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ORIGINAL RESEARCH ARTICLE

Early Detection of Adverse Drug Reaction Signals by Association Rule Mining Using Large-Scale Administrative Claims Data

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Abstract

Introduction Adverse drug reactions (ADRs) are a leading cause of mortality worldwide and should be detected promptly to reduce health risks to patients. A data-mining approach using large-scale medical records might be a useful method for the early detection of ADRs. Many studies have analyzed medical records to detect ADRs; however, most of them have focused on a narrow range of ADRs, limiting their usefulness.

Objective This study aimed to identify methods for the early detection of a wide range of ADR signals.

Methods First, to evaluate the performance in signal detection of ADRs by data-mining, we attempted to create a gold standard based on clinical evidence. Second, association rule mining (ARM) was applied to patient symptoms and medications registered in claims data, followed by evaluating ADR signal detection performance.

Results We created a new gold standard consisting of 92 positive and 88 negative controls. In the assessment of ARM using claims data, the areas under the receiver-operating characteristic curve and the precision-recall curve were 0.80 and 0.83, respectively. If the detection criteria were defined as lift > 1, conviction > 1, and p-value < 0.05, ARM could identify 156 signals, of which 90 were true positive controls (sensitivity: 0.98, specificity: 0.25). Evaluation of the capability of ARM with short periods of data revealed that ARM could detect a greater number of positive controls than the conventional analysis method.

Conclusions ARM of claims data may be effective in the early detection of a wide range of ADR signals.

Key Points

To evaluate the performance of the data-mining approach in detecting ADR signals, we created a global gold standard consisting of 92 positive and 88 negative drug-event pairs based on clinical evidence.

Association rule mining (ARM) on administrative claims data for ADR signal detection has the potential to serve as a complementary tool for existing pharmacovigilance strategies.

1 Introduction

Adverse drug reactions (ADRs) are the undesirable effects associated with the use of medicines. ADRs are estimated to be the fourth leading cause of death in the USA [1, 2]. In addition, late detection of ADRs has been appraised to cause health consequences leading to medical costs of more than $800 million for a single drug type (rofecoxib–myocardial infarction) [3]. A previous review showed that 32% of the drugs that were newly approved by the US Food and Drug Administration (FDA) experienced post-marketing safety events, including withdrawals due to safety concerns and the addition of boxed warnings [4]. Therefore, the health risks associated with ADRs can be significantly reduced if these events are detected in an early and timely manner.

Although clinical trials are normally conducted to assess the safety of drugs, they have numerous limitations, including small sample sizes and short study durations [5]. Therefore, post-marketing surveillance through a spontaneous

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reporting system (SRS) plays an important role in the detection of ADRs associated with a particular drug. One of the major SRSs is the FDA Adverse Event Reporting System (FAERS), which contains information regarding different drug-related symptoms experienced by 11 million patients by the end of 2019. The use of SRSs has proven to be the most effective method of detecting serious ADRs [6–8].

However, the SRS has known limitations, including systematic underreporting and a lack of information on the exposed population [9, 10]. Previous studies have shown that only approximately 6% of serious ADRs are reported to the SRS [11], since it is difficult to determine whether the changes in symptoms experienced by the patient are drug-induced, despite the availability of a few tools that can assess drug-induced adverse reactions [12, 13]. These limitations may reduce the quality of data analysis for detecting ADRs. Therefore, methods that can complement SRS in the effective detection of ADRs are urgently required.

Unlike SRS, electronic medical records (EMRs) and administrative claims data register patient symptoms and medications, regardless of suspected ADRs. Therefore, several past studies have used EMRs for detecting ADRs [14–16]. However, EMRs cannot cover a wider range of patients because it is difficult to track patient's symptoms in an event of transfer to another facility [17]. However, administrative claims data can track a patient's symptoms even if the patient is transferred from one hospital to another. Additionally, the lack of information on prescription drugs and symptoms is very low compared to that in other clinical databases. Therefore, analyzing a large-scale administrative claims database has the potential to actively understand the relationship between drugs and ADRs.

Sequence symmetry analysis (SSA) is a frequently used tool for ADR signal detection based on administrative claims data [18, 19]. Several research works have been undertaken using SSA for administrative claim data to detect ADR signals [20–22], but most of these studies used long-term data (e.g., 17-year period) and examined specific hypotheses about the effects of a particular drug class and subsequent health outcomes. Recently, several studies have assessed a wide range of relationships between drugs and ADRs using prescription databases [23–26]; however, the detection of ADR signals was based on long-term data, and early detection of ADR signals was not examined. It is also difficult to analyze ADRs for which there is no therapeutic drug since the patient's symptoms are not registered in the prescription database.

The objective of this study was to identify methods for the early detection of a wide range of ADR signals using data on patient symptoms registered in an administrative claims database, the first computational approach of the kind.

2 Methods

2.1 Data Sources

2.1.1 US Food and Drug Administration Adverse Event Reporting System (FAERS) Database

Adverse event reports from 2004 to 2019 were obtained from the FDA website (https://www.fda.gov/drugs/drug–approvals–and–databases/fda–adverse–event–reporting–system–faers). Duplicate reports were eliminated as previously reported [27], and the remaining 11,438,031 reports were analyzed. Arbitrary drug names, including trade names and abbreviations, were manually mapped into unified generic names using text mining. ADRs were coded according to the preferred terminology of the Medical Dictionary for Regulatory Activities (MedDRA, http://www.meddra.org/; version 23.0). We used standardized MedDRA Queries (SMQs), consisting of 226 terms for the FAERS analysis.

2.1.2 JADER (Japanese Adverse Drug–Event Report) Database

Adverse event reports from 2004 to 2019 were obtained from the PMDA (Pharmaceuticals and Medical Devices Agency) website (www.pmda.go.jp). The JADER database contains 611,336 reports of adverse events, including data on the date of the first administration of each drug and the onset date of each ADR. The JADER analysis also used the 226 SMQs.

2.1.3 JMDC Insurance Claims Data

Administrative claims data from 2005 to 2019 were purchased from JMDC Inc. (Tokyo, Japan). The dataset contained the monthly medical diagnoses and prescription claims of 7,438,470 employees and their dependents. All diagnoses were encoded using the International Classification of Diseases, 10th Revision (ICD10) codes, and all the medications were mapped to the Anatomical Therapeutic Chemical (ATC) codes. ICD10 codes 'O00-O99', 'Q00-Q99', 'V01-Y98', and 'Z00-Z99' were excluded from this study since these codes are unlikely to be drug induced. Furthermore, we also excluded topical agents, fluid therapies, diagnostic aid drugs, and Chinese herbal drugs (ATC categories: D, K, R, T, and V).

2.2 Identification of the Gold Standard

To evaluate the performance of the data-mining approach in detecting ADR signals, proper reference benchmarks are necessary, which are frequently known as the gold standards. So far, some gold standards have been created to accelerate

pharmacovigilance [23, 28–30]. Ryan et al. [29] created a gold standard by utilizing four events that are vital to pharmacovigilance activities, including myocardial infarction, kidney injury, liver injury, and gastrointestinal bleeding. Harpaz et al. [30] created one that included the date of label change of a drug as per the FDA website. However, to assess the utility of a wide range of ADR signal detection, it is crucial to establish a gold standard across a wide scope of drugs and related adverse events. In addition, without information about the timing of the occurrence of an ADR, it is difficult to assess whether the data-mining approach is effective in realistic simulations. Therefore, we created a new global gold standard based on large-scale ADR self-reports, FAERS, and JADER databases, which included the time-to-onset profile for ADRs. Only reports with the drug code "primary suspect drug" or "secondary suspect drug" were included in this analysis. First, we conducted a disproportionality analysis [6] using the reporting odds ratio (ROR) and its statistical significance (Z score) for each ADR (226 individual SMQs) to examine the association of each drug with a zero-cell correction (adding 0.5 to each count in a 2 × 2 table). In this regard, we divided individuals in the ADR self-reports into the following four groups: (a) individuals who received the drug of interest and exhibited the ADR of interest; (b) individuals who received the drug of interest but did not exhibit the ADR of interest; (c) individuals who did not receive the drug and exhibited the ADR of interest; and (d) individuals who did not receive the drug and did not exhibit the ADR of interest. The ROR and Z scores were calculated using the following equations:

$$\mathrm{ROR} = \frac{a/b}{c/d}$$

$$\mathrm{Z\ score} = \frac{\log(\mathrm{ROR})}{\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

where a, b, c, and d refer to the number of individuals in each group. Positive and negative controls and time-to-onset profiles for ADRs were created based on the following criteria:

2.2.1 Positive Controls

Positive controls were denoted by the drug–event pairs with a causal relationship between the two (true ADRs). ADRs (187 SMQs: excluded that not reported 39 SMQs) that were not reported by chance were identified for each drug using a binomial test as reported previously [31]. We calculate the p-values for all observed ADR occurrences for the drug of interest and performed a Benjamini–Hochberg False Discovery Rate (FDR) correction (using the R function 'binom.test'). If the FDR-corrected p-value was < 0.01, then the ADR value for that drug was 1, reflecting an association, otherwise it was 0. Further, we extracted the drug–event pairs that were determined to be significant (ROR > 1 and Z score > 1.96) in the disproportionality analysis. For each SMQ, one drug was selected from the combination that showed a strong signal in the FAERS and JADER analyses according to the following criteria:

1. Extracted drugs with the top 30 Z score values for each SMQ in FAERS and JADER.
2. For the top three pairs, the product information was checked to determine whether the drug–event pairs were recognized as true associations. The drug was selected if it was supported by another database.
3. If nothing was selected among the top three pairs, the rank was gradually lowered.

