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ORIGINAL RESEARCH ARTICLE

Assessment of the Frequency, Phenotypes, and Outcomes of Acute Liver Injury Associated with Amoxicillin/Clavulanate in 1.4 Million Patients in the Veterans Health Administration

Ayako Suzuki[1,2] · Hans Tillmann[3,4] · James Williams[5] · Ronald G. Hauser[6,7] · Julie Frund[8] · Mizuki Suzuki[9] · Fred Prior[8] · Guruprasad P. Aithal[10] · M. Isabel Lucena[11,12] · Raúl J. Andrade[11,12] · Weida Tong[13] · Christine M. Hunt[1,2,14]

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Abstract

Introduction Drug-induced liver injury is a significant health issue, yet the exposure-based incidence remains to be characterized.

Objective We aimed to assess the frequency, phenotypes, and outcomes of acute liver injury associated with amoxicillin/clavulanate using a large electronic health record system.

Methods Using the Veterans Health Administration electronic health record system, we developed the framework to identify unexplained acute liver injury, defined by alanine aminotransferase and/or alkaline phosphatase elevation temporally linked to prescription records of amoxicillin/clavulanate, a major culprit of clinically significant drug-induced liver injury, excluding other competing causes. The population was subcategorized by pre-existing liver conditions and inpatient status at the time of exposure for the analysis.

Results Among 1,445,171 amoxicillin/clavulanate first exposures in unique individuals [92% men; mean age (standard deviation): 59 (15) years], 6476 (incidence: 0.448%) acute liver injuries were identified. Of these, 4427 (65%) had alternative causes, yielding 2249 (incidence: 0.156%) with unexplained acute liver injuries. The incidence of unexplained acute liver injury was lowest in outpatients without underlying liver disease (0.067%) and highest in inpatients with pre-existing liver conditions (0.719%). Older age, male sex, and American Indian or Alaska Native (vs White) were associated with a higher incidence of unexplained acute liver injury. Cholestatic injury affected 74%, exhibiting a higher frequency with advanced age, inpatient exposure, and pre-existing liver conditions. Hepatocellular injury with bilirubin elevation affected 0.003%, with a higher risk at age >45 years. During a 12-month follow-up, patients with unexplained acute liver injury had a higher adjusted overall mortality risk than those without evident acute liver injury.

Conclusions This framework identifies unexplained acute liver injury following drug exposure in large electronic health record datasets. After validating in other systems, this framework can aid in deducing drug-induced liver injury in the general patient population and regulatory decision making to promote drug safety and public health.

✉ Ayako Suzuki
Ayako.suzuki@duke.edu; ayako.suzuki@va.gov

1 Gastroenterology, Durham Veterans Affairs Health Care System, Durham VA Medical Center, 40 Duke Medicine Cir, Suite DUMC 3913, Durham, NC 27710, USA

2 Gastroenterology, Duke University, Durham, NC, USA

3 Specialty Clinics, Greenville VA Healthcare Center, Greenville, NC, USA

4 Gastroenterology, Hepatology and Nutrition, East Carolina University, Greenville, NC, USA

5 HSR&D, Central Arkansas Veterans Healthcare System, Little Rock, AR, USA

6 Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA

7 Department of Laboratory Medicine, Yale School of Medicine, New Haven, CT, USA

8 Department of Biomedical Informatics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

9 Brody School of Medicine, East Carolina University, Greenville, NC, USA

10 National Institute for Health Research (NIHR) Nottingham Biomedical Research Center at the Nottingham University Hospital NHS Trust and University of Nottingham, Nottingham, UK

11 Servicio de Aparato Digestivo y Farmacología Clínica, Instituto de Investigación Biomédica de Málaga (IBIMA_Plataforma Bionand), Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Malaga, Spain

12 CIBERehd, Madrid, Spain

13 Bioinformatics and Biostatistics, National Center for Toxicological Research, Jefferson, AR, USA

14 VA Cooperative Studies Program Epidemiology Center-Durham, Durham, NC, USA

Graphical Abstract

Drug Safety

PEER-REVIEWED FEATURE

Assessment of the frequency, phenotypes, and outcomes of acute liver injury associated with amoxicillin/clavulanate in 1.4 million patients in the Veteran Health Administration

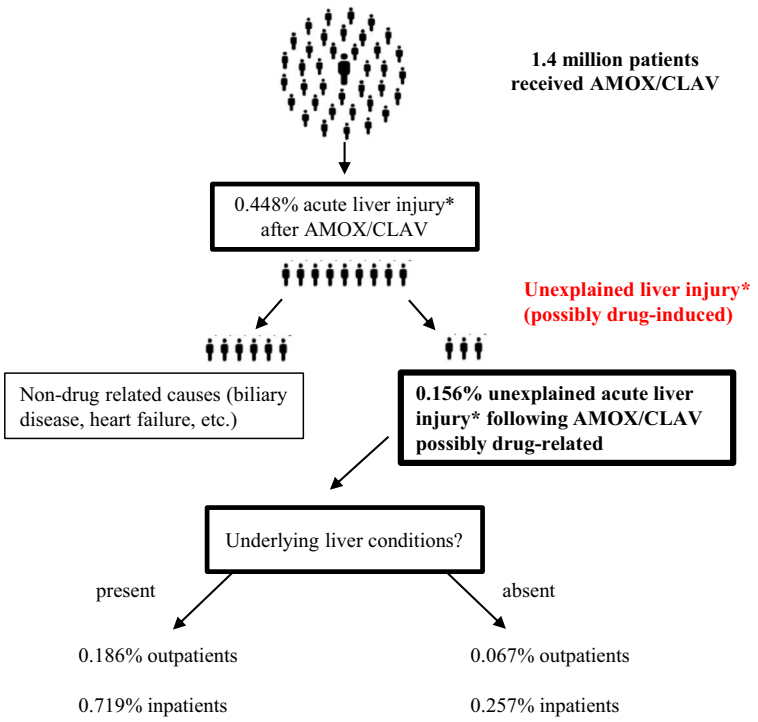
Ayako Suzuki, Hans Tillmann, James Williams, Ronald G. Hauser, Julie Frund, Mizuki Suzuki, Fred Prior, Guruprasad P. Aithal, M. Isabel Lucena, Raúl J. Andrade, Weida Tong, Christine M. Hunt

Objective: assess the frequency, phenotypes, and outcomes of acute liver injury associated with amoxicillin/clavulanate (AMOX/CLAV) using the Veterans Health Administration Electronic Health Record (EHR)

Methods: we developed an EHR framework to identify unexplained acute liver injury, defined by alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) elevation temporally linked to AMOX/CLAV prescription records, excluding other competing causes.

Demographics: 1.4 million AMOX/CLAV first exposures; 92% men; mean age: 59 (15 SD)

Main Findings: Of 6476 acute liver injury events after AMOX/CLAV (incidence: 0.448%), 2 in 3 had non-drug causes, yielding 1 in 3 with unexplained acute liver injury, which is possibly AMOX/CLAV-induced. After validation, this EHR framework can aid in deducing drug-induced liver injury in the general patient population.



