WHICH PATIENTS WITH CHRONIC KIDNEY DISEASE HAVE THE GREATEST SYMPTOM BURDEN? A COMPARATIVE STUDY OF ADVANCED CKD STAGE AND DIALYSIS MODALITY

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SUMMARY

Background: Chronic kidney disease (CKD) leads to a range of symptoms, which are often under-recognised and little is known about the multidimensional symptom experience in advanced CKD.
Objectives: To examine (1) symptom burden at CKD stages 4 and 5, and dialysis modalities, and (2) demographic and renal history correlates of symptom burden.
Methods: Using a cross-sectional design, a convenience sample of 436 people with CKD was recruited from three hospitals. The CKD Symptom Burden Index (CKD-SBI) was used to measure the prevalence, severity, distress and frequency of 32 symptoms. Demographic and renal history data were also collected.
Results: Of the sample, 75.5 % were receiving dialysis (haemodialysis, n = 287; peritoneal dialysis, n = 42) and 24.5 % were not undergoing dialysis (stage 4, n = 69; stage 5, n = 38). Participants reported an average of 13.01 ± 7.67 symptoms. Fatigue and pain were common and burdensome across all symptom dimensions. While approximately one-third experienced sexual symptoms, when reported these symptoms were frequent, severe and distressing. Haemodialysis, older age and being female were independently associated with greater symptom burden.
Conclusions: In CKD, symptom burden is better understood when capturing the multidimensional aspects of a range of physical and psychological symptoms. Fatigue, pain and sexual dysfunction are key contributors to symptom burden, and these symptoms are often under-recognised and warrant routine assessment. The CKD-SBI offers a valuable tool for renal clinicians to assess symptom burden, leading to the commencement of timely and appropriate interventions.

KEY WORDS Chronic kidney disease • Dialysis • Non-dialysis • Symptom burden • Symptom dimensions

BIODATA

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INTRODUCTION

Chronic kidney disease (CKD) is global health issue mostly due to the rising incidence of type two diabetes mellitus and hypertension. CKD creates a significant burden for individuals, often due to numerous troublesome symptoms, particularly in advanced stages of the disease (Abdel-Kader et al. 2009; Caplin et al. 2011). There is a growing body of evidence that CKD symptom burden is negatively correlated Health Related Quality of Life (HRQoL) (Jablonski 2007; Abdel-Kader et al. 2009; Yong et al. 2009; Davison & Jhangri 2010) and increased morbidity and mortality rates (Amro et al. 2014), likely through a reduction in treatment adherence (Davison & Jhangri 2005). Comprehensive reviews identify that the average number of symptoms per patients range between 6 to 20 symptoms (Almutary et al. 2013) and the most prevalent symptoms are fatigue, pain, pruritus, sleep disturbance and poor appetite (Almutary et al. 2013; Murtagh et al. 2007). However, to date, knowledge

about CKD symptoms is limited to a small number of symptoms and their prevalence, and is focused predominantly on those undergoing haemodialysis (HD).

Conceptually, symptoms are a multidimensional construct characterised by prevalence, distress, severity and frequency (Lenz *et al*. 1997). The symptom experience in patients with cancer is better understood when considering the multidimensional nature of the symptoms (Pettersson *et al*. 2014). Overall, the extent of symptom burden for people with CKD is under-recognised and little is known about the multidimensional symptom experience in CKD (Jablonski 2007; Almutary *et al*. 2013). Although the literature has generally focused on the prevalence and impact of individual symptoms among people with CKD, understanding the total symptom burden is the subject of much attention and several multiple-symptom assessment tools are now available (Almutary *et al*. 2013). Most studies of CKD symptoms focus on examining common dimensions (prevalence and distress), but often miss the severity and frequency of symptoms. Only two studies have assessed the multidimensional aspects of symptoms and both of these studies have been limited to the HD population (Jablonski 2007; Danquah *et al*. 2010).

When a clinician focuses only on highly prevalent symptoms, other significant (frequent, distressing or severe) symptoms would remain under-recognised and unrelieved and this will contribute to an increment of the total symptom burden. Assessment of all symptom dimensions helps to estimate the total symptom burden. Thus, assessment of symptom burden must go beyond prevalence to adequately capture the impact of CKD and direct treatment. This study sought to assess the multidimensional nature of symptom burden across advanced CKD stages and dialysis treatment groups. It also aimed to explore demographic and renal history correlates of CKD symptom burden.

