

Risk Assessment of Adverse Drug Reactions in Elderly Patients with Chronic Diseases

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RISK ASSESSMENT OF ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS WITH CHRONIC DISEASES

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ABSTRACT

Introduction: The adverse drug reaction (ADR) is 4-7 times more common in elderly patients. That was also related to changes in pharmacokinetics and pharmacodynamics that triggered the emergence of Drug-Related Problems. **Objective:** The purpose of this study was to assess ADR in elderly patients with chronic diseases using the GerontoNET Score and the Screening Tool of Older Person's Prescriptions (STOPP) criteria. **Methods:** The research design used a cross-sectional study which was analyzed descriptively. The sample consisted of 72 patients, aged over 60 years, accompanied by chronic diseases, and hospitalized at Waluyo Jati Kraksaan Hospital. The exclusion criteria were patients referred to the Intensive Care Unit. Assessment to see the risk of ADR in elderly patients with chronic diseases using the GerontoNet Score while the wrong type of drug is given to elderly patients using the STOPP criteria. The variables contained in the GerontoNET Score are comorbid conditions ≥ 4 (score=1), heart failure (score=1), liver disease (score=1), the number of drugs such as: ≤ 5 (score=0); 6-7 (score=1); ≥ 8 (score=4), history of ADR (score=2), kidney failure (score=1). **Results:** The variable with the most ADR risk factors was the number of drugs ≥ 8 drugs as many as 47 patients (65.3%) with GerontoNET score ≥ 4 as much as 70.8%. The types of drugs included in the STOPP criteria are clopidogrel, Arixtra (fondaparinux), beta-blockers, NSAIDs, and furosemide. **Conclusion:** The risk factor for ADR was the number of drugs ≥ 8 drugs.

ABSTRAK

Latar belakang: Kejadian Reaksi Obat yang Tidak Dikehendaki (ROTD) dialami 4-7 kali lebih banyak pada pasien usia lanjut. Hal ini juga berkaitan dengan perubahan farmakokinetika dan farmakodinamika yang memicu timbulnya Drug Related Problem. **Tujuan:** Tujuan penelitian ini adalah meng-asesmen ROTD pada pasien usia lanjut dengan penyakit kronis menggunakan GerontoNET score dan kriteria Screening Tool of Older People's Prescriptions (STOPP). **Metode:** Desain penelitian menggunakan studi potong lintang yang dianalisis secara deskriptif. Sampel berjumlah 72 pasien dengan usia lebih dari sama dengan 60 tahun disertai dengan penyakit kronis yang menjalani rawat inap di RSUD Waluyo Jati Kraksaan. Kriteria eksklusi adalah pasien yang dirujuk ke Intensif Unit Care. Asesmen untuk melihat resiko ROTD pada pasien usia lanjut dengan penyakit kronis menggunakan GerontoNet Score sedangkan jenis obat yang tidak tepat diberikan pada pasien usia lanjut menggunakan kriteria STOPP. Variabel yang terdapat pada GerontoNET Score berupa kondisi komorbid ≥ 4 (skor=1), gagal jantung (skor=1), gangguan hati (skor=1), jumlah obat yang diterima seperti: ≤ 5 (skor=0); 6-7 (skor=1); ≥ 8 (skor=4), riwayat ROTD (skor=2), gagal ginjal (skor=1). **Hasil:** Hasil penelitian menunjukkan variabel yang mempunyai faktor resiko ROTD terbanyak yaitu jumlah obat yang diterima ≥ 8 macam obat sebanyak 47 pasien (65,3%) dengan GerontoNET score ≥ 4 sebanyak 70,8%. Jenis obat yang masuk dalam kriteria STOPP adalah clopidogrel, arixtra, penghambat beta (beta blocker), NSAID, dan furosemid. **Kesimpulan:** Faktor resiko terjadinya ROTD berupa jumlah obat yang diterima ≥ 8 macam obat.

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Introduction:

An adverse drug reaction event is an unwanted reaction in the body due to a drug-related intervention. Dangerous drug responses can occur in regular doses used by humans for prophylaxis, diagnosis, or therapy (Julianti et al., 2019; Sunny et al., 2018). Several factors influence ADR occurrence, consisting of age, polypharmacy, some comorbidities, inaccuracy in prescribing. A meta-analysis study showed that almost 9% of patients admitted to the hospital due to ADR occurred in the elderly (Gray et al., 2018). The average occurrence of ADR is 4-7 times higher in patients over 65 years of age than young adults (Hashim et al., 2019). Changes in pharmacokinetics and pharmacodynamics have a clinically significant relationship with advancing age, such as drug-related problems (DRP).