2.2.2 Negative Controls

Negative controls consisted of drug–event pairs that did not have a causal relationship between the drug and event and were highly unlikely to be associated. We extracted the drugs and the events that appeared in the positive controls. For each SMQ, drug–event pairs were created by selecting a drug according to the following criteria:

1. For each SMQ, extracted drugs not reported as primary candidates in JADER and those with a ROR < 1 in FAERS analysis.
2. Randomly selected drug per SMQ.
3. The product information and biomedical literature via PubMed were checked to determine whether the drug–event pairs were highly unlikely to be associated. 'Drug-induced event' term was used for PubMed search. If there were no case reports of ADR occurrence or if there were case reports of ADR suppression, the drug was selected.

2.2.3 Time-to-Onset Profiles of ADRs

For positive controls, time-to-onset profiles of ADRs were calculated for each drug–event pair using the JADER database. This database contains information about the start and end dates of administration of the suspected drug and the date of onset of the ADR. We calculated the onset profile and the median duration of onset of an ADR as the time elapsed between the patient's first prescription and the occurrence of the ADR.

2.2.4 Mapping of ADRs to International Classification of Diseases, 10th Revision (ICD10)

ADRs in SRS databases were coded according to the SMQs, while symptoms in JMDC claims data were coded according to the ICD10 code. To evaluate the detection of ADR signals in the JMDC claims data, each ADR of the gold standard needed to be mapped to the ICD10 code. SMQs are ADR categories that group several MedDRA preferred terms (PTs). For each positive control SMQ, we identified the PTs for the paired drug reported in FAERS (up to the top three). JMDC claims data contain 22,925 standard disease names for symptoms, which are linked to 1,500 ICD10 codes. By pairing the top three kinds of PTs and JMDC standard disease names with similar names, SMQ and ICD10 were manually mapped.

2.3 Association Rule Mining (ARM)

ARM is an analytical method that efficiently identifies items with high co-occurrence probability from massive data and is used in medical data analysis to identify undiscovered associations among medications, diagnoses, and clinical outcomes [32]. ARM has been proposed as an approach for pharmacovigilance and pharmacology studies using the SRS database [7, 33–35]. Therefore, we applied ARM to medications and symptoms registered in the claims data and extracted patterns that exceeded a prespecified threshold (i.e., defined as the support measure shown below). We then evaluated its usefulness in detecting ADR signals using our gold standard.

Given a set of transactions (each transaction contains a set of items), an association rule was expressed as $X \rightarrow Y$, where X and Y were sets of items. The support indicated how frequently the rule occurred in the transaction, and was calculated as:

$$\text{Support}\,(X, Y) = P(X \cap Y)$$

The confidence corresponded to the conditional probability P (Y|X), and was calculated as:

$$\text{Confidence}\,(X \rightarrow Y) = \frac{P(X \cap Y)}{P(X)}$$

The lift represented how many times X and Y occurred together, more frequently than the expected number, if they were statistically independent. The lift was calculated as:

$$\text{Lift}\,(X \rightarrow Y) = \frac{\text{Confidence}\,(X \rightarrow Y)}{\text{Support}\,(Y)}$$

The conviction compared the probability of X appearing without Y, if they were dependent on the actual frequency of the appearance of X without Y. The Conviction was calculated as:

$$\text{Conviction}\,(X \rightarrow Y) = \frac{1 - \text{Support}\,(Y)}{1 - \text{Confidence}\,(X \rightarrow Y)}$$

Unlike the lift, conviction is sensitive to rule direction since it also uses the information of the absence of the consequent (lift $(X \rightarrow Y)$ = lift $(Y \rightarrow X)$). In general, lift > 1 was used as the detection standard for the ARM but conviction > 1 was also used in this study [36]. The strength of the drug–event pair association was evaluated by calculating lift and conviction. The statistical significance of the association rule was estimated using the chi-square test. The chi-square value was calculated as follows:

$$\text{Chisquare} = \text{n}\,(\text{Lift} - 1)^2 \frac{\text{Support} * \text{Confidence}}{(\text{Confidence} - \text{Support})\,(\text{Lift} - \text{Confidence})}$$

If there were values less than 10, Fisher's exact test was used instead of the chi-squared test. The ARM was performed using the *Apriori* function of *arules* library in the arules package of R version 4.0.2 software (2020-06-22). In this analysis, we examined whether ARM could be effective for screening ADR signals using administrative claims data.

2.3.1 Preparation for Data-Mining

We used the JMDC claims data and extracted records of drugs and their prescribed months, as well as the ICD10 codes and their registration months. Only the first occurrence of each outcome was noted in this study, and the run-in period or the so-called washout period was set to exclude cases in which the patient had already been prescribed a medication or been diagnosed with a disease before enrolling in the insurance scheme [37]. In this study, we set the minimum support threshold as a small value (1×10^{-10}) because the gold standard created could include ADRs that occurred with a very rare frequency. The performance of ARM using administrative claims data for detecting ADR signals was evaluated via four separate analyses described below. ARM was used to assess the relevance of only two items—drug and event in the drug–event pair. It should be noted that ARM usually analyzes multiple (two or more) sets of items, but in this study, only two item pairs were analyzed. Although this analysis was equivalent to a disproportionality analysis, we used the term ARM in this study according to previous reports in this field.

2.3.2 Performance Calculation and Reproducibility

First, we calculated ARM performance by setting a 6-month run-in period, which was considered a sufficient duration.

ARM was performed on claims data from 2005 to 2019, which contained 162,454,898 records of 6,072,316 patients. Second, to validate the reproducibility of ARM performance, we prepared different datasets by dividing the claims data (Supplementary Table 1 in the Online Supplementary Material (OSM)) into ten groups, based on the timing of patient enrollment, and performed ARM for each dataset wherein different populations were assumed. The performance of ARM was compared with that of SSA [18, 19]. A proof-of-concept study on SSA was published in 1996, and since then the number of SSA-related articles published per year and the total number of articles are on the rise [38, 39]. By using SSA, several ADRs associated with a wide array of organs have been identified [20–22]. Therefore, we considered SSA as a good baseline method for comparing the performance of ARM.

2.3.3 Early Detection of ADRs

To examine ARM performance in the early detection of ADR signals, we prepared datasets with records from January 2018 as a starting point and extended these to 3 and 6 months. To exclude the influence of the number of patients, we continued to follow the same patients (1,337,370 patients). A 3-month run-in period was set instead of 6 months to minimize the decrease in the number of records as much as possible.

2.3.4 Safety Label Changes

We examined whether ARM could detect ADR signals for a new therapeutic drug earlier than the issuance of safety information. Here we focused on the "Ethinyl estradiol drospirenone–Thrombophlebitis" pair from the gold standard because event is difficult to infer from the drug indications and the pair was issued safety information (Rapid Safety Communications) by the regulatory agency. We prepared the dataset from November 2010 (the month in which the drug was marketed) to November 2013 (the month before the safety information was issued).

2.3.5 Evaluation of the Conventional Benchmark

To validate our findings, we determined the performance using the conventional benchmark. In this regard, we used the gold standard proposed by Ryan et al. because it spans four events essential to pharmacovigilance activities [29]. Of the drug–event pairs generated in this previous study, only those drug–event pairs (61 positive controls and 39 negative controls) including drugs marketed in Japan and those for which the level of evidence was considered high were extracted (Supplementary Table 2, OSM) to evaluate the performance of ARM. In this study, four ADRs, namely acute myocardial infarction, acute liver injury, gastrointestinal bleed, and acute kidney injury, were examined, mapping to ICD10 codes I21, K71, K92, and N17, respectively.

2.4 Sensitivity, Specificity, Precision, and F-Measure

To evaluate the effectiveness of ARM in detecting the ADR signal of each drug, the sensitivity, specificity, and precision were calculated. The F-measure was calculated from the harmonic mean of the sensitivity and precision.

3 Results

3.1 Identification of the Gold Standard

A flowchart for the identification of the gold standard is shown in Fig. 1. A disproportionality analysis was performed to examine the association between each ADR and each drug (563,805 ADR–drug pairs). In the volcano plot, Z scores were used instead of p-values to save space (Fig. 2a). In addition, we performed a binomial test to examine whether each ADR was reported more frequently than chance level in patients prescribed the drug. Of 226 individual SMQs, 39 types were excluded from further analyses because they were not reported as ADRs (Supplementary Table 3, OSM). Additionally, 47 SMQs were excluded because of the difficulty encountered while determining whether they were ADRs (e.g., congenital abnormality). Furthermore, 27 SMQs were excluded because of their similarity to other SMQs.

