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Research Article

Drug-Induced Acute Kidney Injury: A Real-World Pharmacovigilance Study Using the FDA Adverse Event Reporting System Database

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Abstract

Background: Comprehensive quantitative and comparative risk data on drug-induced acute kidney injury (AKI) remain limited. Thus, this study aimed to supplement the current data with information from the FDA Adverse Event Reporting System (FAERS) database. **Methods**: Based on the collected AKI-related reports in the FAERS database from 2004 to 2023, we summarized a list of reported nephrotoxic drugs, compiling counts of the most frequently reported single drugs and drug classes. A disproportionality analysis was used to evaluate the AKI risk of reported drugs, and histological and onset time analyses were conducted. **Results**: A total of 1456 drugs were reported as culprit drugs in the 327,561 AKI-related reports in the FAERS database, most of which were antineoplastic agents. Omeprazole was the most frequently reported single drug, followed by furosemide, pantoprazole, esomeprazole, and lansoprazole. Drugs for acid-related disorders were the most commonly reported drug class, followed by agents acting on the renin–angiotensin system, antineoplastic agents, immunosuppressants, and analgesics. In the disproportionality analysis, 1021 drugs showed different degrees of association with the occurrence of AKI, among which eight drugs (spironolactone, mycophenolic acid, enalapril, valsartan, candesartan, gentamicin, vancomycin, and nifedipine) had the largest number of positive signals, with 15 positive signals each. Drugs acting as an antineoplastic agent were the class with the largest number of positive signal drugs in most preferred term groups; however, the imbalance of risk signal distribution among drug classes reflected the subsequent risk differences in relation to AKI. In the histological analysis, tubulointerstitial injury was the most commonly reported type of histological injury. In the onset time analysis, vancomycin presented the shortest median onset time, while the median onset time for lansoprazole was the longest. **Conclusions**: Our study integrated quantitative and comparative AKI risk data for 1456 reported culprit drugs using the FAERS database, which can provide reference information for clinical practice.

Keywords: acute kidney injury; acute renal failure; adverse drug reaction; pharmacovigilance; data mining

1. Introduction

Acute kidney injury (AKI) is a rapid decline in the kidneys' ability to filter metabolic waste products from the blood, which manifests clinically as an abrupt and sustained increase in the serum levels of urea and creatinine with an associated disruption of salt and water homeostasis [1]. It is a common disorder of renal function that affects 7 to 18% of hospital inpatients and 20–200 per million population in the community worldwide [2], significantly increasing the risk of death, economic burden, and the probability of progression to end-stage renal disease and chronic kidney disease [3–5].

There are many known etiologies of AKI, mainly including sepsis, critical illness, circulatory shock, burns, trauma, cardiac surgery, major non-cardiac surgery, poisonous plants and animals, radiocontrast agents, and nephrotoxic drugs [6,7]. Among them, drugs are the third to the fifth leading cause of AKI [8], accounting for about 18%–27% of all AKI cases [9], and even as high as 66% in elderly patients [10]. Due to the prominent position of drugs in the etiology of AKI, the 2012 AKI guideline of the Kidney Disease Improving Global Outcomes (KDIGO) group recommended that the management of potentially nephrotoxic drugs should be the basic intervention measures throughout the four stages of AKI (high risk of AKI, AKI stage 1, 2, and 3) [11]. In this context, it is of great significance for medical professionals to be familiar with the potential nephrotoxicity of drugs to ensure the management quality of AKI.

In clinical practice, medical professionals usually rely on primary, secondary, and (or) tertiary information sources to obtain information on nephrotoxic drugs [8]. However, this process may not run smoothly because of the substantial fragments and discrepancies in nephrotoxicity information provided by various sources [12,13]. In response to this situation, some researchers have carried out literature

review studies to integrate the nephrotoxicity information of drugs, highlight the high-risk drugs causing AKI, and recommend management measures [6,9,14–19]. However, although these studies have made an excellent critical review of the literature and simplified the process for medical professionals to achieve and apply information about drug nephrotoxicity, they cannot provide comprehensive quantitative and comparative risk data of these drugs, which partly limits the practicability of the research results in high-risk drug monitoring, primary suspected drug identification, and drug withdrawal selection. Thus, it is necessary to explore a method to quantify and compare the AKI risk of drugs comprehensively.

At present, the massive real-world adverse event (AE) data in the spontaneous reporting system bring opportunities for understanding the risk characteristics of drugs [20,21]. In terms of kidney safety, the pharmacovigilance database has been widely used to understand the AKI risk of specific drugs [22,23], investigate the most common AKI pathogenic drugs [24], compare the risk differences of AKI among drugs in the same category [25–27], and explore risk characteristics of drug-induced AKI in the special population [28]. To some extent, these studies confirmed the feasibility of using pharmacovigilance databases to explore the risk characteristics of drug-related AKI in the real world. However, although the aforementioned studies provide quantitative AKI risk information of some drugs to varying degrees, it is almost impossible to comprehensively integrate the quantitative risk of drug-induced AKI based on these results due to the differences in drugs investigated, research methods, time span, and population selection. In addition, the potential AKI risks of many drugs have also not been quantitatively evaluated in pharmacovigilance research, which also hinders the comprehensive understanding and integration of drug-related AKI risk characteristics.

In this context, our objective is to assess the AKI risk of all the reported nephrotoxic drugs in the FDA Adverse Event Reporting System (FAERS) in a unified standard, trying to present the whole picture of drug AKI risks from the perspective of pharmacovigilance, so as to provide more comprehensive renal safety information for clinical AKI management.

2. Materials and Methods

2.1 Data Source

The FAERS database is a post-marketing safety surveillance program run by the FDA, which records all AE reports received by the FDA since 2004 and is updated quarterly. The AE data recorded in the FAERS database mainly includes patient demographic characteristics, patient outcomes, report sources (reporter and reporting country), drug information, drug indications, reporting time, and adverse reactions involved [29]. These data are highly structured, and the target information can be called and obtained through the application program interface provided by the *openFDA* platform (https://open.fda.gov/apis/drug/) [30].

2.2 Identifying AE Reports Related to AKI

By using the Medical Dictionary for Regulatory Activities (MedDRA), the FAERS database uniformly converts adverse reaction information into standardized medical terms called Preferred Term (PT). Standardized MedDRA query (SMQ) is an embedded tool provided by MedDRA that can help retrieve the AE reports of interest in the MedDRA-coded pharmacovigilance database. An SMQ usually provides two retrieval strategies: narrow-scope search and broad-scope search. Typically, PTs in the narrow-scope search can more accurately represent the condition or area of interest [31], so we use PTs included in the narrow-scope search of "acute renal failure (SMQ)" in MedDRA version 27.0 to retrieve target reports. The specific PT and corresponding MedDRA codes can be found in **Supplementary Table 1**.

2.3 Risk Signal Detection Method

In this study, we used the reporting odds ratio (ROR) method to detect the risk signal and quantify the risk of AKI induced by different drugs [32]. The ROR method is a classical disproportionality analysis method, and we can calculate its ROR value and corresponding 95% confidence interval (CI) based on the two-by-two contingency table (Table 1). The specific calculation equation is as follows:

$$ROR = \frac{a/c}{b/d} = \frac{ad}{bc} \tag{1}$$

$$95\%\ CI = e^{\ln(ROR) \pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}} \tag{2}$$

Table 1. The two-by-two contingency table for risk signal detection.

	Drug of interest	Other drugs	Total
AE of interest	a	b	a+b
Other AEs	c	d	c+d
Total	a+c	b+d	a+b+c+d

Abbreviation: AE, adverse event.

When target reported quantity (a in Table 1) is greater than or equal to 3 and the lower limit of 95% CI of the ROR value is lower than 1, a positive risk signal is generated, which means that the drug being evaluated has potential risk of inducing AKI; On the contrary, if the target reported quantity or the lower limit of 95% CI of the ROR value does not meet the above criteria, it means a non-positive

Table 2. The co-reported PT indicated glomerular injury, tubular injury, tubulointerstitial injury, and thrombotic injury.

Histological injury type	PT (MedDRA code)
Glomerular injury	glomerulonephritis acute (10018366); glomerulonephritis rapidly progressive (10018378); mesangioproliferative glomerulonephritis (10066453); fibrillary glomerulonephritis (10068279); glomerulonephritis (10018364); glomerulonephritis minimal lesion (10018374); glomerulonephritis membranoproliferative (10018370); glomerulonephritis membranous (10018372); immunotactoid glomerulonephritis (10067871)
Tubular injury	renal tubular acidosis (10038535); renal tubular atrophy (10038536); renal tubular disorder (10038537); renal tubular necrosis (10038540); renal tubular dysfunction (10050335)
Tubulointerstitial injury	tubulointerstitial nephritis and uveitis syndrome (10069034); tubulointerstitial nephritis (10048302)
Thrombotic injury	renal vein thrombosis (10038548); renal vascular thrombosis (10072226); renal-limited thrombotic microangiopathy (10085346); renal artery thrombosis (10038380)

Abbreviation: PT, Preferred Term; MedDRA, Medical Dictionary for Regulatory Activities.

risk signal, suggesting that there is no statistical association between the drug being evaluated and the occurrence of AKI [33].

2.4 Histological Analysis and Onset Time Analysis

Based on the co-reported PT, we marked the histological injury type of reports as glomerular injury, tubular injury, tubulointerstitial injury, and (or) thrombotic injury. The co-reported PT, indicating four types of histological injury, is detailed in Table 2. On this basis, we made statistics on the distribution of the frequent types of renal injuries for main drugs and drug classes to understand their risk difference in histological injury type.

In addition, we used the data on medication time and AKI occurrence time in the report for onset time analysis. Onset time is defined as the interval from the beginning date of drug use to the AKI occurrence date. To ensure the accuracy of the data, we removed records missing drug beginning date or AKI occurrence date, incorrect records (AKI occurrence date before the drug beginning date), and suspected records (drug withdrawal date to AKI occurrence date exceeding 30 days). In this study, medians (interquartile ranges) and Weibull's shape parameter β were used to conduct onset time analysis. According to the Weibull's shape parameter β, the AKI risk with time can be classified into early failure type (the upper limit of 95% CI of β is lower than 1, indicating that the AKI risk decreases with time), random failure type (the 95% CI of β includes 1, indicating that the AKI risk is continuously over time), and wearout failure type (the lower limit of 95% CI of β is higher than 1, indicating that the AKI risk increases with time) [34].

