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Data mining techniques for detecting signals of adverse drug reaction of cardiac therapy drugs based on Jinan adverse event reporting system database: a retrospective study

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ABSTRACT

Objective Cardiac therapy drugs are widely used in the treatment of heart disease. However, the concern regarding adverse events (AEs) of cardiac therapy drugs have been rising. This study aimed to analyse cardiac therapy drug-related AEs using the Jinan adverse event reporting system (JAERS) database mining and conduct a comprehensive evaluation to provide safe medication information for patients.

Design Retrospective observational study.

Setting In this study, cardiac therapy drug-related AEs were detected using the JAERS database from January 2000 to March 2022.

Methods Reports of cardiac therapy drug-related AEs were extracted from JAERS database, and the basic information of patients, reports and common AEs were analysed. Four disproportionality analysis methods, proportional reporting ratio (PRR), reporting odds ratio (ROR), Bayesian Confidence Propagation Neural Network (BCPNN), Medicines and Healthcare products Regulatory Agency (MHRA), were used to detect cardiac therapy drug-related signals. We further checked whether the detected signals exist on drug labels in China and two developed countries, the USA and Japan.

Results In total, 168 314 AEs were reported, of which 4788 were associated with cardiac therapy drugs. Using the PRR, ROR, MHRA and BCPNN method, we detected 52 signals, 52 signals, 33 signals and 43 signals, respectively. Among the 52 signals, 14 were not included on the drug labels of China. One (isosorbide mononitrate—head bilges) was not included on the drug labels of the three countries.

Conclusion We identified 14 new cardiac therapy drug signals that did not appear on drug labels in China and 1 new signal that did not appear on drug labels in 3 counties. A causal link between cardiac therapy drugs and AEs should be evaluated in further studies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addresses a very important issue, as reports of cardiac therapy drugs adverse events (AEs) are increasing, and it analyses two decades of data from Jinan AE reporting system database describing signals of cardiac therapy drugs.
⇒ Data mining was conducted by calculating 4 indices including proportional reporting ratio, reporting odds ratio, Bayesian Confidence Propagation Neural Network and Medicines and Healthcare products Regulatory Agency to detect signals from the use of 11 cardiac therapy drugs.
⇒ Signal-related adverse drug reactions were checked whether exist in drug labels in China and two developed countries, the USA and Japan.
⇒ Limitations of this study are omission, underreporting of adverse drug reactions, lack of clinical information of patients in the spontaneously reported database and the fact that the influence of the disease itself and the interaction of the combined medication were not considered.

INTRODUCTION

According to Report on Cardiovascular Health and Disease Report in China 2021,[1] the number of patients with cardiovascular diseases was about 330 million, among which the number of heart disease patients was about 47.66 million. The death caused by cardiovascular diseases accounted for more than 40% of the total causes of death in urban and rural residents, 46.74% in rural areas and 44.26% in urban areas. Heart disease has a high incidence and mortality in our country, so cardiac therapy drugs are widely used and play an important role in the treatment of heart disease.[2–4] According to the WHO classification of Anatomic Therapeutic Chemistry (ATC),[5] cardiac therapy drugs include cardiac glycosides, vasodilators for cardiac conditions, cardiac excitants other than cardiac glycosides, class I and class III antiarrhythmic agents and other cardiac conditions.

The sales value of cardiovascular system drugs in China reached 35 billion yuan, among which cardiac treatment drugs accounted for the highest proportion, 35.94%, with a value of 12.579 billion yuan. Cardiovascular system drugs were ranked by sales amount, and 11 of the top 20 drugs were cardiac therapy drugs, namely alprostadil, coenzyme complex, Salviae miltiorrhizae and ligustrazine hydrochloride, creatine phosphate sodium, adenosine cyclophosphate, safflower extract and aceglutamide, isosorbide mononitrate, trimetazidine, calcium dibutyryl adenosine cyclophosphate, levosimendan, Salviae miltiorrhizae ligustrazine hydrochloride.[6] With the wide application of cardiac therapy drugs, reports of adverse events (AEs) are increasing, especially some reports that are not listed on drug labels. Therefore, it is necessary to monitor the AEs of cardiac therapy drugs and determine a causal relationship through systematic research on the reported AEs.

