Original Article

DOI: 10.5582/ddt.2024.01090

Characteristics and patterns of adverse event reports in the Japanese Adverse Drug Event Report database over two decades (2004–2023): Exploring findings on sexes and age groups

Hiroyuki Tanaka[1,*], Masaki Takigawa[2], Naohito Ide[3], Toshihiro Ishii[1]

[1] Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, Chiba, Japan;
[2] Department of Clinical Pharmaceutics, Faculty of Pharmaceutical Sciences, Toho University, Chiba, Japan;
[3] Department of Practical Pharmacy, Nihon Pharmaceutical University, Saitama, Japan.

SUMMARY: Recently, increased attention has been paid to the consideration of individual characteristics, including sex and age, in the context of medication use and adverse events. However, the characteristics and patterns of adverse events reported in the Japanese Adverse Drug Event Report (JADER) database stratified by sex and age have not yet been clarified. This study aimed to clarify the characteristics and patterns of adverse event reports in the JADER database over a 20-year period (April 2004–March 2024). Data were stratified into 20 groups based on sex and age (aged 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and ≥90 years). The female/male ratio of adverse event reports in JADER was 0.95. The largest group comprised males in their 70s. Adjusting for the proportion of adverse event reports in each group according to the demographic composition in 2015 highlighted that the reporting rates of adverse events were higher in people aged ≥70 years and that females aged 20–49 years reported more adverse events than males. Medical history, causative drugs, and adverse events reported to JADER were characterized by combinations of sex and age. Our results provide additional insights into the interpretation of previous studies using JADER. In addition, the results of this study will help understand the characteristics of adverse event reports contained in JADER and conduct appropriate subgroup and sensitivity analyses.

Keywords: Japanese Adverse Drug Event Report database, medication safety, pharmacovigilance, reporting patterns, sex–age stratification

1. Introduction

Post-marketing surveillance is essential because not all adverse effects of drugs can be identified in pre-marketing clinical trials. Spontaneous reporting systems for adverse events play an important role in pharmacovigilance by providing information from real-world clinical settings throughout a drug's life. There are a variety of spontaneous adverse event reporting databases in the world, including the World Health Organization's global database of reports on adverse events for medicines and vaccines (VigiBase®) and the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) maintains the Japanese Adverse Drug Event Report (JADER) database, which has accumulated adverse events reported to the PMDA since April 1, 2004.

Various studies have been conducted using databases that report spontaneous adverse events. Most of these are hypothesis-generating studies that utilize signal detection techniques to assess the association between drug use and occurrence of adverse events (*1*). Recently, the use of spontaneous adverse event reporting databases has increased. JADER has also been used in studies to analyze adverse event reporting patterns in specific patient populations, such as children (*2*), the elderly (*3*), pregnant women (*4*), and people living with HIV (*5*), as well as to evaluate the quality of adverse event reporting in Japan (*6*).

Although there are various limitations in interpreting studies using spontaneous adverse event reporting databases, results from studies using FAERS and VigiBase® have been used as evidence that the rate at which females experience adverse drug events is twice that of males (*7,8*). Although pharmacokinetics and pharmacodynamics are typically used to explain these sex differences, many factors can influence the

distribution of adverse event reports by sex, including the well-known disparities in the rates at which males and females use prescription drugs (*9,10*). Conversely, it has been suggested that upon adjusting for sex differences in drug use, the sex differences in adverse event reporting in FAERS may be smaller than previously thought (*11*). Furthermore, studies using VigiBase® have shown that the extent of the sex differences in adverse event reporting is small in the Asian region, including Japan (*8*). Although age, like sex, is a factor that influences disease, medications, vaccination, and the occurrence of adverse events, and may also affect the distribution of adverse event reports, the pattern of adverse event reporting by age in Japan remains unclear.

In this study, adverse event reports stored in the JADER database were stratified by sex and age at 10-year intervals, and the characteristics and patterns of adverse event reports in the various groups classified according to these criteria were analyzed.

2. Materials and Methods

2.1. Data source

Data covering April 2004 to March 2024 were extracted from the JADER database and used in this analysis. In JADER, data are provided in four files: "demo," "drug," "reac," and "hist," and the data in each file can be linked by an identification number. Patient age is rounded to every 10 years (*e.g.*, 10s, 20s, and 30s), although there are also reports of patients registered as first–third trimester pregnancies, infants, children, adults, the elderly, or unknown. As sex and age were the primary variables of interest in this study, only reports in which they could be clearly determined were included in this analysis.

2.2. Demographic data

Information on sex, age, and reporting year is included in the demo file. To characterize adverse event reports by sex and age, the data were stratified into 20 groups based on a combination of sex and age (aged 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and ≥90 years). In Japan, the national population census is conducted every 5 years. It was conducted four times between 2004 and 2023 (2005, 2010, 2015, and 2020). The 2015 data, which were considered to best reflect population trends within the study period, were used in this study. To visualize the age distribution of adverse event reports relative to that of the national population, the number of reports was normalized to the 2015 national population distribution. Population data were obtained from e-Stat (*https://www.e-stat.go.jp/*; accessed on Nov 9, 2024).

2.3. Medical histories

Information related to medical history (history of present illness, medication history, tobacco use, and alcohol use) is included in the hist file. Medical history is not always registered, possibly due to simple reporting errors. In the case of adverse event reports due to vaccination or drugs used during pregnancy and delivery, there may also be no relevant medical history. Medical history was reported based on the preferred term (PT) levels in the Medical Dictionary for Regulatory Activities (MedDRA). The study listed the top ten medical histories in each group, stratified by sex and age. Additionally, the number and percentage of patients with unregistered medical histories were investigated.

2.4. Causative drugs

Information related to drug use is included in the drug file. Drugs are classified into three categories based on their involvement in the occurrence of adverse events: "suspected drug," "drug interaction," and "concomitant drug." In this study, drugs classified as "suspected drug" or "drug interaction" were defined as "causative drug" based on previous research (*12*). We investigated the generic names of the top 10 causative drugs in each group and mapped them to the second level of the (Anatomical Therapeutic Chemical) ATC code (the main therapeutic class) (*https://www.kegg.jp/brite/br08303*, accessed on Nov 9, 2024). Drugs may have more than one ATC code; in such cases, they were counted under all ATC codes. Two coronavirus RNA vaccines, COMIRNATY® (Pfizer-BioNTech) and Spikevax® (Moderna), were used particularly frequently in Japan and were registered in JADER so that they could be recognized by their generic names; thus, they were counted separately. This information is always available, because each report contains at least one causative drug.

2.5. Adverse events

Information related to the adverse events is included in the reac file. Adverse events registered in the JADER database are based on the MedDRA-PT levels. In this study, we mapped all PT-level adverse events reported in each group to the 27 system organ classes (SOCs) at the top of the MedDRA hierarchy and then removed duplicates. PTs may belong to more than one SOC category. In this study, we counted all the SOCs for each case. This information is always available because each report includes at least one PT-level adverse event.

