feeding by PEG.[7,8,10,12] In addition, "Guideline of parenteral and EN for elderly in Europe" does not recommend enteral nutrition to persons with severe dementia as a result of more risks than benefits for persons with severe dementia, and occasionally in early and moderate dementia to ensure energy and nutrient supply and to prevent undernutrition.[17,18] In the present study, we found that approximately 45% of the geriatricians considered that dementia patients with loss of appetite or apraxia for eating should be on tube feeding and that 65% of the geriatricians considered that aspiration-prone frail elderly without comorbidities should also be on tube feeding, which is a relatively high percentage. In a previous study, approximately 60% of physicians in the USA answered that aspiration pneumonia was the indication for PEG placement, and was the most common medical indication.[19] The present finding are consistent with other results; therefore the medical situation in Japan might be quite similar to that in the USA. Indeed, PEG placement to the elderly with repeating aspiration pneumonia or not eating voluntarily with cerebrovascular disease or dementia is indicated in "Guideline of PEG in Japan."[16] In the present study, the questions did not specify the stage of disorders or the level of conditions; therefore our results should be interpreted with caution. However, it is certain that there is no consensus among Japanese geriatricians about tube feeding for the elderly with advanced dementia and there is an urgent need to develop guidelines to decide the risk/benefit ratio in the individual patient to optimize the timing and route of nutritional support. Thus, the indication for tube feeding in the elderly should be widely discussed in the future and hence a guideline should be established to describe the indication of tube feeding in more detail.

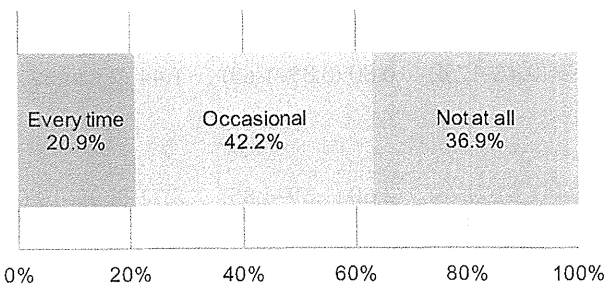

Figure 1 Do you organize a multidisciplinary conference before introducing tube feeding?

"Guideline of parenteral and EN for elderly in Europe" indicates PEG placement if EN is anticipated for longer than 4 weeks.[17,18] In contrast, the present study showed that approximately 80% of the geriatricians consider that survival more than 12 weeks should be expected for PEG placement. PEG is better than NGT for swallowing rehabilitation, and PEG placement

Table 3 Conference members for decision making of tube feeding according to place of employment

	Place of employment of geriatricians					Total
	Hospital $n = 249$	Clinic $n = 80$	Long-term care $n = 17$	Other† $n = 3$	*P*-value	$n = 350$
No. conference members; mean ± standard deviation (total 12 occupations)	4.4 ± 2.0	4.2 ± 1.8	4.3 ± 1.5	4.8 ± 4.2	0.864	4.31 ± 1.9
Conference members						
Attending physician	238 (95.2)	75 (92.6)	17 (100)	3 (100)	–	334 (95.4)
Primary nurse	224 (89.6)	54 (66.7)	15 (88)	3 (100)	–	297 (94.9)
Otolaryngologist	27 (10.8)	10 (12.3)	0 (0)	0 (0.0)	–	37 (10.6)
Certified nurse of dysphagia nursing	42 (16.8)	18 (22.2)	3 (18)	0 (0.0)	–	63 (18.0)
Physical therapist	55 (22.0)	12 (14.8)	4 (24)	1 (33.3)	–	72 (20.6)
Occupational therapist	37 (14.8)	8 (9.9)	4 (24)	1 (33.3)	–	50 (14.3)
Speech therapist	118 (47.2)	23 (28.4)	5 (29)	1 (33.3)	–	147 (42.0)
Dietician	126 (50.4)	37 (45.7)	9 (53)	2 (66.7)	–	174 (49.7)
Pharmacist	37 (14.8)	12 (14.8)	1 (5.9)	1 (33.3)	–	51 (14.6)
Discharge planning coordinator‡	26 (10.4)	14 (17.3)	2 (12)	1 (33.3)	–	43 (12.3)
Medical social worker	89 (35.6)	24 (29.6)	4 (24)	2 (66.7)	–	119 (34.0)
Care manager	46 (18.4)	39 (48.1)	5 (29)	1 (33.3)	–	91 (26.0)

Number (%), *P*-values were tested by ANOVA, $^*P < 0.05$ by Bonferroni. Of the 555 geriatricians, 350 (63.1%) carried out a conference at least once. Respectively, hospital: 249 (69.2%), clinic: 80 (48.2%), long-term care: 17 (85.0%), other: 3 (33.3%). Multiple answers were allowed. †Other included part-time doctors, retired doctors, researchers and so on. ‡They are a registered nurse and work for discharge planning and coordination in the hospital.

Table 4 Multivariate-adjusted odds ratios and 95% confidence intervals for frequency and the conference members according to the indication for tube feeding and interventions for dysphagia before using tube feeding

	Conference				
	Non	Occasional		Every time	
		Participating occupation		Participating occupation	
		Few	Multidisciplinary	Few	Multidisciplinary
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Is the following disorder an indication for TF?					
Head injury or facial trauma	Ref	1.02 (0.55–1.89)	1.15 (0.52–2.57)	0.80 (0.36–1.78)	1.52 (0.62–3.77)
Oropharyngeal malignancy	Ref	0.96 (0.56–1.66)	0.78 (0.41–1.52)	1.05 (0.48–2.31)	1.02 (0.48–2.16)
Neurological disorder	Ref	0.72 (0.34–1.52)	0.56 (0.23–1.34)	1.69 (0.46–6.16)	1.17 (0.39–3.53)
Stroke	Ref	1.41 (0.68–2.90)	1.84 (0.66–5.13)	2.35 (0.68–8.15)	4.03 (0.90–18.05)
Dementia	Ref	0.83 (0.54–1.28)	0.82 (0.48–1.42)	1.86 (1.00–3.44)	1.01 (0.56–1.83)
Aspiration-prone frail elderly without comorbidity	Ref	0.99 (0.63–1.55)	1.23 (0.69–2.19)	1.31 (0.68–2.52)	0.80 (0.44–1.46)
Malnutrition in frail elderly without comorbidity	Ref	0.77 (0.49–1.22)	0.98 (0.56–1.74)	1.30 (0.70–2.42)	1.18 (0.64–2.18)
How long does a patient need to survive after PEG placement? ≧12 weeks†	Ref	0.85 (0.50–1.43)	0.89 (0.46–1.74)	0.80 (0.39–1.63)	1.44 (0.64–3.21)
Intervention for swallowing disorder before using TF					
No. intervention items, ≧ 6 items‡	Ref	2.07 (1.33–3.20)	3.24 (1.81–5.78)	2.60 (1.39–4.85)	8.71 (3.99–19.00)
Consultation					
To otolaryngologist	Ref	1.13 (0.72–1.77)	1.36 (0.78–2.38)	0.94 (0.49–1.80)	1.48 (0.80–2.72)
To speech therapist	Ref	1.51 (0.93–2.46)	4.57 (2.52–8.29)	2.47 (1.28–4.76)	3.82 (2.01–7.27)
To certified nurse of dysphagia nursing	Ref	1.18 (0.65–2.14)	2.16 (1.11–4.23)	1.65 (0.76–3.61)	4.75 (2.43–9.32)
Test					
Repetitive saliva swallowing test	Ref	1.62 (0.98–2.66)	3.89 (2.16–6.99)	3.91 (2.05–7.44)	4.48 (2.37–8.46)
Water swallowing test	Ref	2.08 (1.32–3.28)	1.63 (0.93–2.87)	1.82 (0.96–3.44)	2.95 (1.49–5.88)
Video endoscopy	Ref	1.53 (0.83–2.82)	1.30 (0.59–2.86)	0.97 (0.37–2.53)	2.89 (1.37–6.09)
Video fluorography	Ref	1.62 (1.03–2.56)	2.08 (1.19–3.66)	3.07 (1.64–5.76)	2.28 (1.23–4.22)
Practice and education					
Oral ice-massage	Ref	1.19 (0.67–2.10)	2.19 (1.16–4.14)	2.34 (1.14–4.79)	3.59 (1.82–7.06)
Swallowing exercise	Ref	1.81 (0.97–3.39)	3.47 (1.74–6.91)	4.86 (2.34–10.09)	6.63 (3.27–13.45)
Vocalization exercise	Ref	1.55 (0.71–3.41)	2.96 (1.28–6.83)	2.70 (1.04–7.00)	6.84 (3.02–15.50)
Using semi-solid and liquid foods	Ref	1.83 (1.13–2.96)	2.12 (1.11–4.06)	1.71 (0.86–3.38)	5.96 (2.24–15.84)
Thickening agent	Ref	1.26 (0.73–2.21)	1.93 (0.85–4.39)	1.18 (0.54–2.59)	4.68 (1.36–16.12)
Positioning	Ref	1.46 (0.94–2.26)	2.36 (1.29–4.31)	1.75 (0.93–3.30)	7.22 (2.94–17.71)
Appropriate approach for swallowing	Ref	2.48 (1.59–3.88)	2.82 (1.62–4.92)	2.13 (1.15–3.95)	5.60 (2.94–10.65)
Ways to coping when the aspiration	Ref	1.48 (0.95–2.29)	2.86 (1.63–5.01)	1.24 (0.67–2.29)	5.31 (2.69–10.48)

