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Real-Time Monitoring of Drug-Induced Liver Injury Risk in Patients with Drug Hypersensitivity Histories Using Explainable AI Models

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ABSTRACT

It is mostly unclear how previous drug allergies (PDA) affect the clinical characteristics and prognosis of individuals who have idiosyncratic drug-induced lung injury (DILI). Our goals were to evaluate the clinical presentation and results of DILI patients depending on the presence or absence of PDA and investigate the relationship between allergies and the culprit medications that cause DILI. We examined a well screened group of DILI cases that were registered with the Spanish DILIRegistry. A multivariate logistic model was fitted to predict poor outcomes in DILI, and the bootstrap-enhanced leastabsoluteshrinkage operator approach was utilized in variable selection. 61 (6.7%) of the 912 patients with a DILI initial episode had PDA on file. In comparison to patients without a history of drug allergies, PDA patients were older (p=0.009), had higher levels of aspartate aminotransferase (AST) (p=0.047), a lower platelet count (p=0.011), and a higher liver-related death rate (11% vs. 1.6%, p<0.001). In DILI patients, penicillin was the most prevalent medication linked to PDA (32%). A model incorporating PDA, nR-based liver injury type, female sex, AST, total bilirubin, and platelet count performed exceptionally well in forecasting poor outcomes for patients from the LATINDILI Network (AUC 0.932; 95% CI 0.884 – 0.981) and the Spanish DILI Registry (area under the ROC curve [AUC] 0.887; 95% CI 0.794 – 0.981). In order to identify deteriorating clinical course early, patients with suspected DILI should be tested for PDA.

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Introduction

An adverse drug response (ADR) to the use of traditional pharmaceuticals, herbal remedies, or nutritional supplements is known as idiosyncratic drug-induced liver damage (DILI). It targets hepatocytes and other biological components, endangers patient safety, and causes unanticipated liver and biliary system damage. DILI often shows as a modest, transitory rise of aminotransferases levels that goes away on its own, but in some instances, it may develop into acute liver failure (ALF), which can lead to mortality or the need for a liver transplant [1,2]. Contrarily, drug allergies are a complicated category of unexpected adverse drug reactions (ADRs) that are characterized by a broad range of hypersensitivity responses employing heterogeneous pathways and exhibiting a wide range of clinical characteristics [3].

Little is presently known regarding the potential relationship between DILI and medication allergies, despite the suggestion that DILI and cutaneous hypersensitivity responses may have comparable risk factors [4]. A recent retrospective analysis found that DILI patients with a history of drug allergies had milder clinical outcomes and that having a history of drug allergies did not increase the risk of developing DILI [5]. To far, prospective studies have been carried out on a group of patients with well-characterized DILI, and these results were based on data taken from patients' electronic

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medical records. Therefore, our goals were to assess the relationship between the medicines that cause DILI and allergies, as well as to compare the clinical presentation and fate of DILI patients in the long-term prospective Spanish DILI Registry with and without previous drug allergies (PDA). 1. Techniques Population under study Data was gathered from DILI cases that were registered in the Spanish DILIRegistry between 1994 and February 2022. Comprehensive information on the Spanish DILI Registry has been published elsewhere [6]. Second episodes of DILI, re-exposures, and dose-related intrinsic DILI patients were not included. Every patient was monitored until their liver profiles returned to normal. The local ethics committee approved the study protocol. Written informed permission was provided by each participant. Definition of a Case The outcome of the liver damage has been documented; competing causes have been ruled out; the potential for hepatotoxicity of the suspected drugs and the presence of known risk factors for hepatotoxicity have been taken into consideration; and information is available to establish with certainty the temporal relationship between the start of the drug or toxin exposure and the onset of hepatic disease, as well as between the discontinuation of the suspected agent and the improvement or recovery of the liver dysfunction. Alkaline phosphatase (ALP) ≥2 times ULN, ALT ≥3 times ULN, and total bilirubin (TBL) >2 times ULN are the biochemical criteria for DILI that were first established by the Council for International Organizations of Medical Sciences (CIOMS) [7] and then modified to those suggested by an international DILI expert consensus [8]. Three independent specialists were able to determine the causal association between the suspected medicine and liver damage. The Roussel Uclaf Causality Assessment Method (RUCAM) scale was used to rate only situations that were deemed at least "possible" [9]. The R-value, which is the ratio of ALT or aspartate aminotransferase [AST], whichever is higher/ULN, was used to identify the pattern of liver damage. The cases were categorized as mixed injury (nR>2 and nR<5), cholestatic (nR≤2), or hepatocellular (nR≥5). Mild (TBL<2 times ULN), moderate (TBL≥2 times ULN), severe (TBL≥2 times ULN, and either International Normalized Ratio [INR] ≥1.5, ascites and/or encephalopathy, or other organ failures related to DILI), or fatal (death or transplantation due to DILI) were the classifications used to describe the degree of life harm [8]. The Anatomical Therapeutic Chemical Classification (ATC) was used to categorize the putative culprit medications into categories and subgroups based on their anatomical pharmacology. Previous drug sensitivity The attending physician's review of the patient's medical record served as the basis for prior medication allergies. Pharmacological and clinical information (including PDA information), blood test results, imaging test findings, and the outcome of liver injury were all recorded for each patient using a standardized case report form. Allergies unrelated to medications, allergies that were not properly reported or recorded, or those that the attending physician identified as perhaps not being allergic adverse drug reactions (ADRs), such intolerances, were not regarded as PDA. Analysis of statistics The study's participants' clinical and demographic information was assessed using descriptive statistics. The Student's test or Mann-Whitney test, as applicable, was used to test for differences between groups. For quantitative data, mean and standard deviation (SD), or median and interquartile range (IQR), were shown. Frequency distributions were used to represent the categorical data, and the chi-square test or Fisher's exact test, as applicable, were used to compare the differences. The least absolute shrinkage and selection operator (Lasso) penalized regression approach was used to choose the variables for a logistic regression model. By decreasing the coefficient estimates toward zero and deleting them from the final model, this technique penalizes the absolute value of the estimates. We used a modified Lasso process called the bootstrap-enhanced leastabsolute shrinkage operator (Bolasso) to address the constraints of the Lasso method and avoid the inclusion of pertinent variables [10,11]. Through the selection of variables with non-zero coefficients, predictor factors linked to fatal outcomes (liver-related mortality or liver transplantation) were found in 100 bootstrap samples with replacement. Age, sex, previous drug allergies, liver injury pattern (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 were all included in the

