

# Polypharmacy and Potentially Inappropriate Medications in Stroke Rehabilitation: Prevalence and Impact

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## Research Article

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# Abstract

## Background

Evidence is scarce regarding the polypharmacy and potentially inappropriate medications (PIMs) in rehabilitation medicine.

## Aim

To investigate the prevalence and impact on outcomes of polypharmacy and PIMs in stroke rehabilitation.

## Methods

A retrospective cohort study was conducted with 849 older inpatients after stroke.

Polypharmacy was defined as six or more medications, and PIMs were defined based on Beers criteria 2019. Study outcomes included Functional Independence Measure (FIM)-motor, FIM-cognitive, energy intake, dysphagia, length of hospital stay and the rate of home discharge. To consider the impact of pharmacotherapy during rehabilitation, multivariate analyses were used to determine whether the presence of polypharmacy or PIMs at discharge was associated with outcomes.

## Results

After enrollment, 361 patients (mean age  $78.3 \pm 7.7$  years; 49.3% male) were analyzed. Polypharmacy was observed in 43.8% and 62.9% of patients, and any PIMs were observed 64.8% and 65.4% of patients at admission and discharge, respectively. The most frequently prescribed PIMs included antipsychotics, benzodiazepines, and proton pump inhibitors. Polypharmacy was negatively associated with FIM-motor score ( $\beta = -0.072$ ,  $P = 0.017$ ), FIM-cognitive score ( $\beta = -0.077$ ,  $P = 0.011$ ), energy intake ( $\beta = -0.147$ ,  $P = 0.004$ ), and home discharge (OR: 0.499; 95% CI: 0.280, 0.802;  $P = 0.015$ ). PIMs were negatively associated with energy intake ( $\beta = -0.066$ ,  $P = 0.042$ ) and home discharge (OR: 0.452; 95% CI: 0.215, 0.756;  $P = 0.005$ ).

## Conclusions

Polypharmacy and PIMs are commonly found among older patients undergoing stroke rehabilitation. Moreover, polypharmacy and PIMs are negatively associated with outcomes.

## Impact Of Findings On Practice Statements

1. Polypharmacy and PIMs are commonly found in older patients undergoing rehabilitation after stroke.
2. Polypharmacy and PIMs were negatively associated with rehabilitation outcomes, including ADL, cognitive level, energy intake, a rate of discharge to home.
3. It is necessary to consider the impact of medications, and optimize prescriptions on an individual basis via collaborative multidisciplinary pharmacotherapy.

## Introduction

Polypharmacy is associated with poor outcomes in older people to whom an increased number of medications are often prescribed owing to multimorbidity. Multimorbidity,<sup>1</sup> multiple physicians,<sup>2,3</sup> and prescribing cascades<sup>4</sup> are factors that contribute to polypharmacy. Problems occurring due to polypharmacy are not limited to the large number of medications taken. Various associated problems arise, including altered pharmacokinetics due to decreased physiological functioning, increased risk of adverse drug events from drug interactions, medication errors, and decreased adherence to therapy.<sup>5-8</sup> Particularly, taking six or more medications is associated with the increased occurrence of adverse drug events.<sup>9</sup> Further, polypharmacy is associated with an increased incidence of falls, worsened physical function, and cognitive decline.<sup>10-12</sup>

Potentially inappropriate medications (PIMs), defined as medications that require special attention in older people worsen outcomes in older people. They are medications that cause serious adverse drug events and have inferior efficacy versus safety.<sup>13</sup> For example, benzodiazepines increase risk of cognitive impairment, delirium, falls, and fractures.<sup>14</sup> PIMs are also associated with hospitalization and declining physical function.<sup>15,16</sup>

Pharmacotherapy is important for older patients undergoing rehabilitation. Recently, the concept of rehabilitation pharmacotherapy has been proposed,<sup>17</sup> with a goal of maximizing quality of life (QOL) by reconsidering the prescription of medications that affect activity and participation, and tailoring of rehabilitation considering the content of pharmacotherapy. Polypharmacy at admission has been associated with poor physical function improvement.<sup>18</sup> Further, PIMs are associated with poor cognitive function improvement in older patients undergoing rehabilitation.<sup>19</sup> However, few studies have examined the prevalence and outcomes of polypharmacy and PIMs in older patients undergoing rehabilitation.

## **Aim**

This study aimed to investigate the prevalence and impacts of polypharmacy and PIMs in older patients undergoing stroke rehabilitation.

## **Ethics approval**

This study was approved by the Institutional Review Board (approval no.: 175-2109152, date: 22<sup>nd</sup> September 2021) of the hospital where the study was conducted. Written informed consent could not be obtained because of the constraints imposed by the retrospective study design, although the participants could withdraw from this study at any time by using an opt-out procedure. This study was conducted in accordance with the Declaration of Helsinki and ethical guidelines for medical and health research involving human subjects.

