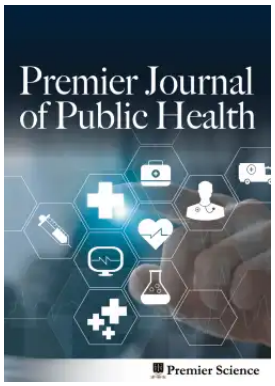

Assessment of Drug-Related Problems Among Haemodialysis Patients: A Multicentre Prospective Study in Pakistan

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ABSTRACT

BACKGROUND

Chronic kidney disease constitutes a major burden on healthcare and has become a major global health issue. Haemodialysis patients receive complicated drug therapy with multiple medications, which necessitates the regular monitoring of drug-related problems (DRPs) among renally compromised patients.

METHOD

A prospective cross-sectional study was undertaken in the Haemodialysis Centre of the Divisional Headquarter Hospital, Mirpur and the District Headquarter Hospital, Kotli, Azad Kashmir. All drug-related issues, including drug interactions (DIs), adverse effects, therapeutic failure, overdosage, subtherapeutic dosage, improper drug selection, indication without drug and drug without indication, were evaluated. The association of demographic and clinical variables with DRPs was assessed through univariable logistic regression.

RESULTS

76.7% of patients were observed to have DRPs during haemodialysis. A total of 228 DRPs were identified in 150 patients, including DIs (73/150 patients, 48.7%), adverse drug reactions (ADRs) (68/150 patients, 45.3%), and failure to receive the drug (50/150 patients, 33.3%). Phosphate binders were the largest source of DRPs, while antihypertensive medicines and PPIs/antacids were the second and third most common causes of DRPs, respectively, in haemodialysis patients. The polypharmacy and comorbid conditions were significantly associated (p value <0.05) with increased odds of DRPs in haemodialysis patients.

CONCLUSION

The study identified numerous DRPs in patients undergoing haemodialysis, including DIs, ADRs, and treatment failure. Polypharmacy and comorbidity were found to have significant associations with DRP occurrence.

Keywords: Hemodialysis drug interactions, Polypharmacy risk factors, Phosphate binder-related issues, Chronic kidney disease medication safety, Prospective multicenter study Pakistan

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Background

Chronic kidney disease (CKD) has become a major global public health issue.[1] It is characterized by anomalies in the structure or function of the kidney that have been present for at least 3 months and have a negative influence on health. CKD is progressive and can be caused by a variety of factors. It is asymptomatic until the glomerular filtration rate (GFR) is very low (less than 30 mL/min).[2,3] The presence of albuminuria is linked to the advancement of end-stage renal disease (ESRD).[1] Kidney disease is one of the most frequent genitourinary diseases in the world, with an estimated 800,000 cases of mortality per year.[4] Kidney disease–related health-care expenditures, particularly the direct costs associated with renal replacement therapy for the management of CKD, constitute a major burden on national health insurance systems.[4] Volume depletion, nephrotoxic drugs, uncontrolled hypertension, anaemia, renal bone disease, metabolic disturbances, skin disease, gastrointestinal complications, uremic bleeding, neurological complications and infections are common causes of sudden deterioration of renal function.[5]

The ESRD is characterised by a GFR of ≤15 mL/min/1.73 m² and encompasses patients requiring maintenance dialysis. Dialysis represents the standard and most effective therapeutic modality for ESRD, serving as a vital means for the removal of metabolic waste products and toxins from the body.[6] Dialysis cannot fully replace lost kidney function; however, diffusion and ultrafiltration can help to manage it to some extent.[7] The dialysis performed through an artificial kidney machine, termed haemodialysis, is the most commonly used dialysis technique. The frequency of haemodialysis is determined by the patient's metabolic and volume status. For most patients with ESRD, a total of 9–16 hours of dialysis per week, typically administered in three sessions, is considered adequate. Once regular haemodialysis is initiated, patients are generally able to tolerate greater fluid and protein intake.[8]

Dialysis patients with ESRD have a complicated drug regimen, receiving about 10–12 drugs per day, the majority of which require multiple doses daily. The complicated health condition often necessitates multiple medications; patients' compliance with their recommended medication regimens might be influenced, leading to drug-related problems (DRPs).[9] DRP refers to any incident in drug treatment that actually or potentially interferes with the patient reaching an endpoint of pharmaceutical care. The incidents of indication without drug (IWD), drug without indication (DWI), failure to receive drug (FRD), subtherapeutic dosage (STD), overdosage (OD), improper drug selection (IDS), adverse drug reactions (ADRs) and drug interactions (DIs) are DRP or medication-related problems.[10]

Despite the need for drug therapy, the patients are often not prescribed the required medications due to poor diagnosis, which leads to an indication without a drug DRP.[11] Alternatively, unnecessary use of medications is a common practice due to self-medication, substance abuse and irrational prescribing leading

Ethical approval: The authorization letters for the conduct of research were obtained through Atson College of Pharmacy, Mirpur, Azad Jammu and Kashmir. The permission was also granted by the DHQ hospitals in Mirpur and Kotli, Azad Kashmir. Ethical Approval numbers: 195/10/EX/ACP/21 and 196/09/EX/ACP/21

Consent: Written informed consent was also taken from the patients who were enrolled in the study.

