MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura 9: OPORTUNIDADES EN HEPATOLOGÍA

“Manejo clínico de la hepatotoxicidad”

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¿Qué es la hepatotoxicidad?

- **Alteración del perfil hepático** causado por fármacos (de prescripción o libre dispensación), productos de herboristería o suplementos dietéticos.
- **Elevación de los valores** de alanino aminotransferasa (ALT), fosfatasas alcalinas (FA) y bilirrubina total (BT)

Criterios bioquímicos para considerar DILI (conferencia de consenso)
ALT ≥ 5 xLimite superior de la normalidad (LSN)
FA ≥ 2 xLSN
ALT ≥ 3 xLSN + BT > 2 xLN

- La elevación aislada de bilirrubina o de gammaglutamil transferasa (GGT) no son suficientes para cualificar como DILI

Estos criterios pueden ser inaplicables en pacientes con enfermedad hepatica basal

Aithal GP,.., Andrade RJ,.., et al *Clin Pharmacol Ther* 2011; 89:806-15.

Manejo clínico de la hepatotoxicidad

- Ser capaz de diagnosticar correctamente una sospecha
  - La expresividad clínica es muy variable…
  - No hay biomarcadores…
- Ser capaz de estimar la evolución y el pronóstico al inicio del cuadro
  - Evolución fulminante y cronicidad
- Ser capaz de tratar correctamente al paciente
  - Nuevos fármacos hepatotóxicos (inmunoterapia) plantean desafíos nuevos
  - ¿Hay algún tratamiento que sea eficaz en acortar la enfermedad o prevenirla?

Manifestaciones clínicas y presentación

- Enormemente **variable** desde **asintomático** detectado por alteraciones del perfil hepático a **necrosis hepática masiva** con fallo hepático fulminante.
- Período de latencia muy variable usualmente < 3 meses desde el inicio del tratamiento.
- Manifestaciones **de alergia asociadas,** ya sea clínicas (fiebre, exantema o reacciones cutáneas mas graves) o de laboratorio (eosinofilia, linfopenia) implican a farmacos como responsables. Presentes en 20-25% de casos.
- Multitud de fenotipos de presentación, **DILI puede simular cualquier enfermedad hepática** aguda o crónica

EASL Clinical Practice Guidelines: DILI. J Hepatol 2019; 70:1222-61
Stephens C,.. Andrade RJ. *J Hepatol* 2021; S0168-8278(21)00043-X. doi: 10.1016/j.jhep.2021.01.029.

Fenotipos de DILI

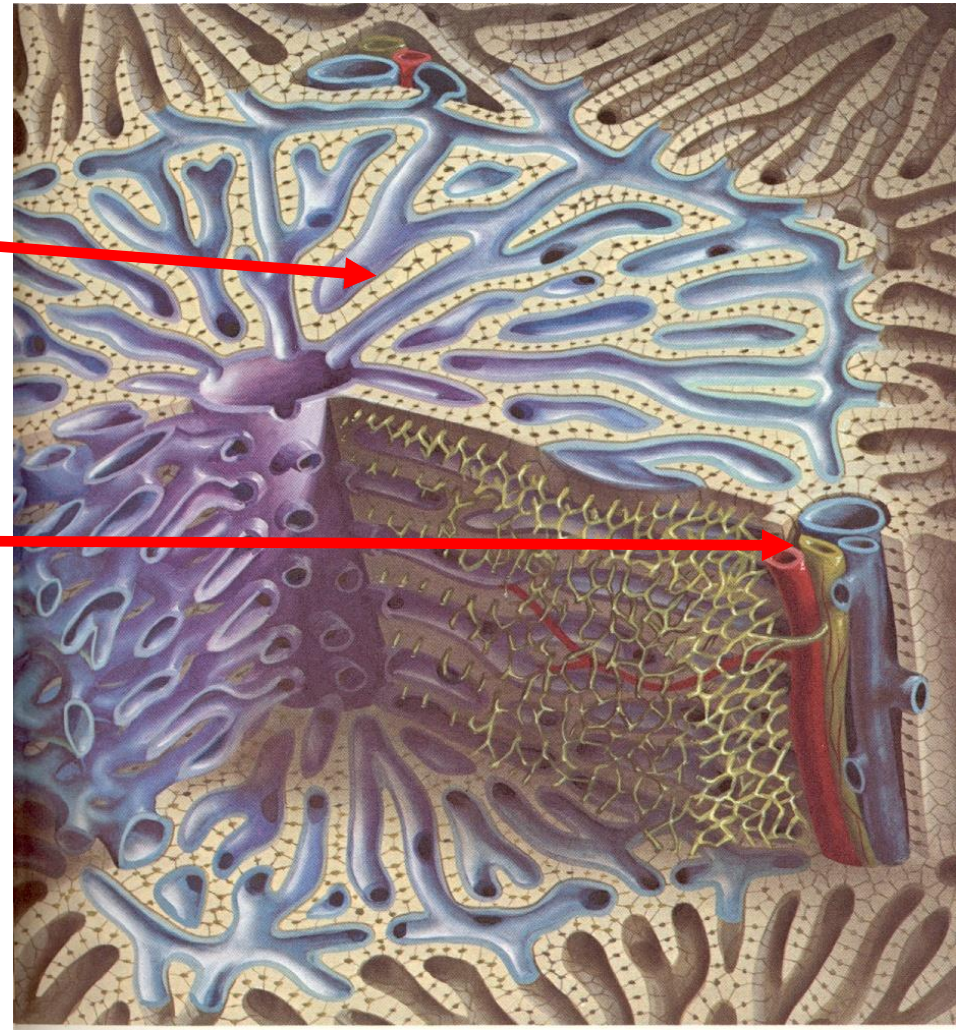
Hepatitis aguda (simulando hepatitis viral)	isoniazida, ketoconazol, ximelagatran
Hepatitis colestásica o mixta	amoxicilina-clavulánico, macrolidos
Necrosis hepatica aguda	Paracetamol, amiodarona IV
Síndrome de hipersensibilidad (DRESS)	Difenilhidantoína, carbamazepina
Esteatosis/ esteatohepatitis	metrotexato, tamoxifeno, irinotecan
Hígado graso agudo y acidosis metabólica	stavudina, tetraciclina, valproate sódico
Hepatitis autoimmune inducida por fármacos	minociclina, nitrofurantoina
Síndrome obstruction sinusoidal	ciclofosfamida, azatioprina
Hiperplasia nodular regenerativa	azatioprina, HAART, bleomicina
Daño hepático inmuno-mediado	ipilimumab, pembrolizumab, nivolumab

- Diferentes manifestaciones clínicas
- Diferentes alteraciones bioquímicas
- Diferente pronóstico

Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting.
https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf

Clasificación DILI

- **HEPATOCELULAR**: elevación predominante de ALT (ALT xLSN/FA xLSN) ≥5
- **COLESTASICO**: elevación predominante de FA (ALT xLSN/FA xLSN) ≤2
- **MIXTO** ALT & FA se incrementan, and 2<ALT xLSN/FA xLSN<5



Bénichou C. *J Hepatol.* 1990; 11: 272-6.
Fontana RJ,…, Andrade RJ,.., et al. *Hepatology* 2010;52:730-42.
Aithal GP,.., Andrade RJ,.., et al *Clin Pharmacol Ther* 2011; 89:806-15.

Algoritmo para un diagnostico ordenado del DILI

Abnormal biochemistry / acute hepatitis

DILI suspicion

Features supporting toxic etiology
Skin involvement, Kidney injury, Previous DILI episodes

Careful enquiry of exposure to HDS, drugs, OTC (record start and stop dates)

STOP ALL NON ESSENTIAL THERAPIES

Potential pitfalls Lack of information (e.g. dose, duration), medications, Hidden HDS and OTCs intake

Search in hepatotoxicity resources (Liver tox)

Calculate biochemical pattern of liver injury

Hep	Mix	Chol
R ≥ 5	2 > R < 5	R ≤ 2

R= ALT x ULN/ALP X ULN

Search for alternative causes

- Viral infections (HAV, HBV, HCV, HEV)
- Alcoholic liver disease, Hepatic ischemia
- Autoantibody titres, ↑ IgG

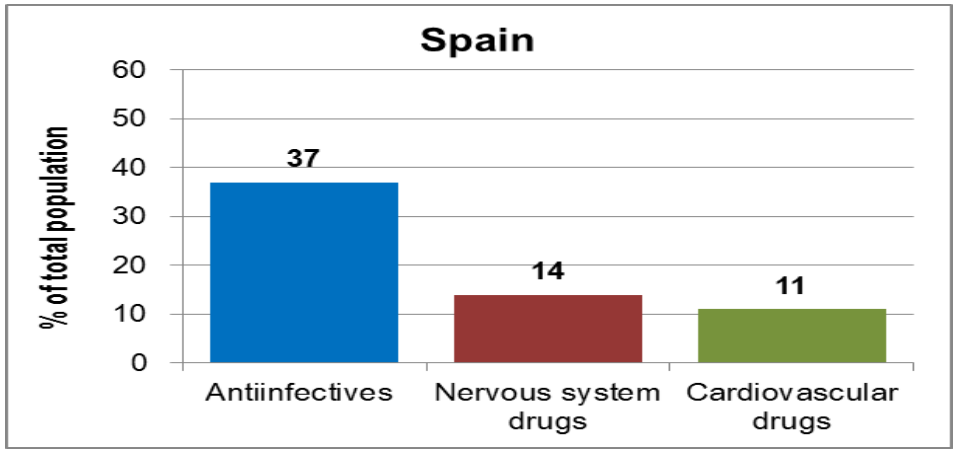
- Benign / malignant biliary obstruction
- Cholestatis autoimmune syndromes (PBC, PSC)

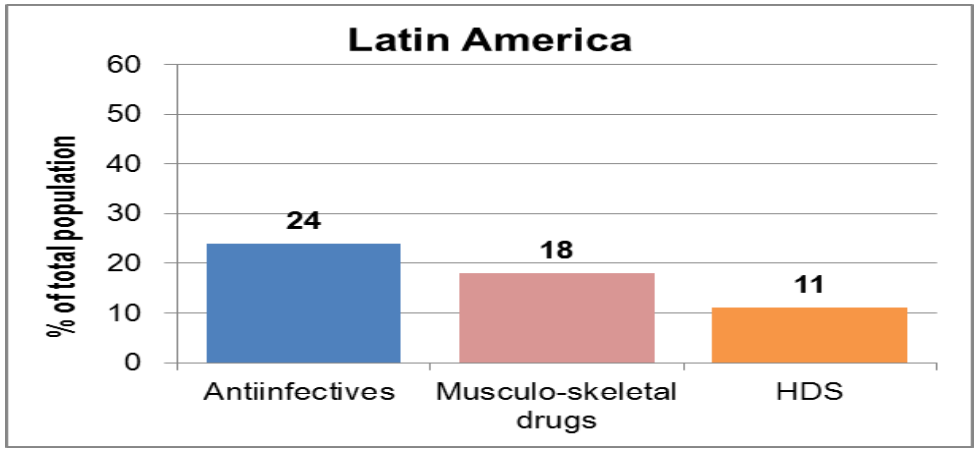
Consider liver biopsy

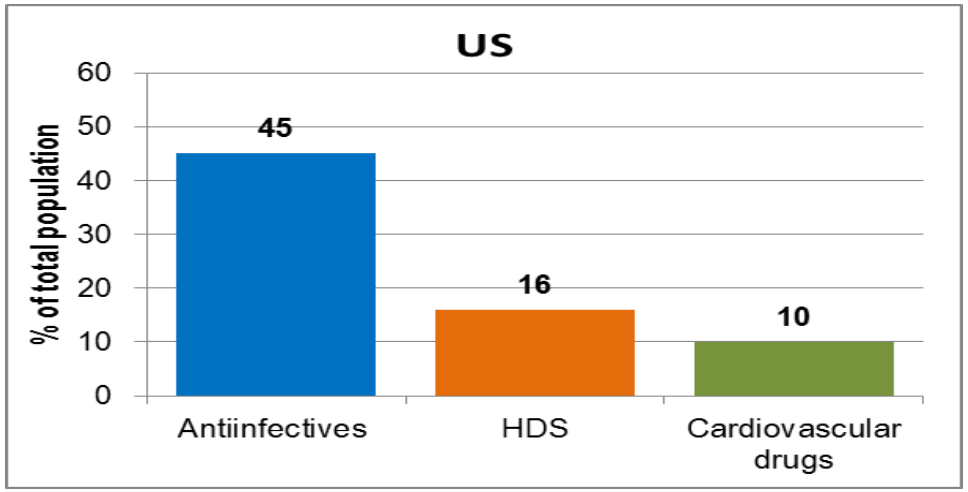
- Negative or incomplete dechallenge
- Acute or chronic atypical presentation (Vascular, MVS, chronic hepatitis)
- Autoimmune hepatitis

