05

^a β represents effect size per SD for continuous variables. BDI, Beck Depression Inventory.

^b $P < 0.001$.

^c $P < 0.05$.

present in 50% of hemodialysis patients but also that 35% of patients with pain were receiving no pharmacologic therapy, and 75% of patients described their treatment of this symptom as inadequate. Efforts to improve the assessment and treatment of pain may be crucial to efforts aimed at improving the quality of life of this patient population.

Overall symptom burden and severity both were associated with impaired HRQoL and depression. Although our study methods do not allow for a determination of cause, these findings highlight the potential interplay of symptoms and these two important patient-related health domains, each of which has been linked to increased morbidity and mortality in patients on dialysis. *Post hoc* analysis of the correlation between BDI scores and a measure of symptom burden that excluded depression-related items on the DSI including sadness, anxiety, and irritability revealed a persistent and strong association between these two domains, reinforcing the validity of this relationship (data not shown). We also found strong relationships between both overall burden and overall severity of symptoms and HRQoL after adjusting for depression and after stratifying the analyses by the presence of depression. In 1999, Merkus *et al.* (13) found that physical symptom burden assessed by a nine-item index contributed substantially to the decrements in HRQoL observed in a cohort of 120 Dutch hemodialysis patients. Similarly, Kimmel *et al.* (12) demonstrated inverse relationships between symptom burden and both HRQoL and patient satisfaction with life. Our results reinforce these findings and suggest that the relationship between symptoms and HRQoL is independent of the effect of depression. Efforts to elucidate the effect of symptom-directed therapy on

HRQoL and to explore the association between symptoms and outcomes such as health resource utilization, hospitalization, and mortality are clearly needed.

This study also exposed the potential clinical utility of the DSI. Standardizing the assessment of symptoms with a validated instrument such as the DSI could potentially facilitate the diagnosis and treatment of common problems such as erectile dysfunction, sleep-disordered breathing, peripheral neuropathy, renal osteodystrophy, and even depression by linking specific symptoms with associated clinical disorders. For example, difficulty with sleep and difficulty with sex may be direct manifestations of underlying pathophysiologic processes such as sleep apnea or erectile dysfunction that are relatively easily diagnosed and may be amenable to medical therapy (38). In fact, erectile dysfunction has been shown to occur in as many as 80% of male dialysis patients, and a series of studies have established the therapeutic efficacy of sildenafil in this patient population (39,40). Efforts to link specific symptoms such as difficulty becoming sexually aroused with disease processes such as erectile dysfunction may greatly assist in attempts to implement targeted interventions to improve HRQoL. Future studies should examine whether standardizing the assessment of symptoms in the clinical arena with the DSI could help providers identify and treat specific disease processes.

It is interesting that we failed to demonstrate that age, ethnicity, diabetic status, time on dialysis, or the presence of a failed transplant affected symptom burden or severity. We did discover that women experience a greater number of symptoms than men. Previous studies have suggested that time on dialysis, age, and ethnicity may influence symptom burden and that

gender may not affect the reporting of specific symptoms such as pain (12,37,41,42). Our findings did not confirm these previous observations. On the basis of our results and contrary to what many clinicians may perceive, diabetic status and a history of failed transplant may not increase symptom burden. Although sampling error may explain these findings, future investigation to clarify the impact of demographic and clinical characteristics including comorbid illness on symptoms may help providers identify the patients who are most likely to be symptomatic.

There are several limitations to our study. First and foremost, we did not collect data on dialysis adequacy, markers of nutritional status such as serum albumin, metabolic parameters such as hemoglobin level, or overall level of comorbid illness. It is possible that our patient population was not receiving adequate doses of renal replacement therapy, had disproportionately low serum albumin and/or hemoglobin concentrations, or experienced a substantial burden of comorbid illness, which would limit the generalizability of our findings. Such phenomena might have increased the number and the severity of reported symptoms. We should note that scores on the IEQ and the BDI in our patients were lower than those seen in previous studies of hemodialysis patients (27,28,43,44). Although selection bias could explain these findings, these observations suggest that our population, collectively, might have been particularly well adjusted to life on dialysis or psychologically healthy. In addition, on the basis of previously published comorbidity data using the Index of Coexistent Diseases, the comorbid illness burden was no different in the two non-VA dialysis facilities from which the large majority of our patients were recruited than in a national sample of patients from the same corporate dialysis chain (45). If our population was in fact relatively healthy, then our results in regard to symptoms would actually underestimate the burden and the severity of symptoms in the general dialysis population. Nonetheless, future studies need to examine the impact of comorbid conditions and metabolic- and dialysis-related treatment parameters on symptom burden. Second, reporting bias may have influenced our results as patients may have viewed participation in the study as an opportunity to receive additional therapy by overreporting the presence and the severity of specific symptoms. We attempted to minimize reporting bias by instructing patients that no data from study surveys would be communicated to their renal providers. Conversely, patients may have underreported potentially embarrassing symptoms such as erectile dysfunction in the context of face-to-face interviews. Future studies should examine the impact of mode of survey administration on symptom reporting as this variable was found to affect reporting of HRQoL in the HEMO study (46). Third, we used the IEQ to measure HRQoL. The IEQ lacks an item on overall HRQoL and has not been as widely used as other HRQoL questionnaires such as the Kidney Disease Quality of Life Questionnaire. However, it is a well-validated measure of HRQoL in the hemodialysis population. Fourth, the DSI was developed and validated in an American and largely urban dialysis population. Its performance characteristics may be different in people of other ethnicities and demographic backgrounds. Last, this was a single geographic

area study, which limits the generalizability of the findings. However, the demographic characteristics of our study patients were generally comparable to the broader American dialysis population.

In summary, we have described the preliminary application of the DSI to a demographically diverse cohort of hemodialysis patients. Physical and emotional symptoms are prevalent and can be severe in this patient population. Furthermore, symptom burden and severity are strongly associated with impaired HRQoL independent of the impact of depression on HRQoL, highlighting the potential role of symptoms in mediating the decrements in quality of life commonly observed in maintenance hemodialysis patients. The DSI is a comprehensive, validated, and concise questionnaire that provides important data that may not be captured adequately by face-to-face patient-provider interactions or by broad HRQoL instruments. Moreover, the DSI is unique in that it focuses solely on symptoms. Efforts to standardize the assessment of symptoms in hemodialysis patients using a validated questionnaire such as the DSI may provide an important opportunity to have a favorable impact on the disease experience of this chronically ill patient group.

Acknowledgments

S.D.W. and L.F.F. were supported by a grant from the Center for Health Equity Research and Promotion at the VA Pittsburgh Healthcare System. S.D.W. was also supported by a VA Health Services Research and Development Career Development Award and by National Institutes of Health Grant T32HL07820-05. L.F.F. was also supported by an Advanced VA Research Career Development Award. R.M.A. was supported by the Project on Death in America Faculty Scholars Program, the Greenwall Foundation, Ladies Hospital Aid Society of Western Pennsylvania, the International Union Against Cancer Yamagiwa-Yoshida Memorial International Cancer Study Grant, and the LAS Trust Foundation.

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