## **Methods**

### **Participants and setting**

This retrospective cohort study included patients admitted to a post-acute care hospital with convalescent rehabilitation wards containing a total of 135 beds. The study period was from January 2015 to December 2020. All stroke patients who were newly admitted to rehabilitation wards were eligible for enrollment in the study. The following exclusion criteria were applied: refusal to participate, missing data, altered consciousness (indicated by a Japan Coma Scale score of 3),<sup>20</sup> overt edema, altered hydration states, pacemaker implantation that might interfere with bioelectrical impedance analysis (BIA), and transfer to other hospitals or wards during rehabilitation. Patients aged  $\geq 65$  years were included in the study. The observation period for each patient corresponded to their period of hospitalization (the date of admission to the date of discharge).

### **Data collection**

Basic information including age, sex, body mass index, main disease for admission, and time from stroke onset to ward admission (days) were recorded. Nutritional status was interviewed by trained registered dietitians using the Mini Nutritional Assessment-Short Form (MNA-SF),<sup>21</sup> which is a validated nutrition screening tool. Dysphagia status was evaluated by trained nurses via the Food Intake Level Scale (FILS),<sup>22</sup> a validated 10-point observer-rated scale for measuring swallowing status. Dysphagia was defined as a FILS score of  $< 7$ . Comorbidities using the Charlson Comorbidity Index (CCI)<sup>23</sup> and premorbid activities of daily living (ADL) using the modified Rankin Scale (mRS)<sup>24</sup> were evaluated by medical doctors.

Within 72 hours of admission, BIA for skeletal muscle mass, hand grip strength (HG), and Functional Independence Measure (FIM) scores<sup>25</sup> indicating physical and cognitive function were measured. The HG of the non-dominant hand (or in case of hemiparesis, the non-paralyzed hand) was measured using a Smedley hand dynamometer (TTM, Tokyo, Japan); with the greatest of three measurements recorded. BIA was measured via a standard protocol using an InBody S10 instrument (InBody, Tokyo, Japan), a validated BIA instrument for which estimations of muscle mass have been reported to be minimally affected by fluid overload.<sup>26</sup> Sarcopenia was diagnosed based on criteria of the Asian Working Group for Sarcopenia 2019 (AWGS2019),<sup>27</sup> when both low skeletal muscle mass index (SMI) and low HG reached cut-off values specific for elderly Asian individuals. The cutoff values for SMI to define sarcopenia in men and women were  $< 7$  and  $< 5.7 \text{ kg/m}^2$ , respectively, whereas the cutoff values for HG to define sarcopenia in men and women were  $< 28$  and  $< 18 \text{ kg}$ , respectively.

During the first week of hospitalization and before discharge, energy and protein intakes were calculated by a nurse or dietitian visually assessing the ratio between the amount of food provided and the actual intake, and were used as daily intakes. In addition, nutrient intake was measured by dividing the weight of energy or protein intake by the patient's body weight.

Total rehabilitation therapy units received during hospitalization (units per day, 1 unit = 20 minutes' therapy) were calculated by reviewing the medical records of patients. To reduce bias, physical therapists, occupational therapists, swallowing-language-hearing rehabilitation therapists, nurses, and doctors who assessed MNA-SF, FILS, CCI, mRS, and FIM, as well as medical social workers who assisted patients

discharged to residential destinations operated independently of those involved in clinical decision-making that affected the treatment and care of enrolled patients.

## Polypharmacy and potentially inappropriate medications

Medication information was investigated via medical chart reviews. Information at admission was routinely listed by a pharmacist, and information at discharge was based on the discharge prescriptions issued by principal physicians. Of all prescriptions, only regularly prescribed oral medications were counted. Medications for transient diseases (e.g., antitussives for colds, antibiotics for urinary tract infections and pneumonia, etc.), medications for use as needed, patch medications, eye drops, intranasal infusers, and over-the-counter drugs were excluded from our analysis. Medications at admission tend to be influenced by acute care, and medications at discharge tend to be influenced by convalescent rehabilitation. Polypharmacy was defined as six or more medications, because it has been reported that risk of adverse drug events is increased in hospitalized patients aged  $\geq 65$  years who take  $\geq 6$  medications.<sup>9</sup>

PIMs are defined based on 2019 Beers criteria of the American Geriatric Society<sup>28</sup> as potentially inappropriate in most older patients. The 2019 Beers criteria is widely used in the field of geriatrics and is one of the tools most frequently used to facilitate the screening of PIMs. PIMs have been evaluated based not only the number of medications taken, but also regarding medication subcategory.

In this study, we examined the impacts of polypharmacy and PIMs at discharge on outcomes to improve our understanding of the influence of pharmacotherapy during convalescent rehabilitation.

