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A STUDY OF DRUG RELATED PROBLEMS IN CHRONIC KIDNEY DISEASE PATIENTS IN HOSPITAL

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ABSTRACT
Patients with chronic kidney disease experience decreased kidney function (as an organ of elimination) and receive various drugs, so they are susceptible to Drug Related Problems (DRP). This study aimed to identify the type of potential DRP and analyzed the influence of gender, age, number of drugs, co-morbidities and length of stay on the incidence of DRP in hospitalized chronic kidney disease patients. This study was a cross-sectional study with retrospective data collection. The subjects of the study were chronic kidney disease patients who underwent hospitalization at a hospital in Surakarta at 2016-2021. The incidence of DRP was analyzed descriptively using the PCNE V9.1 algorithm, while the associations between risk factors and the incidence of DRP was analyzed statistically using the Fisher's Exact Test. Data were obtained from 54 patients whose progress was followed up through medical record. The results showed that 36 patients (66.67%) had DRP while 18 patients (33.33%) did not. In the Problem category there were 22 events while in the Cause category there were 34 events. The results of statistical analysis using the Fisher's Exact Test showed that there were no significant associations between the risk factors (gender, age, number of drugs, number of co-morbidities, length of stay) and the incidence of DRP in hospitalized chronic kidney disease patients.

Keywords: Drug related problems; Chronic kidney disease; Hospital patients

1. INTRODUCTION

The kidney is the main organ for eliminating drugs. Patients with chronic kidney disease experience a decrease in kidney function which is characterized by uremia, in which glomerular filtration and active tubular secretion decrease due to nephron damage. Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt^2, persisting for 3 months or more, irrespective of the cause (KDIGO, 2013). Creatinine clearance describes the function of the kidney to excrete the drug. Low creatinine clearance may increase the risk of drug toxicity or decrease the therapeutic effect. Management of chronic kidney disease is long-term treatment and often uses more than one medication. Patients with chronic kidney disease most often are secondary to diabetes mellitus and cardiovascular disease, thereby increasing the variety of drugs used.

Decreased kidney function as an organ of drug elimination and the variety of drugs used in patients with chronic kidney disease can lead to Drug Related Problems (DRP). A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (PCNE, 2020). Several classification systems of DRP have been used in clinical practice, among them were the most widely used Pharmaceutical Care Network (PCNE). Previous studies have determined numerous risk factors for DRPs in

general patients. The major causes contributing to DRPs were adverse drug reactions and noncompliance (Al Hamid et al., 2014). In addition, the major risk factors associated with DRPs were old age, the number of drugs, heart rate ≥ 80 bpm and comorbidities (Saldanha et al., 2020; Sell & Schaefer, 2020).

There are still limited studies regarding the risk factors for DRP in patients with chronic kidney disease. Patients with chronic kidney disease require special attention because of a decrease in kidney function which further causes changes in the pharmacokinetic and pharmacodynamic profile of drugs. In this population, drug safety is an important concern in order to achieve rational pharmacotherapy. Identification of risk factors plays an important role in preventing DRP. DRP are an important problem in clinical practice and many of them are preventable, so the specific risk factors that facilitate the occurrence of DRP are of considerable interest (Kaufmann et al., 2015). As part of the implementation of pharmaceutical services, pharmacist has responsibility for identifying actual and potential DRP, preventing potential DRP, and overcoming DRP that occurred.

Based on the description above, the purpose of this study was to identify the type of DRP and to analyze the factors of age, gender, the number of drugs, co-morbidities and length of stay that can affect the incidence of DRP in patients with chronic kidney disease in a hospital in Surakarta City. By knowing the DRP and the risk factors for the occurrence of DRP, it is hoped that rational pharmacotherapy will be achieved for the treatment of patients with chronic kidney disease.

2. METHODS

2.1. Study Design

This study was an observational study with a cross-sectional design. Data were taken retrospectively at a hospital in Surakarta City from August 2021 – December 2021. Ethical *approval* was *obtained* from Ethics Commission of Kusuma Husada University (No.91/UKH.L.02/EC/IX/2021).

2.2. Population and Sample

The subjects of this study were chronic kidney disease patients who were hospitalized in a hospital in Surakarta City between 2016-2021 who met the inclusion and exclusion criteria. The inclusion criteria for this study included patients with a diagnosis of chronic kidney disease, at least 18 years old and receiving drug therapy. Exclusion criteria included patients with a history of impaired liver function, patients with Human Immunodeficiency Virus (HIV) acquired immunodeficiency syndrome (AIDS), patients undergoing chemotherapy, patients with kidney transplants.

