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Analysis of sociodemographic factors associated with adverse drug-drug interaction in patients with stable angina pectoris prescribed polypharmacy at outpatient cardiology clinic Ulin Public Hospital Banjarmasin

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ABSTRACT

Background: Drug interactions can lead to either adverse or beneficial effects due to concomitant administration of drugs. The prevalence of drug interactions in patients with cardiovascular diseases has been reported to be high by 83-91%, especially in stable angina pectoris (SAP) patients. Various sociodemographic factors, including age, sex, education level, occupation, marriage status, and hypertension status, have been identified to influence drug interactions. This study aims to determine sociodemographic factors (age, sex, educational background, occupational status, marital status, and history of hypertension) that influence adverse drug-drug interactions in patients with SAP by using medical records.

Methods: It was a retrospective observational study with a cross-sectional approach conducted at the Outpatient Cardiology Clinic, Ulin Public Hospital Banjarmasin, Indonesia, from 2020 to 2021. The drug-drug interactions were determined by using the Lexicomp tool from the UpToDate® website. Prevalence odds ratios (PORs) and 95% confidence intervals (95%CI) were calculated using a logistic regression test.

Results: We identified 84 SAP patients prescribed 335 drug-drug interactions. Most patients were prescribed major polypharmacy (44 patients, 52.38%), and most interactions were under category C, i.e., close monitoring of therapy (220 interactions, 65.67%). Our study demonstrated that a year increase in age was associated with a significantly increased event of adverse drug-drug interaction by 1.106 times (adjusted POR 1.106, 95%CI 1.003-1.220, p=0.043).

Conclusion: In conclusion, among any other sociodemographic factors, only age was significantly associated with an increased event of adverse drug-drug interactions among SAP patients with polypharmacy at Ulin Public Hospital Banjarmasin, Indonesia.

Keywords: sociodemographic factors, adverse drug-drug interaction, polypharmacy, stable angina pectoris.
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INTRODUCTION

Drug interaction is an unexpected effect in addition to the known normal effects after administration of the drug due to a reaction or interactions with any other drugs given concomitantly. In drug-drug interactions, clinically significant changes in drug effect might lead to harmful or profitable outcomes.[1] The prevalence of potential drug-drug interactions in cardiology is highly reported by 83-9. The probability of identification of interacting drug pairs per prescription is eight times higher in patients with cardiovascular diseases (CVDs) compared to other patients in other specialties. Some risk factors that might influence drug interactions include age, sex, genetic pattern, comorbidity, concomitant treatment, food components, and smoking behavior.[2] Modernization is also associated with risk factors such as diabetes mellitus, abnormal blood lipids, high blood pressure, overweight and obesity, unhealthy diet, poor physical activity, low socioeconomic status, and alcoholism.[3]

Adverse drug interactions do not only interfere with therapeutic goals but also lead to increased morbidity, mortality, and health care costs.[2] Also, drug interactions were associated with an increased use of health services, as shown in some research. A study demonstrated that 1% of all patient admissions to the hospital, 0.05% of visits to the emergency department, 0.6% of hospitalization, and 0.1% of hospitalization returns were caused by adverse drug reactions due to drug interactions.[1] Most cases of bleeding remain a major clinical consequence of multiple drug interactions for CVDs. Adverse effects on the cardiovascular system are the most serious, which can result in hospitalization or even death.[4]

Most of the drug-drug interactions were taken part by antiplatelets and anticoagulants. A combination of heparin and aspirin was identified as the main drug-drug interaction, followed by other drugs such as warfarin, diltiazem, and captopril.[1]

