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Identification of Potential Drug Interactions of Patients with Chronic Kidney Disease Based on Lexicomp® Application

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ABSTRACT: One of the factors that cause chronic kidney disease is comorbid diseases. Comorbidities can lead to polypharmacy, which can increase the potential for drug interactions. Potential drug interactions, if not addressed, can increase the incidence of morbidity and mortality. The purpose of the study was to identify potential drug interactions with drugs for patients with chronic kidney disease using the Lexicomp® application in terms of risk level, severity, and recommendations for the treatment of drug interactions. The study was conducted at Ansari Saleh Hospital, Banjarmasin, from January to February 2024. The study sample consisted of 58 patients. Data were analyzed using the Lexicomp® application. The results showed that 56.90% of the patients had potential drug interactions, with 175 cases of potential drug interactions in 53 drug combinations. The percentage of potential drug interactions based on risk level was 31.43% (category B), 61.71% (category C), 4% (category D), and 2.86% (category X). The percentage of potential drug interactions according to severity was 33.71% (minor), 62.29% (moderate), and 4% (major). Treatment recommendations for drug interactions with drugs include not need for action, monitoring therapy, and dose adjustment. Potential drug interactions with drugs for patients with chronic kidney disease using the Lexicomp® application in terms of the majority of risk levels in category C, the severity of most moderate categories, and recommendations for handling drug interactions for the majority need to monitor therapy and dose adjustments. Chronic kidney disease patients have the potential to experience moderate drug-drug interactions of the category, with treatment recommendations that require therapeutic monitoring.

Keywords: handling recommendations; risk of drug interactions; severity of drug interactions

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INTRODUCTION

The global prevalence of chronic kidney disease is 9.5%, with a mortality rate of 2.4% (ISN, 2023). Chronic kidney disease is a health challenge in various countries, including Indonesia (Hustrini, 2023). One of the provinces in Indonesia, South Kalimantan, has a significant prevalence of chronic kidney disease. The population of chronic kidney disease patients in South Kalimantan in 2021 showed that the number of old cases was 430 people, with 347 new cases. Among these chronic kidney disease patients, 20 people died in 2021 (South Kalimantan Province, 2021).

Patients with chronic kidney disease need to undergo continuous pharmacological therapy to maintain the physiological viability of the kidneys, increase the patient's life expectancy, and avoid other disease complications. A group of diseases that can occur includes anemia, metabolic acidosis, diabetes mellitus, pulmonary edema, electrolyte fluid disorders, hypertension, hyperkalemia, and bone disorders. Complications of these diseases lead patients to take a large number of drugs, leading to polypharmacy. The large number of drugs that patients must consume increases the risk of adverse drug reactions (ADRs) caused by drug-drug interactions. The impact of drug interactions on the pharmacokinetic and pharmacodynamic properties of a drug that experiences drug interactions, in addition to drug interactions in patients with chronic kidney disease, can cause multiple organ dysfunction and excess extracellular fluid. It is important to identify the risk of drug-drug interactions to mitigate the increased incidence of morbidity and mortality (Hammoud et al., 2022; Hutagaol, 2017; Narsa et al., 2022; Papotti et al., 2021).

Potential drug interactions can be identified by reviewing the literature and using tools. The Lexicomp® application presents a service to identify the risk of drug interactions with other drugs. According to the study by Marcath et al., Lexicomp could identify one more clinically meaningful interaction among 33.3 patients instead of existing medication interaction approaches (Marcath et al., 2018). Lexicomp® scores well compared to other tools in identifying the risk of drug interactions based on sensitivity, specificity, and performance (Shakeel et al., 2020). Identification of drug interactions with drugs in patients with chronic kidney disease in Indonesia has been studied primarily using the www.drugs.com application (Handayani et al., 2023; Probosiwi et al., 2023; Santosa et al., 2024). The Lexicomp® application provides information on potential drug interactions with drugs based on the level of risk, severity, and recommendations for limiting drug interactions (Lexicomp, 2024). The advantages of the Lexicomp® application include references to each search, a simple design, and a layout that makes it easier for readers to read the information displayed and can be accessed without a cellular signal. Based on this, the study aims to identify potential drug interactions with drugs for patients with chronic kidney disease using the Lexicomp® application in the aspects of risk level, severity, and recommendations for limiting drug interactions. It is hoped that it can describe the safety of drugs and the handling of potential drug interactions to minimize the incidence of drug interactions in patients with chronic renal failure. The researcher provides data on identifying potential drug interactions using Medscape®, Drugs.com®, and DrugBank® tools to enhance health worker awareness and encourage consideration of drug interaction tools in their practice.

