Polypharmacy and the Risk of Adverse Drug Reactions in the Elderly at a Tertiary Referral Hospital in Indonesia: Assessing the Applicability of the GerontoNet Score

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ABSTRACT

Background*:** *Geriatric patients are often subject to polypharmacy, increasing their risk of adverse drug reactions (ADRs). This study evaluated polypharmacy practices, ADR incidence, predictive factors, and the applicability of the GerontoNet Score at a tertiary referral teaching hospital in Indonesia.* ***Methods: *This retrospective study included 340 geriatric inpatients at Dr. Cipto Mangunkusumo Hospital, Jakarta, in 2023. The relationship between demographic data, comorbidities, number of drugs used, and ADR events was analyzed using the Chi-square test. The association between GerontoNet ADR scores and ADR events was also assessed.* ***Results****: The study included 182 (53.5%) male and 158 (46.5%) female patients, with a mean age of 71.9±6.1 years. Of these, 70.9% were aged 65 to 74. A total of 78.8% of patients had ≥ 4 comorbidities. The number of drugs ranged from 3 to 28, with a mean of 10.7 drugs and a median of 10 drugs. ADRs were detected in 26 patients (7.6%), with 17 cases in females and 9 in males (p=0.044). Insulin- and diuretic-induced hypokalemia were the most frequent ADR (13 patients), followed by heparin-induced thrombocytopenia (3 patients). No significant correlation was found between ADRs and age (p=0.505), number of comorbidities (p=0.425), number of drugs (p=0.576), or GerontoNet ADR Score (p=0.530).* ***Conclusion:*** *Polypharmacy is prevalent at Dr. Cipto Mangunkusumo Hospital, yet the incidence of ADRs is relatively low. Most ADRs were related to high-alert drugs, while no significant correlations were found between age, polypharmacy, comorbidities, or GerontoNet Score with ADR events.*

Keywords*: adverse drug reaction, geriatrics, GerontoNet scores, polypharmacy.*

INTRODUCTION

Geriatric patients possess unique characteristics that make them particularly susceptible to adverse drug reactions (ADRs). These characteristics include multiple comorbidities, reduced homeostatic capacity, and diminished organ function. According to the WHO and the International Pharmaceutical Federation, there were 70,000 hospital admissions due to drug-related problems (DRP) in 2016, accounting for 3-6% of all admissions and costing 130 billion dollars annually.[1,2]

Paisansirikul et al.,[3] at King Chulalongkorn Memorial Hospital, Bangkok, reported that 63% of urban older people experienced DRP, and polypharmacy and multiple comorbidities were significantly linked to DRP. Sharon et al.[4] reported 86.09% of DRP and 1.45 DRPs per patient. Drug-related problems contribute to higher complications, higher mortality rates, prolonged hospital stays, decreased quality of life, and increased hospital costs.[5]

Polypharmacy is prevalent among the elderly, often unavoidable due to the need for multiple treatments for various conditions. The direct consequences of polypharmacy include an increased risk of drug-drug interactions and a higher likelihood of adverse drug reactions (ADRs). However, many drug-related problems can be anticipated, and the risk of ADRs should be preventable. The GerontoNet group in the European Union has developed the GerontoNet ADR Risk Score, a tool designed to predict the risk of ADRs in elderly patients.[6] This scoring system is based on five key parameters: the use of more than eight drugs, a history of adverse drug reactions (ADRs), the presence of more than four comorbidities, and the existence of heart failure, renal failure, or liver disease. However, patient characteristics can vary across different hospital settings and population groups, meaning these parameters may not be universally applicable. Al-Ragawi et al.[7] found that 21.9% of patients were improperly classified as high-risk by the GerontoNet ADR Risk Score, despite not being at high risk.

Dr. Cipto Mangunkusumo Hospital is the top referral hospital in Indonesia, receiving complicated cases from various cities around Jakarta and nationwide. The complexity of cases at this hospital requires multidisciplinary approaches, and consequently, multiple treatments are unavoidable. On the other hand, being a teaching hospital, patient treatments are carefully supervised by senior physicians. Additionally, hospital pharmacists anticipate potential drug-drug interactions using specialized software before medications are administered to patients. In this study, we aim to evaluate the practice of polypharmacy, the incidence of ADRs, and their relationships with various predictive factors. We also seek to assess the applicability of the GerontoNet Score to our patients' conditions.

