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ADRVis: an Information Visualization Platform for Adverse Drug Reactions

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Abstract

Adverse drug reactions (ADRs) are a serious threat to people's lives and property safety. Currently, drug instructions are the main way for people to obtain information on ADRs. Due to drugs' limited pre-market clinical trials, adverse reactionsstated in drug instructions are often not sufficient. Avisualization platform for ADRs isput forward to address this problem. Adverse drug events (ADEs) data include actual clinical adverse reactions of drugs detected by drug monitoring administrationand can compensate for the insufficiency of drug instructions. Based on drug instructions and ADEs data, ADRVis isrealized by data analysis, model design and JAVA programming. ADRVis presentsthe relationship of 656 common drugs and their respective ADRs. Three case studies show that the platform has the capacities of visual presentation of ADRs and early warning of drug risks.The platform can provide people more rich information about drugs and help them understand ADRs more accurately and comprehensively.

Keywords: *Adverse drug reactions, Information visualization, Drug risk, Early warning*

1. Introduction

Information visualization is a mapping technique that utilizes visual graphics to represent non-spatial abstract datasets in physical space [1]. It is the transformation of data into a visual form by combining the two most powerful information processing systems, human brain and computer, which enables people to observe, control, research, browse, filter, discover, and understand large-scale data, in order to effectively reveal hidden characteristics and rules among data. Information visualization has been broadly used in human health. Demiris G, *et al.*, demonstrated how informatics applications can support the assessment and visualization of older adults' wellness [2]. Zhang ZY, *et al.*, proposed a framework composed of a suite of cooperating visual information displays to represent the Five Ws (who, when, what, where, and why) and demonstrated its use within a healthcare informatics application [3]. Faisal S, *et al.*, present a systematic review of the literature on information visualization for making sense of personal health information and stated that there were recognized design challenges associated with each of these themes, such as how to best represent data visually and integrate qualitative and quantitative information, other challenges and opportunities have received little attention to date [4]. But, currently, the availability of graphical decision support systems for drug

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information based on visualization techniques in practice is quite limited. Two prime examples are Epocrates (http://epocrates.com/) and UpToDate (http://www.uptodate.com/home). These applications have been shown to be effective in reducing prescribing errors and assisting clinical decision-making [5, 6]. Some researchers have successfully applied information visualization technology in drug safety. For example, Jon Duke, *et al.*, created a decision support system that may help physicians to expedite the reviewing of potential adverse reactions through information visualization [7]. Harpaz, *et al.*, developed a new pharmacovigilance data-mining technique to identify drug groups that share a common set of adverse events in FDA's spontaneous reporting system [8]. Jon Duke, *et al.*, designed the Rxplore, a novel tool for assessing medication side-effects which supports simultaneous lookup of multiple medications and an intuitive visual representation of query results [9]. The iHealth Explorer tool[10], developed by CSIRO and DoHA in Australia, provided data mining and analytic facilities over a web interface over very large data collections. The results of the analysis can then be visualized using various forms of knowledge representation methods. Gert Van Valkenhoef, *et al.*, developed a unifying data model that enabled the development of evidence-based decision support and applied into the ADDIS software, which made ADDIS enable semi-automated construction of meta-analyses, network meta-analyses and benefit-risk decision models, and provides visualization of all results[11]. Through the application of information visualization technology, these works made a great contribution to human health. However, the research based on adverse drug reaction monitoring data and instructions to realize drug information visualization is lack.

According to the WHO definition, Adverse drug reactions (ADRs) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function [12]. Currently, people obtain ADR information mainly from drug instructions (also called drug package inserts). However, the drug instructions may not include all adverse reactions due to limited sample size and observation time during the drug's pre-market clinical trials, which usually leads to inadequate understanding of ADRs information. In order to control ADRs effectively, many countries, including China, have established ADR monitoring agencies to collect data through the Internet. These adverse drug events (ADEs) data includes a lot of actually detected ADRs and makes up for the shortage of the insufficiency of drug instructions. As lacking for information technicians, utilization and exploitation of ADEs data in China is very poor. In order to help people understand ADRs more accurately and comprehensively, we developed an information visualization platform for ADRs.

