**Drug-Induced Liver Injury in Latin America: 10-year experience of the Latin American DILI (LATINDILI) Network**

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**List of abbreviations:** AAS: anabolic androgenic steroids; ALP: alkaline phosphatase; ALT: alanine transaminase; anti-TB: anti-tuberculosis drugs; AST: aspartate aminotransferase; ATC: Anatomical Therapeutic Chemical; Chol: cholestatic; CNS: central nervous system; d: days; DILI: drug induced liver injury; DILIN: Drug-Induced Liver Injury Network; GGT: gamma-glutamyl transferase; Hep: hepatocellular; HDS: herbal and dietary supplements; INR: international normalized ratio; IQR: interquartile range; Mix: mixed; NA: data not available; NSAID: non-steroidal anti-inflammatory drug; RUCAM: Roussel Uclaf Causality Assessment Method; LATINDILI Network: Latin American DILI Network; SD: standard deviation; TBL: total bilirubin; ULN: upper limit of normal; y: years.

**Abstract**

**Background and aims:** Latin America is a region of great interest for studying the clinical presentation of idiosyncratic drug-induced liver injury (DILI). A comprehensive analysis of patients enrolled into the LATINDILI Network over a decade is presented.

**Methods:** Demographics, clinical presentation, histological findings and outcome of prospectively recruited DILI cases in the LATINDILI Network were analyzed. Suspected culprit drugs were classified according to the Anatomical Therapeutic Chemical classification. Causality was assessed using the Roussel Uclaf Causality Assessment Method (RUCAM) scale.

**Results:** Overall, 468 idiosyncratic DILI cases were analyzed (62% women, mean age 49 years). Hepatocellular injury predominated (62%), jaundice was present in 60% of patients and 42% were hospitalized. 4.1% of the cases had a fatal outcome, and 24 (12%) patients developed chronic DILI. The most common drug classes were systemic anti-infectives (31%), musculoskeletal agents (12%), antineoplastic and immunomodulating agents (11%), and herbal and dietary supplements (HDS, 9%). Notably, none of the patients with DILI due to antibacterials or immunosuppressants had a fatal outcome. In fact, Hy's law showed to have drug-specific predictive value, with anti-tuberculosis drugs, nimesulide and HDS associated with the worst outcome, whereas DILI caused by amoxicillin-clavulanate, nitrofurantoin and diclofenac that fulfilled Hy's law did not have a fatal outcome.

**Conclusion:** Features of DILI in Latin America are comparable to other prospective registries. However, the pattern of drugs responsible for DILI differs. An increasing incidence of HDS, with high mortality rate, and likewise nimesulide and nitrofurantoin was noted. Thus, public health policies should raise awareness of the potential adverse effects of these compounds.

**Keywords:** drug-induced liver injury; hepatotoxicity; Latin America; prospective; acute liver failure

**What you need to know**

*Background*

- Latin America is a region that represents a unique scenario for studying the clinical presentation of idiosyncratic drug-induced liver injury (DILI).

*Findings*

- Features of DILI in Latin America are comparable to other prospective registries.
- The different pattern of drugs responsible for DILI highlights an increasing incidence of herbal and dietary supplements, with high mortality rate associated with its use.

*Implications for patient care*

- Regulatory policies are warranted as common DILI-causing drugs in Latin America are either second-line drugs, no longer in use or withdrawn from other markets due to liver toxicity.

## Introduction

Detection of idiosyncratic drug-induced liver injury (DILI) is hampered by its multifactorial and unpredictable nature. Its diagnosis relies on the exclusion of alternative causes. Compounded by the relatively low incidence, heterogeneous presentation and the lack of specific biomarkers, DILI stands out among liver disorders as being particularly challenging to diagnose and treat.[1]

Latin America is a vast and diverse geographical region with different racial, ethnic and genetic backgrounds. Prescribing patterns can differ significantly from those in Western countries, and there is also a high rate of self-medication, which can be seen as a response to problems with drug availability, prescription policies, pharmacovigilance systems and access to health services. Furthermore, the use of traditional medicine and herbal remedies is deeply rooted in these countries. These characteristics make this region an area of great interest for studying differences in drug responses and clinical presentations of DILI.[2]

Previous epidemiological data in this region are mainly derived from small retrospective studies. Prior investigations identified nimesulide, cyproterone acetate, nitrofurantoin, anti-tuberculosis drugs and flutamide as the main agents responsible for DILI[3], while a recent review focused on herbal and dietary supplements (HDS) reported 23 published cases, mainly due to *Centella asiatica* and *Carthamus tinctorius*.[4]

The establishment of prospective DILI registries has been considered the most reliable source of data, as they provide detailed characterization of DILI cases collected according to a structured protocol. Therefore, the creation of a multinational DILI registry in Latin America was considered a necessary strategy to increase awareness of this condition, improve surveillance, facilitate collaboration between healthcare professionals and institutions, and gain further insight into DILI in Latin America. In 2011 the Latin

American DILI (LATINDILI) Network held its first meeting with the support of the Spanish DILI Registry and the Latin American Association for the Study of the Liver.[5]

Here, we present clinical characteristics, outcome, histological features and culprit drugs responsible for DILI in 468 patients included in the LATINDILI Network over a 10-year time period.

## Methods

*Study population*

The LATINDILI Network is a prospective registry that identifies *bona fide* idiosyncratic DILI cases and collects detailed demographics, clinical and laboratory parameters at DILI recognition and during follow-up, imaging and histological information, and outcome of the DILI episode, using a standardized case report form.[5] Being coordinated by the Spanish DILI group, LATINDILI Network has the same operational structure as the Spanish DILI Registry in terms of inclusion criteria, data collection and causality assessment.[6] This study includes all idiosyncratic DILI cases recorded in the LATINDILI Network since its inception until July 2022. Dose-related intrinsic DILI cases, re-exposures, and second episodes of DILI were excluded. The study protocol was approved by local ethics committees, and all subjects provided written informed consent.

The biochemical criteria for DILI and grade of severity of the DILI episode were those proposed by an international expert working group.[7] The pattern of liver injury was classified based on biochemical parameters from the first available blood test after DILI recognition to calculate the R value (alanine aminotransferase [ALT]/upper limit of normal [ULN])÷(alkaline phosphatase [ALP]/ULN). Liver injury was classified into hepatocellular ($R \geq 5$), cholestatic ($R \leq 2$), or mixed injury ($R > 2$ and $< 5$). The causal

relationship between the suspected drug and liver damage was determined by consensus of three independent experts from the coordinating center. Case likelihood categorization was based on Roussel Uclaf Causality Assessment Method (RUCAM) categories.[8]

The definition of Hy's law was R≥5 and total bilirubin >2 times ULN, while nR-based Hy's law was defined as nR≥5 and total bilirubin >2 times ULN.[9] Chronic DILI was defined as incomplete biochemical resolution (liver parameters below ULN) one year after DILI recognition.[10] Eosinophilia was defined as serum eosinophils exceeding 4-6% of total leukocyte count depending on the normal range of individual hospitals, and lymphopenia as serum lymphocytes <10%, both based on blood work at DILI recognition. Rash was defined as acute skin injury with changes in skin texture or color that may appear inflamed or irritated. Hypersensitivity was considered when any of the following features were present at DILI recognition: fever, rash, eosinophilia, lymphopenia, or arthralgia. Comorbidity burden was calculated using Charlson's Comorbidity Index.[11] The suspected culprit drugs were classified according to the Anatomical Therapeutic Chemical classification (ATC) into pharmacological groups and subgroups. Histological findings were classified based on a proposed diagnostic classification.[12]

*Statistical analysis*

For quantitative data, mean and standard deviation (SD), or median and interquartile range (IQR) were presented, and differences between groups were tested using Student's t-test or Mann-Whitney U test, as appropriate. Categorical data were described using frequency distributions, and differences were compared using the chi-square test or Fisher's exact test, as appropriate. Frequencies were calculated based on available data. Prognostic factors of worse outcome (severe or fatal liver injury) were explored through a backward stepwise *logit* model. The C-statistic was used to assess the discriminative power of the model. All results were deemed statistically significant when a two-sided p-

value was lower than 0.05. All analyses were performed using STATA version 17 (Stata Corporation, College Station, TX, USA) and R version 4.3.0 (R Core Team, 2023).