2.6. Statistical analysis

All data were analyzed using Microsoft® Excel® 2018

(Microsoft Corp., Redmond, WA, USA). In the analysis of adverse events at the SOC level, sex differences were considered to exist if the difference in the proportion of reported events between the sexes in each age group was ≥ 3.0%. This is because the occurrence of any particular adverse event may be low. When applying the chi-square test or Fisher's exact test to analyze big data, very small differences can be detected as statistically significant. Conversely, Cramer's V, as used for the effect size of the chi-square test or Fisher's exact test, tends to be low when the data distribution is skewed (*e.g.*, when most of the data points are concentrated in a specific category). Because the purpose of this study was to understand the overview of JADER, statistical significance was not considered important.

2.7. Ethical considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study used only publicly available data and did not involve direct access to study subjects. Therefore, the ethics committee of the author's institution waived the review of this study. All data from JADER were fully anonymized by the relevant regulatory authorities prior to access.

3. Results

3.1. Demographic data

There were 908,928 adverse event reports in the JADER database during the study period, of which 801,163 contained complete information on sex (males, 410,544, females, 390,619; female/male ratio, 0.95) and age. Figure 1 shows the time trend of the number of adverse event reports in the JADER database. A detailed breakdown of the number of adverse event reports for the combinations of sex and age groups is presented in Table 1, and a tree map was created based on this information (Figure 2A). The largest group was males in their 70s, followed by males in their 60s, and females in their 70s. The female/male ratio was < 0.9 in those aged < 10 years and those in their 60s and 70s; it was > 1.1 in those in their 20s, 30s, and 40s, and those ≥ 90 years. Figure 2B shows the tree map created after normalizing the proportion of adverse event reports in

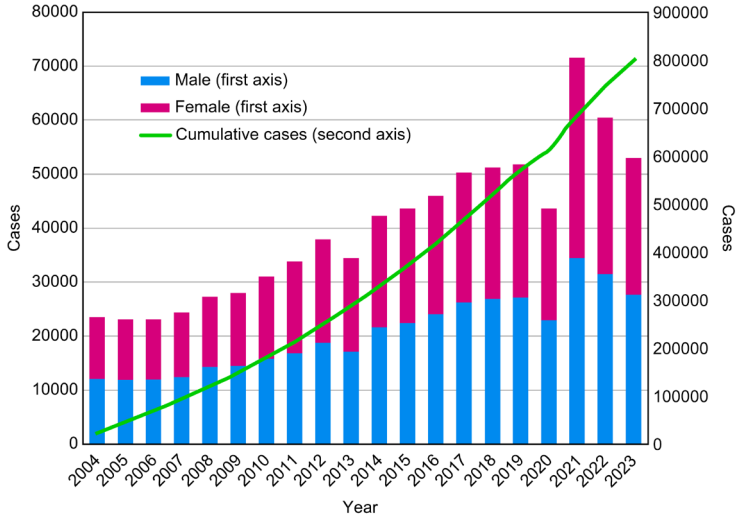

Figure 1. Time trends of the number of adverse event reports in the Japanese Adverse Drug Event Report database.

Table 1. A detailed breakdown of the number of adverse event reports for combinations of sex and age

Age (years)	Male [cases, rate (%)]	Female [cases, rate (%)]	Total [cases, rate (%)]	Female/Male
0–9	15,548 (1.94)	12,122 (1.51)	27,670 (3.45)	0.78
10–19	10,993 (1.37)	11,941 (1.49)	22,934 (2.86)	1.09
20–29	11,187 (1.40)	17,514 (2.19)	28,701 (3.58)	1.57
30–39	17,407 (2.17)	27,339 (3.41)	44,746 (5.59)	1.57
40–49	28,882 (3.61)	35,571 (4.44)	64,453 (8.04)	1.23
50–59	51,183 (6.39)	50,486 (6.30)	101,669 (12.69)	0.99
60–69	97,424 (12.16)	77,160 (9.63)	174,584 (21.79)	0.79
70–79	119,642 (14.93)	91,740 (11.45)	211,382 (26.38)	0.77
80–89	52,869 (6.60)	55,720 (6.95)	108,589 (13.55)	1.05
≥90	5,409 (0.68)	11,026 (1.38)	16,435 (2.05)	2.04
Total	410,544 (51.24)	390,619 (48.76)	801,163 (100)	0.95

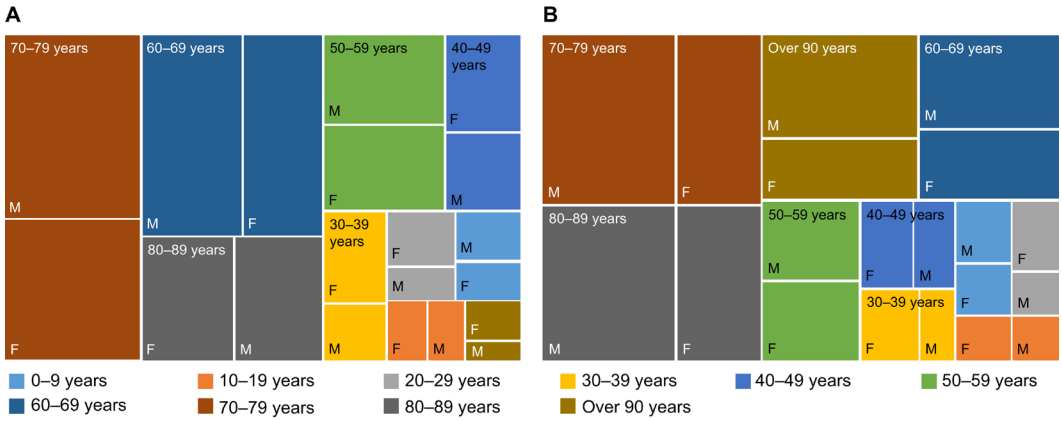

Figure 2. Tree maps based on raw data registered in the Japanese Adverse Drug Event Report database (A) or adjusted to the 2015 Japanese population composition (B). M; male, F; female.

each group to the national population distribution in 2015. Adverse events were reported at a higher rate in the elderly aged ≥ 70 years, and by females more than males in the age group of 20–49 years.

3.2. Medical history

The top ten medical histories for each sex–age group are presented in Table 2. Overall, cancer, infectious diseases, neuropsychiatric disorders, autoimmune diseases, and metabolic syndromes were frequently reported, and their distribution according to sex and age group was similar to that generally known. Hypertension was the most frequently reported medical history in the group aged ≥ 50 years regardless of sex. The rate of unregistered medical histories tended to be higher among the younger age groups than among the older age groups. The concordance rates of the top ten medical histories across different sexes and age groups are shown in Figure 3A. Eight of the top ten medical histories reported for each sex under 10 years of age were common. In other age groups, four to six of the reported top ten medical histories differed between males and females, indicating sex differences in medical history. When examining the concordance rates of medical histories between the age groups for each sex, a high degree of similarity was often observed between adjacent age groups (Figures 3B and 3C). The lowest concordance rate in medical histories between adjacent age groups was observed between males aged 10–19 years and those aged 20–29 years (3/10, 30%), and between females aged < 10 years and those aged 10–19 years (4/10, 40%).