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Bolasso procedure based on traits that may be linked to the worst outcomes. To find the ideal regularization parameter value and provide reliable estimates, ten-fold cross-validation was carried out. The variance inflation factor (VIF) statistic was used to evaluate the multicollinearity of independent variables. The following logistic function was used to construct a multivariable logistic regression model using the chosen variables in order to determine the likelihood of the desired outcome: Outcome probability = 1/ [1+e-(α+βX)] where β stands for the corresponding variable coefficients and α, the intercept, is the model's constant. To depict the model, a nomogram that integrated the independent components was created. The area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the model's discriminating power. In addition to internal validation, the model's performance was evaluated in an external cohort of DILI patients who were part of the Latin American DILI (LATINDILI) Network in order to ascertain its repeatability and generalizability [12]. The LATINDILI Network patients were monitored until their profiles returned to normal. Everybody

R version 4.3.0 (RCoreTeam, 2023) was used for statistical studies, and the "bolasso," "regplot," and "pROC" packages were used. A two-sided p-value was considered statistically significant if it was less than 0.05.

2. Outcomes Of the 1,006 patients in the Spanish DILI Registry, 94 were removed because they were either re-exposed, intrinsic DILI instances, or had experienced a second DILI episode. Records of 68 individuals with potential PDA were subsequently examined among the 912 patients who had a first episode of DILI. Seven of these instances had non-drug-related allergies (such as seasonal, food, or dustmite allergies), were thought to be non-allergic ADRs, or lacked adequate documentation, and were thus not classified as having PDA. In the end, the study comprised 851 instances without PDA (93.3%) and 61 DILI patients with proven PDA (6.7%) (Supplemental Fig. 1). Of the PDA patients, one was identified with Stevens-Johnson syndrome (SJS), and two with DILI accompanied with drug responses with eosinophilia and systemic symptoms (DRESS). Notably, none of them developed into a deadly condition. Features of DILI patients with and without PDA While the proportion of female sex was comparable between groups (59% and 47%, respectively; p=0.075), patients with PDA were older than those without medication allergies (mean age 60 vs. 54 years; p=0.009). There were variations in the kind of liver injury, with the most prevalent damage in both groups being the hepa-tocellular pattern (p=0.233). Similarly, hospitalization rates and the incidence of jaundice were similar for individuals with and without PDA. When compared to those without a history of drug allergies, patients with PDA showed a tendency toward higher AST levels upon DILI detection (median 9.4 vs. 6.2xULN, respectively; p=0.047). On the other hand, DILI patients with PDA had lower ALP levels than those without a history of drug allergies (median 1.4 vs. 1.6xULN, respectively; p=0.045). Additionally, the platelet count was lower in PDA patients than in non-PDA patients (189 vs. 226 ×103/mL; p = 0.011).
The severity of DILIepisode varied significantly (p=0.001), with 3.1% of patients without a history of drug allergy and 15% of patients with PDA experiencing liver-related mortality or liver transplantation. In fact, DILI patients with PDA had a significantly higher liver-related death rate (7 out of 61, 11%) than those without a history of drug allergies (1.6%; p<0.001). However, neither the period to biochemical normalization nor the necessity for liver transplantation or mortality from non-liver-related reasons differed significantly (Table 1). PDA-implicated medications for DILI patients