## Results

A total of 483 DILI cases were included in the LATINDILI Network. Of them, three were intrinsic DILI cases, two were second DILI episodes (due to azathioprine and norethisterone), and ten were positive rechallenge (diclofenac (n=2), clopidogrel, Herbalife® products (n=2), sertraline, ibuprofen, methylprednisolone, *Croton cajucara* Benth, and *Peumus boldus*), and were excluded. Thus, a total of 468 idiosyncratic DILI cases were included in the current study **(Supplemental figure 1)**. The vast majority of DILI cases were caused by a single drug (88%). According to RUCAM scale, 25% were scored as possible, 69% probable, and 6.1% highly probable. Of note, in this cohort, nine cases (1.9%) were drug-induced autoimmune-like hepatitis, and 24 (5.1%) were DILI associated with drug reaction with eosinophilia and systemic symptoms. In-depth characterization of these cases, as well as those with positive rechallenge, has been published elsewhere.[13-15]

### *Demographics, clinical characteristics and outcome*

Most cases were female (62%), with a mean age of 49 years. Patients with hepatocellular damage, however, were younger than those with cholestatic injury (mean age 45 vs. 55 years, respectively; $p<0.001$). Hepatocellular liver damage predominated (62%), while 24% and 14% of cases had cholestatic and mixed injury, respectively. 7.1% of cases had an underlying chronic liver disease, mainly steatosis or metabolic dysfunction-associated steatotic liver disease (64%) and autoimmune hepatitis (15%).

Over half of the patients presented with jaundice (60%), particularly those who developed cholestatic or mixed injury (p=0.005). 42% of cases were hospitalized due to DILI. Median duration of therapy until DILI recognition was 34 days, with patients who had hepatocellular damage having significantly longer duration of therapy than those with mixed injury (40 vs. 26 days, respectively; p=0.002). Furthermore, 22% of patients had positive autoantibody titers, with a higher prevalence among patients with hepatocellular injury than patients with cholestatic damage (26% and 12%, respectively; p=0.006). Moreover, platelet count was diminished in patients with hepatocellular injury compared to those with cholestatic or mixed liver damage (p=0.009).

In terms of severity, half of the patients presented moderate injury (53%), while 6.2% had severe injury, and 4.1% developed acute liver failure (ALF). Cases with cholestatic and mixed pattern mostly developed mild or moderate injury, whereas those with a hepatocellular pattern had a higher proportion of severe injury or developed ALF (p<0.001). Indeed, among the ten cases who died from liver-related causes, nine had hepatocellular damage, as well as the nine cases who underwent a liver transplantation. Lower albumin levels, presence of rash, and increased total bilirubin and ALT levels at DILI recognition were found to be prognostic factors of worse outcome (C-statistic 0.879; 95% confidence interval 0.802-0.955). In addition, among those cases with follow-up until DILI resolution (n=206), 24 (12%) developed chronic DILI **(Table 1)**.

Distribution of DILI patients according to pattern of liver injury, age and sex is shown in **Figure 1**. To determine the influence of pattern of liver injury and age in clinical presentation and outcome of DILI, we divided the cohort into three age groups (≤45 years, 46-64 years, and ≥65 years). Independent of pattern of liver injury, prevalence of comorbidities, such as hypertension and dyslipidemia, and number of concomitant drugs were higher at older age. Moreover, in the hepatocellular DILI cases, we observed a trend

towards longer duration of therapy and latency with increasing age (p=0.012 and p=0.001, respectively), while in cholestatic/mixed cases, the rise in ALP was markedly higher in older patients compared with younger patients **(Supplemental table 1)**.

*Culprit drugs*

The ATC groups and subgroups of drugs associated with the highest number of cases were anti-infectives for systemic use (31%), musculo-skeletal system drugs (12%), and antineoplastic and immunomodulating agents (11%) **(Supplemental table 2)**. Among the 9% of cases due to HDS the most frequent herbal product was *Camellia sinensis* (n=9, 21%), followed by *Garcinia cambogia* (n=6, 14%) and Herbalife® products (n=4, 9.5%), for which the last case was reported in 2012. Stanozolol was the main anabolic androgenic steroid (AAS), accounting for 74% of AAS-DILI cases.

A total of 121 different drugs were responsible for DILI. The most frequent culprit drugs were amoxicillin-clavulanate (n=58, 12%), HDS (n=42; 9.0%), anti-tuberculosis (anti-TB) drugs (n=27; 5.8%), AAS (n=23, 4.9%), nitrofurantoin (n=20; 4.3%) and diclofenac (n=19; 4.1%) (**Table 2)**. Some drugs were predominantly associated with hepatocellular presentation of liver damage (HDS, anti-TB drugs, nitrofurantoin, ibuprofen, methyldopa, or cyproterone acetate), whereas DILI due to amoxicillin-clavulanate, atorvastatin and azathioprine presented with cholestatic damage. Furthermore, some drugs such as methyldopa, nitrofurantoin, azathioprine, nimesulide and fenofibrate were responsible for DILI mainly in women. Notably, we detected that the predictive value of Hy's law was drug-specific, i.e., 20% of DILI patients caused by amoxicillin-clavulanate and 35% of cases due to nitrofurantoin fulfilled Hy's law but none of these patients had a fatal outcome, whereas among those patients with DILI due to HDS, anti-TB drugs or nimesulide who fulfilled Hy's law, 20-50% died or needed a liver transplantation. A

graphical representation of the predictive value of Hy's law stratified by drugs is depicted in **Figure 2**.

When studying the clinical characteristics and outcome of the main therapeutic classes, we observed that most patients were women in all groups, except for AAS (87% of male patients). Hepatocellular injury predominated in DILI due to HDS and non-steroidal anti-inflammatory drugs (NSAIDs). It is also worth noting that 91% of cases due to AAS presented with jaundice, and nearly 70% of cases due to nervous system drugs had hypersensitivity features. Interestingly, the majority of cases due to immunosuppressants had mild liver injury. In addition, none of the patients who had DILI due to antimicrobials or immunosuppressants had a fatal outcome, while HDS cases had the highest rate of ALF (14%) (**Table 3**).

*Histological findings*

A total of 80 patients (17% of the cohort) had a liver biopsy or histological evaluation of the explanted liver (**Table 4**). There was no strict correlation between the biochemical classification of DILI and histological features. The most common finding was cholestatic hepatitis (n=20, 25%), followed by acute cholestasis and acute hepatitis (n=10 each, 13%). In addition, nine patients showed zonal necrosis and five cases developed massive necrosis. 15% of cases showed chronic damage, classified as chronic hepatitis (n=9) or chronic cholestasis (n=3), two of which developed ductopenia. In addition, eight cases had hepatic steatosis, two of which had steatohepatitis and macrovesicular steatosis as the only histological findings, and six had mild steatosis associated with other major pathological findings.

## Discussion

This is the first study to report a comprehensive analysis of DILI cases included in the prospective LATINDILI Network. This network has allowed prospective identification and characterization of more than 450 patients over a decade, underscoring its role as a key tool for compiling well-vetted DILI cases and improving the study of clinical characteristics and outcomes of DILI, the characterization of drugs responsible for liver damage, and the analysis of prescribing patterns in Latin America.

In **Supplemental table 3**, we compared our findings with other international prospective registries.[6,16-19] The mean age of patients in the LATINDILI Network was comparable to those in the Drug-Induced Liver Injury Network (DILIN), but younger than those in the Spanish, Japanese and European DILI registries. In addition, female sex predominated in our cohort as well as in other registries, with the exception of the Indian Network of DILI where less than half of the patients were females. It is possible that differences in demographics and access to health care could explain these disparities.[20]

Hepatocellular damage was the most common pattern of liver injury in DILI patients across all registries, except for the Indian registry. Hepatocellular injury was more common in younger age groups, with an upward trend in the prevalence of cholestatic injury in older age groups, in line with previous findings in the Spanish DILI registry.[21,22] However, the exact mechanisms underlying this age-dependent change in pattern of liver injury remains to be elucidated. Another remarkable finding was the hospitalization rate in the LATINDILI Network, comparable to the DILIN but lower than other registries, despite the similar proportion of DILI cases that presented with jaundice in all cohorts.[6,16-18] One possible explanation for these disparities could be attributed to existing differences in health systems and access to health care across countries and regions.[20]

The proportion of cases with mild or moderate damage was comparable across registries, but the proportion of patients who had developed severe injury or progressed to ALF was

lower than those in the DILIN and the Indian Network of DILI. This overrepresentation of poor outcome in the last two registries compared to the LATINDILI Network could be attributed to a higher comorbidity burden in these populations, which have been associated with an increased risk of death in DILI patients,[23] and the higher hospitalization rate among Indian cases. Remarkably, we observed that there were no cases of death or liver transplantation in DILI cases related to certain drugs despite fulfilling Hy's law, as previously reported in other studies.[6,16] Although the limited number of cases that fulfilled Hy's law prevents us from drawing solid conclusions, this finding suggests that this prognostic model might be drug-specific.

