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Drug-induced Liver Injury in Latin America: 10-year Experience of the Latin American DILI (LATINDILI) Network

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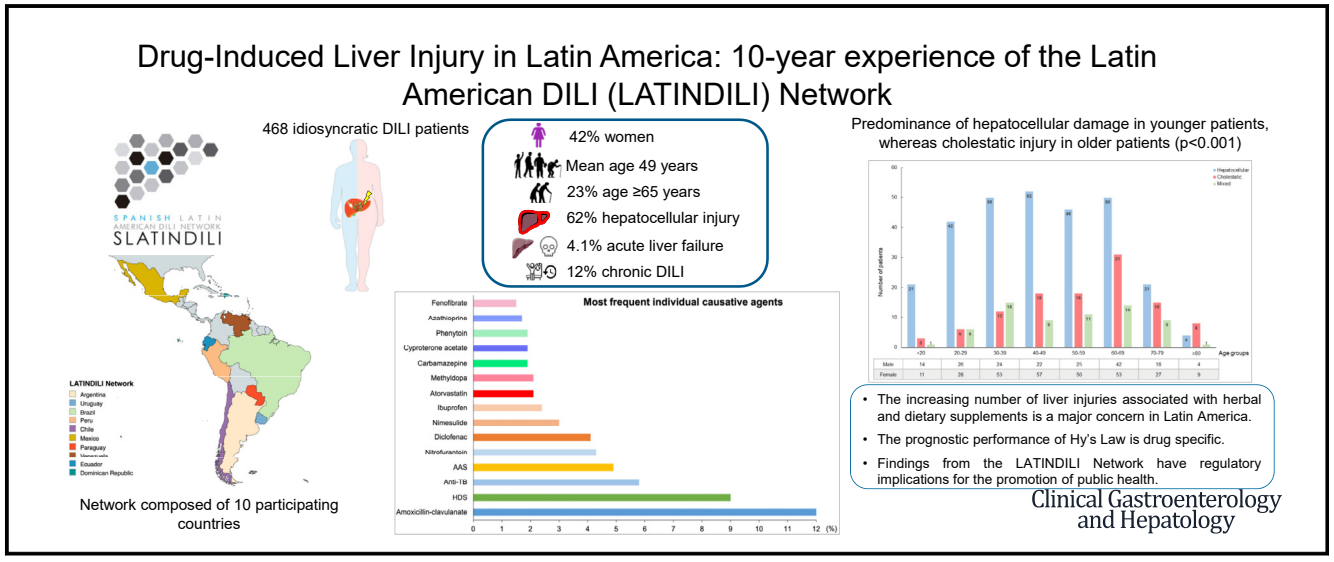

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Abbreviations used in this paper: AAS, anabolic androgenic steroids; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine transaminase; anti-TB, anti-tuberculosis drugs; AST, aspartate aminotransferase; ATC, Anatomical Therapeutic Chemical; DILI, drug induced liver injury; DILIN, Drug-Induced Liver Injury Network; GGT, gamma-glutamyl transferase; HDS, herbal and dietary supplements; NSAID, non-steroidal anti-inflammatory drug; RUCAM, Roussel Uclaf Causality Assessment Method; LATINDILI Network, Latin American DILI Network; ULN, upper limit of normal.

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BACKGROUND & 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. Of the cases, 4.1% had a fatal outcome, and 24 patients (12%) 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 (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 herbal and dietary supplements associated with the worst outcome, whereas DILI caused by amoxicillin-clavulanate, nitrofurantoin, and diclofenac, which 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 herbal and dietary supplements, 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: Acute Liver Failure; Drug-induced Liver Injury; Hepatotoxicity; Latin America; Prospective.

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] whereas 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 health care 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 and 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 3 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 $\geq$5 and total bilirubin >2 times ULN, whereas nR-based Hy's law was defined as nR $\geq$5 and total bilirubin >2 times ULN.[9] Chronic DILI was defined as incomplete biochemical resolution (liver parameters below ULN) 1 year after DILI recognition.[10] Eosinophilia was defined as serum eosinophils exceeding 4% to 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 (ATC) classification 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, or median and interquartile range were presented, and differences between groups were tested using the Student *t*-test or Mann-Whitney *U* test, as appropriate. Categorical data were described using frequency distributions, and differences were compared using the χ^2 test or Fisher 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 2-sided *P*-value was lower than .05. All analyses were performed using STATA version 17 (Stata Corporation) and R version 4.3.0 (R Core Team, 2023).