2.5 Statistical Analysis Steps

Referring to the definition of AE report data fields provided by *openFDA* (https://open.fda.gov/apis/drug/event/searchable-fields/), we can realize the data collection, processing, analysis, and summary of AE report data. Detailed steps are as follows.

First, we used PTs in **Supplementary Table 1** to search the field "patient.reaction.reactionmeddrapt.exact" and set the retrieval time field "receivedate" as "[20040101+TO+20231231]" to determine AE reports related to AKI in the FAERS database from January 1, 2004, to December 31, 2023. Correspondingly, all the AE reports returned by the retrieval will be downloaded and used for subsequent analysis.

Second, we extracted and integrated the basic information of the downloaded AE reports, including annual report quantity, submitter, reporting country, patient sex, patient age, patient outcome, and the report quantity for each PT.

Third, we collected the generic name information of drugs in the field of "patient.drug.openfda.generic_name" and the reported role of the drug in the field of "patient.drug.drugcharacterization". After removing non-primary suspected drugs ("patient.drug.drugcharacterization" field $\neq$ 1), removing drugs missing generic name information ("patient.drug.openfda.generic_name" field is empty), excluding repetitive drug names (drug information in "patient.drug.openfda.generic_name" field is the same), removing ambiguous drugs (e.g., "CHOLESTEROL"), and manually merging drugs with the same active ingredient (e.g., aspirin and acetylsalicylic acid), we finally got a comprehensive nephrotoxic drug list from the FAERS database.

Fourth, the Anatomical Therapeutic Chemical (ATC) classification system (https://atcddd.fhi.no/atc_ddd_index/) was used to code the drug list manually, and we classified drugs into pharmacological or therapeutic subgroups (ATC 2nd level) according to the ATC code definition. On this basis, the most commonly reported single drugs and drug classes in AKI-related reports were counted.

Fifth, the risk signals of each drug involved in the list were detected at the SMQ level and the PT level, respectively. In addition, the distribution characteristics of risk signals were summarized on the basis of the detection results.

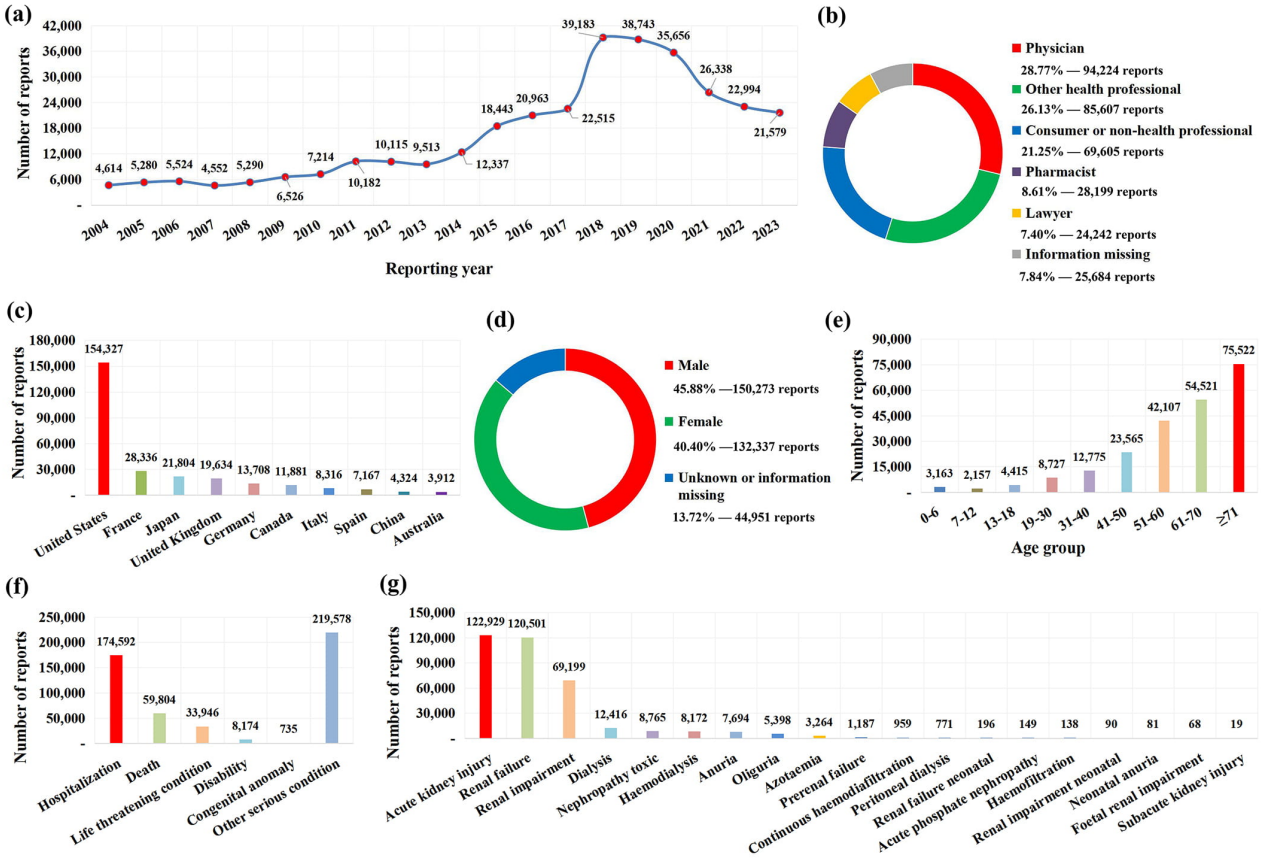


Fig. 1. The basic information and patient characteristics of 327,561 AKI-related reports. (a) Distribution of annual report quantity. (b) The occupational distribution of the submitter. (c) The top 10 reporting countries. (d) The gender distribution of patients. (e) The age distribution of patients. (f) The out-come distribution of patients. (g) The number of adverse event reports associated with each PT.

Finally, based on the co-reported PT and time data, the histological analysis and onset time analysis were conducted.

In this study, R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel 2019 were used for statistical analysis.

3. Results

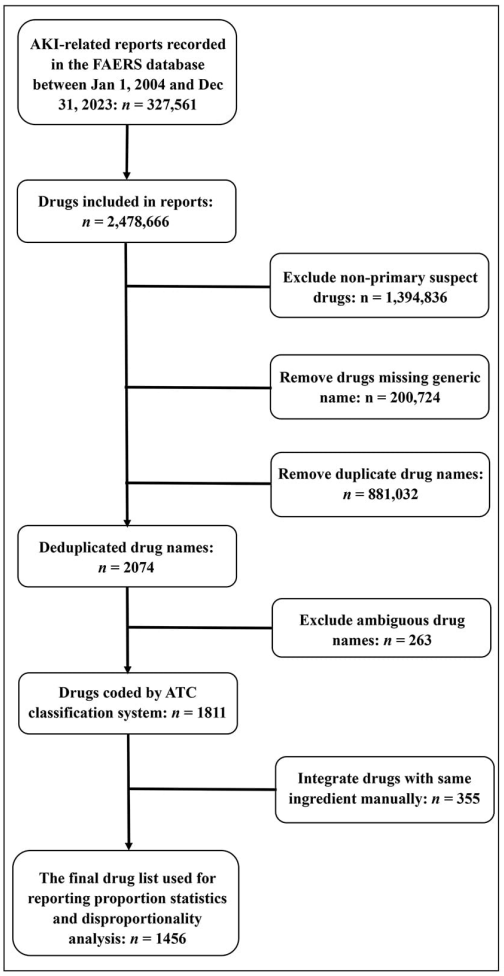
3.1 Descriptive Analysis of AKI-Related Reports in the FAERS Database

During the period from January 1, 2004, to December 31, 2023, the FAERS database accumulated 17,391,308 AE reports. Using 19 PTs in **Supplementary Table 1** to identify target drug nephrotoxicity reports, 327,561 AKI-related reports were finally retrieved for analysis. The number of AKI annual reports received by the FAERS database is shown in Fig. 1a, among which 2018 was the year with the largest reported quantity. In terms of submitters, 208,030 (63.51%) AKI reports were submitted by health professionals (physicians, pharmacists, and other health professionals), among which physicians accounted for the highest proportion (Fig. 1b). The top 10 countries with the largest reported quantity of drug-induced AKI are shown in Fig. 1c, and the United States is the most important source of reports, contributing 154,327 (47.11%) AKI-related reports. The gender distribution of patients is shown in Fig. 1d, and there are more male patients (45.88%) than female patients (40.40%) suffering from drug-induced AKI. Among the AKI-related reports included in the analysis, 226,952 (69.29%) detailed patient age, and the statistical age distribution showed that the occurrence of AKI showed an increasing trend with the age of patients (Fig. 1e). With regard to patient outcomes, more than 50% of drug-induced AKI cases can be classified into serious AE, and even 59,804 (18.26%) cases died (Fig. 1f). The number of reports related to each PT is shown in Fig. 1g, in which "acute kidney injury" is the most frequently reported PT, followed by "renal failure" and "renal impairment".

