VOLUME - 12, ISSUE - 01, JANUARY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Internal Medicine

RELATIONSHIP BETWEEN POLYPHARMACY, LENGTH OF HOSPITALIZATION, AND DELIRIUM AMONG HOSPITALIZED ELDERLY PATIENTS

Dina Aprillia Ariestine* — Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Dr Mansyur 5, Medan, Indonesia *Corresponding Author

Siti Syarifah — Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Sumatera Utara, Dr Mansyur 5, Medan, Indonesia

ABSTRACT

Background: Decreased organ function in the elderly is associated with the aging process, which initiates various chronic diseases and increases the risk of polypharmacy. Meanwhile, polypharmacy tends to provoke adverse drug reactions that prolong the treatment period and increases the risk of delirium in elderly patients. **Aim:** To determine the relationship between polypharmacy, length of hospitalization, and delirium in geriatrics admitted to the Universitas Sumatera Utara Hospital. **Method:** An observational analytical study with a cross-sectional design was carried out at the Universitas Sumatera Utara Hospital. Patients aged 60 years or older who had 2 or more drugs during hospitalization were enrolled, while those with incomplete medical records were excluded. The demographic and clinical data were gathered, processed, and analyzed using the Statistical Package for Social Sciences (SPSS) version 25 software and the P-value of <0.05 was considered significant. **Result:** A total of 116 subjects participated in this study and were dominated by males in the 60-69 years age group. A significant correlation was discovered between polypharmacy and the length of hospitalization ($p=0.012$). Polypharmacy was detected in 67.2% of subjects, 58.6% had an increased risk of drug interactions, 44% had a prolonged length of hospitalization, and 29.3% experienced altered mental status. This showed that several delirium-related drugs were still prescribed to geriatric patients, namely ranitidine (38.7%) and ketorolac (20.2%). **Conclusion:** There is a significant relationship between polypharmacy, length of hospitalization, and delirium in geriatric patients.

KEYWORDS : Delirium, Geriatric, Hospitalization, Polypharmacy.

INTRODUCTION

A growing proportion of the elderly population is being recorded in many countries due to a rapid increase in life expectancy lately. In 2019, the geriatric population was approximately 703 million, and predicted to reach 1.5 billion in 2050 [1]. This has become a challenge for global health authorities. The degeneration that occurs because of aging will reduce the organ's capability to function properly, thereby increasing the risk of various diseases such as hypertension, diabetes, arthritis, chronic heart, and kidney [2, 3]. The presence of diseases leads to more frequent drug prescriptions and ends with polypharmacy [4, 5].

Polypharmacy has become a severe problem, where approximately 30% of geriatrics in developing countries consume many drugs simultaneously. Moreover, it is defined as irrational drug prescribing, which makes patients consume 6 or more drugs simultaneously. Topical medications, herbs, vitamins, and minerals are not included in the definition of polypharmacy [6]. Higher consumption of multiple medications will lead to unwanted events such as drug interactions, side effects, decreased functional status, and increased health-related expenses. This will hamper patients' adherence to medications and trigger geriatric syndrome, which prolongs the length of hospitalization [3].

One of the core problems in polypharmacy is the prescription of the cascade. This occurs when a new medicine is prescribed to treat the adverse drug reaction (ADR) from the previous ones. However, the new administration of medicines can cause another side effect or drug reaction, creating a vicious unending cycle [3]. It was also reported that over-the-counter drugs and supplements contribute to this cycle [7, 8]. A previous study stated that less than half of the patients are willing to discuss their supplements or complementary medicine intake with their healthcare workers [9].

Polypharmacy is also associated with cognitive impairment such as delirium. Several studies reported that polypharmacy is a risk factor for delirium regardless of the type of drugs [10, 11]. However, another investigation discovered a contradictive result, there was no association between polypharmacy and delirium in geriatric patients [12]. Delirium is also called acute confusional state, characterized by acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattentive, disorganized thinking, or an altered level of consciousness [13, 14]. Once the diagnosis of delirium is confirmed, the suspected precipitating factors need to be managed immediately because persistent delirium causes unfavorable outcomes that increase mortality [10].

Based on previous studies, there is an association between polypharmacy and prolonged length of hospitalization [15, 16]. This is because the length of hospitalization increases the number of drugs given, where approximately 60% of patients have more prescribed drugs at discharge [17]. Previous reports have discovered that iatrogenic polypharmacy practices in geriatrics can be prevented with Beers and STOPP/START criteria, which can significantly reduce treatment costs [18, 19]. Therefore, this study aims to determine the relationship between polypharmacy, length of hospitalization, and delirium in geriatric patients admitted to the Universitas Sumatera Utara Hospital.