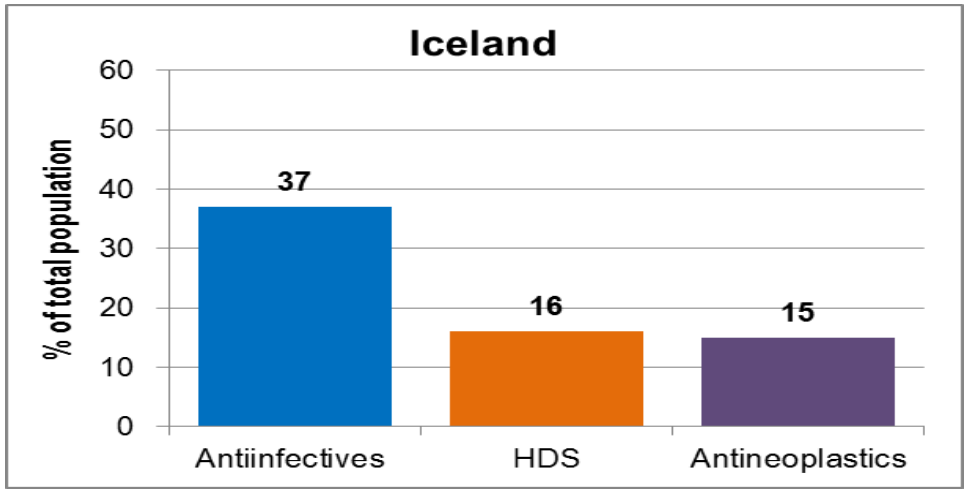
EASL CPG DILI. *J Hepatol 2019*; 70:1222-1261

Most common causative drugs in large DILI populations









Andrade RJ, et al. *Gastroenterology* 2005;129:512–21; Chalasani N, et al. *Gastroenterology* 2015;148:1340–52.e7; Bessone F, et al. *Int J Mol Sci* 2016;17:313; 4. Björnsson ES, et al. *Gastroenterology* 2013;144:1419–25.e3.

DRUG RECORD

TERBINAFINE

OVERVIEW
Terbinafine

Introduction

Terbinafine is an orally and topically active allylamine fungicidal agent which is used to treat superficial fungal infections of the skin and nails. Terbinafine has been clearly linked to rare instances of acute liver injury that can be severe and sometimes fatal.

Background

Terbinafine (ter' bin a feen) is a synthetic allylamine derivative that has potent activity against many dermatophytes that affect skin and nails, including Epidermophyton floccosum, Trichophyton mentagrophytes and Trichophyton rubrum. The antifungal activity of terbinafine is believed to be due to the selective inhibition of fungal squalene epoxidase, which increases squalene to toxic levels, thus killing the fungal cell. Terbinafine was approved for use in the United States in a topical form in 1992 and as an oral antifungal agent in 1998. Topical terbinafine is available over-the-counter as a 1% cream or spray for treatment of dermatophyte infections of the skin (tinea pedis, cruris or corporis). Oral terbinafine is available by prescription only in tablets of 250 mg generically and under the brand name of Lamisal. Oral terbinafine is used in the therapy of onychomycosis or fungal infections of the fingernails or toenails (tinea unguium) typically in a dose of 250 mg once daily for 6 weeks (fingernails) or 12 weeks (toenails). The most common side effects of terbinafine include gastrointestinal disturbances, headache, change in taste and rash.

Hepatotoxicity

Drug induced liver injury due to terbinafine was identified shortly after its introduction into

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Hepatotoxicity

Drug induced liver injury due to terbinafine was identified shortly after its introduction into medical use. Oral therapy with terbinafine is associated with elevations in serum aminotransferases in less than 1% of patients and the elevations are generally asymptomatic and resolve without stopping therapy. The estimated probability of developing elevated serum aminotransferase levels requiring stopping treatment is about 0.31% for 2 to 6 weeks' treatment and 0.44% for treatment longer than 8 weeks.

Clinically apparent liver injury from terbinafine occurs rarely (1 in 50,000 to 120,000 prescriptions), but many case reports and even case series have been described in the literature. Liver injury usually arises within the first 6 weeks of therapy. The pattern of injury can be either hepatocellular or cholestatic initially, but typically evolves into a cholestatic pattern which can be prolonged (Cases 1 and 2). Some cases may progress to vanishing bile duct syndrome. Signs of hypersensitivity (rash, fever, eosinophilia) are not common and, when present, are generally mild-to-moderate in severity. Autoantibody formation is rare. In addition, cases with severe hepatocellular injury with acute liver failure have been described. These instances are marked by precipitous onset with marked elevations in serum aminotransferase levels and progressive jaundice and hepatic failure. Terbinafine has also been implicated in cases of Stevens-Johnson syndrome, in which case the hepatic injury may be overshadowed by rash and allergic symptoms.

Likelihood score: B (highly likely cause of clinically apparent liver injury).

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD
LIVER INJURY/REGENERATION

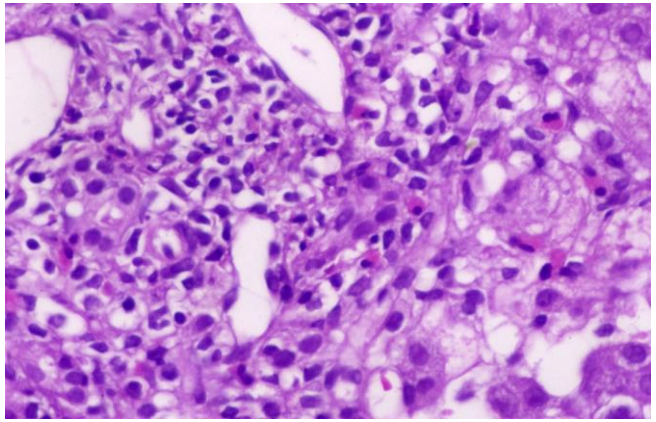
Categorization of Drugs Implicated in Causing Liver Injury: Critical Assessment Based on Published Case Reports

Einar S. Björnsson[1,2] and Jay H. Hoofnagle[3]

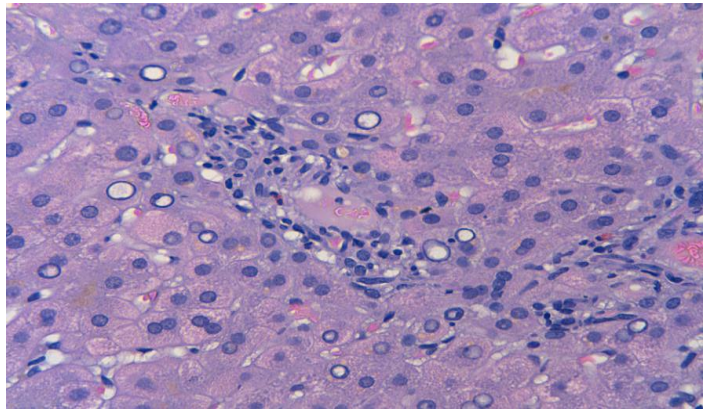
Category A	The drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described
Category B	The drug is reported and known or highly likely to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described
Category C	The drug is probably linked to idiosyncratic liver injury, but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series
Category D	Single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a possible hepatotoxin and only a rare cause of liver injury
Category E	Despite extensive use, no evidence that the drug has caused liver injury. Single case reports may have been published, but they were largely unconvincing. The agent is not believed or is unlikely to cause liver injury
Category E*	The drug is suspected to be capable of causing liver injury or idiosyncratic acute liver injury but there have been no convincing cases in the medical literature. In some situations cases of acute liver injury have been reported to regulatory agencies or mentioned in large clinical studies of the drug, but the specifics and details supportive of causality assessment are not available. The agent is unproven, but suspected to cause liver injury
Category X	Finally, for medications recently introduced into or rarely used in clinical medicine, there may be inadequate information on the risks of developing liver injury to place it in any of the five categories, and the category is characterized as “unknown”

Björnsson ES, Hoofnagle JH. *Hepatology.* 2016;63:590-603.

