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Original Article

Hepatobiliary calculi associated with ceftriaxone treatment: An analysis of FAERS data from 2004 to 2021

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ABSTRACT

Introduction: The role of gender, age, dose and other factors in the adverse reaction process of pseudocholelithiasis caused by ceftriaxone is controversial. In this study, we further explored potential risk factors using the FAERS database.

Methods: The reported odds ratio (ROR) and the information component (IC) of specific candidate factors were calculated by using the ROR method and the Bayesian confidence promotion neural network (BCPNN) method respectively to detect potential risk factors in adverse events(AEs) of ceftriaxone and hepatobiliary calculi(HBC). One candidate factor will be considered as a suspicious signal, or potential risk factors if its lower limit of 95% confidence interval of ROR (ROR025) is greater than 1 and its lower limit of 95% confidence interval of IC (IC025) is greater than 0.

Results: A total of 764 AEs of HBC were used to this analysis to evaluate candidate risk factors: Age group, Gender, Dose. Child (1–12 years): male ROR025 = 6.64, IC025 = 2.42, female ROR025 = 6.66, IC025 = 2.40. Adolescent group (12–18 years): male ROR025 = 5.47, IC025 = 2.08; elderly (≥65 years): female ROR025 = 1.25, IC025 = 0.22.

Conclusions: Gender was not detected as a risk factor for HBC caused by ceftriaxone. However, Male infants, male children, female children, adolescent male, and elderly female were potential risk factors for HBC caused by ceftriaxone based on criteria ROR025 > 1 and IC025 > 0.

1. Introduction

1.1. Ceftriaxone-related pseudocholelithiasis

Ceftriaxone (CTRX), as a third-generation cephalosporin antibiotic, is excreted through renal and biliary channels. CTRX is concentrated in the gall bladder after entering the bile, and the concentration in the bile can reach 20–150 times of the blood concentration [1]. High concentrations of CTRX in bile combine with calcium to form deposits, which can lead to cholestasis or the formation of drug stones [2].

In 1986 , Schaad et al. [3] firstly described precipitations in an adolescent patient's gallbladder associated with CTRX therapy. They proposed a new term reversible ceftriaxone-associated biliary pseudolithiasis" to describe the calculi that disappear after withdrawal of CTRX in 1988 [4]. The Medical Dictionary for Regulatory Activities (MedDRA) also included 'Pseudocholelithiasis' as low-level term (LLT) for the first time in version 10.0 and was upgraded to preferred term (PT) in version 20.1.

Cholelithiasis is rare in childhood, but CTRX-related cholelithiasis and bile mud have been widely reported in children [5–9]. Araz et al. [5] found that the risk of gallstones was greatly increased after the treatment dose of more than 100 mg/(kg·d) in children with high fever of meningitis in this area. Ito et al. [10] also considered that patients with CTRX treatment dose exceeding the normal daily dose and children under 10 years old were high-risk groups of pseudocholelithiasis. However, Heim-duthoy et al. [11], after observing the clinical use of ceftriaxone sodium in 36 young people over 18 years old, considered that the gallstone caused by ceftriaxone sodium was independent of the

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dose and duration of medication. Imafuku et al. 's study [12] proposed that females may be an independent risk factor for adult CTRX-related biliary pseudolithiasis, but the reason for the dominant role of females in adult CTRX-related biliary pseudolithiasis remains unclear. However, gender is not considered as the influencing factor in other studies mentioned above. Therefore, in addition to the consensus that children are the high-risk group, the rest of the views on gender and dose are not consistent. Hence it is necessary to analyze the gender differences in different age groups.

1.2. Signal detection method

Based on spontaneous-reporting system (SRS), classical quantitative detection methods of adverse drug reaction (ADR) signal can be generally divided into two categories: frequency method and Bayesian method [13–17]. The basic idea is to investigate if there is a statistically significant difference between the proportion of two groups showed in Table 1.

