ISSN: 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

Evaluation of potential drug-drug interactions in stage 5 chronic kidney disease patients on routine hemodialysis at Dr. Cipto Mangunkusumo General Hospital, Jakarta

Nusmirna Ulfa[1], Vivian Soetikno[2]*, Ni Made Hustrini[3]

[1]Clinical Pharmacology Study Program, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [2]Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [3]Division of Renal and Hypertension, Department of Internal Medicine, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

https://doi.org/10.22146/ijpther.19437

Submitted: 18-01-2025
Accepted : 20-03-2025

Keywords:
adverse drug reaction;
drug interaction;
hemodialysis;
kidney insufficiency

ABSTRACT

Patients with chronic kidney disease (CKD) face heightened susceptibility to adverse drug reactions (ADRs) owing to alterations in the pharmacokinetics and pharmacodynamics of medications. Patients with Stage 5 CKD receiving hemodialysis (HD) have numerous medications that are eliminated during the HD process. This study aims to assess the prescribing patterns in stage 5 CKD patients undergoing routine HD and their association with drug-drug interactions (DDIs) and the potential for adverse drug reactions (ADRs) resulting from DDIs. This cross-sectional study encompassed stage 5 CKD patients undergoing routine HD at Dr. Cipto Mangunkusumo General Hospital from 2020 to 2021. Data were obtained from the medical records of the HD Unit. An evaluation was performed utilizing the Lexicomp software to discover DDIs. The study had 147 individuals, with 101 different medications taken, the most prevalent being epoetin alfa (70.4%). Eighty nine percent of patients who underwent treatment associated with a potential DDIs, with the bulk of these interactions classified as moderate (88%). Fifty percent of patients were suspected of experiencing ADRs due to DDIs. Diabetes mellitus exhibited a statistically significant association with suspected ADRs attributable to DDIs (p = 0.04). Hypertension was the most predicted ADR resulting from DDIs, and diabetes mellitus significantly contributed to the incidence of ADRs owing to DDIs in patients with stage 5 CKD on routine HD. In conclusion, DDI in patients undergoing routine HD is sometimes unavoidable considering the many comorbidities. The DDI that occurred was moderate in severity and could be managed well at the Dr. Cipto Mangukusumo General Hospital.

ABSTRACT

Pasien dengan penyakit ginjal kronis (PGK) menghadapi kerentanan yang lebih tinggi terhadap reaksi obat yang merugikan (ADR) karena perubahan farmakokinetik dan farmakodinamik obat. Pasien dengan PGK stadium 5 yang menjalani hemodialisis (HD) memiliki banyak obat yang dieliminasi selama proses HD. Penelitian ini bertujuan untuk menilai pola peresepan pada pasien PGK stadium 5 yang menjalani HD rutin dan hubungannya dengan interaksi obat-obat (DDI) dan potensi reaksi obat yang merugikan (ADR) akibat DDI. Penelitian potong lintang ini mencakup pasien PGK stadium 5 yang menjalani HD rutin di Rumah Sakit Cipto Mangunkusumo dari tahun 2020 hingga 2021. Data diperoleh dari rekam medis unit HD. Evaluasi dilakukan dengan menggunakan perangkat lunak Lexicomp untuk menemukan DDI. Penelitian ini melibatkan 147 individu, dengan 101 obat yang berbeda yang dikonsumsi, yang paling umum adalah epoetin alfa (70,4%). Sebanyak 89% pasien yang menjalani pengobatan terkait dengan potensi terjadinya DDI, dengan sebagian besar interaksi ini diklasifikasikan sebagai moderate (88%). Sebanyak 50% pasien diduga mengalami ADR karena DDI. Diabetes melitus menunjukkan hubungan yang signifikan secara statistik dengan dugaan ADR yang disebabkan oleh DDI (p = 0,04). Hipertensi merupakan ADR yang paling diprediksi akibat DDI, dan diabetes melitus berkontribusi secara signifikan terhadap kejadian ADR akibat DDI pada pasien dengan CKD stadium 5 pada HD rutin. Simpulan, DDI pada pasien yang menjalani HD rutin terkadang tidak dapat dihindari mengingat banyaknya komorbiditas. DDI yang terjadi memiliki tingkat keparahan moderate dan dapat ditangani dengan baik di Rumah Sakit Umum Pusat Dr. Cipto Mangukusumo.

