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Association of pharmacist-led deprescribing intervention with the functional recovery in convalescent setting

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So far, no studies investigated the association between pharmacist intervention and rehabilitation outcomes. The aim of study was to establish whether the pharmacist-led deprescribing intervention affects rehabilitation outcomes. This retrospective, observational, single-center, cohort study included consecutive geriatric patients (n = 448) with pharmacist-led intervention between 2017 and 2019. Participants were divided based on pharmacist-led deprescribing and non deprescribing interventions during hospitalization. Demographic data, laboratory data, the Functional Independence Measure were (FIM) analyzed between the groups. Multiple linear regression analysis was performed to analyze the relationship between pharmacist-led deprescribing and FIM total gain. The primary outcome was FIM total gain. The rate of pharmacist intervention during the study period was 92.4%. A multiple linear regression analysis of FMI-T gain, adjusting for confounding factors, revealed that the pharmacist-led deprescribing intervention was independently correlated with FMI-T gain. Particularly, the use of dyslipidemia drugs, antipsychotic drugs, hypnotics, and nonsteroidal anti-inflammatory drugs significantly decreased during hospitalization. The pharmacist-led deprescribing intervention was independently and significantly associated with FIM-T gain. The pharmacist-led deprescribing intervention improved functional recovery in a rehabilitation setting.

1. Introduction

Polypharmacy, defined as the regular use of at least five medications, is a serious problem among older people. Its prevalence increases with age as the elderly are often affected by multiple diseases (Wolff et al. 2002). Adhering to current clinical practice guidelines in caring for older people with multimorbidity may result in polypharmacy, regardless of whether the prescription prevents fatal events or alleviates symptoms (Fick et al. 2001). Polypharmacy is associated with several problems, including drug interactions, adverse drug events, increased healthcare costs, and decreased medication adherence (Mangin et al. 2018). In addition, drug elimination function is usually impaired in older adults, leading to an increase in adverse drug reactions (Mangoni and Jackson 2004). Thus, older patients with polypharmacy may be at increased risk of adverse drug events, which reduces their QOL and ADL.

The concept of rehabilitation pharmacotherapy has been introduced recently (Kose and Wakabayashi 2020). Its objective is to achieve the highest possible level of body function, activity status and QOL in individuals more prone to polypharmacy. Rehabilitation pharmacotherapy applied to drug treatment not only considers the training in rehabilitation but also pharmacotherapy. Therefore, examining rehabilitation and pharmacotherapy in parallel is essential for improving the outcomes of rehabilitation. We have demonstrated that polypharmacy or PIMs affect rehabilitation outcomes (Kose et al. 2018a-d, 2016).

Similar to our report, a recent systematic review reported that PIMs were associated with poorer physical performance comprising the Timed Up and Go test, walking speed, grip strength, time to functional recovery, functional independence, and scale of functioning (Manias et al. 2021). Another systematic review and meta-analysis also reported that PIMs were associated with health-related outcomes such as functional decline or falls (Mekonnen et al. 2021). As such, managing medication use among older adults in convalescent rehabilitation wards is crucial to prevent unnecessary harm and improve the quality of drug use.

Pharmacists are responsible for promoting the proper use of medications and preventing the occurrence of adverse drug events. They have a significant role in facilitating evidence-based information and educating the public on appropriate medicines, especially in convalescent rehabilitation wards. In addition, promoting the least possible use of medications through various means, including

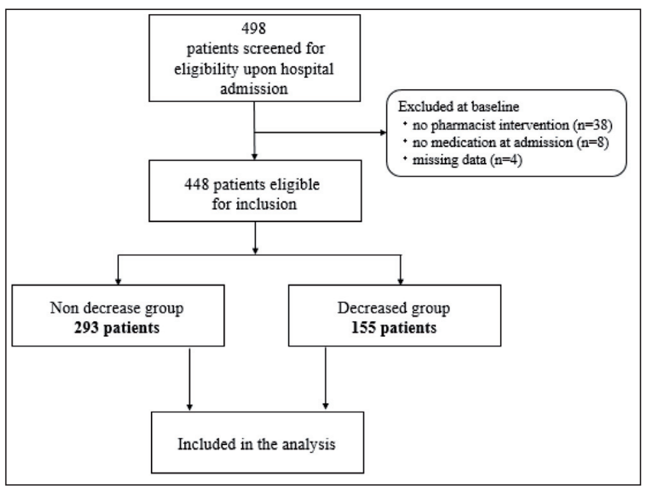

Fig. 1: Flowchart of participant screening, inclusion criteria, and follow-up. The reasons why pharmacists could not intervene are as follows. First, the patient was unable to communicate, mainly due to mental illness, dementia, or severe hearing loss; second, the patient refused to accept the pharmacist's guidance; and finally, there was no prescription.

