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Drug Selection, Dosage Adjustment, and Potential Interaction of Antihypertensive and Antidiabetic for Chronic Kidney Disease with Hemodialysis

(Pemilihan Obat, Penyesuaian Dosis, dan Potensi Interaksi Antihipertensi dan Antidiabetes pada Pasien Penyakit Ginjal Kronis dengan Hemodialisis)

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Abstract: Antihypertensive and antidiabetic drugs in CKD patients on hemodialysis may cause medication-related problems requiring monitoring. This study aimed to evaluate the selection, dosage, and potential drug interactions of antihypertensive and antidiabetic drugs in stage 5 CKD patients with hypertension and/or type 2 diabetes mellitus undergoing hemodialysis in a hospital in Jakarta. A cross-sectional study used the medical records of adult in patients from January - December 2022 with a total sampling method. Out of 101 patients, 97.0% received appropriate drug selection. Dosage adjustments were appropriate in 74.3% of cases. Potential drug interactions between antihypertensive and antidiabetic drugs were found in 90.1% of patients, mostly pharmacodynamic interactions, moderate severity, and requiring monitoring. Statistical analysis showed that age, gender, number of drugs, and length of stay were not associated with the appropriateness of antihypertensive and antidiabetic drug selection ($p > 0.05$). However, there was a relationship between number of drugs ($p=0.033$; OR=2.996) and length of stay ($p=0.024$; OR=3.171) with the appropriateness of drug dosage. The length of stay was also associated with potential drug interactions ($p=0.040$; OR=8.426). Drug selection has been done well, but there is a need for improvement in monitoring dosage adjustments and potential drug interactions by pharmacists in the hospital.

Keywords: Antidiabetic, antihypertensive, chronic kidney disease, drug related problems, hemodialysis.

Abstrak: Penggunaan obat antihipertensi dan antidiabetes pada pasien penyakit ginjal kronik (PGK) dengan hemodialisis dapat berpotensi meningkatkan masalah terkait obat sehingga perlu dilakukan pemantauan. Penelitian ini bertujuan untuk mengevaluasi pemilihan, dosis, dan potensi interaksi obat antihipertensi serta antidiabetes pada pasien PGK stage 5 dengan hipertensi dan/atau diabetes melitus tipe 2 yang menjalani hemodialisis pada sebuah rumah sakit di Jakarta. Studi cross-sectional menggunakan data rekam medis pasien dewasa rawat inap periode Januari – Desember 2022 dengan metode total sampling. Dari total 101 pasien, 97% telah tepat pemilihan obat. Penyesuaian dosis sudah tepat dilakukan pada 74,3%. Potensi interaksi obat antihipertensi dan antidiabetes ditemukan pada 90,1% pasien dengan mayoritas merupakan interaksi farmakodinamik, derajat keparahan moderat, dan membutuhkan pemantauan. Hasil analisis statistik menunjukkan bahwa faktor usia, jenis kelamin, jumlah obat, dan lama rawat inap tidak memiliki hubungan dengan ketepatan pemilihan obat antihipertensi dan antidiabetes ($p > 0,05$). Tetapi, terdapat hubungan antara jumlah obat ($p=0,033$; OR=2,996) dan lama rawat inap ($p=0,024$; OR=3,171) dengan ketepatan dosis obat. Lama rawat inap juga berhubungan dengan potensi interaksi obat ($p=0,040$; OR=8,426). Pemilihan obat telah dilakukan dengan baik tetapi perlu peningkatan pemantauan terhadap penyesuaian dosis dan potensi interaksi obat oleh apoteker di rumah sakit.

Kata kunci: Antidiabetes, antihipertensi, hemodialisis, masalah terkait obat, penyakit ginjal kronis.

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INTRODUCTION

CHRONIC kidney disease (CKD) was one of the global health problems associated with the increasing incidence of hypertension and diabetes mellitus (DM)[1]. Kidney disease improving global outcomes (KDIGO) defines CKD as abnormalities in kidney structure or function for more than 3 months[2]. World Health Organization data shows that CKD-related deaths have reached 850,000 people yearly[3]. Based on data from Riskesdas in 2018, the prevalence of CKD in Indonesia reached 713,783 people, or about 0.38% of the total population[4]. CKD can be classified into 5 stages based on glomerular filtration rate (GFR), where an increase in stage correlates with a decrease in GFR value[2]. Chronic kidney disease epidemiology collaboration (CKD-EPI) method was commonly recommended for calculating GFR because it has been proven to be more accurate compared to Cockcroft-Gault and Modification of diet in renal disease (MDRD) methods[5-7].

The management of CKD includes lifestyle modification (fluid and diet restriction), medication treatment, and renal replacement therapy (dialysis, kidney transplantation)[8]. Renal replacement therapy, especially dialysis, was required to replace kidney function for eliminating body toxins to prevent more severe symptoms and was usually initiated in stage 5 CKD patients (GFR <15 mL/minute/1.73 m^2)[9,10]. Every year, more than 115,000 patients start dialysis therapy, and there has been an increase in the number of CKD patients undergoing hemodialysis from 2007 to 2018 in Indonesia[11]. In CKD patients with hypertension and/or DM undergoing HD, the primary medications were antihypertensive and antidiabetic drugs. Additional medications will be prescribed based on the patient's clinical condition, such as anti-anemia drugs, gastrointestinal drugs, analgesics, and other symptomatic drugs[12].

