Risk of Adverse Drug-Drug Interactions in Heart Failure Patients with Co-Morbidity Chronic Kidney Disease Prescribed Polypharmacy

by Pandji Winata Nurikhwan

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Abstract. Heart failure (HF) is a complex clinical syndrome due to the impairment of myocardial function, valvular or pericardial diseases, or anything interfering blood flow leading to fluid retention. A comorbidity that can accompany HF patients is chronic kidney disease (CKD). This condition requires consumption of several drugs simultaneously (polypharmacy). This study aimed to determine the risk of adverse drug-drug interactions in HF patients with co-morbid CKD prescribed polypharmacy. This is an analytic observational study with a cross-sectional approach in the Cardiac Outpatient Clinic of Ulin Public Hospital, Banjarmasin using medical records from 2020-2021. The interactions were determined using the UpToDate® under the Lexicomp tool. Prevalence Odds Ratio (POR) and 95% Confidence Intervals (95%CI) were determined using Logistic Regression analysis. Of 27 patients, 17 were males (62.96%). Most of the interactions (92.92%) were under category C and the moderate category (82 interactions, 82.83%). For HF patients with CKD, polypharmacy increased the risk of adverse drug-drug interactions by 2.75 times compared to those who were not prescribed polypharmacy, but it was not statistically significant (crude POR 2.75, 95% CI; 0.248-30.512). In conclusion, there is no significant relationship between polypharmacy and the risk of adverse drug-drug interactions in HF patients with CKD.
Keywords: polypharmacy, drug-drug interactions, heart failure, chronic kidney disease, Ulin Public Hospital, Banjarmasin.

1 Introduction

Heart failure (HF) is a complex clinical syndrome as a result of disturbances in myocardial function (systolic and diastolic functions), valve or pericardial diseases, or anything that can interfere blood flow with fluid retention as a result. It is usually manifested as pulmonary congestion, peripheral edema, dyspnoea, and fatigue [1]. As many as 64.3 million people in worldwide is estimated to suffer from HF. In developed countries, the prevalence of HF is generally estimated to be 1% to 2% of the adult population [2]. According to the Sample Registration System (SRS) survey conducted in 2019, heart diseases are the second leading cause of death in Indonesia following stroke [3]. In 2013 the Riset Kesehatan Dasar (Riskesda; Basic Health Research) demonstrated that according to doctors' diagnosis the prevalence of HF in Indonesia is estimated to affect around 229,696-530,068 people (0.13%-0.30%) [4].

HF patients usually have co-morbidities such as chronic kidney disease (CKD). Approximately 70% of the causes of death in patients with CKD are caused by heart diseases. According to Riskesdas in 2018, the prevalence of CKD affected as many as 713,783 people (0.38%) in Indonesia and 11,068 people (0.32%) in the Province of South Kalimantan. The incidence of HF with CKD ranges from 17% to 21% [5].

Drug interactions can be exploited to gain therapeutic advantages and a combination therapy might lead to the optimal treatment. However, these interactions can cause adverse side effects for the patients. Drug interactions commonly occur because of rarely documented and missed observed. Thus the adverse side effects were considered as an increased of disease severity. Around 5-15% of patients are estimated to experience adverse drug interactions that are clinically significant. Risk factors for drug interactions are identified including age, genetic polymorphism, co-morbidities, dosage, number of physicians prescribing drugs, self-medication, and polypharmacy [6].

Polypharmacy can increase the risk of drug-drug interactions. More than 80% of elderly patients take at

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least 1 prescribed drug and more than half of them take 5 or more drugs concomitantly. The higher the number of patients who consume a lot complex drug or regimen, the higher the risk and the more vulnerable to drug-drug interactions [6].

Patients with HF generally have decreased function organs and have co-morbidities that require to take several drugs simultaneously. About 52% of drug categories involved in drug-drug interactions are cardiovascular drugs that lead to an adverse effect on the body ranging from mild to severe levels, such as syncope and the death [6].

There are a limited number of study assessing the risk of adverse drug interaction for patients with cardiovascular diseases patients with co-morbidities. Furthermore, we have not found any studies on the risk of adverse drug-drug interactions specifically for HF patients with comorbidity. Thus, this study aims to assess the risk of adverse drug-drug interaction for HF patients with CKD co-morbid prescribed polypharmacy in Indonesia, especially in South Kalimantan Province. We then performed this study by using secondary data (medical records) at outpatients Cardiology Clinic at Ulin Public Hospital, Banjarmasin, Indonesia.