Table 1: Baseline of demographic characteristics

Characteristics	All patients (n = 448)	Non decreased group (n = 293)	Decreased group (n = 155)	*p* value
Age (y)	82 (76–86)	82 (74–86)	83 (77–88)	0.0012†
Gender *n*, (%)				0.4166§
Male	155 (34.6)	100 (34.1)	55 (35.5)	
Female	293 (65.4)	193 (65.9)	100 (64.5)	
Length of stay (d)	41 (28.3–58)	40 (27–60)	42 (32–55)	0.2862†
Body weight at admission (kg)	50 (42.3–58)	50.1 (43.2–58.5)	48.5 (41.1–55.1)	0.0377†
BMI at admission (kg/m^2)	21 (18.8–23.5)	21.3 (19.1–23.7)	20.3 (18.4–23)	0.0477†
GNRI at admission	84.7 (46.2–94.2)	87.2 (47.5–96.3)	78.4 (43.8–89.9)	0.0007†
Primary diagnosis *n*, (%)				0.0334§
Cerebral infraction	28 (6.3)	45 (15.4)	12 (7.7)	
Intracerebral hemorrhage	57 (12.7)	23 (7.9)	5 (3.2)	
Subarachnoid hemorrhage	16 (3.6)	9 (3.1)	7 (4.5)	
Fracture–related disease	315 (70.3)	193 (65.9)	122 (78.7)	
Hospital-associated deconditioning	2 (0.4)	1 (0.3)	1 (0.7)	
Others	30 (1)	22 (7.5)	8 (5.2)	
Comorbid conditions *n*, (%)				
Cardiac disease	90 (20.1)	58 (19.8)	32 (20.7)	0.8309§
Diabetes mellitus	282 (62.9)	183 (62.5)	99 (63.9)	0.7682§
Hypertension	119 (26.6)	80 (27.3)	39 (25.2)	0.6253§
Parkinson's disease	9 (2)	4 (1.4)	5 (3.2)	0.1818§
Epilepsy	15 (3.3)	12 (4.1)	3 (1.9)	0.2267§
Family cooperation *n*, (%)	368 (82.1)	239 (81.6)	129 (83.2)	0.6633§
HDS-R	23 (19–26)	24 (19–27)	23 (16–26)	0.1349§
Upper limb paralysis *n*, (%)	90 (20.1)	71 (24.2)	19 (12.3)	0.0026§
Higher brain dysfunction *n*, (%)	80 (17.9)	63 (21.5)	17 (11)	0.0056§
No. of medications at admission	6.6 ± 3.3	6.2 ± 3.3	7.5 ± 3.2	<.0001†
No. of medications at discharge	6.3 ± 3.3	6.7 ± 3.4	5.6 ± 2.9	0.0026†
FIM at admission (points)				
FIM–T	73 (55–90)	73 (55–91)	71 (53–89)	0.5749†
FIM–M	46 (30–58)	47 (30.5–60)	46 (30–58)	0.6815†
FIM–C	28 (21–35)	28 (20–35)	28 (22–34)	0.7651†
FIM at discharge (points)				
FIM–T	110 (92–118)	110 (90.5–118)	110 (94–117)	0.8665†
FIM–M	79 (65–85)	79 (64.5–85)	79 (67–84)	0.6526†
FIM–C	31 (25–35)	31 (25–35)	31 (25–35)	0.9209†

Values are mean±standard deviation or median (interquartile range) where appropriate
Abbreviations: BMI, body mass index; FIM, functional independence measure; FIM–C, functional independence measure–cognitive; FIM–M, functional independence measure–motor; FIM–T, functional independence measure–total; GNRI, geriatric nutritional risk index; HDS-R, Hasegawa dementia rating scale-revised
†: Mann–Whitney U test, §: Chi–square test.

pharmacist-led medication reviews to improve health outcomes, is important. Several systematic reviews showing a positive impact of pharmacist-led interventions have been published, but these studies have mostly focused on the impact of the interventions in the community (Fried et al. 2014), nursing homes (Lee et al. 2019), or tertiary care (Teoh et al. 2019) settings. Several studies reported the effects of pharmacists' interventions with older patients in convalescent rehabilitation setting. Assignment of pharmacists to the convalescent rehabilitation ward improved rehabilitation outcomes regardless of time spent in the ward (Nakamichi et al. 2021). Another report showed that pharmacist medication instructions to patients affected patients' medication self-management (Kose et al. 2021a). However, these studies were not specific to pharmacist-led deprescribing. Few studies are available on the impact of deprescribing on rehabilitation outcomes (Kose et al. 2021b). Therefore, the present study aimed to clarify whether the pharmacist-led deprescribing intervention affects rehabilitation outcomes, which is the focus of our study.