2.3. Data Collection Method

The data were taken from the medical records of patients with primary diagnosis of chronic kidney disease. Subsequently, the data were tabulated in Excel data sheets followed by descriptive analysis and statistical analysis from SPSS. Data were included patient characteristics, medical history, history of drug use, and general clinical variables comprised body temperature, leukocyte values, blood pressure, blood sugar level, allergies and medical specialty. Patient characteristics included age, gender, patient diagnosis, the number of drugs, type of co-morbidities and length of stay in hospital. Another material used in this research is a research worksheet and Pharmaceutical Care Network Europe (PCNE) V9.1 algorithm.

2.4. Data Analysis

The DRP was analyzed by descriptive evaluative method. DRP was classified according to the PCNE V9.1 algorithm. DRP that were detected, classified as potential DRP. The classification was only conducted in the *Problems* and *Cause* categories. To find out the associations between risk factors and the occurrence of DRP, the statistical Fisher's Exact Test

(95% CI; α = 0.05) was used because the 2x2 table did not meet the Chi Square criteria, that was, more than 20% of cells had an expected value of less than 5.

3. RESULTS AND DISCUSSION

A total of 54 hospitalized chronic kidney disease patients were followed by their progress notes in the medical record. Data describing the characteristics of the research subjects were in **Table 1**, including gender, age, number of drugs, number of co-morbidities, types of co-morbidities, and length of stay.

Table 1. Patient characteristics (N=54)

No.	Characteristics	Frequency	Percentage (%)
1	**Gender**		
	Men	16	29.63
	Women	38	70.37
2	**Ages (years)**		
	18-25	2	3.70
	26-35	6	11.11
	36-45	2	3.70
	46-55	16	29.63
	56-65	8	14.81
	≥65	20	37.04
3	**Number of co-morbidities**		
	< 3	20	37.04
	≥ 3	34	62.96
4	**Type of comorbidity**		
	Cardiovascular disease	30	55.56
	Diabetes Mellitus (DM)	2	3.70
	Cardiovascular disease and DM	12	22.22
	Other than cardiovascular disease and DM	10	18.52
5	**Number of drugs**		
	1-4	2	3.70
	5-10	24	44.44
	>10	28	51.85
6	**Length of stay**		
	< 7 days	30	57.69
	≥ 7 days	24	46.15

Based on **Table 1**, the number of women was greater than that of men. These results indicated that the prevalence of cases of chronic kidney disease in these hospitals was higher in women than in men. It has been reported internationally that chronic kidney disease (CKD) is more prevalent among women than men (USRDS, 2020). The differences in the underlying pathophysiology of disease might account for these dissimilarities between the sexes (Carrero et al., 2018). Women are more at risk for kidney failure because they are more susceptible to urinary tract infections that can damage kidneys. They also have increased risk for kidney disease due to hypertensive disorders of pregnancy (preeclampsia and gestational hypertension) (Barrett et al., 2020). Menopausal women are at higher risk for CKD than premenopausal women because estrogen may have protective effect on the kidneys (Harris & Zhang, 2020).

Our study found that most patients experienced CKD were geriatric (≥65 years old). It has been known that estimated glomerular filtration rate (eGFR) will declines along with increasing age. Elderly people with advanced CKD have a higher risk of death, kidney failure, myocardial infarction, and stroke than similar people who have a normal or slightly low eGFR (Tonelli & Riella, 2014). The length of stay was mostly for < 7 days (57.69%). The increase in length of stay can be caused by the age factor, because the elderly experience a decrease in physiological functions such as decreased metabolic ability, so that the healing process for a disease will take longer (Fatimah et al., 2023).

The number of comorbidities in chronic kidney patients was dominated by ≥ 3 comorbidities. The highest comorbidities suffered by patients were cardiovascular disease as much as 55.56%, followed by cardiovascular disease and Diabetes Mellitus (DM) as much as 22.22%. Cardiovascular disease was the main cause of death in ESRD (End Stage Renal Disease) patients and contributes to more than half of deaths. Older ESRD patients tend to have a higher prevalence of cardiovascular disease. However, the prevalence of cardiovascular disease is also high among the ages of 22-44 years, although a much higher prevalence occurs at the age of 45 years or older (USRDS, 2020). Patients with chronic kidney disease (CKD) exhibit an increased cardiovascular risk associated with coronary artery disease, heart failure, arrhythmias, and sudden cardiac death. CKD can cause a chronic and systemic proinflammatory state that contributes to vascular and myocardial remodeling processes resulting in atherosclerotic lesions, vascular calcification, and vascular senescence as well as myocardial fibrosis and heart valve calcification. Thus, CKD can mimic accelerated aging of the cardiovascular system (Jankowski et al., 2021).