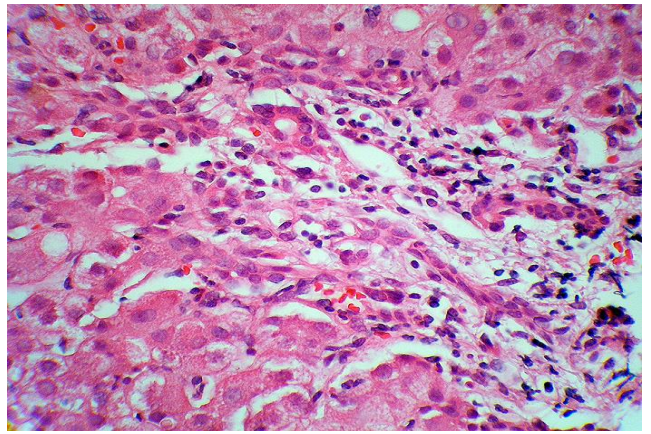
DILI: histología



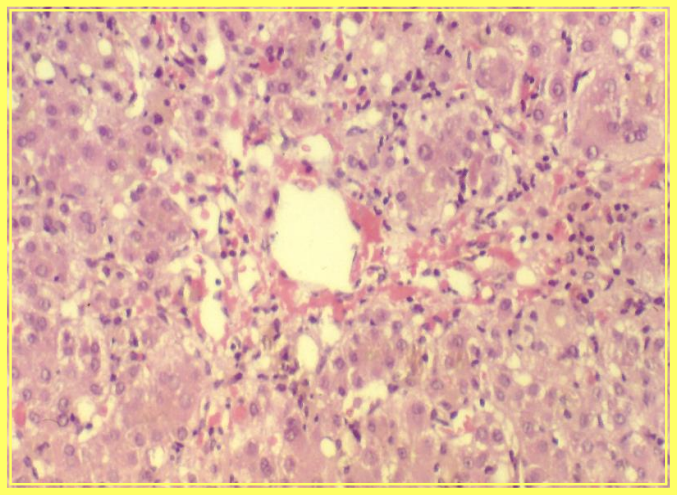
Inflamación portal y eosinófilos



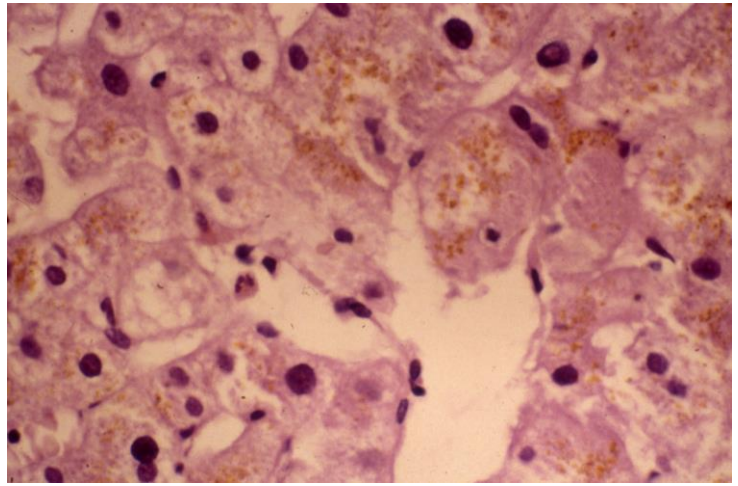
Inflamación lobular y eosinófilos



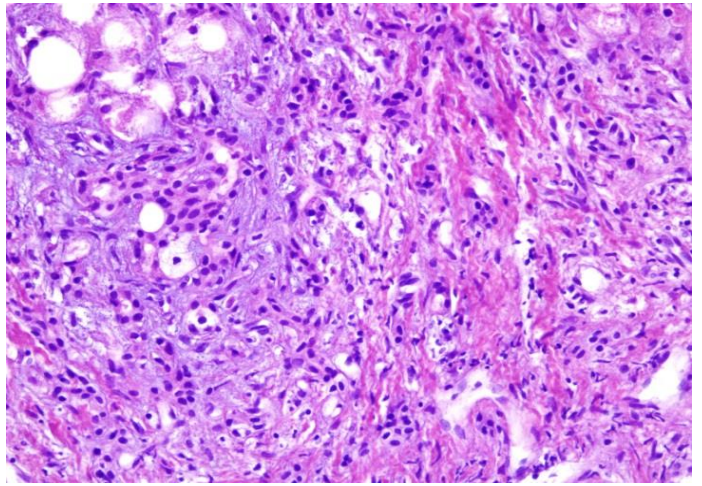
Hepatitis y colestasis



Necrosis centrolobulillar

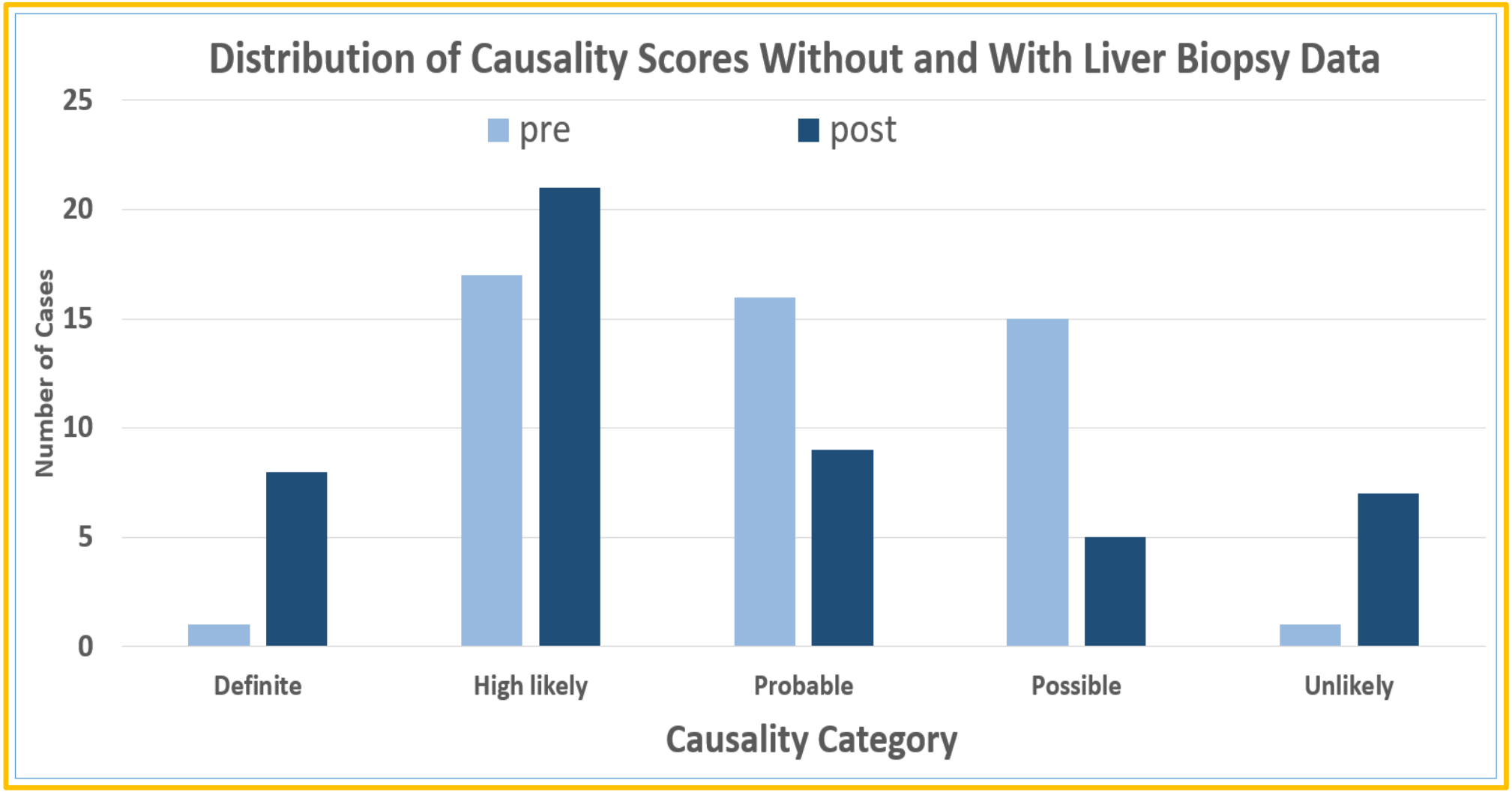


Colestasis pura



Esteatohepatitis con cirrosis

The Value of Liver Biopsy in the Diagnosis of Drug-Induced Liver Injury

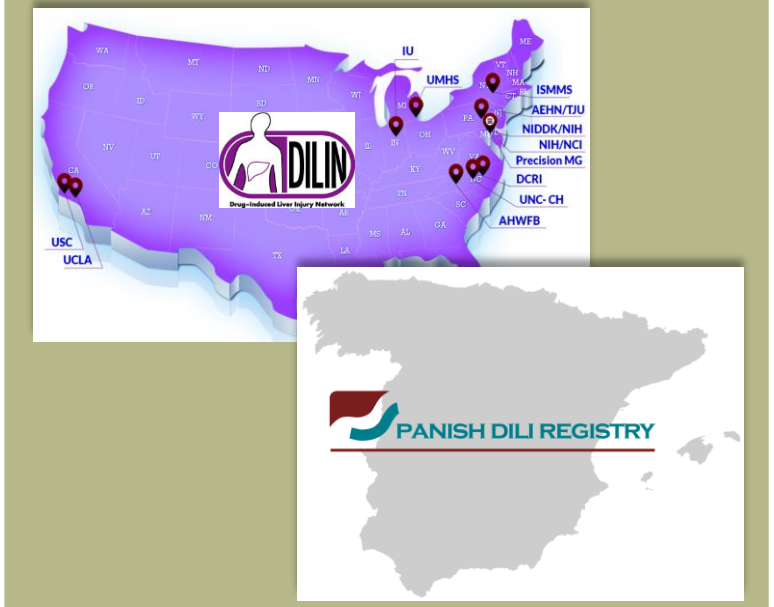


Ahmad J, et al. *J Hepatol.* 2022;76:1070-1078.

RECAM: An Evidence Based Update of RUCAM

Study Population

DILIN & Spanish DILI Registry Cases



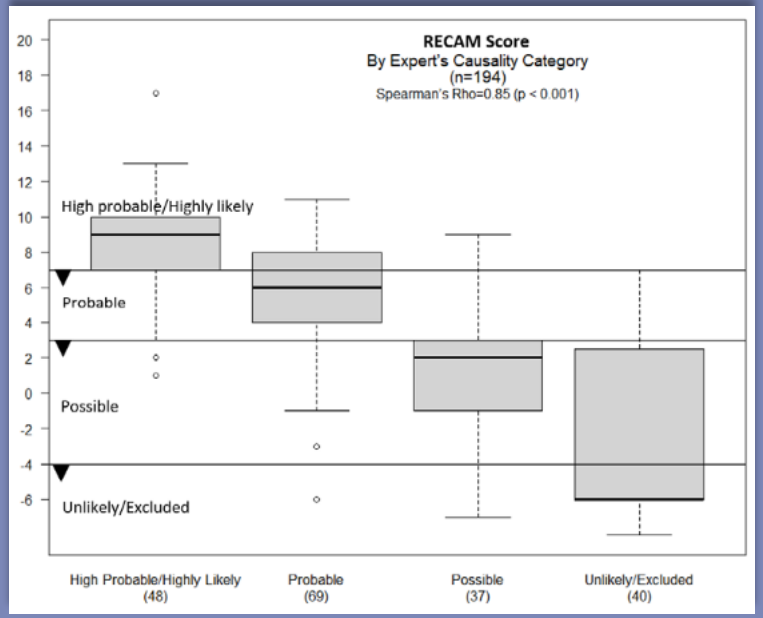
Methods

Updates based on case data, expert opinion, & iterative testing of cases across the spectrum of DILI diagnostic likelihood

RUCAM Criteria	RECAM Changes
1: Latency from start & stop	Both latencies scored. Latency from drug stop only penalizes
2: Dechallenge	Same for cholestatic, mixed and hepatocellular
3. Risk factors (age, alcohol, pregnancy)	✗ *Eliminated* Shown not to be diagnostically helpful
4. Competing medications	✗ *Eliminated* Opted for separate scoring of each suspected agent
5. Competing diagnoses	Updated, expanded and instructions tightened
6: DILI risk	Anchored to *LiverTox®* Likelihood scores
7: Rechallenge	Moved to new domain of "Additional Data"
New Domain	Additional data

Results

Improved separation of diagnostic categories & less subjective scoring



Hayashi PH & Lucena MI,….Andrade RJ, Hoofnagle JH. *Hepatology* 2022.
(http://gihep.com/dili-recam/)

HEPATOLOGY
JOURNAL OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

GENETIC BIOMARKERS (GWAS)

