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Real-World Pharmacovigilance Analysis of Drug-Induced Liver Injury in 18-60 Years: Based on the FDA Adverse Event Reporting System (FAERS)

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Abstract. Drug-induced liver injury (DILI) in adults aged 18–60 years remains understudied despite its clinical heterogeneity and rising incidence. This study aimed to characterize the epidemiology, risk factors, and drug-specific profiles of DILI in this demographic. Utilizing data from the FDA Adverse Event Reporting System (FAERS) (2007–2024), we analyzed 17,464 DILI cases. Four disproportionality methods—Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS)—were employed to identify high-risk drugs. Time-to-onset (TTO) and gender-specific risks were assessed. Seventeen drugs exhibited significant DILI signals. Rifampicin (ROR=19.33, 95%CI: 16.41–22.77), amoxicillin/clavulanic acid (ROR=16.39, 95%CI: 14.48–18.56), and paracetamol (ROR=10.3,95%CI: 9.61–11.04) showed the strongest associations. Non-steroidal anti-inflammatory drugs (NSAIDs) had the shortest median time-to-onset (7 days). Gender subgroup analysis revealed sex-biased hepatotoxicity, with females disproportionately affected by immunosuppressants and males by antibiotics. This large-scale real-world analysis identifies NSAIDs, antibiotics, and immunosuppressants as critical hepatotoxic threats in younger adults. The findings advocate for targeted hepatic monitoring and updated drug labeling to reflect class-specific latency patterns. Gender-tailored risk mitigation strategies are warranted to address sex-based disparities in DILI susceptibility.

Keywords: Drug-induced liver injury, FDA Adverse Event Reporting System, Pharmacovigilance, Epidemiology

1. Introduction

Drug-induced liver injury (DILI) refers to liver damage caused by medications that are widely used in clinical practice, which may involve injury to hepatocytes as well as other liver cells [1-3]. With the continuous introduction of new drugs, the expanding use of pharmaceuticals worldwide, and the

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rapid development of novel therapeutic strategies, the occurrence of DILI has shown an upward trend. Its highly variable clinical presentations and potentially severe outcomes have made it an important public health issue. Although advances have been made in hepatotoxicity prediction, DILI remains challenging to diagnose due to its often non-specific symptoms and the absence of reliable biomarkers. Current estimates suggest an annual incidence of approximately 14 to 19 cases per 100,000 individuals in Western countries and 23.8 cases per 100,000 in China [4]. Prior research indicates that while DILI can affect all age groups, its incidence and pathophysiological mechanisms exhibit certain differences, attributed to variations in liver metabolism, drug treatment patterns, and long-term therapeutic needs among different age cohorts [5,6].

A growing body of research has shown that certain drug categories, including antitumor agents, antituberculosis medications, and antipsychotics, are frequently associated with hepatotoxicity and may contribute to DILI development [7-9]. In addition, drugs with mitochondrial toxicity have been reported to carry a 1.41-fold higher risk of inducing DILI compared to those without such effects [10]. Younger adults may be more susceptible to mitochondrial dysfunction due to relatively lower CYP3A4 activity, whereas older individuals are more prone to bile salt export pump (BSEP) inhibition as a result of polypharmacy [11]. Epidemiological studies have suggested a bimodal age distribution of DILI incidence, with peaks observed in individuals aged 20-40 years—likely related to higher drug exposure—and those over 60 years, where cholestasis, multiple medication use, and metabolic decline play more prominent roles [12,13]. Focusing on populations under 60 years of age may help differentiate two major pathogenic patterns: predominantly idiosyncratic DILI in younger adults and more intrinsic forms in older patients [14,15].

Despite increasing attention to DILI, most epidemiological studies and risk factor analyses have primarily focused either on specific drug-related adverse events or on pediatric populations. In contrast, comprehensive investigations among adults under 60 years of age remain limited, particularly those utilizing large-scale real-world data [14,16]. This age group is exposed to unique risk factors, including lifestyle behaviors, immune-related conditions, and use of medications with higher hepatotoxic potential. Moreover, undetected or unresolved DILI in younger individuals may progress to chronic liver injury, posing long-term health risks. Therefore, a systematic evaluation of the drug spectrum and associated risk factors for DILI in adults under 60 is essential to enhance pharmacovigilance and support more individualized treatment strategies.

