World Smart Medication Day 2023

IUPHAR INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY

A step closer to detecting drug-induced liver injury (DILI) through metabolomics: new logistic regression model as a promising diagnostic tool

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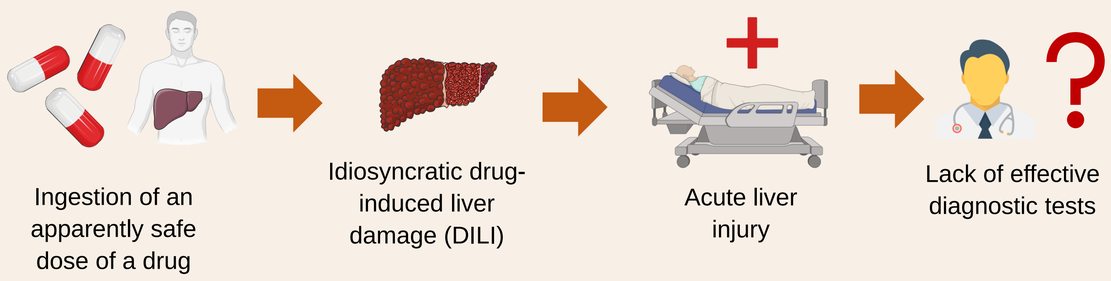
"The analysis of patient serum metabolomics has allowed us to develop a predictive model capable of **detect DILI with 84% accuracy**, through a promising equation **easily transferable to clinical practice**"

Introduction and objectives

Drug-induced liver injury (DILI) is a public health problem and is a leading cause of acute live failure and withdrawal of pharmacological products, even during drug development[1].

Problem: Diagnosis of DILI remains a critical challenge during clinical development for the pharmaceutical industry and clinical practice. To date, there is no test or specific biomarker capable of concluding an accurate diagnosis of this disease[2]. **Our aim** was to identify metabolic variables to design an optimal statistical model that can help clinicians distinguish DILI from other types of liver injury.



Methods

The serum metabolomic profile (UHPLC-MS) and clinical parameters of 26 DILI cases -mostly due to anti-infective drugs- and 34 patients with other forms of acute liver injury (ALI) -mostly viral hepatitis- were used to design and optimize a predictive logistic regression model. The number of variables of the model was optimized using genetic algorithms, selecting only those with the highest accuracy in cross-validation.

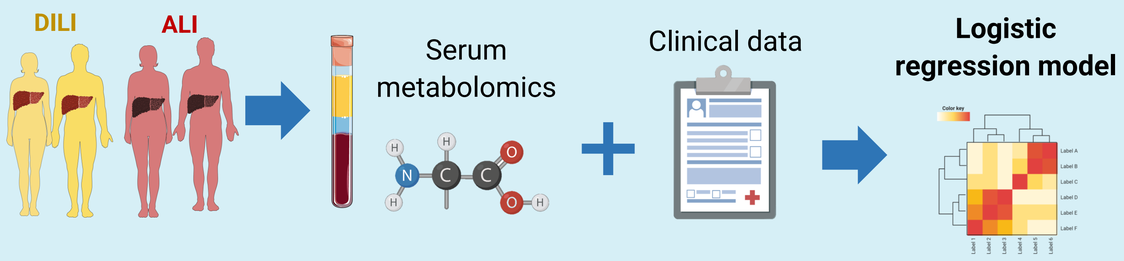


Table 1. Clinical and demographic data of patients

Variable	DILI (n=26)	ALI (n=34)
Age, mean ± SD	50 ± 17	48 ± 20
% Sex (male/female)	57 / 43	53 / 47
BMI	24,6 ± 3,7	23,9 ± 4,1
ALT (UI/L)	424 ± 466	1134 ± 1241
AST (UI/L)	264 ± 368	700 ± 806
γ-GT (UI/L)	551 ± 1270	300 ± 253
TB (mg/dL)	11 ± 13	11 ± 8

Results

Out of 186 initial different metabolic variables, the logistic regression model was generated **incorporating only 5 different metabolites: ALT, leucine, two polyunsaturated fatty acids (22:4n-6 and 20:3n-9) and one lysophosphatidylcholine (PC(O-22:1/0:0))** (Table 2). The AUC of the training cohort and the validation cohort was 0.84 in both cases (Figure 1). This algorithm was developed for implementation in a logistic regression probability equation in which Bi are the coefficients of the model variables and the explanatory variables (Xi) correspond to the concentrations of the metabolites.

