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Effects of polypharmacy on the prevalence of adverse drug events resulting in outpatient visits and hospitalization

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A high proportion of hospitalizations is attributable to the prevalence of adverse drug events. This retrospective study included outpatients and inpatients to determine the prevalence of adverse drug events and if polypharmacy increases it. The prevalence, classification, and causality of adverse drug events were assessed based on medical records, laboratory values, and other data. Multivariate analysis (multiple logistic regression analysis) was performed with the presence or absence of adverse drug events at the time of the visit as the dependent variable and items for which the *P*-value was <0.25 in the univariate analysis as independent variables. The prevalence of adverse drug events was 13.0%, 10.9%, and 16.0% among all patients, the outpatient group, and the inpatient group, respectively. Multivariate analysis showed that polypharmacy (≥5 drugs) significantly increased the risk of adverse drug events in all patients. The prevalence of adverse drug events significantly increased with each additional drug used. We expect that minimizing the number of medications through moderation of the number of prescription drugs and elimination of polypharmacy will reduce the number of outpatient visits and hospitalizations due to adverse drug events.

1. Introduction

A high proportion of hospital consultations is attributable to the prevalence of adverse drug events (ADEs). The rate of outpatient visits and hospitalizations due to ADEs has been reported to vary from 5.5% to 35.0% (Gandhi et al. 2003; Hanlon et al. 1997; Honigman et al. 2001) and 1.3% to 30.4% (Chan et al. 2001; Dartnell et al. 1996; Onder et al. 2002; Parameswaran Nair et al. 2017; Ruiter et al. 2012; Senst et al. 2001; Wawruch et al. 2009), respectively. In Japan, the corresponding rate was reported to be 1.7% (Koinuma et al. 2006). However, the percentage of outpatient visits due to ADEs has not been reported.

Several previous studies have reported the risk factors of ADEs in older outpatients, with polypharmacy suggested to be one of the risk factors (Gandhi et al. 2003; Hajjar et al. 2003). In geriatric wards, the incidence of ADEs was higher in patients who received six or more medications and the frequency of falls was higher in patients who received five or more medications (Kojima et al. 2012a, b). However, there are no reports specific to Japan that show polypharmacy to increase the risk of outpatient visits due to ADEs. Moreover, the scope of a report showing polypharmacy increases hospitalization risk due to ADEs was limited to university hospitals for tertiary care (Angamo et al. 2017).

To develop strategies to reduce the prevalence of ADEs, it would be very useful to investigate ADE prevalence and elucidate the influencing risk factors. Therefore, this retrospective study was aimed at determining ADE prevalence and clarifying whether polypharmacy increases it among patients aged 15 years and higher with outpatient visits and who underwent hospitalization.

Table 1: Background characteristics of the patients studied

	Overall (n = 5,174)	Outpatient group (n = 3,026)	Inpatient group (n = 2,148)
Sex [n (%)]			
Male	2,450 (47.4)	1,324 (43.8)	1,126 (52.4)
Female	2,724 (52.6)	1,702 (56.2)	1,022 (47.6)
Age (mean ± standard deviation)	63.2 ± 20.4	58.9 ± 21.2	69.2 ± 17.6
Number of drug used (mean ± standard deviation)	5.9 ± 4.4	5.4 ± 4.4	6.7 ± 4.3
Length of hospitalization (days, mean ± standard deviation)	–	–	21.3 ± 34.6
Disease [n (%)]			
Certain infectious and parasitic diseases	1,123 (21.7)	808 (26.7)	315 (14.7)
Neoplasms	1,039(20.1)	565 (18.7)	474 (22.1)

	Overall (n = 5,174)	Outpatient group (n = 3,026)	Inpatient group (n = 2,148)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1,091(21.1)	823(27.2)	268 (12.5)
Endcrine, nutritional and metabolic diseases	2,539 (49.1)	1,660 (54.9)	879 (40.9)
Mental and behavioural disorders	1,225 (23.7)	1,029 (34.0)	196 (9.1)
Diseases of the nervous system	1,601 (30.9)	1,339 (44.2)	262 (12.2)
Diseases of the eye and adnexa	1,200 (23.2)	977 (32.3)	223 (10.4)
Diseases of the ear and mastoid process	468 (9.0)	414 (13.7)	54 (2.5)
Diseases of the circulatory system	3,048 (58.9)	1,736 (57.4)	1,312 (61.1)
Diseases of the respiratory system	2,344 (45.3)	1,706 (56.4)	638 (29.7)
Diseases of the digestive system	3,294 (63.7)	2,256 (74.6)	1,038 (48.3)
Diseases of the skin and subcutaneous tissue	1,347(26.0)	1,174 (38.8)	173 (8.1)
Diseases of the musculoskeletal system and connective tissue	1,679 (32.5)	1,328 (43.9)	351 (16.3)
Diseases of the genitourinary system	1,878 (36.3)	1,334 (44.1)	544 (25.3)
Pregnancy, childbirth and the puerperium	98 (1.9)	56 (1.9)	42 (2.0)
Certain conditions originating in the perinatal period	22 (0.4)	22 (0.7)	0 (0.0)
Congenital malformations, deformations and chromosomal abnormalities	6 (0.1)	5 (0.2)	1 (0.0)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1,519 (29.4)	1,445 (47.8)	74 (3.4)
Injury, poisoning and certain other consequences of external causes	624 (12.1)	408 (13.5)	216 (10.1)

