

Factors contributing to the prevalence of potential drug-drug interactions among hospitalized elderly patients in a tertiary hospital in Eastern Java, Indonesia

Shah Faisal¹, Junaidi Khotib², Cahyo Wibisono³, Khusnul Fitri Hamidah⁴, Febriansyah Nur Utomo⁴, Elida Zairina^{2,5,6}



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Authors' affiliations:

¹Department of Pharmacy, CECOS University of IT and Emerging Sciences, Peshawar, Pakistan, ²Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia, ³Universitas Airlangga Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, ⁴Universitas Airlangga Hospital, Surabaya, Indonesia, ⁵Innovative Pharmacy Practice and Integrated Outcome Research (INACORE) Group, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia, ⁶Center of Excellence for Patient Safety and Quality, Universitas Airlangga, Surabaya, Indonesia

Corresponding author:

Elida Zairina
Department of Pharmacy Practice,
Faculty of Pharmacy, Universitas
Airlangga, Jalan Dokter Ir. Haji Soekarno,
Mulyorejo, Surabaya 60115, East Java,
Indonesia
Tel/Fax: +62-031-5933150/
+62-031-5935249
E-mail: elida-z@ff.unair.ac.id

ABSTRACT

BACKGROUND Drug-drug interactions (DDIs) are the primary cause of adverse drug events. However, studies on potential DDIs (pDDIs) in hospitalized older adult patients in Indonesia remain limited. Therefore, this study aimed to investigate the prevalence and potential risk factors of pDDIs in this population.

METHODS A prospective observational study assessing the medical profiles of hospitalized elderly patients was conducted at Universitas Airlangga Hospital from September 2023 to February 2024. Patient characteristics were recorded, and Micromedex® Drug-Reax software was used to check the pDDIs. Ethical approval was obtained for this study (No. 078/KEP/2023). Data were analyzed using SPSS software (version 26).

RESULTS Of the 409 patients, 41.9% of the prescriptions contained pDDIs. Furthermore, 73 prescriptions (17.1%) had at least one pDDI, with 1–6 interactions per prescription. Of the 369 identified pDDIs, 209 (56.6%) were major interactions. Logistic regression analysis revealed increased odds of pDDIs in patients with previous medication use (adjusted odds ratio [aOR] = 2.254; crude odds ratio [cOR] = 1.771), polypharmacy (aOR = 16.309; cOR = 11.709), circulatory diseases (aOR = 4.082; cOR = 4.788), and genitourinary diseases (aOR = 1.819; cOR = 1.855). Conversely, patients with digestive system diseases had a significantly lower risk (aOR = 0.573; cOR = 0.608).

CONCLUSIONS This study found a high prevalence of pDDIs (41.1%) among older hospitalized patients in Indonesia. Modifiable factors, such as polypharmacy and previous medication use, can reduce the risk of pDDIs and avoid adverse events.

KEYWORDS chronic disease, drug interactions, elderly, polypharmacy

Elderly patients are the largest consumers of medication and the most rapidly growing population sector worldwide, making drug treatment for elderly patients a critical aspect of healthcare. In Indonesia, the fourth most populous country worldwide, elderly individuals (≥ 60 years) constitute almost 10% (26.8 million) of the population.¹ Medication use increases with age, commonly leading to polypharmacy in older adults. Polypharmacy, defined as the regular use of

five or more medications simultaneously, is a factor that adds to treatment complexity and influences elderly health.² Specifically, polypharmacy raises the chances of unwanted adverse drug events, such as drug-drug interactions (DDIs), which are particularly common in elderly patients and those with multiple chronic conditions and multiple drug prescriptions.³ Polypharmacy is considered a concern due to its association with undesirable health outcomes, as it

leads to drug interactions that cause adverse reactions and the deterioration of functional status.^{4,5}

In elderly patients, DDIs and inappropriate medications significantly compromise health, leading to affliction, poor quality of life, prolonged hospital stays, greater reliance on ambulatory services, and increased healthcare costs.⁶ Polypharmacy increases the risk of potential DDIs (pDDIs) in the elderly, with prevalence rising as the number of medications used per day increases.^{7,8} One study in the United States reported that three-quarters of the included polypharmacy patients had experienced at least one severe pDDI.⁹ High-risk groups include those on antithrombotic and anticoagulant therapy, intensive care unit patients, individuals with excessive medication use, and those with prolonged hospital stays.¹⁰ Notably, 73.8% of patients hospitalized for seven or more days were at a risk of DDIs.⁹