Evaluating drug-related problems (DRPs) was important as they can potentially affect patient health outcomes and lead to morbidity and mortality[13]. According to Hepler and Strand, DRPs can be categorized as untreated indications, improper drug selection, subtherapeutic dosages, failure to receive drugs, overdosage, adverse drug reactions (ADRs), drug interactions, and drug use without indication[14]. Previous research has shown that the occurrence of improper drug selection, dosage adjustments, and potential drug interactions in CKD inpatients with comorbidities and undergoing hemodialysis was still relatively high[15,16]. Inappropriate drug selection and dosages, especially for medications eliminated through the kidneys, like antihypertensive and antidiabetics, can worsen kidney function and increase drug toxicity levels in the body[17,18]. Drug interactions can also affect medications' effectiveness and blood levels, exacerbating the patient's medical condition[19].

This study aims to evaluate drug-related problems in terms of appropriateness of medication selection, dosages, and potential drug interactions of antihypertensive and antidiabetic medications in CKD inpatients with hypertension and/or type 2 DM undergoing hemodialysis from January to December 2022 at a hospital in Jakarta. This study also analyzes other factors that may influence these three parameters.

MATERIAL AND METHODS

MATERIALS. This study's data source was medical records of CKD inpatients with hypertension and/or type 2 DM undergoing hemodialysis from January-December 2022 at a hospital in Jakarta.

METHODS. Study Design. The study was observational with a cross-sectional study design. This research has obtained ethical clearance from the Hospital Research Ethics Committee with Number B/16/EC/LKS/III/RS/2023. The CKD stage was classified based on GFR using the CKD-EPI equation. Drug selection and dosage appropriateness were determined by comparing patient data with national Indonesia references[20-23] and Merative Micromedex®. Potential drug interactions were analyzed with Lexicomp® drug interactions.

Data Collection and Analyses. A Total sampling data collection was done from the medical records of CKD patients with hemodialysis. The collected data was further analyzed and selected based on predetermined inclusion and exclusion criteria. Sample inclusion criteria were inpatients with stage 5 CKD (GFR <15 mL/minute/1.73 m^2) undergoing hemodialysis during January – December 2022, having hypertension and/or type 2 DM, receiving antihypertensive and/or antidiabetic drugs, and aged 18 years and over. Patients with incomplete treatment of the disease and pregnant or lactating patients were excluded from this study. The data analysis was conducted using IBM® SPSS® Statistics version 26, which consisted of univariate and bivariate analyses.

RESULTS AND DISCUSSION

Sample Characteristics. A total of 101 patients were included in this study. The sociodemographic and clinical characteristics of samples can be seen in Table 1. Samples were predominantly male (58.4%) compared to female patients (41.6%). Males had higher testosterone levels, associated with increased

muscle mass, leading to increased creatinine formation. Increased serum creatinine levels align with a decrease in GFR value as a sign of kidney dysfunction[24]. Most patients were aged 57-93 years (54.5%). Increasing age was directly proportional to decreased renal nephrons and GFR value, putting them at greater risk for renal replacement therapy such as hemodialysis[25, 26]. The frequency of hemodialysis ranged from 1-3 times per week. Two patients (2.0%) undergo HD once a week, 97 patients (96.0%) twice a week, and two patients (2.0%) three times a week. According to Pernefri, HD can be performed 2-3 times per week, but in Indonesia, it was usually done twice a week[9]. The determination of hemodialysis frequency depends on the individual patient's condition, such as the amount of urine per day, urea levels, and serum creatinine levels, to prevent uremia, fluid overload, and potential complications related to CKD[27, 28].

In this study, 67.3% of patients had hypertension, patients with hypertension and type 2 DM (28.7%), and 4.0% had type 2 DM. A study in Scotland also showed that the most common comorbidities in inpatient CKD patients were hypertension, coronary heart disease, and DM[29]. While hospitalized, the patient received various medicines depending on patient comorbidities and clinical condition so that drug changes can occur at certain times during the hospitalization period; 54.50% received 4-14 drugs, and 45.50% received 15-45. The percentage of patients with a length of stay of 1-8 days (55.40%) was higher than those with a length of stay of 9-31 days (44.60%).

Antihypertensive and Antidiabetic Drug Use Profile. Table 2 shows the profile of antihypertensive and antidiabetic used for patients. Antihypertensive prescribed to patients in this study were candesartan (79.21%), amlodipine (54.46%), and furosemide (51.49%). Amlodipine and furosemide were typically given in combination with an ARB as a first-line combination antihypertensive therapy for CKD patients[23]. The most prescribed antidiabetic drugs were insulin glulisine (20.79%) and insulin glargine (14.85%). Insulin glulisine was a rapid-acting insulin commonly given to stage 4-5 CKD patients undergoing hemodialysis. Insulin pharmacokinetics and glucose homeostasis were affected by dialysis and need close monitoring[30]. These patients often experience delayed gastric emptying, so this insulin was typically administered after meals to help adjust the timing of insulin peak with postprandial blood glucose peak[31]. In addition, long-acting insulin, such as glargine, was prescribed to maintain basal insulin levels constantly. Another advantage of using insulin glargine was its reduced risk of nocturnal hypoglycemia, as it has almost no peak effect and can work for up to 24 hours[21]. The study that compared the glargine and NPH insulin showed that the incidence of nocturnal hypoglycemia was 3 times lower in patients using glargine in patient with CKD[32].