Fig. 1 and Supplemental Table 1 provide specifics on the medications that cause the allergy and the DILI event. 32 medications were shown to be the cause of 75 reported drug allergies, with 11 individuals experiencing sensitivities to several medications. Acetylsalicylic acid and codeine (5.3%), ibuprofen, iodinated contrasts, metamizole, streptomycin, and sulphonamides (4% each) were the most often reported individual drugs that caused PDA in DILI patients, followed by penicillin (32%). Anti-infectives were the most common pharmacologic category of pharmaceuticals that caused drug allergies (53%), followed by medications for the musculoskeletal and neurological systems (13% each). The most prevalent therapeutic class producing drug allergies was beta-

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lactams (33%; 63% of anti-infectives), non-steroidal anti-inflammatory medications (12%; 90% of musculoskeletal system medicines), and analgesics and antipyretics (11%; 80% of nervous system drugs). Additionally, the most prevalent culprit medicines causing DILI in patients with PDA were anti-infectives (43%), pharmaceuticals for the neurological system (15%), and drugs for the musculoskeletal system, alimentary tract, and metabolism (9.8% each) (Supplemental Table 2). The medications that induced the allergy and the DILI were part of the same pharmacologic group in 17 instances (28%), and they were part of the same pharmacological subgroup in five cases (8.2%) of PDA. The Fourof

