



Categorisation of Pharmaceutical Adverse Events Using the Japanese Adverse Drug Event Report Database: Characteristic Adverse Drug Events of the Elderly Treated with Polypharmacy

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Abstract

Background Pharmacokinetics and pharmacodynamics of drugs in elderly individuals differ from those in younger adults; thus, adverse drug events (ADEs) are common in older patients with polypharmacy because co-existing comorbidities elevate the risk of ADEs occurring. However, ADEs have not yet been characterised based on the elderly patients of Japanese origin and polypharmacy.

Objective The 100 most commonly reported ADEs were grouped into four classes (Class 1–Class 4) based on elderly patients with polypharmacy.

Patients and Methods In this study, logistic regression analysis was performed using cases recorded in the Japanese Adverse Drug Event Report (JADER) database.

Results ADEs in elderly patients treated with polypharmacy—in whom the risk of electrolyte abnormalities, renal and respiratory disorders, and coagulopathy was high—were categorised as ‘Class 1 [E(+), P(+)]’, while ADEs in elderly patients not treated with polypharmacy—in whom the risk of delirium and fall was high—were categorised as ‘Class 2 [E(+), P(-)]’. When there was no association with being elderly, ADEs associated with polypharmacy that carried a high risk of myelosuppression and infection were categorised as ‘Class 3 [E(-), P(+)]’, and allergic ADEs that were not affected by being elderly or polypharmacy, were categorised as ‘Class 4 [E(-), P(-)]’. Class 1 events as well as Class 3 ADEs occurred more frequently in females than in males, whereas Class 3 ADEs (deep vein thrombosis and pulmonary embolism) occurred more frequently in males.

Conclusions Class 1 and Class 2 ADEs should be investigated in analyses that focus on individual drugs.

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Key Points

Using the Japanese Adverse Drug Event Report database, adverse drug events were categorized into four classes (Class 1–Class 4) based on age (elderly— ≥ 70 years) and polypharmacy (six or more agents).

Among the adverse drug events associated with elderly patients, the risks of electrolyte abnormality, renal disorder, respiratory disorder, and coagulopathy were associated with polypharmacy (Class 1).

Among the adverse drug events associated with elderly patients, the risks of delirium and fall were not associated with polypharmacy (Class 2).

1 Introduction

As a result of changes in physiological function that occur with aging, pharmacokinetics and organic drug responses (i.e. pharmacodynamics) differ between the elderly and the non-elderly [1–5]. Because of this, the risk of adverse drug events (ADEs) is higher in the elderly than in the non-elderly [1–6]. Since co-existing comorbidities tend to increase in frequency with age, there is a tendency for polypharmacy prescribing for the elderly [2, 3, 7, 8]. Polypharmacy, the simultaneous use of multiple medications by patients, has been linked to reduced adherence to medication, prolongation of hospitalisation, readmission to hospital immediately after discharge, mortality, ADE incidence, and elevated risks of drug interaction [3, 4]. Moreover, follow-up prescriptions ('prescription cascades') of concomitant drugs for occurring ADEs also give rise to polypharmacy [4]. This type of polypharmacy treatment in the elderly, which is linked to adverse outcomes, has been reported as a global public health issue [9]. ADEs induced by polypharmacy increase dramatically in patients prescribed five to six drugs [2].

In this way, aging and polypharmacy increase the risk of ADEs. It is said that the geriatric syndromes (such as delirium, falling, dizziness, and urinary incontinence) are non-specific and do not fit into a single deficit diagnosis [10]. In other words, it can be considered that the risk of certain ADEs in elderly patients receiving polypharmacy increases not because of specific drugs but because of an increase in the number of drugs administered. Therefore, we hypothesized that the elderly may be vulnerable to certain ADEs, given that they have higher sensitivity to drugs. Thus, the identification of which ADEs are likely to be caused by aging and polypharmacy would make it easier to observe these ADEs more closely for managing drug treatment effectively in the elderly.

Focusing on cases recorded in the Japanese Adverse Drug Event Report (JADER) database from the perspectives of polypharmacy and aging, we grouped the 100 most commonly reported ADEs into four classes (Class 1–Class 4) and investigated the influence of these two factors on the risk of ADEs.

2 Methods

2.1 Database Information

The JADER was downloaded from the Pharmaceuticals and Medical Devices Agency website (<http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp>). JADER is the database of collected and published cases of ADEs that were reported by pharmaceutical companies and medical

staff, and is used for pharmacovigilance activities. All cases recorded from April 2004 to July 2018 were used. The JADER is composed of four tables: a 'demo' table, a 'drug' table, a 'reac' table, and a 'hist' table, across which each case is linked by the assignment of a common identification number. Data on patients such as age and sex are presented in the 'demo' table, data on drugs used in cases are presented in the 'drug' table, data on ADEs that have occurred in cases are presented in the 'reac' table, and primary disease data are presented in the 'hist' table. For this study, we used the 'demo', 'drug' and 'reac' tables. The 'drug involvement' from the drug table in JADER mentions 'Suspected drug', 'Co-administered drug' or 'Interactions' for each drug. However, this study did not use the 'drug involvement' information as the study did not focus on individual drugs. The study instead examined all the registered drugs. The ADEs used in this study were entered in the database using the preferred terms (PTs) from the Medical Dictionary for Regulatory Activities/J (MedDRA/J), version 21.0. All processing was performed at the PT level.

2.2 Adverse Drug Events (ADEs)

All ADEs recorded in JADER were extracted from the reac table, and the total number of reports was calculated for each. We then ranked the top 100 ADE cases according to their frequency based on the information that we referred to. This study analysed these 100 ADEs. Cases in which none of the 100 ADEs were observed were also included as a control group.

2.3 Data Cleaning

The data-cleaning procedure is shown in Fig. 1. First, cases clearly denoted by 'sex' and 'age' were extracted from the JADER demo table. Then, we used the reac table to prepare combinations of 'identification number-ADEs-date of ADEs,' applying each combination to a single case. ADEs reported with the same identification number were counted as different cases. Then, using the common identification number for each case, we extracted 'sex' and 'age' from the demo table, 'drug name (generic name),' 'date of start of use' and 'date of termination of use' from the drug table, and 'ADEs' and 'date of ADEs occurrence' from the reac table. Year, month and day were used to denote the start of drug use and the termination of drug use, and for the date of ADE occurrence. By excluding drugs that were administered before or after the ADE occurrence, the remaining drugs were considered to have been used at the time of occurrence. Drugs with no clear record of the start or termination dates