DDIs are preventable, but may result in significant adverse effects or ineffective treatment outcomes.¹¹ One study found that 38% of patients are exposed to clinically relevant pDDIs,¹¹ often resulting in predictable and manageable adverse reactions.¹² Although DDIs can cause serious harm to patients, their actual impact remains unclear. In hospitalized patients, pDDIs are estimated to occur in up to 45% of cases, contributing to longer hospital stays and increased healthcare costs.¹³ A systematic review stated that up to 41.3% of hospital admissions were caused by drug-related problems in different health care settings.¹⁴ Another systematic review reported a high prevalence of pDDIs in Indonesia, with estimates ranging from 0.9% to 99%.¹⁵ In this context, the present study aimed to investigate the prevalence and risk factors of pDDIs in elderly patients with chronic diseases admitted to a single teaching hospital in Indonesia. Identifying these factors could help to reduce pDDIs and prevent potential harm to vulnerable populations.

METHODS

Patients

This prospective observational study of older adult patients was conducted in the inpatient department of the Universitas Airlangga Hospital, Surabaya, Indonesia. The study was conducted over six months from September 2023 to February 2024. The inclusion criteria were as follows: patients aged ≥60 years who were admitted to the hospital for at least 24 h, had at

least one chronic condition, understood the purpose and scope of the study, and provided informed consent to participate. Patients who were unable to communicate properly and those with mental conditions were excluded.

Measures

Eligible patients were interviewed to obtain all relevant demographic and clinical data. Medication use and diagnoses at the time of admission were extracted from the medical records, and drug interactions were identified using Micromedex® Drug-Reax (Merative, USA) a system known for its high sensitivity.¹⁶ This software categorizes pDDIs according to severity (minor, moderate, severe, or contraindicated) and documentation quality (fair, good, or excellent). Prescribed medications were cross-checked to ensure accuracy. Polypharmacy was defined as the use of five or more medications at admission.¹⁷ Furthermore, disease conditions were categorized based on the International Classification of Disease Tenth Revision (ICD-10) classification system.

Ethical approval

The Research Ethics Committees of the Faculty of Pharmacy, Universitas Airlangga (No: 29/LE/2022) and Universitas Airlangga Hospital (No: 078/KEP/2023) approved the study protocols, and the study was conducted in compliance with the Declaration of Helsinki.¹⁸

Statistical analysis

Data were analyzed using the statistical package IBM SPSS software version 26, for Windows 10 (IBM Corp., USA). Descriptive data included frequencies and percentages of patient characteristics and the severity and documentation of pDDIs. Chi-square or Fisher's exact tests were conducted to identify any differences between the demographic and clinical characteristics of patients with polypharmacy at discharge. Binary logistic regression analysis was applied to analyze the risk factors associated with pDDIs at the time of discharge. The crude odds ratio (cOR) and adjusted odds ratio (aOR) were calculated for the adjusted model. All available independent variables considered clinically relevant were included in the adjusted model. All variables were entered simultaneously into a multivariable logistic regression to estimate the independent association of each predictor with

pDDIs. For all tests, the statistical significance was set at $p < 0.05$.

RESULTS

This study enrolled 409 hospitalized patients with a mean age of 67.91 years, the majority of whom (52.3%) were male. Among them, 76.3% had previously been prescribed medications, and 30.6% used self-medication. Comorbidities were present in 41.3% (169 patients); 28.6% (117 patients) had respiratory system diseases, and 69.9% (286 patients) had circulatory system diseases. A total of 168 patients (41.1%) had at least one pDDI during admission. This included 83 (38.8%) of all male patients and 85 (43.6%) of all female patients. Significant differences in pDDI prevalence were observed among patients with previous medications, comorbidities, and circulatory, digestive, and genitourinary system disorders (Table 1). In the crude binary logistic regression model, previous use of medications was found to be associated with

an increased risk of developing pDDIs. Patients with polypharmacy at the hospital had higher odds of developing pDDIs during admission. Among the disease conditions, circulatory system diseases were associated with a higher risk of developing pDDIs during the hospital stay. In the adjusted model, polypharmacy and circulatory system diseases were identified as key risk factors as shown in Table 1.