Consistently with what has been described in other Western prospective DILI registries,[6,16,18] amoxicillin-clavulanate was the leading culprit drug responsible for DILI in the LATINDILI Network. Noticeably, HDS were the second most frequent culprit drug in our cohort, accounting for nearly 10% of DILI cases. Such a high incidence of DILI due to HDS has been reported previously in Asian countries, e.g., a nationwide Chinese study found that over 25% of DILI cases were caused by HDS, possibly explained by the widespread use of Traditional Chinese Medicine.[24] Conversely, in our cohort, herbal products were mainly taken for weight loss without medical prescription, as occurs in the United States.[25] The misleading social perception that HDS have no harmful effects, coupled with the increasing number of DILI cases due to these products in recent years[26,27], may indicate that the incidence of herbal-associated liver injury is underreported in Latin America. In addition, given the risk of liver-related death and liver transplantation associated with use of HDS, public health campaigns to raise awareness of these possible consequences are warranted.

In addition, AAS were responsible for nearly 5% of DILI cases. Contrary to what has been described for HDS, the incidence of DILI due to AAS has not shown an upward

trend in Latin America.[26] These patients mostly presented with jaundice, and developed moderate liver injury, although one patient died. Our findings are consistent with two case series, which reported a remarkable prevalence of jaundice, albeit no patients evolved into ALF, and an absence of increased gamma-glutamyl transferase (GGT) levels despite increased ALP levels.[28,29] These normal GGT levels seen in the cholestatic phenotype suggest genetic variations in the *ABCB11* gene, which encodes the bile salt export pump transporter, as this phenomenon also occurs in benign recurrent intrahepatic cholestasis, which results in a deficient transporter causing episodes of cholestasis with spontaneous normalization characterized by normal GGT levels and elevated serum bile salts.[30] In fact, in a DILIN series, up to 20% of patients with AAS hepatotoxicity had mutations in *ABCB11*[29], whilst the estimated frequency of the mutation in the general population is 0.33%.[31]

Contrary to evidence that points towards DILI due to AAS as being a male-driven condition, in this LATINDILI Network cohort AAS-induced liver damage was reported in some female patients. A woman aged 54 years who took halodrol for muscle hypertrophy, with no underlying liver conditions, died due to ALF. Likewise, in an Australian case series of AAS-DILI, mainly composed of males, most of the patients presented with jaundice, were hospitalized and one patient underwent liver transplantation.[32]

Regulatory policies and prescribing patterns can also explain the higher incidence of DILI with certain drugs compared to other countries or regions. For instance, the higher number of cases of nitrofurantoin-induced liver injury in the LATINDILI Network compared with the Spanish DILI Registry could be explained by higher prescription rates for a longer period of time, compared to a more restrictive use of nitrofurantoin in Spain.[33] Likewise, nimesulide, an NSAID that accounts for 3% of cases in the LATINDILI Network, was

never marketed in the United States, was withdrawn from the market in Spain in 2002 due to high incidence of ALF associated with its use[34], and the European Medicines Agency has restricted its use since 2012.[35]

This is the largest cohort of DILI patients analyzed in Latin America. However, some limitations should be acknowledged. We only analyzed clinical data due to the lack of biological samples. Nonetheless, the LATINDILI Network is committed to improve the infrastructure to foster systematic serial collection of biological samples to conduct future pharmacogenetic studies.[27]

In conclusion, the findings from this large cohort of Latin American DILI cases highlight the importance of this prospective registry as a public health tool. The characteristics of DILI in Latin America are comparable to other prospective registries. Nevertheless, the differential pattern of drugs responsible for DILI, with an increasing incidence of HDS and a high mortality rate associated with their use, calls for public health policies to raise awareness of the potential adverse effects of these compounds. In addition, regulatory policies and different prescribing patterns can explain the increased incidence of DILI of certain drugs, such as nitrofurantoin and nimesulide, in Latin American. These findings have regulatory implications for the promotion of public health, as common DILI-causing drugs in Latin America are either second-line drugs, no longer in use or have been withdrawn from other markets due to liver toxicity.

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**Table 1.** Comparison of demographics, clinical characteristics, laboratory parameters and outcome according to pattern of liver injury in 468 cases in the Latin American DILI (LATINDILI) Network.

| | **Total registry n=468** | **Hepatocellular n=289 (62%)** | **Cholestatic n=112 (24%)** | **Mixed n=67 (14%)** | **p value** |
|---|---|---|---|---|---|
| Age (y), mean±SD | 49±18 | 45±17[a] | 55±17 | 51±17 | <0.001 |
| Female sex, n (%) | 290 (62) | 182 (63) | 65 (58) | 43 (64) | 0.607 |
| Body mass index (kg/m$^2$), mean±SD | 26±5.3 | 26±4.9 | 26±6.7 | 26±4.7 | 0.424 |
| Diabetes, n (%) | 31 (6.7) | 16 (5.6) | 12 (11) | 3 (4.5) | 0.156 |
| Hypertension, n (%) | 102 (22) | 60 (21) | 33 (29)[c] | 9 (13) | 0.040 |
| Dyslipidemia, n (%) | 27 (5.8) | 15 (5.2) | 10 (8.9) | 2 (3.0) | 0.224 |
| Underlying hepatic disease, n (%) | 33 (7.1) | 20 (6.9) | 8 (7.1) | 5 (7.5) | 0.966 |
| History of drug allergy, n (%) | 17 (3.8) | 9 (3.3) | 5 (4.6) | 3 (4.6) | 0.723 |
| Charlson comorbidity index, median (IQR) | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0.773 |
| *DILI episode characteristics* | | | | | |
| Jaundice, n (%) | 274 (60) | 151 (54)[a,b] | 76 (68) | 47 (70) | 0.005 |
| Hospitalization, n (%) | 195 (42) | 114 (39) | 54 (48) | 27 (40) | 0.271 |
| Hypersensitivity features, n (%) | 172 (41) | 102 (40) | 43 (43) | 27 (43) | 0.803 |
| Rash, n (%) | 66 (14) | 35 (13) | 18 (16) | 13 (20) | 0.265 |
| Total daily dose (mg), median (IQR) | 250 (86-1,000) | 200 (100-850) | 200 (50-1,875) | 250 (75-2,000) | 0.560 |
| Duration of therapy (d), median (IQR) | 34 (11-83) | 40 (14-93)[b] | 32 (11-76) | 26 (10-44) | 0.013 |
| Time to onset (d), median (IQR) | 30 (11-68) | 33 (11-83) | 28 (13-52) | 27 (14-43) | 0.140 |
| Most frequent culprit drugs, % | | | | | |
| | Amoxicillin-clavulanate (12) | HDS (11) | Amoxicillin-clavulanate (23) | Amoxicillin-clavulanate (21) | |
| | HDS (9.0) | Anti-TB (8.0) | AAS, atorvastatin (5.4) | Nimesulide (9.0) | |
| | Anti-TB (5.8) | Amoxicillin-clavulanate (6.2) | Azathioprine, diclofenac, HDS (4.5) | HDS (7.5) | |
| Concomitant drugs, n (%) | | | | | 0.169 |
| None | 179 (38) | 114 (39) | 39 (35) | 26 (39) | |
| 1-2 | 193 (41) | 127 (44) | 40 (36) | 26 (39) | |
| 3-4 | 68 (15) | 35 (12) | 22 (20) | 11 (16) | |

