Original Article

Comparison of Fatigue, Pain, and Depression in Patients With Advanced Kidney Disease and Cancer—Symptom Burden and Clusters

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Abstract

Context. Although symptom clusters have been studied in the context of cancer, few data exist in chronic and end-stage kidney disease (CKD/ESKD) patients.

Objectives. The objectives of this study were to 1) characterize and compare symptom cluster phenotypes in patients with advanced CKD, ESKD, and cancer and 2) explore predictors of symptom clusters.

Methods. We conducted secondary data analysis of three prospective studies in which pain, depression, and fatigue were assessed in patients with Stage 4–5 CKD, ESKD, and gastrointestinal cancer. Tetrachoric correlations between these symptoms were quantified, and partitioning around medoids algorithm was used for symptom cluster analysis.

Results. In the 82 CKD, 149 ESKD, and 606 cancer patients, no differences in the average fatigue ($P = 0.17$) or pain levels ($P = 0.21$) were observed. Over 80% of patients in each group had at least one symptom. Moderate or severe depressive symptoms were more common in patients with cancer (31% vs. 19% in ESKD vs. 9% in CKD; $P < 0.001$). Mild-moderate correlations were observed between the three symptoms in ESKD and cancer patients. Three distinct clusters were observed in each group. In ESKD, the HIGH cluster (with high probability of pain, depression, and fatigue) had higher body mass index ($P < 0.001$) and antidepressant use ($P = 0.01$). In cancer patients, the HIGH cluster patients were more likely to be female ($P = 0.04$), use antidepressants ($P = 0.04$), and have lower serum albumin ($P < 0.001$) and hemoglobin ($P = 0.03$) compared to the other two clusters.

Conclusion. Although the burden of fatigue, pain, and depressive symptoms for CKD and ESKD patients is similar to patients with gastrointestinal cancer, symptom cluster phenotypes differed between the groups as did the predictors of symptom clusters. J Pain Symptom Manage 2019;57:566–575.

Key Words

Symptom clusters, fatigue, pain, depression, ESKD and cancer

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Introduction

Patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) experience high mortality, substantial symptom burdens, and poor quality of life (QoL).[1] The symptom burden in patients with ESKD may even be similar to that of advanced cancer patients.[2,3] Yet, symptom recognition and management in CKD and ESRD by nephrology providers remains suboptimal.[4]

For cancer patients, pain, fatigue, and depression were the most common and debilitating symptoms identified in the National Institute of Health State-of-Science Consensus statement.[5] This led the Institute of Medicine and several national oncological societies (e.g., American Society for Clinical Oncology, American College of Surgeons) to recommend screening and treatment guidelines for these symptoms in cancer patients.[6] Only recently, the Kidney Disease Improving Global Outcomes Controversies Conference on Supportive Care in 2015 advocated for integration of symptom assessment and management in routine CKD care.[7]

Fatigue is the most common symptom reported by patients with advanced CKD/ESKD and cancer, with a reported prevalence of up to 100%.[2,8] Fatigue substantially impacts QoL in both patient populations.[8,9] Fatigue is one of the most highly prioritized symptoms for which treatment is desired among kidney disease patients and clinicians.[10,11] However, its treatment in CKD/ESKD remains challenging due to the patient-specific manifestations, multifactorial etiology, and incompletely understood pathophysiology.[8,12] Among cancer patients, symptom cluster research has identified that fatigue often coexists with other symptoms such as pain, emotional distress, sleep dysfunction, and depression.[13] This has led to the development of cancer-related fatigue management guidelines by the National Comprehensive Cancer Network and the Fatigue Coalition that emphasize a shift of focus from treating fatigue alone to addressing multiple symptoms.[14] We hypothesized that symptom clusters also exist among kidney disease patients, given the high burden of pain and depressive symptoms in this population.[1] Symptom cluster research in nephrology has been limited to a handful of studies that have been focused on ESKD patients and mostly included non-US cohorts.[15–18] Characterizing symptom clusters in CKD and ESKD patients is a key step to understanding underlying mechanisms and accelerating the development of targeted symptom interventions, as recommended by the National Institute of Health (NIH) 2017 workshop on "Advancing Symptom Science through Symptom Cluster Research.".[19] In addition, comparing symptom cluster phenotypes and their predictors across chronic conditions may help identify potentially modifiable risk factors (such as hemoglobin, albumin, cytokines, and hormonal mediators) and inform the development of specific, individualized interventions to improve patient-centered outcomes.[19]

The aim of our study was to characterize and compare symptoms (fatigue, pain, and depressive symptoms) and symptom cluster phenotypes among advanced CKD, ESKD, and advanced gastrointestinal (GI) cancer patients (i.e., a group of malignancies associated with very high symptom burden and poor QoL).[20] We will also examine potential demographic and disease-specific predictors of symptom clusters among the three patient groups.

Methods

Study Population

The present study is a post hoc analysis of data collected as part of prospective studies of kidney disease and cancer patients. As part of a larger, prospective cohort study of sleep and QoL in adult, English-speaking patients with CKD Stage 4–5 or ESKD (K23DK66006; R01DK77785), we assessed patients' fatigue, pain, and depressive symptoms.[21] Between March 2004 and December 2008, patients were approached during routine nephrology clinic visits, dialysis clinic visits, or initial kidney transplant evaluations at the University of Pittsburgh. This cohort also included patients enrolled in an ancillary Frequent Hemodialysis Network Trials study (FHN; NCT00264758). Exclusions included age less than 18 years and presence of severe active medical or psychiatric illness as has been previously described. Because the main focus of our present study was fatigue, only those patients who completed the fatigue questionnaire (see below) at baseline were included (82 CKD Stage 4–5 and 149 ESKD).

