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Population scale retrospective analysis reveals potential risk of cholestasis in pregnant women taking for omeprazole, lansoprazole, and amoxicillin

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Abstract

In nearly 50% of patients with drug-induced liver injury, the bile flow is impaired known as cholestasis. Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease that happens in pregnancy. Some of the clinical symptoms include pruritus, dark urine, and abnormal liver function tests. A rise of serum bile acids is the most accurate diagnostic evidence. ICP may lead to premature birth, fetal distress, and even postpartum hemorrhage or stillbirth in some severe cases. Higher bile acid levels (>40μmol/L) are associated with higher rates of adverse fetal outcomes. Due to the multifactorial nature of ICP, its etiology is still not fully understood. Therefore, the current treatments of ICP are limited to control symptoms and protect fetuses. Among various causing factors, drug exposure during pregnancy is one common factor, and it can be prevented if we know drugs with increasing risk of cholestasis. Here we analyzed over 9.5 million FDA adverse effect reports to identify drugs with increasing risks of cholestasis as an adverse effect. Patients treated for cholestasis or liver diseases were removed. The odds ratio analysis reveals that lansoprazole (LSPZ), omeprazole (OMPZ) and amoxicillin (AMXC) are associated with an increased risk of cholestasis. LSPZ is associated with increased reported cholestasis by a factor of 2.32 (OR with 95% confidence interval [2.21, 2.43]). OMPZ is associated with increased reported cholestasis by a factor of 2.61 [2.54, 2.69]. AMXC is associated with increased reported cholestasis adverse effect by a factor of 6.79 [6.49, 7.11]. The risk of cholestasis associated with these three drugs is further increased in pregnant women. These findings justify careful reassessment of the safety of the identified three drugs.

Keywords

Adverse effect; drug induced cholestasis; intrahepatic cholestasis of pregnancy; odds ratio

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1. Instruction

In nearly 50% of patients with drug-induced liver injury, the bile flow is impaired known as cholestasis[1]. Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is the most common liver disease in pregnant women. ICP is a condition where bile cannot flow from the liver. The typical clinical symptoms of ICP are intense pruritus without a skin rash, dark urine, and abnormal liver function tests[2–5]. Besides, ICP sometimes is associated with increased risk of postpartum hemorrhage due to disruption of bile acid metabolism, which may also lead to disturbance of absorption of lipophilic vitamins, especially vitamin K[6]. Even more severely, in some cases the ICP can lead to prematurity, the passage of meconium, fetal distress, increasing caesarean section rate, and stillbirth[2, 3, 7–9].

There are no effective therapeutic interventions for ICP. The established treatments focus on controlling the symptoms and protect fetuses. For example, ursodeoxycholic acid is used to decrease the concentration of bile acid to relieve pruritus and hepatic impairment[10–15], but it is not recommended during pregnancy. In addition, some drugs may be used to protect the fetus and increase its maturity, e.g. dexamethasone is used in to speed up the maturity of the baby's lung[16, 17]. Those treatments provide an opportunity for the pregnant woman to get an elective delivery between gestation weeks 37–38 to pre-empt potential stillbirth[12].

One possible reason for lacking effective therapeutic interventions for ICP is that the detailed etiology of ICP is still not clear. Currently, cholestasis is considered to be caused by several potential factors: 1) mechanical blockage of duct; 2) metabolism disruption due to the genetic defects[18–23] or hormone fluctuation (especially for pregnant women)[24, 25]; 3) adverse effects of drug exposure[1, 26–29] or cumulative hazardous effects of environmental chemicals or metabolites[30–32]. As medications are known to be one leading contributor to ICP, and there is no effective treatment for ICP except for withdrawal of the drug[33], so risk factor mitigation is key to prevent negative outcomes. Then to succeed for any prevention efforts, clinicians should have a good understanding of medications associated with cholestasis in all clinical settings.