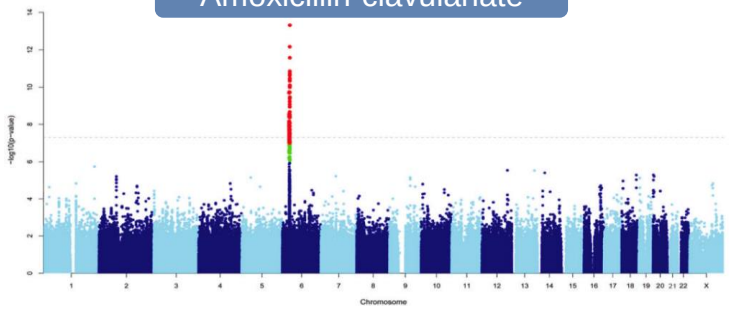
HLA

Test: HLA type	% positive in DILI cases	% + in 'normal' population
*DRB1*15:01 B* 1801, A* 0201*	57%-67% (Amoxicillin-clavulanate)	15%-20%
*B*57:01*	84%-87% (Flucloxacillin)	6%
*A*31:01*	17% (Carbamazepine)	2%
*DRB1*16:01-DQB1*05:02*	25% (Flupirtine)	1%
*A*33:01*	80% (Ticlopidine) 50% (Methyldopa) 50% (Enalapril) 43% (Fenofibrate) 43% (Terbinafine) 40% (Sertraline) 20% (Erythromycin)	1%
*B*35:02*	16% (Minocycline)	0.6%
*B*35:01*	72% (*Green Tea*)	11% (Caucasian)
*B*35:01*	45% (*Polygonum multiflorum*)	3% (Chinese)

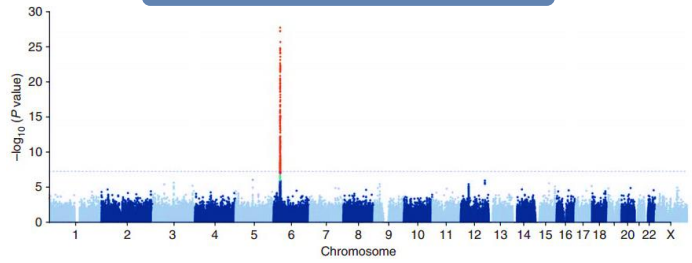
NO HLA

A non synonymus* in the protein tyrosine phosphatase**, non-receptor type 22 gene ***(PTPN22), *rs2476601 OR 1.44*

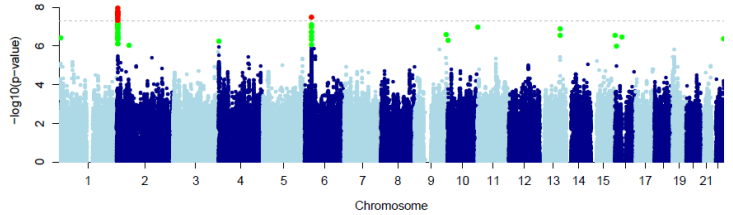
Amoxicillin-clavulanate



Flucloxacillin



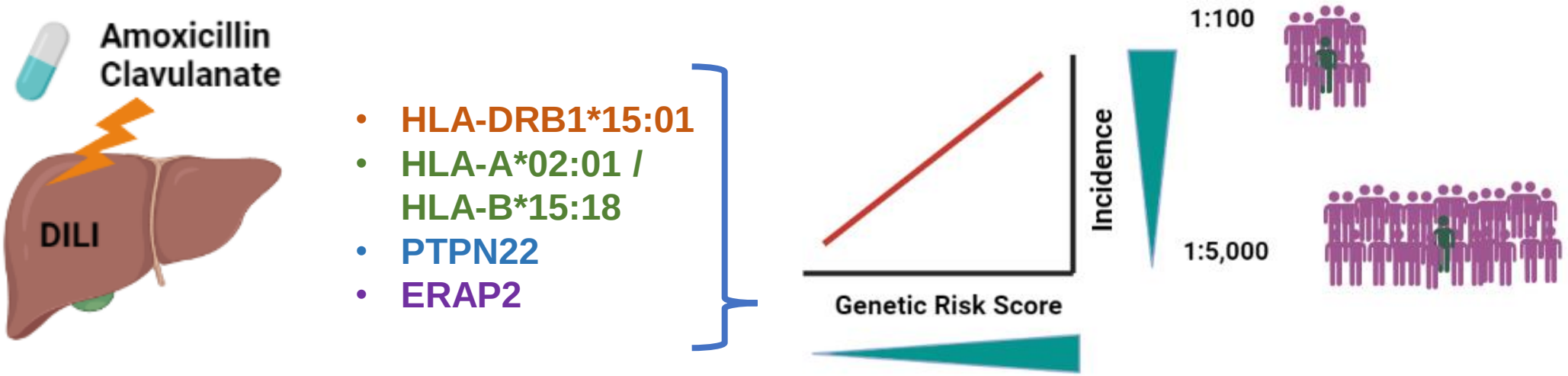
HLA A*33:01



Lucena MI et al, *Gastroenterology* 2011; Daly A et al, *Nat Genet* 2009; Nicoletti P et al., *Gastroenterology* 2017;
Cirulli et al, *Gastroenterology* 2019: Li C et al *Hepatology* 2019; Hoofnagle JH, et al *Hepatology* 2021; EASL CPG DILI. *J Hepatol* 2019;

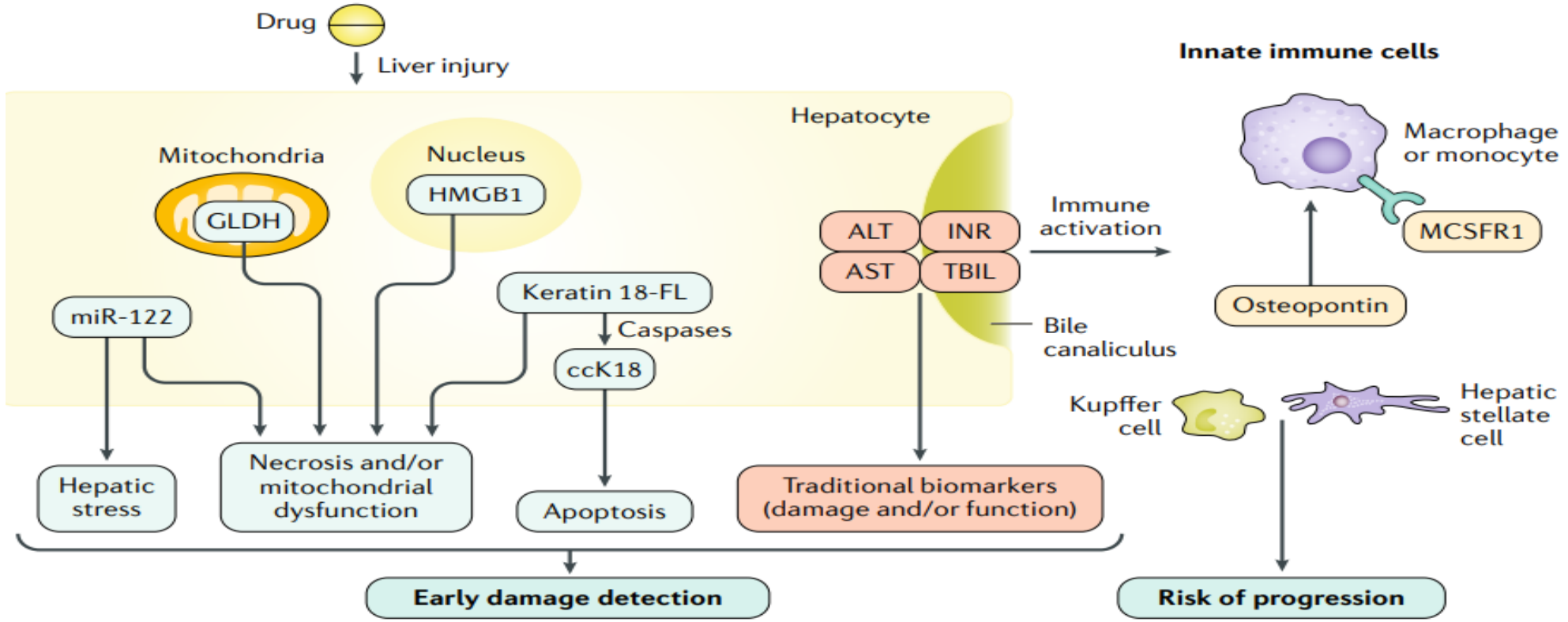
GWAs and general drug susceptibility
Polygenic Risk Score in amoxicillin clavulanate

HLA-DRB1*15:01	HLA-A*02:01 / HLA-B*15:18	PTPN22 Rs2476601 (A)	ERAP2 Rs1363907 (GG)	Freq Cases	Freq Controls	OR	95% CI	P
+	+	-	-	0.15	0.06	5.79	3.89–8.6	$3.9x10^{-18}$
+	+	+	-	0.06	0.01	10.7	6.3-18.0	$7.6x10^{-19}$
+	+	-	+	0.14	0.03	10.7	7.1-16.1	$6.2x10^{-30}$
+	+	+	+	0.05	0.006	18.5	10.4-33	$2.1x10^{-23}$



Nicoleti P…. Andrade RJ MI, Watkins P. Gastroenterology 2023

Nuevos biomarcadores en DILI



Church et al. *Hepatology* 2019; 69:760-773.
Andrade, R.J. et al. Drug-induced liver injury. *Nat. Rev. Dis. Primers* doi.org/10.1038/s41572-019-0105-0

nature communications

Article

https://doi.org/10.1038/s41467-023-36858-6

Tandem mass tag-based quantitative proteomic profiling identifies candidate serum biomarkers of drug-induced liver injury in humans