Almost all patients received more than 5 drugs (polypharmacy). CKD patients are at high risk of drug related problems due to polypharmacy and impaired renal excretion. DRP can lead to decreased quality of life, increased length of hospital stays, increased overall health care costs, and even increased risk of morbidity and mortality (Garedow et al., 2019). Therefore, complex treatment regimens consisting of several types of medications are usually required to treat chronic kidney disease (CKD) and related comorbidities. Patients with CKD require several drugs to treat medical conditions that accompany the development of CKD (such as diabetes mellitus, hypertension, and prevent the development of chronic kidney disease), as well as common complications of CKD (such as hyperlipidemia, anemia, bone and mineral disorders) (Mason & Bakus, 2010).

DRP analysis was based on PCNE V9.1. This study was only carried out in the Problems and Cause categories. Based on the k of the study, it was found that 36 of 54 patients (66.67%) were experienced DRP. A total of 56 cases were found and categorized as Problems and Causes. In the Problem category there were 22 cases while in the Cause category there were 34 cases. The full number of DRP events in the Problem Category and Causes can be seen in **Table 2**.

Table 2. Number of DRP events in the category of problems and causes (N=60)

Category	Code V9.1	Primary Domains	Case Number	Total (N)
Problems	P1	Treatment effectiveness	14	22
	P2	Treatment safety	1	
	P3	Other	7	
Causes	C1	Drug selection	34	34
	C2	Drug form	0	
	C3	Dose selection	0	
	C4	Treatment duration	0	
Total				**56**

3.1. The Problems

The problems consist of treatment effectiveness, treatment safety, and other problems. Based on the analysis of DRP according to PCNE V9.1, the results obtained were 22 events where the most problems were in the category of treatment effectiveness by 14 events (63.64%), followed by treatment safety for 1 event (4.55%), and other problems 7 events (31.82%). The explanation of Problem Category can be seen in **Table 3**.

In the P1.1 subdomain (No effect of drug treatment despite correct use), it showed that all treatment of hospitalized patients with chronic kidney disease had therapeutic effect. In subdomain P1.2 (Effect of drug therapy not optimal) there were 7 events as shown in **Table 4**. The effect of suboptimal drug therapy was dominated by patients who received a combination of antihypertensive drugs but the patient's blood pressure was still high, ranging from 160/100

mmHg to with 217/101 mm Hg. Based on the JNC 8 algorithm, the blood pressure target for hypertensive patients with CKD is <140/90 mmHg (James et al., 2014). The selection of drugs for 3 patients (case No. 1, 21, 26) was correct, namely the ACEI or ARB group combined with other drug classes, while for the patient with case no. 17 the combination of captopril and ramipril could not control the blood pressure because the two drugs had the same mechanism of action on the renin-angiotensin-aldosterone system. In other wise, blood pressure that had not met the target might be caused by psycho-social factors such as lifestyle and medication adherence. Non-pharmacologic lifestyle interventions should be encouraged as adjunctive therapy for hypertension such as regular physical activity, weight control, smoking cessation, stress reduction, and avoiding excessive alcohol intake (Oliveros et al., 2020). In this study, the patient's medication adherence and lifestyle could not be known because data collection was carried out retrospectively. Intervention and strategies such as the use of single pill combination, electronic pill monitors, lowering economic barriers, and collaborative care between pharmacist and primary care provider or cardiologist have been shown to increase adherence rates (Neiman et al., 2017).

