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Evaluation of burden of polypharmacy and potential drug related problems in patients with chronic kidney disease

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Abstract

Aim: The primary aim of the study is to analyze prevalence of polypharmacy, determine factors affecting polypharmacy and identify potential Drug Related Problems (DRPs) in patients with chronic kidney disease (CKD).

Methods: A prospective observational study was conducted among 207 patients diagnosed with chronic kidney disease in a tertiary care hospital for a period of 6 months. Drug-Related Problems were identified, reported and categorized in accordance with the Helper and Strand, 1990 Classification. Binary logistic regression was used to identify the association between dependent variable and independent variables.

Result: The mean age of the study population was 56.64 ±16.64 with male predominance (66%). The prevalence of polypharmacy was 76.8% and prescription pattern was analyzed in different stages of chronic kidney disease was found to be antiulcer drugs (84.5%) and antihypertensive (81.6%) were the most commonly prescribed class of drug. Age, gender, length of hospital stay, comorbidities such as diabetes mellitus and hypertension were determined as the main predictors for polypharmacy (p-value < 0.05). Drug interaction (93.2%) was identified as main Drug-related problem associated with polypharmacy (p-value of 0.022).

Conclusion: Polypharmacy has a positive correlation with advancement of chronic kidney disease which put them at higher risk for drug-related problems. Drug Related Problems may be prevented or reduced by early detection and modification of the above-mentioned predictors.

Keywords: Prescribing pattern; Drug related problem; Chronic kidney disease; Polypharmacy; Drug interaction; Comorbidities

1. Introduction

The Kidney Disease Outcome Quality Initiative (KDOQI) of the National Kidney foundation defined CKD as kidney damage ≥3 months characterised by structural or functional abnormalities of the kidney with or without decreased GFR[1] . KDOQI criteria classifies CKD into five stages on the basis eGFR or evidence of structural renal abnormalities. Early stages of CKD are usually asymptomatic despite the accumulation of metabolites. Symptoms usually begin within the stage 4-5 (eGFR < 30ml/min /1.73m2) which manifest as electrolyte or metabolic rearrangements[2]. CKD is one of the most prominent public health concerns worldwide. The global burden of disease study (GBD) estimated about 1.4 million deaths due to CKD in 2019, making it one of the most prominent causes of global mortality (20% increase from 2010) [3]. Patients with CKD commonly suffer from multiple coexisting conditions that require treatment with several medications. This burden of comorbidities is higher in older adults, who are more vulnerable to negative health outcomes. To mitigate the effects of CKD, early detection and appropriate management is critical. Studies show that

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prompt intervention can slow down or prevent the progression of CKD. However, many patients with CKD delay seeking medical attention due to a lack of awareness of the disease, cultural beliefs, financial constraints, and the insidious nature of the disease. Addressing these barriers to care can improve outcomes and reduce the burden of CKD on patients, families, and the healthcare system. Patients with CKD often suffer from large number of comorbidities including hypertension, diabetes, cardiovascular disease, chronic kidney disease related bone and mineral disorders, anaemia [4].

It is imperative to conduct an in-depth examination of drug utilization patterns over a specific time frame to evaluate the appropriateness of treatment and mitigate the possibility of unintended adverse outcomes, as drug prescription patterns are known to vary considerably based on the population under treatment, the nature of the disease being treated, and the preferences of the treating physicians. The global impact of polypharmacy was emphasized in the WHO's Medication Without Harm challenge study, which identified it as one of the three key areas for action in the organization's 2019 technical statement, urging member nations to prioritize their commitment to pharmaceutical safety. As a result, approximately 22 countries have produced national guidelines for controlling polypharmacy[5,6,7] Another aspect influencing polypharmacy is the presence of multiple organ damage and fluid overload which could disrupt the volume of distribution of several drugs [8]. The presence of uremia and renal insuffiency could also affect the plasma protein binding of several drugs which can increase the unbound fraction of the drug within the circulation thereby resulting in higher interaction potential or direct toxic effects.

Collaboration among healthcare professionals, including doctors, nurses, and pharmacists, is essential for effective management of polypharmacy, as it allows for the pooling of knowledge and expertise [9]. In addition, active involvement, engagement and empowerment of patients are crucial to ensure optimal outcomes. Clinical interventions such as medication reviews which involve the patient or caregiver in the decision-making process, should be implemented to enhance the quality of care and reduce the risk of medication-related harm.

