Establishment of the visualization platform for ADR query and analysis: an example of severe skin adverse reactions caused by sulfonylureas

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Abstract

Background: Driven by the need of medical staff and general public to collect and review adverse drug reactions (ADRs) of interest, we introduced and validated a visualization platform for querying and analyzing data from the FDA Adverse Event Reporting System (FAERS). A case study of the association between sulfonylureas and serious skin adverse reactions was conducted to validate platform usability.

Objective: To build a visualization platform for querying and analyzing data from the FDA Adverse Event Reporting System (FAERS), facilitating the collection and review of adverse drug reactions (ADRs) of interest.

Methods: We performed appropriate data acquisition, cleaning and subsequent platform interface and functional development of available data. In order to evaluate the usability of the platform, we focused on a case study involving serious skin adverse reactions caused by sulfonylureas.

Results: We developed a visualization platform for adverse reaction query and analysis based on FAERS data. The platform consists of five components, including the login page, multi-condition query, drug and adverse reaction query, primary ID query and data download interface. The high usability of the platform was verified by demonstrating the signal mining results of serious skin adverse reactions caused by sulfonylureas and visualizing information.

Conclusions: The visualization platform and verification cases constructed in this study provide a suitable framework and method for drug safety research, which is expected to promote the development of pharmacovigilance.

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Keywords: ADRs; Case Study; FAERS; Pharmacovigilance; Visualization Platform

1 Introduction

In 1992, a French pharmacoepidemiologist formally defined pharmacovigilance (PV) as “all methods of preventing and monitoring adverse drug reactions (ADRs)” [1]. In 2002, the World Health Organization (WHO) further refined it as “a series of science and activities related to the detection, evaluation, recognition and prevention of ADRs and any other drug-related problems” [2]. ADR case reports in the Spontaneous Reporting System (SRS) have been a cornerstone of PV over the past few decades [3]. The FDA Adverse Event Reporting System (FAERS) updates quarterly and collects daily more than 4000 drug safety reports, with the number of reports growing exponentially each year [4]. One of the common tasks routinely performed in a hospital's PV center/department is to collect and review all available data on adverse events (AEs) of interest, thus there is no doubt that PV research is facilitated by comparing FAERS data with everyday clinical practice [5]. While this data source is freely available to the public through external channels [6], researchers often find their access limited due to a lack of programming expertise or familiarity with the FAERS database structure [7].

A key challenge in using FAERS data is data quality: manufacturers, physicians, pharmacists, nurses, and consumers may report the same AEs, leading to data duplication and a lack of standardization. Another challenge is the limited time for clinicians to data retrieval. Studies have shown that the expected time required to complete data retrieval significantly impacts physicians' ability to seek clinical answers [8]. Furthermore, the FDA does not provide statistical visualization analysis, which significantly limits the ability to interpret and analyze the vast and complex FAERS data for further safety signals mining. A visualization platform based on the FAERS data could greatly benefit researchers by facilitating dynamic exploration and rapid extraction of patient data, overcoming some of the inherent challenges in utilizing FAERS data and enhancing the efficiency and efficacy of drug safety research.

Sulfonylureas (SU) are widely used oral hypoglycemic drugs in clinical practice [9]. Glimepiride, as a third-generation long-acting sulfonylurea preparation, is mainly used in type 2 diabetes mellitus whose blood sugar level can’t be effectively controlled by diet, exercise and weight loss. In the latest American Beers criteria in 2019, glimepiride was classified as a potentially inappropriate drug (PIM) for the elderly due to the high risk of severe long-term hypoglycemia in the elderly [10]. Our previous study found that glimepiride was still a highly used PIM in outpatient elderly patients in China [11]. In addition to the clear risk of severe hypoglycemia, there have been cases where patients have experienced severe skin ADRs after using sulfonylureas, and these ADRs were not listed in the drug inserts although the FDA has indicated the risks on the website [12]. Severe skin ADRs have a great impact on the quality of life of patients, and even have life-threatening consequences. Therefore, it is necessary to clarify whether there is a definite link between sulfonylureas such as glimepiride and severe skin ADRs.

Driven by these practical conditions, we developed a visualization platform for ADR query and analysis based on FAERS data, and detailed the processes of data acquisition and cleaning, as well as the subsequent functional and visualization enhancements implemented in the platform. Utilizing the established platform, a pharmacovigilance study was conducted using real-world FAERS data, where we analyzed signals and elucidated the association between severe skin ADRs and sulfonylureas through a case demonstration. Our goal is to enhance the accessibility and utility of FAERS data for medical professionals and the general public by introducing this innovative visualization tool, thereby contributing to the advancement of pharmacovigilance.

2 Materials and methods

2.1 Construction of ADR Query and Analysis Platform

2.1.1 Data download and processing

The data processing work was carried out independently by the team (members were from the Department of Pharmacy, Xiangya Hospital, Central South University and the School of Computer Science, National University of Defense Technology). After an extensive literature search, the terms of interest were determined. The data was extracted and synchronized through Python and MySQL, then merged, deduplicated, and analyzed, finally defining the data table structure. If the case ID was the same, we identified and deleted the duplicate report by comparing the numerical value of primary ID and the order of FDA-DT date [4]. This study considered an AE record to be complete if it contained at least four 'key' demographic fields: event date, age, gender, and reporting country. Records were aggregated by case ID, and missing values were filled with data from other records in the same aggregation, if available [4].

2.1.2 Platform Framework Design

During December 2021, we held several virtual meetings to discuss the framework design of the platform for query and analysis exploiting FAERs data, especially the function of visual statistical analysis. Information visualization could enhance the effect of data presentation, allowing medical staff to observe and browse data in an intuitive and interactive way [13]. Researches have shown that visualization could reduce the cognitive load on physicians and support the

extraction of useful information from complex medical data [14].

The platform was designed with data query and management functions. The query terms were determined after extensive discussion by the team and literature search for the correlation analysis of drugs and ADRs based on the FAERS database in the past three years. The query module had three functions: multi-condition query, drug and ADR query, and primary ID query. In order to support users for further advanced statistical analysis and data mining, we built a data management module, which main function was data download.