The FDA Adverse Event Reporting System (FAERS), a global repository of post-marketing surveillance data, offers a unique opportunity to analyze real-world DILI patterns. Unlike cohort studies limited by sample size, FAERS captures rare events across diverse demographics, enabling robust signal detection [17]. In this study, we utilize the FAERS database to investigate DILI specifically among adults under 60 years old. Our goals are to pinpoint the drugs most commonly associated with DILI reports in this age group, delineate the clinical and demographic features stratified by age, and shed light on potential risk modifiers. By pursuing these aims, we hope to bridge significant gaps in our understanding of DILI epidemiology, ultimately aiding in the improvement of drug safety monitoring, informing evidence-based clinical practices, and shaping regulatory policies tailored to the needs of younger patient populations.

2. Materials and methods

2.1. Main outcome measures

In this study, we extracted reports of drug-induced liver injury from the FAERS database, covering the period from January 1, 2007, to December 31, 2024. To systematically identify relevant cases,

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we screened preferred terms (PTs) using standardized MedDRA queries, focusing specifically on "drug-induced liver injury" and "liver injury."For the analysis of implicated medications, only reports in which a drug was classified as the "primary suspect drug" were retained. This restriction was applied to minimize ambiguity regarding causal attribution and to improve the reliability of subsequent signal detection.

2.2. Statistical analyses

To enhance the robustness of pharmacovigilance signal detection, we applied four complementary disproportionality analysis methods: the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multi-item Gamma Poisson Shrinker (MGPS). Each approach relies on distinct statistical assumptions, allowing for cross-validation of potential drug-event associations. Only drugs that met the predefined significance thresholds across all four algorithms were considered to have a meaningful association with DILI. To further refine the findings, we conducted a univariate regression analysis on the drugs that satisfied the disproportionality criteria. A Bonferroni correction was subsequently applied to adjust for multiple comparisons and reduce the likelihood of false-positive results. To characterize the timing of DILI onset, we calculated the interval between the date of adverse event occurrence (EVENT_DT) and the recorded medication start date (START_DT). This time-to-onset (TTO) metric was then compared across different therapeutic classes to explore variability in latency patterns.

3. Results

3.1. Baseline information on adverse reactions occurrence

Between 2007 and 2024, the FAERS recorded 17,464 reports of DILI involving individuals aged 18-60 years. The mean age of affected patients was 43.2±11.5 years, and females constituted 60.6%. With respect to clinical outcomes, over one-third of patients (35.33%) required hospitalization or experienced a prolonged hospital stay due to DILI. Physicians submitted the largest proportion of reports (5,778 cases, 33.1%), while consumer reports accounted for 14.4% of the total (Table 1).

During the study period from 2007 to 2024, the number of reported DILI cases exhibited an overall upward trajectory, reaching its highest level in 2024. Notably, the increase observed between 2018 and 2024 was substantially greater than that seen from 2007 to 2015. When stratified by sex, female cases were predominantly clustered in the 40-45 age group, whereas male cases were more concentrated among individuals aged 55-60 years (Fig 1A). Prior to 2012, the number of reported cases was comparable between males and females. From 2007 to 2020, both sexes showed similar growth patterns in reporting frequency; however, between 2023 and 2024, female reports rose sharply and markedly outpaced those of males (Fig 1B).

Table 1. Baseline data of drug-induced liver injury reported in the FAERS database from 2007 to 2024

Variables	Overall(n=17464,%)	Year	Cases(%)
Sex		2007	74 (0.4)
Female	10577 (60.6)	2008	186 (1.1)
Male	6688 (38.3)	2009	192 (1.1)

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Table 1. (continued)

missing	199 (1.1)	2010	204 (1.2)
Age		2011	324 (1.9)
Mean (SD)	43.2 (11.5)	2012	431 (2.5)
Median (P25, P75)	44.0 (35.0, 53.0)	2013	635 (3.6)
Occupation of the reporter		2014	697 (4.0)
Consumer	2526 (14.5)	2015	948 (5.4)
Lawyer	62 (0.4)	2016	806 (4.6)
Physician	5778 (33.1)	2017	838 (4.8)
Other health-professional	2892 (16.6)	2018	1296 (7.4)
Pharmacist	700 (4.0)	2019	1246 (7.1)
Unknown	5506 (31.5)	2020	1453 (8.3)
Patient outcome		2021	1601 (9.2)
Hospitalization(Initial or Prolonged)	6170(35.33)	2022	1697 (9.7)
Death	1959(11.22)	2023	1935 (11.1)
Life-Threatening	1596(9.14)	2024	2901 (16.6)
missing	554(3.17)		
Disability	225(1.29)		
Required Intervention to Prevent	12(0.07)		
Congenital Anomaly	3(0.01)		
Other	6945(39.77)		

Note:SD:standard deviation; P25: 25% Percent; P75: 75% Percent.