2. Investigations and results

2.1. Patient background

Patient background characteristics are shown in Table 1. In all, 5,174 patients were surveyed, of whom 47.4% were male. The mean patient age and number of drugs used were 63.2±20.4 years and 5.9±4.4, respectively. The most common (63.7%) diseases were digestive system disorders.

2.2. Adverse drug events

Of the patients surveyed, 13.0% (674/5,174) were investigated because of ADEs. There were 1,011 ADEs that resulted in outpatient visits. Most ADEs were classified as "possible" (75.6%), followed by "probable/likely" (21.7%) and "certain" (2.8%) causes (Table 2A). The numbers of gastrointestinal disorders, investigations, and nervous system disorders were high (42.6%,

Table 2: Adverse drug events

A. Assessment of the causality of adverse drug events [n (%)]	Overall (n = 1,011)	Outpatient group (n = 461)	Inpatient group (n = 550)
Certain	28 (2.8)	11 (2.4)	17 (3.1)
Probable/ likely	219 (21.7)	43 (9.3)	176 (32.0)
Possible	764 (75.6)	407 (88.2)	357 (64.9)
B. Classification of adverse drug events [n (%)]			
Gastrointestinal disorders	247 (42.6)	129 (27.9)	118 (21.5)
Investigations	139 (13.7)	28 (6.1)	111 (20.2)
Nervous system disorders	127 (12.6)	89 (19.3)	38 (6.9)
Metabolism and nutrition disorders	101 (10.0)	36 (7.8)	65 (11.8)
General disorders and administration site conditions	80 (7.9)	45 (9.8)	35 (4.5)
Injury, poisoning and procedural complications	72 (7.1)	34 (7.4)	38 (6.9)
Infections and infestations	31 (3.1)	0 (0.0)	31 (5.6)
Blood and lymphatic system disorders	30 (3.0)	4 (0.9)	26 (4.7)
Skin and subcutaneous tissue disorders	26 (2.6)	18 (3.9)	8 (1.5)
Respiratory, Thoracic and mediastinal disorders	26 (2.6)	9 (2.0)	17 (3.1)
Renal and urinary disorders	26 (2.6)	0 (0.0)	26 (4.7)
Immune system disorders	25 (2.5)	20 (4.3)	5 (0.9)
Cardiac disorders	25 (2.5)	11 (2.4)	14 (2.5)
Vascular disorders	22 (2.2)	16 (3.5)	6 (1.1)
Psychiatric disorders	13 (1.3)	4 (0.9)	9 (1.6)

	Overall (n = 1,011)	Outpatient group (n = 461)	Inpatient group (n = 550)
Ear and labyrinth disorders	10 (1.0)	10 (2.2)	0 (0.0)
Reproductive system and breast disorders	6 (0.6)	5 (1.1)	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (0.3)	2 (0.4)	1 (0.2)
Eye disorders	1 (0.1)	1 (0.2)	0 (0.0)
Hepatobiliary disorders	1 (0.1)	0 (0.0)	1 (0.2)
C. Severity of adverse drug events* [n (%)]			
Grade 1	210 (20.8)	148 (32.1)	62 (11.3)
Grade 2	397 (39.3)	263 (57.0)	134 (24.4)
Grade 3	291 (28.8)	39 (8.5)	252 (45.8)
Grade 4	110 (10.9)	11 (2.4)	99 (18.0)
Grade 5	3 (0.3)	0 (0.0)	3 (0.5)

Each adverse drug event was counted, even when there was more than one adverse drug event per patient.
*Grade refers to the severity of the adverse drug events according to Common Terminology Criteria for Adverse Events v5.0. Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to adverse drug reactions.

13.7%, and 12.6%, respectively; Table 2B). The rates of Grade 1, 2, 3, 4, and 5 ADEs were 20.8%, 39.3%, 28.8%, 10.9%, and 0.3%, respectively (Table 2C).

2.3. Univariate analysis

The *P*-values were <0.25 for 13 diseases as well as for age (≥65 years) and polypharmacy (≥5 drugs) (Table 3).

