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Identification of Probable Drug-Drug and Drug-Food Interactions in Hospitalized Patients With Chronic Renal Disease

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Abstract

Chronic renal disease is a substantial health challenge in numerous countries worldwide, including Indonesia. Chronic renal disease patients frequently experience comorbidities and require multiple medications (polypharmacy). In patients receiving polypharmacy, it is necessary to monitor the occurrence of drug interactions. The current study analyzed the most probable of drug-drug interactions based on severity and management. Furthermore, to analyze the most probable drug-food interactions based on severity and management in patients hospitalized with chronic renal disease. From September to October 2023, a cross-sectional study was carried out using retrospective data gathering. The present study population consists of hospitalized patients with chronic renal disease in 2022. The sampling methodology utilizes the saturated sample method. The tools utilized encompassed the Lexicomp® drug interaction checking application. The severity and management categories for probable drug-drug interactions and drug-food interactions are defined within the Lexicomp® application. The study analyzed medical data from 51 patients in total. The results of the current study showed that there were probable drug-drug interactions in 68.62% and drug-food interactions in 47.06% of patients hospitalized with chronic renal disease. Based on severity, the most probable drug-drug interaction and drug-food interaction is in the moderate category. Based on the management, the most probable drug-drug interaction needs to be monitored, and the most probable drug-food interaction needs to be avoided concurrent administration with food. In patients with chronic renal disease, it is crucial to minimize and handle probable drug-drug and drug-food interactions.

Keywords: Adverse Drug; Medication Interaction; Nutrition; Polypharmacy; Recommendation

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Introduction

The global prevalence of chronic renal disease in 2017 was 697.5 million cases[1]. Chronic renal disease has become a prominent factor contributing to death on a global scale[2]. In 2019, the World Health Organization announced that renal disease ranks among the top ten leading causes of mortality globally[3]. Chronic renal disease is a substantial health challenge in numerous countries worldwide, including Indonesia[4,5]. According from 2023 Health Survey Indonesia, the mean prevalence was 0.18%, indicating that 2 out of every 1,000 individuals were diagnosed with chronic renal disease. Chronic renal disease is a significant issue in Indonesia, ranking among the seven chronic diseases that contribute to the highest mortality rates and health expenditures[6].

Patients with chronic renal disease are one patient population that comes in the category of chronic diseases and requires special care during therapy. Chronic renal disease patients frequently experience comorbidities and require multiple medications (as is known in polypharmacy)[7]. In patients receiving polypharmacy, it is necessary to monitor the occurrence of drug interactions[8].

Drug interactions refer to the interactions that occur between a drug and other drugs that hinder the drug from achieving its desired effect. This concept encompasses the interactions between drugs and other drugs, drugs and food, and drugs and other substances[8,9]. Drug interactions can result in either a reduction or enhancement of the drug's effects[10–13]. The concurrent use of many pharmaceuticals was considered to have probable drug-drug interactions when the theoretical interactions between the prescribed medications were assessed, rather than based on their actual occurrence[11]. Furthermore, considering potential drug-food interactions is crucial for enhancing treatment efficacy[14]. Some food habits of patients, such as consuming green tea, coffee, soy, and grapefruit, had the capacity to interact with drugs[15].

Numerous studies have revealed that the probable of drug-drug interactions is common in chronic renal disease, with prevalence varying between 61.9% and 92.5% in different research[16]. Several studies have investigated probable drug interactions in Indonesian patients with chronic renal disease. However, previous research has mainly examined drug interactions considering their level of severity[7,17–22]. Current suggestions to mitigate probable drug interactions remain insufficient. In Indonesia, the www.drugs.com application is the most widely used device for studying probable drug interactions[7,18,19,21]. Furthermore, the studies conducted in Indonesia focus primarily on the examination of the possibility of drug-drug interactions, while the analysis of drug-food interactions in patients with chronic renal disease remains restricted[7,17–22].

