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Original Article

POTENTIAL DRUG-DRUG INTERACTIONS OF CARDIOVASCULAR DRUGS BASED ON LITERATURE IN GERIATRIC PATIENTS WITH CONGESTIVE HEART FAILURE AT Dr. M. DJAMIL PADANG HOSPITAL

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ABSTRACT

Objective: Congestive Heart Failure (CHF) is a notable cardiovascular disease impacting global morbidity and mortality. Geriatric patients with CHF typically require multiple medications that can potentially cause drug-drug interactions and affect patient therapy outcomes. This study aims to determine the potential drug-drug interactions, the relationship between the average number of cardiovascular drugs per day and the potential drug-drug interactions, and the relationship between the severity of drug-drug interactions and the clinical symptoms and signs of the patients.

Methods: The research method used was analytical observational with retrospective data collection through the medical records of inpatients in 2021. A total of 63 patients were included using the total sampling method.

Results: Results revealed that furosemide was the most commonly prescribed cardiovascular medication (15.27%). Among the participants, 93.65% exhibited potential drug-drug interactions (332 occurrences), with the most frequent involving furosemide and bisoprolol (32 cases). Pharmacodynamic interactions were the dominant mechanism (85.24%), with moderate severity (65.06%) being common. A significant relationship existed between the average number of cardiovascular drugs per day and the potential drug-drug interactions ($p<0.05$). Nonetheless, there was no notable correlation discovered between the severity of the interaction and the presence of symptoms and clinical signs ($p>0.05$).

Conclusion: When considering the high incidence of potential drug-drug interactions, it is expected that clinical pharmacists have the competence to analyze potential drug interactions to prevent harmful effects on patients.

Keywords: Potential drug-drug interactions, CHF, Geriatric, Cardiovascular drugs

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INTRODUCTION

Congestive Heart Failure (CHF) is one of the cardiovascular diseases that is a major cause of morbidity and mortality worldwide. The expected 5 y mortality rates for individuals with heart failure did not decrease between 2000 and 2010 and remained high, with an overall rate of 52.6%. Specifically, it was 24.4% for those aged 60 and 54.4% for those aged 80 [1]. Based on the 2013 Basic Health Research (Riskesdas) findings, about 0.13% of the Indonesian population, roughly equivalent to 229,696 individuals, were reported to have congestive heart failure. In West Sumatra, the prevalence of heart failure consists of 4,456 people (0.13%) based on a doctor's diagnosis and 10,283 people (0.3%) based on a doctor's diagnosis/symptoms [2].

The choice of CHF therapy is based on structural heart abnormalities or symptoms related to the functional capacity of the New York Heart Association (NYHA) [3, 4]. Types of medications used for CHF therapy include diuretics, ACE inhibitors, β-blockers, angiotensin receptor blockers (ARBs), aldosterone antagonists, angiotensin receptor-neprilysin inhibitors (ARNIs), ivabradine, digoxin, and hydralazine and isosorbide dinitrate (H-ISDN); usually, patients are given at least four types of these treatments [3, 5].

Research conducted by Espinosa-Bosch *et al.* (2012) found that the prevalence of drug interactions in hospitals ranged from 15% to 45%, with higher numbers in patients with heart disorders and geriatrics [6]. Geriatrics are generally characterized by the decline in organ function, such as the kidneys and liver, leading to changes in the pharmacodynamics and pharmacokinetics of the drugs they consume. Additionally, geriatric patients often suffer from cardiovascular diseases such as coronary heart disease, heart failure, hypertension, and stroke, requiring multiple treatment therapies [7, 8]. It is estimated that more than 40% of geriatrics aged >65 y use five or more drugs, and at least 12% use ten drugs. The increased use of drugs or polypharmacy can lead to drug interactions [9, 10].

The most common drug interaction in CHF treatment is the combination of potassium-sparing diuretics (spironolactone) and ACE inhibitors or ARBs. The side effect to be cautious of in the case of spironolactone interaction is hyperkalemia. Additionally, the combination of aspirin and beta-blockers is often found to interact during CHF therapy [11]. Dumbreck *et al.* (2015) also reported that common effects of drug interactions in CHF therapy are increased digoxin concentration, bleeding, and the risk of arrhythmias [12].

