Mapping the incidence of drug-induced liver injury worldwide: a systematic review and meta-analysis

Min Li
Capital Medical University Affiliated Beijing Friendship Hospital
Yu Wang
Capital Medical University Affiliated Beijing Friendship Hospital
Tingting Lv
Capital Medical University Affiliated Beijing Friendship Hospital
Jimin Liu
McMaster University Department of Pathology and Molecular Medicine
Yuanyuan Kong
Capital Medical University Affiliated Beijing Friendship Hospital
Jidong Jia
Capital Medical University Affiliated Beijing Friendship Hospital
Xinyan Zhao (zhao_xinyan@ccmu.edu.cn)
Capital Medical University Affiliated Beijing Friendship Hospital https://orcid.org/0000-0002-8016-4368

Research Article

Keywords: drug toxicity, epidemiology, global, disease burden, DILI, hepatotoxicity, gender, age, region, liver injury

Posted Date: April 26th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1557481/v1

Abstract

Background: Drug-induced liver injury (DILI), an increasing etiology of liver dysfunction in hepatology, its incidence has been variably reported worldwide. To better understand the disease burden hence make appropriate preventive and treatment strategies, we conducted this meta-analysis from global perspective.

Methods: PubMed, EMBASE, Web of Science and Cochrane Library were searched for studies on the incidence of DILI published from inception to Aug 1, 2021. According to the predefined criteria, only population-based studies were included. Incidence was calculated as cases per 100,000 person-years with its confidence interval (CI) using random effects model.

Results: A total of 31 studies were included. The overall incidence of DILI was 4.94 (95%CI: 4.05-5.83) per 100,000 person-years. Time-based cumulative meta-analysis suggested that the incidence of DILI had increased over time since 2010. It varied by regions: Asia had the highest incidence, at 17.82 (95%CI: 6.26-29.38) per 100,000 person-years, while America had the lowest, at 1.72 (95%CI: 0.48-2.95) per 100,000 person-years. All studies had a consistent result of higher incidence of DILI in elders; but comparable incidence between male and female (3.42 vs 4.64 per 100,000 person-years). As for the specific implicated drug(s), the incidence of statins induced liver injury was 11.30 (95%CI: 6.48-19.69) per 100,000 person-years, while the incidence among patients using antifungal drugs, antidepressants, paracetamol, antidiabetic, anti-tuberculosis, nonsteroidal anti-inflammatory drugs, anti-thyroid drugs and iron chelator ranged from 0.16 to 180.97 per 100,000 person-years.

Conclusions: The incidence of DILI has been increasing since 2010 worldwide, with the highest incidence in Asia. Understanding the epidemiological characteristics of DILI aids in making specific strategies to deal with the emerging health problems.

Introduction

Drug-induced liver injury (DILI) is emerging as one of the most challenging liver diseases during daily practice. It is associated with high disease burden worldwide.[1] Actually, DILI is the main reason for the withdrawal of many drugs after their marketing.[2] Until now, there are only scattered reports regarding the epidemiology of DILI, but with noticeable variations. In the West, the incidence of DILI has been estimated to be 1.0 in 100,000 to 20.0 in 100,000 person-years in general population.[3] In the East, the incidence of DILI has been estimated to be 12.0 in 100,000 to 23.8 in 100,000 person-years.[4] This variation may be partly due to differences in genetic background, culprit drugs and lack of specific diagnostic biomarkers.

The most common insulting drugs for DILI were antibiotics, including anti-tuberculosis (anti-TB) drugs, Herbal and Dietary Supplement (HDS) and immune checkpoint inhibitors, etc.[5,6] DILI occurred in 5%-33% of patients with TB and affected 9%-30% of patients with human immunodeficiency virus (HIV) infection, who received either anti-TB or antiretroviral therapy.[7,8] Additionally, statins being the most widely prescribed medication could result in rare but severe idiosyncratic liver injury. A European study reported that the incidence rate of DILI is 16 per 100,000 person-years after initiation of statins,[9] and the data from Taiwan described an incidence rate of 768 per 100,000 person-years for patients with chronic liver disease who took statins.[10]

Moreover, DILI accounts for up to 60% acute liver failure and 5–10% mortality, which highlighting the importance to better understand this disease, given that DILI are preventable.[11–13] Thus, to better understand the disease burden hence make appropriate preventive and treatment strategies, we conducted this systematic review and meta-analysis. Our aims were to pool the worldwide incidence of DILI together, characterize the global and regional differences, and highlight the common insulting drugs.

Method

This meta-analysis was reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement, and was registered with PROSPERO (CRD42021272634).

Data sources and search strategy

PubMed, EMBASE, Web of Science and Cochrane Library were searched from inception to Aug 1, 2021 for studies reporting the incidence of DILI, using the following keywords: drug-induced liver injury, drug toxicity, incidence, prevalence, epidemiology and frequency (Supplementary file 1 for full details about the searching strategy and result). In addition, we checked the websites of the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asian-Pacific Association for the study of the Liver (APASL) and International Association for the study of the Liver (IASL) for annual conference abstracts published up to Aug 1, 2021, as well as the reference lists of all relevant articles to identify additional studies. No language restriction was applied.