For positive controls, one drug was selected from the combination showing a strong signal based on the results of the binomial test and disproportionality analysis (Supplementary Table 4, OSM). As an exception, for 12 SMQs (“Cholestasis and jaundice of hepatic origin”, “Haemolytic disorders”, “Haematopoietic cytopenias affecting more than one type of blood cell”, “Ventricular tachyarrhythmias”, “Dyskinesia”, “Gastrointestinal obstruction”, “Biliary tract disorders”, “Gastrointestinal nonspecific dysfunction”, “Gastrointestinal nonspecific symptoms and therapeutic procedures”, “Conjunctival disorders”, “Lipodystrophy”, and “Osteoporosis/osteopenia”), we selected the drugs not included in the top 30 in JADER but with several reports in FAERS and high Z scores. For eight SMQs (“Agranulocytosis”, “Asthma/bronchospasm”, “Dyslipidaemia”, “Hyperglycaemia/new onset diabetes mellitus”, “Embolic and thrombotic events, venous”, “Gallbladder related disorders”, “Hypertension”, and “Tubulointerstitial diseases”), we selected the drugs that followed next to include a wide range of ATC classifications, although there were drugs that met the criteria of being at the top of the list. For two SMQs (“Supraventricular tachyarrhythmias” and “Drug abuse and

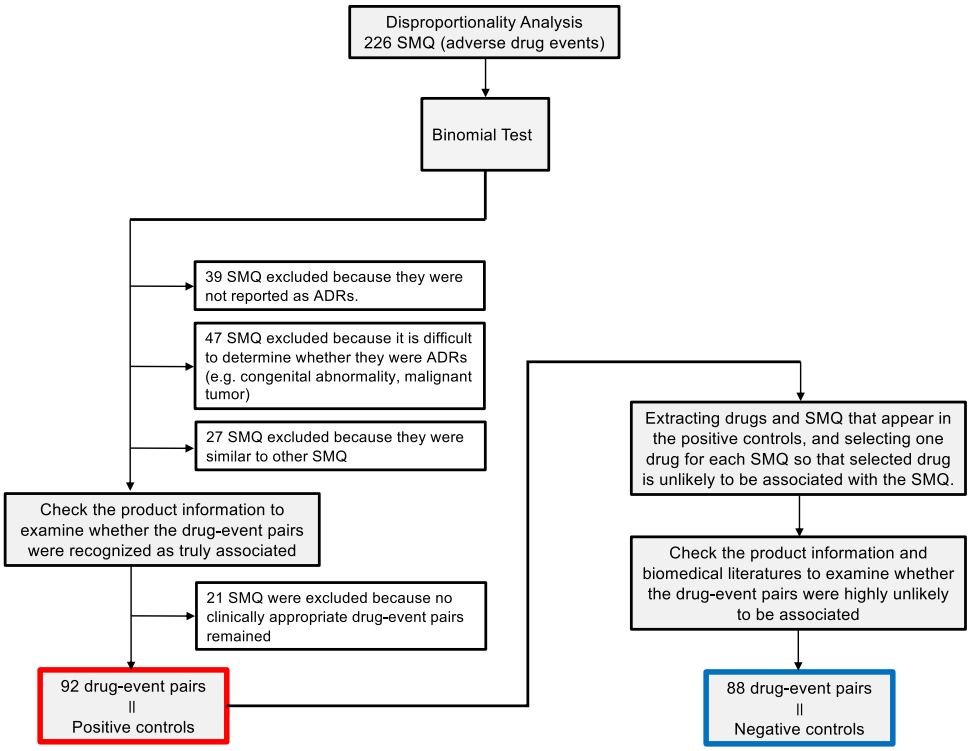


Fig. 1 Flowchart depicting identification of gold standard positive and negative controls through the FDA Adverse Event Reporting System (FAERS) and Japanese Adverse Drug–Event Report (JADER) analysis. *ADRs* adverse drug reactions, *FDA* US Food and Drug Administration, *SMQ* standardized MedDRA Queries

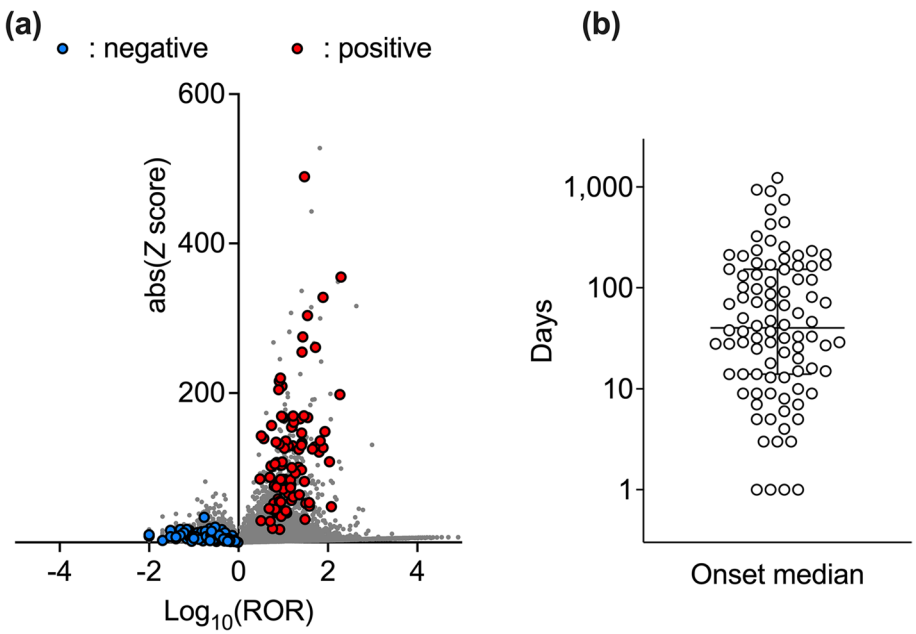


Fig. 2 Features of gold standard based on large-scale ADR self-reports. (**a**) Volcano plots for visualizing the reporting odds ratio (ROR) and its statistical significance (*Z* score) in FAERS data (563,805 drug–event pairs). Ninety-two positive controls were indicated by red circles and 88 negative controls were indicated by blue circles. (**b**) Time-to-onset profile of the 92 positive controls. *ADR* adverse drug reaction, *FAERS* US Food and Drug Administration Adverse Event Reporting System

dependence"), we selected the drugs not supported in the top 30 in FAERS but with high *Z* score in JADER and enough cases in JMDC claims data. For "Taste and smell disorders", we selected the drug that was considered to have less bitterness and was used in a sufficient number of cases in JMDC claims data. For "Retinal disorders", we selected the drug that followed next because of the crucial ADR listed in the warning box of the product information although there were drugs that met the criteria of being at the top of the list. For "Other ischaemic heart disease", we selected the drug not supported in the top 30 in FAERS but with a high *Z* score in JADER. Furthermore, it was considered a serious ADR with high frequency in the package insert. A total of 21 SMQs were excluded because no clinically appropriate drug–event pairs remained (Supplementary Table 3, OSM).

For negative controls, we selected one drug for each SMQ so that the selected drug was unlikely to be associated with the SMQ. We determined that ADRs related to allergy ("Drug reaction with eosinophilia and systemic symptoms syndrome", "Eosinophilic pneumonia", "Asthma/bronchospasm", "Angioedema", "Acute pancreatitis", "Anaphylactic reaction", "Severe cutaneous adverse reactions", and "Hypersensitivity"), gastrointestinal symptoms ("Noninfectious diarrhoea", "Gastrointestinal nonspecific dysfunction", "Gastrointestinal nonspecific inflammation", and "Gastrointestinal ulceration"), electrolyte abnormalities ("Hypokalaemia", "Dehydration", and "Lactic acidosis"), "Hypertension", and anemia ("Haematopoietic erythropenia") could occur with any drug, making it difficult to create drug–event pairs. Since most drugs are metabolized in the liver, we determined that creating drug–event pairs for two SMQs ("Hepatitis, non-infectious" and "Cholestasis and jaundice of hepatic origin") would be difficult. We included three SMQs ("Ventricular tachyarrhythmias", "Disorders of sinus node function", and "Torsade de pointes/QT prolongation") in "Supraventricular tachyarrhythmias" to create negative controls. We also included "Gallbladder related disorders" in "Biliary tract disorders" to create negative controls. We were unable to create drug–event pairs for four SMQs ("Haemodynamic oedema, effusions and fluid overload", "Noninfectious encephalopathy/delirium", "Cardiac failure", and "Gastrointestinal nonspecific symptoms and therapeutic procedures") because no valid drugs were remaining. Finally, to bring the number of negative controls closer to the number of positive controls, in some SMQs, we allowed the selection of one additional drug. The resultant gold standard consisted of 92 positive and 88 negative controls.

Time-to-onset profiles of events were calculated as the time elapsed between the patient's first prescription and the occurrence of the adverse event using the JADER database. In addition, to evaluate the detection of ADR signals in the JMDC claims data, we identified the PTs encompassed by each SMQ, and then frequent PTs were mapped to ICD10 codes (Supplementary Table 5, OSM). Unlike the previously reported gold standards, which were limited to specific events [23, 28–30] and did not include information about the onset of ADRs, our gold standard covered a wide range of drugs and ADRs and also included time-to-onset profiles of ADRs (Table 1; Fig. 2b; Supplementary Table 6, OSM).