Common frequency methods include: proportional reporting ratio (PRR) method, reporting odds ratio (ROR) method, comprehensive standard method, etc. [13] PRR method is the earliest and most basic method used in the early quantitative analysis of SRS, and has been used in the UK adverse reaction monitoring system. The ROR method [14] was first proposed by the core laboratory of the Netherlands Pharmacovigilance Center, and is still widely used in the Netherlands Pharmacovigilance Center. The comprehensive standard method is currently used by the British Medicine and Healthcare Products Regulatory Agency (MHRA), so it is also called MHRA method.

Bayesian method is based on Bayesian logic, which analyzes and describes drugs and corresponding adverse reactions through the probability distribution selected in advance. Since 1998, the World Health Organization (WHO) Uppsala Monitoring Center (UMC) in Sweden has adopted Bayesian confidence propagation neural network (BCPNN) method to detect ADR signals [15,16]. In addition, the GPS method, and the MGPS method, which is further improved and expanded on the basis of the GPS method, have been used in the early ADR signal detection work of the Food and Drug Administration (FDA) [17,18].

In this study, we calculate the ROR025 and IC025 of gender, age, dose factors in the adverse events (AEs) of hepatobiliary calculi (HBC) caused by ceftriaxone using the reports in FDA Adverse Event Reporting System (FAERS) database. HBC refer to all stones occurring in the hepatobiliary system or signs caused by stones.

2. Material and methods

2.1. Data sources and preprocessing

The data included in this study were from publicly available data from the FAERS Database, covering the period from the first quarter of 2004 to the fourth quarter of 2021. FAERS Quarterly Data files was downloaded from the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). We used "ceftriaxone" as the search term for DRUGNAME and PROD_AI entries, and preferred terms (PTs) specified in MedDRA version 23.0 as the search term for PT entries. Before retrieval, we preprocessed the data in FAERS database.

FAERS database contains more than 60 million spontaneously reported AEs, but the database has duplicate reports and missing data. We first performed a de-duplication operation on the FAERS database according to FDA's own requirements, and deleted the data with PRIMARYID, CASEID, DRUG_SEQ as missing values. At the same time, in order to better establish the association between AEs and drugs, we deleted the data of the time of first administration after the event occurrence time. After performing the above procedures, 60,090,091 pairs of suspected drug-AE correspondences were obtained. A total of 764 reports of AE of hepatolithiasis after CTRX treatment were included in signal detection and risk factor analysis (Fig. 1).

Table 1
2*2 contingency table for disproportionality.

	Reports with target AEs	All other AEs reports
Reports with the suspected drugs/factors	a	b
All other dugs/factors reports	c	d

2.2. AE signal detection method

Use 2 × 2 contingency table (Table 1) makes statistical analysis on AE reports of suspicious drugs and other drugs, as well as suspicious risk factors and other factors. Two data mining methods, ROR and information component (IC) of BCPNN, were used to calculate the disproportionation rate to find possible risk factors. By comparing the target AEs reporting ratio of the target drug with that of all other drugs, if the ratio is greater than the set threshold, it is called disproportionality, indicating the generation of potential AE signal. The 95% confidence interval of ROR and IC is calculated according to the formula. If the lower limit of 95% confidence interval of ROR (ROR025) is greater than 1 or the lower limit of 95% confidence interval of IC (IC025) is greater than 0, the signal is considered to be significant. When both signals are positive, we think there is a suspicious signal, or risk factors. The calculation formula of ROR and its 95% confidence interval is as follows:

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

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

All analyses were performed with SAS version 9.4 and R version 4.1.3. Ethics approval and consent to participate are not applicable.

2.3. Treatment of dose

In this study, the daily dose was calculated by multiplying the dose and dose frequency given in the database, and the signal values were analyzed in subgroups according to the daily dose (Table 6). According to the drug instructions of CTRX, children under 12 years old need to be given drugs according to their body weight, so this study conducted subgroup analysis, extracted reports ≤12 years old, and calculated their daily dose.