In order to "run" the query, the subject needed to click the "statistics" button, which would cause visual graphs or tables to be created in a new window on the screen. They included a signal mining result of drug and ADR information exported as a CSV or EXCEL file and other seven visualization graphs, including distribution of patients' age, gender, job occupation and adverse event reporting sources, as well as the situation of report time, outcome and polypharmacy.

2.2 Case study

2.2.1 Data sources

All data in this study were derived from real-world data from the FAERS. We use the ADR analysis and query platform established in the early stage to access the data for subsequent analysis. Data were retrieved from 2015Q1 to 2020Q1 (21 quarters in total) after defining terms of ADRs and drugs. The reasons why we built a single case to test the platform were as follows: (1) we wanted a test environment to experiment with various data integrations; (2) we wanted to validate the rationality of interface and functional design.

2.2.2 Standardization of study drug names

All related generic names and trade names of second- and third-generation sulfonylureas were searched in the Drugbank database for data mapping to ensure the integrity of the search. The results are shown in Multimedia Appendix 1.

2.2.3 Standardization of ADR Terminology

We validated Preferred Term (PT) from MedDRA version 23.0, defined severe cutaneous ADRs using a narrowly defined Standardised MedDRA Queries (SMQ) algorithm, and searched against the defined 18 preferred terms reported (Multimedia Appendix 2).

2.2.4 Data mining methods

The ADR signal monitoring mining algorithms are ratio imbalance measure (DPA) and Bayesian method. DPA included PRR method and ROR method, and Bayesian method included BCPNN method and MGPS method. The above four methods were used in this study.

2.2.5 Data Analysis

Fours ADR signal mining algorithms were used in this study [15], which detection standard judgments were as follows: 1) ROR: the number of reports N≥3 and the lower limit of the ROR 95% confidence interval > 1; 2) PRR: the number of reports ≥3 and PRR≥2 and the chi-square value ≥4; 3) BCPNN: IC025>0 (two-sided test 95% confidence interval lower limit); 4) MGPS: EBGM05>2, N>0 (one-sided test 90% confidence interval lower limit).

3 Results

3.1 Platform framework design

The platform consisted of five components, including the login page, multi-condition query, drug and ADR query, primary ID query and data download interface.

After identifying the platform framework, we initiated the process of transforming the data into visualizations on the platform dashboard, including the selection of appropriate, understandable graphics for each metric, the definition of appropriate data terms and parameters, and the adjustment of graphical assets (such as axis values, table titles and color schemas). The platform provided statistical visualization analysis and generated report, while allowing personalized analysis by filtering conditions, and had the ability to browse individual patient data for more comprehensive information.

3.1.1 User registration and login

Users needed to register an account and indicated the role position (physician, pharmacist, nurse) before logging in the platform. The platform was temporarily limited to testers who had an account (See Figure 1).

3.1.2 Multi-condition query

Users could make targeted queries base on time of occurrence of AEs, age, age group (newborn, infant, young child, adolescent, adult, elderly), gender, reporter occupation (physician, pharmacists, patients, lawyers, and other health professionals), drug name and ADR terms. Most of the conditions were displayed in the form of drop-down menu selection, such as age group and reporter occupation. Other conditions were accompanied by inputting format prompts to ensure the accuracy and personalization of the query (See Figure 2). For “drug”, in order to avoid the influence of irregularity and omission, the generic and trade name of the drug should be searched through the Drugbank database. Similarly, it was recommended to use SMQ algorithm for the term “adverse reaction” [16].

3.1.3 Drug and ADR query, primary ID query

This module realized separate or combined search for drugs and ADRs. In Figure 3, the upper table represented the results of searching for drug names alone, which meant the user want to retrieve all the ADRs. The table below showed the results of limited drug names and ADRs, which meant that the user was interested in the ADRs caused by a specific drug.

In addition, it was well known that the seven data sets were linked through primary ID, and clicking the corresponding primary ID can obtain the complete process of the patient's AEs. Users could also look through data information by directly entering the relevant primary ID (See Figure 4) .

3.1.4 Data management

The platform also provided a data download service. Each column represented a quarter of data, and also recorded the size of the file for users to download. As shown in Figure 5. Due to limited page space, the screenshot only showed part of the data. Each column represented a quarter of data, and the file size was also recorded for users to download. This feature saved time and resources, otherwise users would take several minutes to access and download data from the FAERS official website. In addition, the platform guaranteed real-time updated of data.

3.1.5 Data visualization analysis

Through the statistics button, the platform completed the visual analysis of the data. The content mainly included: patient age distribution, patient gender distribution, AE report source distribution, reporter occupation distribution, reporting time distribution, patient outcome distribution and patient polypharmacy, a total of 7 visual charts. This function helped users to quickly understand the information provided by the data in a clearer and more efficient way. Data visualization analysis was one of the main features of the Platform, which greatly reduced the threshold for users. (See Figure 6-7, taking the search drug glimepiride causing severe skin ADRs as an example)

3.2 Case study

3.2.1 Sulfonylurea-Related ADRs in the FAERS Database

A total of 2,968,834 records in 21 quarters from 2015Q1 to 2020Q1 were included in this study. The records of the use of second-generation and third-generation sulfonylurea drugs and the occurrence of serious skin ADRs are shown in Table 1.

The second-generation and third-generation sulfonylureas all have serious skin ADRs reported, and Gliclazide and glimepiride have a higher reporting rate of ADRs. Among the second-generation sulfonylureas, 6746 cases of ADRs were

recorded with gliclazide, and 123 cases were related to serious skin ADRs. The use of glimepiride, a third-generation sulfonylurea drug, was associated with 77 documented skin ADRs.

3.2.2 Data mining for severe skin ADRs

Table 2 showed the signal values of sulfonylurea-related serious skin ADRs tested by four statistical methods. The signal values of Gliclazide, Glibenclamide, and glimepiride were all statistically significant.

