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IMPACT OF NUMBER OF DRUG TYPES ON CLINICAL OUTCOME IN PATIENTS WITH ACUTE HIP FRACTURE

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Abstract: *Objectives:* This study aims to investigate the impact of the number of drug types on clinical outcomes for patients with acute hip fracture. *Designs:* This is a retrospective cross-sectional study. *Setting:* A hospital-based database constructed by the Japan Medical Data Center. *Participants:* Consecutive patients exhibiting acute hip fractures on admission between April 2014 and November 2017 were included. *Measurements:* Relationships among the numbers of varying drug types of ≥6 and ≤5 as well as clinical outcomes were analyzed in 11,073 patients aged ≥65 years. The primary outcome was defined as the Barthel Index efficiency, with the secondary outcome being the length of hospital stay. *Results:* Median Barthel Index scores at admission and discharge were 5 (interquartile range: 5–20) and 50 (interquartile range: 20–85). The Barthel Index efficiency was significantly higher in the group having received 5 or fewer drug variations taken (1.45 ± 1.77) than in the group receiving 6 or more drug types taken (0.94 ± 1.18) during hospital stays ($p < 0.001$). The length of hospital stay was significantly shorter in the group receiving 5 or fewer drug types taken (29.9 ± 23.8) than in the group having 6 or more drug types taken (44.3 ± 30.3) during hospital stays ($p < 0.001$), with the latter number being independently associated with the Barthel Index efficiency and length of hospital stay. *Conclusions:* Number of drug types of 6 or more were associated with lower Barthel Index efficiency and longer lengths of hospital stays.

Key words: Barthel Index efficiency, hip fracture, number of drug types, polypharmacy, rehabilitation.

Introduction

Polypharmacy has been well known for a long time (1) and has recently attracted increased attention, as it involves drug-related problems during rehabilitation. Reports show that polypharmacy interferes with rehabilitation in stroke patients with chronic kidney disease (CKD) (2). Polypharmacy is common for patients suffering from multiple chronic diseases (3). In addition, it is shown that the number of prescription drugs increases with age along with increased occurrence of complicated diseases, with the number of drugs increasing by 1.3 per disease (4).

Although the definition of polypharmacy has been controversial, reports indicate that there is an increase in the occurrence of adverse effects resulting from the administration of 6 or more drugs in Japan (5). However, there are also reports describing the most popular definition of polypharmacy as the receipt of 5 or more drug types (1). Polypharmacy is recognized as the cause of some serious problems in elderly patients, such as adverse drug reactions, a decline of medication adherence, administration of unnecessary prescriptions, lack of prescriptions for required medicines, overdose, and overlap administration. An additional problem remains that the number of drug types is high, thus the contents of prescriptions are essentially more important, and a comprehensive approach is required to solve this issue.

Polypharmacy affects rehabilitation outcome in some diseases, although the outcome for acute hip fracture is unknown. A report described that the Functional Independence Measure (FIM) efficiency was significantly lower in the polypharmacy group for patients with CKD in a rehabilitation ward (2). Additionally, increases in the number of administered drugs delay the functional improvement of stroke patients and prolong periods preceding hospital discharge (6). There are reports that potentially inappropriate medicines (PIMs) reduce the quality of life in elderly patients undergoing rehabilitation, and increased PIMs limit the functional improvement in stroke patients (7, 8). Polypharmacy and prescription of potentially inappropriate drugs can worsen rehabilitation outcomes, such as daily living activities in patients with acute stroke (2, 8).

In terms of hip fractures, reports indicate that positive rehabilitation outcome is associated with fewer medications for patients with femoral neck fracture (9). PIMs effectively increased long-term mortality and functional recovery in older patients with hip fractures (10, 11). Furthermore, high administration of anticholinergic drugs correlates with a lower functional status at discharge for patients after acute hip fractures (12). These results imply that there is an association between polypharmacy or PIMs and rehabilitation outcome.

However, polypharmacy is still a controversial topic (1, 5, 13, 14), although there are no studies have evaluated the relationship between the number of drug types and rehabilitation outcomes in acute hip fracture.

