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Original Research Article

Determinants and outcomes of hyperpolypharmacy among chronic kidney disease patients in a teaching hospital in Northern Ghana

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ABSTRACT

Background: There is paucity of drug utilization studies among patients with chronic kidney disease (CKD) patients in Ghana. This study aimed to evaluate drug utilization pattern focusing on prevalence of hyperpolypharmacy and its determinants and outcomes among CKD patients in a teaching hospital in northern Ghana.
Methods: A retrospective cross-sectional was conducted among patients with CKD patients in the Tamale Teaching Hospital (TTH).
Results: Drugs acting on the cardiovascular system were the most commonly utilized (n=639/2081, 30.7%). Majority of the CKD patients 107/198 (54.0%) utilized prescriptions with ≥10 drugs concurrently (i.e. hyperpolypharmacy). Patients with 3-4 and ≥5 comorbidities were 5.3 times (AOR=5.3, 95% CI: 1.39-20.30, p=0.015) and about 8-folds (AOR=7.9, 95% CI: 2.04-30.31, p=0.003) more likely to have hyperpolypharmacy respectively. Exposure to hyperpolypharmacy was significantly associated with potential drug-drug interactions; contraindicated (OR=6.3, 95% CI: 2.51-15.92, p<0.001), serious-use alternative (OR=3.2, 95% CI: 1.71-5.73, p<0.001), and monitor closely (OR=3.1, 95% CI: 1.75-5.98, p<0.001), exposure to hyperpolypharmacy resulted in 4-folds higher likelihood to stay >7 days hospitalization (AOR=4.1, 95% CI: 2.26-7.51, p<0.001).
Conclusions: The presence of three or more comorbidities was an independent determinant of hyperpolypharmacy. which was associated with adverse outcomes; increased severity of potential drug-drug interactions and longer hospitalization. Hence, clinicians of TTH need to implement measures to prevent hyperpolypharmacy among CKD patients to help mitigate its associated burden.

Keywords: Chronic kidney disease, Drug utilization pattern, Hyperpolypharmacy, Determinants, Outcomes

INTRODUCTION

At present, global guidelines define CKD as a decline in renal function characterized by glomerular filtration rate (GFR) of lower than 60 ml/min per 1.73 m^2 or markers of kidney damage (i.e. albuminuria; urine albumin to creatinine ratio ≥30 mg/g), or both occurring within a period of three months or more, irrespective of the underlying cause of kidney damage.[1] In 2023, the estimated global prevalence of CKD was around 13.4%, with a range between 11.7% to 15.1% which translates to approximately 700 million individuals worldwide affected by CKD.[2] The prevalence of CKD in Africa has been reported in a systematic review ranging from 2% to 41%.[3] However, the true extent of CKD in most parts of Africa is unknown mainly due to unavailability of national registries and scarcity of studies in the communities.[3] In Ghana, the national prevalence of CKD is not known, although a study have reported an estimated prevalence of CKD among some Ghanaians to be 13.3%.[4]

Drug utilization study is an important component of pharmacoepidemiology which involves describing, analyzing and understanding the extent, nature and determinants of drug exposure in patients.[5] Drug utilization among CKD patients changes with time, population, prescribers, and disease condition; thus, it is necessary to conduct drug utilization research frequently across time to identify these shifts.[6] Furthermore, evaluation of drug utilization pattern among CKD patients is essential identify the current prescribing trends, understand common co-morbidities associated with CKD and study the therapeutic basis of the drug therapy.[7] Generally, it is very challenging to enhance prescribing practices in a specific patient population without information on the pattern of drug use in those patients.[7] Therefore, drug utilization research in CKD patients can help recognize pattern of drug use including drug classes commonly prescribed, and presence of polypharmacy or hyperpolypharmacy.