METHODS
SAMPLE
A cross-sectional design was used to recruit a convenience sample of individuals with CKD stage 4 and 5 CKD from kidney centres and nephrology clinics at three large public hospitals at Saudi Arabia. Data were collected between July 2013 and February 2014. Eligible participants included adults diagnosed with CKD [estimated glomerular filtration (eGFR) <30 ml/min/1.73 m^2] or currently receiving either HD or peritoneal dialysis (PD), who were willing to participate, able to communicate in Arabic, and provide informed consent. Exclusion criteria were cognitive impairment that would preclude voluntary, informed consent, and those with critical conditions.

The study was explained verbally and in writing prior to obtaining voluntary written consent. The instruments were administered and collected by one of the researchers (first author). Assistance was provided by the same researcher (if required) who read out aloud items and possible responses. This procedure assisted with maintaining a consistent approach during data collection and ensured that participants received the same instructions. Other data were extracted from dialysis charts and hospital files. This study was approved by the ethics committees of Queensland University of Technology, King Abdulaziz University Hospital and Jeddah Research Centre.

MEASURES

DEMOGRAPHIC AND DISEASE CHARACTERISTICS
Demographic information that could potentially influence the individual's symptom experience was collected, including age, gender, marital status and level of education. Data were also collected from patient health records, including stage of CKD (measured by eGFR if not receiving dialysis), cause of CKD, duration of renal replacement therapy (RRT) (in years), co-morbidities, and the most recent clinical data (serum albumin, phosphate, calcium, and haemoglobin). Co-morbidities were measured using Davies *et al*.'s (2002) co-morbidity index. This index has seven domains with a maximum score of seven. The scores are graded into three risk groups: grade 0 (zero total score), grade 1 (score 1–2) or grade 2 (score 3–7).

ASSESSMENT OF SYMPTOM BURDEN
Symptoms were assessed using the CKD Symptom Burden Index (CKD-SBI), see Supplemental Material 1 (Almutary *et al*. 2015). The CKD-SBI was modified (with permission) from the Dialysis Symptom Index (Weisbord *et al*. 2004) based on a comprehensive review of available instruments used for CKD symptom assessment. This self-report instrument assesses prevalence, distress, severity and frequency of 32 symptoms and provides an opportunity for other symptoms to be added by participants. The prevalence scale assessed presence or absence of symptoms (Yes/No) and ranged between 0 and 32 symptoms. Other

symptom dimensions are rated on a 0–10 numerical rating scale. Participants rate the "distress" subscale from *none* to *very much*, "severity" from *none* to *very severe*, and "frequency" from *never* to *constant*. A maximum total score for each of these scales is 320 (range 0–320). Higher scores indicate greater symptom distress, severity and frequency. A total symptom burden score of the CKD-SBI is calculated by summing subscale scores (prevalence, distress, severity and frequency) and then multiplying the result by 0.1008 (constant number—a mathematical manoeuvre to convert the total score of CKD-SBI to 100 (Cuyt *et al*. 2008). The total score for the CKD-SBI ranges between 0 and 100. The CKD-SBI was piloted during the translation processes and the psychometric properties have been previously reported (Almutary *et al*. 2015).

STATISTICAL ANALYSES
Data were entered into IBM SPSS Statistics version 21. Counts and percentages for symptom prevalence, and means and standard deviations for symptom distress, severity and frequency were calculated for the whole sample and separately for each CKD group. Differences between groups were examined using chi-square or Fisher's exact tests for categorical data, and one-way ANOVA for continuous variables. All analyses were adjusted for multiple comparisons using the Games-Howell correction to account for the unequal sample size (Huizingh 2007). Normality for each variable was assessed by inspection of histograms, Shapiro-Wilk normality test and skewness, and kurtosis indices. All variables were normally distributed, except three variables (total distress score, total severity score and total frequency score). Therefore, these variables were transformed using square root transformation to follow the normal distribution in order to achieve the assumptions of multiple regression analysis. The sample size of 436 was sufficient to conduct multiple regression analysis for 6 predictors because in this study the ratio of participants to predictors exceeded the recommended ratio of 20:1 (Hair *et al*. 2014). Multiple linear regression analyses were performed to examine associations between demographic and illness factors and symptom burden in advanced CKD. The variables selected to enter into the regression model were based on clinical importance and statistical significance of the bivariate associations. Consequently, six background variables (age, gender, education level, cause of CKD, number of co-morbid conditions, stage and treatment of CKD) were included in each model. Statistical significance was set at $p < 0.01$.