*corresponding author: vivian.soetikno@ui.ac.id

INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition that may culminate in kidney failure, referred to as end-stage renal disease (ESRD) or stage 5 CKD. A study by Prodjosudjadi *et al.*,[1] suggests that 12.5% of Indonesians are afflicted with CKD. Hemodialysis (HD) is the predominant treatment for people with stage 5 CKD. This therapy can not restore kidney function, but it can mitigate its effects, extend lifespan, and enhance the patient's quality of life. According to the United States Renal Data System (USRDS), the incidence of end-stage renal disease (ESRD) in 2018 was 131,636 individuals, reflecting a 2.3% rise from 2017, with 70.7% of patients using dialysis.[2] Data from the Indonesian Renal Registry (IRR) in 2018 indicates that 132,142 stage 5 CKD patients were actively undergoing routine HD therapy, reflecting a 69% increase over 2017.[3]

Patients with stage 5 CKD undergoing HD commonly present with many comorbidities, including hypertension, diabetes mellitus, and cardiovascular disease. They are also susceptible to long-term problems necessitating treatment with many pharmacological agents that can lead polypharmacy. This medication is utilized long-term, hence augmenting the possibility for Drug-drug interactions (DDIs).[3,4] A previous study has demonstrated that the prevalence of DDI in CKD patients varied between 76.1% and 89.1%.[5] Drug-drug interactions are a significant and frequently predictable cause of adverse drug reactions (ADRs).[6] In fact, DDIs are responsible for up to 8% of ADRs in the general population.[7] Moreover, individuals with CKD are especially vulnerable to heightened drug accumulation and ADRs due to alterations in pharmacokinetic and pharmacodynamic characteristics.[8]

The occurrence of DDIs and ADRs is influenced by multiple factors including gender, age, diagnosis, comorbidities, and the type and quantity of medication administered.[9] The rise in the number of medications, along with heart disease, inadequate patient adherence, and a glomerular filtration rate (GFR) of less than 30 ml/min per 1.73 m^2, can elevate the risk of ADRs in patients with CKD.[10] Previous study has identified anticoagulants, antiplatelets, diuretics, digoxin, and narrow therapeutic index medications as some of the causative agents responsible for ADRs in the elderly population.[11] Jiang *et al.*,[12] have demonstrated that antimicrobial agents were the most common implicated pharmacological group which caused ADRs due to DDIs.

A study in Indonesia indicates that 5.01% of elderly CKD patients suffered ADRs likely to be caused by DDIs, with the most prevalent ADRs being hyperkalemia, hypomagnesemia, and hypocalcemia.[13] Nonetheless, prior research has not assessed potential DDIs in stage 5 CKD patients on routine HD as outpatients, with stable circumstances and several drugs. Monitoring DDIs is essential to avert ADRs. Vigilant observation can facilitate the detection of DDIs and provide clinicians with information regarding the likelihood of ADRs, enabling them to exercise greater caution in drug delivery and mitigate undesirable DDIs. This study aimed to assess the prescribing patterns in stage 5 CKD patients undergoing routine HD and their correlation with DDIs and the potential ADRs resulting from these interactions.

MATERIAL AND METHODS

Subjects and design

This cross-sectional study encompassed male and female stage 5 CKD patients on routine hemodialysis, aged 18 yr or older, who visited the Outpatient Department at the Dr. Cipto Mangunkusumo Genral

Hospital. The research was carried out with the authorization from the Institutional Ethics Committee of Universitas Indonesia (#289/UN2. F1/ETIK/PPM.00.02/2021). Data were obtained from medical records (MR) and electronic health records (EHR) between March 2020 and August 2021. Patients with incomplete data were eliminated from the study. A minimum of 96 stage 5 CKD outpatients undergoing routine HD was required based on the sample size calculation. Based on a confidence interval of 95%, an absolute precision of 5%, and a proportion of patients CKD experiencing DDIs and ADRs of 50%, a sample size of 96 was determined. The samples were obtained through a non-probability sampling method that employed the consecutive sampling method. The criteria inclusion were CKD stage 5 patients undergoing HD for at least 3 mo and aged over 18 yr.

Data collection

The collected data encompassed patient details, including name, medical record number, age, gender, and date of outpatient care, alongside clinical data comprising subjective complaints, physical examination findings, diagnosis, comorbidities, and length of hemodialysis therapy. The data encompassed details regarding the patient's therapy, comprising a list of generic drug names, the quantity of pharmaceuticals administered, drug dosage, and the mode of administration documented for the three months preceding the final laboratory result. Individuals with insufficient data were excluded from this study. An evaluation of probable DDIs was conducted using Lexicomp software, which categorized the interactions as minor, moderate, or major. The clinical manifestations and abnormalities in the patient's laboratory results during the last 3 mo of follow-up, which were documented in the medical record and HER, will be used to evaluate ADRs caused by DDIs. The Hartwig scale is used to categorize the severity of ADRs into mild, moderate, and major. ADRs were classified as mild or moderate if they did not necessitate treatment discontinuation, and as major if they necessitated immediately medical attention, caused long-term harm to the patient, or resulted in death.[14]

Statistical analysis

The correlation between variables was assessed using the Chi-square test and logistic regression, with a p-value <0.05 being statistically significant. The statistical analysis was conducted utilizing SPSS version 20.0.