From the reported demographic data, there were 233 records of serious skin ADRs using second- and third-generation sulfonylureas, and 119 (51.07%) were female patients. The median patient age was 73 (IQR 65-77), and 175 patients were ≥65 years old (75.11%). There were significant differences in the gender ratio and age composition of patients who used second- and third-generation sulfonylureas and had severe skin ADRs. In terms of the places where ADRs occurred, the reports of second-generation sulfonylureas mainly came from France (66.67%), the United Kingdom (17.89%) and Japan (5.69%); the reports of third-generation sulfonylureas mainly came from Germany (68.83%), Japan (28.57%), and the United States (2.60%). And the reporters were mainly other health-professional (39.06%). In terms of reporting time, 2018 was the year with the largest number of reports in the past five years. Among the patients who used second- and third-generation sulfonylureas and had severe skin ADRs, 89.27% had multiple medication (number of drugs>5). More importantly, we found serious AE outcomes (Death, Hospitalization - Initial or Prolonged, Life-Threatening, Other Important Medical Event) in all patients with serious cutaneous ADRs (Table 3).

Table 4 showed the results of the detection of ADR signals using the four data mining methods. The narrow SMQ search for serious cutaneous ADRs in MedDRA included eighteen ADR PTs. Among 156 patients with severe skin ADRs using second-generation drugs, Dermatitis bullous, Stevens-Johnson syndrome, Toxic epidermal necrolysis. And two or more methods can detect Toxic epidermal necrolysis, Dermatitis exfoliative generalised, Exfoliative rash, Stevens-Johnson syndrome, Dermatitis bullous, Acute generalised exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms eosinophilia and systemic symptoms a total of seven ADRs PT signals were statistically significant.

Among 77 patients with severe skin ADRs using third-generation drugs, the most common adverse event was Toxic epidermal necrolysis. Dermatitis exfoliative and Erythema multiforme followed. Among them, Toxic epidermal necrolysis, Dermatitis exfoliative, Erythema multiforme, Oculomucocutaneous syndrome, a total of four ADRs PT signals in two types. The above methods are statistically significant.

4 Discussion

4.1 Platform Framework design

In the current work, we adopt a pragmatic approach to utilize available FAERS data for data extraction, parsing, merging and synchronization, missing data processing and structure definition, then designed the interface and functions, described the visual information in detail with a case finally. Taken together, these work illustrated the potential of the platform to support medical staff in the practice of analytics. To the best of our knowledge, no such tool was currently available to the general public or healthcare workers, and we demonstrated an approach to be applied to other data sources for PV.

One study [17] relied on query formulas to obtain data from the FAERS, PubMed and Twitter, filtered and transformed the data, then performed visual analysis, which was similar to our study. The design of the computing framework was elaborated in their study, while we showed more about the function and interface design. This enlightened that we can use multiple sources to improve the usability of the platform and provide more comprehensive information for PV.

Visualizing information enhanced the understanding of reported information. Another study developed the Information Visualization Platform (InfoViP) for drug safety surveillance [15]. It used context-driven interactive visualizations and informatics tools for case series analyses. They conducted three times meeting with a team of seven experts at the FDA Headquarters about the workflow and major functionalities. The design process was more representative and unbiased than us. In terms of data integration, our platform required to manually retrieve the corresponding drug name and ADRs, but InfoViP can map drug labels one by one with external databases. This was undoubtedly the goal of our next research.

One study designed a platform to provide a graphical representation of individual patient records while allowing the view of individual patient-level longitudinal data [5]. our platform can only achieve overall statistical visualization of retrieved results. Pham [8] et al. developed an analytics platform guiding by the User-centred design (UCD) framework. As a design philosophy, the UCD framework supported the creation of tools that users want. Similar to this study, we also took into account the individual needs of users, allowing users to filter and aggregate data, and provided all possible retrieval contents in the form of drop-down menus. In the future, we can use the UCD framework as a guide to fully consider the needs of users and further iterate.

4.2 Sulfonylureas and Serious Skin ADRs

It was estimated that 422 million people worldwide had diabetes, avoidance of ADRs was the most important

feature of treatment that patients value when choosing a treatment regimen [18]. This study revealed an association between sulfonylurea antidiabetic drugs and several specific serious cutaneous ADRs. We performed signal detection for eighteen specific PTs for severe cutaneous ADRs using four methods. In patients on second-generation sulfonylureas, Toxic epidermal necrolysis, Dermatitis exfoliative generalised, exfoliative rash, Stevens-Johnson syndrome, Dermatitis bullous, Acute generalised exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms, a total of seven PTs were statistically significant, indicating that they were associated with the use of drugs. In patients taking glimepiride, Toxic epidermal necrolysis, Dermatitis exfoliative, Erythema multiforme, Oculomucocutaneous syndrome, a total of four PTs were statistically significant. Nishanth et al. in 2018 reported the first case of Glimepiride induced Drug Reaction with Eosinophilia and Systemic Symptoms, which was a life threatening ADR [19]. Bouraoui et al reported a case of fatal Toxic Epidermal Necrolysis probably related to glimepiride in a patient with a previous medical history of hypersensitivity to SMX-TMP [20], which corroborated our findings and suggested that we should be concerned with the relationship between glimepiride and severe skin ADRs.

Elderly patients were at increased risk of polypharmacy due to decreased physical function. Our study showed 89.27% of the patients had multiple drugs (number of drugs>5), and 69.53% of the patients took more than 10 drugs. According to recent research, middle-aged and older adults with diabetes took an average of nine medications a day [21]. Another retrospective study of elder patients with a diagnosis of type 2 diabetes showed that the percentage of patients receiving five or more drugs was 57.1% [22]. A review examined the association with adverse health outcomes of polypharmacy in older adults with type 2 diabetes and the results showed a significant association between polypharmacy and all-cause mortality and myocardial infarction [23]. These findings indicated that attention should be paid to the polypharmacy of these patients.