Table 1 Features of the gold standard based on large-scale ADR self-reports: number of ICD10 categories included in the gold standard

ICD10 category	ICD10 detail	Number of categories
A	Parasitic diseases	7
B	Infectious diseases	6
C	Malignant neoplasms	0
D	Benign neoplasms	13
E	Metabolic disorders	22
F	Psychological disorders	9
G	Nervous disorders	16
H	Eye and ear disorders	18
I	Cardiovascular disorders	23
J	Respiratory disorders	9
K	Gastrointestinal disorders	24
L	Skin disorders	1
M	Musculoskeletal disorders	13
N	Renal disorders	6
R	Symptoms	12
T	Drug-induced reactions	1

ADR adverse drug reaction, *ICD10* International Classification of Diseases, 10th Revision

3.2 Performance Evaluation of ARM

The gold standard presented in this study made it possible to evaluate the performance of ARM in the detection of ADR signals by using the JDMC claims data. In this regard, we analyzed only two items in the drug–event pair. We referred to the method as ARM, although it was reduced to disproportionality analysis. First, we analyzed the claims data from January 2005 to August 2019 and calculated the performance of ARM using our gold standard (Tables 2 and 3). To accommodate extremely small p-values, we calculated $-\log_{10}$ (p-value). Figure 3a shows the receiver-operating-characteristic (ROC) curve, and Fig. 3b shows the precision-recall curve with the lift value as the threshold. The area under the ROC curve (ROC-AUC) was 0.80 and the area under the precision-recall curve (PR-AUC) was 0.83. If the ARM detection criteria were defined as follows: lift > 1, conviction > 1, and p-value < 0.05, 156 signals were identified, of which 90 were true positive controls (sensitivity: 0.98, specificity: 0.25, precision: 0.58, and F-measure: 0.73). SSA identified 59 signals, of which 42 were true positive controls (sensitivity: 0.46, specificity: 0.81, precision: 0.46, and F-measure: 0.56). By both methods, 57 pairs were considered signals, of which 42 pairs were true positive controls. To assess the reproducibility of ROC- and PR-AUC, we divided the claims data into ten parts, and thereafter ARM was repeated for each dataset. The ROC-AUC ranged from 0.71 to 0.77 and the PR-AUC ranged from 0.74 to 0.81 (Fig. 3c, d).

Second, we examined whether ARM was capable of detecting ADR signals with short accumulation periods of data. In this regard, the ARM detection criteria were defined as follows: lift > 1, conviction > 1, and p-value < 0.05 and the performance of ARM was compared with that of SSA. Figure 4a shows the sensitivity of ARM and SSA for ADR signal detection. In the 1-month dataset, ARM achieved a sensitivity of 0.38 (detected 35 positive pairs), whereas SSA

Table 2 ARM and SSA performances for positive controls using JMDC claims data from 2005 to 2019

ICD10	Event	Drug name	ARM				SSA			Log_{10} (ROR)
			Lift	Count	Conviction	$-Log_{10}$ (*p*-value)	ASR	ASR 95%CI Lower	ASR 95%CI Upper	
A04	Pseudomembranous colitis	Piperacillin-tazobactam combination	3.70	1,164	1.0553	510.89	1.46	1.28	1.67	1.47
A09	Gastrointestinal nonspecific inflammation	Ipilimumab	1.57	18	1.4074	1.74	3.12	1.19	8.20	1.35
A41	Sepsis	Cytarabine	242.79	1,042	2.4575	54636.26	3.57	3.04	4.20	1.19
B16	Liver infections	Rituximab	43.45	217	1.1152	1961.60	0.93	0.68	1.27	0.98
B25	Opportunistic infections	Mycophenolic acid	530.15	399	1.5303	45801.71	3.05	2.39	3.88	1.54
D59	Haemolytic disorders	Tacrolimus	129.68	158	1.0419	4387.25	0.80	0.55	1.15	0.91
D61	Haematopoietic erythropenia	Palbociclib	15.66	2	1.0059	2.13	4.80	0.30	76.68	0.94
D61	Haematopoietic cytopenias affecting more than one type of blood cell	Pemetrexed	18.45	8	1.0070	7.69				1.16
D69	Haematopoietic thrombocytopenia	Ribavirin	6.91	70	1.0580	78.87	0.36	0.22	0.59	0.84
D70	Haematopoietic leukopenia	Oxaliplatin	54.58	805	1.2665	9239.08	4.95	4.10	5.99	0.91
D70	Agranulocytosis	Trimethoprim-sulfamethoxazole combination	36.51	3,208	1.1620	24243.12	2.43	2.24	2.65	0.94
D72	Drug reaction with eosinophilia and systemic symptoms syndrome	Allopurinol	3.00	565	1.0102	167.21	0.78	0.65	0.93	2.27
E03	Hypothyroidism	Nivolumab	26.14	197	1.3330	1046.51	2.72	1.96	3.76	1.17
E05	Hyperthyroidism	Amiodarone	7.77	171	1.0574	222.34	1.57	1.14	2.17	1.83
E16	Hypoglycaemia	Insulin glargine	9.18	630	1.0530	1007.48	1.75	1.46	2.09	1.44
E78	Dyslipidaemia	Olanzapine	2.37	4,351	1.1496	827.32	0.95	0.89	1.00	0.97
E86	Dehydration	Furosemide	2.35	13,189	1.2227	2547.78	0.76	0.73	0.79	0.97
E87	Hyponatraemia/SIADH	Indapamide	4.81	397	1.0412	264.67	1.32	1.06	1.63	1.89
E87	Lactic acidosis	Metformin	2.97	1,590	1.0209	462.32	1.52	1.37	1.69	2.29
E87	Hypokalaemia	Furosemide	14.57	7,072	1.1640	19767.89	1.50	1.42	1.59	1.21
E88	Lipodystrophy	Lamivudine	54.61	10	1.1693	116.06	0.64	0.12	3.48	2.03
E88	Tumour lysis syndrome	Bendamustine	27.70	27	1.0777	152.82	2.62	1.03	6.64	1.59
F05	Noninfectious encephalopathy/delirium	Valacyclovir	1.57	209	1.0003	10.82	1.34	1.01	1.77	1.16
F19	Drug abuse and dependence	Mirtazapine	11.55	130	1.0034	275.24	1.22	0.85	1.76	0.82
F32	Depression (excl. suicide and self-injury)	Varenicline	3.10	3,427	1.0822	1104.64	0.85	0.80	0.91	0.97
F38	Hostility/aggression	Paroxetine	20.30	12	1.0004	49.32	2.70	0.56	12.99	1.12
G03	Noninfectious meningitis	Human immunoglobulin	21.98	108	1.0124	472.33	1.47	0.87	2.47	1.27
G04	Noninfectious encephalitis	Atezolizumab		0						1.49
G21	Neuroleptic malignant syndrome	Haloperidol	64.74	1,085	1.0772	14841.48	1.47	1.26	1.71	1.71
G21	Parkinson-like events	Aripiprazole	70.54	3,165	1.0848	47484.63	2.73	2.51	2.98	0.99
G24	Dystonia	Risperidone	8.67	237	1.0119	352.66	2.09	1.55	2.80	1.04
G24	Dyskinesia	Aripiprazole	6.18	378	1.0080	361.25	2.20	1.77	2.73	1.20
G62	Peripheral neuropathy	Bortezomib	6.31	121	1.4737	126.11	1.83	1.25	2.68	1.23

Table 2 (continued)

ICD10	Event	Drug name	ARM				SSA			Log_{10} (ROR)
			Lift	Count	Conviction	$-Log_{10}$ (*p*-value)	ASR	ASR 95%CI Lower	ASR 95%CI Upper	
H02	Ocular motility disorders	Botulinum toxin type A	4.20	257	1.0652	140.42	0.62	0.47	0.81	1.55
H10	Conjunctival disorders	Lamotrigine	1.15	2,880	1.0647	18.26	0.63	0.59	0.68	0.50
H26	Lens disorders	Aflibercept	13.57	1,095	1.4753	2842.93	0.45	0.39	0.53	0.88
H35	Retinal disorders	Hydroxychloroquine	12.01	293	1.4688	662.42	1.76	1.34	2.31	0.75
H40	Glaucoma	Triamcinolone acetonide	2.64	12,802	1.0763	3021.96	0.95	0.92	0.99	1.08
H44	Ocular infections	Aflibercept	17.75	22	1.0065	76.94	4.20	1.50	11.79	1.65
H46	Optic nerve disorders	Ethambutol	159.26	311	1.1778	10637.11	7.87	4.93	12.57	1.58
H91	Hearing impairment	Gentamicin	2.03	901	1.0168	105.89	0.89	0.77	1.02	0.95
I10	Hypertension	Lenvatinib	7.66	53	1.6400	71.85	1.75	0.86	3.57	1.19
I20	Other ischaemic heart disease	Anagrelide	21.46	43	1.5466	186.90	1.44	0.77	2.72	0.92
I21	Myocardial infarction	Celecoxib	2.36	1,835	1.0028	335.90	1.19	1.08	1.30	1.01
I26	Embolic and thrombotic events, venous	Lenalidomide	48.36	9	1.0287	12.26	0.54	0.10	2.96	0.48
I27	Pulmonary hypertension	Dasatinib	29.81	3	1.0092	3.81				0.71
I42	Cardiomyopathy	Trastuzumab	10.83	22	1.0099	43.95	2.71	1.05	6.98	1.42
I45	Torsade de pointes/QT prolongation	Nilotinib	14.57	8	1.0469	6.96	2.71	0.53	13.98	1.11
I48	Supraventricular tachyarrhythmias	Cilostazol	14.29	523	1.0590	1413.75	1.07	0.87	1.30	0.76
I49	Disorders of sinus node function	Donepezil	4.19	164	1.0944	90.24	0.71	0.51	0.98	1.51
I49	Ventricular tachyarrhythmias	Escitalopram (citalopram)	2.71	3,422	1.0484	830.15	0.79	0.73	0.85	0.79
I50	Cardiac failure	Bosentan	19.56	61	1.5033	239.04	0.20	0.10	0.40	0.85
I61	Haemorrhagic central nervous system vascular conditions	Rivaroxaban	10.14	76	1.0109	137.68	1.16	0.73	1.83	0.91
I63	Ischaemic central nervous system vascular conditions	Ranibizumab	8.58	128	1.0567	189.19	0.81	0.57	1.17	0.80
I80	Thrombophlebitis	Ethinyl estradiol-drospirenone combination	3.92	291	1.0134	140.16	3.46	2.63	4.56	1.93
J18	Infective pneumonia	Lenalidomide	6.91	104	1.4195	121.27	2.24	1.50	3.35	0.57
J38	Angioedema	Enalapril	1.94	205	1.0098	21.51	0.84	0.64	1.12	0.68
J82	Eosinophilic pneumonia	Nivolumab	31.13	3	1.0038	3.86	1.04	0.09	11.46	1.34
J84	Interstitial lung disease	Amiodarone	46.13	248	1.0963	2385.70	6.41	4.38	9.40	1.46
J96	Respiratory failure	Diazepam	3.56	10,939	1.0527	4585.02	1.05	1.01	1.10	0.94
J98	Asthma/bronchospasm	Propofol	6.71	2,682	1.0089	2960.24	1.64	1.48	1.83	0.85
K10	Osteonecrosis	Denosumab	11.47	17	1.0034	36.53	3.75	1.32	10.65	1.42
K12	Oropharyngeal conditions (excl. neoplasms, infections and allergies)	Everolimus	9.91	290	2.3103	538.71	1.60	1.20	2.14	0.73
K21	Gastrointestinal nonspecific dysfunction	Alendronate	4.56	5,433	1.6042	3633.18	0.62	0.58	0.65	1.03