3. Results

3.1. Descriptive analysis

The number of record entries and signal values of each PT are shown in Table 2 (the data of PTs is from MedDRA version 23.0). Cholelithiasis, cholestasis and pseudocholelithiasis were the top three PTs, accounting for 59.16% in total. Top three ROR025 and IC025 are pseudocholelithiasis (ROR025 = 3152.00, IC025 = 5.59), bile duct stone (ROR025 = 15.85, IC025 = 3.37) and cholelithiasis (ROR025 = 13.04, IC025 = 3.61).

The clinical characteristics of patients with HBC after CTRX treatment are shown in Tables 3 and 4. Male reports accounted for 45.29%, while female reports accounted for 47.77%. In terms of age groups, Infant group (1–12 months) accounted for 1.05%; children group (1–12 years) accounted for 1.70%; adolescent group (12–18 years) accounted for 5.89%; elderly group (>65 years) accounted for 36.4%.

Result of outcome: Other serious events reports accounted for 47.25%; hospitalization reports accounted for 45.16%; life-threatening

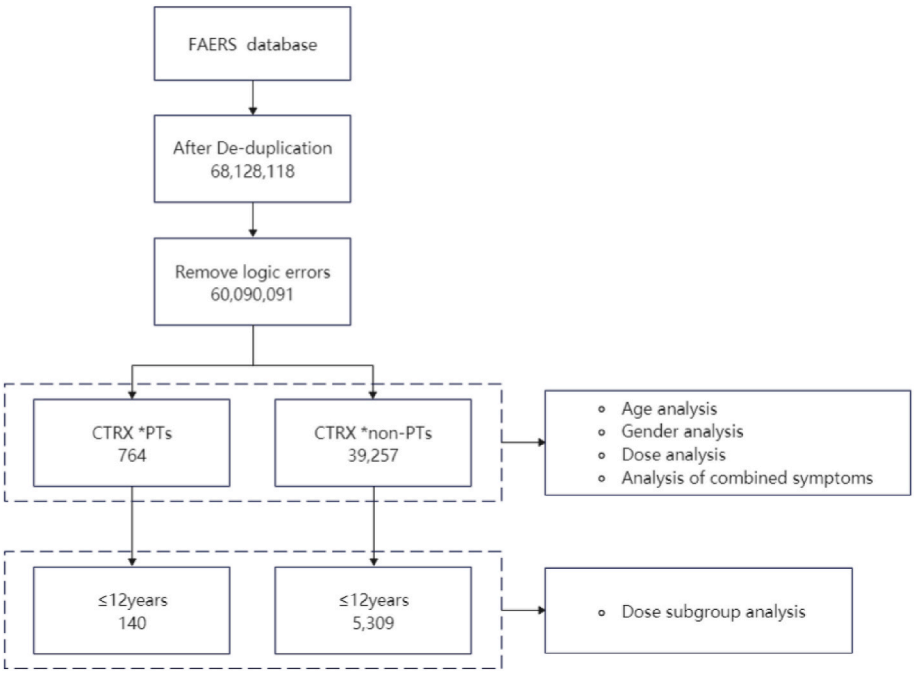

Fig. 1. Flow chart of adverse event report screening.
Fig. 1 shows the processing of adverse event reports in this study.

Table 2
Frequency distribution of CTRX-hepatobiliary calculi AEs.

