



Polypharmacy, Potentially Inappropriate Medications, and Dysphagia in Older Inpatients: A Multi-Center Cohort Study

Shintaro Togashi^{1,2}, Hironori Ohinata³, Taiji Noguchi^{4,5}, Hidetaka Wakabayashi⁶, Mariko Nakamichi⁷, Akio Shimizu⁸, Shinta Nishioka⁹, Ryo Momosaki¹⁰

¹Center for Outcomes Research and Economic Evaluation for Health, National Institute of Public Health, Wako-shi, Japan

²Department of Nursing Care, Sendai Kosei Hospital, Sendai, Japan

³Faculty of Health Sciences, Hokkaido University, Sapporo, Japan

⁴Department of Social Science, Center for Gerontology and Social Science, Research Institute, National Center for Geriatrics and Gerontology, Obu, Japan

⁵Japan Society for the Promotion of Science, Chiyoda, Japan

⁶Department of Rehabilitation Medicine, Tokyo Women's Medical University Hospital, Shinjuku, Japan

⁷Department of Pharmacy, Haradai Hospital, Fukuoka, Japan

⁸Department of Food and Health, Faculty of Health and Human Development, The University of Nagano, Nagano, Japan

⁹Department of Clinical Nutrition and Food Service, Nagasaki Rehabilitation Hospital, Nagasaki, Japan

¹⁰Department of Rehabilitation Medicine, Mie University Graduate School of Medicine, Tsu, Japan

Corresponding Author:

Shintaro Togashi, RN, PHN, PhD
Center for Outcomes Research and
Economic Evaluation for Health,
National Institute of Public Health, 2-3-
6, Minami, Wako-shi 351-0197, Japan
E-mail: togashishintaro.42@gmail.com
ORCID:
<https://orcid.org/0000-0002-1753-4450>

Received: December 6, 2023

Revised: January 5, 2024

Accepted: January 10, 2024

Background: Although the relationship between medication status, symptomatology, and outcomes has been evaluated, data on the prevalence of polypharmacy and potentially inappropriate medications (PIMs) and the association of polypharmacy and PIMs with swallowing function during follow-up are limited among hospitalized patients aged ≥ 65 years with dysphagia. **Methods:** In this 19-center cohort study, we registered 467 inpatients aged ≥ 65 years and evaluated those with the Food Intake LEVEL Scale (FILS) scores ≤ 8 between November 2019 and March 2021. Polypharmacy was defined as prescribing ≥ 5 medications and PIMs were identified based on the 2023 Updated Beers Criteria. We applied a generalized linear regression model to examine the association of polypharmacy and PIMs with FILS score at discharge. **Results:** We analyzed 399 participants (median age, 83.0 years; males, 49.8%). The median follow-up was 51.0 days (interquartile range, 22.0–84.0 days). Polypharmacy and PIMs were present in 67.7% of and 56.1% of patients, respectively. After adjusting for covariates, neither polypharmacy ($\beta=0.05$; 95% confidence interval [CI], -0.04 – 0.13 , $p=0.30$) nor non-steroidal anti-inflammatory medications ($\beta=0.09$; 95% CI, -0.02 – 0.19 ; $p=0.10$) were significantly associated with FILS score at discharge. **Conclusions:** The results of this study indicated a high proportion of polypharmacy and PIMs among inpatients aged ≥ 65 years with dysphagia. Although these prescribed conditions were not significantly associated with swallowing function at discharge, our findings suggest the importance of regularly reviewing medications to ensure the appropriateness of prescriptions when managing older inpatients.

Key Words: Deglutition disorders, Geriatrics, Polypharmacy, Potentially inappropriate medication list

INTRODUCTION

Dysphagia is a serious problem in older people that affects aspiration pneumonia and patient quality of life (QOL).¹⁻³ Dysphagia is

a disorder caused by the disuse of muscles related to swallowing or impairment of the central nervous system.¹ The prevalence of dysphagia varies by setting, with 11%–34% in independent individuals, 29%–47% in inpatients, and 38%–92% in those hospital-

ized for community-acquired pneumonia.²⁾ Dysphagia is associated with adverse events, including aspiration pneumonia, dehydration, poor nutrition, and low QOL.¹⁻³⁾ In addition, these adverse events can result in unexpected rehospitalization, prolonged hospitalization, and increased medical costs due to excess medications.^{4,5)} Similarly, side effects and drug-drug interactions can also cause dysphagia.^{6,7)}

Polypharmacy resulting from excessive medication use has been a growing concern among older people in recent years.⁸⁻¹¹⁾ Although a consensus definition for polypharmacy is lacking,^{11,12)} several reviews^{8,13-15)} have reported that the prevalence of polypharmacy varies widely (10%–90%) owing to age differences, definitions used, chronic conditions, healthcare settings, and geographical settings. Our previous 21-center descriptive study¹⁶⁾ reported a median of six medications (interquartile range [IQR], 4–7) among 467 hospitalized patients aged ≥ 20 years with dysphagia. Additionally, several reviews^{8,10,12,15,17)} reported that although the numerical definitions (2–11 medications) and prevalence of polypharmacy (4%–97%) vary among studies, polypharmacy is consistently associated with adverse events. For example, adverse drug events are associated with anticholinergic drugs, pneumonia,¹⁸⁾ and dysphagia.^{19,20)} A list of potentially inappropriate medications (PIMs) for older people has been established.²¹⁻²⁴⁾ Therefore, polypharmacy and PIMs for older adults are problematic from a health risk perspective.¹¹⁾