Drug interactions can result in adverse side effects. Two-thirds of the patients had a suspected drug-drug interaction-related adverse reaction[17]. To reduce the occurrence of adverse effects caused by drug interactions, it is important to have more knowledge regarding drug interactions. In addition, suggestions for mitigating probable drug interactions could be improving the safety of clinical drug therapies. Drug interactions contribute significantly to hospital admissions, resulting in a significant financial burden[16].

The current study analyzed the most probable of drug-drug interactions based on severity and management. Furthermore, to analyzed the most probable drug-food interactions based on severity and management in patients hospitalized with chronic renal disease.

Methods

From September to October 2023, a cross-sectional study was carried out using retrospective data gathering. The study took place in a public hospital, Ansari Saleh. The hospital provide facility for patients with chronic renal disease in Banjarmasin, South Kalimantan. Electronic medical records were used to collect information such as age, gender, and therapy. The research has been authorized by the Lambung Mangkurat University Medical Faculty, The Committee on Medical Research Ethics on April 2023 (061/KEPK-FK ULM/EC/IV/2023).

The present study population consists of hospitalized patients with chronic renal disease in 2022. The hospitalized patients with chronic renal disease in 2022 that attains the study criteria as the research sample. The sampling methodology utilizes the saturated sample method. The current study included chronic renal disease patients who were getting more than one drug. The inclusion criteria required comprehensive medical records, including age, gender, and detailed information on the therapy, such as the drug name, rules of use, and dosage type. Patients under the age of 18 with chronic renal disease were not included in the study.

The tools utilized encompassed a data collection sheet and the Lexicomp® drug interaction checking application. Lexicomp® demonstrates extremely sensitive and consistently delivers excellent performance. Furthermore, it offers information on the seriousness of drug interactions and provides recommendations on how to prevent and handle drug interactions if they occur[16,23]. The Lexicomp® was utilized to analyze probable drug-drug and drug-food interactions. The software, encompassing all text and other content, is owned by Lexicomp® and is guaranteed by copyright (Copyright 2024 UpToDate Inc. All Rights Reserved) and intellectual property statutes[24].

The severity and management categories in probable drug-drug interactions and drug-food interactions are defined within the Lexicomp® application. The category of severity in probable drug interaction include 16:

1. Minor: relating to minor consequences that can be readily surmounted.
2. Moderate: indicating intermediate consequences that can result in harm to organs;
3. Major: signifying severe consequences that can result in death

Lexicomp® was used to gather management categories regarding probable drug-drug interactions and drug-food interactions. The management categories for handling probable of drug-drug interactions encompass: there is no need to take any action; medication monitoring; modification of the medication is recommended; and avoiding drug combinations is recommended. The management categories for handling probable of drug-food interactions encompass: there is no need to take any action; administer without regard to food; medication monitoring; take with food; administer 30 minutes before food; administer 30 minutes after food; and avoid concurrent administration with food[24].

Results and Discussion

The study analyzed medical data from 51 patients in total. The findings indicated that the age of patient from 18 to 79 years old. Patient characteristics showed that 51% were female and 49% were male, consistent with earlier investigations[25]. According to gender, female patients encountered a higher incidence of potential drug-drug interactions (62%) and food-drug interactions (52%). Previous studies explain that there is no correlation between gender and the occurrence of

potential drug interactions. Nonetheless, the practice of polypharmacy carries the risk of potential drug interactions[26]. Polypharmacy was observed during hospitalization and most of the patients received more than five drugs (Table 1).

The Probable of Drug-Drug Interaction

The results of the current study showed that there were probable drug-drug interactions in 68.62% (35 patients) of patients hospitalized with chronic renal disease. Total 60 various types of probable drug-drug interactions with 190 cases. The present study demonstrates that patients with chronic renal disease experience the highest number of probable drug-drug interactions ranging from 1 to 6 (Table 1). The most probable drug-drug interactions category was moderately severe and required medication monitoring (Table 1). Previous research has demonstrated comparable findings, indicating that most probable drug-drug interactions in patients with chronic renal disease fall into the moderate severity category[7,16,18,19,21,27].