Table 3. The problems

Code V9.1	Primary Domains	Code V9.1	Problem (subdomains)	Case Number	Percentage (%)
P1	Treatment effectiveness	P1.1	No effect of drug treatment despite correct use	0	63.64
		P1.2	Effect of drug treatment not optimal	7	
		P1.3	Untreated symptoms or indication	7	
P2	Treatment safety	P2.1	Adverse drug event (possibly) occurring	1	4.55
P3	Other	P3.1	Unnecessary drug-treatment	7	31.82
		P3.2	Unclear problem/complaint. Further clarification necessary (please use as escape only)	0	
Total cases				22	100.00

Table 4. Subdomains of problems P1.2 (Effect of drug treatment not optimal)

Case Number	Drug	Explanation
1	Ramipril 1x10 mg, amlodipine 1x10 mg, clonidine 2x0.15 mg, bisoprolol 1x5 mg	Blood pressure was still high
6	Na diclofenac po 2x50 mg	Painkillers were inadequate because patients still felt pain after surgery
8	Atorvastatin po 1x20 mg	Antihyperlipidemic drugs were inadequate because total cholesterol, triglyceride and LDL levels were still high
10	Metformin po 3x500 mg	Blood glucose was still high
17	Captopril po 1x25 mg, ramipril po 1x10 mg	Blood pressure was still high
21	Ramipril po 1x10 mg, amlodipine po 1x10 mg, HCT po 1x25 mg, clonidine po 2x0.15 mg	Blood pressure was still high
26	Ramipril po 1x10 mg, amlodipine po 1x10 mg, bisoprolol 1x5 mg, clonidine po 3x0.15 mg	Blood pressure was still high

In the P1.3 subdomain (Untreated symptoms or indications) there were 7 events as shown in **Table 5**. This subdomain was dominated by patients who experienced nausea and vomiting but had not received antiemetic therapy. Patients received one or a combination of omeprazole, sucralfate, ranitidine while they had not received antiemetic therapy. Nausea and vomiting in kidney disease are not associated with excess stomach acid. Serum creatinine and urea in CKD patients can cause patients to lose their appetite, nausea, vomiting, loss of energy and protein,

decrease in carnitine production which causes a decrease in energy production for the skeleton and results in fatigue (Artom et al., 2014).

Table 5. Subdomains of problems P1.3 (Untreated symptoms or indications)

Case Number	Complain	Explanation
3	Diarrhea	The patient had not received antidiarrheal therapy
9	Blood pressure was 150/80 mmHg	The patient's blood pressure was still high, but antihypertensive drugs are no longer given
10	Nausea, vomitting	Had not received antiemetic drugs
14	Nausea, vomitting	Had not received antiemetic drugs
15	Pain during urination	Had not received pain medication yet
16	Nausea	Had not received anti-nausea therapy, because nausea and vomiting in kidney disease were not related to excessive stomach acid
25	Dermatitis	Had not received medicine to treat dermatitis yet

In the P2.1 subdomain (Adverse drug event (possibly) occurring), there was 1 event where the patient was hypotensive. This hypotension most likely occurred due to ADR (adverse drug reactions) from the use of the antihypertensive drug, namely carvendilol and at the same time the patient received tamsulosin to treat BPH. Tamsulosin is an alpha blocker that works selectively on α_{1A} receptors in the prostate, while α_{1B} receptors are found in blood vessels. A study on the use of tamsulosin for BPH in patients aged 40-85 years in the USA showed that there was a associations between the use of tamsulosin and the incidence of severe hypotension (Bird et al., 2013). Therefore, the use of tamsulosin in elderly patients must be wary. In this study, the patient was 77 years old, so the occurrence of hypotension could not be ruled out related to the use of carvendilol and tamsulosin together in elderly patients.

In the P3.1 subdomain (Unnecessary drug-treatment) there were 7 events as shown in **Table 6**. There were several drugs prescribed, but without clear indications or diagnosis. These drugs included suppressors of stomach acid production, the Proton Pump Inhibitor and H-2 blockers. Both of these drug classes usually indicated to reduce gastric acid secretion (Katzung, 2018). Nausea and vomiting is very common in kidney patients and has many causes. These causes include the buildup of uremic toxins and medications metabolites because kidney can't eliminate them, gastroparesis, high level of blood sugar, vestibular dysfunction, motion disorder and increased intra-cranial pressure. Serum creatinine and urea in CKD patients can cause patients to lose their appetite, nausea, and vomiting (Artom et al., 2014). Dimenhydrinate is mostly efficacious for nausea/vomiting caused by vestibular dysfunction, motion disorder and increased intra-cranial pressure. For patients with gastric stasis/gastroparesis, metoclopramide or domperidone may relieve nausea and vomiting (Camilleri et al., 2013).

Unnecessary prescribing of antibiotics also occurred, levofloxacin and ceftriaxone were given to patients without signs of infection, normal temperature was 37 °C, and leukocyte values were still in the range of 4500-11,000/mm^3.

