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Systemic quinolones and risk of acute liver failure III: A nested case–control study using a US electronic health records database

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Abstract

Background and Aim: Quinolones are globally popular antibiotics with proven potency, broad coverage, and reasonable safety. However, some concerns were raised as to their possible association with acute liver failure (ALF). The aim of this study is to assess ALF risk within 30 days of receiving a systemically administered quinolone antibiotic, in individuals with no history of liver/diseases.

Methods: We conducted a nested case–control study using electronic health records from the Cerner Health Facts. The initial cohort (n = 35 349 943) included all patients who were admitted between 2000 and 2016, with no history of liver diseases, and had a minimum medical history of one year. Eligible cases were inpatients who were first diagnosed with ALF between 2010 and 2015. Using incidence density sampling, each case was matched with up to five unique controls by sex, race, age at index encounter, and period-at-risk. We used conditional logistic regression to calculate the odds ratio and 95% confidence interval for ALF risk, upon adjusting for exposure to other medications, and major confounders (diabetes mellitus and alcohol abuse). We used the STROBE Statement for reporting on our study.

Results: We identified 3151 cases and 15 657 controls. Our primary analysis did not reveal an association between quinolones and ALF risk. However, some risk was identified among those with no or few comorbidities, those ≤ 60 years of age, women, men, African Americans, and Caucasians.

Conclusion: Although our study does not suggest an overall association between quinolones and ALF, elevated risks seen in some subgroups warrant further investigation.

Introduction

Quinolones are potent antibiotics characterized by broad coverage, favorable pharmacologic properties, and a reasonable safety profile.[1–4] These attributes enhanced their popularity against a wide range of infections, despite the development of resistance, adverse reactions, and the availability of other alternatives. Whereas adverse reactions to quinolones are predominantly mild to moderate and self-limiting, some have generated serious safety concerns, resulting in revised labeling and even market withdrawal.[1–7]

Drug-induced liver injury is reportedly the most common reason for the premarketing and postmarketing withdrawal of medications,[5,8,9] and the most common cause of acute liver failure (ALF) in the United States and Europe,[5,6,9–11] with a reported annual incidence of 44 000 cases in the United States alone.[12] As one of the most widely used medication groups, antibiotics, including quinolones, may play a role in the development of drug-induced liver injury.[4,13,14]

Acute liver failure is a serious disease involving rapid, progressive, and likely severe loss of hepatic cells, which may involve transient elevations of liver enzymes up to severe liver damage requiring transplantation.[5–7] Such deterioration takes place within 4 weeks[15–19] following exposure to different factors such as medications, nutritional, and herbal supplements, bacteria, viruses, and toxins.[5,6,8,10] Annual ALF incidence in the United States reportedly ranges between one and six per million, while comprising 7% and 6% of liver-related transplants and deaths, respectively.[15]

Possible mechanisms for hepatotoxicity include production of reactive metabolites,[3,4,7] or triggering an immunologic response to the administered quinolone.[3,20] However, a definitive pathophysiology remains to be confirmed.[4,7]

Whereas quinolone-associated ALF risk has been investigated in some epidemiological studies,[4,7,21,22] and spontaneous adverse

event reports,[4–7] only two clinical trials reported such a risk. Our study represents the third part of a multipronged investigation of quinolone-associated ALF risk, which analyzes a major US Electronic health records (EHR) database.

Methods

Study design. Using a nested case–control design, we analyzed inpatient EHR data from the Cerner Corporation's Health Facts Datawarehouse (Health Facts), Kansas City, Missouri, US. This large surveillance system hosts extensive EHR for almost 70 million deidentified patients (approximately 21.6% of the US population of 324 070 652 in 2016 [https://www.census.gov]), that were generated between 2000 and 2016 from nearly 450 million encounters from more than 500 US hospitals. Health Facts contain detailed patient information such as demographics, extensive medical care details, health-care setting, and insurance status.

