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Medication-related problems among adults with chronic kidney disease in Southwest, Nigeria: A Retrospective Study

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ABSTRACT

Background: There is a growing population of patients with chronic kidney disease (CKD) with a high burden of comorbidities and complications that require multiple medications which puts them at risk of medication-related problems (MRPs). This study aims to identify and describe the types of MRPs in CKD patients.

Methods: Current medical records of CKD patients attending the renal clinic of a tertiary hospital in Lagos were reviewed to retrieve data on patient demographics, diagnosis, and medication prescribed. The identified MRPs were categorized using the Pharmaceutical Care Network Europe classification of drug-related problem tool (PCNE DRP). Multivariate regression was utilized to assess the association between the dependent (MRPs) and independent variables (number of comorbidities, doses per day, medications, age, and stage of CKD). Statistical significance was set at $p < 0.05$.

Results: MRPs were identified and categorized in 89 patients (1.54 ± 0.66 MRPs/patient). The prevalent MRPs identified were drug use problems (38.4%), adverse drug reactions (16.2%), drug choice problems (14.1%) and dosing problems (12.1%). The odds of identifying MRPs increased with number of comorbidities [AOR 3.71 (95% CI 1.15-11.98); P <0.002], number of medications [OR 4.03 (95% CI 1.53-10.65); P <0.0001], and number of doses per day [AOR 4.02 (95% CI 1.49-10.89); P <0.0001].

Conclusion: Medication-Related Problems in CKD patients are high, mandating the need for scheduled review by hospital pharmacists to identify and make interventions with the knowledge of the attending clinicians.

1. Introduction

There is a growing global population of chronic kidney disease (CKD) with estimates of 9.1% (697.5 million) recorded cases [1, 2.] Patients with CKD suffer from a high number of comorbidities and consequent pathologic manifestations of impaired kidney function such as anemia, hyperparathyroidism, and CKD-related bone and mineral disease[3], which necessitate the need for multiple medications, both prescription-only and over-the-counter (OTC) medicines, to ameliorate the symptoms and progression of the disease [4-7]. In these patients the alteration in the pharmacokinetic and pharmacodynamic parameters of medications which clinicians must always consider while prescribing is paramount. Clinicians need to ensure these patients' medication safety is achieved via dosage adjustment [8,9].

Given the complexity of pharmacotherapy in patients with CKD, the occurrence of medication events is inevitable during prescribing in any clinical setting [10-12]. Any event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes in patients are referred to as medication-related problems (MRPs) [13]. These problems are a common occurrence in

CKD population with studies revealing 2-3 MRPs/patient in non-dialysis CKD and between 4-8 MRPs/patient in dialysis CKD [11, 12]. Some common MRPs in CKD are adverse drug reactions, drug-drug interactions, inappropriate dose, and poor adherence to medication [10,11,12,14].

In addition, since MRPs are very common in patients with CKD, identification, prevention, and management would require competency and an interdisciplinary approach [15, 16]. Identifying, resolving actual, and preventing potential MRPs is a major role pharmacist in community and hospital practice have assumed with the consent of clinicians [17-19]. MRPs unidentified and unresolved in CKD have a negative impact on desired patient and therapeutic outcomes resulting in reduced quality of life, increased hospital-stay, increased overall healthcare cost and even increasing the risk of morbidity and mortality[20, 21]. Despite numerous studies published on the recognized challenges of MRPs in CKD patients, few studies exist from the developing world. To add to the existing body of knowledge on MRPs in CKD, we reviewed the current medication prescription of CKD patients on a routine consult at the nephrology clinic of a tertiary hospital in Lagos State, South-West, Nigeria.

2. Method

This study was conducted in Lagos University Teaching Hospital (LUTH), a tertiary hospital with over 750 beds serving over 25 million people in Lagos State (6.5176° N, 3.3538° E). This study was carried out among CKD outpatients attending the renal clinic of the nephrology unit. Adult patients (>18 years) diagnosed with CKD (non-dialysis and dialysis) were considered eligible for inclusion. Ethical approval was obtained from the Hospital Research/Ethics Committee of LUTH before commencing the study (ADM/DCST/HREC/APP/334).

