Original Research

EVALUASI RISIKO DAN POLA INTERAKSI OBAT PADA PASIEN HIPERTENSI DENGAN KOMORBIDITAS DI RUMAH SAKIT X SIDOARJO

EVALUATION OF DRUG INTERACTION RISK AND PATTERNS IN HYPERTENSIVE PATIENTS WITH COMORBIDITIES AT X HOSPITAL SIDOARJO

*Eka Putri Nurhidayah[1] *, Faizal Agustino[2], Bella Fevi Aristia[3]*

[1]Department of Clinical and Community Pharmacy, Faculty of Health Sciences, Universitas Anwar Medika, Sidoarjo, Indonesia, 61263

[2]Bachelor of Pharmacy, Faculty of Health Sciences, Universitas Anwar Medika, Sidoarjo, Indonesia

[3] Apothecary Professional Education Program, Faculty of Health Sciences, Universitas Anwar Medika, Sidoarjo, Indonesia

**E-mail: eka.putri@uam.ac.id*

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Abstrak

Hipertensi merupakan penyakit kronis dengan prevalensi tinggi dan sering disertai komorbiditas yang memerlukan polifarmasi, sehingga meningkatkan risiko terjadinya interaksi obat. Penelitian ini bertujuan mengevaluasi risiko dan pola interaksi obat pada pasien hipertensi dengan komorbiditas di ruang rawat inap dengan desain retrospektif observasional menggunakan data rekam medis pasien tahun 2023–2024. Analisis dilakukan secara deskriptif terhadap karakteristik pasien, regimen antihipertensi, serta potensi interaksi obat menggunakan sumber literatur ilmiah dan instrumen analisis interaksi terstandar (Medscape, DrugBank, Drugs.com). Validasi dilakukan secara independen oleh praktisi dan peneliti farmasi klinis. Dari 182 rekam medis, sebanyak 65 rekam medis memenuhi kriteria inklusi. Mayoritas pasien berusia ≥60 tahun (56,9%) dengan jenis kelamin perempuan (55,4%). Sebanyak 56,9% pasien mengalami potensi interaksi obat. Risiko interaksi moderate paling sering melibatkan mekanisme farmakodinamik, khususnya kombinasi aspirin–furosemide, nifedipine–alprazolam, valsartan–insulin glargine, dan candesartan–meloxicam. Potensi interaksi mayor teridentifikasi pada kombinasi valsartan–spironolactone, ramipril–spironolactone yang berpotensi meningkatkan risiko hiperkalemia, serta kombinasi diltiazem–bisoprolol yang memiliki efek aditif terhadap nodus SA/AV. Hal ini menegaskan bahwa pasien hipertensi dengan komorbiditas memiliki risiko tinggi terhadap interaksi obat. Pemantauan klinis dan evaluasi regimen obat secara berkala oleh apoteker klinis diperlukan untuk meningkatkan keamanan dan efektivitas terapi di rumah sakit.

Kata kunci: Hipertensi; Interaksi Obat; Komorbiditas

Abstract

Hypertension is a chronic condition with a high prevalence and is frequently accompanied by comorbidities that require polypharmacy, thereby increasing the risk of drug–drug interactions (DDIs). This study aimed to evaluate the risk and patterns of DDIs among hypertensive inpatients with comorbidities using a retrospective observational design based on medical record data from 2023–2024. Descriptive analyses were conducted on patient characteristics, antihypertensive regimens, and potential DDIs using three drug interaction–checking tools. Validation was conducted independently by a clinical pharmacy practitioner and a clinical pharmacy researcher. Of the 182 medical records reviewed, 65 met the inclusion criteria. Most patients were aged ≥60 years (56.9%) and female (55.4%). A total of 56.9% of patients experienced potential DDIs. Moderate-risk interactions most frequently involved pharmacodynamic mechanisms, particularly aspirin–furosemide, nifedipine–alprazolam, valsartan–insulin glargine, and candesartan–meloxicam. Major potential interactions were identified in combinations such as valsartan–spironolactone and ramipril–spironolactone, which may increase the risk of hyperkalemia, as well as diltiazem–bisoprolol, which has an additive effect on SA/AV nodal conduction.