Although the relationship between medication status, symptomatology, and outcomes has been evaluated, data are limited regarding the prevalence of polypharmacy and PIMs and the association of polypharmacy and PIMs with swallowing function during the follow-up period among hospitalized patients aged ≥ 65 years with dysphagia. Regarding the association with polypharmacy and clinical outcomes, Matsumoto et al.²⁵⁾ reported that polypharmacy on admission was negatively associated with dysphagia and nutritional status on discharge among 257 consecutive stroke patients with sarcopenia in a rehabilitation hospital. Second, Maki et al.²⁶⁾ also reported a significant higher Barthel Index among inpatients in the Japan Medical Data Center claims database aged ≥ 65 years with acute hip fracture who received ≤ 5 medications compared with those who received ≥ 6 medications. Kose et al.¹⁹⁾ reported a negative association between anticholinergics (PIMs) and patient functional state. However, data on the proportion of polypharmacy and PIMs in hospitalized patients aged ≥ 65 years with dysphagia are limited. In addition, information on the association between polypharmacy and PIMs at admission and swallowing function at discharge is scarce. Identifying these associations could help reduce the risk of prolonged hospitalization, overmedication, and increased healthcare costs.^{4,5)}

Therefore, this study aimed to (1) describe the proportion of

polypharmacy and PIMs in hospitalized patients aged ≥ 65 years with dysphagia and (2) evaluate the association of polypharmacy and PIMs with swallowing function at discharge. We hypothesized that the proportion of polypharmacy and PIMs on admission would be high and negatively associated with swallowing function at discharge.

MATERIALS AND METHODS

Study Design

We conducted a 19-site cohort study to describe the prevalence of polypharmacy and PIMs in hospitalized patients aged ≥ 65 years with dysphagia and to evaluate the association of polypharmacy and PIMs with swallowing function at discharge (Supplementary Fig. S1). The results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.²⁷⁾ This study was conducted in accordance with the principles of the Declaration of Helsinki and registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (No. UMIN000038281; Registration date: October 12, 2019). This study was approved by the Institutional Review Board of Yokohama City University Medical Center (No. B190700074; approval date: August 7, 2019). All participants provided written informed consent before enrollment or were given the right to refuse participation on an opt-out form. This study complied with the ethical guidelines for authorship and publication of *Annals of Geriatric Medicine and Research*.²⁸⁾

Data Source

The database was derived from a multicenter cohort study that used the Japanese Sarcopenic Dysphagia Database, which primarily aimed to assess the risk and contributing factors associated with sarcopenic dysphagia,^{16,29)} using the REDCap web-base data-capturing system.³⁰⁾ In the database, we registered dysphagic patients aged ≥ 20 years and with a Food Intake LEVEL Scale (FILS) score of ≤ 8 ³¹⁾ from nine acute-care hospitals, eight rehabilitation hospitals, two long-term care hospitals, and one home-visit rehabilitation team between November 2019 and March 2021 through a standardized questionnaire for data collection.

Study Participants

We included non-consecutive inpatients aged ≥ 65 years with dysphagia, defined as a FILS score of ≤ 8 ³¹⁾ in the database. The exclusion criteria were patients aged 20–64 years and outpatients.

Outcome

The primary outcome was the FILS score at discharge. The

FILS³¹⁾ is used to evaluate swallowing function based on the patients' level of food intake and the following 10-point observer-rated scale (discrete variable, ranging from 0 to 10): scores of 1–3 indicate various degrees of non-oral food intake; scores of 4–6 indicate various degrees of oral food intake and alternative nutrition; scores of 7–8 indicate various degrees of oral food intake alone; a score of 9 indicates no dietary restriction, but with given medical consideration; and a score of 10 indicates normal oral food intake.

Exposure

We defined polypharmacy as the prescription of ≥ 5 medications.^{12,25)} PIMs were identified based on the American Geriatrics Society 2023 Updated Beers Criteria.²¹⁾ We collected medication information from electronic medical chart reviews on participant enrollment. Newly prescribed medication information taken within the 4 weeks before admission was excluded as a washout window. Two researchers (S.T. and M.N.) independently searched for and reviewed the medication codes to identify PIMs (Supplementary Table S1) and discussed with H.W. when necessary. The concordance rate between the researchers was 94.0% (141 of 150 individual medication names). We excluded aspirin and anticoagulant agents such as warfarin and rivaroxaban from our PIM assessment because of insufficient clinical information in our database to assess their appropriateness.

Covariates

We collected the following patient data: age (continuous variable); sex (binary variable); primary disease diagnosed (injuries, cerebral vascular diseases, respiratory diseases, cancer and other diseases); Charlson Comorbidity Index (CCI)³²⁾ (continuous variable); FILS at baseline (discrete variable); and general sarcopenia (binary variable), considered a proxy indication of systemic vulnerability, as diagnosed using the 2019 criteria of the Asian Working Group for Sarcopenia.³³⁾ We plotted a directed acyclic graph that was associated with polypharmacy and swallowing function based on previous studies^{6,7,10,14,25,34–36)} (Supplementary Fig. S2) and discussions with our research team (registered nurses, physical therapists, registered dietitians, pharmacists, and medical doctors).