RESULTS
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS
Sample characteristics are presented in Table 1. The mean age was 48 years (range 18–87 years), 53% were male, 75.5% were receiving dialysis (HD, n = 287; PD, n = 42) and 24.5% were not receiving dialysis (stage 4, n = 69; stage 5, n = 38). Diabetes (31.4%) and hypertension (33.7%) were the main causes of CKD. Those receiving HD were more likely to have longer years on RRT (>5 years; 48.4%) compared to those receiving PD (21.4%). Around half of the participants (59.6%) were married and had at least a secondary education (45.7%) across all CKD groups. Dialysis groups tended to be younger (mean age = 47.15 ± 14.59 vs. 51.60 ± 15.24, t (175.45) = 2.62, p = 0.009) and have more co-morbid conditions (χ^2 (2, N = 436) = 65.67, p < 0.001) compared with those not receiving dialysis. There were no significant differences between groups for other clinical variables.

SYMPTOM CHARACTERISTICS

TOTAL SCORE OF CKD-SBI
A summary of each symptom dimension (prevalence, distress, severity and frequency) for the whole sample is presented in Table 2. The mean total symptom burden score for the whole sample was 18.63 ± 16.02, ranging from 0.81 to 83.36. Table 3 compares the means of each CKD-SBI scale by CKD stage and treatment group. Total symptom burden score was significantly higher in the HD group compared with other CKD groups (F (3, 415) = 31.32, p < 0.001).

SYMPTOM PREVALENCE
On average participants reported 13.01 (SD = 7.67) CKD-related symptoms. Of the 32 possible symptoms, 40.6% were reported by more than 40% of the sample. Four symptoms were found to be most prevalent (≥50%) across all CKD groups: fatigue (77.0%), bone or joint pain (60.3%), itching (59.6%), and decreased appetite (50.5%). The mean number of the symptoms in the dialysis group was more than double the number of symptoms reported by the non-dialysis group (14.65 ± 7.49 vs. 7.51 ± 5.3, t (220) = 10.47, p < 0.001). The most prevalent symptoms in the dialysis groups were fatigue (84.8%), bone joint pain (68.7%), itching (65%) and decreased appetite (56.5%); whereas the non-dialysis group commonly experienced fatigue (54.2%), worry (45.8%), itching (43%) and bone joint pain (34.6%). Although fatigue was the most prevalent symptom across all CKD groups, fatigue was present in almost all patients undergoing PD (95.2%).

	Total (N = 436)	Non-dialysis CKD (n = 107)		Dialysis group (n = 329)	
		Stage 4, (n = 69) (eGFR 15–29 mL/min/1.73 m²)	Stage 5, (n = 38) (eGFR <14 mL/min/1.73 m²)	HD, (n = 287)	PD, (n = 42)
Age, mean, SD	48.29 ± 14.86	51.47 ± 15.42	51.84 ± 15.11	47.71 ± 14.46	43.08 ± 15.09
Gender, n (%)					
Male	231 (53)	38 (55.1)	21 (55.3)	153 (53.3)	19 (45.2)
Education status, n (%)					
Less than Secondary	235 (53.9)	35 (50.7)	22 (57.9)	160 (55.7)	18 (42.9)
Secondary	105 (24.1)	20 (29)	4 (10.5)	68 (23.7)	13 (31)
College or above	94 (21.6)	14 (20.3)	11 (28.9)	58 (20.2)	11 (26.2)
Marital status, n (%)					
Married	260 (59.6)	44 (63.8)	24 (63.2)	169 (58.9)	23 (54.8)
Years on KRT, n (%)					
0–12 months	68 (20.7)	N/A	N/A	55 (19.2)	13 (31)
1.1–5 years	113 (34.3)	N/A	N/A	93 (32.4)	20 (47.6)
5.1–10 years	82 (24.9)	N/A	N/A	73 (25.4)	9 (21.4)
More than 10 years	66 (20.1)	N/A	N/A	66 (23)	–
Comorbid conditions, n (%)					
0	182 (41.7)	57 (82.6)	23 (60.5)	88 (30.7)	14 (33.3)
1–2	224 (51.4)	12 (17.4)	15 (39.5)	173 (60.3)	24 (57.1)
≥3	30 (6.9)	–	–	26 (9.1)	4 (9.5)
Causes of CKD, n (%)					
Diabetic nephropathy	137 (31.4)	23 (33.3)	13 (34.2)	92 (32.1)	9 (21.4)
Hypertensive nephropathy	147 (33.7)	15 (21.7)	13 (34.2)	103 (35.9)	16 (38.1)
Primary glomerular disease	30 (6.9)	3 (4.3)	3 (7.9)	18 (6.3)	6 (14.3)
Unknown aetiology	59 (13.5)	18 (26.1)	1 (2.6)	36 (12.5)	4 (9.5)
Others	63 (14.4)	10 (14.5)	8 (21.1)	38 (13.2)	7 (16.7)
Clinical variables, mean, SD					
Albumin g/L	33.43 ± 5.48	34.41 ± 4.29	34.16 ± 5.23	33.54 ± 4.91	30.45 ± 9.19
Phosphate mmol/L	1.54 ± 0.55	1.39 ± 0.27	1.59 ± 0.36	1.57 ± 0.61	1.54 ± 0.56
Calcium mmol/L	2.17 ± 0.29	2.28 ± 0.29	2.11 ± 0.27	2.17 ± 0.29	2 ± 0.33
Haemoglobin g/L	107.99 ± 17.09	109.14 ± 17.27	106.34 ± 17.05	108.07 ± 17.44	107.12 ± 14.72

Table 1: Sample characteristics.

