

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

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ABSTRACT

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Keywords:

adverse drug reaction; drug interaction; hemodialysis; kidney insufficiency 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 obatobat (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.

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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 Prodiosudiadi 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 endstage 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 longterm 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} А 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 m², 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 (#289/UN2. Universitas Indonesia 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 details, including patient name, medical record number, age, gender, and date of outpatient care, alongside clinical data comprising subjective physical examination complaints, 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 followup, 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).

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

TABLE 1. Baseline characteristics (total n = 147)

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.

II 2707)	
Classification of drugs	Frequency of prescription in 3 mo [n (%)]
CCB	
· Amlodinine	160 (5.8)
• Annoulpine	100(3.0)
• Mileuipine	128 (4.6)
• Diffiazem	24 (0.9)
• Flunarizine	1 (0.04)
ARB	
• Candesartan	75 (2, 7)
• Irbesartan	10(0.4)
• Telmisartan	7 (0 3)
. Valsartan	7 (0.3)
· vaisartait	72 (2:0)
ACEI	
• Captopril	10 (0.4)
 Lisinopril 	8 (0.3)
• Ramipril	68 (2.5)
p DIOCKERS	140 (4 0)
• Bisoprolol	116 (4.2)
• Carvedilol	21 (0.8)
 Propranolol 	6 (0.2)
Statins	
Atorvastatin	30 (1 1)
• Simvastatin	15 (0 5)
	15 (0.5)
PPI	
• Lansoprazole	64 (2.3)
• Omeprazole	24 (0.9)
Antidiabetics	
• Gliquidone	42 (1 5)
• Acarbose	$\frac{12}{3}(0.1)$
· Inculin glarging	3(0.1) 27(1.2)
Insulin dotomir	0(0.2)
• Insulin lienno	9 (0.3)
• Insumi inspio	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)
Anticoaguiants	
• Heparin	1683 (60.8)
• Warfarin	11 (0.4)
• Apixaban	3 (0.11)
• Rivaroxaban	3 (0.11)
Phosphate hinder	
· Calcium carbonate	272 (12 E)
- Calcium acotato	575 (15.5) E (0.2)
• calciulii acelale	5 (0.2)

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

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

Potential DDIs		Frequency	Corrowiter	Internation offects	Machanian of action	
Drug A	Drug B	[n(%)]	Severity	interaction effects	mechanism of action	
Amlodipine	C a l c i u m carbonate	46 (31.3)	Moderate	Antihypertension effect of amlodipine is reduced	Calcium carbonate reduces the antihypertension effect of amlodipine on calcium channels	
Nifedipine	C a l c i u m 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	

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



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).

	Pati	ients	Bivariate ^a		Multyvariate	9 p
Variable	ADR (+) [n (%)]	ADR (-) [n (%)]	OR (95%CI)	р	OR (95% CI)	р
Sex						
• Male	35 (47.3)	39 (52.7)	1 21 (0 62 2 22)	0 56		
• Female	31 (42.5)	42 (57.5)	1.21 (0.03-2.33)	0.50	-	
Age (yr)						
• >65	12 (42.9)	16 (57.1)	0 0 (0 20 2 07)	0.00		
• ≤65	54 (45.4)	65 (54.6)	0.9 (0.39-2.07)	0.80	-	
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)	2.23 (1.11-4.34)	0.02	1.20 (0.60-2.64)	0.54
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)	5.10 (1.1175.15)	0.02	0.55 (0.15-1.56)	0.50
• 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)	1	0.00		0101
• CD						
✓ Yes	26 (47.3)	29 (52.7)	1.17 (0.59-2.28)	0.65	-	
✓ No	40 (43.5)	52 (56.5)		0.05		
 Hepatitis 						
✓ Yes	18 (51.4)	17 (48.6)	1 41 (0 66-3 02)	0.37	_	
✓ No	48 (42.9)	64 (57.1)	1.11 (0.00 3.02)	0.07		
 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)	0.37 (0.22 1.30)	0.23	0.00 (0.22 1.01)	0.01
• Others						
✓ Yes	30 (47.6)	33 (52.4)	1 21 (0 63-2 34)	0.56	_	
✓ No	36 (42.9)	48 (57.1)	1.21 (0.05-2.34)			

TABLE 5.	The relationshi	o of confounding	variables to	ADRs (total n =147)
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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 Kidnev 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.

present study found Our 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

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