Dependent variables: the indication for tube feeding and interventions for dysphagia before introducing tube feeding. Independent variables: frequency and the conference members (ref, non conference; 1, occasional and less than five different health-care professionals; 2, occasional and ≧5 different health care professionals; 3, every time and less than five different health-care professionals; 4, every time and ≧5 different health-care professional. Adjusted for sex, place of employment and clinical experience. †The period expected to survive after PEG was divided into two groups. (1: ≧12 weeks, 0: <12 weeks). ‡Number of intervention items were divided into two groups, which was used median value into 15 items. (1: ≧6 items, 0: <6 items). CI, confidence interval; OR, odds ratio; TF, Tube Feeding.

in patients with stroke and oropharynegeal malignancy was associated with better prognosis; therefore PEG placement is recommended for these disorders by the European guideline.[20] We did not investigate how long PEG is placed in each condition. Thus, knowledge of geriatricians for tube feeding or PEG placement was not sufficiently explored in the present study; however, a period of PEG placement should be considered in each condition.

In Japan, requests for PEG to facilitate care are prevalent, because the staff in nursing homes tend to prefer PEG to time-consuming oral feeding. A multicenter study in the USA showed that feeding tube insertion is independently associated with both clinical characteristics of residents and fiscal, organizational and demographic features of nursing homes.[4] Therefore, these situations might have affected the decision making of geriatricians for tube feeding. Unfortunately, we did not include the question whether or not the request from nursing homes might have affected the decision making for tube feeding in dementia patients. Therefore, we should ask this question next time.

Regarding interventions for swallowing disorder, the mean number of interventions for swallowing disorder before introducing tube feeding was six items, which are not so many. Among the 15 items of interventions before introducing tube feeding, over 70% of the geriatricians answered that "Thickening agent" and "Using semi-solid and liquid foods" were afforded to patients with swallowing disorder. In contrast, consultation with other specialists was not frequently carried out, and care to improve swallowing dysfunction, such as "oral ice-massage," "swallowing exercise" and "vocalization exercise" was not usually carried out either. Therefore, from these data, we think that more interventions would be necessary to care for patients with dysphagia by consulting specialists and multidisciplinary approach.

It is interesting to note the relationship between multidisciplinary conference and knowledge and practice for tube feeding for the elderly. In the present study, we showed that those who have a multidisciplinary team conference for a patient indicated for tube feeding tended to carry out more "interventions for dysphagia before tube feeding" compared with the reference group after multivariate adjustment. Furthermore, the data showed that geriatricians who organize a conference with different health-care professionals carried out more interventions for dysphagia before tube feeding, irrespective of the frequencies of conference. The present study also showed that although there were no differences in the number of conference members and interventions between the geriatricians working in an acute hospital and those in a clinic before introducing tube feeding, the percentage of geriatricians who organized a multidisciplinary conference before introducing tube feeding was higher in the hospital than in the clinic. Therefore, the characteristics of facilities, not doctors themselves, might have affected this outcome. A previous study reported that multidisciplinary CGA is effective for the care of frail older persons admitted to the hospital, because evaluation and management by a multidisciplinary team during hospitalization documented a lower rate of institutionalization after 1 year.[14] Furthermore, decision making for treatment strategy should be discussed in a multidisciplinary team. The multidisciplinary conference would provide a better answer for each elderly patient who requires tube feeding, because they tend to have a complicated background.

Several potential limitations should be considered when interpreting these results. First, a cross-sectional study does not prove any causal relationship. Second, the practice rate of tube feeding in geriatricians was not clearly determined, because the present study was carried out by self-administered questionnaires. Third, the subjects were limited to geriatricians certified by the Japan Geriatrics Society, and also the response rate was not so high. Therefore, selection bias might have occurred. Finally, we did not investigate the number of beds in their place of employment; therefore these results were not completely adjusted by hospital size.

In conclusion, the present data showed that more than half of the board-certified geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. Furthermore, regardless of their clinical experience, approximately 40% of the Japanese geriatricians consider that demented elderly with loss of appetite or apraxia for eating should be on tube feeding. At this moment, there is no consensus among Japanese geriatricians about tube feeding for advanced demented people, and hence the guideline should be established for tube feeding in the elderly. Furthermore, a multidisciplinary team approach is expected to find a better answer for each elderly patient with eating difficulty.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Polypharmacy as a risk for fall occurrence in geriatric outpatients

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Objective: To investigate the predictors of falls, such as comorbidity and medication, in geriatric outpatients in a longitudinal observational study.

Methods: A total of 172 outpatients (45 men and 126 women, mean age 76.9 ± 7.0 years) were evaluated. Physical examination, clinical history and medication profile were obtained from each patient at baseline. These patients were followed for up to 2 years and falls were self-reported to their physicians. The factors associated with falls were analyzed statistically.

Results: A total of 32 patients experienced falls within 2 years. On univariate analysis, older age, osteoporosis, number of comorbid conditions and number of drugs were significantly associated with falls within 2 years. On multiple logistic regression analysis, the number of drugs was associated with falls, independent of age, sex, number of comorbid conditions and other factors that were significantly associated in univariate analysis. A receiver–operator curve evaluating the optimal cut-off value for the number of drugs showed that taking five or more drugs was a significant risk.

Conclusion: In geriatric outpatients, polypharmacy is associated with falls. Intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidity and falls. **Geriatr Gerontol Int 2012; 12: 425–430.**

Keywords: bone/musculo-skeletal, elderly, falls, geriatric medicine, internal medicine, polypharmacy.

Introduction

Previous studies have assessed the risk factors for falls in community-dwelling elderly,[1–3] but not in geriatric outpatients, and history of falls, physical ability and living environment were found to be predictors of falls. Outpatients have different characteristics from community-dwelling elderly, and previous studies have not assessed whether medical comorbidity and therapeutic drugs might be risk factors for falls. Falls in patients on medication are complicated, because some drugs, such as aspirin, can cause serious bleeding when they have injurious falls, and others, such as antihypertensive[4] and hypoglycemic[5,6] agents, can cause falls.

Previously, we reported that polypharmacy was associated with the tendency for falls using four indices of fall tendency in a cross-sectional setting in geriatric outpatients,[7] though that study did not evaluate fall occurrences, and also not in a longitudinal manner. Therefore, we aimed at investigating whether polypharmacy was predictive of fall occurrences in a prospective fashion. For this purpose, we followed geriatric outpatients for up to 2 years, and assessed whether polypharmacy is a risk for fall occurrence, together with other risks.

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The validity of two novel indices of fall tendency, the 22 items fall risk index[8] and the 13 points simple screening test,[3] which were used in our previous study, have been confirmed in community-dwelling elderly, but not in geriatric outpatients. Therefore, in the present investigation, the association of these two indices with falls was also evaluated to confirm their validity in geriatric outpatients in a longitudinal study.