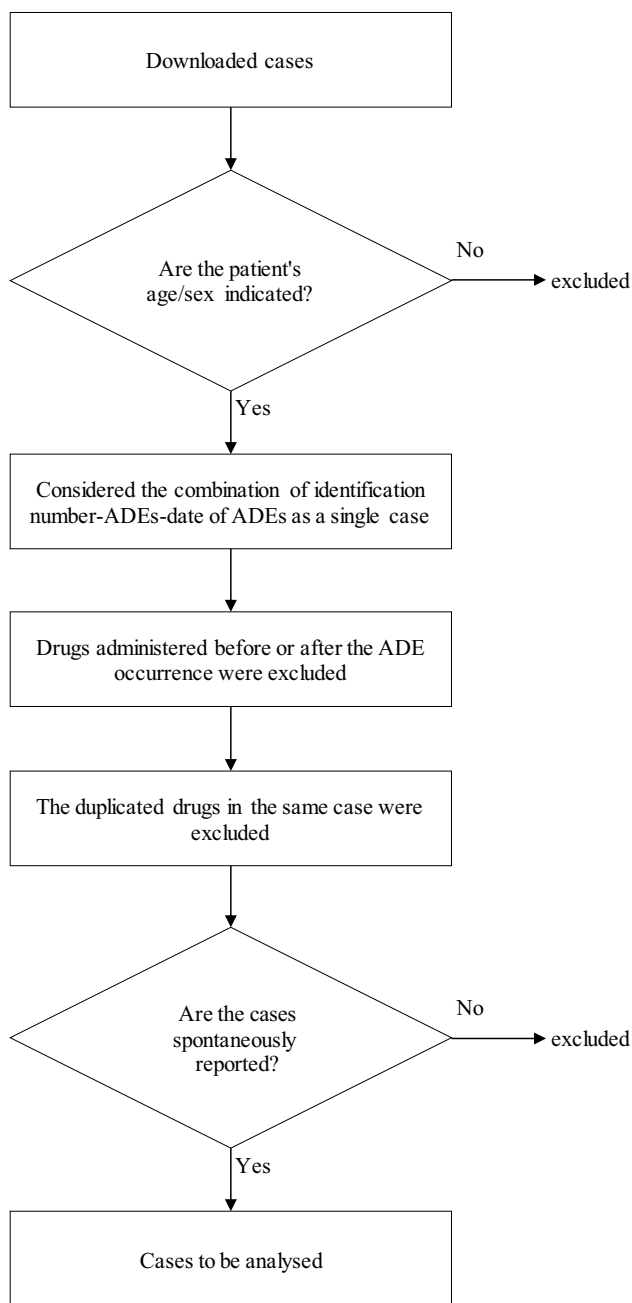


Fig. 1 Data-cleaning procedure. ADE adverse drug event

of use and those that were used at the time of ADE occurrence were regarded as patient-use drugs. When different dosages of the same drug were included in multiple records for a single case, the drug was counted as a single agent. The JADER also includes clinical trial data, thus spontaneously reported cases were included in the analysis, while clinical trial data were excluded.

2.4 Data Analysis

Cases were divided into men and women, and subsequent analyses were conducted separately for each sex. We counted the number of concomitant drugs for each case. Based on previous studies, polypharmacy was defined as cases where the patient was treated with six or more concomitant drugs and non-polypharmacy cases where the patient was treated with less than six drugs [11, 12]. Although ‘elderly’ generally refers to individuals aged 65 years and older, as age is grouped by decade in the JADER, ‘elderly’ was defined as patients aged 70 years or more and ‘non-elderly’ was defined as those aged less than 70 years [13].

In this study, we used logistic regression analysis to analyse the factors ‘elderly’ and ‘polypharmacy’, because it can be used to simultaneously analyse multiple factors [14]. Next, to investigate the influence of elderly and polypharmacy, with x_e as the presence or absence of elderly, and x_p as the presence or absence of polypharmacy with respect to the reporting rate for each ADE in the JADER database, p , we performed logistic regression analysis according to Eq. 1:

$$\ln \frac{p_i}{1 - p_i} = a_{e_i} \times x_{e_i} + a_{p_i} \times x_{p_i} + b_{0_i}. \quad (1)$$

The natural exponential function of the partial regression coefficient (a_e or a_p) derived from logistic regression analysis with Eqs. (2) and (3) being the adjusted odds ratio (adjusted OR), elderly risk (OR_e) and polypharmacy risk (OR_p) were calculated for each ADE. Non-association between ‘elderly’ or ‘polypharmacy’ and ADE onset is represented by OR 1, while it is represented by $OR > 1$ where there is risk of ADE onset. In this study, a significant risk was defined as a 95% confidence interval of OR.