Information on number of cases and used ICD codes are shown in the supporting information (section I). All liver diseases leading to exclusion of cases or controls from our study and a list of hepatotoxic medications are shown in the supporting information (sections II & III), respectively. Complete listings of the odds ratio (ORs), 95% confidence interval (CI), and *P* value for all regression analyses are provided in the supporting information (sections IV, V, & VI). Characteristics of recent similar studies are detailed in the supporting information (section VII).

Identification of case and matched controls. Upon examining all unique encounters, we were able to identify an initial cohort comprising all registered inpatients who were admitted, at any time to any of the Health Facts participating hospitals, with a primary diagnosis of ALF (outcome of interest), with no history of current or prior liver diseases. The International Association for the Study of the Liver (IASL) Subcommittee statement on nomenclature of acute and subacute liver failure defined ALF as "potentially reversible, often sudden, persistent and progressive liver dysfunction (in the absence of pre-existing liver disease) characterized by the occurrence of encephalopathy within 4 weeks from onset of symptoms".[16,18,19]

Using this initial cohort, we excluded all patients with a medical history of less than 1 year in the Health Facts. We then restricted our pool to those with the date of index encounter between 2010 and 2015. This date for a case represents the date of the first encounter where a patient was admitted based on a first-time primary diagnosis of ALF. Meanwhile, for a control, this date represents the date of the latest inpatient encounter without being diagnosed with ALF.

Subsequently, we excluded all patients with missing or inconsistent information on any of the matching variables (sex, race, and age at index encounter). To identify ALF cases, we used specific ICD9 (International Classification of Diseases, Ninth Revision) and ICD10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) codes, which were reported earlier as demonstrating a high positive predictive value for drug-induced hepatotoxicity.[21] We then calculated the period-at-risk for all cases and possible controls, which represents the time spanning between date of the first recorded inpatient encounter, and date of the index encounter.

An optimal variable matching approach[23] was used for matching controls to cases without replacement, where each control was matched to a single case. Each case was matched to up to five controls based on four variables with equal weights: sex, race, age on day of the index encounter (± 1 year), and the period-at-risk (± 1 year).

Medication exposure. As we are interested in exposure to systemic quinolones, all nonsystemic formulations were excluded. Inpatient medication exposure was grouped into four classes: quinolones, hepatotoxic medications (excluding quinolones),[24,25] other antibiotics (excluding quinolones and hepatotoxic antibiotics), and other medications (excluding all antibiotics and hepatotoxic medications). Data on medication exposure were limited to prescriptions filled during inpatient care.

Data analysis

Descriptive analysis. We reported categorical variables as frequencies and percentages, and continuous variables as means with standard deviations. Categorical variables included sex, race (Caucasian, African American, Asian, Hispanic and other); socioeconomic indicators included census region and division; hospital setting (urban/rural); health insurance (insured, noninsured, and missing/unknown); and 30-day exposure to each of the four medication groups and individual quinolones (ever/never). Additional variables included ever/never concurrent diabetes mellitus (complicated and uncomplicated) and alcohol abuse. The diagnosis of complicated/uncomplicated diabetes and alcohol abuse was confirmed based on the identification of specific ICD9/ICD10 codes from patient health records, using the Hude Quan version[26] of the Elixhauser comorbidity index (CMI).[27]

Continuous variables included age at index encounter and comorbidity status, with the age stratified into 10-year groups (0–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, and 81–90). Comorbidity as measured by the score generated via the Hude Quan version[26] of the Elixhauser CMI[27] was stratified into five groups according to the CMI score (0, 1–5, 6–10, 11–15, and 16+). The number of inpatient medication prescriptions filled during the 30-day period preceding the index date was stratified into five groups (0, 1–3, 4–6, 7–10, and 11+).

Regression analysis. We generated a series of conditional logistic regression models to identify the best estimate for quinolone-associated ALF risk, upon adjusting for other medication exposures and major confounders. For each medication group, we fitted a base model with only sex, race, age at index encounter, and the selected medication group (ever/never). This was followed by a minimally adjusted model including all variables in the base model plus all other medication groups (ever/never). Finally, we fitted a maximally adjusted model extending the minimally adjusted model to include all remaining variables. To identify the quinolone(s) with the strongest possible association with ALF risk, we repeated the same series of regression models using exposure to individual quinolones, rather than a class, as predictors of ALF.