METHODS

The study was conducted at Ansari Saleh Hospital, Banjarmasin, South Kalimantan, from January to February 2024. Data collection was retrospective, tracking patient electronic medical record data. The study population used data from the electronic medical record of inpatients diagnosed with chronic kidney disease at Ansari Saleh Banjarmasin Hospital from January to December 2023. The sampling technique used in this study was total sampling. The sample is data from the electronic medical record of hospitalized with chronic kidney disease at Ansari Saleh Banjarmasin Hospital for January-December 2023 who meet the research criteria. The following inclusion criteria were patients with a primary diagnosis of kidney disease (ICD N.18), hospitalized and prescribed ≥ 2 drugs. The researchers excluded samples with referral status to other hospitals or death. Research instruments consisted of data collection sheets and the Lexicomp® application.

Data Analysis

Data analysis using the Lexicomp® application obtained data on potential drug interactions. Lexicomp® is a paid access application. Relevant Lexicomp® information can be accessed at the following link: http://webstore.lexi.com/Information/Product-Information/Lexi-Interact-Fields. The risk level in the Lexicomp® application is classified as A, B, C, D, and X. Severity levels in the Lexicomp® application are divided into minor, moderate, and major. Restriction recommendations are described for each drug based on the Lexicomp® application.

RESULT AND DISCUSSION

Based on data from medical records, 67 medical records were found in the period January - December 2023. Nine medical records were excluded from the study because the primary diagnosis was not kidney disease, resulting in a total of 58 samples that were used for analysis.

This study involved a total sample of 58 participants, of whom 33 experienced potential drug interactions. A total of 25 patients did not experience potential drug interactions. The results showed that patients who potentially experienced drug interactions were more, namely 56.90%, compared to patients who did not experience potential drug interactions, namely 43.10%. The results of this study indicate that the percentage of drug interactions possible in patients with chronic kidney disease is lower than in previous studies. The results of the research by Primadhini et al. stated that chronic renal failure patients who had the potential to experience drug interactions were 106 patients, or 95%, while those who did not have the potential to experience drug interactions were six patients, or 5% (Primadhini et al., 2023). The difference in the number of patients analyzed causes differences in the percentage of potential drug interactions. The potential drug interaction with most drugs is Iron-Omeprazole.

Based on the results obtained, 33 patients who experienced potential drug interactions and 175 cases of potential drug interactions, with 53 drug combinations of potential drug interactions, were obtained. This study identified various levels of risk of possible drug interactions according to categories. Most were in category C. Potential drug interactions based on the level of risk in the Lexicomp® application are divided into five levels, namely A, B, C, D, and X, from a total of 175 cases of drug interactions that occurred (Table 1). Category X indicates a very high risk and is generally contraindicated; an example is the combination of Flunarizine with Cetirizine, which can increase sedation in certain

patients (Lule et al., 2024). On the other hand, Category D requires alternative therapy or close monitoring, such as the combination of furosemide with ketorolac, which can increase the risk of kidney damage. Category C shows significant effects that can still be used with monitoring, such as combining Ceftriaxone with Furosemide, which can trigger nephrotoxicity.

Table 1. The Percentage of Potential Interaction Data (PID) Based on Risk Level

PID Based on Risk Level	Frequency	Percentage (%)
A	0	0
B	55	31.43
C	108	61.71
D	7	4
X	5	2.86
Total	175	100

Category B shows evidence of potential drug interactions with little clinical support, such as the combination of Uron with Omeprazole, which may increase the risk of anemia. Combining iron with PPIs (Omeprazole and Lansoprazole) has potential drug interactions in the absorption phase of pharmacokinetics. Iron is used to increase hemoglobin and serum ferritin in patients with anemia, while PPI inhibits gastric acid production by activating the enzyme H^+, K^+, -ATPase from parietal cells (Kapoh et al., 2021; Syari & Sari, 2021). This interaction results in decreased iron absorption due to increased gastrointestinal pH, which can decrease serum concentrations and the effectiveness of iron therapy, potentially damaging patients with anemia (Drugbank, 2024; Lexicomp, 2024). Category A shows no evidence of significant drug interactions and does not require a specific intervention. The current study did not find category A risk (Sari & Putra, 2024b).