Previous studies on drug interactions in heart failure were conducted by Roblek *et al.* (2014), revealing that 445 out of 778 patients had the potential for drug interactions [11]. Furthermore, Adondis and Mongi (2019), who discussed drug interactions in heart failure patients at the Advent Manado Hospital Inpatient Installation, found drug interactions in 42 patients out of a total of 46 patients [13]. This study aimed to determine the potential for drug interactions, the relationship between the average number of cardiovascular drugs per day and the potential for drug interactions, and the relationship between the severity of drug interactions and the clinical symptoms and signs of patients.

MATERIALS AND METHODS

Research design

This research was conducted in the medical records department of Dr. M. Djamil Hospital Padang from March to May 2023. This study is an analytical observational study with retrospective data involving data collection from patients' medical records during the year 2021 using a total sampling method.

Patient criteria

Data were collected from patients who received cardiovascular drug therapy, were aged≥ 6 0 y, were diagnosed with congestive heart failure (CHF), and had complete examination data (clinical

symptoms such as shortness of breath and edema, as well as clinical signs including blood pressure, pulse rate, and respiratory rate). Data from medical records that were not found, unreadable, or had incomplete examination data were not included in the study.

Data analysis

There exists tools utilized as a point of references for potential drug interactions including The 9th edition of Stockley's Drug Interactions book [14], Drug Interaction Facts book [15], Medscape website [16], and The Drug Interaction Checker database (www. drug. com) developed by Wolters Kluwer Health, the American Society of Health-System Pharmacists, Cerner Multum and Micromedex from Truven Health [17].

Univariate analysis was conducted for each variable in the study, including patient demographics, the average number of cardiovascular drugs per day, cardiovascular drug usage profile, potential drug interactions, interaction mechanisms, and the severity of interactions. All of these were presented of tables displaying the percentage distribution and frequency of each variable. Furthermore, bivariate analysis was used to test the relationship between the average number of cardiovascular drugs per day and the potential for drug interactions (the Mann-Whitney test). Then, the relationship between the severity of drug interactions and clinical symptoms and signs (Fisher's Exact Test). These factors were then hypothetically tested using IBM SPSS for Windows, Version 26 (IBM Corp., Armonk, NY, USA). A value of $p<0.05$ indicates a relationship between the two variables.

Ethical approval

This research received ethical approval from the Health Research Ethics Committee of Dr. M. Djamil Padang Hospital with approval No. LB.02.02/5.7/168/2023.

RESULTS

The results of the study conducted on 63 CHF patients at Dr. M. Djamil Padang Hospital, based on table 1, most of the patients were male (66.57%) and categorized in the elderly group (60-69 y old), with 47 patients (74.6%) and average age (mean = 66.76±5.20).

Table 1: Distribution of patient demographic characteristics

Patient characteristics	Number of patients	Percentage (%)
Gender		
Female	21	33.33
Male	42	66.67
Age (Mean = 66,76±5,20)		
Elderly (60-69 y old)	47	74.6
High-risk elderly (>70 y old)	16	25.4

Fig. 1 shows that the average daily use of cardiovascular medications ranges from 2-6 drugs, with the most common average being four drugs (27%). The average daily use of cardiovascular medications is determined based on the number of cardiovascular drugs patients consume daily during their hospitalization.

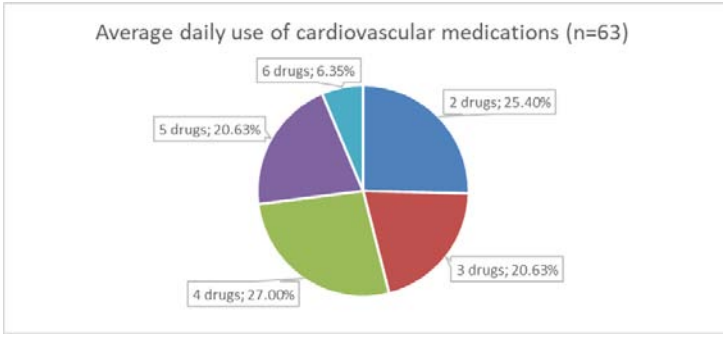

Fig. 1: Average daily use of cardiovascular medications

Among the 334 profiles of cardiovascular drug usage in CHF patients at Dr. M Djamil Padang Hospital, it is evident that the most frequently used cardiovascular drugs, in sequence, are furosemide at 15.27%, bisoprolol at 13.17%, spironolactone at 9.28% and aspirin at 8.98% (fig. 2). According to fig. 3, it was found that 59 patients (93.65%) potentially experienced interactions among cardiovascular drugs.