| | | | | | |
|---|---|---|---|---|---|
| ≥5 | 28 (6.0) | 13 (4.5) | 11 (9.8) | 4 (6.0) | |
| Eosinophilia, n (%) | 88 (21) | 49 (19) | 25 (25) | 14 (22) | 0.383 |
| Lymphopenia, n (%) | 31 (7.2) | 22 (8.5) | 6 (5.6) | 3 (4.8) | 0.554 |
| Positive autoantibody titers, n (%) | 90 (22) | 67 (26)[a] | 12 (12) | 11 (20) | 0.018 |
| *Liver parameters at onset (x ULN), median (IQR)* | | | | | |
| Aspartate aminotransferase (AST) | 6.5 (3.1-17) | 12 (5.4-25)[a,b] | 2.4 (1.6-4.7)[c] | 5.9 (3.4-9.9) | <0.001 |
| Alanine aminotransferase (ALT) | 9.7 (5.4-19) | 14 (8.7-29)[a,b] | 3.4 (2.0-5.4)[c] | 9.1 (6.0-12) | <0.001 |
| Alkaline phosphatase (ALP) | 1.7 (1.0-2.9) | 1.1 (0.8-1.6)[a,b] | 3.6 (2.8-5.5)[c] | 2.5 (2.0-3.6) | <0.001 |
| Total bilirubin | 4.0 (1.0-8.9) | 3.4 (0.8-8.6) | 5.8 (1.1-11) | 4.1 (1.4-7.1) | 0.093 |
| Albumin (g/dL), mean±SD | 3.8±0.7 | 3.8±0.7 | 3.7±0.6 | 4.0±0.5 | 0.176 |
| Platelets (x $10^3$/mL), median (IQR) | 233 (181-284) | 221 (176-274)[a,b] | 255 (197-303) | 256 (210-294) | 0.009 |
| Severity, n (%) | | | | | <0.001 |
| Mild | 173 (37) | 121 (42)[a,b] | 36 (32) | 16 (24) | |
| Moderate | 246 (53) | 126 (44)[a,b] | 70 (63) | 50 (75) | |
| Severe | 29 (6.2) | 23 (8.0)[a,b] | 5 (4.5) | 1 (1.5) | |
| Fatal/liver transplantation | 19 (4.1) | 18 (6.3)[a,b] | 1 (0.9) | 0 (0) | |
| *Outcome* | | | | | |
| Liver-related death, n (%) | 10 (2.1) | 9 (3.1) | 1 (0.9) | 0 (0) | 0.226 |
| Liver transplantation, n (%) | 9 (1.9) | 9 (3.1) | 0 (0) | 0 (0) | 0.057 |
| Death due to other causes, n (%) | 6 (1.3) | 5 (1.7) | 1 (0.9) | 0 (0) | 0.849 |
| Time to resolution (d), median (IQR) | 63 (34-118) | 57 (30-114) | 78 (45-134) | 65 (37-105) | 0.103 |
| Chronic DILI, n (%)[*] | 24 (12) | 12 (9.4) | 9 (20) | 3 (9.1) | 0.153 |

AAS, Anabolic androgenic steroids; Anti-TB, antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide; d, days; HDS, herbal and dietary supplements; IQR, interquartile range (25%-75%); SD, standard deviation; ULN, upper limit of normal; y, years.

[*] Based on patients with follow-up until biochemical resolution.

[a] Hepatocellular vs cholestatic liver damage, $p<0.05$

[b] Hepatocellular vs mixed liver damage, $p<0.05$

[c] Cholestatic vs mixed liver damage, $p<0.05$

**Table 2.** Comparison of clinical presentation of DILI episode according to the 15 most frequent individual causative agents registered in the Latin American DILI (LATINDILI) Network.

| Culprit agents | n (%) | Age (y) | Pattern of DILI, n (%) | | | Female sex n (%) | Eosinophilia n (%) | Lymphopenia n (%) | Hy's law n (%) | True Hy´s law (death/liver transplant) n (%) | nR-based Hy's law n (%) | True nR-based Hy´s law (death/liver transplant) n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Hep | Chol | Mix | | | | | | | |
| Amoxicillin-clavulanate | 58 (12) | 57±16 | 18 (31) | 26 (45) | 14 (24) | 30 (52) | 17 (31) | 6 (11) | 11 (20) | 0 (0) | 11 (20) | 0 (0) |
| HDS | 42 (9.0) | 45±17 | 32 (76) | 5 (12) | 5 (12) | 27 (64) | 6 (16) | 0 (0) | 14 (40) | 3 (21) | 14 (40) | 3 (21) |
| Anti-TB | 27 (5.8) | 40±16 | 23 (85) | 2 (7.4) | 2 (7.4) | 15 (56) | 6 (24) | 4 (16) | 11 (46) | 3 (27) | 11 (46) | 3 (27) |
| AAS | 23 (4.9) | 33±9.1 | 13 (57) | 6 (26) | 4 (17) | 3 (13) | 4 (21) | 0 (0) | 10 (45) | 1 (10) | 11 (50) | 1 (9.1) |
| Nitrofurantoin | 20 (4.3) | 59±13 | 16 (80) | 2 (10) | 2 (10) | 19 (95) | 4 (22) | 2 (11) | 7 (35) | 0 (0) | 7 (35) | 0 (0) |
| Diclofenac | 19 (4.1) | 55±12 | 12 (63) | 5 (26) | 2 (11) | 12 (63) | 2 (11) | 3 (16) | 6 (32) | 0 (0) | 6 (32) | 0 (0) |
| Nimesulide | 14 (3.0) | 57±16 | 8 (57) | 0 (0) | 6 (43) | 12 (86) | 2 (14) | 1 (7.1) | 6 (50) | 3 (50) | 7 (58) | 3 (43) |
| Ibuprofen | 11 (2.4) | 44±15 | 10 (91) | 1 (9.1) | 0 (0) | 6 (55) | 1 (10) | 1 (10) | 4 (40) | 0 (0) | 4 (40) | 0 (0) |
| Atorvastatin | 10 (2.1) | 62±8.6 | 2 (20) | 6 (60) | 2 (20) | 6 (60) | 3 (33) | 0 (0) | 1 (11) | 0 (0) | 2 (22) | 0 (0) |
| Methyldopa | 10 (2.1) | 35±8.8 | 10 (100) | 0 (0) | 0 (0) | 10 (100) | 0 (0) | 0 (0) | 5 (63) | 1 (20) | 5 (63) | 1 (20) |
| Carbamazepine | 9 (1.9) | 43±23 | 4 (44) | 4 (44) | 1 (11) | 6 (67) | 6 (67) | 0 (0) | 1 (14) | 0 (0) | 1 (14) | 0 (0) |
| Cyproterone acetate | 9 (1.9) | 69±7.0 | 9 (100) | 0 (0) | 0 (0) | 0 (0) | 2 (25) | 0 (0) | 7 (78) | 1 (14) | 7 (78) | 1 (14) |
| Phenytoin | 9 (1.9) | 40±17 | 5 (56) | 3 (33) | 1 (11) | 3 (33) | 0 (0) | 1 (13) | 3 (50) | 1 (33) | 3 (50) | 1 (33) |
| Azathioprine | 8 (1.7) | 48±16 | 3 (38) | 5 (63) | 0 (0) | 7 (88) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Fenofibrate | 7 (1.5) | 64±10 | 5 (71) | 1 (14) | 1 (14) | 6 (86) | 1 (14) | 0 (0) | 2 (29) | 0 (0) | 2 (29) | 0 (0) |

AAS, Anabolic androgenic steroids; Anti-TB, antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide; Chol, Cholestatic; DILI, drug-induced liver injury; Hep, hepatocellular; HDS, herbal and dietary supplements; Mix, mixed.

**Table 3.** Demographics, clinical data, severity and outcome according to the Anatomic Therapeutic Classification (ATC) class.