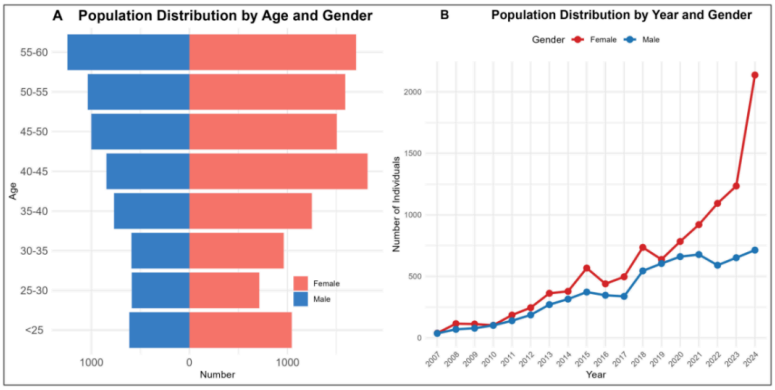

Figure 1. Characteristics of reports involved in Drug-Induced Liver Injury(DILI) from the FAERS database

3.2. Drug signal description verified

Of 959 drugs assessed, 17 met all four disproportionality thresholds and were classified as positive DILI signals (Table 2). These included three antibiotics, three immunosuppressants, and three NSAIDs. The highest ROR estimates were observed for Rifampicin(19.33, 95%CI: 16.41-22.77), Amoxicillin(16.39, 95%CI: 14.48-18.56), Epirubicin (15.34, 95%CI: 13.06-18.02), and Paracetamol (10.30, 95% CI: 9.61-11.04).

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Table 2. Statistical values of drugs associated with drug-induced liver injury

Drug classification	Case	ROR(95%Cl)	PRR(χ^2)	EBGM(EBGM05)	IC(IC025)
Paracetamol	876	10.3 (9.61-11.04)	10.00 (6764.63)	9.55 (9.02)	3.26 (3.15)
Ibuprofen	296	3.73 (3.32-4.18)	3.69 (573.01)	4.27 (4.00)	2.09 (1.98)
Diclofenac	239	5.58 (4.91-6.35)	5.5 (870.75)	3.65 (3.31)	1.87 (1.70)
Atorvastatin	246	3.92 (3.46-4.45)	3.89 (521.63)	15.37 (13.85)	3.94 (3.76)
Rosuvastatin	142	4.14 (3.51-4.89)	4.10 (331.46)	3.85 (3.46)	1.94 (1.76)
Methotrexate	655	4.44 (4.11-4.81)	4.40(1659.06)	5.44 (4.88)	2.44 (2.25)
Tocilizumab	179	4.15 (3.58-4.82)	4.11 (418.39)	6.15 (5.51)	2.62 (2.43)
Leflunomide	118	6.73 (5.61-8.09)	6.61 (559.61)	4.08 (3.60)	2.03 (1.81)
Methylprednisolone	117	6.33 (5.55-7.22)	6.22 (997.05)	14.52 (12.69)	3.86 (3.62)
Alendronic Acid	144	8.82 (7.47-10.42)	8.6 (961.80)	18.07 (15.76)	4.18 (3.94)
Rifampicin	154	19.33 (16.41-22.77)	18.22 (2492.53)	3.76 (3.28)	1.91 (1.67)
Epirubicin	157	15.34 (13.06-18.02)	14.64 (1984.03)	8.53 (7.42)	3.09 (2.85)
Oxaliplatin	138	4.12 (3.48-4.87)	4.07 (318.51)	4.08 (3.55)	2.03 (1.78)
Valproic Acid	147	3.82 (3.24-4.49)	3.78 (299.09)	4.05 (3.52)	2.02 (1.77)
Amoxicillin	266	16.39 (14.48-18.56)	15.6 (3590.22)	5.28 (4.58)	2.4 (2.15)
Azithromycin	137	5.39 (4.55-6.39)	5.31 (477.43)	2.53 (2.18)	1.34 (1.08)
Ciprofloxacin	129	2.55 (2.14-3.04)	2.54 (119.72)	6.57 (5.64)	2.72 (2.45)

Note: 95%CI, 95% confidence interval; χ^2, chi-squared; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM; IC, information component; IC025, the lower limit of 95% CI of the IC. ROR, reporting odds ratio; PRR, proportional reporting ratio.