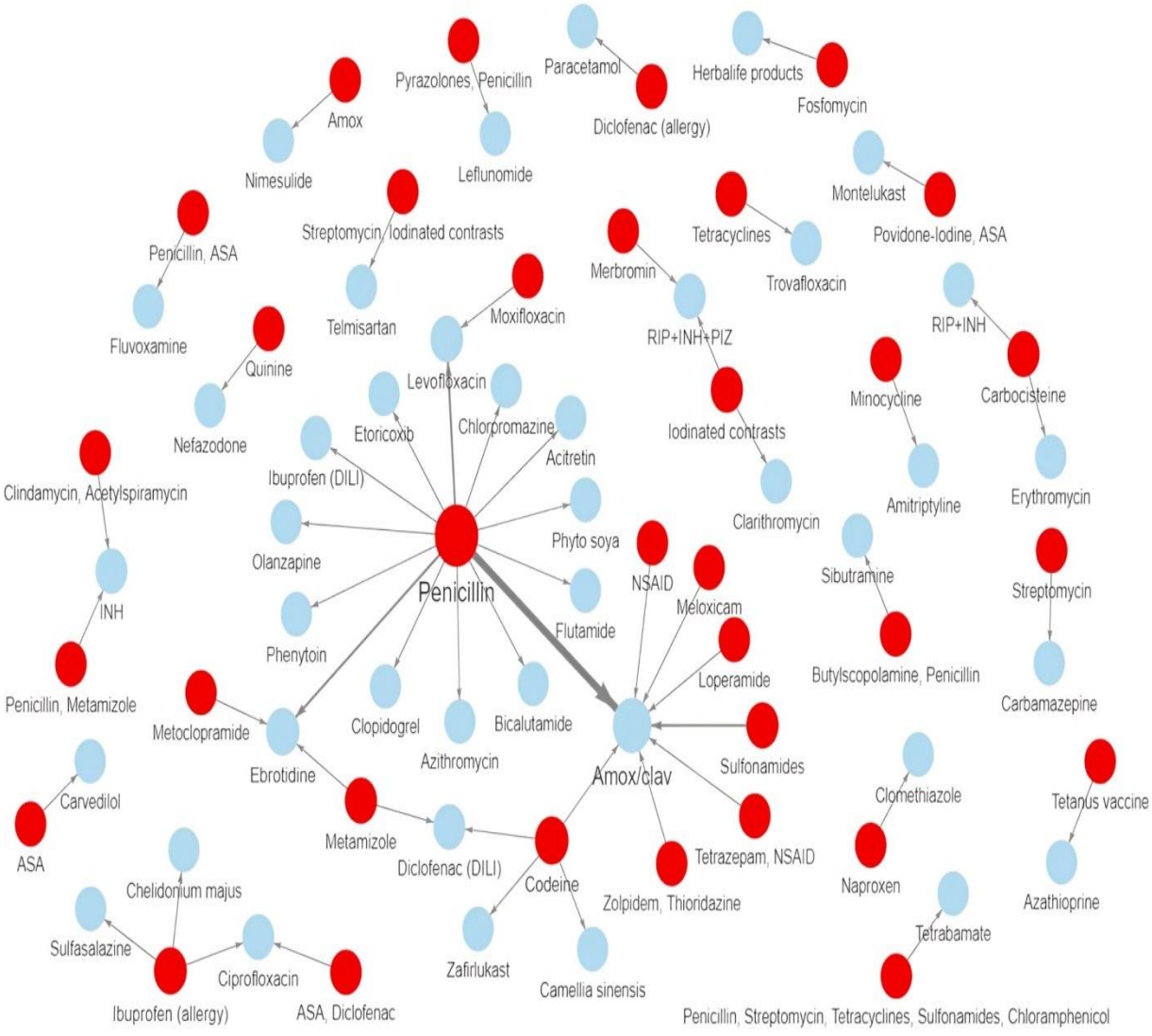

Fig. 1. Association between drugs that caused allergy (in red) and those responsible for DILI (in blue). The frequency of the relationship is proportional to thethickness of the line.

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Table1

Comparisonofdemographics,clinicalcharacteristics,laboratoryparameters and outcome between DILI patients with and without prior drug allergies.

Table2

Comparisonofdemographics,clinicalcharacteristics,laboratoryparameters andoutcomebetweenDILIpatients withpriordrugallergies thatdeveloped a fataloutcome(liver-relateddeathorliver transplantation)andthose withanon-fatal outcome.

	Priordrug allergy (n=61)	Nopriordrugallergy (n=851)	pvalue
Age(years),mean±SD	60±15	54±18	0.009
Female,n(%)	36(59)	402 (47)	0.075
Bodymassindex(kg/m^2),mean±SD	26±3.4	26±3.8	0.432
Diabetesmellitus,n(%)	5(8.2)	110 (13)	0.282
Hypertension,n(%)	11(18)	164 (19)	0.812
Dyslipidaemia,n(%)	8(13)	113 (13)	0.971
Underlyinghepaticdisease,n(%)	9(15)	52 (6.1)	0.016
Currentorformeralcoholdrinker,n (%)	19(32)	198 (25)	0.281
Currentorformersmoker,n(%)	5(8.2)	81 (9.5)	1.000
Typeofliverinjury,n(%)			0.233
Hepatocellular	46(75)	553 (65)	
Cholestatic	7(11)	158 (19)	
Mixed	8(13)	140 (16)	
Durationoftherapy(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
Eosinophilian(%)	15(25)	175 (21)	0.455
Lymphopenian(%)	14(23)	157 (18)	0.384
Arthralgia,n(%)	1(1.6)	15 (1.8)	1.000
Positiveautoantibodytitres,n(%)	6(9.8)	149 (18)	0.123
Laboratoryparameters atDILI			

	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
Bodymassindex,mean±SD	29±6.2	26±3.1	0.214
Diabetesmellitus,n(%)	0(0)	5(9.6)	1.000
Hypertension,n(%)	0(0)	11 (21)	0.192
Dyslipidaemia,n(%)	0(0)	8(15)	0.591
Underlyinghepaticdisease,n(%)	2(22)	7(13)	0.609
Currentorformeralcoholdrinker,n (%)	4(44)	15 (29)	0.445
Currentorformersmoker,n(%)	2(22)	3(5.8)	0.154
Typeofliverinjury,n(%)			0.254
Hepatocellular	9(100)	37 (71)	
Cholestatic	0(0)	7(13)	
Mixed	0(0)	8(15)	
Durationoftherapy(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
Eosinophilian(%)	2(22)	13 (25)	1.000
Lymphopenian(%)	3(33)	11 (21)	0.416
Arthralgia,n(%)	0(0)	1(1.9)	1.000

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recognition(xULN),median(IQR)			
Totalbilirubin	5.7 (1.6–11)	5.0 (1.1–10)	0.567
Aspartateaminotransferase(AST)	9.4 (3.1–32)	6.2 (2.9–19)	0.047
Alanineaminotransferase(ALT)	12(4.4–27)	9.5 (4.8–24)	0.407
Alkalinephosphatase(ALP)	1.4 (0.8–2.1)	1.6 (1.0–2.6)	0.045
Gamma-glutamyltransferase(GGT)	4.5 (2.0–8.8)	5.5 (2.6–10)	0.187
Leucocytes(x10^3/mL),median (IQR)	6.4 (4.9–8.3)	6.6 (5.3–8.2)	0.608
Platelets(x10^3/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-basedHy'slaw,n(%)	27(52)	271 (36)	0.026
Outcome			
Liver-relateddeath,n(%)	7(11)	14(1.6)	<0.001
Livertransplantation,n(%)	2(3.3)	12 (1.4)	0.240
Deathduetoothercauses,n(%)	1(1.6)	12 (1.4)	0.596
Timetoresolution(days),median (IQR)	96(48–294)	109 (57–218)	0.812

