Original Article

Polypharmacy as a risk factor for hospital admission among ambulance-transported old-old patients

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Aim: The aim of this study was to analyze the relationship between polypharmacy and hospital admission in ambulance-transported old-old patients.

Methods: A retrospective cohort study was conducted of consecutive old-old patients (aged ≥ 85 years) transported by ambulance to a community teaching hospital between April and December of 2013. Patients with out-of-hospital cardiopulmonary arrest were excluded. Data were collected from the computerized records on the demographics, chief complaints, vital signs, and level of consciousness at arrival, final diagnoses at discharge, and polypharmacy (≥5 medications). The primary outcome was requirement of hospital admission. We also analyzed symptomatic adverse drug events (ADEs).

Results: Of the 3,084 adults (aged ≥ 18 years) transported to the hospital during the study period, 381 (13%) were old-old patients. Of those, 233 (61%) were women, and 261 (69%) were admitted to the hospital. The mean number of their baseline medications was 6.8 ± 3.9, and 250/347 patients (72%) were suffering from polypharmacy. Twenty-seven of the patients (7%) had symptomatic ADEs. Although the ADEs were not related to polypharmacy (P = 0.437), logistic regression adjustments for age, sex, and vital signs at arrival showed that patients with polypharmacy were more likely to be admitted to the hospital than were patients without (odds ratio: 2.12 [95% CI, 1.03–4.43]; P = 0.042).

Conclusions: Symptomatic ADEs due to polypharmacy were one of the most preventable causative factors leading to hospital admission of old-old patients. Polypharmacy could be a major risk for emergency admission to hospital.

Key words: Adverse drug event, hospital admission, old-old, polypharmacy

INTRODUCTION

THE PROPORTION OF the population that is elderly has been increasing: 1 in 5 people is now elderly. In particular, the proportion of the "old-old", that is, those aged 85 years and older, has been growing rapidly.[1] Thus, the increase in the number of older patients will become the new global issue of medicine. As the frontrunner among nations with aging populations, this issue is particularly urgent for Japan.

Old-old adults tend to use health care services because of multimorbidity and polypharmacy (multiple medication use).[2,3] Polypharmacy is associated with an increased likelihood of inappropriate prescription and adverse drug events (ADEs).[4]

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The aging of the population affects the clinical setting of emergency medicine because the emergency department (ED) sits at a unique crossroads in the sequence of geriatric care, overlapping with the outpatient, inpatient, prehospital, home, and extended care settings. In Japan, the hospital admission rates of elderly patients have also been increasing. Emergency department admission of old-old adults challenges emergency physicians, and polypharmacy is one of the possible risk factors for such admissions. Therefore, the aim of this study was to analyze the relationship between polypharmacy and hospital admissions of ambulance-transported old-old patients.

METHODS

Ethics statement

THE STUDY PROTOCOL was reviewed and approved by the ethics committee of Mito Kyodo General Hospital, University of Tsukuba.

Study design, setting, and participants

This was a retrospective cohort study. We reviewed the medical records of consecutive old-old patients (aged ≥ 85 years) transported to the ED of a community teaching hospital (Mito Kyodo General Hospital, Japan) by ambulance. The period studied was from April to December 2013. Patients with out-of-hospital cardiopulmonary arrest at arrival were excluded from the study.

Data collection

Data on demographics, chief complaints, vital signs, and level of consciousness at arrival, final diagnoses at discharge, and medication numbers and lists were collected from the computerized records. Prescription medications were counted according to classes: calcium channel blockers (CCBs), beta-blockers, angiotensin receptor blockers (ARBs), furosemide, digitalis, antithrombotic agents, anticoagulants, antidiabetics, statins, drugs for osteoporosis including calcium and vitamin D, proton pump inhibitors (PPIs), H2 blockers, analgesics, nonopioids, benzodiazepines, antidementia drugs, drugs for dysuria, and drugs for constipation. Polypharmacy was defined as concurrent use of ≥ 5 baseline medications prescribed at outpatient clinics, according to the most common definition used in international polypharmacy studies.[5–7] The primary outcome was requirement of hospital admission. The secondary outcome was symptomatic adverse drug events (ADEs), which were judged and recorded by the patients' primary doctors including emergency physicians and hospitalists.

