Clinical and Pharmaceutical Sciences Journal

Research article

Potential Drug–Drug Interactions in Antihypertensive Therapy Among Outpatients with Comorbidities: Prevalence, Severity, and Clinical Implications

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Received: 30 November 2025 | Revision: 27 January 2026 | Accepted: 31 January 2026

Abstract

Hypertension is a condition that frequently coexists with comorbidities, often necessitating polypharmacy and consequently increasing the risk of drug-drug interactions (DDIs). This study aimed to analyze the pattern and severity of potential DDIs among hypertensive outpatients with comorbidities at North Lombok Regional General Hospital in 2024. This study employed a descriptive observational design with retrospective data collection. A total of 100 outpatient medical records meeting the criteria were selected via probability sampling from the hospital database during January to December 2024. Among the included patients, 50% were aged >60 years, 60% were female, and 91% were covered by the National Health Insurance. Potential DDIs were assessed using the Drugs.com drug interaction checker and categorized based on severity into major, moderate, and minor. A total of 257 potential DDI events were identified, consisting of 19 major interactions (7.4%), 205 moderate interactions (79.8%), and 33 minor interactions (12.8%). The most frequent major interaction was the combination of spironolactone and candesartan, which poses a significant risk of hyperkalemia and hypotension. Moderate interactions were predominantly observed with the combination of furosemide and bisoprolol, which may increase the risk of hyperglycemia and hypertriglyceridemia. Meanwhile, the most frequent minor interaction was aspirin with bisoprolol, which may reduced beta-blocker antihypertensive effect. In conclusion, this study found that moderate-severity potential DDIs were the most prevalent and could significantly impact therapeutic outcomes in hypertensive patients with comorbidities. These findings highlight the critical role of clinical pharmacists in identifying and mitigating clinically significant interactions through rigorous prescription monitoring, patient education, and optimization of drug therapy. Strengthened monitoring and evaluation of drug regimens are recommended to minimize the risk of adverse drug reactions and enhance patient safety.

Keywords: Antihypertensive drugs, drug–drug interactions, hypertension, outpatients, polypharmacy

Introduction

Hypertension is a chronic condition characterized by persistently elevated blood pressure above normal thresholds. According to the Eighth Joint National Committee (JNC VIII), hypertension in individuals aged ≥60 years is defined as blood pressure ≥150/90 mmHg, while in individuals aged <60 years it is defined as blood pressure ≥140/90 mmHg [1]. According to the Indonesian Health Survey, the prevalence of hypertension in the population aged ≥18 years is 30.8%, positioning it as a major contributor to morbidity and disability in individuals aged ≥15 years [2].

This study focuses on North Lombok Regency, one of the districts in West Nusa Tenggara Province, where 12,704 hypertension cases were reported in 2022 [3]. Local data further confirms its significance, with hypertension being the second most common disease in the regency (11,703 cases in 2023) [4] and ranking among the top 10 diseases at the North Lombok Regional General Hospital (860 cases in 2023).

Hypertension management is complicated by comorbidities that often require polypharmacy, thereby increasing the risk of drug–drug interactions (DDIs), particularly among older adults [5,6]. Previous studies have consistently shown a high prevalence of potential DDIs in hypertensive patients, especially in elderly individuals with multiple comorbidities [7]. In Indonesia, a tertiary hospital study reported that 55.8% of hypertensive inpatients were exposed to potential DDIs, predominantly of moderate severity [8]. However, most existing evidence originates from inpatient settings, tertiary or urban hospitals, or mixed disease populations.

Nevertheless, studies from primary healthcare centers in Indonesia have also reported a high prevalence of moderate-severity DDIs among hypertensive outpatients, underscoring the consistency of this issue across levels of care [9]. Data specifically addressing potential DDIs among hypertensive outpatients in regional hospital settings, such as North Lombok Regency, remain scarce. Differences in prescribing practices, drug availability, formulary restrictions, and patient characteristics may limit the generalizability of findings from other regions to this local context.