Chronic renal failure patients revealed a potential drug interaction at risk level X, according to the findings of Aghili and Kasturirangan. Two combinations of medications found in the study showed possible drug interactions at risk level X. Generally contraindicated in providing the drug combination, the combination of drugs at risk level X should be avoided for the use of the drug, as the gained dangers are greater than the benefits (Aghili & Kasturirangan, 2021). Table 1 presents the percentage of potential interaction data categorized by risk level.

Most potential drug interactions fall into the moderate severity category. The results of the current study align with previous studies (Sari & Putra, 2024b; Susanti et al., 2023). Potential drug interactions based on severity in the Lexicomp® application are divided into 3, namely minor, moderate, and major. Potential drug interactions based on the severity of the drug can cause injury or permanent damage and even threaten the patient's life, requiring contraindications in combination use, such as Clopidogrel with Lansoprazole, which interferes with the antiplatelet effect of Clopidogrel (Lexicomp, 2024). As a thienopyridine prodrug, Clopidogrel requires the metabolism of active metabolites by the enzyme CYP2C19. As a proton pump inhibitor (PPI), lansoprazole inhibits CYP2C19 enzymes by increasing gastric pH. This interaction results in a decrease in the area under the curve of the active metabolite of Clopidogrel by approximately 14%, which can reduce the therapeutic effect and increase the risk of complications such as heart attack after

myocardial infarction or post-percutaneous coronary intervention stent thrombosis (Lexicomp, 2024; Maifitrianti, 2016).

Moderate-level interactions, such as Ceftriaxone with Furosemide, require monitoring, as they can increase the risk of kidney damage (Agustin & Fitrianingsih, 2020; Hakim & Arfania, 2022; Lexicomp, 2024). The findings of this study align with previous research indicating that the combination of Ceftriaxone and Furosemide has the highest potential for moderate-severity drug-drug interactions (Sari & Putra, 2024a). Furosemide is a pharmacological agent classified as a loop diuretic, prescribed primarily for treating hypertension and cardiovascular disease. Individuals with chronic kidney disease generally require diuretics to regulate fluid expansion outside cells and to reduce blood pressure (Sari et al., 2023). Potential interaction in this drug combination involves a mechanism where furosemide can increase the risk of nephrotoxicity, particularly when used with the cephalosporin class of antibiotics (Lexicomp, 2024). Although interactions at a minor level, such as iron with omeprazole, generally do not require intervention, they still need attention to avoid the risk of anemia (Lexicomp, 2024). Table 2 shows the percentage of potential drug interactions, stratified by severity.

Table 2. Percentage of potential drug interactions based on severity

PID Based on Severity	Frequency	Percentage (%)
Minor	59	33.71
Moderate	109	62.29
Major	7	4
Total	175	100

This study found that most patients with chronic kidney disease experienced drug interactions classified as risk category C, indicating moderate severity. Several factors are significantly associated with the incidence of drug-drug interactions, including age, the number of drugs, and the length of hospitalization (Sari et al., 2023; Sari & Putra, 2024). Age is associated with the incidence of drug interactions; An age over 60 has greater potential than an age less than 60. The elderly experience a physiological decline in the body that affects the pharmacokinetic and pharmacodynamic processes of the drugs consumed. The quantity of drugs taken influences the appearance of drug interactions. An increase in the number of drugs used by a patient is correlated with a higher risk of drug interactions. The duration of hospitalization is positively correlated with the potential for drug interactions (Sari et al., 2023).

Recommendations for handling drug interactions with drugs in patients with drug interactions are important to prevent unwanted reactions. Avoid drug combinations with potential interactions and perform clinical management by monitoring specific health parameters such as blood pressure, heart rate, and hypersensitivity reactions. In drug combinations with risk of category C and moderate to significant severity, such as Ceftriaxone-Furosemide, Amlodipine-Furosemide, Candesartan-Potassium Chloride, Diltiazem-Furosemide, Allopurinol-Furosemide, Clonidine-Diltiazem and Clopidogrel-Lansoprazole, therapeutic monitoring and dose adjustment should be considered if necessary (Lexicomp, 2024). Most recommendations to handle potential drug interactions are monitoring therapy and dose adjustments. Table 3 provides recommendations for managing potential drug interactions of moderate and severe severity.