medical case notes of eligible CKD patients were sampled during a renal clinic day. The pharmacists retrieved data using a semi-structured data collecting tool designed a priori to capture the patient's socio-demographics (age, BMI, educational status, occupation), clinical characteristics (presence of comorbidities, laboratory evaluations), and current medication regimen. Each patient's current medication regimen was reviewed for relevant medication-related problems (MRP) utilizing a systematic approach which compares patients' pharmacotherapy with current evidence-based clinical practice guideline recommendations. [4] All identified MRPs were then categorized and grouped using the Pharmaceutical Care Network Europe classification of drug-related problem tool (PCNE DRP)[13]. The PCNE DRP tool is a classification scheme constructed to help health care professionals to document MRP information in their place of practice. The tool is classified into 3 primary domains - problems, causes, and interventions. The problems and causes domains were adopted which both consist of six subdomains – adverse reactions, drug choice problems, dosing problems, drug use problems, drug interactions, and others.

All statistical analysis was carried out on Statistical Package for Social Sciences (SPSS) version 22. Continuous variables were expressed as means ± standard deviations (SDs) while categorical variables as frequency distributions with percentages. Bivariate regression analysis was utilized to describe the association between the dependent variable (medication-related problems) and some independent variables (CKD stage, age, gender, number of comorbidities, number of medications and number of medication doses per day). These associations were expressed using adjusted odds ratio (AORs) with their 95% confidence intervals (CIs) considered statistically significant at p-value < 0.05.

3. Results

The demographics and characteristics of the 89 patients reviewed in this study are presented in Table 1. Most of the patients were male (59.1%) The overall mean age was 56.5 ± 13.8 years with a range of 27 to 82 years. The median number of medications per day was 8 (range: 4 -15) which translates to over 65.1% (n=58) of patients taking over 8 different medications per day. The median number of doses per day was 11 (Range: 4 - 24) (Table 1). Most of the patients were non-dialysis CKD (63.0%) with hypertension (87.6%) and diabetes (30.3%) being the most frequent comorbid conditions (Figure 1). Invariably, antihypertensives are the most prescribed medications with calcium channel blockers (CCBs), angiotensin II receptor blockers (ARBs), and loop diuretics being the most prescribed class (Figure 2).

Table 1: Demographic and Clinical Characteristics of Patients by chronic kidney disease (CKD) stage (n = 89)

	eGFR categories (ml/min/1.73^2)				
	(45-59) CKD Stage **S3a** (n=18)	(30-44) CKD Stage **S3b** (n=25)	(15-29) CKD Stage **S4** (n=17)	(0-15) CKD Stage **S5** (n=29)	TOTAL (n=89)
Age, years; Mean(±SD)	59.1(±13.4)	59.2 (±15.3)	56.9(±13.5)	52.2(±12.7)	56.5 (±13.8)
Gender, n (%)					
Male	11 (61.1)	16 (64.0)	10 (58.8)	16 (55.2)	53 (59.6)
Female	7 (38.9)	9 (36.0)	7 (41.2)	13 (44.8)	36 (40.4)
Educational Status, n (%)					
Primary	1 (5.6)	7 (28.0)	3 (17.7)	6 (20.7)	17 (19.1)
Secondary	12 (66.7)	13 (52.0)	9 (52.9)	17 (58.6)	53 (57.3)
Tertiary	5 (27.7)	5 (20.0)	5 (29.4)	6 (20.7)	23(23.6)
Occupation, n (%)					
Employed	4 (22.2)	5(20.0)	4 (23.5)	6 (20.7)	19 (21.3)
Business	5 (27.8)	8 (32.0)	6 (35.3)	17 (58.6)	36 (40.5)
Dependents	9 (50.0)	12 (48.0)	7 (41.2)	6 (20.7)	34 (38.2)
#Comorbidities, (n, Mean)	27	47	46	81	201 (2.2)
Mean	1.5	1.9	2.7	2.8	2.2
Range	(1 – 3)	(1 – 4)	(2 – 4)	(2 – 5)	(1 – 5)
≥ 3 comorbidities, n (%)	1	5	9	16	31 (33.3%)
Medications (n)	104	166	186	282	738
Mean (±SD)	5.8 (±1.4)	6.6 (±2.4)	11.1 (1.6)	9.7 (±2.2)	8.3 (± 2.9)
Median (Range)	6 (4 – 9)	6 (4 – 12)	11 (8 – 13)	9 (6 – 15)	8 (4 – 15)
≥ 8 medications (n [%])	5	9	17	27	58 (65.2%)
Scheduled doses/day (n)	140	219	262	396	1017
Mean (±SD)	7.8 (±2.76)	8.8 (±3.3)	15.4 (±2.6)	13.7 (±4.3)	11.4 (± 4.6)
Median (Range)	8 (4 - 15)	8 (4 – 17)	15 (12 – 22)	13 (7 - 24)	11 (4 – 24)
≥ 11 dose/day (n [%])	4	7	17	27	55 (61.8%)