Potential confounding. To avoid any possible confounding effect, we a priori excluded all patients with history of any liver disease/condition. We also adjusted for other major confounders, including health status, recognized risk factors (diabetes mellitus and alcohol abuse), socioeconomic status (health insurance and care setting), and concurrent exposure to other medications.

Sensitivity analysis. To isolate the effect of notable differences in comorbidity and inpatient medications between cases and controls, we fitted a third series of regression models to different subgroups of our study population via stratifying by sex, race, comorbidity status (tertiles), and age at index encounter (tertiles).

This study was approved by the Office of Ethics and Research Integrity of the University of Ottawa, Canada (H02-18-05). All analyses were conducted using SAS statistical software Version 9.4 (SAS Institute, NC, USA). We hereby report on our study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines.[28]

Results

Identification of acute liver failure cases. Upon searching all encounters registered in the entire Health Facts, we were able to identify a total of 69 117 801 unique patients. By excluding all inpatients with history of liver diseases, we identified an initial cohort of 66 352 931 patients, which included a pool of 17 890 unique ALF cases.

By removing all patients with a medical history of less than 1 year, we reduced our case pool to 3820 cases (21.4%), which was then restricted to those with an index date between 2010 and 2015 (n = 3356, 18.8%). Excluding those with missing or inconsistent data on any of the matching variables resulted in a final pool of 3151 eligible cases (17.6%). Based on our criteria, we