3.2. The Causes

The Causes consist of primary domains, C1 – C9. Each of these primary domains has subdomains or secondary domains. Information from patient medical records could only be used to identify domains C1 – C4. We could not identify the C5 – C9 domains because we did not follow the patient's progress during treatment.

Based on the results of identification of DRP problems according to PCNE V9.1 domain C1 - C4, it was found that there were 34 incidents where the most problems were in the Drug Selection domain (100%). The causes can be seen in **Table 7**. In the causes of DRP, the secondary domain that occurred most frequently was domain C1.2 (No indication for drugs), which was 32.35%.

Table 6. Subdomains of problems P3.1 (Unnecessary drug-treatment)

Case Number	Drug	Explanation
8	Levofloxacin	There was no indication of infection, the temperature was 37 °C (normal), leukocyte values were still in the range of 4500-11.000/mm^3
9	Ranitidine, omeprazole	Ranitidine and omeprazole are drugs to reduce stomach acid secretion. However, the patient had no indications of dyspepsia, nor complaints related to the stomach or digestive system
13	Omeprazole, sucralfate	There were no indications of dyspepsia, nor complaints related to the stomach or digestive system
15	Ceftriaxon	There was no indication of infection, the temperature was 37 °C (normal), leukocyte values were still in the range of 4500-11.000/mm^3
17	Omeprazole	There were no indications of dyspepsia, nor complaints related to the stomach or digestive system
23	Echinacea	Echinacea is an immune-boosting supplement, however, the patient did not have a viral or bacterial infection that required an increased in the immune response
25	Paracetamol	There were no complaints of pain or fever. According to IONI (2020) the indication for paracetamol is as an analgesic and antipyretic

Table 7. The causes

Code V9.1	Primary Domain	Code V9.1	Cause (subdomain)	Case Number	Percentage (%)
C1	Drug selection	C1.1	Inappropriate drug according to guidelines/formulary	4	11.76
		C1.2	No indication for drug	11	32.35
		C1.3	Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	3	8.82
		C1.4	Inappropriate duplication of therapeutic group or active ingredient	5	14.71
		C1.5	No or incomplete drug treatment in spite of existing indication	7	20.60
		C1.6	Too many different drugs/active ingredients prescribed for indication	4	11.76
C2	Drug form	C2.1	Inappropriate drug form/formulation (for this patient)	0	0.00
C3	Dose selection	C3.1	Drug dose too low	0	0.00
		C3.2	Drug dose of a single active ingredient too high	0	0.00
		C3.3	Dosage regimen not frequent enough	0	0.00
		C3.4	Dosage regimen too frequent	0	0.00
		C3.5	Dose timing instructions wrong, unclear or missing	0	0.00
C4	Treatment duration	C4.1	Duration of treatment too short	0	0.00
		C4.2	Duration of treatment too long	0	0.00
Total cases				34	100.00

In the subdomain C1.1 (Inappropriate drug according to guidelines/formulary) there were 4 incidents which the use of ondansetron in patients with kidney disease to treat nausea and vomiting did not comply with the National Formulary because it was not nausea and vomiting caused by chemotherapy or surgery. In subdomain C1.2 (No indications for drugs) there were 11 events, the full details of which can be seen in **Table 8**. The drugs prescribed without any indication included antibiotic, proton pump inhibitor, H-2 antagonist, antiemetic and analgetic. A patient prescribed several kinds of drugs to treat digestive disorders, those were sucralfate,

curcuma, ondansetron, and ranitidine. Even the patient had not experienced nausea and vomiting anymore but these drugs were still given. The C1.2 subdomain was dominated by PPI and H2-blocker prescribing without any indication of gastric or gastrointestinal disorders, as well as administration of antibiotics without establishing a diagnosis of infection. Paracetamol was also prescribed but the patient did not complain of dizziness, pain or fever. According to PIONAS paracetamol is indicated as an analgesic and antipyretic (BPOM RI, 2020).