In the *EASL Clinical Practice Guidelines, Management of cholestatic liver diseases*[34], some drugs, including sex hormones, medicinal herbs, and NSAIDs, are known to cause hepatocellular or ductular/ductal cholestasis as adverse effects. More drugs need to be assessed. The United States Food and Drug Administration Adverse Event Reporting System (FAERS) is the most comprehensive database of drug-associated adverse event records. Though there exist the prevalence of ICP and the demand for recognizing hepatotoxicity medications in pregnant women, till now, despite several small scale clinical studies about drug-induced cholestasis[35], no study has determined which drugs are most frequently reported with cholestasis or ICP as adverse events in the FAERS database. A systematic evaluation of cholestasis risks of drugs hasn't been conducted. In this paper, we report the first cohort study with over 9.5 million FAERS reports to identify drugs that are associated with high risks of cholestasis as an adverse effect. According to the odds ratio (OR) and usage frequency of each drug, we identified three drugs, lansoprazole, omeprazole,

and amoxicillin that have higher risks of cholestasis, especially for pregnant women. Our analysis reveals and quantifies the potential risks of these three drugs, justifying that more assessments are needed for clinical usage of these drugs for pregnant women.

2. Materials and methods

The whole procedures of the cohort study were shown in the flow chart in Figure 1. This study includes four steps: data collection, data normalization and standardization, cohort selection and statistical analysis.

2.1 Data collection

The study used over 9.5 million reports available from the FDA's Adverse Event Reporting System (FAERS) and Adverse Event Reporting System (AERS) data sets. At the time of the study, the FAERS set contained data from September 2012 to September 2017, and its older AERS set contained data from January 2004 to August 2012. The reports were used to conduct a cohort study for drugs and cholestasis. Both data sets are available online at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm.

2.2 Data normalization and standardization

The FAERS and AERS data sets have adverse event reports collected and shown quarterly, but those quarterly reports not homogenous throughout the whole data sets[36, 37]. For our study, each quarterly data set was downloaded and modified into a text table with consistent table field structure. The column names were homogenized and missing columns in older data sets were added with no values. Even though most of the reports in FAERS and AERS were submitted from the Unites States, there are still many reports submitted from other countries. Therefore, some field contents, such as drug names, date formats, and weight units were translated into consistent names/values. The various forms of drug names were converted to generic drug names corresponding to therapeutic ingredients. All identified misspellings of the drugs were homogenized into consistent values. The final version of the data set contained over 9.5 million reports from the first quarter of 2004 to the third quarter of 2017.

2.3 Cohort selection

A total number of 9,586,673 individual records were collected. Reports with cholestasis or liver disease *indications* were removed from the cohort to avoid confounding factors affecting the frequencies of cholestasis related adverse effects (See the full list of excluded indications in Table S1, S1 Appendix). This data set was named as "ALL", containing 9,425,513 records. Then the "ALL" group was split into two cohorts, patients with cholestasis related effects (named as CHOLESTASIS) and patient without cholestasis related effects (named as non-CHOLESTASIS). The CHOLESTASIS cohort contained all records whose "adverse effect" field contained at least one of the following items: cholestasis, cholestasis of pregnancy, jaundice cholestatic, hepatitis cholestatic, bile duct obstruction, cholestatic pruritus, cholestatic liver injury, and mixed hepatocellular cholestatic injury.

The CHOLESTASIS cohort contained 17,385 records and the non-CHOLESTASIS cohort contained 9,408,128 records. Usage frequencies of each reported drug in both cohorts were calculated[36–38]. Odds ratios (ORs) and natural log odds ratios (LnORs, see definition below) for each drug were calculated. A positive value of LnOR with 95% confidence interval above zero value indicates an increasing risk of CHOLESTASIS.

The "ALL" group was also divided into patients who are pregnant women ("pregnancy" group), male patients ("male" group), female patients ("female" group), and female patients whose ages are from 12 to 55 years old ("female 12–55" group). Each group was split into CHOLESTASIS cohort and non-CHOLESTASIS cohort. The frequencies of each drug in both cohorts were calculated to generate the OR and LnOR values for each drug in each group. For drugs that may be used together, usage frequencies and ORs of several drug combinations were also calculated for all groups. The drugs were ranked by LnOR values of CHOLESTASIS. To assess the potential risks of the selected drugs, ORs and LnORs for common adverse effects of the selected drug were also calculated in the "ALL" group for comparison.