Multimorbidity has been identified to be highly prevalent among patients with CKD. Consequentially, multiple drugs are required to treat the multimorbidity (etiologies, complications and other comorbidities) associated with CKD patients.[8] However, the utilization of multiple drug therapy among CKD patients increases the likelihood of drug therapy related problems including drug dosage inappropriateness, drug-disease interactions, drug-drug interactions, and drug non-adherence) which can impact negatively on the safety and efficacy of drug therapy in CKD patients.[9] Multiple drug utilization categorized as polypharmacy (i.e. concurrent administration of five or more drugs) or hyperpolypharmacy (i.e. concurrent utilization of at least ten drugs), are considered as modifiable risk factors of drug therapy related problems, and are associated with worse clinical outcomes, lower quality of life, and increased healthcare complications in CKD populations.[8-11] Evaluation of polypharmacy or hyperpolypharmacy among CKD patients is important to help in early identification of high-risk CKD subpopulation likely to experience this phenomenon, allowing for implementation of clinical strategies to mitigate adverse health outcomes. Currently, there is a lack of published data regarding hyperpolypharmacy among CKD patients in Ghana. To address this knowledge gap, this study aims to review drug treatment patterns, and identify the extent of hyperpolypharmacy and its determinants and outcomes among CKD patients admitted in the Tamale Teaching Hospital.

METHODS

Study site

This study was conducted in the medical ward of the Tamale Teaching Hospital; a tertiary located in the Tamale metropolis of northern region in Ghana. The hospital serves as a referral center for the entire northern sector of Ghana.

Study design

A retrospective cross-sectional study was conducted from January 2023 to December 2023.

Study population

The study population comprised CKD patients admitted in the medical ward of Tamale Teaching Hospital between January 2023 to December 2023.

Inclusion criteria

Patient with confirmed diagnosis of CKD, who utilized at least one prescribed drug. Confirmed diagnosis of CKD was defined according to the functional and/or structural criteria by the Kidney Disease: Improving Global Outcomes (KDIGO): (a) GFR <60 ml/min/1.73 m^2 for ≥3 months with or without structural abnormalities of the kidney. (b) GFR >60 ml/min/1.73 m^2 and presence of 1 or more marker of kidney damage (albuminuria, urinary sedimentation, persistent hematuria, electrolyte abnormalities, structural abnormalities detected by histology or renal imaging, history of kidney transplantation) for at least 3 months.[12] The GFR of the patients was determined using the 2021 CKD-EPI creatinine equation online calculator.[13]

Exclusion criteria

Patients without confirmed diagnosis of CKD and patients whose renal function tests were either not undertaken or not traceable or with incomplete medical records were excluded from the study.

Sampling

This study included all patients with the inclusion criteria of the study. A total of 198 patients with CKD comprised the study population.

Data collection

We collected data from the hospital's electronic medical record system i.e. Light Wave Hospital Information Management System (LHIMS). Data obtained from the electronic medical record of the patients comprised (sex, age, renal function test, comorbidities, dialysis exposure, days of hospitalization, and in-hospital death). Each patient's prescribed drug treatment information was collected (i.e., generic name of drug, dosage, route of administration, and number of drugs utilized concurrently).

Data analysis

The collected data was cleaned and entered into statistical package for social sciences (SPSS) version 29 (IBM, Illinois, USA) for analysis. Patients characteristics were analyzed as follows sex (male vs female), age (18-39 years [young adults], vs 40-59 years [middle-age adults] vs ≥60

years [elderly]), number of comorbidities (1-2 [low], vs 3-4 [medium] vs ≥5 [high]), and dialysis exposure (no vs yes) and clinical stages of CKD (stage-1 to stage-5) were classified using the estimated GFR criteria by the KDIGO.[12] Clinical outcomes of the CKD patients were analyzed as follows days of hospitalization (1-7 days [normal] vs >7 days [longer]), in-hospital death (no vs yes), and clinically relevant potential drug-drug interactions (pDDIs) [type X; contraindicated, type D; serious-use alternative, and type C; monitor closely] using Medscape drug reference.[14] Drugs utilized were classified using the first level of the WHO Anatomical Therapeutic Chemical (ATC) classification system.[15] The first level of the ATC classification system classifies drugs based on the main anatomical organ or system on which the drug acts. The highest number of drugs utilized concurrently by a patient was used to determine whether the patient was exposed to non-polypharmacy (1-4 drugs), polypharmacy (5-9 drugs) or hyperpolypharmacy (≥10 drugs). The patterns of the main anatomical drug classes utilized were assessed according to patient exposure to non-polypharmacy, polypharmacy, or hyperpolypharmacy. Inferential statistics was conducted to determine the factors and outcomes associated with exposure to hyperpolypharmacy (no vs yes). Patients' characteristics (sex, age, CKD stage, number of comorbidities, and dialysis exposure) were considered as independent variables for analysis of determinants of exposure to hyperpolypharmacy. Multivariate binomial logistic regression was then conducted by including independent variables that were statistically significant (i.e. $p<0.05$) in the initial univariate analysis.