2.4. Multivariate analysis

Figure 1 shows the results of the multivariate analysis using 13 diseases as well as age (65 years or higher) and polypharmacy (≥5 drugs), the *P*-values for all of which were <0.25 in the univariate analysis, as independent variables. ADE prevalence associated with three items including polypharmacy (≥5 drugs) (odds ratio [OR], 2.77; 95% confidence interval [CI], 2.25–3.40; $P < 0.001$)

Table 3: Univariate analysis in all patients

	Adverse drug event		*P*
	Present (n = 674)	Absent (n = 4,500)	
	n (%)	n (%)	
Background of the patients			
Sex (male)	322 (47.8)	2,128 (47.3)	0.836
Age (≥65)	463 (68.7)	2,548 (56.6)	<0.001*
Polypharmacy (≥5)	520 (77.2)	2,290 (50.9)	<0.001*
Disease [n (%)]			
Certain infectious and parasitic diseases	166 (24.6)	957 (21.3)	0.051*
Neoplasms	207 (30.7)	832 (18.5)	<0.001*
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	194 (28.8)	897 (19.9)	<0.001*
Endocrine, nutritional and metabolic diseases	404 (59.9)	2,135 (47.4)	<0.001*
Mental and behavioural disorders	172 (25.5)	1,053 (23.4)	0.225*
Diseases of the nervous system	231 (34.3)	1,370 (30.4)	0.049*
Diseases of the eye and adnexa	189 (28.0)	1,011 (22.5)	0.002*
Diseases of the ear and mastoid process	60 (8.9)	408 (9.1)	0.943
Diseases of the circulatory system	473 (70.2)	2,575 (57.2)	<0.001*
Diseases of the respiratory system	291 (43.2)	2,053 (45.6)	0.245*
Diseases of the digestive system	479 (71.1)	2,815 (62.6)	<0.001*
Diseases of the skin and subcutaneous tissue	180 (26.7)	1,167 (25.9)	0.672
Diseases of the musculoskeletal system and connective tissue	244 (36.2)	1,435 (31.9)	0.027*
Diseases of the genitourinary system	278 (41.2)	1,600 (35.6)	0.005*
Pregnancy, childbirth and the puerperium	3 (0.4)	95 (2.1)	0.001*

	Adverse drug event		*P*
	Present (n = 674)	Absent (n = 4,500)	
	n (%)	n (%)	
Certain conditions originating in the perinatal period	1 (0.1)	21 (0.5)	0.348
Congenital malformations, deformations and chromosomal abnormalities	1 (0.1)	5 (0.1)	0.567
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	203 (30.1)	1,316 (29.2)	0.650
Injury, poisoning and certain other consequences of external causes	90 (13.4)	534 (11.9)	0.281

