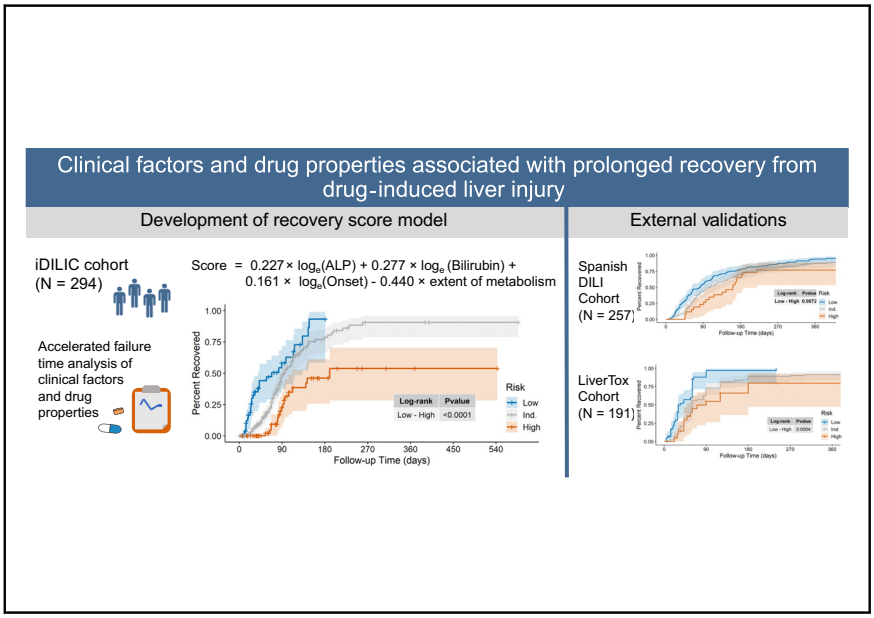
Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL OF HEPATOLOGY

Elevated bilirubin, alkaline phosphatase at onset, and drug metabolism are associated with prolonged recovery from DILI

Graphical abstract



Highlights

- Bilirubin, ALP, time to onset, and drug metabolism influence DILI recovery time.
- Parametric time-to-event method identifies risk factors for prolonged DILI recovery.
- Recovery score model predicts the trajectory of DILI recovery for individual patients.

Authors

Kristin Ashby, Wei Zhuang, Andres González-Jimenez, …, Guruprasad P. Aithal, Ayako Suzuki, Minjun Chen

Correspondence

Minjun.chen@fda.hhs.gov
(M. Chen).

Lay summary

In this study, we investigated whether drug properties and clinical factors are associated with the time it takes to recover from drug-induced liver injury (DILI). We found that total bilirubin, alkaline phosphatase level at DILI onset, time to onset, and extent of drug metabolism were consistently associated with recovery time. Using these factors, we built a model to predict the trajectory of recovery from DILI and validated this model in 2 independent cohorts. Our findings offer important insights into the factors influencing the trajectory of recovery from DILI. Additional investigations and longer follow-ups can be planned in those for whom a delayed recovery is predicted.

https://doi.org/10.1016/j.jhep.2021.03.021
 J. Hepatol. 2021, 75, 333–341

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL OF HEPATOLOGY

Elevated bilirubin, alkaline phosphatase at onset, and drug metabolism are associated with prolonged recovery from DILI

Kristin Ashby[1], Wei Zhuang[1], Andres González-Jimenez[2], Ismael Alvarez-Alvarez[3], M. Isabel Lucena[3], Raúl J. Andrade[3], Guruprasad P. Aithal[4], Ayako Suzuki[5,6], Minjun Chen[1,*]

[1]*Division of Bioinformatics and Biostatistics, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, Arkansas, USA;* [2]*Bioinformatic Platform. Instituto de Investigación Biomédica de Málaga (IBIMA), Málaga, Spain;* [3]*Unidad de Gestión Clínica de Aparato Digestivo, Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain;* [4]*National Institute for Health Research (NIHR) Nottingham Biomedical Research Center at the Nottingham University Hospital NHS Trust and University of Nottingham, Nottingham, UK;* [5]*Division of Gastroenterology, Duke University, Durham, North Carolina, USA;* [6]*Durham VA Medical Center, Durham, North Carolina, USA*

Background & Aims: Although most drug-induced liver injury (DILI) cases resolve after the offending medication is discontinued, time to recovery varies among patients, with 6 –12% developing a chronic disease. Herein, we investigated clinical factors and drug properties as potential risk determinants that influence the time course for DILI recovery and developed a model to predict its trajectory.

Methods: We applied an accelerated failure time model to 294 cases collected by the International Drug-Induced Liver Network Consortium (iDILIC). Factors included in the multivariate recovery score model were selected through univariate analysis. The model was externally validated using 257 cases from the Spanish DILI Registry and 191 cases from the LiverTox database.

Results: Higher serum bilirubin and alkaline phosphatase (ALP) at DILI onset, a longer time to onset, and non-significant drug metabolism were associated with a longer recovery and were included in the recovery score model. We defined high- and low-risk groups based on the scores assigned by the model. The estimated probability of recovery by 6 months was 0.46 (95% CI 0.26–0.61) for the high-risk group and 0.93 (95% CI 0.58–0.99) for the low-risk group in the iDILIC. Model performance was validated in both validation sets. The high- and low-risk cases identified by the model showed a significantly different time course for recovery, with a majority of low-risk cases recovering sooner.

Conclusion: The trajectory of biochemical recovery from DILI is predicted by the extent of drug metabolism, serum bilirubin and ALP at DILI onset. The model can be used to compute an estimated DILI recovery and, when a significant delay is predicted, clinicians may consider additional investigations such as histologic evaluation or extended follow-up.

Lay summary: In this study, we investigated whether drug properties and clinical factors are associated with the time it takes to recover from drug-induced liver injury (DILI). We found that total bilirubin, alkaline phosphatase level at DILI onset, time to onset, and extent of drug metabolism were consistently associated with recovery time. Using these factors, we built a model to predict the trajectory of recovery from DILI and validated this model in 2 independent cohorts. Our findings offer important insights into the factors influencing the trajectory of recovery from DILI. Additional investigations and longer follow-ups can be planned in those for whom a delayed recovery is predicted.