The group(s) within independent variables with $p<0.05$ were considered to significantly associated with hyperpolypharmacy without confounding factors. Regarding analysis of the outcomes of exposure to hyperpolypharmacy (independent variable), clinically significant pDDIs, days of hospitalization and in-hospital death were used as dependent variables. Univariate regression analysis was carried out to determine outcome(s) significantly associated (i.e., $p<0.05$) with exposure to hyperpolypharmacy. Adjusted odds ratio and odds ratio were calculated in the multivariate and univariate logistic regression analysis respectively. These measures were used to assess the strength and direction of the associations between hyperpolypharmacy and its determinants and outcomes.

RESULTS

Characteristics of the study participants

A total of 198 patients with CKD comprised the study participants. More than half of the patients were males 114/198 (57.6%). Patients with age range 18-39 years the highest (n=79, 39.9%), followed by 40-59 years (n=71, 35.9%), and ≥60 years (n=48, 24.2%). There was predominance of patients with CKD stage-5 (n=150, 75.8%). Patients with ≥5 comorbidities were the highest (n=91, 46.0%). About 41% (40.9%) of the CKD patients underwent hemodialysis in (Table 1).

Drug utilization pattern

A total of 2081 drug prescriptions were utilized among the CKD patients. The top-5 main anatomical drug classes utilized included drugs acting on: cardiovascular system (n=639, 30.7%), blood and blood forming organs (n=445, 21.4%), alimentary tract and metabolism (n=424, 20.4%), anti-infectives for systemic use (n=296, 14.2%), and nervous system (n=162, 7.8%) shown in (Figure 1).

Majority of the patients 107/198 (54.0%) utilized prescriptions with ≥10 drugs concurrently (i.e. hyperpolypharmacy), 86/198 (43.4%) utilized prescriptions with 5-9 drugs (i.e. polypharmacy), whereas 5/198 (2.5%) utilized prescriptions with 1-4 drugs (i.e. non-polypharmacy) in (Figure 2).

Drug distribution according to number of drugs utilized concurrently showed that drugs acting on the cardiovascular system were the most commonly utilized among patients with non-polypharmacy; 17/45 (37.8%), polypharmacy; 272/851 (32.0%), and hyperpolypharmacy; 350/1070 (32.7%) in (Figure 3).

Outcomes of drug-utilization among the CKD patients

Clinically significant potential drug-drug interactions (pDDIs) were identified among the CKD patients with the highest been type C; monitor closely 128/198 (64.6%), followed by type D; serious-use alternative 78/198 (39.4%) and type X; contraindicated 39 (19.7%). More than fifty percent of the patients stayed >7 days hospitalization (n=116, 58.6%). In-hospital death occurred among about 10 percent of the CKD patient 20/198 (10.1%) shown in (Table 2).

Determinants and outcomes of hyperpolypharmacy

The number of comorbidities was significantly associated with exposure to hyperpolypharmacy, patients with 3-4 and ≥5 comorbidities were 5.3 times (AOR=5.3, 95% CI: 1.39-20.30, p=0.015) and about 8-folds (AOR=7.9, 95% CI: 2.04-30.31, p=0.003) more likely to have hyperpolypharmacy, respectively (Table 3). Outcomes of drug utilization indicated that patients with hyperpolypharmacy were associated with clinically relevant pDDI; the risk was highest with type X; contraindicated (OR=6.3, CI: 2.51-15.92), p<0.001), followed by type D; serious-use alternative (OR=3.2, CI: 1.71-5.73, p<0.001), and type C; monitor closely (OR=3.1, CI: 1.75-5.98, p<0.001). Patients exposed to hyperpolypharmacy were 4-folds more likely to stay >7 days hospital admission (OR=4.1, CI: 2.26-7.51, p<0.001) in (Table 4).

Table 1: Characteristics of the CKD patients, (n=198).