Abbreviations: alanine aminotransferase (ALT), amoxicillin/clavulanate (AMOX/CLAV)

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Key Points

We developed a temporal framework to assess drug-associated acute liver injury in a large EHR system to provide a broadpopulation-based view of drug-associated liver events.

Taking an exposure-based approach, the incidence of amoxicillin/clavulanate (AMOX/CLAV)-associated acute liver injurywas estimated at 0.156% with potential risk factors of older age, male sex, American Indian or Alaska Native race,hospitalization, and pre-existing liver conditions.

Patients with AMOX/CLAV-associated acute liver injury had a higher adjusted overall mortality risk than those withoutevident acute liver injury during a 12-month follow-up, implicating a broader negative health impact.

1 Introduction

Drug-induced liver injury (DILI) is a significant public health concern and negatively impacts patient health and drug development. In the general population, DILI is uncommon, with an estimated incidence of 14–19 per 100,000, in whom 22% are hospitalized [1, 2]. The incidence rate of acute liver failure due to DILI is estimated at 1 per 1,000,000 person-years; 57% of those leading to liver transplantation or death [3]. The incidence estimates of DILI vary by study population and drugs; the frequency of drug-specific DILI has rarely been estimated through prescription event monitoring in a large population.

Hundreds of marketed pharmaceuticals are known to cause DILI [4]. However, risk factors for developing DILI are largely unknown. In an Icelandic population-based study, the age-standardized incidence of DILI significantly increased with advanced age [1]. However, prescription volume also increases with age; thus, whether older subjects have a higher DILI susceptibility remains unclear [1]. A French population-based study reported a two-fold higher standardized DILI incidence in women than men over age 50 years, yet found no sex difference under age 50 years [2]. A similar trend was observed in the Icelandic population-based study [1]. However, these observations were not exposure based; thus, the DILI preponderance in older women remains uncertain. For select drugs, HLA variants have been highly associated with DILI. These genetic markers exhibit a high negative predictive value and low positive predictive value [5, 6], limiting their clinical use to prospectively predict DILI risk. Thus, DILI remains unpredictable in current practice.

The severity of DILI ranges from asymptomatic liver chemistry elevations to acute liver failure. Most DILI events are self-limited asymptomatic liver enzyme elevations. In the minority exhibiting symptomatic DILI, about one in ten patients develop life-threatening outcomes (i.e., requiring urgent liver transplantation, or death) [7, 8]. These DILI outcomes have been studied in prospective DILI registries [7–9], but the impact of DILI on overall health outcomes has not been qualitatively assessed in the general patient population.

With increasing worldwide use, electronic health record (EHR) datasets provide an opportunity to estimate drug-specific DILI incidence by age, sex, and racial/ethnic groups and assess its health outcomes in the general population. This approach is especially advantageous in studying this infrequent condition. Using a large EHR system, we developed a framework to identify acute liver injury events following amoxicillin/clavulanate (AMOX/CLAV) exposure, unexplained by other non-drug causes. This approach helps to deduce real-world DILI, complements existing resource-intensive DILI registries, and can advance the scope of our clinical knowledge of DILI.

2 Materials and Methods

2.1 Data Source and Study Design

We used the Veterans Health Administration (VHA) Corporate Data Warehouse, a national EHR repository of clinical and administrative data [10], and conducted a descriptive cohort study to identify acute liver injury events that were temporally associated with AMOX/CLAV treatment and unexplained by other causes. Using the identified acute liver injury events, we analyzed the frequency, risk disparities by age, sex, and race/ethnicity, liver injury phenotypes, and overall mortality during the 2-year follow-up. This study was exempted by the Institutional Review Board of Central Arkansas Veterans Healthcare System and Durham Veterans Affairs (VA) as human subject research (Category 4: Secondary Use of Data or Specimens).

2.2 Study Cohort Identification

To define our study cohort, we first identified AMOX/CLAV prescriptions that included any period between 1 October, 1999 and 30 September, 2015, and estimated the days of drug exposure using available outpatient and inpatient prescription records. Most were single prescriptions, without refills or renewals. When recurring prescriptions were observed, these were concatenated into a single drug exposure period

by assuming continuous exposure when the end of the current prescription and the start of the next refill were less than either half of dispensed days supplied of the current prescription or 30 days (whichever was smaller) [11]. Inpatient prescriptions were recorded as individual dispenses. For these fragmented inpatient prescription records, we considered an AMOX/CLAV interruption of < 7 days to represent continuous exposure. Among the overall AMOX/CLAV exposures identified by this algorithm, 44% were repeat exposures (Fig. 1). In this study, we examined only data related to the first documented drug exposure in each individual.

The study cohort was then divided into patients with no known liver disease (termed 'liver healthy') and those with existing liver conditions, using the clinical data available prior to the first exposure (Fig. 1). The cohort was further sub-classified as outpatients or inpatients based on their status when initiating AMOX/CLAV (Fig. 1). More specifically, patients without underlying liver diseases, liver enzyme elevations, hepatitis B viral infection, hepatitis C viral infection, hepatitis E viral infection, or human immunodeficiency virus infection during 36 months before drug exposure comprised a 'liver healthy' population. We extended this baseline period from 12 months in our previous EHR study [11] to 36 months as 12 months was insufficient to characterize pre-existing liver diseases based on a case validation analysis we performed on a randomly selected 18% of identified cases, reviewing available structured data (i.e., laboratory data and International Classification of Diseases, Ninth Revision [ICD-9] codes) in a pilot cohort (data not shown). Chronic liver diseases considered in this study included: chronic hepatitis C or B, alcoholic liver disease, autoimmune hepatitis, biliary cholangitis, secondary biliary cirrhosis, primary and secondary sclerosing cholangitis, hemochromatosis, and nonalcoholic fatty liver disease. Hepatitis B virus infection was identified by ICD-9 codes, positive hepatitis B surface antigen and/or hepatitis B viral DNA during the 36 months prior to the drug exposure. Hepatitis C virus infection and human immunodeficiency virus infection were identified using ICD-9 codes during 36 months prior to the drug exposure. All other diagnoses of chronic liver disease were based on ICD-9 coding or pre-existing liver enzyme elevations.

2.3 Identification of Acute Liver Injury Events Unexplained by Other Causes of Liver Enzyme Elevation

Acute liver injury events were defined within high-risk periods following the AMOX/CLAV exposure. The high-risk period was defined as either (1) from drug initiation to 30 days after drug discontinuation or (2) the first 90 days of drug exposure if treatment exceeded 60 days (Fig. 2), reflecting the time period of most observed DILI cases [12].

Acute liver injury was defined as alanine aminotransferase (ALT) $\geq 5 \times$ the upper limit of normal (ULN) or alkaline phosphatase (ALP) $\geq 2 \times$ ULN when baseline liver chemistries were normal, as specified in the international consensus DILI criteria [13, 14]. If baseline liver chemistries were elevated even once during the 36 months prior to the event, acute liver injury was defined as ALT $\geq 5 \times$ or ALP $\geq 2 \times$ above baseline median values, baseline mean values, or the ULN, whichever was higher, in the 36 months prior to exposure. The event date was defined as the first date when laboratory data met the acute liver injury criteria: ALT $> 5 \times$ ULN (or baseline median/mean value) and/or ALP $>2\times$ ULN (or baseline median/mean value) (Fig. 2).