| | **Antibacterials (n=109)** | **Cardiovascular (n=40)** | **Immunosuppressants* (n=13)** | **NSAID (n=49)** | **CNS (n=39)** | **HDS (n=42)** | **AAS (n=23)** |
|---|---|---|---|---|---|---|---|
| Age (y), mean±SD | 54±18 | 56±17 | 47±14 | 52±15 | 45±18 | 45±17 | 33±9.1 |
| Female sex, n (%) | 66 (61) | 32 (80) | 10 (77) | 34 (69) | 24 (62) | 27 (64) | 3 (13) |
| Body mass index (kg/m$^2$), mean±SD | 27±6.5 | 26±3.3 | 26±5.5 | 26±3.1 | 24±4.6 | 27±7.4 | 25±3.3 |
| Diabetes, n (%) | 7 (6.5) | 5 (13) | 2 (17) | 4 (8.3) | 2 (5.1) | 1 (2.4) | 0 (0) |
| Hypertension, n (%) | 31 (29) | 19 (48) | 5 (42) | 10 (21) | 5 (13) | 2 (4.8) | 1 (4.4) |
| Dyslipidemia, n (%) | 9 (8.3) | 8 (20) | 0 (0) | 1 (2.0) | 2 (5.1) | 3 (7.1) | 0 (0) |
| Underlying hepatic disease, n (%) | 9 (8.3) | 2 (5.0) | 0 (0) | 4 (8.2) | 2 (5.1) | 4 (9.5) | 1 (4.4) |
| History of drug allergy, n (%) | 6 (5.7) | 2 (5.0) | 0 (0) | 2 (4.1) | 1 (2.7) | 2 (5.1) | 3 (13) |
| Type of liver injury, n (%) | | | | | | | |
| Hepatocellular | 48 (44) | 25 (63) | 6 (46) | 35 (71) | 21 (54) | 32 (76) | 13 (57) |
| Cholestatic | 40 (37) | 11 (28) | 7 (54) | 7 (14) | 14 (36) | 5 (12) | 6 (26) |
| Mixed | 21 (19) | 4 (10) | 0 (0) | 7 (14) | 4 (10) | 5 (12) | 4 (17) |
| *DILI episode characteristics* | | | | | | | |
| Jaundice, n (%) | 72 (67) | 21 (55) | 2 (15) | 32 (65) | 23 (61) | 27 (68) | 21 (91) |
| Hospitalization, n (%) | 49 (45) | 14 (35) | 2 (15) | 21 (43) | 21 (54) | 17 (40) | 12 (52) |
| Hypersensitivity features, n (%) | 47 (47) | 8 (21) | 1 (9.1) | 18 (38) | 25 (69) | 12 (31) | 6 (33) |
| Rash, n (%) | 10 (9.5) | 2 (5.1) | 1 (7.7) | 6 (12) | 17 (44) | 4 (9.5) | 2 (8.7) |
| Total daily dose (mg), median (IQR) | 1,875 (350-2,000) | 135 (20-400) | 100 (50-150) | 200 (90-200) | 200 (75-400) | 1,000 (450-1,350) | 50 (29-50) |
| Duration of therapy (d), median (IQR) | 11 (8-22) | 63 (39-119) | 48 (37-64) | 21 (9-42) | 38 (27-64) | 35 (20-64) | 53 (32-124) |
| Time to onset (d), median (IQR) | 20 (8-36) | 57 (31-115) | 37 (19-62) | 21 (8-36) | 31 (15-43) | 29 (9-65) | 54 (25-89) |
| Eosinophilia, n (%) | 25 (24) | 5 (13) | 0 (0) | 5 (11) | 16 (46) | 6 (16) | 4 (21) |
| Lymphopenia, n (%) | 10 (10) | 1 (2.6) | 0 (0) | 6 (13) | 2 (5.6) | 0 (0) | 0 (0) |
| Positive autoantibody titers, n (%) | 25 (26) | 9 (24) | 2 (15) | 12 (26) | 4 (11) | 7 (18) | 4 (20) |
| *Liver parameters at onset (x ULN), median (IQR)* | | | | | | | |
| Aspartate aminotransferase (AST) | 5.4 (2.8-11) | 6.6 (4.7-24) | 3.7 (2.7-6.0) | 8.6 (5.0-23) | 5.3 (2.9-17) | 11 (4.3-22) | 3.0 (1.9-7.9) |
| Alanine aminotransferase (ALT) | 8.8 (4.3-15) | 10 (6.3-23) | 6.1 (4.5-7.5) | 14 (9.0-24) | 9.9 (3.4-23) | 13 (5.8-28) | 5.7 (2.3-9.1) |
| Alkaline phosphatase (ALP) | 2.2 (1.4-3.2) | 1.9 (0.9-3.5) | 2.7 (0.7-3.9) | 1.7 (1.0-2.5) | 2.2 (1.2-4.8) | 1.5 (1.0-2.4) | 1.4 (0.7-2.3) |
| Gamma-glutamyl transferase (GGT) | 8.6 (4.3-12) | 9.1 (4.1-13) | 5.8 (3.4-14) | 6.1 (4.2-9.7) | 7.9 (3.6-20) | 4.6 (1.5-10) | 2.4 (1.0-6.9) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Total bilirubin | 5.4 (1.4-8.0) | 2.9 (0.9-9.8) | 0.4 (0.4-0.6) | 4.7 (1.4-8.8) | 3.7 (0.9-10) | 6.7 (1.5-18) | 9.1 (5.4-14) |
| Severity, n (%) | | | | | | | |
| Mild | 32 (29) | 18 (45) | 12 (92.3) | 16 (33) | 15 (38) | 13 (31) | 0 (0) |
| Moderate | 72 (66) | 19 (48) | 1 (7.7) | 25 (51) | 18 (46) | 22 (52) | 21 (91) |
| Severe | 5 (4.6) | 2 (5.0) | 0 (0) | 4 (8.2) | 3 (7.7) | 1 (2.4) | 1 (4.4) |
| Fatal/liver transplantation | 0 (0) | 1 (2.5) | 0 (0) | 4 (8.2) | 3 (7.7) | 6 (14)[†] | 1 (4.4) |
| nR-based Hy's law, n (%) | 24 (23) | 14 (39) | 0 (0) | 22 (49) | 12 (36) | 14 (40) | 11 (50) |
| *Outcome* | | | | | | | |
| Liver-related death, n (%) | 0 (0) | 0 (0) | 0 (0) | 2 (4.1) | 1 (2.6) | 3 (7.1) | 1 (4.4) |
| Liver transplantation, n (%) | 0 (0) | 1 (2.5) | 0 (0) | 2 (4.1) | 2 (5.1) | 3 (7.1) | 0 (0) |
| Death due to other causes, n (%) | 0 (0) | 0 (0) | 0 (0) | 1 (2.0) | 1 (2.6) | 0 (0) | 1 (4.4) |
| Time to resolution (d), median (IQR) | 65 (38-113) | 51 (37-108) | 142 (43-253) | 57 (33-109) | 60 (40-102) | 53 (25-120) | 81 (45-99) |

AAS, anabolic androgenic steroids; CNS, central nervous system; d, days; HDS, herbal and dietary supplements; IQR, interquartile range (25%-75%); NSAID; non-steroidal anti-inflammatory drug; SD, standard deviation; ULN, upper limit of normal; y, years.

[*] Immunosuppressants included were azathioprine, fingolimod, infliximab, leflunomide, natalizumab, and thalidomide.

[†] *Camellia sinensis*, Lipodex (weight loss supplement), *Garcinia cambogia*, *Senecio brasilensis*, Herbalife® products, and *Peumus boldus*.

**Table 4.** Histological findings according to type of liver injury in the Latin American DILI (LATINDILI) Network.

| Histological features | Total registry n (%) | Hepatocellular n (%) | Cholestatic n (%) | Mixed n (%) |
|---|---|---|---|---|
| Number of cases | 80 | 53 | 22 | 5 |
| *Pattern of damage* | | | | |
| Acute hepatitis | 10 (13) | 10 (19) | 0 (0) | 0 (0) |
| Chronic hepatitis | 9 (11)[∫] | 9 (17) | 0 (0) | 0 (0) |
| Acute cholestasis | 10 (13) | 3 (5.7) | 6 (27) | 1 (20) |
| Chronic cholestasis | 3 (3.8)[*] | 1 (1.9) | 2 (9.1) | 0 (0) |
| Cholestatic hepatitis | 20 (25) | 12 (23) | 6 (27) | 2 (40) |
| *Type of necrosis* | | | | |
| Massive necrosis | 5 (6.3) | 5 (9.4) | 0 (0) | 0 (0) |
| Zonal necrosis | 9 (11) | 6 (11) | 3 (14) | 0 (0) |
| *Steatosis component* | | | | |
| Macrovesicular steatosis | 1 (1.3)[†] | 1 (1.9) | 0 (0) | 0 (0) |
| Steatohepatitis | 1 (1.3)[¶] | 1 (1.9) | 0 (0) | 0 (0) |
| *Others patterns of damage* | | | | |
| Vascular injury | 2 (2.5)[‡] | 0 (0) | 2 (9.1) | 0 (0) |
| Mixed or unclassificable injury | 8 (10) | 4 (7.6) | 3 (14) | 1 (20) |
| Minimal non-specific changes | 2 (2.5)[ǂ] | 1 (1.9) | 0 (0) | 1 (20) |

[*] Culprit drugs: ciprofloxacin (hepatocellular injury); ticlopidine, atorvastatin (cholestatic injury).

[∫] Four cases presented with hepatic fibrosis. Grade of fibrosis: F1, portal fibrosis without septa (n=1, ketoconazole); F2, portal fibrosis with few septa (n=1, isotretinoin); F2/F3, portal and bridging fibrosis, less than 50% (n=1, azithromycin); F4, cirrhosis (n=1, nitrofurantoin).