METHODS

Study Design

This retrospective study utilized the medical records of elderly patients (aged > 65 years) at the Geriatric Division of the Internal Medicine Department at Dr. Cipto Mangunkusumo Hospital in 2023.

Ethics

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital (No: KET 1797/UN2. F2/ETIK/PPM.00.02/2023).

Estimation of Sample Size

The sample size was estimated using the formula for the proportion of a single population: $n = Z^2\alpha \times P \times Q / d^2$, where P represents the proportion of elderly patients receiving more than five drugs, estimated at 80%, Q is (1 - P), and d is the absolute precision, set at 5% as determined by the researcher. With an α value of 5%, Zα of 1.96, a minimum required sample size was 246.

Data Collected

Demographic data included age, sex, comorbidities, and medications received during hospitalization. Clinical diagnoses encompassed central nervous system (CNS) disorders; cardiovascular diseases (heart failure with LVEF < 40%, hypertension, and coronary artery disease); chronic kidney disease (CKD) with a GFR value of < 60 ml/minute.1.73 m^2); pneumonia; diabetes mellitus; and anemia (Hb < 12 g/dL for women or < 13 g/dL for men). The occurrence of adverse drug reactions (ADRs) were determined based on the specific notes by the physicians, if any, or from abnormal laboratory changes, or specific antidote administration. The relationship between ADRs and the suspected medications was assessed using the WHO-UMC causality assessment system. Only definite and probable ADRs were considered for this study. The GerontoNet-ADR

score was calculated based on Onder et al.,6, where: number of drugs < 5 (score 0), number of drugs 5-7 (score 1), number of drugs 8 or more (score 4), history of previous ADRs (score 2), presence of comorbid heart failure, liver disease, or chronic kidney disease with LFG < 60 ml/min, each given a score of 1. Total score of less than 4 was considered low risk, while total score of 4 or more were considered high risk.

Data Analysis

Demographic data, number of drugs, number of comorbidities, and clinical data were reported as descriptive statistics. The relationship between these variables and the presence of ADR was analyzed using the Chi-square test with SPSS version 20.

RESULTS

General Characteristics of the Patients

In this study, 340 medical records of elderly patients were analyzed. There were slightly more male patients (53.5%) than female patients (46.5%). The mean age was 71.9 ± 6.1 years, with a range of 65 to 95 years. The age distribution was predominantly between 65 and 74 years (70.9%). The number of comorbidities varied from 1 to 9, with 78.8% of patients having more than four comorbidities. Number of drugs ranged from 3 to 28 drugs, with a mean of 10.7 drugs and a median of 10 drugs. Nearly all patients (98.2%) experienced polypharmacy, receiving 5 drugs or more. The types of comorbidities were classified according to the organ system, as detailed in **Table 1**.

Table 1. Demographic characteristics of the study subjects

Demographics	Frequency Total (n = 340)	%
Male	182	53.5%
Female	158	46.5%
Age groups		
65-74	242	70.9%
75-84	84	24.7%
>= 85	14	4.1%
Number of Comorbid		
1-3	72	21.2%
4-6	217	63.8%
>= 7	51	15%
Number of Drugs		
1-4	6	1.8%
5-8	95	27.9%
9-12	143	42.1%
13-16	74	21.8%
17-20	20	5.9%
21-24	1	0.3%
25-28	1	0.3%
Types of Comorbidities		
CVD (stroke)	50	14.7%
Coronary Artery Disease	58	17.1%
Hypertension	24	7.1%
Heart failure (LVEF <40%)	30	8.8%
Pneumonia	154	45.3%
CKD (GFR <60 ml/ min.1.73 m2)	74	21.8%
Diabetes	149	43.8
Anemia	159	46.8
Liver disease	102	30%
Electrolyte imbalance	174	51.2%

Adverse Drug Reactions

Adverse drug reactions (ADRs) were detected in 26 of the 340 patients (7.65%). The most common ADR was hypokalemia, occurring in 13 patients, with 9 cases attributed to insulin, 3 cases to furosemide, and 1 case to salbutamol. Heparin-induced thrombocytopenia was the second most frequent ADR, as shown in **Table 2**.