To exclude other causes of ALT and/or ALP acute elevation, we developed ten exclusion criteria (Table 1 of the Electronic Supplementary Material [ESM]), based on the above-mentioned case validation analysis. The algorithms for the ten criteria were applied to clinical/administrative data within -7 to $+90$ days from the event date. For hepatitis C, hepatitis B, and autoimmune hepatitis, only new cases diagnosed within -7 to $+90$ days from the event date were excluded, without having ICD-9 codes or laboratory data indicative of active infection during the 36 months before the event date. Acute liver injury events associated with leukemia, other hematological malignancy, or post-liver transplantation were excluded as information was generally insufficient to identify DILI versus disease-related liver injury in our validation case analysis. Similarly, cases with liver enzyme elevation on the same day as the AMOX/CLAV initiation (i.e., latency of 0 days) were also excluded from the analysis as we could not accurately determine the chronological order of the data. Subjects who did not have liver chemistries during the high-risk period were considered to have not developed clinically significant acute liver injury and were included as controls in the analysis (i.e., untested controls) in addition to tested controls (in which liver enzymes were normal when tested in the high-risk period).

2.4 Phenotypes of Acute Liver Injury

After defining unexplained acute liver injury events, these events were classified as hepatocellular, cholestatic or mixed, applying the internationally agreed DILI phenotype classification [13]. Hepatocellular liver injury was defined as $R \geq 5$, where the R value was calculated as (ALT/ALT ULN)/(ALP/ALP ULN) using the reference range at the time of the event, while cholestatic liver injury was defined as $R \leq 2$ and mixed liver injury as $2 < R < 5$ [13]. The R values were calculated using data closest to the event date (within 24 h after the event date). Cases with insufficient data to classify liver injury type were excluded from the analysis of phenotypes.

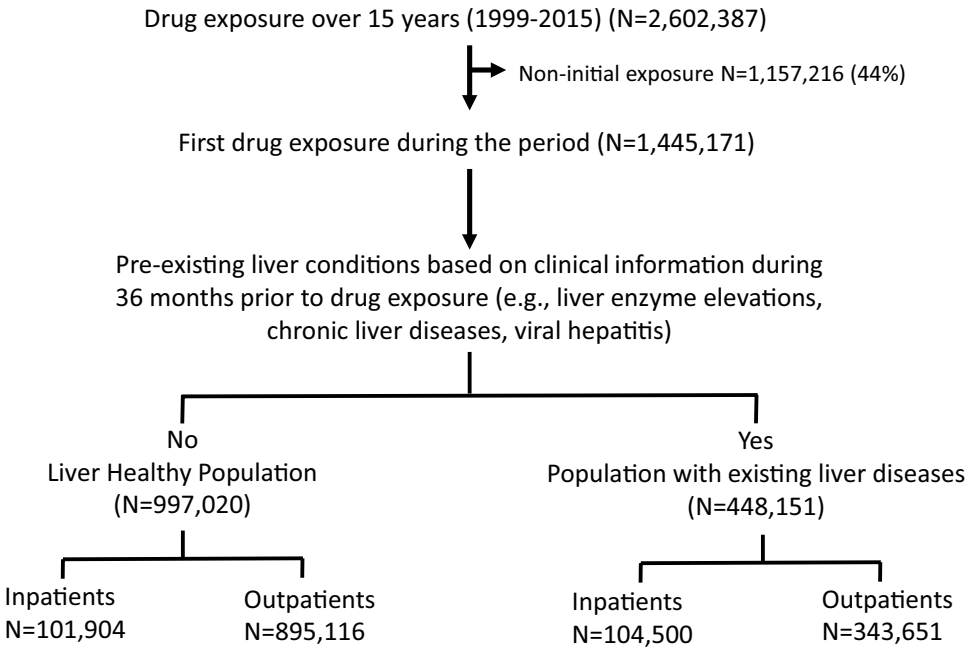

Fig. 1 Selection of study population and sub-classification

In patients with DILI, hepatocellular injury accompanied by serum bilirubin elevation (i.e., Hy's law cases) is considered a sign of potential life-threatening outcomes [15]. We defined hepatocellular injury with bilirubin > 2 × ULN to assess this specific phenotype of acute liver injury (i.e., serious hepatocellular liver injury) [16].

2.5 Outcome Variables

Using the date of death in the Corporate Data Warehouse, overall mortality was identified within 6 months, 12 months, and 24 months after the acute liver injury events. For controls, overall mortality was assessed at 6 months, 12 months, and 24 months after the initiation of drug exposure. Cases associated with an obviously erroneous date of death (e.g., date of death before AMOX/CLAV was prescribed) [N = 719 or 0.4% of total death cases] could not be classified and were removed from this analysis.

2.6 Other Variables

Age, sex, race, and ethnicity at the time of exposure were retrieved from the Corporate Data Warehouse. Age was classified into seven categories: 18–25, 26–35, 36–45, 46–55, 56–65, 66–75, and 75+ years. Race/ethnicity variables were combined to create eight categories: HISPANIC (including all Hispanic subjects regardless of race), non-Hispanic White, non-Hispanic Black, Asian, American Indian or Alaska Native, Native Hawaiian and other Pacific Islander, unknown, and missing.

2.7 Statistical Analysis

The data are presented as mean ± standard deviation, median with 25th and 75th, or proportions (%) as appropriate. For the incidence rate (%), 95% confidence intervals (CIs) were also computed. The age-specific, sex-specific, and race/ethnicity-specific incidence of acute liver injury events were also computed.

We also performed a logistic regression analysis with unexplained acute liver injury event (yes or no) as an outcome and age, sex, race/ethnicity as predictors. Interactions among age, sex, and race/ethnicity were assessed in a multiple logistic regression model. When no significant interaction was noted, a model including age, sex, and race/ethnicity was developed to assess adjusted associations with unexplained acute liver injury events. We also performed multinomial logistic regression to assess factors influencing phenotypes of liver injury using hepatocellular injury as a reference. The analyses were performed using SAS Enterprise version 7.13 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Study Population Characteristics

We identified 2,602,387 total exposures to AMOX/CLAV. Among those, 1,445,171 (56%) were analyzed in this study as the first exposures in unique subjects. Of these, 997,020 exposures were classified as the 'Liver Healthy' population [outpatient: 895,116 (90%), inpatient: 101,904 (10%)] while

