Precision Medication 3 (2026) 100075

Contents lists available at ScienceDirect

Precision Medication

journal homepage: www.keaipublishing.com/en/journals/precision-medication/

# Spatiotemporal trends in the global burden of drug-induced chronic liver diseases in thirty years

Ke Qian[a], Lingyan Yu[b], Jianping Zhu[c], Jieqiong Liu[c], Zhenwei Yu[a,c,d,*]

[a] Shaoxing Campus, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Shaoxing, China
[b] The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[c] Qingchun Campus, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[d] Research Center for Clinical Pharmacy, Zhejiang University, Hangzhou, China

ARTICLE INFO

*Keywords:*
Drug-induced liver injury
Liver cirrhosis
Death rate
Disability-adjusted life year
Joinpoint regression model

ABSTRACT

*Background:* Drug-induced chronic liver disease (DICLD) is concerned due to its threat to health, but there are few data about its global burden. We evaluated the trends in the burden of DICLD in 204 countries in thirty years via the Global Burden of Disease (GBD) database.
*Methods:* Death rates and disability-adjusted life year (DALY) rates of DICLD from 1990 to 2019 were the main outcomes. The global DICLD burden and health development status were assessed by age, sex, year, location, and sociodemographic index (SDI) quintiles. Trends were estimated via a joinpoint regression model (JRM).
*Results:* The global death rates of DICLD declined from 2.59 per 100,000 population in 1990–2.50 per 100,000 population in 2019 (-3.60%), and DALY rates declined from 89.59 per 100,000 population in 1990–82.17 per 100,000 population in 2019 (-8.28%). In 2019, the most severe deaths and DALY losses caused by DICLD were mainly concentrated in Europe, Asia and Africa, with a wide distribution in Europe and the most significant in Eastern Europe. Males had higher death rates and DALY rates than those of females, although they were declining. Old patients, especially those aged > 75 years, had a greater risk of DICLD. The death rates and DALY rates were the highest in low-middle-SDI countries.
*Conclusions:* This study revealed the global burden of DICLD on death rates and DALY rates, which were slightly decreased during the study period. More efforts are needed to better prevent and manage DICLD.

## Introduction

Drug-induced liver injury (DILI) is an adverse reaction to drugs that occurs either as a predictable event when an individual is exposed to toxic doses of some compounds or as an unpredictable event with many drugs in common use.[1] Drugs can be harmful to the liver in susceptible individuals owing to genetic and environmental risk factors.[2] DILI remains a complex issue for medical providers to treat, given the numerous types of potential causal medications and the risk of further severe liver injury. The consequential hepatic injury has been noted to range in severity from mild to severe, even leading to liver failure.[3] Whereas toxic liver damage usually presents as acute hepatitis viral-like syndrome or acute cholestasis, it has long been recognized that DILI can be associated with the development of progressive liver fibrosis and cirrhosis if treatment with the implicated drug is not discontinued.[4] Persistence of DILI has been described after an acute episode of DILI, long after discontinuation of the implicated drug. The prevalence rate of chronic diseases, also known as drug-induced chronic liver disease (DICLD), varied widely among DILI patients from 5.7% to 39%.[5]

DICLD can usually be defined as the persistence in the biochemical abnormalities and/or histological damages for more than a period after drug withdrawal. The period could be 3 months, 6 months or one year according to different definitions.[5] The manifestations of DICLD include non-alcoholic fatty liver disease, vascular lesions, drug induced autoimmune hepatitis, chronic cholestasis leading to vanishing bile duct syndrome and even cirrhosis.[6] Thus, DICLD could cause a remarkable disease burden, including death and disability-adjusted life years (DALYs), which calls for special attention.[7] It is important to inform healthcare systems and policy makers of the importance of DICLD prevention and treatment.

* Corresponding author.
*E-mail addresses:* imqianke@163.com (K. Qian), lingyanyu@zju.edu.cn (L. Yu), zjping@zju.edu.cn (J. Zhu), liujieqiong@zju.edu.cn (J. Liu), yzw_srrsh@zju.edu.cn (Z. Yu).

https://doi.org/10.1016/j.prmedi.2026.100075
Received 9 September 2025; Received in revised form 23 November 2025; Accepted 25 November 2025
Available online 26 March 2026

**Table 1**
Death/DALY rates of DICLD in 1990 and 2019, and EAPCs in death/DALY rates by sex from 1990 to 2019 (per 100,000 population).

| Factor | Deaths | | | DALYs | | |
|---|---|---|---|---|---|---|
| | ASR (95% UI) | | EAPC (95% CI) | ASR (95% UI) | | EAPC (95% CI) |
| | 1990 | 2019 | | 1990 | 2019 | |
| Overall | 2.59 (2.08–3.21) | 2.50 (2.07–2.98) | -0.22 (-0.35 to −0.09) | 89.59 (72.03–110.36) | 82.17 (68.05–98.33) | -0.39 (-0.53 to −0.25) |
| Male | 4.13 (3.40–5.00) | 3.93 (3.30–4.66) | -0.24 (-0.36 to −0.13) | 142.12 (116.30–172.89) | 129.10 (108.00–154.44) | -0.40 (-0.53 to −0.27) |
| Female | 1.14 (0.83–1.52) | 1.17 (0.91–1.47) | -0.08 (-0.25–0.09) | 37.89 (26.86–49.87) | 36.60 (28.51–45.63) | -0.27 (-0.46 to −0.09) |

DICLD: drug-induced chronic liver disease; DALY(s): disability-adjusted life year(s); ASR: age-standardized rate; UI: uncertainty interval; EAPC(s): estimated annual percentage change(s); CI: confidence interval.

Determining the burden of DICLD worldwide is difficult given the diverse cultures, traditions, healthcare systems and lack of consistent reporting systems and definitions. It is not surprising that few data are available. Thus, we carried out this study to analyze the spatiotemporal trends in the global DICLD burden from 1990 to 2019 via the Global Burden of Disease (GBD) study database.

## Methods

### *Data sources*

This study was based on data obtained from the Global Burden of Disease (GBD) study, which is presently being coordinated by the Institute for Health Metrics and Evaluation (IHME). The GBD 2019 study conducted an epidemiological assessment of 256 causes of death, 369 diseases and injuries, and 87 risk factors from 204 countries and territories.[8] The data on DICLD are derived from the GBD 2019, which employs established and standardized methodologies—including case definitions, ICD coding, and statistical modeling—to estimate the burden of chronic liver diseases attributable to drug use. All death and DALY rates in this study are age-standardized and are presented per 100,000 population in all figures and tables. Since the GBD 2019 database does not contain disease data for individuals aged 0–14 years, this age group was excluded from this study. To describe the evolution process of the disease from the initial stage to the late stage in detail, we adopted a five-year age division method.