Table 2. Frequency and types of ADR

ADR event	N = 26	%
Hypokalemia	13	50%
Heparin-induced thrombocytopenia	3	11.5%
Hyperkalemia ec Candesartan	2	7.7
Elevated transaminase	2	7.7%
Antibiotic-associated diarrhea	1	3.8%
GI bleeding ec Rivaroxaban	1	3.8%
Tachycardia	1	3.8%
Extrapyramidal symptom	1	3.8%
Elevated prothrombin time	1	3.8%
Hypocalcemia	1	3.8%

Predictors of ADR

The distribution of predictive factors associated with ADR events is presented in **Table 3**. A significantly higher incidence of ADRs was observed in females (17 cases) compared to males (9 cases) (p = 0.044). However, no significant correlation was found between ADR events and the number of comorbidities (p = 0.425), the number of drugs used (p = 0.562), or the types of comorbidities.

Table 3. Predictor of ADR

Demographics	ADS (n = 26)	No ADR (n = 314)	p
Male	9	173	0.044
Female	17	141	
Age groups:			
65-74	20	221	0.769
75-84	5	80	
>= 95	1	13	
Number of Comorbidities			
1-3	6	66	0.425
4-6	14	203	
>= 7	6	45	
Number of Drugs			
<= 5	0	16	0.562
6-9	8	115	
10-14	14	144	
>= 15	4	39	
Presence of Comorbidities			
Cerebrovascular disease	5 21	45 269	0.498
Coronary artery disease	7 19	51 263	0.164
Hypertension	2 24	22 292	0.704
Heart failure (LVEF <40%)	2 24	28 286	0.592
CKD (eGFR <60 ml/min)	6 20	68 246	0.866
Pneumonia	8 18	146 168	0.122
Diabetes mellitus	11 15	138 176	0.871
Anemia	8 18	151 163	0.089
Liver disease	7 19	95 219	0.722
Electrolyte imbalance	14 12	160 154	0.926

GerontoNet Score versus ADR Events

Table 4 shows the distribution of GerontoNet scores among patients with and without ADRs. Of the 26 patients with ADRs, 24 (92.3%) were correctly classified as having high GerontoNet scores (scores > 4). Conversely, 255 out of 314 patients (81.2%) without ADRs were incorrectly classified as having high GerontoNet scores (highlighted in grey in the table). This indicates that 81.2% of patients had an inappropriate GerontoNet score classification.

DISCUSSION

In this study, we evaluated the pattern of polypharmacy at Dr. Cipto Mangunkusumo Hospital, a leading referral hospital in Indonesia. We collected medical records of 340 elderly patients. As shown in **Table 1**, heavy

Table 4. Association between GerontoNet score with ADR events

GerontoNet Score	0	1	2	3	4	5	6	7	8
Patients with ADR (n)	0	0	2	0	5	10	5	3	1
Patients without ADR (n)	4	11	29	15	22	121	89	22	1

polypharmacy is prevalent at this hospital, with the number of medications ranging from 3 to 27. Over 98% of patients received 5 or more drugs, while only 6 out of 340 (1.8%) received fewer than 5. The proportion of this polipharmacy is higher than the studies in India which reported an incidence of polypharmacy of 78%[8] and 86.09%[4]. The primary reason for this extensive polypharmacy in our study is the presence of multiple comorbidities; nearly 80% of patients have 4 or more comorbidities, as detailed in **Table 1**.

Adverse drug reactions (ADRs) were detected in 26 of 340 patients (7.65%), which is slightly higher than 6.5% as reported by Onder et al.[6], but lower than the 22.9% reported by Al-Ragawi et al.[7] The reasons for these discrepancies are unclear, but variations in population settings and disease complexity may have influenced physicians' prescribing practices.

In the present study, we finally reported the ADRs based on objective findings of abnormal laboratory results, as there were no specific reports of ADR from the physician. Meanwhile, the ADR in the form of subjective complaints of patients could not be recorded due to the retrospective nature of our study and their low reliability. The association between ADRs and specific drugs was determined using the WHO classification, considering only those with a definite or probable association.

The most frequent ADR was hypokalemia, primarily due to insulin use, and some were due to furosemide and salbutamol use. Insulin can cause hypokalemia by stimulating the Na-K-ATPase pump, which promotes the entry of potassium into cells.[9] Furosemide induces hypokalemia through its diuretic effects, which increase the excretion of electrolytes such as sodium, potassium, and magnesium.[10,11] Other studies by Tadjudin et al.[12] have also reported hypokalemia as an ADR. The second most frequent ADR in this study was heparin-induced thrombocytopenia, which occurred in three patients. However, no active bleeding was recorded, as the physician was promptly alerted and heparin was discontinued on the right time.