Statistical Analysis

All analyses were conducted according to polypharmacy exposure. First, we described patient characteristics using standard descriptive statistics of medians and IQRs for continuous variables and numbers (%) for categorical variables. Additionally, we described the medication categories of PIMs based on the 2023 Updated Beers Criteria prescribed at baseline. Second, we used descriptive statistics to summarize and repeated measures two-way ANOVA

(time \times polypharmacy) for the FILS score at discharge by overall and hospital type as effect modifiers owing to differences in patient characteristics and purpose for hospitalization between the three hospital types.

Third, we conducted a complete case analysis as a base-case analysis, considering that the proportion of missing values was $< 5\%$; thus, the effect of selection bias due to missing values was likely to be small^{37,38)} (Supplementary Fig. S3). Because the FILS score is a finite discrete variable, we applied a generalized linear model with a Poisson distribution and log-link function using Huber-type robust estimators (robustbase package in R)³⁹⁾ to evaluate the association of polypharmacy and PIMs with FILS score at discharge. In Model 1, we introduced the FILS score at discharge (discrete variable, ranging from 0 to 10) as the dependent variable and polypharmacy, age, sex, CCI, FILS score at baseline, and hospital type as independent variables in the analytical model. In Model 2, we added general sarcopenia as an independent variable to Model 1 to assume that it was an intermediate factor. In Model 3, we added primary diagnosis at hospitalization as an independent variable to Model 2. Additionally, we applied individual PIM categories with proportions $> 4\%$ as exposure using Models 1–3.

We then conducted a sensitivity analysis. First, we applied a change cut-off value from 5 to 6, which was used as a secondary frequency in a previous systematic review,¹²⁾ to assess differences in the results due to changing the cut-off value for polypharmacy. Second, we applied the multiple imputation approach under the missing-at-random assumption to check the results due to changes with multiple imputation. We generated 50 imputed datasets using the multiple imputation by chained equations (MICE) procedure and pooled the results (mice package in R) using the standard Rubin's rule.^{40,41)} Third, we analyzed the associations using four primary diagnoses (injury, cerebrovascular diseases, respiratory diseases, and cancer) to check for groups with different effect sizes. Finally, for scenario analysis, we excluded participants diagnosed with conditions commonly associated with dysphagia, including esophageal cancer (10th revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10] codes: C15x), laryngeal cancer (C32x), pharyngeal cancer (C14x), stroke (I630, I631–I636, I638, I639, I600–I611, I613–I616, I619, I629, and G459), Alzheimer's disease (G20), head injury (S00x–S19x), Parkinson disease (G20x), and pneumonia (J15x, J18x, and J690) to evaluate the results in participants without common conditions known to cause dysphagia.^{1,42)}

We performed data processing and all statistical analyses using R version 4.0.5 for Mac (R Foundation for Statistical Computing, Vienna, Austria)⁴³⁾ (Supplementary File).

RESULTS

The final analysis included data from 399 patients (Fig. 1). Table 1 shows the demographic and clinical characteristics of the study population. Patients with polypharmacy were more likely to be female, older, have PIMs, have injuries, and have been admitted to rehabilitation hospitals. They were also less likely to have cerebrovascular diseases and be admitted to acute-care hospitals. Of the nine patients with missing medication data, seven were female, five were aged ≥ 85 years, and nine had sarcopenia. The median follow-up period was 51.0 days (IQR, 22.0–84.0 days).

Table 1 and Supplementary Fig. S4 provide information on polypharmacy and PIMs, respectively. A median of 6.0 medications was prescribed (IQR, 4.0–8.0). Polypharmacy, defined as the use of ≥ 5 medications and ≥ 6 medications, was observed in 270 (67.7%) and 231 (57.9%) participants, respectively. Additionally, 224 (56.1%) participants used a median of 1.0 PIMs (IQR, 0.0–1.0). Table 2 presents the medication categories of PIMs at admission.

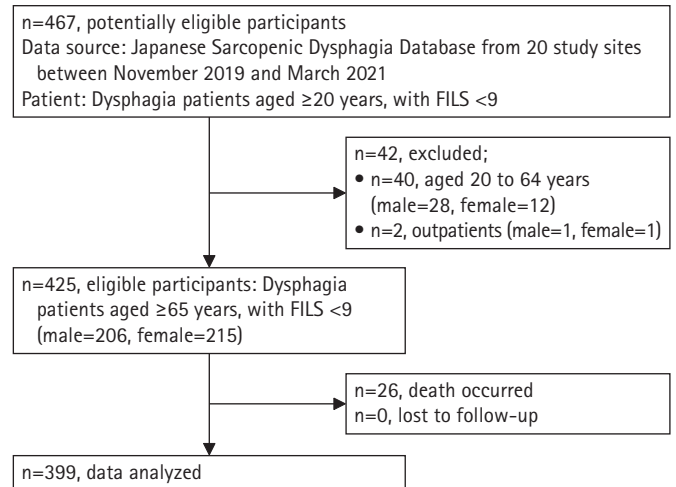


Fig. 1. Study flow. A total of 467 patients were registered in our database. Of these, 42 patients (9.0%) were excluded for the following reasons: 40 patients (8.6%) aged 20–64 years and two outpatients (0.4%). Of the 425 patients (91.0%), 26 patients occurred dead by follow-up period and zero patients had been lost to follow-up. Therefore, 399 patients (85.4%) were analyzed in the study.