RESULTS

A total of 354 medical records were obtained from stage 5 CKD patients undergoing routine HD treatment. Among these, 147 patients satisfied the inclusion criteria for the study. The three most common comorbid diseased found in this study were hypertension, diabetes mellitus, and heart disease. Forty-two point nine (42.9) % of patients presented with additional comorbidities, including ischemic stroke, vertigo, cholelithiasis, liver cirrhosis, osteoarthritis, osteoporosis, epilepsy, and pneumonia (TABLE 1). The most widely used drug classification in this study were antihypertension, antidiabetics, and statins (TABLE 2).

We found that there were 101 types of drugs used in the present study with 2767 prescriptions. Among the 2767 prescriptions, there were five types of drugs that were most often prescribed, namely epoetin alpha, heparin, calcium carbonate, folic acid, and vitamin B12 (TABLE 3).

TABLE 1. Baseline characteristics (total n = 147)

Characteristics	n (%)
Gender	
• Male	74 (50.3)
• Female	73 (49.7)
Age (yo)	
• 18-40	35 (23.8)
• 41-65	85 (57.8)
• > 65	27 (18.4)
Comorbid	
• Hypertension	136 (92.5)
• DM	58 (39.5)
• CD	55 (37.4)
• Hepatitis B	9 (6.1)
• Hepatitis C	26 (17.7)
• Dyslipidemia	21 (14.3)
• Others	63 (42.9)
Number of drugs used	
• ≤ 5	5 (3.4)
• 6-10	94 (63.9)
• > 10	48 (32.7)
Duration of hemodialysis (yr)	
• < 5	83 (56.5)
• 5-10	42 (28.6)
• 10-15	17 (11.6)
• > 15	5 (3.4)

Note: DM= diabetes mellitus; CD: cardiovascular diseases

TABLE 2. Classification of drugs used in the study (total n = 147)

Classification of drugs	n (%)
Antihypertension	
• CCB	100 (68)
• ARB	56 (38.1)
• ACEI	29 (19.7)
• Central adrenolytic	56 (38.1)
• β blockers	48 (32.7)
• Nitrate	7 (4.8)
Oral anti-diabetics	
• Sulfonylureas (gliquidone)	13 (8.8)
• α glucosidase inhibitors (acarbose)	1 (0.7)
Insulin	22 (15)
Statin (atorvastatin, simvastatin)	23 (15.6)

Note: CCB= calcium channel blocker/antagonists; ARB= angiotensin receptor blockers; ACEI: angiotensin converting enzyme inhibitors.

TABLE 3. Frequency distribution of drug frequently prescribed in 3 mo (total n =2767)

Classification of drugs	Frequency of prescription in 3 mo [n (%)]
CCB	
• Amlodipine	160 (5.8)
• Nifedipine	128 (4.6)
• Diltiazem	24 (0.9)
• Flunarizine	1 (0.04)
ARB	
• Candesartan	75 (2.7)
• Irbesartan	10 (0.4)
• Telmisartan	7 (0.3)
• Valsartan	72 (2.6)
ACEI	
• Captopril	10 (0.4)
• Lisinopril	8 (0.3)
• Ramipril	68 (2.5)
β blockers	
• Bisoprolol	116 (4.2)
• Carvedilol	21 (0.8)
• Propranolol	6 (0.2)
Statins	
• Atorvastatin	30 (1.1)
• Simvastatin	15 (0.5)
PPI	
• Lansoprazole	64 (2.3)
• Omeprazole	24 (0.9)
Antidiabetics	
• Gliquidone	42 (1.5)
• Acarbose	3 (0.1)
• Insulin glargine	37 (1.3)
• Insulin detemir	9 (0.3)
• Insulin lispro	17 (0.6)
• Insulin aspart	39 (1.4)
• Insulin glulisin	1 (0.04)
Antianemia	
• Vitamin B12	354 (12.8)
• Epoetin alpha	1949 (70.4)
• Folic acid	367 (13.3)
Anticoagulants	
• Heparin	1683 (60.8)
• Warfarin	11 (0.4)
• Apixaban	3 (0.11)
• Rivaroxaban	3 (0.11)
Phosphate binder	
• Calcium carbonate	373 (13.5)
• Calcium acetate	5 (0.2)

Note: CCB= calcium channel blocker/antagonists; ARB= angiotensin receptor blockers; ACEI: angiotensin converting enzyme inhibitors; PPI= proton pump inhibitors

Most of the patients in our investigation, specifically 131 individuals (89%), underwent treatment associated with probable DDIs (FIGURE 1). Most patients in this study had a moderate category of DDIs (FIGURE 2).