3.2 Potential Nephrotoxic Drugs Reported to the FAERS Database

To obtain a comprehensive list of potentially nephrotoxic drugs recorded in the FAERS database, we collected the generic name information of drugs recorded in the "patient.drug.openfda.generic_name" field of 327,561 AKI-related reports. Due to the existence of combined drugs and concomitant drugs, an AKI-related report usually records multiple drug information, so we finally ex-

(a)



(b)

Antineoplastic agents L01 218 (14.97)	Antibacterials for systemic use J01 76 (5.22)	Antivirals for systemic use J05 69 (4.74)
Immunosuppressants L04 64 (4.40)	Psycholeptics N05 54 (3.71)	Drugs used in diabetes A10 47 (3.23)
Psychoanaleptics N06 44 (3.02)	Analgesics N02 38 (2.61)	AARAS C09 37 (2.54)
OATMP A16 34 (2.34)	Drugs for obstructive airway diseases R03 34 (2.34)	All other therapeutic products V03 31 (2.13)
Cardiac therapy C01 29 (1.99)	Antithrombotic agents B01 28 (1.92)	SHMGS G03 26 (1.79)
Other nervous system drugs N07 24 (1.65)	Antiepileptics N03 23 (1.58)	Ophthalmologicals S01 23 (1.58)
Lipid modifying agents C10 22 (1.51)	Urologicals G04 20 (1.37)	Anesthetics N01 20 (1.37)
Endocrine therapy L02 19 (1.30)	AAP M01 19 (1.30)	Anti-parkinson drugs N04 18 (1.24)
Contrast media V8 18 (1.24)	Drugs for acid related disorders A02 17 (1.17)	Beta blocking agents C07 17 (1.17)
Drugs for constipation A06 16 (1.10)	Diuretics C03 15 (1.03)	Antihistamines for systemic use R06 15 (1.03)
PHHA H01 14 (0.96)	Immunostimulants L03 14 (0.96)	Antiprotozoals P01 14 (0.96)
Antihypertensives C02 13 (0.89)	Muscle relaxants M03 13 (0.89)	AIAAA A07 12 (0.82)
Antianemic preparations B03 12 (0.82)	SHPESHI H02 12 (0.82)	Antimycotics for systemic use J02 12 (0.82)
Vitamins A11 11 (0.76)	Calcium channel blockers C08 10 (0.69)	Antimycobacterials J04 10 (0.69)
Mineral supplements A12 9 (0.62)	Antihemorrhagics B02 9 (0.62)	Other hematological agents B06 9 (0.62)
Calcium homeostasis H05 9 (0.62)	BSPS B05 8 (0.55)	Drugs for treatment of bone diseases M05 8 (0.55)
ODDMSS M09 8 (0.55)	Diagnostic radiopharmaceuticals V09 8 (0.55)	Antiemetics and antinauseants A04 7 (0.48)
Antifungals for dermatological use D01 7 (0.48)	Immune sera and immunoglobulins J06 7 (0.48)	Cough and cold preparations R05 7 (0.48)
DFGD A03 6 (0.41)	Antiseptics and disinfectants D08 6 (0.41)	Other dermatological preparations D11 6 (0.41)
Nasal preparations R01 6 (0.41)	Bile and liver therapy A05 5 (0.34)	Antiobesity preparations A08 5 (0.34)
ACDU D06 5 (0.34)	Other gynecologicals G02 5 (0.34)	Antigout preparations M04 5 (0.34)
Other respiratory system products R07 5 (0.34)	Vasoprotectives C05 4 (0.27)	CDP D07 4 (0.27)
Thyroid therapy H03 4 (0.27)	Anthelmintics P02 4 (0.27)	Therapeutic radiopharmaceuticals V10 4 (0.27)
Stomatological preparations A01 3 (0.21)	Anti-acne preparations D10 3 (0.21)	Diagnostic agents V04 3 (0.21)
Digestives, incl. Enzymes A09 2 (0.14)	Anabolic agents for systemic use A14 2 (0.14)	Peripheral vasodilators C04 2 (0.14)
PTWU D03 2 (0.14)	Antipsoriatics D05 2 (0.14)	GAA G01 2 (0.14)
Ectoparasiticides P03 2 (0.14)	Emollients and protectives D02 1 (0.07)	Pancreatic hormones H04 1 (0.07)

Fig. 2. Identification and classification of reported potential nephrotoxic drugs. (a) Flowchart of reported nephrotoxic drugs identification. (b) Classification and summary of reported nephrotoxic drugs. Abbreviations: AAP, antiinflammatory and antirheumatic products; AARAS, agents acting on the renin-angiotensin system; ACDU, antibiotics and chemotherapeutics for dermatological use; AIAAA, Antidiarrheals, intestinal antiinflammatory and antiinfective agents; BSPS, blood substitutes and perfusion solutions; CDP, corticosteroidal dermatological preparations; DFGD, drugs for functional gastrointestinal disorders; GAA, gynecological antiinfectives and antiseptics; OATMP, other alimentary tract and metabolism products; ODDMSS, other drugs for disorders of the musculo-skeletal system; PHHA, pituitary and hypothalamic hormones and analogues; PTWU, preparations for treatment of wounds and ulcers; SHMGS, sex hormones and modulators of the genital system; SHPESHI, systemic hormonal preparations, excluding sex hormones and insulins.

tracted 2,478,666 pieces of drug generic name information. After excluding non-primary suspect drugs (n = 1,394,836), removing drugs missing generic name information (n = 200,724), and removing duplicate drug names (n = 881,032), we got a preliminary list containing 2074 drug names. Based on this preliminary list, we manually reviewed the generic names of drugs and coded them with the ATC classification system. After excluding ambiguous drug names (n = 263) and manually merging drugs with the same active ingredient (n = 355), we finally obtained a list containing 1456 potentially nephrotoxic drugs for subsequent analysis (Fig. 2a).

Based on the ATC classification system, the 1456 potentially nephrotoxic drugs were further classified into 81 pharmacological or therapeutic subgroups (Fig. 2b). Of the 81 drug categories involved, the number of reported potential nephrotoxic drugs involved in different drug classes varies greatly, among which antineoplastic agents contain the largest number of reported nephrotoxic drugs (n = 218), while emollients and protectives (n = 1) and pancreatic hormones (n = 1) involve the fewest drugs. In addition, we further associated 1456 drugs with 19 PTs (Table 3), among which "renal failure" involved the largest number of reported nephrotoxic drugs (n = 1389), while "foetal renal impairment" involved the least drugs (n = 16).

3.3 Most Frequently Reported Nephrotoxicity Drugs in the FAERS Database

Based on the number of AKI-related reports associated with each PT (Fig. 1g) and the corresponding potential

Table 3. Number of reported nephrotoxic drugs associated with the SMQ group and PT subgroup.

Group	No. (%) of reported nephrotoxic drugs
Acute renal failure (SMQ) [1]	1456 (100.00)
Renal failure (PT)	1389 (95.40)
Acute kidney injury (PT)	1379 (94.71)
Renal impairment (PT)	1330 (91.35)
Dialysis (PT)	993 (68.20)
Oliguria (PT)	924 (63.46)
Anuria (PT)	920 (63.19)
Nephropathy toxic (PT)	892 (61.26)
Haemodialysis (PT)	873 (59.96)
Azotaemia (PT)	821 (56.39)
Prerenal failure (PT)	524 (35.99)
Continuous haemodiafiltration (PT)	459 (31.52)
Peritoneal dialysis (PT)	384 (26.37)
Acute phosphate nephropathy (PT)	149 (10.23)
Haemofiltration (PT)	136 (9.34)
Renal failure neonatal (PT)	117 (8.04)
Neonatal anuria (PT)	80 (5.49)
Renal impairment neonatal (PT)	52 (3.57)
Subacute kidney injury (PT)	34 (2.34)
Foetal renal impairment (PT)	16 (1.10)

[1] This is an SMQ term that contains 19 PTs in this table.

Abbreviations: SMQ, Standardized MedDRA Query.

Table 4. Quantity distribution of positive risk signals in reported nephrotoxic drugs.

No. of positive risk signals	No. (%) of reported nephrotoxic drugs
15	8 (0.55)
14	6 (0.41)
13	14 (0.96)
12	26 (1.79)
11	38 (2.61)
10	43 (2.95)
9	62 (4.26)
8	64 (4.40)
7	70 (4.81)
6	98 (6.73)
5	93 (6.39)
4	126 (8.65)
3	132 (9.07)
2	104 (7.14)
1	137 (9.41)
0	435 (29.88)
Total	1456 (100.00)

nephrotoxic drugs involved (Table 3), we made statistics on the proportional distribution of reported nephrotoxic drugs in AKI-related cases. Fig. 3 shows 10 potential nephrotoxic drugs most frequently reported at the SMQ level and PT level. From the overall (at SMQ level) perspective, the top 10 most frequently reported potential nephrotoxic drugs are omeprazole (n = 36,601), furosemide (n = 32,529), pantoprazole (n = 30,802), esomeprazole (n = 30,272), lansoprazole (n = 27,633), metformin (n = 23,442), acetylsalicylic acid (n = 22,572), amlodipine (n = 21,192), lisinopril (n = 15,564), and metoprolol (n = 15,344) in turn. However, it is worth noting that the most frequently reported potential nephrotoxic drugs may vary greatly across SMQ and different PT levels.

In addition, based on the ATC classification system, we further divided the drugs involved in each PT (Table 3) into 81 different pharmacological or therapeutic subgroups (Fig. 2b) and made statistics on the quantitative and proportional distribution of different drug classes in AKI-related reports. Fig. 4 shows 10 potential nephrotoxic drug classes most frequently reported at the SMQ level and PT level. From the overall (at SMQ level) perspective, the top 10 most frequently reported drug classes are drugs for acid related disorders (n = 67,540), agents acting on the renin-angiotensin system (n = 57,141), antineoplastic agents (n = 56,387), immunosuppressants (n = 53,508), analgesics (n = 49,752), diuretics (n = 48,973), drugs used in diabetes (n = 46,157), beta blocking agents (n = 41,825), antibacterials for systemic use (n = 40,288), and antithrombotic agents (n = 37,544) in turn. It is noteworthy that although most frequently reported drug classes also change across SMQ and different PT levels, the role of "drugs for acid related disorders" and "agents acting on the renin-angiotensin system" is particularly prominent.

3.4 Risk Signal Detection Results of Reported Nephrotoxic Drugs

To better identify high-risk AKI drugs and facilitate risk comparison, we used the ROR method to uniformly quantify the AKI risk of 1456 drugs at SMQ and PT levels. The risk signal detection results of 1456 reported nephrotoxic drugs are detailed in **Supplementary Table 2**. For each drug, there is one risk signal detection result at the SMQ level and 19 at the PT level.

