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Original article

Pill-burden and its association with treatment burden among patients with advanced stages of chronic kidney disease

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is associated with multimorbidity and high treatment burden. Pill-burden is one component of the overall treatment burden. However, little is known about its magnitude and contribution to the overall treatment burden among patients with advanced stages of CKD. This study aimed to quantify the magnitude of pill-burden in dialysis-dependent vs. non-dialysis-dependent advanced-stage CKD patients and its association with treatment burden.

Methods: This was a cross-sectional study for the assessment of pill-burden and treatment burden among non-dialysis and hemodialysis (HD)-dependent CKD patients. Pill-burden was quantified as "number of pills/patient/week" through electronic medical record, while treatment burden was assessed using the "Treatment Burden Questionnaire (TBQ)". Furthermore, oral and parenteral medication burden was also quantified. Data were analyzed using both descriptive and inferential analysis, including Mann – Whitney *U* test and two-way between groups analysis of variance (ANOVA).

Results: Among the 280 patients included in the analysis, the median (IQR) number of prescribed chronic medications was 12 (5.7) oral and 3 (2) parenteral medications. The median (IQR) pill-burden was 112 (55) pills/week. HD patients experienced higher pill-burden than non-dialysis patients [122 (61) vs. 109 (33) pills/week]; however, this difference did not reach statistical significance ($p = 0.81$). The most commonly prescribed oral medications were vitamin D (90.4%), sevelamer carbonate (65%), cinacalcet (67.5%), and statins (67.1%). Overall, patients who had high pill-burden (≥112 pills/week) had significantly higher perceived treatment burden compared to low pill-burden patients (<112 pills/week) [47 (36.2) vs. 38.5(36.7); $p = 0.0085$]. However, two-way ANOVA showed that dialysis status is the significant contributor to the treatment-burden in the high overall pill-burden group ($p < 0.01$), the high oral-medication-burden group ($p < 0.01$), and the high parenteral-medication-burden group ($p = 0.004$).

Conclusions: Patients with advanced CKD experienced a high pill-burden, which increases the treatment burden; however, the dialysis status of the patient is the main factor affecting the overall treatment burden. Future intervention studies should target this population with an aim to reduce polypharmacy, pill-burden, and treatment burden, which may ultimately improve CKD patients' quality of life.

1. Introduction

Chronic kidney disease (CKD) had risen from being the thirteenth to the tenths leading cause of death worldwide, with mortality increase from 813000 in 2000 to 1.3 million in 2019 (World Health Organization, 2020). CKD is associated with several complications and comorbidities, including, anemia, secondary hyperparathyroidism, metabolic acidosis, renal osteodystrophy, gout, and cardiovascular diseases (CVDs) (Bello et al., 2017; Bikbov

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et al., 2020; Jankowski, Floege, Fliser, Böhm, & Marx, 2021; Thomas, Kanso, & Sedor, 2008). End-stage renal disease (ESRD), which is associated with renal replacement therapy (RRT) such as renal transplantation (RT) or hemodialysis (HD), was projected to increase from 2.5 million to 5.4 million cases worldwide by 2030 (Liyanage et al., 2015). ESRD patients on RRT have a worse prognosis due to being at a higher risk of developing CKD complications compared to patients with mild to moderate CKD (Tzanakaki et al., 2014). Likewise, non-dialysis patients with stage 4 or stage 5 CKD who receive conservative management, were also found to experience similar complications to ESRD patients receiving HD (Hansen, Chin, Blalock, & Joy, 2009). Therefore, CKD patients, especially ESRD receiving RRT and non-dialysis patients at advanced stages, are at high risks of multiple health complications.

Consequently, polypharmacy, defined as the concurrent intake of five or more medications on a routine basis (Masnoon et al., 2017), is highly prevalent among patients with CKD (Laville et al., 2018; Mason, 2011). Previous studies have demonstrated that CKD patients, especially those with ESRD who received HD, experienced polypharmacy and increased pill-burden that can reach up to 25 pill/day, with more than 10 medications per day (Chiu et al., 2009; Hayward et al., 2021; Oosten et al., 2021). Of note, this predisposes patients to multiple risks, including, drug-drug interactions, drug-disease interactions, adverse drug reactions, and non-adherence due to high pill-burden (i.e. the number of pills taken per a patient per day) (Aggarwal, Woolford, & Patel, 2020). (Chiu et al., 2009; Hayward et al., 2021; Marienne et al., 2021; Oosten et al., 2021). Therefore, pill-burden is a common health concern in CKD patients.