2. Material and methods

2.1. Design and study participants

A prospective observational study was conducted among inpatients and outpatients in a tertiary care teaching hospital for a duration of 6 months. The following inclusion criteria were employed including inpatients having CKD above ≥18 years of age and who gave consent to participate in the study .The sample size was estimated with 75% confidence interval and 10% precision to be 208 participants. The ethical clearance was obtained from Institutional Ethics Committee (IEC).

2.2. Data Collection

A data collection form was prepared which contain details of patient characteristics including social habits, physical examination, social history, laboratory results, current medication with frequency and dose, comorbidities, length of hospitalization and relevant previous medical and medication histories. The prescribing pattern was studied and DRPs were identified, reported and categorized as per the Helper and Strand,1990 classification.

2.3. Data Analysis

The collected data was analysed by applying suitable statistical method. All extracted data were pooled and analysed using the statistical package SPSS version 16.0. Continuous data were tested for normality.A normally distributed data was expressed as mean ± standard deviation. Binary logistic regression was used to identify the association between dependent variable (polypharmacy) and independent variables (Age, gender, level of education and length of hospital stay, stage of CKD and various comorbidities). P value 0.05 was considered as statistically significant.

2.4. Ethical approval

The study was approved by the BAPUJI PHARMACY COLLEGE Institutional Ethics Committee on human subjects' research. Ref No. BPC/IEC/81/2021 – 22 dated 21st Feb 2022. Subject confidentiality was maintained during and after data collection.

3. Result

A total of 207 participants met the selection criteria were enrolled in the study. Out of which 136 (66%) were males and 71 (34%) were females. Preponderance share of maximum number of age group of 60-69 years (31.9%), followed by very less margin in age group of 20-29 years (4.34%). Mean age of study population was 56.64 ±16.64 (Mean ±SD). Majority of the study population were found in Stage 5 (ESRD). Most common comorbidities were diabetes mellitus 165 (79.7%), hypertension 114 (55%) and ischemic heart disesse 45 (21.7%).The average length of hospital stay was 7.85 days. The prevalence of polypharmacy found to be 77%.

Table 1 Demographic and clinical characteristics

Characteristics	Parameters	Frequency	Percentage(%)
Age	20 – 29	9	4.34
	30 – 39	34	16.42
	40 – 49	24	11.6
	50 – 59	23	11.11
	60 – 69	66	31.9
	≥70	51	24.63
Gender	Male	136	66
	Female	71	34
Level of education	No formal education	39	18.8
	Primary education	42	20.2
	Secondary education	35	16.9
	Higher education	36	17.3
	Degree	48	23.1
	PG degree	7	3.3
Comorbidities	Diabetes mellitus	165	79.7
	Hypertension	114	55
	Ischemic – heart disease	45	21.7
	Hypothyroidism	8	3.8
	Anemia	15	7.2
	Asthma	7	3.3
	Dyslipidemia	8	3.8
Social history	Alcohol	51	24.6
	Smoking	56	27
	Tobacco	12	5.7
Stages of CKD	Stage 1	1	0.48
	Stage 2	6	2.89
	Stage 3a	9	4.34
	Stage 3b	17	8.21
	Stage 4	76	36.7
	Stage 5	98	47.3