2. Model Construction and System Implementation

2.1 Data Analysis

The first task of constructing a visualization platform is to understand the feature of the data. The ADR data were obtained from two sources: the drug-ADR combinations included in drug instructions (Figure 1-III) and those detected by ADR monitoring agencies (Figure 1-II). Some drug-ADR combinations were common between the two groups (Figure 1-I).

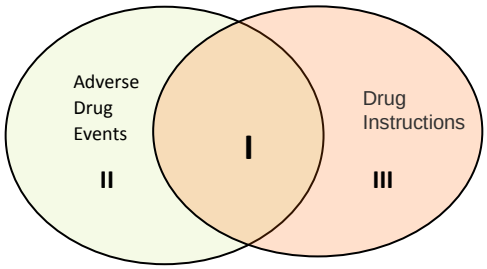

Figure 1. Three Types of Drug-ADR Combinations

Four Tables were needed for this study. The ADEs Table, a total of 4,404 Drug-ADR combinations including 656 common drugs, was provided by China Jiangsu Province ADR Monitoring Center. The data fields included drug code, ADRs code, and event frequency. 7,150 Drug-ADR combinations were retrieved from the Internet for the establishment of drug instructions Table (The data fields include drug code and ADRs code). Due to the differences of data acquisition, the record numbers of the above two Tables were not consistent. The third Table was the drug basic information Table (The data fields include drug code, name, and type). The forth Table was ADRs coding Table(The data fields include ADRs code, name, and affected organs), mainly from the World Health Organization Adverse Reaction Terms(WHO-ART).

2.2 Visualization Legends Design

Three different legends were designed to distinguish the three types of cases in Figure 1 (Table 1).

Table 1. Instructions of Three Legends

Legend	Type	Note
	CASE I	Solid circle, indicating that the ADR of one specific drug was stated in drug instructions and also actually detected.
	CASE II	Solid rectangle, indicating that the ADR of one specific drug was actually detected but not stated in drug instructions.
	CASE III	Hollow dashed circle, indicating that the ADR of one specific drug was stated in drug instructions but not actually detected.

In Table 1, as the case I and case III both denote all ADRs stated in drug instruction of a drug, they share the same shape, circle. The case II uses another shape, rectangle, to denote those ADRs not stated in drug instruction. Due to the frequency of the case I and case II is more than zero, solid shape is used. Contrarily, hollow dashed circle is choosing for the shape of the case III since its frequency of equals zero.

2.2 Visualization Model Design

As one drug has many ADRs, it is one-to-many relationship between them. The Ferris wheel style is just fit to this feature. The overall structure is circular, with the drug as the center connected by the legends of adverse reactions with equal radii. The visualization model is shown in Figure 2.

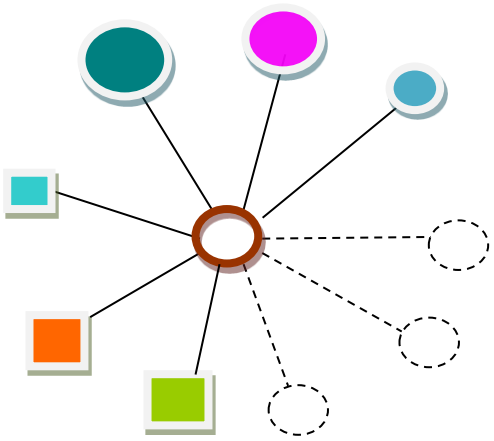

Figure 2. Ferris Wheel Model

The model met the following requirements:

(1) Different legends to distinguish the three different cases (See Table 1).

(2) Graphics with different size to distinguish the frequencies of ADRs. The radii and frequencies were positively correlated, and the legends were arranged clockwise with descending size under the same case.

(3) Different colors to distinguish different types of ADRs. The legend and its name label shared the same color.

(4) Dotted or solid lines to distinguish whether drug-adverse reaction combinations were actually detected.