N/A: not applicable, KRT: kidney replacement therapy, eGFR: estimated glomerular filtration rate, HD: haemodialysis, PD: peritoneal dialysis, SD: standard deviation. '–' When no data were reported for a specific characteristic.

The mean number of symptoms was significantly higher in the HD group compared with other CKD groups (F (3, 432) = 39.49, p < 0.001; see Table 3). Prevalence of symptoms varied between CKD groups. For example, constipation was more prevalent in the PD group (53.7%). Shortness of breath was reported more by stage 5 non-dialysis (39.5%) and the HD group (45.6%) compared with stage 4 (24.6%) and PD groups (26.2%). Supplemental Material 2 (a–d) compares each symptom by CKD group for each symptom dimension. A few symptoms were noted to be similarly prevalent (e.g., swelling in legs, worrying and feeling nervous) regardless of stage or treatment.

SYMPTOM DISTRESS
Participants reported moderate to high symptom distress overall (mean = 57.55 ± 52.27). Five symptoms were found to be most distressing across all CKD groups, exceeding the midpoint on the

10-point scale: fatigue (5.89 ± 3.11), bone or joint pain (5.56 ± 3.2), feeling irritable (5.5 ± 3.46), restless legs (5.47 ± 3.44), and decreased interest in sex (5.14 ± 3.57). Overall, symptom distress was higher in the dialysis group (68.4 ± 53.99) compared to the non-dialysis group (21.33 ± 20.55), (t (397.8) = −12.88, p < 0.001). The mean overall symptom distress score significantly differed between CKD groups (F (3, 417) = 29.24, p < 0.001) where the HD group had the highest symptom distress (72.24) and stage 4 group had the lowest (20.35); see Table 3. The HD group reported greater mean distress levels for shortness of breath, cough, bone joint pain, muscle soreness, light headedness or dizziness, headache, skin problems, sleep disturbance, and sexual problems compared to other groups. Fatigue was one of the most distressing symptoms across all CKD groups and was a highly distressing symptom for the PD group. The PD group reported greater distress for fatigue (F (3, 328) = 7.37, p < 0.001), constipation