These findings highlight that hypertensive patients with comorbidities are at high risk for DDIs. Regular clinical monitoring and systematic medication review by clinical pharmacists are essential to enhance therapeutic safety and effectiveness in hospital settings.

Keywords: Hypertension; Drug-Drug Interactions; Comorbidity

INTRODUCTION

Hypertension is a chronic medical condition characterized by a persistent elevation in blood pressure above normal thresholds, defined as a systolic pressure of ≥140 mmHg and a diastolic pressure of ≥90 mmHg. A diagnosis is established when these values are recorded on at least two separate examinations [1]. As one of the most common cardiovascular disorders worldwide, hypertension continues to pose a substantial global health burden, affecting populations in both developed and developing countries. Often termed a silent killer, hypertension typically manifests without noticeable symptoms in its early stages, causing many individuals to remain unaware of their condition. When left untreated, it can lead to serious complications such as heart disease, stroke, and damage to vital organs [2]. In Indonesia, the prevalence of hypertension has risen markedly. Data from the Riset Kesehatan Dasar indicate an increase from 25.8% in 2013 to 34.1% in 2018 among adults aged over 18 years. An estimated 63,309,620 individuals were living with hypertension, with 427,218 reported deaths. The highest prevalence was observed in the 55–64 age group (55.2%), followed by the 45–54 (45.3%) and 31–44 age groups (31.6%) [3].

Hypertensive patients frequently present with comorbidities such as diabetes mellitus, dyslipidemia, chronic kidney disease, and other cardiovascular conditions. These coexisting illnesses often necessitate the use of multiple medications, resulting in increasingly complex therapeutic regimens. When patients receive more than three medications, the likelihood of drug–drug interactions (DDIs) increase substantially. DDIs may alter the intensity or duration of drug effects and can compromise both treatment efficacy and patient safety. Such interactions may arise from pharmacokinetic mechanisms such as differences in absorption, distribution, metabolism, and elimination, or pharmacodynamic mechanisms involving modifications of physiological responses [1]

The risk of DDIs is particularly elevated in inpatient settings, where patients generally present with more severe clinical conditions, require closer monitoring, and often undergo more frequent adjustments to therapy. The World Health Organization (WHO) emphasizes the importance of identifying and monitoring patients at high risk for DDIs, as unmanaged interactions

may increase the incidence of adverse drug events, prolong hospitalization, and negatively affect clinical outcomes [4]. Several previous studies underscore the high incidence of DDIs among hypertensive patients. Indriani & Oktaviani (2020) reported DDIs in 66.2% (169 cases) of antihypertensive therapy. Similarly, Eliani Tirta et al. (2023) found that most interactions were classified as moderate (71.78%), followed by minor (21.78%) and major (6.45%). The clinical manifestations ranged from edema, nausea, abdominal pain, and fatigue in minor interactions to bradycardia, dizziness, and syncope in moderate interactions [5][6]. Major interactions, although less frequent, may cause severe complications such as rhabdomyolysis, which can be life-threatening and therefore must be avoided. These findings demonstrate that drug interactions remain a significant concern in the management of hypertensive patients particularly those with comorbidities who require multidrug therapy. In inpatient environments, where therapeutic regimens are more dynamic and complex, the potential for harmful interactions becomes even greater. However, studies that specifically evaluate DDI patterns, severity levels, and high-risk drug combinations among hypertensive inpatients remain limited.

This study differs from previous research in Indonesia because it specifically examines the risk of drug–drug interactions in hospitalized hypertensive patients with multiple comorbidities, and utilizes three drug interaction–checker tools simultaneously. Most earlier studies in the country focused on outpatients or populations with limited comorbidities, resulting in fewer and less diverse drug interactions being identified. Conducted in a referral hospital that manages patients with more complex clinical conditions, this study provides a more comprehensive overview of antihypertensive drug interaction patterns in real-world clinical practice. Focusing on hospitalized patients is crucial, as this population typically experiences higher levels of polypharmacy, receives more intensive medication regimens, and undergoes frequent therapeutic adjustments, all of which increase the likelihood of clinically significant DDIs [1][3][7].