As part of prospective research in patients with GI cancer (R21CA127046; R01CA176809), patients with hepatocellular or cholangiocarcinoma, pancreatic, or other solid tumors that had metastasized to the liver were recruited from the University of Pittsburgh's Liver Cancer Center between April 2008 and April 2013.[22] Eligibility criteria included biopsy-proven cancer, age ≥ 21 years, and English fluency. Patients were excluded for active suicidal or homicidal ideation, hallucinations, delusions, or history of a liver transplantation. Similar to the kidney disease cohort, only those patients who completed the fatigue questionnaire at baseline were included in this study (606 cancer patients). The University of Pittsburgh Institutional Review Board approved both studies, and all participants provided written, informed consent.

Sociodemographic, Disease, and Treatment-Specific Factors

Sociodemographic data were collected through self-report. Disease-specific and treatment-related information, including physician-diagnosed medical

conditions, antidepressant, analgesic, and benzodiazepine use, blood pressure, body mass index (BMI), and laboratory values, was collected from the patients' medical record. Because the kidney disease cohort parent study required polysomnography during a home visit, questionnaires were administered in patients' homes. For cancer patients, QoL and symptom questionnaires were administered at diagnosis before initiating treatment through phone interviews.

Fatigue

In both kidney and GI cancer cohorts, the Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scale was used to assess fatigue. The FACIT-F is a 13-item questionnaire that uses a five-point Likert scale ranging from "not at all" to "very much" to measure physical fatigue (e.g., I feel tired), functional fatigue (e.g., trouble finishing things), emotional fatigue (e.g., frustration), and social consequences of fatigue (e.g., limits social activity) over the prior week.[23] Scores range from 0 to 52 with higher scores indicating lower levels of fatigue. The scale has excellent internal consistency and test-retest reliability and has been validated in many populations, including cancer and kidney disease patients.[24,25] We divided the subjects into two groups (FACIT-F scores ≤44 [significant level of fatigue] vs. >44 [nonfatigued]) based on the mean score among the U.S. general population (mean, SD: 43.6, 9.4).[23]

Depressive Symptoms

The Patient Health Questionnaire (PHQ)-9 or the Beck Depression Inventory (BDI) was used to assess depressive symptoms in the CKD/ESKD cohort (BDI in the subset of patients enrolled in the FHN ancillary),[26] and the Center for Epidemiologic Studies Depression Scale (CES-D)[27] was used in the cancer cohort. The PHQ-9, BDI, and CES-D are nine-item, 21-item, and 20-item questionnaires, respectively, which assess depressive symptoms over the prior two weeks with higher scores indicating a greater depressive symptom burden. For the PHQ-9, scores ≥10 are consistent with moderate-to-severe depressive symptoms and are sensitive and specific for a diagnosis of depressive disorder in patients receiving chronic hemodialysis.[28] For the BDI, scores ≥16 are consistent with moderate-to-severe depression in advanced CKD/ESKD.[28] The clinical cutoffs for both these questionnaires are comparable and have been validated in kidney disease patients against the gold standard measure of psychologist-administered Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders.[28] For cancer patients, the CES-D has demonstrated adequate construct validity and reliability for diagnosing depressive symptoms.[27] A CES-D cutoff of ≥22 has been shown to be associated with a diagnosis of depression and comparable to the BDI and PHQ cutoffs for moderate-to-severe depressive symptoms.[29]

Pain

In the kidney disease cohort, pain was assessed using single item from the bodily pain subscale of the SF-36 questionnaire that measures the magnitude of pain ("How much bodily pain have you had during the last four weeks?").[30] Responses range from "none"/"not at all" to "very severe"/"extremely" with subscale scores ranging from 0 (greatest pain) to 100 (least pain). We categorized patients as having clinically significant pain if they had a score ≤50 on this single pain item to be consistent with BP cutoffs (as below). The bodily pain subscale has been used widely in CKD/ESKD and has excellent reliability.[31] The reported average SF-36 bodily pain score for the US general population is 50.1 ± 16.3.[32] In the cancer cohort, pain was measured using the Brief Pain Inventory. The Brief Pain Inventory measures both the intensity of pain (sensory dimension) and interference of pain in the patient's life (reactive dimension). The average intensity of pain was assessed on a 0 (no pain) to 10 (greatest pain) Likert scale, and those with score of ≥5 were classified as having clinically significant pain using the cutoff for at least moderate level of pain.[33]

Statistical Analysis

Baseline demographics, comorbidities, laboratory values, and symptom measures were described using means and SDs for continuous variables and percentages for categorical variables. Univariate comparisons between cohort groups in terms of the three symptoms and baseline demographic, clinical, and laboratory variables were assessed using analysis of variance or Kruskal-Wallis test for continuous variables and chi-square or Fisher exact test for categorical variables. Correlations between fatigue, pain, and depression binary variables were quantified using tetrachoric correlation coefficient.