Positiveautoantibodytires,n(%)	2(22)	4(7.7)	0.212
LaboratoryparametersatDILI recognition (xULN),median (IQR)			
Totalbilirubin	14(9.6–17)	4.2 (1.2–9.7)	<0.001
Aspartateaminotransferase(AST)	26(12–47)	7.8 (2.7–28)	0.024
Alanineaminotransferase(ALT)	21(11–27)	10 (4.2–26)	0.306
Alkalinephosphatase(ALP)	1.2 (0.9–1.8)	1.4 (0.8–2.1)	0.710
Gamma-glutamyltransferase(GGT)	4.0 (3.5–6.2)	4.5 (2.0–8.9)	0.668
Leucocytes(x10^3/mL),median(IQR)	7.6 (6.4–10)	6.0 (4.8–8.0)	0.229
Platelets(x10^3/mL),median(IQR)	127 (103–158)	190 (167–262)	0.013
nR-basedHy'slaw,n(%)	7(88)	20 (45)	0.051

SD stands for standard deviation, ULN for upper limit of normal, and IQR for interquartile range. Laboratory value ranges were regarded as typical reference ranges. These five patients had a history of penicillin allergy, and the DILI episode was subsequently brought on by amoxicillin-clavulanate. In the fifth instance, levofloxacin produced DILI and the patient had a moxifloxacin allergy. Features of DILI patients with PDA according to the results

Additionally, we contrasted the features of DILI patients with PDA who died or had liver transplantation with those who did not (Table 2). Patients who had a fatal result did not significantly vary from those who did not in terms of age or sex.

Every patient that had a fatal result had to be hospitalized, showed jaundice, and had a pattern of hepatocellular damage. Additionally, AST and total bilirubin levels were more than three times higher in instances with a fatal end than in those with a more favorable outcome ($p<0.001$ and $p=0.024$, respectively). SD stands for standard deviation, ULN for upper limit of normal, and IQR for interquartile range. Laboratory value ranges were regarded as typical reference ranges.

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On the other hand, individuals with a fatal result had a considerably lower platelet count than those with a better prognosis (127 vs. 190×103/mL; p = 0.013).
Table 3 provides comprehensive details on the nine DILI subjects with PDA that either died or had liver transplants. Six of these nine individuals had PDA associated with anti-infectives (sulphonamides, amoxicillin, streptomycin, and penicillin), and one patient had an allergy to both butylscopolamine and penicillin. Additionally, one patient had allergies to medications that affect the neurological system (zolpidem, thioridazine), another patient had allergies to quinine, and the final patient had an allergy to ibuprofen. Damoxicillin-clavulanate (n=2), nimesu-lide, ibuprofen, carbamazepine, nefazodone, betalutamide, sibutramine, and herbal medicines (Chelidonium majus) are the causal agents of DILI. creation of a prognostic model In the research population, the Bolasso method found six indicators linked to a fatal result (liver-related mortality or liver transplantation). These characteristics included female sex (1.13), nR-based hepatocellular damage pattern (1.32), total bilirubin (0.118), AST level (0.022), platelet count (-0.006), and medication allergy (mean bootstrap coefficient 1.87).
For every independent variable, VIF values revealed no collinearity. These variables were used to create a multivariable logistic regression model to

Table3
DetailedinformationoncasesofDILIwithpriordrugallergiesthatdevelopedafataloutcome(liver-relateddeathorlivertransplantation).

Sex/ Age(y)	Priordrugallergy	DILIsuspecteddrug	Durationoftherapy(d)	Latency(d)	Rash	Eosinophilia	TBL (xULN)	ALT (xULN)	AST (xULN)	ALP (xULN)
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	*Chelidoniummajus*	5	9	No	No	7.2	50	59	1.2
F/38	Penicillin, butylscopolamine	Sibutramine	15	30	No	No	23	11	12	1.8