Figure 2 shows the relationship between DILI and suspected drugs. The x-axis represents the log-transformed ROR; values above zero indicate that DILI was reported more frequently than other adverse events for a given drug. The y-axis corresponds to the negative log-transformed p-value derived from Fisher's exact test with Bonferroni adjustment. Each point in the plot reflects a specific drug, with its position and color indicating the strength of the drug-DILI association. Drugs located toward the upper right corner and displayed in darker shades represent stronger and more statistically significant signals. Paracetamol and Methotrexate appear with the darkest coloring and are positioned closer to the upper right region. In contrast, Isoniazid and Nitrofurantoin show a pronounced statistical signal despite having relatively small case numbers.

Figure 2. Drug-Induced Liver Injury-related drug volcano plots

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3.3. Induced time latency

The drugs with the shortest median incubation periods were Paracetamol (5.00 days), Methotrexate (5.00 days), and Methylprednisolone (6.00 days), respectively. Fig 3 showed the stacked bar chart of the adverse reaction induction time after the classification of 17 types of drugs and showed that the onset times of adverse reactions for all drugs were relatively concentrated and short. Analysis revealed that the median TTO for Hormonal Agents is the shortest (6.0 days), followed by NSAIDs and Metabolic Modulators, 7.0 days and 9.0 days respectively, whereas the median TTO for Antivirals is the longest (46.0 days).

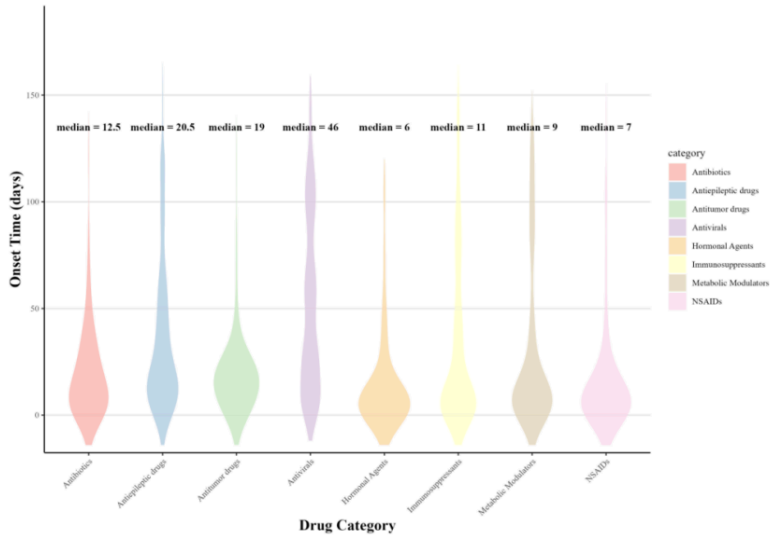

Figure 3. The distribution of onset times for Drug-Induced Liver Injury(DILI) caused by various medications

3.4. Gender subgroup analysis

To assess the impact of gender-related differences on the risk of DILI, we conducted a subgroup analysis using four pharmacovigilance indicators on males and females. Table 3 showed that among the DILI cases reported by females, out of the top 30 drugs, a total of 19 drugs passed all four tests. The top three drugs were Paracetamol (ROR=10.33, 95%CI:9.45-11.28), Methotrexate (ROR=5.03, 95%CI:4.59-5.51), Diclofenac (ROR=8.06, 95%CI:6.98-9.29), and Methylprednisolone (ROR=8.56, 95%CI:7.34-9.98). Additionally, Epirubicin(ROR=17.45, 95%CI:14.78-20.61), Alendronic Acid(ROR=10.9, 95%CI:9.20-12.92), Amoxicillin; Clavulanic Acid(ROR=15.22, 95%CI:12.79-18.11).

Table 3. Statistical values of drugs in females associated with drug-induced liver injury

DRUG	Case	ROR(95%Cl)	PRR(χ^2)	EBGM(EBGM05)	IC(IC025)
Paracetamol	533	10.33 (9.45 - 11.28)	10.03 (4126.49)	9.57 (8.89)	3.26 (3.13)
Methotrexate	499	5.03 (4.59 - 5.51)	4.97 (1510.71)	4.78 (4.43)	2.26 (2.12)
Adalimumab	227	0.46 (0.41 - 0.53)	0.46 (137.61)	0.48 (0.43)	-1.07 (-1.26)
Diclofenac	197	8.06 (6.98 - 9.29)	7.87 (1163.46)	7.74 (6.87)	2.95 (2.74)
Methylprednisolone	170	8.56 (7.34 - 9.98)	8.35 (1086.14)	8.23 (7.24)	3.04 (2.82)
Ibuprofen	163	3.67 (3.14 - 4.28)	3.63 (307.37)	3.59 (3.15)	1.85 (1.62)