To determine symptom cluster phenotypes within each cohort, patients were clustered based on the fatigue, pain, and depression. Binary symptom variables, dichotomized using standard clinical cut points as described earlier, were used to account for the different measurement scales used across the cohorts. Partitioning around medoids was used as clustering algorithm.[34] The idea behind partitioning around medoids is similar to k-means with the added benefit that an actual observation is used as exemplar (medoid) of each cluster. The observations were grouped together to form a cluster based on how similar they are. We used Gower distance to quantify the dissimilarity between observations given that the symptom

variables are of nominal type. Gower distance is a widely used distance metric applicable for mixed data type (continuous or categorical). The number of clusters was chosen graphically based on the number that maximizes the average silhouette width. The silhouette measures how similar an observation is to its own cluster relative to other clusters, with values closer to +1 indicating tighter grouping. Univariate association of baseline variables with symptom clusters was explored using analysis of variance or Kruskal-Wallis test for continuous variables and chi-square or Fisher exact test for categorical variables.

To assess the robustness of our findings after accounting for differences in patient characteristics across the disease groups, we repeated the analyses after matching the CKD patients to the ESRD and cancer patients. Considering the small sample size in the CKD group, variables used for matching were limited to a few variables including age, race, tobacco use, and alcohol use. These variables were chosen as they likely precede the disease and were found to differ in the unmatched sample. Matching was performed via the optimal matching method within a recommended caliper of 0.25 using the propensity score as balancing score. Matching was performed pairwise where CKD patients were matched to ESRD and subsequently to cancer patients.

For all analyses, P values < 0.05 were considered significant. Analyses were performed using R (version 3.5) using the packages dpylr for data management, compareGroups for descriptive tables, ggplot2 for graphics, polycor for tetrachoric correlations, cluster for cluster analyses,[35] and MatchIt for matching.

Results

Baseline Characteristics

For this study, 82 advanced CKD (not on dialysis) patients, 149 dialysis-dependent ESKD patients, and 606 patients with GI cancer were included. Table 1 shows the baseline patient characteristics. Patients with kidney disease were younger, had higher proportion of blacks, and had higher comorbidity burden of diabetes, hypertension, and cardiovascular disease as compared to the cancer group ($P < 0.001$ for all). Antidepressant use was similar in the three groups ($P = 0.29$). Pain medication use was similar in all three groups ($P = 0.15$), but among those reporting significant levels of pain, CKD patients were significantly more likely to be on pain medications than ESKD or cancer groups ($P = 0.01$). CKD and ESKD patients had lower hemoglobin but higher serum albumin than the cancer group ($P < 0.001$ and $P = 0.003$, respectively).

Table 1
Baseline Characteristics

Variable[a]	CKD ($N = 82$), n (%) or Mean (SD)	ESKD ($N = 149$), n (%) or Mean (SD)	Cancer ($N = 606$), n (%) or Mean (SD)	P-value
Age (yrs)	52.1 (14.5)	56.3 (14.7)	61.7 (10.9)	<0.001
Male	57 (69.5%)	93 (62.4%)	392 (64.7%)	0.56
Race				<0.001
White	58 (70.7%)	92 (61.7%)	545 (89.9%)	
Black	19 (23.2%)	55 (36.9%)	49 (8.1%)	
Other	5 (6.1%)	2 (1.3%)	11 (1.8%)	
Education (high school or greater)	75 (91.5%)	126 (84.6%)	493 (81.4%)	0.01
Married	49 (59.8%)	73 (49%)	372 (61.4%)	<0.001
Diabetes	26 (31.7%)	62 (41.6%)	130 (21.5%)	<0.001
Hypertension	72 (87.8%)	108 (72.5%)	278 (45.9%)	<0.001
Cardiovascular disease	19 (23.2%)	46 (30.9%)	91 (15.0%)	<0.001
Tobacco use (ever)	39 (47.6%)	84 (56.4%)	209 (34.5%)	<0.001
Alcohol use	27 (32.9%)	28 (18.8%)	89 (14.7%)	<0.001
Dialysis vintage (months)	n/a	13 (6, 37)[b]	n/a	—
Antidepressant use	12 (14.6%)	21 (14.1%)	114 (18.8%)	0.29
Antidepressant use among those with depressive symptoms	2 (28.6%)	8 (29.6%)	47 (26.9%)	0.94
Benzodiazepine use	5 (6.1%)	8 (5.6%)	34 (5.6%)	0.98
Pain medication use	38 (50.0%)	42 (35.9%)	245 (41.8%)	0.15
Pain medication use among those reporting significant pain	16 (80.0%)	18 (48.6%)	60 (44.1%)	0.01
Body mass index (BMI; kg/m^2)	27.6 (5.4)	27.4 (5.9)	28.5 (6.8)	0.16
Albumin (g/dL)	3.8 (0.6)	3.7 (0.5)	3.6 (0.6)	0.003
Serum Cr (mg/dL)	4 (1.5)	8.0 (3.3)	1.0 (0.6)	<0.001
eGFR (mL/minute/1.73m^2)	18.8 (6.8)	n/a	>60	—
Hemoglobin (g/dL)	11.7 (1.8)	11.7 (1.9)	12.9 (2.2)	<0.001

CKD = chronic kidney disease; ESKD = end-stage kidney disease; BMI = body mass index; eGFR = estimated glomerular filtration rate.
[a]Race missing for one patient; education status missing for 68 patients; marital status missing for seven patients; diabetes missing for 20 patients; HTN missing for 35 patients; cardiovascular disease missing for 18 patients; tobacco use missing for 68 patients; alcohol missing for 47 patients; antidepressant use missing for four patients; benzodiazepine missing for three patients; pain meds missing for 58 patients.
[b]Median (25th percentile, 75th percentile).