This study provides original contributions by addressing these gaps. To our knowledge, it is among the first hospital-based pharmacoepidemiological studies to comprehensively describe the patterns and severity distribution of potential DDIs among hypertensive outpatients with comorbidities in North Lombok Regency. Beyond estimating prevalence, this study identifies the most frequent and clinically significant interacting drug combinations, including major interactions such as spironolactone–candesartan and moderate interactions such as furosemide–bisoprolol, within a real-world outpatient setting. By integrating severity classification with commonly prescribed antihypertensive regimens, the findings generate context-specific and actionable evidence to support clinical pharmacy interventions, medication review strategies, and prescription monitoring systems. In doing so, this study bridges the gap between epidemiological data and practical, institution-level patient safety initiatives in regional hospitals.

Therefore, this study aimed to analyze the pattern and severity of potential drug–drug interactions in antihypertensive therapy among outpatients with comorbidities at North Lombok Regional General Hospital in 2024. In this context, clinical pharmacists play a vital role in mitigating medication-related risks through systematic DDI screening, patient education, and optimization of pharmacotherapy, underscoring the importance of strengthening clinical pharmacy services to improve hypertension management and patient safety [10].

Materials and Methods

Materials

Data were obtained from the hospital's electronic medical record system. The extracted variables included patient sociodemographic characteristics (age and gender), documented comorbid conditions, and complete outpatient medication regimens prescribed during the study visit, including both antihypertensive and non-antihypertensive drugs.

Methods

Study Design and Population

This study employed a descriptive observational design with retrospective data collection. The study population consisted of hypertensive outpatients with documented comorbid conditions who received care at the outpatient department of North Lombok Regional General Hospital from January 1 to December 31, 2024.

As a descriptive retrospective study, the primary objective was to characterize the patterns and severity distribution of potential drug–drug interactions (DDIs), rather than to test specific hypotheses or assess clinical outcomes.

Ethical Considerations

Ethical approval for this study was obtained from the Ethics Committee of Ahmad Dahlan University (approval No.: REC-UAD/01/01/01-2025/014). The requirement for informed consent was waived due to the retrospective nature of the study, which utilized anonymized secondary data from medical records.

Sampling and Sample Size

A probability sampling method using simple random sampling was employed. The sample size was calculated based on the reported population of 860 hypertensive outpatients in the preceding year (2023). Using Slovin's formula with a 10% margin of error, the minimum required sample size was 89.5, which was rounded up to 90 patients to avoid underestimation [14]. To enhance representativeness, a final sample of 100 patient records was included in the analysis.

Inclusion and Exclusion Criteria

Patients were included if they were outpatients aged ≥18 years with a documented diagnosis of hypertension (ICD-10 code I10) and at least one comorbid condition, and were prescribed a regimen of two or more medications that included at least one antihypertensive agent. Exclusion criteria were pregnancy or having incomplete medical records (e.g., missing medication lists or comorbidity documentation).

Data Collection and DDI Identification

Data abstraction followed a standardized protocol. For each included patient, all medications listed in the medical record were entered into the Drugs.com interaction checker. Every possible pairwise drug combination within a patient's regimen was screened. Each identified DDI was recorded along with its assigned severity category.

Data analysis

The analysis was descriptive, aligning with the study's objective. Categorical variables (e.g., sex, comorbidity types, DDI severity) are presented as frequencies and percentages. Continuous variables (e.g., age) are summarized using measures of central tendency and dispersion (mean ± standard deviation or median with interquartile range, as appropriate).

This study did not perform stratified or inferential analyses (e.g., to test associations between patient characteristics and DDI severity). Its purpose is to provide foundational, context-specific evidence on the prevalence and severity distribution of potential DDIs. This baseline profile is crucial for informing immediate clinical pharmacy activities (e.g., targeted medication reviews) and for establishing priorities for future analytical studies that can investigate predictors and clinical outcomes of DDIs in this setting.