## Outcomes

Primary outcomes considered included physical and cognitive function, as assessed by FIM-motor and FIM-cognitive scores<sup>25</sup> at discharge. FIM is divided into a motor domain (FIM-motor) with 13 sub-items and a cognitive domain (FIM-cognitive) with five sub-items. Tasks are rated on a seven-point ordinal scale ranging from total assistance to complete independence. Total FIM scores range from 18 to 126 points, with FIM-motor and FIM cognitive scores ranging from 13 to 91 points and 5 to 35 points, respectively. Low scores indicate dependency.

Secondary outcomes assessed were energy intake, FILS score, dysphagia at discharge, length of hospital stay (LOS), and rate of discharge to home (home discharge). These variables were considered indicators of successful rehabilitation and were used as indicators of quality of care.<sup>29</sup>

## Sample size calculation

The sample size was calculated using data from a previous study, the results of which showed that the FIM-motor score of patients on hospital admission was normally distributed, with a standard deviation of 23.4.<sup>30</sup> With a true mean value difference between groups (patients with and without polypharmacy) of 17,<sup>31</sup> a sample size of at least 31 participants in each group is required to reject the null hypothesis with a power of 0.8 and a value of 0.05.

## Statistical analysis

For parametric data, results were reported as means (standard deviation; SD), while medians and 25th to 75th percentiles (interquartile range [IQR]) were used to describe nonparametric data, and numbers (%) were used to describe categorical data. Comparisons between groups were made using the t-test, Mann-Whitney U test, chi-square test, and McNemar test, depending on the type and correspondence of variables.

Statistical significance was set at  $P < 0.05$ . All analyses were performed using IBM SPSS version 21 (IBM, Armonk, NY, USA).

Multiple linear regression analyses were used to determine whether polypharmacy and PIMs were independently associated with FIM-motor, FIM-cognitive, energy intake, FILS score at discharge, and LOS. Multiple logistic regression analyses were used to determine whether the presence of polypharmacy or PIMs were associated with home discharge. As potential confounders for each outcome, the baseline value (value at admission) for each outcome was included as an adjustment factor. In addition, variables that were shown in previous studies to influence rehabilitation outcomes were used for outcome adjustment. As a result, covariates selected to adjust bias included age, sex (male), LOS, CCI, FIM-motor, and FIM-cognitive on admission, FILS on admission, energy intake on admission, and total rehabilitation therapy (units/day), all of which were previously reported to be clinically relevant predictors of rehabilitation outcomes.<sup>32-36</sup> To reduce bias, adjustment for common confounders was performed via a series of multivariate analyses outcomes. Multicollinearity was assessed via variance inflation factor (VIF), with values ranging from 1 to 10 indicating the absence of multicollinearity.

## Results

A total of 849 patients with stroke were admitted during the study period. Of these, patients who were transferred to other hospitals or wards during rehabilitation (n = 16), who were aged < 65 years (n = 268), and those with missing data (n = 164), altered consciousness (n = 35), or a pacemaker (n = 5) were excluded. After exclusion criteria were applied, 361 patients were included in the analysis (Figure 1).

Baseline characteristics of enrolled participants are summarized in Table 1. Included patients had a mean (SD) age of 78.3 (7.7) years, and 49.3% of participants were male. The median number of medications (IQR) taken on admission was 5 (3–7), and 43.8% of patients were taking  $\geq 6$  medications. The median number of PIMs (IQR) was 1 (0–1); a number that was significantly higher for the patients with polypharmacy versus those without polypharmacy. Median FIM-motor and FIM-cognitive scores (IQR) were 42 [18–64] and 20 [13–27], respectively, suggesting that a large number of patients were physically dependent at baseline. A between-group comparison revealed that CCI was significantly higher, whereas energy intake, protein intake, and rehabilitation units were significantly lower in patients with polypharmacy than in those without polypharmacy at baseline.

Table 1  
Baseline characteristics of participants and between-group comparison of patients with or without polypharmacy