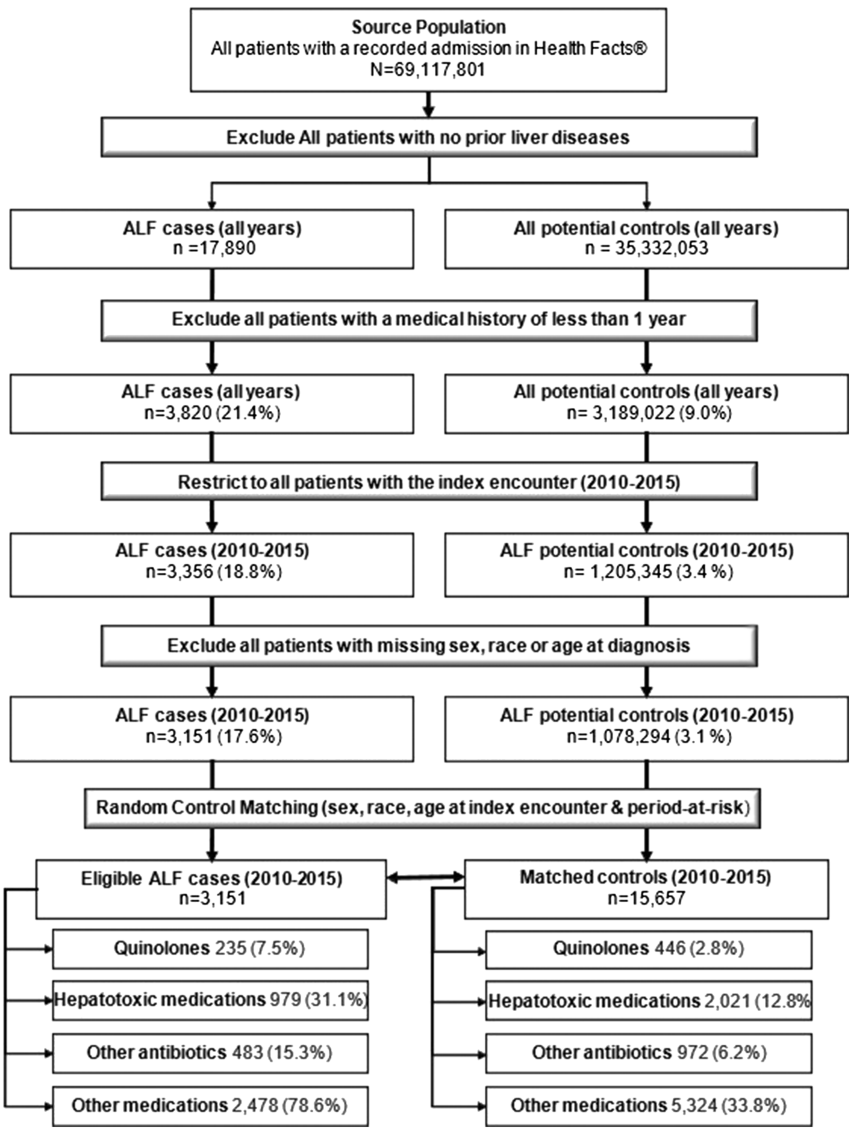

Figure 1 Identification of eligible ALF cases and matching controls (2010–2015). ALF, acute liver failure.

were able to match a total of 15 657 unique controls to the 3151 eligible cases. A total of 29 cases could not be matched to the maximum of five controls sought by our matching algorithm (Fig. 1).

Characteristics of study population. As summarized in Table 1, study population was comprised mainly of Caucasian race (n = 2374; 75.3%), with slightly more women (n = 1677; 53.2%). Incidence of ALF was low (1.1–1.5%) in the early decades of life, increased steadily until the age of 60 years, then plateaued afterwards.

Cases were generally less healthy than controls, with a mean (± SD) CMI score of 7.9 (± 3.3) and 3.3 (± 3.4), respectively. Most cases (56%) were in the mid-range (CMI: 6–10), with the remainder distributed fairly equally on either side of this middle zone. Only 1.5% of cases showed no comorbidities other than ALF. Whereas most controls (49%) were in a healthier zone (CMI: 1–5), 26% showed no comorbidities (CMI: 0), with the remaining controls (26%) were scattered along the higher zones of the index.

Cases showed a higher prevalence of uncomplicated (44% *vs* 23%) and complicated (20% *vs* 8%) diabetes mellitus compared with controls, respectively. Similarly, alcohol abuse in cases (6%) was more than double that in controls (2.5%). Both cases (n = 2695; 85.5%) and controls (n = 13 236; 84.0%) were equally covered by health insurance.

During the 30 days preceding the index encounter, average medication prescriptions filled was two to three times higher among cases compared with controls for all medication groups, reflecting a less favorable health profile for cases relative to controls. Whereas a large majority of cases (93%) and controls (97%) were prescribed no quinolones during the 30-day window, they were prescribed other nonquinolone antibiotics (85% *vs* 93%) or hepatotoxic medications (69% *vs* 87%) during the same period (Table 2).

Levofloxacin and ciprofloxacin were the most commonly filled quinolones for both cases and controls during the 30 days preceding the index date, whereas moxifloxacin had a remarkably low proportion (Table 3).

Regression analysis

Entire study population. Primary analysis of the entire study population showed that systematically administered quinolones are not associated with ALF risk (adjusted odds ratio [aOR]: 1.05 [95% CI: 0.87–1.28]), after adjusting for exposure to other medications, uncomplicated and complicated diabetes mellitus, alcohol abuse, health care setting and insurance status. Repeating the same regression analyses based on individual quinolones produced similar results to a multimedication model including all quinolones simultaneously. Our risk estimates reported herein were generated using the multimedication model. Among the individual quinolones, an increased, nonsignificant ALF risk was detected with moxifloxacin (aOR: 1.46 [95% CI: 0.85–2.50]) and ciprofloxacin (aOR: 1.22 [95% CI: 0.91–1.64]). A summary of ALF risk estimates for medication groups and individual quinolones is provided in Tables 4 and 5, respectively.