Polypharmacy and its associated pill-burden can contribute to "treatment burden" (Morris et al., 2021), defined as "the workload of healthcare and its effect on patient functioning and well-being" (Trakoli, 2021). In the context of CKD, based on patient-reported outcome measures assessing the treatment burden of CKD, treatment regimen measures, distress measures, barriers to self-care measures, and treatment satisfaction measures were the main factors contributing to the overall treatment burden (Eton et al., 2013). Therefore, treatment or medication regimen complexity, which can be explained by pill-burden, is an important contributor to the overall treatment burden. CKD patients, especially those with ESRD undergoing dialysis, have reported an increased treatment burden, and this was associated with a lower adherence to medications, lower patient capacity, and poorer health-related quality of life (HR-QoL) (Al-mansouri et al., 2021; Hounkpatin et al., 2020; Roberti et al., 2018).

To date, little is known about the contribution of pill-burden to the overall treatment burden globally, especially in Middle East countries including Qatar. Although treatment burden and its effect on the HR-QoL of patients at different stages of CKD were previously reported by our research group (Al-mansouri et al., 2021), the magnitude of the pill-burden and its association with treatment burden was not reported, especially among patients with advanced stages of CKD and ESRD. Therefore, the aim of this study was to quantify the magnitude of pill-burden in dialysis-dependent and non-dialysis-dependent advanced stage CKD patients and to investigate its association with treatment burden.

2. Methods

2.1. Study design and setting

A cross-sectional assessment of the pill-burden and its association with the overall treatment burden was conducted among patients with advanced stages of CKD at Fahad Bin Jassim Kidney Center (FBJKC). This is a specialized healthcare facility that is considered as the primary dialysis center, catering for around 50% of all patients receiving dialysis in Qatar, under the Hamad Medical Corporation (HMC).

2.2. Target population and sample size

The target population included all CKD patients at stage 4 (non-dialysis patients with estimated glomerular filtration rate [eGFR] of 15–25 ml/min) and stage 5 (non-dialysis patients and dialysis patients with eGFR < 15 ml/min) who met the study's inclusion criteria. Patients were included if they were: adults (≥18 years old), with advanced CKD (stages 3, 4, or 5) diagnosis, and receiving nephrology care at FBJKC, and being on dialysis or non-dialysis but followed up at 'the low clearance clinic' at FBJKC for at least two months. The patients who were excluded include pregnant women, critically-ill patients, mentally-ill patients, patients with dementia, and those who were unconscious.

The sample size required for the study was calculated with a validated equation (Charan & Biswas, 2013) using critical parameters, including, 95% confidence level, 5% margin of error, and the total number of CKD patients (713 [HD = 533, and non-dialysis = 180]). The minimum calculated sample size required to reach statistical significance was 288 patients. Patient recruitment was done through a sampling-by-convenience method, and potentially eligible participants attending the clinics were identified, approached and consented by a nurse researcher. The potential participants who met the eligibility criteria were consecutively approached and those who declined consent were excluded. We approached 460 eligible participants (HD = 380 and pre-dialysis = 80) out of which only 280 consented (HD = 223 and pre-dialysis = 57). Therefore, several patients (n = 180) declined or were unable to participate in the study.

2.3. Data collection procedures

The sociodemographic and clinical characteristics, and data relating to co-morbidities were collected from 1 June 2017 to 20 November 2017 from the patients' medical records available through the electronic health information system used in FBJKC (i.e. Cerner®). Pill-burden was calculated as 'number of pills per patient per week' after reviewing each patient's medications list through the Cerner®. All chronic medications and their corresponding frequencies and durations were extracted for each patient, and then the total weekly pill-burden was calculated. Weekly pill-burden was calculated for chronic medications only, including oral and parenteral medications. A parenteral medication here refers to any medication administered by routes other than the digestive tract, including intramuscular, intravenous, subcutaneous, and intrathecal medications. However, other medications prescribed for acute illnesses, such as antibiotics, were excluded in the pill-burden determination. Additionally, any prescribed over-the-counter medications (OTC) such as analgesics, antacids, simethicone… etc., were calculated at lowest possible frequency to avoid an overestimation of the pill-burden. Pill-burden was later categorized into a high pill-burden or a low pill-burden based on the median pill-burden of the study sample. A pill-burden lower than the median would be considered low, while a pill-burden that was greater than or equal to the median would be considered high, based on consensus by the study investigators.

Treatment burden was assessed using the Treatment-Burden-Questionnaire (TBQ), developed by Tran et al. (Tran et al., 2014). The TBQ is a 15-item Likert-type scale-based questionnaire designed to measure treatment burden in patients with chronic medical conditions. Each of the items' responses are reported with a Likert scale scores ranging from 0 (not a problem) to 10 (a big

problem). A total score is generated through the summation of each item score to a maximum of 150 points. Of note, a higher score of the TBQ represents a higher treatment burden. An Arabic version of TBQ was translated and linguistically validated based on the principles of good practice for the translation of patient-related-outcomes measures (Al-mansouri et al., 2021; Wild et al., 2005). The questionnaire administration was done through face-to-face structured interviews in a designated room at the study site. More details about this and the use of TBQ to determine the overall treatment burden was published in a companion paper by Al-mansouri et. al. (Al-mansouri et al., 2021).