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to DWI DRP.[12] The inability of a patient to receive the medication prescribed is often due to patient noncompliance, nonadherence, ineffective drug distribution or administration approach and formulation concerns, which may lead to failure in receiving the drug therapy.[13] The sub-therapeutic dosage and OD are also common DRPs that can occur when the medicine dose is not tailored for an individual patient, due to inappropriate dosage intervals or regimen and ineffective excretion of renally excreted drugs.[10] Dosing modifications are essential for drugs cleared by the renal system based on creatinine clearance.[14] Similarly, wrong drug selection despite the inappropriateness in a medical condition, contraindications or an allergy to that drug also leads to DRP.[15] ADRs are also common and can occur at regular doses due to a variety of reasons, including incorrect pharmaceutical administration, delivery of a harmful medicine and pharmacological or allergic reaction.[16,17] Similarly, DIs between drugs used for kidney disease treatment, like calcium salts and iron products, are common in dialysis patients.[16]

DRPs have been reported in up to 81% of hospitalized patients undergoing haemodialysis. The presence of DRPs may lower quality of life, prolong hospital stays, and increase overall health-care expenditures.[18] Four or more medication changes within the past 12 months, concurrent use of five or more drugs and presence of more than three comorbid conditions have all been identified as significant factors associated with DRPs in dialysis patients. Studies have estimated that patients undergoing haemodialysis commonly experience between four and eight DRPs per individual.[19] The study, therefore, aimed to evaluate the DRPs among patients receiving haemodialysis treatment.

Methods

Study Design and Setting

This was a prospective, multicentre observational study designed to estimate the prevalence and patterns of DRPs among patients receiving maintenance haemodialysis. The study outcomes were assessed at a single point per patient (prevalence), and data were collected prospectively during routine clinical care using predefined operational criteria. The study was conducted within the haemodialysis units of the Divisional Headquarters (DHQ) Hospital in Mirpur, as well as the District Headquarters Hospital in Kotli, Azad Kashmir. At both centres, patients typically received maintenance haemodialysis three times per week, with each session lasting approximately four hours. The study was conducted in accordance with STROBE guidelines over a period of three months, from November 2024 to January 2025. During the study period, all eligible patients who were receiving maintenance haemodialysis treatments at one of the centres were screened for inclusion (Figure 1).

Sampling and Sample Size

This research was approached using a consecutive sampling method. All patients at the haemodialysis centres (HDCs) during the designated study period were screened to participate so long as they met our eligibility criteria. Out of the total eligible patients undergoing haemodialysis at the two centres during the recruitment period of three months, a total of 150 patients were recruited for the study. There was no a priori sample size calculation as the study was intended to be a pragmatic, feasibility-based observational assessment aimed at capturing the entirety of cases pertinent

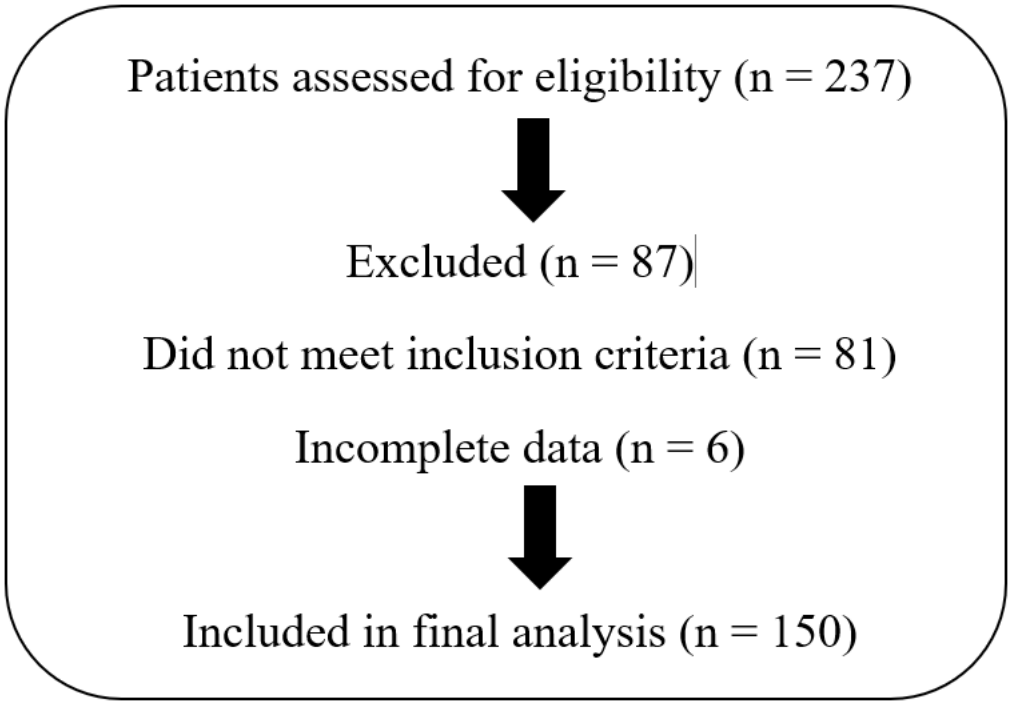

Fig 1 | Summary of screening process

to the setting. In this case, the study aimed to provide a preliminary dataset with which to understand the burden and pattern of DRPs facing patients undergoing haemodialysis in the region of Azad Kashmir.