4.3 Advantages and limitations

In this study, we successfully built a visualization platform for ADR query and analysis, which was also the first multi-functional query and analysis platform based on FAERS data in China. It mainly had the following characteristics: 1) the multi-condition query function realized the personalized needs and meant a lot for the signal mining of AEs for special groups. 2) online viewing of patients' complete adverse event report information through Primary ID, patient privacy was not involved. 3) The visual analysis function was simple and clear, which could help users quickly understand data information and lower the user threshold. We used the visualization platform to access the data for subsequent analysis, and we found the correlation between sulfonylurea antidiabetic drugs and severe skin ADRs from real cases for the first time.

However, it was unclear whether the findings based on the platform will have a positive clinical impact. The platform should be trialed among real clinical practice environment in the future to gain more insights into its design, functionality and performance [8]; secondly, the data only came from the FAERS, and multi-source data should be considered to avoid information bias [24]; Thirdly, it was impossible to quickly and accurately confirm whether the displayed chart was correct, and the corresponding raw data should be attached for verification [25]; In addition, the platform can’t visualize longitudinal data at the individual patient level; Last but not least, in the framework design, we had only carried out preliminary interface and functional design, and more detailed elements hadn’t be considered, diverse functional requirements were also ignored, such as using a multi-dimensional timeline to show the relationship between events on different timelines [26].

5 Conclusions

This paper elaborated the appropriate data acquisition, cleaning and subsequent interface and functional design to develop the visualization platform for ADR query and analysis, then conducted a case study of the association between glimepiride and severe skin ADRs. Based on the platform, this study carried out the signal detection of second- and third-generation sulfonylurea antidiabetic drugs and severe skin ADRs[1]. It was the first time that serious skin ADRs were found to be clearly related to these drugs. This result also validated that the platform can be a powerful tool for medical workers to mine ADR signals. Our goal was to facilitate the utilization of FAERS data by introducing a visualization platform for ADR query and analysis, illustrate potential benefits and challenges and promote the development of PV further.

6 Declarations

6.1 Funding

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Reform Project of Central South University (2022JGB067).

6.2 Conflicts of interest

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6.3 *Data Availability*

The data that support the findings of this study are openly available.

6.4 Authors' contributions

All authors of the University of National Defense Science and Technology carried out data processing and algorithm design. All authors of Xiangya Hospital carried out the platform interface and functional design. Ya-Min Huang and Lu Zhang drafted the manuscript. All authors participated in manuscript revision, and final approval of the submission.

6.5 Ethics approval

No requirements about ethical approval to develop the visualization platform.

6.6 Consent for publication

All authors agreed to submit this version of paper for publication.