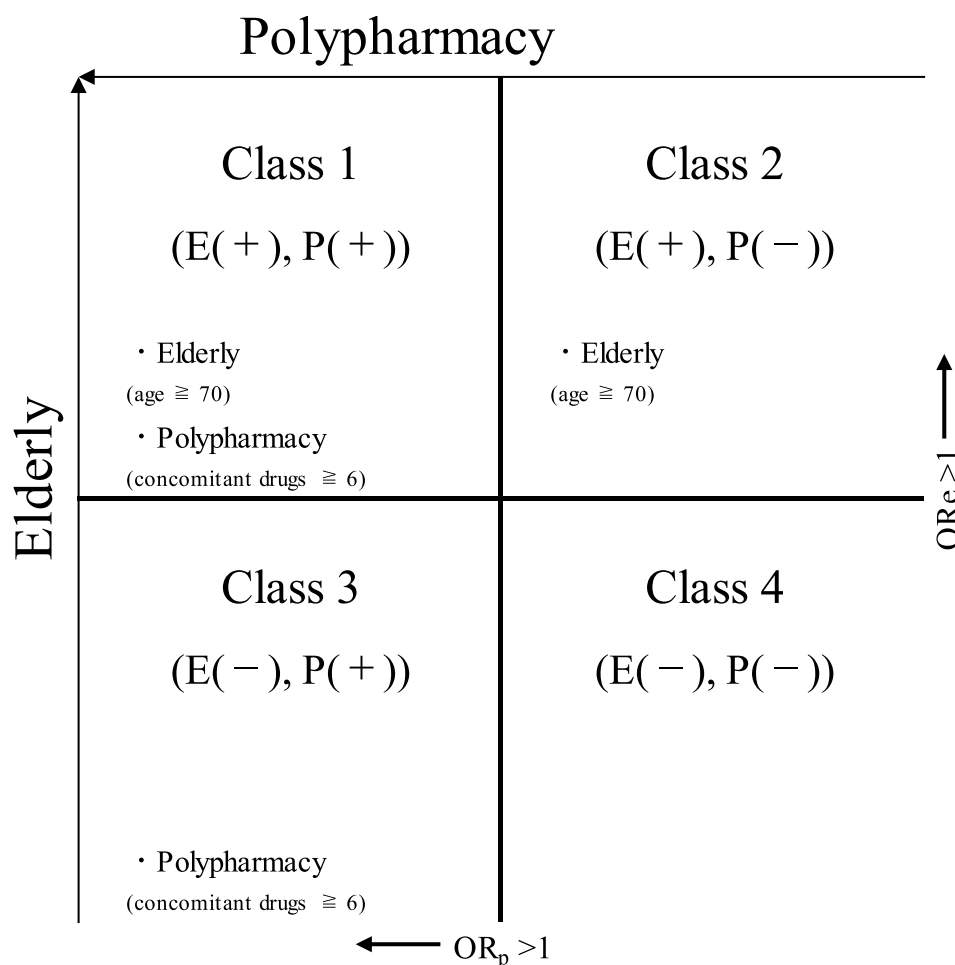
$$OR_{e_i} = e^{a_{e_i}} \quad (2)$$

$$OR_{p_i} = e^{a_{p_i}} \quad (3)$$

2.5 ADE Categorisation

Using OR_e and OR_p derived from logistic regression analysis, 100 types of ADEs were grouped into four classes (Fig. 2). First, ADEs for which OR_e significantly exceeded 1 were grouped into Classes 1 and 2, and all other ADEs were grouped into Classes 3 and 4. Next, of the ADEs categorised as Class 1 and Class 2, those in which OR_p significantly exceeded 1 were grouped into Class 1 [E(+), P(+)] and the remainder into Class 2 [E(+), P(-)]. Again, of the ADEs categorised as Class 3 and Class 4, those in which OR_p significantly exceeded 1 were grouped into Class 3 [E(-), P(+)] and the remainder into Class 4 [E(-), P(-)].

Fig. 2 Categorisation of adverse drug events (ADEs) considering elderly and polypharmacy. OR_e adjusted odds ratio with elderly as a factor for the occurrence of ADEs, OR_p adjusted odds ratio with polypharmacy as a factor for the occurrence of ADEs. E(+), P(+): ADEs where OR_e and OR_p significantly exceeded 1; E(+), P(-): ADEs where only OR_e significantly exceeded 1; E(-), P(+): ADEs where only OR_p significantly exceeded 1; E(-), P(-): ADEs where neither OR_e nor OR_p significantly exceeded 1



3 Results

3.1 ADEs in Identified Cases

Total cases registered in JADER (combinations of identification number-ADE-date of ADE) comprised 355,855 men and 349,460 women. The average number of drugs that the patients used simultaneously was 4.25 ± 4.56 , and the median age of the study group was 70 years. The 100 most common types of ADEs are collated by report number in Table 1; these were subsequently targeted for analysis.

3.2 ADEs That are Associated with Both Elderly and Polypharmacy: Class 1 [E(+), P(+)]

ADEs categorised as Class 1 are presented by sex in Table 2 ((a) Males, (b) Females). The ADEs in Table 2 were ranked in descending order of OR_e and OR_p volume. A total of 19 and 26 male and female ADE types, respectively, were categorised as Class 1. Of these, 16 ADE types were categorised as common to both males and females.

OR_e for males included hypoglycaemia (OR 2.03), bradycardia (OR 2.03), hyperkalaemia (OR 1.76), interstitial lung disease (OR 1.74), and hyponatraemia (OR 1.73). For females, ADEs included hyperkalaemia (OR 3.68), hypoglycaemia (OR 3.42), hyponatraemia (OR 3.18), bradycardia (OR 2.82), and renal failure (OR 2.49).

OR_p for males included hyperkalaemia (OR 1.89), transfusion-related acute lung injury (OR 1.71), dehydration (OR, 1.71), bradycardia (OR 1.49), and respiratory failure (OR 1.43). For females, the ADEs included disseminated drug interaction (OR 2.26), hyperkalaemia (OR 1.90), transfusion-related acute lung injury (OR 1.89), hypokalaemia (OR 1.66), and rhabdomyolysis (OR 1.65).

Many of the ADEs categorised as Class 1 were related to electrolyte abnormalities, renal and respiratory disorders, and coagulopathy. Comparison of male and female ADEs identified as Class 1 revealed that lung disorders, increased blood creatinine, and dizziness were significant for males only, and that ten ADE types (drug interaction, urinary retention, pneumonia aspiration, renal disorder, renal impairment, electrocardiogram QT prolonged, decreased

Table 1 Top 100 adverse drug event (ADE) types considered for analysis

No.	ADEs	No.	ADEs
1	Interstitial lung disease	51	Stomatitis
2	Platelet count decreased	52	Pneumocystis jirovecii pneumonia
3	Hepatic function abnormal	53	Alanine aminotransferase increased
4	Anaphylactic shock	54	Urticaria
5	Neutrophil count decreased	55	Hyponatraemia
6	White blood cell count decreased	56	Blood creatine phosphokinase increased
7	Pyrexia	57	Dizziness
8	Anaemia	58	Aspartate aminotransferase increased
9	Pneumonia	59	Hyperkalaemia
10	Liver disorder	60	Renal disorder
11	Neutropenia	61	Hypertension
12	Drug eruption	62	Bradycardia
13	Diarrhoea	63	Hypokalaemia
14	Renal impairment	64	Anaphylactoid reaction
15	Blood pressure decreased	65	Rash generalised
16	Decreased appetite	66	Delirium
17	Febrile neutropenia	67	Erythema
18	Rash	68	Renal failure
19	Acute kidney injury	69	Pleural effusion
20	Rhabdomyolysis	70	Depressed level of consciousness
21	Thrombocytopenia	71	Urinary retention
22	Pancytopenia	72	Diabetes mellitus
23	Hypoglycaemia	73	Electrocardiogram QT prolonged
24	Cerebral infarction	74	Deep vein thrombosis
25	Nausea	75	Pulmonary embolism
26	Erythema multiforme	76	Dehydration
27	Anaphylactic reaction	77	Melaena
28	Cardiac failure	78	Fall
29	Stevens-Johnson syndrome	79	Drug interaction
30	Haemoglobin decreased	80	Jaundice
31	Altered state of consciousness	81	Herpes zoster
32	Vomiting	82	Blood creatinine increased
33	Shock	83	Lymphoproliferative disorder
34	Seizure	84	Palmar-plantar erythrodysesthesia syndrome
35	Leukopenia	85	Headache
36	Sepsis	86	Transfusion-related acute lung injury
37	Cerebral haemorrhage	87	Cytomegalovirus infection
38	Dyspnoea	88	Pancreatitis acute
39	Loss of consciousness	89	Lung disorder
40	Drug-induced liver injury	90	Respiratory failure
41	Drug reaction with eosinophilia and systemic symptoms	91	Hyperglycaemia
42	Malaise	92	Infection
43	Bone marrow failure	93	Ileus
44	Agranulocytosis	94	Pneumonia aspiration
45	Disseminated intravascular coagulation	95	Toxicity to various agents
46	Gastrointestinal haemorrhage	96	Septic shock
47	Death	97	Tubulointerstitial nephritis
48	Toxic epidermal necrolysis	98	Cellulitis
49	Neuroleptic malignant syndrome	99	Toxic skin eruption
50	Osteonecrosis of jaw	100	Peritonitis

Table 2 Adverse drug events (ADEs) categorised as Class 1 (OR_e and OR_p volumes in descending order)