Table 1. The demographic and clinical data of patients with and without polypharmacy

Variable	Overall (n = 399)	With polypharmacy (n = 270)	Without polypharmacy (n = 120)	Missing on number of medications used (n = 9)
Sex				
Female	211 (52.9)	147 (54.4)	57 (47.5)	7
Male	188 (47.1)	123 (45.6)	63 (52.5)	2
Age (y)	83.0 (78.0–88.0)	84.0 (78.0–88.0)	81.0 (76.0–89.0)	87.0 (84.0–90.0)
65–74	62 (15.5)	36 (13.3)	25 (20.8)	1
75–84	153 (38.3)	100 (37.0)	50 (41.7)	3
≥ 85	184 (46.1)	134 (49.6)	45 (37.5)	5
BMI (kg/m ²)	20.0 (17.3–22.6)	20.0 (17.3–22.6)	20.2 (17.4–22.5)	19.0 (16.6–19.9)
Primary diagnosis				
Injury, poisoning and certain other consequences of external causes	132 (33.1)	103 (38.1)	27 (22.5)	2
Cerebrovascular disease	114 (28.6)	67 (24.8)	45 (37.5)	2
Diseases of the respiratory system	46 (11.5)	27 (10.0)	16 (13.3)	3
Cancer	16 (4.0)	11 (4.1)	5 (4.2)	0
Other diseases	90 (22.6)	62 (23.0)	26 (21.7)	0
Missing data	1 (0.3)	0 (0)	1 (0.8)	0
CCI score	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (0.0–3.0)	2.0 (2.0–4.0)
General sarcopenia	357 (90.1)	262 (90.3)	112 (88.9)	9
Missing data	2 (0.5)	1 (0.3)	1 (0.8)	0
Number of PIMs				
0	175 (43.9)	85 (31.5)	81 (67.5)	9
1	132 (33.1)	103 (38.1)	29 (24.2)	0
2	80 (20.1)	70 (25.9)	10 (8.3)	0
3	11 (2.8)	11 (4.1)	0 (0)	0
4	1 (0.3)	1 (0.4)	0 (0)	0
Hospital type				
Acute hospital	165 (41.4)	104 (38.5)	60 (50.0)	1
Rehabilitation hospital	194 (48.6)	142 (52.6)	44 (36.7)	8
Long-term care hospital	40 (10.0)	24 (8.9)	16 (13.3)	0

Values are presented as number (%) or median (interquartile range). We defined ≥ 5 medication usage as polypharmacy. CCI, Charlson Comorbidity Index; PIMs, potentially inappropriate medications.

The most frequently prescribed PIMs were proton pump inhibitors (PPIs; 45.6%), non-steroidal anti-inflammatory drugs (NSAIDs; 14.9%), antipsychotics (6.4%), and non-benzodiazepines (5.1%).

Table 3 summarizes the repeated-measures two-way ANOVA

(time × polypharmacy) results for the FILS score at discharge among patients with and without polypharmacy across all hospitals (Supplementary Fig. S5) and by hospital type. While each factor (time and/or polypharmacy) showed a significant change in

Table 2. Description of medication categories of PIMs based on the Beers Criteria 2023 prescribed at baseline

Category	Overall (n = 399)	With polypharmacy (n = 270)	Without polypharmacy (n = 120)	p-value
Anticholinergics (%)				
First generation antihistamines	0 (0)	0 (0)	0 (0)	NA
Antiparkinsonian agents	0 (0)	0 (0)	0 (0)	NA
Antispasmodics	0 (0)	0 (0)	0 (0)	NA
Antithrombotics	3 (0.8)	2 (0.7)	1 (0.8)	1.000
Cardiovascular (%)				
Peripheral alpha-1 blockers	5 (1.3)	5 (1.9)	0 (0)	0.311
Central alpha agonists	2 (0.5)	2 (0.7)	0 (0)	0.859
Digoxin	7 (1.8)	6 (2.2)	1 (0.8)	0.426
Nifedipine immediate release	2 (0.5)	2 (0.7)	0 (0)	0.859
Amiodarone	4 (1.0)	4 (1.5)	0 (0)	0.426
Central nervous system (%)				
Antidepressants	1 (0.5)	1 (0.7)	0 (0)	1.000
Antipsychotics	25 (6.4)	22 (8.1)	3 (2.5)	0.060
Benzodiazepines	18 (4.6)	18 (6.7)	0 (0)	0.008
Nonbenzodiazepine	20 (5.1)	18 (6.7)	2 (1.7)	0.069
Isoxsuprine	0 (0)	0 (0)	0 (0)	NA
Endocrine (%)				
Estrogens	0 (0)	0 (0)	0 (0)	NA
Sulfonylureas	4 (1.0)	4 (1.5)	0 (0)	0.426
Gastrointestinal (%)				
Metoclopramide	0 (0)	0 (0)	0 (0.0)	NA
Proton pump inhibitors	178 (45.6)	146 (52.1)	32 (27.7)	< 0.001
Pain medications (%)				
NSAIDs	58 (14.9)	48 (17.8)	10 (8.3)	0.024
Skeletal muscle relaxants	0 (0)	0 (0)	0 (0)	NA
Indomethacin	0 (0)	0 (0)	0 (0)	NA

Values are presented as number (%). We defined ≥5 medication usage as polypharmacy. NSAIDs, non-steroidal anti-inflammatory drugs; NA, not available.