In 131 patients with probable DDIs, the incidence of suspected ADRs was observed in 50% of the patients. Each patient encountered one to two suspected ADRs attributable to DDIs. The most noted probable DDIs was between amlodipine and calcium carbonate, occurring in 31.29% of cases (TABLE 4).

The occurrence of suspected ADRs was 6 occurrences. The predominant incidence of ADRs was hypertension (72%). (FIGURE 3).

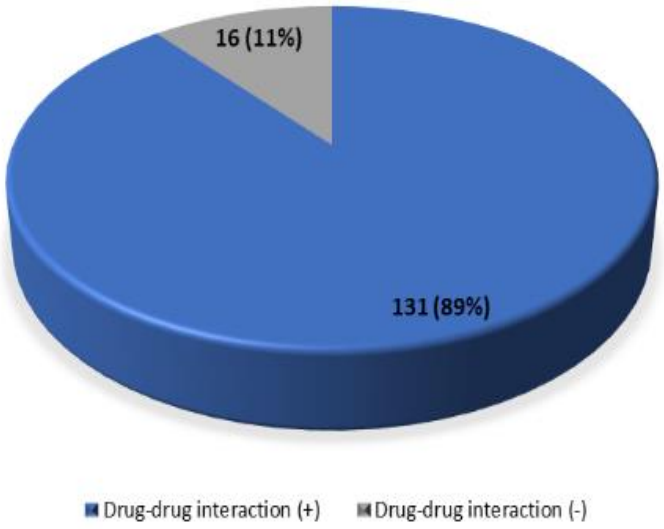

FIGURE 1. Proportion of patients with stage 5 CKD on routine HD with potential DDIs

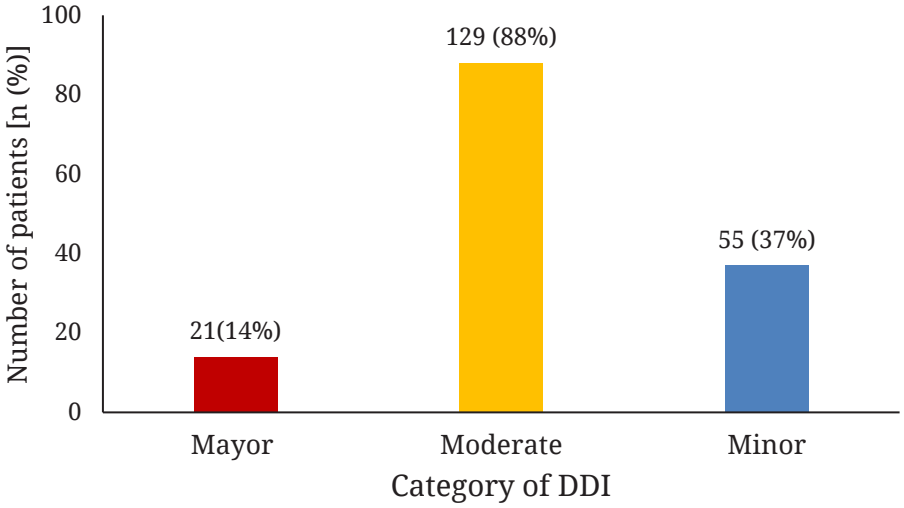

FIGURE 2. Proportion of patients in each category of potential DDIs

TABLE 4. The five most potential DDIs (total n =147)

Potential DDIs		Frequency [n(%)]	Severity	Interaction effects	Mechanism of action
Drug A	Drug B				
Amlodipine	Calcium carbonate	46 (31.3)	Moderate	Antihypertension effect of amlodipine is reduced	Calcium carbonate reduces the antihypertension effect of amlodipine on calcium channels
Nifedipine	Calcium carbonate	33 (22.5)	Moderate	Antihypertension effect of nifedipine is reduced	Calcium carbonate reduces the antihypertensive effect of nifedipine on calcium channels
Candesartan	Heparin	24 (16.3)	Moderate	Hyperkalemia	Candesartan and heparin decrease adrenal aldosterone secretion.
Heparin	Valsartan	22 (15.7)	Moderate	Hyperkalemia	Valsartan and heparin decrease adrenal aldosterone secretion
Epoetin alpha	Ramipril	21 (14.3)	Minor	Therapeutic effect of epoetin alpha is reduced	Unknown