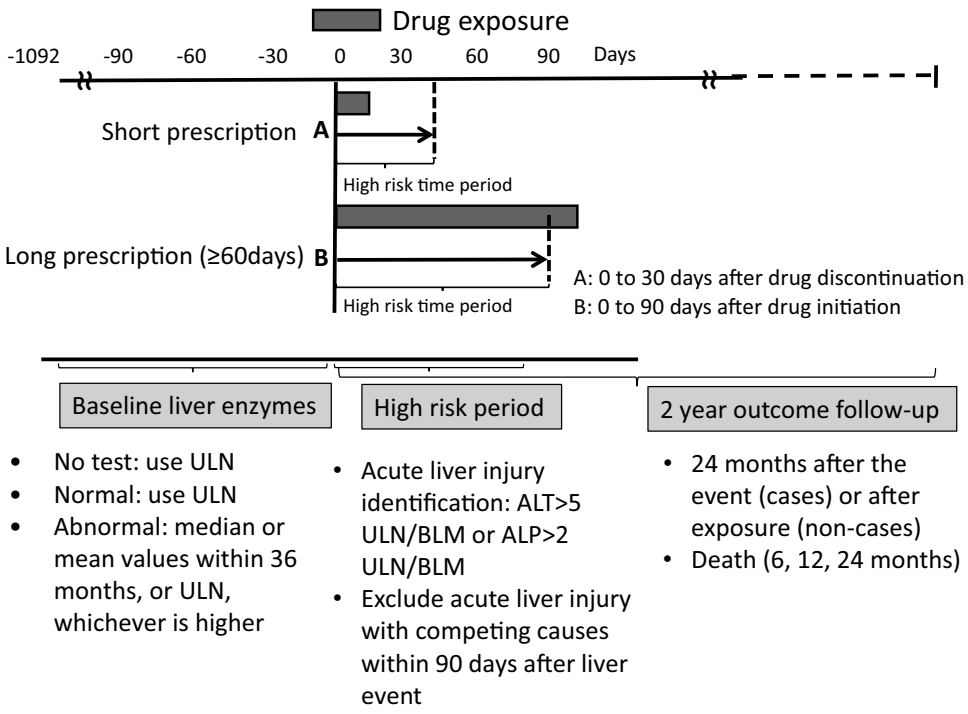

Fig. 2 Study methodology. The figure depicts the definition of high-risk periods based on exposure periods, time windows of baseline period, event period, and follow-up period. The high-risk period was defined using **a** or **b**, whichever is shorter (see Sect. 2). *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *BLM* baseline median/mean, *ULN* upper limit of normal

448,151 exposures were classified as 'other' (i.e., having pre-existing liver conditions) [outpatient: 343,651 (77%), inpatient: 104,500 (23%)] (Fig. 1). Among the first AMOX/CLAV exposures, 85% had liver chemistries measured (ALT and/or ALP) during the preceding 36 months and 32% had liver chemistries during the high-risk period defined based on each exposure. Laboratory availability during the baseline 36 months and high-risk periods are summarized in Table 2 of the ESM by the four sub-population categories (2a) and by age, sex, and race/ethnicity categories (2b).

In the study population**,** most were male (92%), older than 55 years of age (62%), and non-Hispanic White (62%) (Table 1). A total of 6476 acute liver injury events (0.45%) were identified within the high-risk period following the AMOX/CLAV exposure, before excluding alternative causes. The frequency of acute liver injury following AMOX/CLAV was 0.16%, 0.68%, 0.52%, and 2.42% in Liver Healthy outpatients, Liver Healthy inpatients, outpatients with existing liver conditions, and inpatients with existing liver conditions, respectively.

3.2 Unexplained Acute Liver Injury Event Frequency

Of 6476 acute liver injury events, 4227 cases (65%) met criteria for alternative liver conditions (summarized in Table 3 of the ESM). The most frequent competing etiologies include biliary/pancreatic disorders [including malignancies] (30%), heart failure (10.2%), and systemic inflammation/shock (9%). New hepatitis C viral/hepatitis B viral infection, new diagnosis of autoimmune hepatitis, and alcoholic hepatitis were identified in 1.7%, 0.015%, and 1.2% of the cases with acute liver injury, respectively. No cases of acute hepatitis E were identified. After these exclusions, 2249 unexplained acute liver injury events were observed, yielding a frequency of 0.156% [95% CI 0.149–0.162]. In the subpopulations, the lowest frequency of unexplained acute liver injury was seen in Liver Healthy outpatients of 0.067% [95% CI 0.061–0.072], with a higher frequency in Liver Healthy hospitalized patients of 0.257% [95% CI 0.227–0.290] and outpatients with existing liver conditions of 0.186% [95% CI 0.172–0.201]; inpatients with existing liver conditions exhibited the highest frequency of unexplained acute liver injury of 0.719% [95% CI 0.668–0.772]. The frequency of unexplained acute liver injury was lower in the Liver Healthy population vs the population with existing liver conditions ($p < 0.0001$, Chi-square test) and in outpatients versus inpatients ($p < 0.0001$, Chi-square test).

3.3 Age-Specific, Sex-Specific, and Race/Ethnicity-Specific DILI Frequency

The frequency of unexplained acute liver injury following AMOX/CLAV was significantly different by age category, sex, and race/ethnicity (Table 2). For age category, the lowest frequency was observed in age 26–35 years and a higher frequency was observed in older subjects. A higher frequency was also observed in male subjects, American Indian or Alaska Native individuals, and those missing race/ethnicity information in the total population as well as Liver

Healthy Outpatients (p values <0.0001, Chi-square tests) (Table 2).

No significant interactions were noted between age categories, sex, and race-ethnicity in multiple logistic regression (data not shown). In Liver Healthy outpatients (Table 3), the youngest category (18–25 years), age categories above 65 years, and American Indian or Alaska Native were associated with a significantly increased risk of unexplained acute liver injury events; adjusted odds ratio (OR) [95% CI] = 2.2 [1.1–4.2], $p = 0.023$ for age 18–25 years (vs age 26–35 years), 1.8 [1.1–2.8], $p = 0.01$ for age 66–75 years (vs age 26–35 years), 1.7 [1.1–2.7], $p = 0.03$ for age 76+ years (vs age 26–35 years), and 2.3 [1.1–5.3], $p = 0.04$ for American Indian or Alaska Native (vs non-Hispanic White). In comparison to male subjects, female subjects exhibited a decreased risk of unexplained acute liver injury (adjusted OR [95% CI] =0.5 [0.4–0.8], $p = 0.003$).

In the overall population, pre-existing liver conditions and inpatient status were associated with an increased risk of having unexplained acute liver injury events; adjusted OR [95% CI] were 2.8 [2.6–3.1] ($p < 0.0001$) and 3.6 [3.3–4.0] ($p < 0.0001$), respectively (Table 3). Risk differences by age categories, sex, and race-ethnicity in the overall population showed a similar tendency to that observed in the Liver Healthy outpatients.

3.4 Liver Injury Phenotypes

Among the 2249 unexplained acute liver injury events following AMOX/CLAV, most (74%) exhibited cholestatic injury, while 14% were hepatocellular, 11% were mixed, and 5.5% could not be phenotyped. In the overall population, the hepatocellular injury incidence was greatest in the younger group and decreased after age 45 years while the cholestatic injury incidence steadily increased with age over 35 years (Table 4 of the ESM). The proportions of the specific injury types showed consistent patterns, with hepatocellular injury more frequently observed among the young and the proportion of cholestatic injury steadily increasing with age (Fig. 3).