For the cancer patients, the most common etiologies for cancer were hepatitis C (29%), cryptogenic (29%), alcohol alone or in addition to other causes (25%), and nonalcoholic hepatic steatosis (10%). Cirrhosis was present in 42% of the patients, and 17% were noted to have vascular invasion. One-third of the patients had one lesion, 23% had more than five lesions, and average tumor size was 3.9 cm.

Symptom Burden

Table 2 shows the prevalence of patient-reported fatigue, pain, and depressive symptoms in the CKD, ESKD, and cancer patients. Fatigue was highly prevalent, and more than 75% of patients in each group reported having a significant level of fatigue. Surprisingly, the prevalence of fatigue was similar across the three groups ($P = 0.97$). Moreover, the severity of fatigue in each group was very similar ($P = 0.17$), and the average fatigue levels were much higher in these patients as compared to the U.S. general population (Fig. 1).

Similarly, prevalence of clinically significant pain was comparable across the three groups ($P = 0.21$). However, moderate or severe depressive symptoms were much more common in cancer than in kidney disease patients ($P < 0.001$). Nearly 80% of patients in each group had at least one symptom—fatigue, depressive symptoms, or pain (Table 2). These symptoms often coexisted, and 25%–30% of patients in each group had 2 or 3 of the symptoms independent of the patient group (Table 2 and Fig. 2).

Correlations Among Patient-Reported Symptoms

In CKD patients, fatigue was moderately correlated with pain but not with depressive symptoms, and there was no significant correlation between depressive symptoms and pain (Fig. 3). By contrast, in the ESKD group, all three symptoms were moderately correlated with each other (correlation coefficient $r = 0.48–0.55$, $P < 0.001$). Cancer patients also had significant correlations among all three symptoms; however, their strength of correlations was weaker than the ESKD patients (correlation coefficient $r = 0.24–0.49$, $P < 0.001$).

Comparison of Symptom Cluster Phenotypes

Cluster analysis revealed three distinct clusters of fatigue, pain, and depressive symptoms in each patient group. In the kidney disease patients (both CKD and ESKD), the three clusters were as follows: 1) high symptom burden (HIGH)—high levels of all three symptoms, 2) low symptom burden (LOW)—low levels of all three symptoms, and 3) fatigue-pain cluster (FP)—high levels of fatigue and pain, without depression. The cancer patients similarly had three clusters—HIGH and LOW symptom burden clusters were similar, but the third cluster was fatigue-depression (FD) with high levels of fatigue and depression without pain (Fig. 4).

Clinical Predictors of Symptom Clusters

In the CKD group, there was no significant difference among the three clusters in any of the baseline characteristics. In the ESKD group, the HIGH cluster was associated with significantly higher BMI (30.3 kg/m^2 in HIGH vs. 27.7 kg/m^2 in FP vs. 23.6 kg/m^2 in LOW, $P < 0.001$) and higher antidepressant use (22.9% in HIGH vs. 15.5% in FP vs. 0% in LOW, $P = 0.01$) as compared to the other two clusters. In cancer patients, HIGH symptom burden cluster had significantly more females (45% in HIGH vs. 33% in FD vs. 34% in LOW, $P = 0.04$), less alcohol and smoking use, and higher antidepressant use (23% in HIGH vs. 20% in FD vs. 12% in LOW, $P = 0.04$). The HIGH symptom burden cluster also had lower serum albumin (3.5 g/dL in HIGH vs. 3.5 g/dL in FD vs. 3.8 g/dL in LOW, $P < 0.001$) and lower hemoglobin (12.7 g/dL in HIGH vs. 12.9 g/dL in FD vs. 13.4 g/dL in LOW, $P = 0.03$).

Sensitivity Analysis—Analyses of Matched Samples

Matched samples included 80 patients in each disease group after matching on age, race, tobacco use, and alcohol use. Except for chronic conditions (diabetes,

Table 2
Prevalence of Patient-Reported Symptoms in Kidney and Cancer Patients

Measure	CKD, *n* (%) or Mean (SD)	ESKD, *n* (%) or Mean (SD)	Cancer, *n* (%) or Mean (SD)	*P*-value
FACIT-Fatigue total score	34.2 (11.5)	34.5 (11.1)	32.7 (12.1)	0.17
Presence of fatigue (FACIT-F score ≤44)	65 (79.3%)	118 (79.2%)	475 (78.4%)	0.97
Moderate or severe depressive symptoms	7 (8.8%)	27 (19.1%)	177 (30.7%)	<0.001
Clinically significant pain	23 (28.4%)	44 (30.1%)	142 (23.6%)	0.21
Number of symptoms				0.42
Have one symptom	41 (51.9%	59 (42.8%)	239 (41.8%)	
Have two symptoms	20 (25.3%)	36 (26.1%)	178 (31.1%)	
Have all three symptoms	4 (5.1%)	15 (10.9%)	55 (9.6%)	
No symptoms	14 (17.7%)	28 (20.3%)	100 (17.5%)	

CKD = chronic kidney disease; ESKD = end-stage kidney disease; FACIT = Functional Assessment of Chronic Illness Therapy.
Depressive symptom scores were missing in 40 patients, pain missing in eight patients.