DRP in the elderly can occur, one of which is due to polypharmacy. Polypharmacy is a concern in the elderly for several reasons. Older people have a greater risk of developing ADR because of changes in metabolism in the body and decreased drug clearance. This risk will increase with the number of drugs consumed (polypharmacy) (Dagli & Sharma, 2014). In addition, the elderly often experience comorbidities, thereby increasing the prescribing of large amounts of drugs. That also triggers the occurrence of ADR. Prescribing many medications can cause inappropriate treatment in elderly patients (O'Mahony, 2020).

Based on a systematic review study, the prevalence of ADR during hospitalization was 11.5%, and this prevalence increased with comorbidities and polypharmacy in the elderly (Alhawassi, Krass, Bajorek, & Pont, 2014). Research in Indonesia conducted at the Arifin Achmad Hospital showed that of 88 elderly patients, 37 patients had a high risk of experiencing ADR due to polypharmacy and comorbidities (Muharni, Pratiwi, Iswari, Tinggi, & Farmasi, 2019). ADR has a significant effect on health; about 5-7% of

patients admitted to the hospital with ADR, and about 10-20% of all patients admitted to the hospital experience ADR while in hospital (Alhawassi et al., 2014). The study aimed to assess the risk of ADR in elderly patients with chronic disease using the GerontoNET Score and the STOPP criteria. The use of the GerontoNET Score is specifically for elderly patients with chronic conditions. A prospective study showed that the STOPP criteria could significantly identify medication inappropriateness than Beer's criteria, with nearly twice as many medication inaccuracies contributing to hospital admissions in elderly patients (O'Mahony, 2020).

Methods:

The research design used a cross-sectional study and was analyzed descriptively. This study has obtained approval from health research ethics with number E.5.A/008/KEPK-UMM/I/2021. The research sample was elderly patients who underwent hospitalization at the Probolinggo Regency Waluyo Jati Kraksaan RSUD in November 2020 - March 2021. Other health workers accompanied the researcher during data retrieval: Head of Pharmacy Installation and Head of Nurse. The research sample inclusion criteria included elderly patients aged 60 years or more with chronic diseases and who underwent hospitalization at Waluyo Jati Kraksaan Hospital. Exclusion criteria were elderly patients who were referred to the ICU.

The large sample used in this study amounted to 72 patients from 102 elderly patients who were hospitalized. This sample was obtained using 10% precision, the value of the standard variation is 95%, and the prevalence of past research is 25% (O'Connor, Gallagher, Byrne, & O'Mahony, 2012). How to calculate the sample size was used the

$$n = \frac{Z_{1-\alpha/2}^2 p(1-p)}{d^2}$$

Description: $n = 72$ patients; $p = 25\%$; $Z_{1-\alpha/2} = 95\%$; $d = 10\%$. Patients willing to participate in the research are given an approval sheet to be signed (Informed Consent). Then, the researcher saw the patient's medical record data. Researchers would interview patients and health workers if the results of previous drug side effects were not in the patient's medical record.

The assessment was to see the risk of ADR in elderly patients with chronic diseases used the GerontoNET Score. GerontoNET Score contains six variables used to see elderly patients who experience chronic diseases, as in Table 1.

Table 1. Variable GerontoNET Score

Variable	Score
≥ 4 comorbid condition	1
Heart Failure ^a	1
Liver Disease ^b	1
Number of drugs	
≤ 5	0
6-7	1
≥ 8	4
History of ADR	2
Kidney Disorder ^c	1

Annotation :

a = level III and IV according to New York Heart Association (NYHA)

b = increasing of enzyme transaminase two times higher

c = If the glomerular filtration rate is ≤ 60 ml/minute/1.73m²

There were also criteria for the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP), which contains the types of drugs that were not right for elderly patients.