This study employed consecutive enrolment using a pragmatic census approach. All adult patients receiving maintenance haemodialysis at the participating centres during the study period were screened for eligibility and invited to participate. This approach was selected to maximize feasibility and selection bias and reflect routine clinical practice in a resource-constrained dialysis setting.

Inclusion and Exclusion Criteria

Patients meeting the following inclusion criteria were recruited for the study:

1. Having an age of 18 years and above.
2. Having an established diagnosis of ESRD as registered in the medical record.
3. Having received maintenance haemodialysis (i.e., recurrent scheduled haemodialysis) at the Mirpur or Kotli DHQ HDCs during the study.
4. Having adequate clinical and medication information in the medical record for the assessment of DRPs.
5. Being able and willing to sign the approved informed consent form.

Patients were excluded from the study in case they:

1. were under the age of 18,
2. had an acute renal injury rather than CKD,
3. were receiving other forms of renal replacement therapies (for example, peritoneal dialysis) or were conservatively managed without dialysis,
4. had key clinical and medication information that was incomplete or absent; and
5. were unable to give informed consent and had not provided a legally authorized representative.

Data Collection Tool

The data collection tool comprised information on patient demographics, clinical data, laboratory observations, information on current medications in use and assessment of DRPs. The demographics included patient gender, age and marital status. The clinical data included comorbidity status, types of comorbid conditions prevalent in the patient, stage of CKD, total time on haemodialysis, and patient vitals such as blood pressure, body temperature, and heart rate. The laboratory observations collected information on clinical lab values for sodium, potassium, calcium, phosphate, urea and creatinine. The medication information included details of the past and existing medications with generic names and frequency. The assessment of drug-related information collected details on all types of DRPs such as DIs, ADRs, FRD therapy, OD, STD, IDS, IWD and DWI.

Study Procedure

All DRPs were identified by trained clinical pharmacists and conflicts were solved by communicating with a nephrologist. All identified DRPs were independently reviewed by two trained clinical pharmacists. A subset of cases was reviewed in parallel to ensure consistency in the application of definitions. Discrepancies were resolved through consensus discussion, and cases without agreement were referred to a consultant nephrologist for final adjudication. Only a small proportion of cases required arbitration, indicating a high level of agreement between reviewers. The framework proposed by Strand et al.[20] was utilized to categorize DRPs based on predetermined operating parameters (e.g. FRD was considered to be missed doses related to either nonadherence or supply difficulties or an error in administration).[10] FRD was identified through review of medical records and medication charts, supplemented by patient or caregiver interview when documentation was unclear. The assessment focused on the preceding dialysis treatment period (30 days preceding the index dialysis cycle) and outpatient medication use. Classification was made when a clinically indicated drug was neither prescribed nor available to the patient during the assessed period, in the absence of a documented contraindication. The information on DIs was verified from Medscape (version 12.30)[21] and Stockley's *Handbook of Drug Interactions*, 12th Edition. Only clinically significant drug–DIs (DDIs) (moderate or major severity) identified using Stockley's Drug Interactions and Medscape were recorded. OD and STDs were assessed from standard dosing guidelines in the British National Formulary, version 86. IDS was evaluated by evidence-based treatment guidelines of the WHO and NICE. The indication without a drug and the drug without an indication were evaluated through a comprehensive review of clinical notes and medication in consultation with the nurse and nephrologist. ADRs were identified through prospective clinical review of patient records and interviews. The assessment was limited to documenting the presence or absence of suspected ADRs; formal causality assessment using WHO-UMC or Naranjo scales, as well as severity or preventability scoring, was not performed.

The DRP identification followed a clinical adjudication workflow rather than a purely measurement-based classification exercise. Two trained pharmacists independently reviewed cases, but disagreements were resolved in real time through structured discussion and, where required, nephrologist arbitration. Because arbitration occurred as part of the routine adjudication process, the original independent ratings were not preserved in a way that allows a valid post hoc kappa calculation.

Data Analysis

IBM SPSS (Statistical Package for Social Sciences) version 22.0 was used to analyse the data. The demographic and clinical data were presented by descriptive

statistics, while statistical associations between DRPs and demographic and clinical variables were assessed through univariable logistic regression. All regression analyses were univariable in nature and were conducted to explore potential associations between patient characteristics and the presence of DRPs. These analyses should be interpreted as hypothesis-generating rather than confirmatory.

Ethical Considerations

The authorization letters for the conduct of research were obtained through Akson College of Pharmacy, Mirpur, Azad Jammu and Kashmir. Ethical Approval numbers: 195/10/EX/ACP/21 and 196/09/EX/ACP/21. The permission was also granted by the DHQ hospitals in Mirpur and Kotli, Azad Kashmir, respectively. Written informed consent was also taken from the patients who were enrolled in the study. The institutional ethics approvals granted in 2021 remained valid through continuation/revalidation and covered the 2024–2025 data collection period at both participating sites.