The death rate is an important indicator for measuring the level of economic development, the allocation of medical resources, or the public health environment of a country or region. With the development of modern medical models and the transformation of population health concepts, the loss of health status and the evaluation of quality of life are also important. DALYs include both the loss of life caused by premature death caused by disease and the loss of health caused by disability and are important indicators for quantitatively calculating the burden of disease. Our study analyzed the temporal and spatial distribution trends of the burden of DICLD worldwide from 1990 to 2019, using death rates and DALY rates as evaluation indicators.[9] The disease burden was analyzed by age, sex, year, and location. We also evaluated the correlation between the disease burden and the sociodemographic index (SDI), which is an indicator of a country's or region's social development level, considering education rates, economic conditions, and total fertility rates.[10] As a common analytical model in epidemiology, the joinpoint regression model (JRM) divides the overall trend of the DICLD burden into several nodes for fitting, achieving the effect of staged observation and analysis and avoiding the objectivity of traditional methods that are only judged based on linear trends.[11] The annual percentage change (APC) was used to evaluate the internal trends of each independent interval via a piecewise function, whereas the average annual percentage change (AAPC) was used to comprehensively evaluate the global average change trend at multiple intervals.

### *Statistical analyses*

All the estimates were reported as rates per 100 000 people, with 95% uncertainty intervals (UIs). Estimated annual percentage changes (EAPCs) were used to evaluate trends in death rates and DALY rates over a specific period, with 95% confidence intervals (CIs) reported. The indicator was recognized to experience an upward trend if the 95% CI of the corresponding EAPC estimation was $> 0$, to experience a downward trend if the 95% CI was $< 0$ and to be stable if the 95% CI included 0. The JRM was used to calculate the APC, AAPC and 95% CI. The analysis was configured to allow a maximum of 5 joinpoints, which was determined to be optimal for capturing the significant trend transitions over the 30-year study period. The final model was selected using a Monte Carlo permutation test at a significance level of 0.05. The data analysis of APC and AAPC were consistent with those of EAPC, and the difference was statistically significant when the $P$ value was $< 0.05$. A sensitivity analysis confirmed that the primary trends and the significance of the AAPC were robust when varying the maximum number of joinpoints. All analyses were performed with Joinpoint software (version 4.9.1.0) and R software (version 4.3.2).

## Results

### *Trends in death/DALY rates of DICLD in different countries and territories worldwide from 1990 to 2019*

We have assessed the burden of DICLD from 1990 to 2019, and found that the globally death rates and DALY rates have been decreased during this period. As shown in Table 1, the global death rates of DICLD declined from 2.59 (2.08–3.21) per 100,000 population in 1990–2.50 (2.07–2.98) per 100,000 population in 2019 (a relative decrease of 3.60%), and the overall death rates showed a downward trend [EAPC = -0.22 (-0.35 to −0.09)]. The DALY rates declined from 89.59 (72.03–110.36) per 100,000 population in 1990–82.17 (68.05–98.33) per 100,000 population in 2019 (a relative decrease of 8.28%), and the overall DALY rates also showed a downward trend [EAPC = -0.39 (-0.53 to −0.25)] (Table 1).

We further analyzed the trends in the DICLD burden at the country level, and the detailed data are shown in Fig. 1 and Table S1. Although the overall trends are declining, DICLD clearly tends to turn red in some countries, indicating an increase in DICLD deaths and DALYs (Fig. 1). We also selected the countries and areas with the greatest changes in death rates and DALY rates caused by DICLD between 1990 and 2019, and ranked them according to the EAPCs in Table 2. In 2019, Turkmenistan had the highest death rates and DALY rates, but their growth was not the fastest. The fastest growth was in the Republic of Lithuania [EAPC = 5.31 (4.19–6.44)], and the fastest decline was in the Republic of Korea [EAPC = -3.73 (-4.08 to −3.38)]. Europe was the most affected by DICLD, and the Republic of Lithuania, Republic of Armenia, Republic of Belarus, Russian Federation and Ukraine were all located in Eastern Europe, facing serious threats from DICLD (Fig. 2, Table 2).