eGFR: estimated glomerular filtration rate, SD: standard deviation

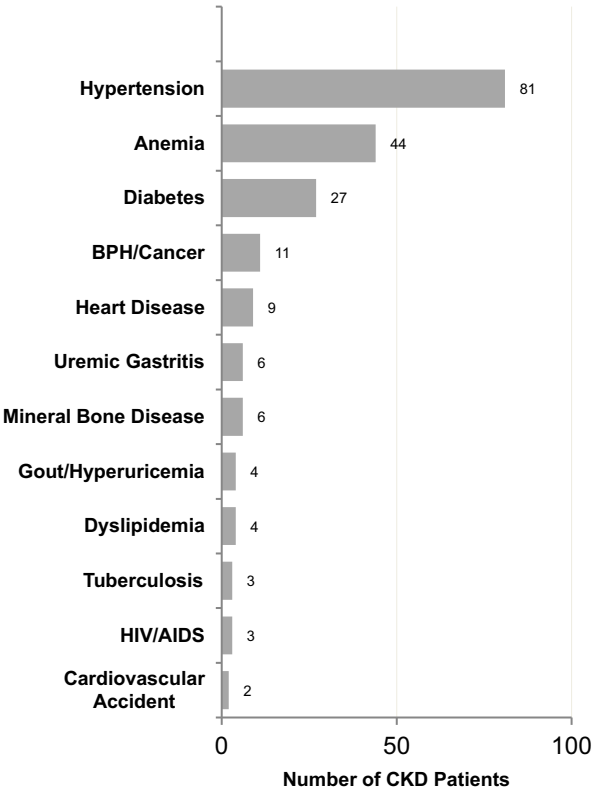

Figure 1 Description of comorbid conditions and complications present in chronic kidney disease patients

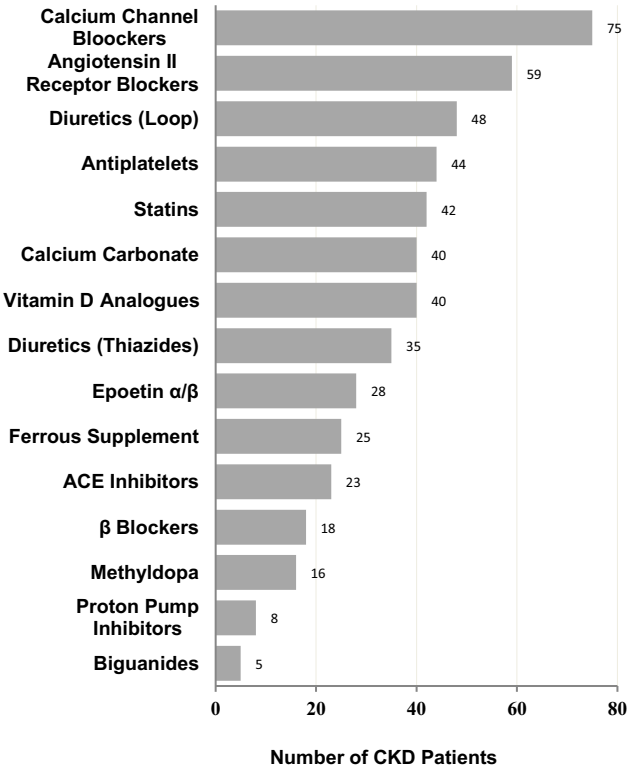

Figure 2 Most commonly prescribed medications to chronic kideny disease patients

Seven hundred and thirty-eight (738) medications were estimated prescribed (Mean ± SD: 8.3 ± 2.9). Ninety-nine (99) MRPs were identified in 64 (72.0%) patients to give an average of 1.54 ± 0.66 MRPs per patient and an overall rate of 18.1 MRPs per 100 medications prescribed. The most prevalent MRP was drug use problem (38.4%). (Table 2). Other MRPs include actual adverse drug reactions (16.2%), potential drug choice/selection problems (14.1%), dosing problems (12.1%), drug-drug interactions (6.1%) and others (13.1%). Cardiovascular and anti-diabetic medications were the most involved with the occurrence of MRPs (Table 3).