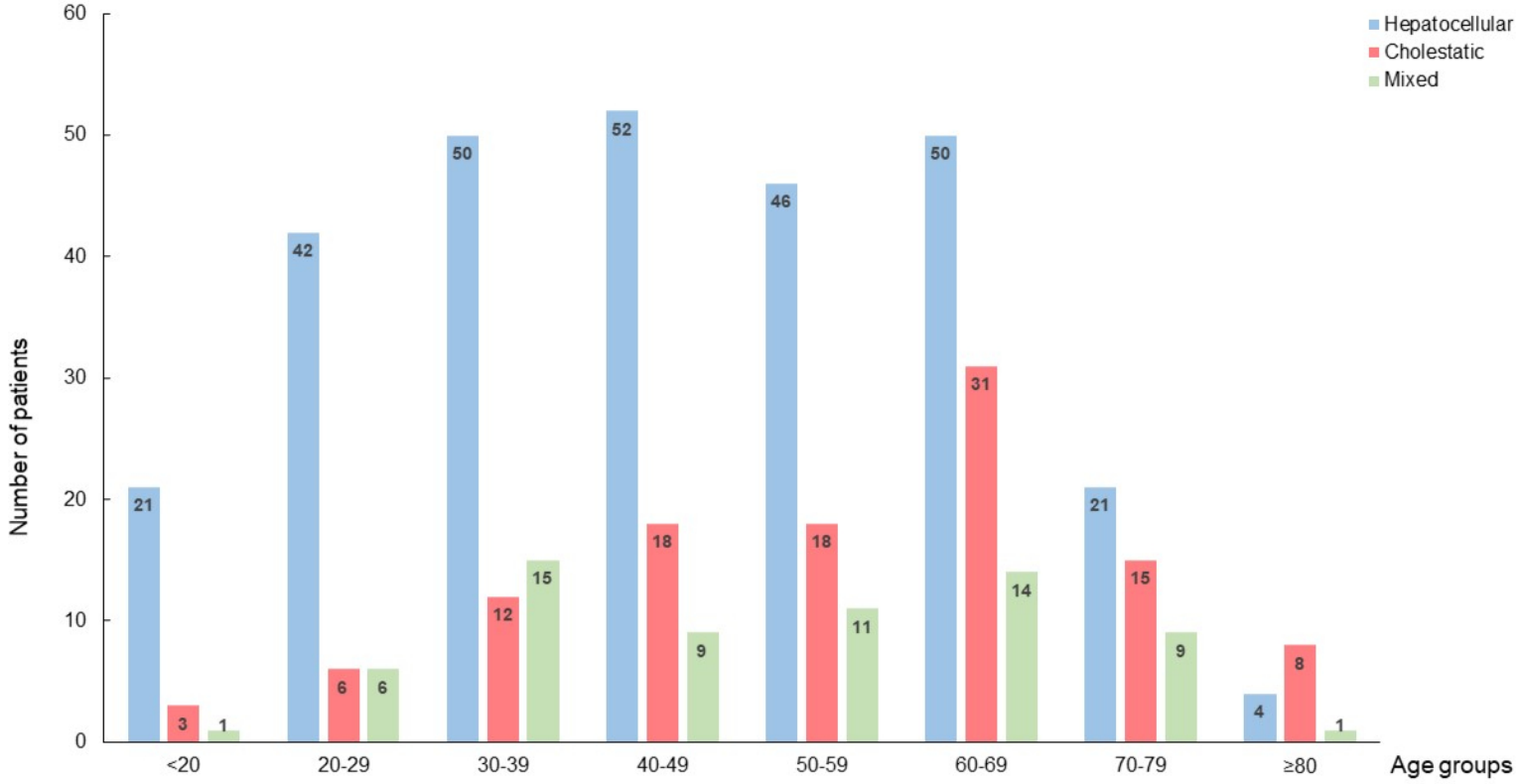
[†] Culprit drug: celecoxib.

[ǂ] Culprit drugs: minocycline (hepatocellular injury); herbal and dietary supplements (mixed injury).

[¶] Culprit drug: antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide.

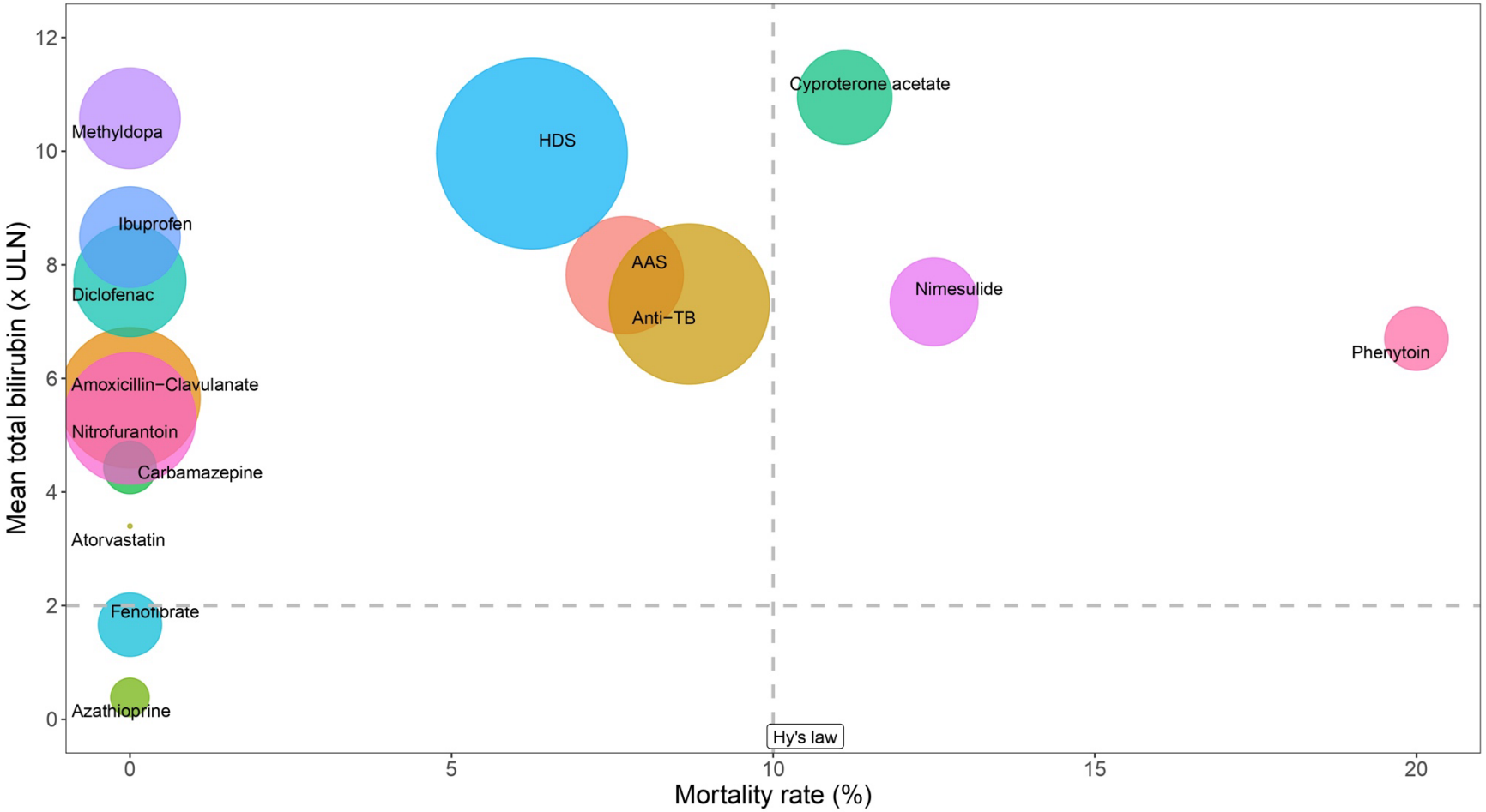
[‡] Culprit drugs: sertraline, oxaliplatin.