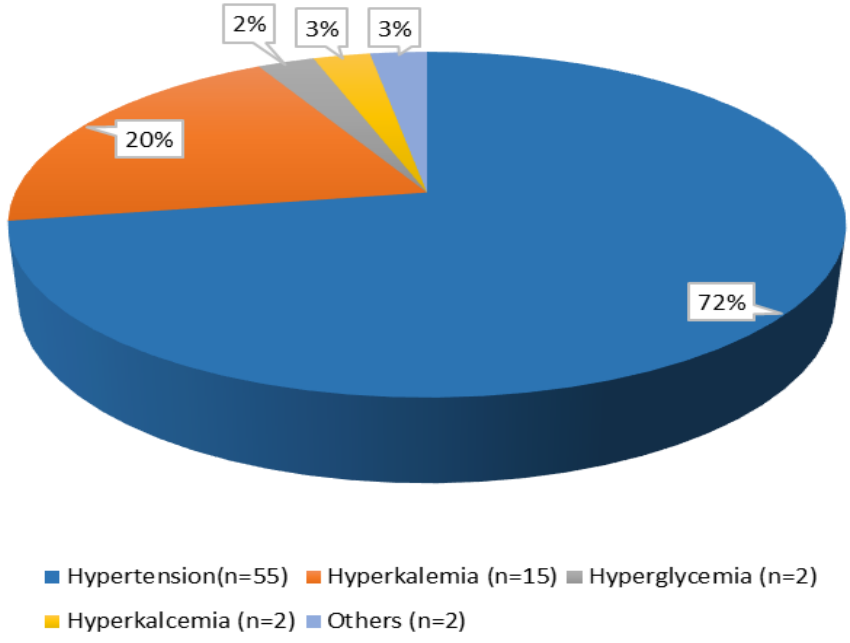

FIGURE 3. Proportion of types ADRs suspected caused by DDIs

In bivariate analysis, a statistically significant relationship was found between drug use greater than 10 (p = 0.02) and hypertension (p = 0.02). Logistic regression analysis showed that comorbidities such as DM had a statistically significant relationship with ADR suspected due to DDI (OR = 2.14; 95% CI = 1.02 - 4.45; p = 0.04) (TABLE 5).

TABLE 5. The relationship of confounding variables to ADRs (total n =147)

Variable	Patients		Bivariate[a]		Multyvariate[b]	
	ADR (+) [n (%)]	ADR (-) [n (%)]	OR (95%CI)	p	OR (95% CI)	p
Sex						
• Male	35 (47.3)	39 (52.7)	1.21 (0.63-2.33)	0.56	-	
• Female	31 (42.5)	42 (57.5)				
Age (yr)						
• >65	12 (42.9)	16 (57.1)	0.9 (0.39-2.07)	0.80	-	
• ≤65	54 (45.4)	65 (54.6)				
Drug number						
• >10	28 (58.3)	20 (41.7)	2.25 (1.11-4.54)	0.02	1.26 (0.60-2.64)	0.54
• ≤10	38 (38.4)	61 (61.6)				
Comorbid						
• Hypertension						
✓ Yes	65 (47.8)	71 (52.2)	9.16 (1.14-73.49)	0.02	0.55 (0.15-1.98)	0.36
✓ No	1 (9.1)	10 (90.9)				
• DM						
✓ Yes	31 (53.4)	27 (46.6)	1.77 (0.91-3.46)	0.09	2.14 (1.02-4.45)	0.04
✓ No	35 (39.3)	54 (60.7)				
• CD						
✓ Yes	26 (47.3)	29 (52.7)	1.17 (0.59-2.28)	0.65	-	
✓ No	40 (43.5)	52 (56.5)				
• Hepatitis						
✓ Yes	18 (51.4)	17 (48.6)	1.41 (0.66-3.02)	0.37	-	
✓ No	48 (42.9)	64 (57.1)				
• Dyslipidemia						
✓ Yes	7 (33.3)	14 (66.7)	0.57 (0.22-1.50)	0.25	0.59 (0.22-1.61)	0.31
✓ No	59 (46.8)	67 (53.2)				
• Others						
✓ Yes	30 (47.6)	33 (52.4)	1.21 (0.63-2.34)	0.56	-	
✓ No	36 (42.9)	48 (57.1)				