(a) Male cases						
No.	ADEs	OR_e	(95% CI)	OR_p	(95% CI)	Female class
1	Hyperkalaemia	1.76	(1.54–2.02)	1.89	(1.65–2.16)	1
2	Bradycardia	2.03	(1.77–2.32)	1.49	(1.30–1.70)	1
3	Hypoglycaemia	2.03	(1.86–2.22)	1.29	(1.18–1.41)	1
4	Transfusion-related acute lung injury	1.43	(1.25–1.64)	1.71	(1.49–1.97)	1
5	Hyponatraemia	1.73	(1.50–1.99)	1.29	(1.11–1.49)	1
6	Interstitial lung disease	1.74	(1.67–1.82)	1.17	(1.12–1.23)	1
7	Dehydration	1.18	(1.00–1.40)	1.71	(1.44–2.02)	1
8	Hypokalaemia	1.48	(1.26–1.74)	1.36	(1.15–1.60)	1
9	<u>Lung disorder</u>	1.48	(1.28–1.72)	1.31	(1.12–1.53)	2
10	Respiratory failure	1.33	(1.14–1.56)	1.43	(1.21–1.68)	1
11	Renal failure	1.41	(1.23–1.63)	1.33	(1.15–1.55)	1
12	Altered state of consciousness	1.29	(1.17–1.42)	1.41	(1.28–1.56)	1
13	Anaemia	1.45	(1.31–1.59)	1.20	(1.08–1.33)	1
14	Thrombocytopenia	1.50	(1.35–1.66)	1.13	(1.02–1.26)	1
15	<u>Blood creatinine increased</u>	1.36	(1.15–1.62)	1.24	(1.03–1.49)	2
16	Acute kidney injury	1.20	(1.10–1.30)	1.36	(1.25–1.47)	1
17	<u>Dizziness</u>	1.30	(1.12–1.50)	1.22	(1.05–1.43)	2
18	Pancytopenia	1.24	(1.13–1.37)	1.12	(1.00–1.24)	1
19	Blood pressure decreased	1.10	(1.02–1.18)	1.16	(1.07–1.26)	1
(b) Female cases						
No.	ADEs	OR_e	(95% CI)	OR_p	(95% CI)	Male class
1	Hyperkalaemia	3.68	(3.12–4.37)	1.90	(1.64–2.21)	1
2	Hyponatraemia	3.18	(2.79–3.64)	1.65	(1.45–1.86)	1
3	Hypoglycaemia	3.42	(3.10–3.78)	1.47	(1.34–1.61)	1
4	Bradycardia	2.82	(2.46–3.24)	1.43	(1.25–1.64)	1
5	Renal failure	2.49	(2.08–2.98)	1.61	(1.35–1.91)	1
6	Dehydration	2.48	(2.05–3.01)	1.60	(1.32–1.93)	1
7	Acute kidney injury	2.35	(2.15–2.58)	1.54	(1.41–1.69)	1
8	Hypokalaemia	2.16	(1.89–2.48)	1.66	(1.45–1.90)	1
9	<u>Drug interaction</u>	1.43	(1.24–1.65)	2.26	(1.96–2.61)	3
10	Transfusion-related acute lung injury	1.61	(1.38–1.88)	1.89	(1.62–2.21)	1
11	<u>Urinary retention</u>	2.32	(1.96–2.76)	1.26	(1.06–1.50)	2
12	<u>Pneumonia aspiration</u>	2.08	(1.66–2.61)	1.38	(1.10–1.74)	2
13	<u>Renal disorder</u>	2.04	(1.74–2.39)	1.25	(1.05–1.47)	4
14	<u>Renal impairment</u>	2.04	(1.86–2.23)	1.21	(1.10–1.33)	2
15	<u>Electrocardiogram QT prolonged</u>	1.72	(1.48–1.99)	1.42	(1.22–1.66)	3
16	Altered state of consciousness	1.71	(1.56–1.87)	1.40	(1.27–1.53)	1
17	<u>Decreased appetite</u>	1.84	(1.65–2.06)	1.21	(1.07–1.35)	2
18	<u>Rhabdomyolysis</u>	1.18	(1.07–1.30)	1.65	(1.49–1.83)	3
19	<u>Cardiac failure</u>	1.70	(1.53–1.89)	1.12	(1.00–1.25)	2
20	Anaemia	1.48	(1.34–1.62)	1.29	(1.17–1.43)	1
21	Pancytopenia	1.58	(1.45–1.73)	1.19	(1.08–1.31)	1
22	Respiratory failure	1.37	(1.14–1.64)	1.31	(1.08–1.59)	1
23	Blood pressure decreased	1.28	(1.18–1.38)	1.22	(1.12–1.33)	1
24	Interstitial lung disease	1.36	(1.29–1.43)	1.10	(1.04–1.16)	1
25	Thrombocytopenia	1.13	(1.00–1.26)	1.29	(1.14–1.45)	1
26	<u>Pneumonia</u>	1.30	(1.19–1.41)	1.11	(1.01–1.22)	2

Underlined ADEs are categorised in a separate Class in the other sex

OR_e adjusted odds ratio with elderly as a factor for the occurrence of ADEs, OR_p adjusted odds ratio with polypharmacy as a factor for the occurrence of ADEs, 95% CI 95% confidence interval of OR_e and OR_p , Female Class class in which ADEs common in females are categorised, Male Class class in which ADEs common in males are categorised

Table 3 Adverse drug events (ADEs) categorised as Class 2 (in OR_e descending order)