Given these gaps, a more comprehensive analysis is required to better understand the risks and patterns of DDIs among hypertensive patients with comorbidities in inpatient settings. This study provides novelty by examining not only the prevalence of DDIs but also their patterns and severity classifications based on therapeutic regimens. The findings are expected to support healthcare professionals particularly clinical pharmacists in enhancing monitoring practices, optimizing pharmacotherapy, and improving patient safety in hospital care.

METHOD

This study employed a retrospective observational design using purposive sampling. It was conducted Inpatient Department of Hospital X in Sidoarjo, a district level referral center that frequently manages hypertensive patients with multiple comorbidities. Medical record data were collected over three months, from March to May 2025, using entries documented in the hospital's electronic medical record system.

The sample consisted of hospitalized patients diagnosed with hypertension and at least one comorbidity. Inclusion criteria required complete demographic and clinical information, concurrent management of comorbid conditions, and relevant laboratory data. Exclusion criteria covered patients with specific infectious diseases such as HIV or tuberculosis and those with pregnancy related hypertension, as these conditions could confound the assessment of drug interactions. The sample size was calculated using Slovin's formula, applied to a finite population of 182 medical records of hypertensive patients with comorbidities documented between 2023 and

2024. The use of Slovin was justified because the population size was known and no preliminary data were available regarding the variability or prevalence of DDIs. Although the formula has recognized limitations in clinical research, it remains acceptable for exploratory descriptive studies. A 5% margin of error was selected to obtain a sufficiently representative minimum sample.

Data were analyzed descriptively, including demographic characteristics such as age, gender, and antihypertensive medications. Potential DDIs were evaluated based on reputable scientific literature and three drugs interaction-checker tools: Medscape, DrugBank, and Drugs.com. Each interaction was categorized as minor, moderate, or major according to the severity ratings defined by these platforms. This assessment was independently performed by one clinical pharmacy practitioner and one clinical pharmacy researcher to strengthen the validity of the findings. This study received ethical approval from the hospital's Ethics Committee and was registered under the number 000.9.2/067/438.5.2.1.1/2024.

RESULT AND DISCUSSION

Out of the 182 medical records reviewed, 65 patient records were identified that met the inclusion criteria and were consistent with the sample size determined using the Slovin formula. Patient characteristics for this study are summarized in Table 1.

Table 1. Patient Characteristics

Characteristics	Category	n (%)
Gender	Male	29 (44,6)
	Female	36 (55,4)
Age (years)	≤40	9 (13,9)
	41-59	19 (29,2)
	≥60	37 (56,9)
DDIs	Present	37 (56,9)
	Absent	28 (43,1)
Number of Comorbidites	2-3	34 (52,3)
	≥4	31 (47,7)
Types of Comorbidities	Diabetes Mellitus	15 (19,2)
	Hypertensive Heart Disease	13 (16,7)
	Cerebrovascular Accident	9 (11,5)
	Heart Failure	8 (10,3)
	Chronic Kidney Disease	8 (10,3)
	Pneumonia	8 (10,3)
	Dyslipidemia	5 (6,4)
	Coronary Heart Disease	4 (5,1)
	Bronchitis	3 (3,8)
	Chronic Obstructive Pulmonary Disease	2 (2,3)
	Acute Exacerbation of Chronic Bronchitis	2 (2,3)
	Tuberculosis	1 (1,3)

Characteristics	Category	n (%)
Number of Antihypertensive Medications Prescribed	1	5 (7,7)
	2	38 (58,5)
	3	22 (33,8)

The patient characteristics in this study indicate that female patients (55.4%) slightly outnumber male patients (44.6%). This difference may be attributed to the increased susceptibility of women to hypertension during the postmenopausal period. According to the state-of the art review by the American Heart Association (2022), the prevalence of hypertension rises sharply after menopause, with more than 40% of postmenopausal women experiencing hypertension exceeding the prevalence observed in age-matched men and contributing to a higher risk of cardiovascular complications [8][9]. Following menopause, cessation of menstrual bleeding reduces the risk of anemia and increases iron stores. However, the decline in estrogen levels simultaneously removes its cardioprotective effects. Estrogen is known to enhance nitric oxide (NO) bioavailability, suppress the renin–angiotensin–aldosterone system (RAAS), and maintain vascular elasticity. Loss of these functions promotes vasoconstriction, arterial stiffness, oxidative stress, and sympathetic nervous system activation [10].