Table 3. Recommendations for handling PDI Based on Risk and Severity Level

No	Combination of PDI (%)	Risk Level	Severity Level	Handling PDI
1	Ceftriaxone-furosemide (6.86%)	C	*Moderate*	Monitor high-dose drug use, particularly in geriatric patients. Assess renal function and calculate the rate of glomerular filtration. Implement a 3-4 hour interval before administering cephalosporin class drugs in combination therapy.
2	Amlodipine-Furosemide (4.57%)	C	*Moderate*	Monitoring of blood pressure and possible adjustment of antihypertensive dosage may be necessary.
3	Candesartan-potassium chloride (4%)	C	*Moderate*	Observe for indicators of hyperkalemia.
4	Diltiazem-Furosemide (3.43%)	C	*Moderate*	Monitoring of blood pressure and possible adjustment of antihypertensive dose may be necessary.
5	Allopurinol-Fluoroquinolones (2.86%)	C	*Moderate*	Observe for indications of hypersensitivity reactions, including fever, rash, and eosinophilia, as well as other adverse effects.
6	Clonidine-Diltiazem (2.86%)	C	*Moderate*	Closely monitor heart rate and blood pressure and inform the patient about the potential onset of new or worsening bradycardia.
7	Codeine-fluconazole (2.86%)	C	*Moderate*	Observe respiratory depression and other adverse effects of the medication and consider decreasing the codeine dosage until a stable therapeutic effect is achieved.
8	Furosemide-Lisinopril (2.86%)	C	*Moderate*	Observe for indications of hypotension.
9	Furosemide-Ramipril (2.86%)	C	*Moderate*	Observe for indications of hypotension.
10	Candesartan-Flunarizine (2.86%)	C	*Moderate*	A decrease in the dose of antihypertensive medication may be necessary.
11	Clopidogrel-Lansoprazole (2.86%)	C	*Major*	Assess clopidogrel pharmacodynamic response
12	Gentamicin-Ketorolac (1.14%)	C	*Moderate*	Observe the enhanced nephrotoxic effects associated with aminoglycosides.
13	Betahistine-Cetirizine (1.14%)	C	*Moderate*	Assess the decline in therapeutic efficacy.
14	Acarbose-Insulin detemir (0.57%)	D	*Moderate*	Evaluate the reduction in insulin dose upon starting therapy with alpha-glucosidase inhibitors and observe the patient for hypoglycemia.
15	Furosemide-Ketorolac (0.57%)	D	*Moderate*	Assess the decreased therapeutic efficacy of loop diuretics.

No	Combination of PDI (%)	Risk Level	Severity Level	Handling PDI
16	Metamizole sodium furosemide (0.57%)	D	*Moderate*	Assess the decreased therapeutic efficacy of loop diuretics.
17	Cetirizine-flunarizine (2.28%)	X	*Moderate*	Nervous system depressants are contraindicated during flunarizine treatment.
18	Metamizole sodium ketorolac (0.57%)	X	*Major*	Ketorolac should not be administered in conjunction with other non-steroidal anti-inflammatory drugs (NSAIDs).

Identification of potential drug interactions can also be analyzed through other tools such as Medscape®, Drugs.com®, com®, and DrugBank®. All three tools are available online and can be accessed free of charge. Medscape®, Drugs.com®, com®, com®, and DrugBank® provide information on the detection of potential drug interactions based on severity (Marcath et al., 2018). The current study presents the results of analyzing potential drug interactions based on these three tools (Table 4 and 5). Therefore, it can provide an overview of potential drug interactions in patients with chronic kidney disease using different tools to detect drug interactions. In addition, it shows the consistency of drug interaction data available from various tools. Therefore, it can serve as a valuable resource for health workers, particularly in Indonesia, to identify drug-drug interactions in patients with chronic kidney disease. Pharmacists should identify drug interactions in pharmaceutical services and know how to handle them.

Table 4. PDI by severity based on Medscape®, Drugs.com®, and DrugBank®

No	Combination of PDI (%)	Medscape®	Drugs.com®	DrugBank®
1	Ceftriaxone-Furosemide (6.857%)	Minor	Moderate	Minor
2	Amlodipine-Furosemide (4.571%)	There are no interactions with other drugs	There are no interactions with other drugs	Minor
3	Candesartan-Potassium Chloride (4%)	-	Major	Moderate
4	Diltiazem-Furosemide (3.429%)	There are no interactions with other drugs	There are no interactions with other drugs	Minor
5	Allopurinol-Fluoroquinolones (2.857%)	There are no interactions with other drugs	Moderate	Moderate
6	Clonidine-Diltiazem (2.857%)	Major	Moderate	Moderate
7	Codeine-Fluconazole (2.857%)	There are no interactions with other drugs	There are no interactions with other drugs	Moderate
8	Furosemide-Lisinopril (2.857%)	Moderate	Moderate	Moderate

