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Analysis of Factors Affecting Potential Drug Interactions in Outpatient Hypertension Patients at Dr. Iskak Tulungagung Hospital

(*Analisis Faktor-Faktor yang Mempengaruhi Potensi Interaksi Obat pada Pasien Hipertensi Rawat Jalan di RSUD Dr. Iskak Tulungagung*)

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ABSTRACT

Background: The global prevalence of hypertension continues to rise, with projections indicating that approximately 29% of adults will be affected by 2025. Hypertension is often accompanied by comorbidities and complications. Hypertension treatment usually involves more than one drug or polypharmacy, increasing the risk of potential interactions. **Objective:** To examine the association between polypharmacy and potential drug-drug interactions in outpatient hypertensive patients. **Material and Method:** Retrospective observational study using a purposive sampling technique. A total of 96 patients were included from January-December 2023. The instruments used were medical records, the Drugs Interaction Checker application on the Drugs.com application, and Medscape. **Results:** Most patients were male (59.38%) and aged 56–65 years (37.50%). Polypharmacy was observed in the majority of patients, with major polypharmacy (>4 drugs) accounting for 48.96%. Potential drug interactions were identified in 65.63% of patients. Pharmacodynamic interactions were more common (58.57%) than pharmacokinetic interactions (41.43%), with moderate severity predominating (78.09%). The number of medications and comorbidities were significantly associated with potential drug interactions ($p < 0.05$). **Conclusion:** The number of drugs and the number of comorbidities affect the potential for drug–drug interactions in outpatients with hypertension at Dr. Iskak Tulungagung Hospital.

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INTRODUCTION

Based on the World Health Organization (2011 in the Ministry of Health, 2013), the prevalence of hypertension throughout the world will continue to experience a significant increase and it is predicted that by 2025, around 29% of adults will suffer from hypertension (Kemenkes, 2013). The prevalence of hypertension in 2018 increased to 34.11% compared to the prevalence of hypertension in 2013, which was 25.8% (Riskesdas, 2013; Balitbangkes RI, 2018; Kemenkes, 2021). Based on official health records from Trenggalek Regency in 2024, hypertension is classified among the ten most prevalent diseases and represents the leading cause of morbidity. The total number of individuals diagnosed with hypertension reached 37,305 cases, comprising 9,444 males and 27,861 females.

Hypertension is a condition in which systolic blood pressure increases more than or equal to 140 mmHg and/or diastolic blood pressure rises more than or equal to 90 mmHg (Kemenkes, 2021). Long-term hypertension is often accompanied by comorbidity and can develop complications because hypertensive patients are at a high risk of experiencing complications and comorbidity (Katzung *et al.*, 2018).

Treatment for hypertension patients usually involves not just one type of drug, but more than one type of drug. This condition is referred to as polypharmacy (Kemenkes, 2021). Polypharmacy is defined as the use of a large number of drugs in one prescription at the same time. Polypharmacy is classified into two, namely minor polypharmacy of 2 - 4 types of drugs and major polypharmacy ≥ 4 types of drugs in one prescription (Romadhoni *et al.*, 2022)

Polypharmacy in hypertension management often heightens risks of drug-drug interactions (DDIs), particularly among older adults or those with comorbidities like diabetes or heart disease. Hypertensive patients face polypharmacy in 81% of cases, far exceeding normotensive groups (65%), with average drug counts around 5-6 per patient leading to DDIs in 48-53%. (Diaconu *et al*., 2021). Because hypertension patients take their medications for extended periods, which can affect therapy and the anticipated efficacy of treatment, it is crucial to discover drug interactions in these individuals (Mukete and Ferdinand, 2016; Parulian *et al*, 2019)

MATERIAL AND METHODS

Methods

This study employed an observational method with an analytical approach and retrospective data collection. This study was conducted at Iskak Tulungagung Hospital in March - April 2024. The population of medical record data of patients with a history of hypertension in the outpatient installation of Dr. Iskak Tulungagung Hospital for the period January - December 2023 was 2641 patients. Medical record information from the most recent visit that satisfied the inclusion requirements served as the study's sample. The sample was determined using the Slovin formula, resulting in 96. The sampling

technique used was non-probability sampling with a purposive sampling type. The instruments used were medical record data, data collection sheets, Drugs Interaction Checker on Drugs.com and Medscape applications.

Data Processing and Analysis

Data were analyzed including univariate, bivariate, and multivariate analysis. In univariate analysis using Microsoft Excel 2013 software which aims to describe the characteristics of polypharmacy and potential drug interactions. Bivariate analysis to determine whether there is a relationship between polypharmacy and potential drug interactions using SPSS version 23 with the chi-square test. Multivariate analysis using multiple logistic regression to determine the factors that most influence the potential for drug interactions.