Table 2 shows the severity and documentation of the pDDIs. During admission, the severity of 209 (56.6%) interactions was major. In addition, majority of the pDDIs, 188 (50.9%) provided fair documentation. Table 3 shows the ten most frequent pDDIs and their severity, documentation, and outcomes. Aspirin and bisoprolol was the most frequent 36 (16.1%) pDDI combination recorded".

DISCUSSION

In the present study, 41.1% of the enrolled patients had pDDIs during admission. This is in contrast

Table 1. Subjects' characteristics and distribution of pDDIs

Patients' characteristics	N = 409	Presence of pDDIs (N = 168)	<i>p</i>	aOR (95% CI)	<i>p</i>	cOR (95% CI)	<i>p</i>
Age (years), mean (SD)	67.91 (6.599)	-	1.04	0.979 (0.938–1.022)	0.337	0.975 (0.946–1.005)	0.105
Gender, n (%)			0.324				0.324
Male	214 (52.3)	83 (38.8)		1.00		1.00	
Female	195 (47.7)	85 (43.6)		0.815 (0.308–2.157)	0.680	0.820 (0.553–1.217)	
Marital status, n (%)			0.379				
Married	367 (89.7)	153 (41.7)		1.00		1.00	
Unmarried	5 (1.2)	3 (60)		3.276 (0.235–45.599)	0.377	2.098 (0.346–12.707)	0.420
Divorced	37 (9.0)	12 (32.4)		0.865 (0.332–2.254)	0.766	0.671 (0.327–1.378)	0.277
Education, n (%)			0.197				
Primary school	85 (20.8)	32 (37.6)		1.00		1.00	
Junior high school	49 (12.0)	27 (55.1)		1.021 (0.402–2.593)	0.965	2.033 (0.996–4.150)	0.051
Senior high school	228 (55.7)	91 (39.9)		0.776 (0.377–1.595)	0.490	1.100 (0.659–1.837)	0.715
University level	47 (11.5)	18 (38.3)		0.295 (0.096–0.903)	0.032	1.028 (0.494–2.141)	0.941
Occupation, n (%)			0.933				
Unemployed	94 (23.0)	35 (37.2)		1.00		1.00	
Government employee	20 (4.9)	8 (40)		0.494 (0.101–2.417)	0.384	1.124 (0.419–3.017)	0.817
Private employee	87 (21.3)	36 (41.4)		0.441 (0.166–1.172)	0.101	1.190 (0.655–2.163)	0.568
Entrepreneur	42 (10.3)	18 (42.9)		0.453 (0.145–1.420)	0.174	1.264 (0.603–2.651)	0.535
Housewife	166 (40.6)	71 (42.8)		1.232 (0.406–3.733)	0.713	1.260 (0.750–2.117)	0.383

Table continued on next page

Table 1. (Continued)

