한국임상약학회지 제33권 제1호
Korean J Clin Pharm, Vol. 33, No. 1, pp. 1–7, 2023

Original Article

Korean Journal of Clinical Pharmacy
Official Journal of
Korean College of Clinical Pharmacy
pISSN 1226-6051 eISSN 2508-786X
https://doi.org/10.24304/kjcp.2023.33.1.1

Potentially Inappropriate Medications and Regimen Complexity on Readmission of Elderly Patients with Polypharmacy: A Retrospective Study

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ABSTRACT

Background: Along with the increase in the elderly population, concerns about polypharmacy, which can cause medication-related problems, are increasing. This study aimed to find out the association between drug-related factors and readmission in elderly patients within 30 days after discharge. **Methods:** Data of patients aged ≥65 years who were discharged from the respiratory medicine ward of a tertiary hospital between January and March 2016 were retrospectively obtained. The medication regimen complexity at discharge was calculated using the medication regimen complexity index (MRCI) score, comorbidity status was assessed using the Charlson comorbidity index (CCI), potentially inappropriate medications (PIMs) were evaluated based on the Beer 2019 criteria, and adverse drug events (ADEs) were examined using the ADE reporting system. Multivariable logistic regression analysis was used to evaluate the effect of medication-related problems on hospital readmission after controlling for other variables. **Results:** Of the 206 patients included, 84 (40.8%) used PIMs, 31 (15%) had ADEs, and 32 (15.5%) were readmitted. The mean age, total medications, MRCI, CCI, and PIMs in the readmission group were significantly higher than those in the non-readmission group. Age significantly decreased the risk of readmission (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.84-0.96) after adjusting for sex, length of hospital stay, and ADEs. The use of PIMs (OR, 2.38; 95% CI, 1.10-5.16) and increased CCI (OR, 1.50; 95% CI, 1.16-1.93) and MRCI (OR, 1.04; 95% CI, 1.01-1.07) were associated with an increased occurrence of readmission. **Conclusion:** PIMs were associated with a significantly greater risk for readmission than MRCI.

KEYWORDS: Elderly, medication regimen complexity, patient readmission, potentially inappropriate medication

Polypharmacy, defined as the concurrent use of five or more medications, is a major public health concern and the potential cause of medication-related problems.[1] Drug treatment for elderly patients with chronic diseases has increased, and polypharmacy is common owing to complex morbidity.[2,3] The prevalence of polypharmacy is high, and the use of 5, 9, 10 drugs or more drugs was reported to be 91, 74, and 65%, respectively, depending on the facilities.[4] Polypharmacy is an indicator of medication-related problems, which is associated with admission and hospitalization in elderly patients.[5,6]

Increased regimen complexity and the use of inappropriate medications have been studied as medication-related problems regarding polypharmacy.[7,8] First, the increase in the number of medications may lead to regimen complexity.[9] George *et al*. (2004) developed a methodology for quantifying regimen complexity as numbers known as the medication regimen complexity index (MRCI).[10,11] This instrument is an open index with no upper limit and consists of sections A (the dosage form), B (dosing frequency), and C (the instructions) of the regimen, which are expressed as the sum of regimen

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Received 2 November, 2022; Revised 27 December, 2022; Accepted 27 December, 2022

complexity.[12] The MRCI can assess medication complexity from the number of medications taken by an individual. It has obtained global validity in various countries.[13-16] and studies have already attempted to find associations with clinical outcomes conducted for different patient groups.[17] Second, the criteria for potentially inappropriate medications (PIMs) have been of major interest within the field of medication use in elderly patients.[18] PIMs are drugs that should be avoided due to the high risk of adverse reactions in elderly populations and are widely applied as screening tools in pharmaceutical interventions.[20]

Several studies aimed at solving medication-related problems have been conducted on elderly patients with polypharmacy using indexes such as the MRCI and PIMs criteria.[9,20] Medication regimen complexity using MRCI has been found to influence health outcomes, including hospital readmission, medication adherence, hospitalization, adverse drug events (ADEs), and emergency room visits.[17] Studies on medication adherence have shown inconsistent results. Although some studies have demonstrated that increased regimen complexity is associated with negative compliance,[12] others have revealed no significant relationship between regimen complexity and adherence without reporting parameter estimates.[22] Regarding hospitalization, studies investigating medication regimen complexity in elderly patients were associated with clinical outcomes such as unplanned hospitalization, 30-day unplanned hospital readmissions, and emergency department visits.[23] The use of PIMs in elderly patients with multiple comorbidities should also be considered as a factor influencing clinical outcomes. A decreased number of PIMs has been found to correlate with an improvement in quality of life, reduction in the number of emergency room visits, and the incidence of the hospitalization.[24,25]