The Jinan Adverse Drug Reaction Monitoring System collects adverse drug reactions reported spontaneously by various medical institutions and pharmaceutical companies in Jinan. The system was established in 2000. More recently, studies are being actively conducted to uncover ADR signals that were not identified at the time of marketing through pharmacodynamic studies using the spontaneous AE reporting system database. The signal is defined as the reported information about the possible causal relationship between the event and the drug, which is unknown or not fully recorded and needs further evaluation.

In this study, we used a data mining approach to detect the signals of 11 cardiac therapy drugs by analysing reported AEs using the Jinan Adverse Event Reporting System (JAERS) database. The signals detected in the JAERS database were compared with drug label information in China and two other countries, the USA and Japan. The purpose of this study was to provide basic data for the safe use of 11 cardiac therapy drugs by evaluating AEs.

MATERIALS AND METHODS

Database and study drug

Data from the JAERS database regarding reported AEs related to 11 cardiac therapy drugs and all other drugs was used in this study. From January 2000 to March 2022, 168 314 reports were accumulated in the JAERS database, including 4788 for target cardiac therapy drugs. Information on patients' ages and genders, as well as suspected drug, is included in this database. Anatomical Therapeutic Chemical Classification Systems (ATC codes) were used for coding drug names, and preferred terms (PTs) in the WHO Adverse Reaction Terminology (WHO-ART) were used for coding AEs.[7] We produced drug–AE pairs for each report using the ATC codes of the reported drugs and the WHO-ART PT of the AEs, on which all descriptive statistics and data mining were based. Since multiple cases of AEs were reported in a given patient, there were 6551 pairs of drug–AE pairs associated with cardiac-targeted therapy drugs.

Table 1 Two-by-two contingency table

	Target ADRs	Other ADRs	Total
Target drugs	A	B	A+B
Other drugs	C	D	C+D
Total	A+C	B+D	A+B+C+D

ADR, Adverse drug reaction.

Statistical analysis

Disproportionality measurement, also known as ratio imbalance measurement, is currently the data mining technique used to identify adverse drug reactions. This method is based on the classic 2×2 contingency table (table 1). The principle is to estimate the ratio of the actual number of adverse reactions associated with a certain drug to the expected number or to the number of other adverse reactions caused by other drugs in the ADR reporting system.[8] If the measured ratio is large enough (imbalance), it is considered as a possible signal. There may be a link between the drug and the adverse reaction.

Proportional reporting ratio (PRR) used by the yellow card database in the UK,[9] reporting odds ratio (ROR) used by the Netherlands Pharmacovigilance Centre,[10] Bayesian Confidence Propagation Neural Network (BCPNN) used by the WHO–Uppsala Monitoring Center (WHO-UMC),[11] Medicines and Healthcare products Regulatory Agency (MHRA) used by UK MHRA[12] were used for quantitative signal detection. Signal generation was conducted as per the conditions shown in table 2.

We defined AEs as signals when they were detected by any of the four indices PRR, ROR, BCPNN or MHRA. The signals detected in the JAERS database were compared with the drug label information in China and two other countries, the USA and Japan (figure 1). All statistical analyses were performed by SPSS V.18.0 and Microsoft EXCEL 2010.

The BCPNN method was used as the reference standard to determine false positive, false negative, true positive and true negative, and the sensitivity, specificity, positive predictive value, negative predictive value and Jordan index were compared. The calculation method is shown in table 3.

Patient and public involvement

None.