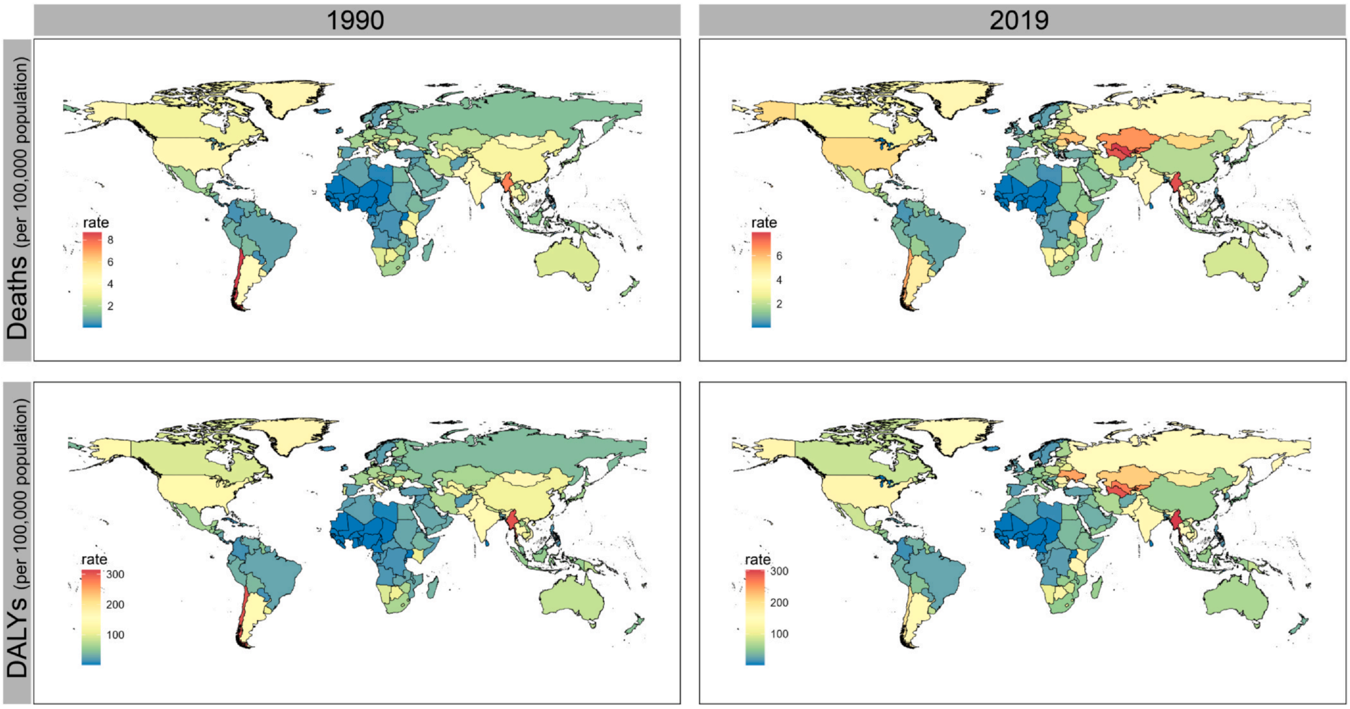


**Fig. 1.** Global prevalence burden of DICLD in 204 countries and territories (per 100,000 population).

*Trends in death/DALY rates of DICLD by age group and sex from 1990 to 2019*

The death rate of DICLD for males declined from 4.13 (3.40–5.00) per 100,000 population in 1990–3.93 (3.30–4.66) per 100,000 population in 2019 (a relative decrease of 4.90%), whereas death rate for females increased from 1.14 (0.83–1.52) per 100,000 population in 1990–1.17 (0.91–1.47) per 100,000 population in 2019 (a relative increase of 2.46%) (Table 1). Even though the death rate for males has declined, males still occupy a high position. The EAPC indicated that the death rate for males tended to decrease, whereas that for females did not significantly change [male: EAPC= -0.24 (-0.36 to −0.13), female: EAPC= -0.08 (-0.25–0.09)] (Table 1).

In terms of DALY rates, the number of males declined from 142.12 (116.30–172.89) per 100,000 population in 1990–129.10 (108.00–154.44) per 100,000 population in 2019 (a relative decrease of 9.17%), whereas the number of females declined from 37.89 (26.86–49.87) per 100,000 population in 1990–36.60 (28.51–45.63) per 100,000 population in 2019 (a relative decrease of 3.40%), both showed decreasing trend [male: EAPC= -0.40 (-0.53 to −0.27), female: EAPC= -0.27 (-0.46 to −0.09)] (Table 1).

From the perspective of age groups, the death rates and DALY rates in the 75- to 95-year-old group increased, whereas those in the 35- to 69-year-old group tended to decrease, and the lowest point appeared in the 40- to 44-year-old group (Fig. 3A, Table S2). There seemed to be an increasing trend in death rates and DALY rates in the 15- to 29-year-old group, but the EAPC interval included 0 and was considered to have no significant change.

*Trends in death/DALY rates of DICLD by 5 SDI quintiles from 1990 to 2019*

Among the countries with 5 sociodemographic index (SDI) quintiles, the low-middle-SDI countries had the highest death rates and DALY rates of DICLD both in 1990 and 2019. The death rates for low-middle-SDI countries increased from 3.26 (2.52–4.15) per 100,000 population in 1990–3.40 (2.71–4.22) per 100,000 population in 2019 (a relative increase of 4.29%) (Fig. 3B).

In addition, the death rates and DALY rates of middle-SDI countries strongly decreased. Its death rate declined from 2.55 (1.99–3.22) per 100,000 population in 1990–2.14 (1.72–2.63) per 100,000 population in 2019 (a relative decrease of 16.08%), and the DALY rates was declined from 88.03 (68.78–110.96) per 100,000 population in 1990–68.72 (55.24–84.25) per 100,000 population in 2019 (a relative decrease of 21.94%). The death rates and DALY rates of middle-SDI countries were the lowest in the 5 SDI quintiles, followed by high-middle-SDI countries (Fig. 3B). However, the EAPCs of the 5 SDI quintiles all included 0, indicating that the death risk of DICLD had no obvious change in each SDI quintile and that the difference has always existed (Table 3).

*JRM analysis of the developmental characteristics of DICLD worldwide from 1990 to 2019*

There were 5 turning points in the global death rate curve of the DICLD from 1990 to 2019, which occurred in 1994, 1999, 2003, 2008 and 2014. The APC indicated that the death rates of DICLD tended to increase in the two periods of 1990–1994 and 1999–2003. However, since 2008–2019, this trend has been fundamentally reversed, and the death rates have begun to decrease significantly, especially during 2008–2014 (Fig. 4A, Table S3).

Moreover, DALY curve also showed a similar trend (Fig. 4B). Specifically, during the two periods of 1990–1995 and 1998–2003, DALY rates tended to increase. However, it showed a downward trend from 2008 to 2019 (Fig. 4B, Table S3). This trend was highly consistent with the changing trend of death rates. Judging from the division of periods, the burden of DICLD stopped increasing after 2003 and it began to gradually reduce since 2008.

In addition, from the perspective of sex, the death rates and DALY rates of males in DICLD were much higher than those of females (Fig. 4). During the period of 2008–2014, it was precisely because of the significant decline of male death rate and DALY rates that the burden of DICLD was greatly reduced. This discovery initially confirmed that males were the main bearers of DICLD burden (Fig. 4, Table S3).

**Table 2**
Death/DALY rates of DICLD in 1990 and 2019, and EAPCs in death/DALY rates in typical countries and territories from 1990 to 2019 (per 100,000 population).