2 Methods

2.1 Research Design and Data Source (Setting)

This was an observational study with cross sectional approach among HF patients with CKD comorbidity at the Cardiology Outpatient Clinic at Ulin Public Hospital Banjarmasin, Indonesia. Ulin hospital is a referral hospital in the province of South Kalimantan and provinces around. The patients' demographic (sex and age) and medical data (co-morbidities and drug used) were retrospectively collected from their medical records over the period 2020-2021. Only adult patients (>18 years old) were included in this study. Our study protocol had been registered to and approved by the Ethic Committee for Health Research, Medical Faculty, Universitas Lambung Mangkurat, Banjarmasin (No. 568/KEPK-FK ULM/EC/XII/2022).

2.2 Research Variables

Variables of interest in this study were number of drugs prescribed by the cardiologists and the risk of drug-drug interactions. For this study, polypharmacy was determined when a patient was prescribed 5 drugs or more simultaneously [7], otherwise non-polypharmacy.

According to UpToDate® website under Lexicomp tool, drug-drug interaction was classified into Category A (no known interaction); Category B (no further actions needed); Category C (benefits over risks, but therapy should be closely monitored to prevent harm); Category D (considering to modify therapy and accurate actions should be taken to reduce toxicity); and Category X (contraindicated) [8]. In this study, we lumped category A, B, and C as "less risk of adverse drug-drug interaction" and category D and X as "high risk of adverse drug-drug interaction". Meanwhile, the

severity of interaction was categorized into **minor** (mild effects, well overcome), **moderate** (moderate effect, may lead to organ damage) and **major** (fatal effect, may lead to the death).

2.3 Statistical Analyses

Demographic and medical data, category of drug-drug interactions, and severity level of the interaction were presented in proportion (%), but number of drugs prescribed was presented in an average number.

In order to estimate the risk of adverse drug-drug interaction among HF patients with CKD prescribed polypharmacy compared to non-polypharmacy, we applied Logistic Regression test. We then presented the data as crude Prevalence Odds Ratios (PORs), 95% Confidence Intervals (95%CIs), and p-value. All the analyses were conducted using a statistical software IBM SPSS version 26. p-value of less than 0.05 was considered statistically significant.

3 Results and Discussion

3.1 Results

We identified 27 HF patients with co-morbid CKD over the period 2020-2021 at the Cardiology Outpatient Clinic, at Ulin Public Hospital, Banjarmasin, Indonesia. Most of the patients were males (17 patients, 63.0%), elderly age (17 patients, 63.0%), and without a history of hypertension (23 patients, 85.2%). In average, 3.7 drugs was prescribed per patient (**Table 1**).

Table 1. Baseline characteristics of heart failure patients with chronic kidney failure

Characteristics	n=27
Sex, n (%)	
• Males	17 (63.0)
• Females	10 (37.0)
Age, n (%)	
• 18-60 years	10 (37.0)
• >60 years	17 (63.0)
Hypertension, n (%)	
• Yes	4 (14.8)
• No	23 (85.2)
Number of drugs prescribed per patient, mean	3.7

For 27 patients, there were 100 drug-drug interactions. Most of the interactions were under category C (92 interactions, 92%), followed by category D and B, i.e., 4 interactions (4%) and 3 interactions (3%), respectively. In contrast, 1 prescription had no known interaction (0%) and no prescription was under category X (0 prescription, 0%) (**Table 2**).

All interactions under category B were classified as moderate. Under category C, interaction between isosorbite dinitrate and candesartan were frequently reported with moderate level of its severity, while under category D, the interaction between warfarin and acetylsalicylic acid was mostly counted with major level of severity (**Appendix**).

According to its severity level, most of drug-drug interactions were moderate (82 interactions, 82.2%), followed by major (11 interactions, 11.1%) and finally minor (6 interactions, 6.1%). Meanwhile, 1 prescription did not have a known interaction (**Table 3**).

As being demonstrated in **Table 4**, HF patients with CKD prescribed polypharmacy were associated with a higher risk of the adverse drug-drug interaction compared to those without polypharmacy by 2.75 times (crude POR 2.750, 95%CI; 0.248-30.512). However, the risk was not statistically significant (p=0.410).

Table 2. Categories of drug-drug interaction

Category	n (%)
● A (no interaction known)	1 (0.0)
● B (no action needed)	3 (3.0)
● C (benefits are outweigh of the risks, but the therapy should be under strict supervision to avoid a potency of harm)	92 (92.0)
● D (considered to modify the therapy and to take the proper action in order to reduce its toxicity)	4 (4.0)
● X (contraindicated, should be avoided)	0 (0.0)
Total	100 (100.0)

Table 3. Level of severity

Category	n (%)
Minor (mild effects, well overcome)	6 (6.1)
Moderate (moderate effect, may lead to organ damage)	82 (82.8)
Major (fatal effect, may lead to the death)	11 (11.1)
Total	99 (100.0)

Table 4. Prevalence odds ratio for the risk of adverse drug-drug interactions for heart failure patients with chronic kidney failure complication prescribed polypharmacy compared to those without polypharmacy