2. Investigations and results

2.1. Descriptive and univariate analyses

A total of 498 participants were included in the study. Of these, 448 were included in the final analysis, excluding 38 participants who did not have pharmacist intervention during the study period, eight participants who had no medication at admission, and four participants with missing data. No participants were transferred to another facility or died during the study period (Fig. 1). The rate of pharmacist intervention during the study period was 92.4%. The reasons why pharmacists could not intervene are as follows. First, the patient was unable to communicate, mainly due to mental illness, dementia, or severe hearing loss; second, the patient refused to accept the pharmacist's guidance; and finally, there was no prescription.

The median age of the participants included in the final analysis was 82 years, with 155 (34.6%) males and 293 (65.4%) females. The major primary diseases were cerebral infarction in 28 participants (6.3%), cerebral hemorrhage in 57 participants (12.7%), a sub-arachnoid hemorrhage in 16 participants (3.6%), fracture-related diseases in 315 participants (70.3%), hospital-associated deconditioning in two participants (0.4%), and others in 30 participants (1%).

Table 1 shows the demographic characteristics of the patients based on the presence (n = 155) and absence (n = 293) of decreased medications by pharmacist intervention. Significant differences were observed for age, BW, BMI, GNRI, primary diagnosis, upper limb paralysis, higher brain dysfunction, and number of medications at admission and dis-charge. In contrast, there was no significant difference between the two groups in other parameters such as gender, length of hospital stay, cardiovascular disease, diabetes mellitus, hypertension, Parkinson's disease, epilepsy, family cooperation, and HDS-R. In comparing FIM-T, FIM-M, and FIM-C at admission and discharge were not significantly different between the two groups.

Table 2 shows the association of FIM-T gain with patient characteristics and FIM at admission and discharge. The items significantly

Table 2: Association between demographic characteristics and FIM-Total gain

Characteristics	All patients (n = 448)	Correlation coefficient	*p* value
Age (y)	82 (76–86)	0.1087	0.0098‡
Gender *n*, (%)			0.5466†
Male	155 (34.6)		
Female	293 (65.4)		
Length of stay (d)	41 (28.3–58)	0.0961	0.0421‡
Body weight at admission (kg)	50 (42.3–58)	–0.0148	0.7569†
BMI at admission (kg/m^2)	21 (18.8–23.5)	0.0445	0.3527‡
GNRI at admission	84.7 (46.2–94.2)	0.0315	0.5098‡
Primary diagnosis *n*, (%)			0.0030§
Cerebral infraction	28 (6.3)		
Intracerebral hemorrhage	57 (12.7)		
Subarachnoid hemorrhage	16 (3.6)		
Fracture–related disease	315 (70.3)		
Hospital-associated deconditioning	2 (0.4)		
Others	30 (6.7)		
Comorbid conditions *n*, (%)			
Cardiac disease	90 (20.1)		0.0281†
Diabetes mellitus	282 (62.9)		0.0842†
Hypertension	119 (26.6)		0.1030†
Parkinson's disease	9 (2)		0.0071†
Epilepsy	15 (3.3)		0.3709†
Family cooperation *n*, (%)	368 (82.1)		0.0007†
HDS-R	23 (19–26)	0.1550	0.0042‡
Upper limb paralysis *n*, (%)	90 (20.1)		0.1314†
Higher brain dysfunction *n*, (%)	80 (17.9)		0.1208†
No. of medications at admission	6.6 ± 3.3	0.0322	0.4971‡
No. of medications at discharge	6.3 ± 3.3	0.0286	0.5455‡
FIM at admission (points)			
FIM–T	73 (55–90)	0.4119	< .0001‡
FIM–M	46 (30–58)	0.4762	< .0001‡
FIM–C	28 (21–35)	0.0409	0.3889‡
FIM at discharge (points)			
FIM–T	110 (92–118)	0.2884	< .0001‡
FIM–M	79 (65–85)	0.2994	< .0001‡
FIM–C	31 (25–35)	0.1764	0.0002‡

Values are median (interquartile range) where appropriate.
P values indicate the association with total FIM gain.
†: Mann–Whitney U test, ‡: Spearman's rank correlation, §: Kruskal–Wallis test.
Abbreviations: BMI; body mass index, FIM; functional independence measure, FIM–T; functional independence measure–total, FIM–M; functional independence measure–motor, FIM–C; functional independence measure–cognitive, GNRI; geriatric nutritional risk index, HDS-R; Hasegawa dementia rating scale-revised

associated with FIM-T gain were age, LOS, primary disease, Parkinson's disease, family cooperation, HDS-R, FIM-T, FIM-M at admission and discharge, and FIM-C at discharge.