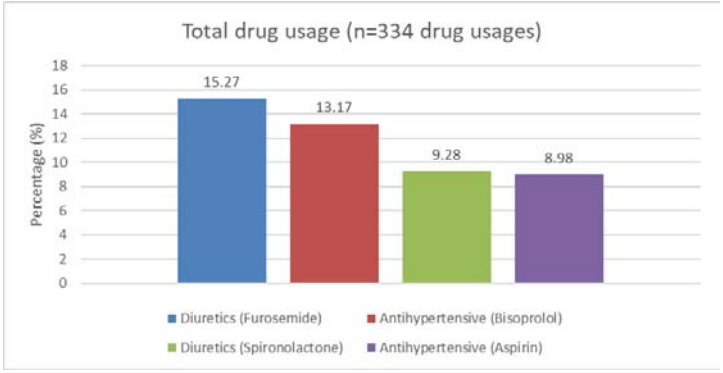

Fig. 2: Profile of cardiovascular drug usage

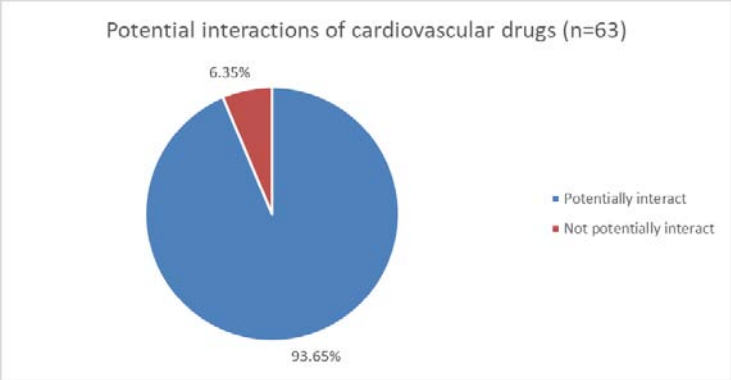

Fig. 3: Potential interactions of cardiovascular drugs

Table 2 describes that there are 332 cases out of 63 medical records of patients who met the inclusion criteria. A total of 78 potential interactions among cardiovascular drugs were found in CHF patients at Dr. M. Djamil Padang Hospital in 2021. The most frequent drug interactions were between furosemide and bisoprolol, furosemide and aspirin, and bisoprolol and spironolactone, with 32, 22, and 20 cases, respectively. Based on the mechanism of drug interactions, it was found that pharmacodynamic interactions occurred in 283 cases (85.24%), followed by pharmacokinetic interactions in 16 cases (4.82%), and unknown interactions in 33 cases (9.94%). Regarding the severity level of drug interactions, it was found that the moderate severity level was the most common in CHF patients at Dr. M. Djamil Padang Hospital, accounting for 216 cases (65.06%).

Table 2: Description of drugs that potentially have interactions, mechanisms, and the severity level of drug interactions