On the basis of the risk signal detection results, we further summarized the risk signal distribution of 15 major drug classes at the SMQ level and PT level to better present the risk characteristics of reported nephrotoxic drugs (Fig. 5). Our results showed that at the SMQ level and most PT levels, the drug classes with the greatest number of positive risk signals were mainly antineoplastic agents, antibacterials for systemic use, and antivirals for systemic use. Meanwhile, we also noticed that the risk signal distribution was unbalanced in some drug classes. For example, most antibacterials for systemic use showed positive risk signals in the SMQ level and most PT levels, while most immunosuppressants showed non-positive risk signals.

Furthermore, we counted the distribution of positive risk signals of 1456 reported nephrotoxic drugs. Our statistical results showed that the sum of positive risk signal

Group	Reporting proportion of the top 10 drugs									
	1	2	3	4	5	6	7	8	9	10
SMQ (n =327,561)	Omeprazole 36,601 (11.17)	Furosemide 32,529 (9.93)	Pantoprazole 30,802 (9.40)	Esomeprazole 30,272 (9.24)	Lansoprazole 27,633 (8.44)	Metformin 23,442 (7.16)	Acetylsalicylic acid 22,572 (6.89)	Amlodipine 21,192 (6.47)	Lisinopril 15,564 (4.75)	Metoprolol 15,344 (4.68)
Acute kidney injury (n =122,929)	Omeprazole 22,973 (18.69)	Pantoprazole 19,809 (16.11)	Esomeprazole 19,711 (16.03)	Lansoprazole 18,137 (14.75)	Furosemide 16,256 (13.22)	Metformin 13,964 (11.36)	Acetylsalicylic acid 10,876 (8.85)	Amlodipine 10,469 (8.52)	Lisinopril 8,855 (7.20)	Dexlansoprazole 7,726 (6.28)
Renal failure (n =120,501)	Omeprazole 17,953 (14.90)	Esomeprazole 16,149 (13.40)	Pantoprazole 14,282 (11.85)	Lansoprazole 13,699 (11.37)	Furosemide 12,389 (10.28)	Acetylsalicylic acid 9,367 (7.77)	Amlodipine 8,158 (6.77)	TD+EMT 8,118 (6.74)	Lisinopril 7,501 (6.22)	Metoprolol 7,172 (5.95)
Renal impairment (n =69,199)	Furosemide 5,698 (8.23)	Amlodipine 4,212 (6.09)	Acetylsalicylic acid 4,113 (5.94)	Omeprazole 3,959 (5.72)	Pantoprazole 3,411 (4.93)	Metformin 3,048 (4.40)	Lansoprazole 3,041 (4.39)	Tacrolimus 3,015 (4.36)	Prednisone 2,854 (4.12)	Metoprolol 2,763 (3.99)
Dialysis (n =12,416)	Lansoprazole 1268 (10.21)	Omeprazole 1020 (8.22)	Furosemide 718 (5.78)	Pantoprazole 691 (5.57)	Darbepoetin alfa 658 (5.30)	Esomeprazole 650 (5.24)	Ambrisentan 598 (4.82)	Acetylsalicylic acid 560 (4.51)	Amlodipine 517 (4.16)	Insulin glargine 469 (3.78)
Nephropathy toxic (n =8,765)	Tacrolimus 1,090 (12.44)	Mycophenolic acid 955 (10.90)	Ciclosporin 763 (8.71)	Vancomycin 709 (8.09)	Methotrexate 619 (7.06)	Prednisone 618 (7.05)	Cisplatin 549 (6.26)	Cyclophosphamide 468 (5.34)	Prednisolone 423 (4.83)	Furosemide 392 (4.47)
Haemodialysis (n =8,172)	Darbepoetin alfa 1,061 (12.98)	Metformin 800 (9.79)	Furosemide 590 (7.22)	Acetylsalicylic acid 497 (6.08)	Omeprazole 436 (5.34)	Amlodipine 429 (5.25)	Lansoprazole 344 (4.21)	Simvastatin 314 (3.84)	Pantoprazole 304 (3.72)	Tacrolimus 297 (3.63)
Anuria (n =7,694)	Metformin 879 (11.42)	Furosemide 740 (9.62)	Amlodipine 522 (6.78)	Acetylsalicylic acid 450 (5.85)	Bisoprolol 295 (3.83)	Tacrolimus 295 (3.83)	Mycophenolic acid 288 (3.74)	Prednisone 284 (3.69)	Omeprazole 276 (3.59)	Ramipril 250 (3.25)
Oliguria (n =5,398)	Furosemide 563 (10.43)	Amlodipine 370 (6.85)	Metformin 336 (6.22)	Acetylsalicylic acid 312 (5.78)	Tacrolimus 251 (4.65)	Prednisone 248 (4.59)	Omeprazole 247 (4.58)	Mycophenolic acid 233 (4.32)	Spironolactone 222 (4.11)	Methylprednisolone 221 (4.09)
Azotaemia (n =3,264)	Furosemide 436 (13.36)	Acetylsalicylic acid 284 (8.70)	Omeprazole 269 (8.24)	Lansoprazole 225 (6.89)	Pantoprazole 213 (6.53)	Amlodipine 208 (6.37)	Metformin 194 (5.94)	Esomeprazole 164 (5.02)	Lisinopril 162 (4.96)	Allopurinol 157 (4.81)
Prerenal failure (n =1,187)	Furosemide 144 (12.13)	Metformin 111 (9.35)	Prednisone 92 (7.75)	Pregabalin 91 (7.67)	Adalimumab 90 (7.58)	Rituximab 83 (6.99)	Methotrexate 82 (6.91)	Amlodipine 79 (6.66)	Etanercept 78 (6.57)	Infliximab 73 (6.15)
Continuous haemodiafiltration (n =959)	Metformin 211 (22.00)	Furosemide 79 (8.24)	Amlodipine 52 (5.42)	Cytarabine 51 (5.32)	Vancomycin 46 (4.80)	Paracetamol 46 (4.80)	Prednisolone 45 (4.69)	Tacrolimus 44 (4.59)	Methotrexate 44 (4.59)	Cyclophosphamide+1 [a] 38 (3.96)
Peritoneal dialysis (n =771)	Darbepoetin alfa 194 (25.16)	Furosemide 50 (6.49)	Lansoprazole 48 (6.23)	Amlodipine 42 (5.45)	Omeprazole 36 (4.67)	Esomeprazole 35 (4.54)	Pantoprazole 34 (4.41)	Insulin glargine 22 (2.85)	Atorvastatin 21 (2.72)	Tacrolimus+1 [b] 21 (2.72)
Renal failure neonatal (n =196)	Diclofenac 36 (18.37)	Paracetamol 18 (9.18)	Furosemide 14 (7.14)	Amlodipine 12 (6.12)	Enalapril 12 (6.12)	Valsartan 12 (6.12)	Ibuprofen 11 (5.61)	Captopril 9 (4.59)	Labetalol 8 (4.08)	Indometacin+3 [c] 8 (4.08)
Acute phosphate nephropathy (n =149)	Acetylsalicylic acid 19 (12.75)	Simvastatin 14 (9.40)	Hydrochlorothiazide 13 (8.72)	Lisinopril 13 (8.72)	Atorvastatin 13 (8.72)	Valsartan 12 (8.05)	Bisacodyl 10 (6.71)	Levothyroxine 10 (6.71)	Calcium 9 (6.04)	Amlodipine 9 (6.04)
Haemofiltration (n =138)	Metformin 19 (13.77)	Dexamethasone 11 (7.97)	Methotrexate 11 (7.97)	Vincristine 10 (7.25)	Cyclophosphamide 9 (6.52)	Cytarabine 9 (6.52)	Levetiracetam 8 (5.80)	Hydrocortisone 7 (5.07)	Prednisone 6 (4.35)	Mitoxantrone+1 [d] 6 (4.35)
Renal impairment neonatal (n =90)	Olmesartan medoxomil 18 (20.00)	Valsartan 15 (16.67)	Acetylsalicylic acid 12 (13.33)	Metoprolol 11 (12.22)	Lisinopril 9 (10.00)	Losartan 7 (7.78)	Nifedipine 5 (5.56)	Candesartan 5 (5.56)	Meropenem 5 (5.56)	Gentamicin+1 [e] 4 (4.44)
Neonatal anuria (n =81)	Furosemide 10 (12.35)	Candesartan 8 (9.88)	Ramipril 7 (8.64)	Metoprolol 6 (7.41)	Valsartan 6 (7.41)	Escitalopram 6 (7.41)	Enalapril 5 (6.17)	Losartan 5 (6.17)	Levothyroxine 5 (6.17)	Vancomycin+1 [f] 5 (6.17)
Foetal renal impairment (n =68)	Ibuprofen 22 (32.35)	Indometacin 15 (22.06)	Valsartan 12 (17.65)	Losartan 8 (11.76)	Metoprolol 6 (8.82)	Insulin glargine 4 (5.88)	Enalapril 3 (4.41)	Olmesartan medoxomil 3 (4.41)	Tacrolimus 3 (4.41)	Sotalol+1 [g] 2 (2.94)
Subacute kidney injury (n =19)	Irbesartan 5 (26.32)	Fenofibrate 5 (26.32)	MET+SIT 3 (15.79)	Dabigatran etexilate 3 (15.79)	Venlafaxine 3 (15.79)	Omeprazole 2 (10.53)	Lansoprazole 2 (10.53)	Captopril 2 (10.53)	Prednisone 2 (10.53)	Bevacizumab+1 [h] 2 (10.53)

Fig. 3. The top 10 most frequently reported single drugs at the SMQ level and PT level. Notes: (a) There is one other drug (acetylsalicylic acid) with the same reporting frequency as that of cyclophosphamide. (b) There is one other drug (cinacalcet) with the same reporting frequency as that of tacrolimus. (c) There are three other drugs (L-methyldopa, candesartan, and nifedipine) with the same reporting frequency as that of indomethacin. (d) There is one other drug (mycophenolic acid) with the same reporting frequency as that of mitoxantrone. (e) There is one other drug (ampicillin) with the same reporting frequency as that of gentamicin. (f) There is one other drug (naproxen) with the same reporting frequency as that of vancomycin. (g) There is one other drug (digoxin) with the same reporting frequency as that of sotalol. (h) There is one other drug (acetylsalicylic acid) with the same reporting frequency as that of bevacizumab. Abbreviations: PT, Preferred Term; TD+EMT, tenofovir disoproxil and emtricitabine; MET+SIT, metformin and sitagliptin; SMQ, Standardized MedDRA Query.

counts of each reported nephrotoxic drug is between 0 and 15 (Table 4). Of the 1456 drugs evaluated, 1021 drugs have at least one positive risk signal, of which eight drugs (spironolactone, nifedipine, enalapril, valsartan, candesartan, gentamicin, vancomycin, and mycophenolic acid) have the largest number of positive risk signals. Correspondingly, there are 435 drugs did not detect any positive risk signals at the SMQ level and PT level, although they were reported as potential etiological drugs of AKI. The details of the sum of positive risk signal counts of each reported nephrotoxic drug are shown in **Supplementary Table 2**.