	<b>Total (N = 361)</b>	<b>Polypharmacy (+) (N = 158)</b>	<b>Polypharmacy (-) (N = 203)</b>	<b>P value</b>
Age, <i>y</i>	78.3 (7.7)	78.6 (7.8)	78.1 (7.7)	0.865*
Sex, <i>male</i>	178 (49.3)	79 (50)	99 (48.7)	0.816***
Stroke type	254 (70.3)	119 (75.3)	135 (66.5)	0.069***
Cerebral infarction	89 (24.6)	32 (20.2)	57 (28)	0.087***
Cerebral hemorrhage	18 (4.9)	7 (4.4)	11 (5.4)	0.669***
Subarachnoid hemorrhage				
Stroke history	98 (27.1)	56 (35.4)	42 (20.7)	0.112***
Premorbid mRS	0 [0-2]	1 [0-3]	0 [0-1]	0.051**
Onset-admission days	13 [10–20]	14 [10–22]	12 [9–18]	0.068**
Paralysis	155 (43.2) / 147 (40.7) / 18 (5.0)	69 (43.7) / 66 (41.8) / 5 (3.2)	87 (42.9) / 81 (39.9) / 13 (6.4)	0.423***
Right / Left / Both	5 [3–6] / 5 [3–6] / 5 [3–6]	5 [3–6] / 5 [3–6] / 5 [3.8-6]	5 [3–6] / 5 [3–6] / 5 [3–6]	0.401**
BRS				
Upper limb / Hand-finger / Lower limb				
FIM, <i>score</i>	63 [33-89]	58 [32-87]	69 [36-90]	0.149**
-Total	42 [18-64]	39 [18-59]	46 [19-66]	0.149**
-Motor	20 [13–27]	19 [12–26]	22 [13–27]	0.171**
-Cognitive				
Swallowing status	7 [7–10]	7 [7–10]	8 [7–10]	0.298**
FILS, <i>score</i>	76 (21.1)	36 (22.8)	40 (19.7)	0.477***
Dysphagia				
CCI, <i>score</i>	3 [1–4]	3 [1–4]	3 [1–3]	0.023**
Nutritional status	6 [5–9]	7 [4–9]	6 [5–9]	0.833**
MNA-SF, <i>score</i>	21.9 [19.8-24.4]	22.66 [20-24.63]	21.7 [19.5-24.3]	0.128**
BMI, <i>kg/m<sup>2</sup></i>	27.7 [23.3-33.2]	26.2 [22.5-31.8]	29 [23.7-34.8]	0.048**
Energy intake, <i>kcal/kg/day</i>	1.0 [0.9-1.2]	1.0 [0.9-1.2]	1.1 [0.9-1.2]	0.024**
Protein intake, <i>g/kg/day</i>				
Muscle-related variables	16.8 [9.2-23.5]	16.7 [9.2-23]	17.6 [8.9-24.4]	0.538**
HG, <i>kg</i>	6.06 [5.03-7]	6.1 [5.03-7]	6.06 [4.99-7.01]	0.831**
SMI, <i>kg/m<sup>2</sup></i>	196 (54.3)	90 (57)	106 (52.2)	0.370***
Sarcopenia				

\* t-test; \*\* Mann-Whitney U test; \*\*\* chi-square test.

<sup>a</sup> Rehabilitation therapy (including physical, occupational, and speech and swallowing therapy) performed during hospitalization (1 unit = 20 min).

Alb, albumin; BMI, body mass index; BRS, Brunnstrom Recovery Stage; CCI, Charlson's Comorbidity Index; CRP, C-reactive protein; FILS, Food Intake Level Scale; FIM, Functional Independence Measure; Hb, hemoglobin; HG, handgrip strength; MNA-SF, Mini Nutritional Assessment-Short Form; mRS, modified Rankin Scale; PIMs, potentially inappropriate medications; SMI, skeletal muscle mass index.

	Total (N = 361)	Polypharmacy (+) (N = 158)	Polypharmacy (-) (N = 203)	P value
Laboratory data	3.55 (0.53)	3.52 (0.56)	3.57 (0.51)	0.293*
Alb, <i>g/dL</i>	1.2 (2.42)	1.22 (2.55)	1.18 (2.31)	0.585*
CRP, <i>g/dL</i>	13.07 (1.93)	12.85 (2.18)	13.2 (1.7)	0.026*
Hb, <i>mg/dL</i>				
Home discharge	228 (63.2)	89 (56.3)	139 (68.5)	0.018***
Length of stay, <i>days</i>	91 [56-139]	91.5 [49.8-139]	90 [60-139]	0.695**
Rehabilitation <sup>a</sup> , <i>units/day</i>	8.2 [7.6-8.6]	8.0 [7.5-8.5]	8.3 [7.7-8.6]	0.018**
Number of total medications	5 [3–7]	8 [6–9]	4 [3–5]	<0.001**
Number of any PIMs	1 [0-1]	1 [1–2]	1 [0-1]	<0.001**
* t-test; ** Mann-Whitney U test; *** chi-square test.				
<sup>a</sup> Rehabilitation therapy (including physical, occupational, and speech and swallowing therapy) performed during hospitalization (1 unit = 20 min).				
Alb, albumin; BMI, body mass index; BRS, Brunnstrom Recovery Stage; CCI, Charlson's Comorbidity Index; CRP, C-reactive protein; FILS, Food Intake Level Scale; FIM, Functional Independence Measure; Hb, hemoglobin; HG, handgrip strength; MNA-SF, Mini Nutritional Assessment-Short Form; mRS, modified Rankin Scale; PIMs, potentially inappropriate medications; SMI, skeletal muscle mass index.				