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Table 3. (continued)

Tocilizumab	163	4.97 (4.25 - 5.81)	4.9 (500.58)	4.84 (4.25)	2.28 (2.05)
Epirubicin	149	17.45 (14.78 - 20.61)	16.55 (2152.93)	16.33 (14.21)	4.03 (3.79)
Secukinumab	147	2.24 (1.9 - 2.64)	2.23 (98.67)	2.21 (1.93)	1.15 (0.91)
Abatacept	145	2.05 (1.74 - 2.42)	2.04 (76.29)	2.03 (1.77)	1.02 (0.78)
Alendronic Acid	140	10.9 (9.2 - 12.92)	10.55 (1198.91)	10.43 (9.05)	3.38 (3.13)
Amoxicillin	135	15.22 (12.79 - 18.11)	14.53 (1684.69)	14.36 (12.41)	3.84 (3.59)
Quetiapine	134	1.86 (1.57 - 2.2)	1.85 (52)	1.84 (1.6)	0.88 (0.63)
Interferon Beta-1A	133	0.74 (0.62 - 0.88)	0.74 (12.02)	0.74 (0.64)	-0.43 (-0.68)
Atorvastatin	132	4.16 (3.5 - 4.94)	4.11 (308.19)	4.07 (3.53)	2.03 (1.77)
Etanercept	131	0.24 (0.21 - 0.29)	0.24 (303.49)	0.25 (0.22)	-1.98 (-2.23)
Lamotrigine	107	2.45 (2.03 - 2.97)	2.44 (90.35)	2.43 (2.07)	1.28 (1)
Leflunomide	95	7.34 (5.99 - 9.01)	7.19 (503.52)	7.14 (6.01)	2.84 (2.54)
Mycophenolic Acid	95	2.36 (1.92 - 2.89)	2.35 (72.99)	2.33 (1.97)	1.22 (0.93)
Trastuzumab	95	2.96 (2.42 - 3.62)	2.94 (120.87)	2.92 (2.47)	1.55 (1.25)
Natalizumab	90	0.37 (0.3 - 0.45)	0.37 (98.18)	0.37 (0.31)	-1.43 (-1.73)
Infliximab	86	0.82 (0.66 - 1.01)	0.82 (3.55)	0.82 (0.68)	-0.29 (-0.6)
Azithromycin	81	5.67 (4.55 - 7.07)	5.58 (303.55)	5.55 (4.61)	2.47 (2.15)
Rifampicin	79	21.79 (17.32 - 27.4)	20.37 (1448.78)	20.22 (16.69)	4.34 (4)
Duloxetine	75	1.7 (1.36 - 2.14)	1.7 (21.42)	1.69 (1.4)	0.76 (0.43)
Isoniazid	75	42.55 (33.38 - 54.24)	37.34 (2642.29)	37.08 (30.26)	5.21 (4.86)
Valproic Acid	75	4.53 (3.6 - 5.7)	4.48 (201.77)	4.45 (3.68)	2.15 (1.82)
Nitrofurantoin	74	16.79 (13.28 - 21.24)	15.95 (1032.87)	15.84 (13.01)	3.99 (3.64)
Pantoprazole	70	4.13 (3.26 - 5.23)	4.08 (162.37)	4.06 (3.33)	2.02 (1.68)
Rituximab	70	1.53 (1.21 - 1.93)	1.53 (12.64)	1.52 (1.25)	0.61 (0.26)

Note: 95%CI, 95% confidence interval; χ^2, chi-squared; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM; IC, information component; IC025, the lower limit of 95% CI of the IC. ROR, reporting odds ratio; PRR, proportional reporting ratio.

In the DILI cases reported by males among the top 30 drugs, 20 drugs passed all four tests (Table 4). The top drugs with notable risk signals were: Paracetamol (ROR=10.4, 95%CI:9.3-11.63), the most frequently reported, indicating a strong association with DILI; Amoxicillin; Clavulanic Acid (ROR=18.94, 95%CI:15.83-22.67), ranking high in disproportionality despite moderate case counts; Rifampicin (ROR=17.29, 95%CI:13.65-21.90) and Fenofibrate (ROR=16.59, 95%CI:12.59-21.86), both showing elevated ROR values and potential for strong risk signals. Additional drugs with notable risk metrics included Methotrexate (ROR=2.98, 95%CI:2.53-3.51) and Ibuprofen (ROR=3.6, 95%CI:3.02-4.28), which had higher case counts but moderate risk ratios. Despite smaller report numbers, Sulfamethoxazole; Trimethoprim (ROR=7.68, 95%CI:5.89-10.0) and Voriconazole (ROR=6.15, 95%CI:4.6-8.22) exhibited elevated disproportionality (Fig 4).