2.4. Data analyses

First, the Kolmogorov-Smirnov test was used to assess data normality to ensure that the choice of statistical tests for data analysis was appropriate and robust. Patients' demographic, clinical characteristics, and the calculated weekly pill-burden were reported using descriptive statistics, including frequencies (percentages) and median (IQR). Mann-Whitney-*U* test was used to compare the weekly pill-burden in HD and non-dialysis, while a Chi-square test of independence was used to compare the groups for categorical data. Analysis of any probable differences in pill-burden was done with Mann-Whitney-U and Kruskal-Wallis tests. A further analysis was conducted to compare the TBQ scores between the dialysis and non-dialysis patients considering the pill-burden category using a two-way between groups analysis of variance test (two-way ANOVA). Data analyses were performed using the Statistical Package for Social Sciences (SPSS), version 24.

2.5. Ethical considerations

The study protocol was approved by the Institutional Review Board of the Medical Research Center (MRC) at HMC under the approval number 16364/16. This was an observational study that did not involve any intervention or invasive procedures, and written informed consent was obtained from all the participants prior to recruitment.

3. Results

3.1. Participants' selection and enrolment

Of the 713 patients with CKD receiving care at FBJKC, 460 eligible patients were approached but only 280 consented to participate in the study (HD = 223, and non-dialysis = 57). Fig. 1 illustrates the process of participant's selection and recruitment. All the data were collected through an electronic medical record system and an interviewer-administered technique, and there were no missing or invalid data.

3.2. Demographic and clinical characteristics of the study participants

The median (IQR) age of the participants was 59 (19) years. The majority of the participants were male (54.6%), married (67.5%), and with secondary school or higher education (59%). Only 31.4% of the CKD patients were employed and the rest were unemployed (39.3%) or retired (29.3%). Most patients reported never smoking (76.8%) or ex-smoking history (18.2%). Table 1 provides further details on the sociodemographic characteristics of the participants.

Regarding the participants' clinical characteristics, 95.4% of them were at CKD stage 5. The median (IQR) duration of follow-up in non-dialysis clinic and the dialysis duration in HD patients were 2 (4) years and 3.1 (4.8) years, respectively. The median Kt/V, the parameter for measuring the efficacy of a HD session for HD patients was 1.7 (0.44) mL/min. The median serum creatinine level for pre-dialysis patients was 301 (460) μmol/L [eGFR of 11 (5.5) mL/min/1.732 m^2]. Hypertension and diabetes were the most prevalent comorbidities among the study participants, accounting for 94.6% and 67.5%, respectively. More information about the co-morbidities among the study participants is represented in Table 2.

3.3. Pill-burden among patients with advanced CKD in Qatar

The utilization of chronic medications and pill-burden per week among the study population are presented in Table 3. In general, the median (IQR) number of medications a patient consumed per day was 12 (5.7) oral medications and 3 (2) parenteral medications. In the sub-group analysis, HD patients were prescribed significantly higher number of parenteral medications relative to non-dialysis patients (median (IQR) of 3 (2) versus 1 (2), respectively ($p < 0.001$). Both HD and non-dialysis patients were prescribed similar number of oral medications [median (IQR) 12 (5), $p = 0.27$]. The median (IQR) weekly pill-burden for the entire study cohort was 112 (55) pills/week. Therefore, 112 was considered as the cut-off for categorizing the total pill-burden as low or high. HD patients experienced a higher pill-burden relative to non-dialysis patients [122 (61) vs. 109 (33) pills/week], but this difference did not reach statistical significance ($p = 0.81$).

The most commonly prescribed oral medications were vitamin D (90.4%), sevelamer carbonate (65%), calcium (Ca) as a phosphate binder or supplement (63.2%), cinacalcet (67.5%), and statins (67.1 %). Medication utilization pattern in HD patients for erythropoiesis-stimulating agents (ESAs), iron, vitamin D, phosphate binders, Ca-supplement and parathyroid hormone (PTH) medication, was significantly higher compared to non-dialysis (Table 3). In contrast, the utilization of diuretics and calcium channel blockers (CCBs) was higher in non-dialysis patients compared to HD patients (50.9% vs. 23.8%; $p < 0.001$) and (75.4 % vs. 57 %; $p = 0.011$), respectively.

