

BUKTI KORESPONDENSI

Jurnal Nasional Terakreditasi Peringkat 3 dan 4

Judul Artikel : *Risk Assessment Of Adverse Drug Reactions In Elderly Patients With Chronic Diseases*

Jurnal : Jurnal Kesehatan dr. Soebandi Vol. 9 No. 2, 26 Oktober 2021

Penulis :

No.	Perihal	Tanggal
1.	Bukti konfirmasi submit artikel	9 Juli 2021
2.	Submit supplementary file (pre-review)	19 Juli 2021
3.	Re-submit untuk perbaikan format penulisan	10 Agustus 2021
4.	Pemberitahuan revisi pertama	5 Oktober 2021
5.	Submit revisi	13 Oktober 2021
6.	Submission diterima	16 Oktober 2021
7.	Proses produksi artikel dan publish artikel	26 Oktober 2021

Bukti Konfirmasi Submit Artikel (9 Juli 2021)

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Re-submit untuk Perbaikan Format Penulisan (10 Agustus 2021)

The screenshot shows a 'Re-submit' notification window from the journal 'Jurnal Kesehatan dr. Soebandi'. The window lists participants: Godeliva Adriani Hendra (godeliva13) and Dyan Wigati (dyanwigati01). It contains two messages: one from Dyan Wigati dated 2021-08-04 09:25 PM regarding a decision to resubmit with specific formatting instructions, and another from Godeliva Adriani Hendra dated 2021-08-10 08:43 PM stating that the revision paper has been attached. A file attachment 'godeliva13, ADR Article.docx' is visible at the bottom.

Re-submit

Participants
Godeliva Adriani Hendra (godeliva13)
Dyan Wigati (dyanwigati01)

Messages

Note	From
Dear author, We have reached a decision regarding your submission and our decision is please resubmit your article with the following notes : In-text citations are shortened (. et al), Reference sources / citations listed in the text are the main reference sources in the form of research reports or articles published in scientific journals in the last 10 years, Citing web pages without "retrieved from" Warm regard,	dyanwigati01 2021-08-04 09:25 PM
Dear editor, I attached the revision paper. Thank you so much for being so attentive. Kind regard, Godeliva A.H	godeliva13 2021-08-10 08:43 PM

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Pemberitahuan Revisi Pertama (5 Oktober 2021)

The screenshot shows a 'Notifications' window from the journal 'Jurnal Kesehatan dr. Soebandi'. The notification is titled '[jkds] Editor Decision' and is dated 2021-10-05 09:32 AM. It informs Godeliva Adriani Hendra that a decision has been reached regarding her submission, 'RISK ASSESSMENT OF ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS WITH CHRONIC DISEASES: English'. The decision is 'Revisions Required'. The notification is signed by Feri Ekaprasetia, with the email address jurnal@stikesdrsoebandi.ac.id. A link to the journal's website is provided at the bottom.

Notifications

[jkds] Editor Decision
2021-10-05 09:32 AM

Godeliva Adriani Hendra:

We have reached a decision regarding your submission to Jurnal Kesehatan dr. Soebandi, "RISK ASSESSMENT OF ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS WITH CHRONIC DISEASES: English".

Our decision is: Revisions Required

Feri Ekaprasetia
jurnal@stikesdrsoebandi.ac.id

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Reviewer's Attachments

File Name	Date
1128 . 306-File Utama Naskah-1124-1-4-20210813.docx	August 28, 2021

Submit Revisi (13 Oktober 2021)

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[jkds] Editor Decision	2021-10-12 05:58 AM
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Godeliva Adriani Hendra:

We have reached a decision regarding your submission to Jurnal Kesehatan dr. Soebandi, "RISK ASSESSMENT OF ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS WITH CHRONIC DISEASES: English".

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Proses Produksi Artikel dan Publish Artikel (26 Oktober 2021)

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

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 furosemide. **Kesimpulan:** Faktor resiko terjadinya ROTD berupa jumlah obat yang diterima ≥ 8 macam obat.

KEYWORD: resiko ROTD, GerontoNET Score, Jenis obat, kriteria STOPP

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 People's Prescriptions (STOPP) criteria. **Methods:** The research design used a cross-sectional study which was analyzed descriptively. The sample consisted of 72 patients, aged more than 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.

KEYWORD: ADR risk, GerontoNET Score, Type of drug, STOPP criteria

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 compared to 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 increase 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 was increasing with comorbidities and polypharmacy in the elderly (Alhawassi et al., 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 et al., 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 was to assess the risk of ADR in elderly patients with chronic disease using the GerontoNET Score and the STOPP criteria.

Comment [S1]: Please elaborate the reason of selecting this scoring and criteria.

METHODS

The research design used a cross-sectional study and was analyzed descriptively. This study has obtained approval from a 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 patients who underwent hospitalization at Waluyo Jati Kraksaan Hospital. Exclusion criteria were elderly patients who are 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 et al., 2012). How to calculate the sample size was used the formula:

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

Description: n = big sample (sample size?); P = prevalence of past research; Z1-A / 22 = normal standard variation; d = precision. Patients willing to participate in the research are given an approval sheet to be signed (Inform Consent). Then, the researcher saw the

Comment [S2]: recheck the correct terminology?



patient's medical record data. Data that was not in the patient's medical record, the researcher conducts interviews with patients and other health workers, such as drug side effects (grammatical error)

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. Variabel 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: ALO, heart failure, diarrhea, anemia with the number of drugs received as many as 12 kinds of medicines.

The second patient had five comorbid: 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 that patients suffered were 14 patients with heart disease (22,2%), such as heart failure, ST-Elevation Myocardial Infarction (STEMI), non STEMI, atrial fibrillation.

The most diagnosis experienced by the patient 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

Comment [S3]: Spelling error



standard value. The number of medications received was 4-16 kinds of medicines, with eight types of drugs on average. There were 3 of 7 patients who 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 patients as many as four patients in anemia and nausea due to rifampicin and isoniazid drugs. Patients with kidney disorders with glomerulus filtration (LFG) ≤ 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 drugs while inpatient (during hospitalization?).

Comment [S4]: If possible, create a chart

Comment [S5]: abbreviation

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)	4 (5,6%)
Pneumonia	9 (12,5%)
Acute Coronary Syndrome (ACS)	6 (8,3%)
Hypertensive Heart Disease (HHD)	1 (1,4%)
Hypertension	6 (8,3%)
Diabetes Mellitus (DM)	5 (6,9%)
Liver Failure	2 (2,8%)
Kidney Failure	2 (2,8%)
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%)
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%)

Tabel 2. ADR Risk Factor (continued)

Variable	Amount (%)
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 NSAIDs (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 NSAIDs, 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 et al., 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 (Eduardo & Tikhonoff, 2017).

Comment [S6]: abbreviation



CONCLUSIONS

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, Arixtra, beta-blockers, furosemide, NSAID class (metamizole, ketorolac).

Comment [S7]: please use generic name

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