Statistical analysis

The baseline and clinical characteristics were compared using a *t*-test for the continuous variables and a χ^2 test for the categorical variables, where appropriate. To compare patients with polypharmacy with those without polypharmacy, multivariate logistic regression models were constructed; odds ratios with 95% confidence intervals (CIs) and probability values were estimated. Dependent variables were a requirement of hospital admission for the primary analysis and symptomatic ADEs for the secondary analysis. The exposure was polypharmacy. To adjust for patient acuity, we chose age, sex, and initial vital signs including mean blood pressure (MBP), respiration rate (RR), and heart rate (HR). They were selected on clinical meaning without a statistical selection. The relationship between the vital signs and the severity of the patient's condition should present as a U curve on an ICU severity scoring system such as the Acute Physiology and Chronic Health Evaluation II (APACHE II).[8] We divided MBP, RR, and HR into three categories according to the interquartile range since we controlled for patients' acuity with precision in the multivariate logistic regression models. We also investigated the characteristics of the ADEs and prescription medication classes to obtain more details regarding old-old patients The two-sided significance level for all tests was $P < 0.05$. All analyses were performed using STATA version 13.1 software (StataCorp, College Station, TX, USA) and JMP version 9.0.2 (SAS Institute, Cary, NC, USA).

RESULTS

OF THE 3,084 adults (aged ≥ 18 years) who were transported to the hospital by ambulance, 381 (13%) were aged ≥85 years; of these, 233 (61%) were women. Data on the number of medications were missing for 34 patients; therefore, 347 patients were used for the analysis. The mean number of their baseline medications was 6.8 ± 3.9 (Min-Max, 0–22); 250 (72%) were suffering from polypharmacy; and 331 (95%) were taking at least one medication. In total, 261 of the ambulance-transported old-old patients (69%) were admitted to the hospital, and 27 of those (7%) had symptomatic ADEs.

The baseline characteristics of the two groups of patients (with polypharmacy and without polypharmacy) were similar for age, sex, initial vital signs, ADEs, and requirement of hospital admission (Table 1).

Table 2 shows the multivariate logistic regression model for hospital admission among the ambulance-transported old-old patients. Patients with polypharmacy were more likely to be admitted to hospital than were patients without polypharmacy. Increased heart rate was also a risk for admission. Table 3 displays the multivariate logistic regression model for ADEs in the ambulance-transported old-old patients. The proportions of the ADEs did not differ significantly between the two groups. None of the vital signs was related to ADEs.

Table 4 shows the clinical characteristics of the ADEs among the old-old patients. Almost all the ADEs were causative factors for admission. Benzodiazepines were one of the main causative medications of ADEs in this population. Table 5 shows the most common prescription medication classes in the old-old patients. Of the 347 patients with data on medications, 140 (40.3%) were taking calcium channel blockers (CCBs); 123 (35.4%), proton pump inhibitors (PPIs); 109 (31.4%), drugs for constipation; 106 (30.5%), angiotensin receptor blockers (ARBs); 96 (27.7%), benzodiazepines; 83 (23.9%), antithrombotic agents; 61 (17.6%), statins; and 47 (13.5%), antidiabetic agents. Anticoagulants and digitalis were prescribed in a small number of the patients (5.8% and 3.5%, respectively).

Table 1. Characteristics of oldest old transported by Emergency Medical Service (EMS)

		Polypharmacy (*n* = 250)	No polypharmacy (*n* = 97)	
	units	Counts (%) or Mean ± SD	Counts (%) or Mean ± SD	*P*-value*
Age	years	90 ± 4	90 ± 4	0.952
Sex (female)		156 (62%)	58 (60%)	0.654
Systolic blood pressure	mmHg	146 ± 30	146 ± 30	0.948
Diastolic blood pressure	mmHg	77 ± 19	78 ± 18	0.708
Respiratory rate	/min	20 ± 5	22 ± 6	0.172
Heart rate	/min	84 ± 21	89 ± 27	0.117
Glasgow Coma Scale		14 ± 2	14 ± 3	0.443
Adverse drug events		19 (8%)	8 (8%)	0.840
Hospital admission		189 (76%)	65 (67%)	0.105

Missing data are systolic blood pressure, *n* = 45; diastolic blood pressure, *n* = 48; respiratory rate, *n* = 107, heart rate, *n* = 51; Glasgow Coma Scale, *n* = 81.
**t*-test for continuous variables, χ^2 test for discrete variables.

Table 2. Multivariate logistic regression model for hospital admission in old-old patients transported to hospital by ambulance (*n* = 226)

		Odds Ratio	95% Confidence Interval		*P*-value
Age, years		1.04	0.95	1.13	0.381
Sex		1.49	0.77	2.88	0.236
Respiratory rate (/min)	Q1 (9–17)	0.91	0.44	1.92	0.801
	reference (18–23)				
	Q3 (24–54)	2.26	0.99	5.52	0.055
Heart rate (/min)	Q1 (30–71)	0.90	0.44	1.90	0.785
	reference (72–97)				
	Q3 (98–199)	8.71	2.80	38.74	<0.001
Mean blood pressure (mmHg)	Q1 (53–87)	0.83	0.37	1.87	0.648
	reference (88–112)				
	Q3 (113–171)	1.36	0.61	3.17	0.464
Polypharmacy		2.12	1.03	4.43	0.042

Q1 = 25% interquartile, Q3 = 75% interquartile.