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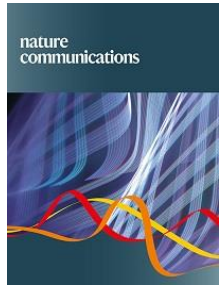
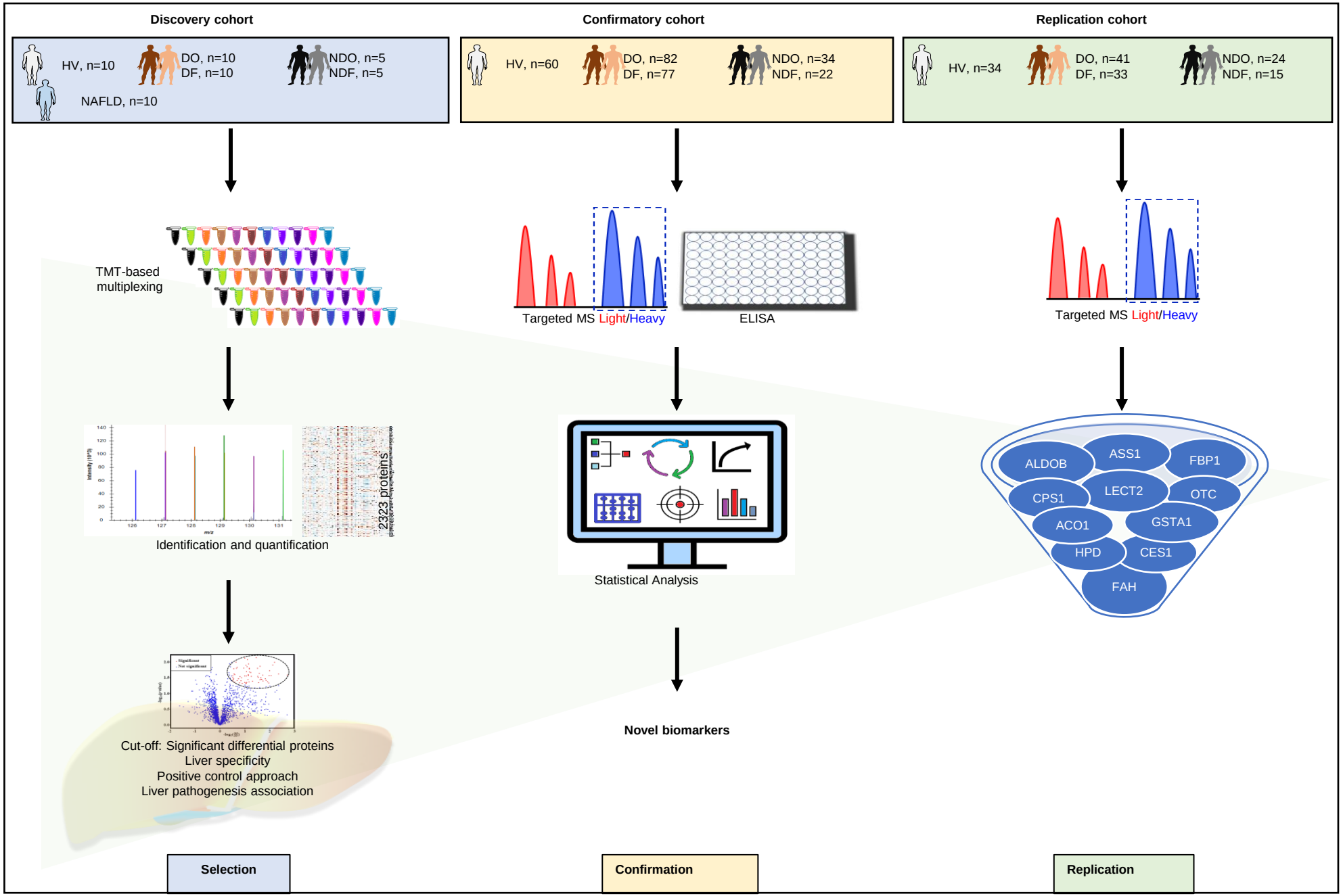
Check for updates



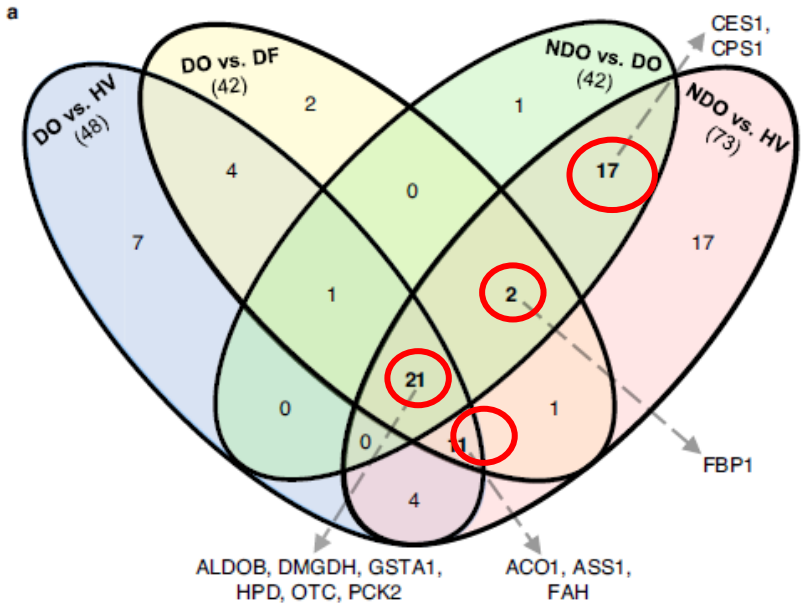
Kodihalli C. Ravindra[1,18], Vishal S. Vaidya[1,18,19] ✉, Zhenyu Wang[1], Joel D. Federspiel[1], Richard Virgen-Slane[1], Robert A. Everley[1], Jane I. Grove[2,3], Camilla Stephens[4,5], Mireia F. Ocana[1], Mercedes Robles-Díaz[4,5], M. Isabel Lucena[4,5], Raul J. Andrade[4,5], Edmond Atallah[2,3], Alexander L. Gerbes[6], Sabine Weber[6], Helena Cortez-Pinto[7], Andrew J. Fowell[8], Hyder Hussaini[9], Einar S. Bjornsson[10,11], Janisha Patel[12], Guido Stirnimann[13], Sumita Verma[14], Ahmed M. Elsharkawy[15], William J. H. Griffiths[16], Craig Hyde[1], James W. Dear[17], Guruprasad P. Aithal[2,3,19] ✉ & Shashi K. Ramaiah[1,19] ✉



Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

Resultados: identificación de biomarcadores candidatos

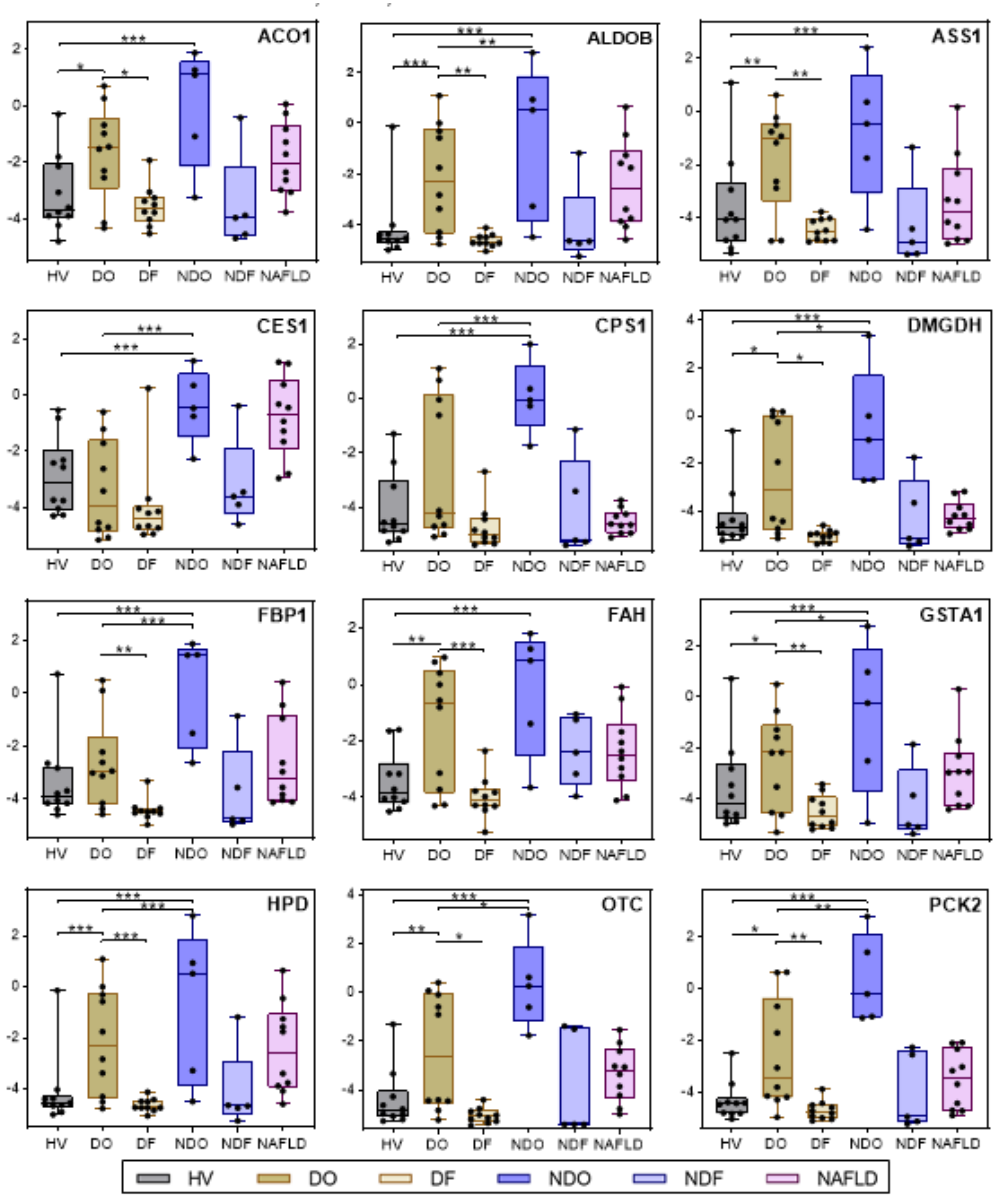
- 2323 proteínas identificados en la cohorte de descubrimiento
- 89 proteínas expresadas diferencialmente (DO vs HV, DO vs DF, NDO vs DO, NDO vs HV
- 51 presentes en al menos dos comparaciones



- 12 seleccionados en base de especificidad hepática y relevancia mecanistica a la biología hepática

Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

Identificación de biomarcadores candidatos



ACO1: Cytoplasmic aconitate hydratase
ALDOB: Frucoseebisphosphate aldolase
ASS1: Argininosuccinate synthase

CES1: Liver carboxylesterase 1
CPS1: Carbamoylphosphate synthase
DMGDH: Demethylglycine dehydrogenase

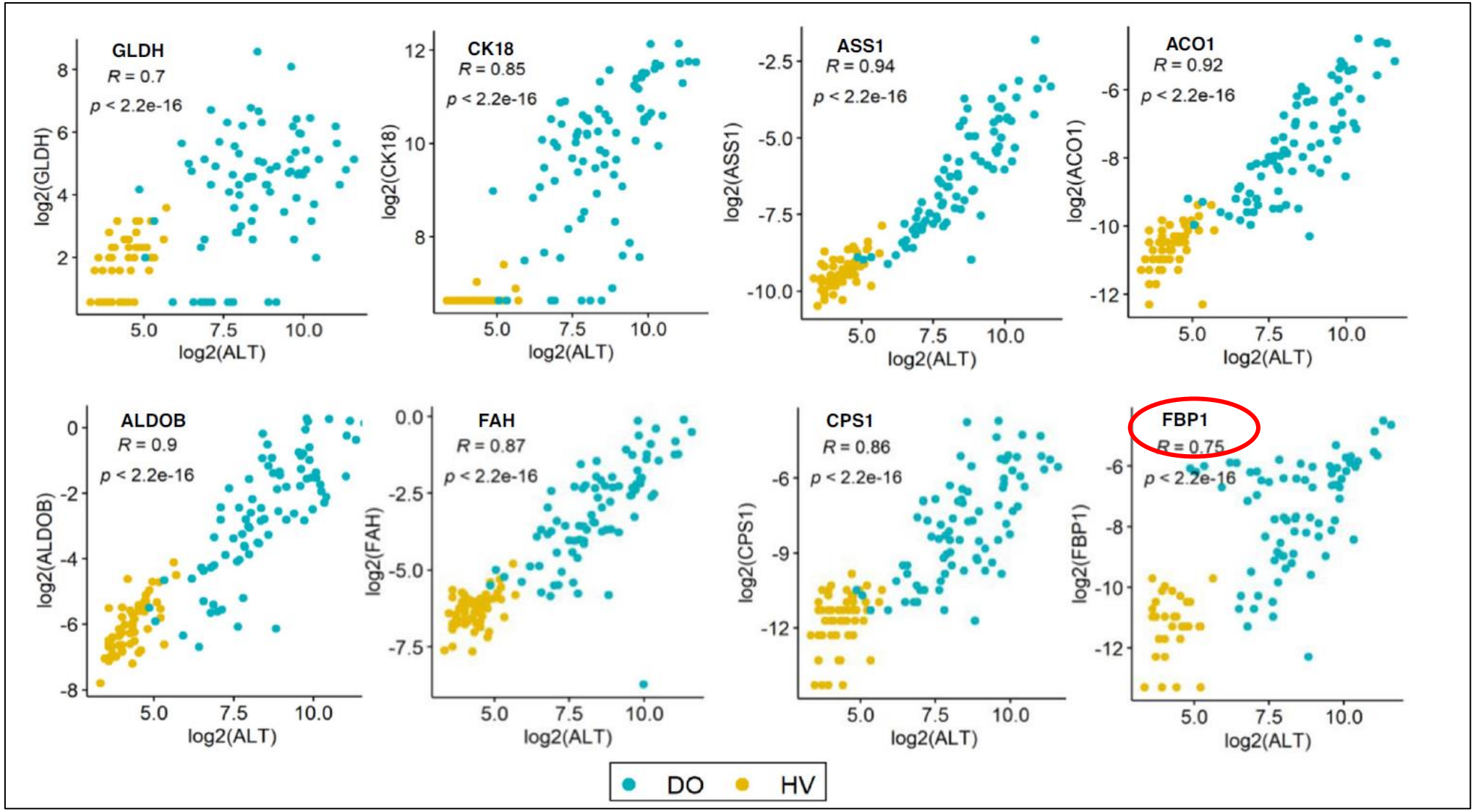
FBP1: Fructose-1,6-bisphosphatase 1
FAH: Fumarylacetoacetase
GSTA1: Glutathione S-transferase