Note: DM= diabetes mellitus; CD= cardiovascular diseases

DISCUSSION

The predominant age group in this study is between 41 and 65 yr. After the age of 40 yr, the glomerular filtration rate diminishes by around 10 mL/min every decade.[15] Hypertension was the most prevalent comorbid condition in this study. This ratio aligns with the characteristics of HD patients as indicated by the IRR statistics. Three in CKD, peripheral vascular resistance rises, and glomerular function diminishes, potentially resulting in renal ischemia, which subsequently elevates renin release and induces hypertension. The most frequently recommended antihypertensive

medications are calcium antagonists, particularly dihydropyridines, which are typically not subject to dialysis. Several studies indicate that the calcium antagonist class can lower predialysis blood pressure relative to the placebo group, with no ADRs reported in these studies.[16] Amlodipine can decrease the occurrence of stroke, myocardial infarction, coronary revascularization, and peripheral vascular angioplasty by 47%.[17]

Epoetin alfa was the most often prescribed medication. Erythropoietin administration is advised for stage 5 CKD patients undergoing HD. Erythropoietin is a hematopoietic growth factor mostly synthesized by the kidneys in peritubular cells and proximal tubules, with minor production occurring in the liver.[18,19] The prevalence of anemia in CKD escalates as the glomerular filtration rate declines. Fourteen studies conducted in Bali indicated that the prevalence of anemia among CKD patients receiving regular HD was 96.2%. The administration of erythropoietin can elevate hematocrit and hemoglobin levels while decreasing the necessity for transfusion. As per Kidney Disease Improving Global Outcomes (KDIGO) guidelines, erythropoietin therapy is advised when hemoglobin levels fall below 10 g/dL and alternative sources of anemia have been excluded.[20] Furthermore, the 2010 Indonesian Nephrology Association (PERNEFRI) guideline stipulates that the target hemoglobin level following erythropoietin therapy is 10-12 g/dL.[21]

The presence of many comorbidities in stage 5 CKD patients undergoing routine HD frequently causes polypharmacy. The rise in the quantity of medications correlates with an increased possibility for DDIs.[22,23] Drug interactions may elevate toxicity or diminish the efficacy of the involved medications, constituting a clinically significant adverse interaction.[24]

The study revealed that 89% of patients had possible DDIs. Other studies indicate that the prevalence of DDIs in CKD patients varies from 27.5% to 95.9%.[25-27] The extensive variation in PIO occurrence between studies is attributable to factors like comorbidities, pre-existing problems, the quantity and kind of prescribed drugs, CKD stage, study design, and the software employed to detect potential drug-drug interactions.[28] In this study, the majority of patients had moderate propensity for DDIs. Both moderate and severe DDIs can yield ADRs; however, severe interactions provide a heightened danger, potentially being life-threatening and need rapid medical intervention, whilst moderate interactions may require therapeutic changes or increased monitoring.

Our present study found no suspected ADRs attributable to probable interactions in the major category, which includes interactions that pose a risk of life-threatening or irreversible harm. This may be ascribed to various variables, including the clinician's anticipation of ADRs related to probable DDIs. Furthermore, laboratory data and patient complaints concerning potential DDIs were derived from information documented in the patient's medical record, which was reviewed at a single instance. Moreover, patients in the primary group were predominantly under 60 years of age, a feature that may influence the likelihood of suspected ADRs resulting from DDIs. The likelihood of ADRs escalates with advancing age.[28]

Bivariate analysis results indicated a strong correlation between the use of more than 10 medicines and the presence of hypertension with the incidence of ADRs resulting from DDIs. Marquito *et al.* indicated that concomitant diabetes mellitus, hypertension, and obesity in patients with end-stage renal disease are risk factors linked to the occurrence of DDIs.[23] Furthermore, Saleem et al. discovered that age, polypharmacy, hypertension, and duration of

hospitalization were associated with the occurrence of possible DDIs.[29] The elevated quantity of medications may result in DDIs, thus augmenting the incidence of ADRs.[4]

The primary limitation of this study is that the evaluation of potential DDIs should be contrasted with several referrals. This study examined a single reference, specifically the Lexicomp program. This study may not accurately establish the causality of ADRs, as it was not a prospective study and did not consider other factors that may influence the development of ADRs, such as patient adherence to medication. The study was further constrained by the availability and precision of patient medical records, as differences may exist between electronic health records and other medical records, particularly in patients undergoing HD. This study's benefit is in being the first investigation assessing the possibility for DDIs in stage 5 CKD patients on routine HD as outpatients, characterized by stable circumstances and the administration of multiple maintenance medications.