Introduction

Drug-induced liver injury (DILI) is a clinically significant adverse reaction. Although most DILI resolves after discontinuation of the culprit medication, the time to recovery varies among patients, with 6–12% of cases eventually developing chronic liver injury.[1,2]

Chronic liver injury may result in fibrosis, bile duct loss, and cirrhosis; and negatively impacts quality of life.[1–4] Currently, the understanding of underlying mechanisms driving the trajectory of DILI recovery is limited. Certain clinical factors have been reported as risk factors for prolonged DILI recovery, but the results are not entirely consistent. For example, Fontana *et al.*[1] reported that a cholestatic pattern of DILI was more frequent in persistent DILI cases, while Medina-Caliz *et al.*[3] did not find a significant association between chronicity and cholestatic pattern. Age was another clinical factor that was significant in some studies, but insignificant in others.[1,3,5] A prospective study conducted by the U.S. Drug-Induced Liver Injury Network described 17% of DILI cases as chronic based on abnormal serum biochemistries 6 months after enrollment,[5,6] and Medina-Caliz *et al.* of the Spanish DILI Registry found that 8% of DILI cases persisted for more than 1 year.[3]

One reason for the inconsistencies among studies may stem from the different definitions of chronic DILI. Chronic cases are defined by abnormal serum chemistry values for an extended period of time, either 6 months[5,6] or 1 year.[3,7] Although these studies categorized cases as chronic based on biological or medical rationales, time to the resolution of abnormal serum chemistry values is a continuous variable, and these different cut-offs may have led to inconsistent observations.

Keywords: Drug-induced liver injury; prolonged recovery; scoring model; risk factor; accelerated failure time.
Received 9 October 2020; received in revised form 22 March 2021; accepted 23 March 2021; available online 18 May 2021
* Corresponding author. Address: Division of Bioinformatics and Biostatistics, National Center for Toxicological Research, U.S. Food and Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, USA; Fax: 870-543-7865.
E-mail address: Minjun.chen@fda.hhs.gov (M. Chen).
https://doi.org/10.1016/j.jhep.2021.03.021

In this study, we did not focus on chronicity, but on time to recovery after DILI. We used an accelerated failure time model to explore host factors and drug properties and to identify the potential risk factors that could influence the time course of DILI recovery after discontinuation of the culprit medications. Further, we defined a model and score based on these factors (*i.e.* bilirubin and alkaline phosphatase (ALP) at DILI onset, time to onset, extent of hepatic metabolism) and validated the model using 2 independent cohorts, with 257 cases from the Spanish DILI Registry[8] and 191 DILI cases collected from the National Institutes of Health (NIH) LiverTox database.[9]

Materials and methods

iDILIC cohort

Cases in this study were part of the International DILI Consortium (iDILIC), a large collaborative study with recruitment centers across Europe, Asia, and Australia. These 720 cases were from batches 1 and 2 of the fourth release of iDILIC. Batch 3 from the fourth release was excluded because follow-up serum biochemistries were not reported. All participants provided written informed consent and each study had been approved by the appropriate national or institutional ethical review boards.

Inclusion criteria for cases in the iDILIC cohort were based on clinical chemistry criteria for DILI as defined by Aithal *et al.*[7] which states that a qualified case must either have alanine aminotransferase (ALT) elevated at least fivefold above the upper level of normal (ULN), or at least a twofold elevation of ALP above the ULN, or elevated levels of ALT at least threefold above the ULN with bilirubin concentrations also more than twofold above the ULN. Cases were also assessed using the Roussel Uclaf Causality Assessment Method (RUCAM) scoring system and expert review by a panel of 3 hepatologists.

Only cases with a RUCAM causality scale of probable (*i.e.*, a score of greater than or equal to 6) were included. In addition, only patients with initial and follow-up serum biochemistries and without long intervals (more than 6 months) between the final elevated and the normalized serum biochemistry dates were included. We excluded cases in which preexisting liver disease was present and only included causal drug combinations that occurred more than 5x in the iDILIC cohort. For example, amoxicillin-clavulanate and sulfamethoxazole-trimethoprim are frequently given in combination. However, causal drug combinations such as diclofenac and flucloxacillin, which are not frequently given in combination and occurred less than 5x in the cohort, were excluded. To avoid conflict with the validation cohort, we excluded cases collected by the Spanish DILI group. The final analysis included 294 cases. Fig. 1 describes the inclusion and exclusion criteria.

Patient follow-up and recovery

In order to study DILI recovery, we collected information regarding the length of patient follow-up and patient status, in terms of biochemical recovery, at final follow-up. Patient recovery was defined as the return of a patient's serum biochemistries to normal (1xULN). Time to recovery, or time followed, was calculated in days from the day of withdrawal of the offending medication[10,11] to the date when liver serum biochemistries normalized (1xULN) or the last day of follow-up. Patients with serum ALT, aspartate aminotransferase (AST), ALP, or bilirubin that did not return to 1xULN were censored at the date of their last recorded follow-up. Four patients that died or required a liver transplant were censored at the date of their last recorded follow-up. Both censored cases and cases that returned to 1xULN are included in the regression modeling of the accelerated failure time analysis, which is a parametric time-to-event analysis. As long as parametric assumptions are met, the time-to-event analysis can utilize cases with and without complete follow-up, resulting in a more representative cohort.

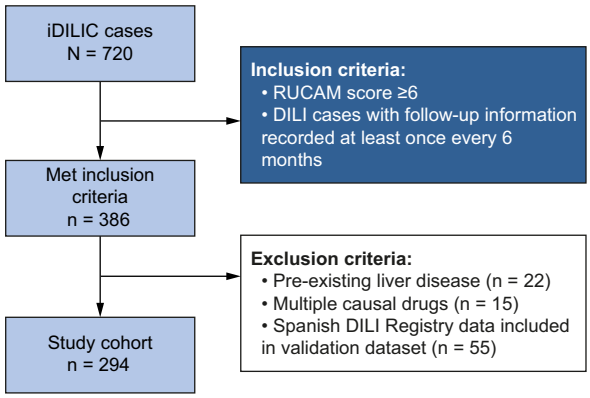


Fig. 1. Inclusion and exclusion criteria in the iDILIC cohort. iDILIC, International Drug-Induced Liver Network Consortium.

To test the non-informative censoring assumption, we assessed the distributions of serum liver tests in censored cases compared to cases that were followed to complete biochemical recovery to evaluate if censored cases have a recovery trajectory comparable to individuals with continued follow-up within this cohort. As shown in Fig. S1, the distribution of serum bilirubin in censored cases is similar to the distribution in cases with complete follow-up, indicating that censoring in this study is non-informative. The analysis on serum ALP and ALT also showed a similar trend (data not shown). Thus, we can reasonably assume that censored cases would likely have a recovery trajectory comparable to that of individuals with continued follow-up.

Host factors

Patient data were collected from the iDILIC clinical data. Clinical information included medical history, concomitant medications, liver enzymes, and other clinical features (Table 1). The type of liver injury was categorized as hepatocellular, mixed, or cholestatic using the R value at DILI diagnosis, as described by Benichou *et al.*[12] We defined DILI onset as the date of DILI diagnosis and the time to DILI onset as the days from the initial drug intake to the DILI diagnosis. Liver biochemistry tests that were taken at DILI diagnosis were also included. Delayed drug discontinuation was defined as the number of days from DILI diagnosis to drug discontinuation. DILI severity categories were defined by Aithal *et al.*[7] Mild cases are those which met aforementioned clinical biochemistry criteria for DILI, moderate cases met criteria for DILI and had bilirubin values greater than 2x the ULN, and severe cases met moderate criteria and had one of the following: ascites, encephalopathy, international normalization ratio >1.5, and/or other organ failure due to DILI.

Drug properties

In this study, we included drug properties associated with clinically significant hepatotoxicity, which were identified by Chen *et al.*[13]: daily dose, lipophilicity, and extent of hepatic

Table 1. Clinical characteristics in 294 iDILIC cases.

		Injury type		
	Entire cohort (n = 294)	**Cholestatic (n = 77)**	**Hepatocellular (n = 103)**	**Mixed (n = 114)**
Sex (n,%)				
Female	175 (60%)	40 (52%)	63 (63%)	70 (61%)
Male	119 (40%)	37 (48%)	38 (37%)	44 (39%)
Age (years)				
Mean (range)	61 (14–91)	66 (32–91)	56 (14–83)	62 (19–85)
Missing (n,%)	1 (0%)	0 (0%)	1 (1%)	0 (0%)
Age-Sex (n,%)				
Under 55 female	72 (25%)	9 (12%)	36 (35%)	27 (24%)
Under 55 male	30 (10%)	6 (8%)	14 (14%)	10 (9%)
Over 55 female	102 (35%)	31 (40%)	28 (27%)	43 (38%)
Over 55 male	90 (31%)	31 (40%)	25 (24%)	34 (30%)
Body mass index				
Mean (SD)	26.1 (±4.5)	25.4 (±4.2)	26.2 (±4.3)	26.3 (±4.9)
Missing (n,%)	17 (5.8%)	5 (6.5%)	7 (6.8%)	5 (4.4%)
Clinical presentation (n,%)				
Jaundice	69 (23%)	20 (26%)	21 (20%)	28 (25%)
Hospital admission	204 (69%)	53 (69%)	72 (70%)	79 (69%)
Missing	4 (1%)	1 (1%)	3 (3%)	0 (0.0%)
Hypersensitivity	8 (3%)	1 (1%)	4 (4%)	3 (3%)
Time to onset (days)				
Mean (SD)	43.2 (±80.7)	38.6 (±49.1)	54.2 (±86.2)	36.4 (±91.7)
Median (range)	25 (1–955)	29 (4–365)	26 (1–519)	22 (1–955)
Follow-up (days)				
Mean (SD)	81.8 (±73.6)	97.1 (±79.2)	68.3 (±64.8)	83.7 (±75.5)
Median (range)	68 (1–587)	82 (1–543)	53 (3–391)	68 (6–587)
Censored (n, %)	154 (52%)	46 (30%)	47 (31%)	61 (40%)
Mean (SD)	85.3 (±91.8)	106.2 (±98.3)	65.9 (±78.3)	84.5 (94.3)
Median (range)	58.5 (1–587)	83 (1–543)	39 (3–391)	55 (6–587)
Time to recovery* (days)				
Recovered (n, %)	140 (48%)	31 (22%)	56 (40%)	53 (38%)
Mean (SD)	79.2 (±47.9)	86.4 (±40.9)	71.8 (±53.0)	82.7 (±45.9)
Median (range)	73 (10–259)	82 (20–194)	66 (10–231)	76 (11–259)
Laboratory parameters at DILI onset				
ALT (/ULN), mean (SD)	12.8 (±13.6)	5.0 (±3.5)	22.3 (±18.8)	9.6 (±4.5)
AST (/ULN), mean (SD)	10.0 (±12.1)	3.6 (±2.7)	16.3 (±15.9)	7.3 (±6.9)
Missing, n (%)	178 (61%)	50 (28%)	57 (32%)	71 (40%)
ALP (/ULN), mean (SD)	2.9 (±2.4)	4.7 (±3.5)	1.6 (±0.9)	3.0 (±1.3)
Bilirubin (/ULN), mean (SD)	5.2 (±4.7)	6.5 (±6.6)	4.4 (±4.1)	5.1 (±3.3)
Severity (n,%)				
Mild	42 (14%)	12 (16%)	17 (17%)	13 (11%)
Moderate	244 (84%)	61 (79%)	84 (82%)	99 (87%)
Severe	3 (1%)	1 (1%)	0 (0%)	2 (2%)
Fatal or transplant	4 (1%)	2 (3%)	2 (2%)	0 (0%)
Missing	1 (0%)	1 (1%)	0 (0%)	0 (0%)
RUCAM causality score (n,%)				
Definite or highly probable	113 (38%)	26 (34%)	40 (39%)	47 (41%)
Probable	181 (62%)	51 (66%)	63 (61%)	67 (59%)
Comorbidities (n,%)				
Diabetes mellitus	9 (3%)	4 (5%)	3 (3%)	2 (2%)
Hypertension	55 (19%)	19 (25%)	18 (17%)	18 (16%)
Tuberculosis	7 (2%)	0 (0%)	7 (7%)	0 (0%)
Lipid metabolism disorders	5 (2%)	2 (3%)	0 (0%)	3 (3%)
Psoriasis	11 (4%)	4 (5%)	4 (4%)	3 (3%)
Dermatitis	8 (3%)	2 (3%)	1 (1%)	5 (4%)
Missing	24 (8%)	8 (10%)	5 (5%)	11 (10%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; DILI, drug-induced liver injury; iDILIC, International Drug-Induced Liver Network Consortium; RUCAM, Roussel Uclaf Causality Assessment Method. Hypersensitivity: fever, rash, and/or eosinophilia; Severity, Mild: elevated ALT/ALP meeting DILI criteria; Moderate: elevated ALT/ALP meeting DILI criteria and bilirubin ≥ 2xULN; Severe: elevated ALT/ALP, bilirubin ≥ 2xULN, and 1 of the following: ascites, encephalopathy, international normalization ratio >1.5 and/or other organ failure due to DILI; Fatal: death or transplantation due to DILI.
*Time to recovery includes only cases that resolved within the follow-up time.

metabolism. Information on drug properties was retrieved from the U.S. Food and Drug Administration's (FDA) Liver Toxicity Knowledge Base[14] and literature sources. The extent of hepatic drug metabolism was defined as high when ≥50%; otherwise, it was low, following the definition by Lammert *et al.*[15] The drug properties of drug combinations were combined by taking the maximum value. Causal drugs and their frequencies are shown in Table S1.

Spanish DILI Registry cohort

To further validate the model, we applied the recovery score prediction to 257 cases collected by the Spanish DILI Registry.[8] These cases had a median follow-up time of 97 days (range 0–3,353 days). The inclusion criteria were the same as the criteria used for the main iDILIC cohort, including the requirement that follow-up serum biochemistries were recorded at least once every 6 months. Causal drugs and their frequencies in the Spanish DILI cohort are shown in Table S2.

The study protocol was approved by the local Ethics Committee at the Virgen de la Victoria University Hospital in Málaga, Spain, and all participants gave informed consent.

LiverTox cohort

We downloaded 389 case reports from the NIH LiverTox database[9] for an independent validation analysis. The case reports included liver biochemistries, DILI severity, pattern of injury, time to onset, age, sex, causal drug, and recovery time. After removing cases in which dietary supplements were responsible and those missing initial serum biochemistries, 191 cases with a median follow-up time of 60 days (range 4-300 days) remained. Table S3 includes LiverTox drug frequencies.

Statistical methods

Univariate analysis

Accelerated failure time (AFT) models were used for time-to-event analysis, where the event was DILI recovery as defined by the return of ALT, ALP, and bilirubin to normal values or 1xULN. In order to identify clinical factors and drug properties affecting DILI recovery, we first screened clinically relevant variables in a univariate analysis. These potential clinical risk factors included sex, age, time to onset, and liver biochemistries (bilirubin, ALP, and ALT) at DILI onset. We also included drug properties: daily dose, extent of metabolism, and lipophilicity, and transformed time to onset and the liver serum biochemistry values (ALT, ALP, and bilirubin) to their natural logarithms.

Two drugs, amoxicillin-clavulanate and flucloxacillin, accounted for 28% (n = 82) and 27% (n = 79) of the total cases in this iDILIc cohort (n = 294), respectively. Therefore, we conducted the univariate analysis in the entire cohort, in subsets including only amoxicillin-clavulanate or flucloxacillin, and in a subset that excluded cases associated with these 2 dominant causal drugs.

Development of DILI recovery time model

We next built a multivariate AFT model using factors approaching significance (p <0.1) in the univariate analysis of the entire cohort. A factor was not selected if its correlation with other factors was 0.3 or greater or if it was significantly associated with other factors (p <0.01) (*i.e.* collinearity). We assessed the AFT distribution and goodness-of-fit (detailed in the supplementary methods) and then used the model to calculate the recovery score and divide cases into high-, indeterminate-, and low-risk groups. Cases with a score of 1 standard deviation above the mean or greater were classified as high-risk for delayed recovery, those within 1 standard deviation of the mean were classified as indeterminate-risk, and those with a score 1 standard deviation below the mean or lower were classified as low-risk.

The defined multivariate score model was validated by predicting prolonged recovery cases from the Spanish DILI Registry and the NIH LiverTox cohorts. The risk score cut-offs defined in the original study population were used to categorize these cases into high-, indeterminate-, and low-risk groups. Recovery rates were determined using the Kaplan-Meier method, and the log-rank test was used to compare the recovery time between the high- and low-risk groups. We also considered performance in specific subgroups based on injury type, case severity, and RUCAM scores.

Other statistical analyses

Descriptive statistics, mean, and standard deviation were used to describe continuous variables, and frequency and percent were used to describe categorical variables. All analyses were performed using R (version 3.6.1)[16] and the survival[17] package for the accelerated failure time model, htmlTable[18] for clinical and drug tables, car[19] for Q-Q plots, and survminer[20] for Kaplan-Meier plots. Code for the Kaplan-Meier estimator of residuals was adapted from Rizopoulos.[21]

Results

Clinical characteristics of the study population

After applying inclusion and exclusion criteria (Fig. 1), 294 cases remained. Of these, 140 cases recovered within the follow-up period, and 154 either did not recover or were lost to follow-up. Mean/median follow-up time was 82/68 days (range 1–587 days). The average age was 59 years (range 14–91 years), and 60% of the cases were female. A majority of patients (94.2%) were Caucasian, 3.4% were Asian, and the remaining 2.4% were of another/unknown race. The pattern of liver injury was cholestatic in 26% of cases, hepatocellular in 35%, and mixed in 39%. Among cases that recovered, the mean/median time to biochemical recovery was 79/73 days (range 10–259 days). In censored cases that were lost to follow-up before they fully recovered, the mean/median follow-up time was 84/59 days (range 1–587 days). Clinical characteristics and comorbidities of the 294 cases are shown in Table 1.

Antibiotics were responsible for 68.4% of cases, followed by non-steroidal anti-inflammatory drugs (6.5%) and anti-hyperlipidemics (3.4%). Amoxicillin-clavulanate and flucloxacillin were the most frequently implicated drugs and were causal in 82 (27.9%) and 79 (26.9%) cases, respectively. Additional drug frequencies are shown in Table S1.

Univariate analysis

Results for the AFT univariate analysis are shown in Table 2. In the entire cohort, a 1-unit increase in $\log_e$ of bilirubin times the upper limit of normal at DILI onset was associated with a 46% longer recovery time (p <0.001), and ALP was associated with a 50% longer recovery time (p <0.001). Moderate-to-severe (*vs.* mild) clinical severity was associated with a 109% longer recovery time and was statistically significant (p <0.001). Hepatocellular injury was associated with a 54% shorter recovery time compared with cholestatic injury (p <0.001). A higher bilirubin value also was associated with a prolonged recovery in the amoxicillin-clavulanate and the flucloxacillin subgroups. Longer time to DILI onset was associated with prolonged recovery time in the amoxicillin-clavulanate subgroup, but not in the flucloxacillin subgroup.

ALT at DILI onset, age, and sex were not significant in any of the subgroups. In ancillary analyses, we analyzed a subset that excluded both amoxicillin-clavulanate and flucloxacillin cases,

Table 2. Univariate accelerated failure time estimates of the impact of host factors and drug properties on the time to biochemical recovery.

	Entire cohort, time ratio (95% CI) n = 294	Amoxicillin-clavulanate, time ratio (95% CI) n = 82	Flucloxacillin, time ratio (95% CI) n = 79
Age	1.00 (1.00–1.01)	1.01 (0.99–1.02)	1.00 (0.99–1.02)
Age below median (61 years)	0.98 (0.77–1.25)	0.99 (0.73–1.36)	1.00 (0.62–1.62)
Sex (male)	0.85 (0.67–1.09)	0.82 (0.60–1.10)	0.66 (0.41–1.06)†
Injury type			
Hepatocellular	**0.54 (0.40–0.73)*****	**0.59 (0.40–0.85)****	0.83 (0.39–1.80)
Mixed	0.79 (0.58–1.06)	**0.67 (0.47–0.96)***	0.76 (0.43–1.36)
Severity: moderate-severe *vs.* mild	**2.09 (1.54–2.83)*****	–	–
Log_e of ALT at onset (xULN)	0.96 (0.83–1.11)	0.87 (0.71–1.06)	1.02 (0.64–1.62)
Log_e of ALP at onset (xULN)	**1.50 (1.25–1.81)*****	1.23 (0.94–1.62)	1.44 (0.80–2.63)
Log_e of bilirubin at onset (xULN)	**1.46 (1.31–1.62)*****	**1.41 (1.15–1.72)*****	**1.44 (1.03–1.99)***
Log_e of time to onset (days)	1.12 (1.00–1.26)†	**1.33 (1.13–1.56)*****	0.95 (0.66–1.36)
Drug exposure (days)	1.00 (1.00–1.00)	1.01 (0.97–1.04)	1.03 (0.98–1.09)
Delayed drug discontinuation	1.02 (0.99–1.05)	–	–
Extent of metabolism (≥50%)	**0.52 (0.40–0.66)*****		
Daily dose	1.00 (1.00–1.00)		
Lipophilicity (LogP)	1.00 (0.92–1.08)		

Univariate accelerated failure time estimates of the percentage differences in time to biochemical recovery. Covariates with a time ratio ≥1 are associated with a prolonged time to recovery. For example, a time ratio of 0.54 indicates that hepatocellular injury is associated with a 54% decrease in time to recovery, as compared to cholestatic injury. A time ratio of 1.46 implies that a 1-unit increase in loge of bilirubin times the upper limit of normal at DILI onset will increase time to recovery by 46%. Results are shown in the entire cohort and 2 subgroups, one comprised only of amoxicillin-clavulanate cases and the other only of flucloxacillin cases. Not enough data was available to estimate severity and delayed drug discontinuation in the amoxicillin-clavulanate and flucloxacillin cases. Numbers in bold indicate statistical significance. *p <0.05; **p <0.01; ***p <0.001, †p <0.1. ALP, alkaline phosphatase; ALT, alanine aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal.

and the results were similar to the entire cohort (data are not shown). In addition, we considered injury types classified by nR;[22] however, a large portion of cases (60%) lacked AST values, and ALT alone was used for their classification. The results were similar, with only 3 mixed injury cases reclassified into the hepatocellular injury type using nR.

Drug properties were tested in the entire cohort. Offending drugs eliminated primarily through hepatic metabolism were significantly associated with a 52% shorter recovery time (Table 2), compared to those without significant hepatic metabolism. This association remained significant even without amoxicillin-clavulanate and flucloxacillin cases (time ratio 0.61; 95% CI 0.42–0.89, p = 0.0095).

DILI recovery time model

Total bilirubin, ALP at DILI onset, time to onset, and extent of drug metabolism were selected for the multivariate analysis (see Table 3), which we used to calculate recovery score. Severity and injury type were not selected, since they were correlated with other selected variables. A score model for DILI recovery derived from the AFT log-normal approach was defined as follows:

Recovery score = 0.227*log_e(ALPxULN at onset) + 0.277 *log_e(bilirubinxULN at onset) + 0.161*log_e(time to onset) – 0.440*(significant hepatic metabolism of culprit drug).

The range of possible recovery scores was -0.60 to 2.03, where a higher score indicated a greater likelihood of prolonged recovery.

The cases were categorized into high-risk for prolonged recovery (recovery score >1.30), and low-risk (recovery score ≤0.44) to evaluate the association between the calculated scores and the trajectory of DILI recovery. Cases between the thresholds were indeterminate. As shown in Fig. 2A, the risk groups had a significantly different time course for recovery (p <0.0001). Specifically, the probability of recovery by 6 months for the high-risk group was estimated as 46% (95% CI 0.26–0.61) compared to 93% for the low-risk group (95% CI 0.58–0.99). The estimated probability of recovery by 3, 6, and 9 months was consistently higher in the low-risk group, as shown in Table 4.

As seen in Fig. S2, cases with a RUCAM score of ≥8 (i.e. definite or highly probable) showed a clearer separation between the high-risk *vs.* low-risk groups (p <0.0001, log-rank test), compared to those with a score of <8. This suggests that the model performs better when applied to higher-quality data.

Model validation

We then validated the model by predicting delayed recovery in 257 cases from the Spanish DILI Registry. The high- and low-risk cases identified by the model showed a significantly different time course for recovery (Fig. 2B, p = 0.0072).

We also validated the model in 191 cases downloaded from LiverTox and applied the recovery score model to the LiverTox cases, categorizing them into risk groups. The difference in

Table 3. Multivariate log-normal accelerated failure time model for DILI recovery score.

Covariates	β	SE	TR	95% CI	p value
Log_e ALP (xULN) at DILI onset	0.227	0.086	1.25	1.06-1.48	0.008
Log_e bilirubin (xULN) at DILI onset	0.277	0.054	1.32	1.19-1.47	<0.001
Log_e of time to onset (days)	0.161	0.049	1.17	1.07-1.29	0.001
Extent of metabolism (>50%)	-0.440	0.127	0.64	0.50-0.83	<0.001

β is used as the coefficient of the recovery score model.
Number of observations = 294, Number of events = 140, R-squared = 0.219.
Likelihood ratio X^2 test = 72.24 (df = 4, p <0.0001). Scale = 0.729.
DILI, drug-induced liver injury; SE, standard error; TR, time ratio; ULN, upper limit of normal.

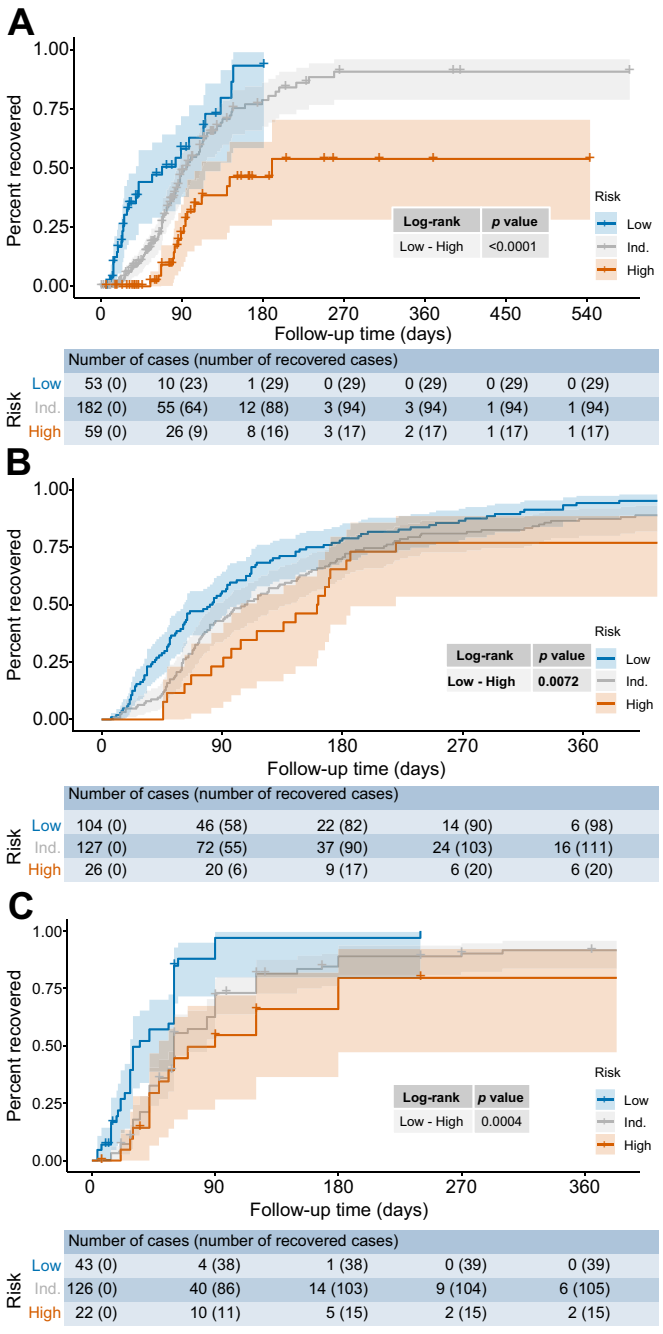


Fig 2. Kaplan-Meier cumulative event rates for time to recovery. Cases were divided into high-, indeterminate-, and low-risk groups using the recovery score model. (A) In the iDILIC cohort (n = 294), the difference between high- and low-risk groups was significant, according to the log-rank test (p <0.0001). (B) In the Spanish cohort (n = 257), recovery in the high- and low-risk groups was significantly different according to the log-rank test (p = 0.0072). (C) In the LiverTox cohort (n = 191), the difference between the low- and high-risk groups was significant according to the log-rank test (p = 0.0004). (This figure appears in color on the web.)

recovery between the high- and low-risk groups was statistically significant when using a log-rank test (Fig. 2C, p = 0.0004).

Table S4 compares clinical characteristics of the iDILIC, LiverTox, and Spanish DILI Registry cohorts grouped by follow-up time.

Discussion

In this study, we modeled the recovery trajectory after DILI injury using clinical factors and drug properties with an accelerated failure time model in a large cohort of well-characterized patients with acute DILI. We found that total bilirubin, ALP at DILI onset, time to onset, and importantly, extent of drug metabolism, were consistently associated with DILI recovery time. A scoring model based on these factors was developed from 294 DILI cases and validated in an independent cohort of 257 samples from the Spanish DILI Registry[8] and 191 DILI cases from the LiverTox database.[9]

Primary strengths of our study are the substantial size of the cohort, strict inclusion criteria, and external validation in diverse cohorts. The 294 well-defined DILI cases, verified by expert review and causality assessment, were retrieved from the iDILIC, which is part of the International Serious Adverse Event Consortium (iSAEC)[23] and includes clinical and offending medication information from patients recruited primarily from DILI centers across Europe. In our study, only cases with a RUCAM score of ≥6 were included and those with preexisting conditions were removed. The recovery score model performed better when applied to cases with a RUCAM of ≥8, suggesting that the model performs well in the higher-quality cases (Fig. S2).

Further, we considered performance in specific subgroups, including injury types and severity. We found that the model performed best for hepatocellular cases, separating them into distinct groups (Fig. S3A, log-rank p = 0.0084). Similar results were found in the Spanish and LiverTox validation sets, as seen in Fig. S4 and S5, respectively. In addition, the model performed better for moderate-to-severe DILI cases than for mild DILI cases; granted, there are fewer mild cases (Fig. S6). Although this trend again was not seen in the Spanish cohort (Fig. S7), it was seen in the LiverTox cases, which were classified into severity groups based on LiverTox methodology (Fig. S8).

Importantly, the model was successfully validated using 2 external cohorts with different causal drug distributions: the Spanish DILI cohort and the LiverTox cohort. Compared to the LiverTox and Spanish DILI cohorts, the iDILIC cohort in this study had similar demographics in terms of sex but was slightly older, *i.e.* the average age at DILI diagnosis was 59 years in this cohort, *vs.* 55 years in the Spanish cohort and 49 years in the LiverTox cohort.[3,5] It is worth noting that antimicrobials were the main culprit, accounting for 68% of cases in the study cohort, which is higher than the 37% in the Spanish cohort and the 45% in the LiverTox cohort.[3,5] Specifically, our cohort included 28% amoxicillin-clavulanate and 27% flucloxacillin cases, which led to a greater portion of mixed (39%) and cholestatic (26%) cases. Likewise, amoxicillin-clavulanate was the most frequent offending drug in Spanish cases. On the contrary, the LiverTox cohort included only 3 amoxicillin-clavulanate cases and no flucloxacillin cases (Table S3). As a result, a relatively shorter recovery course was observed in the LiverTox cohort because recovery from treatment with these 2 drugs may take longer. Because the LiverTox cohort is derived from a collection of representative case reports, it has a more even distribution of drugs, including 148 unique drugs, of which 113 occurred only once within the cohort.

In this study, rather than reducing statistical power by using a cut-off point to define chronic cases, we considered patient time to recovery as a continuous variable. Using a continuous variable

Table 4. Clinical characteristics of the high- and low-risk groups for prolonged DILI recovery.

		Risk category	
	Total (n = 294)	Low, recovery score ≤0.44 (n = 53)	High, recovery score >1.30 (n = 59)
Probability of recovery (95% CI)			
3 months	0.45 (0.37–0.51)	0.58 (0.38–0.72)	0.22 (0.08–0.35)
6 months	0.74 (0.65–0.80)	0.93 (0.58–0.99)	0.46 (0.26–0.61)
9 months	0.85 (0.75–0.91)	0.93 (0.58–0.99)	0.54 (0.28–0.70)
Time to onset			
Mean (SD)	43.2 (±80.7)	28.6 (±27.5)	65.2 (±130.9)
Median (range)	25 (1–955)	22 (1–150)	33 (5–955)
Follow-up (days)			
Mean (SD)	81.8 (±73.6)	50.7 (±43.9)	109.6 (±91.5)
Median (range)	68 (1–587)	31 (6–181)	86 (6–543)
Censored (n, %)	154 (52.4%)	24 (45.3%)	42 (71.2%)
Time to recovery*			
Mean (SD)	79.2 (±47.9)	51.6 (±44.0)	96.6 (±34.0)
Median (range)	73 (10–259)	29 (10–147)	89 (55–190)
Injury type (n,%)			
Cholestatic	77 (26%)	10 (19%)	28 (48%)
Hepatocellular	103 (35%)	30 (57%)	8 (14%)
Mixed	114 (39%)	13 (25%)	23 (39%)
Laboratory parameters at onset			
ALT (/ULN), mean (SD)	12.8 (±13.6)	12.0 (±18.0)	9.8 (±8.0)
AST (/ULN), mean (SD)	10.0 (±12.1)	7.8 (±6.1)	10.9 (±16.5)
Missing	178 (61%)	26 (49%)	38 (64%)
ALP (/ULN), mean (SD)	2.9 (±2.4)	2.1 (±2.5)	4.3 (±3.3)
Bilirubin (/ULN), mean (SD)	5.2 (±4.7)	1.1 (±1.1)	10.0 (±6.3)
Extent of metabolism (n,%)			
≥50 %	85 (29%)	42 (79%)	2 (3%)
<50 %	209 (71%)	11 (21%)	57 (97%)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal.
*Time to recovery includes only cases that resolved within the follow-up time.

has statistical advantages over those classified by hard thresholds (*e.g.* 6 months). Categorizing continuous variables, however, has well-documented statistical disadvantages,[24,25] which can result in a considerable loss of statistical power and increase the risk of false positives. Even cut-off points based on medical rationales can be problematic for borderline cases. Here, biochemical recovery after liver injury is a continuous process that may occur well before or after 6 months. The AFT analysis also allowed us to individualize the trajectory of patient recovery and include cases without complete follow-up information.

We employed the AFT model rather than the Cox proportional hazards model. The Cox model is semi-parametric and does not assume that the survival times or outcome must follow a certain statistical distribution. It does, however, rely on the assumption of constant proportional hazard ratios, and a violation of such will result in an improper fitting of the model and incorrect inferences.[26] We found that the recovery time data violated the assumptions of proportional hazards. Alternatively, the AFT model does not assume proportional hazards and is easier to interpret but does require a parametric distribution for the survival times. The AFT multivariate model fit the log-normal distribution well, except for departures at the tail of the distribution, where very few cases remained.

Total bilirubin at DILI onset was consistently associated with the length of time to DILI recovery across drugs in the entire cohort and in the drug-specific subsets. Previous studies have identified bilirubin as significantly associated with chronic[3] or persistent[1] DILI, but not at DILI onset; however, Medina-Caliz *et al.* found that bilirubin was significantly elevated in chronic cases in the second month after onset and that jaundice at onset was a risk factor for DILI chronicity. A recent retrospective study found that prolonged bilirubin decline from the peak value to its half of the peak value was an independent risk factor for chronic DILI.[27] Some studies defined chronic DILI as 6 months or 1 year from onset;[3,5,28,29] whereas our study relied on an AFT model rather than a binary cut-off, giving us more statistical power with which to identify influential factors (*i.e.*, total bilirubin at onset). Of note, our extended analysis showed that the initial bilirubin value remained significant when tested in all injury type subgroups: hepatocellular (time ratio 1.63; 95% CI 1.35–1.97; p <0.0001), mixed (time ratio 1.43; 95% CI 1.20–1.69; p <0.0001), and cholestatic (time ratio 1.24; 95% CI 1.04–1.47, p = 0.019).

ALP at onset was significant in the entire cohort and in the subgroup that excluded both amoxicillin-clavulanate and flucloxacillin cases (p = 0.026). A similar finding was previously reported in other studies of DILI chronicity.[1,3,29] As in other studies, ALT was not a significant predictor of recovery time.

Injury type was significant in the entire cohort (p = 0.001) but was not significant in the amoxicillin-clavulanate and flucloxacillin subgroups. Notably, both of these drugs have a high prevalence of cholestatic and mixed cases, with 25% and 58% of flucloxacillin cases, and 33% and 41% of amoxicillin-clavulanate, attributable to cholestatic and mixed injury, respectively. Previous studies differed as to the role of injury type, with some finding differences in injury type,[1,5] whilst other studies did not.[3]

Significance of age also was inconsistent, with some studies reporting a higher frequency of chronic DILI cases in older patients,[1,3] while another reported a higher frequency of younger patients with chronic DILI.[5] Still others reported no significant association with age.[4,29] Interestingly, it has been suggested that the prevalence of certain medications in specific age categories

may influence the significance of age in chronic DILI.[1] Since certain drugs have unique clinical signatures, it is possible the inconsistencies between studies were due in part to the different drug frequencies and drug properties. In addition, some of these studies considered elevated liver biochemistries at 6 months as chronic or persistent DILI; others considered that time to be at 12 months.

Besides clinical factors, drug factors such as lipophilicity, dose, and metabolism can also influence DILI phenotypes[30,31] or DILI risk.[13,15,32,33] In this study, we found that the extent of hepatic metabolism of offending drugs was significantly associated with recovery time. Potential mechanisms of the association between non-significant hepatic metabolism and prolonged recovery have yet to be elucidated. However, a few aspects are worthy of discussion. Drugs with significant hepatic metabolism (*e.g.* diclofenac) have been linked to hepatocellular injury and severe DILI outcomes.[15,34] At the same time, drugs with insignificant hepatic metabolism usually are reactive, and some have been reported to directly bind immune cells to stimulate responses in susceptible patients, possibly leading to prolonged recovery. For example, flucloxacillin was reported to form covalent bonds with peptide-HLA complexes,[35] and amoxicillin can bind directly to MHC-peptide complexes.[36] It is likely that the chronic presentation of nitrofurantoin-induced liver injury occurs via similar mechanisms.[37]

A possible limitation of our study is that it is retrospective, and case follow-up time was influenced in part by the clinician decision. In the iDILIC cohort, only 5 patients were followed for at least 12 months; because the model was built on this cohort, extending it past 12 months is beyond the range of the model. As such, our model was designed to predict the trajectory of a patient's recovery and might not predict chronic DILI that persists for ≥1 year after DILI onset. Herein, we have defined DILI recovery as determined by liver enzyme data, and very few cases included histological data for supporting evaluations. Overall statistically, the model works for the entire cohort; however, when applied to subgroups based on the type of liver injury, the model performs best when applied to hepatocellular cases. This likely is due to mechanistic differences in the development of different kinds of liver injury. Further study is required to model cholestatic DILI and DILI extending beyond 12 months. We also noted that 2 drugs, amoxicillin-clavulanate and flucloxacillin, were the offending medications in a large proportion (55%) of cases. In our study, we specifically investigated the subpopulations taking these 2 drugs. Additionally, this cohort included very few targeted therapies and only 1 tyrosine kinase inhibitor case; thus, the model may not be applicable to that particular therapeutic class or patient population. Further data including additional therapeutic classes and patient populations would improve the performance of the model in a broader population.

A major challenge of DILI clinical management is that the patient's clinical course is difficult to predict based on the initial findings at the time of DILI diagnosis. Our model provides a tool to predict the trajectory of the patient's recovery after drug discontinuation, discerning low *vs.* high risk of having a prolonged recovery, using a simple model that is easy to implement in clinical practice. Patients whose liver tests have not normalized after suspected DILI may have persistent symptoms, such as itching, which reduce quality of life. The frequent investigations and clinic visits associated with prolonged recovery may also add to the cost of care of these patients, increasing the overall burden on health services. By assigning patients to high- or low-risk groups, the recovery score model could assist clinicians in determining which patients need additional work-up, such as magnetic resonance cholangiopancreatography or liver biopsy (*e.g.* to look for secondary sclerosing cholangitis or ductopenia) informing patient care and follow-up.

In conclusion, we identified drug-related factors and clinical manifestations, in the form of degree of bilirubin and ALP elevation at the onset of DILI, that have statistically significant associations with prolonged recovery. The model we developed is robust, maintaining significance in drug-specific subgroups, as well as in a separate cohort which included a number of different drugs.

Abbreviations

AFT, accelerated failure time; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; International Drug-Induced Liver Network Consortium; RUCAM, Roussel Uclaf causality assessment; ULN, upper limit of normal.

Financial support

The present study has been supported by the internal funds of the US Food and Drug Administration

Conflict of interest

A.S has consulted for Pfizer Inc and the other authors declare that they have no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions'

MC conceived and designed the study; KM, MC, and AG analyzed the data and drafted the manuscript; AS, GA, ML, RA, MC, and KM interpreted the data. WZ contributed to data analysis, model building, and interpretation. AG, IAA, MIL, and RA collected and processed the cohort used for validation. MC, WZ, AS, MIL, and GA participated in critical revision of the manuscript. All authors contributed to the critical review and final approval of the manuscript.

Data availability statement

The International DILI Consortium (iDILIC) is a large collaborative study with recruitment centers across Europe, Asia, and Australia (https://dataportal.saeconsortium.org/). The data can be requested from the iDILIC consortium. The Spanish DILI Registry database is a privately owned database maintained by the registry's coordinating center in Malaga, Spain. The database is not publicly available.

Disclaimer

The views presented in this article do not necessarily reflect those of the U.S. Food and Drug Administration. Any mention of commercial products is for clarification and is not intended as an endorsement. The National Institutes of Health LiverTox data is publicly available (https://www.ncbi.nlm.nih.gov/books/NBK547852/).

Acknowledgements

We thank Dr. Jurgen Borlak and the 3 anonymous reviewers for their insightful comments and constructive suggestions. A sincere thank you to Joanne Berger for her diligent proofreading of this paper. We acknowledge iSAEC for providing the access to the iDILIC data used in this study. MIL, RJA, IAA, AG, AS, and GPA are members of European Cooperation in Science & Technology (COST) Action CA17112 Prospective European DILI Network.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.03.021.

References

Author names in bold designate shared co-first authorship

[1] Fontana RJ, Hayashi PH, Barnhart H, Kleiner DE, Reddy KR, Chalasani N, et al. Persistent liver biochemistry abnormalities are more common in older patients and those with cholestatic drug induced liver injury. Am J Gastroenterol 2015;110:1450–1459.
[2] Hayashi PH, Bjornsson ES. Long-term outcomes after drug-induced liver injury. Curr Hepatol Rep 2018;17:292–299.
[3] **Medina-Caliz I**, **Robles-Diaz M**, Garcia-Muñoz B, Stephens C, Ortega-Alonso A, Garcia-Cortes M, et al. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. J Hepatol 2016;65:532–542.
[4] Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol 2009;50:511–517.
[5] Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015;148. 1340-1352. e1347.
[6] Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-induced liver injury network (DILIN) prospective study. Drug Saf 2009;32:55–68.
[7] Aithal G, Watkins P, Andrade R, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89:806–815.
[8] Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512–521.
[9] Hoofnagle JH. LiverTox: a website on drug-induced liver injury. Drug-Induced Liver Disease. Elsevier; 2013. p. 725–732.
[10] Andrade RJ, Lucena MI, Kaplowitz N, García-Muṇoz B, Borraz Y, Pachkoria K, et al. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. Hepatology 2006;44:1581–1588.
[11] Björnsson E, Kalaitzakis E, Av Klinteberg V, Alem N, Olsson R. Long-term follow-up of patients with mild to moderate drug-induced liver injury. Aliment Pharmacol Ther 2007;26:79–85.
[12] Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol 1993;46:1331–1336.
[13] **Chen M**, **Suzuki A**, Borlak J, Andrade RJ, Lucena MI. Drug-induced liver injury: interactions between drug properties and host factors. J Hepatol 2015;63:503–514.
[14] Chen M, Zhang J, Wang Y, Liu Z, Kelly R, Zhou G, et al. The liver toxicity knowledge base: a systems approach to a complex end point. Clin Pharmacol Ther 2013;93:409–412.
[15] Lammert C, Bjornsson E, Niklasson A, Chalasani N. Oral medications with significant hepatic metabolism at higher risk for hepatic adverse events. Hepatology 2010;51:615–620.
[16] R Core Team. R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
[17] Therneau TM, Lumley T. Package 'survival'. Survival analysis Published on CRAN. 2014.
[18] Gordon M, Gragg S, Konings P. htmlTable: advanced Tables for Markdown/HTML. R package version, vol. 1; 2018.
[19] Fox J, Weisberg S. An R companion to applied regression (Third). Sage; 2019.
[20] Kassambara A, Kosinski M, Biecek P. survminer: drawing Survival Curves using'ggplot2', vol. 1; 2017. R package version 03.
[21] Rizopoulos D. EP03: survival analysis in R companion. 2020. Section 3.4.
[22] Robles–Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina–Cáliz I, González–Jimenez A, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147. 109-118. e105.
[23] Holden AL. The innovative use of a large-scale industry biomedical consortium to research the genetic basis of drug induced serious adverse events. Drug Discov Today Tech 2007;4:75–87.
[24] Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;332:1080.
[25] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006;25:127–141.
[26] Chapman J, O'callaghan C, Hu N, Ding K, Yothers G, Catalano P, et al. Innovative estimation of survival using log-normal survival modelling on ACCENT database. Br J Canc 2013;108:784–790.
[27] Zhu W, Wang L, Zhao X, Wang T, Shi X, Ou X, et al. Prolonged interval of total bilirubin decline is an early independent predictive factor of chronic persistent drug-induced liver injury. Hepatol Res 2020;50:224–232.
[28] Aithal P, Day C. The natural history of histologically proved drug induced liver disease. Gut 1999;44:731–735.
[29] Fontana RJ, Hayashi PH, Gu J, Reddy KR, Barnhart H, Watkins PB, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology 2014;147. 96-108. e104.
[30] Gonzalez-Jimenez A, McEuen K, Chen M, Suzuki A, Robles-Diaz M, Medina-Caliz I, et al. The influence of drug properties and host factors on delayed onset of symptoms in drug-induced liver injury. Liver Int 2019;39:401–410.
[31] Vuppalanchi R, Gotur R, Reddy KR, Fontana RJ, Ghabril M, Kosinski AS, et al. Relationship between characteristics of medications and drug-induced liver disease phenotype and outcome. Clin Gastroenterol Hepatol 2014;12:1550–1555.
[32] Chen M, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. Hepatology 2013;58:388–396.
[33] McEuen K, Borlak J, Tong W, Chen M. Associations of drug lipophilicity and extent of metabolism with drug-induced liver injury. Int J Mol Sci 2017;18:1335.
[34] Boelsterli UA. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. Toxicol Appl Pharmacol 2003;192:307–322.
[35] Waddington JC, Meng X, Illing PT, Tailor A, Adair K, Whitaker P, et al. Identification of flucloxacillin-haptenated HLA-B* 57: 01 ligands: evidence of antigen processing and presentation. Toxicol Sci 2020;177:454–465.
[36] Horton H, Weston S, Hewitt C. Allergy to antibiotics: T-cell recognition of amoxicillin is HLA-DR restricted and does not require antigen processing. Allergy 1998;53:83–88.
[37] Kelly BD, Heneghan MA, Bennani F, Connolly CE, O'Gorman TA. Nitrofurantoin-induced hepatotoxicity mediated by CD8 T cells. Am J Gastroenterol 1998;93:819–821.