| Location | Metric | ASR (95% UI) | | EAPC (95% CI) |
|---|---|---|---|---|
| | | 1990 | 2019 | |
| **Trends with Increasing Rates** | | | | |
| Republic of Lithuania | Deaths | 0.62 (0.34–1.02) | 2.36 (1.40–3.64) | 5.31 (4.19–6.44) |
| | DALYs | 24.09 (13.12–40.73) | 94.12 (55.76–142.68) | 5.41 (4.27–6.57) |
| Republic of Kazakhstan | Deaths | 2.04 (1.41–2.88) | 6.63 (4.72–9.19) | 4.83 (4.07–5.60) |
| | DALYs | 65.31 (46.24–90.19) | 216.73 (152.31–299.63) | 4.87 (3.92–5.82) |
| Republic of Armenia | Deaths | 0.45 (0.24–0.79) | 1.52 (0.90–2.40) | 4.81 (4.11–5.51) |
| | DALYs | 15.59 (8.17–28.39) | 53.12 (31.43–82.31) | 4.86 (4.07–5.56) |
| Republic of Belarus | Deaths | 0.95 (0.68–1.30) | 2.75 (1.81–4.03) | 4.42 (3.22–5.64) |
| | DALYs | 31.81 (23.20–42.82) | 101.66 (67.55–147.72) | 4.71 (3.40–6.03) |
| Russian Federation | Deaths | 1.21 (0.99–1.46) | 3.84 (3.07–4.75) | 4.06 (3.13–4.99) |
| | DALYs | 42.02 (34.73–50.48) | 149.67 (119.67–185.71) | 4.48 (3.45–5.53) |
| Ukraine | Deaths | 1.81 (1.50–2.17) | 5.94 (4.60–7.60) | 3.96 (3.09–4.83) |
| | DALYs | 62.08 (51.86–74.06) | 243.88 (188.29–312.24) | 4.53 (3.55–5.52) |
| Turkmenistan | Deaths | 3.25 (1.91–4.88) | 7.16 (5.03–11.01) | 3.01 (2.69–3.32) |
| | DALYs | 116.74 (68.22–170.40) | 291.90 (189.53–423.30) | 3.33 (3.01–3.65) |
| Republic of Chad | Deaths | 0.03 (0.01–0.05) | 0.05 (0.03–0.10) | 2.63 (2.51–2.75) |
| | DALYs | 0.83 (0.40–1.54) | 1.78 (0.86–3.29) | 2.75 (2.64–2.86) |
| Lebanese Republic | Deaths | 0.74 (0.37–1.27) | 1.40 (0.59–2.51) | 2.61 (2.38–2.84) |
| | DALYs | 24.61 (12.33–43.58) | 44.02 (19.27–77.46) | 2.45 (2.19–2.71) |
| Kingdom of Morocco | Deaths | 0.64 (0.34–1.12) | 1.23 (0.72–1.97) | 2.44 (2.23–2.65) |
| | DALYs | 21.50 (11.39–37.75) | 37.42 (21.44–60.63) | 2.16 (1.98–2.35) |
| **Trends with Decreasing Rates** | | | | |
| Republic of Korea | Deaths | 1.65 (0.99–2.57) | 0.74 (0.50–1.09) | -3.73 (-4.08 to −3.38) |
| | DALYs | 63.71 (37.41–99.54) | 24.40 (16.62–35.53) | -4.25 (-4.58 to −3.91) |
| Hungary | Deaths | 1.32 (0.70–2.41) | 0.83 (0.46–1.39) | -3.33 (-3.84 to −2.28) |
| | DALYs | 51.59 (25.96–93.80) | 29.15 (16.43–48.58) | -3.87 (-4.41 to −3.32) |
| Republic of Italy | Deaths | 4.60 (3.87–5.35) | 2.23 (1.91–2.58) | -2.78 (-2.94 to −2.61) |
| | DALYs | 141.94 (122.97–160.92) | 61.45 (53.25–70.51) | -3.15 (-3.32 to −2.97) |
| Portuguese Republic | Deaths | 2.63 (1.62–3.97) | 1.39 (0.97–1.98) | -2.51 (-2.61 to −2.41) |
| | DALYs | 97.31 (59.15–141.21) | 46.58 (32.70–65.74) | -2.89 (-3.02 to −2.76) |
| Republic of Singapore | Deaths | 0.47 (0.30–0.68) | 0.25 (0.16–0.35) | -2.41 (-2.59 to −2.23) |
| | DALYs | 15.86 (10.49–22.69) | 7.03 (4.87–9.79) | -3.06 (-3.23 to −2.88) |
| Republic of Mauritius | Deaths | 6.94 (5.08–9.19) | 4.14 (2.99–5.54) | -2.38 (-2.67 to −2.09) |
| | DALYs | 242.29 (181.50–319.01) | 137.60 (98.04–184.00) | -2.58 (-2.89 to −2.27) |
| People's Republic of China | Deaths | 3.34 (2.68–4.11) | 1.84 (1.45–2.29) | -2.22 (-2.37 to −2.07) |
| | DALYs | 111.76 (88.17–139.00) | 55.83 (44.04–68.72) | -2.58 (-2.72 to −2.44) |
| Grand Duchy of Luxembourg | Deaths | 2.54 (1.82–3.59) | 1.44 (1.03–2.01) | -2.18 (-2.30 to −2.05) |
| | DALYs | 85.55 (62.05–117.93) | 43.69 (31.34–60.26) | -2.59 (-2.68 to −2.49) |
| Republic of Slovenia | Deaths | 4.16 (2.60–6.53) | 2.55 (1.65–3.81) | -1.89 (-2.15 to −1.64) |
| | DALYs | 146.00 (93.21–220.97) | 78.89 (51.45–115.78) | -2.39 (-2.64 to −2.13) |
| Republic of Maldives | Deaths | 4.21 (2.44–6.19) | 2.69 (1.98–3.57) | -1.81 (-2.03 to −1.58) |
| | DALYs | 132.11 (77.41–197.61) | 71.25 (53.11–93.00) | -2.42 (-2.71 to −2.12) |

DICLD: drug-induced chronic liver disease; DALY(s): disability-adjusted life year(s); ASR: age-standardized rate; UI: uncertainty interval; EAPC(s): estimated annual percentage change(s); CI: confidence interval.

The AAPC interval for the overall death rates indicated that the change was insignificant. However, the overall DALY rates showed a downward trend. Both the death rate and DALY rate for males tended to decrease (Table 4). Although the changes in the overall death rates or DALY rates of females were insignificant, the APCs during certain time periods exhibited statistically significant differences. This further confirmed that males faced a greater risk of death in DICLD. Over time, the male death rate and DALY rate gradually decreased, leading to a reduction in the burden of DICLD.

## Discussion

To the best of our knowledge, this is the first study to evaluate the global burden of DICLD, thereby filling a critical evidence gap left by previous investigations that were largely confined to clinical case reports and specific drug analyses. Our systematic, population-level assessment reveals that the overall global death and DALY rates of DICLD have decreased from 1990 to 2019. The male death rate decreased significantly, whereas the female death rate remained stable. Both sexes showed a decrease in DALY rates. DICLD was affected by age, and individuals aged over 75 years had more severe burden. The low-middle-SDI countries had the highest death rates and DALY rates among all countries. Moreover, 5 turning points in the global death rate curve of DICLD were identified in this study.

Our study provides a comprehensive evaluation of the distribution of the DICLD burden and its 30-year change patterns on a global scale. The death rates and DALY rates caused by DICLD have shown a downward trend over time, but the death rate decreased by only 3.60% at the end of this study. Our study emphasizes the necessity of preventive strategies for DICLD. In terms of prevention, rational use of drugs is highly important to avoid any side effects.[12] It is necessary to strictly grasp the indications and correct dosage and methods of medication and increase the supply of medication safety consulting services.[13] We should accelerate the promotion of scientific knowledge and methods for liver protection and provide a sound medical welfare system.