Examining the injury types by subpopulations (Table 4), cholestatic injury predominated across all subpopulations, with higher proportions in subjects with pre-existing liver conditions and inpatients compared with the Liver Healthy subjects and outpatients, respectively ($p < 0.0001$, Chi-square test). In the overall population, pre-existing liver conditions and inpatient status were associated with an increased likelihood of having cholestatic injury versus hepatocellular injury compared with the complementary groups; adjusted ORs [95% CI] were 1.5 [1.1–2.0] ($p = 0.0077$) and 1.7 [1.2–2.2] ($p = 0.001$) [Table 5 of the ESM]. In Liver Healthy outpatients, older age categories (vs age 26–35 years) were associated with an incremental increase in the likelihood of having cholestatic injury versus a hepatocellular injury (Table 5 of the ESM). No significant associations were noted for sex. Black race (vs White) was associated with a 50% increased likelihood of having cholestatic injury versus hepatocellular injury (adjusted ORs [95% CI] =1.5 [1.00–2.12], $p = 0.048$) in the overall population although the association did not reach a statistical significance in the Liver Healthy outpatients (Table 5 of the ESM).

Among those with hepatocellular injury, all 303 cases had bilirubin data within 30 days after acute liver injury events, and 43/303 (14.2%) overall met criteria for serious liver injury (with total bilirubin > 2 × ULN). In cholestatic injury and mixed injury, elevated total bilirubin (> 2 × ULN) was observed in 15.6% (246/1573) and 16.2% (39/241), respectively. No serious hepatocellular injury cases were observed among female subjects in this male-dominant population nor in Liver Healthy outpatients. The prevalence of serious hepatocellular injury was higher in older age groups; the

Table 1 Demographic characteristics of the study population

	Total		Liver healthy outpatients	
	$N = 1,445,171$		$N = 895,116$	
	Age: 59.3 ± 14.9 years [a]		Age: 58.3 ± 15.4 years [a]	
	N	Percentage	*N*	Percentage
Age group, years				
18–25	22,448	1.55	18,800	2.10
26–35	89,086	6.16	68,289	7.63
36–45	133,720	9.25	91,214	10.19
46–55	298,763	20.67	176,074	19.67
56–65	421,685	29.18	248,021	27.71
66–75	259,925	17.99	163,762	18.30
76 +	218,512	15.12	127,965	14.30
Missing	1032	0.07	991	0.11
Sex				
Female	119,043	8.24	92,362	10.32
Male	1,326,007	91.75	802,658	89.67
Missing	121	0.01	96	0.01
Race/ethnicity				
AI/AN	7627	0.53	4564	0.51
Asian	6303	0.44	4161	0.46
Black	248,750	17.21	151,337	16.91
Hispanic	84,383	5.84	49,614	5.54
NH/PI	10,031	0.69	6507	0.73
Unknown	77,647	5.37	47,980	5.36
White	921,373	63.76	576,109	64.36
Missing	89,057	6.16	54,844	6.13

AI/AN American Indian or Alaska Native, *NH/PI* Native Hawaiian and Other Pacific Islander

[a]Mean ± standard deviation

proportions with severe hepatocellular injury in those less than and greater than age 45 years were 8.6% versus 15.9 % in the overall population. Age over 45 years significantly increased the likelihood of serious hepatocellular liver injury (adjusted OR and 95% CI = 4.0 [1.2–13.5], $p = 0.027$) versus age ≤45 years after adjusting for non-Hispanic White race. Because of the low event frequencies, the evaluation of disparities in severe hepatocellular injury by sex and race/ethnicity was limited.

3.5 6-Month, 12-Month, and 24-Month Overall Mortality

Overall mortality was consistently higher in unexplained acute liver injury cases compared with cases without evident liver injury following the drug exposure, except for the mortality in inpatients with and without pre-existing liver conditions for 13–24 months (Table 5). Age, sex, race/ethnicity, pre-existing liver conditions, and inpatient status were significantly associated with overall mortality (data not shown). After adjusting for these variables in the model, unexplained acute liver injury cases exhibited a five-fold increased risk of overall mortality within 6 months (adjusted OR [95% CI] = 5.0 [4.5–5.6], $p < 0.0001$), 50% increased risk for 7–12 months (adjusted OR [95% CI] = 1.5 [1.3–1.8], $p < 0.0001$), and no association with overall mortality after 12 months.

Serious hepatocellular injury cases tended to be associated with an increased mortality versus non-serious unexplained acute liver injury cases within 6 months (19/43 [44.2%] among serious injury vs 619/2012 [30.8%] among others, $p = 0.06$); after adjusting for age over 45 years, race/ethnicity, and subpopulations, adjusted OR [95% CI] of overall mortality within 6 months for serious hepatocellular injury cases was 2.4 [1.2–4.6], $p = 0.010$ (only men were included as no serious hepatocellular injury cases were identified among women). No association of serious hepatocellular injury with overall mortality was observed after 6 months.

Table 2 Incidence of unexplained acute liver injury following amoxicillin/clavulanate exposure in the total population and liver healthy outpatients

	Total		Liver healthy outpatients	
Number of cases	2249		596	
Incidence	0.16%		0.07%	
	N	Incidence	*N*	Incidence
Age group[a], years				
18–25	21	0.09	14	0.07
26–35	65	0.07	25	0.04
36–45	128	0.10	45	0.05
46–55	411	0.14	114	0.06
56–65	678	0.16	154	0.06
66–75	499	0.19	132	0.08
76 +	447	0.20	112	0.09
Missing	0	0.00	0	0.00
Sex[a]				
Female	76	0.06	30	0.03
Male	2173	0.16	566	0.07
Missing	0	0.00	0	0.00
Race/ethnicity[a]				
AI/AN	16	0.21	6	0.13
Asian	8	0.13	4	0.10
Black	356	0.14	91	0.06
Hispanic	117	0.14	32	0.06
NH/PI	10	0.10	2	0.03
Unknown	116	0.15	25	0.05
White	1227	0.13	337	0.06
Missing	399	0.45	99	0.18

AI/AN American Indian or Alaska Native, *NH/PI* Native Hawaiian and Other Pacific Islander, *$p < 0.0001$ among age categories, sex, and race/ethnicity

4 Discussion

Using 15 years of VHA EHR data and international DILI liver chemistry thresholds, we identified more than one million unique patients exposed to AMOX/CLAV and 2249 unexplained acute liver injury events. The incidence of unexplained acute liver injury was highest among inpatients with pre-existing liver conditions and lowest among Liver Healthy outpatients. Older age, male sex, and American Indian or Alaska Native were associated with a higher incidence of unexplained acute liver injury following AMOX/CLAV exposure. In this predominantly older male population in which female subjects are 8% of the overall population and 3.4% (76 cases) of unexplained acute liver injury, cholestatic injury was most frequently observed. Over age 35 years, the incidence of acute cholestatic liver injury steadily increased while the incidence of acute hepatocellular liver injury gradually declined with age. Among hepatocellular injury cases, 14.2% were classified as serious hepatocellular injury, with an overall incidence of 0.003%. Although the incidence of acute hepatocellular liver injury declined with age, the likelihood of serious cases among hepatocellular injury cases was four-fold higher in patients over age 45 years than those younger. During a 12-month follow-up, unexplained acute liver injury was associated with increased overall mortality versus cases without evident acute liver injury after adjusting for other factors.