Table 8. Subdomain of causes C1.2 (No indication for drug)

Case Number	Drug	Explanation
8	Levofloxacin	No indication of infection. Patient complained of low back and shoulder pain, flatulence, dizziness, fatigue, tingling from the back of the neck, shoulders to spine. Patient diagnosed with CKD, CHF, Hypertension Heart Disease, DM, Dyslipidemia, PVC
9,23	Ranitidine	There was no indication of peptic ulcer or other digestive disorders
9,13,17	Omeprazole	There was no indication of peptic ulcer or other digestive disorders
13	Sucralfate	There was no indication of peptic ulcer or other digestive disorders
15	Ceftriaxone	There was no indication of infection, the patient did not complain of fever, normal body temperature, normal leukocyte count
23	Ondancetron	The patient did not experience nausea and vomiting
23, 25	Paracetamol	The patient did not complain of dizziness, pain or fever. Paracetamol is indicated as an analgesic and antipyretic

In the subdomain C1.3 (Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements) there were 3 events as shown in **Table 9**. In this subdomain there were 2 cases where ceftriaxone iv and calcium carbonate were given together. This could be fatal because combination of calcium-containing preparations with intravenous ceftrixone can cause precipitation of ceftriaxone in the lungs and kidneys which is very dangerous. If the two drugs will be administered together, they must be separated for at least 48 hours (Suwandi & Pahlavi, 2016).

Table 9. Subdomain of causes C1.3 (Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements)

Case Number	Drug	Explanation
13,15	Ceftriaxone iv and calcium carbonate	Concurrent use of calcium-containing preparations with intravenous ceftrixone can cause very dangerous precipitation of ceftriaxone in the lungs and kidneys. Their use must be separated by at least 48 hours
14	Aspilet, clopidogrel, warfarin, heparin	The concomitant use of antiplatelet and anticoagulant drugs can trigger bleeding

In the C1.4 subdomain (Inappropriate duplication of therapeutic group or active ingredient) there were 5 events, the full details of which can be seen in **Table 10**. There were 2 cases where combination of ramipril and captopril were administered to patients with hypertension. Ramipril and captopril are antihypertensives in the same class of therapy, namely ACE inhibitors, so they are not appropriate when used together. The combination of antihypertensives in the same class also occurred in a patient, that was the use of bisoprolol and carvendilol together. Both are antihypertensive drugs belonging to the beta blocker. The combination of the two could increase the antihypertensive effect in the form of beta-adrenergic receptor blockade. According to JNC 8, first-line antihypertensive drugs in hypertensive patients with CKD are ACE inhibitors or ARBs alone or in combination with other therapeutic class drugs (James et al., 2014). If the blood pressure target is not reached, it can be titrated up to the maximum dose or combined with other therapeutic class drugs.

Table 10. Subdomain of causes C1.4 (Inappropriate duplication of therapeutic group or active ingredient)

Case Number	Drug	Explanation
4,12	Ramipril and captopril	Ramipril and captopril are antihypertensives in the same therapy group, namely ACE inhibitors, so they are not appropriate when used together
9	Ketorolac and mefenamic acid	Ketorolac and mefenamic acid are anti-inflammatory and analgesics in the NSAID category. The concomitant use of them was inappropriate and could triggers GI bleeding. The doctor also prescribed ranitidine and omeprazole in this patient possibly to prevent GI bleeding
10	Antalgin injection and ketorolac injection	Ketorolac and antalgin are anti-inflammatory and analgesics in the NSAID category. The concomitant use of them was inappropriate and could triggers GI bleeding.
14	Bisoprolol dan carvedilol	Bisoprolol dan carvedilol are antihypertensive drugs in the same class, namely beta blockers. The combination of the two can increase the antihypertensive effect in the form of beta-adrenergic receptor blockade

In the subdomain C1.5 (No or incomplete drug treatment in spite of existing indication) there were 7 events as shown in **Table 11**. There were 3 cases of patients who experienced nausea and vomiting but had not received antiemetic therapy. Patient with case number 10 received sucralfate and ranitidine, patient with case number 14 only received curcuma, patient with case number 16 received ranitidine. Nausea and vomiting in patients with kidney disease frequently caused by high levels of creatinine in the blood. Dialysis is an effective way to reduce blood creatinine levels. Through dialysis, the various waste products and metabolites are removed from the body (Daugirdas et al., 2015). For patients with multiple comorbidities, a shift is made to conservative management using all proper treatments apart from dialysis. For patients with gastric stasis/gastroparesis, metoclopramide or domperidone may relieve nausea and vomiting (Camilleri et al., 2013).