(5) Certain mathematical model for establishing positional relationships among all legends to ensure overall symmetry and aesthetics (See Figure 3).

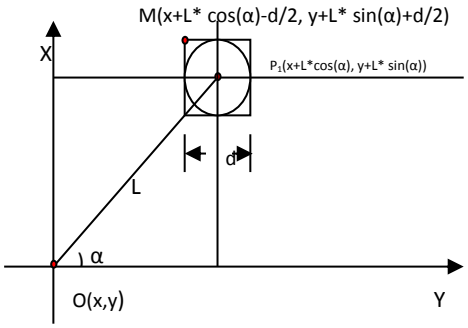

Figure 3. Mathematical Model for Positional Relationships of Legends

The mathematical model design is as follows:

(1) Construct a coordinates system. Point *O* denotes as a drug instance and locates in the center of java draw panel. (*x*, *y*) is the coordinate value of *O* and it is a fixed value in this system.

(2) Point P_1 represents the first ADR of the drug and its coordinate value is $(x + L * \cos(\alpha), y + L * \sin(\alpha))$. *L* is a fixed value and represents the length of OP_1. α is the angle between horizontal ordinate *OY* and OP_1 and it can be calculated from 360/*n* (*n* is the total amount of ADRs of the drug). So the coordinate value of the *i*th Point P_i can be got by $(x + L * \cos(i * \alpha), y + L * \sin(i * \alpha))$, i=1,2,3,,,*n*.

(3) In this system, shape (circle or square) with point P_i as center is selected to indicate an ADR instance. The diameter of the shape is *d*. The size of *d* is determined by the frequency of ADRs and it can be calculated by $\pi(d/2)^2/c$, where *c* is a constant.

(4) In the draw function of java, coordinate (*x*, *y*) indicates the location of the upper-left corner of the shape, and all values are measured in pixel units. Therefore, while drawing a shape, $M_{(x + L * \cos(i * \alpha) - d/2,\ y + L * \sin(i * \alpha) + d/2)}$ is the coordinate value of draw functions.

2.3 Area of Statistical Information Design

Compared to graph, text can provide more quantitative information description. In ADRVis platform, we embed a textual area of statistical information about ADRs of three cases. These information included ADR name, frequency, whether stated in drug instruction and PRR value. Frequency was the total amount of a target ADR of this drug, which has been detected by Jiangsu Province ADR Monitoring Center of China during two years.

PRR is a popular statistic method for ADR signal detection based on disproportionality theory [13]. The formula of PPR method is as follows:

$$PRR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \quad (1)$$

Where, a, b, c and d can be found in Table 2.

Table 2. Two-by-two Contingency Table

	Candidate ADR	All other ADRs
Candidate drug	a	b
All other drugs	c	d

PRR value represents the disproportion degree of a candidate Drug-ADR combination. According to the criteria of ADR signal detection, when $a \geq 2$ and $PRR \geq 3$, the correspondingcombination will be considered as a suspect sign. Thus, we highlighted such a suspect signal with "*" before the *PRR* value in this platform.

2.4 Visualization System Implementation

Under the Windows 7 operating system environment, MyEclipse (Enterprise Workbench, Version 8.5) was used as the development tool to achieve ADR information visualization system by the JAVA language (Figure 4, system main interface).