Non-communicable disease, such as stable angina pectoris (SAP), is one of the manifestations of complaints in CVDs, which contributes to one of the most globally burdened diseases.[1,5] Epidemiological data showed that 45% of 9.4 million deaths are caused by coronary heart disease (CHD), the highest cause of death in the world. It is also estimated that the death rate will increase to 23.3 million in 2030.[4,6] According to Riset Kesehatan Dasar (Riskesdas) Indonesia data in 2018, the incidence of SAP in Indonesia increases yearly.[7] As shown in many low- and middle-income countries, the burden of CVDs and its risk factors are high in Indonesia. Prevalence of hypertension and obesity in adult people (aged 18 and over) also increased by 32% and 47%, respectively, during 2013–2018.[7] Cardiovascular problems that occur in South Kalimantan Province are dependent on causal factors, including genetic factors, environment, behavior, health services. These factors play a role in high cases of hypertension in this province. Several studies at Ulin Public Hospital, Banjarmasin, indicated that people with heart disease had risk factors such as hypertension, dyslipidemia, age more than 45 years, male sex, and smoking.[8,9]

Management of SAP includes pharmacotherapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). Pharmacotherapy for SAP, including antiplatelet drugs, anti-ischemic drugs, statins, and other therapies, aims to control risk factors for CVDs as well as therapy for other complications and comorbidity. Patients with CVD are very susceptible to drug interactions due to old age, polypharmacy, and the influence of CVD itself on drug metabolism.[2]

We have not found any studies assessing the association between sociodemographic factors and the risk of harmful drug interactions in Ulin Public Hospital, Banjarmasin, Indonesia. Therefore, this study aims to discover several sociodemographic risk factors associated with these adverse drug-drug interactions in SAP patients with polypharmacy at the Outpatient Cardiology Clinic at Ulin Public Hospital, Banjarmasin, Indonesia, in 2020-2021.

METHODS

Study design and setting

We performed an analytical cross sectional observational study among adult patients with SAP at Ulin Public Hospital, Banjarmasin, Indonesia, from 2020 to 2021. This referral, tertiary, and teaching hospital is in South Kalimantan Province. It serves patients within the province and some provinces nearby, such as Central and East Kalimantan. All the data were collected from patients' medical records at the Outpatient Cardiology Clinic. A patient with SAP was diagnosed by a cardiologist. A diagnosis of SAP was established from history taking, physical examination, a representation of electrocardiography (ECG), a treadmill test, a multi-slice computed tomography (MCTA) angiography, and a directional coronary atherectomy (DCA) catheter. Blood and other examinations were not regularly used to establish the diagnosis, but blood levels of Creatinine Kinase-MB, Troponin I/T, HbA1 and lipid profiles, and x-ray examinations could be performed to determine cardiovascular risk factors. Patients were considered as having polypharmacy when they received at least 6 drugs in one prescription. This study used a total sampling method, and all SAP patients who sought treatment at the outpatient clinic of Ulin Public Hospital, Banjarmasin, Indonesia, in 2020-2021 were included in the study. Patients with incomplete medical records data were excluded from the study.

Research variables

In this population-based study, all research variables (drug prescribed, age, sex, education level, occupation, marital status, and history of hypertension) were collected from patients' medical records. Drug-drug interactions were determined using the Drug Interaction Checker tool Lexicomp® from the UpToDate website. These interactions are then classified into Category A (no interaction known), Category B (no action needed), Category C (benefits outweigh the risks, but the therapy should be under strict supervision to avoid a potency of harm), Category D (considered to modify the therapy and to take the proper action in order to reduce its toxicity), and finally Category X (contraindicated, should be avoided). The drug-drug interactions were then grouped into 2 categories, which are (1) no and low risk of adverse drug-drug interaction (Category A, B, and C) and (2) high risk of adverse drug-drug interactions (Category D and X).

Statistical analysis

The prevalence odds ratio (POR) and 95% confidence interval (CI) for the association between sociodemographic factors and the adverse drug-drug interaction were estimated using logistic regression analysis. Adjusted POR was calculated with adjustment for all risk factors. Missing values were handled by applying complete-case analysis. All analyses were performed using IBM Statistic SPSS version 26, and a p-value <0.05 was considered statistically significant.