Study selection

Observational studies were eligible for inclusion if they met the following criteria: 1) Longitudinal or registry studies were conducted in a general population or selected population (eg, patients treated with statins, oral antifungal drugs or paracetamol, etc.). 2) Incidence rate of DILI was reported or calculable. 3) Patients with DILI was identified by the RUCAM score, ICD code, or clinical, laboratory, and pathological profiles with exclusion of other liver diseases. For studies reporting on similar populations or overlapped enrollment period, we used the most recent study or the study with the greater amount of person-year. Reviews, editorials, letters, guidelines and protocols as well as articles only focused on basic science research were excluded.

Data extraction and quality assessment

Two investigators (M.L. and Y.W.) independently assessed the eligibility of studies and extracted data in duplicate. Any disagreements on study inclusion or interpretation of data were resolved by consulting senior investigator (XY.Z.). The extracted data included study information (first author, region of study, study design, study period), patients' characteristics (age and gender), details of incidence rate (number of DILI cases, number of total population, annual incidence with 95% confidence interval (CI), diagnostic criteria and source of cases. Study period was defined as the year of patients' enrollment.

Two investigators assessed study quality according to seven previously published criteria, including defined catchment, accurate denominator, population-based case finding, standardized disease diagnosis, blinding to demographic factors, inclusion criteria, and leakage study.[14] This quality rating system scored from 0 (highest degree of bias) to 7 (lowest degree of bias).

Statistical analysis

Characteristics of enrolled studies were described. Heterogeneity among studies was quantified by I^2 test. An I^2 statistic above 50% was considered substantial heterogeneity. Random-effect models were used to calculate the pooled incidence rates as well as their 95% CIs.

Firstly, we estimated the overall incidence rate of DILI in the general population. Studies reporting on selected population were analyzed separately (eg, patients treated with statins). Then, a subgroup analysis was conducted on the basis of clinical considerations: regions (Asia vs. Europe vs. America), median time of patients' enrollment (before 2000 vs. 2000-2010 vs. after 2010), source of patients' data (Insurance/administrative databases vs. hospital-based case series vs. physicians' report), study quality (≥5 score vs. <5 score), and study design (prospective vs. retrospective). Additionally, a meta-regression was performed to explore the heterogeneity caused by regions, median time of patients' enrollment, source of patients' data, study quality and study design. Cumulative meta-analyses were performed to decide how estimates changed as subsequent studies were added to the pool.

In sensitivity analyses, we restricted our analysis to studies with causality assessment, studies published after the detection of hepatitis C at year of 1990,[15] as well as excluding the study of Goldberg et al which reported the incidence of drug-induced acute liver failure. Begg's and Egger's test were performed to evaluate publication bias. STATA software version 15.0 (Stata

Corp, College Station, TX, USA) and R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for meta-analysis. P value <0.05 was considered statistically significant.

Result

Study Characteristics

The initial search yielded 3,901 non-duplicated studies. A total of 110 studies were identified as potentially meeting our inclusion criteria and full-text of the studies were reviewed. After reviewing, another 79 studies were further excluded mainly due to lack of extractable or calculable incidence data, or different study population (ie. none general population-based study). Finally, a total of 31 studies were included in this meta-analysis (Figure 1). List of included studies were showed in supplementary file 2.

The characteristics of individual study were summarized in table 1 and supplementary table 1. The quality assessment of each paper included in the study was shown in supplementary table 2. The average score in the quality assessment was 4.8. The major risks of bias existed in “blinding to demographic variables” domain due to blind the person/panel who diagnosed cases to certain demographic characteristics, and “leakage study” domain due to lack of attempting to identify the original cases.

The pooled annual incidence of DILI

The overall incidence of DILI among the general population was 4.94 (95% CI: 4.05-5.83) per 100,000 person-years (14 studies,supplementary file 2 for reference list). There was high heterogeneity among the studies (I^2=99%, P<0.01, Supplementary Figure 1). Figure 2 showed the incidence of DILI of each country with at least one study.

Pooled result of five studies showed the incidence of DILI in terms of hepatocellular, cholestatic and mixed patterns was 1.51 (95%CI: 0.72-2.29), 0.78 (95%CI: 0.37-1.18) and 0.58 (95%CI: 0.21-0.96) per 100,000 person-years, respectively (Supplementary Figure 2).

The DILI incidence varied by regions, as noted in table 2. The incidence was 17.82 (95%CI: 6.26-29.38) per 100,000 person-years (2 studies) in Asia, 3.89 (95%CI: 2.81-4.97) per 100,000 person-years in Europe (7 studies), and 1.72 (95%CI: 0.48-2.95) per 100,000 person-years in America (5 study).