2.4 Data analysis

2.4.1 Descriptive statistics—The common adverse effects of selected drugs were taken from www.drugs.com. Frequencies for common adverse effects and CHOLESTASIS of selected drug were calculated using Equation 1 in all groups[36–38].

$$Frequency = \frac{(Number\ of\ records\ with\ CHOLESTASIS\ exposed\ drug)}{(Number\ of\ records\ exposed\ drug)} \quad \text{(Equation 1)}$$

2.4.1 Comparative statistics—Drug usage report rates were compared via the natural log Odds Ratio (LnOR) by *Equation 2*:

$$ln(OR) = ln\left(\frac{a/b}{c/d}\right) \quad \text{(Equation 2)}$$

a = Number in an adverse effect group with drug-exposed

b = Number in an adverse effect group with no drug-exposed

c = Number in control group with drug-exposed

d = Number in control group with no drug-exposed

Standard Error (*SE*) of the LnOR value was calculated using *Equation 3*:

$$SE = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \quad \text{(Equation 3)}$$

where a, b, c, and d were defined in *Equation 2*.

Error bars were given in 95% confidence interval by *Equation 4*:

$$\text{Limit} = \text{LnOR} \pm 1.96\ SE \quad \text{(Equation 4)}$$

3. Results and discussions

3.1 Drugs with high LnORs for cholestasis

After data collection, normalization and standardization, cohort selection and statistical analysis based on FAERS/AERS database, LnORs of CHOLESTASIS with 95% confidence intervals and usage frequencies of all 3,331 drugs reported in the "ALL" group were calculated and ones of 200 drugs whose frequencies were bigger than 0.20% were shown in Table S2 (see in S2 Appendix). Drugs with high risks of CHOLESTASIS were selected based on the following criteria: 1) the 95% confidence interval of LnOR of CHOLESTASIS of the drug is larger than 0.69, corresponding to OR larger than two; 2) the number of records containing the drug in CHOLESTASIS cohort is larger than 300; 3) frequency of causing CHOLESTASIS of the drug in "pregnancy" group is larger than 4%; 4) the number of the drug associated CHOLESTASIS records in "pregnancy" group is larger than 20.

Three drugs, amoxicillin (AMXC), omeprazole (OMPZ), and lansoprazole (LSPZ), were selected based on these criteria. The detailed statistics of each drug and some external information (the pregnancy category by the US FDA and the ATC code) were shown in Table 1. These three drugs showed high LnORs for cholestasis.

3.2 Adverse drug reactions (ADRs) comparison

The selected drugs, OMPZ, LSPZ, and AMXC are frequently used, and abundantly present in the FAERS and AERS reports (OMPZ: 260,202; LSPZ: 102,591; AMXC: 66,448). To assess the potential risks of those three drugs, cholestasis as an ADR was compared with other frequently reported adverse events for each drug. The OR values of their common ADRs were also calculated in the "ALL" group. The LnOR values of common ADRs of these drugs, including CHOLESTASIS for comparison, are shown in Figure 2.

Figure 2a shows the LnORs of various ADRs calculated for OMPZ. Among various common ADRs of OMPZ, CHOLESTASIS has the second largest LnOR value (0.96±0.03). The top LnOR value is the "regurgitation" term that is associated with the main indication for OMPZ. LnOR values for CHOLESTASIS are among the top five ADRs for LSPZ (0.84±0.05, Figure 2b) and the highest compared to other ADRs for AMXC (LnOR =1.92±0.05, Figure 2c).