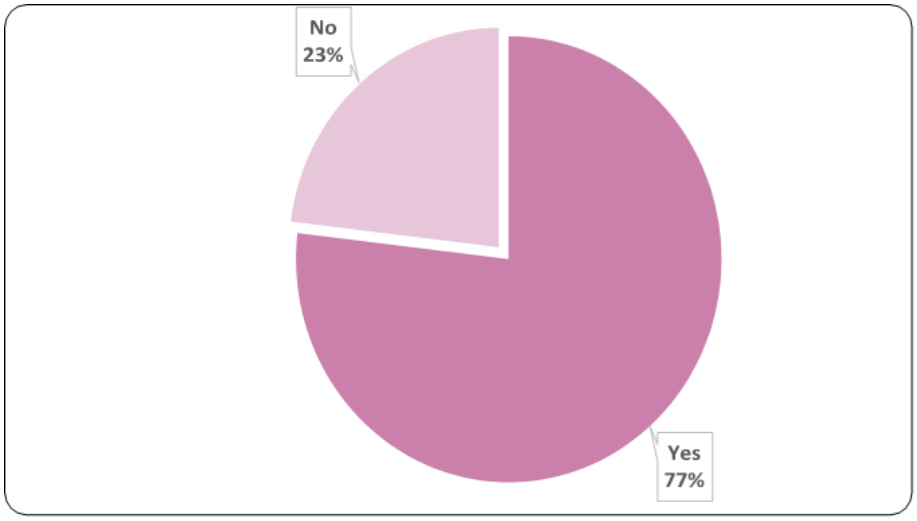

Figure 1 Prevalance of polyphramacy

Table 2 Distribution based on stages of CKD with polypharamcy

Parameters	Frequency	Percentage(%)
Stage 1	1	0.62
Stage 2	5	3.14
Stage 3a	5	3.14
Stage 3b	14	8.8
Stage 4	55	34.5
Stage 5	79	49.6

Prevalence of polypharmacy was 76.8% out of which 49.6% were found to be in Stage 5 CKD.

3.1. Analysis of Prescription Pattern and Polypharmacy

An assessment of prescribing pattern in the study population revealed that predominant segment of the study population was antiulcer drug (84.5%) followed by antihypertensive (81.6%), antibiotics (79.2%) antifungal(5.7%) and antiviral (5.3%) drugs were the least prescribed drug class (Table 3).

Table 3 Prescribing pattern of study population

Parameters	Frequency	Percentage (%)
Antihypertensive	169	81.6
Antibiotics	164	79.2
Antidiabetics	118	57
Diuretics and antidiuretics	124	59.9
Analgesics	125	60.3
Antiulcer	175	84.5
Antiplatelet	71	34.2
Cardiovascular agents	54	26

Nutrition supplements		142	68.5
Antifungal		12	5.7
Antiviral		11	5.3
Antihyperlipidemic		52	25.1
Bronchodilators		65	31.4
Others	Antiemetics	41	19.8
	Alkalizing agent	33	15.8
	Laxatives	27	13.0