Time-based cumulative meta-analysis showed an overall increase of the incidence of DILI over time (Figure 3). Subgroup analysis showed that the highest incidence among studies whose patients’ enrollment were after 2010 (15.14 per 100,000 person-years, 95%CI: 0.00-30.39) compared to those enrolling patients at 2000-2010 (4.44 per 100,000 person-years, 95%CI: 0.84-8.05), and before 2000 (2.55 per 100,000 person-years, 95%CI: 1.63-3.47).

We found that the DILI incidence varied among the reporting sources. The incidence was 11.78 per 100,000 person-years (95%CI: 1.32-22.24) among studies whose DILI cases were reported by physicians and 9.57 per 100,000 person-years (95%CI: 5.06-14.09) among those whose cases were identified based on hospital case series, compared to 1.61 per 100,000 person-years (95%CI: 0.82-2.41) for studies using insurance/administrative databases. Moreover, the pooled estimates of DILI incidence were higher in studies with prospective design and studies with quality score<5.

Incidence of DILI: Subgroup analysis by age and gender

The DILI incidence by age group was not pooled in this meta-analysis because of the high variability of age groups used. Nonetheless, consistent higher incidence in old age group was observed (Supplementary Figure 3). For example, in the study conducted in Iceland, the incidence of DILI ranged from 8.5 per 100,000 person-years (95% CI: 3.7-16.8) in people aged 15-24 years to 41 per 100,000 person-years (95% CI: 18.7-77.8) in people aged 80-106 years.[16]

Five studies reported the incidence of DILI in male and female separately, but with inconsistent results (Supplementary Figure 3). The pooled results of these studies showed similar incidence of DILI between male (3.42 per 100,000 person-years,

95%CI: 1.83-5.00) and female (4.64 per 100,000 person-years, 95%CI: 2.74-6.55). Heterogeneity was substantial in both female and male sets (I^2=96%, I^2=98%).

Incidence of DILI: By given drug(s)

As to the incidence of drug-specific DILI among the users, we found that the incidence of statins-induced DILI was 11.30 per 100,000 person-years (95% CI: 6.48-19.69, five studies). Notably, rosuvastatin users had a slighter lower incidence of DILI (8.31 per 100,000 person-years, 95% CI: 2.21-31.18) compared with other statins users (12.60 per 100,000 person-years, 95% CI: 7.44-21.34) (Table 3) (supplementary file 2 for reference list).

The incidence of antifungal, antidepressants, paracetamol and antidiabetic drugs induced DILI was 63.46 (95%CI: 33.39-120.57, three studies), 3.83 (95%CI: 0.97-15.03, three studies), 0.16 (95%CI: 0.02-1.08, two studies), and 18.20 (95%CI: 1.51-219.20, two studies) per 100,000 person-years, respectively. Only one study reported the incidence of anti-TB, non-steroidal anti-inflammatory drugs (NSAIDs), anti-thyroid drugs (ATD), and oral iron chelator induced liver injury, respectively.

Meta-regression

Univariate and multivariate meta-regression analysis was conducted to explore the reasons accounting for the high heterogeneity observed in our meta-analysis (Supplementary Table 3). The results showed that region distribution could partly explain this high heterogeneity among the studies (P<0.05).

Sensitivity analysis and publication bias

The pooled estimate was 7.42 per 100,000 person-years (95%CI: 5.52-9.32) for studies with case ascertainment by causality assessment, 5.90 per 100,000 person-years (95%CI: 4.85-6.95) for studies published after the detection of hepatitis C of 1990 year, and 6.02 per 100,000 person-years (95%CI: 4.85-7.18) after removing the study of Goldberg DS et al. The sensitivity analysis showed a slightly increase in the pooled estimates, mainly because most of the studies included in the sensitivity analysis were relatively recent published studies. This was consistent with the temporal trend of DILI incidence over time.

There was no evidence of publication bias as assessed neither by Begg's nor Egger's test for meta-analyses (p=0.32 and p=0.08).

Discussion

We found that the global incidence of DILI among the general population was 4.94 per 100,000 person year, with the highest incidence reported in Asia compared with that in Europe and America. Additionally, the DILI incidence has increased since 2010.

There is marked geographic variation of DILI incidence. In fact, the incidence of DILI was 17.82 per 100,000 person-years in Asia, 3.89 per 100,000 person-years in Europe, and 1.72 per 100,000 person-years in America. Not surprisingly, meta-regression analysis also showed that the high heterogeneity could be partly explained by regions' variability. The reason for the observed difference in DILI incidence between Asia and other regions is unclear but one potential explanation might be related to the usage of HDS. In Asian countries, HDS are the most common causes of DILI (26.81%), while HDS induced DILI currently represent less than 10% of all cause DILI in Western countries.[6,17] In addition, about 20% of DILI cases were attributed to anti-TB drugs.[6] Asian countries have the highest TB burden, which may further contribute to higher risk of DILI development.[18] The cornerstone of TB therapy is at least a 6-month course of isoniazid, rifampicin, pyrazinamide, and ethambutol. All these anti-TB drugs have potential hepatotoxicity and could lead to a higher incidence of DILI (180.97 per 100,000 person-years).[19,20] The potential geographic variation of the incidence of DILI would be informative in more appropriately allocation of the medical resources in order to design sustainable health recommendation and reduce associated costs. However, the incidences of DILI in Asian were only reported from China and Korea, which has limitation of extrapolation to the whole Asian countries. We advocated future studies to be conducted in order to deeply understand the potential high DILI incidence in Asia.