CONCLUSION

A total of 101 medicine types are prescribed, amounting to 2,767 prescriptions for patients. Epoetin alfa is the most often prescribed medication. Fourteen percent of patients experience possible interactions in the major category, 88% in the moderate category, and 37% in the minor category. Comorbid DM is identified as a potential source of adverse drug reactions attributed to DDIs.

Recommendations for additional research involve undertaking a prospective study to evaluate the clinical relevance of each DDI and to precisely ascertain the causation classification of ADRs. It is advised that clinicians perform diligent regular monitoring of patients with DDIs to mitigate the risk of ADRs. Furthermore, as all HD machines included in the study are high flux, it is imperative to consider medications that can traverse the dialysis membrane, namely those with a molecular weight less than 20,000 and a low volume of distribution, to ensure adequate monitoring of these substances.

CONFLICT OF INTEREST

None

ACKNOWLEDGMENT

The authors wish to convey their appreciation to the MR Centre and HD Unit at the Dr. Cipto Mangunkusumo General Hospital for their support during the data gathering phase. We express gratitude to the University of Indonesia for financing this research via the PUTI grant (NKB-4681/UN2.RST/HKP.05.00/2020).

REFERENCES

1. Prodjosudjadi W, Suhardjono, Suwitra K, Pranawa, Widiana IG, Loekman JS, *et al*. Detection and prevention of chronic kidney disease in Indonesia: initial community screening. Nephrology (Carlton) 2009; 14(7):669-74. https://doi.org/10.1111/j.1440-1797.2009.01137.x
2. System USRD [Internet]. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020 [cited 2020 March 17]. https://odphp.health.gov/healthypeople/objectives-and-data/data-sources-and-methods/data-sources/united-states-renal-data-system-usrds
3. Indonesia Renal Registry. Report of

Indonesian renal registry, 11th ed. Jakarta: Perkumpulan Nefrologi Indonesia (Pernefri), 2018.
4. Sharif-Askari FS, Syed Sulaiman SA, Saheb Sharif-Askari N, Al Sayed Hussain A. Development of an adverse drug reaction risk assessment score among hospitalized patients with chronic kidney disease. PLoS One 2014; 9(4):e95991. https://doi.org/10.1371/journal.pone.0095991
5. Fasipe OJ, Akhideno PE, Nwaiwu O, Adelosoye AA. Assessment of prescribed medications and pattern of distribution for potential drug-drug interactions among chronic kidney disease patients attending the Nephrology Clinic of Lagos University Teaching Hospital in Sub-Saharan West Africa. Clin Pharmacol 2017; 9:125-32. https://doi.org/10.2147/CPAA.S147835
6. Liu R, AbdulHameed MDM, Kumar K, Yu X, Wallqvist A, Reifman J. Data-driven prediction of adverse drug reactions induced by drug-drug interactions. BMC Pharmacol Toxicol 2017; 18(1):44. https://doi.org/10.1186/s40360-017-0153-6
7. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. Expert Opin Drug Saf 2012; 11(1):83-94. https://doi.org/10.1517/14740338.2012.631910
8. Velenosi TJ, Urquhart BL. Pharmacokinetic considerations in chronic kidney disease and patients requiring dialysis. Expert Opin Drug Metab Toxicol 2014; 10(8):1131-43. https://doi.org/10.1517/17425255.2014.931371
9. Rodrigues MCS, Oliveira Cd. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. Rev Lat Am Enfermagem 2016; 24:e2800-e. https://doi.org/10.1590/1518-8345.1316.2800
10. Laville SM, Gras-Champel V, Moragny J, Metzger M, Jacquelinet C, Combe C, *et al*. Adverse drug reactions in patients with CKD. Clin J Am Soc Nephrol 2020; 15(8):1090-102. https://doi.org/10.2215/CJN.01030120
11. Cahir C, Curran C, Walsh C, Hickey A, Brannigan R, Kirke C, *et al*. Adverse drug reactions in an ageing PopulaTion (ADAPT) study: Prevalence and risk factors associated with adverse drug reaction-related hospital admissions in older patients. Front Pharmacol 2023; 13:1029067. https://doi.org/10.3389/fphar.2022.1029067
12. Jiang H, Lin Y, Ren W, Fang Z, Liu Y, Tan X, *et al*. Adverse drug reactions and correlations with drug-drug interactions: A retrospective study of reports from 2011 to 2020. Front Pharmacol 2022; 13:923939. https://doi.org/10.3389/fphar.2022.923939
13. Magro L, Arzenton E, Leone R, Stano MG, Vezzaro M, Rudolph A, *et al*. Identifying and characterizing serious adverse drug reactions associated with drug-drug interactions in a spontaneous reporting database. Front Pharmacol 2020; 11:622862. https://doi.org/10.3389/fphar.2020.622862
14. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992; 49(9):2229-32.
15. Adibe MO, Ewelum PC, Amorha KC. Evaluation of drug-drug interactions among patients with chronic kidney disease in a South-Eastern Nigeria tertiary hospital: a retrospective study. Pan Afr Med J 2017; 28:199. https://doi.org/10.11604/pamj.2017.28.199.13622
16. Georgianos PI, Agarwal R. Pharmacotherapy of hypertension