**Figure 1.** Distribution of pattern of liver injury in DILI patients according to age and sex.




| | <20 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | ≥80 |
|---|---|---|---|---|---|---|---|---|
| Male | 14 | 26 | 24 | 22 | 25 | 42 | 18 | 4 |
| Female | 11 | 28 | 53 | 57 | 50 | 53 | 27 | 9 |

**Figure 2.** Predictive value of the classic Hy's law by specific drugs in the LATINDILI Network.



**Supplemental table 1.** Comparison of demographics, clinical characteristics, laboratory parameters and outcome between different age groups according to pattern of liver injury.

| | Hepatocellular damage | | | | Cholestatic/mixed damage | | | |
|---|---|---|---|---|---|---|---|---|
| | **≤ 45 years n=145** | **46-64 years n=92** | **≥ 65 years n=49** | **p value** | **≤ 45 years n=60** | **46-64 years n=61** | **≥ 65 years n=56** | **p value** |
| Female sex, n (%) | 92 (63) | 57 (62) | 32 (65) | 0.924 | 34 (57) | 43 (70) | 30 (54) | 0.133 |
| Body mass index (kg/m$^2$), mean±SD | 25±4.9 | 26±5.2 | 26±3.6 | 0.069 | 25±4.5 | 28±8.0 | 25±4.5 | 0.040 |
| Diabetes, n (%) | 4 (2.8) | 8 (8.8) | 4 (8.2) | 0.075 | 2 (3.3) | 4 (6.6) | 9 (16) | 0.054 |
| Hypertension, n (%) | 16 (11) | 25 (28) | 19 (40) | <0.001 | 2 (3.3) | 13 (21) | 27 (48) | <0.001 |
| Dyslipidemia, n (%) | 2 (1.4) | 6 (6.5) | 7 (14) | 0.001 | 0 (0) | 7 (11) | 5 (8.9) | 0.018 |
| Underlying hepatic disease, n (%) | 9 (6.2) | 8 (8.7) | 3 (6.1) | 0.745 | 1 (1.7) | 7 (11) | 5 (8.9) | 0.088 |
| History of drug allergy, n (%) | 6 (4.4) | 2 (2.3) | 1 (2.1) | 0.661 | 1 (1.7) | 5 (8.3) | 2 (3.7) | 0.224 |
| *DILI episode characteristics* | | | | | | | | |
| Jaundice, n (%) | 82 (59) | 43 (48) | 25 (53) | 0.274 | 41 (68) | 42 (69) | 39 (71) | 0.952 |
| Hospitalization, n (%) | 60 (41) | 33 (36) | 20 (41) | 0.685 | 33 (55) | 23 (38) | 24 (43) | 0.147 |
| Hypersensitivity features, n (%) | 53 (41) | 33 (41) | 16 (37) | 0.911 | 22 (42) | 22 (41) | 25 (46) | 0.819 |
| Rash, n (%) | 20 (14) | 12 (13) | 3 (6.5) | 0.420 | 16 (27) | 6 (10) | 8 (15) | 0.044 |
| Total daily dose (mg), median (IQR) | 300 (90-1,000) | 200 (100-750) | 200 (100-500) | 0.628 | 175 (50-1,200) | 300 (75-1,920) | 350 (80-1,938) | 0.325 |
| Duration of therapy (d), median (IQR) | 33 (11-82) | 42 (19-93) | 70 (21-129) | 0.012 | 32 (13-56) | 27 (11-53) | 26 (8-60) | 0.399 |
| Time to onset (d), median (IQR) | 23 (8-65) | 40 (14-88) | 69 (16-120) | 0.001 | 28 (8-54) | 27 (15-38) | 29 (13-47) | 0.846 |
| Concomitant drugs, n (%) | | | | 0.008 | | | | 0.010 |
| None | 69 (48) | 34 (37) | 11 (22) | | 31 (52) | 22 (36) | 12 (21) | |
| 1-2 | 58 (40) | 43 (47) | 25 (51) | | 17 (28) | 23 (38) | 25 (45) | |
| 3-4 | 10 (6.9) | 13 (14) | 11 (22) | | 9 (15) | 14 (23) | 10 (18) | |
| ≥ 5 | 8 (5.5) | 2 (2.2) | 2 (4.1) | | 3 (5.0) | 2 (3.3) | 9 (16) | |
| Eosinophilia, n (%) | 28 (21) | 15 (18) | 6 (13) | 0.554 | 10 (19) | 13 (24) | 16 (30) | 0.425 |
| Lymphopenia, n (%) | 15 (12) | 5 (6.0) | 2 (4.6) | 0.281 | 2 (3.6) | 4 (7.0) | 3 (5.5) | 0.841 |
| Positive autoantibody titers, n (%) | 35 (26) | 19 (23) | 13 (32) | 0.596 | 6 (12) | 8 (14) | 9 (19) | 0.632 |
| *Liver parameters at onset (x ULN), median (IQR)* | | | | | | | | |
| Aspartate aminotransferase (AST) | 11 (5.1-22) | 13 (5.6-27) | 13 (6.2-22) | 0.423 | 3.7 (1.8-6.2) | 3.4 (1.7-6.2) | 3.3 (2.3-7.1) | 0.395 |
| Alanine aminotransferase (ALT) | 14 (8.1-30) | 16 (9.1-32) | 12 (8.5-23) | 0.333 | 5.1 (2.3-8.0) | 5.0 (2.8-7.7) | 5.3 (3.4-9.8) | 0.486 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Alkaline phosphatase (ALP) | 1.1 (0.8-1.5) | 1.2 (0.8-1.6) | 1.2 (0.8-1.8) | 0.323 | 2.8 (2.1-3.7) | 3.1 (2.4-5.3) | 4.0 (2.7-5.7) | 0.002 |
| Total bilirubin | 3.4 (0.8-8.4) | 2.9 (0.9-8.9) | 3.8 (0.9-10) | 0.782 | 5.5 (1.3-9.9) | 4.6 (1.0-7.6) | 5.0 (1.4-9.7) | 0.576 |
| Severity, n (%) | | | | 0.359 | | | | 0.295 |
| Mild | 58 (40) | 42 (46) | 19 (39) | | 18 (30) | 19 (31) | 15 (27) | |
| Moderate | 68 (47) | 39 (42) | 18 (37) | | 42 (70) | 40 (66) | 37 (66) | |
| Severe | 10 (6.9) | 5 (5.4) | 8 (16) | | 0 (0) | 1 (1.6) | 4 (7.1) | |
| Fatal/liver transplantation | 8 (5.6) | 6 (6.5) | 4 (8.2) | | 0 (0) | 1 (1.6) | 0 (0) | |
| *Outcome* | | | | | | | | |
| Liver-related death, n (%) | 4 (2.8) | 3 (3.3) | 2 (4.1) | 0.901 | 0 (0) | 1 (1.6) | 0 (0) | 1.000 |
| Liver transplantation, n (%) | 4 (2.8) | 3 (3.3) | 2 (4.1) | 0.901 | 0 (0) | 0 (0) | 0 (0) | - |
| Death due to other causes, n (%) | 1 (0.7) | 2 (2.2) | 2 (4.1) | 0.202 | 0 (0) | 1 (1.6) | 0 (0) | 1.000 |
| Time to resolution (d), median (IQR) | 57 (30-114) | 53 (33-136) | 60 (26-95) | 0.886 | 80 (43-116) | 68 (37-141) | 71 (53-109) | 0.974 |

d, days; IQR, interquartile range (25%-75%); SD, standard deviation; ULN, upper limit of normal.

**Supplemental table 2.** Anatomic Therapeutic Classification (ATC) groups according to pattern of liver injury in Latin American DILI (LATINDILI) Network.

| Pharmacological group and subgroup | Total registry (n=468) | Hepatocellular (n=289) | Cholestatic (n=112) | Mixed (n=67) |
|---|---|---|---|---|
| **A (Alimentary tract and metabolism)** | **5 (1.1)** | **1 (0.4)** | **1 (0.9)** | **3 (4.5)** |
| A02 (Drugs for acid related disorders) | 1 (0.2) | - | 1 (0.9) | - |
| A03 (Drugs for functional gastrointestinal disorders) | 1 (0.2) | - | - | 1 (1.5) |
| A07 (Antidiarrheals, intestinal anti-inflammatory / antiinfective agents) | 2 (0.4) | - | - | 2 (3.0) |
| A10 (Drugs used in diabetes) | 1 (0.2) | 1 (0.4) | - | - |
| **B (Blood and blood forming organs)** | **4 (0.9)** | **1 (0.4)** | **3 (2.7)** | **-** |
| B01 (Antithrombotic agents) | 4 (0.9) | 1 (0.4) | 3 (2.7) | - |
| **C (Cardiovascular system)** | **40 (8.6)** | **25 (8.7)** | **11 (9.8)** | **4 (6.0)** |
| C01 (Cardiac therapy) | 3 (0.6) | - | 3 (2.7) | - |
| C02 (Antihypertensives) | 11 (2.4) | 11 (3.8) | - | - |
| C08 (Calcium channel blockers) | 1 (0.2) | - | 1 (0.9) | - |
| C10 (Lipid modifying agents) | 25 (5.3) | 14 (4.8) | 7 (6.3) | 4 (6.0) |
| **D (Dermatologicals)** | **9 (1.9)** | **6 (2.1)** | **-** | **3 (4.5)** |
| D01 (Antifungals for dermatological use) | 4 (0.9) | 2 (0.7) | - | 2 (3.0) |
| D05 (Antipsoriatics) | 1 (0.2) | - | - | 1 (1.5) |
| D10 (Anti-acne preparations) | 4 (0.9) | 4 (1.4) | - | - |
| **G (Genito urinary system and sex hormones)** | **29 (6.2)** | **23 (8.0)** | **3 (2.7)** | **3 (4.5)** |
| G01 (Gynecological antiinfectives and antiseptics) | 1 (0.2) | 1 (0.4) | - | - |
| G03 (Sex hormones and modulators of the genital system) | 28 (6.0) | 22 (7.6) | 3 (2.7) | 3 (4.5) |
| **H (Systemic hormonal preparations)*** | **13 (2.8)** | **6 (2.1)** | **5 (4.5)** | **2 (3.0)** |
| H02 (Corticosteroids for systemic use) | 4 (0.9) | 4 (1.4) | - | - |
| H03 (Thyroid therapy) | 9 (1.9) | 2 (0.7) | 5 (4.5) | 2 (3.0) |
| **J (Anti-infectives for systemic use)** | **146 (31)** | **77 (27)** | **43 (38)** | **26 (39)** |
| J01 (Antibacterials for systemic use) | 109 (23) | 48 (17) | 40 (36) | 21 (31) |
| J02 (Antimycotics for systemic use) | 4 (0.9) | 3 (1.0) | - | 1 (1.5) |
| J04 (Antimycobacterials) | 29 (6.2) | 23 (8.0) | 2 (1.8) | 4 (6.0) |
| J05 (Antivirals for systemic use) | 4 (0.9) | 3 (1.0) | 1 (0.9) | - |