Table 2 summarizes details regarding the prescription of PIMs at admission and discharge. The most frequently prescribed medications were antipsychotics, benzodiazepines, proton pump inhibitors (PPI), and non-steroidal anti-inflammatory drugs (NSAIDs). Use of first-generation antihistamines and peripheral alpha-1 blockers, antipsychotics, and benzodiazepines significantly increased during hospitalization. One or more PIMs were taken by 234 (64.8%) patients at admission and 236 (65.4%) at discharge.

Table 2  
Comparison of PIMs prescribed at admission and discharge based on the Beers Criteria 2019

Drug category	At admission (N = 361)	At discharge (N = 361)	P value
Total	234 (64.8)	236 (65.4)	0.612
Anticholinergics	0 (0)	4 (1.1)	0.015
First-generation antihistamines			
Antiparkinsonian agents	2 (0.6)	1 (0.3)	0.445
Trihexyphenidyl			
Antispasmodics	0 (0)	0 (0)	-
Antithrombotics	2 (0.6)	1 (0.3)	0.601
Dipyridamole, oral short-acting			
Cardiovascular	7 (1.9)	14 (3.9)	0.012
Peripheral alpha-1 blocker	1 (0.3)	1 (0.3)	0.409
Amiodarone	1 (0.3)	0 (0)	0.501
Disopyramide	6 (1.7)	4 (1.1)	0.110
Digoxin	0 (0)	0 (0)	-
Nifedipine (immediate release)			
Central nervous system	1 (0.3)	3 (0.8)	0.231
Antidepressants	23 (6.4)	34 (9.4)	0.015
Antipsychotics	0 (0)	0 (0)	-
Barbiturates	22 (6.1)	84 (23.3)	<0.001
Benzodiazepines			
Endocrine	11 (3)	0 (0)	<0.001
Insulin (sliding scale)	18 (5)	17 (4.7)	0.671
Sulfonylureas (long acting)			
Gastrointestinal	4 (1.1)	3 (0.8)	0.151
Metoclopramide	191 (52.9)	154 (42.7)	<0.001
PPI			
Pain medications	21 (5.8)	34 (9.4)	0.031
NSAIDs			
McNemar test was used to compare PIMS at admission and discharge.			
NSAIDs, non-steroidal anti-inflammatory drugs; PIMs, potentially inappropriate medications; PPI, proton pump inhibitors			

In both patients with and without polypharmacy, FIM-motor, FIM-cognitive, FILS scores, and energy intake significantly increased from admission to discharge (**Supplemental Table 1**). Results of the univariate analysis of outcomes at admission and discharge revealed that patients with polypharmacy had significantly longer hospital stay durations (98 [59–142] vs. 86.5 [51–134]), and lower FIM-motor scores (74 [42–86] vs. 82 [65.8–88]), FIM-cognitive scores (27 [18–32] vs. 31 [23.8–34]), FILS scores (10 [8–10] vs. 10 [9–10]), energy intake (kcal/kg) (28.3 [25.1–32.6] vs. 30.5 [26.2–35.6]), and home discharge rates (56.4% vs. 74.6%) than those without polypharmacy.

Table 3 summarizes results of multivariate analyses of patient outcomes associated with polypharmacy. Polypharmacy was independently and negatively associated with FIM-motor score ( $\beta = -0.072$ ,  $P = 0.017$ ), FIM-cognitive score ( $\beta = -0.077$ ,  $P = 0.011$ ), energy

intake ( $\beta = -0.147$ ,  $P = 0.004$ ), and home discharge (OR: 0.499; 95% CI: 0.280, 0.802;  $P = 0.015$ ).