Table 3. Description of outcome according to hospital type

Variable	Overall	With polypharmacy	Without polypharmacy	p-value ^{a)}
Overall	399	270	120	Polypharmacy (< 0.001)
FILS at baseline	7.0 (4.0–8.0)	7.0 (6.0–8.0)	7.0 (2.0–7.0)	Times (< 0.001)
FILS at follow-up	8.0 (7.0–8.0)	8.0 (7.0–8.0)	8.0 (7.0–8.0)	Time × Polypharmacy (0.411)
Acute care hospital	164	104	60	Polypharmacy (0.040)
FILS at baseline	6.0 (1.0–7.0)	6.0 (1.0–7.0)	4.5 (1.0–7.0)	Times (< 0.001)
FILS at follow-up	7.0 (7.0–8.0)	7.0 (7.0–8.0)	7.0 (6.0–8.0)	Time × Polypharmacy (0.615)
Rehabilitation hospital	186	142	44	Polypharmacy (0.086)
FILS at baseline	7.0 (7.0–8.0)	7.0 (7.0–8.0)	7.0 (6.8–8.0)	Times (< 0.001)
FILS at follow-up	8.0 (7.0–8.0)	8.0 (7.0–8.0)	8.0 (7.0–8.0)	Time × Polypharmacy (0.643)
Long-term care hospital	40	24	16	Polypharmacy (0.364)
FILS at baseline	7.0 (6.0–8.0)	8.0 (6.5–8.0)	7.0 (4.0–7.0)	Times (0.051)
FILS at follow-up	8.0 (6.8–8.0)	7.5 (6.8–8.0)	8.0 (6.8–8.2)	Time × Polypharmacy (0.146)

Values are presented as number or median (interquartile range). We defined ≥5 medication usage as polypharmacy.

FILS, Food Intake LEVEL Scale.

^{a)}Using a two-way ANOVA for Times×Polypharmacy.

FILS score, the interaction term (time \times polypharmacy) did not significantly change for either the overall participants (time \times polypharmacy, $p = 0.41$) or hospital type.

Table 4 presents the results of the association between polypharmacy and PIMs on admission and the FILS score at discharge. After adjusting for covariates, neither polypharmacy nor PIMs individual category was significantly associated with FILS score at discharge ($\beta = 0.05$; 95% confidence interval [CI], -0.04 – 0.13 ; $p = 0.30$) in base-case and sensitive analysis. Regarding the PIMs individual category, NSAID use was not associated with FILS score at discharge ($\beta = 0.09$; 95% CI, -0.02 – 0.19 ; $p = 0.10$). These results demonstrate trends similar to those observed in the sensitivity analysis, where the change cutoff value of polypharmacy and the MICE approach (Table 4).

In the sub-group analysis, participants with cancer ($\beta = 0.39$; 95% CI, -0.21 – 0.99) showed a higher point estimate compared with overall ($\beta = 0.05$; 95% CI, -0.04 – 0.13) and the other sub-group ($\beta = 0.07$; 95% CI, -0.10 – 0.25 in injury; $\beta = 0.05$; 95% CI, -0.11 – 0.20 in cerebrovascular diseases; $\beta = 0.05$; 95% CI, -0.22 – 0.32 in respiratory diseases) in Model 2 in complete case analysis although no statistically significant differences were observed (Supplementary Table S2, S3). Among cancer patients without polypharmacy ($n = 5$), two had laryngeal cancer, one had lung cancer, one had stomach cancer, and one had pancreatic cancer.

In the scenario analysis, the results, after excluding participants diagnosed with conditions commonly associated with dysphagia, were generally similar to those of the base case analysis (Supple-

mentary Tables S4, S5).

DISCUSSION

This multicenter cohort study is the first to reveal the proportions of polypharmacy and PIM categories on admission among hospitalized patients aged ≥ 65 years with dysphagia and to evaluate the association of polypharmacy and PIM categories with swallowing function at discharge. In summary, we observed high proportions of polypharmacy and PIMs but no significant association between these prescribing conditions and swallowing function at discharge. These findings suggest that regular medication reviews^{8,44,45} for older adults with polypharmacy could help prevent frailty and maintain good body function, activities, participation, and QOL.^{6,7}

First, the proportions of polypharmacy and PIMs were 68% and 56%, respectively, among hospitalized patients aged ≥ 65 years with dysphagia. The high proportion of polypharmacy was similar to that in a recent systematic review,⁴⁴ which reported a pooled proportion of 71% (95% CI, 57–86) among patients aged ≥ 60 years with frailty as a hospitalized subgroup from 14 studies. The proportion of PIMs in our study is higher than those reported in previous reviews,^{34,45} which reported proportions of 9% and 57% among older patients with frailty⁴⁵ and cancer,³⁴ respectively. From a clinical viewpoint, patients with multimorbidity are more likely to have polypharmacy and prescription of PIMs. The risks of polypharmacy and PIMs are likely to increase with comorbidities and complications^{13,21} and could be harmful to older people.^{11,21}