Parameter	N	Percent (%)
Sex		
Male	114	57.6
Female	84	42.4
Age (in years)		
18-39	79	39.9
40-59	71	35.9
≥60	48	24.2
CKD stage		
Stage-1	4	2.0
Stage-2	9	4.5
Stage-3	20	10.1
Stage-4	15	7.6
Stage-5	150	75.8
Comorbidities		
1-2	21	10.6
3-4	86	43.4
≥5	91	46.0
Dialysis		
No	117	59.1
Yes	81	40.9

Table 2: Outcomes of drug utilization among the CKD patients, (n=198).

Parameters	N	Percent (%)
Potential drug-drug interactions		
Type X; Contraindicated	39	19.7
Type D; serious-use alternative	78	39.4
Type C; monitor closely	128	64.6
Days of hospitalization		
1-7	82	41.4
>7	116	58.6
In-hospital death		
No	178	89.9
Yes	20	10.1

#a patient can be exposed to more one type of potential drug-drug interaction.

Table 3: Determinants of hyperpolypharmacy among the CKD patients, (n=198).

Parameters	Hyperpolypharmacy		P value	OR	P value	AOR
	No, (n=91)	Yes, (n=107)				
Sex						
Female	32 (35.2)	52 (48.6)		Ref		
Male	59 (64.8)	55 (51.4)	0.058	0.6 (0.32-1.02)		
Age range (in years)						
13-39	30 (33.0)	49 (45.8)	0.601	1.3 (0.61-2.63)		
40-59	40 (44.0)	31 (29.0)	0.179	0.6 (0.29-1.26)		
≥60	21 (23.1)	27 (25.2)		Ref		
CKD stage						
Stage 1	3 (3.3)	1 (0.9)		Ref		
Stage 2	4 (4.4)	5 (4.7)	0.322	3.8 (0.27-51.37)		
Stage 3	13 (14.3)	7 (6.5)	0.700	1.6 (0.14-18.58)		
Stage 4	5 (5.5)	10 (9.3)	0.161	6.0 (0.49-73.45)		
Stage 5	66 (72.5)	84 (78.5)	0.251	3.8 (0.39-37.55)		
Comorbidities						
1-2	18 (19.8)	3 (2.8)		Ref		Ref

Continued.

Parameters	Hyperpolypharmacy		P value	OR	P value	AOR
	No, (n=91)	Yes, (n=107)				
3-4	42 (46.2)	44 (41.1)	0.005*	6.3 (1.73-22.91)	0.015*	5.3 (1.39-20.30)
≥5	31 (34.1)	60 (56.1)	<0.001*	11.6 (3.18-42.48)	0.003*	7.9 (2.04-30.31)
Dialysis						
No	65 (71.4)	52 (48.6)		Ref		Ref
Yes	26 (28.6)	55 (51.4)	0.001*	2.6 (1.46–4.78)	0.125	1.7 (0.87-3.18)

*Statistically significant at p<0.05, OR; odds ratio, AOR; adjusted odds ratio

Table 4: Outcomes of hyperpolypharmacy among the CKD patients (n=198).

Hyperpolypharmacy			P value	OR
	Type X; contraindicated pDDIs			
	No (n=159)	**Yes (n=39)**		
No	85 (53.5)	6 (15.4)	<0.001*	Ref
Yes	74 (46.5)	33 (84.6)		6.3 (2.51–15.92)
	Type D; serious-use alternative pDDIs			OR
	No (n=120)	**Yes (n=78)**		
No	68 (56.7)	23 (29.5)	<0.001*	Ref
Yes	52 (43.3)	55 (70.5)		3.2 (1.71–5.73)
	Type C; monitor closely pDDIs			OR
	No (n=70)	**Yes (n=128)**		
No	45 (64.3)	46 (35.9)	<0.001*	Ref
Yes	25 (35.7)	82 (64.1)		3.1 (1.75–5.98)
	Days of hospitalization			OR
	1–7 days (n=82)	**>7 days (n=116)**		
No	54 (59.3)	37 (40.7)	<0.001*	Ref
Yes	28 (26.2)	79 (73.8)		4.1 (2.26–7.51)
	In-hospital death			OR
	No (n=178)	**Yes (n=20)**		
No	83 (91.2)	8 (8.8)	0.574	Ref
Yes	95 (88.8)	12 (11.2)		1.3 (0.51–3.36)

*Statistically significant at p-value < 0.05, OR; odds ratio, pDDIs; potential drug-drug interactions.