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.

Results

A total of 483 DILI cases were included in the LATINDILI Network. Of them, 3 were intrinsic DILI cases, 2 were second DILI episodes (due to azathioprine and norethisterone), and 10 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 (Supplementary Figure 1). The vast majority of DILI cases were caused by a single drug (88%). According to the RUCAM scale, 25% were scored as possible, 69% probable, and 6.1% highly probable. Of note, in this cohort, 9 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; $P < .001$). Hepatocellular liver damage predominated (62%), whereas 24% and 14% of cases had cholestatic and mixed injury, respectively. Of the cases, 7.1% had an underlying chronic liver disease, mainly steatosis or metabolic dysfunction-associated steatotic liver disease (64%) and autoimmune hepatitis (15%).

Over one-half of the patients presented with jaundice (60%), particularly those who developed cholestatic or mixed injury ($P = .005$). Forty-two percent 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; $P = .002$). 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; $P = .006$). Moreover, platelet count was diminished in patients with hepatocellular injury compared with those with cholestatic or mixed liver damage ($P = .009$).

In terms of severity, one-half of the patients presented moderate injury (53%), whereas 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 ($P < .001$). Indeed, among the 10 cases who died from liver-related causes, 9 had hepatocellular damage, as well as the 9 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 3 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 ($P = .012$ and $P = .001$, respectively), whereas in cholestatic/mixed cases, the rise in ALP was markedly higher in older patients compared with younger patients (Supplementary 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%) (Supplementary 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 (ie, 20% of patients with DILI 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% to 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, whereas 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

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, *years*	49 ± 18	45 ± 17[a]	55 ± 17	51 ± 17	< .001
Female sex	290 (62)	182 (63)	65 (58)	43 (64)	.607
Body mass index, kg/m^2	26 ± 5.3	26 ± 4.9	26 ± 6.7	26 ± 4.7	.424
Diabetes	31 (6.7)	16 (5.6)	12 (11)	3 (4.5)	.156
Hypertension	102 (22)	60 (21)	33 (29)[c]	9 (13)	.040
Dyslipidemia	27 (5.8)	15 (5.2)	10 (8.9)	2 (3.0)	.224
Underlying hepatic disease	33 (7.1)	20 (6.9)	8 (7.1)	5 (7.5)	.966
History of drug allergy	17 (3.8)	9 (3.3)	5 (4.6)	3 (4.6)	.723
Charlson comorbidity index	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	.773
DILI episode characteristics					
Jaundice	274 (60)	151 (54)[a,b]	76 (68)	47 (70)	.005
Hospitalization	195 (42)	114 (39)	54 (48)	27 (40)	.271
Hypersensitivity features	172 (41)	102 (40)	43 (43)	27 (43)	.803
Rash	66 (14)	35 (13)	18 (16)	13 (20)	.265
Total daily dose, *mg*	250 (86–1000)	200 (100–850)	200 (50–1875)	250 (75–2000)	.560
Duration of therapy, *days*	34 (11–83)	40 (14–93)[b]	32 (11–76)	26 (10–44)	.013
Time to onset, *days*	30 (11–68)	33 (11–83)	28 (13–52)	27 (14–43)	.140
Most frequent culprit drugs, %	Amoxicillin–clavulanate (12) HDS (9.0) Anti–TB (5.8)	HDS (11) Anti–TB (8.0) Amoxicillin–clavulanate (6.2)	Amoxicillin–clavulanate (23) AAS, atorvastatin (5.4) Azathioprine, diclofenac, HDS (4.5)	Amoxicillin–clavulanate (21) Nimesulide (9.0) HDS (7.5)	
Concomitant drugs					.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	88 (21)	49 (19)	25 (25)	14 (22)	.383
Lymphopenia	31 (7.2)	22 (8.5)	6 (5.6)	3 (4.8)	.554
Positive autoantibody titers	90 (22)	67 (26)[a]	12 (12)	11 (20)	.018
Liver parameters at onset, × *ULN*					
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)	< .001
ALT	9.7 (5.4–19)	14 (8.7–29)[a,b]	3.4 (2.0–5.4)[c]	9.1 (6.0–12)	< .001
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)	< .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)	.093
Albumin, *g/dL*	3.8 ± 0.7	3.8 ± 0.7	3.7 ± 0.6	4.0 ± 0.5	.176
Platelets, × $10^3/mL$	233 (181–284)	221 (176–274)[a,b]	255 (197–303)	256 (210–294)	.009
Severity					< .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)	