Table 1. Samples sociodemographic and clinical characteristics.

Characteristics	Frequency (n = 101)	Percentage (%)
Gender		
Male	59	58.40
Female	42	41.60
Age		
18-56 years	46	45.50
57-93 years	55	54.50
Frequency of Hemodialysis		
Once a week	2	2.00
Twice a week	97	96.00
Three times a week	2	2.00
Comorbidities		
Hypertension	68	67.30
Type 2 Diabetes Mellitus	4	4.00
Hypertension and Type 2 Diabetes Mellitus	29	28.70
Others[a]		
Anemia	40	39.60
Hypertensive Heart Disease	20	19.80
Sepsis	14	13.86
Non-Hemorraghic Stroke	10	9.90
Pneumonia	10	9.90
Number of Drugs		
4-14	55	54.50
15-45	46	45.50
Length of Stay		
1-8 days	56	55.40
9-31 days	45	44.60

[a]Other comorbidities that patients have, in addition to hypertension and type 2 diabetes. The data presented are the top 5 comorbidities based on the number of patients.

Appropriateness of Antihypertensive and Antidiabetic Drug Selection. Based on Table 2, one patient (100%) experienced an inappropriate administration of captopril because it was used concurrently with candesartan, but the hospital pharmacist intervened by discontinuing the administration of captopril to that patient. Captopril, an ACE inhibitor, should not be combined with candesartan, an ARB, as it risks increased side effects such as hypotension, hyperkalemia, and renal failure[23, 33, 34]. The study of Gregg et al. found that adverse drug reactions of ARB or ACE inhibitors lead to treatment discontinuation(35). Furthermore, there were two patients (100%) who experienced an inappropriate administration of hydrochlorothiazide, a thiazide diuretic, which was not recommended for patients with GFR < 10 mL/min/1.73 m², hemodialysis patients, and patients with gout history[33, 36]. The hospital pharmacist has not addressed this issue. The selection of antidiabetic drugs in this study was appropriate because none of the antidiabetic drugs chosen were contraindicated for the patient's clinical conditions. Overall, 98 patients (97.0%) were prescribed appropriate antihypertensive and/or antidiabetic drugs, while three patients (3.0%) experienced inappropriate selection of antihypertensive drugs (Figure 1).

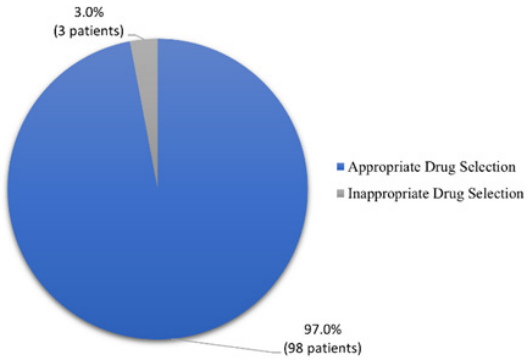

Figure 1. Appropriateness of antihypertensive and antidiabetic drug selection.

Appropriateness of Antihypertensive and Antidiabetic Dosage Adjustment. In this study, the antidiabetic dosages were appropriate because they did not exceed the frequency and dose allowed. However, there were inappropriate dosage of antihypertensive drugs found, namely carvedilol, nifedipine, clonidine, candesartan, furosemide, spironolactone, amlodipine, bisoprolol, and methyldopa (Table 2). Carvedilol (63.16%) was the most frequently administered antihypertensive drug with inappropriate dosage because it was given once daily. Carvedilol was usually used 2 times a day because its plasma half-life was around 7-10 hours[37]. Overall, 74.3% received appropriate dosage adjustment of antihypertensive and/or antidiabetic drugs, while 25.7% experienced inappropriate dosage adjustment (Figure 2).

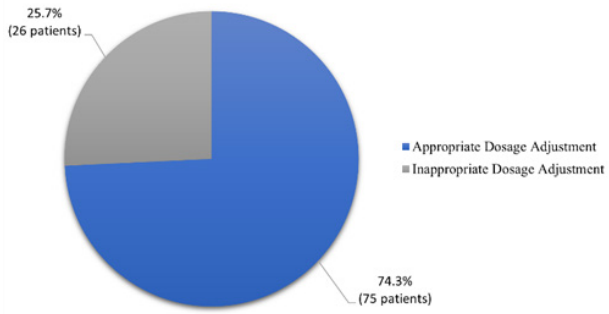

Figure 2. Appropriateness of antihypertensive and antidiabetic dosage adjustment.

Antihypertensive and Antidiabetic Potential Drug Interactions. This study found 238 potential drug interactions involving antihypertensive and antidiabetic, consisting of 30 antihypertensive-antihypertensive interactions, 3 antidiabetic-antidiabetic interactions, 16 antihypertensive-antidiabetic interactions, 163 antihypertensive-other drugs interactions, and 26 kinds of antidiabetic-other drugs interactions. The majority had moderate severity (83.6%) with pharmacodynamic interaction mechanism (57.6%) and were category C, which means it required monitoring of therapy for 78.6% (Table 3).