d: days; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; DILI: liver damage brought on by drugs; M: Male; F: Female; ULN: upper limit of normal range; y: years; TBL: total bilirubin. Liver transplantation. Liver parameters at DILI recognition. Ranges of laboratory results were regarded as the normal of reference ranges.This is how to calculate the likelihood of a deadly outcome: Probability(fataloutcome)=1. One plus e-(—5·572+1·780×1+1·459×2+1·166×3+ 0·131×4+0·012×5–0·007×6)] Drug allergy is represented by X1 in the formula above, nR-based hepatocellular damage by X2, female sex by X3, total bilirubin by X4, AST level (x ULN) by X5, and platelet count by X6. As shown in Fig. 2, a nomogram was developed to illustrate the expected odds that each patient will have liver-related mortality or need a liver transplant. Furthermore, examples of estimated probability for two randomly chosen patients—one with PDA and the other without—from the Spanish DILI Registry are shown in Supplemental Fig. 2. In the Spanish DILI Registry cohort, the model's AUC was 0.887 (95% CI 0.794–0.981), indicating a high level of discriminating ability. Furthermore, the LATINDILINetwork's 468 DILI patients were employed for external validation (Supplemental Table 3). The model's AUC (AUC 0.932; 95% CI 0.884 – 0.981) was in agreement with the one observed in the Spanish cohort (Fig. 3).
1.Conversation

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This research is the first to evaluate the impact of a previous medication allergy in a large cohort of genuine DILI patients with prospective follow-up. According to our research, individuals with DILI who had a history of medication allergies had more severe liver damage and a non-negligible higher chance of dying from liver disease. The primary pharmacologic group responsible for drug allergies and DILI was anti-infectives.
The information that is currently available about how medication allergies affect DILI outcomes is limited and sometimes conflicting, most likely due to methodological variations amongst the research that have examined this topic. According to a USDrug-InducedLiverInjuryNetwork research, individuals who died or had liver transplants within six months of the commencement of DILI had a somewhat greater incidence of self-reported medication allergies.