3.5 Histological Analysis and Onset Time Analysis

Based on the co-reported PT, we summarized the frequent types of renal injuries for the main drugs and drug classes (Table 5). According to the available data, tubulointerstitial injury is the most commonly reported histological injury type, followed by tubular injury, glomerular injury, and thrombotic injury. Notably, for certain drugs (acetylsalicylic acid) and drug classes (antineoplastic agents and immunosuppressants), renal tubular injury is the most frequently reported histological injury type.

Based on the available time data, we described the onset time distribution characteristics for the top 50 most frequently reported single drugs (Table 6). The median onset time of different drugs varies greatly, among which the median time of vancomycin (5.00 days, 95% CI 2.00–11.00) is the shortest, and the median time of lansoprazole (1427.00 days, 95% CI 222.75–2924.50) is the longest. In Weibull's parameter analysis, all 50 drugs showed early failure type.

4. Discussion

Drug-induced AKI is an important clinical problem widely concerned by health workers. In the clinical management of drug-induced AKI, timely identification and withdrawal of potential nephrotoxic drugs play a cornerstone role [11]. However, due to the lack of unified quantitative indicators to judge the risk of AKI caused by different drugs, the determination and withdrawal of pathogenic drugs are still highly dependent on the personal experience of medical staff. Aiming at this problem, we reviewed 327,561 AE reports related to AKI in the FAERS database over the past 20 years to investigate the association between the occurrence of AKI and drug use. To our knowledge, such a large sample is unprecedented, which provides a

Group	Reporting proportion of the top 10 drug classes									
	1	2	3	4	5	6	7	8	9	10
SMQ (*n* =327,561)	DARD A02 67,540 (20.62)	AARAS C09 57,141 (17.44)	Antineoplastic agents L01 56,387 (17.21)	Immunosuppressants L04 53,508 (16.34)	Analgesics N02 49,752 (15.19)	Diuretics C03 48,973 (14.95)	Drugs used in diabetes A10 46,157 (14.09)	Beta blocking agents C07 41,825 (12.77)	Antibacterials J01 40,288 (12.30)	Antithrombotic agents B01 37,544 (11.46)
Acute kidney injury (*n* =122,929)	DARD A02 37,826 (30.77)	AARAS C09 28,590 (23.26)	Diuretics C03 24,574 (19.99)	Analgesics N02 24,044 (19.56)	Drugs used in diabetes A10 23,444 (19.07)	Antibacterials J01 21,305 (17.33)	Beta blocking agents C07 20,851 (16.96)	Antineoplastic agents L01 20,066 (16.32)	Antithrombotic agents B01 17,809 (14.49)	Lipid modifying agents C10 15,463 (12.58)
Renal failure (*n* =120,501)	DARD A02 28,470 (23.63)	AARAS C09 20,537 (17.04)	Analgesics N02 20,027 (16.62)	Immunosuppressants L04 19,439 (16.13)	Antineoplastic agents L01 17,867 (14.83)	Diuretics C03 17,767 (14.74)	Antivirals J05 16,228 (13.47)	Beta blocking agents C07 16,188 (13.43)	Drugs used in diabetes A10 15,825 (13.13)	Lipid modifying agents C10 14,700 (12.20)
Renal impairment (*n* =69,199)	Immunosuppressants L04 14,613 (21.12)	Antineoplastic agents L01 14,206 (20.53)	AARAS C09 10,670 (15.42)	DARD A02 10,170 (14.70)	Diuretics C03 9,221 (13.33)	Analgesics N02 8,697 (12.57)	SHPESHI H02 8,242 (11.91)	Antithrombotic agents B01 7,695 (11.12)	Beta blocking agents C07 7,619 (11.01)	Antivirals J05 7,415 (10.72)
Dialysis (*n* =12,416)	DARD A02 2,234 (17.99)	Immunosuppressants L04 1,749 (14.09)	Antihypertensives C02 1,529 (12.31)	Drugs used in diabetes A10 1,399 (11.27)	Antineoplastic agents L01 1,186 (9.55)	Analgesics N02 1,166 (9.39)	Antithrombotic agents B01 1,089 (8.77)	Antianemic preparations B03 1,058 (8.52)	Diuretics C03 1,048 (8.44)	AARAS C09 1,027 (8.27)
Nephropathy toxic (*n* =8,765)	Immunosuppressants L04 2,700 (30.80)	Antineoplastic agents L01 2,458 (28.04)	Antibacterials J01 1,643 (18.75)	SHPESHI H02 1,532 (17.48)	Antivirals J05 1,351 (15.41)	DARD A02 678 (7.74)	Analgesics N02 649 (7.40)	AARAS C09 618 (7.05)	Diuretics C03 540 (6.16)	AAP M01 466 (5.32)
Haemodialysis (*n* =8,172)	Antianemic preparations B03 1,245 (15.23)	Drugs used in diabetes A10 1,126 (13.78)	Immunosuppressants L04 1,122 (13.73)	DARD A02 1,093 (13.37)	AARAS C09 976 (11.94)	Analgesics N02 945 (11.56)	Antibacterials J01 894 (10.94)	Antineoplastic agents L01 878 (10.74)	Diuretics C03 857 (10.49)	SHPESHI H02 779 (9.53)
Anuria (*n* =7,694)	AARAS C09 1,302 (16.92)	Drugs used in diabetes A10 1,169 (15.19)	Analgesics N02 1,062 (13.80)	Diuretics C03 1,020 (13.26)	Antineoplastic agents L01 1,001 (13.01)	Immunosuppressants L04 989 (12.85)	Beta blocking agents C07 975 (12.67)	Antibacterials J01 974 (12.66)	SHPESHI H02 865 (11.24)	DARD A02 832 (10.81)
Oliguria (*n* =5,398)	Antibacterials J01 858 (15.89)	Diuretics C03 848 (15.71)	Antineoplastic agents L01 817 (15.14)	AARAS C09 789 (14.62)	Immunosuppressants L04 768 (14.23)	Analgesics N02 762 (14.12)	SHPESHI H02 750 (13.89)	DARD A02 679 (12.58)	Psycholeptics N05 596 (11.04)	Beta blocking agents C07 554 (10.26)
Azotaemia (*n* =3,264)	AARAS C09 619 (18.96)	DARD A02 606 (18.57)	Diuretics C03 583 (17.86)	Antineoplastic agents L01 547 (16.76)	Analgesics N02 531 (16.27)	Immunosuppressants L04 441 (13.51)	Beta blocking agents C07 434 (13.30)	SHPESHI H02 394 (12.07)	Drugs used in diabetes A10 380 (11.64)	Antibacterials J01 368 (11.27)
Prerenal failure (*n* =1,187)	Antineoplastic agents L01 370 (31.17)	AARAS C09 241 (20.30)	Diuretics C03 197 (16.60)	Immunosuppressants L04 187 (15.75)	Drugs used in diabetes A10 180 (15.16)	Analgesics N02 175 (14.74)	DARD A02 167 (14.07)	SHPESHI H02 160 (13.48)	Antithrombotic agents B01 139 (11.71)	Beta blocking agents C07 131 (11.04)
Continuous haemodiafiltration (*n* =959)	Drugs used in diabetes A10 232 (24.19)	Antineoplastic agents L01 144 (15.02)	AARAS C09 116 (12.10)	Diuretics C03 113 (11.78)	Antibacterials J01 111 (11.57)	Immunosuppressants L04 110 (11.47)	Analgesics N02 107 (11.16)	SHPESHI H02 101 (10.53)	Psycholeptics N05 88 (9.18)	DARD A02 85 (8.86)
Peritoneal dialysis (*n* =771)	Antianemic preparations B03 211 (27.37)	Immunosuppressants L04 103 (13.36)	DARD A02 97 (12.58)	AARAS C09 79 (10.25)	Antibacterials J01 77 (9.99)	Diuretics C03 67 (8.69)	CCB C08 58 (7.52)	Beta blocking agents C07 56 (7.26)	Drugs used in diabetes A10 52 (6.74)	SHPESHI H02 50 (6.49)
Renal failure neonatal (*n* =196)	AARAS C09 60 (30.61)	AAP M01 56 (28.57)	Analgesics N02 28 (14.29)	Diuretics C03 21 (10.71)	Beta blocking agents C07 21 (10.71)	CCB C08 20 (10.20)	Antibacterials J01 18 (9.18)	Antihypertensives C02 14 (7.14)	Immunosuppressants L04 10 (5.10)	DARD+1 [a] A02 9 (4.59)
Acute phosphate nephropathy (*n* =149)	AARAS C09 53 (35.57)	Lipid modifying agents C10 40 (26.85)	DARD A02 26 (17.45)	Analgesics N02 24 (16.11)	Diuretics C03 19 (12.75)	AAP M01 19 (12.75)	Mineral supplements A12 15 (10.07)	Beta blocking agents C07 14 (9.40)	Psychoanaleptics N06 14 (9.40)	CCB+1 [b] C08 13 (8.72)
Haemofiltration (*n* =138)	Antineoplastic agents L01 30 (21.74)	Immunosuppressants L04 27 (19.57)	Drugs used in diabetes A10 22 (15.94)	SHPESHI H02 21 (15.22)	Antivirals J05 20 (14.49)	Antibacterials J01 14 (10.14)	DARD A02 11 (7.97)	Antiepileptics A03 11 (7.97)	Antithrombotic agents B01 7 (5.07)	AARAS+2 [c] C09 6 (4.35)
Renal impairment neonatal (*n* =90)	AARAS C09 54 (60.00)	Beta blocking agents C07 15 (16.67)	Analgesics N02 14 (15.56)	Antibacterials J01 8 (8.89)	CCB C08 6 (6.67)	AAP M01 5 (5.56)	Antiepileptics N03 4 (4.44)	Diuretics C03 3 (3.33)	SHPESHI H02 2 (2.22)	Antineoplastic agents+1 [d] L01 2 (2.22)
Neonatal anuria (*n* =81)	AARAS C09 38 (46.91)	Beta blocking agents C07 13 (16.05)	Diuretics C03 12 (14.81)	AAP M01 11 (13.58)	Psychoanaleptics N06 11 (13.58)	Cardiac therapy C01 8 (9.88)	Antibacterials J01 8 (9.88)	Antianemic preparations B03 6 (7.41)	Analgesics N02 6 (7.41)	Psycholeptics+1 [e] N05 5 (6.17)
Foetal renal impairment (*n* =68)	AARAS C09 26 (38.24)	AAP M01 23 (33.82)	Beta blocking agents C07 8 (11.76)	Drugs used in diabetes A10 5 (7.35)	Immunosuppressants L04 5 (7.35)	Cardiac therapy C01 2 (2.94)	Lipid modifying agents C10 1 (1.47)	NR	NR	NR
Subacute kidney injury (*n* =19)	AARAS C09 8 (42.11)	Lipid modifying agents C10 7 (36.84)	Drugs used in diabetes A10 4 (21.05)	Antithrombotic agents B01 4 (21.05)	Psychoanaleptics N06 3 (15.79)	DARD A02 2 (10.53)	Diuretics C03 2 (10.53)	SHPESHI H02 2 (10.53)	Antineoplastic agents L01 2 (10.53)	Analgesics+1 [f] N02 2 (10.53)