Based on Table 4, the potential for antihypertensive drug interactions with other drugs with a major severity level and being in the X category was the interaction between carvedilol and salbutamol (6.93%), where carvedilol can reduce the bronchodilator effect of salbutamol. Therefore, it was necessary to avoid using carvedilol in patients taking salbutamol. Another potential category X drug interaction was spironolactone and potassium chloride (1.98%), which could cause hyperkalemia. Therefore, in patients receiving spironolactone, it was recommended to avoid using potassium chloride especially patients with serum potassium concentration > 5.2 mmol/L should avoid using spironolactone[33, 36].

Overall, potential drug interactions involving antihypertensives and antidiabetics were found in 91 patients (90.1%), while in 10 patients (9.9%), with no potential drug interaction (Figure 3).

Factor Associated with Appropriateness of Antihypertensive and Antidiabetic Drug Selection. The results of statistical analysis in Table 5 showed that gender (p = 0.569), age (p = 0.590), number of drugs (p = 0.590), and length of stay (p = 1.000) did not have a significant relationship with the appropriateness of antihypertensive and antidiabetic drug selection. This result was similar to other studies where there was no significant relationship between age, gender, and length of stay with the incidence of inappropriate drug selection. Research in Italy and India found a

Table 2. Drug selection and dosage adjustment of antihypertensive and antidiabetic.

Drug Names	Frequency, n = 101 (%)[a]	Drug selection, n (%)[b]		Drug dosage adjustment, n (%)[b]	
		Appropriate	Inappropriate	Appropriate	Inappropriate
Antihypertensives					
ACEi (ACE inhibitor)					
Captopril	1 (0.99)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)
Ramipril	3 (2.97)	3 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)
ARB (Angiotensin Receptor Blocker)					
Candesartan	80 (79.21)	80 (100.0)	0 (0.0)	77 (96.25)	3 (3.75)
Irbesartan	2 (1.98)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)
Telmisartan	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Valsartan	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
CCB (Calcium Channel Blocker)					
Amlodipine	55 (54.46)	55 (100.0)	0 (0.0)	54 (98.18)	1 (1.85)
Nicardipine	16 (15.84)	16 (100.0)	0 (0.0)	16 (100.0)	0 (0.0)
Nifedipine	12 (11.88)	12 (100.0)	0 (0.0)	3 (25.0)	9 (75.0)
Diuretics					
Hydrochlorothiazide	2 (1.98)	0 (0.0)	2 (100.0)	2 (100.0)	0 (0.0)
Furosemide	52 (51.49)	52 (100.0)	0 (0.0)	50 (96.15)	2 (3.85)
Spironolactone	8 (7.92)	8 (100.0)	0 (0.0)	6 (75.0)	2 (25.0)
Beta Blockers					
Bisoprolol	29 (28.71)	29 (100.0)	0 (0.0)	28 (96.55)	1 (3.45)
Metoprolol	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Carvedilol	19 (18.81)	19 (100.0)	0 (0.0)	7 (36.84)	12 (63.16)
Others					
Alpha-1 Blockers					
Terazosine	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Central Alpha-2 Agonists					
Clonidine	22 (21.78)	22 (100.0)	0 (0.0)	18 (81.82)	4 (18.18)
Methyldopa	1 (0.99)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Antidiabetics					
Sulfonylurea					
Gliquidone	10 (9.90)	10 (100.0)	0 (0.0)	10 (100.0)	0 (0.0)
DPP-4 Inhibitors					
Linagliptine	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Insulins					
Insulin Aspart	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Insulin Glargine	15 (14.85)	15 (100.0)	0 (0.0)	15 (100.0)	0 (0.0)
Insulin Glulisine	21 (20.79)	21 (100.0)	0 (0.0)	21 (100.0)	0 (0.0)
Insulin Lispro	1 (0.99)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)

[a]Percentage: Patients used the drug/101 (patient total) x 100%, [b]Percentage: Patients/patients used the drug x 100%.

Table 3. Potential drug interactions involving antihypertensive and antidiabetic.

Classifications	Total (n = 238)	Percentage (%)
Severity		
Minor	30	12.60
Moderate	199	83.60
Major	9	3.80
Mechanism		
Pharmacodynamic	137	57.60
Pharmacokinetic	31	13.00
Unknown	70	29.40
Interaction Categories[a]		
B	33	13.90
C	187	78.60
D	16	6.70
X	2	0.80

[a]B = No action needed; C = Monitor therapy; D = Consider therapy modification; X = Avoid combination.

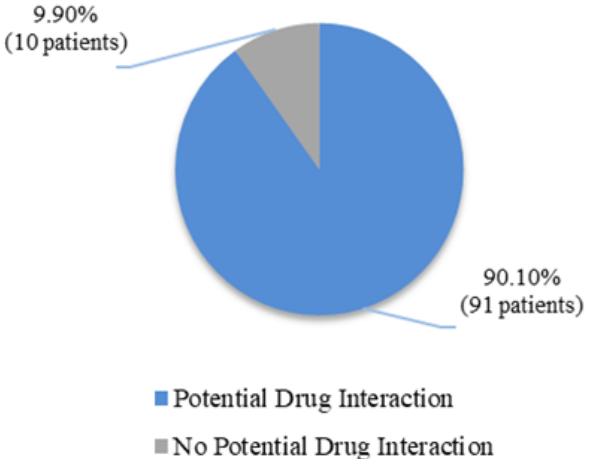

Figure 3. Antihypertensive and antidiabetic potential drug interactions.