Table 2: Categories of Medication-Related Problems by chronic kidney disease (CKD) stage using PCNE DRP (n = 89)

	eGFR categories (ml/min/1.73^2)				
	S3a	**S3b**	**S4**	**S5**	**Total**
Adverse Reactions	2	2	4	8	16 (16.2)
Drug Choice Problems	3	3	3	5	14 (14.1)
Dosing Problems	1	2	5	4	12 (12.1)
Drug Use Problems	3	10	11	14	38 (38.4)
Interactions	0	3	2	1	6 (6.1)
Others	1	2	3	7	13 (13.1)
MRP by CKD Stage, n (%)	**10** (10.)	**22** (22.2)	**28** (28.3)	**39** (39.4)	
Mean (±SD)	1.1(±0.33)	1.47(±0.52)	1.87(±0.74)	1.56(±0.71)	1.54(±0.66)
Number of patients ≥ 2 MRP	1	7	10	11	29 (45.3)

*PCNE DRP : Pharmaceutical Care Network Europe classification of drug-related problem tool ; eGFR : estimated glomerular filtration rate, MRP: Medication-Related Problems, SD: standard deviation

Table 3: Detailed description of medications involved with Medication-Related Problems (n=99) in chronic kidney disease (CKD) patients (N= 89)

1.	**Adverse Reactions**
	Side effect(s) suffered (non-allergic)
	Nifedipine 30XL – headache
	Aspirin 75mg – induced GERD
	Tenofovir 300mg – induced nephropathy
	Torsemide 20mg/Furosemide 40mg – Hypokalemia in CHD
	Zidovudine - anemia
	Side effect suffered (allergic)
	Torsemide 20/40/100mg - dry throat
	IV Iron sucrose reaction
	Lisinopril 20mg - induced dry cough
	ARV (Nevirapine) – NVP Skin reaction
P1.3	*Toxic effects suffered* - Nil
2.	**Drug Choice Problems**
P2.1	*Inappropriate drug (not most appropriate for indication)*
P2.2	*Inappropriate drug form (not most appropriate for indication)*
	Inappropriate duplication of a therapeutic group or active ingredient
	Torsemide 20mg + Furosemide 40mg BD
	Losartan 50mg OD + Twynsta® 80/10 (telmisartan/amlodipine)
	Contra-indications for drug (Warning)
	Metformin 1g BD in patient(s) with eGFR < 45ml/min)
	Diclofenac 75mg/100mg in CKD
	Glimepiride 4mg OD in patient(s) with eGFR < 30ml/min
	Saxagliptin 2.5mg in ESRD on HD
	Gliclazide 60mg (in patient(s) eGFR < 30 – not recommended)
P2.5	*No clear indication for drug use* - Nil
	No drug prescribed but clear indication
	Congestive Heart Disease – no antiplatelet

3.	**Dosing Problems**
P3.1	*Drug dose too low or dosage regime not frequent enough* - Nil
	Drug dose too high or dosage regime too frequent
	Metformin 1g BD (eGFR <50ml/min)
	Nifedipine 40mg TDS (control release)
	Atenolol 50mg BD (eGFR = 18.6ml/min)
	Vildagliptin 50mg BD (eGFR < 50ml/min)
	Slow K 600mg BD in CKD (risk of hyperkalemia)
	Tenofovir 300mg OD (eGFR < 30ml/min)
	Gliclazide 60mg in ESRD
P3.3	*Duration of treatment too short*
P3.4	*Duration of treatment too long*
4.	**Drug Use Problems**
	The Drug not taken/administered at all (compliance)
	Minoxidil Tab (not available in the market)
	Financial problem (can't afford medication)
	Clinic defaulters/ Patient sees no need
	Poor compliance with HD (2 - 3x weekly)
P4.2	*Wrong drug taken/administered*
5.	**Interactions**
	Potential interaction
	Omeprazole 20mg + Clopidogrel 75mg
	Atenolol + Losartan + Furosemide prescription – Elevates K^+
P5.2	*Manifest interaction*
6.	**Others**
P6.1	*Patient dissatisfied with therapy despite taking drug(s) correctly* - Nil
	Insufficient awareness of health and diseases (possibly leading to future problems)
	Patient not aware of health status; Poor knowledge of disease
P6.3	*Unclear complaints. Further clarification necessary*
P6.4	*Therapy failure (reason unknown)*