Our framework identified the overall incidence of unexplained acute liver injury as 0.156%. The incidence of unexplained acute liver injury increased tenfold from 0.067%

Table 3 Adjusted OR of unexplained acute liver injury following amoxicillin/clavulanate exposure by age group, sex, and race/ethnicity

	Total population		Liver healthy outpatients	
	Adjusted OR with 95% CI	*P* value	Adjusted OR with 95% CI	*P* value
Age categories, years				
18–25	1.52 [0.93–2.50]	0.0980	2.15 [1.11–4.15]	0.0232
26–35	Reference		Reference	
36–45	1.05 [0.77–1.42]	0.7788	1.28 [0.78–2.12]	0.3307
46–55	1.19 [0.91–1.56]	0.2107	1.53 [0.98–2.39]	0.0629
56–65	1.34 [1.03–1.74]	0.0310	1.41 [0.91–2.18]	0.1265
66–75	1.52 [1.16–2.00]	0.0025	1.76 [1.13–2.76]	0.0130
76 +	1.33 [1.01–1.75]	0.0439	1.70 [1.07–2.70]	0.0253
Sex				
Female	0.65 [0.51, 0.83]	0.0006	0.54 [0.36, 0.81]	0.0031
Male	Reference		Reference	
Race/ethnicity				
AI/AN	1.76 [1.10–2.80]	0.0181	2.34 [1.05–5.26]	0.0389
Asian	1.12 [0.56–2.25]	0.7465	1.76 [0.66–4.73]	0.2605
Black	1.10 [0.98–1.24]	0.1099	1.11 [0.88–1.40]	0.3942
Hispanic	1.05 [0.87–1.26]	0.6351	1.11 [0.78–1.60]	0.5587
NH/PI	0.83 [0.44–1.54]	0.5492	0.54 [0.13–2.16]	0.3815
Unknown	1.10 [0.91–1.32]	0.3489	0.95 [0.64–1.41]	0.8061
White	Reference		Reference	
Existing liver conditions				
No	Reference		N/A not applicable	N/A not applicable
Yes	2.84 [2.58–3.13]	< 0.0001		
Patient status				
Outpatients	Reference		N/A not applicable	N/A not applicable
Inpatients	3.61 [3.28–3.98]	< 0.0001		

Multiple logistic regression models were performed, excluding cases with missing information on age, sex, or race/ethnicity, resulting in the total population ($N = 1{,}355{,}606$) and the Liver Healthy Outpatient population ($N = 839{,}773$). *P* values were from Wald tests

AI/AN American Indian or Alaska Native, *CI* confidence interval, *N/A* , *NH/PI* Native Hawaiian and Other Pacific Islander, *OR* odds ratio

in Liver Healthy outpatients to 0.719% in inpatients with existing liver conditions, depending on the subpopulation. Among inpatients, the DILI incidence (due to any drug) of 0.14–1.4% [17, 18] is much higher than that estimated in the general population of 0.014–0.019% [1, 2]. As methods differed by study, we cannot directly compare these estimates. However, using a standardized method, our analysis showed that the incidence of unexplained acute liver injury following AMOX/CLAV exposure was three-fold higher among inpatients versus outpatients after adjusting for other factors, which suggests that DILI incidence may be higher among patients with other acute illness. Of note, prophylactic anti-coagulation therapy with heparin among patients in critical care is a standard practice. At VHA, among eligible patients (without contraindications) at admission who were at an increased risk of venous thromboembolism (~ 20%), about 63% of patients would have received heparin during acute care (~ 12.6%) [19, 20]. Thus, a small fraction of acute liver injury (up to 3%) may be explained by significant liver enzyme elevation caused by heparin administration [21]. Our study also showed that both outpatients and inpatients with existing liver diseases showed a higher risk of unexplained acute liver injury following AMOX/CLAV exposure. No robust data exist to assess the risk of developing DILI in patients with existing liver disease. The impact of chronic liver disease on DILI risk may differ, depending on

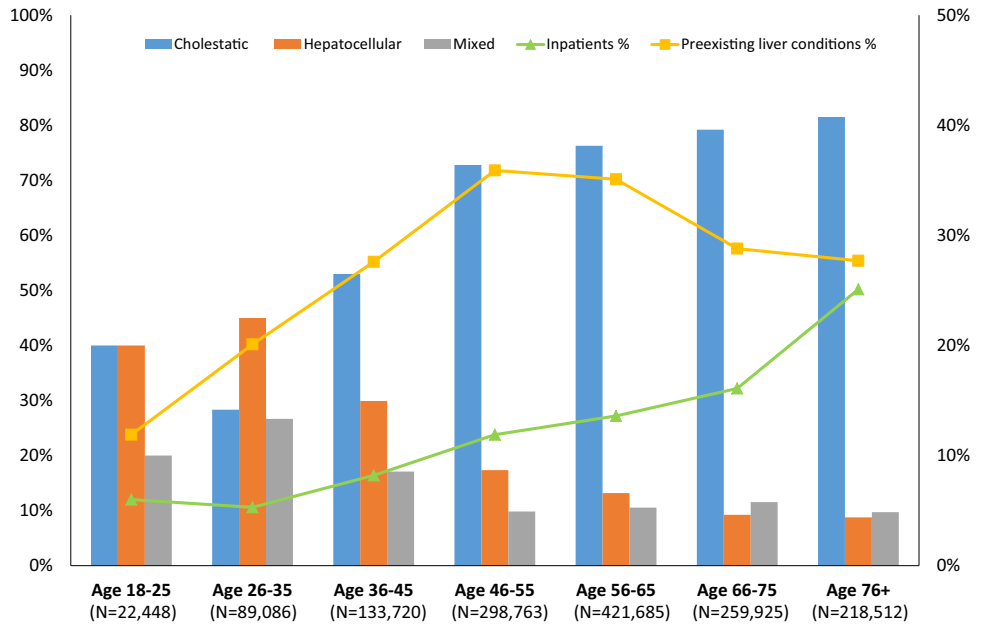

Fig. 3 Proportions of drug-induced liver injury types to total numbers of drug-induced liver injury cases in different age categories along with proportions of inpatients and subjects with pre-existing liver conditions. The figure shows proportions of different drug-induced liver injury types (cholestatic, hepatocellular, and mixed injury) in different age categories (left vertical axis) along with proportions of inpatients and subjects with pre-existing liver conditions to numbers of subjects in each age category (right vertical axis). This study population is predominantly male, of which female subjects are only 8% of the population, with 3.4% of unexplained acute liver injury cases