Table 4. Potential drug interactions involving antihypertensive and antidiabetic.

Drug-drug combinations	Number of patients, n = 101 (%)	Mechanism type	Severity (category[a])
Antihypertensive + Antihypertensive[b]			
Bisoprolol + Clonidine	11 (10.89)	Pharmacodynamic	Moderate (D)
Carvedilol + Clonidine	6 (5.94)	Pharmacodynamic	Moderate (D)
Candesartan + Captopril	1 (0.99)	Pharmacodynamic	Moderate (D)
Carvedilol + Methyldopa	1 (0.99)	Pharmacodynamic	Moderate (D)
Candesartan + Spironolactone	6 (5.94)	Pharmacodynamic	Major (C)
Ramipril + Spironolactone	1 (0.99)	Pharmacodynamic	Major (C)
Spironolactone + Valsartan	1 (0.99)	Pharmacodynamic	Major (C)
Candesartan + Furosemide	39 (38.61)	Pharmacodynamic	Moderate (C)
Amlodipine + Furosemide	27 (26.73)	Pharmacodynamic	Moderate (C)
Clonidine + Furosemide	16 (15.84)	Pharmacodynamic	Moderate (C)
Antidiabetic + Antidiabetic			
Insulin Glulisine + Insulin Glargine	11 (10.89)	Pharmacodynamic	Moderate (C)
Gliquidone + Insulin Glargine	2 (1.98)	Pharmacodynamic	Moderate (C)
Insulin Glulisine + Gliquidone	2 (1.98)	Pharmacodynamic	Moderate (C)
Antihypertensive + Antidiabetic			
Furosemide + Insulin Glulisine	9 (8.91)	Pharmacokinetic	Moderate (C)
Furosemide + Insulin Glargine	6 (5.94)	Pharmacokinetic	Moderate (C)
Bisoprolol + Gliquidone	5 (4.95)	Pharmacodynamic	Moderate (C)
Bisoprolol + Insulin Glulisine	4 (3.96)	Pharmacodynamic	Moderate (C)
Bisoprolol + Insulin Glargine	3 (2.97)	Pharmacodynamic	Moderate (C)
Carvedilol + Insulin Glulisine	2 (1.98)	Pharmacodynamic	Moderate (C)
Carvedilol + Insulin Glargine	2 (1.98)	Pharmacodynamic	Moderate (C)
Carvedilol + Gliquidone	2 (1.98)	Pharmacodynamic	Moderate (C)
Furosemide + Gliquidone	2 (1.98)	Pharmacokinetic	Moderate (C)
Hydrochlorothiazide + InsulinGlulisine	1 (0.99)	Pharmacodynamic	Moderate (C)
Bisoprolol + Linagliptin	1 (0.99)	Pharmacodynamic	Moderate (C)
Hydrochlorothiazide + Gliquidone	1 (0.99)	Pharmacodynamic	Moderate (C)
Others[c]			
Antihypertensive + Other Drugs			
Carvedilol + Salbutamol	7 (6.93)	Pharmacodynamic	Major (X)
Spironolactone + Potassium Chloride	2 (1.98)	Pharmacodynamic	Major (X)
Clonidine + Codeine	3 (2.97)	Pharmacodynamic	Major (D)
Clonidine + Tramadol	2 (1.98)	Pharmacodynamic	Major (D)
Antidiabetic + Other Drugs			
Insulin Glulisine + Norepinephrine	9 (8.91)	Pharmacodynamic	Moderate (C)
Insulin Glulisine + Levofloxacin	5 (4.95)	Pharmacodynamic	Moderate (C)
Insulin Glargine + Norepinephrine	4 (3.96)	Pharmacodynamic	Moderate (C)
Insulin Glargine + Levofloxacin	4 (3.96)	Pharmacodynamic	Moderate (C)

[a]C= Monitor therapy; D = Consider therapy modification; X = Avoid combination; [b]Potential drug interactions shown were 10 based on severity and category; [c] Potential drug interactions shown were 4 based on severity and category.

significant relationship between the number of drugs and the incidence of inappropriate drug selection, where polypharmacy can increase the probability of inappropriate drug selection[37-39]. In this study, the number of patients who received 15-46 drugs during hospitalization experienced more inappropriateness in drug selection compared to patients who received 4-14 drugs during hospitalization.

Factors Associated with Appropriateness of Antihypertensive and Antidiabetic Dosage Adjustment. Table 6 shows the number of drugs (p=0.033) and length of stay (p=0.024) had a significant relationship with the appropriateness of antihypertensive and antidiabetic dosage adjustment, where patients who received 4-14 drugs tended to be 2.996 times higher received appropriate dosage of antihypertensive and antidiabetic than patients who received 15-45 drugs. In addition, patients treated for 1-8 days tended to be 3.171 times more likely to get the appropriate antihypertensive and antidiabetic dosage than patients treated for 9-31 days. Longer lengths of stay cause more drugs patients to receive due to the possibility of the patient's illness severity. Therefore, the longer the hospitalization, the greater the number of drugs given, making it more challenging to check and monitor dosage adjustments for each drug[40, 41]. In this study, gender (p=0.885) and age (p=0.763) did not have a significant relationship with the appropriateness of dosage adjustment. These results align with previous studies in Pakistan and Ethiopia[41, 42].