Table 1 Characteristics of cases and matched controls

Characteristic	No. (%) of patients or mean (± SD)		*P* value
	Cases	Controls	
Total no. of participants	3151	15 755	
Sex[†]			**0.97**
Women	1677 (53.2%)	8391 (53.3%)	
Men	1474 (46.8%)	7364 (46.7%)	
Race class[†]			**0.98**
Caucasians	2374 (75.3%)	11 910 (75.6%)	
African Americans	589 (18.7%)	2925 (18.6%)	
Asians	44 (1.4%)	217 (1.4%)	
Hispanics	10 (0.3%)	41 (0.3%)	
Others	134 (4.3%)	662 (4.2%)	
			1.0000
Age group[†]			
0–10	46 (1.5%)	230 (1.5%)	
11–20	35 (1.1%)	175 (1.1%)	
21–30	83 (2.6%)	414 (2.6%)	
31–40	137 (4.4%)	686 (4.4%)	
41–50	228 (7.2%)	1137 (7.2%)	
51–60	526 (16.7%)	2,632 (16.7%)	
61–70	707 (22.4%)	3537 (22.5%)	
71–80	758 (24.1%)	3788 (24.0%)	
81–90	631 (20.0%)	3156 (20.0%)	
			< **0.0001**
Census region			
South	1141 (36.2%)	5333 (33.9%)	
North East	947 (30.1%)	3646 (23.2%)	
Midwest	568 (18.0%)	4564 (29.0%)	
West	495 (15.7%)	2207 (14.0%)	
Missing	0 (0.0%)	5 (0.1%)	
			0.0049
Hospital setting			
Urban	2,543 (80.7%)	12,358 (78.5%)	
Rural	608 (19.3%)	3,392 (21.5%)	
Missing	0	5 (0.09%)	
			0.0131
Health insurance			
Insured	2695 (85.5%)	13 236 (84.0%)	
Noninsured	72 (2.3%)	504 (3.2%)	
Unknown/missing	384 (12.2%)	2015 (12.8%)	
			< **0.0001**
Payer group			
Government	2090 (66.3%)	8751 (55.5%)	
HMO/managed care	604 (19.2%)	4483 (28.5%)	
Self-pay	72 (2.3%)	502 (3.2%)	
Other	1 (0.0%)	4 (0.0%)	
Unknown/missing	384 (12.2%)	2015 (12.8%)	
Comorbidity score	**7.90 (±3.3)**	**3.35 (± 3.5)**	< **0.0001**
0	65 (2.1%)	4098 (25.7%)	
1–5	664 (21.1%)	7710 (49.0%)	
6–10	1,753 (55.7%)	3282 (20.8%)	
11–15	647 (20.6%)	689 (4.4%)	
16–20	19 (0.6%)	19 (0.12%)	
Confounders			
Diabetes—uncomplicated	1397 (44.4%)	3785 (24.0%)	< 0.0001
Diabetes—complicated	651 (20.7%)	1372 (8.7%)	< 0.0001
Alcohol abuse	176 (5.6%)	383 (2.4%)	< 0.0001

[†]Matching variables.

Table 2 Thirty-day exposure, by medication group, prior to the index date

Medication group		Mean (± SD); *P* value or no. (%) of filled prescriptions		*P* value
		Cases	Controls	
Quinolones		**0.11 (± 0.44); < 0.0001**	**0.04 (± 0.27); < 0.0001**	
	0	2916 (92.5%)	15 164 (97.2%)	< 0.0001
	1–3	229 (7.3%)	440 (2.8%)	
	4–6	6 (0.2%)	6 (0.1%)	
	7–10	0 (0%)	0 (0%)	
	11+	0 (0%)	0 (0%)	
Hepatotoxic		**0.76 (± 1.59); < 0.0001**	**0.27 (± 0.91); < 0.0001**	
	0	2172 (68.9%)	13 734 (87.2%)	< 0.0001
	1–3	777 (24.7%)	1744 (11.1%)	
	4–6	163 (5.2%)	226 (1.4%)	
	7–10	31 (1.0%)	44 (0.3%)	
	11+	8 (0.3%)	7 (0%)	
Other antibiotics		**0.32 (± 0.91); < 0.0001**	**0.13 (± 0.62); < 0.0001**	
	0	2668 (84.7%)	14 783 (93.8%)	< 0.0001
	1–3	418 (13.3%)	833 (5.3%)	
	4–6	61 (1.9%)	121 (0.8%)	
	7–10	4 (0.1%)	17 (0.1%)	
	11+	0 (0%)	1 (0%)	
Other medications		**10.11 (± 17.50); < 0.0001**	**3.77 (± 11.01); < 0.0001**	
	0	673 (21.4%)	10 431 (66.2%)	< 0.0001
	1–3	1528 (48.5%)	3322 (21.1%)	
	4–6	92 (2.9%)	239 (1.5%)	
	7–10	62 (2.0%)	176 (1.1%)	
	11+	796 (25.3%)	1,587 (10.1%)	