3.3 Results of drug-induced cholestasis during Pregnancy

To explore whether pregnancy, gender, and age correlate with drug-induced cholestasis, we calculated the CHOLESTASIS occurrence in five predefined groups (See Cohort selection in Methods and in Figure 3). The "pregnancy" group is associated with significantly higher frequencies of CHOLESTASIS than other groups for all three drugs, while the gender and age don't make significant differences. On the drug side, except for the "pregnancy" group, AMXC is associated with significantly higher frequencies of CHOLESTASIS than OMPZ

and LSPZ. This is consistent with the higher OR of CHOLESTASIS for AMXC than OMPZ and LSPZ (Figure 3). To further dissect the risks of drug-induced cholestasis, we analyzed the frequencies of cholestasis occurrence in each of the following age ranges, (12, 20), [20, 25), [25, 30), [30, 35), [35, 40), [40, 45), [45, 50), and [50, 55). Shown in Table S3, the [35, 40) group has a higher occurrence frequency of cholestasis for AMXC, OMPZ, and LSPZ. However, the record sizes of those age groups are relatively small, which may result to relatively high uncertainties.

3.4 Drug combinations

We found that out of the 24 records in which LSPZ is associated with CHOLESTASIS in the "pregnancy" group, 23 records also contain OMPZ and AMXC. Therefore, the high CHOLESTASIS frequency of LSPZ results from the combination with OMPZ and AMXC. We calculated the CHOLESTASIS occurrences and ORs of various combinations of the three drugs, shown in Table 2. The combination of OMPZ, LSPZ, and AMXC showed a high OR of CHOLESTASIS (LnOR: 3.70±0.37) in the "ALL" group, with the CHOLESTASIS occurrence frequency being 100% (23/23) in the "pregnancy" group and 6.97% in the "ALL" group (3⁄445). Other drug combinations are also associated with high odds ratios of CHOLESTASIS in the "ALL" group. But the number of reports with drug combinations in the "pregnancy" group is relatively small (only 23 reports) that increased the 95% confidence range. However, the "ALL" group was sufficiently large, and the combinations were excluded from the OR calculations. Based on the single drug OR values we concluded that the cholestasis causing effects of drug combinations are not dominated by a single drug.

3.5 Discussion

Our study based on the 9.5 more million FAERS/AERS records suggested that AMXC, LSPZ, and OMPZ are associated with increased risks of cholestasis, especially for pregnant women. Since cholestasis may lead to further complications in women and fetuses, the usage of these three drugs for pregnant women should be carefully considered.

Our results are further supported by the *EASL Clinical Practice Guidelines*. The *EASL Clinical Practice Guidelines: Management of cholestatic liver diseases*[34] includes a list of drugs that are known to be associated with cholestasis, containing AMXC, but not OMPZ and LSPZ. Amoxicillin-clavulanic acid which is used frequently is known to be associated with hepatocellular or ductular/ductal cholestasis. From our results, the high OR of CHOLESTASIS of AMXC (LnOR: 1.92±0.05) further confirms the risk of AMXC. The ORs of OMPZ (LnOR: 0.84±0.05) and LSPZ (LnOR: 0.96±0.03), also illustrated the elevated risks of cholestasis of these two drugs.

In addition, AMXC and OMPZ association with cholestasis, hepatocellular injury or cholestatic injury of hepatotoxicity were also noticed in several case studies[27, 39–42], with AMXC being the most prominent [43–48]. Cholestasis risk of OMPZ has also been reported as some cases[14, 49–51]. However, no report about the cholestasis risk of LSPZ has been published to our knowledge.

AMXC, OMPZ, and LSPZ are relatively common in daily life, so their using safety should be more considered during pregnancy. AMXC is one of the most widely used antibiotics in many countries[42–48]. Although it is considered to be relatively safe, AMXC may cause liver injury in some cases, even after AMXC was treated with the patient only 5–12 days[52]. The cholestasis risk of AMXC is relatively well-known, as many cases have been reported. Our cohort analysis in this paper further quantified the risk of AMXC with large population data. OMPZ and LSPZ are broadly used proton pump inhibitors (PPIs). Even though the embryonic and fetal toxicity of OMPZ has been pointed out in the *American Gastroenterological Association Institute Medical Position Statement*[14], cholestasis risks of them haven't been systematically studied, other than some case reports in which OMPZ might induce cholestatic hepatitis or liver injury[50, 53, 54]. Our results demonstrated their risks of causing cholestasis and quantify the risks based on the populational scale retrospective study. So their risks should be considered when giving them to pregnant women.