LECT2: leukocyte cell-derived, Chemotaxin 2, did not meet significance threshold, but was elevated in DO vs NDO

HPD: 4-hydroxyphenylpyruvate dioxygenase
OTC: Ornithine carbamoyl transferase
PCK2: mitocondrial phosphoenolpyruvate carboxykinase 2

Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

Evaluación de la especificad de daño hepático de los nuevos biomarcadores candidatos: Correlación de Spearman

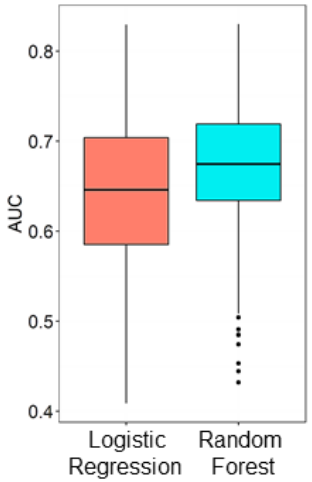


Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

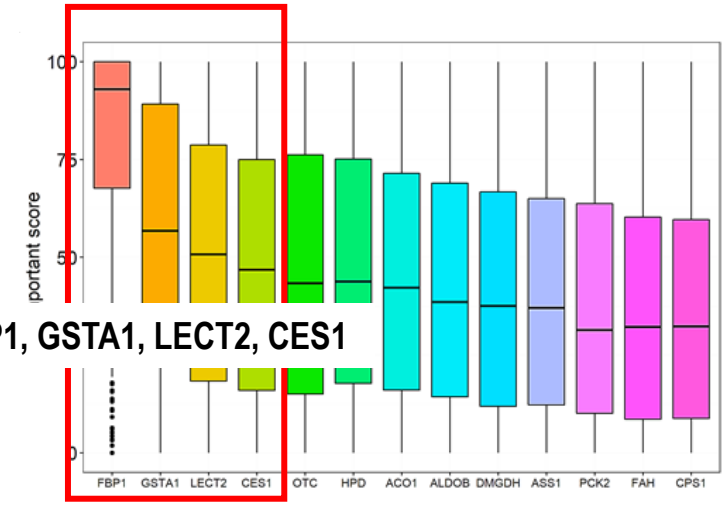
Modelos multivariantes para distinguir DO y NDO

Todos los biomarcadores candidatos

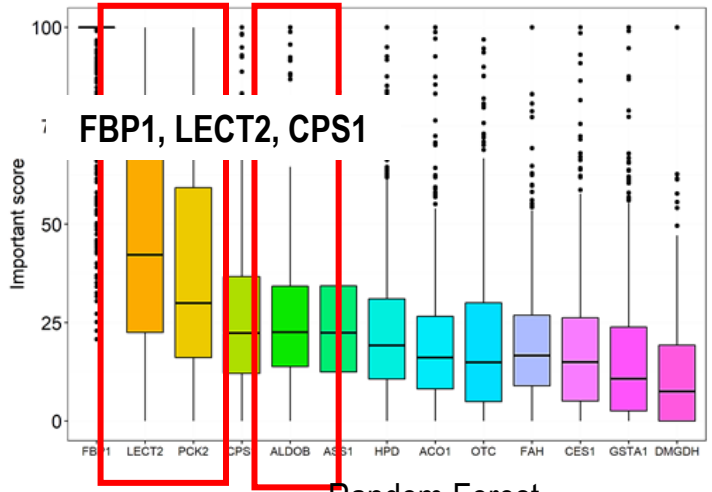
AUC
LR: 0.65
RF: 0.68



Importance score basado en 500 bootstrapping



Logistic regression



Random Forest

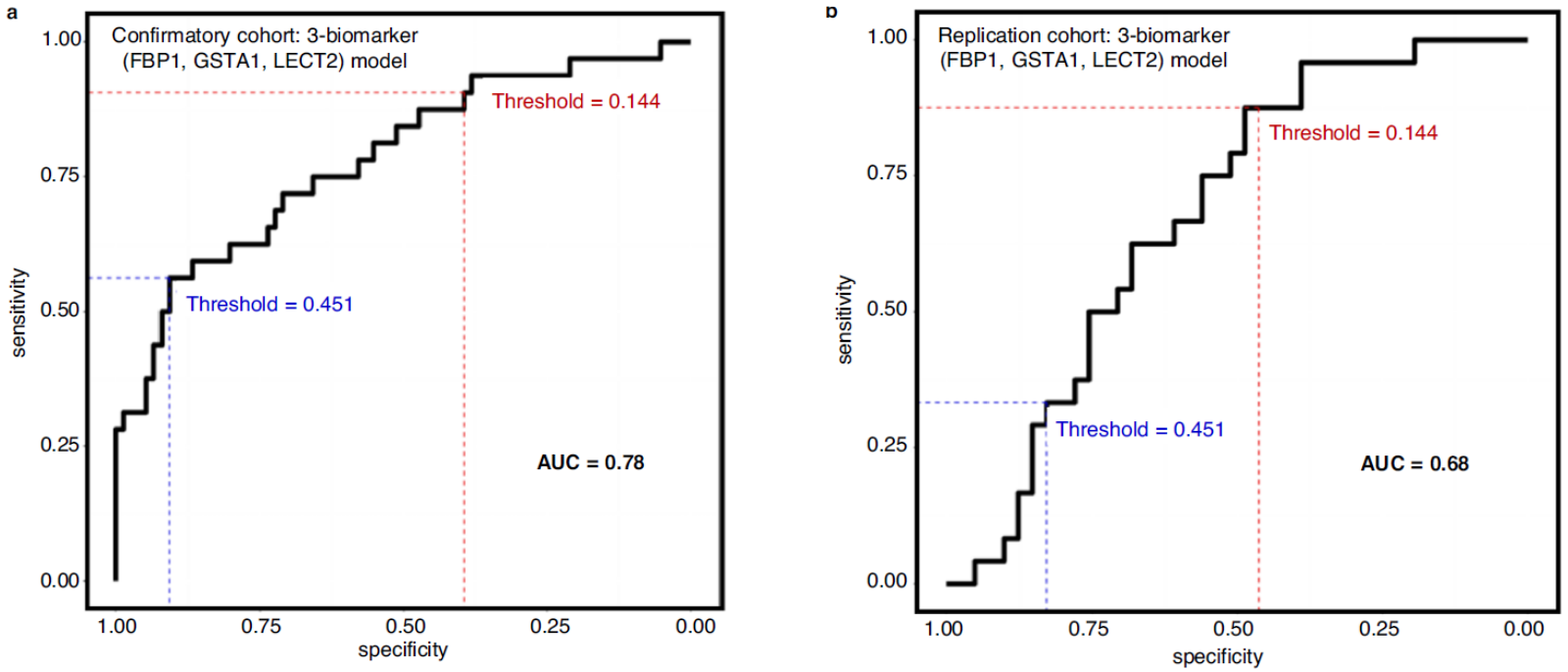
Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

Modelos multivariantes para distinguir NDO vs DO

Method	Biomarkers/Models	AUC of confirmatory cohort between NDO vs. DO	AUC of replication cohort between NDO vs. DO
Logistic regression	FBP1 + GSTA1	0.75	0.69
	FBP1 + GSTA1 + LECT2	0.78	0.68
	FBP1 + CES1 + LECT2	0.78	0.64
Random forest	FBP1 + LECT2	1.00	0.64
	FBP1 + LECT2 + CPS1	1.00	0.61

Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

Modelos multivariantes para distinguir NDO y DO



Mejor modelo: **FBP1 + GSTA1 + LECT2**
No mejoraba cuando añadieron ALT

Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

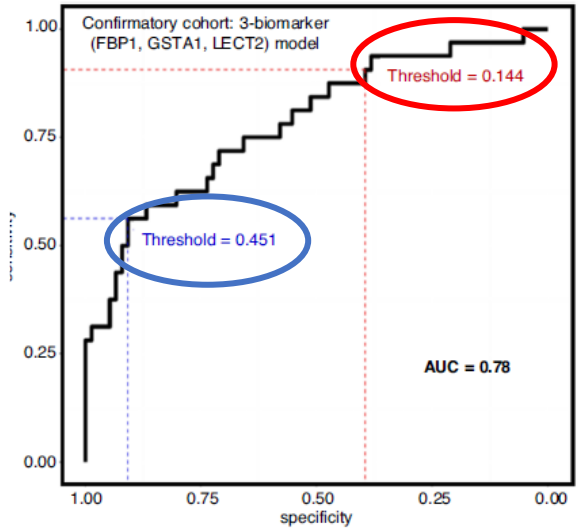
Aplicación clínica

“Screen–and-confirm approach”

- Usar biomarcadores convencionales para identificar daño hepático
- Usar nuevos biomarcadores para “confirmar” DILI

FBP1 + GSTA1 + LECT2

- Valores “cut-off” con especificidad y sensibilidad alto identificados



Usar para “rule-out” o “rule-in” DILI

Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

Aplicación clínica. Ejemplos

1. Breau et al. 2019: 11.3% de pacientes con ALT o AST >1000 IU/L son DILI

Probabilidad de DILI antes prueba con nuevo modelo: 11.3%
Usando el valor de cut-off 0.45
Probabilidad de DILI después prueba con nuevo modelo (+): 21%

2. Donaghy et al. 2013: 15% de pacientes con ictericia son DILI

Probabilidad de DILI antes prueba con nuevo modelo: 15%
Probabilidad de DILI después prueba con nuevo modelo (+): 27%

3. Suzuki et al. 2022: 35% de pacientes con ALT ≥ 5 xLSN o FA ≥ 2 xLSN dentro de 90 días después comenzar tratamiento con amoxicilina-clavulánico son DILI