No	Drugs that potentially have interactions		Mechanism	Severity level	Total cases
	Drug A	Drug B			
1	Furosemide	Bisoprolol	PD[a,d]	Moderate[b,c]	32
2		Ramipril	PD[d]	Moderate[c]	18
3		Aspirin	PD[a,d]	Minor[c]	22
4		Digoxin	PD[b,c]	Moderate[b,c]	4
5		Candesartan	PD[a]	Moderate[c]	4
6		Carvedilol	PD[d]	Moderate[c]	2
7		Imidapril	PD[d]	Moderate[c]	2
8		Amiodarone	PD[b]	Major[b,c]	3
9		Hydrochlorothiazide	PK[b]	Moderate[b,c]	1
10		Captopril	PD[d]	Moderate[c]	1
11	Bisoprolol	Aspirin	*Unknown*[b]	Minor[b,c]	15
12		Candesartan	PD[a,d]	Moderate[c]	4
13		Spironolactone	PD[b]	Moderate[c,b]	20
14		Digoxin	PD[b,c]	Moderate[c,b]	3
15		Amlodipine	PD[d]	Moderate[c]	7
16		Amiodarone	PD[b]	Moderate[c]	4
17		Dobutamine	PD[d]	Moderate[c]	1
18		Norepinephrine	PD[d]	Moderate[c]	1
19		Valsartan	PD[a,d]	Moderate[c]	1
20		Ticagrelor	PD[d]	Minor[c]	2
21		Hydrochlorothiazide	PD[b]	Moderate[b,c]	1
22	Ramipril	Aspirin	PD[b]	Moderate[b,c]	12
23		Spironolactone	PD[a]	Major[c]	12
24		Amlodipine	PD[b]	Minor[b,c]	5
25		Heparin	PK[d,b]	Moderate[b,c]	2
26		Nitroglycerin	PD[d]	Moderate[c]	5
27		Nicardipine	PD[b]	Minor[b,c]	2
28		Digoxin	*Unknown*[b]	Moderate[b,c]	3
29		ISDN	PD[d]	Moderate[c]	2
30		Enoxaparin	PD[d]	Moderate[c]	3
31	Candesartan	Spironolactone	PD[b,d]	Major[b,c]	16
32		Imidapril	PD[a,d]	Major[c]	1
33		Aspirin	PD[b]	Moderate[b,c]	12
34		Heparin	PK[b]	Moderate[b,c]	3
35		Enoxaparin	PK[d]	Moderate[c]	5
36	Spironolactone	Aspirin	PK[b]	Minor[b,c]	1
37		Enoxaparin	PD[d]	Moderate[c]	2
38		Warfarin	PD[b]	Minor[b,c]	6
39		Captopril	PD[a,d]	Major[c]	1
40		Dabigatran	PD[d]	Moderate[c]	2
41		Imidapril	PD[a,d]	Major[c]	3
42		Digoxin	PK[b]	Minor[b,c]	3

No	Drugs that potentially have interactions		Mechanism	Severity level	Total cases
	Drug A	Drug B			
43		Valsartan	PD[a,d]	Major[c]	1
44		Ticagrelor	PD[d]	Moderate[c]	2
45		Heparin	PD[b]	Moderate[b,c]	1
46		Propanolol	PD[b]	Moderate[c,b]	1
47	Aspirin	Warfarin	PD[b]	Major[b,c]	5
48		Enoxaparin	PD[d]	Moderate[c]	7
49		Ticagrelor	PD[d]	Moderate[c]	5
50		Rivaroxaban	PD[d]	Major[c]	1
51		Clopidogrel	*Unknown*[b]	Moderate[b,c]	12
52		Imidapril	PD[d]	Minor[c]	1
53		Nitrogliserin	PD[d]	Minor[c]	6
54		Valsartan	PD[a,d]	Moderate[c]	1
55		Nicardipine	PD[d]	Moderate[c]	1
56		Carvedilol	PD[b]	Minor[b,c]	1
57		Amlodipine	PD[d]	Moderate[c]	4
58		Heparin	PD[b]	Moderate[b,c]	3
59		Captopril	PD[d]	Minor[c]	1
60	Nitroglycerin	Heparin	*Unknown*[d]	Moderate[c]	2
61		Nicardipine	PD[b]	Moderate[b,c]	1
62		Amlodipine	PD[b]	Moderate[b,c]	1
63		Nifedipine	PD[b]	Moderate[b,c]	2
64	Amlodipine	Carvedilol	PD[b]	Moderate[b,c]	1
65		Ticagrelor	PD[d]	Minor[c]	1
66		Propanolol	PD[b]	Moderate[b,c]	1
67	Ticagrelor	Enoxaparin	PD[d]	Moderate[c]	1
68		Clopidogrel	PD[d]	Moderate[c]	2
69		Amiodarone	PD[d]	Moderate[c]	1
70	Amiodarone	Digoxin	*Unknown*[b]	Major[b,c]	1
71		Warfarin	PK[b]	Major[b,c]	2
72		Dabigatran	PD[d]	Moderate[c]	1
73		Clopidogrel	PD[b]	Moderate[b,c]	2
74	Warfarin	Heparin	PD[b,d]	Major[b,c]	2
75		Clopidogrel	PD[b]	Moderate[b,c]	2
76		Enoxaparin	PD[d]	Major[c]	2
77	Clopidogrel	Enoxaparin	PD[d]	Major	4
78		Heparin	PD[b]	Moderate[b,c]	1

Description: a: *Stockley's Drug Interaction* (2009) b: *Drug Interaction Facts* (2008) c: *Drugs. com* (2023) d: *Medscape* (2023)
PD: Pharmacodynamic (85.24%); PK: Pharmacokinetic (4.82%); and Unknown (9.94%)
Major (16.87%); Moderate (65.06%); and Minor (18.07%)

In table 3, it is found that out of 59 patients potentially experiencing drug interactions, they consumed two drugs (13 patients), three drugs (12 patients), four drugs (17 patients), five drugs (13 patients), and six drugs (4 patients). Based on the normality test, it was determined that the distribution of numerical data for the average daily use of cardiovascular drugs in CHF patients is not normal, with a $p<0.05$. Therefore, an alternative test, the Mann-Whitney test, was conducted. Based on table 6, the result obtained a p-value of 0.021, which means $p<0.05$. Statistically, it can be concluded that there is a significant relationship between the average daily use of cardiovascular drugs and the potential for drug interactions (H1 accepted).