Results and Discussion

Sociodemographic Characteristics and Clinical Interpretation

A total of 100 hypertensive outpatients with comorbidities were included in the study. Half of the patients were aged >60 years (50%, n = 50), followed by those aged 36–60 years (49%, n = 49) and 18–35 years (1%, n = 1). This age distribution reflects the progressive nature of hypertension, in which age-related vascular remodeling, increased arterial stiffness, and endothelial dysfunction contribute to both disease onset and complication development [11]. Female patients constituted a larger proportion of the study population (60%, n = 60) compared with males (40%, n = 40). This pattern is consistent with epidemiological data showing increased hypertension prevalence among postmenopausal women, likely related to estrogen decline and its effects on vascular tone and endothelial function [12,13]. Most patients were covered by Indonesia's National Health Insurance (91%, n = 91), indicating substantial reliance on public health insurance for chronic disease management. Insurance coverage has been associated with improved access to healthcare services and continuity of pharmacotherapy, which are critical in long-term hypertension management [14]. The sociodemographic and administrative characteristics of hypertensive outpatients are presented in Table 1.

Table 1. Sociodemographic and Administrative Characteristics of Hypertensive Outpatients (n = 100)

Sociodemographic Characteristics		Frequency (n)	Percentage (%)
Age (years)	≥18-35	1	1
	36-60	49	49
	>60	50	50
Gender	Female	60	60
	Male	40	40
Insurance	National Health Insurance	91	91
	Other	9	9

Comorbidity Profile

A total of 145 comorbid conditions were identified among the 100 patients, indicating that multiple comorbidities per patient were common. Cardiovascular comorbidities were the most prevalent (44.1%, n = 64), followed by endocrine disorders (17.2%, n = 25) and neurological conditions (15.2%, n = 22). Cardiovascular comorbidities primarily included coronary artery disease, cardiomegaly, and cardiomyopathy, conditions that are pathophysiologically linked to prolonged blood pressure elevation through mechanisms such as left ventricular hypertrophy and accelerated atherosclerosis [5,11,15]. Endocrine disorders were dominated by type 2 diabetes mellitus,

a well-recognized comorbidity that synergistically increases cardiovascular and renal risk when coexisting with hypertension [16].

Neurological comorbidities, including peripheral neuropathy, vertigo, and anxiety disorders, were also common and may contribute to complex medication regimens, thereby increasing the risk of polypharmacy-related DDIs [17]. Chronic kidney disease and hyperuricemia, categorized under renal and urological disorders, were present in 4.8% of cases, reinforcing the established bidirectional relationship between hypertension and renal dysfunction [18]. The distribution of comorbidities by organ system and specific diseases among hypertensive outpatients is presented in Table 2.

Table 2. Distribution of comorbidities by organ system and specific diseases among hypertensive outpatients at North Lombok Regional General Hospital in 2024 (n = 145 comorbidities)

Organ System	Specific diseases	Frequency (n)	Percentage (%)
Cardiovascular	Coronary artery disease, cardiomegaly, cardiomyopathy	64	44.1
Endocrine	Type 2 diabetes mellitus, hyperthyroidism	25	17.2
Nervous system	Neuropathy, vertigo, anxiety disorder	22	15.2
Digestive	Gastroesophageal reflux disease, dyspepsia, constipation	9	6.2
Musculoskeletal	Low back pain, osteoarthritis	7	4.8
Kidney and Urology	Chronic kidney disease, hyperuricemia	7	4.8
Reproductive	Ovarian cyst, benign prostatic hyperplasia	5	3.5
Respiratory	Upper respiratory tract infection, acute bronchitis	4	2.8
Hepatobiliary	Chronic liver disease, gallbladder polyp	2	1.4

Note: Several patients had more than one comorbid condition.

Pattern and Severity of Potential Drug-Drug Interactions (DDIs)

Screening of antihypertensive medication regimens identified a total of 257 potential drug–drug interactions (DDIs). As shown in Table 3, moderate-severity interactions were most common (79.8%, n = 205), followed by minor (12.8%, n = 33) and major interactions (7.4%, n = 19). The predominance of moderate DDIs indicates a substantial clinical burden, as these interactions may reduce therapeutic efficacy or necessitate dose adjustments and close monitoring [8,17]. Although predictors of high-severity DDIs were not formally assessed in this study, the observed patterns suggest that polypharmacy, clustering of cardiovascular–endocrine comorbidities, and frequent use of renin–angiotensin system inhibitors and diuretics may contribute to increased interaction risk. These findings highlight the importance of proactive medication review and pharmacist-led prescription screening in outpatient hypertension care. The majority of identified potential drug–drug interactions were classified as moderate in severity, as presented in Table 3.