Patients' characteristics	N = 409	Presence of pDDIs (N = 168)	<i>p</i>	aOR (95% CI)	<i>p</i>	cOR (95% CI)	<i>p</i>
Monthly income in IDR (million), n (%)			0.625				
<3	278 (68.0)	110 (39.6)		1.00		1.00	
3–6	109 (26.7)	49 (45)		1.978 (0.857–4.564)	0.110	1.247 (0.797–1.951)	0.333
>6	22 (5.4)	9 (40.9)		2.835 (0.555–14.473)	0.210	1.057 (0.437–2.557)	0.902
Previous medications, n (%)	312 (76.3)	138 (44.2)	0.020	2.254 (1.167–4.354)	0.016	1.771 (1.090–2.877)	0.021
Visit to multiple health care prescribers, n (%)	97 (23.7)	42 (43.3)	0.610	0.993 (0.519–1.897)	0.982	1.127 (0.711–1.787)	0.610
Self-medications, n (%)	125 (30.6)	48 (38.4)	0.466	1.374 (0.763–2.475)	0.290	0.852 (0.554–1.310)	0.466
Comorbidity, n (%)	169 (41.3)	79 (46.7)	0.050	0.994 (0.916–1.080)	0.894	-	-
Length of hospital stay (days), mean (SD)	5.45 (3.242)	-	0.426	0.891 (0.431–1.842)	0.756	1.489 (0.999–2.221)	
Polypharmacy at hospital, n (%)	209 (51.1)	91 (43.5)	0.060	16.309 (8.847–30.064)	<0.001	11.709 (7.192–19.061)	<0.001
Blood and blood forming organs, n (%)	39 (9.5)	16 (41)	0.995	0.688 (0.268–1.770)	0.438	0.998 (0.510–1.951)	0.995
Endocrine, nutrition, and metabolic disorders, n (%)	213 (52.1)	93 (43.7)	0.268	0.965 (0.496–1.880)	0.917	1.250 (0.842–1.857)	0.268
Disease of the circulatory system, n (%)	286 (69.9)	146 (51)	0.000	4.082 (1.949–8.548)	<0.001	4.788 (2.857–8.022)	<0.001
Diseases of the respiratory system, n (%)	117 (28.6)	40 (34.2)	0.070	0.697 (0.351–1.384)	0.302	0.666 (0.426–1.040)	0.074
Diseases of the digestive system, n (%)	149 (36.4)	50 (33.6)	0.019	0.573 (0.320–1.028)	0.062	0.608 (0.400–0.924)	0.020
Diseases of the genitourinary system, n (%)	63 (15.4)	34 (54)	0.024	1.819 (0.829–3.991)	0.135	1.855 (1.080–3.185)	0.025
Diseases of the nervous system, n (%)	9 (2.2)	5 (55.6)	0.372	1.183 (0.222–6.305)	0.844	1.817 (0.481–6.871)	0.379
Neoplasms, n (%)	15 (3.7)	4 (26.7)	0.248	0.310 (0.073–1.324)	0.114	0.510 (0.160–1.630)	0.256
Skin and subcutaneous disorders, n (%)	68 (16.6)	21 (30.9)	0.061	0.383 (0.184–0.799)	0.010	0.590 (0.338–1.030)	0.063
Connective tissue disorders, n (%)	3 (0.7)	1 (33.3)	0.784	1.258 (0.086–18.430)	0.867	0.716 (0.064–7.956)	0.785
Diseases not elsewhere classified, n (%)	147 (35.9)	55 (37.4)	0.260	1.229 (0.697–2.169)	0.476	0.788 (0.521–1.193)	0.260

CI=confidence interval; IDR=Indonesian rupiah; pDDIs=potential drug-drug interactions; SD=standard deviation

Table 2. Severity and documentation of potential drug-drug interactions (pDDIs) during admission

Category	n (%) (n = 369)
Severity	
Minor	1 (0.3)
Moderate	158 (42.8)
Major	209 (56.6)
Contraindicated	1 (0.3)
Documentation	
Fair	188 (50.9)
Good	94 (25.5)
Excellent	87 (23.6)

with a prior study on geriatric patients in a private hospital, which found a higher prevalence (65%), with cases ranging from 1 to 17 pDDI per patient.⁸ In Indonesia, pDDI prevalence varies widely across healthcare settings, with an estimated range of 0.9–99%.¹⁵ The high prevalence in this study may be due to the inclusion of patients with at least one chronic condition, and that patients with chronic conditions tend to receive more drugs strongly linked to pDDIs.¹⁹ Hospital settings also influence pDDI rates, with variations linked to differences in screening

tools, medical documentation, and medication history recording. In some countries, the insufficient implementation of these measures contributes to a higher pDDI prevalence.¹³

We found that 56.6% of pDDIs were statistically significant. In contrast, a local study on pDDIs among hypertensive patients reported a significantly lower rate (9.8%),²⁰ possibly due to differences in the interaction checker software and study samples. Additionally, this study focused on chronically hospitalized elderly patients, who are inherently more vulnerable to multiple drug use and major pDDIs. The most common pDDI in our study was between aspirin and bisoprolol, which significantly lowered diastolic blood pressure. Although the effect of aspirin on blood pressure remains debatable, low-dose aspirin has been linked to a reduction in blood pressure.²¹ Further, its interactions with bisoprolol may compromise its effect on lowering blood pressure, as it affects the receptor systems.