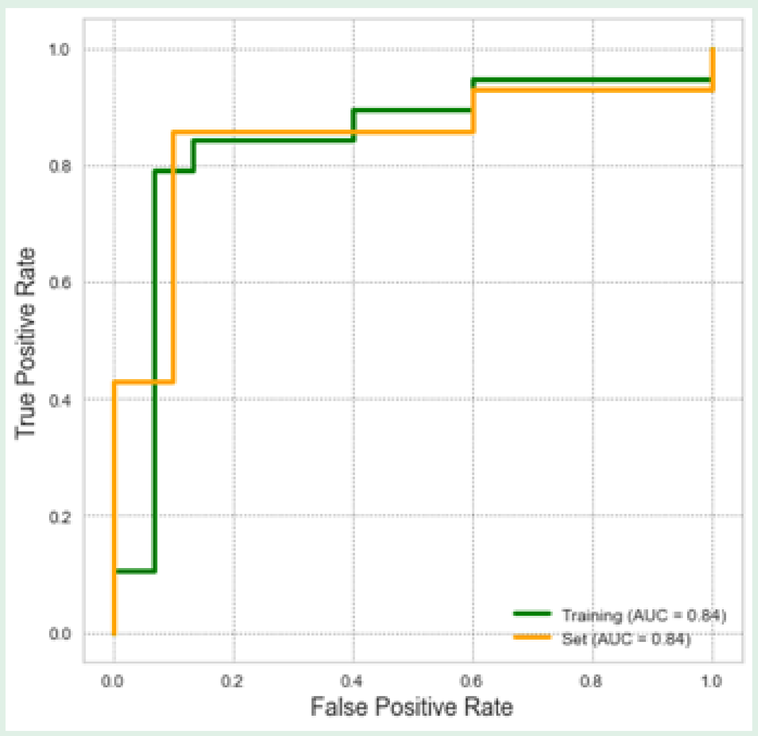
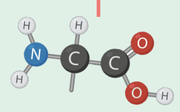


Figure 1. ROC curves. Models were built in the training cohort (60% samples) and evaluated in the validation cohort (40% samples).

Table 2. Coefficients of the metabolites chosen for the development of the logistic regression model.

Variable	Coef (B_i)	SE
β0	2,472	1,841
PC(O-22:1/0:0)	-1,273	0,808
ALT (U/L)	0,002	0,001
22:4n-6	0,732	0,928
20:3n-9	0,504	0,711
Leucine	-7,253	3,087

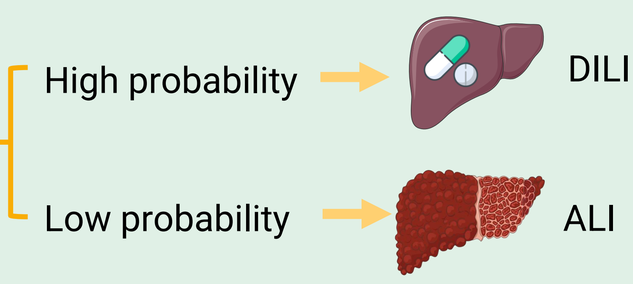


Metabolite concentration

Example:

$$\text{Probability of DILI} = 1 - \frac{e^{B_0 + \sum_{i=1}^{N} B_i X_i}}{1 + e^{B_0 + \sum_{i=1}^{N} B_i X_i}}$$

Diagnostic



Conclusions

Metabolomic profiling can help distinguish drug-induced liver injury from other causes of liver injury. Using serum concentrations for 5 metabolites into **logistic regression equation that can be easily translated to clinical, it was possible to predict the probability of a case being DILI or ALI** with an AUC of 0.84. However, it is necessary to refine the model and to validate these results in a larger cohort of patients to test the robustness of the algorithm and to analyse its performance.

References

1. Andrade RJ, et al.,. Drug-induced liver injury. Nat Rev Dis Primers. 2019 Aug 22;5(1):58.
2. Aithal GP, et al., Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011 Jun;89(6):806-15.

Funding: CIBERehd-ISCiii, FEDER PI18/00901, PI19/00883, PI21/01248, UMA18-FEDERJA-193, PY18-3364, PEMP-0127-2020, I-PFIS (IFI21-00034).

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