Table 11. Subdomain of causes C1.5 (No or incomplete drug treatment in spite of existing indication)

Case Number	Complain	Explanation
3	Diarrhea	The patient had not received antidiarrheal therapy
10,14,16	Nausea, vomitting	The patient had not received antiemetic therapy such as domperidone or metoclopramide
15	Pain	The patient had not received analgesic therapy to treat pain during urination
16,19	Cough	The patient had not received cough medicine

In the subdomain C1.6 (Too many different drugs/active ingredients prescribed for indication) there were 4 events as shown in **Table 12**. More than 5 drugs prescribed to treat digestive disorders such as sucralfate, curcuma, ondansetron, ranitidine, omeprazole injection, hyoscine injection, metoclopramide, and lansoprazole. The use of excessive medications can increases the risk of adverse drug effects, including falls and cognitive impairment, potential drug-drug interactions, and drug-disease interactions, in which a medication prescribed to treat one condition worsens another or causes a new one. As the number of drugs taken increases, the risk of ADR increases exponentially. Polypharmacy may also lead to decreased medication compliance, poor quality of life, and unnecessary drug expenses (Dagli & Sharma, 2014). Patient diagnosed with ischemia compensated cordis was given 4 blood thinning drugs those were aspirin, clopidogrel, warfarin, and heparin. Concomitant use of blood-thinning drugs must be careful because they can trigger intracranial hemorrhage (Mohammed et al., 2013).

Table 12. Subdomain of causes C1.6 (Too many different drugs/active ingredients prescribed for indication)

Case Number	Indication	Drug
7	Nausea	Sucralfate, curcuma, ondansetron, ranitidine. Patients who were not nauseous were still given these drugs
10	Nausea, vomiting, abdominal pain	Omeprazole injection, hyoscine injection, sucralfate, ranitidine
14	compensated cordis (extensive anterior ischemia)	Many blood thinners: aspirin, clopidogrel, warfarin, heparin. Concomitant use of blood thinners can trigger a brain hemorrhage or intracerebral hemorrhage
26	Nausea, vomiting	Metoclopramide, ondancetron, lansoprazole, sucralfate

In C2, C3, and C4 domains there were no DRP events, those meant the dosage form, dose selection and duration of therapy in hospitalized chronic kidney disease patients were appropriate. Patients with chronic kidney disease require special attention because of a decrease in kidney function which further causes changes in the pharmacokinetic and pharmacodynamic profile of drugs. Impaired renal function can affect the pharmacokinetics and pharmacodynamics of drugs through several mechanisms. Kidney disease can affect the process of drug distribution through the mechanism of changes in volume of distribution and drug-plasma protein binding. The drug will compete with the urea toxin to bind to the plasma protein albumin (Klammt et al., 2012). Patients with chronic kidney disease are susceptible to changes in both clearance (CL) and volume of distribution (Vd) (Lea-Henry et al., 2018). Prescribing to patients with kidney disease requires knowledge about the drug especially the pharmacokinetics of drugs and how much the patient's physiology changes. Generally, drugs in patients with uremia or kidney impairment have prolonged elimination half-lives and a change in the apparent volume of distribution (Shargel & Yu, 2016). All disturbances in the pharmacokinetics of drugs can result in changes in the therapeutic response and safety of the drug. Changes in therapeutic response can be seen from the Problem Category, sub-category P1 (Effectiveness of Therapy), where a total of 14 cases were found, while drug safety can be seen from the Problem Category, sub-category P2 (Therapeutic Safety), where a total of 1 case was found.

3.3. Risk Factors for DRP

It has been reported that the major risk factors associated with DRP were old age, polypharmacy and comorbidities (Al Hamid et al., 2014). The multipathological conditions that are often experienced by CKD patients require that patients consume large amounts of drugs. Thus, can increase the risk of DRP events. On the other hand, aging also affects kidney function. The kidneys gradually experience a decrease in their physiological functions with increasing age. The liver's ability to metabolize drugs decreases so that drugs tend to stay longer in the geriatric patient's body and will prolong the effects of the drug and increase the risk of ADR (Alomar, 2014). **Table 13** presents the results of the analysis using the Fisher's Exact Test.

In this study, there was no significant associations between age and the incidence of DRP, so age was not a risk factor for DRP (p value > 0.05). Even though there was a difference in the proportion, the difference in the proportion was less than 20%, which means that was not clinically significant. The number of co-morbidities and polypharmacy were also not a risk factor for DRP (p > 0.05). It has been reported that the number of diseases, advanced age, and polypharmacy were associated with a great prevalence of DRP (Garin et al., 2021). Geriatric patients are at high risk of DRP exposure due to several factors, such as multiple disease, receiving many drugs, and cognitive factors (Sell & Schaefer, 2020). The multipathologic condition experienced by CKD patients requires the patient consume large amounts of drugs. Prescription more than 7 drugs in a day was known to increase the risk of DRP (Saldanha et al., 2020). Most DRPs encountered were prevalent among adult patients taking medicines for cardiovascular diseases and diabetes (Al Hamid et al., 2014). The greater number of drugs will increase the risk of drug interactions, synergism, and duplication (Alomar, 2014). The results of

this study were different from previous studies, possibly because the majority of subjects received polypharmacy (n = 52; 96.30%) where polypharmacy is a risk factor for DRP. The lack of variation in the subjects causes inadequate statistical results.