Research Ethics Test

Prior to starting the study, an ethical clearance was conducted, specifically at the Health Research Ethics Commission of Dr. Iskak Tulungagung Hospital (number 070/3266/24.09/2024) and the Research Ethics Commission of Institut Ilmu Kesehatan Bhakti Wiyata Kediri (number 679/FF/EP/I/2024).

RESULTS AND DISCUSSION

Characteristics of Research Samples

The results showed that most participants were male 57 patients (59.38%), while females accounted for 39 patients (40.62%). The results of this study are in line with the research of Setyoningsih (2022) which explained that patients with hypertension with the male gender tended to be higher, namely 21 patients (51.2%) than female patients 20 patients (48.8%). This is because hypertension is associated with the lifestyle of most men, namely an unhealthy lifestyle and other risk factors such as obesity or being overweight, excessive salt intake, stress, smoking habits, and low alcohol tolerance, resulting in consuming alcohol in larger amounts (Princewel *et al*., 2019; Setyoningsih and Zaini, 2022; Tumanduk *et al*., 2019).

Hypertensive patients in the late elderly category (56 - 65 years) have a high percentage, namely (37.50%) as many as 36 patients. This corroborates the findings of Gaol's research (2022), which shows that the largest percentage of respondents – 42 individuals, or 40% - are between the ages of 56 and 65. This may be brought on by reaching the last stages of old age, which means that as people age, their physical health and bodily functions will deteriorate faster. This can lead to a decline in health conditions, a weakened immune system, and a lack of body reaction to disease prevention (Gaol and Simbolon, 2022; Yuwono, Ridwan, and Hanafi, 2017).

Patients with the Social Security Administrative Body (Badan Penyelenggara Jaminan Sosial, abbreviated as BPJS) service type had the highest results, namely 75 patients (78.13%). These findings are consistent with Rahmawati's research from 2021, which found that the anticipated number of BPJS participants has grown. This could be because health services are improving and the program is becoming more modern over time (Rahmawati *et al*., 2021).

The main diagnosis in this study was mostly not a diagnosis of hypertension or hypertension as a secondary diagnosis of 59 patients (61.46%), this result was caused because hypertension did not occupy the top position in the recapitulation of the top 10 outpatient diseases at Dr. Iskak Tulungagung Hospital. The number of drugs in this study was grouped based on Romadhoni (2022). Classified into two classifications, namely minor polypharmacy (2 - 4 types) of drugs in one prescription and major polypharmacy (> 4 types of drugs) in one prescription. The results of this study were that the number of drugs > 4 had the highest percentage, namely 47 patients (48.96%). This is consistent with Romadhoni's study from 2022, which found that patients who took more than four medications had the best outcomes, with 107 prescriptions and a 54.9% percentage. Prescribing in hypertensive patients is very susceptible to polypharmacy because, in addition to hypertension medication, patients also tend to have other comorbid diseases, thus increasing the risk of polypharmacy (Romadhoni *et al*., 2022). General characteristics of the patients can be seen in table 1.

Table 1. General Characteristics of Patients

Patient Characteristics	Total	Percentage (%)
Gender		
Male	57	59.38
Female	39	40.62
Age (year)		
Late Adolescence 17-25	2	2.08
Early Adults 26-35	2	2.08
Late Adults 36-45	8	8.33
Early Seniors 46-55	20	20.83
Late Seniors 56-65	36	37.50
Seniors >65	28	29.17
Type of Service		
BPJS		
-BPJS Mandiri	40	
-BPJS PBI	35	41.67
General	21	36.46
		21.88
Primary Diagnosis	37	38.54
Hypertension		61.46

Potential Drug Interaction Analysis

Based on the results of the analysis of potential drug interactions in Table 2, the analysis of potential drug interactions shows that there is potential for interactions in 63 patients with the highest percentage (65.62%), while in patients who do not have the potential for interactions, there are 33 patients (34.38%). These results support a previous study conducted by Iskandar (2021) which shows that the potential for drug interactions has a higher result (67%) compared to no potential for drug interactions (33%). This can be caused by various factors, namely the severity of the disease, the age of the patient, and the administration of polypharmacy therapy (Iskandar *et al*., 2021).

Table 2. Potential Drug Interactions

Potential Drug Interactions	Total	Percentage (%)
Potential for Interaction	63	65.62
No Potential for Interaction	33	34.38
Total	96	100

Analysis of Potential Interactions Based on Working Mechanism

The potential for interaction based on the mechanism of action can be seen in Table 3. The pharmacodynamic mechanism has the highest results (58.57%) consisting of antagonistic (32.67%) and synergistic (25.90%) pharmacodynamic mechanisms compared to the pharmacokinetic mechanism (41.43%). This is consistent with Yuswar *et al's* study (2022) which showed that pharmacodynamic working mechanisms interaction was higher (93%) and was composed of antagonistic pharmacodynamics (53%) and synergistic mechanisms (40%), as well as pharmacokinetic mechanisms (7%) (Yuswar *et al*., 2022).