MATERIALS AND METHODS

This observational analytical study with a cross-sectional design was carried out at the Universitas Sumatera Utara Hospital from February 2019 to October 2021. Institutional Review Board approved this study of Universitas Sumatera Utara, register number 724/KEP/USU/2021. Patients aged 60 years and older who have received 2 or more drugs during hospitalization were included. The data were gathered from patients' medical records, including demographic and clinical variables, therefore, those with incomplete information were excluded. Subsequently, the data collected were processed and analyzed using Statistical Package for Social Sciences (SPSS) version 25 software. The relationship between polypharmacy and length of hospitalization was determined using the chi-square test, where a p-value of <0.05 was considered significant. Beers criteria were used to determine the drugs associated with delirium.

RESULTS

A total of 116 subjects were willing to participate in this study

and their characteristics are summarized in Table 1. The samples were dominated by male (56.9%), with the 60-69 years age group (63.8%). Approximately 14.7%, 12.9%, and 12.1% of subjects received 5, 10, and 4 drugs during hospitalization, respectively, as shown in Table 2.

From Table 1, polypharmacy was detected in 67.2% of subjects, and risk for drug interaction was anticipated among 58.6% of respondents. The probability of drug interaction was determined using the Drug Interactions Checker on the Medscape website. Only 56% were categorized in short hospitalization periods, while the rest had prolonged periods, which is defined as more than 5 days. Decreased consciousness is one of the signs of delirium and observed in 29.3% of subjects. Diabetes (30.8%) was the most common comorbidity in the samples, followed by hypertension (25.3%). According to Beers criteria, some drugs need to be avoided in geriatrics. However, drugs such as ranitidine, ketorolac, aspirin, alprazolam, ibuprofen, mefenamic acid, and nifedipine are still prescribed. The most commonly prescribed drugs were ranitidine (38.7%), followed by ketorolac (20.2%), as presented in Table 3. According to the chi-square test, there was a statistically significant relationship between polypharmacy and length of hospitalization in geriatrics, with a p-value of 0.012 (Table 4).

DISCUSSION

This study discovered that the prevalence of polypharmacy in geriatric patients is high, reaching 78 of 116 subjects. They had more than 5 drugs during their hospitalization in the Universitas Sumatera Utara Hospital. The aging process in geriatrics leads to multi-organ dysfunction and comorbidities, which increase the causes of multi-drug prescription risk, leading to polypharmacy [20].

Polypharmacy can increase the risk of side effects and adverse drug interactions. A study stated that patients who take 5 or more drugs have an 88% higher risk of experiencing adverse events than those who consume fewer drugs. It was also reported that patients who consume 5 to 9 drugs simultaneously have a 50% probability of experiencing an adverse reaction. Similarly, those who consume 20 or more drugs have a 100% probability [21]. Nonsteroidal anti-inflammatory drugs (NSAIDs), cardiovascular medicines, diuretics, antibiotics, anticonvulsants, benzodiazepines, and diabetic drugs frequently cause adverse effects [18].

Based on these results, it was discovered that most geriatrics are at risk for adverse reactions to drug interactions (58.6%). This showed that taking more than 2 types of drugs will increase the risk of adverse events. Moreover, an adverse drug interaction is an unanticipated pharmacological or reduced therapeutic effect that occurs due to the simultaneous consumption of drugs [8]. Adverse events can also alter drug pharmacokinetics due to changes in absorption, distribution, metabolism, or excretion and ultimately lead to pharmacodynamics disturbances [22].

The results also showed that diabetes (30.8%) was the most common comorbidity, followed by hypertension (25.3%). Diabetes often occurs in the elderly because their pancreas cannot produce an adequate quantity of insulin. The inability of target organs to effectively use insulin can also be a possible mechanism [23]. Diabetes is also a significant cause of polypharmacy because of the necessity to treat diabetic complications such as microvascular or macrovascular complications [24].

Polypharmacy is the cause of a prolonged length of hospitalization and increased healthcare visits after discharge [25]. In this study, 51 subjects (44%) were hospitalized for more than 5 days. Several predictors that may affect the length of hospitalization are characteristics or clinical states of the subjects, medical intervention, patient management, and hospital administration problem [26]. The health-related expense is in line with the length of hospitalization [27]. A previous study identified some risk factors related to hospitalizations for geriatrics, which include advanced age, past hospitalization, male gender, the presence of comorbidities or severe diseases, functional disturbances or disabilities, solitary living, and some behavioral factors, namely lack of exercise, falls, and poor intake [28].