The results of the analysis of this study showed that patients with chronic renal disease hospitalized with the most probable drug-drug interactions Domperidone-Ciprofloxacin at the minor category, Ceftriaxone-Furosemide drug interactions at the moderate category and Codeine-Cetirizine drug interactions at the major category (Table 2). The research conducted by Sari and Maulana in 2024 revealed that the most occurrence of drug interaction at major category was between Codeine and Cetirizine[16]. However, previous research revealed disparities in the probability of drug-drug interactions in the minor and moderate categories because the research examined drug-drug interactions in patients with outpatient chronic renal disease[16]. Prescription patterns vary between inpatients and outpatients, resulting in changes in the probable drug-drug interactions.

Codeine-Cetirizine was the most occurrence of drug at the highest level of severity. Cetirizine may enhance the sedative impact of codeine, possibly due to its depressive effect on the central nervous system. According to the Food and Drug Administration (FDA) of the United States, the combination of opioids with medications that suppress the central nervous system (CNS) can result in severe side effects, such as slowed or labored breathing and even death. If feasible, it is advised not to combine codeine and cetirizine due to probable drug interactions. These medications should only be used together if other treatment alternatives are insufficient[24].

The most frequent occurrence of Ceftriaxone-Furosemide is often observed at a moderate severity level. Both medications exhibit drug interaction processes. Specifically, furosemide can potentially enhance the nephrotoxic effect of cephalosporins, such as ceftriaxone. The probable interaction is due to the combined nephrotoxic effects. It is recommended to closely monitor renal function when administering furosemide and ceftriaxone[24].

The Probable of Drug-Food Interaction

The probable drug-food interactions in patients with chronic renal disease were 47.06% (24 patients). Total 21 various types of probable drug-food interactions with 116 cases. Each patient has the probable drug-food interaction from 1 to 2. There exists a notable correlation between the prescribed drug number and the number of drug-food interactions that pose a risk to the patient[28,29]. Most of the patients received more than five drugs in this current study.

The current study analyzed probable drug-food interactions based on severity. Most probable drug-food interactions in patients with chronic renal disease are of moderate severity. However, there are probable

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drug-food interactions at severe severity, including Domperidone/grapefruit juice and Clopidogrel/grapefruit juice (Table 3). Based on research by Koni et al. (2022) explained that most drugs interact with grapefruit[30].

Based on the management of potential drug-food interactions, the most common is need to avoid using drugs with food. The drugs that have the most probable drug-food interaction in patients with chronic renal disease include lansoprazole, atorvastatin and diltiazem (Table 4). Previous research showed varying results, indicating that the medications with the highest degree of interaction with food include omeprazole and aspirin[31].

The food items or nutrients that have the potential to interact with drugs in the current research are grapefruit juice, caffeine, fiber, foods rich in pectin, and soybean (Table 4). The study conducted by Kose et al. (2021) demonstrated comparable findings, indicating that grapefruit and high-fiber diets frequently exhibit potential medication interactions[31]. The current study explored nutritionist records relating to the dietary regimens of individuals with chronic renal disease and revealed that the majority patients followed dietary plan such as low sodium, low sugar, or low protein. It is necessary to conduct screenings to identify foods that may have interactions with drugs being taken by patients. Pharmacists can collaborate with nutritionists at health facilities to accomplish this task.