DISCUSSION

WE HAVE HERE shown that polypharmacy is one of the major risks for hospital admission through the emergency department among old-old adults. To the best of our knowledge, only a few reports about polypharmacy have focused on old-old patients. In our population, the mean number of baseline medications (6.8 ± 3.9) met the definition of polypharmacy (≥ 5 medications). Tsoi *et al.* reported the clinical characteristics of old-old patients in Canada and showed that these patients received a mean number of 6.8 medications per day. They suggested that multimorbidity and polypharmacy were highly prevalent in old-old adults.[9] Hohl *et al.* also showed that young-old patients (aged 65 years and older) who visited the emergency department received an average of 4.2 ± 3.1 medications per day (range, 0–17), with 90.8% receiving at least one medication.[7] As expected, in our study, the number of medications being taken by old-old

Table 3. Multivariate logistic regression model for adverse drug events in old-old patients transported to hospital by ambulance ($n = 226$)

		Odds Ratio	95% Confidence Interval		*P*-value
Age, years		1.05	0.91	1.22	0.538
Sex		1.11	0.42	3.16	0.830
Respiratory rate (/min)	Q1 (9–17)	1.37	0.42	4.49	0.595
	reference (18–23)				
	Q3 (24–54)	1.24	0.36	4.17	0.725
Heart rate (/min)	Q1 (30–71)	2.03	0.65	6.27	0.218
	reference (72–97)				
	Q3 (98–199)	0.85	0.21	2.98	0.800
Mean blood pressure (mmHg)	Q1 (53–87)	2.35	0.76	7.38	0.136
	reference (88–112)				
	Q3 (113–171)	1.57	0.43	5.28	0.478
Polypharmacy		0.67	0.25	1.92	0.437

Q1 = 25% interquartile, Q3 = 75% interquartile.

patients was greater than that being taken by young-old patients. Our target population (aged ≥ 85 years) comprised 13% of all ambulance transports, and their admission rate was also very high (70%), similar to the findings of a previous report.[10] These high percentages of ambulance transportation and admission rates of old-old patients highlight the trend towards a rapidly growing aging population in Japan.

Although we showed that polypharmacy was significantly related to requirement of hospital admission after controlling for patient acuity levels using their vital signs at arrival, our results did not prove a causal relationship between polypharmacy and ADEs. To the best of our knowledge, no reports have been published comparing the ADEs of old-old patients with polypharmacy with those of old-old patients without polypharmacy. Evidence suggests that the risk of prescribing error, high-risk prescribing, and ADEs are increased as the number of drugs prescribed rises.[11] A previous report also showed that polypharmacy was related to inappropriate medication use.[12] Another report suggested that a higher number of medications was associated with higher rates of ADEs.[7] However, we could not explain which comes first, the chicken or the egg: whether it is polypharmacy or multimorbidity that leads to hospital admission.

Hohl *et al.* reported that 11% of the patients aged older than 65 years who visited the ED had ADEs.[7] This percentage was higher than that of the patients with ADEs found in our study. A likely explanation is that these patients included not only those with symptomatic ADEs but also those taking inappropriate medications. We might have detected such a relationship if we had used the Beers criteria.[13] In our study, almost all ADEs were causative factors for admission because we confirmed only symptomatic ADEs noted by the patients' primary physicians. Therefore, we might have missed potential ADEs. Since Hohl *et al.*'s study reported only descriptive statistics, further research is needed to compare patients with and without polypharmacy.

Our results on baseline medications were similar to those of previous reports. Oral anticoagulants or antiplatelet agents, antidiabetic agents, and agents with a narrow therapeutic index were frequently implicated medicines.[7] The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project showed that three medication classes (oral anticoagulant or antiplatelet agents, antidiabetic agents, or agents with a narrow therapeutic index) caused 48% of all ED visits for ADEs in older patients.[14] However, in our study, benzodiazepines were the most implicated drug. The proportion of benzodiazepines was much greater than those of previous studies, despite benzodiazepines being considered one of the common inappropriate medications prescribed to older adults.[12]

We showed the most common prescription medication classes in old-old adults. Major implicated drugs such as anticoagulants or antiplatelet agents, antidiabetic agents, and agents with a narrow therapeutic index were relatively less prescribed than expected. Physicians might hold back on prescribing drugs associated with worse adherence, such as oral anticoagulants or agents with a narrow therapeutic index. On the other hand, drugs that are easy to prescribe, such as drugs for constipation and benzodiazepines, were frequent. The relationship between benzodiazepines and ADEs in older adults has been documented.[7]

Table 4. Characteristics of adverse drug events in the old-old patients of this study