Factors Associated with Antihypertensive and Antidiabetic Potential Drug Interactions. Table 7 showed that length of stay had a significant relationship with potential drug interactions (p = 0.040). Patients with a duration in hospital for 1-8 days tend to be 8.426-fold not to experience drug interactions than patients with a more extended stay of 9-31 days (OR = 8.426). The result showed in the Table 7. Another study in Northwest Ethiopia also showed that the longer the hospitalization period and received more drugs (p = 0.005; p = 0,035 respectively) caused increasing the probability of potential drug interactions experienced by patients[43]. Drug interactions that may occur can cause unwanted drug effects, so this requires monitoring by health workers.

Table 5. Factor associated with appropriateness of antihypertensive and antidiabetic drug selection.

Factors	Drug Selection (n =101)		Total, n (%)	p value	Odds Ratio (OR) (95% Cl)
	Appropriate	Inappropriate			
Gender					
Male	58 (59.2)	1 (33.3)	59 (58.4)	0.569[a]	2.900 (0.254 – 33.073)
Female	40 (40.8)	2 (66.7)	42 (41.6)		
Age					
18-56 years	44 (44.9)	2 (66.7)	46 (45.5)	0.590[a]	0.407 (0.036 – 4.643)
57-93 years	54 (55.1)	1 (33.3)	55 (54.5)		
Number of drugs					
4-14	54 (55.1)	1 (33.3)	55 (54.5)	0.590[a]	2.455 (0.215 – 27.971)
15-45	44 (44.9)	2 (66.7)	46 (45.5)		
Length of stay					
1-8 days	54 (55.1)	2 (66.7)	56 (55.4)	1.000[a]	0.614 (0.054 – 6.993)
9-31 days	44 (44.9)	1 (33.3)	45 (44.6)		

[a]*Fisher Exact* test

Table 6. Factors associated with appropriateness of antihypertensive and antidiabetic dosage adjustment.

Factors	Dosage Adjustment (n =101)		Total, n (%)	p value	Odds Ratio (OR) (95% Cl)
	Appropriate	Inappropriate			
Gender					
Male	43 (57.3)	16 (61.5)	59 (58.4)	0.885[a]	0.840 (0.337 – 2.093)
Female	32 (42.7)	10 (38.5)	42 (41.6)		
Age					
18-56 years	33 (44.0)	13 (50.0)	46 (45.5)	0.763[a]	0.786 (0.321 – 1.921)
57-93 years	42 (56.0)	13 (50.0)	55 (54.5)		
Number of drugs					
4-14	46 (61.3)	9 (34.6)	55 (54.5)	0.033[a*]	2.996 (1.180 – 7.610)
15-45	29 (38.7)	17 (65.4)	46 (45.5)		
Length of stay					
1-8 days	47 (62.7)	9 (34.6)	56 (55.4)	0.024[a*]	3.171 (1.246 – 8.065)
9-31 days	28 (37.3)	17 (65.4)	45 (44.6)		

[a]*Continuity Correlation Chi-Square* test; [*]There is significant difference that indicated by p value < 0.05

Table 7. Factors associated with antihypertensive and antidiabetic potential drug interactions.

Factors	Potential Drug Interactions (n =101)		Total, n (%)	p value	Odds Ratio (OR) (95% Cl)
	Not Found	Found			
Gender					
Male	7 (70.0)	52 (57.1)	59 (58.4)	0.516[a]	1.750 (0.425 – 7.202)
Female	3 (30.0)	39 (42.9)	42 (41.6)		
Age					
18-56 years	6 (60.0)	40 (44.0)	46 (45.5)	0.506[a]	1.913 (0.505 – 7.240)
57-93 years	4 (40.0)	51 (56.0)	55 (54.5)		
Number of Drugs					
4-14	8 (80.0)	47 (51.6)	55 (54.5)	0.106[a]	3.745 (0.754 – 18.065)
15-45	2 (20.0)	44 (48.4)	46 (45.5)		
Length of Stay					
1-8 days	9 (90.0)	47 (51.6)	56 (55.4)	0.040[a*]	8.426 (1.025 – 69.253)
9-31 days	1 (10.0)	44 (48.4)	45 (44.6)		

[a] *Fisher Exact* test; [*]There is significant difference that indicated by p value < 0.05.

In this study, we found that the variables of gender (p = 0.516), age (p = 0.506), and number of drugs (p = 0.106) did not have a significant relationship with potential drug interactions. Another study also found no significant relationship between gender and age with potential drug interactions[44]. However, studies in Ethiopia and Pakistan, Slovenia, Brazil found a significant relationship between the number of drugs and the potential for drug interactions, where an increase in the number of drugs corresponded to an increase in the potential for drug interactions[45-47]. The difference in results could be due to the potential drug interactions studied in our study focusing only on the potential drug interactions involving antihypertensive and antidiabetic drugs.