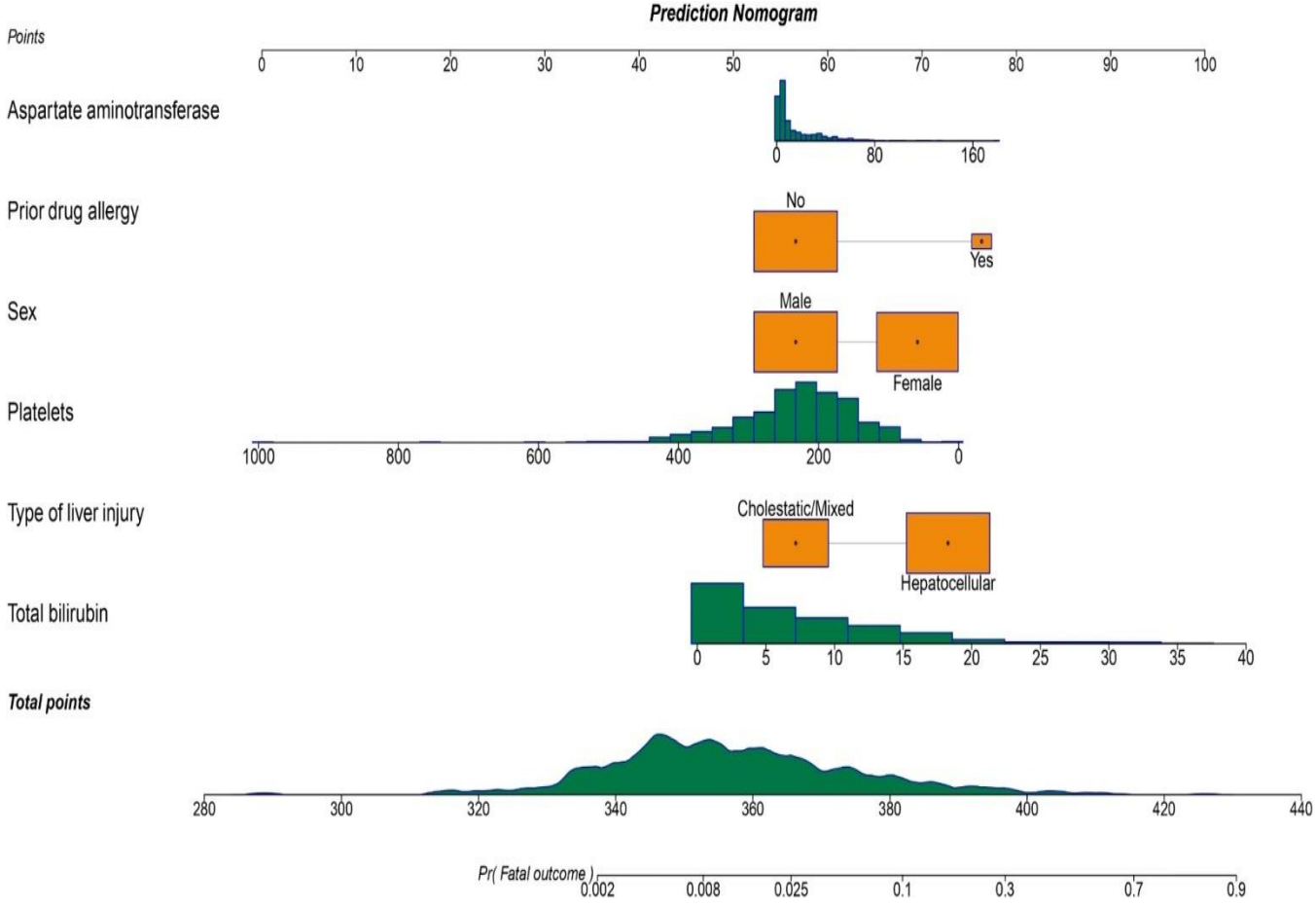

Fig.2. Prognosticnomogrammodeloffataloutcome(liver-relateddeath/livertransplantation).Quantitativevariablesdistributionisrepresentedbythedensityof bar plots. Categorical variables distribution is reflected by the size of the boxes.

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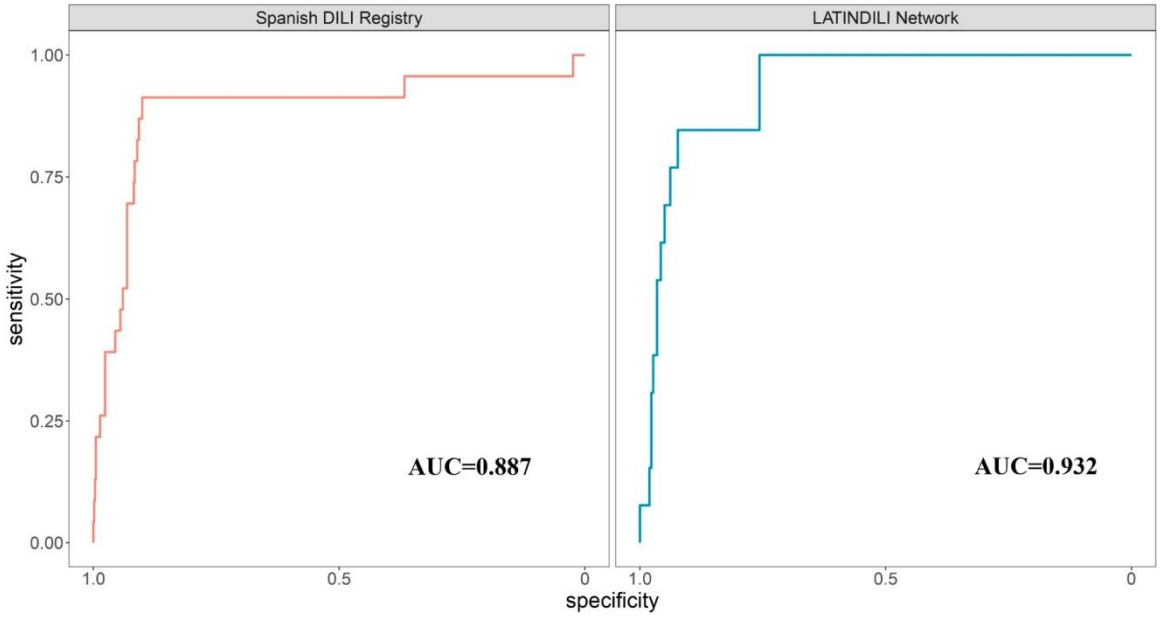

Fig.3. Receiveroperatingcurve(ROC)andareaunderthecurve(AUC)