PT	Count	Percent (%)	IC025	ROR025
Cholelithiasis	274	35.86	**3.61**	**13.04**
Cholestasis	109	14.27	**2.66**	**6.79**
Pseudocholelithiasis	69	9.03	**5.59**	**3152.00**
Hepatitis cholestatic	68	8.90	**2.70**	**7.36**
Jaundice	56	7.33	**1.03**	**2.12**
Cholecystitis	51	6.68	**2.08**	**4.70**
Bile duct stone	40	5.24	**3.37**	**15.85**
Hyperbilirubinaemia	40	5.24	**1.61**	**3.36**
Cholecystitis acute	28	3.66	**1.83**	**4.27**
Bile duct obstruction	8	1.05	**0.86**	**2.87**
Jaundice cholestatic	7	0.92	−0.36	0.90
Ocular icterus	6	0.79	−0.24	**1.06**
Jaundice neonatal	3	0.39	−0.87	0.77
Yellow skin	2	0.26	-	-
Cholecystitis chronic	1	0.13	-	-
Gallbladder obstruction	1	0.13	-	-
Hyperbilirubinaemia neonatal	1	0.13	-	-
Total	764	100.00	2.79	7.14

Table 2 shows the counts, proportions, IC025 and ROR025 of all PTs of CTRX-related hepatobiliary calculi.
-The signal value cannot be calculated if the number of records is less than 3.
Bold indicates that the signal values are meaningful: IC025 > 0, ROR025 > 1.

reports accounted for 1.05%; death reports accounted for 1.44%. In terms of occurrence countries and regions, reports from Japan accounted for 30.37%. Dechallenge positive reports accounted for 31.81%.

3.2. Analysis of age and sex

Table 3 shows the results of gender and age signal values. Male signal value result: ROR025 = 0.81, IC025 = −0.23; female signal value result: ROR025 = 1.02, IC025 = −0.06. Child signal value result: ROR025 = 1.45, IC025 = 0.41; adolescent signal value result: ROR025 = 1.91, IC025 = 0.78; elderly signal value result: ROR025 = 1.19, IC025 = 0.10.

3.3. Gender analysis in age groups

Table 5 shows the differences in gender distribution among different age groups. In neonates, the number of AEs reported in females was less than 3, so no signal value was reported; Male: ROR025 = 2.04, IC025 = 0.52. In the children group, Male: ROR025 = 6.64, IC025 = 2.42; Female: ROR025 = 6.66, IC025 = 2.40. In the adolescent group, males: ROR025 = 5.47, IC025 = 2.08. In the elderly group, Female: ROR025 = 1.25, IC025 = 0.22.

3.4. Analysis of onset time

A total of 240 reports described the onset time of AEs after administration. AEs occurred on average 18.25 days after administration, and the earliest AEs occurred on the day of administration. When analyzing the onset time of different age groups, it was found that the average onset time of the elderly group was 9.99 days.

3.5. Dosage analysis

For all age dose analysis results: 0–1 g/d group: ROR025 = 7.84, IC025 = 2.72; 1–2 g/d group: ROR025 = 14.61, IC025 = 3.65; 2–4 g/d group: ROR025 = 20.54, IC025 = 3.75; >4 g/d group did not report signal values because the number of reports was less than 3.

Results of dose analysis for ≤12 years: 0–20 mg/kg/d dose group and 20–40 mg/kg/d dose group did not report signal values because the number of reports was less than 3; 40–80 mg/kg/d group: ROR025 = 7.76, IC025 = 1.61; >80 mg/kg/d group: ROR025 = 18.46, IC025 = 3.13.

3.6. Analysis of combined symptoms

Concurrent symptom data of 619 patients from these 764 reports were also extracted in this study. A total of 253 AEs occurred in 619 patients, and 1345 cases were accumulated, with an average of 2.17 AEs per patient. 44.26% of patients had cholelithiasis, 11.15% had pseudocholelithiasis, 6.46% had bile duct stones, and 17.61% had cholestasis. Jaundice was present in 9.05% of patients, cholestatic jaundice in

Table 3
Sex and age of patients with hepatobiliary calculi of CTRX.