Symptom	Symptom prevalence n (%)	Symptom distress[a] mean, SD	Symptom severity[a] mean, SD	Symptom frequency[a] mean, SD
Constipation	168 (38.5)	4.87 ± 3.11	4.48 ± 3.02	4.41 ± 3.07
Nausea	175 (40.1)	3.67 ± 3.13	3.51 ± 3.14	3.67 ± 3.15
Vomiting	86 (19.7)	3.9 ± 3.36	3.59 ± 3.31	3.4 ± 3.41
Diarrhoea	101 (23.2)	3.55 ± 3.19	3.82 ± 3.23	3.8 ± 3.23
Decreased appetite	220 (50.5)	4.31 ± 3.3	4.12 ± 3.13	4.62 ± 3.26
Muscle cramps	198 (45.4)	4.34 ± 3.07	4.13 ± 3.25	3.75 ± 3.12
Swelling in legs	156 (35.8)	3.51 ± 3.09	3.14 ± 2.85	3.43 ± 3.11
Shortness of breath	174 (39.9)	3.46 ± 3.12	2.73 ± 2.8	3.02 ± 2.89
Light headedness or dizziness	180 (41.3)	4.03 ± 3.19	3.46 ± 3.07	3.68 ± 3.15
Restless legs	105 (24.1)	5.47 ± 3.44	4.23 ± 3.76	4.42 ± 3.81
Numbness or tingling in feet	193 (44.3)	4.32 ± 3.39	3.74 ± 3.32	3.97 ± 3.63
Feeling tired or lack of energy	337 (77.3)	5.89 ± 3.11	5.78 ± 3.05	6.35 ± 3.05
Cough	152 (34.9)	4.51 ± 3.36	4.41 ± 3.23	4.48 ± 3.44
Dry mouth	123 (28.2)	4.26 ± 3.28	3.78 ± 3.19	4.29 ± 3.53
Bone or joint pain	263 (60.3)	5.56 ± 3.2	5.24 ± 3.32	5.45 ± 3.25
Chest pain	144 (33)	3.88 ± 3.21	3.55 ± 3.24	3.13 ± 3.09
Headache	178 (40.8)	4.55 ± 3.37	4.1 ± 3.39	4.07 ± 3.33
Muscle soreness	201 (46.1)	4.44 ± 3.11	4.28 ± 3.07	4.37 ± 3.28
Difficulty concentrating	172 (39.4)	4.1 ± 3.15	3.73 ± 3.06	4.11 ± 3.09
Dry skin	214 (49.1)	4.56 ± 3.39	4.77 ± 3.33	5.44 ± 3.42
Itching	260 (59.6)	4.91 ± 3.39	4.76 ± 3.21	5.43 ± 3.49
Worrying	196 (45)	4.47 ± 2.93	4.38 ± 2.95	4.76 ± 3.05
Feeling nervous	170 (39)	4.09 ± 2.75	3.99 ± 2.91	4.17 ± 3.02
Trouble falling asleep	214 (49.1)	4.88 ± 3.28	4.71 ± 3.22	5.29 ± 3.39
Trouble staying asleep	123 (28.2)	4.47 ± 3.36	4.6 ± 3.34	4.91 ± 3.56
Feeling irritable	145 (33.3)	5.5 ± 3.46	5.06 ± 3.54	5.01 ± 3.54
Feeling sad	173 (39.7)	3.94 ± 3.00	4.16 ± 2.99	4.59 ± 3.1
Feeling anxious	149 (34.2)	4.68 ± 3.19	4.62 ± 3.02	4.65 ± 3.12
Depression	138 (31.7)	3.47 ± 2.88	3.63 ± 2.83	4.31 ± 2.87
Decreased interest in sex	161 (36.9)	5.14 ± 3.57	6.6 ± 3.46	6.8 ± 3.51
Difficulty becoming sexually aroused	151 (34.6)	4.96 ± 3.64	6.31 ± 3.59	6.47 ± 3.67
Nocturia	69 (15.8)	3.00 ± 2.75	2.42 ± 2.22	2.91 ± 2.48
Overall subscale, mean, SD	13.01 ± 7.67	57.55 ± 52.27	55.45 ± 51.74	58.76 ± 50.48

Table 2: Symptom dimensions for the whole sample (N = 436).

SD: standard deviation. [a]Possible range for symptom mean scores was 0–10.

(F (3, 162) = 5.19, p = 0.002) and decreased appetite (F (3, 213) = 4.32, p = 0.006) compared to other groups. There were no significant differences in the distress levels of psychological symptoms such as feeling sad, worry, feeling anxious, feeling nervous and depression among groups. However, feeling sad tended to be a more distressing symptom for people at CKD stage 5.

SYMPTOM SEVERITY
The mean overall symptom severity score was 55.45 ± 51.74. Five symptoms were found to be most severe across all CKD groups: decreased interest in sex (6.6 ± 3.46), difficulty becoming sexually aroused (6.31 ± 3.59), fatigue (5.78 ± 3.05), bone or joint pain (5.24 ± 3.32) and feeling irritable (5.06 ± 3.54). Mean overall symptom severity was highest in the HD group (70.39), followed by PD (34.1), stage 5

(22.09) and stage 4 (19.9), F (3, 416) = 29.8, p < 0.001, see Table 3. Those with stage 5 who were not receiving dialysis tended to reported higher severity of sadness (5.13 ± 2.99) compared with other groups, but this did not reach statistical significance (F (3, 166) = 2.11, p = 0.10). Fatigue was more severe in the PD group (F (3, 326) = 6.1, p < 0.001) compared to other CKD groups. Sleep disturbance, skin problems, bone or joint pain, cough, muscle soreness, and sexual problems were more severe in the HD group. There was no significant difference in the mean severity of the psychological symptoms between all CKD groups.

SYMPTOM FREQUENCY
The mean overall symptom frequency was 58.76 ± 50.48. Eight symptoms were found to occur most frequently overall: decreased interest in sex (6.8 ± 3.51), difficulty becoming

	Non-dialysis		Dialysis		
Scale	Stage 4, (n = 69) mean, SD	Stage 5, (n = 38) mean, SD	HD, (n = 287) mean, SD	PD, (n = 42) mean, SD	p value
Total symptom burden	7.35 ± 6.4	8.1 ± 8.04	23.36 ± 16.99	12.04 ± 6.58	<0.001
Symptom prevalence	7.35 ± 5.25	7.77 ± 5.53	15.32 ± 7.65	10 ± 4.02	<0.001
Symptom distress	20.35 ± 18.2	23.06 ± 24.35	72.24 ± 55.88	41.18 ± 24.76	<0.001
Symptom severity	19.9 ± 19.4	22.09 ± 24.43	70.39 ± 55.32	34.1 ± 20.77	<0.001
Symptom frequency	25.24 ± 21.53	27.46 ± 26.66	73.5 ± 53.63	34.18 ± 19.78	<0.001

Table 3: Compare mean overall scales by CKD groups.