Table 1. Continued

	Total registry (N = 468)	Hepatocellular (n = 289; 62%)	Cholestatic (n = 112; 24%)	Mixed (n = 67; 14%)	*P* value
Outcome					
Liver-related death	10 (2.1)	9 (3.1)	1 (0.9)	0 (0)	.226
Liver transplantation	9 (1.9)	9 (3.1)	0 (0)	0 (0)	.057
Death due to other causes	6 (1.3)	5 (1.7)	1 (0.9)	0 (0)	.849
Time to resolution, *days*	63 (34–118)	57 (30–114)	78 (45–134)	65 (37–105)	.103
Chronic DILI[d]	24 (12)	12 (9.4)	9 (20)	3 (9.1)	.153

Note: Data are presented as number (%), median (interquartile range), or mean ± standard deviation.
AAS, Anabolic androgenic steroids; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Anti-TB, antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide; AST, aspartate aminotransferase; DILI, drug induced liver injury; HDS, herbal and dietary supplements; ULN, upper limit of normal.
[a]Hepatocellular vs cholestatic liver damage, $P < .05$.
[b]Hepatocellular vs mixed liver damage, $P < .05$.
[c]Cholestatic vs mixed liver damage, $P < .05$.
[d]Based on patients with follow-up until biochemical resolution.

acute hepatitis (n = 10 each; 13%). In addition, 9 patients showed zonal necrosis, and 5 cases developed massive necrosis. Fifteen percent of cases showed chronic damage, classified as chronic hepatitis (n = 9) or chronic cholestasis (n = 3), 2 of which developed ductopenia. In addition, 8 cases had hepatic steatosis, 2 of which had steatohepatitis and macrovesicular steatosis as the only histological findings, and 6 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 Supplementary 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 one-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 patients with DILI 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

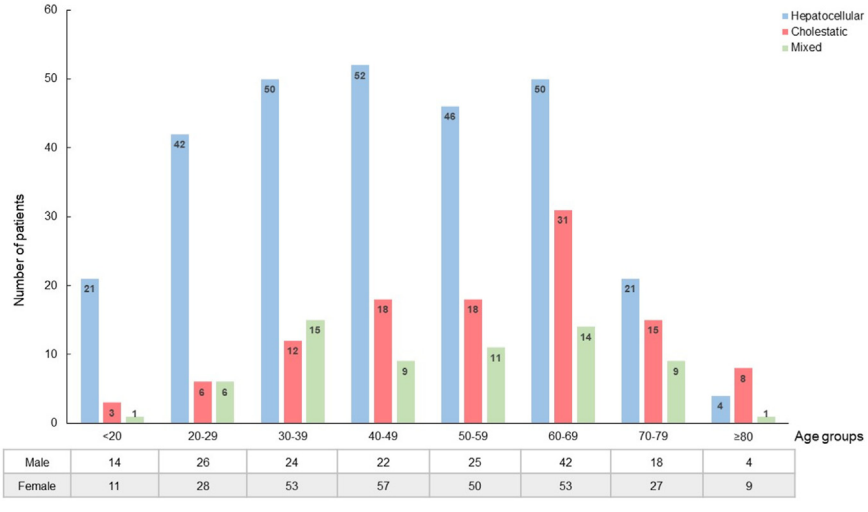

Figure 1. Distribution of pattern of liver injury in patients with DILI according to age and sex.