Table 3  
Multivariate analyses for patient outcomes of polypharmacy

	FIM-motor at discharge*		FIM-cognitive at discharge*		FILS at discharge*		Energy intake at discharge*		LOS*		Home discharge**	
	$\beta$	P value	$\beta$	P value	$\beta$	P value	$\beta$	P value	$\beta$	P value	OR (95% CI)	P value
Age	-0.093	0.012	-0.132	<0.001	-0.129	0.003	0.146	0.006	-2.989	0.003	0.975 (0.952, 0.997)	0.026
Sex (male)	0.037	0.180	-0.002	0.935	-0.014	0.738	-0.126	0.013	-0.511	0.610	1.045 (0.634, 1.755)	0.817
LOS	0.165	<0.001	0.194	<0.001	0.193	<0.001	0.095	0.158	-	-	1.006 (0.999, 1.012)	0.102
CCI	-0.048	0.158	-0.018	0.572	-0.056	0.190	-0.107	0.046	0.362	0.718	0.923 (0.778, 1.094)	0.354
FIM-motor on admission	0.531	<0.001	0.175	0.002	0.186	0.012	-0.162	0.077	-0.864	<0.001	1.046 (1.027, 1.065)	<0.001
FIM-cognitive on admission	0.214	<0.001	0.673	<0.001	0.140	0.019	-0.001	0.988	0.949	0.343	1.071 (1.029, 1.115)	0.001
FILS on admission	0.177	<0.001	0.089	0.468	0.459	<0.001	0.055	0.438	-1.444	0.150	1.123 (1.000, 1.261)	0.050
Energy intake on admission	-0.030	0.286	-0.041	0.170	-0.005	0.890	0.230	<0.001	-0.108	0.314	0.987 (0.967, 1.007)	0.192
Rehabilitation therapy	0.001	0.973	0.041	0.181	0.027	0.433	-0.008	0.873	-1.739	0.083	1.016 (0.917, 1.125)	0.761
<b>Polypharmacy</b>	-0.072	0.017	-0.077	0.011	-0.025	0.411	-0.147	0.004	0.171	0.535	0.499 (0.280, 0.802)	0.015

\* Multivariate linear regression analysis; \*\* Multivariate logistic regression analysis

CCI, Charlson's Comorbidity Index; FILS, Food Intake Level Scale; FIM, Functional Independence Measure; LOS, length of stay

In both patients with and without PIMs at discharge, FIM-motor, FIM-cognitive, FILS scores, and energy intake significantly increased from admission to discharge (**Supplemental Table 2**). Results of univariate analyses of outcomes at admission and discharge in patients with and without PIMs revealed home discharge (57.6% vs. 73.6%) occurred less frequently in patients with PIMs than in those without. No other between-group differences in outcomes were observed.

Table 4 summarizes results of multivariate analyses of patient outcomes associated with PIMs. PIMs were independently and negatively associated with energy intake ( $\beta = -0.066$ ,  $P = 0.042$ ) and home discharge (OR: 0.452; 95% CI: 0.215, 0.756;  $P = 0.005$ ), while no associations with other outcomes were identified.

Table 4  
Multivariate analyses for patient outcomes of PIMs based on the Beers Criteria 2019

	FIM-motor at discharge*		FIM-cognitive at discharge*		FILS at discharge*		Energy intake at discharge*		LOS*		Home discharge**	
	$\beta$	P value	$\beta$	P value	$\beta$	P value	$\beta$	P value	$\beta$	P value	OR (95% CI)	P value
Age	-0.076	0.027	-0.122	<0.001	-0.130	0.003	0.149	0.006	-0.125	0.003	0.975 (0.939, 1.013)	0.199
Sex (male)	0.018	0.578	-0.006	0.846	-0.011	0.791	-0.137	0.008	-0.017	0.668	1.023 (0.615, 1.701)	0.931
LOS	0.164	<0.001	0.193	<0.001	0.191	<0.001	0.097	0.152	-	-	1.044 (1.022, 1.065)	0.067
CCI	-0.055	0.102	-0.028	0.388	-0.057	0.182	-0.124	0.021	0.015	0.714	0.894 (0.753, 1.062)	0.202
FIM-motor on admission	0.590	<0.001	0.177	0.002	0.191	0.010	-0.164	0.077	-0.665	<0.001	1.044 (1.022, 1.065)	<0.001
FIM-cognitive on admission	0.234	<0.001	0.684	<0.001	0.141	0.018	0.019	0.799	0.055	0.344	1.066 (1.019, 1.115)	0.006
FILS on admission	0.122	<0.001	0.082	0.058	0.462	<0.001	0.051	0.479	-0.087	0.125	1.123 (1.012, 1.279)	0.041
Energy intake on admission	-0.036	0.265	-0.035	0.248	-0.025	0.537	0.240	<0.001	-0.003	0.936	0.987 (0.965, 1.011)	0.290
Rehabilitation therapy	0.030	0.359	0.048	0.118	0.008	0.842	0.007	0.892	-0.072	0.075	1.058 (0.930, 1.204)	0.389
<b>PIMs</b>	-0.008	0.771	-0.010	0.734	0.032	0.433	-0.066	0.042	0.035	0.403	0.452 (0.215, 0.756)	0.005
* Multivariate linear regression analysis; ** Multivariate logistic regression analysis												
CCI, Charlson's Comorbidity Index; FILS, Food Intake Level Scale; FIM, Functional Independence Measure; LOS, length of stay; PIMs, potentially inappropriate medications												

## Discussion

In this cohort study, the prevalence and impacts of polypharmacy and PIMs in older patients undergoing stroke rehabilitation were assessed. We wish to highlight the following three novel findings: (1) polypharmacy and PIMs were frequently observed in this cohort, (2) polypharmacy was negatively associated with ADL recovery and home discharge, and (3) PIMs were negatively associated with home discharge.