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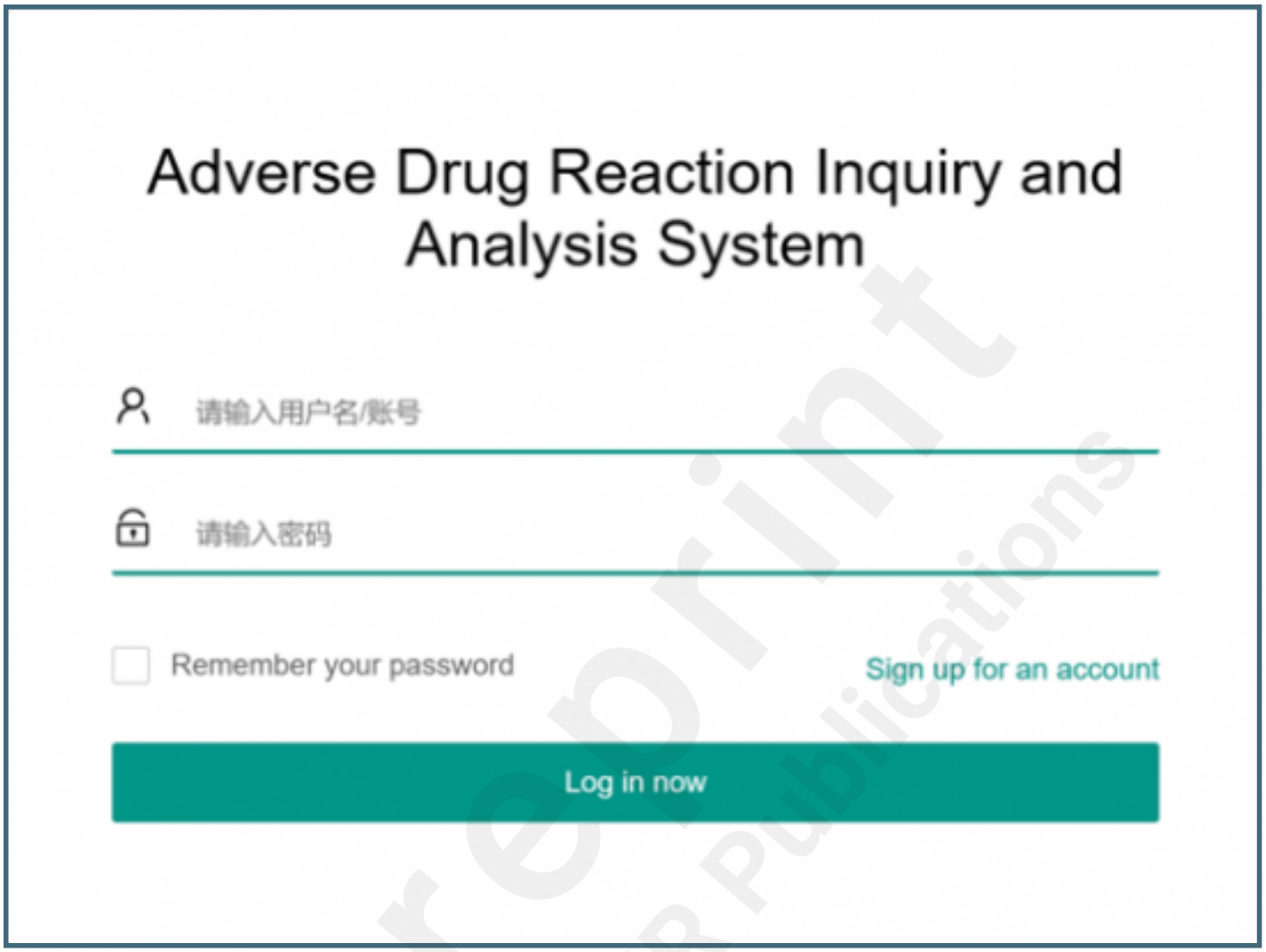
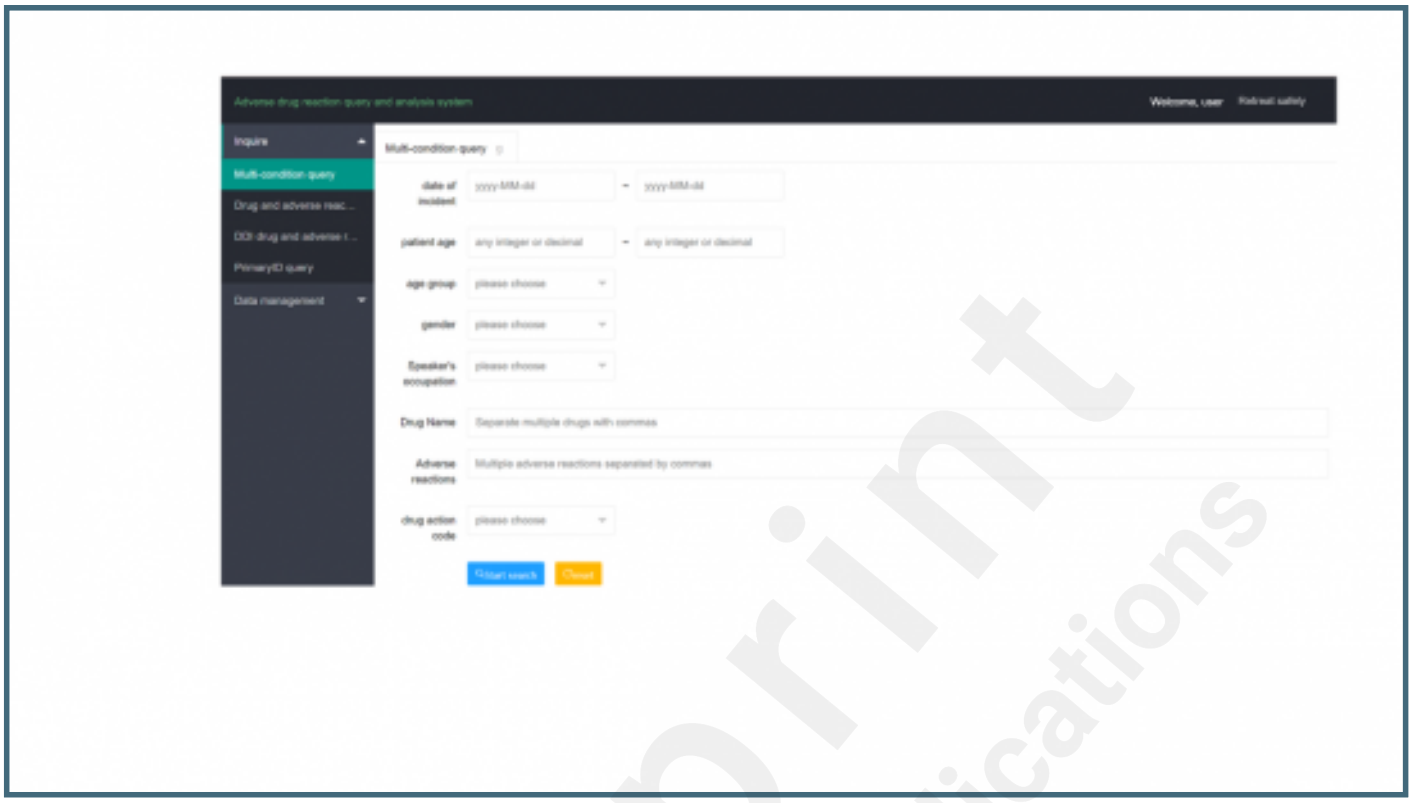
Supplementary Files

Figures

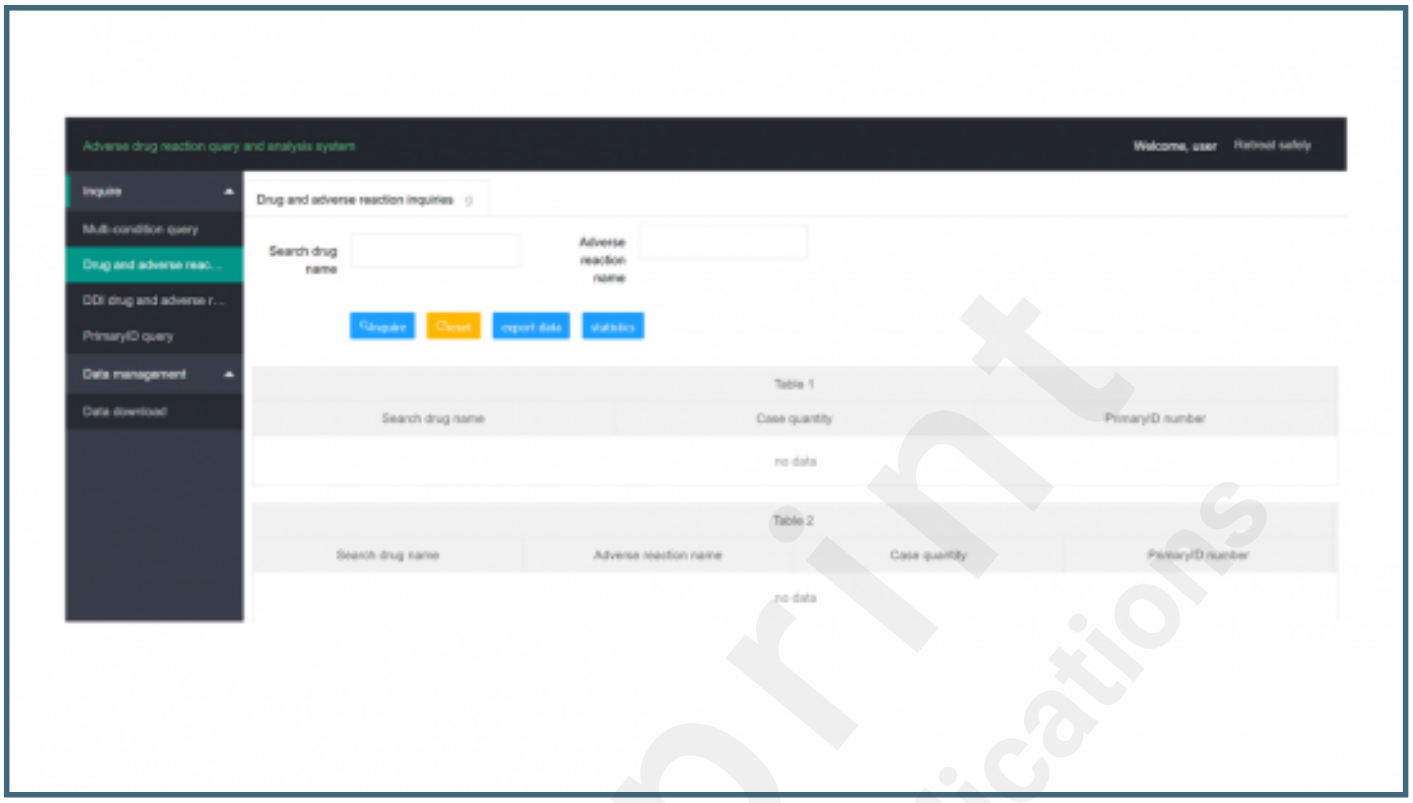
User login interface.