CONCLUSION

Hospital pharmacists' role in monitoring therapy patients with CKD undergoing HD with hypertensive and diabetic mellitus needs improvement. In this study, we found that the drug selection was mostly appropriate. However, dosage adjustment and potential drug interaction became a concern in this study because we found that inappropriate dosage adjustment was increased in patients receiving more drugs and longer hospitalized. In addition, the number of drugs also intensified the potential drug interaction in the patient receiving antihypertensive and antidiabetic.

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REFERENCES

1. Gliselda VK. Diagnosis dan manajemen penyakit ginjal kronis (PGK). Jurnal Medika Hutama. 2021;2(04 Juli):1135-41.
2. Rossing P, Caramori ML, Chan JC, Heerspink HJ, Hurst C, Khunti K, et al. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney International. 2022;102(5):S1-S127.
3. de Souza W, de Abreu LC, Silva LGd, Bezerra IMP. Incidence of chronic kidney disease hospitalisations and mortality in Espírito Santo between 1996 to 2017. PLoS One. 2019;14(11):e0224889.
4. Riskesdas LN. Kementerian Kesehatan Republik Indonesia. Badan Penelitian Dan Pengembangan Kesehatan. 2018.
5. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. Jama. 2012;307(18):1941-51.
6. Jalalonmuhali M, Lim SK, Md Shah MN, Ng KP. MDRD vs. CKD-EPI in comparison to 51Chromium EDTA: a cross sectional study of Malaysian CKD cohort. BMC nephrology. 2017;18(1):1-6.
7. Hunter-Dickson M, Drak D, Anderson M, Shamu T, Chimbetete C, Dahwa R, et al. Comparison of CG, CKD-EPI [AS] and CKD-EPI [ASR] equations to estimate glomerular filtration rate and predict mortality in treatment naïve people living with HIV in Zimbabwe. BMC nephrology. 2023;24(1):1-6.
8. Cahyani AAAE, Prasetya D, Abadi MF, Prihatiningsih D. Gambaran diagnosis pasien pra-hemodialisa di RSUD Wangaya Tahun 2020-2021. Jurnal Ilmiah Hospitality. 2022;11(1):661-6.
9. Pernefri PNI. Konsensus dialisis. Jakarta: Pernefri. 2003. 21–34.
10. Putra IGSS, Islamiah A. Gambaran klinis dan laboratoris penderita penyakit ginjal kronis yang menjalani hemodialisis di RSUD Muara Teweh, Barito Utara, Kalimantan Tengah. Intisari Sains Medis. 2023;14(1):538-42.
11. Indonesia PN. 11th Report of Indonesian renal registry 2018. Jakarta: Perhimpunan Nefrologi Indonesia. 2018;1–46.12.
12. Insani N, Manggau MA, Kasim H. Analisis efektivitas terapi pada pasien anemia gagal ginjal hemodialisis di RSUP Dr. Wahidin Sudirohusodo Makassar. Majalah Farmasi dan Farmakologi. 2018;22(1):13-5.
13. Adusumilli P, Adepu R. Drug related problems: an over view of various classification systems. Asian J Pharm Clin Res. 2014;7(4):7-10.
14. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. American journal of hospital pharmacy. 1990;47(3):533-43.
15. Handayani N, Faisal M, Rusli R. Drug interaction studies in patients with kidney failure inpatient at Panglima Sebaya Hospital, Tanah Grogot. Jurnal Sains dan Kesehatan. 2023;5(4):500-6.
16. Tuloli TS, Madania M, Mustapa MA, Tuli EP. Evaluasi penggunaan obat pada pasien gagal ginjal kronik yang menjalani hemodialisis di RSUD Toto Kabila Periode 2017-2018. Parapemikir: Jurnal Ilmiah Farmasi. 2019;8(2):25-32.
17. Lucida H, Trisnawati R, Suardi M. Analisis aspek farmakokinetika klinik pasien gagal ginjal pada IRNA penyakit dalam RSUP Dr. M. Djamil Padang. Jurnal Sains Dan Teknologi Farmasi. 2011;16(2):144-55.
18. Zhao P, Vieira MdL, Grillo JA, Song P, Wu TC, Zheng JH, et al. Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. The Journal of Clinical