*, $P<0.05$

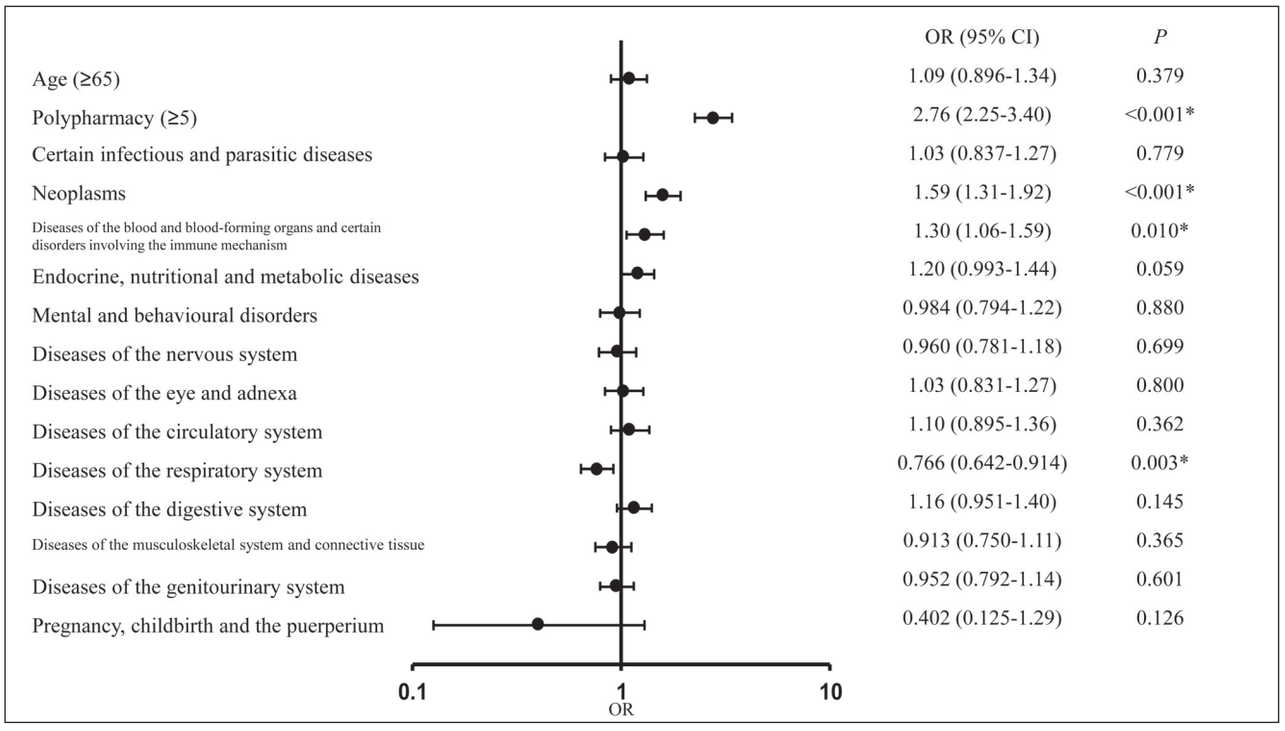

Fig. 1: Multivariate analysis in all patients
*, $P<0.05$; OR,odds ratio; CI, confidence interval

and "neoplasm" (OR, 1.59; 95% CI, 1.31–1.92; $P < 0.001$), was significantly higher than that associated with the remaining items. Furthermore, the ADE rate was significantly lower for "diseases of the respiratory system" (OR, 0.766; 95% CI, 0.642–0.914; $P = 0.003$) than those for the remaining items.
Each additional drug was associated with a 1.12-fold (95% CI, 1.09–1.14; $P < 0.001$) increase in the prevalence of ADEs as the results of the multivariate analysis with the number of drug used instead of polypharmacy (≥5 drugs).

2.5. Stratification analysis

2.5.1. Outpatient group

2.5.1.1. Patient background

The number of patients surveyed in the outpatient group was 3,026, of whom 43.8% were male. The mean age and number of drugs used in the group were 58.9 ± 21.2 years and 5.4 ± 4.4, respectively. "Diseases of the digestive system" were the most common (74.6%) in this group.

2.5.1.2. Adverse drug events

Of the outpatients surveyed, 10.9% (331/3,026) were investigated because of ADEs. The number of ADEs that resulted in outpatient visits were 461. Most ADEs were classified as "possible" (88.2%), followed by "probable/likely" (9.3%) and "certain" (2.4%) causes (Table 2A). The most common conditions were gastrointestinal disorders (27.9%), nervous system disorders (19.3%), and general disorders and administration-site conditions (9.8%) (Table 2B). The rates of ADEs of Grade 1, 2, 3, 4, and 5 were 32.1%, 57.0%, 8.5%, 2.4%, and 0.0%, respectively (Table 2C).

2.5.1.3. Univariate analysis

The *P*-values were <0.25 for 14 diseases as well as for age (≥65 years) and polypharmacy (≥5 drugs) (Table 4).

2.5.1.4. Multivariate analysis

Figure 2 shows the results of multivariate analysis using 14 diseases as well as age (65 years or higher) and polypharmacy (≥5 drugs) ($P < 0.25$ in the univariate analysis) as the independent variables and the presence of ADEs at the time of examination as the dependent variable. The ADE prevalence associated with two categories was significantly higher than that for the remaining categories: polypharmacy (≥5 drugs; OR, 2.73; 95% CI, 2.04–3.67; $P < 0.001$) and "Neoplasms" (OR, 1.38; 95% CI, 1.03–1.85; $P = 0.029$). In addition, the ADE rate associated with "Diseases of the muscu-

Table 4: Univariate analysis in the outpatient group

	Adverse drug event		*P*
	Present (n = 331)	Absent (n = 2,695)	
	n (%)	n (%)	
Background of the patients			
Sex (male)	140 (42.3)	1,184 (43.9)	0.597
Age (≥65)	191 (57.7)	1,284 (47.6)	0.001*
Polypharmacy (≥5)	234 (70.7)	1,207 (44.8)	<0.001*
Disease [n (%)]			
Certain infectious and parasitic diseases	102 (30.8)	706 (26.2)	0.076*
Neoplasms	88 (26.6)	477 (17.7)	<0.001*
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	105 (31.7)	718 (26.6)	0.057*
Endcrine, nutritional and metabolic diseases	218 (65.9)	1,442 (53.5)	<0.001*
Mental and behavioural disorders	133 (40.2)	896 (33.2)	0.014*
Diseases of the nervous system	184 (55.6)	1,155 (42.9)	<0.001*
Diseases of the eye and adnexa	131 (39.6)	846 (31.4)	0.003*
Diseases of the ear and mastoid process	53 (16.0)	361 (13.4)	0.203*
Diseases of the circulatory system	224 (67.7)	1,512 (56.1)	<0.001*
Diseases of the respiratory system	184 (55.6)	1,522 (56.5)	0.769
Diseases of the digestive system	273 (82.5)	1,983 (73.6)	<0.001*
Diseases of the skin and subcutaneous tissue	154 (46.5)	1,020 (37.8)	0.003*
Diseases of the musculoskeletal system and connective tissue	156 (47.1)	1,172 (43.5)	0.218*
Diseases of the genitourinary system	156 (47.1)	1,178 (43.7)	0.241*
Pregnancy, childbirth and the puerperium	3 (0.9)	53 (2.0)	0.275
Certain conditions originating in the perinatal period	1 (0.3)	21 (0.8)	0.503
Congenital malformations, deformations and chromosomal abnormalities	1 (0.3)	4 (0.1)	0.440
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	184 (55.6)	1,261 (46.8)	0.003*
Injury, poisoning and certain other consequences of external causes	46 (13.9)	362 (13.4)	0.798