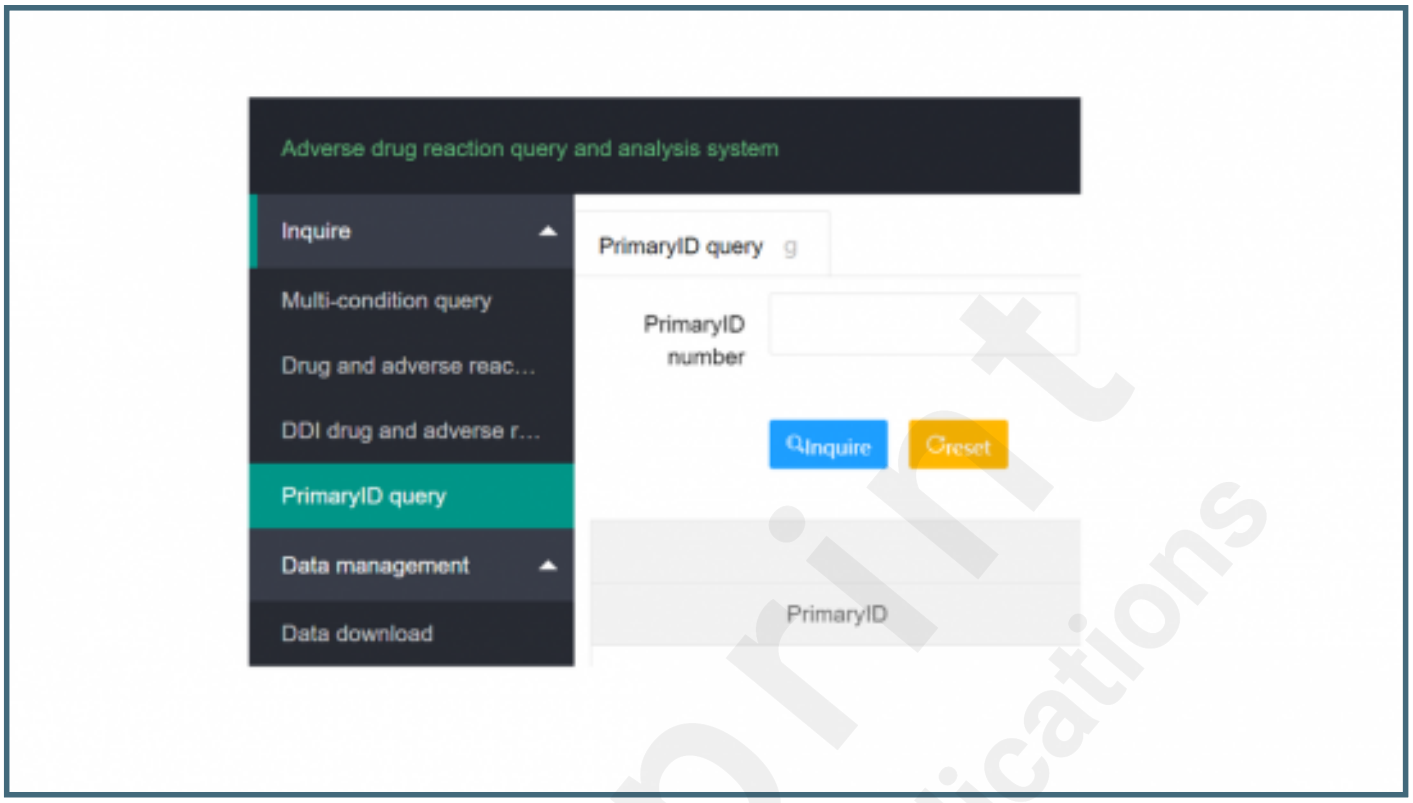
Multi-condition query interface.