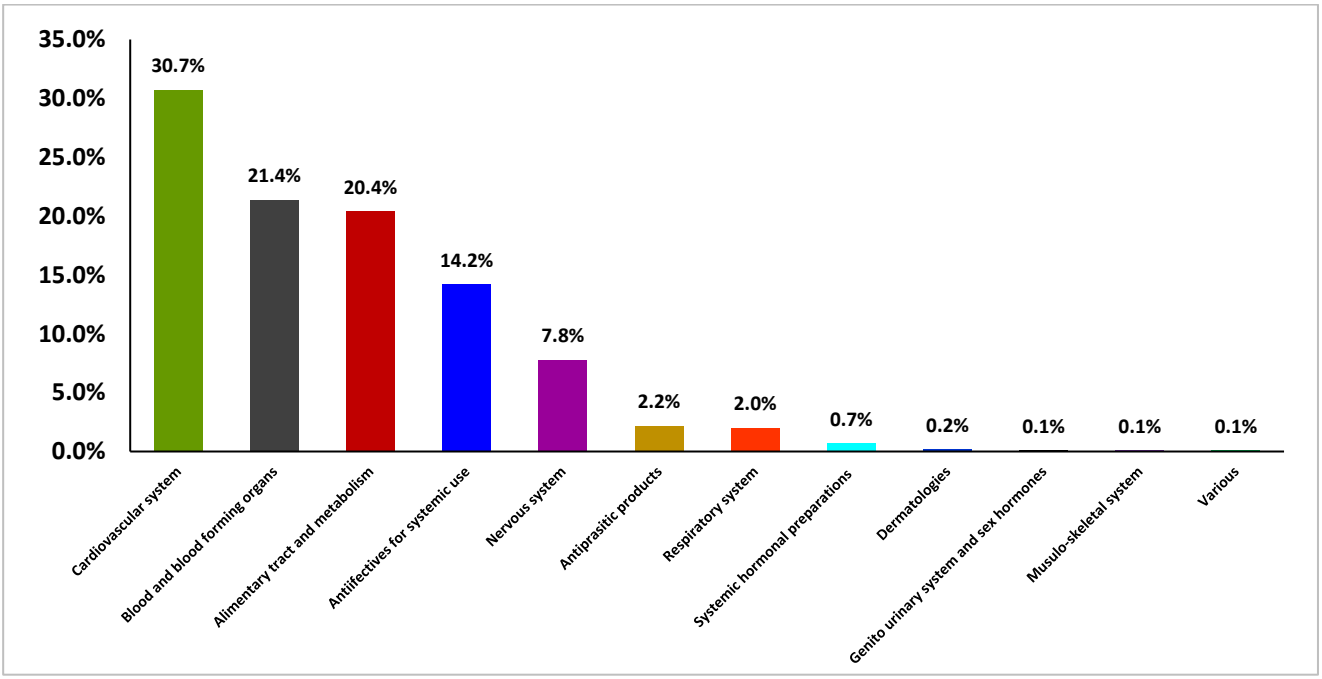

Figure 1: ATC main anatomical drug classes utilized among the CKD patients.