Methods

Patients

From 2006 to 2007, a total of 190 consecutive patients aged 65 years or older who were receiving treatment for chronic diseases, such as hypertension, dyslipidemia, diabetes and osteoporosis, who were seen every 2–4 weeks at the outpatient clinic of the Research Institute of Aging Science, Tokyo, were enrolled. All the patients were able to walk independently and their condition was stable. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information including past history of stroke, myocardial infarction, malignancy and prescribed drugs was obtained from each patient at baseline from the medical chart recorded by the physician in charge. However, 18 patients were excluded, because they were lost to follow up soon after enrolment and the medical information was not fully obtained. All prescribed drugs had not been changed in the included patients for at least 2 months before enrolment. The patients were followed up for 2 years.

Occurrence of falls

During the follow-up period, the patients and their family members responded to the annual questionnaire asking about the occurrence of falls within the past year. The questionnaire was repeated for 2 years.

Indices of fall tendency

After enrolment, the patients were examined for two indices to investigate the fall tendency. These were (i) a questionnaire of the 22 items portable fall risk index;[8] and (ii) the 13 points simple screening test to assess the fall tendency.[3]

Ethical consideration

The present study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Data analysis and statistical methods

Values are expressed as mean ± standard deviation. In order to analyze the relationship between falls and comorbidity or drugs, variables were compared using Student's *t*-test or χ^2-test as appropriate. Significant factors found in univariate analysis were included in multivariate logistic regression analysis to determine the association of falls with other variables. Receiver-operating curve (ROC) analysis was carried out to identify the optimal cut-off value of the number of drugs for predicting falls within 2 years. The value with the highest sum of sensitivity and specificity was used as the optimal cut-off value. Logistic regression analysis was carried out to assess the validity of the two indices of fall tendency, adjusted by age and sex. *P*-values <0.05 were considered statistically significant. Data were analyzed using JMP version 8.0.1 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline medical information and two indices of fall tendency were evaluated in 172 patients (Table 1). Drugs prescribed in less than 5% of the patients are not shown. Because only patients who were in a stable condition and were able to walk independently were included, patients with Parkinson's disease, severe paresis or painful arthralgia were not included. Calcium channel blockers prescribed in the present study were all long-acting agents, and the prescribed aspirin dosage was 100 mg in all cases. Only a few patients were receiving insulin therapy, sulfonylureas, angiotensin converting enzyme inhibitors, β-blockers, α-blockers, non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics or antiparkinsonian drugs.

After 1 year, all patients, except for one who died of congestive heart failure, were followed up ($n = 171$, follow-up rate 99.4%). Falls occurred in 22 patients. Only a higher age was associated with falls within 1 year on univariate analysis (non-fallers: 76.4 ± 6.8 years, fallers: 81.0 ± 6.9 years, $P = 0.004$).

After another year (2 years after enrolment), one patient had died of lung cancer, and five patients were lost to follow up. A total of 165 patients were evaluated (follow-up rate 95.9%), and 10 patients had fallen during the second year; thus a total of 32 patients had fallen within 2 years. As shown in Table 2, higher age, osteoporosis, number of comorbid conditions and number of drugs were significant factors associated with falls. To determine the association of falls with these significant factors, multivariate logistic regression analysis was carried out, and as shown in Table 2, the number of drugs was the only factor that was significantly associated with falls within 2 years.

As polypharmacy was assumed to be a risk for falls within 2 years, the cut-off of the number of the drugs was analyzed. Figure 1 shows the ROC curves to define the optimal cut-off point in relation to falls within

Table 1 Characteristics and univariate analysis of association with fallers and non-fallers within 2 years and risk factors

Total		Non-fallers ($n = 133$)	Fallers ($n = 32$)	P-value (Fallers vs. Non-fallers)
Age (years)	77.0 ± 7.0	76.3 ± 6.9	80.0 ± 6.9	0.007
Body mass index (kg/cm^2)	22.7 ± 3.2	22.7 ± 3.3	22.7 ± 3.1	0.98
No. comorbid conditions	1.9 ± 1.1	1.8 ± 1.1	2.3 ± 0.9	0.009
No. drugs	3.2 ± 2.8	2.8 ± 2.7	4.9 ± 2.5	<0.0001
Female ($n = 122$)	–	72.9%	78.1%	0.66
Hypertension ($n = 106$)	–	62.4%	71.8%	0.41
Dyslipidemia ($n = 76$)	–	47.3%	40.6%	0.56
Diabetes ($n = 23$)	–	12.8%	18.8%	0.40
Osteoporosis ($n = 59$)	–	30.8%	56.3%	0.01
History of stroke ($n = 6$)	–	2.3%	9.4%	0.09
History of myocardial infarction ($n = 3$)	–	0.8%	6.3%	0.10
History of cancer ($n = 8$)	–	5.3%	3.1%	0.99
Calcium channel blocker ($n = 59$)	–	33.3%	46.9%	0.16
Angiotensin II receptor blocker ($n = 56$)	–	33.3%	37.5%	0.68
Statin ($n = 40$)	–	23.5%	28.1%	0.65
Aspirin ($n = 31$)	–	19.0%	24.1%	0.61
Bisphosphonate ($n = 9$)	–	4.6%	9.4%	0.38
H2-blocker ($n = 9$)	–	3.8%	12.1%	0.80
Proton pump inhibitor ($n = 11$)	–	5.3%	12.1%	0.23
Hypnotic ($n = 31$)	–	16.7%	28.1%	0.14

Values are expressed as mean ± SD ($n = 165$).

Table 2 Logistic regression analysis of association of falls within 2 years with age, sex, other significant factors found in univariate analysis, and polypharmacy

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/1 year)	1.08 (1.03–1.13)†	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.98 (0.29–3.23)	0.75 (0.23–2.38)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)†	2.76 (0.92–7.38)	3.02 (0.96–6.15)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	0.90 (0.55–1.47)	0.99 (0.62–1.56)
No. drugs (/drug)	1.29 (1.12–1.48)‡	1.30 (1.08–1.57)*	–
Five or more drugs ($n = 0$, Y = 1)	5.04 (2.25–11.3)‡	–	4.50 (1.66–12.2)†

*$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$. CI, confidence interval.

2 years: the area under the ROC was 0.731, and the optimal cut-off value of the number of drugs was five (sensitivity 0.576, specificity 0.788). Logistic regression analysis showed that taking five or more drugs was significantly associated with an increased risk of falls (odds ratio 4.5, 95% CI 1.7–12.2) after adjustment for age, sex, osteoporosis and number of comorbid conditions (Table 2).

Also, the association between falls and two indices of fall tendency was evaluated to confirm the validity of each index in geriatric outpatients. As both indices included the questionnaire asking whether patients were "taking five or more drugs," the number of drugs was excluded from this analysis because of duplication in the statistical model. As shown in Table 3, the 22 items fall risk index showed a tendency towards an association with falls within 2 years, odds ratio 1.12 (95% CI 1.00–1.26; $P = 0.05$), whereas the 13 points screening test was significantly associated with falls after adjustment for age, sex and other factors significantly associated in the univariate analysis. Therefore, these indices are considered to be good predictors of falls in geriatric outpatients, as has been shown in community-dwelling elderly subjects.

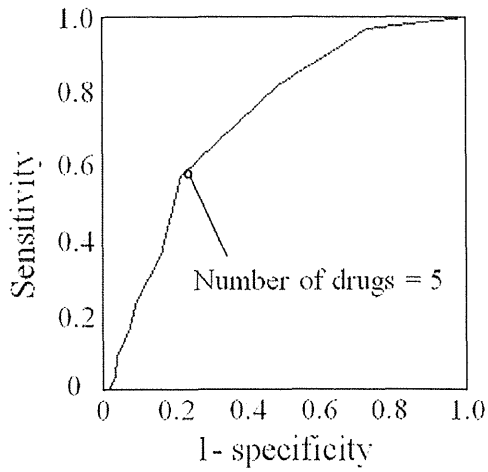

Figure 1 Receiver–operating curves to define optimal cut-off value of number of drugs at baseline in relation to falls within 2 years. Area under the curve was 0.731, optimal cut-off value of the number of drugs was five (sensitivity = 57.6%, specificity = 78.8%).