HD: haemodialysis, PD: peritoneal dialysis, SD: standard deviation.

sexually aroused (6.47 ± 3.67), fatigue (6.35 ± 3.05), bone or joint pain (5.45 ± 3.25), dry skin (5.44 ± 3.42), itching (5.43 ± 3.49), trouble falling asleep (5.29 ± 3.39) and feeling irritable (5.01 ± 3.54). Mean overall symptom frequency was highest in the HD group (73.5), followed by PD (34.18), stage 5 (27.46) and stage 4 (25.24), $F_{(3, 415)} = 29.92$, $p < 0.001$, see Table 3. Fatigue was reported frequently by all CKD groups but more frequently occurred in the PD group. Those not receiving dialysis (stage 4 and 5) were more likely to report a higher frequency of psychological symptoms (worrying, feeling sad and depression) but this did not reach statistical significance. Sleep disturbance, skin problems, bone or joint pain, restless legs, light headedness or dizziness and cough were reported more frequently by the HD group.

ASSOCIATIONS BETWEEN SAMPLE CHARACTERISTICS AND SYMPTOM BURDEN

Multiple regression analyses were performed to explore demographic and renal history correlates of CKD symptom burden (see Table 4). Age, gender and stages of CKD were found to be independently associated with total symptom burden, distress, severity and frequency of the symptom. Following the results reported above, HD treatment was the strongest predictor ($\beta = 0.58$–0.53, $p < 0.001$) of greater symptom burden across all CKD-SBI scales. Older age was associated with higher scores for all CKD-SBI scales ($\beta = 0.19$–0.16, $p < 0.001$–0.002). Being female was also associated with higher scores all CKD-SBI scales ($\beta = 0.14$–0.11, $p = 0.002$–0.009), except symptom prevalence.

DISCUSSION

This study examined the multidimensional symptom burden experienced by people in advanced stages of CKD. To our knowledge this is the first study that examined four symptom dimensions across disease stages and treatment groups in advanced CKD. Although two previous studies considered multiple symptom dimensions, both included only people receiving HD (Jablonski 2007; Danquah *et al*. 2010). Each dimension of symptom has contributed to estimate the total symptom burden. Our findings show that total symptom burden was higher in the dialysis group, compared to the non-dialysis group. Multidimensional assessment of symptoms is vital to better understand the total symptom burden, and to develop effective management through minimising the distress, severity and frequency of symptoms.

Fatigue and bone or joint pain were found as the most prevalent and distressing symptoms, while sexual problems were the most severe and frequent symptoms, regardless of CKD stage. The results of this study highlight an important feature that symptoms are multidimensional. For instance, the most prevalent symptoms are not necessarily the most severe or distressing symptoms, and that other symptoms are less important in respect of their severity but are frequently experienced. In this study, nausea and decreased appetite were reported frequently but with lesser degree in their severity levels among people at stage 4 CKD. In clinical settings, however, symptom assessment commonly focuses on examining the severity level of the most prevalent symptoms, such as pain (Jablonski 2007). Uni-dimensional symptom assessment provides incomplete information as distressing and frequent symptoms could remain under-recognised and unrelieved which will contribute to an increment of the total symptom burden. We emphasise the importance of assessing the multidimensional aspects of symptoms to better understand symptom burden in those with CKD in order to provide more effective management.

Overall symptoms were more burdensome in the dialysis group, in particular among those receiving HD, which indicates that dialysis therapy may contribute to increased symptom burden.