2.2. *Multiple linear regression analysis*

Among the candidate factors extracted from the univariate analysis for the presence or absence of a decrease in the number of medications following pharmacist intervention, the explanatory factors that were significantly associated with FIM-T gain by multiple regression analysis were FIM-T at admission, decrease in the number of medications, HDS-R, higher brain dysfunction, family cooperation, LOS, and epilepsy (Table 3).

Table 3: Multiple regression analysis for FIM–Total gain

Variable	Unstandardized coefficient				t	VIF	*p* value
	β	Standard error	95% CI of β				
FIM–T at admission	0.681	0.043	0.596	0.766	15.81	1.731	< .0001
Deacreased in the no. of medications	1.555	0.786	0.008	3.102	1.98	1.114	0.049
GNRI at admission	0.007	0.030	–0.052	0.066	0.22	1.097	0.823
HDS–R	1.342	0.138	1.070	1.613	9.73	1.577	< .0001
Higher brain dysfunction	–3.045	1.436	–5.870	0.220	–2.12	2.833	0.035
Cerebral infraction	–4.900	3.238	–11.267	1.475	–1.51	2.672	0.132
Intracerebral hemorrhage	–2.183	2.432	–6.967	2.602	–0.01	2.394	0.370
Subarachnoid hemorrhage	–1.107	3.484	–7.962	5.748	–0.32	2.360	0.751
Fratcture–related disease	–0.413	2.356	–5.049	4.223	–0.18	3.882	0.861
Hospital-associated deconditioning	–3.687	7.869	–19.169	11.796	–0.47	4.245	0.634
Others	–4.945	3.205	–11.254	1.359	–1.54	1.237	0.124
No. of medications at admission	–0.087	0.248	–0.575	0.400	–0.35	1.377	0.725
Family cooperation	5.423	1.017	3.453	7.394	5.41	1.154	< .0001
LOS	–0.120	0.035	–0.190	–0.051	–3.40	1.367	0.001
Age	–0.079	0.117	–0.308	0.151	–0.67	1.496	0.501
Hypertension	1.119	0.770	–0.396	2.633	1.45	1.078	0.147
Diabetes mellitus	–1.198	0.945	–3.057	0.661	–1.27	1.202	0.206
Epilepsy	–6.949	2.043	–10.969	–2.929	–3.40	1.175	0.001
Cardiac disease	–1.307	1.020	–3.134	0.699	–1.28	1.196	0.201
Parkinson's disease	–2.815	2.414	–7.564	1.934	–1.17	1.107	0.244
Constant	47.784	11.520	25.118	70.450	4.15		< .0001

Abbreviation; CI, confidence interval; FIM–T, functional independence measure total; GNRI, geriatric nutrition risk index; HDS–R, Hasegawa dementia rating scale-revised; LOS, length of stay; VIF, variance inflation factor
$R^2 = 0.5328$, $p = <.0001$

2.3. *Comparison of prescription medications at admission and discharge*

Figure 2 shows the percentage of prescribed medications at admission and discharge. Dyslipidemia drugs, antipsychotic drugs, hypnotics, and NSAIDs decreased significantly from admission to discharge. On the other hand, osteoporosis drugs increased significantly from admission to discharge.

3. Discussion

The most important finding of this study is that the pharmacist-led deprescribing intervention was independently and significantly associated with FIM-T gain. i.e., deprescribing may positively affect the improvement of ADL by rehabilitation. The second most important finding is that the prescribed rate of dyslipidemia drugs, antipsychotic drugs, hypnotics, and NSAIDs significantly decreased from admission to discharge. This finding suggests that the deprescribing of these drugs contributed to the improvement of ADLs through rehabilitation.

The pharmacist-led deprescribing intervention was associated with the improvement of ADL by rehabilitation. We have reported that the deprescribing of PIMs affects the improvement of ADLs (Kose et al. 2021b). The present study showed that pharmacists made efforts to support patients' medication use by understanding patients' medication history, symptoms, and laboratory data, and deprescribing based on the appropriate use of medications led to improvement in ADLs. This finding was similar to a previous report (Kose et al. 2021b). Therefore, pharmacist-led deprescribing intervention is crucial for improving ADL in clinical practice, and active intervention for prescribing is necessary. Japan is becoming a super-aged society, with the proportion of older adults aged ≥65 years exceeding a quarter of the total population. Older adults are more susceptible to various diseases, which inevitably lead to an increased use of medications, and polypharmacy has become a problem. Therefore, our results are socially and clinically significant in that the pharmacist-led deprescribing intervention contributed to the improvement of ADL.