Discussion

The risk of falls has been assessed in community-dwelling elderly, and history of falls, physical ability and living environment were found to be predictors of falls. Also, in nursing home residents, cognitive function, gait disturbance and urinary incontinence are reported to be risk factors for falls,[9,10] and length of stay, disease condition, surgical procedures and some specific drugs are reported to be risk factors in hospital inpatients.[11,12]

Nevertheless, the risks in geriatric outpatients have not been sufficiently assessed, although assessment of fall risk in geriatric outpatients is important; their medical conditions or drugs might cause falls, and drugs, such as antiplatelet agents or anticoagulants, might cause critical bleeding after a fall. Also, physicians could prevent falls in their patients by giving advice during regular consultations, if risk factors are identified.

In our previous cross-sectional study assessing geriatric outpatients, polypharmacy was significantly correlated with indices of fall tendency, and the present follow-up study of geriatric outpatients showed the impact of polypharmacy on falls within 2 years. Statistical analyses showed that polypharmacy was a risk factor for falls, independent of age, sex and comorbidity.

Besides polypharmacy, several medications and comorbid conditions have been reported as risks for falls.[13–22] Among these, diabetes,[5,6] insomnia,[13] hypnotics,[13–15] antiarrhythmics[22] and antihypertensive agents[14] were not significantly associated with fall risk in the present study. Just 11 patients (45.9% of diabetic patients) were prescribed hypoglycemic agents, such as a sulfonylurea ($n = 8$) or insulin ($n = 3$), and the relatively low rate of prescription of hypoglycemic agents might have affected our result. Neither hypnotics nor antihypertensives were associated with falls. This result might be a result of the small sample size. Anti-arrhythmics were taken by just three patients (digoxin: $n = 2$, class IA anti-arrhythmic drug: $n = 1$). Other drugs, such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonian agents,[19,22] might increase fall risk; however, no patient used these drugs in the present study. In the present study, most of the patients were in a stable condition throughout the 2 years, though their drugs were changed gradually according to their medical conditions during the observation period. We only used the number of drugs at baseline for statistical analysis; however, the number of drugs increased from 3.2 ± 2.8 to 3.9 ± 3.0 during the 2 years. There were 17 patients whose number of drugs had been decreased, 70 patients not changed and 78 patients increased. The number of drugs after 2 years was also associated with falls ($P < 0.0005$). The optimal cut-off point for the number of drugs was again five (area under ROC curve 0.780, sensitivity 0.576, specificity 0.788). Furthermore, the changes in number of drugs were also associated with falls ($P < 0.05$), and the optimal cut-off point for the change in number of drugs was +1 (area under ROC curve 0.649, sensitivity 0.727, specificity 0.409).

Table 3 Logistic regression analysis of association between 2-year fall occurrences with two indices of fall tendency; 22 items fall risk index and 13 points simple screening test

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/year)	1.08 (1.03–1.15)**	1.06 (0.99–1.13)	1.06 (1.00–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.75 (0.23–2.43)	0.79 (0.24–2.56)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)**	2.56 (0.96–6.82)	2.61 (0.98–6.95)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	1.24 (0.83–1.86)	1.32 (0.88–1.97)
Fall risk index (/item)	1.23 (1.11–1.37)***	1.12 (1.00–1.26)	–
Simple screening test (/point)	1.19 (1.06–1.33)**	–	1.14 (1.01–1.29)*

*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$. CI, confidence interval.

Consequently, polypharmacy, especially taking five or more drugs, should be considered a risk for falls.

There were several limitations of the present study. First, the falls were self-reported by the patients. Although all the patients had no overt dementia, they might have forgotten the incident of falling. We attempted to count the total fall occurrences in each patient; however, we could not differentiate the repeated falls in the second year from the fall occurrence in the first year. In fact, we asked 22 patients who reported falls in the first year about fall occurrence during the second year, but they did not accurately recall whether they experienced falls in the first or second year. Second, five patients were lost to follow up at 2 years for unknown reasons. The follow-up ratio was acceptable, although some of the patients might have fallen, have been no longer able to come to the clinic and moved to nursing homes. This might have slightly influenced the result. Also, the cause of falls in polypharmacy patients is not explained. Potentially inappropriate medications, which could cause adverse drug reactions, are usually seen in patients with polypharmacy, and falls might be the consequence of adverse drug reactions, such as dizziness, instability and light-headedness. Pathophysiological assessments and drug-reducing interventions are expected to elucidate the causal relationship.

Additionally, we showed that the 22-item fall risk index and its simple screening test were useful to predict falls in geriatric outpatients. Although both indices have been validated in community-dwelling elderly people, the present finding also showed their association with fall risk among geriatric outpatients. The difference of statistical significance between fall risk index and simple screening test might be a result of small sample size or the difference in the contribution of each item to total scores between the two indices. "Taking five or more drugs" accounts for only one item out of the 22-item fall risk index; in contrast, the same questionnaire accounts two points in the 13-point simple screening test. Because polypharmacy was a strong risk factor of falls in elderly outpatients in the present study, the proportion of polypharmacy in the scores might have caused the discrepancy. Taken together, it is likely that 13-point screening test was more suitable to our subjects who were taking several medicines.

In summary, the present study showed that geriatric outpatients with polypharmacy were at a high risk of falls, especially those receiving five or more drugs. Our finding might add new information for pharmacotherapy and geriatric research in elderly patients with chronic diseases. Intervention studies examining the effect of drug reduction for the prevention of falls are required in the future.

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Disclosure statement

The authors declare no conflict of interest.

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FACTORS ASSOCIATED WITH PROLONGED HOSPITAL STAY IN A GERIATRIC WARD OF A UNIVERSITY HOSPITAL IN JAPAN

To the Editor: We read with interest the article by Lakhan and colleagues,[1] which showed the high prevalence and worsening of geriatric syndrome during acute care hospitalization. Because falls, incontinence, impairment in activities of daily living (ADLs), and other geriatric syndrome components increase the care burden and limit discharge planning in acute care hospitals, geriatric syndrome might cause prolonged hospital stays. A prolonged hospital stay is one of the major determinants of medical cost and is thus a serious problem in geriatric medicine. Previous studies have shown that clinical events during hospitalization,[2,3] basic ADLs,[4] and nonmedical factors such as delayed transfer to a nursing facility or disagreement on the discharge plan among family members[5] are risk factors for prolonged hospital stay. Furthermore, because older adults have multiple comorbid conditions and are susceptible to adverse drug reactions (ADRs), these factors might be related to length of hospital stay. To test this hypothesis, the association between geriatric conditions such as geriatric syndrome, ADLs, and ADRs and prolonged hospital stay were comprehensively investigated using the database of the geriatric ward of the University of Tokyo Hospital from 1995 to 2010. The ethics committee of the Graduate School of Medicine, University of Tokyo approved this study.

All records of patients aged 65 and older from 1995 to 2010 were reviewed. Data on length of stay, acute hospitalization, ADRs, body mass index (BMI), number of diseases and drugs, geriatric syndrome, and Barthel Index were collected. Twenty-three components of geriatric syndrome such as falls, cognitive impairment, urinary incontinence, constipation, and insomnia were included in the analysis. Records lacking information on any of the variables were excluded. Cases of scheduled short-term hospitalization were excluded. Finally, the records of 1,616

Table 1. Characteristics of Study Patients and Analyses for Length of Hospital Stay (N = 1,616)

Characteristic	Value	Univariate Analysis (R or Hospital Stay, Days, Mean ± SD)	Standardized Regression Coefficient
Age, mean ± SD	78.3 ± 7.0	0.001	−0.099[d]
Sex, *n* (%)			
Female	778 (48.1)	26.8 ± 20.2	
Male	838 (51.9)	27.6 ± 24.6[a]	
Acute hospitalization, *n* (%)			
Yes	300 (18.5)	26.2 ± 21.0	
No	1,316 (81.5)	31.8 ± 28.2[a,d]	
Adverse drug reaction, *n* (%)			
Yes	190 (11.8)	26.4 ± 19.5	0.078[c]
No	1,426 (88.2)	33.3 ± 38.1[a,d]	
Body mass index, kg/m^2, mean ± SD	22.0 ± 4.1	−0.59[d]	−0.062[b]
Barthel Index (points out of 100), mean ± SD	83.1 ± 26.1	−0.178[d]	−0.13[d]
Number of diseases, mean ± SD	5.3 ± 2.3	1.43[c]	0.082[c]
Number of drugs, mean ± SD	6.8 ± 3.6	0.411[b]	–
Number of geriatric syndrome components, mean ± SD	4.6 ± 3.6	1.66[d]	0.19[d]

All data were collected soon after admission. For sex, acute hospitalization, and adverse drug reactions, a simple *t*-test was performed for univariate analysis, and values are expressed as mean ± standard deviation (SD).