Probabilidad de DILI antes prueba con nuevo modelo: 35%
Probabilidad de DILI después prueba con nuevo modelo (+): 53%

Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

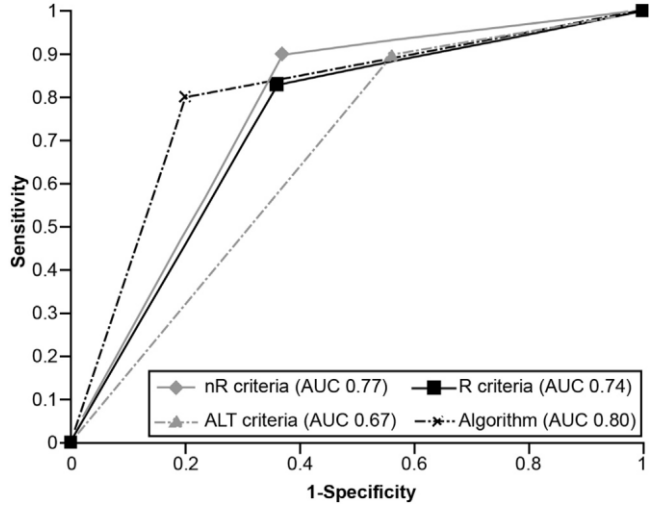
Prediciendo el riesgo de fallo hepático fulminante en DILI: Hy´s Law

- Hyman Zimmerman (1960'): combinación de **ictericia** and **lesión** hepática de tipo **hepatocelular** en DILI predecía un **10%–50% mortalidad** debida a fallo hepático

- Definición de los casos "Hy's Law " usada por la FDA en desarrollo de fármacos: ALT> 3 LSN y BT > 2 LSN sin elevación significativa de la FA (1-2 casos que cumpliesen Hy's law predecían numerosos casos de fallo hepático y muerte si el fármaco llegaba al mercado).

"Nueva Hy's Law" propuesta por el Spanish DILI Registry: nR [(ALT o AST cual sea mas elevada/LSN)/(FA/LSN)] >5 + BT>2 LSN[1]

	ALT >3 ULN; TBL >2 ULN	R ≥5; TBL >2 ULN	nR ≥5; TBL >2 ULN
Sensitivity	90%	83%	90%
Specificity	44%	67%	63%
AUROC	0,67	0,74	0,77

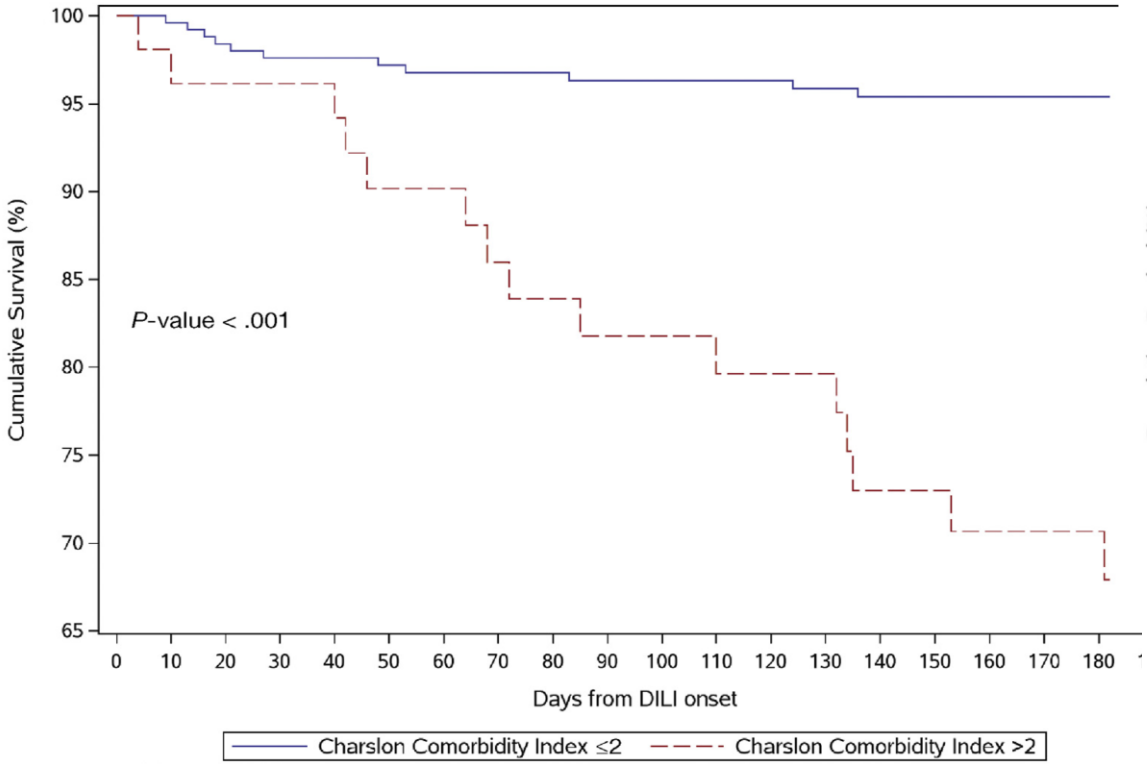


La nR Hy's law identificó mejor el riesgo de muerte que la Hy's law tradicional en una cohorte de DILI independiente[2]

1. Robles–Diaz,.., Andrade RJ. *Gastroenterology* 2014;147:109–118
2. Hayashi, et al. *Hepatology,* 2017; 66:1275-1285

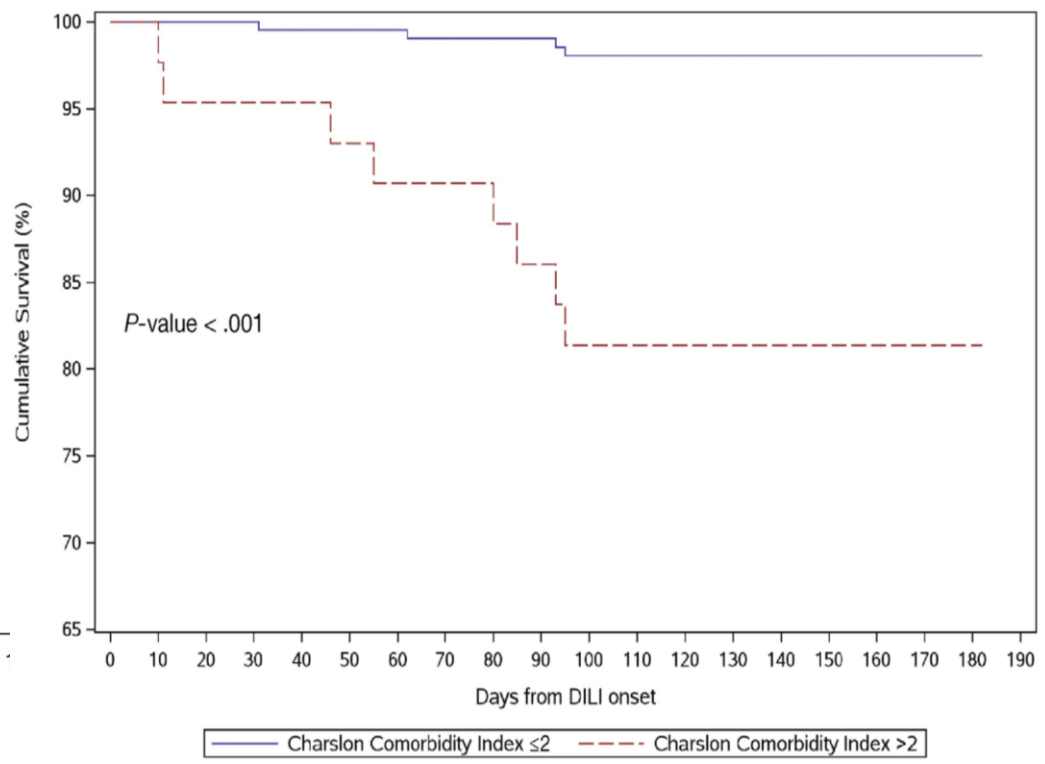
Otros factores pronósticos en DILI (mas allá de la Hy's law): comorbilidad

Indiana cohort



Participants at risk							
CCI ≤ 2	253	238	227	216	211	206	188
CCI > 2	53	49	43	39	36	31	26

North Carolina cohort



Participants at risk							
CCI ≤ 2	220	214	206	199	195	188	180
CCI > 2	43	41	39	37	35	33	32

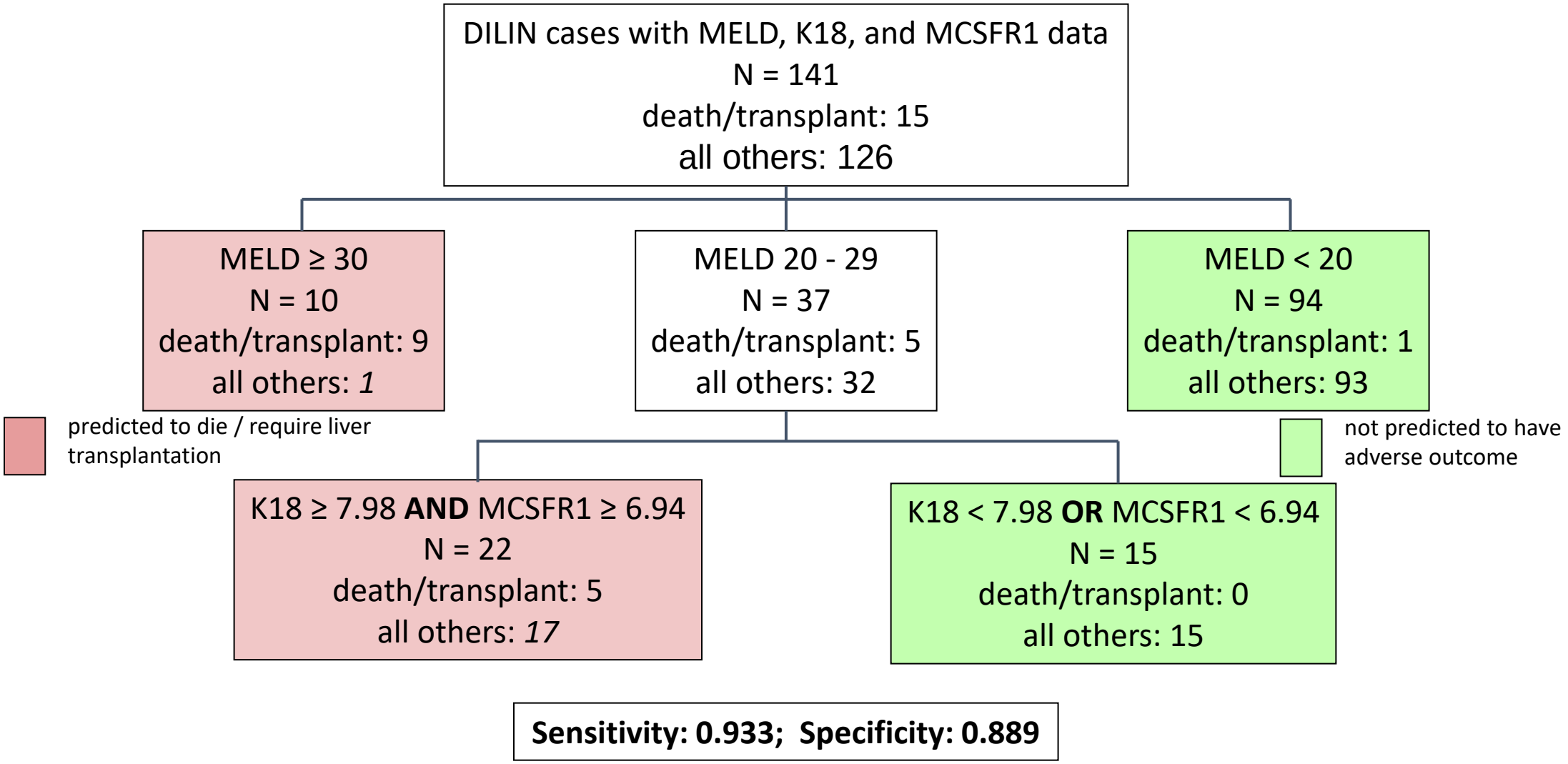
Ghabril M, et al. *Gastroenterology* 2019; 1

Factors at Presentation Associated With 6-Month Overall Mortality in Patients With Suspected Drug-Induced Liver Injury (n=306)

	Simple logistic regression		Multiple logistic regression	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Comorbidity category				
Reference category none/mild comorbidity (CCI >2)	---	---	---	---
Significant comorbidity (CCI >2)	8.7 (3.7–20.3)	<.0001	5.6 (2.2–14.1)	<.001
MELD	1.14 (1.08–1.20)	<.0001	1.10 (1.04–1.17)	<.001
Albumin, g/dL	0.26 (0.15–0.46)	<.0001	0.40 (0.20–0.78)	.007
Age, y	1.03 (1.005–1.054)	0.02	---	---

Ghabril M, et al. *Gastroenterology* 2019; 157:1245-1252.e3.