Table 4. Association of polypharmacy and PIMs with dysphagia at discharge

	Model 1				Model 2				Model 3			
	β	SE	95% CI	p-value	β	SE	95% CI	p-value	β	SE	95% CI	p-value
Base analysis												
-Complete case analysis												
Polypharmacy definition ≥ 5	0.03	0.04	-0.04, 0.13	0.324	0.05	0.04	-0.04, 0.13	0.296	0.05	0.04	-0.04, 0.14	0.263
Sensitive analysis												
Polypharmacy definition ≥ 6	0.03	0.04	-0.04, 0.11	0.386	0.03	0.04	-0.05, 0.11	0.447	0.04	0.04	-0.04, 0.12	0.389
PIMs individual category												
Proton pump inhibitors	0.02	0.04	-0.06, 0.10	0.587	0.02	0.04	-0.05, 0.10	0.537	0.03	0.04	-0.05, 0.10	0.513
NSAIDs	0.09	0.05	-0.02, 0.19	0.103	0.08	0.05	-0.03, 0.18	0.143	0.08	0.05	-0.03, 0.18	0.156
Antipsychotics	0.02	0.08	-0.13, 0.17	0.808	0.01	0.08	-0.14, 0.16	0.877	0.03	0.08	-0.13, 0.18	0.734
Non-benzodiazepines	-0.02	0.09	-0.19, 0.15	0.832	-0.02	0.09	-0.19, 0.15	0.832	-0.02	0.09	-0.19, 0.16	0.844
Benzodiazepines	-0.02	0.09	-0.20, 0.16	0.843	-0.02	0.09	-0.2, 0.16	0.831	-0.02	0.09	-0.21, 0.16	0.796
-Multiple imputation approach												
Polypharmacy definition ≥ 5	0.05	0.04	-0.04, 0.13	0.287	0.05	0.04	-0.04, 0.13	0.293	0.05	0.04	-0.04, 0.14	0.264
Polypharmacy definition ≥ 6	0.03	0.04	-0.04, 0.11	0.357	0.03	0.04	-0.05, 0.11	0.313	0.04	0.04	-0.04, 0.12	0.293

FILS, Food Intake LEVEL Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PIMs, potentially inappropriate medications; β , unstandardized coefficient; SE, Standard error; CI, confidence interval.

Model 1 represents “polypharmacy (without polypharmacy=0, as reference, or with polypharmacy=1) + age + gender + primary diagnosis at hospitalization + Charlson Comorbidity Index + FILS at baseline + hospital type were introduced into the analytical models,” Model 2 represents “Model 1 + general sarcopenia were introduced into the analytical models,” and Model 3 represents “Model 2 + primary diseases were introduced into the analytical models.”

Polypharmacy and PIMs are associated with increased risks of malnutrition, sarcopenia, falls, frailty, dysphagia, and cognitive impairment in older adults.^{6,7,10,11,13} Moreover, prescribed medications are often not changed despite improved clinical conditions.⁴⁶ As a result, the risk of drug-drug interactions and prescription cascades increases. Therefore, healthcare providers should focus on routinely sorting polypharmacy because PIMs are likely to cause dysphagia as a side effect of drugs.

Second, contrary to our hypothesis, polypharmacy was not associated with swallowing function at discharge among hospitalized patients aged ≥ 65 years with dysphagia in the base case and sensitivity analyses. Our study showed different results to those of a previous single-center cohort study²⁵ that reported a negative association between polypharmacy and swallowing function using the Functional Oral Intake Scale (FOIS) at discharge among stroke inpatients with sarcopenia in a convalescent rehabilitation ward. However, another study³⁶ reported no association between polypharmacy and swallowing function in patients with stroke. Our findings showed a significant impact of time on FILS improvement, with a smaller trend in polypharmacy. According to previous studies,^{25,35,36,47} polypharmacy may inhibit the recovery of swallowing function by causing sarcopenia, malnutrition, and impaired activities of daily living. Moreover, these associations were modified using rehabilitation therapy and nutritional support.

Third, each category of PIMs was unrelated to swallowing function at discharge. This result differs from that of a previous study¹⁹ that reported a negative association between increased anticholinergic drug use during hospitalization and swallowing function at discharge among older inpatients with stroke in a convalescent rehabilitation ward. In the present study, none of the patients were prescribed anticholinergic drugs as PIMs on admission, and all had dysphagia. In contrast, in the previous study, the frequency of anticholinergic drug use on admission was 30%, and half of the patients had dysphagia (median FOIS score of 6; IQR, 5–7).¹⁹ One potential cause of these discrepancies is differences in the participants' backgrounds. In addition, our results showed that PPIs, NSAIDs, and antipsychotics were the most frequently prescribed PIMs. The risks of long-term intake have been reported.^{21,48} However, we did not examine the association between the change in prescribing PIMs during hospitalization and the improvement of dysphagia because we did not collect medication information at follow-up.¹⁶ Further research is needed to examine the association between changes in the prescription of PIMs during hospitalization and the improvement of dysphagia.

An intriguing finding was that the cancer type could influence the association between polypharmacy and swallowing function at discharge. Contrary to our hypothesis, our results showed that

polypharmacy was likely to be positively associated with FILS score at discharge in patients with cancer, although the number of patients was limited (Supplementary Tables S2, S3). Additionally, the proportion of cancer types differed between participants with and without polypharmacy. Given the small sample size, further research on the association between polypharmacy and dysphagia in patients with cancer is needed.

This study had some limitations. First, the measurement error in medication information could have resulted in an underestimation of the frequency of PIMs and their association with the outcome because of zero values (3.9%), missing numbers of medications (2.1%), and missing medication information (7.3%), despite using a standardized questionnaire. Second, the nature of this observational study design could not determine causality because of unmeasured confounding factors. However, this might have had a limited impact on the results because we considered the major confounding factors in previous studies^{6,7,10,14,25,34,49,50} (Supplementary Fig. S2) and multidisciplinary team discussions.