Therefore, in this study, we aimed to investigate the impact of the number of drug types on clinical outcomes in patients with acute hip fracture.

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Methods

Study design and data sources

We performed a retrospective cross-sectional study using a hospital-based database constructed by the Japan Medical Data Center (JMDC). The database contains the Diagnosis Procedure Combination (DPC) which is used for health policy planning. The details of the DPC database are described in previous reports (15, 16). The DPC survey was conducted between April 2014 and November 2017 in patients with acute hip fractures. There are up to 100 participating hospitals with 3 million patients spanning Japan. The DPC database includes the following patient data: age and sex; diagnosis and comorbidities at admission and discharge, all recorded with text data in Japanese according to the International Statistical Classification of Diseases, 10th Revision (ICD-10). All data for diagnoses and comorbidities in this study were recorded by attending physicians.

Ethical considerations

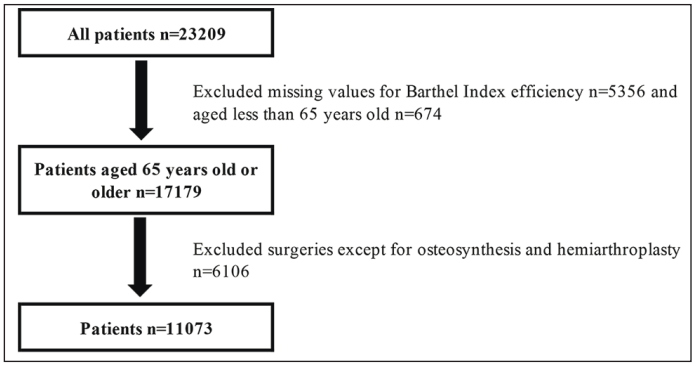
The requirement for informed consent was waived due to the anonymous nature of the data. Study approval was obtained from the Institutional Review Board of Teikyo University. This study was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Study population

We identified patients aged 65 years or older who were admitted to participating hospitals with a diagnosis of acute hip fracture (ICD-10, code S70). We excluded inpatients with missing values for Barthel Index (BI) efficiency or having undergone certain surgeries, except for osteosynthesis and hemiarthroplasty (Figure 1).

Figure 1

Study flow from the data extraction from database



Study flow from the data extraction from database. A total of 23,209 patients were admitted to participating hospitals with a diagnosis of acute hip fracture (ICD-10, code S70). After exclusion of those individuals who did not meet the inclusion criteria, 11073 patients were included.

The number of drugs administered during hospital stays was collected from the DPC database. The total number of drugs administered during hospital stays is used in this study but does not include external medicine. Medicines used as needed are included.

Measurements

Age categories at admission were classified into the following: 65-74 years old (pre-old), 75-89 years old (old), and ≥90 years (oldest-old). Rehabilitation outcome was defined as activities of daily living, which were assessed using the BI. The BI score is calculated using the following categories: 1) feeding, 2) moving back and forth between a wheelchair and bed, 3) grooming, 4) using a toilet, 5) bathing, 6) walking on a level surface, 7) moving up and down stairs, 8) dressing, 9) bowel continence, and 10) bladder continence. Evaluation of the 10 aforementioned categories were divided into 2–4 levels, with scoring from 0–100. Higher scores indicated higher degree of personal ADL capacity (17).

Comorbidities were evaluated according to Charlson Comorbidity Index (CCI) (18) using the ICD-10 code. Each comorbidity category has an associated weight (1–6), based on the adjusted risk of mortality or use of resources. The sum of all the maximum weight is 24 points, including congestive heart failure (2 points), dementia (2 points), chronic pulmonary disease (1 point), rheumatologic disease (1 point), mild liver disease (2 points), diabetes with chronic complications (1 point), hemiplegia or paraplegia (2 points), renal disease (1 point), any malignancy including leukemia and lymphoma (2 points), moderate or severe liver disease (4 points), metastatic solid tumors (6 points), and AIDS or human immunodeficiency virus infection (4 points).