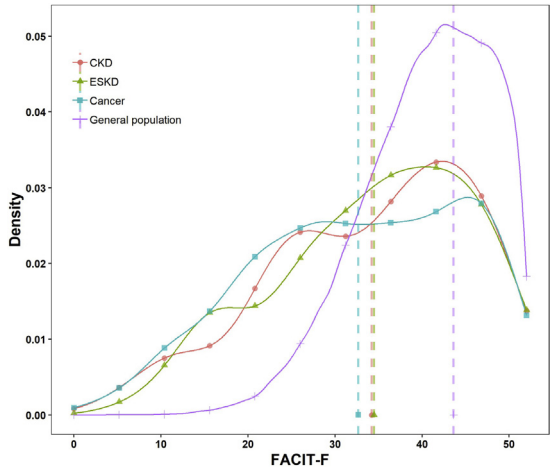

Fig. 1. Distribution of fatigue scores among patients with advanced CKD, ESKD, and cancer compared to the U.S. general population. Higher FACIT-F score indicate less fatigue. Density on y-axis shows the probability of distribution of patients. Dotted line depicts the mean FACIT-F score in each patient cohort. General population curve extrapolated from Cella (2002). CKD = chronic kidney disease; ESKD = end-stage kidney disease; FACIT-F = Functional Assessment of Chronic Illness Therapy—Fatigue.

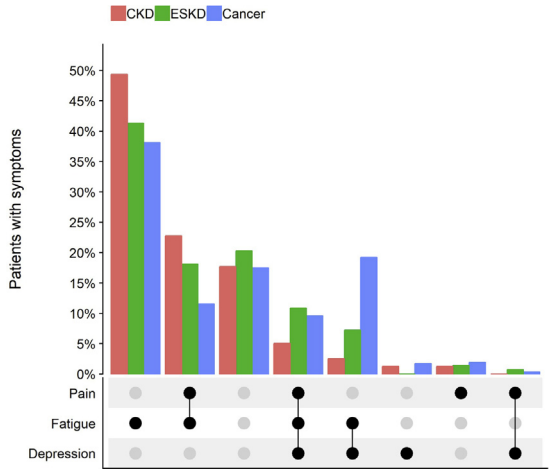

Fig. 2. Symptom burden among patients with advanced CKD, ESKD, and cancer. Black dots at the bottom indicate presence of symptom, and lines connecting the dots indicate symptom co-occurrence. Bar plots on top show percent of patients with the symptom or symptoms. CKD = chronic kidney disease; ESKD = end-stage kidney disease.

hypertension, CVD) and laboratory variables (creatinine and hemoglobin) that were likely influenced by the disease, most baseline variables were similar across the disease groups (Supplementary Table 1). Similar to the unmatched comparisons, prevalence of symptoms was similar across the groups except for depressive symptoms, which was again found to be more prevalent in cancer patients (Supplementary Table 2). Cluster analyses also revealed symptom clusters similar to the unmatched sample (Supplementary Fig. 1).

Discussion

In our study, 75% of patients with CKD and ESKD reported fatigue and one-third reported pain, and the rates of these symptoms were similar to those in patients with advanced GI cancer. Symptom burden in kidney disease patients was similarly high as in cancer patients, and 80% of all patients in each group had at least one symptom. We found that fatigue, pain, and depression often coexist and are highly correlated in the ESKD and cancer patients. Distinct symptom clusters existed in each cohort and were very similar in advanced CKD or ESKD, but somewhat different in cancer patients. Patients with CKD and ESKD were more likely to report fatigue and pain, whereas cancer patients were more likely to have fatigue and depression. Finally, we identified clinical predictors associated with each symptom cluster, such as low albumin, low hemoglobin, and high body mass index, which may be modifiable and provide targets for treatment in clinical practice.

Our study adds to the existing literature on symptom clusters among CKD and ESKD and is the first study to compare this across disease states. Such symptom cluster phenotyping and comparisons across chronic diseases may help identify common underlying biological mechanisms and similarities, which may be the first step to developing effective treatments. We showed that two clusters (HIGH pain, depression, and fatigue; and LOW pain, depression, and fatigue) were similar in CKD, ESKD, and advanced cancer patients. However, the third cluster was distinct—patients with CKD and ESKD were more likely to report fatigue and pain, whereas cancer patients were more likely to have fatigue and depression. We found that the rate of pain was similar among advanced CKD, ESKD, and advanced cancer patients. Despite this, less than half of the ESKD and cancer patients with clinically significant pain reported using analgesic medications. Pain has been recognized as the fifth vital sign by the Institute of Medicine and has a significant negative impact on QoL.[36] Unfortunately, in the era of opioid overuse, providers are even more wary of prescribing appropriate medications to control pain adequately. There is an urgent need for improved pain management and pain research among patients with chronic diseases.

An interesting finding of our study is that patients reported similar levels of fatigue in all three patient cohorts and that this level was much higher than general population norms.[23] The prevalence of fatigue is similar to prior studies in kidney disease and cancer patients.[8,12,23,37] Moreover, we showed that fatigue coexisted with pain and depressive symptoms as distinct clusters in each group. Our findings are similar to