Table 3 Analysis of Potential Interactions Based on Working Mechanism

Interaction Mechanism	Total	Percentage (%)
Pharmacokinetics	104	41.43
Pharmacodynamic	147	58.57
Total	251	100

In this study, the most frequent potential pharmacokinetic interaction was amlodipine with bisoprolol. The resulting interaction effect is an increase in serum concentrations caused by several calcium channel blockers inhibiting the CYP450 metabolism of beta blockers that are metabolized in the liver (Drugs.com, 2024). One of the effects that occur due to this interaction is bradycardia, sinus blockade of the heart, and decreased heart rate (Oktianti *et al*., 2023; Sakti Pambudi and Rista Rini, 2024).

The potential for interaction with pharmacodynamic mechanisms is most common in bisoprolol with valsartan, which is associated with unfavorable outcomes in morbidity and mortality in patients with heart failure (Drugs.com, 2024). According to Razoki's 2023 research, combining valsartan and bisoprolol may result in an interaction that affects cardiac morbidity and mortality (Razoki *et al*., 2023).

Analysis of Potential Interactions Based on Severity Level

The potential for drug interactions is categorized based on the severity of the interaction which can be seen more completely in Table 4. The severity level is divided into minor, moderate, and major. The results of the study showed that the potential for drug interactions based on the moderate severity level had the highest results (78.09%), followed by the minor severity level (12.35%), and the last with the lowest results was the major severity level (9.56%). The findings of this study are consistent with Yuswar *et al* (2022) which shows that interactions based on moderate severity levels yield the best results (72%), followed by minor severity levels (22%), and major severity levels (6%) (Yuswar *et al*., 2022).

Table 4 Analysis of Potential Drug Interactions Based on Severity

Severity Level	Total	Percentage (%)
Minor	31	12.35
Moderate	196	78.09
Major	24	9.56
Total	251	100

The potential for drug interactions with a minor level of severity is most often found in furosemide and aspirin because the potential for this interaction can cause the antihypertensive effect of furosemide to be reduced by aspirin. Aspirin causes fluid and salt retention, which is contrary to the diuretic effect. Management that can be done is by monitoring blood pressure and sodium (Preston, 2015).

The potential for moderate-severity interactions is most often found in amlodipine and atorvastatin. The possibility of amlodipine and atorvastatin drug interactions can result in elevated blood levels of atorvastatin and adverse effects like liver damage and rhabdomyolysis, a rare and dangerous disorder that damages skeletal muscle tissue and can occasionally result in kidney damage or death (Razoki *et al.*, 2023).

Valsartan and spironolactone were discovered to have potentially major medication interactions. In order to lessen or prevent the incidence of hypotension, it is advised to utilize a lower starting dose of

valsartan or to reduce the dose of spironolactone due to the possible interaction's hypotensive effects. If given together, it causes an increased risk of hyperkalemia. Management of this interaction is recommended to monitor potassium levels (Mahamudu *et al*., 2017).

Analysis of Factors Affecting Potential Drug Interactions

The results of the analysis can be seen in Table 5. It was found that there was a relationship between polypharmacy and the potential for drug interactions as evidenced by a p-value of 0.041. There was also a relationship between the number of complications and comorbidities with the potential for drug interactions as evidenced by a p-value of 0.0287 where the Sig value < 0.05, then H0 is rejected and Ha is accepted, which means there is a relationship.

Table 5. Analysis of the Relationship between Polypharmacy and Potential Drug Interactions

	Characteristics	Potential for Interaction	No Potential Interaction	*p-value*
Gender	Male	38	19	0.795
	Female	25	14	
Age (year)	Late adolescence 17-25	2	0	0.741
	Early Adults 26-35	1	1	
	Late Adults 36-45	5	3	
	Early Seniors 46-55	14	6	
	Late Seniors 56-65	21	15	
	Seniors >65	20	8	
Type of Service	*BPJS Mandiri*	27	13	0.526
	BPJS PBI	21	14	
	General	15	6	
Primary Diagnosis	Hypertension	22	16	0.197
	Not Hypertension	41	17	
Number of Complications and Comorbidity (per diagnosis)	One	3	7	0.027
	Two	31	17	
	Three	19	9	
	Four	6	0	
	Five	4	0	

This study shows that the results of the bivariate analysis on the variable number of drugs (polypharmacy) have a p-value of 0.041, which means that there is a relationship between polypharmacy and the potential for drug interactions. The p-value of the chi-square test of 0.041, which is less than the alpha value of 0.05 as a benchmark, indicates that there is a significant correlation between the polypharmacy variable and the drug interaction variable when prescribing (Romadhoni *et al*., 2022). There was also a correlation between the number of comorbid complications and the p-value of 0.027, according to the findings of the bivariate analysis utilizing the chi-square test. These findings are consistent with the study by Chaliks (2021) that showed a substantial correlation between comorbidities and the likelihood of drug interactions, with a p-value of 0.028 (Chaliks *et al.*, 2021).