RESULTS

As shown in table 4, cardiac therapy drug reports are categorised by their characteristics. The 4788 reports included 2237 (46.7%) from males and 2551 (53.3%) from females. According to age, patients aged 41–65 (48.0%) had the highest frequency of AEs, followed by

Table 2 Signal data mining algorithms and their signal-generating-satisfied conditions

Indices	Signal-generating-satisfied conditions	Definition
PRR	PRR 95% CI>1 and n≥3	$PRR=(A/(A+B))/[C/(C+D)$ $SE(lnPRR)=((1/A-1/(A+B)+1/C-1/(C+D))^{-1/2}$ $95\%\ CI=e^{ln(PRR)\pm1.96SE(lnPRR)}$
ROR	PRR 95% CI>1 and n≥3	$ROR=(A/C)/(B/D)=(AD)/(BC)$ $SE(lnROR)=(1/A+1/B+1/C+1/D)^{-1/2}$ $95\%CI=e^{ln(ROR)\pm1.96SE(lnROR)}$
MHRA	PRR≥2, A≥3, $\chi^2\geq4$	$PRR=(A/(A+B))/(C/(C+D))$ $\chi^2=((\lvert AD-BC\rvert-n/2)^2n)/((A+B)(A+C)(C+D)(B+D))$
BCPNN	IC95% CI lower limit>0	$IC=\log_2(p(x,y))/(p(x)p(y))=\log_2(A(A+B+C+D))/((A+B)(A+C))$, $IC=E(IC_{ij})$ $SD=(V(IC_{ij}))^{-1/2}$, $\gamma_{ij}=1$, $\alpha_i=\beta_j=1$, $\alpha=\beta=2$, $c_{ij}=A$ $c_i=A+B$, $c_j=A+C$, $N=A+B+C+D$ $\gamma=\gamma_{ij}((N+\alpha)(N+\beta))/((c_i+\alpha_i)(c_j+\beta_j))$ $E(IC_{ij})=\log_2((c_{ij}+\gamma_{ij})(N+\alpha)(N+\beta))/((N+\gamma)(c_i+\alpha_i)(c_j+\beta_j))$ $=\log_2((c_{ij}+\gamma_{ij})\gamma)/(N+\gamma)$ $V(IC_{ij})=(((N-c_{ij}+\gamma-\gamma_{ij})/((c_{ij}+\gamma_{ij})(1+N+\gamma))+((N-c_i+\alpha-\alpha_i)/((c_i+\alpha_i)(1+N+\alpha))+((N-c_j+\beta-\beta_j)/(c_i+\beta_j)(1+N+\beta)))/(\log2)^2$

BCPNN, Bayesian Confidence Propagation Neural Network; IC, information score; MHRA, Medicines and Healthcare products Regulatory Agency; PRR, proportional reporting ratio; ROR, reporting odds ratio.

patients aged>65 (43.5%), patients aged 18–40 (7.0%) and patients aged<18 (1.6%) years with the lowest frequency.

In this study, we detected 52 signals using the PRR method, 52 signals using the ROR method, 33 signals using the MHRA method and 43 weak signals using the BCPNN method (online supplemental table 1). We compared the detected signals with the drug labels of three countries. Head bilges of isosorbide mononitrate was an unlabelled AE in three countries. Fever of isosorbide mononitrate was an unlabelled AE in China but labelled in both the USA and Japan. The neck discomfort of isosorbide mononitrate was an unlabelled AE in both China and Japan but labelled in the USA. Dizziness of isosorbide mononitrate was an unlabelled AE in Japan but labelled in both the USA and China. Vertigo and cold sweat of isosorbide mononitrate were labelled AE in China but unlabelled both the USA and Japan. Jitter of alprostadil was an unlabelled AE in both China and the USA but labelled in Japan. Other AE of alprostadil was unlabelled in the USA. Fever of coenzyme complex, calcium dibutyryl adenosine cyclophosphate and creatine phosphate sodium, rhinobyon and increased tearing of safflower extract and aceglutamide, extrasystoles of levosimendan, chest tightness, fever and vision abnormal of Salviae miltiorrhizae ligustrazine hydrochloride were unlabelled AEs in China. These drugs were not approved