Table 4 Acute liver injury phenotype by subpopulations

	Total population	Outpatients, liver healthy	Outpatients, existing liver conditions	Inpatients, liver healthy	Inpatients, existing liver conditions
Number of cases	2126	553	607	255	711
Cholestatic injury	74.4%	64.0%	74.0%	70.6%	84.1%
Hepatocellular injury	14.3%	19.2%	14.5%	16.1%	9.6%
Mixed injury	11.4%	16.8%	11.5%	13.3%	6.3%
Isolated ALP elevation	13.8%	12.1%	13.3%	15.7%	14.8%

Unclassified cases ($N = 123$) were excluded from the analysis, $p < 0.0001$ for injury types by subpopulations

ALP alkaline phosphatase

the disease stage, injury types, and existing disease conditions. Further analysis of this research question is needed. DILI registry studies report an older male predominance of AMOX/CLAV-DILI, implying that older age and male sex could be potential risk factors of AMOX/CLAV hepatotoxicity [22, 23]. This exposure-based analysis provides additional evidence to support this data, demonstrating an independent contribution of older age and male sex to the risk of unexplained acute liver injury following AMOX/CLAV exposure. At the VHA, the distribution of male and female subjects differ by age. As female subjects are generally younger than the male patients, our estimates for sex differences were computed after adjusting for age and the stratification by pre-existing liver disease and exposure status (inpatients vs outpatients); the estimates may have been influenced by bias inherent to this specific population. Our incidence exceeds the 0.043% incidence of AMOX/CLAV-DILI reported in the Icelandic population-based study [1] and 0.033% in a Kaiser study [11]. The incidence of DILI depends on the composition of the study population. Our study population comprises 92% men with mean age of 59 years. Given the increased risk of unexplained acute liver injury in older male subjects, the predominantly male population might explain the higher incidence in our study. Of note, the frequency of available liver enzyme measurements during the high-risk period varied 30–40% by age, sex, and

Table 5 Overall mortality for 0–6 months, 7–12 months, and 13–24 months in subjects with unexplained acute liver injury following amoxicillin/clavulanate exposure versus controls

	Total ($N = 1,444,452$)a		Outpatients				Inpatients			
			Liver healthy ($N = 894,708$)		Pre-existing liver conditions ($N = 343,437$)		Liver healthy ($N = 101,850$)		Pre-existing liver conditions ($N = 104,457$)	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
0–6 Month mortality		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$
Unexplained acute liver injury	687	30.56%	93	15.60%	178	27.86%	86	32.82%	330	43.94%
Other acute liver injury	1851	43.82%	267	30.41%	501	43.95%	182	42.03%	901	50.82%
Cases without evident acute liver injury	60,621	4.22%	16,682	1.87%	11,962	3.50%	12,961	12.81%	19,016	18.66%
7–12 Month mortality		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p = 0.6188$		$p = 0.0003$
Unexplained acute liver injury	190	8.45%	35	5.87%	53	8.29%	18	6.87%	84	11.19%
Other acute liver injury	309	7.32%	48	5.47%	99	8.68%	30	6.93%	132	7.45%
Cases without evident acute liver injury	38,776	2.70%	15,361	1.72%	9,881	2.89%	6089	6.02%	7445	7.30%
13–24 Month mortality		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p = 0.5392$		$p = 0.0005$
Unexplained acute liver injury	175	7.78%	46	7.72%	46	7.20%	21	8.02%	62	8.26%
Other acute liver injury	290	6.87%	48	5.47%	92	8.07%	30	6.93%	120	6.77%
Cases without evident acute liver injury	61,928	4.31%	28,109	3.15%	15,758	4.61%	8481	8.38%	9580	9.40%

[a]Seven hundred and nineteen cases (0.4% of the total death cases) were excluded from the analysis (see Sect. 2)

inpatient status, which may have influenced the detection of asymptomatic liver enzyme elevations. While detected risk disparities exceeded this range of variation, the results should be interpreted cautiously.

The incidence of cholestatic injury steadily increased with age, while the incidence of hepatocellular injury gradually declined. This finding is consistent with the age-related differences in liver injury type observed in well-characterized DILI registries [24, 25]. Interestingly, we observed a U-shaped association between age and the frequency of cholestatic injury, with the lowest incidence of cholestatic injury at age 25–35 years. This is also consistent with published DILI reports [26]. While intriguing, whether adolescents/young adults show a distinct response to injury is unclear at this point, pending future investigation. The incidence of serious hepatocellular injury (i.e., unexplained hepatocellular injury accompanied by elevated serum bilirubin) was 0.003% in overall population, which is 30-fold higher than the reported incidence of drug-induced acute liver failure among subjects without chronic liver injury (0.0001% or 1 in 1,000,000 person-years) [3]. Our study also revealed that the proportion of serious hepatocellular injury cases (i.e., Hy's law cases in DILI) increased with age, while the incidence of hepatocellular injury declined. This may be explained by an aging-related decrease in liver regeneration [27], as seen in acute hepatitis A; hepatitis A hospitalization rates steadily increase in those over age 40 years [28]. A recent study in a large DILI registry also reported worse outcomes among older patients with hepatocellular injury [29]. These findings suggest that older age is a risk determinant of severe outcomes in acute hepatocellular injury, regardless of the etiology. The Spanish DILI registry recently demonstrated an equivalent prevalence of Hy's law cases across age groups [25]; this finding is likely explained by the generally lower prevalence of hepatocellular injury in the older population. In our analysis, older age groups with hepatocellular injury were associated with a higher prevalence of Hy's law cases (data not shown). Our study also showed that 13% of the acute liver injury cases presented with isolated ALP elevation. Whether this isolated ALP elevation reflects a later phase of injury or incomplete exclusion of other causes cannot be determined.

Higher mortality was observed in those with unexplained acute liver injury than in those without during a 2-year follow-up period. After adjusting for other factors, unexplained acute liver injury was associated with a five-fold increased risk of overall mortality within 6 months, a 50% increased risk during 7–12 months, and no association with overall mortality after 12 months. Pre-existing comorbidities might have contributed to this increased mortality risk. This requires further elucidation and is beyond the scope of this study.

Our study has several strengths. The 9.8 million patients receiving integrated VHA care (https://www.va.gov/vetdata/docs/Quickfacts/VA_Utilization_Profile_2017.pdf) provided one of the largest exposure cohorts of a single drug. We included cases with unexplained acute liver injury and two controls: without evident injury (i.e., normal controls) and with acute liver injury caused by other etiologies (i.e., disease controls) in the outcome analysis. Further, our study used a higher threshold (e.g., ALT 5 × ULN) to increase specificity [13]. The framework we developed is distinct from the conventional epidemiological DILI case finding approach [1, 2] as ours does not count physician's recognition or DILI diagnosis. Real-time monitoring followed by a hepatologist review identified 12 times more DILI cases compared with a standard care strategy (i.e., referral), implicating a significant number of patients with DILI would be missed through a referral-based approach [30]. Thus, proactive case identification through real-time monitoring [30] or EHR data [31] would complement our current understanding of real-world DILI. A potential racial disparity in the severity was implicated based on the findings of all-cause DILI within the prospective US Drug-Induced Liver Injury Network registry, although no differences in the severity was observed in a small cohort of AMOX/CLAV-DILI [32]. Having tested/untested control subjects, our study did not reveal a significant difference between White and Black in the incidence or 6-month mortality (data not shown). Acute liver injury due to biliary disease, ischemic hepatitis, and sepsis occurring during drug exposure is frequently erroneously classified as DILI by non-specialists [33] and is also reported in published DILI cases [34]. Congruent with these reports, we found that non-drug acute liver injury affected two of three following drug exposure, while one in three did not have any competing etiologies around the time of event (i.e., unexplained acute liver injury associated with AMOX/CLAV). Further, among reported DILI cases, the majority of unrelated cases lack a temporal relationship between events and drug exposures [33]. A key strength of our framework to identify drug-associated acute liver injury following exposures is its exclusion of these non-drug causes based on the time of the diagnosis, specific combinations of diagnosis, laboratory data, and injury patterns while taking account of baseline conditions to provide a broad population-based view of AMOX/CLAV-associated liver injury.