Although the overall burden is decreasing, it can be seen from the world map that the death rates and DALY rates of DICLD in some countries showed an increasing trend, such as the Republic of Lithuania and the Republic of Kazakhstan are increasing. There were also some countries where the risk of DICLD death was decreasing, such as Republic of Korea and Hungary. There were many reasons for this difference in different countries and territories, including different living habits, natural ecological environment, demographic

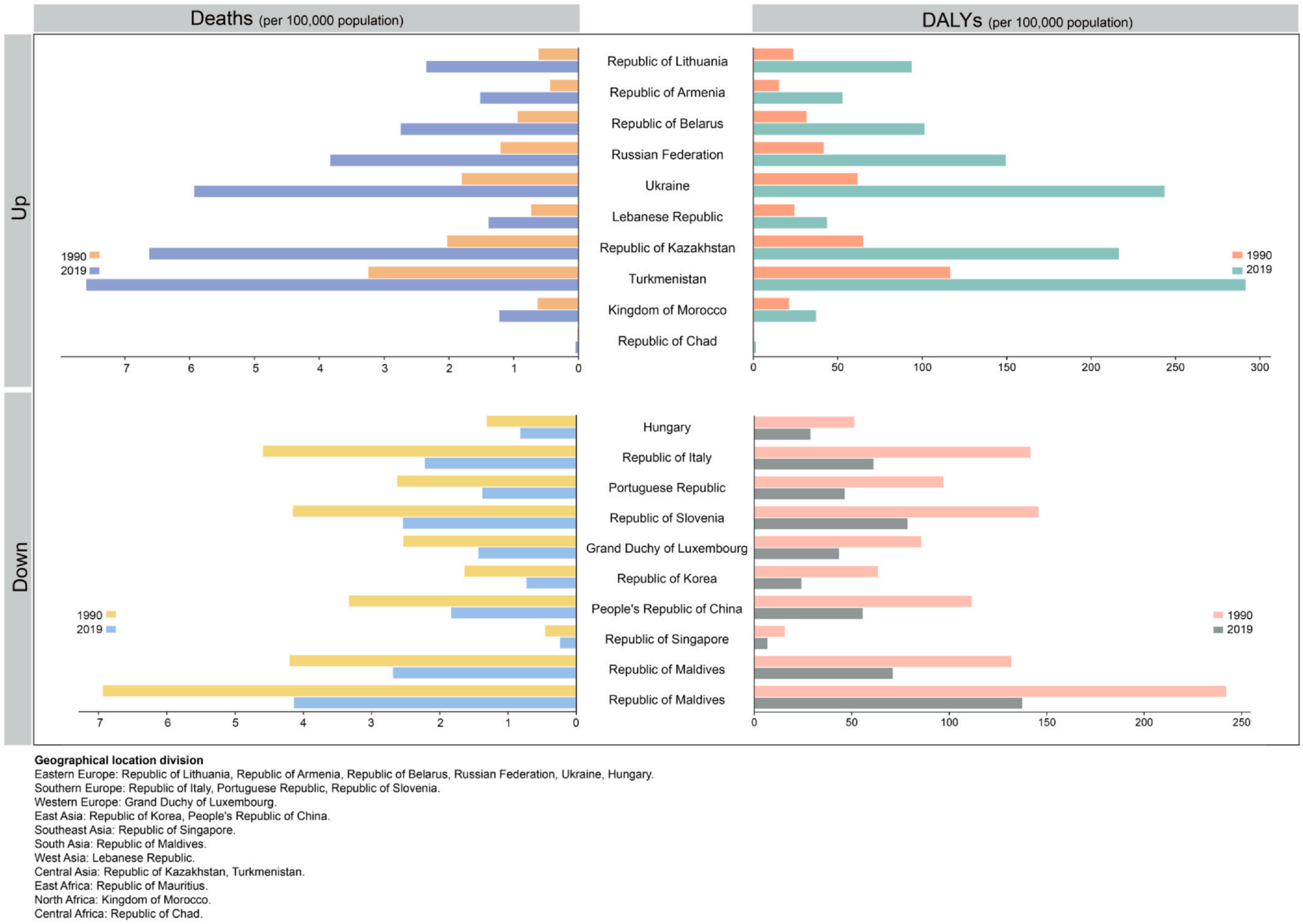


**Fig. 2.** Death/DALY rates in countries and territories with the deepest impact of DICLD in 1990 and 2019 (per 100,000 population).

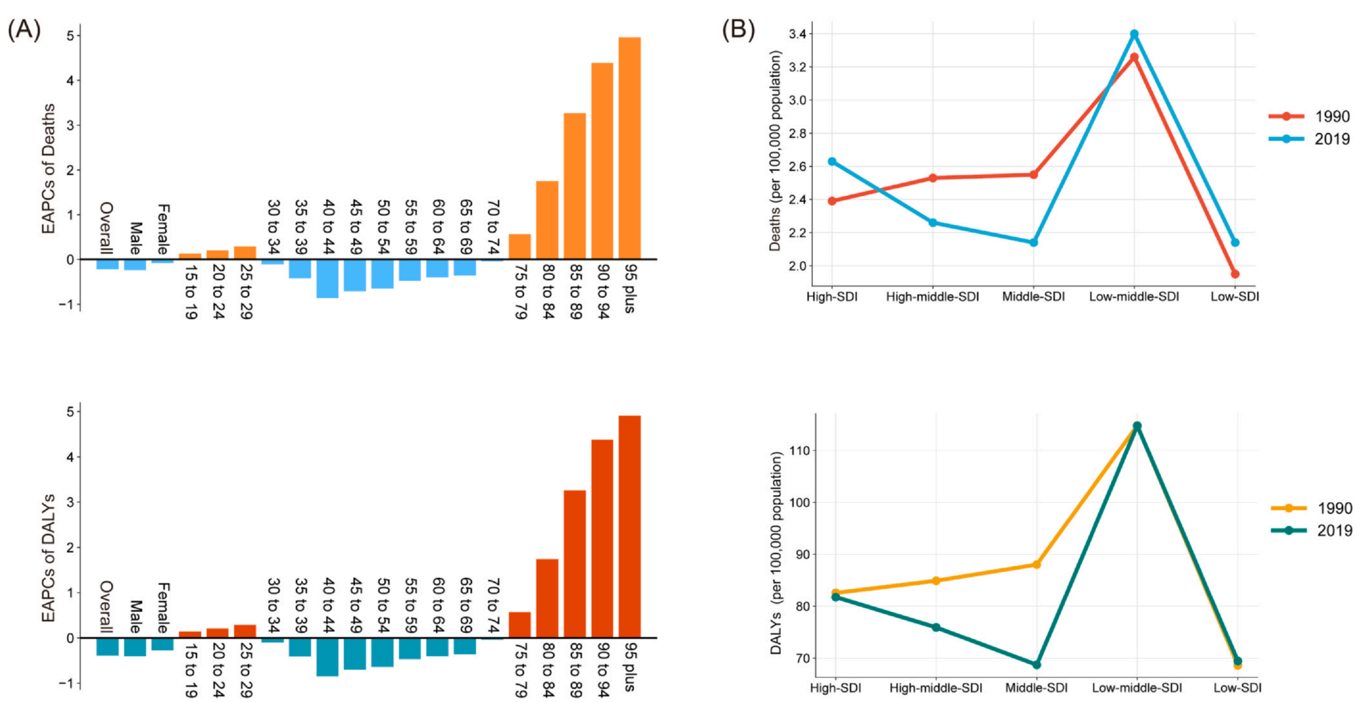


**Fig. 3.** Global burden trends of DICLD (per 100,000 population). (A) EAPCs in death/DALY rates by different sex and age groups. (B) Death/DALY rates by 5 SDI quintiles.