(a) Male cases						
No.	ADEs	OR_e	(95% CI)	OR_p	(95% CI)	Female class
1	Urinary retention	3.34	(2.93–3.82)	0.79	(0.69–0.91)	1
2	Fall	2.29	(1.93–2.73)	1.04	(0.87–1.25)	2
3	Cardiac failure	2.17	(1.94–2.43)	1.07	(0.95–1.20)	1
4	Osteonecrosis of jaw	2.14	(1.83–2.52)	0.60	(0.50–0.73)	2
5	Gastrointestinal haemorrhage	2.14	(1.89–2.43)	0.77	(0.67–0.89)	2
6	Pneumonia aspiration	2.14	(1.81–2.52)	1.14	(0.96–1.35)	1
7	Melaena	2.08	(1.78–2.43)	0.91	(0.77–1.07)	2
8	Cerebral haemorrhage	1.88	(1.70–2.07)	0.89	(0.80–0.99)	2
9	Pleural effusion	1.81	(1.54–2.12)	1.00	(0.84–1.18)	2
10	Cerebral infarction	1.79	(1.62–1.97)	0.73	(0.65–0.82)	2
11	Delirium	1.70	(1.49–1.94)	1.01	(0.87–1.16)	2
12	Decreased appetite	1.55	(1.40–1.72)	1.07	(0.96–1.20)	1
13	Platelet count decreased	1.46	(1.37–1.56)	0.97	(0.90–1.04)	2
14	Depressed level of consciousness	1.40	(1.21–1.63)	1.06	(0.90–1.24)	2
15	Pneumonia	1.40	(1.30–1.51)	1.02	(0.94–1.11)	1
16	Lymphoproliferative disorder	1.40	(1.16–1.68)	0.11	(0.06–0.16)	2
17	Death	1.26	(1.10–1.43)	0.62	(0.53–0.73)	2
18	<u>Hypertension</u>	1.25	(1.05–1.50)	0.69	(0.56–0.85)	4
19	Renal impairment	1.17	(1.08–1.26)	1.02	(0.94–1.11)	1
(b) Female cases						
No.	ADEs	OR_e	(95% CI)	OR_p	(95% CI)	Male class
1	Gastrointestinal haemorrhage	3.69	(3.15–4.33)	1.05	(0.90–1.22)	2
2	Melaena	3.22	(2.69–3.86)	0.93	(0.77–1.11)	2
3	Fall	3.05	(2.63–3.54)	0.88	(0.75–1.03)	2
4	Delirium	2.89	(2.47–3.38)	1.11	(0.94–1.29)	2
5	Cerebral haemorrhage	2.61	(2.31–2.97)	0.83	(0.72–0.95)	2
6	Blood creatinine increased	2.16	(1.71–2.73)	1.15	(0.90–1.47)	1
7	Osteonecrosis of jaw	2.16	(1.95–2.39)	0.71	(0.63–0.80)	2
8	Death	1.99	(1.69–2.34)	0.67	(0.55–0.81)	2
9	Cerebral infarction	1.91	(1.71–2.13)	0.63	(0.55–0.72)	2
10	<u>Haemoglobin decreased</u>	1.46	(1.24–1.72)	0.88	(0.73–1.07)	4
11	Lymphoproliferative disorder	1.42	(1.26–1.60)	0.10	(0.07–0.13)	2
12	<u>Infection</u>	1.26	(1.04–1.54)	0.50	(0.38–0.64)	4
13	Platelet count decreased	1.23	(1.15–1.32)	0.97	(0.90–1.06)	2
14	Lung disorder	1.21	(1.01–1.45)	1.06	(0.87–1.30)	1
15	Depressed level of consciousness	1.21	(1.07–1.37)	1.05	(0.91–1.20)	2
16	Pleural effusion	1.20	(1.02–1.43)	1.12	(0.93–1.35)	2
17	<u>Shock</u>	1.20	(1.09–1.32)	0.89	(0.80–1.00)	4
18	Dizziness	1.20	(1.06–1.35)	0.94	(0.82–1.07)	1
19	<u>Stomatitis</u>	1.19	(1.02–1.38)	1.01	(0.85–1.19)	4

Underlined ADEs are categorised in a separate Class in the other sex

OR_e adjusted odds ratio with elderly as a factor for the occurrence of ADEs, OR_p adjusted odds ratio with polypharmacy as a factor for the occurrence of ADEs, 95% CI 95% confidence interval of OR_e and OR_p , Female Class class in which ADEs common in females are categorised, Male Class class in which ADEs common in males are categorised

appetite, rhabdomyolysis, cardiac failure, pneumonia) were significant for females only.

3.3 ADEs That are Associated with Elderly and Not With Polypharmacy: Class 2 [E(+), P(-)]

ADEs categorised as Class 2 are presented by sex in Table 3 ((a) Males, (b) Females). The ADEs in Table 3 were ranked in descending OR_e order. A total of 19 male and female ADE types, respectively, were categorised as Class 2. Of these, 12 were categorised as being common to both males and females. OR_e for males presented high values for urinary retention (OR 3.34), fall (OR 2.29), cardiac failure (OR 2.17), osteonecrosis of the jaw (OR 2.14), and gastrointestinal haemorrhage (OR 2.14). For females, high values were found for gastrointestinal haemorrhage (OR 3.69), melaena (OR 3.22), fall (OR 3.05), delirium (OR 2.89), and cerebral haemorrhage (OR 2.61). Except for mental and nervous disorders, various ADEs were categorised in Class 2. Hypertension was common to males, while decreased haemoglobin, infection, shock and stomatitis were common to females.

3.4 ADEs That are Associated with Polypharmacy and Not With Elderly: Class 3 [E(-), P(+)]

Class 3 ADEs are presented by sex in Table 4 ((a) Males, (b) Females). ADEs in Table 4 and OR_p are ranked in descending order. In total, 14 and 20 ADE types common to both males and females, respectively, were categorised as Class 3. Of these, nine were common to both males and females.

OR_p for males included drug interaction (OR 2.16), agranulocytosis (OR 1.62), rhabdomyolysis (OR 1.60), erythema (OR 1.41), and toxic skin eruption (OR 1.31). For females, the ranking was sepsis (OR 1.60), cellulitis (OR 1.48), hyperglycaemia (OR 1.47), neuroleptic malignant syndrome (OR 1.45), and erythema (OR 1.39).

In Class 3, the PTs infectious diseases and decreased white blood cell count predominated. Septic shock and decreased white blood cell count were categorised as common to males, while sepsis, cellulitis, hyperglycaemia, acute pancreatitis, increased blood creatine phosphokinase, Stevens–Johnson syndrome, jaundice, increased aspartate aminotransferase, toxic epidermal necrolysis, vomiting, and drug-induced liver injury were categorised as common to females.

3.5 ADEs That are Not Associated with Either Polypharmacy or Elderly: Class 4 [E(-), P(-)]

Class 4 ADEs are presented by sex in Table 5 ((a) Males, (b) Females). OR_e and OR_p volumes are ranked in ascending

order to clarify that ADEs were unaffected by elderly or polypharmacy. A total of 48 and 35 ADE types were categorised as male and female, respectively. Of these, 32 were common to both sexes. Class 4 ADEs were dominated by allergic symptoms, including anaphylactic reaction.

3.6 Summary of the Results

ADE classes are presented in Fig. 3.

4 Discussion

Class 2 ADEs [E(+), P(-)], including the PTs delirium and fall, have previously been identified as those with a high risk of occurrence in elderly patients treated with polypharmacy [10]. However, these ADEs were associated with the elderly but not with polypharmacy in this study. Moreover, it is difficult to distinguish between symptoms associated with drugs and those associated with aging, and symptoms may actually include symptoms of aging.

Conversely, the results of the present study support existing reports that the risk of Class 1 ADEs [E(+), P(+)], including electrolyte abnormalities [15–17], renal disorder [3] and pneumonia aspiration [18, 19], in elderly patients treated with polypharmacy is high. Dehydration and electrolyte imbalance are common in elderly persons, who have a high threshold value for throat dryness; moreover, polypharmacy including diuretics and selective serotonin receptor inhibitors has been reported [15–17] to increase these risks. In addition to the reduction in renal function associated with the elderly [3], multi-drug combinations of non-steroidal anti-inflammatory drugs, hypotensive drugs and diuretics have been reported to increase the risk of renal disorders. Similarly, reduced mobility in the elderly leads to decreased swallowing function, and multi-drug combinations including those with muscle-relaxing properties and diuretics carry a risk of pneumonia aspiration [18, 19].