Table 3: The relationship between the average daily use of cardiovascular drugs and the potential drug interaction

Potential drug interaction	n	Average daily use of cardiovascular drugs					p-value
		mean±SD. error	95% CI		Min.	Max.	
			Lower	Upper			
Yes	59	3.71±0.160	3.39	4.03	2	6	0.021
No	4	2.25±0.250	1.45	3.05	2	3	

Table 4 shows that the $p>0.05$, which means there is no significant relationship between the severity level of drug interactions and the clinical symptoms experienced by patients (H0 accepted). Table 5 illustrates that there is no relationship between the severity level of drug interactions and the clinical signs experienced by CHF patients ($p>0.05$).

Table 4: The relationship between severity level and clinical symptoms

Clinical symptoms	Severity level	Status			p-value
		Improvement (%)	No change (%)	Worsening (%)	
Short of breath	Major	55.3%	42.1%	2.6%	0.613*
	Moderate and Minor	71.4%	28.6%	0%	
Edema	Major	31.6%	68.4%	0%	1.000**
	Moderate and Minor	28.6%	71.4%	0%	

*Fisher's exact test, **Continuity correction[b]

Table 5: The relationship between severity level and clinical signs

Clinical signs	Severity level	Status			p-value
		Improvement (%)	No change (%)	Worsening (%)	
Blood Pressure	Major	23.7%	57.9%	18.4%	0.136*
	Moderate and Minor	4.8%	66.7%	28.6%	
Pulse	Major	13.2%	78.9%	7.9 %	0.806*
	Moderate and Minor	19.0%	71.4%	9.5%	
Respiratory Rate	Major	39.5%	55.3%	5.3%	0.625*
	Moderate and Minor	28.6%	61.9%	9.5%	

*Fisher's exact test

DISCUSSION

The age characteristics in this study were categorized according to Minister of Health Regulation No. 25 of 2016. Aging can lead to decreased heart function, resulting in heart failure in older people [18]. Heart failure is considerably more common in the elderly population, with a rate of 4.3% observed in individuals aged 65 to 70 in 2012. Projections indicate a continuous rise in this figure, with the prevalence of heart failure estimated to potentially reach 8.5% by the year 2030 [19]. This statement is supported by a study conducted by Bosch (2019). He stated that heart failure is highly associated with aging and comorbidities, which makes the process of diagnosing heart failure in the elderly population more challenging [20].

In general, polypharmacy is divided into three categories: minor (2-3 medications), moderate (4-5 medications, and major (>5 medications). The majority of patients aged over 65 underwent some level of polypharmacy, with a significant number experiencing major polypharmacy [21]. From a study conducted by Maharani (2018), it is known that the occurrence of drug interactions in geriatric patients is approximately 20%, becoming one of the causes of adverse drug reactions [22]. This research aligns with a study conducted by Olii (2014), which found that the average number of prescribed cardiovascular drugs was between 4-5 [23].

Furosemide and spironolactone belong to the diuretic drug class and are typically administered to CHF patients with signs of congestion (Class I or Stage B). As the first-line treatment for CHF patients, diuretics can help reduce edema and heart swelling in left-sided heart failure patients to make heart pumping more effective. Furosemide is a loop diuretic that inhibits the Na-K-Cl transporter in the loop of Henle, while spironolactone is a potassium-sparing diuretic for patients with hypokalemia [4]. Diuretics are the most commonly used because CHF patients at Dr. M. Djamil Padang Hospital are often diagnosed with left-sided heart failure and pleural effusion, which requires reducing fluid in the pleural cavity. Wulandari (2015) and Nopitasari (2020) also revealed that diuretics are the most widely used drugs for CHF patients [24]. Bisoprolol is the second most frequently prescribed drug to patients. Bisoprolol and carvedilol belong to the Beta Blocker class, which can improve ventricular function and reduce CHF mortality [25].