Pharmacists play an important role in drug safety in clinical practice and the elimination of useless polypharmacy. Pharmacists are responsible for assessing drug efficacy, identifying potential adverse drug events, and determining the appropriateness of prescriptions through medication review. Several studies have examined the effects of pharmacist-led interventions on polypharmacy. Hashimoto et al. investigated the outcomes of interdisciplinary drug therapy interventions by pharmacists among older residents of special elderly nursing homes. The authors noted that the pharmacist intervention was associated with a trend toward fewer PIMs and falls (Hashimoto et al. 2020). However, the sample size was small (55 patients), and the outcomes included a decrease in PIMs and the occurrence of falls, i.e., the patients' ADLs were not assessed. Additionally, Balsom et al. examined the effective-

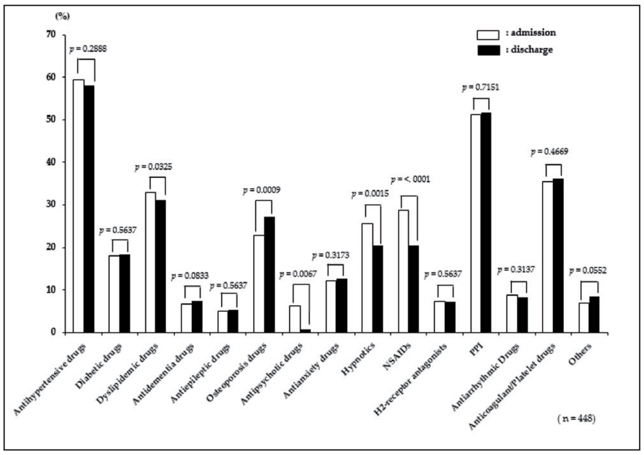

Fig. 2: Comparison of prescription drugs at admission and discharge. The McNemar test was used to compare the prescription drugs at admission and discharge. Abbreviation; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor

ness of pharmacist-led deprescribing in residents of a long-term care facility (Balsom et al. 2020). The authors concluded that a pharmacist-led deprescribing intervention could reduce the number of unnecessary and potentially harmful medications taken by long-term care residents. Furthermore, Komagamine and Hagane (2017) evaluated the effect of a pharmacist-led intervention to improve polypharmacy in older patients hospitalized for hip fracture. The primary composite outcome was death or the first occurrence of any new fracture. The authors concluded that intervention for polypharmacy was associated with a reduction in PIMs but not an improvement in clinical outcomes (Komagamine and Hagane 2017). As is evident from the above, the outcome of studies examining the effect of pharmacists' intervention on polypharmacy is mostly drug reduction. A few studies outside Japan have reported ADL and QOL as outcomes (Syarifuddin et al. 2019; Mahdavi et al. 2021). A systematic review has also appeared, but large heterogeneity has been noted (Thillainadesan et al. 2018). This study differs from previous reports in that the pharma-cist-led deprescribing intervention improved the ADL of the patients. As far as we know, there is no study in Japan in which pharmacist-led deprescribing intervention improved ADL, which is important for patients. Accordingly, this is a strength of this study and a new finding that has not been reported previously.

The use of dyslipidemia drugs, antipsychotic drugs, hypnotics, and NSAIDs decreased by approximately 2%, 6%, 5%, and 8%, respectively, from admission to discharge. Statins decrease CoQ10 production by inhibiting mitochondrial oxidative phosphorylation and inducing mitochondrial apoptosis (Mollazadeh et al. 2021). Decreased CoQ10 results in decreased adenosine triphosphate production and energy deficiency, which may in-duce frailty and sarcopenia. In this study, statins accounted for the majority of dyslipidemia drugs. Therefore, the discontinuation of statins may have suppressed the decrease in CoQ10 production and led to the elimination of energy deficiency, resulting in the improvement of ADL.

Antipsychotics and hypnotics are known to directly inhibit the nervous system and be responsible for drowsiness and sedation, causing motor and functional impairment and decreased levels of consciousness. In addition, many benzodiazepines are fat-soluble, and their distribution volume increases in the older people and obese, who have an in-creased proportion of adipose tissue, making them more prone to adverse effects. Most of the hypnotics used in this study were benzodiazepines. Accordingly, these drugs' hypnotic and sedative effects and also their muscle relaxant effects may have affected ADL.

Some of the most common side effects of NSAIDs are gastrointestinal disorders. Gastrointestinal disorders caused by NSAIDs are often asymptomatic, and symptoms may worsen if the patient continues to take the medications without being aware of them. In addition, gastrointestinal disorders may lead to loss of appetite and decreased food intake. Decreased food intake can lead to sarcopenia and frailty, resulting in malnutrition. A systematic review has shown that malnutrition in older patients admitted to a rehabilitation hospital has a negative effect on functional recovery and QOL after discharge (Marshall et al. 2014). Thus, rehabilitation in a malnutritional state is not expected to be sufficiently effective. In addition, rehabilitation leads to further worsening of the malnutritional state. As such, it is conceivable that the deprescribing of NSAIDs may have indirectly enhanced rehabilitation by reducing the occurrence of gastrointestinal disorders and malnutrition.