The PTs decreased white blood cell count and infectious diseases predominate among the Class 3 ADEs [E(-), P(+)] that are common to both sexes. This indicates that there is an age-independent risk of myelosuppression with combinations of anti-cancer agents, which subsequently increase the risk of infections. In addition, given that many Class 4 ADEs [E(-), P(-)] were found to be allergic in nature, the high risk of allergy-type ADEs unrelated to polypharmacy or elderly should be considered.

In this study, sex differences in the occurrence of ADEs were investigated. ADEs of which the risk of onset is associated with polypharmacy occurred more frequently in women (Tables 2, 3), which may suggest that women

Table 4 Adverse drug events (ADEs) categorised as Class 3 (in OR_p descending order)

(a) Male cases						
No.	ADEs	OR_e	(95% CI)	OR_p	(95% CI)	Female class
1	Drug interaction	1.05	(0.91–1.21)	2.16	(1.87–2.49)	1
2	Agranulocytosis	0.69	(0.60–0.79)	1.62	(1.42–1.84)	3
3	Rhabdomyolysis	0.86	(0.80–0.93)	1.60	(1.48–1.73)	1
4	Erythema	0.91	(0.78–1.06)	1.41	(1.20–1.66)	3
5	Toxic skin eruption	0.69	(0.57–0.84)	1.31	(1.07–1.60)	3
6	<u>Septic shock</u>	0.80	(0.66–0.97)	1.28	(1.05–1.55)	4
7	Electrocardiogram qt prolonged	1.17	(0.98–1.39)	1.25	(1.04–1.49)	1
8	Anaphylactic shock	0.70	(0.67–0.74)	1.22	(1.15–1.28)	3
9	Neuroleptic malignant syndrome	0.31	(0.26–0.35)	1.19	(1.05–1.34)	3
10	Hepatic function abnormal	0.88	(0.83–0.93)	1.17	(1.11–1.25)	3
11	Drug eruption	0.71	(0.65–0.78)	1.16	(1.05–1.27)	3
12	Disseminated intravascular coagulation	1.11	(0.98–1.25)	1.16	(1.01–1.32)	3
13	Pyrexia	0.87	(0.82–0.94)	1.13	(1.05–1.22)	3
14	<u>White blood cell count decreased</u>	0.88	(0.80–0.97)	1.11	(1.01–1.23)	4
(b) Female cases						
No.	ADEs	OR_e	(95% CI)	OR_p	(95% CI)	Male class
1	<u>Sepsis</u>	0.91	(0.79–1.05)	1.60	(1.38–1.84)	4
2	<u>Cellulitis</u>	1.13	(0.93–1.38)	1.48	(1.20–1.81)	4
3	<u>Hyperglycaemia</u>	0.90	(0.75–1.08)	1.47	(1.22–1.77)	4
4	Neuroleptic malignant syndrome	0.49	(0.42–0.57)	1.45	(1.26–1.67)	3
5	Erythema	0.62	(0.54–0.72)	1.39	(1.20–1.59)	3
6	<u>Pancreatitis acute</u>	0.65	(0.54–0.78)	1.38	(1.14–1.66)	4
7	Disseminated intravascular coagulation	1.06	(0.92–1.22)	1.38	(1.19–1.59)	3
8	<u>Blood creatine phosphokinase increased</u>	0.92	(0.79–1.07)	1.34	(1.14–1.57)	4
9	Toxic skin eruption	0.75	(0.63–0.89)	1.31	(1.09–1.56)	3
10	<u>Stevens-Johnson syndrome</u>	0.70	(0.63–0.77)	1.29	(1.16–1.42)	4
11	<u>Jaundice</u>	1.04	(0.88–1.24)	1.26	(1.05–1.51)	4
12	<u>Aspartate aminotransferase increased</u>	0.87	(0.74–1.03)	1.24	(1.04–1.47)	4
13	<u>Toxic epidermal necrolysis</u>	0.81	(0.70–0.93)	1.23	(1.06–1.42)	4
14	Anaphylactic shock	0.68	(0.64–0.72)	1.19	(1.12–1.27)	3
15	<u>Vomiting</u>	1.11	(1.00–1.22)	1.18	(1.05–1.31)	4
16	<u>Drug-induced liver injury</u>	0.57	(0.50–0.65)	1.15	(1.01–1.31)	4
17	Pyrexia	0.74	(0.69–0.80)	1.14	(1.06–1.23)	3
18	Agranulocytosis	0.62	(0.55–0.69)	1.13	(1.01–1.26)	3
19	Drug eruption	0.61	(0.56–0.67)	1.12	(1.03–1.22)	3
20	Hepatic function abnormal	0.79	(0.75–0.84)	1.09	(1.02–1.16)	3

Underlined ADEs are categorised in a separate Class in the other sex

OR_e adjusted odds ratio with elderly as a factor for the occurrence of ADEs, OR_p adjusted odds ratio with polypharmacy as a factor for the occurrence of ADEs, 95% CI 95% confidence interval of OR_e and OR_p , Female Class class in which ADEs common in females are categorised, Male Class class in which ADEs common in males are categorised

are more sensitive to the effects of polypharmacy than are men [20, 21]. However, the type of drug used was not included in the analysis conditions. Thus, detailed investigations focusing on the types of drugs used are necessary for a detailed discussion on the reasons for these sex differences.

This study has the following limitations: since this study focused on the 100 most common ADE types reported in the JADER database, it is possible that ADEs categorised as Class 1 were not the only events that carry a high risk of occurrence in elderly patients treated with polypharmacy: other ADEs may carry a high risk of occurrence in

Table 5 Adverse drug events (ADEs) categorised as Class 4 (OR_e and OR_p volumes in ascending order)