3.3. Causative drugs

The top ten causative drugs in each group, classified by the combination of sex and age, are listed in Table 3. Prednisolone ranked among the top ten causative drugs in most groups, followed by Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) and tacrolimus hydrate. The distribution of the ATC codes for the top ten causative drugs according to sex and age is shown in Figure 4. The causative drugs reported in females had a wider distribution of ATC codes than those in males (27 *vs.* 23). Drugs belonging to the B01 class (antithrombotic agents) were frequently reported in both males and females aged ≥ 80 years. Drugs belonging to the J07 class (vaccines) were frequently reported in younger age groups. Drugs belonging to the L01 class (antineoplastic agents) were reported more frequently in the 10–19 and 40–79-year age groups, indicating a bimodal distribution. Drugs belonging to the L04 class (immunosuppressants) were reported more frequently in the 10–49-year age group in both males and females.

3.4. Adverse events

Figure 5 shows the reporting rate of SOC-level adverse events in each group divided by sex and age. Among those in their 10s to 40s, there were many SOC-level adverse events, with a difference of 3% or more in reporting rates between males and females. The reporting rate of nervous system disorders among teenage girls was particularly high. The reporting rates of infections and infestations were higher in males than in females aged 10–39 years. Immune system disorders were reported more frequently in females than in males aged between 20–49 years, and more frequently in males than in females in their 70s and 80s. Cardiac disorders were reported more frequently in females than in males in the 10s age group. The reporting rate of vascular disorders was higher in females than in males aged 10–49 years. The reporting rate of respiratory, thoracic, and mediastinal disorders was higher in males than in females over 60 years old. The reporting rates of skin and subcutaneous tissue disorders were higher in females than in males aged 10–59 years. Musculoskeletal and connective tissue disorders were reported more frequently in females than in males in

Table 2. The top ten medical histories for each sex–age group

Medical history	Number of cases	Rate (%)	Medical history	Number of cases	Rate (%)
Male, 0–9 years			**Female, 0–9 years**		
Influenza	526	3.38	Epilepsy	436	3.60
Asthma	516	3.32	Influenza	312	2.57
Epilepsy	472	3.04	Acute lymphocytic leukemia	289	2.38
Kawasaki's disease	419	2.69	Asthma	279	2.30
Acute lymphocytic leukemia	334	2.15	Kawasaki's disease	228	1.88
Patent ductus arteriosus	272	1.75	Patent ductus arteriosus	221	1.82
Nephrotic syndrome	268	1.72	Pyrexia	169	1.39
Factor VIII deficiency	198	1.27	Nephrotic syndrome	164	1.35
Pyrexia	196	1.26	Neuroblastoma	153	1.26
Attention deficit hyperactivity disorder	193	1.24	Premature baby	146	1.20
Unregistered	6,496	41.78	Unregistered	5,221	43.07
Male, 10–19 years			**Female, 10–19 years**		
Influenza	619	5.63	Epilepsy	531	4.45
Epilepsy	588	5.35	Acute lymphocytic leukemia	321	2.69
Acute lymphocytic leukemia	413	3.76	Influenza	274	2.29
Attention deficit hyperactivity disorder	404	3.68	Asthma	254	2.13
Colitis ulcerative	311	2.83	Acute myeloid leukemia	180	1.51
Asthma	288	2.62	Systemic lupus erythematosus	174	1.46
Autism spectrum disorder	270	2.46	Colitis ulcerative	173	1.45
Intellectual disability	215	1.96	Rhinitis allergic	168	1.41
Nephrotic syndrome	215	1.96	Non-tobacco user	148	1.24
Rhinitis allergic	206	1.87	Schizophrenia	143	1.20
Unregistered	3,372	30.67	Unregistered	4,974	41.65
Male, 20–29 years			**Female, 20–29 years**		
Schizophrenia	648	5.79	Schizophrenia	749	4.28
Colitis ulcerative	503	4.50	Depression	575	3.28
Epilepsy	431	3.85	Epilepsy	558	3.19
Depression	298	2.66	Systemic lupus erythematosus	430	2.46
Crohn's disease	270	2.41	Non-tobacco user	315	1.80
HIV infection	204	1.82	Colitis ulcerative	311	1.78
Insomnia	193	1.73	Dysmenorrhea	306	1.75
Intellectual disability	164	1.47	Asthma	286	1.63
Non-tobacco user	153	1.37	Insomnia	260	1.48
Hypertension	152	1.36	Bipolar disorder	234	1.34
Unregistered	3,731	33.35	Unregistered	6,446	36.80
Male, 30–39 years			**Female, 30–39 years**		
Schizophrenia	1,167	6.70	Schizophrenia	1,114	4.07
Hypertension	673	3.87	Systemic lupus erythematosus	816	2.98
HIV infection	586	3.37	Depression	759	2.78
Depression	493	2.83	Rheumatoid arthritis	626	2.29
Epilepsy	488	2.80	Asthma	573	2.10
Colitis ulcerative	440	2.53	Epilepsy	564	2.06
Diabetes mellitus	353	2.03	Hypertension	510	1.87
Hyperuricemia	346	1.99	Insomnia	493	1.80
Crohn's disease	343	1.97	Breast cancer	420	1.54
Insomnia	335	1.92	Non-tobacco user	418	1.53
Unregistered	5,116	29.39	Unregistered	8,982	32.85
Male, 40–49 years			**Female, 40–49 years**		
Hypertension	2,526	8.75	Breast cancer	1,775	5.00
Schizophrenia	1,627	5.63	Hypertension	1,553	4.37
Diabetes mellitus	1,470	5.09	Schizophrenia	1,366	3.84
Hyperuricemia	884	3.06	Rheumatoid arthritis	1,274	2.46
Hyperlipidemia	804	2.78	Depression	876	2.26
Depression	783	2.71	Uterine leiomyoma	854	2.11
Type 2 diabetes mellitus	764	2.65	Asthma	803	2.10
Tobacco user	725	2.51	Diabetes mellitus	749	2.03
Alcohol use	677	2.34	Systemic lupus erythematosus	748	1.92
Insomnia	672	2.33	Metastases to lymph nodes	722	1.87
Unregistered	7,265	25.15	Unregistered	10,188	28.64

Table 2. The top ten medical histories for each sex–age group (continued)