Table 13. Factors associated with DRP among CKD patients

Risk factor	Number of patients		P value	OR
	DRP	Not DRP		
Age (years)				
Geriatrics (≥ 65)	14 (70.0%)	6 (30.0%)	0.771	1.273
Non geriatrics (<65)	22 (64.7%)	12 (35.3%)		
Gender				
Males	12 (75.0%)	4 (25.0%)	0.532	1.75
Females	24 (63.2%)	14 (36.8%)		
Number of Co-morbidities				
< 3	12 (60.0%)	8 (40.0%)	0.552	0.625
≥ 3	24 (70.6%)	10 (29.4%)		
Type of Co-morbidities				
Cardiovascular and DM	30 (68.2%)	14 (31.8%)	0.715	1.429
Non cardiovascular and DM	6 (60.0%)	4 (40.0%)		
The numbers of drug				
<5	2 (100.0%)	0 (0.0%)	0.547	1.529
≥5	34 (65.4%)	18 (34.6%)		
Length of Stay (days)				
< 7	14 (58.3%)	10 (41.7%)	0.264	1.964
≥ 7	22 (73.3%)	8 (26.7%)		

Information: Significant if $p < 0.05$ using Fisher's Exact Test

The proportion of male patients who experienced DRP was 75%, while the women was 63.2%. In this study, gender was not a risk factor for DRP because the p value was > 0.05. The results of this study were in line with previous studies. Gender was not associated with a higher risk of developing DRP (Garin et al., 2021). However, there is controversy on the impact of gender on the risk of developing DRP especially in clinical practice (Alomar, 2014; Garin et al., 2021; Kaufmann et al., 2015).

Length of stay shows the efficiency of treatment and the effectiveness of therapy. Problems involving medication are associated with a higher number of hospitalizations, long-term hospitalizations, admission to emergency services, additional visits to the doctor's office, additional prescriptions and death (Al Hamid et al., 2014). In this study, length of stay was not a risk factor for DRP (p value > 0.05). The proportion of patients with length of stay <7 days who experienced DRP was 73.3%, while patients with length of stay ≥7 days who experienced DRP was 58.3%. Even though there was actually a difference in proportions, based on statistical analysis the difference was not significant. The result of this study was in line with previous study that the patients who were hospitalized for 5–10 days were found to have the highest number of DRPs compared to the patients with length of stay <4 days. However, no association was found between the length of stay and incidence of DRPs with the Chi-square test (Movva et al., 2015).

Pharmacists who have the responsibility of carrying out pharmaceutical service duties can assist clinicians in exploring patient complaints and evaluating whether there are duplications or the presence of drugs that may be used to treat unwanted effects from other drugs. Thus can reduce unnecessary drug prescribing. With the PCNE algorithm, the nature, prevalence, and incidence of DRP can be identified. It is also intended to help health professionals, especially pharmacists, to document DRP information in the pharmaceutical service. Identification of risk factors also plays an important role in preventing DRP. By knowing the factors that triggers the incidence of DRP, it will make it easier for clinicians to provide appropriate therapy to patients and make it easier for pharmacists to provide education to patients. In a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

4. CONCLUSION

Based on the results of this study, of the 54 patients whose progress was followed through medical records, it was found that 36 patients (66.67%) experienced potential DRP while 18 patients (33.33%) did not experience potential DRP. In the Problem category there were 22 incidents while in the Cause category there were 34 incidents. The results of statistical analysis using the Fisher's Exact Test showed that there were no significant associations between the risk factors for gender, age, number of drugs, number of co-morbidities, and length of stay for the incidence of potential DRP in hospitalized chronic kidney disease patients.

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Authors' Contributions and Responsibilities

The authors made substantial contributions to the conception and design of the study. The authors took responsibility for data analysis, interpretation, and discussion of results. The authors read and approved the final manuscript.

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The authors declare no competing interest.

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