**Table 3**
Death/DALY rates of DICLD in 1990 and 2019, and EAPCs in death/DALY rates by the 5 SDI quintiles from 1990 to 2019 (per 100,000 population).

| Factor | Deaths | | | DALYs | | |
|---|---|---|---|---|---|---|
| | ASR (95% UI) | | EAPC (95% CI) | ASR (95% UI) | | EAPC (95% CI) |
| | 1990 | 2019 | | 1990 | 2019 | |
| High-SDI | 2.39 (1.98–2.91) | 2.63 (2.26–3.06) | 0.36 (-0.60–1.33) | 82.60 (68.52–100.47) | 81.76 (70.92–94.83) | 0.01 (-0.98–1.02) |
| High-middle-SDI | 2.53 (2.09–3.04) | 2.26 (1.91–2.69) | -0.37 (-1.71–0.98) | 84.92 (70.65–101.79) | 75.94 (63.94–89.87) | -0.33 (-1.68–1.03) |
| Middle-SDI | 2.55 (1.99–3.22) | 2.14 (1.72–2.63) | -0.78 (-2.22–0.68) | 88.03 (68.78–110.96) | 68.72 (55.24–84.25) | -1.06 (-2.54–0.45) |
| Low-middle-SDI | 3.26 (2.52–4.15) | 3.40 (2.71–4.22) | 0.03 (-1.17–1.23) | 114.79 (88.92–145.59) | 114.75 (91.58–141.86) | -0.15 (-1.37–1.09) |
| Low-SDI | 1.95 (1.41–2.61) | 2.14 (1.57–2.83) | 0.31 (-0.63–1.25) | 68.62 (49.33–91.80) | 69.45 (50.70–93.59) | 0.01 (-0.92–0.95) |

DICLD: drug-induced chronic liver disease; DALY(s): disability-adjusted life year(s); SDI: sociodemographic index; ASR: age-standardized rate; UI: uncertainty interval; EAPC(s): estimated annual percentage change(s); CI: confidence interval.

characteristics, medical technology and national health awareness, and DICLD has become a public health problem that cannot be ignored.[14–16] More efforts are needed for these countries.

Our study revealed a clear sex disparity in the burden of DICLD. Although both sexes were affected, males consistently carried a heavier burden from 1990 to 2019, with higher death and DALY rates than females. While the decline in male deaths over this period was more significant, their absolute rates remained disproportionately high. The biological and behavioral underpinnings of this disparity are likely multifactorial and complex. Crucially, evidence suggests that the relationship between sex and DICLD is not uniform but is often drug-specific. For instance, certain medications, such as anabolic steroids, are associated with DILI almost exclusively in males, while others like nitrofurantoin and methylprednisolone pose a greater risk to females.[17,18] This underscores that sex-linked differences in drug exposure, metabolism, and concomitant comorbidities (e.g., alcohol-related liver disease) may be key confounders driving the overall male predisposition observed in our study.[19–21] Further epidemiological and mechanistic studies are needed to delineate the precise contributions of these factors.

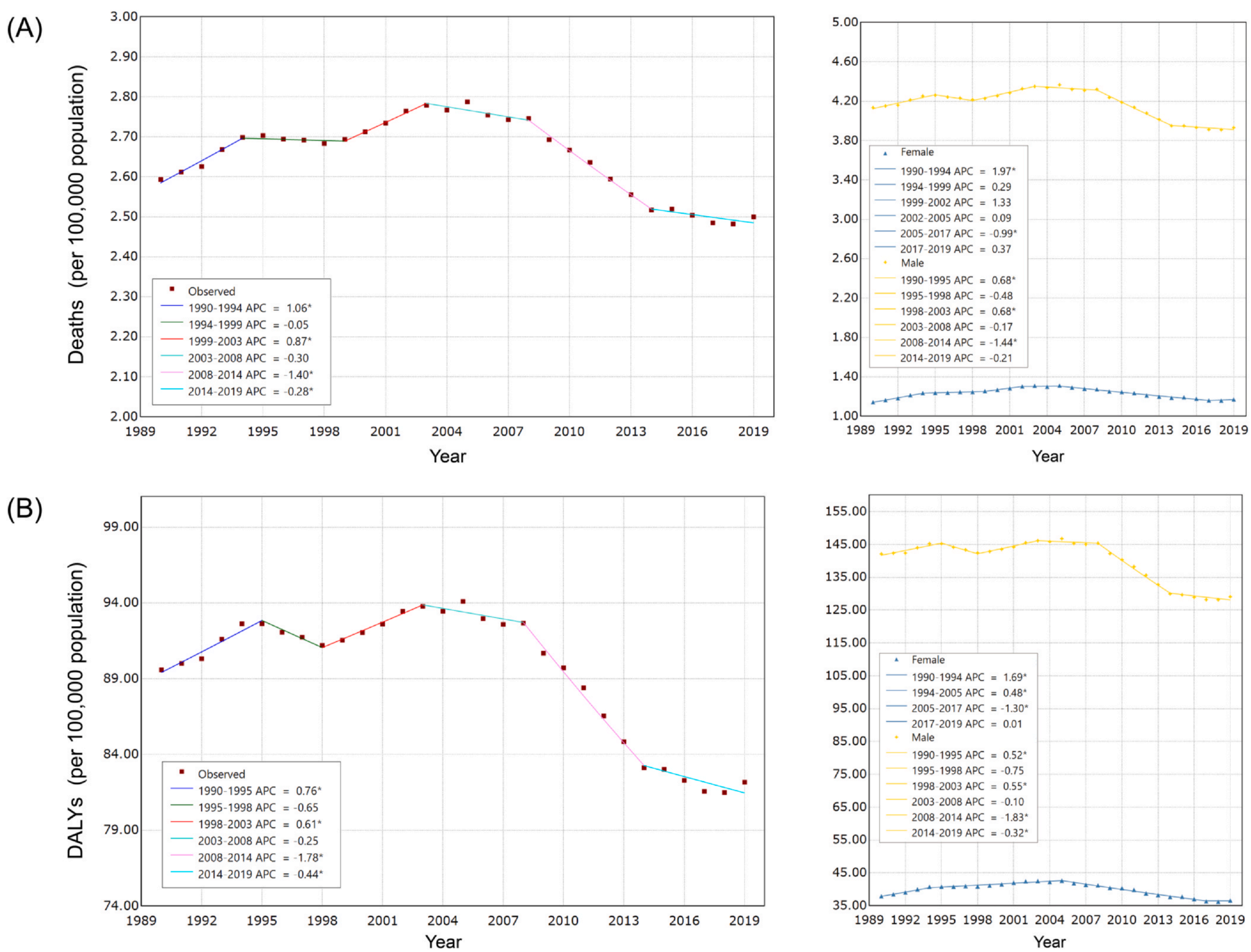


**Fig. 4.** Temporal trend of the global burden of DICLD from 1990 to 2019 (per 100,000 population). (A) Overall trend in death rates. (B) Overall trend in DALY rates. *: $P$ value $<$ 0.05.