Fig. 4. The top 10 most frequently reported drug classes at the SMQ level and PT level. Notes: (a) There is one other drug class, cardiac therapy (C01), with the same reporting frequency as that of drugs for acid related disorders (A02). (b) There is one other drug class, drugs for constipation (A06), with the same reporting frequency as that of calcium channel blockers (C08). (c) There are two other drug classes, beta blocking agents (C07) and analgesics (N02), with the same reporting frequency as that of drugs for agents acting on the renin-angiotensin system (C09). (d) There is one other drug class, antidiarrheals, intestinal antiinflammatory/antiinfective agents (A07), with the same reporting frequency as that of antineoplastic agents (L01). (e) There is one other drug class, thyroid therapy (H03), with the same reporting frequency as that of psycholeptics (N05). (f) There is one other drug class, immunosuppressants (L04), with the same reporting frequency as that of analgesics (N02). Abbreviations: CCB, calcium channel blockers; DARD, drugs for acid related disorders; NR, no report; SHPESHI, systemic hormonal preparations, excluding sex hormones and insulins.

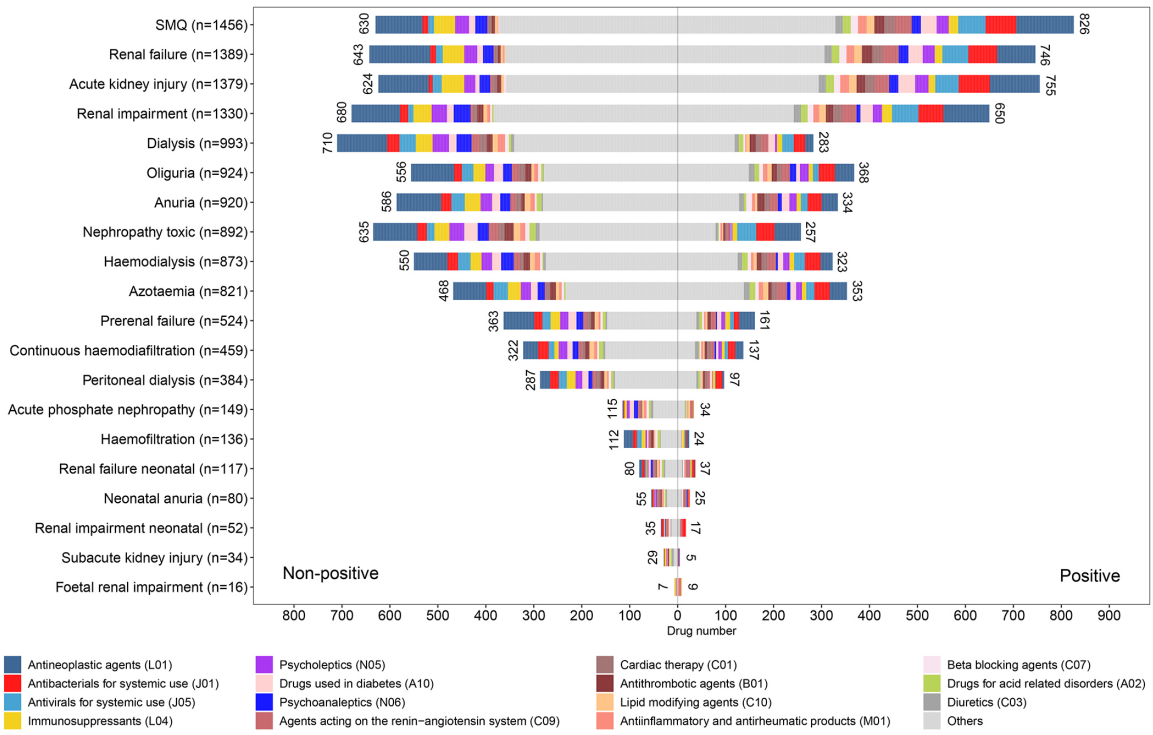


Fig. 5. The risk signal distribution of 15 major drug classes at the SMQ level and PT level.

Table 5. Distribution of histological injury type for the top 10 most frequently reported single drugs and drug classes.

Medicine	Total cases*	Glomerular injury	Tubular injury	Tubulointerstitial injury	Thrombotic injury
Single drug					
Omeprazole	4413	133 (3.01)	702 (15.91)	3776 (85.57)	13 (0.29)
Furosemide	1465	84 (5.73)	549 (37.47)	908 (61.98)	20 (1.37)
Pantoprazole	3600	122 (3.39)	618 (17.17)	3005 (83.47)	20 (0.56)
Esomeprazole	3928	97 (2.47)	621 (15.81)	3373 (85.87)	11 (0.28)
Lansoprazole	3848	142 (3.69)	446 (11.59)	3404 (88.46)	9 (0.23)
Metformin	943	49 (5.20)	447 (47.40)	506 (53.66)	16 (1.70)
Acetylsalicylic acid	1204	46 (3.82)	842 (69.93)	751 (62.38)	11 (0.91)
Amlodipine	1300	114 (8.77)	482 (37.08)	798 (61.38)	15 (1.15)
Lisinopril	1223	62 (5.07)	482 (39.41)	768 (62.80)	2 (0.16)
Metoprolol	914	53 (5.80)	330 (36.11)	591 (64.66)	4 (0.44)
Main drug classes					
Drugs for acid related disorders	6259	250 (3.99)	1260 (20.13)	5034 (80.43)	32 (0.51)
AARAS	2664	168 (6.31)	1038 (38.96)	1625 (61.00)	31 (1.16)
Antineoplastic agents	1788	236 (13.20)	886 (49.55)	784 (43.85)	41 (2.29)
Immunosuppressants	1813	338 (18.64)	968 (53.39)	625 (34.47)	45 (2.48)
Analgesics	2665	110 (4.13)	1073 (40.26)	1632 (61.24)	26 (0.98)
Diuretics	2167	127 (5.86)	833 (38.44)	1341 (61.88)	27 (1.25)
Drugs used in diabetes	1735	73 (4.21)	788 (45.42)	966 (55.68)	20 (1.15)
Beta blocking agents	1962	123 (6.27)	734 (37.41)	1216 (61.98)	26 (1.33)
Antibacterials for systemic use	3384	124 (3.66)	1453 (42.94)	2066 (61.05)	11 (0.33)
Antithrombotic agents	1138	63 (5.54)	475 (41.74)	646 (56.77)	36 (3.16)

Abbreviations: AARAS, agents acting on the renin-angiotensin system.

* A case may record multiple histological injury types at the same time, so the total number of cases often exceeds the sum of the cases of the four histological injury types.

solid foundation for our comprehensive investigation of the nephrotoxicity risk of drugs.

In this study, we present the etiological drug characteristics of AKI from multiple dimensions. First, we summarized a list of 1456 reported nephrotoxic drugs, involving 81 drug classes (Fig. 2). Among the 1456 reported nephrotoxic drugs, our results showed that the largest number of drugs belong to antineoplastic agents (Fig. 2b). Although it is well-known that the kidney is one of the main target organs affected by the toxic effects of antineoplastic agents, either traditional chemotherapeutics or novel molecularly targeted agents [35], antineoplastic agents did not show an obvious dominant position among reported nephrotoxic drugs in previous pharmacoepidemiologic studies [9,13–15,24,36]. There are two possible explanations for the high proportion of antineoplastic agents in the drug list. One possible explanation is that there is a large base of antineoplastic agents used in the real world, which may increase the proportion of antineoplastic agents in the integrated drug list. Another possible explanation is that antineoplastic agents do play an important role in the occurrence of AKI in the clinical setting, whereas our study opportunistically caught a glimpse of it. However, for whatever reason, with the development and application of new antineoplastic drugs and therapies, the problem of antineoplastic agent-induced AKI has become increasingly prominent and has attracted wide attention [37–39]. Therefore, it is necessary for medical staff to have a deeper understanding of the AKI risk related to antineoplastic agents and provide timely prevention and treatment.