In some cases, pharmacists could not reduce the number of medications. The reasons for failure to reduce medication were that the prescribed drug was necessary for disease control and was highly effective, that the risk of withdrawal symptoms was high and difficult to correct, or that the patient did not provide consent. When reducing number of medications, attention must be paid to minimizing the risk of disease exacerbation and withdrawal symptoms. Older patients should be carefully evaluated because they are at higher risk of developing symptomatic changes after drug reduction.

This study has several limitations. First, it was an observational study conducted at a single Japanese civilian hospital. Thus, our results may not be generalizable to other clinical settings or countries. However, our results may be useful in an aging population such as that in Japan or when the prescribing trends are similar. Second, we could not evaluate whether the reduced medication was restarted or not after discharge. Third, the content of the rehabilitation program was not considered. Finally, the dosage of medications was not taken into account.

In conclusion, our results highlighted that pharmacist-led deprescribing intervention was independently and significantly associated with FIM-T gain. It is desirable to examine the relationship between pharmacist-led deprescribing intervention and ADL in prospective cohort studies.

4. Experimental

4.1. Study design and participants

This retrospective cohort study included 498 consecutive participants admitted to the convalescence rehabilitation ward at Ogaki Tokushukai Hospital between January 2017 and June 2019. The inclusion criteria were as follows: 1) the patient is ≥65 years old, and 2) the patient had a pharmacist's intervention. The exclusion criteria were as follows: 1) lack of a pharmacist's intervention; 2) not taking medication at admission; 3) transfer to another facility during the study period; 4) death during the study period; 5) missing data. In addition, participants were categorized into two groups, i.e., those whose number of medications was decreased by the pharmacist's intervention during hospitalization (the "decrease group") and those whose number of medications was not reduced (the "nondecrease group").

4.2. Data collection

Data on the participants' basic information included their age, gender, LOS, BW, BMI, GNRI, primary diagnosis, comorbidities, family cooperation, HDS-R, upper limb paralysis, higher brain dysfunction, number of medications, and FIM. For the analysis, the number of medications and FIM at admission and discharge were used. For the other items, the data at admission were used.

The GNRI, a nutritional risk index, was calculated based on the serum Alb concentration and BW using the following equation: GNRI = [14.89 × Alb concentration (g/dL)] + [41.7 × (actual BW/ideal BW)]. The weight and Alb were measured at admission. The ideal BW was defined as a BMI of 22.0 kg/m^2 rather than using the Lorentz formula (Shah et al. 2006); there is reportedly no difference in GNRI when the Lorentz formula is used to estimate the ideal BW or this parameter is assumed to have a BMI value of 22.0 kg/m^2. We divided patients into two groups according to GNRI at admission: low GNRI (<92), indicating moderate or severe nutritional risk, and high GNRI (≥92), indicating low or no nutritional risk [20].

4.3. Assessment of ADLs

Indicators of ADL such as FIM and the Barthel index are used for evaluation during the recovery period (Chumney et al. 2010). Notably, the reliability of FIM has been confirmed in a meta-analysis of 11 studies (Ottenbacher et al. 1996). Therefore, we used FIM for the ADL measurement. The FIM score, which includes 13 lower-order items regarding FIM-M and 5 lower-order items regarding FIM-C, is one of the most common measures of ADL (Nathans et al. 2020). Each item is scored on a scale of 1 point (total assistance) to 7 points (complete independence). FIM-T score therefore ranges from 18 to 126 points. FIM scores were determined at admission and discharge by a multidisciplinary rehabilitation team, including a rehabilitation physician, a physical therapist, an occupational therapist, and a speech-language-hearing therapist. Appropriate rehabilitation was offered to all participants based on clinical judgment, regardless of their FIM score, disease severity, or LOS.

4.4. Details of pharmacist's intervention

Pharmacists play specialized and important roles in the wards (Nathans et al. 2020). Pharmacists' recommendations for safer alternatives to reduce the risk of side effects without compromising the achievement of desired therapeutic goals are crucial (Fritsch et al. 2019). The activities of the pharmacists in this study are listed below. Two pharmacists work full-time in the convalescent rehabilitation ward and also participate in the rehabilitation conferences.

- Dose adjustment according to clinical laboratory values (particularly liver and kidney function).
- Discontinuation or reduction of medications that cause drug–drug interactions.
- Discontinuation or reduction of doses of overlapping drugs and drugs of the same class.
- Whether or not to continue aimlessly administered drugs, considering their efficacy and the risk of developing side effects.
- Discontinuation or reduction of doses of suspected drugs that may be the cause of adverse drug reactions.