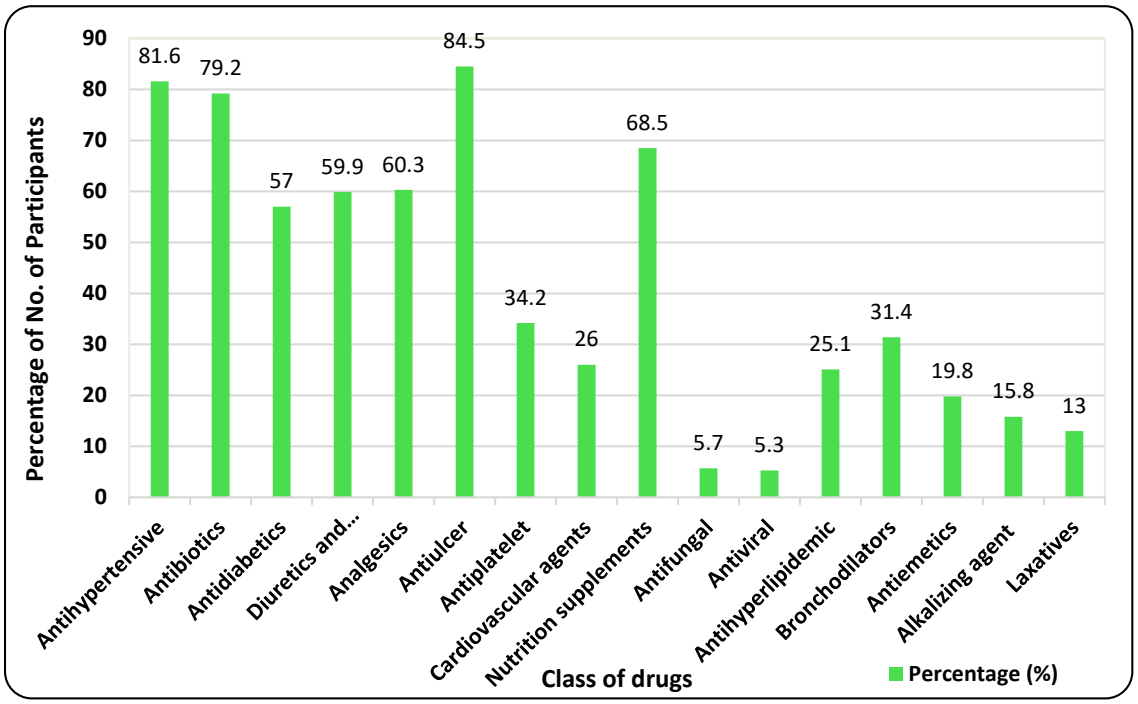

Figure 2 Distrubution of different class of drugs

Table 4 Distribution of Factors Associated with Polypharmacy

Risk Factors	No. of Cases	Odd's ratio	95% C.I.		P value
			Lower	Upper	
Age					
20-29	9	Ref	-	-	0.011*
30-39	34	5.029	1.080	23.404	
40-49	24	4.962	1.743	14.126	
50-59	23	2.588	0.789	8.489	
60-69	66	1.746	0.489	6.229	
≥70	51	1.122	0.395	3.187	
Gender					0.001*
Male	136	4.840	1.945	12.049	

Female	71	Ref	-	-	
Hospital Stay					0.001*
≤ 5	27	Ref	-	-	
6-10	117	13.697	1.073	174.796	
11-15	46	0.994	0.088	11.213	
+16-20	10	2.300	0.191	27.723	
> 20	7	1.169	0.057	23.913	
Comorbidities					
Diabetes mellitus	165	0.592	0.295	1.190	0.001*
Hypertension	114	0.402	0.180	0.896	0.026*
Ischemic heart disease	45	0.448	0.172	1.165	0.050
Hypothyroidism	8	1.591	0.261	9.691	-
Anemia	15	1.353	0.253	7.228	0.614
Asthma	7	1.319	0.234	7.447	0.050
Hyperlipidemia	16	1.003	0.298	3.377	0.754
Dyslipidemia	8	1.591	0.261	9.691	0.050

Various risk factors associated with polypharmacy were examined including age, gender, level of education, hospital stay and stages of CKD. Age, gender, hospital stay and comorbidities such as Diabetes Mellitus and Hypertension were significantly associated with polypharmacy (p value <0.005)

Table 5 Distribution of Drug Related Problems

Drug related problems	**Frequency**	**Percentage (%)**
Drug interactions	193	93.2
Adverse drug reactions	16	7.7
Inappropriate drug	65	31.4
Contraindication	64	30.9
Drug duplication	48	23.2
Drug overdose	50	24.2
Medication error	71	34.3
Drugs without indication	50	24.2
Indication without drug	48	23.2

A total of 605 DRPs were identified among 207 patients. The most common DRP was Drug Interaction 193 (93.2%) were attributed as the main cause of Drug related problem followed by medication error 71 (34.3%) inappropriate drug 65 (31.4%) and contraindication 64 (30.9%). Severe drug interactions were comparatively higher (48.75%) than moderate (44.06%) and minor (7.18%). Most common class of drugs responsible for interaction were antihypertensives, loop diuretics, antacids and antiplatelets. The average number of DRP per prescription was 2.90±1.22 (Table 5).

Table 6 Distribution Based on Drug Related Problem and Polypharmacy

Parameter	Polypharmacy				p – value
	Yes	Percentage	No	Percentage	
Drug interaction	159	76.8	48	23.1	0.022*
Adverse drug reaction	14	6.7	2	0.95	0.235
Inappropriate drug	49	23.6	16	7.7	0.435
Contraindication	49	23.6	15	7.2	0.543
Drug duplication	36	17.3	12	5.7	0.436
Drug overdose	41	19.8	9	4.3	0.212
Medication error	52	25.1	19	9.17	0.239
Drug without indication	41	19.8	10	4.8	0.343
Indication without drug	36	17.3	12	5.7	0.435

Various domains of Drug Related Problems were compared with polypharmacy, drug interaction was significantly associated with polypharmacy (p value 0.022).

4. Discussion

The present study was conducted to evaluate burden of polypharmacy and to determine potential DRPs among chronic kidney disease patients. The mean age of the study participants was 56.64±16.64 which was on par with the study conducted by Hailu B Y et al.,[10] Older age are at increased risk of polypharmacy which is mainly attributed to their concomitant illness, physical difficulties and cognitive decline.