To further understand the causative drugs of AKI, based on the integrated drug list obtained from the FAERS database, we made statistics on the most frequently reported nephrotoxic single drugs and drug classes at the SMQ level and PT level, respectively (Figs. 3,4). As a whole, “antineoplastic agents” is the drug class with the third largest number of AKI reports at the SMQ level (Fig. 4), which further demonstrates that the use of antineoplastic agents is an important trigger of AKI. In addition, it is noteworthy that although only 17 (1.17%) of the 1456 reported nephrotoxic drugs were classified as “drugs for acid related disorders” (Fig. 2b), it is still the drug class with the largest number of AKI reports among the 81 kinds of drug classes. Meanwhile, in the statistics of single drugs at the SMQ level, four drugs (omeprazole, pantoprazole, esomeprazole, and lansoprazole) are among the top 10 most frequently reported nephrotoxic drugs (Fig. 3). The existing literature also suggested that “drugs for acid related disorders” and the drugs they contain are closely related to AKI [40–42]. Therefore, the above evidence suggests that we should pay more attention to the use of “drugs for acid related disorders” in future clinical practice, to identify and intervene in possi-

Table 6. Characteristics of onset time for the top 50 most frequently reported single drugs.

SN	Drugs	Cases	Median (IQR)/days	Weibull distribution parameter		
				α (95% CI)	β (95% CI)	Failure type
1	Omeprazole	4784	841.50 (146.00–2313.25)	1311.54 (1242.98–1380.11)	0.61 (0.59–0.62)	Early failure
2	Furosemide	3705	29.00 (4.00–294.00)	117.23 (107.81–126.65)	0.41 (0.40–0.42)	Early failure
3	Pantoprazole	2722	266.00 (11.00–1360.50)	445.45 (405.07–485.84)	0.44 (0.43–0.46)	Early failure
4	Esomeprazole	5036	990.00 (294.00–2137.25)	1230.22 (1182.96–1277.48)	0.75 (0.73–0.77)	Early failure
5	Lansoprazole	1790	1427.00 (222.75–2924.50)	1753.63 (1612.42–1894.85)	0.65 (0.63–0.68)	Early failure
6	Metformin	1595	355.00 (18.00–1593.50)	533.04 (473.03–593.05)	0.46 (0.44–0.48)	Early failure
7	Acetylsalicylic acid	1064	235.00 (19.00–1070.75)	464.41 (402.35–526.47)	0.48 (0.46–0.51)	Early failure
8	Amlodipine	1309	174.00 (28.00–837.00)	371.86 (330.00–413.72)	0.51 (0.49–0.54)	Early failure
9	Lisinopril	1096	543.00 (70.00–1577.75)	708.50 (633.26–783.74)	0.58 (0.55–0.61)	Early failure
10	Metoprolol	927	298.00 (26.00–1233.00)	525.05 (448.40–601.71)	0.47 (0.45–0.50)	Early failure
11	Prednisone	976	41.00 (8.00–324.50)	144.94 (123.93–165.96)	0.45 (0.43–0.47)	Early failure
12	Paracetamol	978	14.00 (1.00–104.00)	55.30 (45.67–64.94)	0.38 (0.36–0.40)	Early failure
13	Simvastatin	692	745.00 (134.00–1946.00)	975.00 (861.07–1088.93)	0.67 (0.62–0.71)	Early failure
14	Levothyroxine sodium	639	401.00 (96.00–1300.00)	718.23 (614.69–821.77)	0.59 (0.55–0.63)	Early failure
15	Allopurinol	1050	31.00 (9.00–464.00)	171.59 (146.26–196.92)	0.42 (0.40–0.44)	Early failure
16	Dexlansoprazole	397	625.00 (194.00–1234.00)	974.31 (831.05–1117.58)	0.77 (0.71–0.83)	Early failure
17	Gabapentin	805	224.00 (13.00–922.00)	348.87 (294.66–403.09)	0.48 (0.45–0.50)	Early failure
18	Tacrolimus	1268	31.00 (5.00–213.00)	107.76 (92.87–122.66)	0.41 (0.39–0.43)	Early failure
19	Spironolactone	1190	50.00 (14.00–344.00)	160.43 (141.48–179.38)	0.50 (0.48–0.53)	Early failure
20	Ibuprofen	1201	10.00 (3.00–160.00)	80.70 (67.32–94.07)	0.36 (0.35–0.38)	Early failure
21	Tenofovir disoproxil and emtricitabine	2299	1078.00 (365.00–2191.00)	1553.80 (1474.41–1633.19)	0.91 (0.88–0.94)	Early failure
22	Clopidogrel	585	172.00 (16.00–1040.00)	366.82 (301.97–431.66)	0.49 (0.46–0.52)	Early failure
23	Mycophenolic acid	731	43.00 (7.00–286.00)	124.85 (104.13–145.56)	0.46 (0.43–0.48)	Early failure
24	Methotrexate	1213	31.00 (2.00–596.00)	138.84 (117.32–160.37)	0.37 (0.36–0.39)	Early failure
25	Bisoprolol	798	87.00 (15.00–423.75)	215.86 (181.93–249.78)	0.47 (0.44–0.49)	Early failure
26	Dexamethasone	2341	14.00 (5.00–65.00)	49.26 (44.85–53.67)	0.48 (0.47–0.50)	Early failure
27	Ergocalciferol	336	290.00 (67.75–987.50)	542.14 (439.91–644.37)	0.62 (0.57–0.67)	Early failure
28	Rosuvastatin	598	160.00 (22.50–1002.50)	401.55 (332.40–470.69)	0.49 (0.46–0.53)	Early failure
29	Carvedilol	532	294.00 (39.00–1279.50)	568.19 (474.67–661.71)	0.56 (0.52–0.60)	Early failure
30	Insulin glargine	474	175.00 (11.00–820.00)	316.83 (250.38–383.29)	0.46 (0.42–0.49)	Early failure
31	Losartan	572	311.50 (59.75–1105.50)	625.89 (531.17–720.62)	0.59 (0.55–0.63)	Early failure
32	Ramipril	695	110.00 (16.00–791.50)	313.45 (260.92–365.99)	0.47 (0.44–0.50)	Early failure
33	Lenalidomide	2404	35.00 (10.00–185.50)	105.63 (97.30–113.96)	0.54 (0.52–0.55)	Early failure
34	Tenofovir disoproxil	614	1251.50 (369.00–2882.00)	1895.44 (1687.83–2103.05)	0.84 (0.78–0.90)	Early failure
35	Atorvastatin	465	266.00 (26.00–1461.00)	533.35 (430.59–636.11)	0.51 (0.47–0.54)	Early failure
36	Vancomycin	1107	5.00 (2.00–11.00)	9.70 (8.66–10.73)	0.59 (0.56–0.61)	Early failure
37	Hydrochlorothiazide	536	268.50 (24.50–1380.25)	509.34 (416.40–602.27)	0.50 (0.46–0.53)	Early failure
38	Famotidine	374	19.00 (3.00–376.00)	113.10 (82.55–143.65)	0.39 (0.36–0.42)	Early failure
39	Rivaroxaban	2147	74.00 (13.00–310.00)	147.34 (135.49–159.18)	0.56 (0.54–0.58)	Early failure
40	Prednisolone	597	28.00 (7.00–177.00)	91.80 (75.15–108.44)	0.46 (0.43–0.49)	Early failure
41	Ciprofloxacin	689	17.00 (5.00–512.00)	120.38 (96.26–144.51)	0.38 (0.36–0.40)	Early failure
42	Salbutamol	433	406.00 (81.00–1275.00)	650.23 (537.32–763.15)	0.57 (0.53–0.61)	Early failure
43	Apixaban	886	39.00 (8.00–230.75)	109.54 (94.70–124.38)	0.51 (0.48–0.54)	Early failure
44	Methylprednisolone	855	6.00 (2.00–25.00)	28.43 (23.13–33.73)	0.38 (0.37–0.40)	Early failure
45	Oxycodone	640	37.00 (6.00–304.00)	125.15 (102.63–147.68)	0.45 (0.42–0.47)	Early failure
46	Pregabalin	539	53.00 (4.00–343.00)	135.48 (108.22–162.73)	0.44 (0.41–0.47)	Early failure
47	Valsartan	481	211.00 (16.00–571.00)	315.54 (254.64–376.44)	0.50 (0.46–0.53)	Early failure
48	Alprazolam	444	95.50 (2.00–1094.25)	241.98 (178.19–305.78)	0.37 (0.34–0.40)	Early failure
49	Adalimumab	604	438.50 (102.00–1155.25)	698.68 (605.13–792.22)	0.66 (0.62–0.70)	Early failure
50	Amoxicillin	1030	11.50 (4.00–485.75)	111.31 (91.88–130.74)	0.37 (0.36–0.39)	Early failure

Abbreviations: CI, confidence interval; IQR, interquartile range.

ble renal damage in the process of drug use in time. Similarly, the AKI risks of some other listed high-reporting drug classes (e.g., diuretics [43], antibacterials [44], and agents acting on the renin-angiotensin system [45]) and drugs (e.g., furosemide [46], vancomycin [47], and enalapril [48]) have also been confirmed in previous literature. Therefore, to some extent, the results mentioned above reflect the most commonly reported nephrotoxic drugs in the real world and can provide some reference information for managing nephrotoxic drugs. However, we also noticed that some drugs that are considered to have low nephrotoxicity (e.g., metformin, amlodipine, and metoprolol) also have high reporting frequency. There are two possible explanations for this abnormal report accumulation. One possible explanation is that it reflects the unknown renal injury model. For example, a recent animal study showed that metformin, even at low doses, exacerbated experimentally induced AKI and increased mortality in mice [49], but this effect has not been confirmed in the population. Another possible explanation is that diabetes and cardiovascular disease are two of the four main types of chronic diseases [50], but as mainstream therapeutic drugs, metformin, amlodipine, and metoprolol inevitably have a huge consumption base and corresponding high AKI report accumulation, even though they have a low risk of kidney injury.