DRP Identification and Adjudication

The categorization of DRPs follows the common framework of Strand et al.[20], which defines the following: IWD, DWI, FRD, STD, OD, IDS, ADRs and DDIs.

- IWD: An IWD case was assigned to a patient who had a documented clinical indication without any prescribed therapy, i.e., the presence of persistent hypertension in a patient had no recorded antihypertensive. Example: A patient with pre-dialysis consistently suffers from >160/100 mmHg blood pressure but no antihypertensive was recorded.
- DWI: No clinical justification for a medication based on diagnosis, vitals or any laboratory results. Example: Continuing the use of proton pump inhibitors when there is no gastritis or reflux symptoms, or no ulcer risk.
- FRD: Cases of nonadherence, inability to afford the medication, supply chain issues or documented medication administration omissions in the original hospital documentation. Example: A phosphate binder given three times a day, but only intermittently filled due to cost.
- STD: When dosages for ESRD patients were recorded that were below recommended or when dosing frequency was too wide to achieve a therapeutic effect within a reasonable length of time. Example: Erythropoietin was prescribed at a lower than recommended weekly dose despite the presence of untreated clinically significant anaemia.
- OD: When dosages exceeded what is recommended based on renal adjustments. Example: Gabapentin was prescribed at 600 mg/day when there was severe renal impairment requiring a lower dose.
- IDS: When a medication is clinically inappropriate or contraindicated for the patient's condition. Example: A dialysis patient who has uncontrolled hypertension and a high risk for GI bleeding, and who uses NSAIDs.
- ADRs: The presence or absence of suspected ADRs was determined based on clinical judgment, patient-reported symptoms, known adverse effect profile, and symptom resolution upon withdrawal. ADRs were recorded as suspected events without causality, severity, or preventability grading. Example: Hypercalcaemia and pruritus after starting calcium-based phosphate binder therapy.
- DDIs: These interactions were validated using Stockley's Drug Interactions and Medscape Interaction Checker. Only the interactions rated "clinically significant" (moderate or severe) were included. For example, Co-administration with calcium-containing binders reduces the absorption of orally administered iron or beta-blockers.

Results

Characteristics of Study Participants

A total of 150 patients with CKD were surveyed, comprising 53.3% males and 46.7% females. The participants' ages ranged from 18 to 85 years, with a mean age of 48.24 ± 15.82 years. The majority (60.7%) were between 31 and 60 years of age, and 80.7% were married. More than half of the patients (57.3%) had been undergoing haemodialysis for 1–4 years (13–48 months), while 15.3% had been on haemodialysis for over 4 years (>48 months). Polypharmacy was prevalent in 90.7% patients and 96.7% patients were in stage 5 CKD (Table 1).

Most patients reported experiencing multiple DRPs; 115 out of the 150 patients (76.7%) reported experiencing at least 1 DRP. On a patient basis, 73 patients (48.7%) suffered from DI-related problems, 68 patients (45.3%) experienced ADR-related problems, and 50 patients (33.3%) experienced FRD-related problems. Across the patients, there were a total of 228 DRP events. Out of which DI contributed 73 events (32.0%) of the total DRP problems, ADRs contributed 68 events (29.8%), FRD caused 50 events (21.9%), and the other categories caused the remaining 37 events. Patients were receiving a mean of 6.55 medications (SD 1.51) at the time of assessment, with counts ranging from 3 to 9 medications per patient, indicating a high prevalence of polypharmacy in the study population. Of the 150 patients included, 90 were enrolled from DHQ Hospital Mirpur and 60 from DHQ Hospital Kotli. Out of 228 DRPs, 141 were reported from DHQ Mirpur and 87 from DHQ Kotli.

Clinical Characteristics

Several comorbid conditions were reported in surveyed patients. A total of 140 patients (93.3%) had comorbidities. Out of these, 120 (80.0%) had hypertension, 30 (20.0%) had anaemia, 29 (19.3%) had type I diabetes mellitus, 26 (17.3%) had hepatitis C and 16 (10.7%) had diabetes mellitus type II. Cerebrovascular diseases were the least prevalent comorbidities (Table 2).

Laboratory Observations and Vitals

All surveyed patients had normal respiratory rates and were afebrile. Also, every patient had higher levels of

Table 1 | Characteristics of Surveyed CKD Patients

Characteristics	Frequency	Percentage
Gender		
Male	80	53.3
Female	70	46.7
Mean age	48.24 ± 15.82 years	
Age groups		
30 years or less	24	16.0
31–45 years	40	26.7
46–60 years	51	34.0
More than 60 years	35	23.3
Marital status		
Single	23	15.3
Married	121	80.7
Divorced/widowed	6	4.0
Duration of haemodialysis treatment		
12 or fewer months (1 year or less)	41	27.3
13–48 months (>1–4 years)	86	57.3
49–96 months (>4–8 years)	18	12.0
More than 96 Months (>8 years)	5	3.3
Stage of chronic kidney disease		
Stage 4	5	3.3
Stage 5	145	96.7
Polypharmacy (≥5 drugs)		
Yes	136	90.7
No	14	9.3