			hepatobiliary calculi AEs	Other AEs	IC025	ROR025
Sex	Male		346 (45.29%)	18383 (46.83%)	−0.23	0.81
	Female		365 (47.77%)	17148 (43.68%)	−0.06	**1.02**
	Unisex		7 (0.92%)	203 (0.52%)		
	Unknown		0 (0.00%)	12 (0.03%)		
	MISS[a]		46 (6.02%)	3509 (8.94%)		
Age	Neonate	≤1 months	8 (1.05%)	308 (0.78%)	−0.72	0.66
	Infant	1–12 months	13 (1.70%)	592 (1.51%)	−0.68	0.65
	Child	1–12 years	119 (15.58%)	3698 (9.42%)	**0.41**	**1.45**
	Adolescent	12–18 years	45 (5.89%)	925 (2.36%)	**0.78**	**1.91**
	Adult	18–65 years	223 (29.19%)	15898 (40.5%)	−0.68	0.52
	Elderly	≥65 years	301 (39.4%)	12572(32.02%)	**0.10**	**1.19**
	MISS[a]		55 (7.20%)	5264(13.41%)		

Table 3 shows the clinical features of patients with hepatobiliary calculi on CTRX and any other drugs. The numbers and percentages are displayed.
AEs, adverse events; IC025, the lower end of the 95% confidence interval of IC; ROR025, the lower limit of the 95% confidence interval of ROR.
Bold indicates that the signal values are meaningful: IC025 > 0, ROR025 > 1.
The age group includes the upper limit of the range and does not include the lower limit of the range (except for neonate and the elderly).
[a] Missing value in FAERS database.

Table 4
Outcome, countries and regions, and dechallenge of patients with hepatobiliary calculi of CTRX.

		hepatobiliary calculi AEs	Other AEs	IC025	ROR025
Outcome	Death	11 (1.44%)	3648 (9.29%)	−3.46	0.08
	Life-threatening	8 (1.05%)	2497 (6.36%)	−3.50	0.08
	Hospitalization	345 (45.16%)	14205 (36.18%)	**0.13**	0.26
	Disability	3 (0.39%)	305 (0.78%)	−2.49	0.16
	Congenital anomaly	0 (0.00%)	53 (0.14%)		
	RI[b]	8 (1.05%)	350 (0.89%)	−0.87	0.58
	Other serious	361 (47.25%)	15609 (39.76%)	**0.06**	**1.18**
	MISS[a]	28 (3.66%)	2590 (6.6%)		
Countries and regions	Japan	232 (30.37%)	1604 (4.09%)	**2.47**	**8.71**
	France	115 (15.05%)	3756 (9.57%)	**0.34**	**1.37**
	MI (Unknown)	105 (13.74%)	5681 (14.47%)	−0.38	0.76
	Spain	57 (7.46%)	1207 (3.07%)	**0.80**	**1.93**
	USA	39 (5.10%)	10006 (25.49%)	−2.75	0.11
	Italy	29 (3.80%)	2417 (6.16%)	−1.23	0.41
	China	23 (3.01%)	1456 (3.71%)	−0.91	0.53
	Portugal	19 (2.49%)	851 (2.17%)	−0.51	0.73
	Cyprus	8 (1.05%)	2 (0.01%)	**1.57**	**1.27**
	Greece	8 (1.05%)	159 (0.41%)	**0.02**	**8.71**
Dechallenge	Positive	243 (31.81%)	5441 (13.86%)	**0.94**	**2.48**
	Negative	16 (2.09%)	576 (1.47%)	−0.29	0.87
	Does not apply	95 (12.43%)	5443 (13.87%)	−0.33	0.79
	Unknown	104 (13.61%)	7630 (19.44%)	−0.95	0.47
	MISS[a]	306 (40.05%)	20167 (51.37%)		

Table 4 shows the results of patients with hepatobiliary calculi using CTRX and any other drugs, country and dechallenge. The numbers and percentages are displayed.
AEs, adverse events; IC025, the lower end of the 95% confidence interval of IC; ROR025, the lower limit of the 95% confidence interval of ROR.
Bold indicates that the signal values are meaningful: IC025 > 0, ROR025 > 1.
[a] Missing value in FAERS database.
[b] Required intervention to prevent permanent impairment/damage.