A total of 34 patients (29.3%) had decreased level of consciousness, which is one of the clinical manifestations of delirium. Moreover, delirium is a syndrome characterized by acute onset of fluctuation in mental status, inattention, disorganized thinking, or altered level of consciousness [14]. Although polypharmacy can induce delirium and also worsens the situation [11], it is not the sole cause of delirium. There are several etiologies categorized as modifiable and non-modifiable. Some potential etiologies are modifiable such as medications, sensory impairment, immobilization, and acute neurological diseases.

The non-modifiable factors include advanced age, previous history of delirium, male, and multiple comorbidities [30]. Delirium patients often require more interventions and take a longer time to reach an eligible cognitive and physical state to discharge from intensive care. Consequently, delirium will affect the length of hospitalization in geriatric patients [31].

Although several medications are associated with delirium, they are still commonly prescribed in this study. Such practice was against Beers criteria, which stated that NSAIDs and benzodiazepines are not recommended to be prescribed for geriatric patients. Furthermore, Beers criteria is a modality to evaluate the quality of care, treatment cost, and the pattern of drug use among geriatrics [18]. This category includes ranitidine, ketorolac, aspirin, alprazolam, ibuprofen, mefenamic acid, and nifedipine. Ranitidine needs to be avoided in those at risk for delirium due to its potential to induce or worsen delirium. Ketorolac can increase the risk of gastrointestinal bleeding, peptic ulcer, and acute kidney injury in geriatrics. Alprazolam is a drug that belongs to the benzodiazepine group. In general, benzodiazepines can increase the risk of cognitive impairment, delirium, falls, and fractures in geriatrics. Nifedipine is a calcium channel blocker that can cause hypotension and risk for myocardial ischemia in geriatrics and has been reported to induce delirium [18].

This is the first study to determine the relationship between polypharmacy, length of hospitalization, and delirium in geriatrics, particularly in Indonesia. The results are expected to contribute additional references based on the practice of polypharmacy and its effect on geriatric patients during hospitalization. The limitations include other confounding factors that influenced the length of hospitalization and delirium, which were not analyzed. Therefore, further similar studies are recommended to consider these factors.

CONCLUSION

There is a significant relationship between polypharmacy, length of hospitalization, and delirium in geriatric patients. The results showed that polypharmacy is among the cause of a prolonged length of hospitalization and can induce delirium. Although several medications are associated with delirium, drugs such as ranitidine and ketorolac are still commonly prescribed.

Acknowledgement

The authors would like to thank all subjects who had participated in this study.

Conflict Of Interest Disclosure
The authors declare that there are no conflicts of interest.

Funding
This research received financial support from TALENTA, Universitas Sumatera Utara, Medan, Indonesia

Table 1 The characteristics of sample distribution

Characteristics	n=116
Gender, n (%) Male Female	66 (56.9) 50 (43.1)
Age, n (%) 60-69 years 70-79 years >80 years	74 (63.8) 36 (31.0) 6 (5.2)
Polypharmacy, n (%) Yes No	78 (67.2) 38 (32.8)
Risk for Drug interaction, n (%) Yes No	68 (58.6) 48 (41.4)
Decreased confusion, n (%) Yes No	34 (29.3) 82 (70.7)
Length of hospitalization, n (%) Short (<5 days) Long(> 5 days)	65 (56) 51 (44)
Comorbid, n (%) Diabetes Hypertension Coronary artery disease Chronic kidney disease Anemia Tuberculosis Acute kidney injury Moderate head injury Dyslipidemia Congestive heart failure COPD	45 (30.8) 37 (25.3) 5 (3.4) 3 (2.1) 2 (1.4) 2 (1.4) 1 (0.7) 1 (0.7) 1 (0.7) 1 (0.7) 1 (0.7)

Table 2 Frequency samples based on number of drugs prescribed

Amount of drugs given	Frequency	%
2	2	1.7
3	5	4.3
4	14	12.1
5	17	14.7
6	13	11.2
7	12	10.3
8	8	6.9
9	11	9.5
10	15	12.9
11	6	5.2
12	2	1.7
13	3	2.6
15	1	0.9
16	4	3.4
17	1	0.9
18	1	0.9
20	1	0.9

Table 3 List of drugs that should be avoided based on Beers criteria

Types of drugs	n (%)
Ranitidine	67 (38.7)
Ketorolac	35 (20.2)
Aspirin	3(1.7)
Alprazolam	2 (1.2)
Ibuprofen	1 (0.6)
Mefenamic acid	1 (0.6)
Nifedipin	1 (0.6)

Table 4 The association between polypharmacy and the hospitalization period.