Medical history	Number of cases	Rate (%)	Medical history	Number of cases	Rate (%)
Male, 50–59 years			**Female, 50–59 years**		
Hypertension	6,535	12.77	Hypertension	4,201	8.32
Diabetes mellitus	3,813	7.45	Rheumatoid arthritis	3,109	6.16
Type 2 diabetes mellitus	1,840	3.59	Breast cancer	2,807	5.56
Metastases to lymph nodes	1,782	3.48	Diabetes mellitus	2,020	4.00
Metastases to lung	1,696	3.31	Metastases to lymph nodes	1,501	2.97
Hyperuricemia	1,593	3.11	Metastases to bone	1,459	2.89
Tobacco user	1,584	3.09	Hyperlipidemia	1,385	2.74
Hyperlipidemia	1,569	3.07	Metastases to lung	1,353	2.68
Schizophrenia	1,519	2.97	Metastases to liver	1,279	2.53
Alcohol use	1,382	2.70	Schizophrenia	1,256	2.49
Unregistered	11,870	23.19	Unregistered	12,740	25.23
Male, 60–69 years			**Female, 60–69 years**		
Hypertension	16,271	16.70	Hypertension	10,693	13.86
Diabetes mellitus	9,178	9.42	Rheumatoid arthritis	6,235	8.08
Metastases to lymph nodes	4,377	4.49	Diabetes mellitus	4,729	6.13
Metastases to lung	3,867	3.97	Breast cancer	3,573	4.63
Type 2 diabetes mellitus	3,856	3.96	Hyperlipidemia	3,155	4.09
Atrial fibrillation	3,396	3.49	Osteoporosis	3,143	4.07
Hyperuricemia	3,263	3.35	Metastases to lymph nodes	2,509	3.25
Tobacco user	3,254	3.34	Metastases to lung	2,478	3.21
Hyperlipidemia	3,108	3.19	Metastases to bone	2,205	2.86
Alcohol use	3,076	3.16	Constipation	2,072	2.69
Unregistered	19,854	20.38	Unregistered	16,903	21.91
Male, 70–79 years			**Female, 70–79 years**		
Hypertension	22,472	18.78	Hypertension	17,274	18.83
Diabetes mellitus	11,799	9.86	Rheumatoid arthritis	7,424	8.09
Atrial fibrillation	6,780	5.67	Diabetes mellitus	6,681	7.28
Metastases to lymph nodes	5,214	4.36	Osteoporosis	6,428	7.01
Type 2 diabetes mellitus	4,710	3.94	Hyperlipidemia	4,277	4.66
Metastases to lung	4,377	3.66	Atrial fibrillation	3,444	3.75
Benign prostatic hyperplasia	4,083	3.41	Dyslipidemia	2,910	3.17
Non-small cell lung cancer	4,075	3.41	Constipation	2,906	3.17
Chronic kidney disease	4,075	3.41	Insomnia	2,717	2.96
Hyperuricemia	3,915	3.27	Type 2 diabetes mellitus	2,647	2.89
Unregistered	23,712	19.82	Unregistered	19,904	21.70
Male, 80–89 years			**Female, 80–89 years**		
Hypertension	11,238	21.26	Hypertension	12,797	22.97
Atrial fibrillation	4,892	9.25	Osteoporosis	5,914	10.61
Diabetes mellitus	4,857	9.19	Atrial fibrillation	4,163	7.47
Benign prostatic hyperplasia	2,948	5.58	Diabetes mellitus	3,890	6.98
Chronic kidney disease	2,684	5.08	Rheumatoid arthritis	3,286	5.90
Prostate cancer	2,610	4.94	Hyperlipidemia	2,268	4.07
Type 2 diabetes mellitus	2,153	4.07	Constipation	2,187	3.92
Cerebral infarction	2,068	3.91	Chronic kidney disease	2,184	3.67
Hyperuricemia	1,975	3.74	Dementia	2,045	3.57
Constipation	1,807	3.42	Dyslipidemia	1,987	3.41
Unregistered	11,317	21.41	Unregistered	12,697	22.79
Male, ≥90 years			**Female, ≥90 years**		
Hypertension	1,077	19.91	Hypertension	2,595	23.54
Atrial fibrillation	560	10.35	Osteoporosis	1,091	9.89
Benign prostatic hyperplasia	372	6.88	Atrial fibrillation	992	9.00
Diabetes mellitus	336	6.21	Dementia	758	6.87
Prostate cancer	323	5.97	Diabetes mellitus	671	6.09
Chronic kidney disease	322	5.95	Cardiac failure	646	5.86
Cardiac failure	293	5.42	Cardiac failure chronic	637	5.78
Cardiac failure chronic	289	5.34	Chronic kidney disease	581	5.27
Cerebral infarction	259	4.79	Constipation	553	5.02
Dementia	257	4.75	Dementia Alzheimer's type	531	4.82
Unregistered	1,357	25.09	Unregistered	2,921	26.49

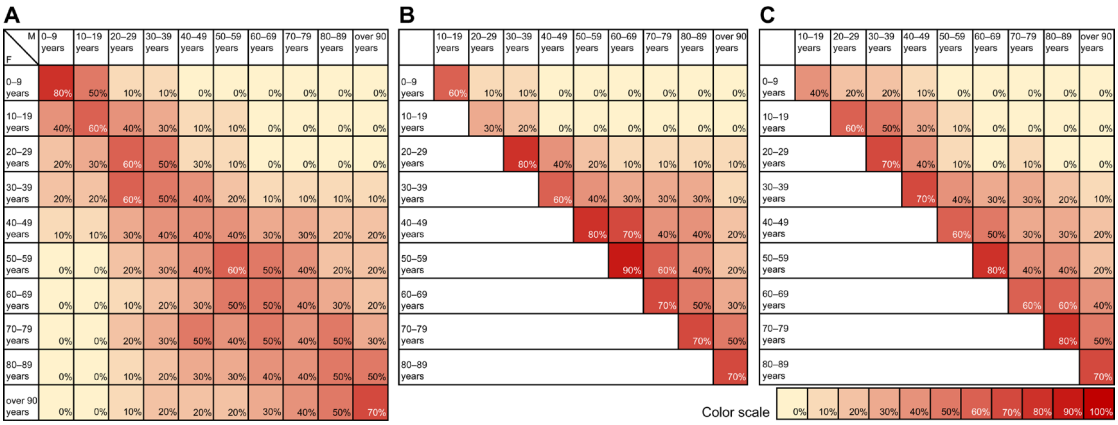

Figure 3. Concordance rate of the top ten medical histories. **A**; females *vs.* males, **B**; male, **C**; female.

the 10s and 80s age groups. Reports of pregnancy, puerperium, and perinatal conditions were mostly concentrated in the under 10, 20s, and 30s age groups, with a higher reporting rate among females than among males in the 20s and 30s age groups. The reporting rate of reproductive system and breast disorders was higher in females than in males aged between 20–49 years. The reporting rates of metabolic and nutritional disorders were higher in females than in males aged ≥ 90 years.

4. Discussion

In this study, we clarified the characteristics and reporting patterns of adverse event reports accumulated in the JADER database over a 20-year period, stratified by sex and age. The results of this study provide important insights that deepen the understanding of research using JADER.

The number of adverse event reports in the JADER database is increasing. Between 2020 and 2022, the number of reports may have varied due to changes in the healthcare system following the COVID-19 pandemic, increased use of the COVID-19 vaccine, and delays in adverse event reporting due to the workload faced by healthcare workers (*13*). In the United States, data have been accumulated in the Vaccine Adverse Event Reporting System (VAERS), which is a monitoring system that identifies immunization safety issues (*14*). However, the post-marketing adverse events of drugs accumulate in the FAERS. Recent studies have shown that the rapid increase in adverse event reports associated with the COVID-19 vaccine affects the results of signal detection based on disproportionality analysis using JADER, VigiBase® and EudraVigilance (*15-18*). Therefore, it is recommended that these databases be analyzed after excluding COVID-19 vaccine reports. In contrast, the FAERS was unaffected by the pandemic because all COVID-19 vaccine reports were included in a separate VAERS database. Currently, a system for collecting spontaneous reports of adverse events specific to vaccination has not been established in Japan; however, the establishment of a vaccine-specific adverse event reporting system should be discussed in the future.