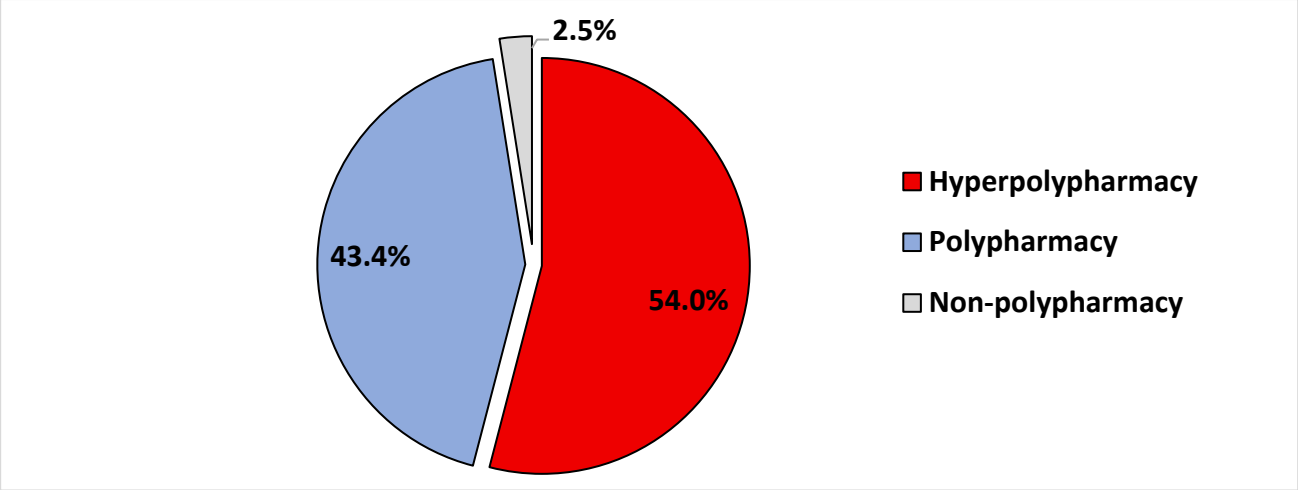

Figure 2: Number of drugs utilized among the CKD patients.

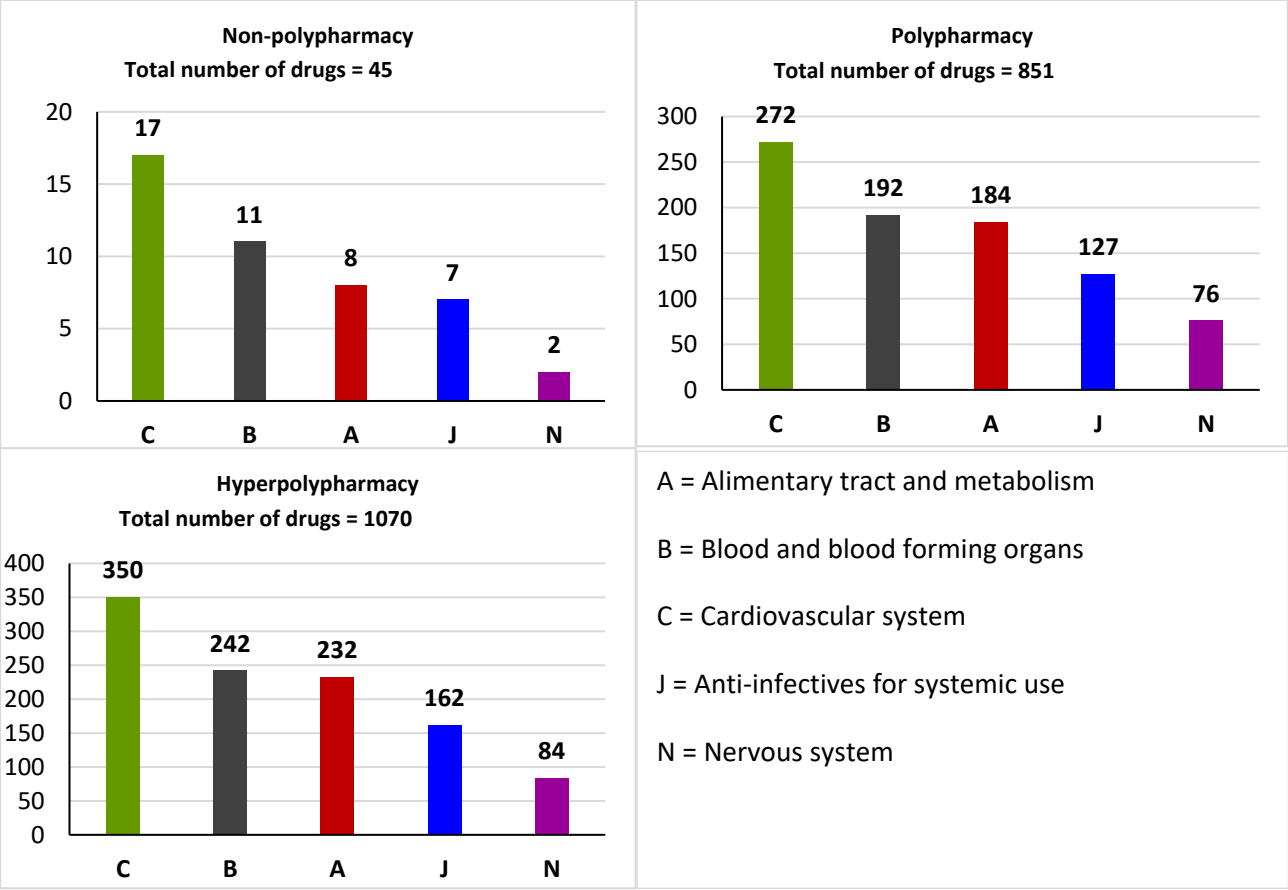

Figure 3: Top-5 main anatomical drug classes pattern by number of drugs utilized.