**Table 4**
AAPC results of the global burden of DICLD from 1990 to 2019.

| Factor | Deaths | | | DALYs | | |
|---|---|---|---|---|---|---|
| | Joinpoints | AAPC (95% CI) | *P* value | Joinpoints | AAPC (95% CI) | *P* value |
| Both | 5 | -0.1 (-0.3–0.0) | 0.063 | 5 | -0.3 (-0.5 to −0.1) | 0.002 |
| Male | 5 | -0.2 (-0.3–0.0) | 0.014 | 5 | -0.3 (-0.5 to −0.2) | < 0.001 |
| Female | 5 | 0.1 (-0.2–0.3) | 0.529 | 3 | -0.1 (-0.3–0.0) | 0.127 |

DICLD: drug-induced chronic liver disease; DALY(s): disability-adjusted life year(s); AAPC: average annual percentage change; CI: confidence interval.

Additionally, aging has an impact on the burden of DICLD. The death rates and DALY rates of DICLD began to increase from the age of 45 years, and the risk increased along with the ages. While a young liver has an astounding capacity for regeneration after liver injury, the hepatic reserve decreases over time, particularly after age 60 years.[22] On the other hand, as people aging, their physical function decreases, their immune system weakens, and they are more susceptible to DICLD.[23] Additionally, polypharmacy is prevalent in old patients, which increases the risk of DICLD.[24] Thus, prevention and treatment of DICLD is an area of special concern for the elderly population.

There were significant differences in the burden of DICLD among different SDI countries, and this difference has not undergone a transformation. From 1990–2019, the countries with the heaviest disease burden of DICLD were low-middle-SDI, ranking first all the time. The relatively lower burden in high-middle-SDI countries may be related to the rapid development of medical technology, more assessible medical resources and the improvement of people's health awareness in these SDI countries in recent 30 years.[25] However, the observed low burden in low-SDI countries is likely multifactorial. While lower drug consumption might be a potential contributor[26], it is also plausible that substantial underdiagnosis and under-reporting due to limited healthcare access are the primary drivers for the low recorded rates.

Our study also indicated that the global death rates of DICLD showed a particularly prominent downward trend from 2008 to 2014, and the changes in DALY rates tended to be consistent, indicating that the DICLD related prevention and control measures taken globally in the past decade have had a certain positive effect. For example, World Hepatitis Day on July 28, 2011, may have drawn high attention to DICLD and promoted the popularization of DICLD screening and prevention measures.[27] With advancement in medical technology and innovations in drugs, the diagnosis and treatment level of DICLD has been continuously improved, which has improved the survival rate and quality of life of patients.[28–30]

This study is subject to several limitations inherent to the GBD 2019. First, a fundamental constraint is the general lack of sufficient DICLD-related data globally. This issue stems from the absence of a unified diagnostic standard and inadequate screening, which often leads to diagnosis only at late disease stages. Consequently, our analysis is constrained by a lack of case records spanning the full disease spectrum. Second, our findings are inherently influenced by the GBD's modeling processes. We rely on statistically imputed and adjusted estimates rather than raw data, which introduces a layer of uncertainty. Furthermore, significant differences in data quality among countries, a key issue tied to the variability of national reporting systems, pose another challenge. These disparities are mainly due to the maturity of medical record systems, the uniformity of data collection standards, and unequal investments in healthcare resources. Although the GBD employs robust techniques to adjust for these disparities, residual bias from under-diagnosis in regions with limited healthcare resources is likely to persist. Therefore, our findings are best interpreted as reflecting the 'diagnosed and reported' burden rather than the true burden in the general population, and this must be considered when interpreting the observed spatiotemporal trends. Finally, uncertainties exist regarding disease coding and statistical interpretation. The specific codes used may not capture all DICLD cases uniformly, and regional differences in coding practices could lead to misclassification. Moreover, EAPC results with wide confidence intervals should not be overinterpreted without corroborating evidence. Readers are therefore urged to consider these methodological and data-related uncertainties when interpreting the study's findings.

## Conclusion

This study assessed the global burden of DICLD and revealed that DICLD is a serious issue that threatens the health of people worldwide. The death rates and DALY rates caused by DICLD have decreased over time, but at a small extent. DICLD still represents a serious disease burden in some countries and areas, especially in Eastern Europe. Male patients, older patients, and those who live in low-middle-SDI countries have a greater burden of DICLD. Our study strongly highlights the importance and necessity of global DICLD prevention and management efforts, which will help alleviate the burden of global DICLD and maintain global health.

## Abbreviations

| | |
|---|---|
| DICLD | drug-induced chronic liver disease; |
| DILI | drug-induced liver injury; |
| GBD | Global Burden of Disease; |
| DALY(s) | disability-adjusted life year(s); |
| SDI | sociodemographic index; |
| EAPC(s) | estimated annual percentage change(s); |
| ASR(s) | age-standardized rate(s); |
| JRM | joinpoint regression model; |
| APC | annual percentage change; |
| AAPC | average annual percentage change; |
| IHME | Institute for Health Metrics and Evaluation; |
| UI(s) | uncertainty interval(s); |
| CI(s) | confidence interval(s). |

## Declarations

Not applicable.

## CRediT authorship contribution statement

**Lingyan Yu:** Formal analysis. **Jianping Zhu:** Formal analysis. **Jieqiong Liu:** Formal analysis. **YU Zhenwei:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Ke Qian:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Data availability

The raw data are available at https://vizhub.healthdata.org/gbd-results/.


## Funding

Not applicable.


## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


## Acknowledgements

Not applicable.

## Financial support and sponsorship

None.


## Patient and public involvement statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

## Authors' other information

Not applicable.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prmedi.2026.100075.