The results of the relationship between the number of complications of accompanying illnesses (comorbidities) and also the number of drugs (polypharmacy) with the occurrence of drug interactions can be caused by the factor of the number of drugs used and the patient suffering from several accompanying illnesses that require additional drug therapy, thus causing an increase in drug interactions that occur in patients (Parulian *et al*., 2019).

Meanwhile, the results of the analysis of patient characteristics, namely gender (p-value 0.795), age (p-value 0.741), type of service (p-value 0.526), and main diagnosis (p-value 0.197) were not significant with potential drug interaction ($p > 0.05$). These findings are consistent with the research of Ekasafitri (2022), which explains why the age component has a p-value of 0.396 and the gender factor has a p-value of 0.296. The p-value for this factor is $p > 0.05$, which means that there is no relationship between gender and age factors with the incidence of drug interactions (Ekasafitri., 2022).

Accordingly, the number of comorbid conditions (comorbid problems) and the number of prescription medications (polypharmacy) are the variables that can affect the likelihood of drug interactions in this study. This can be brought about by the fact that, in addition to their primary illness and their comorbid problems, hypertensive individuals have comorbid conditions that necessitate the use of many medications for treatment. As a result, these patients receive additional therapy, which leads to the use of more medications.

Analysis of the Most Influential Factors with Potential Drug Interactions

Analysis was conducted to identify the factors most strongly associated with the potential for drug interactions. Multivariate analysis was carried out using multiple logistic regression to determine the factors that have the most influence on the potential for drug interactions. The results of the bivariate analysis that had a p-value < 0.25 were entered into a multiple logistic regression analysis, including the number of complications of comorbidities and the number of drugs (polypharmacy) because both showed a significant influence. The results of the multivariate analysis can be seen in Table 6.

Table 6. Multivariate Analysis of Factors Influencing Potential Drug Interactions

Variable	**B**	**S.E**	**Wald**	**df**	**Sig**	**Exp(B)**	**95% C.I. Lower**	**95% C.I. Upper**
Step 1 Number of complications and comorbidities	1.307	0.396	10.908	1	0.001	3.696	1.701	8.029
Number of Drugs	-2.569	0.737	12.156	1	0.000	0.077	0.018	0.325
Constant	1.993	1.067	3.485	1	0.062	7.334		

The results of the multivariate analysis using multiple logistic analysis in Table 6 show that the number of complications and comorbidities have the greatest influence on the potential for drug interactions, as indicated by a value of p=0.001, OR=3.696 (95% CI 1.701-8.029). From the Odds Ratio value, it can be seen that the number of complications and accompanying diseases has a 3.696x chance of causing potential drug interactions.

The results of this study support the research of Shareef *et al*. (2025) which demonstrate that comorbidity burden is the dominant determinant of potential drug–drug interactions (pDDIs) among older adults prescribed NSAIDs, exceeding the influence of age alone and closely interacting with polypharmacy. Higher Charlson Comorbidity Index scores and greater medication counts independently predicted pDDIs, with cardiovascular comorbidities contributing most prominently. The high prevalence of major interactions particularly involving aspirin combinations underscores the clinical vulnerability of this population. Overall, the study supports the need for systematic medication review, targeted deprescribing, and routine use of interaction-screening tools in older patients with multimorbidity to mitigate preventable adverse drug events (Shareef *et al*., 2025).

CONCLUSION

The therapy patterns given to outpatients with hypertension at Dr. Iskak Tulungagung Hospital in 2023 were in the non-polypharmacy category (5.21%), minor polypharmacy of 2 - 4 drugs (45.83%) and major polypharmacy > 4 drugs (48.96%). The administration of therapy with a potential interaction of 65.63% and no potential interaction of 34.38%. The description of the potential interaction in the pharmacokinetic mechanism is 41.43% and pharmacodynamics is 58.57%. Factors influencing the potential for drug interactions in outpatients with hypertension at Dr. Iskak Tulungagung Hospital in 2023 are the number of drugs and the number of complications and comorbidities.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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