Outcomes

The primary outcome was personal ADL capacity measured as follows, BI efficiency (BI at discharge minus BI at admission)/length of hospital stay (19, 20), and the secondary outcome was the length of hospital stay. We compared the outcomes in hip fracture patients aged 65 years or older into two groups: either those having 6 or more drug types or those with 5 or fewer drug types taken during hospital admission. Previous studies have also shown that patients taking 6 or more drugs are associated with a high risk of adverse drug reactions (5) and low grade of functional independence efficiency (2).

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS) version 22 software (IBM, Armonk, NY, USA) was used for statistical analyses. Parametric data are presented as means ± standard deviations and nonparametric data as medians and interquartile ranges. The chi-square test was used to compare the proportions of the categorical data. T-test were performed to compare the averages of the continuous variables. Multiple regression analysis was conducted to examine whether the number of drugs administered during hospital stays was independently associated with the length of hospital stay,

Table 1
Patients' baseline characteristics

		Total n=11073	Number of drug types during hospital stay ≥6 n=8371	Number of drug types during hospital stay ≤5 n=2702	p-value
Age(%)	Pre-old (65-74years old)	1339(12.1)	919(11.0)	420(15.5)	<0.001[b***]
	Old (75-89 years old)	6665(60.2)	5149(61.5)	1516(56.1)	
	Oldest-old (≥90 years)	3069(27.7)	2303(27.5)	766(28.3)	
Gender(%)	Male	2237(20.2)	1688(20.2)	549(20.3)	0.863[b]
	Female	8836(79.8)	6683(79.8)	2153(79.7)	
Fracture type (%)	Femoral neck	5518(49.8)	4206(50.2)	1312(48.6)	0.304[b]
	Trochanteric penetrating	5108(46.1)	3818(45.6)	1290(47.7)	
	Others	447(4.0)	347(4.1)	100(3.7)	
Number of beds(%)	20-99	107(1.0)	85(1.0)	22(0.8)	<0.001[b***]
	100-199	2389(21.6)	1816(21.7)	573(21.2)	
	200-299	2152(19.4)	1723(20.6)	429(15.9)	
	300-499	4018(36.3)	2999(35.8)	1019(37.7)	
	500+	2407(21.7)	1748(20.9)	659(24.4)	
Charlson Comorbidity Index(%)	0	6597(59.6)	4719(56.4)	1878(69.5)	<0.001[b***]
	1	817(7.4)	718(8.6)	99(3.7)	
	2	2924(26.4)	2313(27.6)	611(22.6)	
	3 and more	735(6.6)	621(7.4)	114(4.2)	
Number of rehabilitation sessions/week	Median(25%-75%)	3.0(1.7-5.6)	3.3(2.0-6.3)	2.1(1.3-3.6)	<0.001[a***]
Barthel Index on admission ±SD		18.0±27.3	18.5±27.6	16.8±26.3	0.004[a**]
Barthel Index on discharge ±SD		50.7±34.2	50.6±33.9	51.1±35.2	0.569[a]
Body Mass Index ±SD		20.7±3.6	20.8±3.6	20.5±3.5	0.003[a**]
Type of surgery	Osteosynthesis(%)	7514(64.0)	5459(62.7)	2055(67.6)	<0.001[b***]
	Hemiarthroplasty(%)	4233(36.0)	3246(37.3)	987(32.4)	

Abbreviation: SD, standard deviation; a: t-test, *P <0.05, **P <0.01, ***P <0.001; The data analyzed excludes patients with missing values for Barthel Index (BI) efficiency or having undergone certain surgeries, except for osteosynthesis and hemiarthroplasty for patients aged 65 years or older.