Although polypharmacy affects the increase in regimen complexity and PIM use, investigations considering both factors as medication-related problems have been limited. A study reported an increase in complexity and a decrease in PIMs after admission[26]; another evaluated PIMs and regimen complexity in medication adherence as medication-related factors.[27] However, studies considering both factors in elderly patients are lacking. Therefore, this study aimed to evaluate PIMs and regimen complexity as drug-related factors affecting readmission rates.

Materials and Methods

Design, setting, and subjects

This was a single-center, retrospective, cross-sectional study to evaluate the effect of PIMs and MRCI scores on readmission of elderly patients within 30 days. All patients discharged from the respiratory medicine ward of a university hospital, Incheon metropolitan city, Republic of Korea, between January 2016 and March 2016 were included in the study. Elderly patients aged ≥65 years and those prescribed at least one discharge drug were included. Patients with more than two readmissions during the observation period were analyzed based on the first admission period. Patients who were not prescribed discharge medications were excluded. The study was approved by the Institutional Review Board of the Institutional Review Board of Inha Hospital (IRB# 2022-05-002).

Data collection

All patient-level information was extracted from the electronic medical records (EMRs) of the hospital. Data on the characteristics of patients, including sex, age, length of hospital stay, Charlson comorbidity index (CCI) score, and types of health insurance, were obtained. All the medication numbers on discharge were checked and patients were classified according to whether corresponded to polypharmacy, defined as the use of five or more medications. The regimen complexity of discharge medications was analyzed by the Korean version of the MRCI (MRCI-K), which has been previously validated.[12] MRCI was measured in sections A (dosage forms), B (dosing frequency), and C (additional directions). Each section is calculated and defined as the sum of the regimen complexity, with higher numbers indicating higher complexity.

To determine hospital readmission within the 30-day discharge period, all cause readmissions during follow-up were evaluated individually based on their respective discharge dates from the EMRs. Patients readmitted to the same tertiary care hospital were included in the follow-up data.

Comorbidity status was assessed at baseline using the CCI, given the well-established link between previous hospitalizations and hospital readmission.[28] PIMs were evaluated on discharge

medications using risk assessment criteria targeting the elderly (Beer 2019 criteria).[18] The presence of PIMs was determined not for all drugs that met the criteria for PIMs, but for those drugs after considering the clinical condition and other medications. The identified presence of ADEs after admission in patients were evaluated using the ADE reporting system, which were above "possible" recorded based on the WHO-UMC (Uppsala Monitoring Center), Naranjo algorithm . The presence of PIMs and ADEs was also assessed.

Statistical analyses

Descriptive statistics analysis was conducted for all baseline variables, including age, sex, CCI, and length of hospital stay. The CCI was used to adjust baseline differences in the comorbid conditions in patients. Several baseline variables such as age, hospital length of stay, CCI and MRCI were evaluated to determine whether differences existed between readmission and non-readmission groups using independent t tests. Chi-square tests were utilized to determine whether groups differed by proportion with PIMs, ADEs and polypharmacy. The correlation between variables and the MRCI score was assessed using Pearson's correlation. To determine the possible risk factors for the 30-day readmissions, bivariate analysis was performed using independent-sample t-tests, the Mann-Whitney U test, and chi-squared distribution. Multivariable logistic regression analysis was performed to determine the efficacy of the MRCI score in predicting the potential for 30-day hospital readmission. The Durbin Watson statistic and multi-collinearity analysis were performed as a test for checking correlation for each each independent variable before regression analysis. The Hosmer-Lemeshow test and backward stepwise method were performed to determine the final regression model, a p-value<0.05 was accepted as indicating a statistical significance in the multivariate model. Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp. Armonk, NY). Statistical significance was set at p<0.05.