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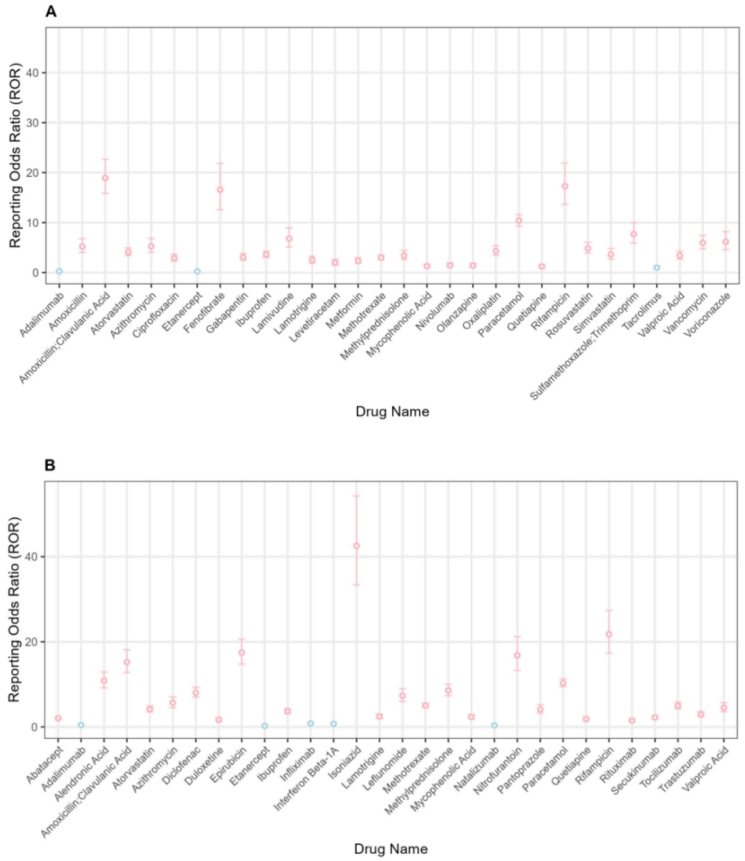

Figure 4. Sexal analysis of the top 30 drugs with the highest number of drug-induced liver injury(DILI) reported in the FAERS database

Notes: (A) Analysis of the top 30 drugs with the highest number of drug-induced liver injury(DILI) in males. (B) Analysis of the top 30 drugs with the highest number of drug-induced liver injury(DILI) in females.

Table 4. Statistical values of drugs in males associated with drug-induced liver injury

DRUG	Case	ROR(95%Cl)	PRR(χ^2)	EBGM(EBGM05)	IC(IC025)
Paracetamol	334	10.4 (9.3 - 11.63)	10.05 (2596.95)	9.6 (8.74)	3.26 (3.1)
Methotrexate	149	2.98 (2.53 - 3.51)	2.96 (189.51)	2.91 (2.54)	1.54 (1.3)
Ibuprofen	131	3.6 (3.02 - 4.28)	3.56 (237.65)	3.51 (3.04)	1.81 (1.56)
Amoxicillin	130	18.94 (15.83 - 22.67)	17.75 (2022.13)	17.42 (14.99)	4.12 (3.86)
Atorvastatin	112	4.09 (3.39 - 4.93)	4.04 (252.77)	3.99 (3.41)	2 (1.72)
Gabapentin	83	3.06 (2.46 - 3.8)	3.04 (112.3)	3.01 (2.51)	1.59 (1.27)
Rosuvastatin	83	4.85 (3.9 - 6.03)	4.78 (245.77)	4.73 (3.94)	2.24 (1.92)
Vancomycin	80	5.94 (4.75 - 7.42)	5.83 (317.62)	5.77 (4.79)	2.53 (2.2)
Oxaliplatin	78	4.3 (3.44 - 5.39)	4.25 (192.33)	4.21 (3.49)	2.07 (1.75)
Rifampicin	74	17.29 (13.65 - 21.9)	16.28 (1053.56)	16.11 (13.22)	4.01 (3.66)
Valproic Acid	72	3.39 (2.68 - 4.28)	3.36 (118.57)	3.34 (2.74)	1.74 (1.4)
Adalimumab	69	0.25 (0.2 - 0.32)	0.25 (154.55)	0.26 (0.21)	-1.96 (-2.3)
Metformin	69	2.34 (1.84 - 2.97)	2.33 (51.83)	2.31 (1.89)	1.21 (0.86)
Ciprofloxacin	68	2.89 (2.27 - 3.67)	2.87 (82.19)	2.85 (2.33)	1.51 (1.16)