The medicines that have the highest probability of interacting with food are lansoprazole and atorvastatin (Table 4). First, the analysis of the current study indicates that lansoprazole has the potential to interact with food. Extended therapy (lasting ≥2 years) can result in impaired absorption of dietary vitamin B12 and the consequent shortage of vitamin B12[24]. Lansoprazole belongs to the class of drugs known as proton pump inhibitors. Swarnakari et al. (2022) research indicates that prolonged and excessive usage of proton pump inhibitors can lead to a deficit in vitamin B12 32. Unlike the research conducted by Alifiar (2016), this study indicates that meals can decrease the bioavailability of lansoprazole by 70%, thus diminishing its effectiveness[33]. Lansoprazole absorption may be hindered by the presence of meals[33]. A study conducted by Abdollahi et al. (2018) reveals that omeprazole, a type of proton pump inhibitor, can potentially interact with food in hospitalized patients. Omeprazole inhibits vitamin B12 absorption. Administration avoid consuming meals high in vitamin B12 before or during the administration of the medication[27].

Second, the analysis of the current study indicates that atorvastatin has the potential to interact with grapefruit juice. Consuming grapefruit juice can elevate atorvastatin levels in the bloodstream. The primary cause of this interaction is attributed mainly to certain components found in grapefruit juice that have the ability to hinder the activity of CYP3A4 24. The findings of this investigation are comparable to the outcomes of Koni et al. (2022) 29. The interaction between atorvastatin and grapefruit juice is classified as moderate. Therefore, it is necessary to refrain from consuming big amounts of grapefruit juice[24].

Considering potential drug-food interactions is crucial for enhancing treatment efficacy. Pharmacists and clinical personnel should prioritize monitoring commonly prescribed medications that have the potential to interact with food[14]. Several suggestions exist for managing potential drug-food interactions (Table 4). Furthermore, to mitigate drug-related issues, it is crucial to provide the patient with education regarding the interactions between drugs and food[34].

These findings emphasize the crucial role of pharmacist and healthcare workers in avoiding and managing drug-drug interactions and drug-food interactions. Researchers should consider examining potential drug-drug interactions and potential drug-food interactions in various disorders utilizing alternative screening tools for interactions. Conducting research on factors associated to potential drug-drug interactions and potential drug-food interactions is crucial as well.

Conclusion

The most probable drug-drug interaction based on severity and management was Ceftriaxone-Furosemide (moderate), which required medication monitoring in patients hospitalized with chronic renal disease. Furthermore, the most probable drug-food interaction based was lansoprazole-food contains vitamin B12 and the need to avoid consuming meals high in vitamin B12.

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Conflict of Interest

None declared.

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Table 1. Socio-demographics of patient with hypertension

The Probable of Drug-Drug Interaction		Frequency (%)
Prescribed drug number	2-4	6 (11.76%)
	≥5	45 (88.24%)
Number of drug-drug interaction	1-6	30 (85.71%)
	≥7	5 (14.29%)
Severity	Minor	10 (16.67%)
	Moderate	42 (70%)
	Major	8 (13.33%)
Management	There is no need to take any action	11 (18.33%)
	Medication monitoring	37 (61.67%)
	Modification of the medication is recommended	11 (18.33%)
	Avoiding drug combinations is recommended	1 (1.67%)

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Table 2. The Probable of Drug-Drug Interaction Based on Severity and Management

The Probable of Drug-Drug Interaction	Frequency	Management
Minor (top 5)		
Domperidone-Ciprofloxacin	7	There is no need to take any action
Ferrous sulphate-Calcium Polystyrene Sulphonate	3	There is no need to take any action
Ferrous sulphate -Lansoprazole	3	There is no need to take any action
Ondansetron-Metronidazole	3	There is no need to take any action
Paracetamol-Ondansetron	2	There is no need to take any action
Moderate (top 5)		
Ceftriaxone-Furosemide	13	Medication monitoring
Candesartan-Furosemide	12	Medication monitoring
Dutasteride-Sucralfate	10	Modification of the medication is recommended
Domperidone- Chlorpheniramine maleate	7	Medication monitoring
Sodium Chloride- Chlorpheniramine maleate	7	Avoiding drug combinations is recommended
Major (top 5)		
Codeine-Cetirizine	12	Modification of the medication is recommended
Ciprofloxacin- Sucralfate	10	Modification of the medication is recommended
Codeine-Braxidin® (clidinium-chlordi-azepoxide)	3	Modification of the medication is recommended
Phenytoin-Dexamethasone	2	Modification of the medication is recommended
Ceftriaxone-Calcium Gluconate	1	Modification of the medication is recommended