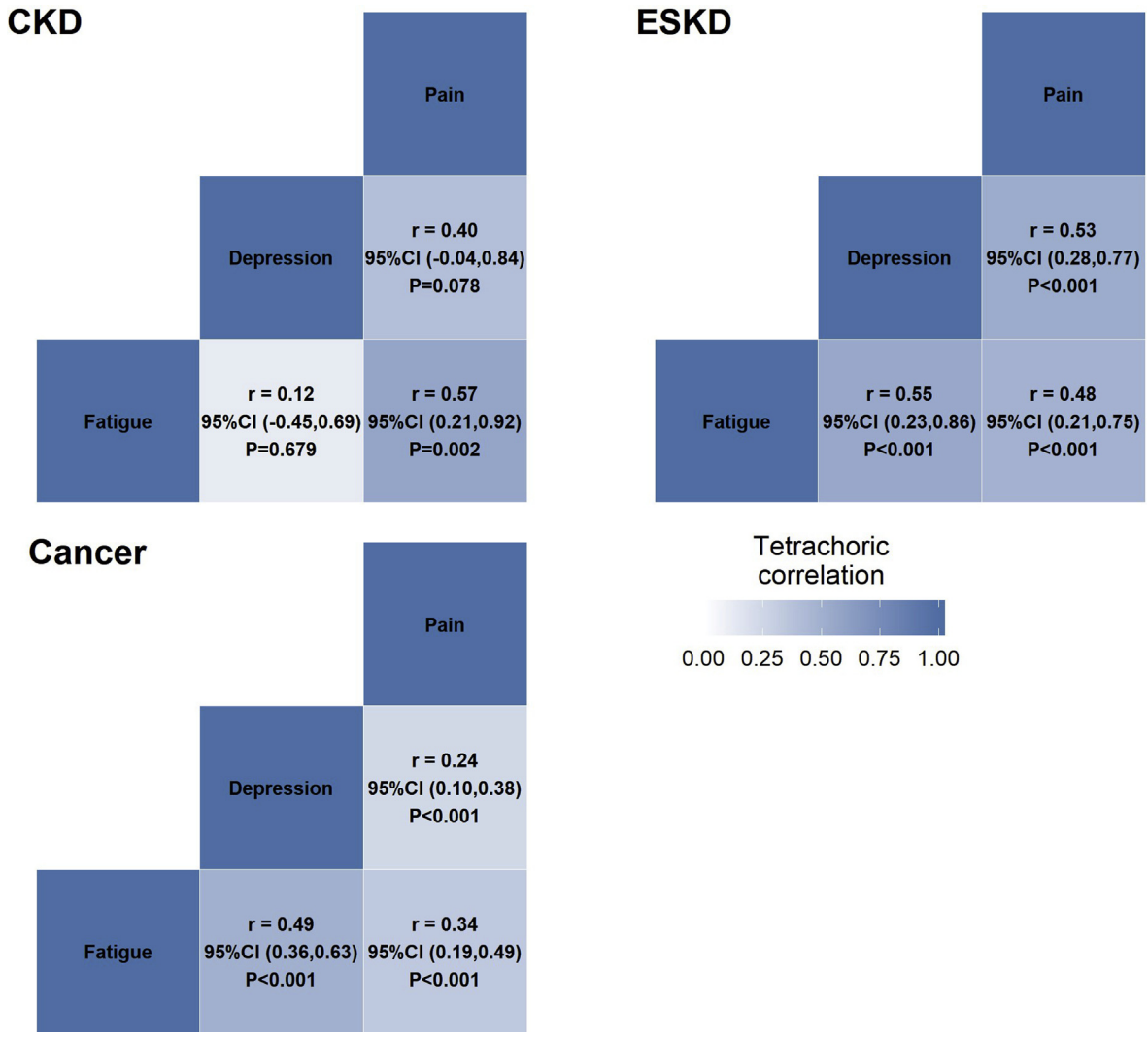

Fig. 3. Correlations of patient-reported symptoms in 1) CKD patients, 2) ESKD patients, and 3) cancer patients. Darker shade indicates higher strength of correlation. CKD = chronic kidney disease; ESKD = end-stage kidney disease.

those from a systematic review by Moens at al. who found that fatigue and pain had a prevalence of more than 50% in patients with advanced cancer and ESKD.[2] Another small pilot study reported similar symptom burden and psychological distress among patients with non−dialysis-dependent advanced CKD and terminal cancer.[3] Despite advances in CKD treatments and dialysis technique, treatment options for fatigue in kidney disease remain limited.[8] Repeatedly, fatigue has emerged as one of the most highly prioritized symptoms for which a treatment is desired by diverse kidney disease patients.[10,11] Given the similar frequency and severity of fatigue in kidney and oncology patients, oncology research into this symptom may provide some insights into novel treatment interventions in nephrology.

In the oncology literature, fatigue has been well known to exist as part of a symptom cluster, often with pain and emotional distress.[13] Although the concept of symptom clusters and targeted treatments for a fatigue-symptom cluster in cancer was proposed over a decade ago, symptom cluster research is relatively new in the field of nephrology. A handful of studies have evaluated symptom clusters in dialysis patients and have identified a cluster of "tiredness, sleeping problems, and muscle weakness"—categorized as the energy/vitality cluster.[38,39] Others have clustered fatigue with "uremic symptoms."[16,17] However, these mostly non-U.S. studies are limited by a lack of inclusion of psychological symptoms in the clusters and the use of nonvalidated questionnaires.[15,16,38−40] There are even lesser data on symptom cluster phenotypes among patients with advanced CKD. The only prior study in patients with CKD Stages 2−4 that evaluated symptom clusters enrolled 140 Korean patients, identified five clusters, and showed similar results with