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Table 4. (continued)

Quetiapine	68	1.21 (0.95 - 1.53)	1.21 (2.37)	1.2 (0.98)	0.27 (-0.08)
Olanzapine	62	1.41 (1.1 - 1.81)	1.41 (7.3)	1.4 (1.14)	0.49 (0.12)
Amoxicillin	57	5.2 (4 - 6.77)	5.12 (188)	5.08 (4.08)	2.35 (1.96)
Mycophenolic Acid	57	1.27 (0.98 - 1.65)	1.27 (3.2)	1.27 (1.02)	0.34 (-0.04)
Sulfamethoxazole;Trimethoprim	57	7.68 (5.89 - 10)	7.49 (318.89)	7.43 (5.96)	2.89 (2.51)
Azithromycin	56	5.25 (4.02 - 6.84)	5.16 (187.18)	5.13 (4.11)	2.36 (1.97)
Methylprednisolone	56	3.4 (2.61 - 4.44)	3.37 (93.09)	3.35 (2.69)	1.75 (1.36)
Fenofibrate	54	16.59 (12.59 - 21.86)	15.66 (737.93)	15.54 (12.34)	3.96 (3.56)
Lamotrigine	51	2.46 (1.87 - 3.25)	2.45 (43.61)	2.44 (1.93)	1.29 (0.88)
Levetiracetam	51	1.98 (1.5 - 2.61)	1.97 (24.36)	1.97 (1.56)	0.97 (0.57)
Lamivudine	50	6.78 (5.11 - 8.98)	6.63 (238.2)	6.59 (5.2)	2.72 (2.31)
Tacrolimus	49	0.98 (0.74 - 1.3)	0.98 (0.02)	0.98 (0.77)	-0.03 (-0.44)
Nivolumab	48	1.44 (1.08 - 1.91)	1.43 (6.27)	1.43 (1.13)	0.52 (0.1)
Etanercept	47	0.22 (0.16 - 0.29)	0.22 (131.49)	0.22 (0.18)	-2.16 (-2.58)
Simvastatin	47	3.61 (2.7 - 4.82)	3.58 (86.91)	3.56 (2.79)	1.83 (1.41)
Voriconazole	47	6.15 (4.6 - 8.22)	6.03 (196.66)	6 (4.7)	2.58 (2.16)

Note: 95%CI, 95% confidence interval; χ^2, chi-squared; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM; IC, information component; IC025, the lower limit of 95% CI of the IC. ROR, reporting odds ratio; PRR, proportional reporting ratio.

4. Discussion

We analyzed DILI cases in individuals aged 18-60 using the FAERS database. Since 2007, the number of reported cases in this age group has steadily increased, reaching a peak in 2024. Among 959 drugs associated with DILI, we focused on the 30 most frequently reported. Disproportionality analysis identified 17 drugs with particularly strong associations. These results provide insight for more tailored DILI management and highlight adverse reactions that could be considered for drug labeling. While generally consistent with known hepatotoxic profiles, the findings also draw attention to immunosuppressants and NSAIDs as notable but often overlooked risks in younger adults [18,19].

The upward trend in DILI reports from 2007 to 2024, particularly the sharp rise after 2018, may reflect increased awareness of hepatotoxicity, changes in prescribing patterns, or the introduction of new medications with underrecognized hepatic risks. The predominance of females (60.6%) aligns with prior studies suggesting sex-based differences in drug metabolism and immune responses [5], potentially increasing susceptibility to DILI in women. The age distribution peak in females (40-45 years) compared to males (55-60 years) could be linked to hormonal influences or gender-specific medication use, such as, oral contraceptives in younger women and cardiovascular drugs in older males [20].

Due to the lack of an exact denominator for drug use, it is impossible to determine the actual incidence of DILI caused by each drug, to compare the risk differences between drugs. To address this issue, we introduced disproportionality analysis as an alternative to quantify the DILI risk of each drug. Previous studies have reported drug-induced allergies [17], as well as hepatotoxicity of drugs such as CDK4/6 inhibitors [21], Enoxaparin [22], and antipsychotics [23], using this method. This study identified 17 high-risk drugs associated with DILI in 18-60-year-old people, with

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Rifampicin (ROR=19.33, 95%CI: 16.41-22.77), Amoxicillin/Clavulanic Acid (ROR=16.39, 95%CI: 14.48-18.56), and Paracetamol (ROR=10.3, 95%CI: 9.61-11.04) demonstrating the strongest signals. These findings align with established Hepatotoxicity profiles, where Rifampicin and Amoxicillin/Clavulanic acid are well-documented causes of idiosyncratic liver injury, and paracetamol overdose is a leading cause of acute liver failure [24-26]. Notably, Immunosuppressants and NSAIDs also featured prominently, underscoring the need for vigilance in chronic use.