Table 3 Thirty-day exposure by the individual quinolones

Medication group	No. (%) of filled prescriptions		*P* value
	Cases	Controls	
Ciprofloxacin	101 (3.2%)	167 (1.1%)	< 0.0001
Levofloxacin	125 (4.0%)	262 (1.7%)	< 0.0001
Moxifloxacin	27 (0.9%)	40 (0.3%)	< 0.0001

Stratification by sex. Quinolones showed a marginal, nonsignificant increase in ALF risk in women (aOR: 1.16 [95% CI: 0.88–1.54]), that was predominantly driven by both moxifloxacin (aOR: 1.43 [95% CI: 0.57–3.61]) and ciprofloxacin (aOR: 1.30 [95% CI: 0.88–1.91]).

Stratification by race. Quinolones showed a substantial, nonsignificant increase in ALF risk in African Americans (aOR: 1.43 [95% CI: 0.88–2.30]), that was also predominantly driven by moxifloxacin (aOR: 2.70 [95% CI: 0.96–7.60]). Additionally, ciprofloxacin showed an increased, nonsignificant ALF risk in Caucasians (aOR: 1.25 [95% CI: 0.90–1.74]).

Stratification by age. In the youngest age tertile (0–60), quinolones showed a significant ALF risk (aOR: 1.91 [95% CI: 1.21–3.00]), which was reduced and lost its significance (aOR: 1.30 [95% CI: 0.95–1.78]) in the middle age tertile (61–75). No risk was found in the eldest age tertile (76 years and older). All individual quinolones showed an elevated but nonsignificant ALF risk in the youngest two tertiles, whereas only moxifloxacin continued to show a nonsignificant risk in the eldest age group.

Stratification by comorbidity. By stratifying the study population into tertiles based on their scores, those with the lowest comorbidity burden (CMI: 0–6) showed a significant 156% increase in ALF risk (aOR: 2.56 [95% CI: 1.54–4.27]) with use of quinolones. In the healthiest group (CMI: 0–6), only ciprofloxacin showed a fourfold significant increase in ALF risk (aOR: 5.11 [95% CI: 2.39–10.94]). No quinolones showed any significant ALF risk in the moderate to high CMI groups.

Effect of major confounders. Complicated diabetes mellitus was associated with a significant ALF risk in the primary analysis examining the entire unstratified study population (aOR: 2.09 [95% CI: 1.85–2.36]). This risk was similar across all races, slightly higher in women, and decreased slightly with advancement of age.

Similarly, alcohol abuse was also associated with a significant ALF risk in the primary analysis (aOR: 1.92 [95% CI: 1.55–2.39]), the healthiest subgroup (CMI: 0–6), women, Caucasians more than African Americans, and in the youngest more than the middle age tertiles.