Polypharmacy and PIMs are frequently observed in older patients. Here, 43.8% and 62.9% of patients had polypharmacy at admission and discharge, respectively. Further, the number of medications increased during hospitalization. To the best of our knowledge, this is the first study to assess both the number of medications prescribed for convalescent stroke and change occurring during hospitalization. A median of 1 PIMs prescription was observed in the study population. The most frequently prescribed PIMs included antipsychotics, benzodiazepines, PPI, and NSAIDs both at admission and discharge. PPIs were the most commonly prescribed PIMs at admission, likely because PPIs are prescribed for the prevention of stress ulcers in the acute phase of stroke and for the prevention of gastric ulcers with antithrombotic drugs for the secondary prevention of cerebral infarction. Post-stroke patients often have underlying diseases such as

hypertension, dyslipidemia, and diabetes mellitus, and suffer from various complications such as spasticity, pain, dysuria, cognitive dysfunction, insomnia, and depression after stroke onset. Polypharmacy and PIM risk likely increases if pharmacotherapy is blindly introduced for these comorbidities and complications.

Polypharmacy was negatively associated with ADL recovery and home discharge. A previous study reported that polypharmacy at admission was negatively associated with physical function improvement in older patients undergoing rehabilitation after stroke.<sup>18</sup> However, prescriptions at admission to rehabilitation hospitals are strongly affected by acute-care treatment just after stroke onset, and the influence of pharmacotherapy during convalescent rehabilitation has not been considered. The present study examined the impact of the number of medications at discharge on patient outcomes. Findings suggested that pharmacotherapy during convalescent rehabilitation affects outcomes. Our findings agreed with a previous study that revealed increases in numbers of medications prescribed during hospitalization were negatively associated with ADL improvement and home discharge in a similar population.<sup>37</sup> The present study also showed that polypharmacy was negatively associated with energy intake. Although previous reports have shown that polypharmacy is associated with falls<sup>10</sup> and malnutrition,<sup>38</sup> it has only been suggested that there is a similar association in stroke patients undergoing rehabilitation. Here, no association was found between polypharmacy and dysphagia status. Dysphagia in stroke is likely more affected by the disease itself than medications. Future high-quality prospective studies are needed to examine mechanisms underlying this association.

PIMs were negatively associated with home discharge. Previous studies revealed that PIMs at discharge are negatively associated with cognitive function improvement in older patients undergoing stroke rehabilitation,<sup>19</sup> and that physical function improvement is likely to be poor in patients with low ADL at baseline when PIMs increase during hospitalization.<sup>39</sup> In this study, PIMs at discharge were associated with home discharge but not with physical or cognitive function. Factors associated with the home discharge of patients undergoing rehabilitation include physical dysfunction,<sup>40</sup> physical inactivity,<sup>41</sup> cognitive decline,<sup>42</sup> dysphagia, and sarcopenia.<sup>43</sup> Therefore, PIMs may have either directly or indirectly been associated with these factors, and, therefore, indirectly affect home discharge. In this study, we examined the impact of PIMs on outcomes. No association between PIMs and physical or cognitive function was found, due to the low proportion of antipsychotics<sup>44</sup> and benzodiazepines<sup>14</sup> that were reported to negatively impact ADL improvement in the study population. Therefore, an examination of the effects of specific drugs on outcomes is needed in the future.

Medication management or pharmacotherapy is important in older patients undergoing rehabilitation. While rehabilitation focuses on training for functional recovery, pharmacotherapy tends to focus on disease treatment.<sup>17</sup> It has been reported that medications prescribed for acute treatment continue to be prescribed thereafter.<sup>45,46</sup> Therefore, the review of prescriptions when patients transition from acute care to rehabilitation is needed. PPI for stress ulcer prevention and antipsychotics for delirium are typical examples of medications introduced in the acute phase of stroke that are PIMs. In the process of functional recovery, it is also necessary to examine whether symptomatic prescriptions for complications are administered randomly.<sup>47</sup> Since this study suggests that both numbers of medications and PIMs are associated with rehabilitation outcome quality, both the content and impact of medications must be considered to optimize prescriptions management on an individual basis. Therefore, multidisciplinary team medicine led by pharmacists is necessary.

The present study had some limitations. First, it was a retrospective cohort study performed at a single hospital in Japan, which limits its generalizability. Second, effects of individual medications were not considered. Due to the nature of the study design, we were unable to examine medications that cause polypharmacy or specific medications that are more likely to be introduced in patients undergoing rehabilitation. Moreover, in addition to PIM, drugs that are useful for older patients and should be considered for initiation should be presented.<sup>48</sup> Therefore, further research is needed to determine how specific drugs affect rehabilitation outcomes.