As expected, the present study confirmed that polypharmacy was a significant risk factor for pDDIs, with patients taking multiple medications having higher odds of developing pDDIs than their counterparts. These findings align with several prior studies investigating polypharmacy as a predominant risk factor for pDDIs.^{12,22–25} However, polypharmacy

Table 3. Top 10 most frequent potential drug-drug interactions (pDDIs) and its severity, documentation, and outcome

Drugs combinations	n (%), (N = 369)	Severity	Documentation	Outcome
Aspirin + bisoprolol	36 (16.1)	Moderate	Good	May result in reduced antihypertensive effect.
Clopidogrel + atorvastatin	21 (9.4)	Moderate	Excellent	May result in decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.
Candesartan + furosemide	17 (7.6)	Major	Fair	May result in severe hypotension and deterioration in renal function.
Candesartan + spironolactone	15 (6.7)	Moderate	Fair	May result in increased risk of hyperkalemia.
Aspirin + spironolactone	10 (4.5)	Major	Good	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.
Amlodipine + clopidogrel	9 (4.0)	Major	Excellent	May result in decreased antiplatelet effect and increased risk of thrombotic events.
Amlodipine + metformin	8 (3.6)	Moderate	Fair	May result in an increased risk of hyperglycemia and potential loss of glycemic control.
Aspirin + furosemide	8 (3.6)	Major	Fair	May result in an increased risk of salicylate toxicity and reduced diuretic effectiveness and possible nephrotoxicity.
Glimepiride + metformin	7 (3.1)	Major	Fair	May result in an increased risk of hypoglycemia.
Clopidogrel + nifedipine	7 (3.1)	Major	Excellent	May result in decreased antiplatelet effect and increased risk of thrombotic events.

should not be assumed to indicate poor care, as its impact needs to be interpreted in the clinical context of individual patients. Clinicians should distinguish between appropriate and inappropriate polypharmacy to reduce inappropriate polypharmacy and severe pDDIs. Although pDDI screening programs classify the concomitant administration of antiplatelets and anticoagulants as high-risk pDDIs (category D) owing to the risk of bleeding, they may still be appropriate for patients with ischemic heart disease and atrial fibrillation. As such, pDDI screening programs cannot replace clinical judgment.

In the present study, patients with circulatory system diseases had a higher risk of developing pDDIs in both the crude and adjusted models. This agrees with a prior study that confirmed that patients with circulatory system diseases have higher odds of developing pDDIs,²⁶ likely owing to evidence-based cardiovascular treatments requiring multiple medications to treat a particular disease.²⁷ Furthermore, patients with genitourinary system disorders have higher odds of developing pDDIs than do their counterparts. Consistent with prior studies, other factors with higher odds for pDDIs included comorbid conditions and the use of previous medications.³

This study provides deep insights into the prevalence, severity, documentation, and PDDI risk factors in hospitalized older patients in Indonesia. These findings highlight the need for healthcare prescribers and clinical pharmacists to closely monitor high-risk groups and their medications. The routine use of interaction checker tools and software in healthcare settings will help to avoid the risk of DDIs. Additionally, this study can help stakeholders establish guidelines and educate healthcare professionals about the risk of pDDIs in older adults to prevent adverse outcomes. However, this study was limited to a single secondary care hospital. Further multicenter studies with larger sample sizes are warranted.

In conclusion, the current study revealed a high prevalence of 168 (41.1%) pDDIs among hospitalized elderly patients, and confirmed that polypharmacy is a predominant risk factor for pDDIs. Moreover, we found that patients with polypharmacy and circulatory system diseases were at a higher risk of developing pDDIs (cOR = 4.788). Additionally, results showed that comorbid conditions, genitourinary system diseases, and digestive system diseases significantly contributed

to a higher pDDI risk. Overall, these results indicate that guidelines for the management of older adult patients are required to avoid the implementation of inappropriate therapies that could induce pDDIs, which, in turn, will decrease the risk of adverse health outcomes.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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