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, *years*	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.

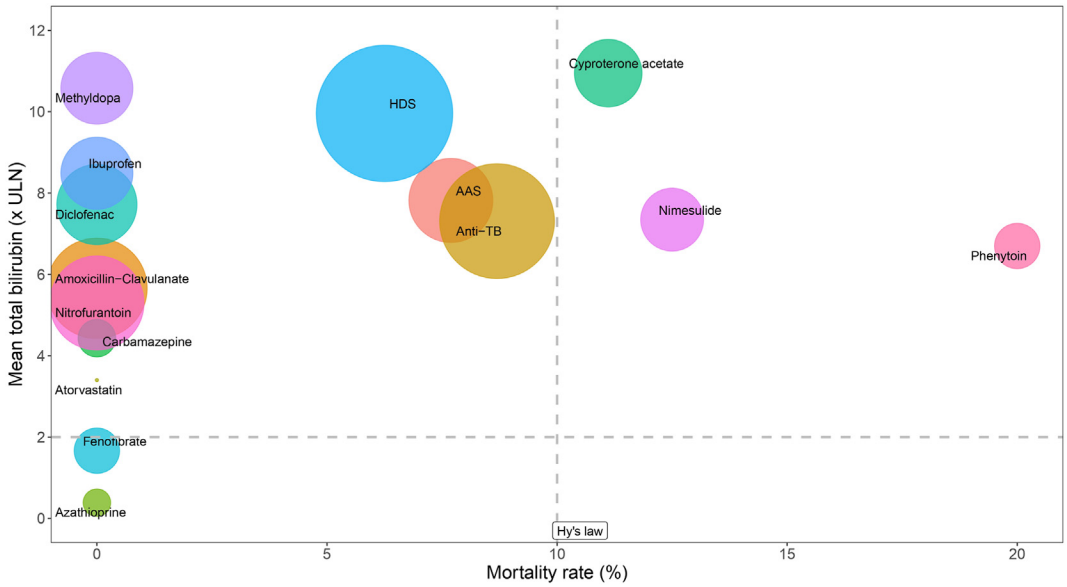

Figure 2. Predictive value of the classic Hy's law by specific drugs in the LATINDILI Network.

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 2 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 patients with DILI[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 (eg, 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 1 patient died. Our findings are consistent with 2 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], whereas the

Table 3. Demographics, Clinical Data, Severity, and Outcome According to the ATC Class

	Antibacterials (n = 109)	Cardiovascular (n = 40)	Immunosuppressants[a] (n = 13)	NSAID (n = 49)	CNS (n = 39)	HDS (n = 42)	AAS (n = 23)
Age, *years*	54 ± 18	56 ± 17	47 ± 14	52 ± 15	45 ± 18	45 ± 17	33 ± 9.1
Female sex	66 (61)	32 (80)	10 (77)	34 (69)	24 (62)	27 (64)	3 (13)
Body mass index, kg/m^2	27 ± 6.5	26 ± 3.3	26 ± 5.5	26 ± 3.1	24 ± 4.6	27 ± 7.4	25 ± 3.3
Diabetes	7 (6.5)	5 (13)	2 (17)	4 (8.3)	2 (5.1)	1 (2.4)	0 (0)
Hypertension	31 (29)	19 (48)	5 (42)	10 (21)	5 (13)	2 (4.8)	1 (4.4)
Dyslipidemia	9 (8.3)	8 (20)	0 (0)	1 (2.0)	2 (5.1)	3 (7.1)	0 (0)
Underlying hepatic disease	9 (8.3)	2 (5.0)	0 (0)	4 (8.2)	2 (5.1)	4 (9.5)	1 (4.4)
History of drug allergy	6 (5.7)	2 (5.0)	0 (0)	2 (4.1)	1 (2.7)	2 (5.1)	3 (13)
Type of liver injury							
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	72 (67)	21 (55)	2 (15)	32 (65)	23 (61)	27 (68)	21 (91)
Hospitalization	49 (45)	14 (35)	2 (15)	21 (43)	21 (54)	17 (40)	12 (52)
Hypersensitivity features	47 (47)	8 (21)	1 (9.1)	18 (38)	25 (69)	12 (31)	6 (33)
Rash	10 (9.5)	2 (5.1)	1 (7.7)	6 (12)	17 (44)	4 (9.5)	2 (8.7)
Total daily dose, *mg*	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, *days*	11 (8–22)	63 (39–119)	48 (37–64)	21 (9–42)	38 (27–64)	35 (20–64)	53 (32–124)
Time to onset, *days*	20 (8–36)	57 (31–115)	37 (19–62)	21 (8–36)	31 (15–43)	29 (9–65)	54 (25–89)
Eosinophilia	25 (24)	5 (13)	0 (0)	5 (11)	16 (46)	6 (16)	4 (21)
Lymphopenia	10 (10)	1 (2.6)	0 (0)	6 (13)	2 (5.6)	0 (0)	0 (0)
Positive autoantibody titers	25 (26)	9 (24)	2 (15)	12 (26)	4 (11)	7 (18)	4 (20)
Liver parameters at onset, × *ULN*							
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)
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)
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)
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							
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)[b]	1 (4.4)