Where the FDA Pregnancy Categories of these three drugs were shown in Table 1, their pregnancy categories should be re-assigned carefully. For clinical practice, the FDA Pregnancy Category is the main and most straightforward resource when physicians rely on to treat pregnant patients. Currently, OMPZ is a Category C drug, which means that the drug showed adverse effects on the fetus in an animal study but there are no adequate and well-controlled studies in humans. AMXC and LSPZ are Category B drugs, meaning that animal studies failed to show adverse effects on the fetus and there are no adequate studies in humans. However, our finding based on over 9.5 million clinical records provide some evidence of potential risks of cholestasis with OMPZ, LSPZ and AMXC. Exposure to them during pregnancy is associated with higher risks for cholestasis that may increase the likelihood of premature birth, fetal distress, and even postpartum hemorrhage or stillbirth[6,7]. These findings call for new consideration and possibly reassignment of Pregnancy Categories for OMPZ, LSPZ and AMXC.

However, this study also has some limitations. The records in the FAERS/AERS system only represent a subset of actual cases because of the voluntary submission nature of FAERS and AERS system. Therefore, data in FAERS/AERS may over-represent patients with adverse effects, and overlook patients who didn't experience adverse effects after taking the drugs.

4. Conclusions

There is some information about drug exposure during pregnancy causing adverse events in kinds of clinical databases. The OR and frequency of cholestasis as an adverse effect of drugs were analyzed based on over 9.5 million FAERS/AERS records. The drugs with both high OR values and frequencies in the "ALL" group and in the "pregnancy" group were picked out. The database OR analysis revealed that LSPZ was associated with increased reported cholestasis by a factor of 2.32 (OR with 95% confidence interval [2.21, 2.43]). OMPZ was 2.61 [2.54, 2.69]. AMXC was 6.79 [6.49, 7.11]. The risk of cholestasis associated with these three drugs is further increased in pregnant women. Even though with some inherent limitation, our cohort study which is based on over 9.5 million records can still provide some evidence with clinical values. Of course, further studies are needed to