Table 3. Severity Distribution of Identified Potential DDIs (n = 257)

Severity	Number of Interactions (n)	Percentage (%)
Major	19	7.4
Moderate	205	79.8
Minor	33	12.8

Major-level interaction of drugs

A total of 19 major potential drug–drug interactions (DDIs) were identified, representing 7.4% of all interactions. The specific combinations, their frequencies, and potential clinical implications are summarized in Table 4. These interactions are clinically significant, as they are associated with serious adverse effects and typically require active intervention or therapy modification [17]. The most frequent major drug–drug interactions among hypertensive outpatients with comorbidities are summarized in Table 4.

Table 4. Most Frequently Identified Major Drug–Drug Interactions Among Hypertensive Outpatients with Comorbidities (n = 19).

Drug Combination	Cases (n)	Percentage (%)	Effects / Clinical Impact
Spironolactone + Candesartan	7	36.8	Hyperkalemia, hypotension
Amlodipine + Simvastatin	3	15.8	Increased risk of rhabdomyolysis
Spironolactone + Ramipril	2	10.5	Hyperkalemia
Clopidogrel + Rosuvastatin	1	5.3	Increased risk of musculoskeletal toxicity
Gemfibrozil + Simvastatin	1	5.3	Increased risk of rhabdomyolysis
Omeprazole + Clopidogrel	1	5.3	Reduced antiplatelet effect
Potassium chloride + Candesartan	1	5.3	Hyperkalemia
Potassium chloride + Spironolactone	1	5.3	Hyperkalemia
Warfarin + Aspirin	1	5.3	Increased bleeding risk
Warfarin + Clopidogrel	1	5.3	Increased bleeding risk

Note: Percentages are calculated based on the total number of major DDIs (n = 19).

The most frequent major DDI was spironolactone combined with candesartan (7 cases, 36.8%). This pattern likely reflects prescribing practices in patients with hypertension complicated by heart failure with reduced ejection fraction (HFrEF) or resistant hypertension, where both agents are guideline-recommended for improving morbidity and mortality [19]. However, in patients with diabetes or chronic kidney disease—conditions prevalent in this cohort—this combination significantly increases the risk of severe hyperkalemia due to synergistic inhibition of the renin-angiotensin-aldosterone system and potassium-sparing effects [20]. These findings underscore the importance of routine monitoring of serum potassium and renal function, particularly in outpatient settings, especially among elderly patients exposed to polypharmacy and potentially inappropriate medications [17,20].

Other major DDIs, such as amlodipine with simvastatin, illustrate risks associated with polypharmacy in cardiovascular management. Amlodipine can inhibit simvastatin metabolism, elevating statin exposure and increasing the risk of rhabdomyolysis [21]. Awareness of such interactions highlights the need for careful medication reconciliation and the consideration of safer alternatives, such as atorvastatin or pravastatin, when clinically appropriate.Overall, these findings provide actionable insights for clinical practice. They identify high-priority drug combinations for targeted pharmacist-led interventions, suggest the implementation of monitoring protocols and prescribing alerts, and emphasize a multidisciplinary approach to optimize patient safety while maintaining therapeutic efficacy.