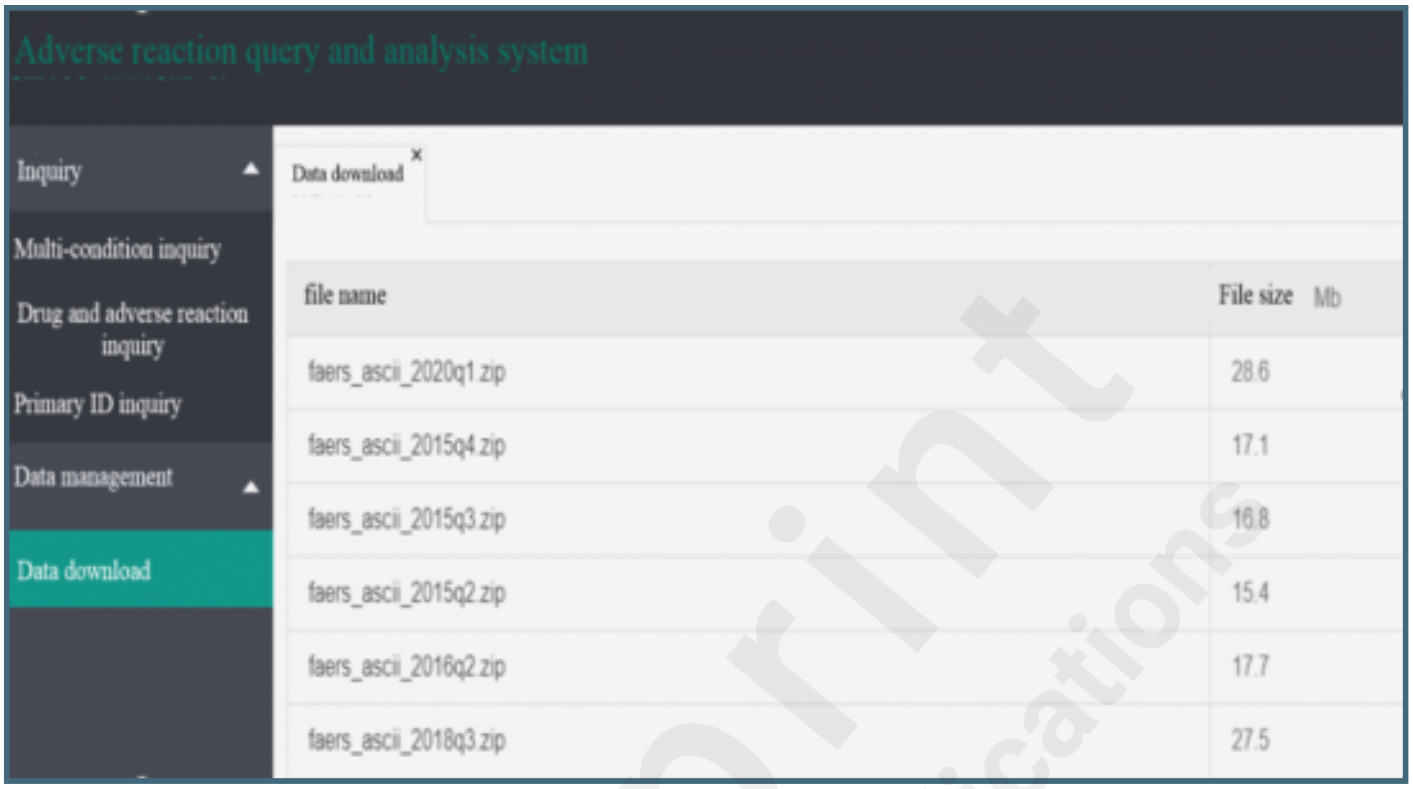
Drug and ADR query interface.



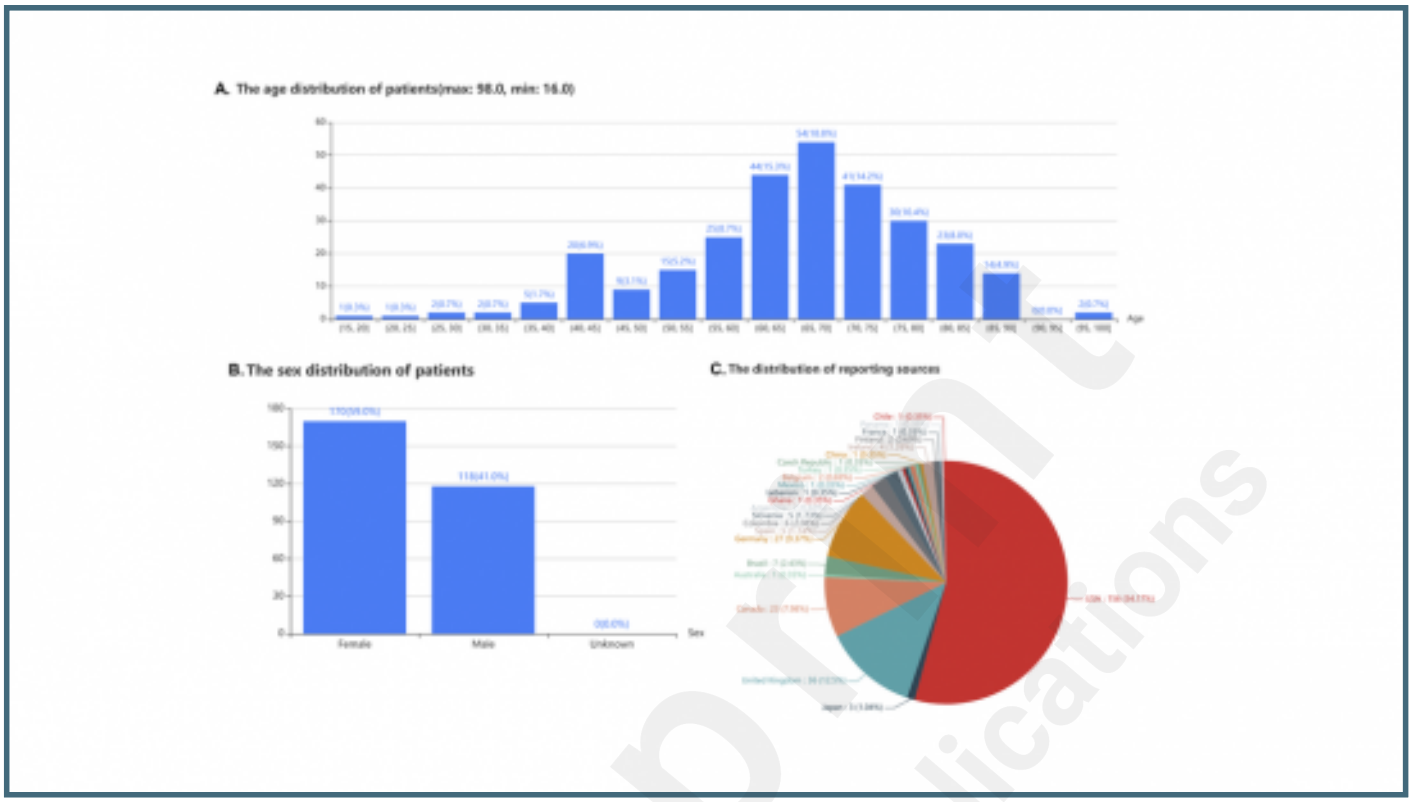
Primary ID query interface.