Cumulative meta-analysis showed that the incidence of DILI had been significantly increased since 2010, with the highest incidence from 2010 to 2020 (15.14 per 100,000 person-years). Progress in the consensus-based diagnostic criteria and standardized DILI nomenclature and instruments were made by the global collaborative efforts in 2010.[21] This resulted in better understanding and recognition of DILI worldwide, which might also contribute to the increase in DILI incidence.

We also observed that DILI incidence increased with age. Youths appeared to be less susceptible to DILI than older population. Less frequently use of implicated drugs, lower doses, or inherent differences in DILI susceptibility may contribute to the observed lower incidence of DILI in young population. Whether gender is a risk factor for susceptibility to DILI remains controversial. Among five studies containing gender-specific DILI incidence, female individuals have been reported to have higher,[16,22] comparable,[23-24] or even lower [25] incidence of DILI. It is worth to note among these gender-containing studies that female patients accounted for more than or nearly half of the cases.

In addition to the incidence of all cause DILI, we also estimated the incidence of specific drug(s) induced DILI. The statins are among the most common implicated drugs, which is a preventive therapy for cardiovascular disease. Results showed that rosuvastatin may have a slightly lower incidence of DILI compared with non-rosuvastatin statins users. Our data also demonstrated that the incidence of DILI in patients using antifungal, antidepressants, paracetamol, antidiabetic, anti-TB, NSAIDs, antithyroid ATD and iron chelator ranged from 0.16 to 180.97 per 100,000 person-years. But no study incidence of HDS induced liver injury at population level is lacking and further study is indicated. The risk of developing DILI varied greatly among drug users due to pharmacokinetic and immunological actors.

An important strength of our study is that it comprises, to our knowledge, the most comprehensive data geographically and chronologically on DILI incidence, which is derived from population-based studies to date. Also, we chose studies based on the incidence of DILI in general population which could better represent actual incidence of DILI in general population. Meanwhile, our study had several limitations. Firstly, patients exposure to other certain drugs (eg. antiretroviral agents, HDS) are believed to be at increased risk of drug hepatotoxicity. However, these studies were not included in our study due to the inclusion criteria of selecting studies conducted not base on the general population. Secondly, only ten countries in Europe (UK, Iceland, Spain, Sweden, Denmark and France), America (USA and Canada) and Asia (China and South Korea) were included in our study, no data on the incidence of DILI from Africa, and Oceania. Therefore, the incidence of DILI in our study might not truly reflect the DILI incidence in these continents. Thirdly, the high heterogeneity in the pooled results was not fully explained. Finally, some studies only included hospitalized DILI cases, this may result in an underestimation of the incidence of DILI.

Conclusion

This meta-analysis has pooled the incidence of all-cause DILI and demonstrated the increasing trend of DILI incidence in population-based studies. This global overview might serve as a reference for clinicians during their clinical practice. Certain factors, including age, region, source of patients, and study design et al, may be associated with different incidence of DILI. Understanding these differences may help prevent hence reduce the incidence of DILI.

Declarations

Data Availability: The original contributions presented in the study are included in the article/Supplementary Material. Additional data are available on request from the corresponding author.

Animal Research (Ethics): Not applicable.

Consent to Participate (Ethics): This study does not contain any studies with human participants or animals performed by any of the authors.

Consent to Publish (Ethics): Not applicable.

Clinical Trials Registration: Not applicable.

Author Contribution:

Study concept and design: Zhao XY.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Li M, Wang Y.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Li M.

Study supervision: Zhao XY.

Conflict of Interest: There are no conflicts of interest.

Funding: This work was supported by grants from the National Natural Science Foundation of China-Youth Science Fund (No. 82103902).