[a]*P*-values are for comparison to female or no. Pearson correlation coefficients (R) are shown for the remaining factors in univariate analysis. All variables shown were included in stepwise regression analysis, and factors significantly associated were analyzed in multiple regression analysis (coefficient of determination = 0.32).

[b]$P < .05$.

[c]$P < .005$.

[d]$P < .001$.

patients were analyzed (mean age 78.3 ± 7.0, 52% male). All data were obtained soon after admission. Values are expressed as means ± standard deviations and were analyzed using JMP version 9.0.2 (SAS Institute, Inc., Cary, NC). $P < .05$ was considered statistically significant.

Mean length of stay was 27.3 ± 22.6 days (range 1–322 days). The results of univariate and multivariate analyses for length of stay are shown in Table 1. Multiple stepwise regression analysis showed that ADRs, number of diseases, and number of geriatric syndrome components were positively associated with longer hospital stay, whereas age, BMI, and Barthel Index were negatively associated. The number of geriatric syndrome components was significantly associated with hospital stay independent of number of diseases.

The present analysis demonstrated that geriatric factors such as ADRs, multiple diseases, low BMI, ADL dependence, and number of geriatric syndrome components were associated with longer hospital stay in a large group. The finding that ADRs are a risk for prolonged hospital stay is consistent with a previous report,[6] and ADL dependence has been reported as a risk in a smaller group.[4] Furthermore, the number of geriatric syndrome components and undernutrition were risk factors for prolonged hospital stay in a large-scale study. Frailty, which is also known to be a risk factor,[7] was not examined independently in the present study, but ADL dependence and undernutrition, both of which are major components of frailty, were found to be risk factors, so it is reasonable to assume that frailty was associated with length of hospital stay in the current cohort as well. The present study revealed that the accumulation of geriatric syndrome components was a risk factor for prolonged hospital stay independent of multiple diseases and, presumably, frailty. Thus, geriatric syndrome should be comprehensively managed during hospitalization. The reason for the negative association between age and length of stay is unclear, but the presence of young-old patients with disability or complicated conditions on the geriatric ward might have influenced the results.

In summary, the present study provides new insight into the significance of geriatric conditions in relation to prolonged hospital stay in older adults. ADL dependence, undernutrition, ADRs, and geriatric syndrome should be carefully assessed and interventions provided when caring for older inpatients.

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ACTIVITIES OF DAILY LIVING RATHER THAN DEPRESSIVE SYMPTOMS INCREASE THE RISK OF MORTALITY IN JAPANESE COMMUNITY-DWELLING ELDERLY PEOPLE: A 4-YEAR LONGITUDINAL SURVEY

To the Editor: The article entitled "Depressive Symptoms Increase the Risk of Mortality in Older Mexican Community-Dwelling Adults" by Piña-Escudero et al.[1] deeply impressed us. Although it has been shown that older adults with depressive symptoms (DSs) have fewer quality-adjusted life years than those with chronic medical conditions,[2] Piña-Escudero et al. in their 2-year longitudinal study, showed that DSs increase mortality risk regardless of multiple covariates such as medical conditions and disability in activities of daily living (ADL). Similarly, results of a meta-analysis of 25 studies suggest that depression increases the risk of mortality,[3] although those studies did not assess ADL in detail. The risk of mortality in Japanese community-dwelling elderly people is reported herein, focusing on DSs and ADLs in a 4-year longitudinal survey.

The study population included 1,818 community-dwelling individuals aged 65 and older in Tosa Town, Japan; 1,600 (88.0%) participants who completed self-reported geriatric questionnaires in 2006 were included in the study. The questionnaires consisted of questions on ADLs and the 15-item Geriatric Depression Scale (GDS-15).[4] For ADL assessment, participants rated their

RELATIONSHIP BETWEEN TESTOSTERONE AND COGNITIVE FUNCTION IN ELDERLY MEN WITH DEMENTIA

To the Editor: A decrease in sex hormones with aging has been reported to be related to psychosomatic disorders such as late-onset hypogonadism syndrome, frailty, and cognitive impairment in adult men.[1] For example, a community-based cross-sectional study has shown that elderly men with a lower blood concentration of bioavailable testosterone have more-severe impairment of cognitive function.[2] Moreover, a longitudinal study indicated that serum free testosterone (FT) concentration could predict memory performance and cognitive status in elderly men,[3] but it is unknown whether lower testosterone concentration is related to cognitive impairment in individuals with dementia, because the previous studies primarily focused on a healthy community-based population. Also, few studies have addressed the relationship between testosterone and cognitive function in elderly Japanese men.

One recent cross-sectional study showed that total testosterone and FT concentration were associated with activities of daily living (ADLs) in institutionalized elderly men.[4] This study also revealed that a relationship between testosterone and cognitive function could be found even in institutionalized elderly men with physical or neuropsychiatric dysfunction. Thus, whether lower testosterone concentration is related to deterioration of ADL in elderly men with cognitive impairment was longitudinally investigated.

Fifty-two male outpatients attending the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were recruited (mean age 77.0 ± 5.5, range 65–87). Participants' clinical backgrounds were hypertension, 48.9%; diabetes mellitus, 12.2%; and dyslipidemia, 38.1%. None had a history of stroke. Comprehensive geriatric assessment was performed based on basic ADLs (Barthel Index),[5] instrumental ADLs (Lawton and Brody IADLs, 0–5 points in men),[6] cognitive function (Mini-Mental State Examination (MMSE)),[7] mood (Geriatric Depression Scale (GDS), 15 items),[8] and vitality (Vitality Index, 10-point scale).[9] This assessment was repeated 1, 2, and 3 years after baseline assessment at the first visit to the clinic. At the first visit, blood was drawn after an overnight fast and FT concentration was measured using radioimmunoassay. FT values ranged from 1.0 to 53.0 pmol/L (mean ± SD 30.4 ± 11.0 pmol/L). Participants were classified into three groups according to tertile according to the baseline FT value (Figure 1), and the parameters from the comprehensive geriatric assessment were compared between groups and visits. Statistical data were analyzed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). One-way analysis of variance (ANOVA) was applied for comparisons between groups, and the Fisher post hoc test was applied when significant ($P < .05$). One-way repeated ANOVA was used for comparisons between baseline and the 1-, 2-, and 3-year visits, and the Fisher post hoc test was applied when significant ($P < .05$).

There were no significant differences between groups in age (high, 75.3; middle, 76.6; low, 79.0), basic ADLs (high, 96.9; middle, 99.1; low, 95.3 points), MMSE (high, 23.2; middle, 25.1; low, 23.1 points), GDS-15 (high, 5.1; middle, 4.1; low, 4.6 points), and Vitality Index (high, 9.1; middle, 9.1; low, 8.8 points) at baseline, whereas IADLs tended to be lower (high, 4.1; middle, 4.1; low, 3.4 points, $P = .06$) in the low FT tertile group than in the other groups.

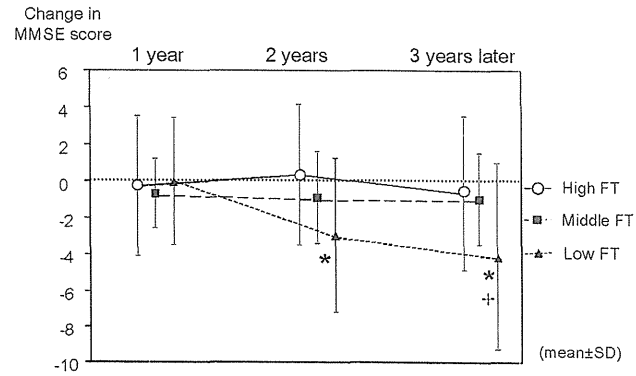

Figure 1. Change in Mini-Mental State Examination (MMSE) score according to tertile of serum free testosterone (FT) level in men. FT tertile: high, >36.1 pmol/L, n = 17; middle, 29.1–35.4 pmol/L, n = 17; low, <28.8 pmol/L, n = 18. *$P < 0.05$ vs highest FT group, +$P < 0.05$ vs middle FT group.