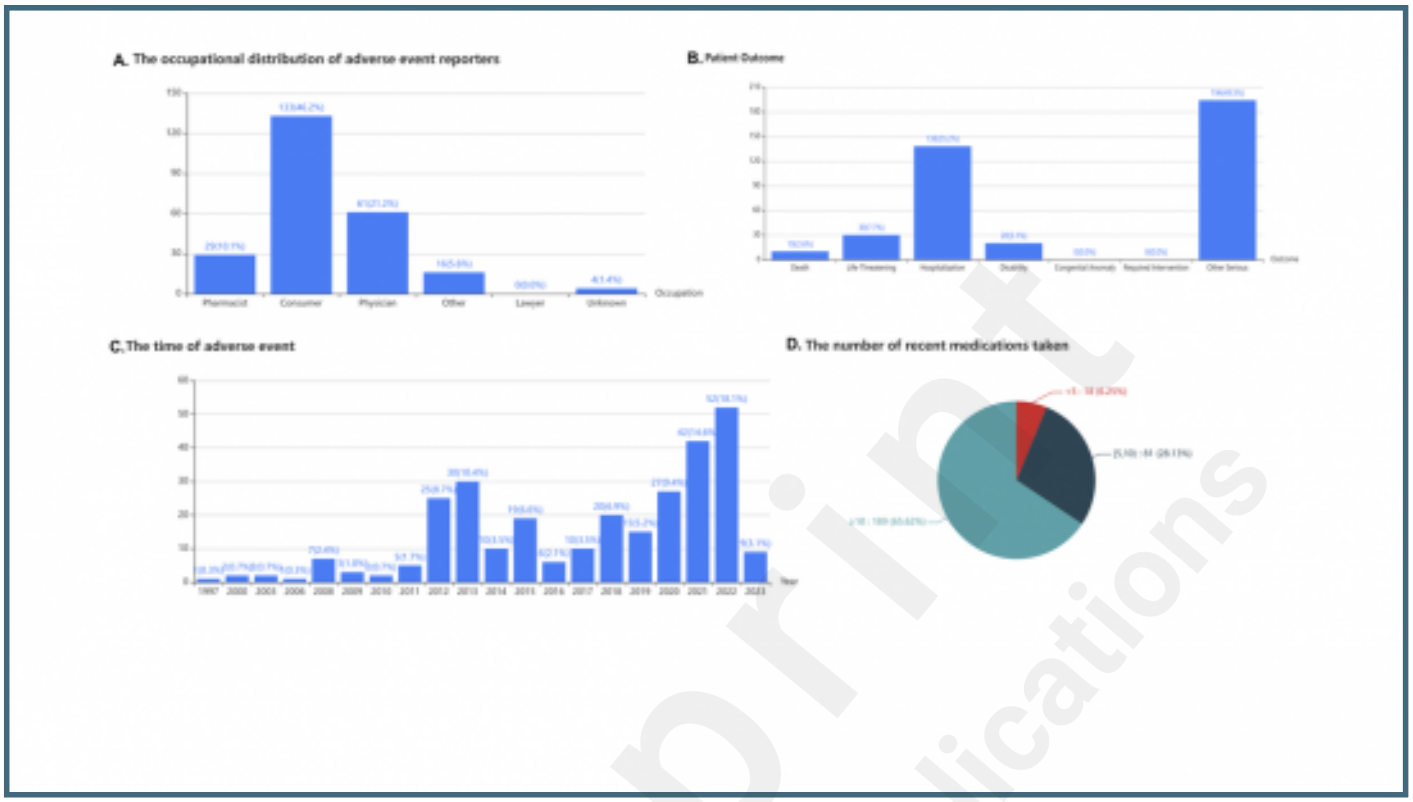
Data management interface.



Results displayed in the platform. A. Distribution of age. B. Distributionof gender. C.Distribution of adverse event reporting sources.



Results displayed in the platform. A. Distribution of reporters’ job occupation; B. Distribution of report time; C.Distribution of outcome; D. Situation of patient's polypharmacy.



Multimedia Appendixes

Table 1 ADRs associated with sulfonylureas in FAERS database.
URL: http://asset.jmir.pub/assets/865b6c3df63fb2c3674fa193c4d5af22.docx

Table 2 The Signal for Severe skin ADRs (Narrow SMQ) associated with SU.
URL: http://asset.jmir.pub/assets/dc205b9d74070026d6f9bf53f60b2523.docx

Table 3 Demographic characteristics of the records.
URL: http://asset.jmir.pub/assets/a4c33b5886ca7712e1fac6f168cb75ba.docx

Table 4 The Signal for ADR.
URL: http://asset.jmir.pub/assets/a42f9c3979959ef7be5364bc0c07ec19.docx

The data mapping of drug name.
URL: http://asset.jmir.pub/assets/6a167f28533e6ce57680b8d9f94fbb55.docx

Definitions of severe skin adverse reactions.
URL: http://asset.jmir.pub/assets/d9926102f71fa208bd3a2487ca7e9171.docx