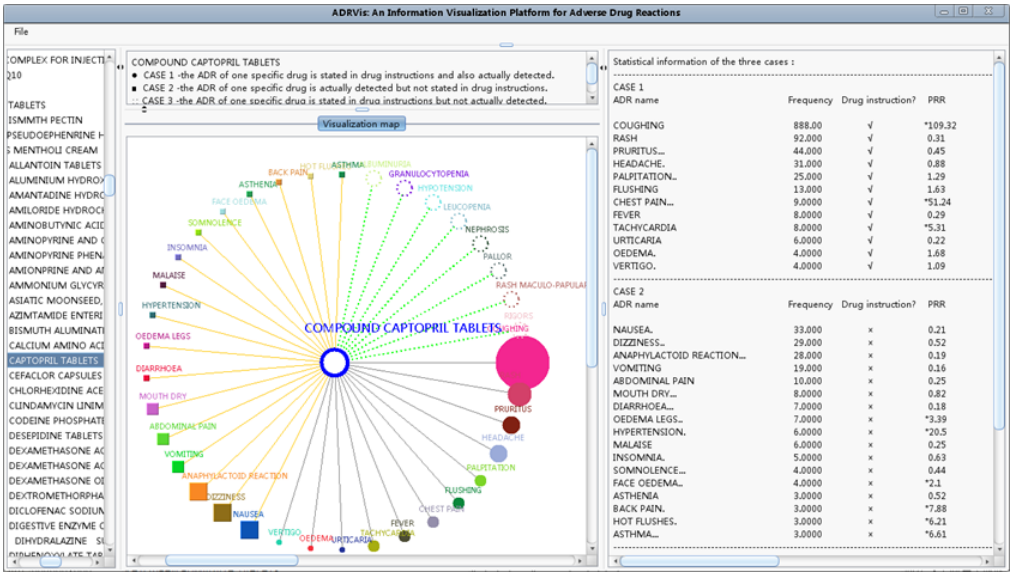

Figure 4. ADRVis Main Interface

The main interface was divided into four zones. The navigation on the left had a tree-structure, with all drugs sorted by names to facilitate users' searching; the intermediate lower region was the visualization map area for the correlations between drugs and adverse reactions using the Ferris wheel model. The upper middle region contains the legend for the visualization map area. The right side was the area of statistical information of the three cases by using texts, numbers, and other characters.

The visualization map of the drug-Compound Captopril Tablets is shown in Figure 4. Users can click the navigation tree to choose a drug. All the solid lines represent the ADRs that have been actually detected and the dashed lines are on the contrary. From this figure, we can explore the most frequent ADR of the drug is coughing easily. Users can realize quantitative analysis of ADRs information for the drug through the area of statistical information.

3. Cases Study

The correlations between drugs and adverse reactions were established with ADRVis. The visualization system not only was able to display the distribution of ADRs but also provided a certain early warning of drug risks.

3.1. Case study I

Amoxicillin is the most widely used antibiotics with as many as 38 different ADRs. Its classification information is chemical medicine – anti-microbial drug – antibiotics – penicillin. We select it to expatiate the three cases of the drug.