| | | | | |
|---|---|---|---|---|
| **L (Antineoplastic and immunomodulating agents)** | **50 (11)** | **36 (12)** | **12 (11)** | **2 (3.0)** |
| L01 (Antineoplastic agents) | 31 (6.6) | 25 (8.7) | 4 (3.6) | 2 (3.0) |
| L02 (Endocrine therapy) | 6 (1.3) | 5 (1.7) | 1 (0.9) | - |
| L04 (Immunosuppressants) | 13 (2.8) | 6 (2.1) | 7 (6.3) | - |
| **M (Musculo-skeletal system)** | **55 (12)** | **39 (13)** | **9 (8.0)** | **7 (10)** |
| M01 (Antiinflammatory and antirheumatic products) | 49 (10) | 35 (12) | 7 (6.3) | 7 (10) |
| M02 (Topical products for joint and muscular pain) | 2 (0.4) | 2 (0.7) | - | - |
| M03 (Muscle relaxants) | 2 (0.4) | 1 (0.4) | 1 (0.9) | - |
| M04 (Antigout preparations) | 2 (0.4) | 1 (0.4) | 1 (0.9) | - |
| **N (Nervous system)** | **39 (8.3)** | **21 (7.3)** | **14 (13)** | **4 (6.0)** |
| N03 (Antiepileptics) | 27 (5.8) | 16 (5.5) | 8 (7.1) | 3 (4.5) |
| N05 (Psycholeptics) | 5 (1.1) | 1 (0.4) | 4 (3.6) | - |
| N06 (Psychoanaleptics) | 7 (1.5) | 4 (1.4) | 2 (1.8) | 1 (1.5) |
| **P (Antiparasitic products, insecticides, and repellents)** | **10 (2.1)** | **8 (2.8)** | **-** | **2 (3.0)** |
| P01 (Antiprotozoals) | 1 (0.2) | 1 (0.4) | - | - |
| P02 (Anthelmintics) | 9 (1.9) | 7 (2.4) | - | 2 (3.0) |
| **S (Sensory organs)** | **3 (0.6)** | **1 (0.4)** | **-** | **2 (3.0)** |
| S01 (Ophthalmologicals) | 3 (0.6) | 1 (0.4) | - | 2 (3.0) |
| **- Herbal and dietary supplements** | **42 (9.0)** | **32 (11)** | **5 (4.5)** | **5 (7.5)** |
| **- Anabolic androgenic steroids** | **23 (4.9)** | **13 (4.5)** | **6 (5.4)** | **4 (6.0)** |

* Excluding sex hormones and insulins.

**Supplemental table 3.** Demographics, clinical characteristics and outcome of drug-induced liver injury in prospective registries.

| | LATINDILI Network (n=468) | Spanish DILI registry (n=843)[6] | DILIN (n=899)[16] | Indian Network of DILI (n=1,288)[17] | Pro-Euro DILI Registry (n=246)[18] | Japanese DILI registry (n=307)[19] |
|---|---|---|---|---|---|---|
| Age (y), mean±SD | 49±18 | 54±18 | 49±17 | 43±17 | 56±18 | 59±16 |
| Female sex, % | 62 | 48 | 59 | 49 | 57 | 59 |
| Underlying hepatic disease, % | 7.1 | 6.3 | 9.9 | NA | 3.6 | NA |
| Type of liver injury, % | | | | | | |
| Hepatocellular | 62 | 57 | 54 | 30 | 62 | 64 |
| Cholestatic | 24 | 21 | 23 | 43 | 19 | 16 |
| Mixed | 14 | 22 | 23 | 27 | 20 | 20 |
| Jaundice, % | 60 | 69 | 70 | 67 | 60 | NA |
| Hospitalization, % | 42 | 60 | 29 | 68 | 70 | NA |
| Time to onset (d), median (IQR) | 30 (11-68) | 25 (10-62) | 36 (19-88) | NA | NA | NA |
| Most frequent culprit drugs, % | | | | | | |
| | Amoxicillin-clavulanate (12) | Amoxicillin-clavulanate (23) | Amoxicillin-clavulanate (10) | Anti-TBC (46) | Amoxicillin-clavulanate (12) | Anti-inflammatory drugs, antimicrobial drugs (11) |
| | HDS (9.0) | Anti-TBC (4.5) | Isoniazid (5.3) | Complementary and alternative medicines (14) | Flucloxacillin (11) | Anticancer drugs (10) |
| | Anti-TB (5.8) | Ibuprofen (3.0) | Nitrofurantoin (4.7) | Anti-epileptic drugs (8.1) | Atorvastatin (8.0) | Dietary supplements, drugs for the gastrointestinal system (9.0) |
| Herbal and dietary supplements, % | 9.0 | 3.4 | 16 | 13.9 | 6.0 (including AAS) | 15 |
| Anabolic androgenic steroids, % | 4.9 | 2.6 | NA | NA | NA | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| Liver parameters at onset, mean±SD | | | | | | |
| Aspartate aminotransferase (AST) | 13±17 (x ULN) | 15±21 (x ULN) | NA | 220 (119-438) (IU/L)‡ | 9.7 (4.6-21) (x ULN)‡ | NA |
| Alanine aminotransferase (ALT) | 16±18 (x ULN) | 19±22 (x ULN) | 825±1,105 (IU/L) | 241 (110-519) (IU/L)‡ | 13 (6.6-25) (x ULN)‡ | 676±800 (IU/L) |
| Alkaline phosphatase (ALP) | 2.4±2.3 (x ULN) | 2.2±2.1 (x ULN) | 288±254 (IU/L) | 180 (123-287) (IU/L)‡ | 2.0 (1.2-3.3) (x ULN)‡ | 708±646 (IU/L) |
| Total bilirubin | 6.6±7.6 (x ULN) | 7.0±6.9 (x ULN) | 6.7±6.6 (mg/dL) | 8.3±10 (mg/dL) | 3.2 (0.7-7.0) (x ULN)‡ | 3.1±4.4 (mg/dL) |
| Severity, % | | | | | | |
| Mild | 37 | 31 | 24 | NA | 43 | NA |
| Moderate | 53 | 59 | 50 | NA | 45 | NA |
| Severe | 6.2 | 6.2 | 19 | 23 | 8.1 | NA |
| Fatal/transplantation | 4.1 | 3.7 | 7 | 9.6 | 4.0 | NA |
| Liver-related death, n (%) | 10 (2.1) | 18 (2.1) | 27 (3.0) | 79 (6.1) | 3 (1.2) | 0 (0) |
| Liver transplantation, n (%) | 9 (1.9) | 13 (1.5) | 36 (4.0) | NA | | 0 (0) |
| Death due to other causes, n (%) | 6 (1.3) | 14 (1.7) | 29 (3.2) | 77 (6.0) | | 1 (0.3) |

DILI, Drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; d, days; IQR, interquartile range (25%-75%); SD, standard deviation; ULN, upper limit of normal; y, years; Anti-TB, antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide; NA, data not available.

‡ Median and interquartile range (25-75%).

**Supplemental Figure 1.** Flow chart of the study.