*, $P<0.05$

loskeletal system and connective tissue" was significantly lower (OR, 0.734; 95% CI, 0.559–0.964; $P = 0.026$).
Each additional drug was associated with a 1.09-fold (95% CI, 1.06–1.13; $P < 0.001$) increase in the prevalence of ADEs as the results of the multivariate analysis with the number of drug used instead of polypharmacy (≥5 drugs).

2.5.2. Inpatient group

2.5.2.1. Patient background

The number of patients surveyed in the inpatient group was 2,148; 52.4% of the participants were male. The mean age and number of drugs used were 69.2±17.6 years and 6.7±4.3, respectively; the median length of stay was 11 days (range: 1–1048 days). The most common diseases (61.1%) were "diseases of the circulatory system."

2.5.2.2. Adverse drug events

Of the patients surveyed, 16.0% (343/2,148) were hospitalized due to an ADE. The number of ADEs resulting in hospitalizations was 550. Most ADEs were classified as "possible" (64.9%), followed by "probable/likely" (32.0%) and "certain" (3.1%) causes (Table 2A). The numbers of gastrointestinal disorders, investigations, and metabolism and nutrition disorders were high (21.5%, 20.2%, and 11.8%, respectively; Table 2B). The rates of ADEs of Grade 1, 2, 3, 4, and 5 were 11.3%, 24.4%, 45.8%, 18.0%, and 0.5%, respectively (Table 2C).

2.5.2.3. Univariate analysis

The *P*-values for 12 diseases as well as age (≥65 years) and polypharmacy (≥5 drugs) were <0.25. "Pregnancy, childbirth and the puerperium," "Certain conditions originating in the perinatal period," and "Congenital malformations, deformations and chromosomal abnormalities" were not analyzed because the number of patients was too small.

2.5.2.4. Multivariate analysis

Figure 3 shows the results of the multivariate analysis using 12 diseases as well as age (≥65 years), polypharmacy (≥5 drugs), all of which had a $P < 0.25$ in the univariate analysis, as independent variables. There was a significant increase in the ADE prevalence associated with 13 items, including polypharmacy (≥5 drugs) (OR, 2.00; 95% CI, 1.44–2.76; $P < 0.001$) and "Certain infectious and parasitic diseases" (OR, 1.42; 95% CI, 1.01–1.98; $P = 0.043$). Each additional drug was associated with a 1.10-fold (95% CI, 1.06–1.13; $P < 0.001$) increase in ADE prevalence as the results of the multivariate analysis with the number of drug used instead of polypharmacy (≥5 drugs).

3. Discussion

In this study, we retrospectively analyzed patients with outpatient visits who underwent hospitalization to determine ADE prevalence and whether it was increased because of polypharmacy. The overall ADE prevalence was 13.0%: 10.9% and 16.0% in the outpatient and inpatient groups, respectively. A meta-analysis of 17 studies in