DISCUSSION

Characteristics of the study participants

This study revealed male predominance among the CKD patients which is analogous to an earlier observation in Ghana and Cameroon.[16,17] Contrary, it is reported that there is higher female prevalence of CKD globally.[18] The young population (13–39 years) were the highest with CKD, a parallel finding was reported in a prior study in Ghana.[19] However, divergent results of geriatric population prevalence of CKD were documented in Somalia, and Italy.[20,21] About three-quarters (75.8%) of the patients presented with CKD stage-5. Previous studies have reported predominance of CKD stage-5 with higher percentage 92.0%, but also a lower rate of 61.0% than current proportion.[22,23] There was higher proportion of patients with high number of comorbidities (i.e., ≥5)

probably due to the predominance of CKD stage-5 (i.e. end-stage renal disease) in the present patients, because it is known that is not until advance stages of CKD that there will be clinical manifestation of CKD complications.[24]

Drug utilization pattern

The study identified that, the following ATC main anatomical classes of drugs: cardiovascular system (group C), blood and blood forming organs (group B), alimentary tract and metabolism (group A), anti-infectives for systemic use (group J) and nervous system (group N) were the commonly utilized drugs. Earlier studies among CKD patients had reported comparable findings, although variations exists in the sequence of the drug classes.[7,25]

Drug classes acting on the cardiovascular system were the highest utilized among the CKD patients. Parallel findings to the current observation were recognized from previous studies in Asia.[26,27] A study assessing international prescribing pattern in Europe similarly reported drug classes acting on the cardiovascular system to be the most frequently prescribed among CKD patients in Poland, Germany, Netherlands, Italy and United Kingdom.[28] This, implies that generally cardiovascular comorbidities may be the most prevalent among CKD patients as may be the likely inference in the present study.

The second commonly prescribed drug class were blood and blood forming organs which comprised 21.4% of the total prescriptions, a similar finding of 21.38% was noticed in an earlier publication.[29] However, the present utilization rate is notably higher than reports from a similar setting of tertiary care hospitals, 14.1-17.2%.[30,31] The high utilization of blood and blood forming organs drugs likely reflects a high burden of anemia within the study population.

Alimentary tract and metabolism drugs were the third highest utilized drug class among the CKD patients which accounted for 20.4% of the prescriptions. Although, earlier in United Kingdom, Alruqayb et al reported that alimentary tract and metabolism drugs were rather the highest prescribed drugs among CKD patients, nevertheless the percentage recorded 22.0% was comparable to our finding. On the hand, the present proportion is much lower than the documented 44.86% in India.[27,29] This may imply that there may be a variation in the geographical prevalence of comorbidities among CKD patients.

Anti-infectives for systemic use represented 14.2% of the overall drugs utilized. From literature, a utilization range of 1.04-10.11% of group J drugs in CKD patients have been published.[7,27,29] Hence, the utilization rate of anti-infectives for systemic use in our setting is higher than the literature reference. suggesting that, infections may be a common comorbidity such as diabetes, CKD mineral bone disorders among the CKD patients which require utilization of group A drugs.

Drugs acting on the nervous system consisted 7.8% of the total prescriptions. A higher proportion of drugs acting on the nervous system compared to present result was recorded in a former study in Europe; 13.5%.[25] On the other hand, extremely lower percentages of drugs acting on the nervous system were reported in earlier publications in Asia; 1.46-3.5%.[7,27] The likely variation in the geographical utilization of drugs acting on the nervous system may be due to differences in setting comorbidity prevalence among the CKD patients in our setting.