Table 2 (continued)

ICD10	Event	Drug name	ARM				SSA			Log_{10} (ROR)
			Lift	Count	Conviction	$-Log_{10}$ (*p*-value)	ASR	ASR 95%CI Lower	ASR 95%CI Upper	
K25	Gastrointestinal ulceration	Aspirin	3.54	13,486	1.2848	5860.83	1.19	1.14	1.23	0.96
K52	Noninfectious diarrhoea	Irinotecan	5.07	182	1.0583	132.42	0.54	0.39	0.74	0.81
K56	Gastrointestinal obstruction	Adalimumab	18.95	152	1.0922	565.91	1.04	0.75	1.46	0.74
K63	Gastrointestinal perforation	Bevacizumab	4.46	484	1.1332	293.39	0.18	0.14	0.24	1.06
K71	Cholestasis and jaundice of hepatic origin	Amoxicillin-clavulanate combination	1.52	390	1.0005	16.64	1.25	1.02	1.54	1.41
K76	Hepatitis, non-infectious	Isoniazid	3.04	539	1.1813	174.33	1.07	0.89	1.28	1.36
K80	Gallstone related disorders	Ceftriaxone	2.41	6,337	1.0147	1198.30	0.94	0.89	0.99	1.18
K81	Gallbladder related disorders	Octreotide	21.66	85	1.0631	366.51	0.43	0.26	0.72	0.82
K83	Biliary tract disorders	Isoniazid	4.63	25	1.0078	16.52	1.77	0.73	4.31	1.22
K85	Acute pancreatitis	Sitagliptin	4.57	610	1.0128	374.27	0.77	0.66	0.91	1.38
K92	Gastrointestinal haemorrhage	Rivaroxaban	3.22	381	1.0439	130.32	1.25	1.02	1.54	1.47
L51	Severe cutaneous adverse reactions	Lamotrigine	2.55	62	1.0044	13.72	1.40	0.82	2.38	1.22
M31	Vasculitis	Propylthiouracil	18.47	19	1.0077	69.58	3.99	1.16	13.79	2.07
M32	Systemic lupus erythematosus	Adalimumab	28.84	62	1.0362	364.10	0.81	0.48	1.36	0.74
M62	Rhabdomyolysis/myopathy	Simvastatin	3.04	258	1.0280	79.07	0.72	0.56	0.92	1.72
M77	Tendinopathies and ligament disorders	Levofloxacin	1.71	57,088	1.0235	4592.38	1.18	1.16	1.20	1.89
M81	Osteoporosis/osteopenia	Prednisolone	3.40	16,747	1.0373	6604.06	2.25	2.17	2.34	0.67
N12	Tubulointerstitial diseases	Vancomycin	10.08	379	1.0506	679.44	1.34	1.08	1.66	1.41
N17	Acute renal failure	Vancomycin	104.91	709	1.1093	15881.53	0.85	0.70	1.03	1.02
N39	Proteinuria	Bevacizumab	6.55	403	1.1178	421.52	1.93	1.57	2.36	1.41
R11	Gastrointestinal nonspecific symptoms and therapeutic procedures	Varenicline	1.43	6,654	1.0795	218.59	1.10	1.04	1.16	0.51
R21	Hypersensitivity	Amoxicillin	2.79	8,917	1.0063	2637.58	1.27	1.22	1.33	0.94
R43	Taste and smell disorders	Clarithromycin	1.82	17,991	1.0042	2142.80	1.92	1.85	1.99	0.88
R44	Psychosis and psychotic disorders	Oseltamivir	1.95	18,536	1.0110	2179.70	0.52	0.50	0.54	1.00
R56	Convulsions	Imipenem-cilastatin combination	0.99	52	0.9999	0.02	0.57	0.31	1.02	1.06
R60	Haemodynamic oedema, effusions, and fluid overload	Dasatinib	11.66	52	1.1787	113.11	1.78	0.99	3.18	0.70
R73	Hyperglycaemia/new onset diabetes mellitus	Quetiapine	2.90	399	1.0175	110.83	0.80	0.66	0.98	0.90
T78	Anaphylactic reaction	Rocuronium	1.30	6,339	1.0066	104.00	0.72	0.69	0.76	1.80

ARM association rule mining, *ASR* Adjusted Sequence Ratio, *excl.* excluding, *ICD10* International Classification of Diseases, 10th Revision, *ROR* reporting odds ratio, *SSA* sequence symmetry analysis

Table 3 ARM and SSA performance for negative controls using JMDC claims data from 2005 to 2019

ICD10	Event	Drug name	ARM				SSA			Log_{10} (ROR)
			Lift	Count	Conviction	$-Log_{10}$ (*p*-value)	ASR	ASR 95%CI Lower	ASR 95%CI Upper	
A04	Pseudomembranous colitis	Amiodarone	1.21	64	1.0042	0.94	1.02	0.60	1.72	−0.09
A04	Pseudomembranous colitis	Olanzapine	1.75	706	1.0148	51.79	0.73	0.63	0.85	−0.41
A41	Sepsis	Diazepam	5.23	2,050	1.0105	1571.40	1.50	1.35	1.66	−0.09
A41	Sepsis	Donepezil	14.57	53	1.0344	147.32	2.11	1.16	3.85	−0.36
B16	Liver infections	Aripiprazole	2.00	194	1.0024	22.37	0.95	0.71	1.28	−1.09
B16	Liver infections	Furosemide	11.20	1,284	1.0254	2618.68	0.67	0.60	0.76	−0.32
B25	Opportunistic infections	Cilostazol	7.14	41	1.0040	48.41	1.18	0.60	2.34	−0.19
B25	Opportunistic infections	Paroxetine	1.86	37	1.0006	3.91	0.67	0.35	1.28	−0.92
D59	Haemolytic disorders	Varenicline	1.82	18	1.0003	2.00	1.14	0.44	2.93	−0.95
D61	Haematopoietic cytopenias affecting more than one type of blood cell	Varenicline	1.42	18	1.0002	0.87	0.97	0.38	2.45	−1.92
D69	Haematopoietic thrombocytopenia	Aflibercept	2.63	78	1.0153	18.31	1.14	0.72	1.80	−0.22
D70	Agranulocytosis	Botulinum toxin type A	2.12	27	1.0044	4.20	1.97	0.90	4.31	−2.00
D70	Agranulocytosis	Insulin glargine	7.66	336	1.0268	426.41	1.07	0.85	1.34	−1.15
D70	Haematopoietic leukopenia	Ranibizumab	1.93	16	1.0037	2.13	0.86	0.32	2.31	−1.22
E03	Hypothyroidism	Irinotecan	3.63	96	1.0268	41.36	0.97	0.65	1.45	−0.52
E03	Hypothyroidism	Levofloxacin	1.79	18,725	1.0079	1724.19	1.14	1.11	1.18	−0.01
E05	Hyperthyroidism	Oxaliplatin	1.90	57	1.0073	6.14	0.43	0.23	0.79	−0.42
E05	Hyperthyroidism	Celecoxib	2.00	5,987	1.0081	697.06	0.97	0.92	1.02	−0.47
E16	Hypoglycaemia	Palbociclib	1.54	3	1.0033	0.51	0			−0.55
E16	Hypoglycaemia	Pemetrexed	1.81	12	1.0050	1.44	1.56	0.46	5.34	−0.58
E78	Dyslipidaemia	Ceftriaxone	1.61	36,028	1.0612	2062.27	0.95	0.93	0.97	−0.44
E87	Hyponatraemia/SIADH	Aflibercept	5.61	186	1.0502	156.07	1.58	1.18	2.12	−0.54
E88	Lipodystrophy	Sitagliptin	6.49	663	1.0150	676.23	1.10	0.93	1.29	−0.81
E88	Lipodystrophy	Quetiapine	6.81	282	1.0159	306.81	0.75	0.58	0.98	−0.60
E88	Tumour lysis syndrome	Ribavirin	13.13	39	1.0339	96.60	0.48	0.25	0.92	−0.88
E88	Tumour lysis syndrome	Lamotrigine	3.98	93	1.0081	46.43	0.92	0.61	1.38	−1.66
F19	Drug abuse and dependence	Simvastatin	2.44	5	1.0005	1.25	1.12	0.19	6.70	−0.30
F19	Drug abuse and dependence	Bendamustine		0						−1.57
F32	Depression (excl. suicide and self−injury)	Rivaroxaban	1.76	391	1.0284	30.22	1.05	0.86	1.29	−0.76
F38	Hostility/aggression	Alendronate		0						−0.52
F38	Hostility/aggression	Aspirin	1.08	1	1.0000	0.22	0			−0.63
G03	Noninfectious meningitis	Oxaliplatin	0.91	2	0.9999	0.19	1.68	0.11	26.94	−0.19
G04	Noninfectious encephalitis	Insulin glargine	8.93	27	1.0021	42.63	0.73	0.31	1.73	−0.56
G21	Neuroleptic malignant syndrome	Adalimumab	2.08	4	1.0012	0.89	0			−1.60