At the 1-year visit, there was no difference in change in MMSE score from baseline between the groups, although the decrease in MMSE score was larger in the low FT tertile group than in the middle and high tertile groups at the 2- and 3-year visits (Figure 1). Also, MMSE scores were lower in the low FT tertile group at the 2- ($P = .009$) and 3-year ($P < 0.001$) visits than at baseline, whereas they were not lower in the middle and high tertile groups. In contrast, there was no such trend in basic ADLs, IADLs, GDS scores, and Vitality Index.

Multiple regression analysis was performed with a decrease in MMSE score as a dependent variable and age; ADLs; body mass index; presence of hypertension, diabetes mellitus, or hyperlipidemia; and FT concentration as independent variables to consider factors affecting cognitive impairment, according to a previous report.[4] Blood FT concentration was found to be an independent predictor of decrease in MMSE score at the 3-year visit ($\beta = 0.492$, $P = .02$).

A number of investigations support the biological plausibility of a protective effect of testosterone against cognitive dysfunction. The present findings from memory clinic outpatients are consistent with previous findings observed in elderly community-based men, showing a relationship between FT concentration and cognitive performance.[3] Furthermore, the present findings indicate that a lower FT concentration could lead to a faster decline in cognitive function in elderly Japanese men who already show cognitive impairment. This study provides fundamental data for the future study of hormone replacement therapy for cognitive decline in elderly adults with low FT.

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BASELINE INSTRUMENTAL ACTIVITIES OF DAILY LIVING AND INCIDENT DEMENTIA

To the Editor: Sikkes et al.[1] have written an important paper showing that individuals without dementia with impairment in at least one of nine instrumental activities of daily living (IADLs) at baseline had a significantly higher incidence of dementia at 12 months (24.4%) than individuals without IADL impairment at baseline (16.7%) (P = .04). Their 531 participants who were followed for 12 months were relatively young (mean age 69.6), so it was decided to duplicate their study from prospective data from the Wyong Hospital Memory Clinic, 100 km north of Sydney. From 415 individuals attending a memory clinic, community-dwelling individuals aged 60 and older who were free of dementia at baseline and had a Mini-Mental State Examination score (MMSE[2]) of 25 to 30 and a follow-up MMSE and Montreal Cognitive Assessment (MoCA), range 0 (worst) to 30 (best)[3] at 12 months were selected in a consensus conference of a geriatrician (PJ) and a clinical nurse consultant (EH). Each individual's family rated IADLs on the Nottingham scale,[4] which ranged from 0 (worst) to 22 (best). Twenty-two of 82 (27%) converted to dementia at 12 months, compared with Sikkes conversion rate of 20.8% at 24 months—the most likely reason for this difference was that mean age (79.1) was 9.5 years older than theirs (69.6). Stats Direct Version 2.7.8b (StatsDirect Ltd, Altrincham, UK) from November 2011 was used to compare converters and nonconverters. Mean age of the 22 converters at baseline was significantly higher that that of the 60 nonconverters (82.0 ± 5.8 vs 78.0 ± 6.8, P < .01), mean IADL score at baseline was significantly lower (13.1 ± 5.3 vs 16.1 ± 4.0, P = .0236), MMSE score at baseline was by definition lower (25.6 ± 0.73 vs 27.5 ± 1.50, P < .001), and MoCA score at baseline was lower (19.2 ± 3.5 vs 22.8 ± 3.9, P < .001). At 12 months, IADL (11.4 ± 5.6 vs 15.4 ± 4.5, P = .004), MMSE score (21.6 ± 4.5 vs 27.4 ± 1.6, P < .001), MoCA (16.8 ± 3.6 vs 22.8 ± 4.2, P < .001) remained significantly lower in converters.

The Nottingham IADL covers seven of the nine IADL items that Sikkes used, excluding medications and finances. Women are more likely than men to perform five of the Nottingham IADL items unless the men live alone with no home care services: cleaning the kitchen, making a hot snack, washing small items of clothing, doing a full clothes wash, and doing housework.

Although the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for dementia include a decline in social and occupational function, there is a surprising lack of research into IADLs as a predictor of incident dementia. This is an important topic for future research and ongoing studies are being conducted in three cohorts: Wyong Memory Clinic; general medical inpatients with delirium or subsyndromal delirium—a prospective randomized controlled trial, Central Coast Australia Delirium Intervention Study; and PhD study, PR DEFEAT DELIRIUM, in outpatients at high risk for incident delirium. One study[5] with 255 community-dwelling individuals attending a memory clinic who were followed an average of 13 months has been published. The 11.4% of participants with antithyroid antibodies had similar outcomes at 12 months with respect to IADLs, decline in IADLs, MMSE and MoCA scores, and transfer to residential care.

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High risk of adverse drug reactions in elderly patients taking six or more drugs: Analysis of inpatient database

Dear Editor,

Polypharmacy is frequently seen in elderly patients, largely because of the existence of multiple comorbid conditions. All medications have the potential for harm as well as benefit, and thus, physicians must make difficult trade-offs between both sides of guideline-directed care.[1,2] Some drugs are reported to increase adverse drug reactions (ADR), and have been listed as potentially inappropriate medications (PIM), which should not be used generally in elderly patients.[3–5] However, it is still complicated for general practitioners to check PIM for each patient. As polypharmacy is a well-known risk for ADR,[6,7] and the frequency of PIM use rises sharply according to the number of drugs,[7] the optimal number of drugs defining polypharmacy might be of substantial help for physicians. Therefore, we aimed to determine the cut-off number of drugs in relation to ADR using the inpatient database of our geriatric department.

All records of patients aged 65 years or older who were admitted to the Department of Geriatric Medicine, The University of Tokyo Hospital, Tokyo, Japan, from 1995 to 2010 were reviewed. Retrospective use of the patient database was approved by the ethics committee of The University of Tokyo. Records lacking information on ADR or the number of drugs and patients taking no drugs were excluded. Finally, we analyzed the records of 2412 patients (mean ± SD age = 78.7 ± 7.3 years, male 51.3%). ADR was defined as unintended or undesired harmful effects presumably caused by drugs. The occurrence of ADR was assessed before discharge by the physician in charge, and other data were obtained soon after admission. Odds ratios with 95% confidence intervals for ADR were obtained by logistic regression analysis. The receiver operating characteristic (ROC) curve was assessed to define the optimal number of drugs in relation to ADR. Data were analyzed using JMP version 9.0.2 (SAS Institute, Cary, NC, USA).

The number of prescribed drugs per patient was 6.6 ± 3.6 (mean ± SD; range = 1–30), and ADR were observed in 252 patients (10.5%). Patients with ADR were taking more drugs than those without ADR (7.6 ± 3.8 *vs* 6.4 ± 3.5 drugs, $P < 0.0001$ by unpaired *t*-test). ADR was significantly associated with the number of drugs in unadjusted and age- and sex-adjusted logistic regression analysis (data not shown). When ADR were analyzed according to the number of drugs by quintile, the odds ratio of ADR was significantly higher in the groups taking six or more drugs (Fig. 1). Furthermore, ROC analysis showed that the optimal cut-off number of drugs was six, although the sensitivity of 0.560 and specificity of 0.710 were not high, with a small area under the curve of 0.591.

Previously, elderly outpatients taking five to eight drugs were reported to be at greater risk of ADR-related hospitalization than those taking zero to four drugs.[6] Also, we have reported that taking five or more drugs is a risk factor for falls in outpatients.[8] Taking these findings together, it might be reasonable to consider six or more drugs as the cut-off of polypharmacy in terms of ADR in elderly patients. The present study had some limitations; the results were obtained from inpatients managed by geriatricians, and thus might not extend to general outpatients. Next, this database did not have information for types of ADR; so they could not be clarified in detail in the present. According to our previous study, hematological, neurological and

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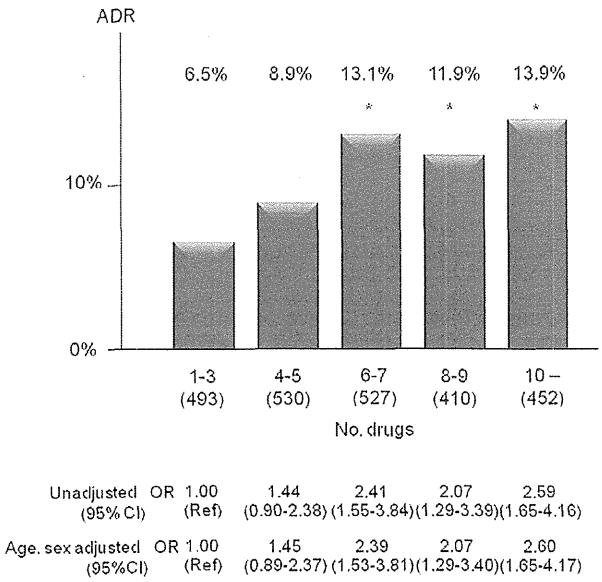

Figure 1 Frequency of adverse drug reactions according to quintile of number of prescribed drugs. Unadjusted and age–sex adjusted odds ratios (95% confidence interval) of adverse drug reactions are shown. $^{*}P < 0.05$ versus one to three drugs. OR, odds ratio.

cardiovascular events were reported to be more frequent than ADR in elderly inpatients,[9] and so, these are possibly the major types in the present study. Also, ROC analysis did not fit well for the present cohort.