		Length of stay		P Value
		Short	Long	
Polypharmacy	Yes	35	39	0.012
	No	30	12	
Total		65	51	

REFERENCES

1. UNITED NATIONS, DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS, POPULATION DIVISION. *World population aging 2019: highlights.* United Nations; 2019. Available from: https://www.un.org/en/development/desa/population/publications/pdf/aging/WorldPopulationAging2019-Highlights.pdf. [Accessed: May 14, 2022].
2. DAGLI RJ., SHARMA A. *Polypharmacy: a global risk factor for elderly people.* J Int Oral Health. 2014; **6**: i–ii.
3. VAUGHAN CP, JOHNSON, II TM. *Incontinence*. In: Halter JB, Ouslander JG, Studenski S, High KP, Asthana S, Supiano MA, Ritchie C, editors. Hazzard's Geriatric Medicine and Gerontology, 7ed. McGraw Hill; 2017. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=1923&sectionid=144522371. [Accessed: May 14, 2022].
4. ZULKARNAINI A., MARTINI RD. *Overview of polypharmacy of geriatric patients in several polyclinics of dr. M. Djamil General Hospital, Padang*. Jurnal Kesehatan Andalas. 2019; **8**:1. DOI: http://dx.doi. org/10. 25077/ jka. v8i1S.916.
5. DUERDEN M., AVERY T., PAYNE R. *Polypharmacy and medicines optimisation*. The King's Fund; 2013. Available from: https://www.kingsfund.org.uk/publications/polypharmacy-and-medicines-optimisation. [Accessed: May 14, 2022].
6. JOHANSSON T., ABUZAHRA ME., KELLER S., MANN E., FALLER B., SOMMERAURER C., *et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis*. Br J Clin Pharmacol. 2016; **82**:532-548. DOI: https://doi.org/10.1111/bcp.12959.
7. NGUYEN T., WONG E., CIUMMO F. *Polypharmacy in older adults: practical applications alongside a patient case*. J Nurse Pract. 2020; **16**:205-209. DOI: https://doi.org/10.1016/j.nurpra.2019.11.017.
8. SAHNE BS. *An Overview of Polypharmacy in Geriatric Patients*. In: Zawada ET, editor. Challenges in Elder Care. IntechOpen; 2016. DOI: 10.5772/64793.
9. ROLITA L., FREEDMAN M. *Over-the-counter medication use in older adults*. J Gerontol Nurs. 2008; **34**:8-17. DOI: 10.3928/00989134-20080401-08.
10. HEIN C., FORGUES A., PIAU A., SOMMET A., VELLAS B., NOURHASHEMI F. *Impact of polypharmacy on occurrence of delirium in elderly emergency patients*. J Am Med Dir Assoc. 2014; **15**: 850. DOI: https://doi.org/10.1016/j.jamda.2014.08.012.
11. KURISU K,. MIYABE D., FURUKAWA Y., SHIBAYAMA O., YOSHIUCHI K. *Association between polypharmacy and the persistence of delirium: a retrospective cohort study*. Biopsychosoc Med. 2020; **14**:25. DOI: 10. 1186/s13030-020-00199-3.
12. MOOREY HC., ZAIDMAN S., JACKSON TA. *Delirium is not associated with anticholinergic burden or polypharmacy in older patients on admission to an acute hospital: an observational case control study*. BMC Geriatr. 2016; **16**:162. DOI: 10.1186/s12877-016-0336-9.
13. ECHEVERRÍA MLR., PAUL M., DOERR C. *Delirium (Nursing)*. In: StatPearls. Treasure Island: StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK568723/. [Accessed: May 14, 2022].
14. GARPESTAD E., DEVLIN JW. *Polypharmacy and delirium in critically ill older adults: recognition and prevention*. Clin Geriatr Med. 2017; **33**:189-203. DOI: 10.1016/j.cger.2017.01.002.
15. FUKUBA N., NISHIDA M., HAYASHI M., FURUKAWA N., ISHITOBI H., NAGAOKA M., et al. *The relationship between polypharmacy and hospital-stay duration: a retrospective study*. Cureus. 2020; **12**:e7267. DOI: 10.7759/cureus.7267.
16. FABBIETTI P., RUGGIERO C., SGANGA F., FUSCO S., MAMMARELLA F., BARBINI N., et al. *Effects of hyperpolypharmacy and potentially inappropriate medications (PIMs) on functional decline in older patients discharged from acute care hospitals*. Arch Gerontol Geriatr. 2018; **77**: 158-162. DOI: 10.1016/j.archger.2018.05.007.
17. NOBILI A., LICATA G., SALERNO F., PASINA L., TETTAMANTI M., FRANCHI C., et al. *Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards*. Eur J Clin Pharmacol. 2011; **67**:507-519. DOI: 10.1007/s00228-010-0977-0.
18. FICK DM., SEMLA TP., STEINMAN M., BEIZER J., BRANDT N., DOMBROWSKI R., et al. *American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults*. J Am Geriatr Soc. 2019; **67**: 674-694. DOI: 10.1111/jgs.15767.
19. O'MAHONY D. *STOPP/START criteria for potentially inappropriate medications/potential prescribing omissions in older people: origin and progress*. Expert Rev Clin Pharmacol. 2020; **13**: 15-22. DOI: 10.1080/ 17512433. 2020.1697676.
20. HOEL RW., CONNOLLY RMG., TAKAHASHI PY. *Polypharmacy management in older patients*. Mayo Clin Proc. 2021; **96**: 242-256. DOI: 10.1016/ j.mayocp. 2020.06.012.
21. ISHIGURO A., SATO R., NAGAI N. *Development of a new Japanese guideline on drug interaction for drug development and appropriate provision of information*. Drug Metab Pharmacokinet. 2020; **35**: 12-17. DOI: 10.1016/j.dmpk.2019.11.009.
22. VAN DEN ANKER J., REED MD., ALLEGAERT K., KEARNS GL. *Developmental*