Results:

The risk factor of the ADR obtained as many as 72 patients (Table 2), where the data was a risk factor for ADR, which consists of: the sex is more suffered by men by 62.5%, the average age of 73 years of the patient

(age 60 - 96 years). Most diagnosis with stroke is 23.6%. Comorbid ≥ 4 as many as three patients, the first patient has four comorbidities: Acute Lung Oedema (ALO), heart failure, diarrhea, anemia with the number of drugs received as many as 12 kinds of medicines.

The second patient had five comorbid: tuberculosis (TB), heart failure, ALO, anemia, azotemia, with; the number of drugs received as many as ten types of medicines. The third patient has four comorbidities: heart failure, diabetes mellitus, dyspepsia, azotemia, with the number of drugs received as many as 12 kinds of medicines. The most severe comorbidities patients suffered were 14 with heart disease (22,2%), including heart failure, ST-Elevation Myocardial Infarction (STEMI), non STEMI, atrial fibrillation.

The most diagnosis experienced by the patient (Table 2) was a stroke of 23.6% (17 patients) with 0-3 comorbid; the average patient has one kind of comorbid. The number of drugs received by patients was 5-17 kinds of medicines, averaging ten types of medication during hospitalization. Patients who experienced heart failure were 11 (15.3%) with 0-3 comorbid, with the patient had one kind of comorbid on average. The number of drugs received by patients is 4-18 kinds of medicines, with an average of 12 types of drugs. Seven patients (9.7%) experienced liver disorders with transaminase enzymes >2 times standard value. The number of medications received was 4-16, with eight types of drugs on average. 3 of 7 patients experienced an increase in ALT/AST due to tuberculosis drugs (TBC).

Patients who have a history of ADR were four patients (5.6%). ADR is experienced by as many as four patients in anemia and nausea due to rifampicin and isoniazid drugs. Patients with kidney disorders with glomerular filtration rate (GFR) ≤ 60 ml/min/1.73m² as many as four patients (5.6%) get 5-13 kinds of drugs, with

an average of 9 types of medications during hospitalization.

Table 2. ADR Risk Factor

Variable	Amount (%)
Patient	72 (100)
Gender:	
Male	45 (62,5)
Female	27 (37,5)
Average of age (years)	73
Diagnose:	
Stroke	17 (23,6%)
Heart Failure	11 (15,3%)
TBC	8 (11,1%)
Chronic Obstructive Pulmonary Disease (COPD)	9 (12,5%)
Pneumonia	6 (8,3%)
Acute Coronary Syndrome (ACS)	1 (1,4%)
Hypertensive Heart Disease (HHD)	6 (8,3%)
Hypertension	5 (6,9%)
Diabetes Mellitus (DM)	2 (2,8%)
Liver Failure	2 (2,8%)
Kidney Failure	1 (1,4%)
Abdominal and Pelvic Pain	1 (1,4%)
≥ 4 comorbid	3 (4,2%)
Comorbid Type:	
TBC	10 (13,9%)
COPD	13 (18%)
Hypertension	12 (16,7%)
Heart Disease	14 (22,2%)
Dyspepsia	11 (15,3%)
Anemia	8 (11,1%)
Diabetes Mellitus	6 (8,3%)

Table 2. ADR Risk Factor (continued)

Variable	Amount (%)
Acute Lung Oedema (ALO)	6 (8,3%)
Urinary Tract Infection	3 (4,2%)
Renal Failure	1 (1,4%)
Diarrhea	1 (1,4%)
Ascites	1 (1,4%)
Azotemia	2 (2,8%)
Heart Failure NYHA III & IV	11 (15,3%)
Liver Disease	7 (9,7%)
The number of drugs:	
≤ 5	8 (11,1%)
6-7	17 (23,6%)
≥ 8	47 (65,3%)
History of ADR	4 (5,6%)
Renal Failure GFR ≤60 ml/ menit/1,73m ²	4 (5,6%)

Based on GerontoNET Score (Table 3), as many as 51 patients (70.83%) got a score of ≥ 4 , which was at risk of ADR. Variables that were at risk of ADR were the number of drugs received by patients ≥ 8 kinds of drugs (65.3%) with the primary disease suffered by the patient was a stroke (23.6%), and the most comorbid was heart disease (22.2%).

Table 3. GerontoNET Score

Score	Number of patients	(%)
< 4	21	29,2
≥ 4	51	70,8

I was judging from the STOPP criteria, and seven elderly patients were at risk of developing ADR (Table 4).