3.4. Effect of pill-burden on treatment burden

The detailed findings of the perceived treatment burden measured with the TBQ among these CKD patients was previously reported by Al-mansouri et al. (Al-mansouri et al., 2021). Further analysis was conducted to determine the relationship between pill-burden and perceived treatment burden. Treatment burden was significantly higher among patients who received greater number of oral or parenteral medications. Patients who were prescribed more than 12 oral medications per day perceived significantly higher treatment burden compared to the lower category [47 (37) vs. 36 (35.5); $p = 0.006$]. Similarly, patients who received higher parenteral medications (4–7) experienced significantly higher treatment burden compared to lower parenteral medication consumers (<4) [50.5 (38.7) vs. 36.5 (32.5); $p < 0.001$]. Additionally, patients who had higher pill-burden per week (112–239 pills/week) had significantly higher treatment burden compared to patients with lower pill burden (22–111 pills per week) [47 (36.2) vs. 38.5 (36.7); $p = 0.0085$].

However, further analysis conducted to compare the HD and the non-dialysis groups showed that only the dialysis status (HD vs. non-dialysis) significantly affected the treatment-burden and the TBQ score. That is, overall, HD patients had an overall higher treatment burden compared to non-dialysis patients in both high-pill burden group and low-pill burden group [48.1 (22.1) and 43.4 (24.1) for HD vs. 28.3 (24.8) and 31.5 (18.4) for non-dialysis respectively; $p < 0.001$ for the dialysis status effect and $p = 0.827$ for the pill-burden category effect]. Similarly, when comparing at the level of oral medication burden, the TBQ score was