Table 2 | Prevalence of Comorbidity Among Surveyed Patients

Comorbidity Status	Frequency	Percentage
Comorbidity		
Yes	140	93.3
No	10	6.7
Hypertension		
Yes	120	80.0
No	30	20.0
Type 1 diabetes mellitus		
Yes	16	10.7
No	134	89.3
Type 2 diabetes mellitus		
Yes	29	19.3
No	121	80.7
Cerebrovascular issues		
Yes	3	2.0
No	147	98.0
Hepatitis C		
Yes	26	17.3
No	124	82.7
Anemia		
Yes	30	20.0
No	120	80.0
Others		
Yes	9	6.0
No	141	94.0

creatinine in their bodies than usual (0.7–1.2 mg/dL). The 97.3% patients (146) had higher than normal uric acid levels (hyperuricemia), 32.0% (48) had elevated phosphate levels and 9.3% (14) were hyperkalemic. Hypocalcemia was prevalent in 34.0% (51) of patients (Table 3).

Evaluation of Drug-Related Problems

A total of 228 DRPs were identified among 150 patients, corresponding to a mean of 1.52 DRPs per patient (median = 2.0, minimum = 0, maximum = 5, IQR = 1.0, range = 5). In our study, 76.7% of patients (n = 115) had drug-related difficulties during haemodialysis. DIs were reported in 73 patients, ADRs in 68 patients and failure to get the drug in 50 patients. The least frequent DRPs reported were OD, STD and DWI (Figure 2).

In total, there were 228 incidents of DRPs, from which the most commonly observed were DIs in 32.0% (n = 73) incidents, ADRs in 29.8% (n = 68), and failure to receive the drug therapy in 21.9% (n = 50) cases. Phosphate binders were prescribed to the majority of patients and were the largest source of DRPs in haemodialysis patients. There were 36 patients with DIs, 31 patients with ADRs, 28 patients with therapeutic failure, 7 patients with IWDs and 4 patients with incorrect drug selection with phosphate binders. Antihypertensive medicines were the second most common cause of DRPs, with 21 DIs and 13 ADRs in haemodialysis patients, and PPIs/Antacids were another source of DRPs, with ADRs in 8 patients, DIs in 7 patients, and treatment failure in 6 patients, respectively. Anticoagulant-related DRPs primarily were due to medications used during dialysis sessions, particularly intradialytic unfractionated heparin. The oral anticoagulants were not the main contributors to anticoagulant-related DRPs (Table 4).

The association between demographic and clinical factors was assessed by applying univariable logistic regression with a significant p value of less than 0.05. The results showed that gender and age have no significant relationships with DRPs. Similarly, the duration of haemodialysis treatment and CKD stage also do not influence DRP occurrences. However, patients with polypharmacy have a significant association (p value <0.05) and have 4.3 times higher odds of experiencing DRPs compared to those taking fewer drugs. Similarly, patients with comorbidities are significantly associated and 4.18 times more likely to develop DRPs than those without comorbidities (Table 5).

Discussion

The goal of this study was to analyse DRPs among haemodialysis patients to improve their quality of life. This was the first study in the state of AJ&K to analyse DRPs in HDCs. The study successfully addressed a gap in

Table 3 | Vitals and Laboratory Observations of Surveyed CKD Patients

Vitals and Laboratory Observations	Frequency	Percentage
Heart rate		
Normal	141	94.0
Bradycardia	2	1.3
Tachycardia	7	4.7
Blood pressure		
Normal	25	16.7
Hypotensive	5	3.3
Hypertensive	120	80.0
Respiratory rate		
Normal	150	100.0
Body temperature		
Afebrile	150	100.0
Sodium levels		
Normal	116	77.3
Hyponatremia	33	22.0
Hypernatremia	1	0.7
Potassium levels		
Normal	136	90.7
Hyperkalemic	14	9.3
Calcium levels		
Normal	96	64.0
Hypocalcemia	51	34.0
Hypercalcemia	3	2.0
Phosphate levels		
Normal	101	67.3
Hypophosphatemia	1	0.7
Hyperphosphatemia	48	32.0
Uric acid levels		
Normal	3	2.0
Hypouricemia	1	0.7
Hyperuricemia	146	97.3
Creatinine levels		
Hyper-creatinine levels	150	100.0

the assessment of DRPs of haemodialysis patients and gathered data using standard DRP categories. The prospective aspect of this study allowed for more possibilities to capture DRPs. Drug-related issues were found in 115 of the 150 surveyed patients. The most prevalent DRPs in haemodialysis patients were DIs, ADRs and FRDs. Failure to receive medication was linked to a high number of medications per prescription. The majority of patients received phosphate binders because of elevated phosphate levels and many suffered from DIs, adverse reactions and therapeutic failure. Antihypertensive medications were also a common cause of DRPs in haemodialysis patients. Although DDIs were recorded at the drug-class level, phosphate binders were frequently implicated, consistent with known interactions involving reduced absorption of iron, antibiotics, and thyroid medications. The second most common DIs observed were of antihypertensives drug class. For example, ACE inhibitors or angiotensin receptor blockers interact with potassium supplements, and beta-blockers were observed to interact with calcium channel blockers. These interactions are well described in standard interaction references and are particularly relevant in haemodialysis populations receiving complex polypharmacy.