We found no correlation between gender, the number of comorbidities, the number of drugs used, with the occurrence of ADR events. In contrast, Onder et al.[6] found that the use of more than 8 drugs was the strongest predictor of ADR events, with a previous history of ADRs being the second strongest predictor. However, Al-Ragawi et al.[7] reported no association between a previous history of ADRs and subsequent ADR events. In our study, previous ADR histories could not be retrieved due to retrospective design of the study, and no such records were found in the medical files. ADRs manifested as subjective symptoms can be difficult to distinguish from disease symptoms. Additionally, the cultural background of our patients, who have relatively low to moderate levels of education, also complicates the accurate recall of previous ADRs.

In contrast to the findings by Onder et al.[6], the number of comorbidities and the presence of certain illnesses did not show a significant association with ADR events in our study. The reasons for these differing results are not clear. However, the relatively low incidence of ADRs in our study may have contributed to these non-significant findings.

GerontoNet ADR risk score

The GerontoNet ADR Risk Score, developed by Onder et al.[6] is a practical tool for predicting ADRs in geriatric patients. In this study, the GerontoNet ADR Risk Score was determined based on the following criteria: at least four comorbid conditions, heart failure, liver disease, the number of drugs used, a history of ADRs, and the presence of renal failure. This study used a prospective design and it was revealed that 71% of cases were correctly predicted using this tool. However, different populations may have unique characteristics that can affect the applicability of this method in various medical settings. Hefner et al.[13] conducted a study on psychiatric patients. Despite the good predictive ability of the GerontoNet ADR risk score, this group suggested incorporating other parameters, such as serum drug concentration, as another factor that determines the occurrence of an ADR. Petrovic et al.[14] identified different predictive factors for ADRs than those proposed by the GerontoNet ADR Risk Score, namely low body mass index, Mini-Mental State Examination (MMSE) score of >24/30 points,

and the presence of osteoarthritis as significant predictors. Additionally, the Brighton Adverse Drug Reactions Risk (BADRI) Model highlighted different predictive factors, including the use of more than 8 drugs, hyperlipidemia, an elevated white cell count, use of anti-diabetic agents, and a length of stay greater than 12 days. In our study, none of the ADR predictive factors showed an association with ADR events. Instead, it appears that the nature of the drugs-particularly high-alert drugs such as insulin, heparin, and diuretics-plays a crucial role in determining the occurrence of ADRs.

The calculation of the GerontoNet score in our patients showed that 255 out of 314 patients (81.2%) without ADR events were incorrectly classified as having high GerontoNet scores. This suggests that the GerontoNet ADR Risk Score has low applicability to our patient population. Various methods exist for predicting ADRs, such as the Medication Appropriateness Index (MAI), which have yielded different results. Population settings can influence these outcomes, as demonstrated in a meta-analysis by Stevenson et al.[15] and Atmaja et al.[16] These meta-analyses reported that various ADR prediction methods yielded widely variable results, and no single assessment tool has proven effective for all situations.

Dr. Cipto Mangunkusumo Hospital, a top national referral and teaching hospital, employs a multidisciplinary approach to patient care. Drug prescribing is closely supervised by senior physicians and guided by interaction checker software. We believe that these practices have contributed to the relatively low incidence of ADRs observed in our study.

Study Limitations

The main limitation of this study is its retrospective design, with data based on medical records completed by treating physicians who were not fully aware of the study's aims concerning ADR collection. As a result, subjective symptoms of probable ADRs may not have been recorded. Additionally, the similarity between ADR symptoms and disease symptoms made it challenging to identify ADRs. However, we used abnormal laboratory findings as primary indicators of ADR events, to ensure that these laboratory changes accurately reflected adverse drug reactions.

CONCLUSION

From the above study, we can conclude that polypharmacy is prevalent at Dr. Cipto Mangunkusumo Hospital, yet ADR incidence was relatively low. This polypharmacy is due to the complexity of cases at this tertiary care facility. The close supervision of prescribing practices, supported by interaction software, might have contributed to a relatively low incidence of ADRs. GerontoNet ADR Risk Score does not appear to be well-suited for this patient population.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest in this study.

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