The adjusted ORs and 95% CI for the primary and subgroup analyses for both confounders are detailed in the supporting information (section VI). Results for the base and (maximally) adjusted models for the primary analysis examining the entire study

Table 4 Base and adjusted odds ratios (aOR) for ALF risk with all medication groups

Population and medication group	Base OR (95% CI)	*P* value	Adjusted aOR (95% CI)	*P* value
Entire study population				
Quinolones	2.80 (2.38–3.31)	< 0.0001	1.05 (0.87–1.28)	0.6075
Hepatotoxic medications	3.17 (2.90–3.48)	< 0.0001	**1.37 (1.23–1.54)**	< **0.0001**
Other antibiotics	2.80 (2.49–3.16)	< 0.0001	1.03 (0.89–1.20)	0.6528
Non-antibiotics	7.61 (6.91–8.37)	< 0.0001	**6.52 (5.86–7.25)**	< **0.0001**
By comorbidity level (tertiles)				
CMI:0–6				
Quinolones	5.43 (3.58–8.22)	< 0.0001	**2.56 (1.54–4.27)**	**0.0003**
Hepatotoxic medications	3.05 (2.49–3.73)	< 0.0001	1.28 (0.99–1.66)	0.0651
Other antibiotics	3.66 (2.82–4.75)	< 0.0001	1.16 (0.84–1.62)	0.3694
Non-antibiotics	8.35 (7.03–9.93)	< 0.0001	**7.89 (6.49–9.59)**	< **0.0001**
CMI:7–9				
Quinolones	1.27 (0.83–1.94)	0.2799	0.87 (0.54–1.42)	0.5762
Hepatotoxic medications	1.19 (0.92–1.53)	0.1805	0.82 (0.61–1.10)	0.1798
Other antibiotics	1.58 (1.15–2.18)	0.0054	1.31 (0.90–1.92)	0.1605
Non-antibiotics	3.14 (2.37–4.15)	< 0.0001	**3.03 (2.22–4.13)**	< 0.**0001**
CMI:10+				
Quinolones	1.12 (0.69–1.83)	1.830	0.80 (0.44–1.44)	0.4567
Hepatotoxic medications	1.52 (1.11–2.06)	0.0084	1.08 (0.73–1.60)	0.7158
Other antibiotics	1.09 (0.73–1.61)	0.6879	0.78 (0.48–1.26)	0.3036
Non-antibiotics	2.62 (1.86–3.70)	< 0.0001	**2.58 (1.68–3.96)**	< 0.**0001**

CI, confidence interval; OR, odds ratio.

Table 5 Base and adjusted odds ratios (aOR) for acute liver failure in relation to use of individual quinolones

Population and Quinolone Used	Base OR (95% CI)	*P* value	Adjusted aOR (95% CI)	*P* value
Entire study population				
Ciprofloxacin	2.74 (2.12–3.54)	< 0.0001	1.22 (0.91–1.64)	0.1754
Levofloxacin	2.35 (1.88–2.93)	< 0.0001	0.90 (0.70–1.15)	0.3966
Moxifloxacin	2.92 (1.75–4.89)	< 0.0001	1.46 (0.85–2.50)	0.1720
By comorbidity level (tertiles)				
CMI:0–6				
Ciprofloxacin	8.1 (4.32–15.23)	< 0.0001	5.11 (2.39–10.94)	< 0.0001
Levofloxacin	3.42 (1.89–6.19)	< 0.0001	1.44 (0.72–2.86)	0.3015
Moxifloxacin	3.45 (0.68–17.44)	0.1346	1.98 (0.35–11.33)	0.4420
CMI:7–9				
Ciprofloxacin	1.58 (0.71–3.48)	0.2604	1.21 (0.51–2.84)	0.6658
Levofloxacin	1.02 (0.61–1.73)	0.9341	0.67 (0.37–1.22)	0.1884
Moxifloxacin	2.09 (0.48–9.00)	0.3240	1.66 (0.37–7.36)	0.5061
CMI:10+				
Ciprofloxacin	0.91 (0.40–2.03)	0.8107	0.69 (0.28–1.72)	0.4261
Levofloxacin	1.10 (0.60–2.02)	0.7584	0.86 (0.43–1.74)	0.6810
Moxifloxacin	3.51 (0.61–20.32)	0.1609	1.26 (0.17–9.32)	0.8240

CI, confidence interval; OR, odds ratio.

population and the subgroup analysis based on comorbidity score are presented in this manuscript in Table 4 for all medication groups and Table 5 for the individual quinolones. Detailed results for all regression models for all analyses are provided in the supporting information (sections IV–VI).