Age, years	Sex	Implicated Medications	Adverse drug event	No. of medications	Final diagnosis at discharge	Disposition
85	F	Theophylline	Tachycardia	5	Pneumonia	Ad
86	M	Aspirin, Clopidogrel	Blood-stained sputum	9	Lung Cancer	Ad
86	F	Furosemide, Losartan + Hydrochlorothiazide	Vertigo, Vomit, Altered mental state	13	Cerebral infarction	Ad
86	F	Carvedilol	Altered mental state, Bradycardia	8	Bradycardia	Ad
86	F	Glycerin enema	Constipation	4	Rectal perforation	Ad
87	F	Donepezil, Carvedilol, Benzodiazepines	Syncope	10	Syncope	Ad
87	M	Pregabalin, Limaprost alfadex	Syncope	4	Syncope	Home
87	F	Benidipine	Orthostatic hypotension	6	Orthostatic hypotension	Ad
87	M	Digoxin, Benzodiazepines	Delirium	10	Delirium	Ad
87	M	Mexiletine	Anuresis	12	Anuresis	Ad
88	M	Aspirin	Thalamic hemorrhage	2	Thalamic hemorrhage	Ad
88	M	Influenza vaccination	Anaphylactic shock	12	Anaphylactic shock	Ad
89	F	Digoxin	Bradycardia (Af)	3	Digitalis intoxication	Ad
89	F	Spironolactone	Hyponatremia	10	Hyponatremia	Ad
89	M	Aspirin	Chronic subdural hematoma	9	Chronic subdural hematoma	Ad
90	F	Benzodiazepines	Altered mental state	7	Hyperkalemia	Ad
90	F	Benzodiazepines	Aspiration	8	Aspiration pneumonia	Ad
90	F	Benzodiazepines	Aspiration	9	Aspiration pneumonia	Ad
91	F	Benzodiazepines	Altered mental state	3	Altered mental state	Ad
92	M	Digoxin	Bradycardia (Af)	7	Digitalis intoxication	Ad
92	M	Naftopidil	Fall	4	Hypovolemia	Home
92	M	Tramadol	Nausea Dizziness	6	Nausea Dizziness	Home
93	M	Aspirin	Subcortical hemorrhage	3	Subcortical hemorrhage	Ad
94	M	Lansoprazole	Diarrhea	10	Collagenous colitis	Ad
94	F	Benzodiazepines	Aspiration	5	Aspiration pneumonia	Ad
94	F	Benzodiazepines	Fall	6	Hip fracture	Ad
95	F	Benzodiazepines	Altered mental state	4	Somnolentia	Home

Ad, admission.

Table 5. The most common prescription medication classes in the old-old patients of this study (n = 347)

Medication class	n	%
CCBs	140	40.3%
PPIs	123	35.4%
Drugs for constipation	109	31.4%
ARBs	106	30.5%
Benzodiazepines	96	27.7%
Antithrombotic agents	83	23.9%
Analgesics, nonopioids	70	20.2%
Statins	61	17.6%
Furosemide	53	15.3%
Drugs for dysuria	50	14.4%
Antidiabetics	47	13.5%
Drugs for osteoporosis including Ca and Vit D	44	12.7%
Beta-blockers	41	11.8%
H2 blockers	38	11.0%
Antidementia drugs	35	10.1%
Anticoagulants	20	5.8%
Digitalis	12	3.5%

ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; PPIs, proton pump inhibitors.

If medication-related problems were ranked as a disease, ADEs would be the fifth leading cause of death in the United States.[13] A heightened awareness of this issue and systematic screening for use of the above medications should lead to better detection of ADEs in the ED. The ADEs caused by those drugs might be preventable.

This study suffers from several limitations. The admission criteria determined by the primary physician were important factors because the primary outcome was requirement of hospital admission. Also, a patient's circumstances might influence the admission criteria. For example, the primary physician might be more likely to admit a patient to hospital before the weekend, or a patient living at a health-care facility might be more likely to be admitted to hospital than a patient living at home. We did not control for these potential confounders. However, the primary outcome, requirement of hospital admission, is still important in clinical practice as a medical service. Soft outcomes, such as admission, are actually more useful than hard outcomes, such as death, in this study setting. Moreover, polypharmacy itself could be a surrogate maker of composite such as nutrition, the level of activities of daily living, dementia comorbidity, and residence. We did not have data on who prescribed the medications. Polypharmacy might have been caused by prescription by multiple clinics. Communicating with the patient's primary physician is probably also crucial. Further studies are needed to analyze such a possible causal relationship.

In conclusion, old-old patients admitted to hospital after being transported to the hospital by ambulance were likely to be taking a number of baseline prescription medications. Some of them had symptomatic adverse drug events, which was one of the most preventable causative factors leading to hospital admission. Polypharmacy could be one of the red flags for hospital admission through the ED.

CONFLICT OF INTEREST

NONE.

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