In recent years, increased attention has been paid to the consideration of individual characteristics, including sex and age, in the context of medication use and adverse drug events (*19*). As the spontaneous adverse event reporting database does not contain baseline information on drug use, it is not possible to calculate the incidence of adverse events. Nonetheless, many researchers are recognizing the benefits of using spontaneous adverse event reporting databases and are further exploring methodologies to identify the risk of adverse events by sex and age (*7,20*). We support the promotion of this type of research but believe that a prerequisite is to understand the characteristics of the information contained in spontaneous adverse event report databases. However, the characteristics and patterns of adverse event reporting in the JADER database stratified by sex and age have not yet been clarified. In this study, the female/male ratio of all adverse event reports registered in JADER was 0.95, and no sex differences were observed. This fact appears to be supported by the results of an analysis in the Asian region using VigiBase® (*8*). In contrast, when groups were compared based on combined sex and age, sex differences in adverse event reporting were evident within certain groups. In general, sex and age affect the incidence of side effects. Sex-specific drug prescriptions may confound the assessment of associations between other medications and adverse event reports. For example, drug treatments for breast cancer, dysmenorrhea, prostate cancer, and benign prostatic hyperplasia generally have sex-specific adverse effects. These issues extend to other confounding factors such as age and concomitant medications. Older age and the concomitant use of medications are known risk factors for side effects (*21*). Females tend to live longer than males and take more medications simultaneously (*22,23*), which could induce further aggregate

Table 3. The top ten causative drugs in each group classified by the combination of sex and age

Sex	Age (years)	Causative drugs [ATC code; number of cases]
Male	0–9	Hemophilus b conjugate vaccine (tetanus toxoid conjugate) [J07; 1,447], Pneumococcal 13-valent conjugate vaccine [J07; 1,195], Live attenuated human rotavirus vaccine, oral [J07; 809], Recombinant adsorbed hepatitis B vaccine (yeast-derived) [J07; 691], Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (sabin strain) combined vaccine [J07; 631], Influenza HA vaccine [J07; 623], Tacrolimus hydrate [L04, D11; 597], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 454], Freeze-dried live attenuated mumps vaccine [J07; 420], Oseltamivir phosphate [J05; 412]
	10–19	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 714], Tacrolimus hydrate [L04, D11; 532], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 493], Methotrexate [L01, L04; 374], Cyclosporine [L04, S01; 366], Zanamivir hydrate [J05; 311], Etoposide [L01; 287], Carbamazepine [N03; 285], Cyclophosphamide hydrate [L01; 282], Acetaminophen [N02, 279]
	20–29	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 649], Coronavirus (SARS-CoV-2) RNA vaccine (Spikevax®) [J07; 598], Tacrolimus hydrate [L04, D11; 489], Mesalazine [A07; 374], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 368], Mycophenolate mofetil [L04; 262], Cyclosporine [L04, S01; 261], Infliximab (genetical recombination) [L04; 219], Carbamazepine [N03; 214], Loxoprofen sodium hydrate [M02; 210]
	30–39	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 684], Tacrolimus hydrate [L04, D11; 661], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 607], Mycophenolate mofetil [L04; 478], Cyclosporine [L04, S01; 432], Loxoprofen sodium hydrate [M02; 392], Clozapine [N05; 388], Coronavirus (SARS-CoV-2) RNA vaccine (Spikevax®) [J07; 350], Infliximab (genetical recombination) [L04; 333], Carbamazepine [N03; 323]
	40–49	Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 962], Tacrolimus hydrate [L04, D11; 899], Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 829], Nivolumab (genetical recombination) [L01; 782], Ribavirin [J05; 644], Mycophenolate mofetil [L04; 643], Clozapine [N05; 587], Cyclosporine [L04, S01; 555], Ipilimumab (genetical recombination) [L01; 512], Peginterferon alfa-2b (genetical recombination) [L03; 479]
	50–59	Nivolumab (genetical recombination) [L01; 2,329], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 1,553], Ribavirin [J05; 1,479], Ipilimumab (genetical recombination) [L01; 1,353], Tacrolimus hydrate [L04, D11; 1,311], Cisplatin [L01; 1,215], Oxaliplatin [L01; 1,200], Bevacizumab (genetical recombination) [L01; 1,143], Pembrolizumab (genetical recombination) [L01; 1,069], Peginterferon alfa-2b (genetical recombination) [L03; 1,052]
	60–69	Nivolumab (genetical recombination) [L01; 5,496], Pembrolizumab (genetical recombination) [L01; 3,128], Bevacizumab (genetical recombination) [L01; 3,049], Cisplatin [L01; 2,770], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 2,745], Ipilimumab (genetical recombination) [L01; 2,660], Oxaliplatin [L01; 2,525], Fluorouracil [L01; 2,269], Methotrexate [L01, L04; 2,242], Ribavirin [J05; 2,131]
	70–79	Nivolumab (genetical recombination) [L01; 6,985], Pembrolizumab (genetical recombination) [L01; 4,788], Ipilimumab (genetical recombination) [L01; 3,614], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 3,041], Bevacizumab (genetical recombination) [L01; 2,869], Aspirin [A01, B01, N02; 2,413], Carboplatin [L01; 2,393], Tegafur, gimeracil and oteracil potassium [L01; 2,339], Cisplatin [L01; 2,312], Methotrexate [L01, L04; 2,244]
	80–89	Apixaban [B01; 1,591], Nivolumab (genetical recombination) [L01; 1,507], Aspirin [A01, B01, N02; 1,454], Pembrolizumab (genetical recombination) [L01; 1,260], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 1,202], Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 1,188], Clopidogrel sulfate [B01; 1,110], Rivaroxaban [B01; 1,026], Warfarin potassium [B01; 780], Ipilimumab (genetical recombination) [L01; 760]
	Over 90	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 277], Apixaban [B01; 243], Aspirin [A01, B01, N02; 135], Rivaroxaban [B01; 133], Edoxaban tosilate hydrate [B01; 114], Enzalutamide [L02; 113], Irradiated red blood cells, leukocytes reduced [B05; 105], Leuprorelin acetate [L02, 98], Roxadustat [B03, 93], Clopidogrel sulfate [B01; 78]

associations. This study revealed that more than half of the adverse event reports included in JADER were from individuals aged 60–89 years. Furthermore, after adjusting the adverse event reports included in JADER to the national population distribution in 2015, it was highlighted that adverse events were reported more frequently in elderly individuals aged ≥ 70 years, and that in individuals aged 10–49 years, the reporting rate of adverse events was higher in females than in males. When comparing JADER with other spontaneous adverse event reporting databases, it is important to provide detailed descriptions of the demographics of each database.