in contrast to those who made it out alive [13]. In contrast, patients with PDA tended to have better clinical outcomes and less severe liver damage in a more recent retrospective single-center research that included electronic medical records and an ICD code [5]. The authors admit that this approach has a modest positive predictive value for identifying patients with DILI [14]. Furthermore, there were relatively few serious effects in this investigation. Conversely, DILI patients that were added to the Spanish DILI Registry were prospectively discovered in the clinical environment and then subjected to a thorough review [6]. Additionally, previous studies found that PDA rates among DILI patients were very high, ranging from 32% to 44% [5,15]. In contrast, a decreased prevalence of PDA (6.7%) was seen in our research. This discrepancy may be ascribed to variations in data collecting techniques and a thorough examination of the instances that were included in order to only document authentic PDA. It is uncertain what biological foundation this relationship has. According to our results, individuals with DILI may have a poorer prognosis if they already have immune system dysregulation. With the discovery of genetic risk alleles linked to immunological responses and autoimmunity, the adaptive immune system's involvement in the pathophysiology of DILI is becoming more clear [1,16]. Given the similarities between drug allergy and DILI, it is therefore possible—albeit speculative at this time—that patients with PDA have an immune memory to drug substances that enhances their immune response and raises their risk of developing ALF and, possibly, liver-related death. Despite the fact that substances with comparable molecular structures might trigger this reaction, we found just five instances where the antibiotics that caused the allergy and DILI were members of the same therapeutic class. Consequently, it is probable that the relationship between PDA and DILI prognosis goes beyond cross-reactive reactions. Exosomes carrying peptide-HLA complexes and drug-modified intracellular proteins may have been released as a result of early liver damage produced by the allergy-causing medication [17, 18]. Dendritic cells have the ability to absorb these exosomes, which may result in a T cell response that is unique to the medication as well as one that is particular to the heliver. In addition to the immunopathological processes implicated in DILI, these latter immune cells may create an autoimmune response and more severe liver damage upon exposure to the second medication that causes cellular stress in the liver. However, even though this idea has a strong biological foundation, further research is necessary to clarify the molecular mechanisms that lead to the poor outcome of patients with DILI who have a history of medication allergies. An R-based pattern of hepatocellular damage was another indicator of a poorer outcome. The significance of AST in DILI evaluation and prognosis is shown by the finding that R-based hepatocellular damage was a stronger predictor than R-based hepatocellular damage [19]. In fact, this pattern of liver impairment was observed in all nine individuals with a history of allergies who either died (liver-related) or had liver transplantation, and five of them had AST levels that were noticeably higher than ALT levels. These

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cases also showed a noticeably lower platelet count. Hepatocellular injury was consistently linked to a decreased platelet count in a prior examination of data from the Spanish DILI registry [6]. ALF and its consequences are often associated with thrombocytopenia and qualitative platelet abnormalities. As a result, the link between a low platelet count and a poor prognosis in DILI may not be unique to this illness but rather has to do with the development of ALF. The cause is complex and most likely has more to do with rising platelet consumption than declining production. The degree of thrombocytopenia and the severity of the systemic inflammatory response syndrome and multi-organ failure in patients with ALF were found to be strongly correlated in previous cohort studies [20]. This suggests that the prothrombotic and proinflammatory effects of platelet-derived microparticles may be involved in the prognosis of ALF. Furthermore, individuals with pre-existing liver illness, typically those with cirrhosis, often have a decreased platelet count [21]. However, only two out of nine PDA patients who had a fatal result had a pre-existing liver illness, even though previous research has linked the presence of an underlying chronic disease to a poorer prognosis [6]. It is doubtful that any underlying chronic problems were undetected since all patients enrolled in the Spanish DILI Registry had a clinical examination [6]. Therefore, it seems that the negative correlation between ALF and a reduced platelet count is independent of the existence of pre-existing chronic liver disorders. Furthermore, prior research has shown a greater frequency of females in DILI cases that proceed to ALF [22,23]. This is probably due to the impact of sex-specific hormones on hepatic drug metabolism and the control of pro-inflammatory cytokines that start in the liver [24]. It is an attractive strategy to employ prediction algorithms to determine DILI outcomes. Elevated ALP and total bilirubin over defined limits (1.1 and 2.8 times the ULN, respectively) in the second month after DILI beginning were reported as the best cut-off values to predict DILI chronicity in an analysis of the Spanish DILI Registry [25]. Similarly, a newly created model showed that patients with higher bilirubin and ALP levels at DILI recognition, longer times to DILI onset, and prolonged drug metabolism recovered from their DILI episode more slowly [26]. Additionally, Wang et al. found that a number of variables, such as male sex, advanced age, elevated AST and total bilirubin, delayed prothrombin time, and a lower platelet count, were linked to the failure of biochemical parameters to resolve within 12 months after DILI detection [27]. We set out to create a method for predicting fatal outcomes in DILI patients in light of our results. In order to provide a user-friendly nomogram with high prediction power for both Spanish and Latin American DILI patients, we illustrated the machine learning-based method. Consequently, this tool's internal and external validity suggest that it might make prognostic stratification at the bedside easier. Themainstrengthofthepresentworkliesintheutilizationofhigh- quality data obtained from a large cohort of well-characterizedDILI 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. None- theless, certain limits should be noted. The evaluation of PDA was based on the patient's medical record, representing the daily clinicalpractice,butthenumberofcasesinwhichskinsensitizationtests were done to validate the diagnosis was unclear. Therefore, any reported drug allergies that lacked enough evidence or were thought to be connected to medication side effects, intolerances, or other types of ADR were deemed not to be PDA in order to maintain the internal validity of our results. Furthermore, these individuals did not regularly undergo genetic evaluation. Future studies that address this gap are thus strongly encouraged since they may shed more light on the part PDA plays in DILI.

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