No	Combination of PDI (%)	Medscape®	Drugs.com®	DrugBank®
9	Furosemide-Ramipril (2.857%)	Moderate	Moderate	There are no interactions with other drugs.
10	Candesartan-Flunarizine (2.857%)	-	-	Minor
11	Clopidogrel-Lansoprazole (2.857%)	Moderate	Moderate	Moderate
12	Gentamicin-Ketorolac (1.143%)	Minor	Moderate	Moderate
13	Betahistine-Cetirizine (1.143%)	-	-	Moderate
14	Acarbose-Insulin detemir (0.571%)	Moderate	There are no interactions with other drugs.	Moderate
15	Furosemide-Ketorolac (0.571%)	Minor	Moderate	Moderate
16	Metamizole sodium-Furosemide (0.571%)	-	-	Moderate
17	Cetirizine-Flunarizine (2.28%)	-	-	Moderate
18	Metamizole sodium-ketorolac (0.571%)	-	-	Moderate

Identifying drug interactions of chronic kidney disease patients according to severity shows differences in results between tools for detecting potential drug interactions. More research is needed to compare tools for detecting potential drug interactions, especially in the use of drugs for patients with kidney disease. Therefore, reliable tools for detecting drug interactions can be obtained for health workers in health facilities. In addition, regarding recommendations for handling potential drug interactions, the Lexicomp® tools are the most complete for providing information. However, the DrugBank® tool provides minimal information on treatment recommendations. DrugBank® tools can be used to find information on severity and mechanism.

Table 5. Recommendations for the handling of PDI Based on Medscape®, Drugs.com®, and DrugBank®

No	Combination of PDI (%)	Medscape®	Drugs.com®	DrugBank®
1	Ceftriaxone-Furosemide (6.857%)	-	Adjustment of dosage is necessary	-
2	Amlodipine-Furosemide (4.571%)	-	-	-

No	Combination of PDI (%)	Medscape®	Drugs.com®	DrugBank®
3	Candesartan-Potassium Chloride (4%)	Therapy monitoring required	Adjustment of dosage is necessary	-
4	Diltiazem-Furosemide (3.429%)	-	-	-
5	Allopurinol-Fluoroquinolones (2.857%)	-	Require monitoring of therapy or cessation of allopurinol use	-
6	Clonidine-Diltiazem (2.857%)	Refrain from the concurrent use or alternation of drugs where feasible.	Requirement for dose modification or therapeutic oversight	-
7	Codeine-Fluconazole (2.857%)	-	-	-
8	Furosemide-Lisinopril (2.857%)	Therapy monitoring required	Adjustment of dosage is necessary.	-
9	Furosemide-Ramipril (2.857%)	Therapy monitoring required	Adjustment of the dose is necessary.	-
10	Candesartan-Flunarizine (2.857%)	-	-	-
11	Clopidogrel-Lansoprazole (2.857%)	Therapy monitoring required	Consider altering the medication if possible	-
12	Gentamicin-Ketorolac (1.143%)	Therapy monitoring required	Therapy follow-up required	-
13	Betahistine-Cetirizine (1.143%)	-	-	-
14	Acarbose-Insulin detemir (0.571%)	Follow-up of therapy required	-	-
15	Furosemide-Ketorolac (0.571%)	Therapy monitoring required.	Adjustment of the dosage is necessary.	-
16	Metamizole sodium-Furosemide (0.571%)	-	-	-
17	Cetirizine-Flunarizine (2.28%)	-	-	-
18	Metamizole sodium-ketorolac (0.571%)	-	-	-

The study's limitations encompass a restricted sample size and data confined to individuals documented in the electronic medical record. Future research should investigate pharmacist knowledge, attitudes, and actions regarding identifying probable drug-drug interactions.

CONCLUSION

When using the Lexicomp® application, it is important to consider the risk level of most category C drugs, the severity of most moderate interactions, and recommendations for limiting drug interactions; therefore, potential drug interactions with medications for patients with chronic kidney disease often require monitoring and dose adjustments.

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AUTHOR CONTRIBUTION

OMS: Ideas, design, literature search, data analysis, manuscript preparation, and manuscript editing.
PNA: Data collection; data analysis.
AMPP: Design; Definition of intellectual content.

ETHICS APPROVAL

The research design obtained a recommendation of eligibility from the Research Ethics Commission Team of the Faculty of Pharmacy of Muhammadiyah University of Banjarmasin, with No. 031/UMB/KE/I/2024.

CONFLICT OF INTEREST (If any)

None to declare.

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