in chronic dialysis patients. Clin J Am Soc Nephrol 2016; 11(11):2062-75. https://doi.org/10.2215/CJN.00870116
17. Mugendi GA, Mutua FM, Natale P, Esterhuizen TM, Strippoli GFM. Calcium channel blockers for people with chronic kidney disease requiring dialysis. Cochrane Database Syst Rev 2020; 10(10):CD011064. https://doi.org/10.1002/14651858.CD011064.pub2
18. Tadvi N, Hussain S. Analysis of prescription pattern in patients on maintenance hemodialysis. Indian J Pharm Pharmacol 2020; 7(2):125-9. https://doi.org/10.18231/j.ijpp.2020.021
19. Suwitra K. Penyakit Ginjal Kronik. Dalam: Setiati S, Sudoyo AW, Alwi I, Simadibrata M, Setiyohadi B, Syam AF, editor. Buku ajar ilmu penyakit dalam. Edisi 6. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia 2014. 2159-65.
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2024; 105(4S):S117-S314. https://doi.org/10.1016/j.kint.2023.10.018
21. PERNEFRI – Perhimpunan Nefrologi Indonesia. Konsesus dialisis [Internet]. 2003 [cited 2020 Jun 16]. https://www.pernefri.org/konsensus/Konsensus%20Dialisis.pdf
22. Spanakis M, Roubedaki M, Tzanakis I, Zografakis-Sfakianakis M, Patelarou E, Patelarou A. Impact of adverse drug reactions in patients with end stage renal disease in Greece. Int J Environ Res Public Health 2020; 17(23):9101. https://doi.org/10.3390/ijerph17239101
23. Marquito AB, Fernandes NM, Colugnati FA, de Paula RB. [Identifying potential drug interactions in chronic kidney disease patients]. J Bras Nefrol 2014; 36(1):26-34. https://doi.org/10.5935/0101-2800.20140006
24. Nusair MB, Al-Azzam SI, Arabyat RM, Amawi HA, Alzoubi KH, Rabah AA. The prevalence and severity of potential drug-drug interactions among adult polypharmacy patients at outpatient clinics in Jordan. Saudi Pharm J 2020; 28(2):155-60. https://doi.org/10.1016/j.jsps.2019.11.009
25. Sgnaolin V, Engroff P, DeCarli GA, Figueiredo A. Assessment of used medications and drug-drug interactions among chronic renal failure patients. Scientia Medica 2014; 24(4).
26. Papotti B, Marchi C, Adorni MP, Potì F. Drug-drug interactions in polypharmacy patients: The impact of renal impairment. Curr Res Pharmacol Drug Disc 2021; 2:100020. https://doi.org/10.1016/j.crphar.2021.100020
27. Bucşa C, Farcas A, Cazacu I, Daniel-Corneliu L, Achimas A, Mogosan C, *et al*. How many potential drug-drug interactions cause adverse drug reactions in hospitalized patients? Eur J Intern Med 2013; 24(1):27-33. https://doi.org/0.1016/j.ejim.2012.09.011
28. Shimizu Y, Io H, Hagiwara S, Gohda T, Hamada C, Horikoshi S, *et al*. Concomitant use of clopidogrel and proton pump inhibitors may attenuate the prognosis of coronary heart disease in hemodialysis patients. Diálisis y Trasplante 2012; 33(3):75-83 https://doi.org/10.1016/j.dialis.2011.07.001
29. Saleem A, Masood I, Khan TM. Clinical relevancy and determinants of potential drug-drug interactions in chronic kidney disease patients: results from a retrospective analysis. Integr Pharm Res Pract 2017; 6:71-7. https://doi.org/10.2147/IPRP.S128816