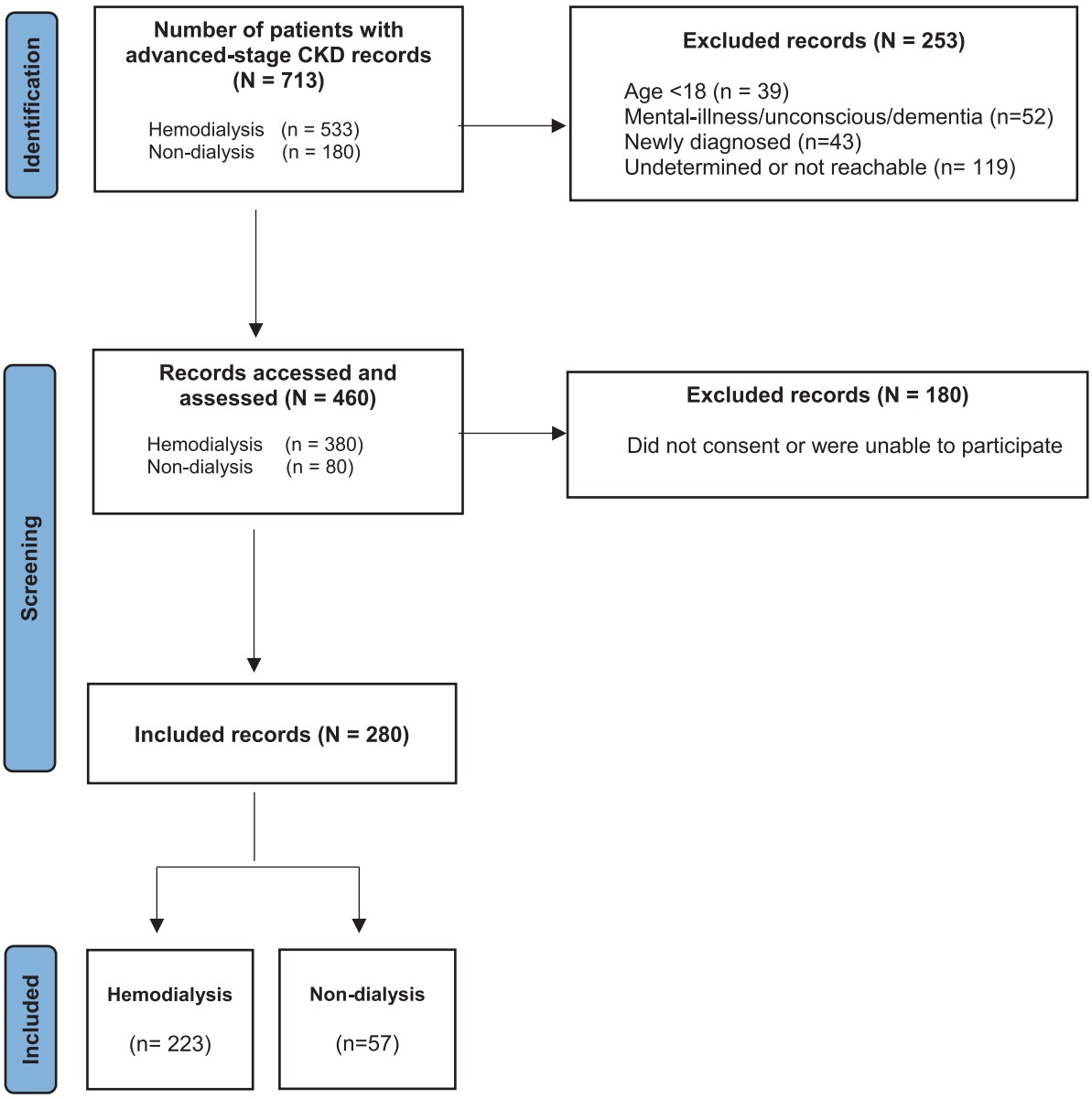

Fig. 1. Flow diagram of the process of CKD patients' enrollment into the study.

higher for the HD patients who had high and low pill-burden compared to the non-dialysis patients [50.1 (22.2) and 41.7 (23.5) for the HD group vs. 27.5 (19.3) and 31.5 (22.9) for the non-dialysis group; $p < 0.001$ for the dialysis status effect and 0.534 for the oral-pill-burden effect. Similar results were obtained when comparing the TBQ in dialysis and non-dialysis patients who have high parenteral medications burden vs. those who have low parenteral medications burden. The detailed TBQ scores are reported along with the significant p-values in Table 4.

4. Discussion

Patients with CKD commonly experience pill-burden as a complication of polypharmacy (Aggarwal et al., 2020). Polypharmacy is associated with many adverse outcomes including drug-drug interactions, poor adherence, and decreased QoL. This decline in QoL may be explained by the increased pill-burden which adds to the treatment burden (Parker & Wong, 2019). In this study, we sought to determine the magnitude of the pre-existing pill-burden among patients with CKD in Qatar and to investigate its association with the overall treatment burden. The findings revealed that most advanced stages-CKD patients in experienced a high pill-burden. Moreover, the increase in pill-burden was significantly associated with a corresponding increase in overall treatment burden as per the TBQ results.

To date, limited studies have quantified the medication burden in the context of CKD. For instance, in a study conducted among elderly CKD patients in France, patients were on a median of nine medications per day with antihypertensive agents, antithrombotic agents, and anti-anemics as the most commonly used medications (Roux-Marson et al., 2020). Another study from Germany reported a similar conclusion; however, the most commonly prescribed medications that contributed to polypharmacy and medication burden were antihypertensives, statins, allopurinol, and vitamin D supplements (Schmidt et al., 2019). In addition, recent findings have demonstrated that more than 90% of the CKD patients received five or more medications daily, and 43% were on 10 or more daily medications (Hayward et al., 2021). Similarly, a study conducted in the United Arab Emirates also concluded that CKD

Table 1
Sociodemographic characteristics of the study participants (N = 280).

Variable	Hemodialysis (n = 223)	Non-dialysis (n = 57)	Total (N = 280)	P-value*
Median (IQR)				
Age	60 (20)	55 (18)	59 (19)	0.24**
n (%)				
Gender				0.581
Male	120 (53.8)	33 (57.9)	153 (54.6)	
Female	103 (46.2)	24 (42.1)	127 (45.4)	
Smoking status				0.722
Never smoker	172 (77.1)	43 (75.4)	215 (76.8)	
Former smoker	39 (17.5)	12 (21.1)	51 (18.2)	
Current smoker	12 (5.4)	2 (3.5)	14 (5)	
Educational level				0.006
No education	72 (32.3)	18 (31.6)	90 (32.1)	
Primary	23 (10.3)	2 (3.5)	25 (8.9)	
Secondary	74 (33.2)	11 (19.3)	85 (30.4)	
College/ University	54 (24.2)	26 (45.6)	80 (28.6)	
Marital status				0.034
Married	142 (63.7)	47 (82.5)	189 (67.5)	
Single	35 (15.7)	6 (10.5)	41 (14.6)	
Divorced	14 (6.3)	0 (0)	14 (5)	
Widow	32 (14.3)	4 (7)	36 (12.9)	
Employment status				< 0.001
Unemployed	92 (41.3)	18 (31.6)	110 (39.3)	
Employed	56 (25.1)	32 (56.1)	88 (31.4)	
Retired	75 (33.6)	7 (12.3)	82 (29.3)	

* P-value was calculated using Pearson's chi-squared (X^2) test unless otherwise specified.
** P-value was calculated using Mann – Whitney *U* test.

Table 2
Clinical characteristics of the study participants (N = 280).