Table 3 (continued)

ICD10	Event	Drug name	ARM				SSA			Log_{10} (ROR)
			Lift	Count	Conviction	$-Log_{10}$ (*p*-value)	ASR	ASR 95%CI Lower	ASR 95%CI Upper	
G21	Parkinson−like events	Bortezomib		0						−0.54
G24	Dyskinesia	Rivaroxaban	2.57	25	1.0024	6.03	1.23	0.56	2.69	−1.08
G24	Dyskinesia	Rituximab	1.91	6	1.0014	1.00	0.60	0.11	3.28	−1.12
G24	Dystonia	Vancomycin	2.11	23	1.0017	3.61	0.74	0.32	1.72	−0.45
G62	Peripheral neuropathy	Enalapril	2.30	1,351	1.0854	230.73	0.79	0.71	0.88	−0.11
G62	Peripheral neuropathy	Bosentan	1.59	16	1.0373	1.28	0.32	0.10	1.01	−0.53
H02	Ocular motility disorders	Lenalidomide	2.70	16	1.0336	4.53	0.62	0.22	1.80	−0.73
H10	Conjunctival disorders	Insulin glargine	1.00	3,248	1.0017	0.11	0.91	0.84	0.97	−0.40
H26	Lens disorders	Everolimus	5.40	66	1.1271	54.00	1.07	0.65	1.75	−0.26
H26	Lens disorders	Trimethoprim-sulfamethoxazole combination	3.55	1,995	1.0700	820.23	1.21	1.11	1.33	−0.34
H35	Retinal disorders	Piperacillin-tazobactam combination	2.69	1,255	1.0517	301.25	0.85	0.76	0.96	−1.00
H40	Glaucoma	Irinotecan	1.27	141	1.0117	2.41	0.33	0.23	0.48	−1.12
H40	Glaucoma	Mycophenolic acid	4.92	234	1.2035	166.98	0.87	0.66	1.14	−0.07
H44	Ocular infections	Allopurinol	2.86	41	1.0007	11.79	0.70	0.38	1.30	−0.14
H46	Optic nerve disorders	Metformin	2.64	131	1.0016	30.43	1.22	0.85	1.74	−0.34
H91	Hearing impairment	Metformin	1.48	1,222	1.0078	44.07	0.92	0.82	1.04	−0.31
I20	Other ischaemic heart disease	Propylthiouracil	2.90	116	1.0338	32.99	0.78	0.53	1.16	−0.50
I21	Myocardial infarction	Isoniazid	3.06	16	1.0043	5.63	1.38	0.50	3.79	−0.61
I26	Embolic and thrombotic events, venous	Valacyclovir	1.51	240	1.0003	10.24	1.10	0.85	1.42	−0.59
I27	Pulmonary hypertension	Levofloxacin	1.49	502	1.0002	22.29	1.29	1.07	1.54	−0.49
I42	Cardiomyopathy	Imipenem-cilastatin combination	3.41	20	1.0024	8.28	1.24	0.50	3.11	−0.63
I48	Supraventricular tachyarrhythmias	Ethambutol	3.16	27	1.0091	9.59	0.78	0.35	1.78	−0.42
I61	Haemorrhagic central nervous system vascular conditions	Haloperidol	16.92	298	1.0192	974.94	0.49	0.36	0.67	−0.36
I63	Ischaemic central nervous system vascular conditions	Oseltamivir	0.80	4,722	0.9986	59.58	1.23	1.16	1.31	−0.62
I80	Thrombophlebitis	Levofloxacin	1.98	9,526	1.0045	1225.67	1.19	1.14	1.25	−0.24
J18	Infective pneumonia	Indapamide	1.05	403	1.0026	0.53	1.07	0.88	1.30	−0.25
J84	Interstitial lung disease	Ethinyl estradiol-drospirenone combination	0.72	23	0.9995	0.94	3.50	1.44	8.52	−0.43
J96	Respiratory failure	Ethinyl estradiol-drospirenone combination	1.42	449	1.0084	13.58	1.35	1.12	1.63	−0.60
K10	Osteonecrosis	Aripiprazole	2.32	30	1.0004	5.75	1.45	0.70	3.01	−1.27
K12	Oropharyngeal conditions (excl. neoplasms, infections and allergies)	Bosentan	2.28	24	1.0886	4.73	1.17	0.52	2.60	−0.37
K56	Gastrointestinal obstruction	Denosumab	5.40	116	1.0211	92.27	1.87	1.29	2.71	−0.55

Table 3 (continued)

ICD10	Event	Drug name	ARM				SSA			Log_{10} (ROR)
			Lift	Count	Conviction	$-Log_{10}$ (*p*-value)	ASR	ASR 95%CI Lower	ASR 95%CI Upper	
K56	Gastrointestinal obstruction	Lamivudine	3.14	1	1.0102	0.56				− 0.06
K63	Gastrointestinal perforation	Risperidone	1.24	727	1.0082	8.41	0.72	0.62	0.83	− 0.83
K80	Gallstone related disorders	Clarithromycin	1.25	24,737	1.0026	398.24	1.34	1.30	1.37	− 0.28
K80	Gallstone related disorders	Rivaroxaban	4.46	288	1.0368	171.24	1.02	0.80	1.30	− 0.54
K83	Biliary tract disorders	Triamcinolone acetonide	2.29	570	1.0028	92.96	1.44	1.22	1.70	− 1.04
K92	Gastrointestinal haemorrhage	Hydroxychloroquine	1.30	21	1.0057	0.65	0.51	0.15	1.75	− 0.33
K92	Gastrointestinal haemorrhage	Botulinum toxin type A	2.22	135	1.0238	21.18	0.84	0.60	1.19	− 1.30
M31	Vasculitis	Donepezil	6.17	4	1.0023	2.36	2.08	0.22	20.04	− 0.31
M32	Systemic lupus erythematosus	Mirtazapine	3.35	149	1.0030	55.06	0.67	0.48	0.93	− 0.69
M32	Systemic lupus erythematosus	Gentamicin	2.10	74	1.0014	10.29	0.80	0.50	1.29	− 0.48
M62	Rhabdomyolysis/myopathy	Ranibizumab	2.97	83	1.0270	24.92	1.00	0.65	1.54	− 1.38
M62	Rhabdomyolysis/myopathy	Ethinyl estradiol-drospirenone combination	2.45	531	1.0198	101.93	1.28	1.08	1.52	− 1.35
M77	Tendinopathies and ligament disorders	Trastuzumab	1.63	104	1.0209	6.54	0.77	0.52	1.14	− 0.73
M77	Tendinopathies and ligament disorders	Anagrelide	1.35	5	1.0116	0.51	2.65	0.44	15.88	− 1.07
M81	Osteoporosis/osteopenia	Cytarabine	11.09	288	1.1787	584.84	2.45	1.89	3.18	− 0.39
N12	Tubulointerstitial diseases	Aripiprazole	2.05	432	1.0056	52.40	1.09	0.90	1.32	− 0.70
N17	Acute renal failure	Escitalopram (citalopram)	1.87	85	1.0008	8.39	1.36	0.88	2.11	− 0.14
N39	Proteinuria	Diazepam	2.36	7,031	1.0265	1252.26	1.16	1.10	1.22	− 0.28
R43	Taste and smell disorders	Triamcinolone acetonide	2.38	1,411	1.0071	252.38	0.95	0.86	1.06	− 0.24
R44	Psychosis and psychotic disorders	Octreotide	0.84	13	0.9981	0.29	0.14	0.03	0.63	− 0.37
R44	Psychosis and psychotic disorders	Aflibercept	0.63	23	0.9957	1.64	0.86	0.37	1.98	− 1.03
R56	Convulsions	Anagrelide		0						− 0.18
R73	Hyperglycaemia/new onset diabetes mellitus	Amoxicillin	1.08	8,798	1.0007	14.23	1.05	1.00	1.09	− 0.52

ARM association rule mining, *ASR* Adjusted Sequence Ratio, *excl.* excluding, *ICD10* International Classification of Diseases, 10th Revision, *ROR* reporting odds ratio, *SSA* sequence symmetry analysis