RESULTS

Within the study period (2020-2021), we identified 84 patients with SAP at the outpatient cardiology clinic at Ulin Public Hospital Banjarmasin, Indonesia. They were late adults, on average 54.74±9.77 years old. Most of them were males (51 patients, 60.71%), without finishing elementary school (28 patients, 33.33%), self-employed (24 patients, 28.57%), married (69 patients, 82.14%), having comorbidity hypertension (45 patients, 53.57%), and being prescribed 10-12 drug (polypharmacy major) (44 patients, 52.38%). Of 82 patients with SAP prescribed polypharmacy, 44 of them were prescribed 10-12 drugs concomitantly (polypharmacy major) (52.38%), followed by polypharmacy minor (6-9 drugs) and hyper polypharmacy (>12 drugs), i.e., 38 patients (45.24%) and 2 patients (2.38%), respectively. Some missing information was found in some variables, i.e., educational background (29 patients, 34.52%), occupation (42 patients, 50.00%) and marital status (14 patients, 16.67%).

Table 1. Baseline characteristics of patients with stable angina pectoris prescribed polypharmacy at out-patients cardiology clinic Ulin Public Hospital Banjarmasin, Indonesia 2020-2021

Characteristics	n = 84
Age, mean (year, sd)	54.74 ± 9.77
Sex, n (%)	
• Female	33 (39.29)
• Male	51 (60.71)
Educational background, n (%)	
• Graduate & Postgraduate	4 (4.76)
• Elementary Schools - High Schools	23 (27.38)
• Did not graduate from school	28 (33.33)
• Unknown	29 (34.52)
Occupation, n (%)	
• Civil Governments	11 (13.10)
• Unemployed	7 (8.33)
• Self-employed	24 (28.57)
• Unknown	42 (50.00)
Marital Status, n (%)	
• Single	1 (1.19)
• Married	69 (82.14)
• Unknown	14 (16.67)
Hypertension, n (%)	
• No	39 (46.43)
• Yes	45 (53.57)
Polypharmacy, n (%)	
• Hyperpolypharmacy (>12 drugs)	2 (2.38)
• Polypharmacy Major (10-12 drugs)	44 (52.38)
• Polypharmacy Minor (6-9 drugs)	38 (45.24)

Table 2. Frequency of drug-drug interactions according to its risk severity among patients with stable angina pectoris prescribed polypharmacy at Ulin Public Hospital, Banjarmasin, Indonesia

Risk Severity	n=335
• A (no interaction known), n (%)	34 (10.15)
• B (no action needed), n (%)	73 (21.79)
• C (benefits are outweigh of the risks, but the therapy should be under strict supervision to avoid a potency of harm), n (%)	220 (65.67)
• D (considered to modify the therapy and to take the proper action in order to reduce its toxicity), n (%)	8 (2.39)
• X (contraindicated, should be avoided), n (%)	0 (0.00)

Baseline characteristics of patients with SAP are shown in Table 1.

We identified 335 drug-drug interactions for 84 patients with SAP. Based on their risk level of severity, most of them (220 drug-drug interactions, 65.67%) were under Category C, i.e., pharmacotherapy should be closely monitored, followed by Category B, and Category A, i.e., 73 interactions (21.79%) and 34 interactions (10.15%), respectively. We found no drug-drug interactions (0 drug-drug interaction, 0%) was under category X, i.e., drug combination that should be avoided (Table 2). The most common drug-drug interaction under category B was clopidogrel and atorvastatin (10 prescriptions, 2.99%), while under category C was nitroglycerine-bisoprolol (16 prescriptions, 4.78%), and category D was simvastatin-diltiazem (2 prescriptions, 0.60%) and simvastatin-amlodipine (2 prescriptions, 0.60%).