The bivariate linear analysis reveal male gender and age were associated with lower odds of experiencing MRP while patients with ≥ 3 comorbidities [AOR 3.71 (95% CI 1.15-11.98); P <0.002], ≥ 8 medications [AOR 4.03 (95% CI 1.53-10.65); P <0.0001], ≥ 11 doses per day [AOR 4.02 (95% CI 1.49-10.89); P <0.0001], and lower stages of CKD gave higher odds of MRPs occurrence (Table 4).

Table 4: Bivariate analysis model for predictors of medication-related problems in chronic kidney disease (CKD) patients (n=89)

Clinical Characteristics	AOR (95% CI)	*p*-value	*r*
Age group (years)			
18 – 40	ref		
41 – 60	0.63 (0.11 – 3.46)		
>60	0.15 (0.03 – 0.72)		
Gender			
Female	ref		
Male	1.09 (0.43 – 2.72)		
Comorbidities			
0 – 2			
,,			
No of Medications			
< 8			
≥ 8			
No of Doses/Day			
< 11			
≥ 11			
Stage (eGFR – mL/min/1.73m^2)			
S3a (45 – 59)	ref		
S3b (30 – 44)	0.44 (0.04 – 5.01)		
S4 (15 – 29)	1.83 (0.12 – 27.8)		
S5 (< 15)	2.44 (0.19 – 31.77)		

*Statistically significant; eGFR: estimated glomerular filtration rate

4. Discussion

This study has revealed that the occurrence and frequency of MRPs in CKD can be attributed to various factors. We observed that the odds of MRPs occurrence in CKD patients' prescriptions increased with the number of comorbidities. Hypertension, anemia, and diabetes were the most common comorbidities observed in this study conforming to a recent data presentation for the United States Renal Data System on CKD patients.[22]Similar studies carried out in some developing countries also revealed comparable comorbidities in CKD patients.[16, 23-25] Hypertension, diabetes, cardiovascular disease, and anemia are the most common comorbid conditions in CKD patients and their prevalence increases as CKD progresses.[22] Although our study did not measure the impact of these comorbidities on patient outcomes, however, studies have shown they contribute to increased mortality in this disease population[26]. This has led to treatment strategies focused on adequate blood pressure control, strict glycemic control, and reduction of proteinuria.[4,26]

A high occurrence of comorbid conditions coupled with the manifestation of complications in CKD patients demands the need for multiple medications and a higher number of doses per day to mitigate symptoms and slow down the

progression of the disease.[4,5,7] This study revealed higher odds of MRPs occurrence with an increasing number of medications and number of doses per day. Data from this study alludes to evidences from studies published on the increasing number of medications as an independent predictor of MRPs in CKD patients.[5, 7, 19, 27] Most studies prefer to use the term polypharmacy defined numerically as intake of five or more medications per day.[27,28] However, systematic reviews have revealed the need to focus on adopting the term 'appropriate polypharmacy' in order to differentiate between the prescribing of 'many' and 'too many' drugs instead of a simple numerical count of medications, which is of limited value in practise.[27] Clinicians have always postulated that patients with CKD are often managed with a combination of medications that are clinically necessary and appropriate to manage their numerous comorbidities and complications. Hence, appropriate polypharmacy in our study population is many and too many at lower stages of the CKD. In addition to earlier factors identified responsible for occurrence of MRPs, this study also revealed higher odds of MRPs in patients with lower stages of CKD. This, not surprising, is similar to evidences from other studies which identified lower stages of CKD as independent predictors of MRPs[7,16,21].