Pharmacology. 2012;52(S1):91S-108S.
19. Rengga MPE, Kono RB, Beama CA. Analisis interaksi obat penyakit ginjal kronik di RSUD Prof. Dr. WZ Johannes Kupang. MPI (Media Pharmaceutica Indonesiana). 2021;3(3):179-87.
20. Ashley C, Dunleavy A. The renal drug handbook: the ultimate prescribing guide for renal practitioners: CRC Press; 2018.
21. Indonesia PE. Pedoman petunjuk praktis terapi insulin pada pasien diabetes mellitus 2021. Jakarta: PB PERKENI. 2021.
22. Kementrian Kesehatan Republik Indonesia. Pedoman nasional pelayanan kedokteran tata laksana diabetes melitus tipe 2 dewasa. Kementrian Kesehatan Republik Indonesia; 2020.
23. Kementrian Kesehatan Republik Indonesia. Pedoman nasional pelayanan kedokteran tata laksana hipertensi dewasa. Kementrian Kesehatan Republik Indonesia; 2021.
24. Zhao JV, Schooling CM. The role of testosterone in chronic kidney disease and kidney function in men and women: a bi-directional Mendelian randomization study in the UK Biobank. BMC medicine. 2020;18(1):1-10.
25. Denic A, Lieske JC, Chakkera HA, Poggio ED, Alexander MP, Singh P, et al. The substantial loss of nephrons in healthy human kidneys with aging. Journal of the American Society of Nephrology: JASN. 2017;28(1):313-20.
26. Dybiec J, Szlagor M, Młynarska E, Rysz J, Franczyk B. Structural and functional changes in aging kidneys. International Journal of Molecular Sciences. 2022;23(23):15435.
27. Shafiee MA, Chamanian P, Shaker P, Shahideh Y, Broumand B, editors. The impact of hemodialysis frequency and duration on blood pressure management and quality of life in end-stage renal disease patients. Healthcare; 2017;5(3):52.
28. Chauhan R, Mendonca S. Adequacy of twice weekly hemodialysis in end stage renal disease patients at a tertiary care dialysis centre. Indian journal of nephrology. 2015;25(6):329-33.
29. MacRae C, Mercer SW, Guthrie B, Henderson D. Comorbidity in chronic kidney disease: a large cross-sectional study of prevalence in Scottish primary care. British Journal of General Practice. 2021;71(704):e243-e9.30.
30. Garla V, Kanduri S, Yanes-Cardozo L, Lien LF. Management of diabetes mellitus in chronic kidney disease. Minerva Endocrinologica. 2019;44(3):273-87.
31. Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with chronic kidney disease. Clinical diabetes and endocrinology. 2015;1(1):1-9.
32. Betônico CC, Titan SMO, Lira A, Pelaes TS, Correa-Giannella MLC, Nery M, et al. Insulin glargine U100 improved glycemic control and reduced nocturnal hypoglycemia in patients with type 2 diabetes mellitus and chronic kidney disease stages 3 and 4. Clinical therapeutics. 2019;41(10):2008-20. e3.
33. Kalaitzidis RG, Elisaf MS. Treatment of hypertension in chronic kidney disease. Current hypertension reports. 2018;20:1-10.
34. Sinha AD, Agarwal R. Clinical pharmacology of antihypertensive therapy for the treatment of hypertension in CKD. Clinical Journal of the American Society of Nephrology: CJASN. 2019;14(5):757-64.
35. Gregg LP, Richardson P, Herrera MA, Akeroyd J, Jafry S, Gobbel G, et al. Documented adverse drug reactions and discontinuation of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in chronic kidney disease. American Journal of Nephrology. 2023;54(3-4):126-35.
36. Lexicomp. Drug Interactions Analysis: Wolters Kluwer; 2023.
37. Barbieri MA, Rottura M, Cicala G, Mandraffino R, Marino S, Irrera N, et al. Chronic kidney disease management in general practice: a focus on inappropriate drugs prescriptions. Journal of clinical medicine. 2020;9(5):1346.
38. Sharma R, Chhabra M, Vidyasagar K, Rashid M, Fialova D, Bhagavathula AS. Potentially inappropriate medication use in older hospitalized patients with type 2 diabetes: a Cross-sectional study. Pharmacy. 2020;8(4):219.
39. Youssef A, Almubarak A, Aljohnai M, Alnuaimi M, Alshehri B, Al-ghamdi G, et al. Contraindicated medications administered to inpatients with renal insufficiency in a Saudi Arabian hospital that has a computerized clinical decision support system. Journal of Taibah University Medical Sciences. 2015;10(3):320-6.
40. Fukuba N, Nishida M, Hayashi M, Furukawa N, Ishitobi H, Nagaoka M, et al. The relationship between polypharmacy and hospital-stay duration: a retrospective study. Cureus. 2020; 12(3): e726741.
41. Zeleke TK, Birhan TY, Abdela OA. Medicine dose adjustment practice and associated factors among renally impaired patients in Amhara Regional State, Ethiopia. International Journal of Nephrology. 2021;2021:1-9.
42. Saleem A, Masood I. Pattern and predictors of medication dosing errors in chronic kidney disease patients in Pakistan: a single center retrospective analysis. PLoS One. 2016;11(7):e0158677.
43. Dagnew EM, Ergena AE, Wondm SA, Sendekie AK. Potential drug-drug interactions and associated factors among admitted patients with psychiatric disorders at selected hospitals in Northwest Ethiopia. BMC Pharmacology and Toxicology. 2022;23(1):88.
44. Marquito AB, Fernandes NMdS, Colugnati FAB, Paula RBd. Identifying potential drug interactions in chronic kidney disease patients. Brazilian Journal of Nephrology. 2014;36:26-34.
45. Bhagavathula AS, Berhanie A, Tigistu H, Abraham Y, Getachew Y, Khan TM, et al. Prevalence of potential drug–drug interactions among internal medicine ward in University of Gondar Teaching Hospital, Ethiopia. Asian Pacific Journal of Tropical Biomedicine. 2014;4:S204-S8.

46. Biase TMMA, Silva MT, Galvao TF. Potential drug interactions in adults living in the Brazilian Amazon: A population-based case-control study, 2019. Exploratory research in clinical and social pharmacy. 2021;3:100056.

47. Bačar Bole C, Nagode K, Pišlar M, Mrhar A, Grabnar I, Vovk T. Potential drug-drug interactions among patients with schizophrenia spectrum disorders: prevalence, association with risk factors, and replicate analysis in 2021. Medicina. 2023;59(2):284.