Results

The baseline characteristics are presented in Table 1. In total, 206 elderly patients at discharge were included in this study. The mean age of the patients was 78.4 years (SD, 7.1 years), and 43.2% were men. The average number of medications at discharge was 6.2±3.4. The mean MRCI score (28.6±14.4) observed in sections A, B, and C was 2.4 (SD, 1.6; range, 1-10 points), 11.9 (SD, 6.1; range, 1-18 points), and 14.4 (SD, 8.3; range, 2-44 points), respectively. The polypharmacy, defined as the use of 5 or more drugs, accounted for 64.5% of 133 patients and did not differ between the two groups. A total of 84 (40.8%) patients used PIMs, 31 (15%) had ADEs, and 32 (15.5%) had hospital readmission 30 days after index discharge. There were no significant differences in the length of hospital stay with and without readmission at the 30-day follow-up. The total number of medications, MRCI, and CCI in the readmission

Table 1. Characteristics of the 206 elderly patients admitted to hospital based on the occurrence of a 30-day all cause readmission

Variable	Total	Readmission		
	(n=206)	Yes (n=32)	No (n=174)	p-value
Age (mean±SD)	78.4±7.1	76.1±6.4	78.7±7.09	0.05
Length of hospital stay (Mean±SD)	14.6±3.4	14.4±12.6	14.5±13.1	0.96
Medication (Mean±SD)	6.2 (3.4)	7.9±4.0	5.9±3.1	0.01
Polypharmacy (≥5 medications) n (%)	133 (64.5)	24 (75)	109 (62.6)	0.17
Section A (Mean±SD)	2.4±1.6	2.9±1.5	2.3±1.6	0.06
Section B (Mean±SD)	11.9±6.1	14.3±7.3	11.3±5.7	0.04
Section C (Mean±SD)	14.4±8.3	18.5±10.3	13.6±7.6	0.01
MRCI (Mean±SD)	28.6±14.4	35.7±17.3	27.3±13.4	0.01
CCI (Mean±SD)	5.2±1.6	5.8±1.8	5.0±1.5	0.01
ADEs n (%)	31 (15.0)	4 (12.5)	27 (15.5)	0.79
PIMs n (%)	84 (40.8)	20 (62.5)	64 (36.8)	0.01

ADE, adverse drug event; CCI, Charlson comorbidity index; MRCI, medication regimen complexity index; PIM, potentially inappropriate medication

group were significantly higher than those in the non-readmission group. Comparable results were observed for the PIMs (Table 1).

Although the MRCI score was strongly correlated with the number of drugs (r=0.96, p<0.001), it was weakly correlated with the length of hospital stay (0.22, p<0.001) (Table 2).The most frequent PIMs were first-generation antihistamines, followed by antipsychotics and benzodiazepines (Table 3).

Age significantly affected the odds of readmission within 30 days (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.84-0.96). PIMs, CCI, and MRCI significantly increased the odds of readmission within 30 days, indicating increased occurrence (OR, 2.24; 95% CI, 1.07-4.67), (OR, 1.50; 95% CI, 1.16-1.93), and (OR, 1.04; 95% CI, 1.01-1.07), respectively (Table 4).

Table 2. Correlation between the Medication Regimen Complexity Index scores and the characteristics of the 206 patients included in the study

	Section A	Section B	Section C	MRCI
Medication number	0.32*	0.88*	0.95*	0.96*
Age	0.01*	0.12	0.49	0.21
Sex	0.19*	0.22*	0.01	0.08
CCI	-0.05	-0.03	0.09	0.03
Length of hospital stay	0.09	0.16*	0.25*	0.22*

CCI, Charlson comorbidity index score; MRCI, medication regimen complexity index *p<0.05.

Table 3. Most frequent potential inappropriate medications

Organ System	Therapeutic Category	Frequency, n (%)
Anticholinergics	First-generation antihistamines	46 (45)
Anticholinergics	Antispasmodics	1 (0.9)
Central nervous system	Benzodiazepines	14 (13.8)
Central nervous system	Nonbenzodiazepine	2 (2)
Central nervous system	Antipsychotics	18 (17.6)
Endocrine	Sulfonylureas	5 (4.9)
Endocrine	Megestrol	8 (8)
Gastrointestinal	Metoclopramide	4 (3.9)
Pain medications	Non-cyclooxygenase-selective	4 (3.9)
Total		102

Table 4. Multivariable analysis for predictive factors of 30-day all cause hospital readmission

Variables	Adjusted OR	95% CI		p-value
Men sex	0.98	0.40	2.37	0.88
Age	0.89	0.84	0.96	0.01
Length of hospital stay	0.99	0.95	1.03	0.73
ADE	0.61	0.17	2.09	0.39
Polypharmacy (≥5 medications)	0.64	0.17	2.39	0.51
MRCI	1.04	1.01	1.07	0.01
CCI	1.50	1.16	1.93	0.01
PIM	2.24	1.07	4.69	0.03

ADE, adverse drug event; CCI, Charlson comorbidity index; MRCI, medication regimen complexity index; OR, odd ratio; PIM, potentially inappropriate medication 95% CI, 95% confidence interval.