1.13%, fever and vomiting in 1.94%, nausea in 1.13%, abdominal pain in 1.78%, and epigastric pain in 1.29%. At the same time, there were more severe patients with cholecystitis (8.24%), acute cholecystitis (4.52%), acute cholangitis (1.78%), and acute pancreatitis (1.62%), which may require some intervention in the treatment. Symptom study also found reports of HBC combined with urinary calculi: hydronephrosis (1.94%), postrenal renal failure (1.94%), ureteral calculi (1.13%), anuria (0.81%), urinary calculi (0.81%), nephrolithiasis (0.81%).

4. Discussion

4.1. HBC based on age and sex

The results showed that children, adolescents and the elderly were considered as risk factors for pseudocholelithiasis caused by ceftriaxone. It also showed that there was no difference in gender distribution of CTRX-related HBC as a whole, but gender differences were found in different age groups. Among patients under the age of 18, male generally showed higher signal values than female, except that neonate did not participate in the discussion due to too few reports. Since the number of reports in the infant group is relatively small, although it can produce effective signal values of ROR025 and IC025, its results may also have some limitations. We can see that when an age group is subdivided by sex, it shows different results than when analyzing age alone. By comparing the results of these two analyses, it can be seen that the positive signals of the adolescent group may come from men, while women aged 12–18 years are not the risk group for such AE. In the children group, both men and women showed positive signal values, and the signal values of both groups were greater than those of the corresponding young men. This difference in age distribution may be related to the special physiological and anatomical structure of children. Children's biliary tract is thinner and longer, which makes CTRX difficult to be excreted through the biliary tract and easy to deposit in the biliary

Table 5
Sex under age group of patients with hepatobiliary calculi of CTRX.

		hepatobiliary calculi AEs	Other AEs	IC025	ROR025
Neonate	Male	6 (0.79%)	785 (0.52%)	−0.73	0.68
≤1 months	Female	1 (0.13%)	562 (0.37%)	-	-
Infant	Male	8 (1.05%)	389 (0.26%)	**0.52**	**2.04**
1–12 months	Female	5 (0.65%)	317 (0.21%)	−0.14	1.3
Child	Male	62 (8.12%)	1537 (1.01%)	**2.42**	**6.64**
1–12 years	Female	52 (6.81%)	1240 (0.82%)	**2.40**	**6.66**
Adolescent	Male	32 (4.19%)	843 (0.55%)	**2.08**	**5.47**
12–18 years	Female	10 (1.31%)	2275 (1.50%)	−1.12	0.47
Adult	Male	93 (12.17%)	27240 (17.92%)	−0.87	0.51
18–65 years	Female	127 (16.62%)	40956 (26.94%)	−0.97	0.45
Elderly	Male	139 (18.19%)	24719 (16.26%)	−0.11	0.95
≥65 years	Female	160 (20.94%)	22942 (15.09%)	**0.22**	**1.25**

Table 5 shows the gender results by age group in patients with hepatobiliary calculi treated with CTRX or all other drugs. The numbers and percentages are displayed.
AEs, adverse events; IC025, the lower end of the 95% confidence interval of IC; ROR025, the lower limit of the 95% confidence interval of ROR.
-The signal value cannot be calculated if the number of records is less than 3.
Bold indicates that the signal values are meaningful: IC025 > 0, ROR025 > 1.
The age group includes the upper limit of the range and does not include the lower limit of the range (except for neonate and the elderly).