Discussion

The number of ALF cases identified in the Health Facts was remarkably low prior to 2010 and after 2015. Whereas we think the former was probably due to the gradual enrollment of participating hospitals, the latter marked the shift of coding from ICD-9 to ICD-10 codes, which could be confirmed by lack of any ICD-10 codes in all identified ALF cases in all years. As such, we decided to focus our study on the interval between 2010 and 2015, which included the bulk of all recorded ALF cases.

By excluding cases or controls with history of liver diseases, and adjusting for major confounders, we aimed at isolating the effect of medications on ALF risk. Our primary analysis of the entire study population showed no evidence of increased ALF risk within 30 days following the "inpatient" exposure to quinolones. However, a possible risk was seen in those with the lowest CMI score (predominantly driven by ciprofloxacin), and in patients up to 60 years of age (predominantly driven by moxifloxacin. A non-significant ALF risk was identified in both women and men (could be attributed to ciprofloxacin and moxifloxacin), in African Americans (by moxifloxacin and ciprofloxacin) and in Caucasians (by ciprofloxacin). Consistent with earlier studies,[29–31] alcohol abuse and complicated diabetes showed increased ALF risk.

Recent pharmacovigilance studies showed closer results,[4,7,21,22] despite differences in study design, target population, case definition, case identification, and control selection process. Characteristics and results of these studies are summarized in supporting information (section VII). Earlier observational studies also reported sporadic occurrences of hepatotoxicity with ciprofloxacin,[14,32,33] moxifloxacin,[14,34–36] and levofloxacin.[14,37–41]

To the best of our knowledge, this is the first large-scale assessment of quinolone-associated ALF using a substantive database with extensive inpatient EHRs for nearly 21% of the US population. We opted for a nested case–control study design rather than a cohort design, due to the former's computational efficiency given its smaller sample size, opportunity for time-based exposure assessment, and accounting for the effects of different potential confounders at different times.[42–44] Moreover, missing observations are expected to have a lesser impact in the nested case–control design, and eventually both designs would be expected reach comparable risk estimates.[45–47]

Using inpatient EHRs provided an opportunity for accurately assessing the temporality of association between ALF and prior medication exposure, and also for adjusting for major confounders such as comorbidities and concurrent medication exposure. Using an inpatient medication management system ensured medication compliance because all filled medications are most likely delivered by hospital staff.

Restricting the inclusion to our study to patients with a minimum of 1-year medical history enabled a more extensive assessment of confounding by patients' comorbidity status on ALF risk, although this came at the expense of losing additional ALF cases with short or no medical history.

A major limitation involved the lack of information on outpatient medication history, considering the fact that 50–80% of antibiotics are prescribed in physician offices rather than hospitals.[48,49] This major limitation should be addressed in future studies. Despite the significant efforts devoted to the cleaning and linking of our data, and similar to other EHR databases,[50,51] our database is subject to limitations such as misclassification of demographics, comorbidities, medications, outcomes or other clinical details.

Conclusion

Overall, our study did not identify evidence to support an association between ALF and systemically administered quinolones. Whereas we identified an association in some subpopulations, as pointed out in our study, we cannot completely rule out the possibility of an overall association based on our examination of such database. Further attention must be paid to quinolone exposure by specific subgroups such as with ciprofloxacin in persons with low CMI score (0–6); moxifloxacin in persons aged 60 years or younger; ciprofloxacin and moxifloxacin in both women and men; moxifloxacin and ciprofloxacin in African Americans and ciprofloxacin in Caucasians. Further studies with additional information on outpatient medication use would be useful in confirming the present findings.

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Declaration of conflict of interest

All authors who contributed to both this study and manuscript report no conflict of interest in relation to the planning for and conducting this study as well as production of this manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. All new ALF cases recorded in the Healthfacts database, by year (2000–2016).
Figure S2. Final group of fully eligible ALF cases, by year of diagnosis (2010–2015).
Table S1. ICD Codes for identifying cases of acute liver failure (ALF).
Table S2. ICD codes for excludable liver conditions.