Moreover, the MRP analysis in this study reflects the dilemma of multiple medications and the consequent occurrence of adverse events solely borne by the patients. It could be presumed that the observed MRPs can contribute to treatment failure and eventual high mortality rate of CKD. Problems that are related to medications can either be actual (real or that has affected outcomes) or potential (likely or that is going to affect outcomes) in nature.[13] Drug use problems such as issues on medication non-adherence, clinic appointments defaulting and unavailability of medicines at the pharmacy were the most prevalent MRP identified in this study. In developing countries, non-adherence represents a major problem in health care constituting a barrier to achieving optimal CKD outcomes.[29] Rosenthal *et al* published the association of non-adherence with uncontrolled hypertension and higher rates of mortality in hemodialysis patients.[30]. A recent qualitative systematic review by Nielsen and colleagues revealed that barriers to medication adherence in CKD were the costs of buying medications and lack of understanding of the indications and effects of medications.[31] Drug use problems obtained from this study are within published estimates of 17 - 74% among patients with CKD and also within 3 - 80% among patients on hemodialysis.[32–34]

Adverse drug events were another subset of MRPs suffered by these patients which are either allergic and non-allergic side effects of medications such as aspirin triggering gastroesophaegeal reflux disease (GERD); angiotensin-converting enzyme inhibitors (Lisinopril) causing unproductive dry cough; loop diuretics (Torsemide) causing hypokalemia and dry cough; amitryptilline induced drowsiness; and antiretroviral (nevirapine) induced skin reaction were all documented in the patients' medical case notes. Although this study presented a 15.7% adverse drug reaction (ADR) which points to the fact that these patients are vulnerable and would also require the services of a pharmacist to help minimize these ADRs. Laville *et al* reported a comparable figure of 14.4% serious ADR after a two-year cohort study in patients with CKD on ambulatory care.[10] Most of these adverse events observed are attributed to the pharmacologic activity of the medications and the increased plasma half-life attributed to reduced renal clearance. They are preventable with appropriate dose adjustment considering the pharmacodynamics and pharmacokinetic alteration of medications by the disease.[35-37]

In addition, this study population also had MRPs categorized as drug choice problems, dosing problems and drug-drug interactions. These three constitute drug selection challenges in CKD patients. We confirmed that oral antidiabetics or hypoglycemic agents were the most frequently involved in dosage problems and non-conformity to the available guidelines.[38, 39] Oral antidiabetics and hypoglycemic agents like metformin, sulphonylureas and dipeptidyl peptidase-4 inhibitors were prescribed at higher doses than recommended in guidelines. These higher doses are part of the medication safety issues often considered at lower stages of the disease.[7,8] Studies have reported that some oral hypoglycemics such as metformin and sulphonylureas predisposes CKD patients to lactic acidosis and hypoglycemia.[8,9] Studies by Mongaret *et al*, Adibe *et al,* and Huang *et al* also reported similar results of oral antidiabetics or oral hypoglycemic agents over-dosage and non-conformity to guidelines.[15, 17, 40] Other medications prescribed in this study at higher doses in lower stages of CKD include β blockers, calcium channel blockers, and tenofovir. Drug-drug interaction is also another potential MRPs in CKD patients with the possibility of resulting in subtherapeutic doses or adverse events.[14, 41] This study identified some clinically significant drug–drug interactions which include omeprazole and clopidogrel -

decreased metabolism of clopidogrel to its active metabolite by omeprazole (hepatic enzyme inhibitor); atenolol, losartan and furosemide combination causing potassium retention in CKD.

Lastly, an appreciable number of the study population was insufficiently aware of their health status coupled with low knowledge of the disease and medication as documented by the clinicians and nephrologist in the patients' record. Studies by Oluyombo *et al*, Welch *et al* and Lopez-Vargas *et al* had revealed low to moderate knowledge of individuals and patients about the risk factors, diagnosis and complications of CKD which could be a contributor to medication non-adherence and consequent poor treatment outcomes.[42–44]

This present study has several limitations, and the results are interpreted in this light. The approach used to identify and categorize MRPs was based on review of patients' medical record and stated recommendations in the guidelines. We could not account for information other than those in patients' records or those documented by the clinicians during consult. Also, this study results might not be generalized to an entire population of CKD patients due to the small sample size that was reviewed. Thus, these findings may be biased toward reporting more of the easily identifiable MRPs.

5. Conclusion

This study has documented a significant occurrence of MRPs in CKD patients revealing the clinical importance of regular evaluation of prescriptions in this disease population by pharmacists to identify and possibly make necessary interventions with the knowledge of the clinicians or nephrologists. The number of comorbidities, number of medications and lower stages of CKD were independent predictors of MRP occurrence in CKD in this study. The occurrence of these factors makes potential or actual MRPs in CKD inevitable.

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Conflict of interest

The authors have no competing interests to declare.

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