Table 2
Comparison of clinical outcomes

	Total n=11073	Number of drug types during hospital stay ≥6 n=8371	Number of drug types during hospital stay ≤5 n=2702	p-value
Barthel Index efficiency	1.06±1.37	0.94±1.18	1.45±1.77	<0.001[a***]
Length of hospital stay	40.8±29.5	44.3±30.3	29.9±23.8	<0.001[a***]
Barthel Index gain	32.70±33.42	32.18±33.31	34.30±33.70	0.004[a**]

a. t-test, *P <0.05, **P <0.01, ***P <0.001; BI efficiency was calculated as follows: (BI at discharge minus BI at admission)/length of hospital stay.

and was not associated with BI efficiency. The independent variables were age, sex, type of fracture, number of beds, CCI, number of rehabilitation sessions per week, BI on admission, body mass index, and type of surgery. A p-value < 0.05 was determined statistically significant.

Results

A total of 23,209 inpatients with acute hip fracture on admission were identified in the JMDC DPC database during the study period. We excluded 674 patients who were less than 65 years old and 5,356 patients with missing values. In addition, 6,106 types of surgery (with the exceptions of osteosynthesis

Table 3
Multiple regression analysis for Barthel Index efficiency

	95% confidence interval			
Variables	**β**	**Lower**	**Upper**	**p-value**
(Constant)	4,880	4,513	5,247	<0.001***
Age	-0,041	-0,044	-0,037	<0.001***
Gender	-0,146	-0,206	-0,086	<0.001***
Type of fracture	0,008	-0,042	0,059	0,750
Number of beds	0,001	0,000	0,001	0.001**
Charlson Comorbidity Index	-0,151	-0,174	-0,128	<0.001***
Number of rehabilitation sessions	-0,003	-0,003	-0,002	<0.001***
Barthel Index on admission	-0,019	-0,019	-0,018	<0.001***
Body Mass Index	0,007	0,000	0,013	0,057
Type of surgery	0,036	-0,023	0,095	0,235
Number of drug types during hospital stay ≥6	-0,363	-0,419	-0,306	<0.001***

*P <0.05, **P <0.01, ***P <0.001

Table 4
Multiple regression analysis for lengh of hospital stay

	95% confidence interval			
Variables	**β**	**Lower**	**Upper**	**p-value**
(Constant)	36,259	29,412	43,105	<0.001***
Age	0,013	-0,052	0,078	0,701
Gender	0,756	-0,37	1,882	0,188
Type of fracture	-4,017	-4,956	-3,007	<0.001***
Number of beds	-0,028	-0,031	-0,024	<0.001***
Charlson Comorbidity Index	0,271	-0,162	0,704	0,220
Number of rehabilitation sessions	0,324	0,316	0,333	<0.001***
Barthel Index on admission	0,017	0,000	0,034	0.044*
Body Mass Index	0,086	-0,040	0,212	0,182
Type of surgery	-1,313	-2,414	-0,212	0.019*
Number of drug types during hospital stay ≥6	7,700	6,644	8,755	<0.001***

*P <0.05, **P <0.01, ***P <0.001

and hemiarthroplasty) were excluded. Thus, 11,073 patients total were included in this study, which was divided into two groups: those with 6 or more drug types (8,371 patients, 75.6%) and those with 5 or less (2,702 patients, 24.4%) drug types taken during hospital admission.

Table 1 summarizes the patients' baseline characteristics in each group. There were 2,237 males (20.2%). The number of patients who were pre-old (65-74years old), old (75-89 years old), oldest-old (≥90 years) were 1,339 (12.1%), 6,665 (60.2%), and 3,069 (27.7%), respectively. The number of patients suffering from femoral neck fractures or trochanteric penetrating fractures was 5,518 (49.8%) and 5,108 (46.1%), respectively. BI scores at admission and discharge were 18.0 ± 27.3 and 50.7 ± 34.2, respectively.

Table 2 shows a comparison of the outcome of BI efficiency and length of hospital stay. BI efficiency was significantly higher in the group with 5 or fewer drug types taken (1.45 ± 1.77) than in the group with 6 or more drug types taken (0.94 ± 1.18) during hospital stays ($p < 0.001$). Moreover, the length of hospital stays was significantly shorter in the group with 5 or fewer drug types taken (29.9 ± 23.8) than in the group with 6 or more drug types taken (44.3 ± 30.3) during hospital stay (p <

0.001).