References

1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019 Jan;70:151–71.
2. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 2016;14:10.
3. Björnsson ES. Epidemiology and risk factors for idiosyncratic drug-induced liver injury. Semin Liver Dis. 2014;34:115–22.
4. Shen T, Liu Y, Shang J, Xie Q, Li J, Yan M, Xu J, Niu J, Liu J, Watkins PB, Aithal GP, Andrade RJ, Dou X, Yao L, Lv F, Wang Q, Li Y, Zhou X, Zhang Y, Zong P, Wan B, Zou Z, Yang D, Nie Y, Li D, Wang Y, Han X, Zhuang H, Mao Y, Chen C. Incidence and Etiology of Drug-Induced Liver Injury in Mainland China. Gastroenterology. 2019;156:2230–41.e11.
5. Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, Devarbhavi H, Merz M, Lucena MI, Kaplowitz N, Aithal GP. Drug-induced liver injury. Nat Rev Dis Primers. 2019 Aug;22:5:58.
6. Miller ED, Abu-Sbeih H, Styskel B, Nogueras Gonzalez GM, Blechacz B, Naing A, Chalasani N. Clinical Characteristics and Adverse Impact of Hepatotoxicity due to Immune Checkpoint Inhibitors. Am J Gastroenterol. 2020 Feb;115:251–61.
7. Kargar M, Mansouri A, Hadjibabaie M, Javadi M, Radfar M, Gholami K. Anti-tuberculosis drugs adverse reactions: a review of the Iranian literature. Expert Opin Drug Saf. 2014;13:875–91.
8. Yimer G, Ueda N, Habtewold A, Amogne W, Suda A, Riedel KD, Burhenne J, Aderaye G, Lindquist L, Makonnen E, Aklillu E. Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. PLoS ONE. 2011;6:e27810.
9. Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. J Hepatol. 2012;56:374–80.
10. Chang CH, Chang YC, Lee YC, Liu YC, Chuang LM, Lin JW. Severe hepatic injury associated with different statins in patients with chronic liver disease: a nationwide population-based cohort study. J Gastroenterol Hepatol. 2015;30:155–62.
11. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM, U.S. Acute Liver Failure Study Group. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947–54.
12. Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003;349:474–85.
13. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76.
14. Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, Murray RM, Jones PB. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. PLoS ONE. 2012;7:e31660.

15. Weiner AJ, Truett MA, Rosenblatt J, Han J, Quan S, Polito AJ, Kuo G, Choo QL, Houghton M, Agius C, et al. HCV testing in low-risk population. Lancet. 1990;336:695.
16. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25.
17. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transpl. 2004;10:1018–23.
18. World Health Organization. Global tuberculosis report 2016. Geneva, Switzerland: WHO Report; 2016. Available at: https://www.aidsdatahub.org/global-tuberculosis-report-2016-who-2016.
19. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. Lancet. 2003;362:887–99.
20. Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, Guarner C, Forné M, Solà R, Castellote J, Rigau J, Laporte JR. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther. 2007;25:1401–9.
21. Fontana RJ, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, Hoofnagle JH. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology. 2010;52:730–42.
22. Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, Lenoir C, Lemoine A, Hillon P. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology. 2002;36:451–5.
23. Ibáñez L, Pérez E, Vidal X, Laporte JR. Grup d'Estudi Multicènteric d'Hepatotoxicitat Aguda de Barcelona (GEMHAB). Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol. 2002;37:592–600.
24. Almdal TP, Sørensen TI. Incidence of parenchymal liver diseases in Denmark, 1981 to 1985: analysis of hospitalization registry data. The Danish Association for the Study of the Liver. Hepatology. 1991;13:650-5.
25. Duh MS, Walker AM, Kronlund KH Jr. Descriptive epidemiology of acute liver enzyme abnormalities in the general population of central Massachusetts. Pharmacoepidemiol Drug Saf. 1999;8:275–83.

Tables

Table 1. Characteristics of included studies reporting incidence of DILI

First Author, year	Country	Study design, Study period	No. of DILI cases	Total population	Age	Male proportion	Diagnostic criteria	Source of Patients
Shen T, 2019	China	Retrospective 2012-2014	13691	\	40-59*	50.83%	Clinical diagnosis	Hospital-based case series
Vega M, 2017	USA	Prospective 2014	20	729779	\	\	Clinical diagnosis	Physicians report
Goldberg DS, 2015	USA	Retrospective 2004-2010	27	4281530	47(32-57)	33.33%	ICD/Clinical diagnosis	Insurance/ administrative databases
Björnsson ES, 2013	Iceland	Prospective 2010-2012	96	251860	55(38-69)	44%	Clinical diagnosis	Physicians report
Suk KT, 2012	South Korea	Prospective 2005-2007	371	\	49(16-79)**	36.70%	Clinical diagnosis	Hospital-based case series
De Valle MB, 2006	Sweden	Retrospective 1995–2005	77	300000	58(41-68)	44%	Clinical diagnosis	Hospital-based case series
Andrade RJ, 2005	Spain	Prospective 1998-2003	461	\	53	51%	Clinical diagnosis	Insurance/ administrative databases
de Abajo FJ, 2004	UK	Retrospective 1994-1999	128	1636792	\	\	ICD/Clinical diagnosis	Insurance/ administrative databases
Sgro C, 2002	France	Prospective 1997-2000	34	81301	56(40-70)	35.3%	Clinical diagnosis	Physicians report
Ibáñez L, 2002	Spain	Prospective 1993-1998	107	2700000	62(17-91)**	49.5%	Clinical diagnosis	Insurance/ administrative databases
Duh MS, 1999	USA	Retrospective 1992–1993	50	124511	53.2±19.4	53.2%	ICD/Clinical diagnosis	Insurance/ administrative databases
Byron D, 1996	Canada	Retrospective 1987-1994	67	650000	\	\	\	Hospital-based case series
Almdal TP, 1991	Denmark	Retrospective 1981-1985	512	\	\	\	Diagnoses terms	Insurance/ administrative databases
Beard K, 1986	USA	Retrospective 1977-1981	12	280000	53(35-68.5)	8.33%	Diagnoses terms	Insurance/ administrative databases

DILI: drug-induced liver injury.