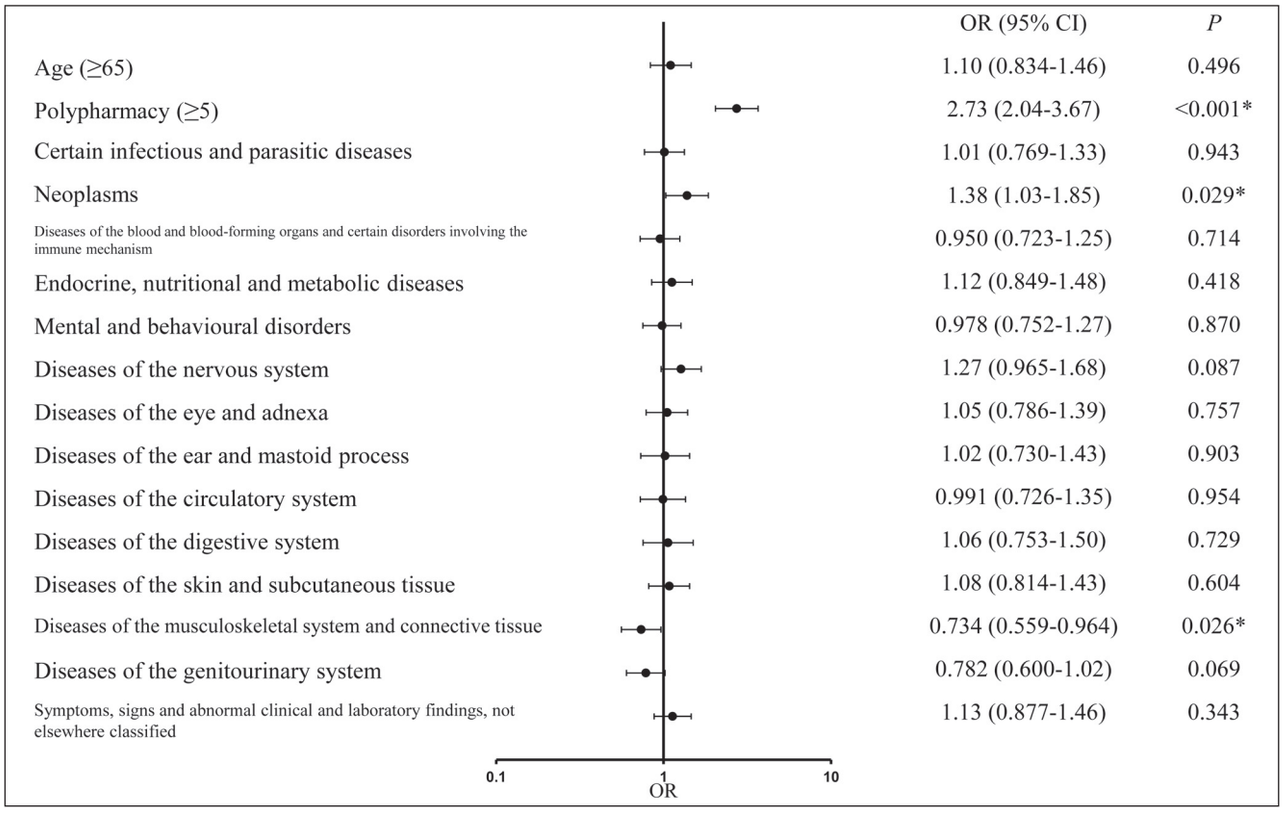

Fig. 2: Multivariate analysis in the outpatient group
*, $P<0.05$; OR; odds ratio; CI, confidence interval

older adults reported 16.6% of the patients were hospitalized due to ADEs (Beijer and de Blaey 2002). This finding was similar to that in this study, although the meta-analysis only included older adults and did not include ADEs due to anticancer drugs.

Overall, the most frequent ADEs in this study were gastrointestinal disorders, including nausea, constipation, and diarrhea. For drugs that can cause ADEs such as gastrointestinal disorders, the possibility of ADEs should be mentioned in advance at the time of medication administration, and measures for ADE prevention and symptom alleviation should be taught.

Regarding the severity of the ADEs that resulted in outpatient visits and hospitalizations, 40.0%, 10.8%, and 64.4% of all patients, the outpatient group, and the inpatient group, respectively, experienced a serious ADE of grade 3 or higher. The rate of serious ADEs was higher the inpatient group (64.4%) than in the outpatient group (10.8%). Gandhi et al. (2003) reported that serious ADEs accounted for 13% of all ADEs resulting in outpatient visits. The rate of serious ADEs in the above-mentioned study was similar to that in the present study. Further, Onder et al. (2002) reported the percentage of ADEs resulting in hospitalization was 19.4% of serious ADEs. The rate of serious ADEs in the above-mentioned study was lower than that in the present study, which is attributable to the different indicators used to assess ADE severity.

Multivariate analysis showed polypharmacy (≥5 drugs) significantly increased the risk of outpatient visits and hospitalization due to ADEs in all patients and outpatient and inpatient groups. Polypharmacy increased ADE prevalence in hospitalized patients in the previous reports (Angamo et al. 2017; Chan et al. 2001; Kojima et al. 2012a, b; Onder et al. 2002; Wawruch et al. 2009). Furthermore, polypharmacy (≥6 drugs) was reported to increase the risk of hospitalization due to ADEs (Angamo et al. 2017).

The results of this study indicated that polypharmacy increases the outpatient visit and hospitalization risks in both inpatients and outpatients. In this study, the ADE prevalence was significantly higher with each additional drug used (1.12-, 1.09-, and 1.10-fold in all patients, the outpatient group, and the inpatient group, respectively). Gandhi et al. (2003) reported a 10% increase in ADE prevalence when the number of drugs increased by one drug. The results of the aforementioned study were mostly in agreement with those of the present study. Those results suggested that reducing the number of medications through interventions such as moderation of prescription drugs may reduce ADE prevalence.