changes in pharmacokinetics and pharmacodynamics. J Clin Pharmacol. 2018; **58**: S10-S25. DOI: 10.1002/jcph.1284.

23. MUSTHAKIMAH RHI., INDRA RH., YUNIARTIKA W. *An overview of the factors that cause complications of diabetes in the elderly at Kartasura Health Center*. Universitas Muhammadiyah Surakarta; 2019. Available from: http://eprints.ums.ac.id/id/eprint/73408. [Accessed: May 14, 2022].
24. DOBRICĂ E., GĂMAN M., COZMA M., BRATU OG., STOIAN AP., DIACONU CC. *Polypharmacy in type 2 diabetes mellitus: insights from an internal medicine department*. Medicina (Kaunas). 2019; **55**: 436. DOI: 10.3390/medicina55080436.
25. MASNOON N., SHAKIB S., KALISCH-ELLETT L., CAUGHEY GE. *What is polypharmacy? A systematic review of definitions*. BMC Geriatr. 2017; **17**: 230. DOI: 10.1186/s12877-017-0621-2.
26. SINAJA CA., GUNAWAN S. *Polypharmacy in the elderly in nursing homes: focus on cardiovascular drug use*. Tarumanagara Med J. 2020; **3**: 226-232. DOI: http://dx.doi.org/10.24912/tmj.v3i1.9755.
27. SASMITA ED., PRATIWI A. *The relationship between personal characteristics of the patient and length of stay of the moderate care patient at the Prof. Dr. R. Soeharso Orthopedic Hospital, Surakarta*. Universitas Muhammadiyah Surakarta; 2017. Available from: http://eprints.ums.ac.id/id/eprint/37682. [Accessed: May 14, 2022].
28. GJESTSEN MT., BRØNNICK K., TESTAD I. *Characteristics and predictors for hospitalizations of home-dwelling older persons receiving community care: a cohort study from Norway*. BMC Geriatr. 2018; **18**:203. DOI: 10.1186/s12877-018-0887-z.
29. FONG TG., TULEBAEV SR., INOUYE SK. *Delirium in elderly adults: diagnosis, prevention and treatment*. Nat Rev Neurol. 2009; **5**: 210-220. DOI: 10.1038/nrneurol.2009.24.
30. TARU MY., BAMIDELE LI., FAITH AO., ANNAH GB., MAYOWA OK., YUSHAU AA. *Delirium and Length of Hospital Stay among Medical Inpatients in Jos University Teaching Hospital, North-Central Nigeria*. Open J Psychiatry. 2018; **8**: 297–314.
31. DZIEGIELEWSKI C., SKEAD C., CANTURK T., WEBBER C., FERNANDO SM., THOMPSON LH., et al. *Delirium and Associated Length of Stay and Costs in Critically Ill Patients*. *Crit Care Res Pract*. 2021; **2021**: 6612187. DOI: 10.1155/2021/6612187.