Table 3. Continued

	Antibacterials (n = 109)	Cardiovascular (n = 40)	Immunosuppressants[a] (n = 13)	NSAID (n = 49)	CNS (n = 39)	HDS (n = 42)	AAS (n = 23)
nR-based Hy's law	24 (23)	14 (39)	0 (0)	22 (49)	12 (36)	14 (40)	11 (50)
Outcome							
Liver-related death	0 (0)	0 (0)	0 (0)	2 (4.1)	1 (2.6)	3 (7.1)	1 (4.4)
Liver transplantation	0 (0)	1 (2.5)	0 (0)	2 (4.1)	2 (5.1)	3 (7.1)	0 (0)
Death due to other causes	0 (0)	0 (0)	0 (0)	1 (2.0)	1 (2.6)	0 (0)	1 (4.4)
Time to resolution, *days*	65 (38–113)	51 (37–108)	142 (43–253)	57 (33–109)	60 (40–102)	53 (25–120)	81 (45–99)

Note: Data are presented as number (%), median (interquartile range), or mean ± standard deviation.
AAS, Anabolic androgenic steroids; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Anti-TB, antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide; AST, aspartate aminotransferase; ATC, Anatomic Therapeutic Classification; CNS, central nervous system; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; GGT, gamma-glutamyl transferase; NSAID; non-steroidal anti-inflammatory drug; ULN, upper limit of normal.
[a]Immunosuppressants included were azathioprine, fingolimod, infliximab, leflunomide, natalizumab, and thalidomide.
[b]*Camellia sinensis*, Lipodex (weight loss supplement), *Garcinia cambogia*, *Senecio brasiliensis*, Herbalife products, and *Peumus boldus*.

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 and were hospitalized, and 1 patient underwent liver transplantation.[32]

Regulatory policies and prescribing patterns can also explain the higher incidence of DILI with certain drugs compared with 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 with 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 patients with DILI 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]

Conclusion

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 America. 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.

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)[b]	9 (17)	0 (0)	0 (0)
Acute cholestasis	10 (13)	3 (5.7)	6 (27)	1 (20)
Chronic cholestasis	3 (3.8)[a]	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)[c]	1 (1.9)	0 (0)	0 (0)
Steatohepatitis	1 (1.3)[e]	1 (1.9)	0 (0)	0 (0)
Other patterns of damage				
Vascular injury	2 (2.5)[d]	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)[f]	1 (1.9)	0 (0)	1 (20)

DILI, Drug-induced liver injury.
[a]Culprit drugs: ciprofloxacin (hepatocellular injury); ticlopidine, atorvastatin (cholestatic injury).
[b]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).
[c]Culprit drug: celecoxib.
[d]Culprit drugs: minocycline (hepatocellular injury); herbal and dietary supplements (mixed injury).
[e]Culprit drug: antituberculosis medications, either alone or the combination of isoniazid, rifampicin and/or pyrazinamide.
[f]Culprit drugs: sertraline, oxaliplatin.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.06.030.

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Data availability
Data available on request from the authors.