The evaluated ratio of males and females are found to be 66% and 34% which indicates male dominance over female patients, this is similar to the study conducted by Atray P et al.,[11] which evaluated male predominance among CKD patients.

During the study period, it was observed that almost half of the CKD patient population had a hospital stay ranging from 6-10 days, which was associated with increased risk of polypharmacy. This finding is in line with previous study conducted by Fukuba N et al.,[12] have reported a positive association between polypharmacy and the length of hospital stay in CKD patients. The presence of polypharmacy increases the risk of potential adverse events and medication-related complications, which in turn can speculate the hospital stay.

Diabetes mellitus, hypertension, ischemic heart disease were the most common comorbidities which coincides with the studies conducted by Fasipe O J et al.,[13] and subeesh vk et al.,[14] which identified hypertension and diabetes mellitus as the most common comorbidity among CKD patients. High blood pressure as well as inadequate glycemic control can result in progressive damage to blood vessel supplying blood to the nephrons resulting in renal impairment.

Majority of study participants had stage 5 CKD followed by stage 4 which resemblant with the study conducted by Mamadi R K et al.,[15] This sheds light on the fact that the number of patients going to ESRD stage is progressively increasing overtime due to lack of appropriate prescribing and patient awareness.

Polypharmacy was observed in 157 out of the total 207 study participants (76.8%). This finding is consistent with a study conducted by Fasipe OJ et al.,[11] which reported a high prevalence of polypharmacy (85.3%) among 105 CKD patients. This indicates that polypharmacy is significantly common necessitating the need to monitor therapy especially for CKD patients because it can significantly increase risk of possible adverse outcomes.

Antiulcer, antihypertensive and antibiotics drugs were the most prescribed drugs which allied with the study conducted by Santra S et al.,[16] which recognized antihypertensive, antiulcer, mineral supplements as most prescribed medication class.

The independent factors which predicted the risk of polypharmacy were age, gender, length of hospital stay and comorbidity such as diabetes mellitus and hypertension which is identical to the study conducted by Wang Y et al.,[17] Salwe J K et al.,[18] and Schmidt M I et al.,[19]

A total of 605 DRPs were identified where the mean number of DRPs per prescription were 2.908 ± 1.22 which is similar to a study conducted by Chan C D et al.,[20] which identified 2.2±1.6 DRPs per prescription. This can be attributed to the proactive role of clinical pharmacist in timely detecting and reporting DRPs to the relevant health care providers.

Drug interactions accounted for the most among DRPs followed by medication error, inappropriate drug and contraindication which is parallel to the study conducted by Subeesh V K et al.,[14] in which drug interactions were the most commonly occurring DRP followed by indication without drug and frequency error.

To our best knowledge our study was the first study which evaluated various domains of drug related problems (Helper and Strands Classification) with polypharmacy where drug interactions was found to be significantly associated with polypharmacy. Antihypertensives, loop diuretics, antiplatelets, anti-ulcer drugs were most commonly associated with drug interactions.

The study has bought to limelight the prevalence and associated risk factor related to polypharmacy alongside the DRPs commonly occurring within CKD patients. Our study had several strengths, it is among its first to evaluate individual DRP with polypharmacy (Helper and Strand Classification). The study also identified prevalence and potential risk factors associated with polypharmacy. Our study had few limitations such as it being single centered study with comparatively less sample size. We were not able to determine OTC medication taken by the patients. Future studies are required to improve the health care outcomes by deploying interventional registries or DRP alert systems to document professional activities.

5. Conclusion

The outcomes of this study have emphasized the prevalence and burden of polypharmacy among chronic kidney disease patients, alongside concomitant comorbidities and the necessity to take proactive measures to avoid the onset of drug-related complications among these patients. The root cause of inappropriate prescriptions among such a vulnerable population is a lack of appropriate guidelines for prescribing. Drug prioritizing strategies may indeed be beneficial in optimizing the impact of pharmacological interventions. Continual identification and resolution of DRPs by a complete pharmaceutical care team can help to improve the health status and quality of life of these patients.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

The study was approved by the BAPUJI PHARMACY COLLEGE Institutional Ethics Committee on human subjects' research. Ref No. BPC/IEC/81/2021 – 22 dated 21st Feb 2022. Subject confidentiality was maintained during and after data collection.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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