Table 3. Assessment of Probable Drug-Food Interaction Based on Severity

Severity	The Probable of Drug-Food Interaction	Effect
Minor	Ciprofloxacin/caffeine	Ciprofloxacin may increase the serum concentration of Caffeine and Caffeine Containing Products[24]
	Diltiazem/grapefruit juice	Grapefruit Juice can enhance the levels of Diltiazem in the bloodstream[24]
	Digoxin/fiber	Pectin may decrease the serum concentration of Cardiac Glycosides[24]
	Levothyroxine/grapefruit juice	Grapefruit Juice can reduce the levels of Levothyroxine in the bloodstream[24]
	Atorvastatin/grapefruit juice	Consuming grapefruit juice can elevate atorvastatin levels in the bloodstream[24]
	Simvastatin/grapefruit juice	Grapefruit Juice may increase the serum concentration of Simvastatin [24]
Moderate	Levothyroxine/caffeine	Levothyroxine may enhance the adverse/ toxic effect of sympathomimetics (caffeine). Specifically, the risk of coronary insufficiency may be increased in patients with coronary artery disease[24]
	Levothyroxine/soybean product	Soybean may diminish the therapeutic effect of Thyroid Products[24]
	Digoxin/food high in pectin	Pectin may decrease the serum concentration of Cardiac Glycosides[24]
Major	Domperidone/grapefruit juice	Grapefruit juice may increase the serum concentration of Domperidone[24]
	Clopidogrel/grapefruit juice	Grapefruit Juice may decrease serum concentrations of the active metabolite of Clopidogrel[24]

Table 4. The Probable of Drug-Food Interaction Based on Management

Management	Drug Class	The Probable of Drug-Food Interaction		Frequency
		Drug	Food / Nutrient	
There is no need to take any action	Antihypertensive	Diltiazem	Grapefruit juice	9
Total				**9**
Administer without regard to food	5 Alpha-Reductase Inhibitor	Dutasteride	Food general but not interact significantly	5
	Antibiotic	Cefixime	Food general	5
	Antihypertensive	Spironolactone	Food general	3
	Analgesic Combination	Paracetamol-Tramadol	Food general	2
		Levofloxacin	Food general	2
	Decongestant	Pseudoephedrine	Food general	2
	Gastrointestinal drug	Ondansetron	Food general	5
	Histamine H1 Antagonist	Cetirizine	Food general	3
Total				**27**
Medication monitoring	Antibiotic	Ciprofloxacin	Caffeine	8
	Gastrointestinal drug	Lansoprazole	Vitamin B12	20
Total				**28**
Take with food	Antiplatelet	Aspirin	Food general	3
	Antibiotic	Metronidazole	Food general	4
	Calcium salts	Calcium carbonate	Food general	4
Total				**11**
Administer 30 minutes before food	Thyroid Product	Levothyroxine Sodium	Soybean, grapefruit juice, caffeine	5
Total				**5**
Administer 30 minutes after food	Alpha 1 Blocker	Tamsulosin	Food general	5
Total				**5**
Avoid concurrent administration with food	Antiplatelet	Clopidogrel	Grapefruit juice	8
	Antiarrhythmic agent	Digoxin	Fiber or food high in pectin	2
	Gastrointestinal drug	Domperidone	Grapefruit juice	6
	HMG-CoA Reductase Inhibitor	Atorvastatin	Grapefruit juice	11
		Simvastatin	Grapefruit juice	4
Total				**31**