Therefore, it should be kept in mind that although the high reporting frequency of drugs in the FAERS database partly reflects the possible nephrotoxicity of some drugs, the high reporting frequency is not absolutely equivalent to the high AKI risk, because the difference in drug use base in the real world will greatly affect this figure. However, the inherent limitations of the spontaneous reporting database make it impossible for us to calculate the actual incidence of AKI of various drugs with existing data to evaluate and compare the AKI risks of various drugs. In this context, we introduced the disproportionality analysis to evaluate the risk of AKI caused by different drugs and used the risk signal detection result as an alternative quantitative index of incidence to represent the AKI risk of drugs [20]. Although previous studies have also tried to quantify the AKI risk of drugs by applying the disproportionality analysis, the drugs they evaluated were usually limited to a specific class, such as immune checkpoint inhibitors [39], antibiotics [51], and sodium-glucose-cotransporter-2 inhibitors [52]. Meanwhile, due to the differences in research methods and research time span, the above research results cannot be integrated to perform an AKI risk comparison across drug classes. By contrast, our study expanded the evaluated drugs to 1456 drugs reported in the FAERS database in the recent 20 years (**Supplementary Table 2**), which provides resources for comparing AKI risks among drugs in a wide range under a unified standard, thus providing better support for timely identification and withdrawal of drugs causing AKI. For example, if a patient suspected drug-induced AKI is using cefazolin and diclofenac at the same time, cefazolin (ROR, 5.36; 95% CI, 5.00–5.74) is more likely to be the culprit drug than diclofenac (ROR, 2.03; 95% CI, 1.97–2.09) according to the signal detection results (**Supplementary Table 2**). In this regard, we can stop cefazolin or adjust cefazolin to other alternative medications accordingly in clinical practice. Similarly, if we find that there are drugs with high AKI risk signal strength in the prescription, we can especially strengthen the monitoring of patients' renal function, so as to identify emerging kidney injury in time.

In addition, based on the risk signal detection results at the SMQ level and PT levels, we further summarized the AKI risk characteristics of 1156 drugs. On the one hand, we made statistics on the sum of positive risk signal counts of each drug and found that 1021 drugs have at least one positive risk signal at the SMQ level or PT levels (Table 4), revealing the statistical relationship between these drugs and AKI. To some extent, the sum of positive risk signal counts of drugs can be used as a simplified indicator reflecting the correlation strength between drugs and AKI [31]. For example, vancomycin with 15 positive risk signals theoretically has a higher AKI risk than cefixime with three positive risk signals (**Supplementary Table 2**), suggesting that the nephrotoxicity of vancomycin should be focused on in clinical use. Accordingly, we can locate some key drugs, and paying attention to these drugs is beneficial to the prevention, diagnosis, and treatment of drug-induced AKI. However, for some drugs with a large number of positive risk signals, the interpretation of AKI risk still needs to be cautious. For example, although there are case reports suggesting that nifedipine can induce acute interstitial nephritis [53], larger studies have shown the beneficial effect of nifedipine (calcium channel blocker) on renal outcomes and can be used as a selectable first-line therapy in non-proteinuric chronic kidney disease [54,55]. Therefore, for drugs that are potentially beneficial to renal outcomes or treat kidney-related diseases, positive risk signals should perhaps be understood as a statistical relationship between drugs and diseases rather than a causal relationship. On the other hand, we integrated the risk signal distribution characteristics of the main drug classes at the SMQ level and PT levels (Fig. 5). Our results showed that "antineoplastic agents" was the drug class with the largest number of positive signal drugs at the SMQ level and most PT levels, which once again highlights its triggering effect on AKI and reminds us to pay enough attention to it. Besides, our result also reveals the differences in the proportion of risk signal distribution between some drug classes. Theoretically, a drug class with a higher proportion of positive risk signals has a higher overall AKI risk than a drug class with a lower proportion [31]. In this regard, our results provide a new perspective to understand the AKI risk difference among drug classes.

Besides summarizing the reporting frequency and risk signals of drugs, we also explored the histological injury

type distribution of the main drugs and drug classes (Table 5). In previous studies, although it is known that the same drug may cause multiple histological types of renal injury [56], the distribution of drugs for histological injury type is not clear. Our study showed that tubulointerstitial injury is the most commonly reported histological injury type for most drugs and drug classes. In drug-induced tubulointerstitial injury, the drugs for acid related disorders (omeprazole, pantoprazole, esomeprazole, and lansoprazole) were obviously dominant. In a previous study, Gérard AO and colleagues [57] used the World Health Organization Safety Database (VigiBase) to identify drugs responsible for tubulointerstitial nephritis and also highlighted the central role of proton pump inhibitors (PPIs), which also supported our results. Therefore, for patients with a rapid decline in renal function during drug (particularly PPIs) use, tubulointerstitial injury may be the primary suspicion after excluding other non-drug causes. However, it should also be noted that some other drugs may have different histological injury characteristics. For example, it is reported that both tubulointerstitial injury and tubular injury can be induced by non-steroidal anti-inflammatory drugs [56], but our results showed that tubular injury induced by acetylsalicylic acid is more frequently reported than tubulointerstitial injury. In this regard, it is necessary to understand the histological characteristics of renal injury caused by different drugs further because they are of great significance in treatment selection.

Additionally, we further evaluated the time relationship between the occurrence of AKI and the start of medication. In previous studies, the average time of vancomycin-induced AKI was 24.9 days from the start of therapy [58]. Our results showed that the median time of vancomycin-induced AKI is 5 days, which is significantly shorter than the above-mentioned time interval. However, it has also been reported that the higher trough values of vancomycin are associated with shorter time intervals and increased histopathological damage [47,59]. For the patients with initial vancomycin trough values exceeding 20 mg/L, the median time to AKI of vancomycin is about 6 days [60], which is basically consistent with our research results. Therefore, one possible explanation for the discrepancy is that the reporting preference (more likely to do spontaneous reports about severe reactions) makes the cases with high initial vancomycin trough values concentrated [61], and leads to a significantly shorter time interval. In our study, lansoprazole has the longest median time interval of AKI (1724 days), and we noticed that other PPIs also have similar long-time intervals. In previous studies, although the association between PPIs and AKI occurrence has been widely confirmed, the time relationship has not been elaborated in detail. In fact, due to unrecognized tubulointerstitial injury, long-term PPI use was usually associated with an increased risk of chronic kidney disease and kidney failure [56], which may partly explain the long-term interval of PPIs. However, it is noteworthy that although the median time interval of different drugs varies greatly, they are all classified as early failure types in Weibull's shape parameter β, indicating that the AKI risk decreases with time. Undoubtedly, different drugs have different onset time characteristics in inducing AKI, so it is necessary for us to further understand the onset time characteristics of different drugs to help identify the possible culprit drugs.

Although this study presents the etiological drug characteristics of AKI from multiple dimensions, it also has to emphasize its limitations. First, although multiple PTs were used in this study to enhance the identification of drug-induced AKI cases, a non-standard diagnostic approach may still bring bias, and it is also difficult to ensure that the inherent AKI in a specific clinical scenario (e.g., the COVID-19 pandemic) will not be wrongly attributed to drugs [62]. Second, as an AE reporting system with a voluntary nature, the problems of underreporting, duplicate reporting, Weber effect, and notoriety bias inevitably exist in the FAERS database, which may damage the accuracy of our AKI risk signal detection results [33]. Third, many factors (e.g., patient age, sex, and accompanying disease) can affect the occurrence of AKI [63], but we can't shield the influence of these factors on the AKI risk signal detection results. Fourth, our study mainly focused on the AKI risk of a single drug, but an AKI report usually records multiple drugs. The drug-drug interaction may indeed influence the quantification of AKI risk of drugs, but it is not deeply explored in this study. Fifth, the Weibull distribution analysis was used to explore the changes of AKI risk caused by different drugs with time in this study, but this method is usually used to identify lifetime distribution in reliability engineering and may bring unexpected methodological bias, so it is necessary to supplement the verification of external validity in future research. Finally, due to the lack of a model linking drug report accumulation with drug prescription/drug use frequency data, we cannot precisely compare AKI risks of different drugs by calculating the incidence. Although the results of risk signal detection are used as a substitute index of incidence to quantitatively evaluate the AKI risk of different drugs, its essence is the statistical association between drugs and AKI occurrence rather than causality. In some cases, such an association is indirect or even misleading, so it is necessary to apply additional evaluation tools (e.g., Bradford-Hill criteria) to verify the causal relationship between drug use and AKI [64].

5. Conclusions

The FAERS database has a large population, wide geographic coverage, and publicly available accessibility, which have qualified it as an important resource for investigating the potential adverse reaction risk of drugs. In this study, we provided a comprehensive review of the culprit drugs of AKI in the FAERS database, summarized a list of 1456 reported nephrotoxic drugs in the past 20 years, and

made statistics on the top 10 frequently reported nephrotoxic drugs and drug classes. In addition, we applied disproportionality analysis to evaluate the AKI analysis of 1456 drugs uniformly, integrated the distribution characteristics of AKI risk signals of drugs on this basis, and found that 1021 drugs were associated with the occurrence of AKI to different degrees. Meanwhile, based on co-reported PT and available time data, we further explored the histological injury characteristics and onset time characteristics of reported culprit drugs. Although our study has unavoidable limitations due to the inherent nature of spontaneous reporting databases, it also provides a real-world perspective for understanding the AKI risk of drugs and can provide reference information for the identification and withdrawal of causative drugs in the clinic.

Availability of Data and Materials

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Author Contributions

Conceptualization, DL and QD; methodology, JZ and RZ; software, JZ and DL; data curation, JZ, RZ, YW, FW, TZ and DL; formal analysis, JZ, RZ, YW, FW, TZ and DL; writing—original draft preparation, JZ and RZ; writing—review and editing, RZ, JZ, YW, FW, TZ, DL, QD; visualization, DL; funding acquisition, DL and QD. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not Applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJP44094.

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