Discussion

This study evaluated the risk of regimen complexity and PIMs as medication-related factors for readmission of elderly patients with polypharmacy within 30 days of discharge. Two primary findings exhibited a correlation. First, statistically significant differences were found in regimen complexity calculated as the MRCI and PIMs between readmission and non-admission. Second, PIMs, rather than regimen complexity, can be considered the risk of readmission as they had higher ORs (OR, 2.24; 95% CI, 1.07-4.67) than MRCI had (OR, 1.04; 95% CI, 1.01-1.07). The regimen complexity of the elderly patients in this study showed a similar score distribution, consistent with previous studies;[29-31] however, a difference was observed—the instructions occupied a large proportion of the score.

A previous study demonstrated that regimen complexity could predict the potential for patients to experience ADEs and unplanned hospital readmission, although the relationship between regimen complexity and readmission rate has not been clearly established. The risk of unplanned 30-day readmissions in patients with a higher MRCI score was 5.45 times greater than in those with a lower MRCI score.[33] Another study reported that readmission due to medication numbers as highly correlated with increased MRCI scores. There was a statistically significant difference in section B scores between the readmission and non-readmission groups. The frequency at admission was shown to be a predictor of drug-related readmission within 30 days after discharge.[34] This accords with earlier researches, which showed that there were statistically significant differences in medication complexity, primarily section B and section C, during hospitalization. These results also agree with the findings of other studies, in which medication complexity increased the risk of readmission rate after adjusting for covariates, although it did not significantly affect readmission compared to the CCI and presence of PIMs.[23]

PIM criteria has been used as a drug indicator that has a clinical impact such as hospitalizations on drug use in the elderly.[32] In this study, the proportion of patients taking PIM was 84 (40.8%), and the most frequent drug was identified as first-generation antihistamines. These medications were found as one of the ingredients of the combination drug that could be overlooked in medication reviews. The use of PIMs showed a risk predictor that increased the readmission rate, and this finding supports previous research into medication related problems in elderly patients.[35-37]

In contrast to earlier findings, however, study results show that age decreases the readmission rate.[38] Further study is required to to investigate the association between the factors of mortality, transfer rate and readmission in elderly patients. In addition, although the effect of polypharmacy on the readmission rate was a significant risk factor in previous studies,[37] polypharmacy did not affect hospitalization, unlike CCI, PIMs and MRCI, when both groups of polypharmacy showed high levels. A possible explanation for this might be that MRCI and PIMs could be a useful indicator for medication reviews where polypharmacy is common.

Solving medication-related problems in elderly patients is challenging due to polypharmacy, comorbidity, and age-related physiological changes. As increased regimen complexity and PIMs use have been associated with negative clinical outcomes, making efforts through comprehensive medication reviews to reduce the burden of medication use in elderly patients will become recommened.[39] Our results support the importance of a comprehensive approach, including PIMs and regimen complexity, when evaluating drug use in elderly patients. Pharmacists need to play a role in reducing regimen complexity and PIMs during medication review via multi-disciplinary cooperation. Furthermore, for the practical use of medication related factors, its clinical validity must be confirmed by its correlation with clinical results. Further studies are required to confirm this finding.

This study had some limitations. First, it was a single-center, retrospective study. Second, although CCI was used to evaluate the clinical condition of patients, the multi-factorial analysis of elderly patients was insufficient; therefore, further research considering multiple variables such as comorbidity diseases, medications and socioeconomic factors in elderly patients is required.

Conclusions

The results of this study revealed statistically significant differences in regimen complexity and PIMs between readmission and non-admission. Based on our findings, regimen complexity and PIMs after adjusting covariants can be considered to increase the risk of all cause readmission in elderly patients.

Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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