Medical history analysis showed that eight of the top ten medical histories were shared by males and females under 10 years of age, confirming the high concordance rate of medical history. In other age groups, four to six items differed between males and females, confirming sex differences in medical history. Sex is a key factor in many aspects of healthcare, including pregnancy and childbirth, prevalence of chronic diseases, healthcare utilization, and medication use (*19*). Previous studies

Table 3. The top ten causative drugs in each group classified by the combination of sex and age (continued)

Sex	Age (years)	Causative drugs [ATC code; number of cases]
Female	0–9	Hemophilus b conjugate vaccine (tetanus toxoid conjugate) [J07; 1,284], Pneumococcal 13-valent conjugate vaccine [J07; 1,082], Live attenuated human rotavirus vaccine, oral [J07; 731], Recombinant adsorbed hepatitis B vaccine (yeast-derived) [J07; 594], Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio (sabin strain) combined vaccine [J07; 536], Tacrolimus hydrate [L04, D11; 534], Influenza HA vaccine [J07; 367], Rotavirus vaccine, live, oral, pentavalent [J07; 348], Pneumococcal polysaccharide conjugate vaccine [J07; 323], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 315]
	10–19	Recombinant adsorbed bivalent human papillomavirus-like particle vaccine (derived from Trichoplusia ni cells) [J07; 1,567], Coronavirus (SARS-CoV-2) RNA vaccine(COMIRNATY®) [J07; 642], Recombinant adsorbed quadrivalent human papillomavirus virus-like particle vaccine (yeast origin) [J07; 551], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 550], Tacrolimus hydrate [L04, D11; 453], Methotrexate [L01, L04; 338], Acetaminophen [N02, 282], Etoposide [L01, 267], Cyclosporine [L04, S01; 366], Mycophenolate mofetil [L04; 245]
	20–29	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 1,714], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 629], Tacrolimus hydrate [L04, D11; 543], Lamotrigine [N03; 487], Coronavirus (SARS-CoV-2) RNA vaccine (Spikevax®) [J07; 422], Loxoprofen sodium hydrate [M02; 387], Ritodrine hydrochloride [G02; 341], Drospirenone and ethinylestradiol betadex [G03; 324], Carbamazepine [N03; 310], Cyclosporine [L04, S01; 300]
	30–39	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 2,027], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 998], Tacrolimus hydrate [L04, D11; 878], Ritodrine hydrochloride [G02; 615], Loxoprofen sodium hydrate [M02; 549], Lamotrigine [N03; 542], Human menopausal gonadotrophin [G03; 518], Methotrexate [L01, L04; 467], Human chorionic gonadotrophin [G03; 463], Mycophenolate mofetil [L04; 422]
	40–49	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 2,802], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 1,292], Tacrolimus hydrate [L04, D11; 1,023], Methotrexate [L01, L04; 943], Paclitaxel [L01; 745], Bevacizumab (genetical recombination) [L01; 729], Cyclophosphamide hydrate [L01; 638], Pembrolizumab (genetical recombination) [L01; 551], Mycophenolate mofetil [L04; 508], Loxoprofen sodium hydrate [M02; 473]
	50–59	Methotrexate [L01, L04; 2,330], Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 2,298], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 1,959], Bevacizumab (genetical recombination) [L01; 1,362], Pembrolizumab (genetical recombination) [L01; 1,360], Paclitaxel [L01; 1,233], Tacrolimus hydrate [L04, D11; 1,219], Ribavirin [J05; 1,147], Carboplatin [L01; 900], Cyclophosphamide hydrate [L01; 865]
	60–69	Methotrexate [L01, L04; 4,714], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 3,065], Ribavirin [J05; 2,305], Bevacizumab (genetical recombination) [L01; 2,174], Pembrolizumab (genetical recombination) [L01; 2,057], Nivolumab (genetical recombination) [L01; 1,742], Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 1,593], Paclitaxel [L01; 1,576], Peginterferon alfa-2b (genetical recombination) [L03; 1,568], Tacrolimus hydrate [L04, D11; 1,443]
	70–79	Methotrexate [L01, L04; 5,418], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 3,217], Nivolumab (genetical recombination) [L01; 2,247], Pembrolizumab (genetical recombination) [L01; 2,144], Bevacizumab (genetical recombination) [L01; 1,797], Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 1,744], Lenalidomide hydrate [L04; 1,393], Dexamethasone [A01, C05, D07, D10, H02, R01, S01, S02, S03; 1,355], Carboplatin [L01; 1,224], Ipilimumab (genetical recombination) [L01; 1,208]
	80–89	Methotrexate [L01, L04; 1,892], Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 1,577], Apixaban [B01; 1,494], Prednisolone [A01, A07, C05, D07, H02, R01, S01, S02, S03; 1,316], Aspirin [A01, B01, N02; 1,031], Valaciclovir hydrochloride [J05; 986], Rivaroxaban [B01; 932], Alendronate sodium hydrate [M05; 870], Pregabalin [N02; 783], Clopidogrel sulfate [B01; 776]
	Over 90	Coronavirus (SARS-CoV-2) RNA vaccine (COMIRNATY®) [J07; 624], Apixaban [B01; 541], Valaciclovir hydrochloride [J05; 347], Aspirin [A01, B01, N02; 253], Rivaroxaban [B01; 241], Irradiated red blood cells, leukocytes reduced [B05; 204], Edoxaban tosilate hydrate [B01; 199], Furosemide [C03; 181], Glimepiride [A10; 177], Sacubitril valsartan sodium hydrate [C09; 173]

have shown that approximately 27% of the cases enrolled in JADER were patients with cancer treated with antineoplastic agents (*24*). In this study, breast cancer, a cancer specific to women, was ranked in the top ten for those in their 20s to 60s, while prostate cancer, a cancer specific to men, was ranked in the top ten for those in their 80s and older. Furthermore, when comparing the medical histories between age groups, high similarities were often found between adjacent age groups in both males and females. The lowest concordance rates in medical history between adjacent age groups were between the 10s and 20s for males (3/10, 30%) and between < 10 years and 10–19 years for females (4/10, 40%). This information may be useful for performing subgroup analyses.