A substantial proportion of patients with hypertension and comorbidities were aged ≥60 years (56.9%), underscoring the predominance of hypertension in the elderly population. This pattern aligns with findings from Fryar et al. (2024), who reported an age-related increase in hypertension prevalence, rising from 23.4% in individuals aged 18–39 years to 52.5% in those aged 40–59 years, and reaching 71.6% in adults aged ≥60 years. Ageing is associated with structural and functional vascular changes, including reduced arterial elasticity, increased fibrosis, and vascular remodeling. These alterations elevate peripheral vascular resistance and blood pressure, thereby establishing advanced age as a major risk factor for hypertension [11][12].

Regarding comorbidity distribution, Diabetes Mellitus was the most prevalent condition (15 patients; 19.2%), followed by Hypertensive Heart Disease (HHD) (13 patients; 16.7%) and stroke/Cerebrovascular Accident (CVA) (9 patients; 11.5%). These findings indicate that metabolic and cardiovascular disorders constitute the predominant comorbidities among hypertensive patients. This is consistent with the study by Hurst et al. (2015), which included more than 55,000 individuals with type 2 diabetes and demonstrated that over half (55.35%) also had hypertension. The strong association between the two conditions stems from shared risk factors, including obesity, unhealthy dietary patterns, and physical inactivity, as well as metabolic disturbances in diabetes that accelerate vascular damage and contribute to elevated blood pressure. Hypertension has also been identified as a major determinant of hypertensive heart disease, particularly heart failure. Evidence from Messerli et al. (2017), involving 5,143 subjects with up to 20 years of follow-up, revealed that hypertension preceded the onset of heart failure in 91% of incident cases. This underscores that hypertension is not merely a risk factor but a key comorbid condition directly driving the pathological progression toward heart failure. Chronic elevation of blood pressure induces left ventricular hypertrophy, diastolic dysfunction, and other structural

alterations that culminate in hypertensive heart disease, making HHD one of the most critical and clinically significant comorbidities among hypertensive patients [13][14].

In terms of pharmacotherapy, the shift from monotherapy to combination therapy involving two to three antihypertensive agents observed in this study reflects individualized treatment approaches tailored to patient variability. Combination therapy has been shown to provide superior blood pressure reduction and facilitate faster achievement of therapeutic targets, particularly in patients with multiple comorbidities and treatment-resistant hypertension. These findings support existing clinical practice recommendations, positioning combination therapy as a more appropriate and effective strategy compared with monotherapy in complex hypertensive populations [15].

Table 2. Category of DDIs

Drug A (Affecting)	Drug B (Affected)	Interaction Type	Severity	Frequency
Aspirin	Furosemide	Pharmacodynamic	Moderate	8
Nifedipine	Alprazolam	Pharmacodynamic	Moderate	4
Atorvastatin	Valsartan	Pharmacodynamic	Moderate	3
Valsartan	Insulin Glargine	Pharmacodynamic	Moderate	3
Candesartan	Meloxicam	Pharmacodynamic	Moderate	2
Heparin	Candesartan	Pharmacodynamic	Moderate	2
Valsartan	Spironolactone	Pharmacodynamic	Major	8
Candesartan	Spironolactone	Pharmacodynamic	Major	3
Spironolactone	Ramipril	Pharmacodynamic	Major	1
Diltiazem	Bisoprolol	Pharmacodynamic	Major	1

Several clinically relevant DDIs were identified among hypertensive patients with multiple comorbidities (Table 2). Most of the interactions involved pharmacodynamic mechanisms that may influence therapeutic response or safety outcomes.

The combination aspirin–furosemide represents one of the moderate DDIs observed. Low-dose aspirin reduces renal prostaglandin synthesis, which may attenuate the natriuretic and diuretic effects of furosemide. As reported by Isabel et al. (2018), this interaction can contribute to suboptimal diuresis and potential fluid retention, particularly in patients with cardiac comorbidity. Although no acute diuretic resistance was documented in this dataset, routine monitoring of renal function and volume status remains clinically indicated when both drugs are used [16]. Another interaction of interest is nifedipine–alprazolam, where both agents may reduce sympathetic tone through different pathways. Nifedipine induces vasodilation through L-type calcium channel blockade, while alprazolam exerts CNS depressant effects via GABA enhancement. This pharmacodynamic overlap may increase susceptibility to hypotension or dizziness. Findings from Ji et al. (2019) on CNS depressant combinations support the need for caution, especially in older adults [17]. The atorvastatin–valsartan combination aligns with earlier observations noting possible myopathy risk when sacubitril/valsartan is used concurrently with statins [18]. Although this study did not capture laboratory-confirmed rhabdomyolysis, the documented mechanism suggests that clinical monitoring for muscle-related symptoms remains appropriate during