## Conclusions And Implications

In conclusion, polypharmacy and PIMs are commonly found in older patients undergoing rehabilitation after stroke. Moreover, polypharmacy and PIMs were negatively associated with rehabilitation outcomes. To maximize the effects of rehabilitation, it is necessary to consider the impact of medications, and optimize prescriptions on an individual basis via collaborative multidisciplinary pharmacotherapy.

## Declarations

### Statements and Declarations

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: Nothing to declare.

**Funding sources:** This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

**Brief summary:**

Polypharmacy and PIMs are commonly found among older patients undergoing stroke rehabilitation. Moreover, polypharmacy and PIMs are negatively associated with rehabilitation outcomes. To maximize the effects of rehabilitation, it is necessary to consider the impact of medications via collaborative multidisciplinary pharmacotherapy.

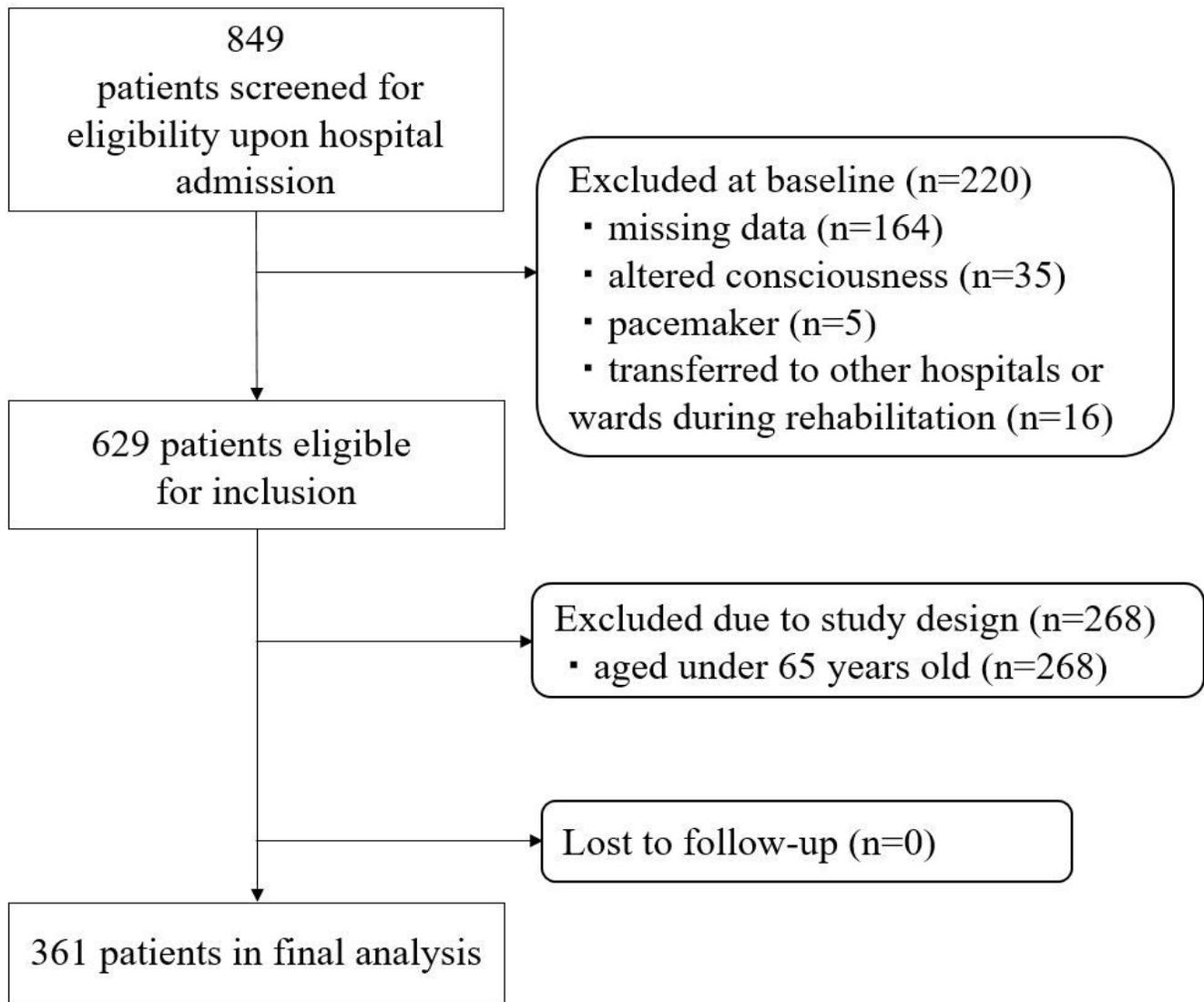
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## Figures



**Figure 1**

Flowchart of participant screening, inclusion criteria, and follow-up.

## Supplementary Files

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