Poly-pharmacy, n (%)	Adverse drug-drug interactions, n (%)		p-value	Crude POR (95%CI)
	High Risk	Less Risk		
Yes	3 (75.0)	79 (82.3)	0.410	2.750 (0.248-30.512)
No	1 (25.0)	17 (17.7)		1

CI= confidence intervals; POR = prevalence odds ratio

3.2 Discussion

In our study most commonly drugs found in drug-drug interaction were furosemide (38 interactions, 38%), isosorbide dinitrate (33 interactions, 33%), and candesartan (22 interaction, 22%). Interaction under category C with the most major severity were ramipril – spironolactone and candesartan – spironolactone. The use of Angiotensin Converting Enzymes-I (ACE-I) or Alpha Receptor Blockers (ARB) drugs in combination with spironolactone may increase serum potassium by ±0.19 mEq/L compared to use single drug of ACE-I or ARB [8]. A combination of isosorbide dinitrate and candesartan has a moderate level of severity. Candesartan is able to increase antihypertension effect of isosorbite dinitrate. This combination may cause organ damage.

Drug-drug interactions under category D consisted of Warfarin – Acetylsalicylic acid, Captopril – Valsartan, and Ramipril – Candesartan. Interaction of Warfarin – Acetylsalicylic Acid has the greatest potential for adverse drug-drug interactions in this study due to its severity level major and fall under category D. Low-dose acetylsalicylate acid and warfarin can be used together in a certain case with close monitoring for increasing signs and symptoms of bleeding. Higher doses of acetylsalicylic acid and other salicylates generally should be avoided. A combination of warfarin and acetylcalycilic acids might be fatal, such as the death. The later drug might increase anti coagulation effect of warfarin.

Captopril–Valsartan and Ramipril–Candesartan interactions include interactions between ACE-I and ARBs drug classes. If the combination should be used, the patients should be monitored very closely for a greater therapeutic response expected for the combination, including monitoring of blood pressure, kidney function, and potassium concentration. For increasing the likelihood of successful initiation. An ACE-I or ARB should be initiated at a lower dose and titrate more slowly if accompanied by chronic kidney failure [9].

A study conducted by Akbar et al concluded that a ratio of potential adverse drug-drug interactions that are not detrimental and detrimental, i.e., 3.6:1 among patient population with general cardiovascular diseases. While the ratio in this research was 2.75:1. It indicates that HF patients with CKD co-morbidity are less likely to experience the adverse interactions than for those general cardiovascular patients [8]. With these risks, caution is needed and accuracy in prescribing drugs, especially in polypharmacy, as well monitoring the patient after being given the drug [6, 10].

The risks of potential adverse drug-drug interactions increase if the number of drugs consumed increase. About 13% of patients taking 2 drugs experienced adverse drug-drug interactions. For those who take 4 drug and >7 drugs the interactions increase to 38% and 82%, respectively [11]. A study by Akbar et al, demonstrated that there was a significant relationship between the number of drugs by >12 and its interactions, even though there was no significant relationship between the number of drugs by 6-12 and drug interactions [9]. Meanwhile, a research conducted by Fatin et al among patients with pneumonia showed that the number of drugs by >6 was associated with 10.1 times of adverse drug-drug interactions [12]. It indicates that a patient's diagnosis and the type of drug also affect adverse drug-drug interactions.

3.3 Potential Clinical Implication

Our findings provide a scientific evidence on the potency of higher risk of adverse drug-drug interaction

for HF patients with CKD prescribed polypharmacy. Clinicians should then carefully take into consideration the use of polypharmacy for those patients, especially for elderly. Ultimately, the risks of harm or even fatal incidents affecting patients are being able to avoid.

A review of patient prescriptions for potential adverse drug-drug interactions should be performed by using a proper software and/or clinical pharmacists experienced in drug interactions. In addition, it is necessary to monitor patients' responses and related side effects to find adverse interaction reactions [13].

3.4 Strengths and Limitations

We need to mention several strengths in this study. First, to the best of our knowledge this is the first study assessing the risk of adverse drug-drug interaction for HF patients with CKD prescribed polypharmacy in Indonesia, especially Banjarmasin. Second, Lexicomp® is the most commonly used tool to assess drug interaction. It also classifies drug-drug interaction based on its severity. Finally, this tool has high sensitivity and specificity.

However, this study is a subject to several weakness. First, instead of the actual adverse events, adverse drug-drug interactions were defined theoretically by using a computer tool as a proxy. It might lead to a misclassification bias of the outcome. Second, our concern is the issue of small sample size. Lack of sample size may lead to inability to detect small differences or association between our variables of interest. Third, we did not adjust our model to several potential confounder contributing to the risk of adverse drug-drug interaction such as sex, age, co-morbidities, genetic polymorphism, drug dosage, number of physicians prescribed, and self medication. Finally, the tool Lexicomp® does not provide information on interactions for more than 2 drugs. This tool has low reliability.