Determining drug interactions was done theoretically based on the administration of drugs on the same day, taking into consideration the time and date of administration. The high number of potential drug interactions among CHF patients is due to comorbidities in many patients. Furthermore, the treatment of heart failure often involves multiple combinations of cardiovascular drugs, leading to polypharmacy and drug interactions. A study on polypharmacy in the elderly affirmed a rise in problems associated with medications, including interactions between different drugs [26, 27]. Similar to Akbar's research, it is asserted that the likelihood of drug interactions is widespread. According to their findings, every patient had at least one potential drug interaction [28]. This highlights the importance of thinking about potential drug interactions when planning treatment to protect patients from any negative effects [29].

Based on the research findings, it can be observed that the drug interaction mechanism of pharmacodynamics occurs much more frequently compared to the other two mechanisms. This is consistent with research conducted by Adondis (2019) and Fitria (2023), which found that pharmacodynamic interactions had a high percentage, specifically 46.7% and 66.7% [13, 30]. The most common drug interaction in pharmacodynamic interactions was the interaction between furosemide and bisoprolol, with 32 cases. The mechanism between furosemide and bisoprolol is their simultaneous use can enhance the cardiovascular effects of bisoprolol [15, 16]. An example of a pharmacokinetic interaction is the interaction between digoxin and spironolactone. Spironolactone can increase the serum levels of digoxin and decrease renal clearance [15-17].

Specifically, for the severity level of drug interactions, it is known that the moderate level is most commonly found in research based on a literature review. In the moderate severity level, the most frequent interaction was between furosemide and bisoprolol, with 32 cases. The interaction between these two drugs can enhance the cardiovascular effects of bisoprolol, necessitating close monitoring of the patient's cardiovascular status and potential dosage adjustments for bisoprolol. The most common interaction at the major severity level was between candesartan and spironolactone, with 16 cases. Simultaneous use of candesartan and spironolactone can lead to an increase in blood potassium levels and can cause hyperkalemia, which, in severe cases, can result in kidney damage, arrhythmias, muscle paralysis, and even cardiac arrest. Close monitoring of blood potassium levels and consideration of dosage adjustments or the use of alternative drugs is required if there are symptoms of drug interactions in patients [14, 15, 17].

Thus, it can be concluded that the more drugs are administered, the greater the likelihood of drug interactions. This research is consistent with a study by Annisa (2022), which found a significant relationship between the number of drugs and drug interactions in hospitalized geriatric patients [31]. The findings of this study are inconsistent with the research conducted by Suryaman in 2023, where no notable connection was established between the use of multiple medications (polypharmacy) and drug interactions in patients with Congestive Heart Failure who also have chronic kidney disease as a comorbidity. Nevertheless, Suryaman's study (2023) did report that polypharmacy increases the risk of experiencing drug interactions by a factor of 2.75 when compared to individuals who are not using multiple medications [32].

Based on the research analysis, it was found that there is no significant relationship between the severity level of drug interactions and the clinical symptoms and signs of patients. Shortness of breath experienced by congestive heart failure patients is influenced not only by the severity of drug interactions but also by other factors such as stress, obesity, and lung infections like pneumonia [33]. Meanwhile, other factors that can lead to edema and left and right heart failure include limited mobility, malnutrition, and kidney failure associated with low albumin levels [34]. Other research highlights the significance of factors in the overall blood circulation connected to stress and inflammation in the origin and progression of heart failure [35].

CONCLUSION

Our study concluded that there is a high prevalence of potential drug interaction in CHF patients, particularly interaction involving pharmacodynamic mechanisms, most of which were of moderate severity. We found a significant relationship between the average

daily use of cardiovascular drugs and the potential for drug interactions ($p<0.05$), while there is no significant relationship between the severity level of drug interactions and the clinical symptoms and signs of patients ($p>0.05$). Therefore it is expected that clinical pharmacists possess the competency to analyze potential drug-drug interactions to prevent harmful effects on patients.

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AUTHORS CONTRIBUTIONS

Rahmi Yosmar: Conceptualization, Supervision, Resources, Review and Editing; Dita Permatasari: Supervision, Writing–Original Draft, Writing–Review and Editing, Funding acquisition; and Nur Alima Husna: Methodology, Writing–Original Draft. All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

There is no conflict of interest from all the authors

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