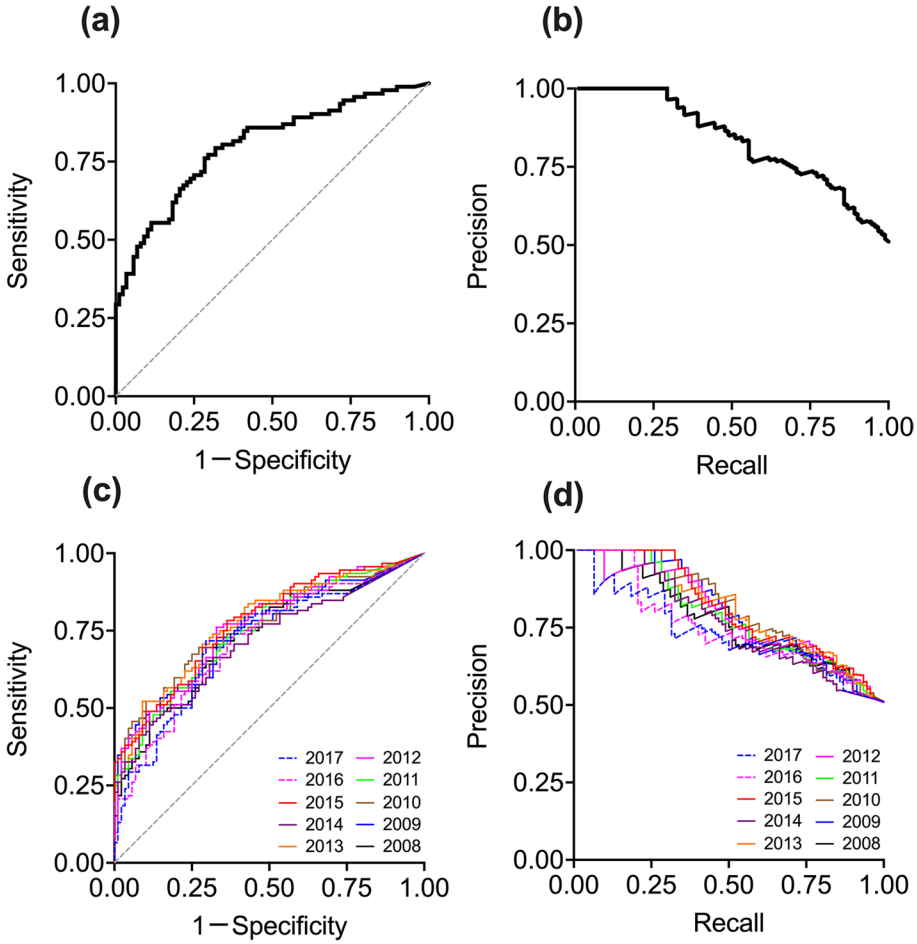


Fig. 3 Performance and reproducibility of ARM for detecting ADR signals. ROC Curve (**a**) and precision-recall curve (**b**) using JMDC claims data from 2005 to 2019 (6,072,316 patients and 162,454,898 records). ROC curves (**c**) and precision-recall curves (**d**) using JMDC claims data divided into 10 datasets. The number of patients and records for each dataset are shown in Supplementary Table 1, Online Supplementary Material. *ADR* adverse drug reaction, *ARM* association rule mining, *ROC* receiver-operating characteristic

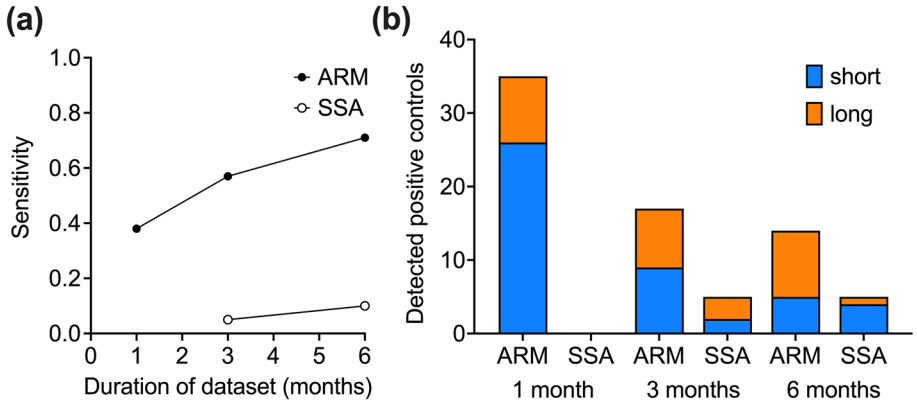


Fig. 4 Comparison of ARM and SSA performance in detecting ADR signals. (**a**) Sensitivity of ARM and SSA using short-period datasets. (**b**) Number of detected positive control signals by the time-to-onset profile of ADRs (short = onset less than or equal to 90 days, long = onset more than 90 days). *ADR* adverse drug reaction, *ARM* association rule mining, *SSA* sequence symmetry analysis

was not applicable because it was impossible to consider the order in this dataset (Fig. 4a). In the 3-month dataset, ARM achieved a sensitivity of 0.57 (detected additional 17 positive pairs), while the SSA achieved a sensitivity of 0.05 (detected five positive pairs), and the five positive pairs detected by SSA were all included in the 52 positive pairs detected by ARM (Supplementary Table 7, OSM). In the 6-month dataset, ARM achieved a sensitivity of 0.71 (detected additional 14 positive pairs but lost one detected positive signal), while the SSA achieved a sensitivity of 0.1 (detected additional five positive pairs but lost one detected positive signal), and the nine positive pairs detected by SSA were all included in the 65 positive pairs detected by ARM (Supplementary Table 7, OSM). We also compared the performance of ARM and SSA using the time-to-onset profile of ADRs, which were classified into two categories (short: median ≤ 3 months; long: median > 3 months) and found that ARM detected multiple short classification events in

the 1-month dataset and greater number of pairs than SSA in both categories (Fig. 4b).

Third, we examined whether ARM could detect ADR signals of drugs immediately after launch in the early post-approval period. In this section, we focused on "Ethinyl estradiol drospirenone–Thrombophlebitis" pair from the gold standard in our analysis and the ARM detection criteria were defined as: lift > 1, conviction > 1, and p-value < 0.05. Although safety information for thrombosis was issued 39 months after ethinyl estradiol drospirenone was marketed, ARM detected a thrombosis signal 14 months after approval (Fig. 5). These results indicate that the ADR signals detected by ARM could serve as a tool to complement the publication of safety information on new therapeutic drugs.

Fourth, we calculated performance using the conventional benchmark. The ROC-AUC was 0.65 and the PR-AUC was 0.78 (Fig. 6a, b). The ARM detection criteria were defined as follows: lift > 1, conviction > 1, and p-value < 0.05 and the performance of ARM was compared with that of SSA. In the full dataset from January 2005 to August 2019, ARM identified 85 signals, of which 54 were true positive controls (sensitivity: 0.89, specificity: 0.21, precision: 0.64, and F-measure: 0.74). SSA identified 23 signals, of which 15 were true positive controls (sensitivity: 0.25, specificity: 0.79, precision: 0.65, and F-measure: 0.36). By both methods, 21 pairs were considered signals, of which 14 pairs were true positive controls (Supplementary Table 8, OSM). In the 1-month dataset, ARM achieved a sensitivity of 0.13 (detected eight positive pairs) (Fig. 7; Supplementary Table 9, OSM). In the 3-month dataset, ARM achieved a sensitivity of 0.28 (detected additional ten positive pairs but lost one detected positive signal). In the 6-month dataset, ARM achieved a sensitivity of 0.43 (detected additional ten positive pairs but lost one detected positive signal). SSA showed no signal for any of the pairs in 1-, 3-, and 6-month datasets.

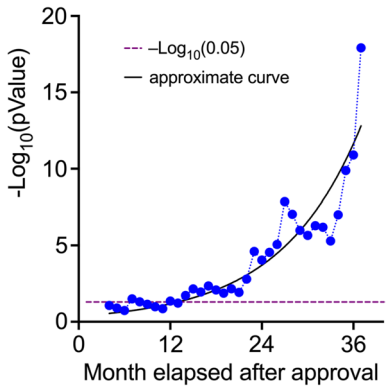


Fig. 5 Detection of ADR signals by ARM using drugs immediately after launch in the early post-approval period: "Ethinyl estradiol drospirenone–Thrombophlebitis" pair. *ADR* adverse drug reaction, *ARM* association rule mining

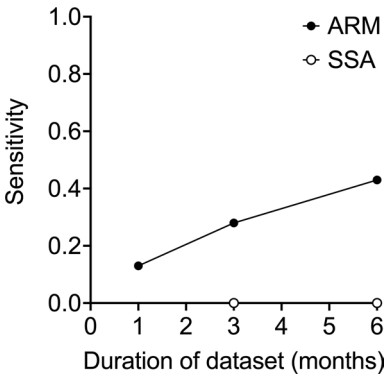
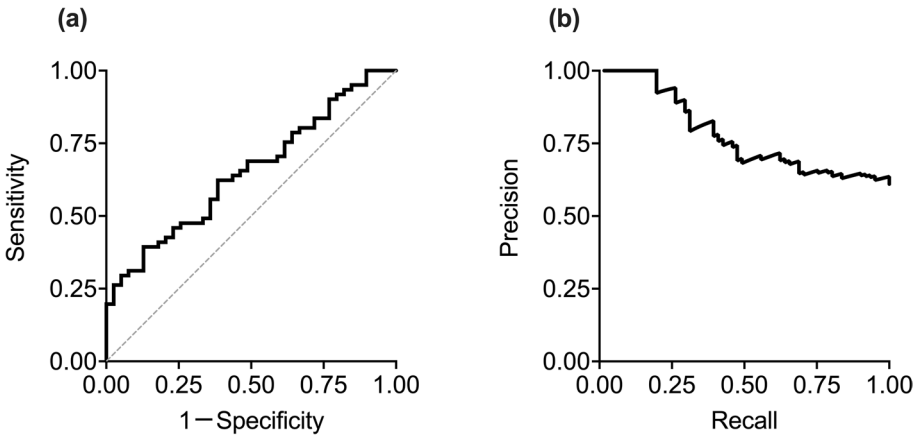


Fig. 7 Sensitivity of ARM and SSA in the conventional benchmark using short-period datasets. *ARM* association rule mining, *SSA* sequence symmetry analysis

Fig. 6 Performance of ARM for detecting ADR signals in the conventional benchmark. ROC Curve (**a**) and precision-recall curve (**b**) using JMDC claims data from 2005 to 2019. *ADR* adverse drug reaction, *ARM* association rule mining, *ROC* receiver-operating characteristic



4 Discussion

In this study, we created a global gold standard of ADRs consisting of 92 ADR–drug pairs as the positive controls and 88 pairs as the negative controls, after rational selection through statistical analyses of large-scale ADR self-reports to assess the ability of a data-mining approach to detect a broad range of ADRs. Our gold standard consisted of drugs with diverse anatomical, therapeutic, and chemical properties, as well as a wide range of ADRs. In addition, it incorporated clinically noteworthy drug–event pairs because gold standards based on SRS are problematic in clinical settings. Furthermore, it contained time-to-onset profiles of the ADRs. This gold standard enabled us to quantify and evaluate the extent to which known ADRs can be detected using a data-mining approach.