(a) Male cases						
No.	ADEs	OR _e	(95% CI)	OR _p	(95% CI)	Female class
1	Cytomegalovirus infection	0.33	(0.26–0.41)	0.74	(0.60–0.92)	4
2	Drug reaction with eosinophilia and systemic symptoms	0.37	(0.33–0.42)	0.77	(0.68–0.88)	4
3	Diabetes mellitus	0.49	(0.41–0.59)	0.65	(0.53–0.79)	4
4	Headache	0.44	(0.33–0.56)	0.85	(0.65–1.09)	4
5	Tubulointerstitial nephritis	0.53	(0.44–0.63)	0.74	(0.61–0.88)	4
6	Palmar-plantar erythrodysesthesia syndrome	0.95	(0.75–1.19)	0.44	(0.31–0.59)	4
7	Anaphylactoid reaction	0.43	(0.37–0.51)	1.15	(0.99–1.34)	4
8	Anaphylactic reaction	0.51	(0.46–0.56)	1.02	(0.92–1.13)	4
9	Pancreatitis acute	0.50	(0.42–0.59)	1.04	(0.88–1.22)	3
10	Peritonitis	0.69	(0.57–0.84)	0.79	(0.63–0.97)	4
11	Urticaria	0.52	(0.45–0.60)	1.09	(0.94–1.26)	4
12	Neutrophil count decreased	0.92	(0.84–1.01)	0.65	(0.58–0.73)	4
13	Infection	0.99	(0.82–1.19)	0.61	(0.48–0.76)	2
14	Drug-induced liver injury	0.74	(0.65–0.84)	0.84	(0.72–0.96)	3
15	Pulmonary embolism	0.58	(0.47–0.72)	1.11	(0.89–1.37)	4
16	Pneumocystis jirovecii pneumonia	0.90	(0.78–1.04)	0.72	(0.61–0.85)	4
17	Stevens-Johnson syndrome	0.62	(0.56–0.69)	1.06	(0.95–1.18)	3
18	Deep vein thrombosis	0.70	(0.56–0.86)	0.95	(0.75–1.18)	4
19	Rash generalised	0.78	(0.66–0.92)	0.85	(0.71–1.02)	4
20	Erythema multiforme	0.73	(0.64–0.83)	0.92	(0.80–1.05)	4
21	Alanine aminotransferase increased	0.75	(0.64–0.87)	0.90	(0.76–1.06)	4
22	Bone marrow failure	0.99	(0.88–1.11)	0.68	(0.59–0.79)	4
23	Neutropenia	0.84	(0.75–0.92)	0.81	(0.72–0.91)	4
24	Rash	0.67	(0.60–0.74)	1.02	(0.92–1.14)	4
25	Leukopenia	0.85	(0.73–0.98)	0.82	(0.70–0.97)	4
26	Blood creatine phosphokinase increased	0.66	(0.59–0.74)	1.06	(0.94–1.20)	3
27	Stomatitis	0.88	(0.75–1.03)	0.80	(0.66–0.96)	2
28	Toxicity to various agents	0.64	(0.54–0.76)	1.15	(0.96–1.37)	4
29	Seizure	0.77	(0.69–0.85)	0.98	(0.87–1.09)	4
30	Liver disorder	0.78	(0.72–0.84)	1.04	(0.96–1.12)	4
31	Hyperglycaemia	0.84	(0.71–0.99)	0.97	(0.80–1.16)	3
32	Shock	0.97	(0.89–1.06)	0.87	(0.78–0.96)	2
33	Toxic epidermal necrolysis	0.73	(0.63–0.84)	1.16	(1.00–1.35)	3
34	Aspartate aminotransferase increased	0.83	(0.71–0.96)	1.02	(0.86–1.21)	3
35	Nausea	0.87	(0.76–0.98)	1.00	(0.87–1.14)	4
36	Diarrhoea	0.97	(0.88–1.07)	0.94	(0.84–1.04)	4
37	Herpes zoster	0.81	(0.63–1.04)	1.13	(0.87–1.47)	4
38	Febrile neutropenia	1.04	(0.93–1.15)	0.89	(0.79–1.00)	4
39	Sepsis	0.86	(0.76–0.98)	1.08	(0.94–1.23)	3
40	Malaise	1.02	(0.89–1.16)	0.93	(0.80–1.08)	4
41	Loss of consciousness	1.10	(0.99–1.22)	0.90	(0.80–1.01)	4
42	Haemoglobin decreased	1.17	(1.00–1.38)	0.84	(0.70–1.01)	2
43	Ileus	1.05	(0.88–1.25)	0.96	(0.79–1.16)	4
44	Renal disorder	1.05	(0.92–1.20)	0.97	(0.83–1.12)	1
45	Jaundice	1.05	(0.90–1.22)	0.97	(0.82–1.14)	3
46	Cellulitis	0.90	(0.71–1.14)	1.14	(0.89–1.46)	3
47	Vomiting	1.00	(0.88–1.14)	1.13	(0.98–1.29)	3
48	Dyspnoea	1.05	(0.94–1.16)	1.11	(0.99–1.23)	4

Table 5 (continued)