Our subgroup analysis highlights significant gender-based differences in DILI risk profiles, underscoring the importance of developing gender-specific pharmacovigilance approaches. Among the top 30 reported drugs, women demonstrated a higher sensitivity to hepatotoxic signals; Certain drugs, notably Isoniazid with a reported female ROR of 42.55 (compared to an unspecified male ROR) and Epirubicin with an EBGM05 exceeding 15 in women, demonstrated remarkable disproportionality in female patients despite lower case numbers. This suggests an inherent gender-specific susceptibility to these medications. An American prospective cohort study revealed that acetaminophen overdose and specific drug reactions have surpassed viral hepatitis as the leading cause of acute liver failure, disproportionately affecting women more than men [27]. This trend contrasts sharply with Paracetamol, which demonstrated comparable ROR values between genders, possibly due to its widespread use as a primary analgesic rather than gender-specific toxicity.

The underlying mechanisms responsible for these differences likely involve complex interactions among pharmacokinetics, hormonal environments, and immune system responses. As an example, Methotrexate, which was reported almost 3.4 times more often in females, exhibited a significantly ROR in women (5.03, 95%CI: 4.59 - 5.51) compared to men (2.98, 95%CI: 2.53 - 3.51). This could stem from sex-specific metabolic pathways or higher prescribing rates for autoimmune conditions in females. Similarly, elevated ROR of Diclofenac in females may relate to progesterone-enhanced cytochrome P450 2C9 activity, increasing reactive metabolite formation. Conversely, Amoxicillin-Clavulanic Acid showed stronger hepatotoxic signals in males, potentially implicating androgen-regulated immune activation or reporting biases linked to antibiotic prescribing patterns [28,29].

The discrepancy between case counts and disproportionality metrics underscores complex risk dynamics. Despite having fewer female cases (n=79 versus 74 in males), Rifampicin demonstrated a higher ROR in females compared to males, even exceeding the reported ROR for Paracetamol, Methotrexate, and Adalimumab. This could potentially be attributed to interactions between estrogen and Rifampicin, which may alter hepatic transporter expression [30]. On the other hand, the predominantly male signal for Fenofibrate, which was not observed in females, might indicate sex hormone-mediated differences in lipid metabolism. These observations are consistent with preclinical data showing reduced susceptibility to certain hepatotoxins in ovariectomized rodents, which is reversible with estrogen supplementation [31]. Previous studies have indicated high liver toxicity associated with Tocilizumab, corroborating the findings of this study [32]. Notably, the reported cases of DILI related to this drug were considerably more frequent among women than men, a gender disparity that remains unacknowledged in the drug's instructions. Consequently, we suggest that the increased sensitivity of liver function in women be considered, and monitoring efforts be intensified during the administration of this drug.

The observed TTO heterogeneity across drug classes carries clinical implications. A study on NSAIDs and DILI indicates that the latency period for DILI induced by NSAIDs (Celecoxib, Meloxicam, and Oxaprozin) is shorter (31.0, 22.5, and 16.0 days, respectively), which is consistent with the results of this article [33]. NSAIDs (median TTO: 7.0 days) likely induce rapid hepatocellular injury via direct mitochondrial toxicity, whereas Antivirals (median TTO: 46.0 days) may involve delayed immune-mediated mechanisms. Leflunomide latency (median TTO: 119.5

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days) aligns with its long half-life and cumulative toxicity. The results suggest that drugs with a longer median incubation period in the 18-60 age group should be regularly followed up to ensure good drug prognosis.

While disproportionality analysis (ROR) is a robust tool for signal detection, it cannot establish causality due to inherent limitations of spontaneous reporting systems, including underreporting and confounding by indication. Additionally, TTO estimates may be skewed by recall bias or incomplete medical records. Future studies should integrate electronic health records to validate latency periods and adjust for covariates.

5. Conclusion

Clinicians should prioritize hepatic monitoring for high-risk drugs (rifampicin, paracetamol), particularly in vulnerable populations. Regulatory agencies might consider updating drug labels to reflect class-specific TTO patterns. For instance, liver enzyme levels every 6 months during long-term medication, while the recommendation for NSAIDs is to monitor liver function within 7 days after prescription.

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