Table 6
Dose grouping of patients with hepatobiliary calculi of CTRX.

		hepatobiliary calculi AEs	Other AEs	IC025	ROR025
All age groups	0–1 g/d	57	2193	**2.72**	**7.84**
	1–2 g/d	138	3127	**3.65**	**14.61**
	2–4 g/d	56	816	**3.75**	**20.54**
	>4 g/d	0	65	-	-
	MISS[a]	513	33056		
	Any other drugs	152007	59898063	−0.02	0.12
≤12 years	0–20 mg/kg/d	1	7	-	-
	20–40 mg/kg/d	2	32	-	-
	40–80 mg/kg/d	9	159	**1.61**	**7.76**
	>80 mg/kg/d	26	253	**3.13**	**18.46**
	MISS[a]	102	4147		
	Any other drugs	5309	1455533	−0.09	0.10

Table 6 shows the dose results of CTRX in patients of all ages and under 12 years of age with hepatobiliary calculi. The numbers and percentages are displayed.
AEs, adverse events; IC025, the lower end of the 95% confidence interval of IC; ROR025, the lower limit of the 95% confidence interval of ROR.
The dose range contains the upper limit but not the lower limit.
-The signal value cannot be calculated if the number of records is less than 3.
Bold indicates that the signal values are meaningful: IC025 > 0, ROR025 > 1.
[a] Missing data in FAERS database or not available through data calculation.

tract and gallbladder to form biliary mud or even stones [19]. In the grouping of the elderly ≥65 years old, the results show that women have positive signals, and they are more likely to have the AE of CTRX-related HBC. Comparing the results of adolescents and adults, the change of this signal value with age may be related to the age difference of female hormone secretion.

However, considering the physiological differences caused by sex among different age groups, and combining the results of this study, it may be more appropriate to consider gender and age rather than separate analysis.

4.2. Dosage of CTRX

Some studies considered that low dose of CTRX can avoid the occurrence of pseudolithiasis [9], but the results of this study show that even 0–1 g/d dose, HBC AEs still occurred, and the signal is positive. No record of daily dose > 4 g/d was reported in the database, and the signal value > 4 g/d could not be calculated due to the missing dose. The results showed that with the increase of dose, the signal value of adverse reactions was significantly enhanced, suggesting that the occurrence of AEs in CTRX hepatobiliary system stones was dose-related.

Meanwhile, the dose for children should be converted according to body mass in the dosing schedule, which may exceed the recommended dose when given as an adult dose. Despite missing data, a large proportion of children were exposed to a dose of more than 80 mg/kg/d. Although there is no signal value of daily dose <40 mg/kg/d for comparison, the daily dose of >40 mg/kg/d also shows a positive signal value, and the signal is stronger when it is > 80 mg/kg/d, so the higher daily dose may be the reason for the occurrence of AEs in children with CTRX related hepatolithiasis. Other previous studies in children also found that CTRX dose of more than 2 g/d or more than 100 mg/kg/d, long-term treatment duration of CTRX, rapid injection and fasting are risk factors for CTRX-related biliary pseudolithiasis [5,9,20–22].

4.3. Onset time and symptoms

The results of this study showed that the average onset time of CTRX-related HBC was 18.25 days after administration, and AEs occurred at the earliest on the day of administration, which was later than the results reported in previous studies [4]. The discovery of HBC in the database may occur later than the actual occurrence of the calculi, since patients often do not present with biliary symptoms, such as upper abdominal pain. Rapid occurrence and rapid regression are the clinical characteristics of CTRX induced pseudolithiasis. The FAERS database did not contain the data of the end time of AEs, so the natural regression time of HBC caused by CTRX was not statistically calculated in this study.

Many clinical reports have observed that CTRX-related HBC often have no obvious symptoms [23–25], so it is not easy to be detected in the early stage of medication. This study also found that only 15.19% patients with abdominal pain, nausea, vomiting and other symptoms. Therefore, it is necessary to consider whether it is necessary to use imaging methods to detect the occurrence of pseudolithiasis after stage medication in order to adjust the subsequent medication regimen. It is also necessary to consider whether the patients with asymptomatic gallbladder abnormalities found in imaging examination need drug intervention and short-term imaging review in the future.