The previous research conducted in Indonesia in 2018 on haemodialysis patients also reported DRPs related to excessive dosage,[22] while inappropriate drug selection and DI were frequently reported drug therapy problems in a study conducted in Nigeria in 2017.[23] Li[24] conducted a comprehensive medication assessment and reconciliation of haemodialysis patients in Singapore and reported an average DRP of 3.1 in each patient. Rama et al.[25] conducted a study in India and reported widespread prevalence of DIs in CKD patients, with the most common interactions between ascorbic acid and cyanocobalamin and clonidine and metoprolol.

The study's findings provided much-needed information on DRP evaluation and the involvement of the role of pharmacists and other health-care professionals in identifying DRPs, preventing possible DRPs, and resolving actual DRPs for improved clinical outcomes in patients with CKD. Measures, such as correction of the dosage regimen, reduction of medication interactions, checking for negative consequences, examining for comorbidities that might require dose adjustments and monitoring of combination therapy, should be adopted to prevent drug-related issues. Phosphate binder–related DRPs were common, consistent with the complexity of CKD–MBD management. These findings highlight the importance of appropriate binder selection, administration timing relative to interacting medications, and monitoring for calcium-related adverse effects, particularly in resource-limited settings.

Patients suffering from advanced stages of CKD show serious biochemical and physiological changes, which may put them at a higher risk when it comes to effects caused by medication. Abnormal renal clearance, changes in protein distribution, alteration of protein binding, irregularities in absorption in the GI tract and disruption of certain metabolic pathways all contribute to altered pharmacokinetic and pharmacodynamic responses, hence making it unfeasible to apply standardized dosing for numerous patients in haemodialysis.[5,7] Together with the extensive polypharmacy, these changes increase the risk of DDIs, adverse outcomes and lack of intended efficacy to a great extent.[9]

A recent study showed that during the study period, phosphate binders contributed the greatest proportion of DRPs. As patients with CKD suffer from chronic hyperphosphatemia due to the severe loss of renal phosphate excretion, which is an integral part of CKD, this finding is understandable.[5] Consequently, phosphate binders are frequently prescribed to mitigate the

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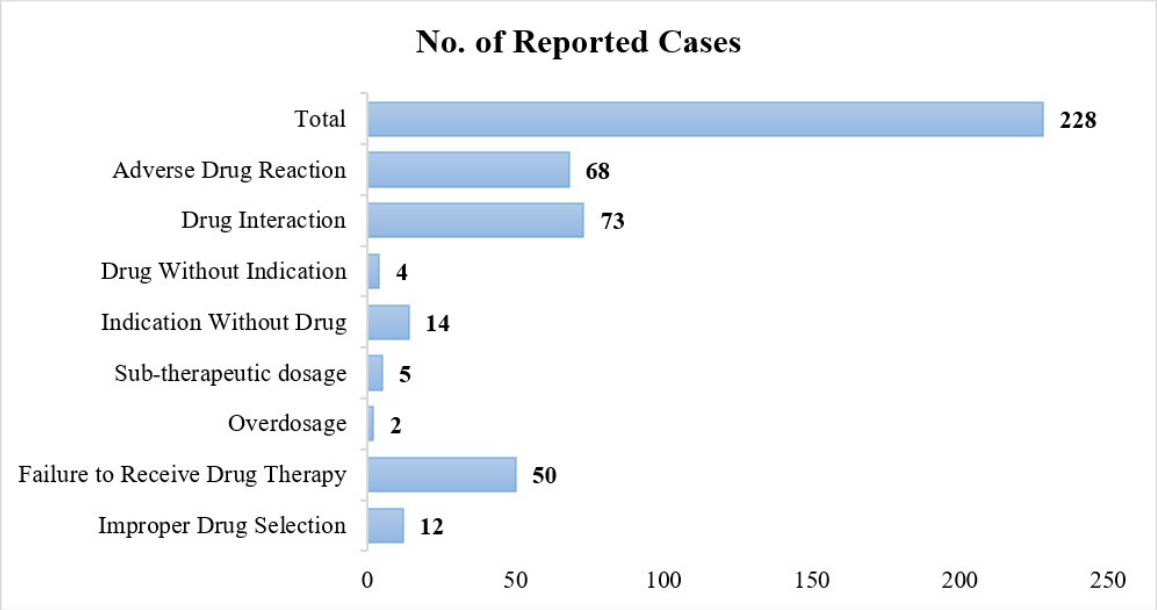

Fig 2 | Prevalence of DRPs by number of reported cases

Table 4 | Prevalence of Drug-Related Problems by Drug Class (*N* = 228)

Drug Classes	IDS	FRD	OD	STD	IWD	DWI	DI	ADRs	Total	% of total DRPs (*N* = 228)
Antihypertensives	2	8	0	1	1	1	21	13	**47**	**20.61%**
Anticoagulants	0	2	1	1	1	0	4	2	**11**	**4.82%**
Antidiabetics	1	2	0	2	2	0	1	4	**12**	**5.26%**
Antianaemic	0	1	0	0	0	0	0	1	**2**	**0.88%**
NSAIDs	1	1	0	0	1	0	2	4	**9**	**3.95%**
Phosphate binders	4	28	0	0	7	2	36	31	**108**	**47.37%**
Multivitamins	3	2	1	1	2	0	2	5	**16**	**7.02%**
PPIs/antacids	1	6	0	0	0	1	7	8	**23**	**10.09%**
	12	**50**	**2**	**5**	**14**	**4**	**73**	**68**	**228**	