Moderate Drug–Drug Interactions

A total of 205 moderate-severity potential DDIs were identified, constituting the majority (79.8%) of all interactions. These are summarized in Table 5. Moderate DDIs may result in clinical deterioration or reduced efficacy but are often manageable through monitoring or dosage adjustment [17]. The most frequent moderate interaction was furosemide combined with bisoprolol (21 cases, 10.2%), which may cause hyperglycemia and hypertriglyceridemia, particularly relevant for diabetic patients. Management of this interaction includes monitoring serum potassium, blood glucose, and blood pressure [22]. Other common combinations included amlodipine with bisoprolol (15 cases, 7.3%), which primarily increases the risk of hypotension and requires dose adjustment and careful monitoring, and spironolactone with bisoprolol (11 cases, 5.4%), which may contribute to metabolic and electrolyte disturbances, particularly in patients with diabetes or renal impairment. Interactions between beta-blockers and insulin, including insulin glargine and insulin aspart (total n = 16, 7.8%), may result in hypoglycemia and masked adrenergic symptoms, highlighting the importance of glucose monitoring in diabetic patients [23]. The most frequent moderate drug–drug interactions are presented in Table 5.

Table 5. Most Frequent Moderate DDIs (n = 205)

Drug combination	Cases (n)	Percentage (%)	Effects / Clinical Impact
Furosemide + Bisoprolol	21	10.2	Increase the risk of hyperglycemia and hypertriglyceridemia
Amlodipine + Bisoprolol	15	7.3	Hypotension
Spironolactone + Bisoprolol	11	5.4	Increase the risk of hyperglycemia and hypertriglyceridemia
Bisoprolol + Insulin Glargine	10	4.9	Hypoglycemia
Furosemide + Lansoprazole	7	3.4	Hypomagnesemia
Candesartan + Insulin Glargine	7	3.4	Hypoglycemia
Simvastatin + Lansoprazole	7	3.4	Increased statin exposure, Rhabdomyolysis
Bisoprolol + Insulin Aspart	6	2.9	Hypoglycemia
Bisoprolol + Meloxicam	5	2.4	Reduced antihypertensive effect, Hypertension
Clopidogrel + Lansoprazole	5	2.4	Reduced antiplatelet effect

Note : Percentages are calculated relative to the total number of moderate interactions (n = 205). The top 10 combinations account for 45.9% of all moderate interactions.

Additional moderate interactions involved furosemide or candesartan with proton pump inhibitors such as lansoprazole (n = 14, 3.4–3.4%), which may cause hypomagnesemia or alter drug efficacy, and simvastatin with lansoprazole (7 cases, 3.4%), which can increase statin exposure and the risk of rhabdomyolysis [21]. Other combinations, including bisoprolol with meloxicam (5 cases, 2.4%) and clopidogrel with lansoprazole (5 cases, 2.4%), may reduce antihypertensive or antiplatelet efficacy, respectively [24]. Collectively, the top ten moderate-severity combinations accounted for 45.9% of all moderate DDIs, reflecting common polypharmacy patterns in outpatient hypertensive populations.

These observed patterns are consistent with prior studies reporting beta-blocker–diuretic and beta-blocker–insulin combinations as leading contributors to moderate-severity interactions in hypertensive outpatients [17]. The

findings underscore the predictable risks associated with polypharmacy in patients with multiple comorbidities, particularly cardiovascular and metabolic disorders. Clinically, these interactions are generally manageable through structured monitoring and dose adjustment; however, systematic medication review, vigilant clinical follow-up, and patient education remain essential components of safe pharmacotherapy [25].

Minor Drug–Drug Interactions

A total of 33 minor DDIs were identified. Minor interactions generally have limited clinical impact, but monitoring is recommended. The most frequent minor drug–drug interactions identified in this study are presented in Table 6.

Table 6. Most Frequent Minor DDIs (n = 33)

Drug Combination	Cases (n)	Percentage (%)	Effects / Clinical Impact
Aspirin + Bisoprolol	17	51.5	Reduced beta-blocker antihypertensive effect; potential loss of blood pressure control
Aspirin + Lansoprazole	6	18.2	Reduced aspirin bioavailability
Amlodipine + Lisinopril	2	6.1	Hypotension
Aspirin + Spironolactone	2	6.1	Reduced diuretic effect
Amlodipine + Ramipril	1	3.0	Hypotension
Aspirin + Nitroglycerin	1	3.0	Hypotension
Captopril + Amlodipine	1	3.0	Hypotension
Paracetamol + Clidinium	1	3.0	Reduced paracetamol absorption
Sucralfate + Bisoprolol	1	3.0	Reduced beta-blocker bioavailability
Warfarin + Simvastatin	1	3.0	Increased risk of rhabdomyolysis