In all patients, neoplasms, diseases of the blood and blood-forming organs, and immune system disorders were suggested to be risk factors for hospital consultations due to ADEs. In the outpatient group, neoplasms were suggested to be a risk factor of outpatient visits due to ADEs. In the inpatient group, 12 diseases were suggested to be risk factors of hospitalization due to ADEs. Diseases that increase the hospitalization risk due to ADEs include renal dysfunction, hepatic dysfunction, and dementia (Angamo et al. 2017; Parameswaran Nair et al. 2017; Wawruch et al. 2009). In this study, "neoplasm" was identified as a risk factor in all patients and the outpatient and inpatient groups. A "neoplasm" can greatly compromise health. Furthermore, drugs for treating "neoplasms" are generally associated with a high ADE prevalence. For patients with "neoplasms," greater attention to signs of ADEs may help prevent outpatient visits and hospitalizations due to ADEs.

This study investigated ADE prevalence in patients with outpatient visits and who underwent hospitalization. Polypharmacy (≥5 drugs) was identified as a factor that significantly increased ADE prevalence. We also found that the ADE prevalence increased 1.10-fold with the addition of each drug. In this study, we found that the risk of ADEs increased as the number of drugs received increased. We believe that the risk of ADEs can be reduced by minimizing the number of drugs received through interventions such as prescription drug moderation.

The limitations of this study include its retrospective nature and that it was conducted at a single institution. Therefore, future multicenter prospective studies should be conducted to obtain further evidence.

Table 5: Univariate analysis in the inpatient group

	Adverse drug event		*P*
	Present (n = 343)	Absent (n = 1,805)	
	n (%)	n (%)	
Background of the patients			
Sex (male)	182 (53.1)	944 (52.3)	0.814
Age (≥65)	272 (79.3)	1,264 (70.0)	<0.001*
Polypharmacy (≥5)	286 (83.4)	1,083 (60.0)	<0.001*
Disease [n (%)]			
Certain infectious and parasitic diseases	64 (18.7)	251 (13.9)	0.025*
Neoplasms	119 (34.7)	355 (19.7)	<0.001*
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	89 (25.9)	179 (9.9)	<0.001*
Endcrine, nutritional and metabolic diseases	186 (54.2)	693 (38.4)	<0.001*
Mental and behavioural disorders	39 (11.4)	157 (8.7)	0.125*
Diseases of the nervous system	47 (13.7)	215 (11.9)	0.368
Diseases of the eye and adnexa	58 (16.9)	165 (9.1)	<0.001*
Diseases of the ear and mastoid process	7 (2.0)	47 (2.6)	0.706
Diseases of the circulatory system	249 (72.6)	1,063 (58.9)	<0.001*
Diseases of the respiratory system	107 (31.2)	531 (29.4)	0.519
Diseases of the digestive system	206 (60.1)	832 (46.1)	<0.001*
Diseases of the skin and subcutaneous tissue	26 (7.6)	147 (8.1)	0.829
Diseases of the musculoskeletal system and connective tissue	88 (25.7)	263 (14.6)	<0.001*
Diseases of the genitourinary system	122 (35.6)	422 (23.4)	<0.001*
Pregnancy, childbirth and the puerperium	0 (0.0)	42 (2.3)	-
Certain conditions originating in the perinatal period	0 (0.0)	0 (0.0)	-
Congenital malformations, deformations and chromosomal abnormalities	0 (0.0)	1 (0.1)	-
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	19 (5.5)	55 (3.0)	0.034*
Injury, poisoning and certain other consequences of external causes	44 (12.8)	172 (9.5)	0.077*