IDS=improper drug selection, FRD=failure to receive drug, OD=overdosage, STD=subtherapeutic dosage, IWD=indication without drug, DWI=drug without indication, DI=drug interactions, and ADRs=adverse drug reactions.
The table reports event-level DRPs, not patient-level data. Counts represent drug-related problem events; individual patients may have contributed more than one DRP.

absorption of dietary phosphate and to avoid the complications of secondary hyperparathyroidism and vascular calcification. However, phosphate binders also predispose patients to DRPs. All polyvalent cationic binders, including calcium-based binders, have the ability to non-selectively bind to other concomitantly administered oral drugs in the intestine, thereby causing clinically significant therapeutic reductions of those drugs and therapeutic failures, in particular antihypertensive, iron and antibiotic drugs.[16,25] Additionally, calcium-based and phosphate binders can also cause hypercalcemia, gastrointestinal sequelae and vascular calcification, all of which are ADR.[5] Furthermore, a considerable number of phosphate binders require several doses throughout the day, which considerably increases the volume of tablets, an important predictor of poor adherence among patients on haemodialysis.[13] This volume of tablets, coupled with nonadherence, results directly in FRD therapy, another common DRP identified in our study. It is the combined set of biological, psychological and physiological factors that provides the most valid explanation for phosphate binders leading the pack, even surpassing antihypertensives and gastrointestinal drugs, in the volume of DRPs for this study.

Our findings related to DRPs in patients receiving phosphate binders, antihypertensives, and other CKD-related therapies should be viewed in light of contemporary clinical guidelines. The KDIGO 2024 clinical practice guideline for evaluation and management of CKD underscores the importance of accurate drug dosing, avoidance of nephrotoxins, and integration of comprehensive care across CKD stages, including those requiring renal replacement therapy.[26] For management of metabolic complications such as mineral and bone disorders, the existing KDIGO CKD–MBD

Table 5 | Univariable Logistic Regression of Factors Related to DRPs

Demographic and Clinical Factors	Total Patients	Presence of Drug-Related Problem		Logistic Regression		
		Yes	No	OR	CI	*p* Value
Gender						
Male	80	60	20	Ref		
Female	70	55	15	1.085	0.478–2.465	0.846
Age groups						
30 years or less	24	19	5	Ref		
31–45 years	40	32	8	1.152	0.300–4.418	0.836
46 to 60 years	51	38	13	0.763	0.217–2.689	0.674
More than 60 years	35	26	9	0.508	0.133–1.945	0.323
Duration of haemodialysis treatment						
12 or fewer months (1 year or less)	41	32	9	Ref		
13–48 months (>1–4 years)	86	65	21	0.845	0.325–2.198	0.730
49–96 months (>4–8 years)	18	14	4	0.898	0.222–3.627	0.879
More than 96 months (>8 years)	5	4	1	2.112	0.141–31.561	0.588
Stage of chronic kidney disease						
Stage 4	5	4	1	Ref		
Stage 5	145	111	34	0.975	0.100–9.542	0.983
Comorbidity						
No	10	5	5	Ref		
Yes	140	110	30	4.184	1.035–16.907	**0.045**
Polypharmacy (≥5 drugs)						
No	14	7	7	Ref		
Yes	136	108	28	4.338	1.309-14.383	**0.016**

guideline update continues to inform phosphate control and PTH modulation, which are directly relevant to binder-related DRPs observed in our cohort.[27]

Limitations of the Study

Some limitations must be discussed in regard to this study. One of these limitations is generalizability. The study was conducted at only two dialysis centres in Azad Kashmir, which comprise a total of 150 dialysis patients. The small sample size and very specific target population might have implications for the generalizability of the study. This study employed a multicentre prospective observational design, which is good for identifying DRPs. However, this design does not allow for the determination of causality, nor does it account for fluctuations in the use of medications, adherence to use or the patient's clinical status in the span of a single dialysis cycle. Furthermore, self-reporting and documentation of non-adherent ADRs might have gone unnoticed in the case of documentation of a patient with mild or non-specific symptoms. Furthermore, the absence of full medication reconciliation is due to the restriction of medications that patients have been treated with, which might have caused a first detection or prescription of a drug. Overall, there is a potential for one-sided prejudice, which is referred to as, through the use of clinical judgement in the determination of DRPs. Additionally, ADRs were identified based on their presence or absence, and a formal assessment of ADR severity or preventability was not performed. As a result, the clinical impact of individual ADRs could not be graded. Although the study was conducted in a multicentre setting, formal site-level comparative analyses were not undertaken, which limits the assessment of variability in DRP patterns across centres. Also, outpatient medication lists were primarily obtained from records and patient interviews; incomplete reconciliation may have led to under- or over-identification of DRPs. The list of medicines mentioned in the patient records was assumed to be used by the patient and was not reconciled with pharmacy records or through interviews with the patient/caregiver, which is also a limitation.