Predictor	Total symptom burden (F=20.34 p<0.001, adjusted R^2=0.318)			Prevalence (F=15.46, p<0.001, adjusted R^2=0.259)			Distress (F=16.19, p<0.001, adjusted R^2=0.275)			Severity (F=17.36, p<0.001, adjusted R^2=0.29)			Frequency (F=15.49, p<0.001, adjusted R^2=0.266)		
	B	β	95% CI (β adjusted)	B	β	95% CI (β adjusted)	B	β	95% CI (β adjusted)	B	β	95% CI (β adjusted)	B	β	95% CI (β adjusted)
Age	0.02	0.16**	0.01, 0.03	0.10	0.19***	0.05, 0.16	0.04	0.16**	0.01, 0.06	0.04	0.16**	0.01, 0.06	0.04	0.18**	0.02, 0.07
Female	0.39	0.14**	0.08, 0.71	1.07	0.07	−0.32, 2.47	0.92	0.14**	0.36, 1.48	0.71	0.15**	0.13, 1.28	0.89	0.14**	0.32, 1.46
Education level															
Illiterate	Ref														
Secondary	−0.27	−0.06	−0.68, 0.14	0.44	0.02	−1.4, 2.25	−0.56	−0.07	−1.31, −0.19	−0.47	−0.06	−1.22, 0.28	−0.34	−0.05	−1.08, 0.4
College or above	−0.42	−0.09	−0.84, 0.01	−0.39	−0.02	−2.26, −1.48	−0.91	−0.11*	−1.69, −0.12	−0.79	−0.11*	−1.57, −0.02	−0.51	−0.07	−1.28, 0.26
Diabetes	−0.17	−0.04	−0.52, 0.18	−1.23	−0.72	−2.78, 0.32	−0.22	−0.03	−0.87, 0.42	−0.35	−0.05	−0.99, 0.29	−0.19	−0.03	−0.83, 0.44
Comorbid conditions															
0	Ref														
1–2	0.17	0.05	−0.18, 0.52	0.34	0.02	−1.19, 1.86	0.47	0.07	−0.16, 1.10	0.22	0.03	−0.41, 0.85	0.02	0.003	−06, 0.65
3≥	0.12	0.02	−0.56, 0.79	0.21	1.51	−2.75, 3.17	0.17	0.01	−1.06, 1.39	0.22	0.02	−0.99, 1.45	0.02	−0.001	−1.22, 1.18
CKD stage															
Stage 4	Ref														
Stage5	0.12	0.02	−0.51, 0.74	0.64	0.02	−2.13, 3.4	0.12	0.01	−1.07, 1.31	0.14	0.01	−1.04, 1.32	0.15	0.01	−1.01, 1.32
HD	2.27	0.58***	1.81, 2.73	9.22	0.55***	7.19, 11.2	3.77	0.54***	2.90, 4.63	3.88	0.55***	3.03, 4.73	3.62	0.53***	2.78, 4.46
PD	1.05	0.16**	0.39, 1.71	3.85	0.14**	0.96, 6.74	1.98	0.17**	0.76, 3.21	1.64	0.14**	0.43, 2.85	1.21	0.11*	−0.01, 2.4

Table 4: Multiple regression analyses predicting total symptom burden, prevalence, distress, severity and frequency.

*p < 0.05; **p < 0.01; ***p < 0.001.
Note: B = unstandardised regression coefficient, β = standardised regression coefficient (it allows for a direct comparison between coefficients as to their relative explanatory power of the dependent variable (Hair et al. 2014).

We found that the most burdensome symptoms in HD group were more related to the physical symptoms. These unpleasant symptoms have been previously documented among people with HD (Jablonski 2007; Danquah *et al*. 2010; Caplin *et al*. 2011). Although, the pathophysiological mechanisms underlying these symptoms are still not fully understood (Thong *et al*. 2009), treatment modality was the strongest contributor to symptom burden in this study. Despite a high percentage of missing data (20%) in the questions assessing symptoms associated with sexual problems, which could be due to the cultural background of the sample, this study found that sexual problems were the most severe and frequent symptoms in the HD group. Similar findings have been reported in other studies involving other cultural groups (Abdel-Kader *et al*. 2009; Yong *et al*. 2009). Patients regardless of cultural background tend not to report sexual symptoms unless the clinician specifically asks about it. Developing a standardised assessment method that helps patients to freely express their views on sensitive issues is needed.

Interestingly, fatigue was more dominant in the PD group compared with other groups. This finding is consistent with that of a previous study that investigated impact of fatigue on daily activity in people with end stage kidney disease (Bonner *et al*. 2010). Persistent fatigue could be an indicator of poor HRQoL (Bonner *et al*. 2010) and may reflect the dialysis adequacy and patient outcomes (Artom *et al*. 2014). Early assessment and management of fatigue may indirectly improve other symptoms, such as sleep disturbance or depression (Artom *et al*. 2014). Given this, more attention to fatigue assessment, especially for PD patients is warranted and development of interventions that focus on energy conservation is needed.