Variable	Hemodialysis (n = 223)	Non-dialysis (n = 57)	Total (N = 280)	P-value*
Median (IQR)				
Serum creatinine (μmol/L)	-	301 (460)	301 (460)	-
eGFR (ml/min/1.73m^2)	-	11 (5.50)	11 (5.50)	-
Dialysis duration (months)	37 (50)	-	37 (50)	-
Kt/V (ml/min)	1.7 (0.44)	-	1.7 (0.44)	-
Hgb (%)	11.3 (1.4)	11 (1.5)	11.3 (1.4)	0.006**
Hct (%)	34.9 (4.7)	33.8 (4.5)	34.8 (4.55)	0.025**
Ferritin (mcg/L)	709 (432)	161 (226.7)	38 (5)	< 0.001**
Number of comorbidities	3 (2)	2 (3)	3 (2)	< 0.001**
n (%)				
CKD stage (eGFR)				< 0.001
CKD stage 3 (30 – 59 ml/min)	0 (0)	2 (3.5)	2 (0.7)	
CKD stage 4 (15 – 29 ml/min)	1 (0.4)	10 (17.5)	11 (3.9)	
CKD stage 5 (< 15 ml/min)	222 (99.6)	45 (78.9)	267 (95.4)	
Hypertension				< 0.001
No	5 (2.2)	10 (17.5)	15 (5.4)	
Yes	218 (97.8)	47 (82.5)	265 (94.6)	
Diabetes				0.066
No	66 (29.6)	25 (43.9)	91 (32.5)	
Type 1	15 (6.7)	1 (1.8)	16 (5.7)	
Type 2	142 (63.7)	31 (54.4)	173 (61.8)	
Dyslipidemia				0.814
No	141 (63.2)	37 (64.9)	178 (63.6)	
Yes	82 (36.8)	20 (35.1)	102 (36.4)	
Cardiac disease				0.005
No	126 (56.5)	39 (68.4)	165 (58.9)	
CAD	42 (18.8)	18 (31.6)	60 (21.4)	
Angina	1 (0.4)	0 (0)	1 (0.4)	
Cardiomyopathy	6 (2.7)	0 (0)	6 (2.1)	
Heart failure	4 (1.4)	0 (0)	4 (1.4)	
Valvular heart disease	2 (0.9)	0 (0)	2 (0.7)	
Other	42 (18.8)	0 (0)	42 (15)	
Eye disease				0.075
No	170 (76.2)	50 (87.7)	220 (78.6)	
Diabetic retinopathy	29 (13)	7 (12.3)	36 (12.9)	
Blindness	6 (2.7)	0 (0)	6 (2.1)	
Others	18 (8.1)	0 (0)	18 (6.4)	

* P-value was calculated using Pearson's chi-squared (X^2) test unless otherwise specified.
** P-value was calculated using Mann-Whitney *U* test.

Table 3
Chronic medications and pill burden per week in patients with CKD in Qatar (N = 280).

Variable	Hemodialysis (n = 223)	Non-dialysis (n = 57)	Total (N = 280)	P-value*
Median (IQR)				
Total number of oral medications	12 (5)	12 (5)	12 (5.7)	0.27**
Total number of parental medications	3 (2)	1 (2)	3 (2)	**< 0.001****
Total pill burden/week	122 (61)	109 (33)	112 (55)	0.81**
n (%)				
ESA				**< 0.001**
No	30 (13.5)	26 (45.6)	56 (20)	
Yes	193 (86.5)	31 (54.4)	244 (80)	
Iron				**< 0.001**
No	29 (13)	43 (75.4)	72 (25.7)	
Yes	194 (87)	14 (24.6)	208 (74.3)	
Vitamin D				**< 0.001**
No	14 (6.3)	13 (22.8)	27 (9.6)	
Yes	209 (93.7)	44 (77.2)	253 (90.4)	
Phosphate binders				**< 0.001**
No	62 (27.8)	36 (63.2)	98 (35)	
Yes	161 (72.2)	21 (36.8)	182 (65)	
Ca^{+} supplements				**< 0.001**
No	62 (26.8)	41 (71.9)	103 (36.8)	
Yes	161 (72.2)	16 (28.1)	177 (63.2)	
PTH medications				**< 0.001**
No	48 (21.5)	43 (75.4)	91 (32.5)	
Yes	175 (78.5)	14 (24.6)	189 (67.5)	
ACEIs				0.424
No	200 (89.7)	49 (86)	243 (86.8)	
Yes	23 (10.3)	8 (14)	37 (13.2)	
ARBs				**< 0.001**
No	204 (91.5)	39 (68.4)	243 (86.8)	
Yes	19 (8.5)	18 (31.6)	37 (13.2)	
Diuretics				**< 0.001**
No	170 (76.2)	28 (49.1)	198 (70.7)	
Yes	53 (23.8)	29 (50.9)	82 (29.3)	
Beta blockers				0.333
No	94 (42.2)	20 (35.1)	114 (40.7)	
Yes	129 (57.8)	37 (64.9)	166 (59.3)	
Calcium channel blockers				**0.011**
No	96 (43)	14 (24.6)	110 (39.3)	
Yes	127 (57)	43 (75.4)	170 (60.7)	
Statins				0.070
No	79 (35.4)	13 (22.8)	92 (32.9)	
Yes	144 (64.6)	44 (77.2)	188 (67.1)	
Anti-diabetic medication				**0.010**
No	78 (35)	28 (49.1)	106 (37.9)	
Mono oral ± insulin	36 (16.1)	10 (17.5)	46 (16.4)	
Dual oral ± insulin	10 (4.5)	5 (8.8)	15 (5.4)	
Triple oral ±insulin	0 (0)	1 (1.8)	1 (0.4)	
Combination injectable therapy	99 (44.4)	13 (22.8)	112 (40)	
Anticoagulant				0.792
No	205 (91.9)	53 (93)	258 (92.1)	
Yes	18 (8.1)	4 (7)	22 (7.9)	
Analgesic				0.153
No	159 (71.3)	46 (80.7)	205 (73.2)	
Yes	64 (28.7)	11 (19.3)	75 (26.8)	