Clinical Implications of the Study

This study examines the management of patients receiving haemodialysis and the implications of the study (Figure 3). The impacts of DRPs and the need for therapy, medication reviews, adjustments to the therapy and medication levels are discussed in detail. These patients are especially vulnerable; there are documented reviews that support the need for therapy and medication reviews. Instructions regarding DRPs created by clinicians are documented and should be used in DRPs created by all antihypertensives for DRPs in combination with phosphate. As demonstrated in this study, the inclusion of DRPs created by clinicians and the study by pharmacists should result in considerably better medication safety through the inclusion of structured medication management in hospitals providing medication reviews. The DRPs, as documented in the findings of this study, support the need for DRPs that should result in better care to ESRD patients by improving DRPs and care for patients and should be used in all countries of the world.

International studies provide evidence suggesting that pharmacist or health-care professional-led reviews of medications may ease some of the medication-related issues of patients with CKD and those on haemodialysis. A cluster randomized controlled trial found that structured clinical pharmacist interventions, in dialysis units, resulted in a significant decrease in the DRPs per patient and positively impacted the compliance of prescribers with the prescribing directives.[28] In the same way, another systematic review of the pharmacist interventions in patients on dialysis, there were a number of studies which demonstrated the same decrease in medication errors, improved DRPs and better outcomes of the patients.[29] A clinical nephrology pharmacist prospectively illustrated that there was a considerable acceptance of the pharmacist's recommendations by the physicians, which effectively resulted in the important optimization of the patients' pharmacotherapy.[30] All of these studies show that there is a need to incorporate medication review, coordinated prescribing audits, and pharmacist availability on the units to

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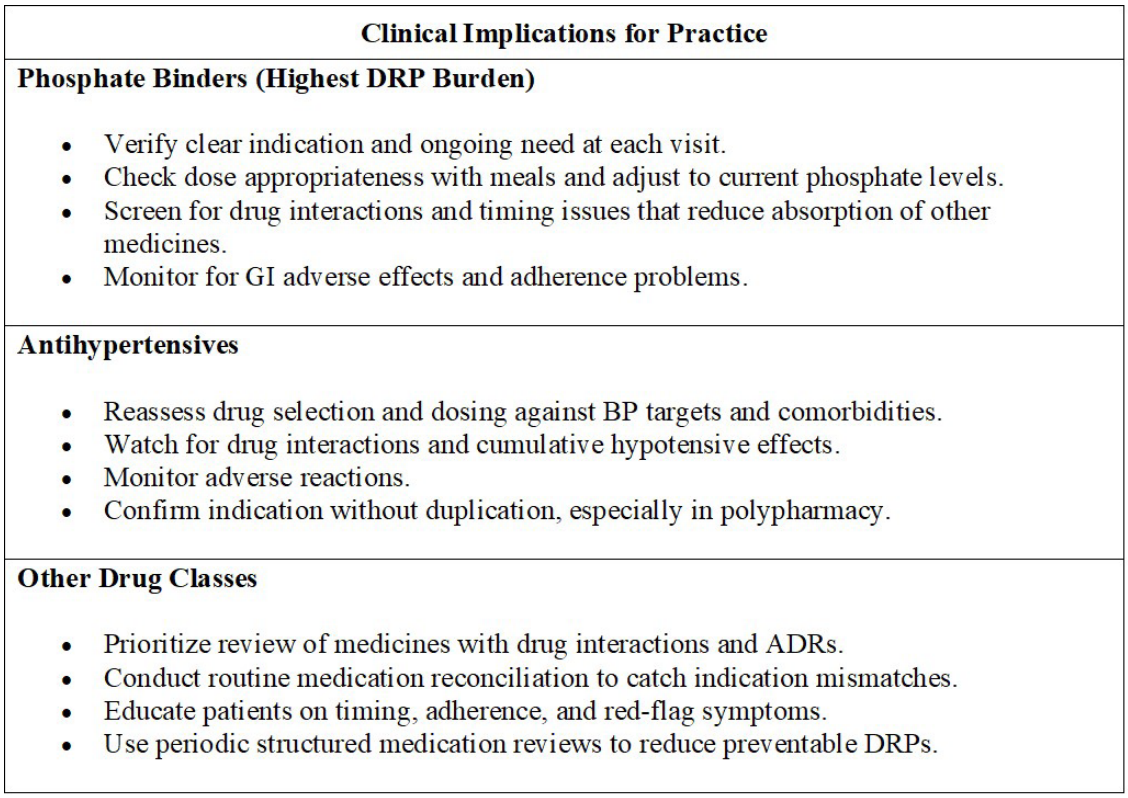

Fig 3 | Clinical implications for practice

reduce the preventable DRPs and provide effective care for the patients.

Conclusion

In conclusion, many DRPs were identified in HDCs, including DIs, ADRs, untreated conditions and treatment failure. This could be attributed to a lack of multidisciplinary services, which are provided by teams of physicians, nurses and clinical pharmacists who all share the goal of preventing DRPs.

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