*, $P<0.05$

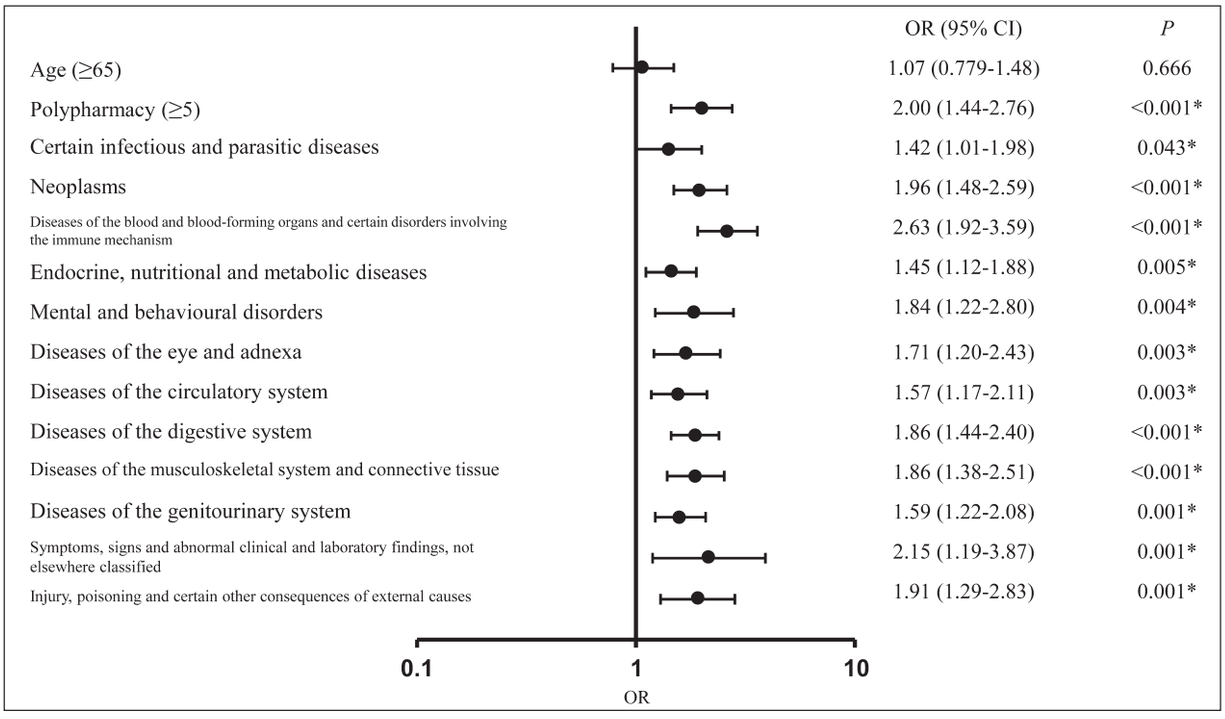

Fig. 3: Multivariate analysis in the inpatient group
*, $P<0.05$; OR; odds ratio; CI, confidence interval

This study revealed that polypharmacy is a risk factor of outpatient visits and hospitalization due to ADEs. It is hoped that minimizing the number of medications received through interventions such as the optimization of prescription drugs and elimination of polypharmacy will reduce the number of outpatient visits and hospitalizations due to ADEs.

4. Experimental

4.1. Eligible patients

Patients who met all of the following criteria were eligible for inclusion: patients aged 15 years or higher who were outpatients and underwent hospitalization without reservation at Gifu Municipal Hospital (Japan) between July 1, 2015, and December 31, 2015, patients who received one or more medications at the time of the outpatient visit or hospitalization, and patients who were not using investigational new drugs.

4.2. Survey details

The survey was conducted retrospectively using electronic medical records. The survey items included sex, age, medications used at the time of outpatient visits and hospitalization, and length of inpatient stay; disease; presence and severity of ADEs; laboratory values; and records of physicians, pharmacists, and nurses. Diseases were classified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (WHO 2016).

4.3. Evaluation method for adverse drug events

The outcome was ADE prevalence. ADEs were extracted by referring to the Global Trigger Tool (Institute for Healthcare Improvement 2003). The classification and severity of adverse drug events were evaluated based on the data retrieved from the medical records and clinical laboratory values. The Common Terminology Criteria for Adverse Events version 5.0, based on Medical Dictionary for Regulatory Activities Japanese Version (MedDRA/J) (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use 2020), was used to evaluate the ADE classification and severity. ADE causality was categorized using the Causality Assessment System published by the Uppsala Monitoring Centre (WHO-UMC 2012) into three levels: "certain," "probable/likely," and "possible." Two pharmacists with at least ten years of clinical experience, and when necessary, a physician extracted the details of ADEs and assessed their severity classification and causality and suspected drugs.

4.4. Statistical analysis

Patients were divided into two categories depending on their age: those aged lower than 65 years and those aged 65 years and higher. Polypharmacy was defined as the concurrent use of five or more drugs (Gnjidic et al. 2012) and categorized as the use of less than five drugs and use of five or more drugs.
Univariate analysis (Fisher's exact test) was performed to examine differences in the proportion of patients seen because of ADEs, stratified by sex, age, polypharmacy, and disease status. Multivariate analysis (multiple logistic regression analysis) was performed considering the presence or absence of ADEs at the time of the outpatient visit and hospitalization as the dependent variable and items with a P-value of <0.25 in the univariate analysis as the independent variable. The multivariate analysis was also performed with the number of drug used instead of polypharmacy (≥5 drugs). Univariate and multivariate analyses were also performed for the outpatient group and the inpatient group (hospitalized patients). Statistical analyses were performed using IBM SPSS statistics 24.0J software (Armonk, New York).

4.5. Ethical considerations

This study was approved by the ethics committees of Gifu Municipal Hospital (approval number: 349) and Gifu Pharmaceutical University (approval number: 28-8).

Conflict of interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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