experimentally assess the risk of these drugs (AMXC, OMPZ, and LSPZ), and even to elucidate the mechanisms. Ultimately, their potential risks, after experimentally confirmed, should be clearly pointed out and considered in clinical practices. This approach is an effective tool for mining drug-induced cholestasis from FAERS databases and it is transferable to other diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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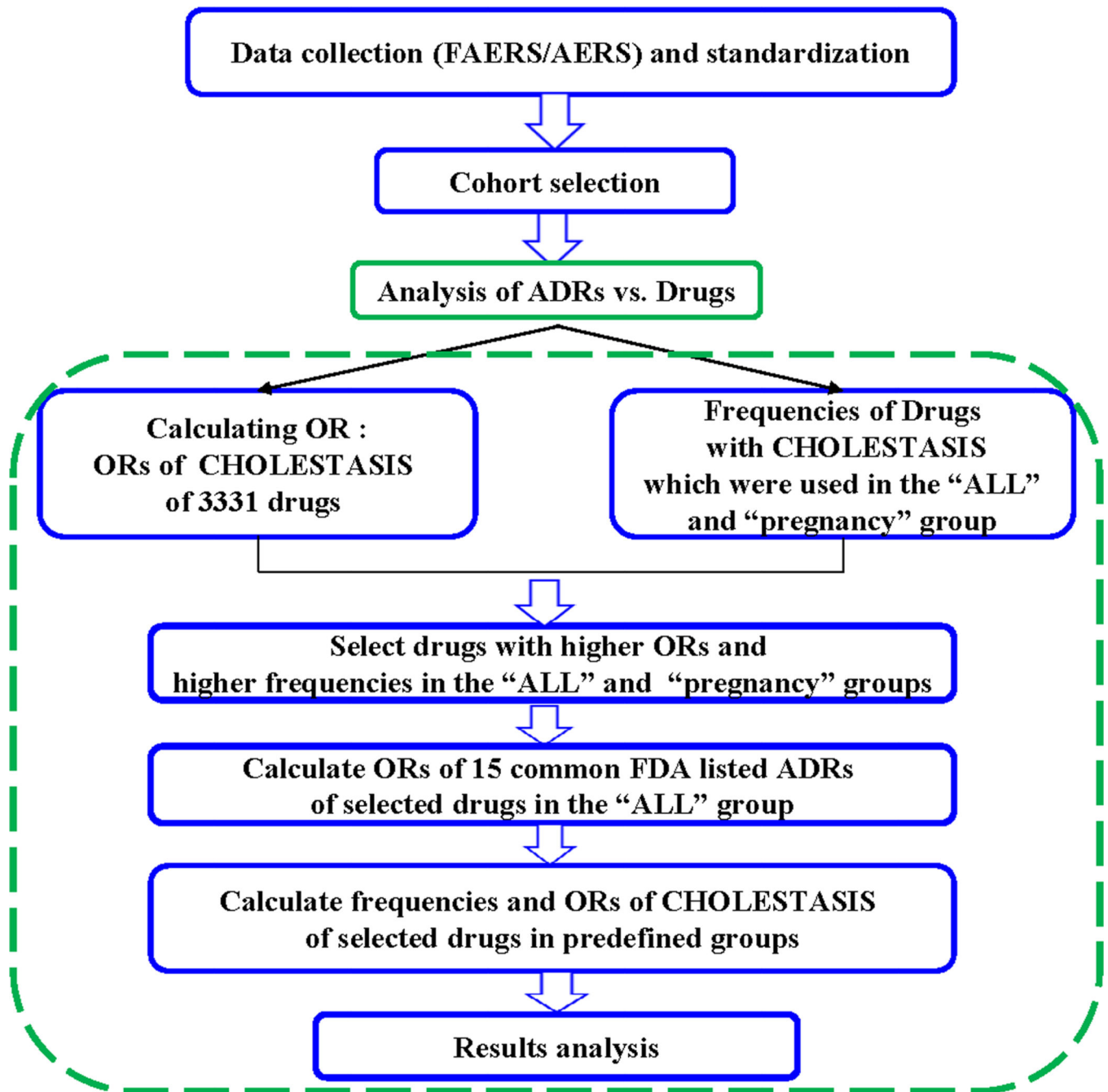
Figure 1.
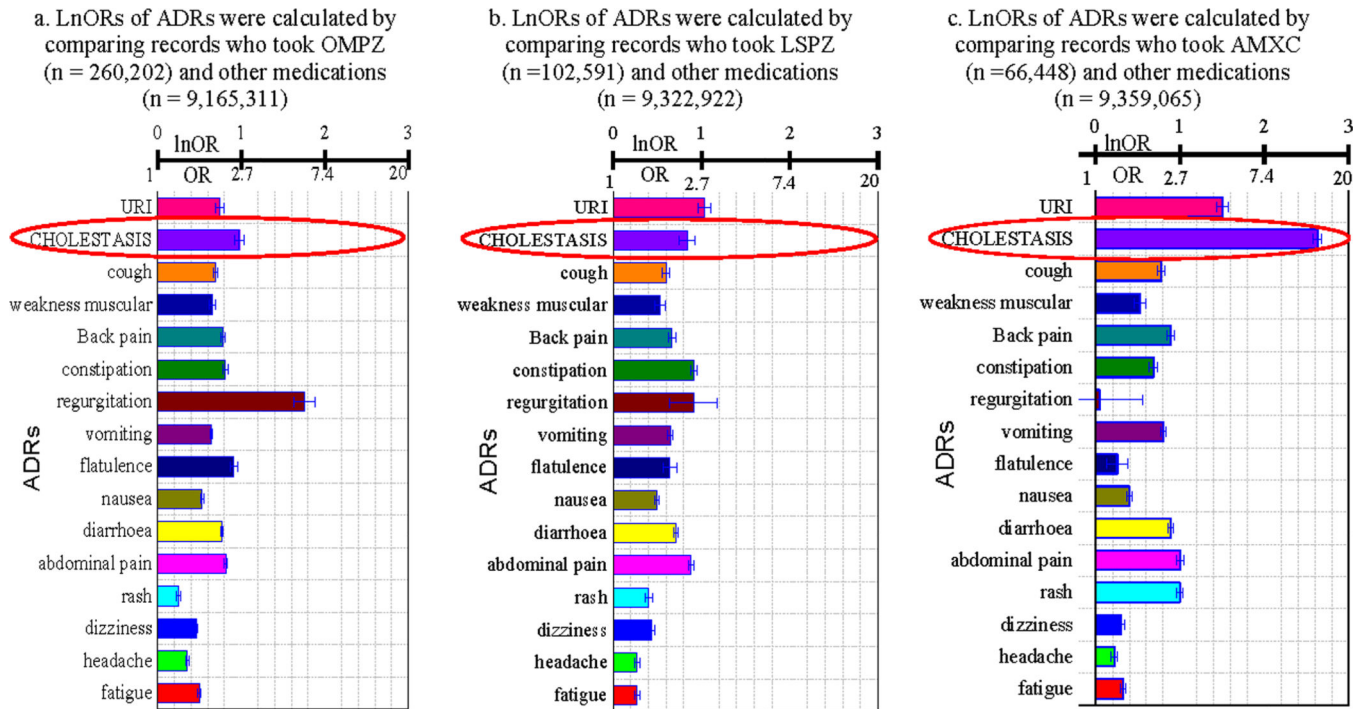Flow chart of the procedures of the cohort study.