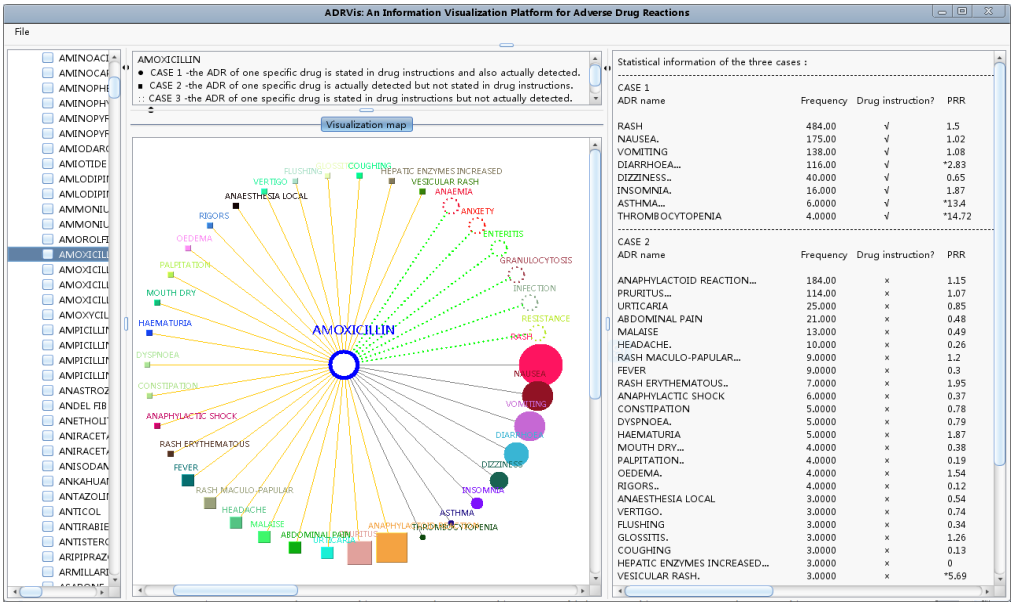

Figure 5. Visualization Map of Amoxicillin's ADRs

Figure 5 is the visualization map of Amoxicillin. A lot of ADRs in all three situations were involved with this drug, and the majority of detected ADRs were not stated in drug instructions (the rectangle shapes in the map). Therefore, physicians, patients, pharmaceutical producing enterprises, and drug administration should all pay closer attention to this drug. The statistical analysis was performed with three cases:

(1) The most frequent ADRs, stated in drug instructions and had been actually detected, were rash (a=484, PRR=1.5) and it accounted for about 33.87% of the total ADRs frequency of this drug. The others were nausea (a=175, PRR=1.02), vomiting (a=138, PRR=1.08) and diarrhoea (a=116, PRR=2.83). Although asthma(a=6, PRR=13.4) and thrombocytopenia (a=4, PRR=14.72) had low frequency, the PRR of them were more larger than 2. Thus, the two ADRs should be cared about.

(2) The detected ADRs that were not stated in drug instructions were listed in Table 3. Anaphylactoid reaction (a=184) and Leucopenia neonatal (a=114) had been shown to be two relatively more frequent ADRs, along with severe ADRs such as anaphylactic shock (a=6). Vesicular rash(a=3, PRR=5.69) was a suspect signal to be highlighted. However, these ADRs were not stated in drug instructions. Therefore, this sub-dataset was particularly important as reference for doctors and pharmaceutical producing enterprises.

Table 3. Actually Detected ADRs of Amoxicillin but not Stated in Drug Instructions

ADR	Frequency	Drug instruction?	PRR
Anaphylactoid reaction	184	×	1.15
Leucopenia neonatal	114	×	1.07
Urticaria	25	×	0.85
Abdominal pain	21	×	0.48
Malaise	13	×	0.49
Headache	10	×	0.26
Rash maculo-papular	9	×	1.2
Fever	9	×	0.3
Erythematous rash	7	×	1.95
Anaphylactic shock	6	×	0.37

(3) The ADRs that were stated in drug instructions but not actually detected include anemia, anxiety, enteritis, granulocytosis, infection and resistance.

3.2. Case Study II

Iopromide is a non-ionic low-osmolality contrast agent for angiography, brain and abdominal CT scans, and urethrography. Its classification information is chemical medicine – diagnostic drug – diagnostic imaging drug – contrast (Figure 6). As Iopromide is a drug which alarmed by China Food and Drug Administration in 2013, we choose it to demonstrate the ability of early warning for drug risks of this platform.

A total of 20 types of ADRs were involved with iopromide. However, only 6 of them were actually detected. The undetected ADRs included asphyxia, coma, dyspnoea and other serious adverse reactions. Those that were both included in drug instructions and actually detected were anaphylactoid reaction(a=12,PRR=2.81), rash(a=6,PRR=0.69), vomiting(a=6,PRR=1.77), and nausea(a=4,PRR=0.87), while those detected but not stated in drug instructions included anaphylactic shock (a=6,PRR=13.98), and pruritus (a=4,PRR=1.41). Anaphylactoid reaction and anaphylactic shock are two suspect signals.

Overall, this drug has some serious ADRs, as stated in drug instructions or actually detected, thus close attention is required for it. On February 6, 2013, China Food and Drug Administration released the Adverse Drug Reaction Information Bulletin (No. 52), which alerted the severity of iopromide's ADRs and advised cautious use of this drug. This is consistent with our analysis results. The detection data used in this system was only two years data of one province of China, indicating the system has the ability of early warning for drug risks.