*Dominated age range; ** Data was presented as median with ranges.

Table 2. Subgroup analysis of the incidence of DILI

	No. of Studies	No. of DILI	Person-years	Incidence/100,000 person-years	I^2
Overall	14	15653	146794623	4.94 (4.05-5.83)	99%
Regions					
Asia	2	14062	60616877	17.82 (6.26-29.38)	98%
Europe	7	1415	62967372	3.89 (2.81-4.97)	98%
America	5	176	23210374	1.72 (0.48-2.95)	96%
Time of patients' enrollment					
Before 2000	7	910	51336843	2.55 (1.63-3.47)	99%
2000-2010	4	936	36689211	4.44 (0.84-8.05)	99%
After 2010	3	13807	58768569	15.14 (0.00-30.39)	99%
Source of patients					
Insurance/administrative databases	7	1297	77116957	1.61 (0.82-2.41)	99%
Hospital-based case series	4	14206	68189703	9.57 (5.06-14.09)	99%
Physicians report	3	150	1487963	11.78 (1.32-22.24)	98%
Quality assessment score					
≥5	9	551	42873214	2.90 (2.08-3.72)	98%
<5	5	15102	103921409	8.08 (5.13-11.03)	99%
Study design					
Prospective	6	1089	32518621	8.44 (3.46-13.43)	99%
Retrospective	8	14564	114276002	3.77 (2.56-4.98)	99%

DILI: drug-induced liver injury.

Table 3. Incidence of specific drug(s) induced DILI

Medication	No. of Studies	No. of DILI	Person-years	Incidence/100,000 person-years	I^2
Statins	5	94	688556	11.30 (6.48-19.69)	65%
Rosuvastatin	5	4	48092	8.31 (2.21-31.18)	0%
Statins rather than rosuvastatin	5	90	640464	12.60 (7.44-21.34)	60%
Antifungal drugs	3	86	160864	63.46 (33.39-120.57)	92%
Antidepressants	3	490	7240830	3.83 (0.97-15.03)	100%
Paracetamol	2	14	18616592	0.16 (0.02-1.08)	97%
Antidiabetic	2	13	246444	18.20 (1.51-219.20)	98%
Anti-TB	1	12	7795	180.97 (39.15-832.25)	-
NSAIDs	1	16	177550	9.00 (6.00-15.00)	-
ATD	1	24	54991	44.80 (26.61-75.41)	-
Iron chelator	1	23	4012659	0.57 (0.36-0.86)	-

Anti-TB: anti-tuberculosis; NSAID: Non-steroidal anti-inflammatory drugs; ATD: anti-thyroid drugs.