In the analysis of the causative drugs, reporting

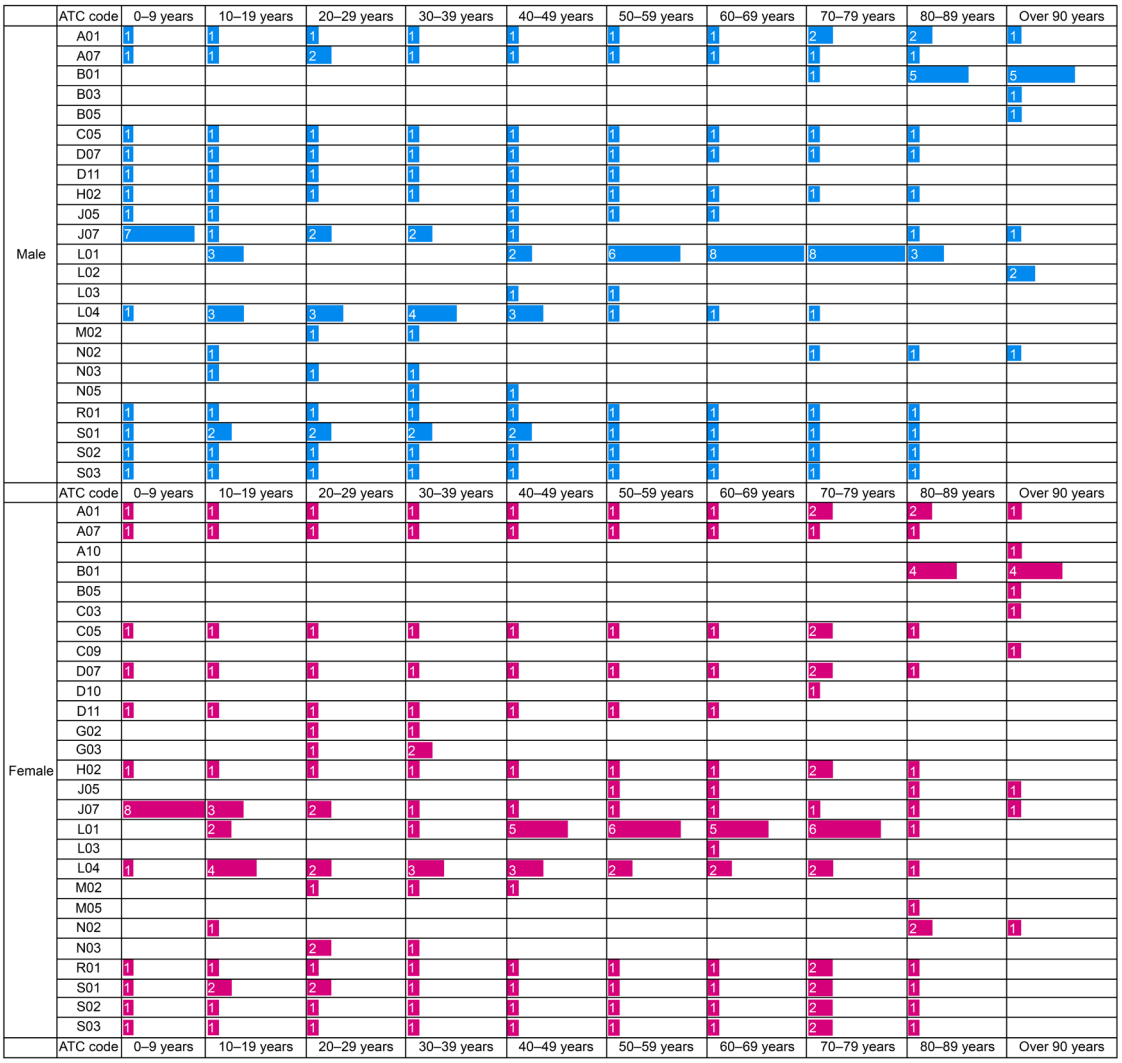

Figure 4. Distribution of ATC codes for the top ten causative drugs by sex and age.

patterns were identified by visualizing the distribution of frequently reported drug names and their ATC codes in groups stratified by sex and age. The causative drugs seem to be clearly influenced by factors such as sex and age, as well as susceptibility to disease and routine vaccinations. In particular, the number of reported vaccines [J07], immunosuppressants [L04], antineoplastic agents [L01], and antithrombotic agents [B01] was characterized by age. Prednisolone was the most commonly reported causative drug in this study, but differences in the administration route and dosage form were not considered. In other words, prednisolone has many ATC codes and indications, which may have influenced the results of this study. Despite vaccinations against COVID-19 only beginning in February 2021, COMIRNATY® ranked in the top ten in 15 of 20 age–sex groups and was the second most commonly reported causative drug overall. Understanding these facts will aid in the correct interpretation of spontaneous adverse event reports and their results. Additionally, analyzing adverse events at the SOC level allowed us to visualize adverse events that were more common or rarer in certain sex or age groups. When conducting subgroup analyses in studies using JADER data for particularly rare events or drugs occurring in specific patient populations, caution is required, as there may not be sufficient reporting. Adverse events seem to be influenced by factors such as sex, age, susceptibility to disease, vaccination, and medication use. The high number of reports on nervous system disorders among teenage girls is largely due to the influence of the human papillomavirus vaccination. Previous research has revealed a sex difference in the number of vaccine-related adverse events reported in JADER between those under 10 years of age and those aged 10–19 years (*25*).

One limitation of this study is that it did not consider actual drug use in Japan. We adjusted for sex and age using the 2015 Japanese population distribution; however, to calculate a more accurate adverse event reporting rate, it may be necessary to adjust for the demographic data of individuals who received medical care. However, this is not easy because JADER includes adverse event reports related to prescription drugs, vaccines, and over-the-counter drugs.