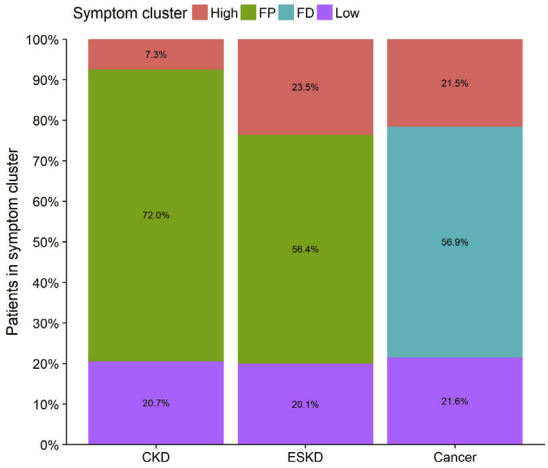

Fig. 4. Percent of patients in each cluster among CKD, ESKD, and cancer patients. Symptom clusters are as follows: 1) High: high probability of fatigue, moderate-severe pain, and moderate-severe depressive symptoms, 2) FP: high probability of fatigue with moderate probability of pain but without depression, 3) FD: high probability of fatigue with moderate probability of depression but without pain, and 4) Low: low probability of symptoms (fatigue, mild pain, and mild depression). CKD = chronic kidney disease; ESKD = end-stage kidney disease.

an observed cluster of "insufficient energy and pain." This cluster was cited most frequently, was reported to be most severe or overwhelming, and was negatively correlated with QoL.[18]

Among cancer patients, the cluster consisting of high levels of fatigue and depression has been found by other research teams.[41] Although almost a third of cancer patients reported depressive symptoms in the clinical range, less than 30% of them reported antidepressant use. Although depression was less common in kidney disease—9% of CKD and 19% of ESKD, use of antidepressants was similarly low at about 30%. Possible reasons for low antidepressant use in these patients may include underrecognition or undertreatment, unacceptability of medications due to pill burden, or poor efficacy of antidepressants in these populations.[4,42,43] Newer treatment options for depression in kidney disease patients, such as adjuvant psychotherapy, collaborative care interventions and incorporation of patient preferences in depression management remain to be tested. To this end, our ongoing Technology Assisted Collaborative Care (TACcare) trial (Clinical trials NCT03440853) will test the effectiveness of a collaborative care intervention targeting symptom clusters (fatigue, pain, and depression) on symptom levels and inflammatory mediators in 150 ESKD patients on hemodialysis.[44]

Our study begins to explore the predictors of symptom clusters in patients with kidney disease. The lack of significant associations between symptom clusters and a number of sociodemographic, clinical, and biochemical variables in kidney disease patients in our study is similar to previous findings in dialysis patients.[16,39] This is in contrast to advanced cancer patients, in which we observed meaningful associations between sociodemographic factors and biochemical variables and specific symptoms, as has been previously described.[45] It may be that in advanced CKD and ESKD patients, there are other predictors that are not routinely captured. These may include patient's coping strategies, perceived social support, and cultural beliefs that may affect their subjective perception of symptoms.[46] In addition, there may be untested biochemical or genetic mechanisms. For instance, in cancer patients, symptoms and symptom cluster have been found to be independently associated with proinflammatory cytokines as well as hypothalamic-pituitary disturbances causing elevations in cortisol, ACTH, epinephrine, and norepinephrine.[47] Genome-wide associations with symptom clusters have also begun to be explored. Illi and colleagues found that a minor allele of IL4 rs2243248 was linked to high levels of pain, fatigue, sleep disturbances, and depression in a sample of cancer patients.[48] Future studies in kidney disease patients should explore these novel inflammatory, hormonal, and genetic predictors of symptoms and symptom clusters.

The study has many strengths including the large sample size of patients, use of validated instruments to assess the three symptoms with available clinical cutoffs to be able to compare across instruments, and comparison of symptom clusters across chronic diseases. Limitations of the study included the lack of other symptoms that may also have high rates in CKD, ESKD, and cancer patients (e.g., sleep, nausea and vomiting, loss of appetite, itching) and may have confounding associations with fatigue, pain, and depressive symptoms. In addition, the studies used different instruments to assess pain and depression across patient cohorts. Finally, the prevalence of depressive symptoms among CKD patients in our study was lower than that reported in the literature, thus may have confounded our results.[49]

Conclusion

The findings of this study represent one of the first studies comparing symptom clusters across different chronic diseases. Patients with CKD and ESRD have similar burden of pain, fatigue, and depressive symptoms compared to those with cancer. These symptoms often coexist and are highly correlated but form distinct symptom clusters among these patient groups and may suggest differences in the underlying biological or genetic mechanisms. We identified some modifiable clinical predictors of these symptom clusters;

however, further research is warranted to better understand the pathophysiological mechanisms. In addition, future research should evaluate additional symptoms to better characterize symptom clusters such as sleep disturbances, nausea and vomiting, loss of appetite and monitor longitudinal changes in symptoms and symptom clusters over time.

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The authors declare no conflicts of interest.