In conclusion, the results of this study revealed a high prevalence of polypharmacy and PIMs among hospitalized older adult patients with dysphagia. Although we did not identify an adverse association between polypharmacy and PIMs and subsequent swallowing function during the follow-up period, our findings suggest that regularly reviewing medications for the appropriateness of their prescriptions might help prevent frailty and maintain high body function, activities, participation, and QOL. In this study, the most frequently prescribed medications were PPIs and NSAIDs. Based on the indications for these drugs, the prophylactic use of PPIs to prevent NSAID-induced complications suggests that regular pain monitoring should inform the concurrent discontinuation of both PPIs and NSAIDs once they are no longer required. Additionally, even for PPIs prescribed alone, there is a defined duration of appropriate use, beyond which the risks of long-term intake have been reported. Therefore, the need for ongoing PPI therapies must be reviewed and reassessed to mitigate their potential adverse effects.

ACKNOWLEDGMENTS

We thank all the collaborators from the Japanese Working Group on Sarcopenic Dysphagia for their clinical work, data collection, and data registration.

CONFLICT OF INTEREST

The researchers claim no conflicts of interest.

FUNDING

This study was supported by the JSPS-KAKENHI, Grant Number

19H03979, during the conduct of the study.

AUTHOR CONTRIBUTIONS

Conceptualization, ST, HO, HW, SN, RM; Analysis and interpretation of data, ST, HO, TN, HW; Writing—original draft preparation, ST, HO, TN; Writing—review and editing, ST, HO, TN, HW, MN, AS, SN, RM; Funding acquisition, HW.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via <https://doi.org/10.4235/agmr.23.0203>.

REFERENCES

- Clave P, Shaker R. Dysphagia: current reality and scope of the problem. *Nat Rev Gastroenterol Hepatol* 2015;12:259-70.
- Baijens LW, Clave P, Cras P, Ekberg O, Forster A, Kolb GF, et al. European Society for Swallowing Disorders: European Union Geriatric Medicine Society white paper: oropharyngeal dysphagia as a geriatric syndrome. *Clin Interv Aging* 2016;11:1403-28.
- Sakai K, Sakuma K. Sarcopenic dysphagia as a new concept. In: Dionysiotis Y, editors. *Sarcopenic dysphagia as a new concept*. Rijeka, Croatia: IntechOpen; 2017.
- Bonilha HS, Simpson AN, Ellis C, Mauldin P, Martin-Harris B, Simpson K. The one-year attributable cost of post-stroke dysphagia. *Dysphagia* 2014;29:545-52.
- Altman KW, Yu GP, Schaefer SD. Consequence of dysphagia in the hospitalized patient: impact on prognosis and hospital resources. *Arch Otolaryngol Head Neck Surg* 2010;136:784-9.
- Kose E, Wakabayashi H. Rehabilitation pharmacotherapy: a scoping review. *Geriatr Gerontol Int* 2020;20:655-63.
- Yoshimura Y, Matsumoto A, Momosaki R. Pharmacotherapy and the role of pharmacists in rehabilitation medicine. *Prog Rehabil Med* 2022;7:20220025.
- Rochon PA, Petrovic M, Cherubini A, Onder G, O'Mahony D, Sternberg SA, et al. Polypharmacy, inappropriate prescribing, and deprescribing in older people: through a sex and gender lens. *Lancet Healthy Longev* 2021;2:e290-300.
- Mehta RS, Kochar BD, Kennealy K, Ernst ME, Chan AT. Emerging approaches to polypharmacy among older adults. *Nat Aging* 2021;1:347-56.
- Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse outcomes of polypharmacy in older people: systematic review of reviews. *J Am Med Dir Assoc* 2020;21:181-7.
- Kojima T. The need for actions against polypharmacy in older people with frailty. *Ann Geriatr Med Res* 2018;22:111-6.
- Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy?: a systematic review of definitions. *BMC Geriatr* 2017;17:230.
- Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. *Ther Adv Drug Saf* 2020;11:2042098620933741.
- Prokopidis K, Giannos P, Reginster JY, Bruyere O, Petrovic M, Cherubini A, et al. Sarcopenia is associated with a greater risk of polypharmacy and number of medications: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2023;14:671-83.
- Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. *Eur Geriatr Med* 2021;12:443-52.
- Mizuno S, Wakabayashi H, Fujishima I, Kishima M, Itoda M, Yamakawa M, et al. Construction and quality evaluation of the Japanese sarcopenic dysphagia database. *J Nutr Health Aging* 2021;25:926-32.
- Ganz DA, Latham NK. Prevention of falls in community-dwelling older adults. *N Engl J Med* 2020;382:734-43.
- Kose E, Hirai T, Seki T. Assessment of aspiration pneumonia using the Anticholinergic Risk Scale. *Geriatr Gerontol Int* 2018;18:1230-5.
- Kose E, Hirai T, Seki T, Okudaira M, Yasuno N. Anticholinergic load is associated with swallowing dysfunction in convalescent older patients after a stroke. *Nutrients* 2022;14:2121.
- Castejon-Hernandez S, Latorre-Vallbona N, Molist-Brunet N, Cubi-Montanya D, Espauella-Panicot J. Association between anticholinergic burden and oropharyngeal dysphagia among hospitalized older adults. *Aging Clin Exp Res* 2021;33:1981-5.
- By the 2023 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2023;71:2052-81.
- Davidoff AJ, Miller GE, Sarpong EM, Yang E, Brandt N, Fick DM. Prevalence of potentially inappropriate medication use in older adults using the 2012 Beers criteria. *J Am Geriatr Soc* 2015;63:486-500.
- Clark CM, Shaver AL, Aurelio LA, Feuerstein S, Wahler RG Jr, Daly CJ, et al. Potentially inappropriate medications are associated with increased healthcare utilization and costs. *J Am Geriatr Soc* 2020;68:2542-50.
- Renom-Guiteras A. Potentially inappropriate medication among people with dementia: towards individualized decision-making. *Eur Geriatr Med* 2021;12:569-75.
- Matsumoto A, Yoshimura Y, Nagano F, Bise T, Kido Y, Shimazu S, et al. Polypharmacy and its association with dysphagia and