We assessed an early and simple detection scheme for ADR signals based on the ARM of the administrative claims data. Although many studies have analyzed medical records to detect ADR signals, most of these research works focused on a narrow range of ADRs. In the present study, we quantitatively evaluated the active detection of 180 kinds of drug–event pairs using our gold standard. Figure 3a, b show the ROC-AUC and PR-AUC values (both greater than 0.8), indicating that ARM can attain reasonable specificity and precision while preserving sensitivity. Figure 3c, d show that the ROC-AUC and PR-AUC were above 0.7 in ten datasets with varying numbers of patients and records, indicating that ARM can reproducibly achieve reasonable performance. For lift > 1, conviction > 1, and p-value < 0.05, ARM had high sensitivity but low specificity, while SSA tended to have low sensitivity but high specificity. Most of the positive drug–event pairs had higher lift values (Tables 2, 3); therefore, the sensitivity, specificity, and precision were calculated for varying lift thresholds (Table 4). As a result of varying lift including conviction, the F-measure showed the maximum at 0.78 when lift was > 2.301 and conviction > 1.0025 in the full dataset (sensitivity: 0.85, specificity: 0.66, and precision: 0.72). The optimal lift and conviction values varied depending on the database. Since it is crucial to detect ADRs as early as possible, we emphasized the performance metrics calculated from positive predictions like sensitivity. Increasing the lift including the conviction threshold at the expense of sensitivity may enhance pharmacovigilance while maintaining a balance between sensitivity and specificity.

Table 4 Ability of ARM to detect signals for varying lift thresholds

Lift	Sensitivity	Specificity	Precision	F-measure
1	0.98	0.25	0.58	0.73
2	0.87	0.49	0.64	0.74
3	0.75	0.73	0.74	0.75
4	0.64	0.81	0.78	0.70
5	0.57	0.83	0.78	0.65

ARM association rule mining

We evaluated whether ARM could detect ADR signals with short accumulation periods of data. We believe that no study has examined whether early detection of ADR signals can be achieved using small amounts of data, to date. Figure 4 indicates that ARM has a higher sensitivity than SSA as a baseline method. SSA, which is also referred to as a self-controlled method, is superior to ARM in that it considers the order of appearance of drugs and events and minimizes the confounding effects of time-varying risk factors [40]. However, SSA is difficult to detect in a short period because of the insufficient number of records, as only patients for whom both drugs and events are registered are included in the analysis. In contrast, ARM does not consider sequencing or control for confounding factors such as patient background, which is likely to result in a higher number of pseudo-associations [41]. Therefore, we calculated not only the sensitivity but also specificity and precision, as well as compared the performance of ARM and SSA (Supplementary Fig. 1, OSM). In this regard, ARM showed higher sensitivity than SSA while maintaining specificity. In the short-term data, several drugs and events included in the gold standard could not be paired, and co-occurrence probability could not be calculated, so it is possible that specificity and precision were maintained. We think that the longer the analysis period, the more extra drug–event pairs are created, resulting in a higher number of pseudo-associations. Despite the above disadvantage, the results indicate that ARM has the potential for the early detection of ADR signals in shorter dataset durations.

In the conventional benchmark, the ROC- and PR-AUC tended to be lower compared to our gold standard. The number of cases with four kinds of ADR mapped to the ICD10 codes tended to be relatively small. This might affect the model's performance. However, since there were many positive drug–event pairs with top lift values, these were considered to have a balanced accuracy by increasing the threshold value. In the short accumulation period data, ARM detected more positive control pairs than SSA, consistent with our gold standard.

Furthermore, as a more realistic simulation, we performed an ARM focusing on the "Ethinyl estradiol drospirenone–Thrombosis" pair. In our analysis, since the run-in period was set, only newly prescribed drugs and newly reported events were included. Although ARM did not consider the sequence, the study showed that ARM may be a very powerful tool for examining the safety of novel therapeutics using a short-term dataset. Recently, several models have been reported for detecting ADR signals of new

therapeutic drugs, using information such as pharmacological targets [42, 43]. Although these models showed high performance, they did not target first-in-class drugs. However, ARM using administrative claims data does not have this limitation. In fact, our gold standard included the CDK4/6 inhibitor palbociclib, which was approved in December 2017 in Japan as a first-in-class drug, and ARM was able to detect the ADR signal of this drug (Table 2).

ARM using administrative claims data has the potential to accelerate safety communication by enabling early identification of post-marketing safety concerns. However, signals detected by ARM cannot replace expert clinical review. There may be some possible limitations to the use of claims data for ADR signals detection. First, we analyzed the symptoms that do not necessarily correspond to ADRs because symptoms related to drug indications as well as those associated with the disease were also extracted from claims data. Claims data might not have the detailed and accurate information needed for some studies since these are used for administrative or billing purposes. To reduce these limitations, at least drug–event pairs where the ATC codes and ICD10 codes suggested that they belong to the same organ must be eliminated. Second, we need to address the differences in terminology between claims data and standard ADR vocabulary. The mapping between ADRs and ICD10 has been established to some extent by the Unified Medical Language System (UMLS). However, there are some difficulties in systematically mapping ADRs to ICD10 even with UMLS [44, 45]. Therefore, in this study, each SMQ was manually mapped to ICD10, wherein some patient information may be lost owing to incomplete mapping from ADRs codes to ICD10. These might have affected the performance of ADR signal detection in the present study. Third, reimbursement is requested by the 10th of the following month in Japan. In addition, several months are required before the claims data can be included in the database. Even if the data can be utilized smoothly in the future, there will be a lag of up to 1 month, and it may be difficult to detect ADR signals less than 1 month after approval using the administrative claims data. There may be other limitations to ARM. The false discoveries in ARM appear to arise in the following situations: first, ARM is not an ordinal analysis, so we estimated causality based on the strength of the association. If there were no reverse order pairs (drug→event or event→drug), the analysis value of SSA was 0 or null, which could not be evaluated and was not detected as a signal. However, ARM will calculate co-occurrence probabilities even if the pair is not necessarily drug→event, leading to false positives. Second, the effects of confounding factors, including reverse causation, time-dependent confounding, and mutual indication, are inevitable [19, 46]. Especially in ARM, it is difficult to distinguish which drug is the cause of the ADRs when several medicines are used together in combination treatment. Furthermore, if there is strong comorbidity between two symptoms, it is difficult to distinguish which symptom is the ADR. Third, even if we increase the lift including conviction thresholds to reduce false positives, a high lift value may not necessarily pair with ADR. If both the drug and the event occur rarely and the drug–event pair co-occurs by chance, the lift is extremely high. To rule out the co-occurrence of drug–event pairs with extremely high scores, the support threshold needs to be increased. In practice, however, it is necessary to reduce false-positive signals not only by the ARM but also by a combination of other analytical methods and finally by human procedures.

Despite the above limitations, our findings show that it reduces the delay in the identification of important ADRs, indicating that it may be used as a complementary tool to SRS. Our gold standard is expected to be useful for ADR signal detection using EMRs as well as other healthcare databases. In the future, using this gold standard, we plan to extend our study to utilize time-series analysis, medical check-up data of patients, and information regarding concomitant medications to improve the accuracy of ADR signal detection.

5 Conclusions

We created a reliable and sufficiently large gold standard for ADR detection based on clinical big-data analysis. This gold standard enabled us to evaluate the performance of the data-mining approach for screening ADR signals. This study suggests that ARM may be effective in the early detection of a wide range of ADR signals and can function as a complementary tool to existing pharmacovigilance strategies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-023-01278-4.

Declarations

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Conflict of interest The authors declare that they have no potential conflicts of interest that might be relevant to the content of this article.

Availability of data and materials The FAERS datasets analyzed during the current study are available on the FDA website (https://www.fda.gov/drugs/drug–approvals–and–databases/fda–adverse–event–reporting–system–faers). The JADER datasets analyzed during the current study are available in the PMDA website (www.pmda.go.jp). The JMDC Claims data that support the findings of this study are available from JMDC Inc. (Tokyo, Japan) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from JMDC.

Ethical approval Not applicable

Consent to participate Not applicable

Consent for publications Not applicable

Code availability Custom code generated in this study is available at: https://github.com/HirokiYamamoto0222/ARM-on-Claims-data.

Author contributions HY and SK wrote the manuscript; HY and SK designed the research; HY performed the research; HY analyzed the data; KN, GK, TN and CT provided technical advice. All authors read and approved the final version.

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