* P-value was calculated using Pearson's chi-squared (X^2) test unless otherwise specified.
** P-value was calculated using Mann – Whitney *U* test.

Table 4
The effect of oral medications, parenteral medications, and pill burden on treatment burden score among patients with CKD.

TBQ Mean Score (SD)				
	Dialysis status			**P-value***
	Hemodialysis (n = 223)	**Non-dialysis (n = 57)**	**Total (N = 280)**	
Oral medications category				< 0.001for the dialysis status
4 - 12 medications	41.7 (23.5)	31.5 (22.9)	39.3 (23.7)	
> 12 medications	50.1 (22.2)	27.5 (19.3)	46.3 (23.3)	
Parenteral medications category				0.004 for the dialysis status
0 - 3 medications	42.2 (21.9)	30.5 (21.7)	38.8 (22.5)	
> 3 medications	51.1 (23.9)	15.0 (8.5)	50.3 (24.3)	
Overall pill burden category				< 0.001 for the dialysis status
< 112 pill/week	43.4 (24.1)	31.5 (18.4)	40.8 (23.5)	
≥ 112 pill/week	48.1 (22.1)	28.3 (24.8)	44.3 (23.9)	

* P-value was calculated using two-way between groups analysis of variance.

patients experienced higher medication burden due to polypharmacy (Shouqair, Rabbani, & Kurian, 2021). In our study, the cohort's median number of medications per day was 12. As for the pill-burden, in our study it was reported to be around 112 pills/week (i.e. 16 pills/day). However, the majority of previous studies did not detail the complete picture of the medication regimens, including doses and frequencies. Therefore, previous studies have not reported pill-burden, but rather explained medication burden in terms of number of medications per day. To our knowledge, limited studies have explained medication burden in terms of pill-burden. In one of these studies that was performed in the USA to explain pill-burden, the median pill-burden for CKD patients on dialysis was reported to be 19 pills/day and it reached up to 25 pill/day in one-quarter of the studied cohort (Chiu et al., 2009). Our cohort's median pill-burden was somewhat lower which may be due to the fact that we included both non-dialysis and HD patients. This assumption can be further supported by our results which demonstrated that the pill-burden in the HD group was around 122 pills/week (i.e. 17.4 pills/day), which is correlated to the findings of the USA study and confirms that dialysis patients have a higher pill-burden. In addition, the different settings, healthcare systems, management protocols, and patient cohorts may be additional factors to explain the differences.

Baseline characteristics may have impacted the findings of the pill-burden and the treatment burden. For instance, the high proportion of patients with no or low-level of formal education might have affected the overall treatment burden having a higher treatment burden compared to their peers with high-level of education (Al-mansouri et al., 2021). In addition, when comparing the pill-burden among HD and non-dialysis groups, HD patients experienced a higher pill-burden. This is possibly because the HD patients have more advanced ESRD compared to the non-dialysis patients, which predisposes them to more complications and other comorbidities. Furthermore, there were statistically significant higher differences in the prevalence of baseline hypertension and cardiac diseases among patients with HD compared to their non-dialysis counterparts (Hounkpatin et al., 2020). Thus, these patients would expectedly consume more medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and other medications used for the treatment of these comorbidities. Therefore, the pill-burden was higher in the HD group compared to the non-dialysis group.