Figure 2.
Ln odds ratios (LnORs) of 15 common FDA-listed ADRs as well as CHOLESTASIS of
OMPZ (2a), LSPZ (2b), and AMXC (2c). Odds ratios were calculated by comparing records
which contain selected drugs and records containing other medications. URI: Upper
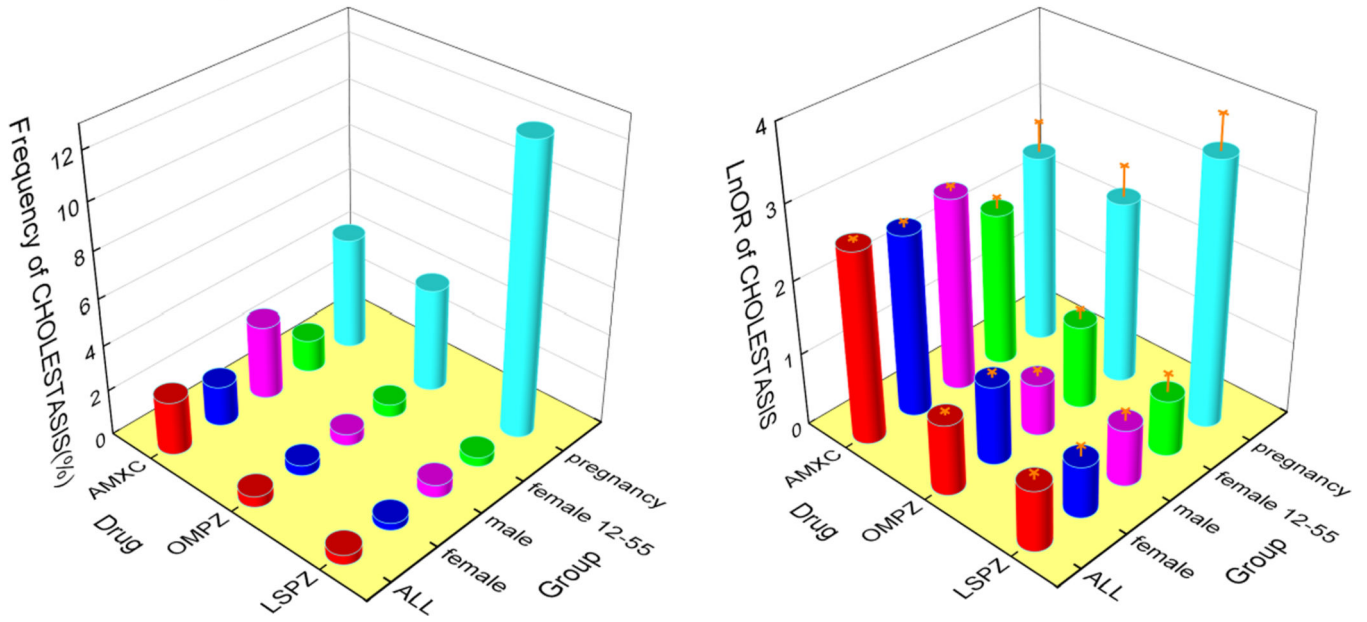respiratory infection.