Tables 3 and 4 show the multiple regression analysis of the BI efficiency and length of hospital stay. The 6 or more drug types taken during hospital stays group were independently associated with BI efficiency and length of hospital stays.

Discussion

We investigated the impact of the number of drug types administered on the clinical outcomes in patients with acute hip fractures. The present study suggested that 6 or more drug types affect rehabilitation outcomes. From this result, it can be said that it is necessary to cope with polypharmacy with respect to not only multidrug combinations but also inappropriate prescriptions and underuse in order to improve the rehabilitation outcome in elderly patients with acute hip fractures.

In this study, the BI efficiency was significantly lower in elderly patients with polypharmacy; however, this may be due to the adverse events associated with drugs, including polypharmacy and the comorbidities. The evaluation of using the number of medicines taken during hospitalization was performed with respect to the rehabilitation outcomes considering that the adverse events occur even with a small number of medications. Therefore, the evaluation of the contents of medicines would also be an issue in the future. In addition, we would like to consider rehabilitation outcome research in polypharmacy via the intervention of the pharmacist. It is important to make an effort to come up with the only necessary medicines for elderly people who are hospitalized with hip fractures. Particularly for the elderly, there are many comorbidities, and the number of drugs tends to be large and requires attention.

Prescription of 6 or more drug types is associated with a longer length of hospital stay. It is reported that the factors of long-term hospital stay in patients with femoral proximal fractures are as follows: infectious complications, admission to private hospitals, a period from hospitalization to surgery greater than 3 days, and a period from surgery to the beginning of rehabilitation being greater than 1 day (21). The previous study does not evaluate factors such as polypharmacy or number of drug types that can be expressed numerically. In particular, with respect to the length of hospital stay, the use of clinical path that is the shortest and most efficient path in clinical setting significantly declined lengths of stay and mortality in the acute care hospital setting (22). However, most of the previous studies were conducted for facility-finished medical care settings. A recent study concluded that reduced hospital stays and mortality depend on critical system differences for treatment of hip fractures in distinct countries (23). The present study used a DPC database for acute hospitals, and it can be said that a shorter hospital stay leads to a reduction in medical expenses.

Both rehabilitation and pharmacotherapy are important concerning acute hip fracture recovery. Rehabilitation is usually prescribed following surgery in these patients. Moreover, Wakabayashi et al. suggested that pharmacotherapy rehabilitation conducted during the treatment should consider the contents of training in rehabilitation (24). Huiskes et al. reported that drug review during a short-term intervention period has little effect on clinical outcome and no effect on the quality of life (25). Moreover, Komagamine et al. evaluated the effectiveness of an intervention in the improvement of appropriate polypharmacy. However, they conclude that it did not improve the clinical outcome, but only reduced PIMs (26). A recent study showed that a multidisciplinary approach is associated with a decline in the duration of hospital stay, mortality, and postoperative complications with patients undergoing hip fracture surgery (27). Therefore, a combination of rehabilitation and pharmacotherapy seems to be important in improving clinical outcomes in patients with acute hip fracture.

This study had a few limitations. First, nearly half of all patients were excluded from analyses due to missing values, or were excluded based on the received type of surgery. Second, the DPC database is insufficient with respect to details or information in some areas. Contents of rehabilitation and degree of fracture, cognitive impairment, frailty, sarcopenia, cachexia, and details of Barthel Index measurement were not evaluated in the present study. Further studies are necessary to evaluate the association between the content and categories of prescription and rehabilitation outcomes following acute hip fracture.

In conclusion, inpatients with acute hip fractures having received 6 or more types of drugs are associated with a lower BI efficiency and longer durations of hospital stays. By reducing the number of drug types to 5 or fewer, activities related to daily living may be improved and hospital stay durations shortened.

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Conflict of interest: The authors declare no conflict of interest.

Ethical Standards: This study was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki. Study approval was obtained from the Institutional Review Board of Teikyo University.

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