- malnutrition among stroke patients with sarcopenia. *Nutrients* 2022;14:4251.
26. Maki H, Wakabayashi H, Nakamichi M, Momosaki R. Impact of number of drug types on clinical outcome in patients with acute hip fracture. *J Nutr Health Aging* 2019;23:937-42.
 27. von Elm E, Altman DG, Egger M, Pocock SJ, Gotsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.
 28. Noh JH, Jung HW, Ga H, Lim JY. Ethical guidelines for publishing in the annals of geriatric medicine and research. *Ann Geriatr Med Res* 2022;26:1-3.
 29. Togashi S, Wakabayashi H, Ohinata H, Nishioka S, Kokura Y, Momosaki R. Sensitivity and specificity of body mass index for sarcopenic dysphagia diagnosis among patients with dysphagia: a multi-center cross-sectional study. *Nutrients* 2022;14:4494.
 30. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
 31. Kunieda K, Ohno T, Fujishima I, Hojo K, Morita T. Reliability and validity of a tool to measure the severity of dysphagia: the Food Intake LEVEL Scale. *J Pain Symptom Manage* 2013;46:201-6.
 32. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676-82.
 33. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc* 2020;21:300-7.
 34. Chen LJ, Trares K, Laetsch DC, Nguyen TN, Brenner H, Schottker B. Systematic review and meta-analysis on the associations of polypharmacy and potentially inappropriate medication with adverse outcomes in older cancer patients. *J Gerontol A Biol Sci Med Sci* 2021;76:1044-52.
 35. Nagai T, Wakabayashi H, Nishioka S, Momosaki R. Functional prognosis in patients with sarcopenic dysphagia: an observational cohort study from the Japanese sarcopenic dysphagia database. *Geriatr Gerontol Int* 2022;22:839-45.
 36. Matsumoto A, Yoshimura Y, Nagano F, Bise T, Kido Y, Shimazu S, et al. Polypharmacy and potentially inappropriate medications in stroke rehabilitation: prevalence and association with outcomes. *Int J Clin Pharm* 2022;44:749-61.
 37. Graham JW. Missing data analysis: making it work in the real world. *Annu Rev Psychol* 2009;60:549-76.
 38. Dong Y, Peng CY. Principled missing data methods for researchers. *Springerplus* 2013;2:222.
 39. Cantoni E, Ronchetti E. Robust inference for generalized linear models. *J Am Stat Assoc* 2001;96:1022-30.
 40. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
 41. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377-99.
 42. Takizawa C, Gemmell E, Kenworthy J, Speyer R. A systematic review of the prevalence of oropharyngeal dysphagia in stroke, Parkinson's disease, Alzheimer's disease, head injury, and pneumonia. *Dysphagia* 2016;31:434-41.
 43. R Core Team. R: a language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation; 2019 [cited 2024 Feb 25]. Available from: <https://www.R-project.org/>.
 44. Toh JJY, Zhang H, Soh YY, Zhang Z, Wu XV. Prevalence and health outcomes of polypharmacy and hyperpolypharmacy in older adults with frailty: a systematic review and meta-analysis. *Ageing Res Rev* 2023;83:101811.
 45. Randles MA, O'Mahony D, Gallagher PF. Frailty and potentially inappropriate prescribing in older people with polypharmacy: a bi-directional relationship? *Drugs Aging* 2022;39:597-606.
 46. Kuijpers MA, van Marum RJ, Egberts AC, Jansen PA; OLDY (OLD people Drugs & dYsregulations) Study Group. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol* 2008;65:130-3.
 47. Wakabayashi H, Kakehi S, Kishima M, Itoda M, Nishioka S, Momosaki R. Impact of registered dietitian and dental hygienist involvement on functional outcomes in patients with dysphagia: triad of rehabilitation, nutrition, and oral management. *Eur Geriatr Med* 2023;14:1301-6.
 48. Vinke P, Wesselink E, van Orten-Luiten W, van Norren K. The use of proton pump inhibitors may increase symptoms of muscle function loss in patients with chronic illnesses. *Int J Mol Sci* 2020;21:323.
 49. Matsumoto A, Yoshimura Y, Nagano F, Shimazu S, Shiraiishi A, Kido Y, et al. Potentially inappropriate medications are negatively associated with functional recovery in patients with sarcopenia after stroke. *Aging Clin Exp Res* 2022;34:2845-55.
 50. Nagai T, Wakabayashi H, Nishioka S, Momosaki R. Importance of early assessment and multioccupational interventions in sarcopenic dysphagia and aspiration pneumonia. *Geriatr Gerontol Int* 2023;23:153-4.