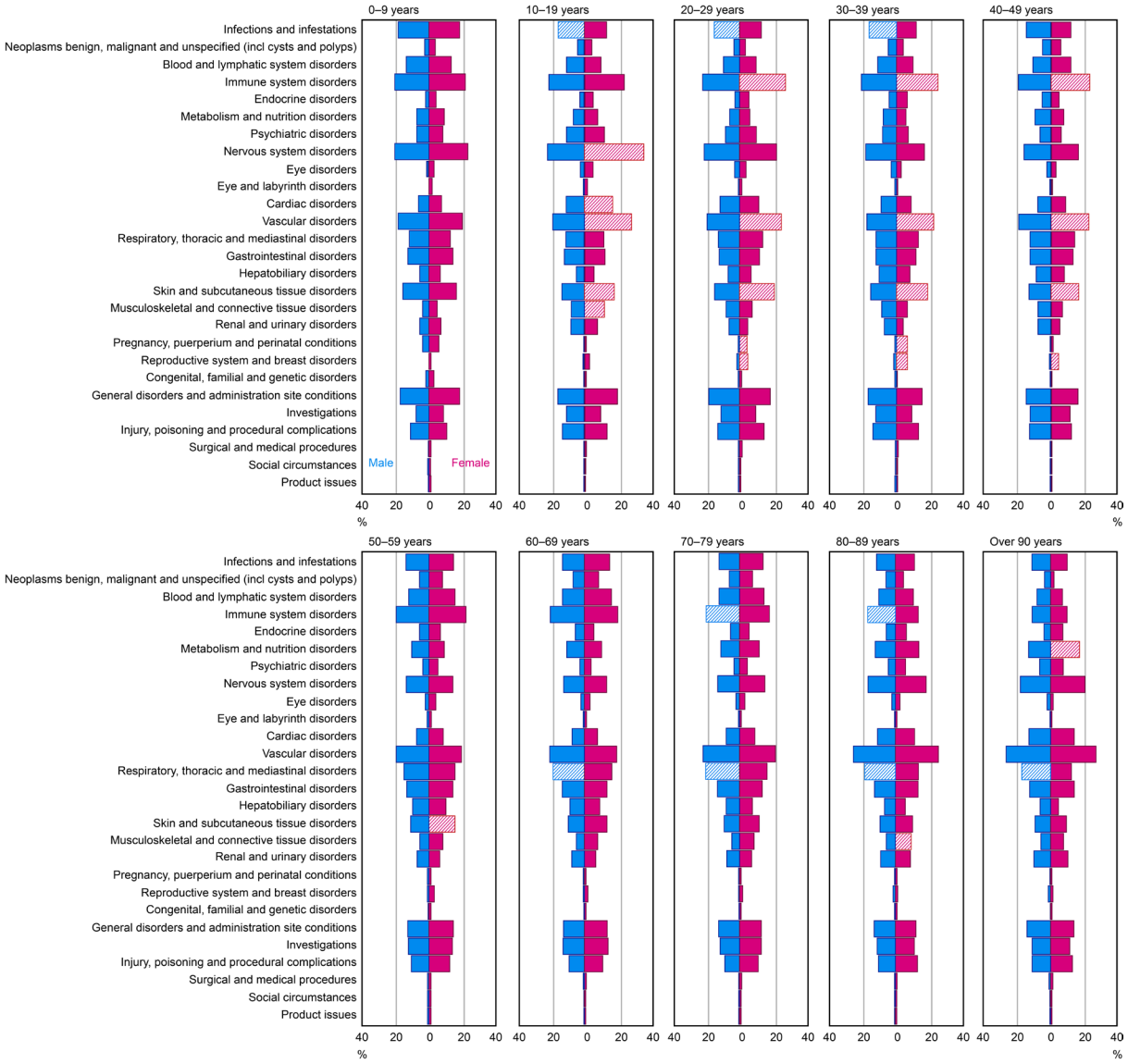

Figure 5. Reporting rate of system organ class-level adverse events in each group classified by the combination of sex and age. For system organ class-level adverse events where there is a difference of ≥ 3% in the reported proportion between males and females, the larger value is shaded.

In this study, we analyzed the characteristics and reporting patterns of adverse events included in the JADER database, focusing on sex and age. These results provide additional insights into the interpretation of previous studies using JADER. In addition, the results of this study will help understand the characteristics of adverse event reports contained in JADER and conduct appropriate subgroup and sensitivity analyses.

Acknowledgements

We would like to acknowledge Editage (*https://www.editage.com/*) for English language editing.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Michel C, Scosyrev E, Petrin M, Schmouder R. Can disproportionality analysis of post-marketing case reports be used for comparison of drug safety profiles? Clin Drug Investig. 2017; 37:415-422.
2. Noda A, Sakai T, Obara T, Miyazaki M, Tsuchiya M, Oyanagi G, Murai Y, Mano N. Characteristics of pediatric adverse drug reaction reports in the Japanese Adverse Drug Event Report database. BMC Pharmacol Toxicol. 2020; 21:36.
3. Chisaki Y, Aoji S, Yano Y. Analysis of adverse drug reaction risk in elderly patients using the Japanese Adverse Drug Event Report (JADER) database. Biol Pharm Bull. 2017; 40:824-829.
4. Sakai T, Ohtsu F, Sekiya Y, Mori C, Sakata H, Goto N. Methodology for estimating the risk of adverse drug reactions in pregnant women: analysis of the Japanese Adverse Drug Event Report database. Yakugaku Zasshi. 2016; 136:499-505. (in Japanese)

5. Tanaka H, Satoh M, Takigawa M, Onoda T, Ishii T. Characteristics of adverse event reports among people living with human immunodeficiency virus (HIV) in Japan: Data mining of the Japanese Adverse Drug Event Report database. Drug Discov Ther. 2023; 17:183-190.
6. Tsuchiya M, Obara T, Miyazaki M, Noda A, Takamura C, Mano N. The quality assessment of the Japanese Adverse Drug Event Report database using vigiGrade. Int J Clin Pharm. 2020; 42:728-736.
7. Yu Y, Chen J, Li D, Wang L, Wang W, Liu H. Systematic analysis of adverse event reports for sex differences in adverse drug events. Sci Rep. 2016; 6:24955.
8. Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine. 2019; 17:100188.
9. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biol Sex Differ. 2020; 11:32.
10. Sportiello L, Capuano A. Sex and gender differences and pharmacovigilance: a knot still to be untied. Front Pharmacol. 2024; 15:1397291.
11. Rushovich T, Gompers A, Lockhart JW, Omidiran I, Worthington S, Richardson SS, Lee KMN. Adverse drug events by sex after adjusting for baseline rates of drug use. JAMA Netw Open. 2023; 6:e2329074.
12. Tanaka H, Yoshiba Y, Watanabe T, Satoh M, Ishii T. Analysis of patients with hypomagnesemia using the Japanese Adverse Drug Event Report database (JADER). J Pharm Pharm Sci. 2018; 21:46-53.
13. Hauben M, Hung E. Effects of the COVID-19 pandemic on spontaneous reporting: Global and national time-series analyses. Clin Ther. 2021; 43:360-368.e5.
14. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015; 33:4398-4405.
15. Montes-Grajales D, Garcia-Serna R, Mestres J. Impact of the COVID-19 pandemic on the spontaneous reporting and signal detection of adverse drug events. Sci Rep. 2023; 13:18817.
16. Yamaoka K, Fujiwara M, Uchida M, Uesawa Y, Shimizu T. The influence of the rapid increase in the number of adverse event reports for COVID-19 vaccine on the disproportionality analysis using JADER. In Vivo. 2023; 37:345-356.
17. Matsuo H, Tanaka H, Endo K, Ishii T. Influence of rapidly increased numbers of reports on adverse events of the COVID-19 vaccine in the Japanese pharmacovigilance database on disproportionality analysis of antineoplastic drug-associated adverse cardiovascular events. Expert Opin Drug Saf. 2024; 1-5. doi: 10.1080/14740338.2024.2448830.
18. Micallef B, Dogné JM, Sultana J, Straus SMJM, Nisticò R, Serracino-Inglott A, Borg JJ. An exploratory study of the impact of COVID-19 vaccine spontaneous reporting on masking signal detection in EudraVigilance. Drug Saf. 2023; 46:1089-1103.
19. Alwhaibi M, Balkhi B. Gender differences in potentially inappropriate medication use among older adults. Pharmaceuticals (Basel). 2023; 16:869.
20. Zhao Z, Liu R, Wang L, Li L, Song C, Zhang P. A computational framework for identifying age risks in drug-adverse event pairs. AMIA Jt Summits Transl Sci Proc. 2022; 2022:524-533.
21. Zazzara MB, Palmer K, Vetrano DL, Carfì A, Onder G. Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med. 2021; 12:463-473.
22. Maxwell CJ, Mondor L, Pefoyo Koné AJ, Hogan DB, Wodchis WP. Sex differences in multimorbidity and polypharmacy trends: A repeated cross-sectional study of older adults in Ontario, Canada. PLoS One. 2021; 16:e0250567.
23. Orlando V, Mucherino S, Guarino I, Guerriero F, Trama U, Menditto E. Gender Differences in Medication Use: A drug utilization study based on real world data. Int J Environ Res Public Health. 2020; 17:3926.
24. Matsuo H, Endo K, Tanaka H, Onoda T, Ishii T. Fact-finding survey and exploration of preventive drugs for antineoplastic drug-induced oral mucositis using the Japanese Adverse Drug Event Report database. Sci Pharm. 2024; 92:34.
25. Noda A, Sakai T, Tsuchiya M, Oyanagi G, Obara T, Mano N. Characteristics of adverse events following immunization reporting in children: The Japanese Adverse Drug Event Report database. Vaccines (Basel). 2020; 8:357.

Received November 30, 2024; Revised January 30, 2025; Accepted February 19, 2025.

**Address correspondence to:*
Hiroyuki Tanaka, Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan.
E-mail: hiroyuki.tanaka@phar.toho-u.ac.jp

Released online in J-STAGE as advance publication February 26, 2025.