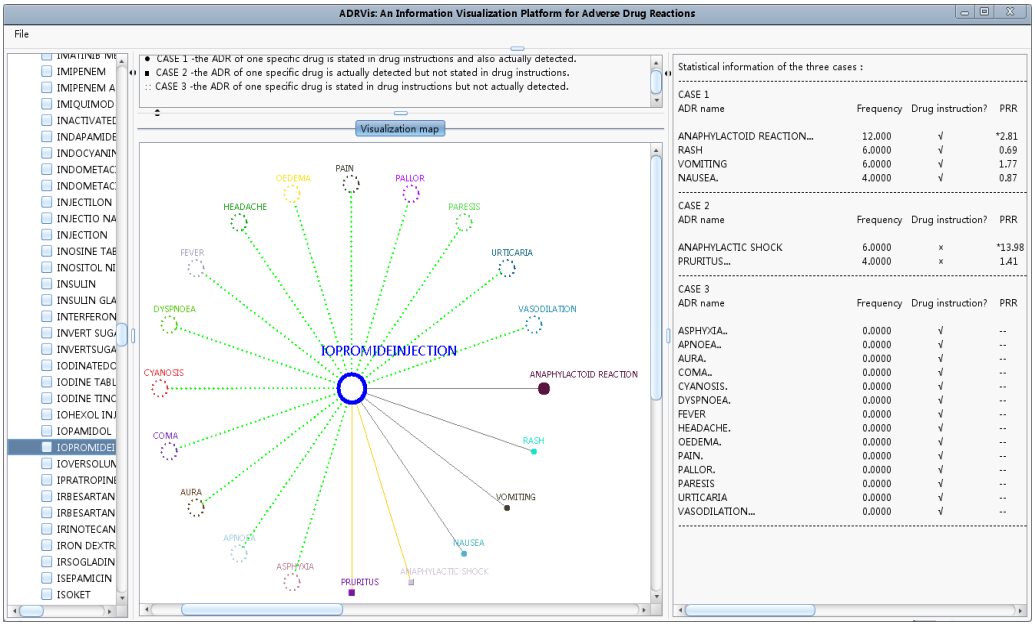

Figure 6. Visualization Map of Iopromide's ADRs

3.3. Case Study III

Iopromide is a non-ionic low-osmolality contrast agent for angiography, brain and abdominal CT scans, and urethrography. Its classification information is chemical medicine – diagnostic drug – diagnostic imaging drug – contrast (Figure 6). As Iopromide is a drug which alarmed by China Food and Drug Administration in 2013, we choose it to demonstrate the ability of early warning for drug risks of this platform.