Although medication-burden is very important, previous research showed that it is only one of multiple factors influencing the overall treatment burden (Gallacher et al., 2014). Treatment burden is considered a comprehensive measure than pill-burden since it was shown to be directly associated with other health complications in different health conditions, including, non-adherence to medications, increased mortality and morbidity, and poorer HR-QoL (Mohammed, Moles, & Chen, n.d.; Tesfaye et al., 2020). In the context of CKD, patients were proven to experience a lower HR-QoL due to perceived treatment burden (Al-mansouri et al., 2021; Ducharlet et al., 2019; Tesfaye et al., 2020). Furthermore, treatment burden was quantified and well-correlated to HR-QoL, and a decrease in HR-QoL was reported with an increase in treatment burden among patients with CKD (Al-mansouri et al., 2021). Nonetheless, the contribution of medication burden or pill-burden to the overall treatment burden was not yet established. Therefore, in the current study, we explained the association between medication burden, represented as pill-burden, and treatment burden in patient with advanced CKD. Overall, we demonstrated that pill-burden has a direct association with treatment burden in this patient population. However, when taking both the pill-burden with the dialysis status (being on HD or non-dialysis), the effect of pill-burden to the overall treatment burden did not reach significance, and the dialysis status was the main driver for the treatment burden. This conclusion was consistent across three categories of pill-burden, the overall bill-burden (high pill burden represented as $\geq$ 112 pill/ week or low pill-burden defined as < 112 pills/week), the oral medications burden (high or low categories), and the parenteral medications-burden (high or low). To our knowledge, this association between the number of chronic medications or pill-burden, and treatment burden, taking the dialysis status into account was not investigated quantitatively in previous studies. However, previous qualitative studies have reported that intensified treatment regimens were associated with increased treatment burden in CKD and multimorbid patients (Eton et al., 2012; van Merode, van de Ven, & van den Akker, 2018). Nonetheless, whether or not it was attributed to the dialysis status or the pill-burden itself was not reported previously.

Our study has several strengths. First, it did not only describe polypharmacy in advanced CKD patients, but also quantified pill-burden per patient per week. Therefore, the study considered the complete picture of the patients' medication regimen complexity. Second, it is the first study to quantitatively demonstrate the correlation between pill-burden in different categories and overall treatment burden. Third, it is a well-designed observational study that has the strengths of observational studies, so data is more natural and based on real-world evidence. However, similar to any other research, it has some inherent limitations. First, this was cross-sectional study that captured treatment-related and pill-burden at a single point in time. This limited capturing of the burden of CKD complications such as anemia, calcium-phosphate imbalance, renal osteodystrophy, hyperparathyroidism, electrolyte imbalances. Therefore, the treatment burden might have been underestimated in this study. A longitudinal prospective study may provide a more comprehensive picture of how pill and treatment burden change over time in this population. Second, the interviewer administration of the TBQ was subject to social desirability and recall bias. Moreover, pill-burden was calculated using data available in electronic health record system which may be incomplete and may not account for other OTC chronic medications used by the patient. Lastly, this study was restricted to patients who were able to understand Arabic and/or English languages only, so treatment-related burden cannot be generalized to other patients who speaks different languages.

The findings of this study confirm the high medication-burden and treatment-burden experienced by patients with ESRD. The study sheds light on the categories of ESRD patients who experience pill-burden the most, i.e. HD patients. In addition, it summarized the most consumed medications by ESRD patients which contribute to their pill-burden, as well as the most common comorbidities they experience. Therefore, using the findings of our studies, some targeted clinical interventions can be made to decrease pill-burden. In previous literature, the use of combined formulations of medications (e.g. the use of tablets that combine two or three classes of antihypertensive medications instead of using each alone), the use of extended-release formulations with lower frequencies (e.g. using 60 mg gliclazide modified release tablets once a day instead of 30 mg tablets twice a day for the treatment of diabetes) were shown to reduce pill-burden and to be more cost-saving (Farrell, French Merkley, & Ingar, 2013). Therefore, similar more simplified drug regimens can be implemented for advanced-stage CKD patients to reduce the number of pills they consume. Further interventional studies to test the effect of these strategies, and other strategies, aimed to reduce pill-burden in CDK patients can be implemented for better clinical outcomes.

5. Conclusion

Increased treatment burden is a main cause for adverse clinical and patient-reported outcomes. Herein, we quantified medication

burden represented as pill-burden per patient per week for advanced CKD patients in Qatar, considering the complete medication regimens complexity. The findings suggest that patients in advanced stages of CKD experienced a high pill-burden, and pill-burden directly influenced the overall treatment burden. Future interventional studies should target this patients-population with the aim of reducing polypharmacy, pill-burden, treatment burden, which may ultimately improve CKD patients' HR-QoL. In addition, further research should be conducted to investigate the magnitude of other treatment burden components in CKD patients and their influence on treatment burden, especially in the context of Middle East countries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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