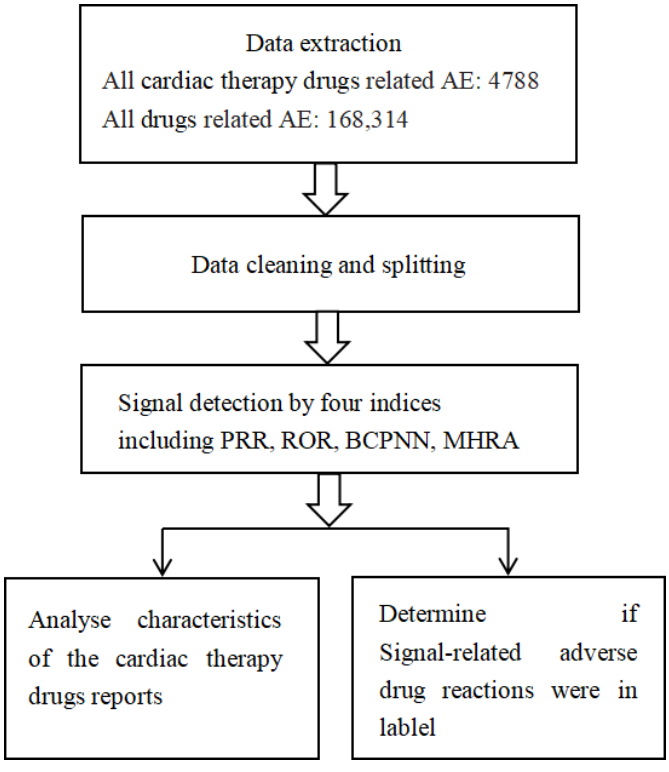

Figure 1 The protocol of the study procession. AE, adverse event; BCPNN, Bayesian Confidence Propagation Neural Network; MHRA, Medicines and Healthcare products Regulatory Agency; PRR, proportional reporting ratio; ROR, reporting OR.

Table 3 Fourfold table for calculating sensitivity and specificity

	BCPNN (+)	BCPNN (–)	Total
Other method (+)	a	b	a+b
Other method (–)	c	d	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity=a/(a+c); specificity=d/(b+d); positive predictive value=a/(a+b); negative predictive value=d/(c+d); Jorden index=(a/(a+c))+(d/(b+d))−1.

Table 4 Characteristics of reports associated with cardiac therapy drugs from 2000 to 2022

Characteristics	Reports, n	%
Gender		
Male	2237	46.7
Female	2551	53.3
Unknown	0	0
Age		
<18	75	1.6
18–40	334	7.0
41–65	2297	48.0
>65	2082	43.5
Total	4788	100

in both the USA and Japan. Headache of trimetazidine was an unlabelled AE in Japan but labelled in China.

The comparison of the four methods was mainly based on sensitivity, specificity, positive predictive value, negative predictive value and Jordan index. These indicators are calculated by comparing the signal values detected by the three methods with those detected by the BCPNN method (table 5).

DISCUSSION

In this study, we detected 52 signals associated with cardiac therapy drugs by analysing the spontaneous AE reporting system database reported to JAERS from 2000 to 2022. Most signal-related AEs are already in drug instructions.

Isosorbide mononitrate was the most widely used one of cardiac therapy drugs, which had the most ADRs. There are four adverse reaction signals that are not listed on drug labels. Fever, neck discomfort and vertigo have been included in other country instructions. Head bilges and vertigo may be related to isosorbide mononitrate mainly dilating peripheral veins, causing blood to accumulate in the periphery, resulting in insufficient circulating blood volume and cerebral ischaemia.[13 14] The mechanism of fever and neck discomfort has not been reported yet.

The indications and usage of alprostadil in China and Japan are similar, both are used to improve cardiovascular and cerebrovascular microcirculation disorders. However, the usage in the USA is completely different for treating erectile dysfunction. Therefore, the ADRs in the US label are quite different from those in the Chinese and Japanese labels, and the ADRs of the detected signals on the Chinese label are not listed in the American label. There are many literature reports on the adverse reactions of alprostadil-induced anaphylactic shock,[15–18] accompanied by jitter in the limbs. Among the three cases of jitter

Table 5 Comparison of various signal detection methods (drug–adverse events)