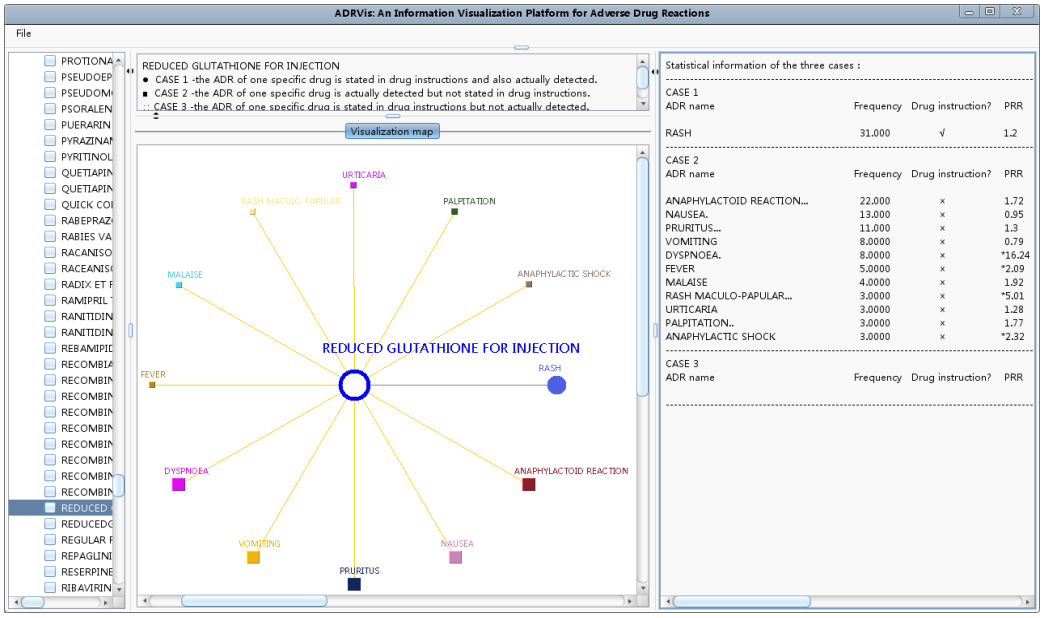

Figure 7. Visualization Map of Reduced Glutathione for Injection

Due to drugs' limited pre-market clinical trials, adverse reactions stated in drug instructions are often not sufficient. Many new ADRs are found in clinical use. In this case study, Reduced glutathione for injection is chosen to validate this kind of situation. The drug is composed of glutamic acid, cysteine and glycine is a kind of natural synthetic peptide in the human cytoplasm and has an important role to maintain cell biological function. Its indications include: anemia, acute respiratory distress syndrome, sepsis, viral hepatitis, digestive diseases, infectious diseases, respiratory medicine and so on. The visualization map of the drug was shown in Figure 7.

From Figure 7, we could see only one ADR of this drug, *rash*, was stated in its drug instruction. The drug instruction stated that *rash* was very rarely seen, which was in conflict with the frequency of actually detected. In our data, the frequency of this ADR was 31. It was a biggish number and accounted for about 27.2% of the total amount of this drug. We also could find that 11 ADRs had been actually detected but not stated in its drug instruction and 4 suspect signals were generated, which were *dyspnoea*(a=8, PRR=16.24), *fever*(a=5, PRR=2.09), *rash maculo-papular* (a=3, PRR=5.01) and *anaphylactic shock*(a=3, PRR=2.32). Therefore, due to the drug has some serious ADRs and its drug instruction is insufficient, we suggest that pharmaceutical manufacturers make on the actual clinical survey and revise the drug instructions

4. Discussion

In this study, we put forward a prototype system for ADR information visualization. But to be truly applied to the practice, there are many aspects should be improved in the further work.

First of all is the data problem. It only contains two years ADEs data of one province in china and the drug instruction data was collected from the Internet. Therefore, this platform had yet not provided very sufficient and accurate information for users. In next work, we will enhance the data quantity and data quality of this system.

Another problem is visualization element design. As the color of legends is random and not one-to-one relationship between ADR and color, which made users can't distinguish the difference of ADRs. In order to make clear which system organ would be effected by a drug, a good idea to resolve the shortcoming is to associate a specific color

to ADR classes, such as red for cardiology, blue for gastrointestinal system, etc.. The textual labels were with uniform size and some of them were overlapping, which made the labels poor readability. Thus, adjustable-size textual labels would be considered in the further research.

Besides the above, this system is designed for all types of users, such as patients, physicians, medicine administration, pharmaceutical manufacturers and so on, which leads to poor system user distinguish degrees. As different type users have different medical knowledge and do not have the same needs, we will give full consideration to the different user demands and provide them personalized functions respectively.

5. Conclusion

A visualization system of adverse drug reactions, ADRVis, was developed based on drug instructions and ADEs data. The relationships between 656 drugs with their respective ADRs were visualized by this system, which was successfully tested with three typical drugs. The system was not only able to display both drug-ADR combinations that were stated in drug instructions and those that were actually detected, but also owned a certain early ADRs warning function. It was also able to differentiate three cases of ADRs: those both mentioned in drug instructions and ADEs, those not mentioned in drug instructions but in ADEs, and those stated in drug instructions but not in ADEs. It applied a variety of visual elements including graphics, size, and color, along with the use of forms including texts and numbers to describe the ADRs information. Therefore, this system can provide a visualization platform for the general public, drug administration, clinicians, and pharmaceutical producing enterprises to understand adverse drug reactions and evaluate drug risks.

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Conflicts of Interest Statement

The authors of this article have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this article.

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