Figures

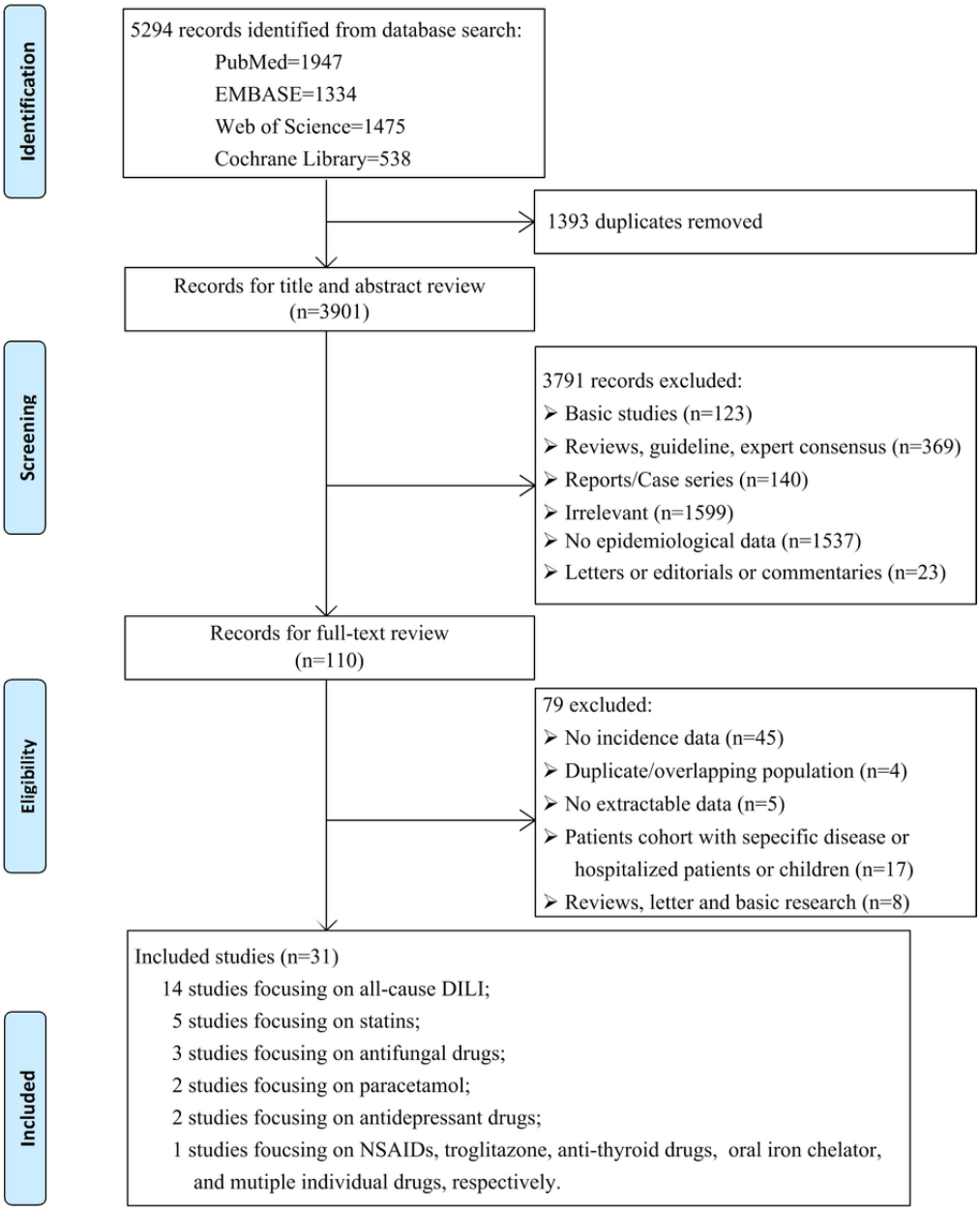

Figure 1

Study selection

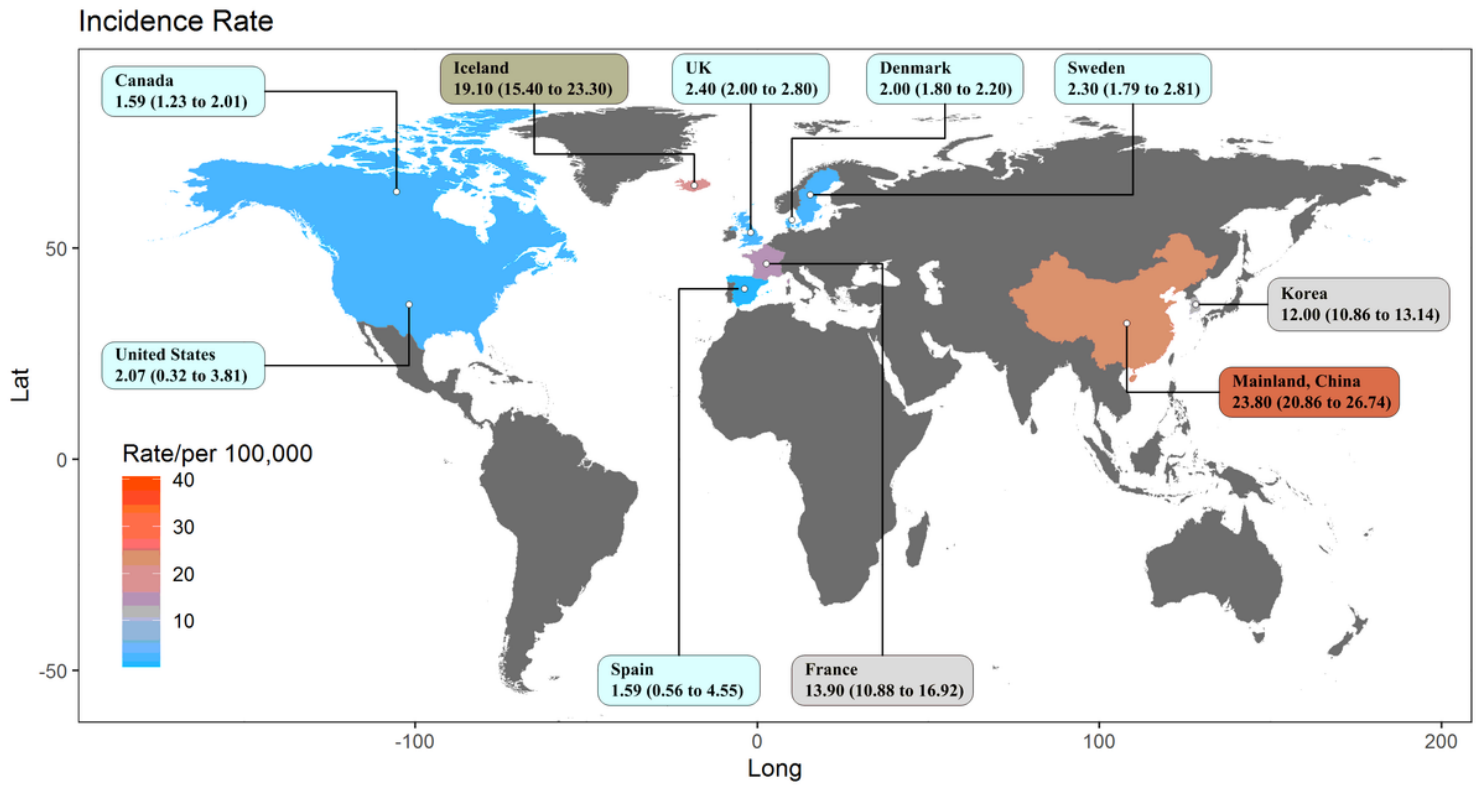

Figure 2

Geographical incidence of DILI