Figure 3.
Frequencies (3a) and Ln odds ratios (LnORs) (3b) of CHOLESTASIS of selected drugs in the five predefined groups. The 95% confidence intervals are shown in orange.

Table 1

Frequencies and ORs of CHOLESTASIS information of selected drugs.

Drug name	N_{C+all}	N_{all}	$Freq_{C/all}$	lnOR	Error	N_P	N_{C+P}	$Freq_{C/P}$	Pregnancy Category	ATC code
OMPZ	1197	260202	0.46%	0.96	0.03	621	28	4.51%	C	A02BC01, A02BD01, A02BD05
AMXC	498	41168	1.21%	1.92	0.05	445	27	6.07%	B	A02BD01, A02BD03, A02BD04, A02BD05, A02BD06, A02BD07, A02BD10, A02BD11, J01CA04, J01CR02.
LSPZ	431	102591	0.42%	0.84	0.05	192	24	12.50%	B	A02BC03, A02BC53, A02BD02, A02BD03, A02BD07, A02BD09, A02BD10

N$C+all$, Number of records with CHOLESTASIS and the drug in the "ALL" group; Nall, Number of records containing the drug in the "ALL" group; FreqC/all, Frequency of CHOLESTASIS after taking the drug in the "ALL" group; NP, Number of drug in pregnancy group; N$C+P$, Number of records with CHOLESTASIS and the drug in the "pregnancy" group; FreqC/P, Frequency of CHOLESTASIS after taking the drug in the "pregnancy" group.

Table 2

Frequencies and ORs of CHOLESTASIS information if three drugs were used in different combinations in ALL group.

Drug combination	N_{C+all}	N_{all}	$Freq_{C/all}$	OR	lnOR	Error	N_P	N_{C+P}	$Freq_{C/P}$
AMXC+OMPZ+LSPZ	31	445	6.97%	40.59	3.70	0.37	23	23	100.00%
AMXC+OMPZ-LSPZ	170	6793	2.50%	14.02	2.64	0.15	21	2	9.52%
AMXC+LSPZ-OMPZ	31	2864	1.08%	5.93	1.78	0.35	5	0	0.00%
LSPZ+OMPZ-AMXC	27	4731	0.57%	3.11	1.13	0.38	6	0	0.00%
AMXC-LSPZ-OMPZ	1279	56346	2.27%	13.49	2.60	0.06	542	4	0.74%
OMPZ-LSPZ-AMXC	974	250340	0.39%	2.18	0.78	0.06	574	3	0.52%
LSPZ-OMPZ-AMXC	342	94558	0.36%	1.98	0.69	0.11	158	1	0.63%

N_{C+all}, Number of records with CHOLESTASIS and the drug combination in the "ALL" group; N_{all}, Number of records containing the drug combination in the "ALL" group; $Freq_{C/all}$, Frequency of CHOLESTASIS after taking the drug combination in the "ALL" group; N_P, Number of drug combination in the "pregnancy" group; N_{C+P}, Number of records with CHOLESTASIS and the drug combination in the "pregnancy" group; $Freq_{C/P}$, Frequency of CHOLESTASIS after taking the drug combination in the "pregnancy" group.