In summary, the present study provided the cut-off number of drugs for screening of elderly patients at high risk of ADR. Prospective studies and intervention studies examining the effect of drug reduction on ADR and comorbid conditions are required to confirm this finding.

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C-kit-positive acute myelogenous leukemia effectively treated with imatinib: A case report and review of the literature

It is highly advisable to choose a strategy to improve the quality of life (QOL), rather than a curative strategy, such as conventional chemotherapy, for very elderly patients with acute myelogenous leukemia (AML). Molecular targeted therapy might also be considered as an important strategy to take into account.[1]

An 88-year-old man was referred to Juntendo University Urayasu Hospital in Chiba, Japan, because of fever and headache in April 2004. The spleen was enlarged to 5 cm below the left costal margin. White blood cell (WBC) count was $61.1 \times 10^4/\mu L$, with 29% blasts and 6.5% basophils. Other data were hemoglobin (Hb) 10.6 g/dL, platelet (plt) $41.0 \times 10^4/\mu L$, lactate dehydrogenase (LDH) 685 IU/L, uric acid (UA) 10.0 mg/dL and C-reactive protein (CRP) 14.6 mg/dL. Bone marrow was myeloid hyperplasia with 27% blasts. Flow cytometer showed that the leukemic cells were positive for myeloperoxidase, CD7, CD13, CD15, CD33, CD34 and c-kit (CD117). Because the leukocytosis with blasts, mild basophilia and splenomegaly resembled blast crisis of chronic myeloid leukemia, and furthermore the patient was very old, imatinib 600 mg daily was tried. Fortunately, imatinib was effective before chromosome analysis later showed trisomy 8. Although the rate of blasts in the peripheral WBC was almost constant, the number of WBC decreased and red blood cells transfusion (RBCT) was not required soon. The patient could leave hospital on day 28 and he had a good QOL. On day 90, the WBC count was 5000/μL with 28% blasts, and Hb and plt were stable; furthermore, the spleen was not palpable. Although generalized edema and pleural effusion occurred as side-effects of imatinib on day 110, they improved with furosemide. However, on day 130, the number of WBC gradually increased,

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LETTERS TO THE EDITOR

Gastrointestinal hemorrhage and antithrombotic drug use in geriatric patients

Dear Editor,

Recent guidelines recommend the aggressive use of antithrombotic medications in patients at high risk of thrombotic events. Although the risk of thrombosis increases with age, critical bleeding related to antithrombotic drug use is frequently seen in older patients.[1] Thus, guideline-directed use of antithrombotic medications might cause more harm than benefits among older patients with multiple comorbid conditions.[2,3] To increase the benefit-to-harm ratio, geriatricians might take care to stratify the risks and totally manage the patients. We hypothesized that such geriatricians' approaches lead to harmless use of antithrombotic medications. For this purpose, we carried out a case–control study to investigate the association between gastrointestinal hemorrhage and antithrombotic drug use.

We analyzed the inpatient registry of the Department of Geriatric Medicine, University of Tokyo Hospital between 1996 and 2007 (2249 patients) to identify patients ≥60 years-of-age who were admitted to the department as a result of gastrointestinal hemorrhage. The database was searched using the keywords of gastrointestinal hemorrhage, melena, hematemesis and anemia. Then, medical records of the extracted patients were reviewed. Finally, a total of 47 patients were defined to fulfil the criteria. Next, using risk-set sampling, we selected four controls per case matched for age, sex and the timing of hospitalization from the same inpatient registry. The data were obtained on prescriptions of antithrombotic drugs (aspirin, warfarin, cilostazol and ticlopidine) and anti-ulcer drugs (proton pump inhibitors and H2 blockers), and comorbid conditions.

Among the cases, causes of gastrointestinal hemorrhage were ulcer (48.9%), cancer (8.5%), ischemic colitis (6.3%), colon diverticulum (4.2%), Mallory–Weiss syndrome (4.2%) and hemorrhoid (2.1%), and 21.2% remained uncertain. As shown in Table 1, 17 cases and 71 controls were taking antithrombotic drugs. Of them, aspirin was most frequently prescribed both in case and control groups. There was no significant difference between case and control groups in the prescription rate of antithrombotic drugs ($\chi^2 = 0.20$, $P = 0.65$) and that of aspirin ($\chi^2 = 0.43$, $P = 0.51$). Furthermore, unadjusted logistic regression analyses showed that antithrombotic drug use and antiulcer drug use was not associated with gastrointestinal hemorrhage. The odds ratio of antithrombotic drug use for gastrointestinal hemorrhage was 0.91 (95% CI 0.46–1.81) after adjustment by age, sex and anti-ulcer drug use. Exclusion of the patients with cancer-related hemorrhage did not fundamentally influence the analytical results (data not shown).

This small case–control study showed no association of admission as a result of gastrointestinal hemorrhage with the use of antithrombotic drugs or aspirin among older patients. As most of the patients were managed by geriatricians in our department, the finding might be limited to the particular facility or cohort, but might not be extended to the general population. It is suggested, however, that geriatricians can make an appropriate decision on the indication and management of antithrombotic drugs for older patients. Although no studies have shown comparable findings in terms of gastrointestinal bleeding, geriatric evaluation and management has been reported to be effective to reduce serious adverse drug events.[4] A recent review on the management of antiplatelet agents[5] also recommended comprehensive strategies to reduce the risk of hemorrhagic complications. Prospective studies with a large sample size are required to confirm this issue. Nevertheless, it is certain that the use of antithrombotic

Table 1 Age, sex and medication use in case and control subjects, and unadjusted odds ratios for gastrointestinal hemorrhage

	Cases ($n = 47$)	Controls ($n = 189$)	Odds ratio (95% CI)
Age (years)	78 ± 10	77 ± 9	1.02 (0.98–1.06)
Men (women = 0, men = 1)	29 (61.7%)	120 (63.5%)	0.93 (0.48–1.79)
Antithrombotic drugs (no = 0, yes = 1)	16 (34.0)	71 (37.5)	0.86 (0.44–1.68)
Aspirin (no = 0, yes = 1)	10 (21.3)	49 (25.9)	0.77 (0.36–1.67)
Anti-ulcer drugs (no = 0, yes = 1)	18 (38.2)	45 (23.8)	0.67 (0.35–1.29)

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medi cations should be carefully determined by considering the risk/benefit balance of each patient.

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Pituitary insufficiency: A cause of hypoglycemia in an elderly diabetic patient

Dear Editor,

Hypoglycemia most likely occurs in the elderly as a result of poor glucose tolerance. The most common cause of hypoglycemia in elderly patients is antidiabetic drugs. Adrenal insufficiency, insulinoma and pituitary insufficiency are rare causes of hypoglycemia in older age.[1] Particularly in old patients, non-specific findings, such as weakness, fatigue and loss of appetite caused by pituitary insufficiency, might be attributed to aging.[2] Here, we reported an elderly patient with diabetes mellitus and hypopituitarism, presenting with refractory hypoglycemia and acute renal failure under therapy with oral antidiabetic drugs.