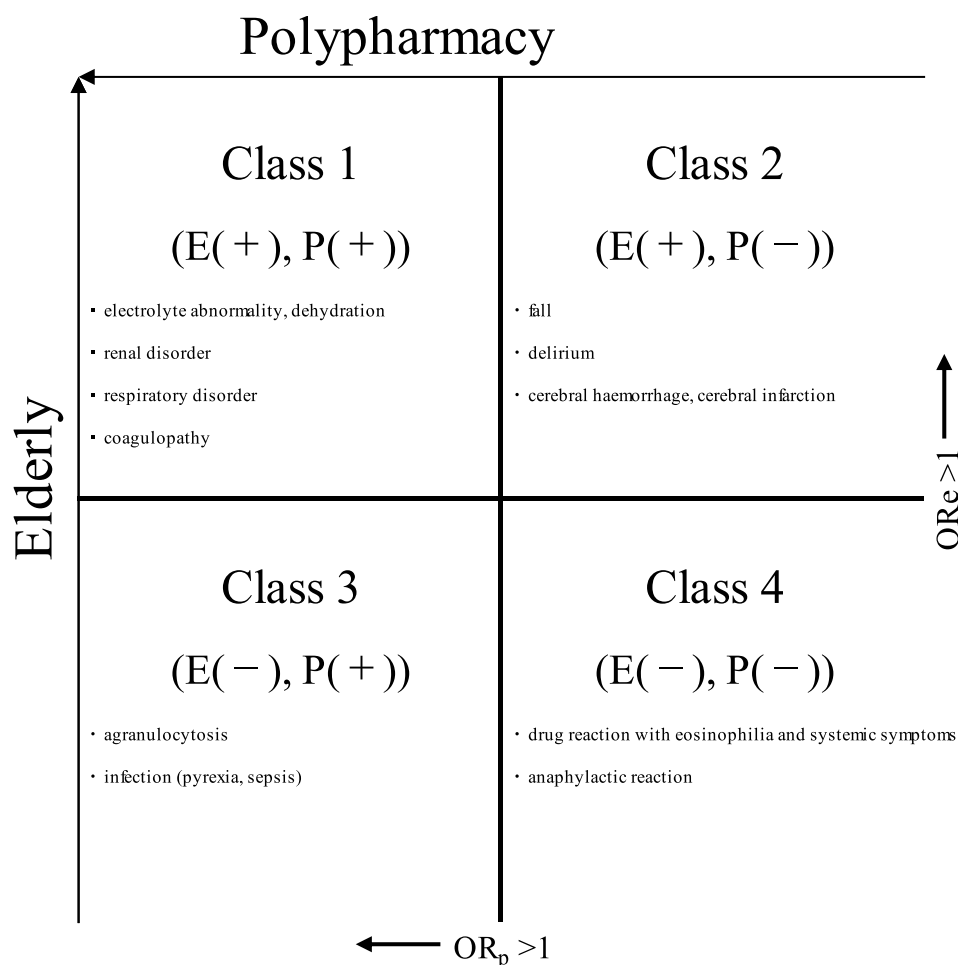
(a) Female cases						
No.	ADEs	OR _e	(95% CI)	OR _p	(95% CI)	Male class
1	Headache	0.31	(0.25–0.37)	0.59	(0.49–0.71)	4
2	Anaphylactoid reaction	0.36	(0.30–0.42)	1.03	(0.88–1.21)	4
3	Cytomegalovirus infection	0.46	(0.36–0.57)	0.84	(0.66–1.06)	4
4	Anaphylactic reaction	0.39	(0.35–0.43)	1.00	(0.90–1.10)	4
5	Palmar-plantar erythrodysesthesia syndrome	0.79	(0.61–1.02)	0.51	(0.36–0.71)	4
6	Pulmonary embolism	0.55	(0.47–0.64)	0.81	(0.69–0.95)	4
7	Drug reaction with eosinophilia and systemic symptoms	0.47	(0.41–0.53)	0.98	(0.86–1.11)	4
8	Neutrophil count decreased	0.73	(0.65–0.81)	0.64	(0.56–0.73)	4
9	Neutropenia	0.61	(0.54–0.68)	0.82	(0.73–0.93)	4
10	Deep vein thrombosis	0.70	(0.61–0.81)	0.72	(0.61–0.85)	4
11	Urticaria	0.49	(0.42–0.56)	1.07	(0.93–1.23)	4
12	Febrile neutropenia	0.61	(0.53–0.70)	0.87	(0.75–1.00)	4
13	Diabetes mellitus	0.54	(0.44–0.66)	1.00	(0.82–1.23)	4
14	Tubulointerstitial nephritis	0.65	(0.54–0.78)	0.85	(0.69–1.05)	4
15	Rash	0.56	(0.51–0.61)	1.05	(0.96–1.16)	4
16	Erythema multiforme	0.71	(0.64–0.80)	0.84	(0.74–0.94)	4
17	Seizure	0.71	(0.65–0.79)	0.84	(0.75–0.95)	4
18	Malaise	0.70	(0.61–0.79)	0.94	(0.81–1.08)	4
19	Peritonitis	0.79	(0.65–0.96)	0.84	(0.66–1.04)	4
20	Hypertension	0.88	(0.73–1.06)	0.76	(0.60–0.94)	2
21	Bone marrow failure	1.07	(0.95–1.21)	0.66	(0.56–0.76)	4
22	Leukopenia	0.71	(0.61–0.82)	1.00	(0.85–1.17)	4
23	Liver disorder	0.73	(0.68–0.79)	0.97	(0.90–1.06)	4
24	Toxicity to various agents	0.69	(0.59–0.80)	1.05	(0.89–1.23)	4
25	Dyspnoea	0.78	(0.70–0.86)	1.00	(0.89–1.12)	4
26	Rash generalised	0.82	(0.72–0.95)	1.05	(0.90–1.22)	4
27	Nausea	0.89	(0.80–0.99)	0.98	(0.88–1.10)	4
28	Herpes zoster	0.85	(0.70–1.02)	1.06	(0.86–1.30)	4
29	Alanine aminotransferase increased	0.81	(0.69–0.95)	1.12	(0.94–1.32)	4
30	White blood cell count decreased	0.87	(0.80–0.95)	1.05	(0.95–1.16)	3
31	Loss of consciousness	0.99	(0.90–1.09)	0.93	(0.83–1.03)	4
32	Diarrhoea	0.92	(0.83–1.01)	1.04	(0.93–1.16)	4
33	Ileus	1.16	(0.95–1.42)	0.86	(0.68–1.07)	4
34	Septic shock	0.86	(0.71–1.05)	1.22	(0.99–1.49)	3
35	Pneumocystis jirovecii pneumonia	1.07	(0.95–1.20)	1.04	(0.91–1.18)	4

OR_e adjusted odds ratio with elderly as a factor for the occurrence of ADEs, OR_p adjusted odds ratio with polypharmacy as a factor for the occurrence of ADEs, 95% CI 95% confidence interval of OR_e and OR_p, Female Class class in which ADEs common in females are categorised, Male Class class in which ADEs common in males are categorised

polypharmacy-treated patients. In addition, because ADEs were categorised using only basic data (age, sex and number of concomitant drugs) in the JADER, questions as to whether Class 1-categorised ADEs were really caused by polypharmacy, or whether other factors (e.g. background diseases or individual drugs) were involved highlight the need for studies from both pharmacological and physiological perspectives.

In conclusion, analysis of ADEs considering polypharmacy and the elderly revealed that the risk of the 100 most common ADEs reported in the JADER database could be categorised as follows: electrolyte abnormalities, renal and respiratory disorders, and coagulopathy in Class 1 [E(+), P(+)]; delirium, falls in Class 2 [E(+), P(-)]; myelosuppression arising from anti-cancer multi-drug combinations in Class 3 [E(-), P(+)]; and allergy-type ADEs in Class

Fig. 3 Typical adverse drug events (ADEs) categorised into each class. OR_e adjusted odds ratio with elderly as a factor for the occurrence of ADEs, OR_p adjusted odds ratio with polypharmacy as a factor for the occurrence of ADEs. E(+), P(+): ADEs where OR_e and OR_p significantly exceeded 1; E(+), P(-): ADEs where only OR_e significantly exceeded 1; E(-), P(+): ADEs where only OR_p significantly exceeded 1; E(-), P(-): ADEs where neither OR_e nor OR_p significantly exceeded 1



4 [E(-), P(-)]. These categories may provide potentially beneficial information for the future pharmaceutical management of elderly patients. In particular, the grouping of some ADEs into Class 2 that are considered classifiable as Class 1 in existing reports highlights the need for studies from pharmacological and physiological perspectives. In this study, we grouped ADEs by age (elderly— ≥ 70 year) and polypharmacy (six or more agents) without specifying the drugs. Since the risk of ADEs grouped in Class 1 increased in the elderly using six or more drugs, monitoring is particularly important for elderly patients under polypharmacy. However, the risk of Class 2 ADEs increased in the elderly who were taking fewer than five drugs, and Class 2 ADEs should therefore always be monitored very cautiously in the elderly. Further investigations that focus on drug types are warranted.

Declarations

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Conflict of interest All authors declare that they have no conflicts of interest.

Data availability The datasets supporting the conclusions of this article are available in the Pharmaceuticals and Medical Devices Agency repository, <https://www.pmda.go.jp/>.

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Consent Not applicable.

Author contributions AN, NI and DK contributed to the conception and initial design of the manuscript. AN was the major contributor to the design and writing of the manuscript. MM and DK contributed to the final design and writing of the manuscript. SO contributed to the project administration. AN and NH contributed to the data curation, methodology, software and formal analysis. SN and SOh contributed to the review and editing. DK contributed to the conceptualization. All authors read and approved the final manuscript.

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