The most frequent minor interaction was aspirin combined with bisoprolol (17 cases, 51.5%), which may attenuate beta-blocker efficacy and contribute to hypotension, followed by aspirin with lansoprazole (6 cases, 18.2%), which may reduce aspirin's antiplatelet bioavailability. Although classified as minor, the warfarin–simvastatin interaction warrants clinical attention, as simvastatin may increase warfarin exposure and INR, highlighting the need for monitoring interactions involving narrow-therapeutic-index drugs even at lower severity levels (Mar et al., 2022). The predominance of aspirin-related interactions reflects the widespread use of low-dose aspirin for secondary cardiovascular prevention and the frequent co-prescription of proton pump inhibitors for gastrointestinal protection, as also observed in community pharmacy studies in Indonesia [8]. Consistent with previous evidence, these minor DDIs may still carry clinically relevant consequences through pharmacodynamic or pharmacokinetic mechanisms and therefore require appropriate clinical vigilance [17].

Therefore, minor DDIs often represent therapeutic trade-offs rather than simple oversights, requiring nuanced clinical judgment. Translating these findings into practice, clinical pharmacists can implement targeted interventions to optimize therapy. For patients on aspirin and bisoprolol, pharmacists should verify the indication for aspirin, emphasize adherence, counsel patients on signs of hypotension, and monitor blood pressure and heart rate during follow-up. For aspirin co-administered with PPIs such as lansoprazole, pharmacists should educate patients on optimal timing of administration, engage prescribers to review the necessity of long-term PPI use, and suggest alternatives like H2-receptor antagonists for lower-risk patients when appropriate, balancing gastrointestinal protection with antiplatelet efficacy. At the system level, these high-frequency minor interactions can be integrated into prescription screening software alerts with guidance for counseling or monitoring, ensuring consistent intervention. By framing minor DDIs as indicators of complex therapeutic balancing, pharmacists shift from passive identifiers to active managers of chronic therapy, mitigating even subtle risks and supporting cumulative therapeutic goals to enhance the quality and safety of pharmacotherapy in outpatient settings. This study is limited by its reliance on prescribed medication data without assessing patient adherence or actual clinical outcomes, which may lead to under- or overestimation of the real impact of drug–drug interactions. The single-center, cross-sectional design also limits generalizability to other outpatient populations. Additionally, factors such as renal or hepatic function, over-the-counter, and herbal medication use were not systematically captured, which could influence interaction risk. Future research should employ prospective designs with clinical outcome monitoring and evaluate the effectiveness of pharmacist-led interventions in mitigating DDI-related risks among hypertensive outpatients.

Conclusion

This study highlights that polypharmacy management in hypertensive outpatients with comorbidities is a complex challenge, predominantly characterized by a substantial burden of moderate-severity potential DDIs, which accounted for 79.8% of all identified interactions. While major and minor DDIs were less frequent, the frequent

occurrence of spironolactone-candesartan combinations and other high-risk moderate interactions underscores scenarios requiring careful monitoring. The observed DDI patterns likely reflect standard yet multifaceted pharmacotherapy for cardiovascular and metabolic comorbidities, where the benefits of combined therapy often outweigh manageable risks under structured follow-up and pharmacist-led monitoring, consistent with findings in similar outpatient populations.

Acknowledgment

The authors express their gratitude to the management and staff of North Lombok Regional General Hospital for their support and facilitation of this research.he authors thank to Ahmad Dahlan University for supporting this study.

Declarations

Author contribution	:	Ade contributed to research conceptualization, data collection, and analysis. Prita acted as corresponding author and provided critical review. Imaniar, Woro, Andriana and Bilal contributed to data interpretation and manuscript review. All authors have read and approved the final manuscript.
Funding statement	:	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflict of interest	:	The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Ethics Declaration	:	This study was approved by the Research Ethics Committee of Ahmad Dahlan University (approval No: REC-UAD/01/01/01-2025/014).
Additional information	:	The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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