prolonged use. An interaction involving glucose homeostasis was observed with valsartan–insulin glargine. Valsartan may enhance insulin sensitivity through AT1 receptor blockade, thereby increasing the potential for hypoglycemia when administered with exogenous insulin. The mechanism described by Andra (2016) supports the need for careful titration and blood glucose monitoring, particularly in patients with variable dietary intake or advanced age [19]. The addition of NSAIDs in patients on RAS inhibitors is a well-established issue, reflected in the candesartan–meloxicam combination. NSAIDs may elevate blood pressure and reduce natriuresis, contributing to extracellular volume expansion. Evidence from a randomized crossover study demonstrated increases in systolic and diastolic blood pressure in hypertensive individuals receiving NSAIDs, as well as reduced renal sodium excretion. Furthermore, the risk of acute kidney injury with NSAID use in combination with RAS inhibitors is described by Kujvenhoven et al. (2013). These data emphasize the importance of limiting NSAID exposure in patients receiving ARBs. The interaction heparin–candesartan also appeared in the dataset. Both agents can reduce aldosterone levels and predispose patients to hyperkalemia. This interaction is generally categorized as moderate but clinically relevant in patients with reduced renal reserve. Regular electrolyte monitoring is recommended when the combination cannot be avoided [20].

Major DDIs identified in this study primarily involved the renin–angiotensin–aldosterone system. The valsartan–spironolactone combination was present in several patients. Both drugs reduce potassium excretion through complementary mechanisms and may increase serum potassium levels. Although Pflug et al. (2017) reported an average potassium rise of 0.19 mEq/L, Ojala et al. (2020) documented both potential and actual cases of hyperkalemia in similar regimens. In this dataset, most cases remained potential rather than actual, likely due to preserved renal function and routine laboratory monitoring. A comparable mechanism was found in the ramipril–spironolactone interaction. As with ARBs, ACE inhibitors reduce aldosterone formation and may enhance the potassium-retaining effect of spironolactone. Findings from Ojala et al. (2020) highlight the importance of regular potassium assessment, especially after therapy initiation or dose escalation. Lastly, the diltiazem–bisoprolol interaction represents a major pharmacodynamic DDI involving additive depression of SA/AV nodal conduction. The risk of bradycardia, hypotension, or conduction disturbances is well documented, with Saedder et al. (2019) reporting serious cardiovascular events in similar combinations. Although no acute events were noted in this retrospective dataset, the mechanistic rationale supports avoiding the combination where alternatives exist [21][22].

Overall, the DDIs potential identified in this retrospective analysis align with mechanisms previously described in the literature and highlight the importance of systematic medication review in hypertensive patients with multimorbidity. Pharmacodynamic overlap particularly within the RAAS pathway, calcium channel blockers, CNS depressants, and NSAIDs accounts for most interactions and warrants continued clinical vigilance. Laboratory and clinical monitoring showed no evidence of actual adverse outcomes related to the identified potential DDIs. Serum potassium levels remained within normal limits, and no episodes of hypotension or bradycardia were observed in patients exposed to drug combinations associated with these risks. Thus, although several moderate to major interactions were detected, they did not manifest clinically and were categorized as potential interactions only.

CONCLUSION

This study identified several potential DDIs in hypertensive inpatients with comorbidities. However no clinically evident adverse outcomes were observed, indicating that these interactions remained potential rather than actual events. Clinical implications should be emphasized, particularly the need for routine monitoring of serum potassium in patients receiving combinations such as ARBs with spironolactone, as well as hemodynamic monitoring for drug pairs associated with hypotension or bradycardia. Strengthening these monitoring practices may help prevent potential interactions from progressing into clinically significant events. These findings highlight the importance of systematic medication review and close clinical monitoring to minimize interaction-related risks in this population.

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