Supplementary Data

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Appendix

Table 1
Baseline Characteristics After Matching

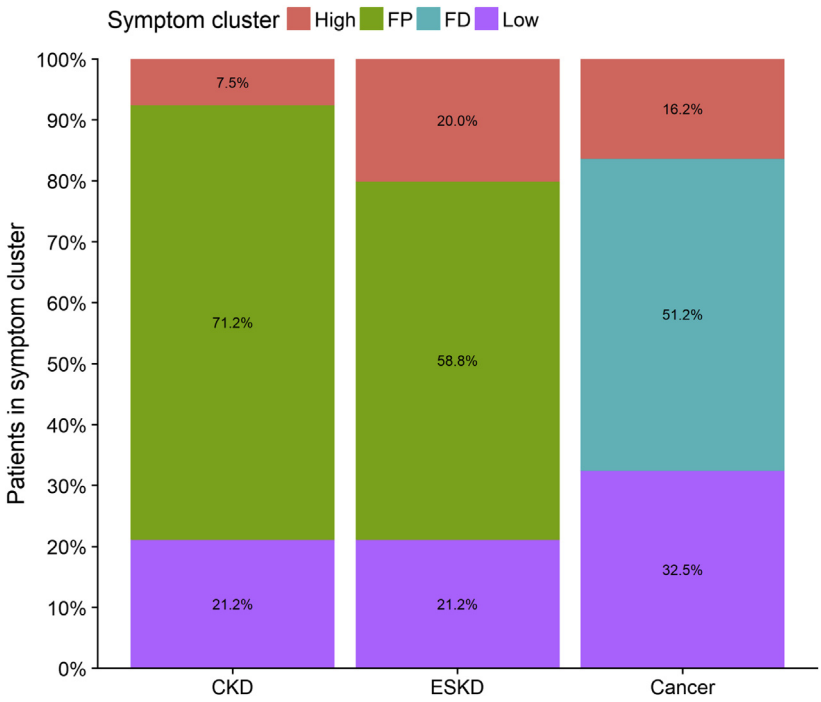
Variable[a]	CKD ($N = 80$), n (%) or Mean (SD)	ESKD ($N = 80$), n (%) or Mean (SD)	Cancer ($N = 80$), n (%) or Mean (SD)	P-value
Age (yrs)	52.0 (14.1)	52.6 (15.3)	54.1 (13.5)	0.62
Male	55 (68.8%)	55 (68.8%)	44 (55.0%)	0.68
Race				0.28
White	58 (72.5%)	58 (72.5%)	61 (76.2%)	
Black	18 (22.5%)	20 (25.0%)	12 (15.0%)	
Other	4 (5.0%)	2 (2.5%)	7 (8.8%)	
Education (high school or greater)	75 (93.8%)	73 (91.2%)	65 (90.3%)	0.72
Married	47 (58.8%)	44 (55.0%)	50 (63.3%)	0.57
Diabetes	26 (32.5%)	30 (41.7%)	14 (17.7%)	0.005
Hypertension	71 (94.7%)	57 (81.4%)	26 (32.9%)	<0.001
Cardiovascular disease	19 (24.1%)	23 (30.3%)	8 (10.1%)	0.007
Tobacco use (ever)	39 (48.8%)	37 (46.2%)	44 (55.0%)	0.52
Alcohol use	27 (33.8%)	22 (27.5%)	33 (41.2%)	0.19
Antidepressant use	12 (15.0%)	11 (13.8%)	15 (19.0%)	0.64
Benzodiazepine use	5 (6.25%)	4 (5.00%)	6 (7.59%)	0.76
Pain medication use	37 (50.0%)	21 (31.8%)	38 (50.0%)	0.05
Body mass index (BMI; kg/m^2)	27.8 (5.4)	26.8 (6.0)	27.4 (5.9)	0.57
Albumin (g/dL)	3.78 (0.6)	3.79 (0.5)	3.70 (0.5)	0.57
Serum Cr (mg/dL)	4.00 (1.5)	7.74 (2.9)	0.83 (0.2)	<0.001
Hemoglobin (g/dL)	11.7 (1.78)	11.6 (2.16)	12.9 (1.80)	<0.001

CKD = chronic kidney disease; ESKD = end-stage kidney disease.
[a]Education status missing for eight patients; marital status missing for one patient; diabetes missing for nine patients; HTN missing for 16 patients; cardiovascular disease missing for six patients; antidepressant use missing for one patient; benzodiazepine missing for one patient; Pain meds missing for 24 patients.

Table 2
Prevalence of Patient-Reported Symptoms in Kidney and Cancer Patients After Matching

Measure	CKD, *n* (%) or Mean (SD)	ESKD, *n* (%) or Mean (SD)	Cancer, *n* (%) or Mean (SD)	*P*-value
FACIT-Fatigue total score	34.1 (11.6)	34.6 (12.1)	34.9 (12.3)	0.93
Presence of fatigue (FACIT-F score ≤44)	63 (78.8%)	63 (78.8%)	54 (67.5%)	0.17
Moderate or severe depressive symptoms[a]	7 (9.0%)	16 (20.8%)	20 (27.0%)	0.02
Clinically significant pain[a]	22 (27.8%)	24 (30.8%)	14 (17.7%)	0.14
Number of symptoms				0.32
Have one symptom	40 (51.9%)	32 (42.7%)	28 (38.4%)	
Have two symptoms	19 (24.7%)	17 (22.7%)	17 (23.3%)	
Have all three symptoms	4 (5.19%)	10 (13.3%)	6 (8.22%)	
No symptoms	14 (18.2%)	16 (21.3%)	22 (30.1%)	

CKD = chronic kidney disease; ESKD = end-stage kidney disease; FACIT = Functional Assessment of Chronic Illness Therapy.
[a]Depressive symptom scores were missing in 11 patients, pain missing in four patients.



Supplementary Fig. 1. Percent of patients in each cluster among CKD, ESKD, and cancer patients after matching. Symptom clusters are as follows: 1) High: high probability of fatigue, moderate-severe pain, and moderate-severe depressive symptoms; 2) FP: high probability of fatigue with moderate probability of pain but without depression; 3) FD: high probability of fatigue with moderate probability of depression but without pain; and 4) Low: low probability of symptoms (fatigue, mild pain, and mild depression). CKD = chronic kidney disease; ESKD = end-stage kidney disease.