Our EHR study has several limitations. As our predominantly older White male veteran population may not have been sufficiently powered to address sex and racial/ethnic disparities, our findings should be applied with caution to deduce AMOX/CLAV-DILI in other patient populations. Our study is also limited by its reliance on laboratory testing to identify acute liver injury as laboratory testing frequency may have influenced its incidence. We considered patients with no available liver enzyme data during 3 years

prior to AMOX/CLAV exposure as having no existing liver disease while patients with no liver enzyme measures during the high-risk period as untested controls. These assumptions may have caused some misclassification as asymptomatic patients could have elevated liver enzymes. However, this limitation would apply to most clinical DILI studies, including population-based and prospective registry studies, unless liver enzymes are periodically monitored after drug exposure; patients who do not seek medical attention are not identified. Liver enzyme data availability is influenced by clinical testing needs and physician preference. Thus, restricting the study cohort to only subjects with available liver enzyme data would significantly skew the population. Regardless, our findings should be interpreted in the context of the study design and assumptions. The VA population is associated with a higher rate of polypharmacy because of a high prevalence of chronic disease. Thus, the defined "unexplained acute liver injury following amoxicillin/clavulanate exposure" may contain some cases related to drug–drug interaction and/or other concomitant medications. Further, as demonstrated in Table 2a of the ESM, laboratory availability varied by subpopulation (27–54%) and demographics (19–35%) during the high-risk period. Thus, the risk variations observed in this study may be partly explained by the variations in laboratory data availability. Combining diagnostic codes and laboratory data with liver injury phenotypes at the time of the event, our algorithms comprehensively assessed and excluded key competing causes of acute liver injury. Despite the rigorous approach, this study poses a potentially substantial limitation; the exclusion of competing etiologies may be incomplete because of the lack of laboratory data, diagnostic work-ups, and/or under-coding diagnoses. For instance, the frequency of acute hepatitis E diagnosis in the study cohort was 0.015% during the entire study period and none around the time of events, which is substantially lower than the frequency reported in the US general population [35]. Furthermore, a 10-year Icelandic population-based analysis of DILI associated with five oral anticoagulation treatments identified liver enzyme elevations in 14.5% and completed manual chart review of temporally related cases [36]. Among these, 82% of cases had non-drug etiologies, 17% had insufficient information, and only three DILI cases related to rivaroxaban were identified in the cohort [36]. Another study of pembrolizumab-associated liver enzyme elevations performed a manual chart review and reported that most liver enzyme elevations were related to pre-existing hepatic metastases while DILI affected one third of the cases [37]. These two studies using a manual chart review for case adjudication reported non-drug etiologies in 71–82% of the liver injury cases in comparison with 65% in the current study. Although the patient populations differ, considerable non-DILI cases may be contained among those with unexplained acute liver injury following AMOX/CLAV in this study. There are different ways to define drug-associated acute liver injury [13, 38, 39], which should be selected based on the study's purpose. We utilized an ALT 5 × ULN and ALP 2 × ULN threshold (or 5 × and 2 × representative baseline value, respectively, whichever is higher) to identify clinically important acute liver injury. In patients with advanced liver disease or cirrhosis, acute liver injury can present as none to a mild liver enzyme elevation along with bilirubin elevation or other signs of decompensation. Such events require capture using a different algorithm, which is beyond the scope of this initial report. Additionally, acute liver injury can be superimposed on systemic inflammation, septic shock, post-liver transplantation, hematopoietic malignancies, and many other competing etiologies. In such complex cases, discerning additional acute insults from existing disease is clinically challenging, and sometimes, impossible even with thorough clinical assessment. As our approach is not designed to study such complex cases, most were excluded.

5 Conclusions

In summary, we identified AMOX/CLAV-associated liver injury after excluding non-drug causes to provide a broad population-based view in a large national EHR dataset at the VHA. We found a higher incidence of unexplained acute liver injury in older subjects, male subjects, and American Indians/Alaska Natives. Inpatients and those with underlying liver conditions exhibited about a three-fold higher risk of unexplained acute liver injury. Overall, cholestatic injury predominated in this population and increased with age, inpatient status, and underlying liver conditions. The incidence of hepatocellular injury declined with age, yet once individuals over age 45 years develop acute hepatocellular injury, they have a higher risk of serious injury associated a two-fold increased mortality. Overall, we observed a higher 12-month mortality among those with unexplained acute liver injury than in those without evident acute liver injury. Our large exposure-based study provides a broad view of drug-associated acute liver injury, which cannot otherwise be easily assessed using conventional analyses. Upon validating this framework, our methodology can be applied to other patient populations to aid in depicting drug-associated acute liver injury in the general patient population while complementing current DILI research and drug safety approaches.

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Declarations

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Conflicts of interest/competing interests The authors have no conflicts of interest that are directly relevant to the content of this study.

Ethics approval The study was approved by the Institutional Review Board and the Research and Development Committee of Central Arkansas Veterans Healthcare System (FWA: 00002261) and Durham Veterans Affairs Health Care System (FWA:00001600).

Consent to participate The Institutional Review Boards at the Central Arkansas Veterans Healthcare System and Durham Veterans Affairs Health Care System determined that this study met exempt human subjects research criteria Category 4 (i.e., use of existing data) and an informed consent form is not applicable.

Consent for publication Not applicable.

Availability of data and material The US Department of Veterans Affairs (VA) places legal restrictions on access to veteran's healthcare data, which includes both identifying data and sensitive patient information. The analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement, per VA privacy and data security policies and regulatory constraints. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center at vog.av@CeRIV.

Code availability Coding strategies used in this study are available upon request.

Authors' contributions Conceptualization: AS, CMH, HT, FP, GPA, MIL, RJA, WT; data curation: JW, RGH; analysis: AS, JW; coding/code validation: JF, MS; funding acquisition: AS; methodology: AS, CMH, HT, JW, RGH, FP; project administration: AS, CMH; supervision: AS; validation: AS, MS; writing original draft: AS; writing, review and editing: AS, HT, JW, RGH, JF, MS, FP, GPA, MIL, RJA, WT, CMH. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The corresponding author further affirms that the article is an honest, accurate, and transparent account of the study. All the authors and acknowledged individuals in the paper read and approved the final version.

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