Symptom burden in advanced CKD were predicted by HD treatment, older age and female gender. Dialysis treatment was the strongest predictor of symptom burden in particularly in those receiving HD. Older age was also found as one of the predictors of increased symptom burden in this study. In the general healthy population, older people experience more deterioration in physiological functions as well as symptom burden, so it is not surprising in the CKD population (Zhang *et al*. 2014; Eckerblad *et al*. 2015). These findings may help clinicians to recognise the patients who are at high-risk of experiencing a greater symptom burden and then to facilitate implementation of early and timely management and referral (e.g. palliative care team for symptom control). Women were also more likely to report greater symptom burden than men. Similarly, other studies suggest that male patients in Western countries seem to be less willing to report symptoms (Danquah *et al*. 2010; Caplin *et al*. 2011). In Middle Eastern countries, male patients possibly report fewer symptoms due to cultural reasons (men should be more patient and tolerant, and avoid expressing their feelings in public). This finding may also reflect the fact that women with CKD experience a higher symptom burden than men. For example, evidence suggests that increased depression and anxiety in women is associated with physiological factors such as hormonal changes (Albert 2015). Consequently, depression may lead to increased fatigue and sleep disturbance. Thus, we strongly suggest that clinicians should take into consideration gender diversity and cultural backgrounds during the assessment of symptoms. Surprisingly, co-morbid conditions did not predict symptom burden. This may be because most of the participants in this study had relatively few co-morbidities. However, more studies are needed to confirm the associations between all of these previous factors and symptom burden because of the few reports in the literature, which have investigated some of these relationships (Abdel-Kader *et al*. 2009; Danquah *et al*. 2010).

There were some limitations for this study. More sophisticated research designs are needed to explore symptom burden in CKD such as longitudinal research. Despite the large sample size, the numbers in the stage 5 conservative management and PD groups were relatively small which may reduce the generalisability of these results. We used the CKD-SBI to assess symptom burden, and although the validity and reliability of this instrument has been demonstrated, it has not been used in other cultural groups.

IMPLICATIONS FOR PRACTICE

In this study, it has been argued that the symptom experience should not be considered uni-dimensional because many prevalent symptoms are not necessarily the most distressing or severe. However, people with CKD experience a variety of symptoms as part of their daily lives and achieving total absence of these symptoms may not be a feasible objective. Therefore, management of CKD symptoms should be directed towards reducing the total symptom burden rather than simply preventing occurrence of individual symptoms. Given this, reducing the distress, severity and frequency of symptoms is crucial to alleviate the total symptom burden. In addition,

minimising the levels of distress, severity and frequency of the symptoms may reflect an effective intervention and may be used to evaluate the implementation of symptom management strategies. Thus, multidimensional assessment of symptom burden is required at different stages and trajectory of CKD is needed to better understand the total symptom burden, and to develop effective management.

Fatigue was overwhelming in advanced CKD regardless of the disease stages and treatment modalities. Fatigue, pain and sexual dysfunction are key contributors to symptom burden, and these symptoms are often under-recognised and warrant routine assessment. Strategies to minimise the distress, severity and frequency of these symptoms are required to diminish the total symptom burden in CKD.

Burden of psychological symptoms was comparable among all CKD groups. The psychological stressors in patients not undergoing dialysis might be explained by the early and growing impact of the complexity of CKD treatment on coping mechanisms, roles in the family, social support, reduced physical function, sexual dysfunction and impending dialysis treatment (Cantekin *et al*. 2014). Given the high burden of psychological symptoms among patients not on dialysis, psychologists or counsellors should also be involved in multidisciplinary teams for this group. Strategies to assist patients to cope with CKD and its complex management may improve adherence and this may also assist with slowing disease progression.

Finally, information about the factors that affect the symptom burden should alert clinicians about people at high-risk of experience greater symptom burden. Thus, people who are older age, female or receiving dialysis treatment, require comprehensive symptom assessments and further attention to facilitate implementation of early and timely management and referral.

CONCLUSION

Symptom burden is high in CKD stage 4 and 5. In CKD, symptom burden is better understood when considering the multidimensional aspects of a range of physical and psychological symptoms. Efforts to reduce the distress, severity and frequency of symptoms may lead to reduction of symptom burden in people with CKD. The CKD-SBI offers a valuable tool for renal clinicians to assess symptom burden at all CKD stags and treatment modalities, leading to the commencement of timely and appropriate interventions.

CONFLICTS OF INTEREST

No conflict of interest has been declared by the authors.

AUTHOR CONTRIBUTIONS

Each of the co-authors has contributed significantly. HA: designed the study, conducted data collection, statistical analyses and drafted the manuscript. AB; CD: participated in the research design and made critical revisions to the manuscript. All authors approved the final manuscript.

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SUPPORTING INFORMATION

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Table S1. CKD-symptom burden index.

Table S2. Symptom characteristics in each CKD group.