4.5. Main outcome measurement

This study used the FIM-T gain as the main outcome measurement, calculated as the change in the FIM-T score from admission to discharge.

4.6. Sample size calculation

A study size analysis was performed using Power and Sample Size Calculation Software (Version 3.0, 2009, William D. Dupont, PhD, and Walton D. Plummer, Department of Biostatistics, Vanderbilt University; available from http: //biost at.mc.vande rbilt .edu/wiki/Main/Power SampleSize). A previous study in Japan indicated that the mean FIM gain of stroke patients in convalescent rehabilitation wards was 19.7±18.5 (Miyai et al. 2015), from which we hypothesized that there was an overall increase of 5 in the FIM gain because of pharmacist-led deprescribing intervention. To detect a mean difference of 5 in the FIM gain (with a standard deviation of 18.5) among two groups at a ratio of 1:1, we required 216 patients per group to achieve a power $(1 - \beta)$ of 0.8 and an α of 0.05. Thus, based on the incidence in Ogaki Tokushukai Hospital, we planned to include approximately 2 years of data to ensure sufficient statistical power.

4.7. Statistical analysis

All statistical analyses were performed using JMP Pro (Version 15, SAS Institute, Cary, NC, USA). Data with a normal distribution were described by mean±standard deviation. If not normally distributed, data were described by median (interquartile range 25^{th}–75^{th} percentiles). A p-value of <0.05 was considered statistically significant.

Student's t-test, Mann–Whitney U-test, Kruskal–Wallis test, and Chi–square test were used to analyze the differences between groups. Spearman's rank correlation test was carried out to detect the correlation coefficients between the factors. Finally, a multiple linear regression analysis was used to examine whether FIM-T gain was independently associated with a pharmacist-led deprescribing intervention. This included adjustment for co-variates such as age, LOS, FIM-T at admission, decrease in number of medications, GNRI, HDS-R, higher brain dysfunction, primary diagnosis (cerebral infraction, intracerebral hemorrhage, subarachnoid hemorrhage, fracture–related disease, hospital-associated deconditioning, and others), number of medications at admission, family cooperation, Comorbid conditions (cardiac disease, diabetes mellitus, hypertension, Parkinson's disease, and epilepsy). Only one variable was included in the multiple linear regression analysis if there was a strong internal correlation between explanatory variables ($p < 0.01$). This is reasonable from a medical and pharmacological point of view.

Multicollinearity was assessed using the variance inflation factor. The McNemar test was used to compare prescription at admission and discharge.

4.8. Ethics approval

The present study was performed according to the Declaration of Helsinki and was approved by the Joint Ethics Committee of the Tokushukai Group (registration number: TGE01809–066).

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References

Balsom C, Pittman N, King R, Kelly D (2020) Impact of a pharmacist-administered deprescribing intervention on nursing home residents: a randomized controlled trial. Int J Clin Pharm 42: 1153–1167.

Chumney D, Nollinger K, Shesko K, Skop K, Spencer M, Newton RA (2010) Ability of functional Independence measure to accurately predict functional outcome of stroke-specific population: systematic review. J Rehabil Res Dev 47: 17–29.

Fick D (2001) Potentially inappropriate medication use in a Medicare managed care population: association with higher costs and utilization. J Manag Care Pharm 7: 407–413.

Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK (2014) Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J am Geriatr Soc 62: 2261–2272.

Fritsch MA, Shelton PS (2019) Geriatric polypharmacy: pharmacist as key facilitator in assessing for falls risk: 2019 update. Clin Geriatr Med 35: 185–204.

Hashimoto R, Fujii K, Shimoji S, Utsumi A, Hosokawa K, Tochino H, Sanehisa S, Akishita M, Onda M (2020) Study of pharmacist intervention in polypharmacy among older patients: Non-randomized, controlled trial. Geriatr Gerontol Int 20: 229–237.

Kinugasa Y, Kato M, Sugihara S, Hirai M, Yamada K, Yanagihara K, Yamamoto K. (2013) Geriatric nutritional risk index predicts functional dependency and mortality in patients with heart failure with preserved ejection fraction. Circ J 77: 705–711.

Komagamine J, Hagane K (2017) Intervention to improve the appropriate use of polypharmacy for older patients with hip fractures: an observational study. BMC Geriatr 17: 288.

Kose E, Endo H, Hori H, Hosono S, Kawamura C, Kodama Y, Yamazaki T, Yasuno N (2021a) Pharmacist medication instructions are associated with continued medication self-management in older adults: a retrospective observational study. J Pharm Health Care Sci 7: 11.

Kose E, Hirai T, Seki T (2018b) The association of increased drugs use with activities of daily living and discharge outcome among elderly stroke patients. Int J Clin Pharm 40: 599–607.