## References


1. Andrade RJ, Chalasani N, Björnsson ES, et al. Drug-induced liver injury. *Nat Rev Dis Prim.* 2019;5:58. https://doi.org/10.1038/s41572-019-0105-0
2. Chidiac AS, Buckley NA, Noghrehchi F, Cairns R. Paracetamol (acetaminophen) overdose and hepatotoxicity: mechanism, treatment, prevention measures, and estimates of burden of disease. *Expert Opin Drug Metab Toxicol.* 2023;19:297–317. https://doi.org/10.1080/17425255.2023.2223959
3. Chayanupatkul M, Schiano TD. Acute Liver Failure Secondary to Drug-Induced Liver Injury. *Clin Liver Dis.* 2020;24:75–87. https://doi.org/10.1016/j.cld.2019.09.005
4. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharm Ther.* 2011;89:806–815. https://doi.org/10.1038/clpt.2011.58
5. Ortega-Alonso A, Andrade RJ. Chronic liver injury induced by drugs and toxins. *J Dig Dis.* 2018;19:514–521. https://doi.org/10.1111/1751-2980.12612
6. Bessone F, Robles-Diaz M, Hernandez N, Medina-Caliz I, Lucena MI, Andrade RJ. Assessment of Serious Acute and Chronic Idiosyncratic Drug-Induced Liver Injury in Clinical Practice. *Semin Liver Dis.* 2019;39:381–394. https://doi.org/10.1055/s-0039-1685519
7. Björnsson ES, Andrade RJ. Long-term sequelae of drug-induced liver injury. *J Hepatol.* 2022;76:435–445. https://doi.org/10.1016/j.jhep.2021.10.011
8. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020;396:1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9
9. Global Burden of Disease 2019 Cancer Collaboration, Kocarnik JM, Compton K, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *JAMA Oncol.* 2022;8:420–444. https://doi.org/10.1001/jamaoncol.2021.6987
10. Younossi ZM, Wong G, Anstee QM, Henry L. The Global Burden of Liver Disease. *Clin Gastroenterol Hepatol.* 2023;21:1978–1991. https://doi.org/10.1016/j.cgh.2023.04.015
11. Hincapie-Castillo JM, Goodin A. Using Joinpoint regression for drug utilization research: Tutorial and case study of prescription opioid use in the United States. *Pharmacoepidemiol Drug Saf.* 2023;32:509–516. https://doi.org/10.1002/pds.5606
12. Maćków M, Dziubyna T, Jamer T, et al. The Role of Dietary Ingredients and Herbs in the Prevention of Non-Communicable Chronic Liver Disease. *Nutrients.* 2024;16. https://doi.org/10.3390/nu16203505
13. Rosso N, Marin V, Giordani A, et al. The Pros and the Cons for the Use of Silybin-Rich Oral Formulations in Treatment of Liver Damage (NAFLD in Particular). *Curr Med Chem.* 2015;22:2954–2971. https://doi.org/10.2174/0929867322666150729114235
14. Lin C-Y, Huang S-C, Tzou S-J, et al. Tendon Disorders in Chronic Liver Disease: A Retrospective Cohort Study in Taiwan. *Int J Environ Res Public Health.* 2023;20:4983. https://doi.org/10.3390/ijerph20064983
15. Yan C, Hu W, Tu J, Li J, Liang Q, Han S. Pathogenic mechanisms and regulatory factors involved in alcoholic liver disease. *J Transl Med.* 2023;21:300. https://doi.org/10.1186/s12967-023-04166-8
16. Shen T, Liu Y, Shang J, et al. Incidence and Etiology of Drug-Induced Liver Injury in Mainland China. *Gastroenterology.* 2019;156:2230–2241.e11. https://doi.org/10.1053/j.gastro.2019.02.002
17. Tillmann HL, Rockey DC. Signatures in drug-induced liver injury. *Curr Opin Gastroenterol.* 2020;36:199–205. https://doi.org/10.1097/MOG.0000000000000636
18. DiPaola F, Molleston JP, Gu J, et al. Antimicrobials and Antiepileptics Are the Leading Causes of Idiosyncratic Drug-induced Liver Injury in American Children. *J Pedia Gastroenterol Nutr.* 2019;69:152–159. https://doi.org/10.1097/MPG.0000000000002383
19. George N, Chen M, Yuen N, Hunt CM, Suzuki A. Interplay of gender, age and drug properties on reporting frequency of drug-induced liver injury. *Regul Toxicol Pharm.* 2018;94:101–107. https://doi.org/10.1016/j.yrtph.2018.01.018
20. Amacher DE. Female gender as a susceptibility factor for drug-induced liver injury. *Hum Exp Toxicol.* 2014;33:928–939. https://doi.org/10.1177/0960327113512860
21. Floreani A, Bizzaro D, Shalaby S, Taliani G, Burra P. Special Interest Group Gender in Hepatology of the Italian Association for the Study of the Liver (AISF). Sex disparity and drug-induced liver injury. *Dig Liver Dis.* 2023;55:21–28. https://doi.org/10.1016/j.dld.2022.06.025
22. Cieslak KP, Baur O, Verheij J, Bennink RJ, van Gulik TM. Liver function declines with increased age. *Hpb.* 2016;18:691–696. https://doi.org/10.1016/j.hpb.2016.05.011
23. Kamimura K, Sakamaki A, Kamimura H, et al. Considerations of elderly factors to manage the complication of liver cirrhosis in elderly patients. *World J Gastroenterol.* 2019;25:1817–1827. https://doi.org/10.3748/wjg.v25.i15.1817
24. Wang Z, Liu T, Su Q, et al. Prevalence of Polypharmacy in Elderly Population Worldwide: A Systematic Review and Meta-Analysis. *Pharmacoepidemiol Drug Saf.* 2024;33:e5880. https://doi.org/10.1002/pds.5880
25. Mazidimoradi A, Momenimovahed Z, Khalajinia Z, Allahqoli L, Salehiniya H, Alkatout I. The global incidence, mortality, and burden of uterine cancer in 2019 and correlation with SDI, tobacco, dietary risks, and metabolic risk factors: An ecological study. *Heal Sci Rep.* 2024;7:e1835. https://doi.org/10.1002/hsr2.1835
26. Tucker EL, Cao Y, Fox ER, Sweet BV. The Drug Shortage Era: A Scoping Review of the Literature 2001-2019. *Clin Pharm Ther.* 2020;108:1150–1155. https://doi.org/10.1002/cpt.1934
27. Malhotra K, Bawa A, Singla A, et al. Digital impact of world hepatitis day: Formulating evidence-based recommendations for promoting healthcare awareness events. *J Educ Health Promot.* 2023;12:288. https://doi.org/10.4103/jehp.jehp_1755_22
28. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *Am J Gastroenterol.* 2021;116:878–898. https://doi.org/10.14309/ajg.0000000000001259
29. Ginès P, Castera L, Lammert F, et al. Population screening for liver fibrosis: Toward early diagnosis and intervention for chronic liver diseases. *Hepatology.* 2022;75:219–228. https://doi.org/10.1002/hep.32163
30. McGill MR, Jaeschke H. Biomarkers of drug-induced liver injury. *Adv Pharm.* 2019;85:221–239. https://doi.org/10.1016/bs.apha.2019.02.001