Method	Condition (A≥values listed)	Sample size	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Jorden index
Reporting odds ratio	3	286	1.00	0.96	0.83	1.00	0.96
	4	221	1.00	0.98	0.90	1.00	0.98
	5	172	1.00	0.99	0.94	1.00	0.99
	6	148	1.00	0.99	0.97	1.00	0.99
	7	132	1.00	0.99	0.96	1.00	0.99
	11	92	1.00	1.00	1.00	1.00	1.00
Proportional reporting ratio	3	286	1.00	0.96	0.83	1.00	0.96
	4	221	1.00	0.98	0.90	1.00	0.98
	5	172	1.00	0.99	0.94	1.00	0.99
	6	148	1.00	0.99	0.97	1.00	0.99
	7	132	1.00	0.99	0.96	1.00	0.99
	11	92	1.00	1.00	1.00	1.00	1.00
Medicines and Healthcare products Regulatory Agency	3	286	0.73	1.00	0.97	0.95	0.72
	4	221	0.89	0.99	0.97	0.98	0.88
	5	172	0.88	0.99	0.97	0.97	0.87
	6	148	0.86	1.00	1.00	0.97	0.86
	7	132	0.83	1.00	1.00	0.96	0.83
	11	92	0.81	1.00	1.00	0.95	0.81

ADR in the Jinan database, one case was tremor accompanied by nausea and vomiting, and two cases were only one ADR of tremor. Whether there is a relationship between jitter and anaphylactic shock, whether it is a precursor symptom of anaphylactic shock, and then taking corresponding preventive measures, requires clinical trials to further research.

The drugs of coenzyme complex, Salviae miltiorrhizae and ligustrazine hydrochloride, creatine phosphate sodium, safflower extract and aceglutamide, calcium dibutyryl adenosine cyclophosphate, levosimendan, Salviae miltiorrhizae ligustrazine hydrochloride have not been approved for marketing abroad, but they are widely used for cardiac therapy in China, and they are used in large quantities, posing safety risks. The risk signals detected in this study that are not listed on labels are of great value for further research on postmarketing drug safety supervision.

Some research groups have also detected signals for cardiovascular drugs in other countries. WHO confirmed the following ADR signals through BCPNN method: pericarditis was associated with propranolol but not with other β-blockers; captopril and other ACE inhibitors have been linked to coughing.[19] French confirmed the following ADR signals through ROR method: Cardiovascular drugs other than nitrates did not significantly affect stroke.[20] Signals of rhabdomyolysis and renal failure were detected in the US years through Multivariable Gamma-Poisson Distribution Test Method before cerivastatin was withdrawn from the market.[21] Detection of signals using adverse drug reaction database can provide early information on adverse drug reactions, which is important for protecting patients from adverse drug reactions.

Compared with BCPNN, PRR and ROR methods have better sensitivity, while MHRA method has better specificity. The higher the sensitivity indicated the lower the false negative rate (missed diagnosis rate). The higher the specificity indicated the lower the false positive rate (misdiagnosis rate). In our previous article, we obtained the performance indices based on out-of-sample performance using receiver operating characteristic curve (ROC curve).[22] The area under the ROC curve of PRR, ROR and MHRA methods were greater than 0.9, which indicates that the three methods have good risk signal recognition.

It should be noted that reporting the ADR signal detected by the four methods can only indicate that the drug has a statistical correlation with the ADR signal, which has a hinting effect. However, this study did not consider the influence of the disease and the combined medication's interaction on the safety signal. Moreover, omission, under-reporting and lack of patients' clinical information in the spontaneously reported database will also affect the analysis results.

CONCLUSIONS

Through the signal mining from the JAERS database, this study exploratively analysed and evaluated the signal risk of serious and other important ADRs represented by cardiac therapy drugs, and provided a reference for their rational clinical application. We detected signals of cardiac therapy drugs and compared those information among the labels of 2 countries, and found that 14 AEs were not included on the drug labels of China and 1 AE was not included on the drug labels of the three countries. The ADR signal detected by ratio imbalance measurement is based on the statistical correlation of the number of ADRs reported. Whether there is a biological relationship between drugs and ADRs needs to be further studied and evaluated.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval As the present study used secondary healthcare data, it was exempted from review by the ethics committee of Shandong Provincial Third Hospital, and informed consent from patients was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All data relevant to the study are included in the article and online supplemental table 1.

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