Kose E, Hirai T, Seki T (2018c) Psychotropic drug use and cognitive rehabilitation practice for elderly patients. Int J Clin Pharm 40: 1292–1299.

Kose E, Hirai T, Seki T, Hayashi H (2018a) Role of potentially inappropriate medication use in rehabilitation outcomes for geriatric patients after strokes. Geriatr Gerontol Int 18: 321–328.

Kose E, Hirai T, Seki T, Hidaka S, Hamamoto T (2018d) Anticholinergic load negatively correlates with recovery of cognitive activities of daily living for geriatric patients after stroke in the convalescent stage. J Clin Pharm Ther 43: 799–806.

Kose E, Hirai T, Seki T, Yasuno N (2021b) The impact of decreasing potentially inappropriate medications on activities of daily living in a convalescent rehabilitation setting. Int J Clin Pharm 43: 577–585.

Kose E, Maruyama R, Okazoe S, Hayashi H (2016) Impact of polypharmacy on the rehabilitation outcome of Japanese stroke patients in the convalescent rehabilitation ward. J Aging Res 2016: 7957825.

Kose E, Wakabayashi H (2020) Rehabilitation pharmacotherapy: A scoping review. Geriatr Gerontol Int 20: 655–663.

Lee SWH, Mak VSL, Tang YW (2019) Pharmacist services in nursing homes: A systematic review and meta-analysis. Br J Clin Pharmacol 85: 2668–2688.

Marshall S, Bauer J, Isenring E (2014) The consequences of malnutrition following discharge from rehabilitation to the community: a systematic review of current evidence in older adults. J Hum Nutr Diet 27: 133–141.

Mangin D, Bahat G, Golomb BA, Mallery LH, Moorhouse P, Onder G, Petrovic M, Garfinkel D (2018) International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and Recommendations for Action. Drugs and Aging 35: 575–587.

Mangoni AA, Jackson SH (2004) Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 57: 6–14.

Manias E, Kabir MZ, Maier AB (2021) Inappropriate medications and physical function: a systematic review. Ther Adv Drug Saf 12: 20420986211030371.

Mekonnen AB, Redley B, Courten BD, Manias E (2021) Potentially inappropriate prescribing and its associations with health-related and system-related outcomes in hospitalised older adults: A systematic review and meta-analysis. Br J Clin Pharmacol 87: 4150–4172.

Mahdavi H, Esmaily H (2021) Impact of educational intervention by community pharmacists on asthma clinical outcomes, quality of life and medication adherence: A systematic review and meta-analysis. J Clin Pharm Ther 46: 1254–1262.

Miyai I, Sonoda S, Nagai S, Takayama Y, Inoue Y, Kakehi A, Kurihara M, Ishikawa M. (2015) Results of new policies for inpatient rehabilitation coverage in Japan. Neurorehabil Neural Repair 25: 540–547.

Mollazadeh H, Tavana E, Fanni G, Bo S, Banach M, Pirro M, Haehling SV, Jamialahmadi T, Sahebkar A (2021) Effects of statins on mitochondrial pathways. J. Cachexia Sarcopenia Muscle 12: 237–251.

Nakamichi M, Wakabayashi H, Nishioka S, Nagano A, Nishiyama A, Fujiwara D, Momosaki R (2021) Impact of pharmacists on the improvement of activities of daily living and nutritional status of convalescent stroke patients. JJARN 5: 96–105.

Nathans AM, Bhole R, Finch CK, George CM, Alexandrov AV, March KL (2020) Impact of a pharmacist-driven poststroke transitions of care clinic on 30 and 90-Day Hospital Readmission Rates. J Stroke Cerebrovasc Dis 29: 104648.

Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC. (1996) The reliability of the functional independence measure: a quantitative review. Arch Phys Med Rehabil 77: 1226–1232.

Shah B, Sucher K, Hollenbeck CB (2006) Comparison of ideal body weight equations and published height-weight tables with body mass index tables for healthy adults in the United States. Nutr Clin Pract 21: 312–319.

Syarifuddin S, Nasution A, Dalimunthe A, Khairunnisa (2019) Impact of pharmacist intervention on improving the quality of life of patients with type 2 diabetes mellitus. Open Access Maced J Med Sci 7: 1401–1405.

Teoh KW, Khan TM, Chaiyakunapruk N, Lee SWH (2019) Examining the use of network meta-analysis in pharmacy services research: a systematic review. J Am Pharm Assoc 59: 787–791.

Thillainadesan J, Gnjidic D, Green S, Hilmer SN (2018) Impact of deprescribing interventions in older hospitalised patients on prescribing and clinical outcomes: a systematic review of randomised trials. Drugs Aging 35: 303–319.

Wolff JL, Starfield B, Anderson G (2002) Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med 162: 2269–2276.