4 Conclusion

Our study indicated that HF patients with CKD co-morbid prescribed polypharmacy were associated with a high risk of adverse drug-drug interaction by 2.75 times compared to those without polypharmacy. However, this association was not statistically significant (crude POR 2.75, 95%CI 0.248-30.512).

5 Acknowledgment

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Appendix

Category	Drug-drug Interaction	Quantity (n)	Level of severity	Effect(s)
A	Warfarin - Atorvastatin	1	-	-
B	Acetylcalicylic acid - CaCO₃	1	Minor	$CaCO_3$ decreases serum calicylic consentration
	Levofloxacin - Candesartan	1	Moderate	Candesartan increases aritmogenic effect of levofloxacin. Levofloxacin increases nephrotoxic effect of candesartan
	Warfarin - Spironolacton	1	Moderate	Spironolacton decreases anticoagulant effect of warfarin
C	Isosorbide dinitrate - Candesartan	9	Moderate	Candesartan increases hypotension effect of isosorbide dinitrate
	Candesartan - Furosemide	8	Moderate	Furosemide increases hypotension and nephrotoxic effects of candesartan.
	Bisoprolol - Furosemide	7	Moderate	Furosemide increased hypotension effect of bisoprolol
	Isosorbide dinitrate - Bisoprolol	7	Moderate	Bisoprolol increases hypotensive effect of isosorbide dinitrate
	Isosorbide dinitrate - Furosemide	7	Moderate	Furosemide increases hypotensive effect of isosorbide dinitrate
	Spironolcaton - Furosemide	6	Moderate	Furosemide increases hypotensive effect of spironolacton
	Furosemide - Acetylcalicylic acid	5	Moderate	Acetylcalicylic acid reduces diuretic effect of furosemide. Furosemide increases serum calicylic consentration
	Isosorbide dinitrate - Amlodipine	4	Moderate	Amlodipine increases hypotensive effect of isosorbide dinitrate
	Ramipril - Furosemide	4	Moderate	Furosemide increases hypotensive and nephrotoxic effects of ramipril.
	Spironolacton - Acetylcalicylic acid	4	Minor	Acetylcalicylic acid reduces therapeutic effects of spironolacton
	Ramipril - Spironolacton	4	Major	Spironolacton increases hyperkalemia effect of ramipril
	Isosorbide dinitrate - Ramipril	3	Moderate	Ramipril increases hypotensive effect of isosorbide dinitrate
	Isosorbide dinitrate - Spironolacton	3	Moderate	Spironolacton increases hypotensive effect of isosorbide dinitrate
	Spironolacton - Candesartan	3	Major	Candesartan increases hyperkalemia effect of spironolacton
	Amlodipine - CaCO₃	2	Moderate	$CaCO_3$ reduces therapeutic effects of amlodipine
	Clopidogrel - Amlodipine	2	Moderate	Amlodipine reduces therapeutic effects of clopidogrel
	Spironolacton - Atorvastatin	2	Moderate	Atorvastatin increases detrimental/toxic effects of spironolacton, specifically theoretically it increases reduced effect of endogen steroid activity
	Bisoprolol - Digoxin	2	Moderate	Bisoprolol increases bradycardia effect of another drug and vice versa
	Digoxin - Spironolacton	2	Moderate	Spironolacton increases serum digoxin concentration and impair a test for determination of digoxin concentration; false increased or decreased concentration of digoxin
	Clopidogrel - Lansoprazole	1	Major	Lansoprazole reduces serum concentration of active metabolite of clopidogrel
	Allopurinol - Furosemide	1	Moderate	Furisemide increases detrimental/toxic effects and increases serum concentration of allopurinol, specifically furosemide increases oxypurinol concentration, active metabolites of allopurinol
	Allopurinol - Ramipril	1	Major	Ramipril increases potency of allergic reaction or hypersensitivity towards allopurinol
	Allopurinol - Captopril	1	Major	Captopril increases potency of allergic reaction or hypersensitivity towards allopurinol
	Captopril - CaCO₃	1	Moderate	$CaCO_3$ decreases serum captopril concentration
	Nifedipine - CaCO₃	1	Moderate	$CaCO_3$ decreases therapeutic effect of nifedipine
	Vitamin D - CaCO₃	1	Moderate	$CaCO_3$ increases detrimental.toxic effects of vitamin D analog
D	Warfarin -	2	Major	Calicylic increases anticoagulant effect of warfarin

	Acetylcalicylic acid			
	Captopril - Valsartan	1	Moderate	Valsartan increases toxic effect of captopril and serum captopril concentration
	Ramipril - Candesartan	1	Moderate	Candesaran increases toxic effect and serum ramipril concentration of ramipril
X	-	0	-	-

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