4.4. Country specific data

In our research results, we described the national and regional distribution of CTRX-related HBC. However, because the database does not contain the ethnic information of patients, we cannot further obtain the physiological relationship between CTRX-related HBC and ethnic groups. However, such differences in AE reports at the country level can still reflect some phenomena.

If we do not consider the difference in the incidence of AEs caused by ethnic differences, the examination means relying on imaging methods, the correct diagnosis of AEs themselves, and whether medical personnel can accurately report AEs in the spontaneous reporting system will also cause a large difference in the number of AE reports. CTRX-related HBC is not as obvious as the skin reaction of drug eruption or the adverse reaction of changes in such indicators as hemogram, liver and kidney

function that can be monitored through laboratory examination. It needs more to be diagnosed and found by computer tomography (CT) scanning, ultrasound and other imaging examinations. Therefore, its diagnostic rate may be affected by the diagnostic and treatment habits of medical personnel and the use rate of imaging examination methods among countries.

4.5. Prognosis and intervention of HBC

Previous studies have reported that the reversibility of pseudolithiasis disappeared after the cessation of CTRX [4–6], and 31.81% of the drug deactivation test in this study also reported positive results, indicating that the AEs of HBC were reversed after the cessation of drugs. There have also been reports of drug or surgical intervention after CTRX associated gallstones [26–28]. Due to the reversible characteristics of CTRX-related pseudolithiasis after drug withdrawal, it is suggested that in the process of clinical treatment, attention should be paid to the judgment of the symptoms of patients, to avoid unnecessary medical measures to the patients caused additional economic burden or secondary damage to the body.

Most reports show that pseudolithiasis improves and is cured after CTRX discontinuation, but there are still case reports of patient death [23]. This study also found statistical reports of death and life-threatening outcomes in CTRX-related HBC (Table 2). Doi et al. [23] reported a case of an 82-year-old woman who was found to have small stones and sludge in the gallbladder and common bile duct on CT scan at 15 days after continuous 5 days of 5 g/d CTRX. She was diagnosed with grade II acute cholangitis and grade 1 acute pancreatitis. The patient's heart failure was exacerbated by the hydration required for acute pancreatitis. She later developed multiple organ failure and died on day 17. This suggests that the severity of comorbidities affects the intervention and outcome of patients. In the process of treatment, the patient's situation should be individualized judgment, to avoid excessive treatment of pseudocholelithiasis should also be timely given corresponding treatment measures to avoid the exacerbation of the disease. In addition, at the beginning of treatment, if the patient is judged to be a high-risk group for CTRX-related pseudocholelithiasis and the prognosis is likely to be poor, CTRX should be avoided and other antibiotics should be used for treatment.

5. Conclusion

On the whole, gender is not a risk factor for HBC caused by ceftriaxone (ROR025 > 1 but IC025 < 0). In different age groups, male infants (ROR025 = 2.04 > 1, IC025 = 0.52 > 0), male children (ROR025 = 6.64 > 1, IC025 = 2.42 > 0), female children (ROR025 = 6.66 > 1, IC025 = 2.40 > 0), adolescent male (ROR025 = 5.47 > 1, IC025 = 2.08 > 0), and elderly female (ROR025 = 1.25 > 1, IC025 = 0.22 > 0) were potential risk factors for HBC caused by ceftriaxone. No matter what dose of ceftriaxone, compared with other drugs, it showed positive signals in the cause of HBC, and with the increase of dose, the signal value increased. CRTX-associated HBC generally resolve spontaneously after drug withdrawal without other intervention, but for patients with severe symptoms, drug or surgical intervention may be required.

Author contributions

Contributor Zhaohang Li and Guanpeng Qi were responsible for data download and access. Xin Liu, Ze Xu, Juman Ma and Aijun Zhang conducted the experimental design. Xin Liu and Ze Xu wrote all the programs involved in the study. Zuojing Li, Fenfang Wei, Ling Zhong provide help for the algorithms and experimental methods involved in this paper. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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