Table 4. Types of Drugs according to STOPP Criteria

No	STOPP Criteria	Number of patients
1.	Anticoagulants and antiplatelet Clopidogrel and Arixtra co-administered in one patient with coronary heart disease	3
2.	Endocrine System Beta-blockers are used in patients with DM	2
3.	Musculoskeletal System Administration of diclofenac sodium in heart failure patients	1
4.	Cardiovascular System Loop diuretics a first-line single therapy treatment for high blood pressure patients (furosemide)	1
Total case		7

Discussion:

The risk factor of ADR, in the form of increased age, kidney disorders, comorbidity, polypharmacy, the use of improper drugs (Alhawassi et al., 2014; Dagli & Sharma, 2014). The results of this study were found to have increased the number of medications received by old-age patients ≥ 8 as many as 47 patients (65.3%). Based on a prospective study, every additional treatment recipe in elderly patients caused an increase in ADR risk by 9%. The increase in the number of



drugs had a connection with the inaccuracy in the prescribed. Potentially inappropriate medications called STOPP had a meaningful relationship with increased ADR risk (O'Connor et al., 2012). Fifty-one patients (70.8%) have GerontoNET Score ≥ 4 , where the high risk of ADR occurred. According to O'Connor (2012) research, 50% of patients had an increased risk of ROTD with GerontoNET Score ≥ 4 .

The next most significant risk factor for ADR due to heart disease comorbid (22.2%). Inappropriate administration of drugs in elderly patients, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Calcium Channel Blockers (CCBs), thiazolidinediones, cilostazol in heart failure patients (Lucenteforte et al., 2017).

In this study, seven patients (9.7%) experienced an increase in ALT/AST more than twice the expected value, three patients due to TB treatment. A retrospective study in Cork, Ireland, found a significant difference between age with hepatotoxicity (mean age = 52.95 years) and no hepatotoxicity (mean age = 41.33 years). Hepatotoxicity is more important in elderly patients where an increase in AST occurs at week ten after administration of TB drug therapy (Cusack, Chawke, O'Brien, O'Connor, & O'Connor, 2017). A prospective research study conducted over 12 months found patients with elevated ALT (28%) due to intravenous therapy such as loop diuretics (furosemide), inotropic, vasopressors, beta-blockers (Ambrosy et al., 2013).

The types of drugs included in the STOPP criteria in this study were clopidogrel and Arixtra (4.2%), beta-blockers (1.39%), NSAIDs (9.72%), furosemide (6.9%). According to a systematic literature review, ten types of fatal drugs in treatment neglect, such as NSAIDs, beta-blockers, warfarin, furosemide, methotrexate, digoxin (Saedder et al., 2014).

In this study, patients received furosemide (6.9%) and beta-blockers (1.4%). Beta-blockers such as propranolol undergo

first-pass metabolism in the liver. In elderly patients, it can lead to decreased hepatic clearance and more prolonged elimination $t_{1/2}$ (Alvarez & Mukherjee, 2011). Furosemide causes electrolyte balance disorders by inducing sodium loss into the urine to lead to hepatic encephalopathy (O'Mahony, 2020).

The combination drug Arixtra (fondaparinux) with clopidogrel was given to 3 patients (4.2%). Combining anticoagulant and antiplatelet drugs is more effective than antiplatelet alone for initial therapy and long-term management of acute coronary syndromes. Still, the combination of these drugs can increase the risk of bleeding in patients with acute coronary syndromes and heart valve patients (Barnes, 2020).

In patients with congestive heart failure and diabetes, the use of beta-blockers may affect blood sugar control. This study used beta-blockers of 1.39%. Beta-adrenergic stimulation increased insulin and glucagon secretion as well as glycogenolysis, gluconeogenesis, and lipolysis. Beta-blockers can prolong, expand, or change the symptoms of hypoglycemia. In addition, beta-blockers can potentially increase blood sugar concentrations, and the mechanism of action of beta-blockers is opposite to anti-diabetic drugs (Edoardo & Tikhonoff, 2017).

Conclusion:

There was more than 70% risk of ROTD in Waluyo Jati Kraksaan Hospital. The types of drugs included in the STOPP criteria in elderly patients were clopidogrel, fondaparinux sodium, beta-blockers, furosemide, NSAID class (metamizole, ketorolac).

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