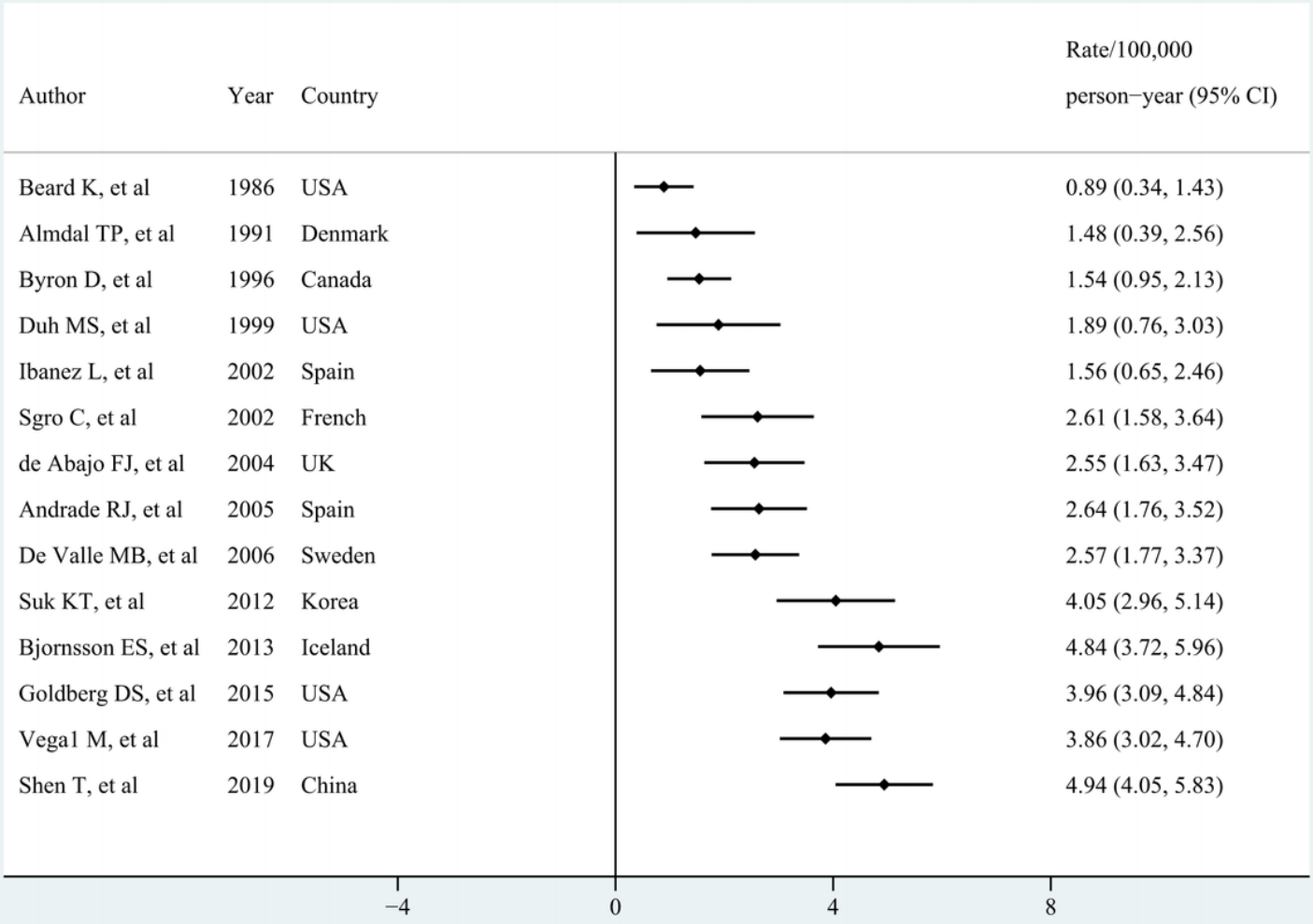

Figure 3

Cumulative meta-analysis of incidence of DILI over time

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx