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Prior drug allergies are associated with worse outcome in patients with idiosyncratic drug-induced liver injury: A machine learning approach for risk stratification

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ABSTRACT

The impact of prior drug allergies (PDA) on the clinical features and outcomes of patients who develop idiosyncratic drug-induced liver injury (DILI) is largely unknown. We aimed to assess the clinical presentation and outcomes of DILI patients based on the presence or absence of PDA and explore the association between culprit drugs responsible for DILI and allergy. We analysed a well-vetted cohort of DILI cases enrolled from the Spanish DILI Registry. Bootstrap-enhanced least absolute shrinkage operator procedure was used in variable selection, and a multivariable logistic model was fitted to predict poor outcomes in DILI. Of 912 cases with a first episode of DILI, 61 (6.7%) had documented PDA. Patients with PDA were older ($p = 0.009$), had higher aspartate aminotransferase (AST) levels ($p = 0.047$), lower platelet count ($p = 0.011$) and higher liver-related mortality than those without a history of drug allergies (11% vs. 1.6%, $p < 0.001$). Penicillin was the most common drug associated with PDA in DILI patients (32%). A model including PDA, nR-based type of liver injury, female sex, AST, total bilirubin, and platelet count showed an excellent performance in predicting poor outcome in patients from the Spanish DILI Registry (area under the ROC curve [AUC] 0.887; 95% confidence interval [CI] 0.794 – 0.981) and the LATINDILI Network (AUC 0.932; 95% CI 0.884 – 0.981). Patients with suspected DILI should be screened for PDA as they would require a close monitoring for early detection of worsening clinical course.

Abbreviations: ADR, adverse drug reaction; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATC, Anatomical Therapeutic Chemical; AUC, area under the curve; Bolasso, bootstrap-enhanced least absolute shrinkage operator; CI, confidence interval; CIOMS, Council for International Organizations of Medical Sciences; DILI, drug-induced liver injury; INR, International Normalized Ratio; IQR, interquartile range; Lasso, least absolute shrinkage and selection operator; PDA, prior drug allergies; ROC, receiving operating characteristic; RUCAM, Roussel Uclaf Causality Assessment Method; SD, standard deviation; TBL, total bilirubin; ULN, upper limit of normal; VIF, Variance Inflation Factor.

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1. Introduction

Idiosyncratic drug-induced liver injury (DILI) is an adverse drug reaction (ADR) to the use of conventional medications, herbal products or dietary supplements. It poses a risk to patient safety and leads to unexpected liver and biliary system damage, targeting hepatocytes and other cellular compartments. DILI usually manifests as a mild transient elevation of aminotransferases levels that resolves spontaneously, but in some cases, it may progress to acute liver failure (ALF), necessitating liver transplantation or resulting in death [1,2]. Drug allergies, on the other hand, constitute a complex type of unpredictable ADR characterized by a wide variety of hypersensitivity reactions involving heterogeneous mechanisms and displaying a wide range of clinical features [3].

While it has been suggested that DILI and cutaneous hypersensitivity reactions might share common risk factors [4], little is currently known about the possible interaction between DILI and drug allergies. A recent retrospective study concluded that a history of drug allergy did not increase the likelihood of developing DILI, and that DILI patients with prior drug allergies experienced milder clinical outcomes [5]. However, these findings were based on information extracted from patients' electronic medical records, and to date no prospective studies have been conducted on a population of patients with well-characterized DILI.

Therefore, we aimed to compare the clinical presentation and outcome of DILI patients in the long-term prospective Spanish DILI Registry with and without prior drug allergies (PDA), and to evaluate the association between the drugs responsible for DILI and allergy.

2. Methods

2.1. Study population

Information from DILI cases enrolled in the Spanish DILI Registry from 1994 to February 2022 was collected. In-depth details about the Spanish DILI Registry have been reported elsewhere [6]. Dose-related intrinsic DILI cases, re-exposures and second episodes of DILI were excluded. All patients underwent follow-up until liver profile normalization. The study protocol was approved by local ethics committee. All subjects gave their written informed consent.

2.2. Case definition

In DILI cases, information is available to establish with certainty the temporal relationship between the start of the drug or toxin exposure and the onset of the liver disease, and between the discontinuation of the suspected agent and the improvement or recovery of the liver dysfunction; competing causes have been excluded; the potential for hepatotoxicity of the suspected drugs and the presence of known risk factors for hepatotoxicity have been considered; and the outcome of the liver damage has been recorded.

The biochemical criteria for DILI were those initially defined by the Council for International Organizations of Medical Sciences (CIOMS) [7], and later adapted to those proposed by an international DILI expert consensus, i.e., alanine aminotransferase (ALT) $\geq$5 times the upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq$2 times ULN, or ALT $\geq$3 times ULN along with total bilirubin (TBL) >2 times ULN [8]. The causal relationship between the suspected drug and liver damage was determined by three independent experts. Only cases that were scored at least "possible" when applying the Roussel Uclaf Causality Assessment Method (RUCAM) scale were included [9].

The pattern of liver injury was defined using the nR value, i.e., (ALT or aspartate aminotransferase [AST], whichever highest/ULN) ÷ (ALP/ULN). Cases were classified as hepatocellular (nR $\geq$5), cholestatic (nR $\leq$2), or mixed injury (nR >2 and nR <5). The severity of liver injury was graded as mild (TBL <2 times ULN), moderate (TBL $\geq$2 times ULN), severe (TBL $\geq$2 times ULN, and either International Normalized Ratio [INR] $\geq$1.5, ascites and/or encephalopathy, or other organ failures due to DILI), or fatal or transplantation (death or transplantation due to DILI) [8].

The suspected culprit drugs were classified according to the Anatomical Therapeutic Chemical classification (ATC) into anatomical pharmacological groups and subgroups.

2.3. Prior drug allergies

Prior drug allergies were based on the evaluation of the medical record by the attending physician. For each patient, a structured case report form was used to record pharmacological and clinical data (including information on PDA), blood test results, imaging tests to rule out other causes of liver damage, and the outcome of liver injury. Allergies unrelated to drugs, allergies not adequately documented or reported, or those suspicious of being non-allergic ADRs, such as intolerances, as reported by the attending physician, were not considered as PDA.

2.4. Statistical analysis

Descriptive statistics were used to examine demographic and clinical data of the subjects included in the study. For quantitative data, mean and standard deviation (SD), or median and interquartile range (IQR) were presented, and differences between groups were tested with the Student's t-test or Mann-Whitney U test, as appropriate. Categorical data were described using frequency distributions, and differences were compared using the chi-square test or Fisher's exact test, as appropriate.

In order to select the variables of a logistic regression model, the least absolute shrinkage and selection operator (Lasso) penalized regression method was used. This method penalizes the absolute value of coefficient estimates by shrinking them towards zero, and then dropping them from the final model. To deal with the limitations of Lasso method and prevent the inclusion of irrelevant variables, we applied a modified Lasso procedure, known as the bootstrap-enhanced least absolute shrinkage operator (Bolasso) [10,11].

In this procedure, predictor factors associated with fatal outcome (liver-related death or liver transplantation) were identified in 100 bootstrap samples with replacement through the selection of variables with non-zero coefficients. Based on characteristics that could be potentially associated with worst outcomes the following variables were included in the Bolasso procedure: age, sex, prior drug allergy, pattern of liver injury (hepatocellular vs. cholestatic/mixed), underlying hepatic disease, smoking status (current/former vs. non-smoker), alcohol consumption (current/former vs. non-drinker), eosinophilia, TBL, ALT, AST and ALP levels at DILI recognition, and platelet count. Ten-fold cross-validation was performed to determine the best value of the regularization parameter and obtain stable estimates. Multicollinearity of independent variables was assessed through the variance inflation factor (VIF) statistic.

To calculate the probability of the outcome of interest, a multivariable logistic regression model with the selected variables was fitted using the following logistic function:

$$\text{Probability (outcome)} = 1 / [1 + e^{-(\alpha + \beta X)}]$$

where α, the intercept, is the constant of the model, and β represents the respective variable coefficients.

A nomogram integrating the independent factors was drawn to visualize the model. The discriminatory capability of the model was evaluated with the area under the receiver operating characteristic (ROC) curve (AUC). In addition to internal validation, to determine its reproducibility and generalizability, the model performance was assessed in an external cohort of DILI patients included in the Latin American DILI (LATINDILI) Network [12]. Patients from the LATINDILI Network were followed-up until liver profile normalization. All

statistical analyses were conducted using R version 4.3.0 (R Core Team, 2023), using the "bolasso", "regplot" and "pROC" packages. A two-sided p-value lower than 0.05 was deemed statistically significant.

3. Results

Of the 1,006 patients included in the Spanish DILI Registry, 94 were excluded for being intrinsic DILI cases, second DILI episodes or re-exposure. Among the remaining 912 patients with a first episode of DILI, records of 68 patients with possible PDA were further evaluated. Of these, seven cases had allergies unrelated to drugs (e.g., seasonal, food, dust mite allergies), were suspected of being non-allergic ADRs, or were not documented clearly, and were thus not considered as having PDA. Ultimately, 61 DILI patients with documented PDA (6.7%) and 851 cases without PDA (93.3%) were included in the analysis **(Supplemental Fig. 1)**. Among patients with PDA, two of them presented with DILI associated with drug reactions with eosinophilia and systemic symptoms (DRESS), and another was diagnosed with Stevens-Johnson syndrome (SJS). Of note, none of them progressed to a fatal outcome.

3.1. Characteristics of DILI patients with and without PDA

Patients with PDA were older than those without drug allergies (mean age 60 vs. 54 years; $p = 0.009$), while the distribution of female sex was similar across groups (59% and 47%, respectively; $p = 0.075$). There were no differences in the type of liver damage, with the hepatocellular pattern being the most common damage in both groups ($p = 0.233$). Likewise, the prevalence of jaundice and hospitalization rates were comparable between patients with and without PDA.

Patients with PDA exhibited a trend towards higher AST levels at DILI recognition compared with those without history of drug allergies (median 9.4 vs. 6.2 x ULN, respectively; $p = 0.047$). Conversely, ALP levels were lower in DILI patients with PDA than in those without history of drug allergies (median 1.4 vs. 1.6 x ULN, respectively; $p = 0.045$). Furthermore, patients with PDA showed a lower platelet count than those without PDA (189 vs. 226 $\times 10^3$/mL; $p = 0.011$).

There were significant differences in the severity of DILI episode ($p = 0.001$), with 15% of patients with PDA progressing to liver-related death or liver transplantation, compared to 3.1% of patients without a history of drug allergies. Indeed, liver-related mortality rate was notably higher in DILI patients with PDA (7 out of 61, 11%), compared to the 1.6% of cases without a history of drug allergies ($p < 0.001$). However, there were no significant differences in the need for liver transplantation, death due to non-liver related causes, or time until biochemical normalization (Table 1).

3.2. Drugs implicated in PDA in DILI patients

The drugs causing the allergy and the DILI episode are illustrated in Fig. 1 and detailed in Supplemental Table 1. A total of 32 drugs were identified as responsible for 75 reported drug allergies, with 11 patients having allergies to more than one drug. The most common specific drug responsible for PDA in DILI patients was penicillin (32%), followed by acetylsalicylic acid and codeine (5.3% each), and ibuprofen, iodinated contrasts, metamizole, streptomycin and sulphonamides (4% each).

The main pharmacologic group of drugs causing drug allergies was anti-infectives (53%), followed by musculoskeletal and nervous system drugs (13% each). Beta-lactams (33%; 63% of anti-infectives), non-steroidal anti-inflammatory drugs (12%; 90% of musculoskeletal system drugs), and analgesics and antipyretics (11%; 80% of nervous system drugs) constituted the most common therapeutic class causing drug allergies. Moreover, in patients with PDA, the most common culprit drugs causing DILI belonged to the categories of anti-infectives (43%), nervous system drugs (15%), and musculoskeletal system and alimentary tract and metabolism drugs (9.8% each) (Supplemental Table 2).

In 17 cases with PDA (28%), the drugs that caused the allergy and the DILI belonged to the same pharmacologic group, and in five cases (8.2%), they belonged to the same pharmacological subgroup. Four of

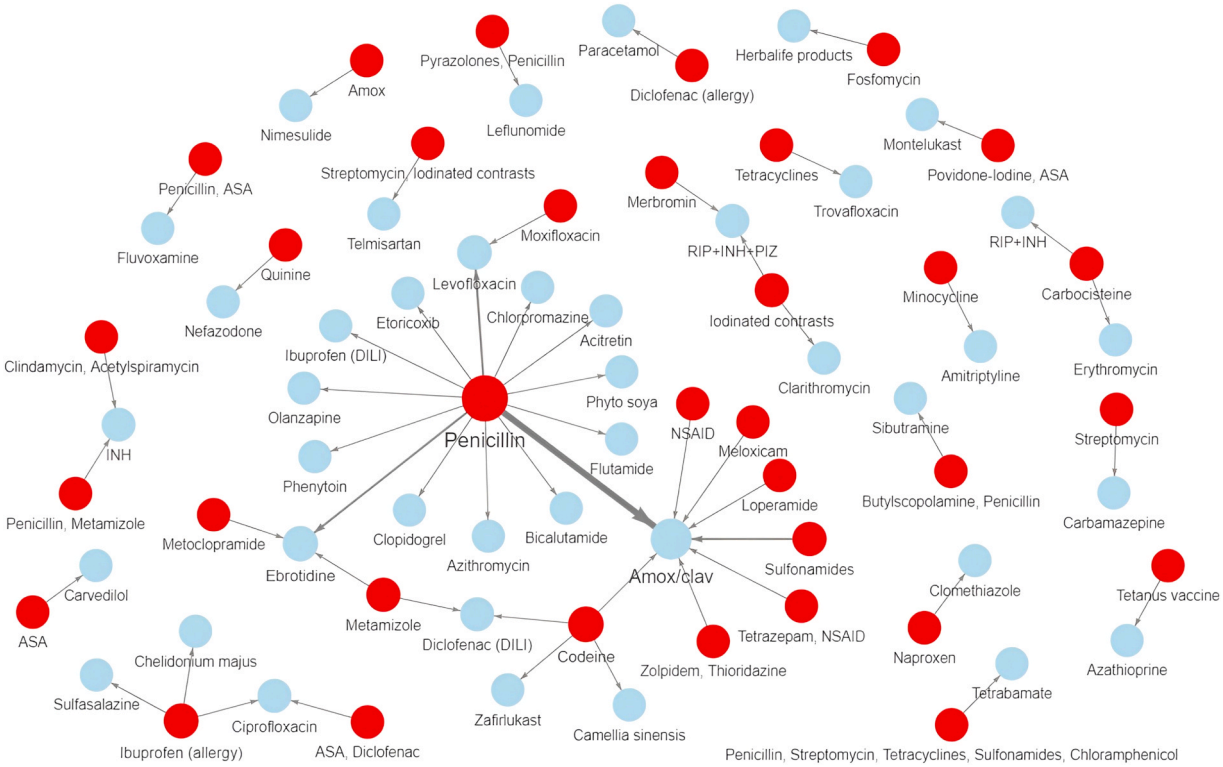

Fig. 1. Association between drugs that caused allergy (in red) and those responsible for DILI (in blue). The frequency of the relationship is proportional to the thickness of the line.

Table 1
Comparison of demographics, clinical characteristics, laboratory parameters and outcome between DILI patients with and without prior drug allergies.

	Prior drug allergy (n = 61)	No prior drug allergy (n = 851)	p value
Age (years), mean ± SD	60 ± 15	54 ± 18	0.009
Female, n (%)	36 (59)	402 (47)	0.075
Body mass index (kg/m^2), mean±SD	26 ± 3.4	26 ± 3.8	0.432
Diabetes mellitus, n (%)	5 (8.2)	110 (13)	0.282
Hypertension, n (%)	11 (18)	164 (19)	0.812
Dyslipidaemia, n (%)	8 (13)	113 (13)	0.971
Underlying hepatic disease, n (%)	9 (15)	52 (6.1)	0.016
Current or former alcohol drinker, n (%)	19 (32)	198 (25)	0.281
Current or former smoker, n (%)	5 (8.2)	81 (9.5)	1.000
Type of liver injury, n (%)			0.233
Hepatocellular	46 (75)	553 (65)	
Cholestatic	7 (11)	158 (19)	
Mixed	8 (13)	140 (16)	
Duration of therapy (days), median (IQR)	27 (10–72)	29 (8–67)	0.544
Latency (days), median (IQR)	24 (10–72)	26 (10–60)	0.739
Jaundice, n (%)	40 (66)	579 (68)	0.691
Hospitalization, n (%)	35 (57)	455 (53)	0.554
Fever, n (%)	8 (13)	100 (12)	0.750
Rash, n (%)	7 (11)	57 (6.7)	0.187
Eosinophilia n (%)	15 (25)	175 (21)	0.455
Lymphopenia n (%)	14 (23)	157 (18)	0.384
Arthralgia, n (%)	1 (1.6)	15 (1.8)	1.000
Positive autoantibody titres, n (%)	6 (9.8)	149 (18)	0.123
Laboratory parameters at DILI recognition (x ULN), median (IQR)			
Total bilirubin	5.7 (1.6–11)	5.0 (1.1–10)	0.567
Aspartate aminotransferase (AST)	9.4 (3.1–32)	6.2 (2.9–19)	0.047
Alanine aminotransferase (ALT)	12 (4.4–27)	9.5 (4.8–24)	0.407
Alkaline phosphatase (ALP)	1.4 (0.8–2.1)	1.6 (1.0–2.6)	0.045
Gamma-glutamyl transferase (GGT)	4.5 (2.0–8.8)	5.5 (2.6–10)	0.187
Leucocytes (x 10^3/mL), median (IQR)	6.4 (4.9–8.3)	6.6 (5.3–8.2)	0.608
Platelets (x 10^3/mL), median (IQR)	189 (156–237)	226 (177–276)	0.011
Severity, n (%)			0.001
Mild	20 (33)	255 (30)	
Moderate	28 (46)	509 (60)	
Severe	4 (6.6)	61 (7.2)	
Fatal	9 (15)	26 (3.1)	
nR-based Hy's law, n (%)	27 (52)	271 (36)	0.026
Outcome			
Liver-related death, n (%)	7 (11)	14 (1.6)	< 0.001
Liver transplantation, n (%)	2 (3.3)	12 (1.4)	0.240
Death due to other causes, n (%)	1 (1.6)	12 (1.4)	0.596
Time to resolution (days), median (IQR)	96 (48–294)	109 (57–218)	0.812

IQR: interquartile range; SD: standard deviation; ULN: upper limit of normal. Ranges of laboratory values were considered as normal of reference ranges.

these five cases exhibited a previous allergy to penicillin, and subsequently, amoxicillin-clavulanate caused the DILI episode. In the fifth case, the patient was allergic to moxifloxacin, and DILI was caused by levofloxacin.

3.3. Characteristics of DILI patients with PDA based on the outcome

We further compared the characteristics of DILI patients with PDA who experienced a fatal outcome (liver-related death or liver transplantation) and those who did not (Table 2). There were no significant differences neither in age nor sex between patients who developed a fatal outcome and those who did not.

All patients who developed a fatal outcome presented with a hepatocellular injury pattern, exhibited jaundice, and required hospitalization. Furthermore, total bilirubin and AST values were more than 3-fold increase in cases with a fatal outcome compared to those with a more favourable outcome ($p < 0.001$ and $p = 0.024$, respectively).

Table 2
Comparison of demographics, clinical characteristics, laboratory parameters and outcome between DILI patients with prior drug allergies that developed a fatal outcome (liver-related death or liver transplantation) and those with a non-fatal outcome.

	Fatal outcome (n = 9)	Non-fatal outcome (n = 52)	p value
Age (years), mean±SD	57 ± 14	61 ± 15	0.532
Female, n (%)	7 (78)	29 (56)	0.286
Body mass index, mean±SD	29 ± 6.2	26 ± 3.1	0.214
Diabetes mellitus, n (%)	0 (0)	5 (9.6)	1.000
Hypertension, n (%)	0 (0)	11 (21)	0.192
Dyslipidaemia, n (%)	0 (0)	8 (15)	0.591
Underlying hepatic disease, n (%)	2 (22)	7 (13)	0.609
Current or former alcohol drinker, n (%)	4 (44)	15 (29)	0.445
Current or former smoker, n (%)	2 (22)	3 (5.8)	0.154
Type of liver injury, n (%)			0.254
Hepatocellular	9 (100)	37 (71)	
Cholestatic	0 (0)	7 (13)	
Mixed	0 (0)	8 (15)	
Duration of therapy (days), median (IQR)	21 (12–50)	29 (9–75)	1.000
Latency (days), median (IQR)	30 (9–71)	23 (10–72)	0.934
Jaundice, n (%)	9 (100)	31 (60)	0.021
Hospitalization, n (%)	9 (100)	26 (50)	0.007
Fever, n (%)	2 (22)	6 (12)	0.336
Rash, n (%)	1 (11)	6 (12)	1.000
Eosinophilia n (%)	2 (22)	13 (25)	1.000
Lymphopenia n (%)	3 (33)	11 (21)	0.416
Arthralgia, n (%)	0 (0)	1 (1.9)	1.000
Positive autoantibody titres, n (%)	2 (22)	4 (7.7)	0.212
Laboratory parameters at DILI recognition (x ULN), median (IQR)			
Total bilirubin	14 (9.6–17)	4.2 (1.2–9.7)	< 0.001
Aspartate aminotransferase (AST)	26 (12–47)	7.8 (2.7–28)	0.024
Alanine aminotransferase (ALT)	21 (11–27)	10 (4.2–26)	0.306
Alkaline phosphatase (ALP)	1.2 (0.9–1.8)	1.4 (0.8–2.1)	0.710
Gamma-glutamyl transferase (GGT)	4.0 (3.5–6.2)	4.5 (2.0–8.9)	0.668
Leucocytes (x 10^3/mL), median (IQR)	7.6 (6.4–10)	6.0 (4.8–8.0)	0.229
Platelets (x 10^3/mL), median (IQR)	127 (103–158)	190 (167–262)	0.013
nR-based Hy's law, n (%)	7 (88)	20 (45)	0.051

IQR: interquartile range; SD: standard deviation; ULN: upper limit of normal. Ranges of laboratory values were considered as normal of reference ranges.

Conversely, platelet count was significantly lower in patients with a fatal outcome than in those with a better prognosis (127 vs. 190 $\times 10^3$/mL; $p = 0.013$).

Detailed information of the nine DILI cases with PDA who died or underwent liver transplant is shown in Table 3. Among these nine cases, six patients had PDA related to anti-infectives (penicillin, amoxicillin, streptomycin, sulphonamides), with one case having an allergy to penicillin and butylscopolamine. Moreover, one case had allergies to nervous system drugs (zolpidem, thioridazine), another patient was allergic to quinine, and the last one to ibuprofen. The causative agents responsible of DILI included amoxicillin-clavulanate (n = 2), nimesulide, ibuprofen, carbamazepine, nefazodone, bicalutamide, sibutramine and herbal products (*Chelidonium majus*).

3.4. Establishment of a prognostic model

The Bolasso procedure identified six factors associated with a fatal outcome (liver-related death or liver transplantation) in the study population. These factors included drug allergy (mean bootstrap coefficient 1.87), nR-based hepatocellular injury pattern (1.32), female sex (1.13), total bilirubin (0.118), AST level (0.022), and platelet count (−0.006). VIF values showed no collinearity for all independent variables. Using these factors, a multivariable logistic regression model was fitted to

Table 3
Detailed information on cases of DILI with prior drug allergies that developed a fatal outcome (liver-related death or liver transplantation).

Sex / Age (y)	Prior drug allergy	DILI suspected drug	Duration of therapy (d)	Latency (d)	Rash	Eosinophilia	TBL (x ULN)†	ALT (x ULN)†	AST (x ULN)†	ALP (x ULN)†
F / 73	Quinine	Nefazodone	50	47	No	No	17	27	44	0.4
F / 66	Amoxicillin	Nimesulide	252	238	No	No	14	25	47	1.4
F / 61	Zolpidem, thioridazine	Amoxicillin-clavulanate	21	71	No	No	27	1.8	2.9	0.9
F / 44	Penicillin	Ibuprofen	12	7	No	No	9.6	10	26	2.9
F / 56	Streptomycin	Carbamazepine	29	4	Yes	Yes	11	56	68	2.9
F / 68*	Sulphonamides	Amoxicillin-clavulanate	11	12	No	Yes	15	13	8.1	0.4
M / 73	Penicillin	Bicalutamide	367	557	No	No	8.8	21	22	1.2
M / 37*	Ibuprofen	*Chelidonium majus*	5	9	No	No	7.2	50	59	1.2
F / 38	Penicillin, butylscopolamine	Sibutramine	15	30	No	No	23	11	12	1.8

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; d: days; DILI: drug-induced liver injury; F: Female; M: Male; TBL: total bilirubin; ULN: upper limit of normal range; y: years.
Ranges of laboratory values were considered as normal of reference ranges.
* Liver transplantation.
† Liver parameters at DILI recognition.

estimate the probability of a fatal outcome as follows:

$$\text{Probability (fatal outcome)} = 1 / [1 + e^{-(-5{\cdot}572 + 1{\cdot}780\times1 + 1{\cdot}459\times2 + 1{\cdot}166\times3 + 0{\cdot}131\times4 + 0{\cdot}012\times5 - 0{\cdot}007\times6)}]$$

In the formula above, X1 represents drug allergy; X2, nR-based hepatocellular injury; X3, female sex; X4, total bilirubin; X5, AST level (x ULN); and X6, platelet count.

A nomogram was created to visualize the predicted probabilities individual patients have of progressing to liver-related death or liver transplantation, depicted in Fig. 2. Additionally, Supplemental Fig. 2 provides examples of predicted probabilities for two randomly selected patients from the Spanish DILI Registry, one with PDA and the other without PDA.

The AUC of the model was 0.887 (95% CI 0.794 – 0.981) in the Spanish DILI Registry cohort, suggesting an excellent discrimination capability. In addition, a total of 468 DILI patients included in the LATINDILI Network were used for external validation (Supplemental Table 3). The AUC of the model was consistent with the one found in the Spanish cohort (AUC 0.932; 95% CI 0.884 – 0.981) (Fig. 3).

4. Discussion

This study represents the first assessment of the role of prior drug allergy in a large cohort of *bona fide* DILI cases with prospective follow-up. Our findings show that DILI patients with a history of drug allergy experienced a more serious liver injury and exhibited a non-negligible increased risk of liver-related death. Anti-infectives were the main pharmacologic group causing both drug allergies and DILI.

The existing evidence regarding the impact of drug allergies in the outcome of DILI is scarce and somehow contradictory, probably as a result of methodological differences in the studies that addressed this issue. A US Drug-Induced Liver Injury Network study found a slightly higher prevalence of self-reported drug allergies in patients who died or underwent liver transplantation within six months of DILI onset

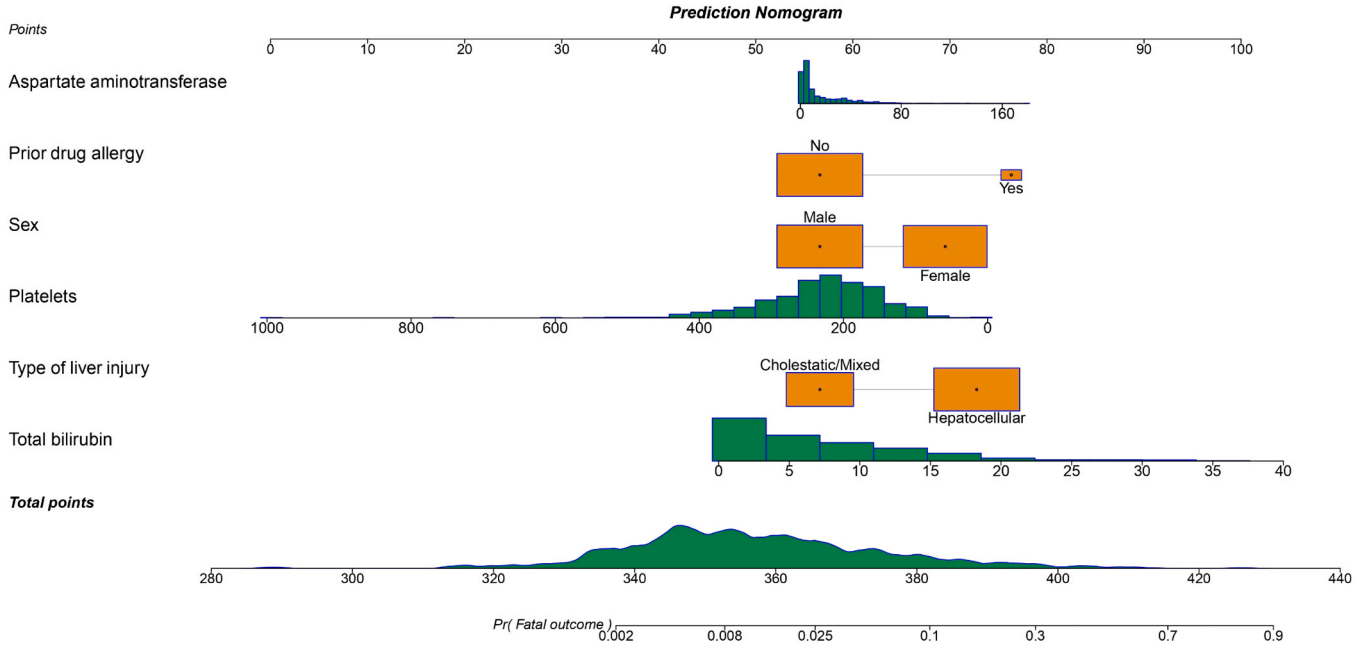

Fig. 2. Prognostic nomogram model of fatal outcome (liver-related death/liver transplantation). Quantitative variables distribution is represented by the density of bar plots. Categorical variables distribution is reflected by the size of the boxes.

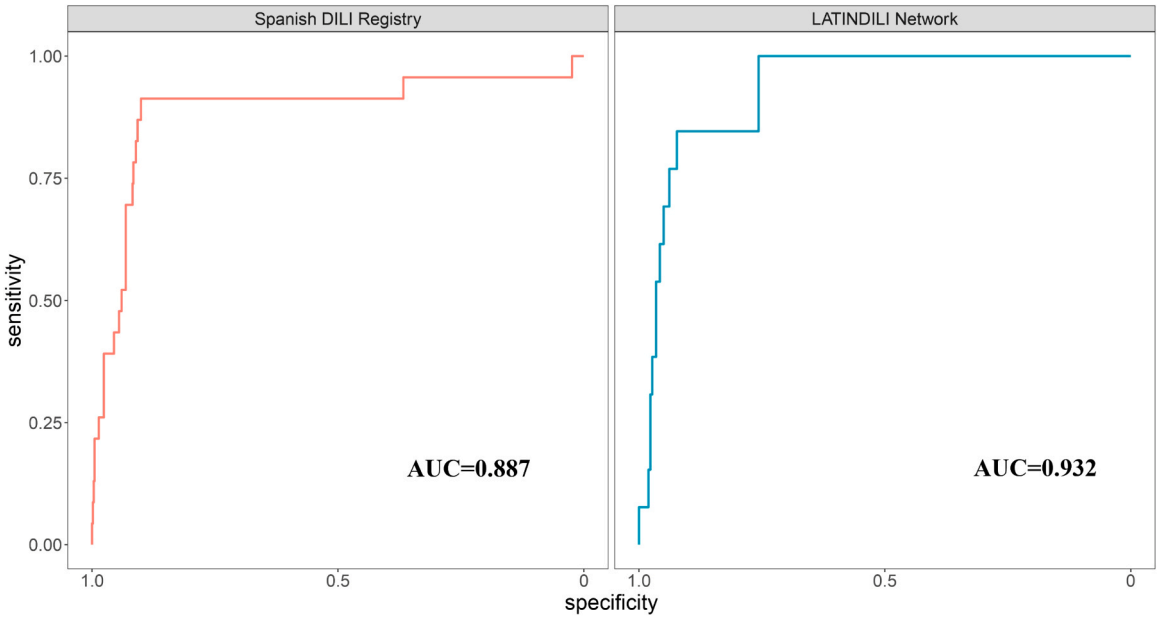

Fig. 3. Receiver operating curve (ROC) and area under the curve (AUC) analysis for model internal and external validation.

compared to those who survived [13]. In contrast, in a more recent retrospective single-centre study using electronic medical records and an ICD code, patients with PDA tended to have less severe liver damage and better clinical outcomes [5]. As acknowledged by the authors this method has low positive predictive value for identifying DILI patients [14]. In addition, the number of severe outcomes was very small in this study. On the contrary, DILI cases included in the Spanish DILI Registry were prospectively identified in the clinical setting and underwent a comprehensive evaluation before their inclusion in the registry [6].

Furthermore, earlier investigations reported remarkably high rates of PDA among patients with DILI, with values ranging from 32% to 44% [5,15]. In contrast, our study revealed a lower prevalence of PDA (6.7%). This variance can be attributed to differences in data collection methodology and an exhaustive review of included cases to exclusively record genuine PDA.

The biological basis for this association is unknown. Our findings suggest that a pre-existing dysregulation of the immune system may favour a worse outcome in patients with DILI. The role of the adaptive immune system is becoming more evident in DILI pathogenesis, with the identification of genetic risk alleles known to be involved in immune responses and autoimmunity [1,16]. Hence, although speculative at this time, in the light of the shared mechanisms between drug allergy and DILI, a plausible explanation could be that patients with PDA have a pre-existing immune memory to drug haptens, which amplifies the immune response and increases the likelihood of progressing to ALF and, potentially, to liver-related death. Although this response can be triggered by compounds with similar chemical structures, we identified only five cases in which the drugs responsible for allergy and DILI, all antibiotics, belonged to the same therapeutic class.

Therefore, the association between PDA and DILI prognosis likely extends beyond cross-reactive responses. One hypothesis could be that the drug responsible for the allergy caused an initial liver damage that led to the release of exosomes containing peptide-HLA complexes and drug-modified intracellular proteins [17,18]. These exosomes can be taken up by dendritic cells and generate not only a drug-specific T cell response but also a specific T cell response against the liver. These latter immune cells, after the exposure to the second drug that produces a cellular stress in the liver, could generate an autoimmune response, and, in addition to the immunopathological mechanisms involved in DILI, cause a more severe liver damage. Nevertheless, despite the plausible biological basis of this hypothesis, future studies are warranted to elucidate the molecular pathways that contribute to the poor outcome of DILI patients with a history of drug allergy.

Another predictor of worse prognosis was a nR-based hepatocellular injury pattern. The fact that nR-based hepatocellular damage was found to be a better predictor than R-based hepatocellular damage highlights the importance of AST in DILI assessment and prognosis [19]. Indeed, all nine cases with a history of allergies who died (liver-related) or underwent a liver transplantation exhibited this pattern of liver injury, and five of them presented with marked elevations of AST over ALT. Furthermore, these cases displayed a significantly lower platelet count. Consistently, a previous analysis of data from the Spanish DILI registry revealed an association between hepatocellular damage and a diminished platelet count [6]. Thrombocytopenia and qualitative platelet defects are commonly linked to ALF and its complications. Therefore, the association between low platelet count and poor prognosis in DILI may not be specific to this disease but rather related to ALF development. The cause is multifactorial and is likely more related to increased platelet consumption rather than decreased production. Prior cohort studies reported a strong correlation between the degree of thrombocytopenia and the severity of the systemic inflammatory response syndrome and multi-organ failure in ALF patients, suggesting that the release of platelet-derived microparticles with prothrombotic and proinflammatory effects may play a role in the prognosis of ALF [20]. Moreover, lower platelet count is a common alteration in patients with pre-existing liver disease, usually those with cirrhosis [21]. Nonetheless, albeit presence of an underlying chronic disease has been associated with worse outcome in prior studies [6], only two out of nine patients with PDA who progressed into a fatal outcome had a pre-existing liver disease. Given the clinical evaluation performed on every patient included in the Spanish DILI Registry [6], it is unlikely that there were any unreported underlying chronic conditions. Thus, the detrimental association between lower platelet count and ALF seems to be independent of the presence of pre-existing chronic liver diseases.

Moreover, previous studies have reported a higher prevalence of females in DILI cases progressing to ALF [22,23], likely attributed to the influence of sex-specific hormones on hepatic drug metabolism and the regulation of pro-inflammatory cytokines originating in the liver [24].

The use of predictive models to ascertain DILI outcome is an appealing approach. In an analysis of the Spanish DILI Registry, elevated ALP and total bilirubin above specified thresholds (1.1 and 2.8 times the ULN, respectively) in the second month after DILI onset were reported as

the best cut-off values to predict DILI chronicity [25]. Likewise, in a recently developed model, patients with increased bilirubin and ALP levels at DILI recognition, longer time to DILI onset and extended drug metabolism were seen to have a prolonged recovery of their DILI episode [26]. Furthermore, Wang *et al.* identified several factors, including female sex, older age, higher AST and total bilirubin, prolonged prothrombin time and lower platelet count, associated with non-resolution of biochemical parameters within 12 months after DILI recognition [27]. In the light of our findings, we aimed to develop a tool for predicting fatal outcome in DILI patients. Thus, we depicted the machine learning-based algorithm into an easy-to-use nomogram that yielded an excellent predictive power in both Spanish and Latin American DILI patients. Therefore, the internal and external validity of this tool indicate that it might facilitate prognostic stratification at the bedside.

The main strength of the present work lies in the utilization of high-quality data obtained from a large cohort of well-characterized DILI patients included in a long-term prospective registry following a rigorous and standardized methodology. In addition, the external validity of our model was confirmed in patients from the LATINDILI Network, who were enrolled following the same methodology. Nonetheless, some limitations should be acknowledged. The assessment of PDA was based on the patient's medical record, reflecting the daily clinical practice, but the number of cases in which skin sensitization tests were performed to confirm the diagnosis was unknown. Therefore, to ensure the internal validity of our findings, any reported drug allergies that lacked sufficient documentation or were suspected of being related to drug side effects, intolerances, or other forms of ADR were considered as not being PDA. Moreover, genetic assessment was not routinely performed in these patients. Thus, future research addressing this gap is highly warranted as it might provide further insights about the role played by PDA in DILI.

5. Conclusions

In conclusion, we found that a history of drug allergy is an independent predictor of fatal outcome in DILI patients. This detrimental association seems to be primarily driven through non-related cross-reactive responses. Patients with PDA presenting with hepatocellular damage, jaundice and lower platelet count were more likely to develop a fatal outcome. As a result, patients with suspected DILI should have a thorough pharmacologic history and be screened for prior drug allergies. DILI patients with PDA require close monitoring for early detection of worsening clinical course. The developed calculator based on a validated model could be a useful tool in risk stratification of these patients.

CRediT authorship contribution statement

Romero-Flores Rocío: Investigation, Writing – review & editing. **Alvarez-Alvarez Ismael:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Robles-Diaz Mercedes:** Resources, Writing – review & editing. **Medina-Caliz Inmaculada:** Investigation, Resources, Writing – review & editing. **Sanabria-Cabrera Judith:** Resources, Writing – review & editing. **Andrade Raúl J.:** Supervision, Writing – review & editing. **García-Cortés Miren:** Investigation, Resources, Writing – review & editing. **Lucena M Isabel:** Conceptualization, Supervision, Writing – review & editing. **Solis-Muñoz Pablo:** Data curation, Investigation, Writing – original draft. **Hernandez Nelia:** Resources, Validation, Writing – review & editing. **Niu Hao:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Bessone Fernando:** Resources, Validation, Writing – review & editing. **Cabello María R.:** Writing – review & editing. **Pinazo-Bandera José M.:** Resources, Writing – review & editing. **Ortega-Alonso Aida:** Resources, Writing – review & editing. **Bonilla-Toyos Elvira:** Resources, Writing – review & editing.

Declaration of Competing Interest

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

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.107030.

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