In this study, there was a prevalence of (54.0%) hyperpolypharmacy. The proportion is similar to 57.8% in Germany, however lower compared to 70.98% in Croatia.[8,28] Nevertheless, the current result is moderately higher relative to the findings of 45.1% in Italy and 47.84% in Australia.[28,32] The pattern of the number of drugs utilized by the CKD patients indicated that hyperpolypharmacy was the most common in our cohort, followed by polypharmacy. Consistent observational pattern was also realized in an earlier publication in Japan.[33] However, divergent result of polypharmacy been the most prevalent followed by hyperpolypharmacy was observed in the United States of America.[34] The differences in the prevalence pattern of hyperpolypharmacy and polypharmacy may be attributed to the national variations in prescribing practices, as well the average number of comorbidities among the CKD patients in the different studies. In this study, there was a prevalence of (54.0%) hyperpolypharmacy. This proportion is comparable to the rate of 57.8% obtained in Germany, however lower than the 70.98% observed in Croatia. 8,28 Nevertheless, the current result is moderately higher relative to the findings of 45.1% in Italy and 47.84% in Australia.[28,32] The current prevalence of hyperpolypharmacy is undesirable because hyperpolypharmacy has been identified to significantly increase the risk of drug-interactions, and other potentially inappropriate medication use.[34] There is a need for patient-centered, team-based approach including deprescribing, medication reconciliation, and regular medication reviews by the clinical team in the hospital as this may help reduce the risk of hyperpolypharmacy.

Drugs acting on the cardiovascular system were the top-most utilized among patients with non-polypharmacy, polypharmacy and hyperpolypharmacy. The heart and kidneys are so deeply intertwined, a relationship known as the cardiorenal syndrome where failure in one organ almost invariably accelerates failure in the other organ.[35] CKD is essentially a state of accelerated cardiovascular damage, and treatment requires aggressive management of blood pressure, and fluid balance and cholesterol making cardiovascular drugs fundamental to therapy in CKD patients.

Determinants and outcomes of hyperpolypharmacy

The number of comorbidities present in a patient was a determinant of hyperpolypharmacy and the observation aligns with previous findings by Adjeroh et al.[34] Patients with moderate to high number of comorbidities (i.e. 3-4 to ≥5) were more likely to experience hyperpolypharmacy compared to patients with a minor comorbidity (1-2). Increased number of comorbidities consequently increases the number of drugs for the treatment of the comorbidities which leads to increased risk of hyperpolypharmacy.

In the present study, hyperpolypharmacy was strongly associated with clinically relevant potential drug-drug interactions, it has been known that concurrent use of multiple drugs creates an exponential, rather than linear, increase in the probability of drug-drug interactions and adverse drug reactions.[36;37] Drugs may overlap in their pharmacodynamic and pharmacokinetic processes and such overlaps increase the likelihood of interactions as the number of prescribed drugs increases.[38] A very worrisome trend was observed with regards to the hyperpolypharmacy outcome of potential drug-drug interactions, the risk of association increased with the severity of the potential drug-drug interactions. The risk of the association was most profound for contraindicated interactions, been highest with contraindicated, followed by serious-use alternative and monitor closely potential drug-drug interactions. This trend implies that the CKD patients are more likely to experience life-threatening adverse drug reactions known to be associated with severe potential drug-drug interactions.

Hyperpolypharmacy was significantly associated with longer days of hospitalization with patients exposed to hyperpolypharmacy been four-folds more likely to experience longer hospitalization. This observation is consistent with the findings, in a former study in Switzerland where there was higher length of hospitalization among patients who had hyperpolypharmacy compared to those without hyperpolypharmacy.[32] Multiple drug administration (as in hyperpolypharmacy) is thought to cause adverse drug events that will prolong length of hospital admission of patients.[39] Conversely, longer hospitalization can lead to further increase in the number of drugs utilized, as longer hospital admission has been found to increase patient risk of hospital acquired infections in Ghana leading to more drugs being utilized.[40]

CONCLUSION

This is the first drug utilization study to assess drug utilization pattern and hyperpolypharmacy and its associated determinants and outcome among CKD patients at hospital in Ghana Hence, it provide a reference point for subsequent studies in the future. Drugs acting on the cardiovascular system were the most frequently utilized among the CKD patients. The presence of three or more comorbidities was an independent risk factor of hyperpolypharmacy. Exposure to hyperpolypharmacy was significantly associated with increased severity of potential drug-drug interactions and longer days of hospitalization. The findings underscore the critical need for targeted interventions to avert the occurrence of hyperpolypharmacy as this may help mitigate the adverse outcomes associated with this complex treatment regimen in CKD patients.

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