Among all potential variables, we found that only age was significantly associated with adverse drug-drug interaction. This study indicated that a year of increased age was associated with a slightly increased event of adverse drug-drug interaction by 1.106 times (adjusted POR 1.106, 95%CI; 1.003-1.220, p=0.043). In contrast, variables sex, occupation, and history of hypertension were not significantly associated with adverse drug-drug interactions (p>0.05). Some sub-categories in research variables were not able to be statistically analyzed (not applicable, NA) due to no actual (observed) value (zero) in at least one cell, such as variables of educational status and marital status. Complete data on the PORs for each variable on the association between sociodemographic factors and the risk of adverse drug-drug interactions for SAP patients prescribed polypharmacy is presented in Table 3.

DISCUSSION

In our study, patients with SAP were late adults with an average age of about 55. Previous studies supported this finding. Muhibbah et al. (2019) and Adisasmito et al. (2018) showed that patients with a high risk of heart disease were over 45 years old.[8,9] Global epidemiological data specifically demonstrated that angina pectoris affects people aged 45-64 years, increasing by >10% in those aged 65-84.[3]

Among all predicting factors for adverse drug-drug interactions, our study demonstrated that only age was associated with a higher event of adverse drug-drug interactions. One year increase in age was significantly associated with an increased risk of adverse drug-drug interaction by 1.106 (adj. POR 1.106, 95%CI; 1,003-1,220, p=0.043) for patients with SAP. Any other sociodemographic factors such as male sex, self-employment, and comorbidity of hypertension might also be associated with a higher adverse drug-drug interaction, i.e., adj. POR 4.040 (95%CI, 0.364-44.815), 2.236 (0.057-87.604), and 1.492 (0.085-26.324), respectively, for these patients. However, this association was not statistically significant. It might be caused by the fact that our sample size was small. Hence, there was insufficient power to detect a relatively weak association between these factors and the adverse interaction.[10] Meanwhile, the PORs for the association between education levels, unemployment status, marital status and drug interaction could not be statistically analyzed due to zero observed numbers in at least one cell.

Atorvastatin reduces the antiplatelet effect of clopidogrel, but this interaction is

unnecessary as this interaction has limited or no clinical data to support it. Meanwhile, bisoprolol increases the hypotensive effect of nitroglycerin. However, this combination's clinical effect outweighs its adverse risks. Nevertheless, this treatment should be closely monitored for its adverse event.

Drug-drug interaction between simvastatin-amlodipine should be considered to change to decrease its toxicity. Amlodipine can increase the serum concentration of simvastatin. Some studies demonstrated that amlodipine increases total simvastatin (simvastatin acid and all metabolites) by 30%, leading to a higher AUC of simvastatin. However, the lipid-lowering effect of simvastatin is similar when these drugs are either given separately for 4 hours or concomitantly.[11,12] A concomitant therapy of simvastatin-diltiazem should also be considered to change. Co-administration of diltiazem increases the AUC of simvastatin and maximum serum concentration (Cmax) by 2-5 times and 2 times, respectively. The AUC of the active metabolite simvastatin acid increased 2.7-fold concomitant with diltiazem.[13] A cohort study in Taiwan proved that patients receiving statins metabolized by CYP3A4 (such as simvastatin, lovastatin, or atorvastatin) in combination with channel blockers CYP3A4 calcium inhibitors (such as amlodipine, diltiazem, and verapamil) have a significantly higher risk of acute kidney injury, hyperkalemia, acute myocardial infarction, and acute ischemic stroke compared with those who were receiving a statin that is not metabolized by CYP3A4.[14] Multiple case reports also described myalgia, rhabdomyolysis, and hepatitis are associated with the concomitant use of diltiazem-simvastatin.[15]

Potential Clinical Implication

This study demonstrated scientific evidence that age is closely associated with the risk of adverse drug-drug interaction for SAP patients prescribed polypharmacy. The older patients are more susceptible to this harmful interaction. Hence, clinicians should consider giving more than 6 drugs in one prescription to older patients. Ultimately, the harm or even fatal incident might be prevented.