A 67-year-old woman was referred to geriatric clinic with symptoms of confusion, irritability, slowness of speech and movements, loss of appetite, nausea, and vomiting. A physical examination of her vital signs showed blood pressure 80/50 mmHg, pulse rate 104/min, body temperature 37.7°C and respiration 24/min. The patient was lethargic with incomplete cooperation (Karnofsky performance score of 30%). She had been taking metformin 2000 mg/day and gliclazide 30 mg/day with the diagnosis of diabetes for 2 years. In the biochemical examination, blood glucose, blood urea-nitrogen, creatinine, sodium and potassium were 32 mg/dL, 60 mg/dL, 3.2 mg/dL, 132 mmol/L and 4.9 mmol/L, respectively. After she was admitted to the geriatric clinic, her glucose infusion was given. Our initial evaluation of the clinical and laboratory parameters suggested that it could be acute renal failure as a result of dehydration and hypoglycaemia, which were the consequence of the prolonged effect of gliclazide. For this reason, oral antidiabetic drugs were discontinued, and glucose infusion was carried out. During her clinical follow up, we realized that her kidney functions had substantially increased. However, hypoglycemia persisted. Afterwards, all of the persistent hypoglycemia, hyponatremia and hypotension were evaluated, and the results were considered to be hypocortisolemia. The patient's other laboratory results, which were obtained during a hypoglycemia period, are presented in the Table 1. The basal serum cortisol (1.38 μg/dL) and adrenocorticototropic hormone levels (less than 0.3 U/L) showed strong evidence of cortisol deficiency. Due to these results, pituitary insufficiency was diagnosed. However, magnetic resonance imaging and magnetic resonance angiography did not show any structural or vascular abnormalities in the hypophysis and brain. Once prednisolone (7.5 mg/day) treatment

Table 1 Endocrinological laboratory results

Parameters		Normal range
Blood cortisol	1.38 ug/dL	6.2–19.4 ug/dL
TSH	0.055 uIU/mL	0.4–4.2 uIU/mL
Free T4	13.24 pmol/L	10.3–23.2 pmol/L
IGF-1	1.00 mg/L	1.73–5.11 mg/L
GH	<3 μg/L	
PRL	0.57 ng/mL	3–20 ng/mL
FSH	2.02 mIU/mL	25.8–134.8 mIU/mL
LH	1.36 mIU/mL	7.7–58.5 mIU/mL
Estradiol	27.96 pg/mL	5–54.7 pg/mL
C peptide	1.02 ng/mL	0.9–7.1 ng/mL
Insuline	2.83 μU/mL	3–28 μU/mL

All the laboratory results were measured between 08.00 hours and 09.00 hours, and confirmed by a second determination.
FSH, follicule stimulating hormone; GH, growth hormone; IGF1, insulin-like growth factor-1; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone; T4, thyroxine.

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マンスリーレクチャー

Geriatrics
老年内科
標榜をめざして

東京大学医学部附属病院老年病科
特任准教授
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第19回 高齢者高血圧の管理

はじめに

高齢者，特に後期高齢者にとって，心筋梗塞や脳梗塞などの循環器疾患は最も重要な死因である．特に脳卒中は重篤な後遺症を引き起こして患者の日常生活動作（ADL）を悪化させ，家族の介護負担を増大させる．そして，これらの疾患における最も重要な危険因子は高血圧である．

本稿では，高齢者における高血圧の管理に関して，注意すべき点について概説する．

疫　学

収縮期血圧値は加齢とともに上昇する．そのため高血圧の有病率も加齢とともに上昇し，日本では高齢者の約60％が高血圧症に罹患していると推測されている．高齢者においても一般成人と同様に，高血圧は心血管疾患の発症リスクを高めることが知られている．実際に大規模な疫学調査によれば，血圧上昇による冠動脈疾患や脳卒中の発症リスクの増大は，高齢になるほどその傾きが緩くなるものの，各年代において認められることが報告されている[1]．

日本における代表的な疫学研究である久山町研究においても，心血管疾患の発症リスクは，70歳台までは収縮期血圧140mmHg以上の場合に有意に上昇することが報告されている．しかしながら，興味深いことに80歳以上では，有意なリスクの上昇は収縮期血圧180mmHg以上から認められている[2]．

したがって，日本高血圧学会の「高血圧治療ガイドライン2009」では，高血圧の診断基準として高齢者においても一般成人と同様に140／90mmHg以上と設定しているが，この数字がただちに治療，特に薬物治療の対象血圧値となるわけではない．

高齢者高血圧の特徴

(1) 孤立性収縮期高血圧

加齢に伴い収縮期血圧値は上昇するが，拡張期血圧値は中年以降むしろ低下し，結果として脈圧が増大する．したがって，高齢者においては収縮期血圧値のみが高くなる（孤立性）収縮期高血圧を呈する場合が多くなる．

収縮期血圧値の上昇や脈圧の増大は，虚血性心疾患や脳卒中のみならず，心不全，心房

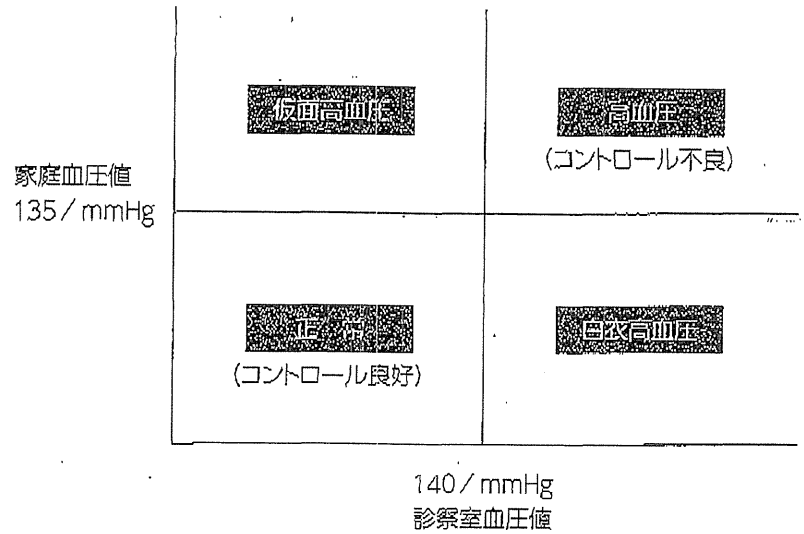

図1　仮面高血圧と白衣高血圧

細動など，高齢者において代表的に認められる心血管疾患の発症リスクを高めることが知られている．この脈圧の増大は，大動脈壁の伸展性の低下(stiffnessの増加)に伴うwindkessel (ふいご) 機能の低下によるものと考えられている．

(2) 血圧の動揺性

血圧の動揺性も高齢者高血圧の特徴である．高齢者では，頸動脈や大動脈弓に存在する圧受容器を介する血圧調節機能が低下しているため，血圧が変動しやすい．そのため診断に際しては，家庭用自動血圧測定器などを利用して，日や時間を変えて繰り返し血圧を測定する必要がある．

また，起立性低血圧や食後低血圧も高率に認められる．白衣高血圧，仮面高血圧，早朝高血圧などにも注意が必要である (図1)．

高齢者高血圧に対する大規模臨床試験

60歳以上の高齢者高血圧に対する降圧薬治療の効果に関する9つの主要な試験のメタ解析によると，降圧薬治療により全死亡が12%，脳卒中による死亡が36%，冠動脈疾患による死亡が25%減少と，いずれも有意な発症抑制効果が認められている[3]．

しかしながら，これらの試験の多くは主に前期高齢者を対象としたものであること，また収縮期血圧160mmHg以上の者を対象としていること，降圧薬による治療後の収縮期血圧値は140～150mmHg程度であることなどから，後期高齢者あるいは超高齢者の高血圧ではどうなのか，140～159mmHg程度の比較的軽症の高血圧ではどうなのか，どこまで降圧すればよいのか (降圧目標値)，J型現象は存在するのか，などについては十分な検討がなされているとは言えない状況であった．

実際に，降圧目標値に関してはJ型カーブの存在を示唆するような結果も報告されている．例えばSHEP (Systolic Hypertension in the Elderly Program)試験では，150mmHg未満の群で最も脳卒中発症抑制効果が強く，一方で，140mmHg未満の群では有意な抑制効果が認められなかった[4]．

最近，80歳以上の高血圧患者を対象としたHYVET (Hypertension in the Very Elderly trial) 試験の結果が発表された[5]．3845