Table 3. Socio-demographic factors associated with adverse drug-drug interaction among patients with stable angina pectoris prescribed polypharmacy at Ulin Public Hospital, Banjarmasin, Indonesia

Variables	Adverse drug-drug interaction					
	No-low risk	High risk	Crude POR (95%CI)	*p-value*	Adjusted POR (95%CI)[¥]	*p-value*
Age, mean (year ± sd)	54.67 ± 9.76	58.38 ± 10.10	1.044 (0.964-1.131)	0.292	1.106 (1.003-1.220)	0.043*
Sex, n (%)				0.686		0.255
• Females	29 (87.88)	4 (12.12)	1		1	
• Males	47 (92.16)	4 (7.84)	0.749 (0.184-3.045)		4.040 (0.364-44.815)	
Education level, n (%)				0.745		
• Undergraduate/postgraduate	4 (100.00)	0 (0.00)	NA		NA	NA
• Elementary school/high schools	23 (100.00)	0 (0.00)	NA		NA	NA
• No schools	23 (82.14)	5 (17.86)	1		1	
Occupation, n (%)				0.731		
• Civil government	10 (90.91)	1 (9.10)	1		1	
• Unemployment	7 (100.00)	0 (0.00)	NA		NA	NA
• Self-employment	23 (95.83)	1 (4.17)	0.506 (0.031-8.286)		2.236 (0.057-87.604)	0.667
Marital status, n (%)				0.779		
• Single	1 (100.00)	0 (0.00)	NA		NA	NA
• Married	63 (91.30)	6 (8.70)	1		1	
Hypertension, n (%)				0.153		
• No	34 (87.18)	5 (12.82)	1		1	
• Yes	42 (93.33)	3 (6.67)	0.304 (0.082-1.481)		1.492 (0.085-26.324)	0.785

Note: CI= confidence intervals; NA = not applicable; POR = prevalence odds ratios; [¥]Adjusted for age, sex, education level, occupation, marital status, and hypertension status; *statistically significant (p<0.05)

Strengths and Limitations

There are several strengths found in this study. This study is the first study assessing sociodemographic factors that influence drug-drug interactions in SAP patients in Indonesia, specifically in Banjarmasin. Also, Lexicomp® is an up-to-date tool to analyze drug interactions supported by the latest references. This tool classifies drug-drug interaction according to its level of severity. It is highly specific and sensitive.

Nevertheless, some limitations need to be mentioned. First, adverse drug-drug interactions were defined theoretically by using a computer tool (Lexicomp® from the UpToDate website) as a proxy for the real adverse events. It might lead to misclassification bias of the outcome. Second, PORs for some predicting factors for drug-drug interactions cannot be statistically calculated because we found no actual numbers, at least in one cell. Hence, conclusions about the association for these variables cannot be drawn. Third, we did not include some other variables that might also contribute to these adverse interactions for SAP patients prescribed polypharmacy, such as smoking behavior, body mass index, and many other co-morbidities. Finally, this study involved relatively small sample size. Thus, the power to detect small differences or effects is low.

CONCLUSION

Our study demonstrated that age is the only variable associated with high-risk adverse drug-drug interactions for patients with SAP patients who are prescribed polypharmacy. An increased age by 1 year is associated with 1.106 times higher risk of adverse drug-drug interactions.

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AUTHOR CONTRIBUTION

All authors contributed to this study. FFA designed the study, collected and analyzed the data, and drafted the manuscript. MB analyzed and interpreted the data and finalized the manuscript. IY and PWN designed the study and criticized the manuscript. DLA criticized the manuscript. All authors agreed to publish.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

The Committee of Medical Research Ethics of Medical Faculty, Universitas Lambung Mangkurat, Banjarmasin, has approved our research protocol with letter No. 547/KEPK-FK ULM/EC/XII/2022.

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