Incorporación de K18 y MCSFR1 al MELD



Church RJ,...; Andrade RJ, et al. *Hepatology* 2019; 69: 760-773

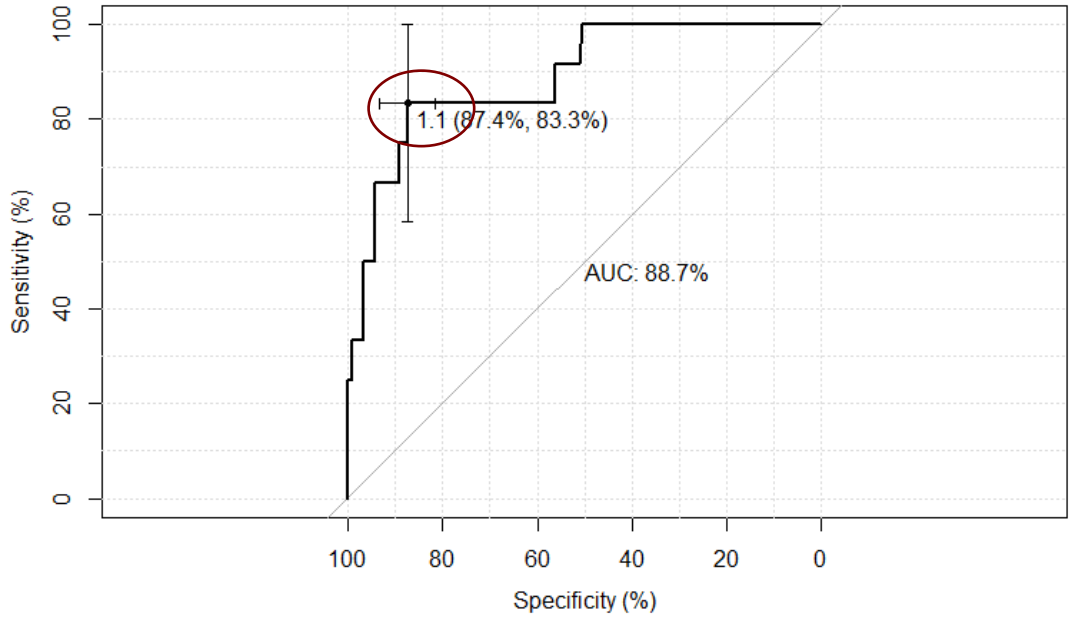
Predictores de cronicidad en DILI: resultados en 298 pacientes

	Acute, ≤1 year (N=273)	Chronic, >1 year (N=25)	*p* value
Female n (%)	151 (55)	16 (64)	0.4
Age mean y (range)	52 (14-88)	63 (30-83)	**0.002**
Clinical presentation, n (%)			
Jaundice	156 (58)	20 (80)	**0.032**
Hospital admission	110 (45)	17 (77)	**0.004**
Type of liver injury, n (%)			0.6
Hepatocellular	185 (68)	15 (60)	
Mixed	44 (16)	4 (16)	
Cholestatic	44 (16)	6 (24)	
Laboratory parameters at onset, mean (range)			
Total Bilirubin (mg/dL)	5 (0.13-33)	7 (0.4-28)	0.1
ALT (x ULN)	19 (0.6-134)	20 (2.5-71)	0.9
GGT (xULN)	7 (0.2-49)	14 (0.3-79)	0.08
ALP (x ULN)	1.8 (0.2-16)	3 (0.4-11)	**0.05**
Severity, n (%)			**0.003**
Mild + moderate	261 (97)	21 (84)	
Severe	9 (3)	4 (16)	
Associated diseases, n (%)			
Diabetes	27 (10)	7 (28)	**0.006**
Hypertension	31 (25)	10 (50)	**0.019**
Dyslipidemia	36 (13)	11 (44)	**<0.001**

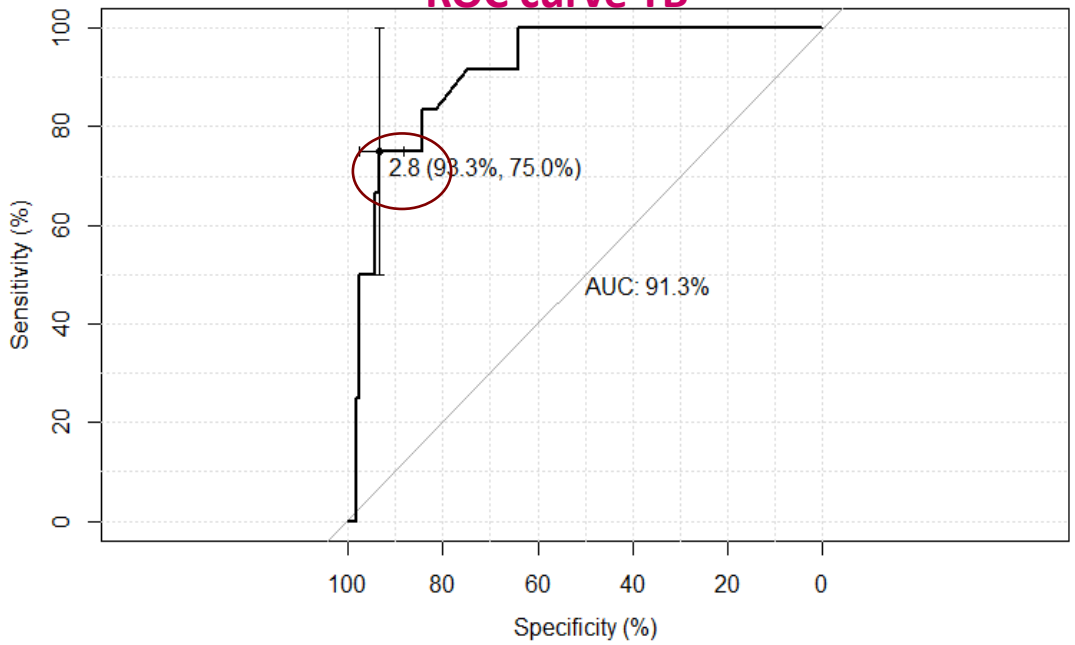
Medina-Cáliz I,…, Andrade RJ. *J Hepatol* 2016; 65:532-42.

Predictores de cronicidad en DILI: resultados en 298 pacientes

ROC curve ALP



ROC curve TB



Laboratory parameters at 30-60 days from DILI onset

ALP	ACUTE N=119	CHRONIC N=12	*p*<0.001
≤1.1	104	2	
>1.1	15	10	

Specificity: 87.4%
Sensitivity: 83.3%

Specificity: 93.3%
Sensitivity: 75%

TB	ACUTE N=120	CHRONIC N=12	*p*<0.001
≤2.8	112	3	
>2.8	8	9	

Medina-Cáliz I,…, Andrade RJ. *J Hepatol* 2016; 65:532-42.

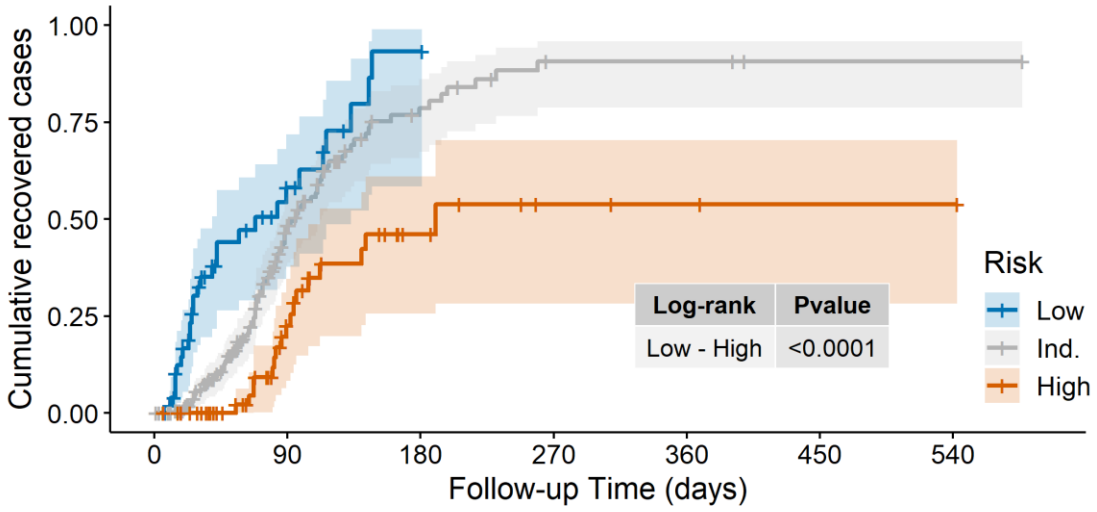
Clinical factors and drug properties associated with prolonged recovery from drug-induced liver injury

Development of Recovery Score Model

iDILIC cohort (N=294)

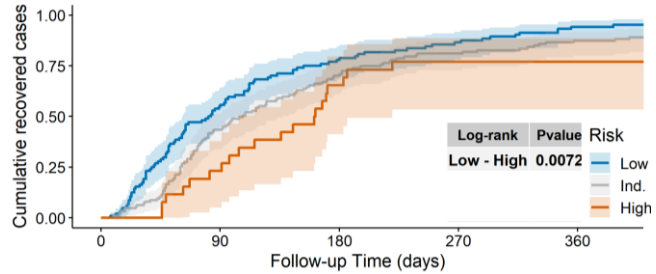
Accelerated failure time analysis of clinical factors and drug properties

$$\text{Score} = 0.227 \times \log_e(\text{ALP}) + 0.277 \times \log_e(\text{Bilirubin}) + 0.161 \times \log_e(\text{Onset}) - 0.440 \times \text{extent of metabolism}$$

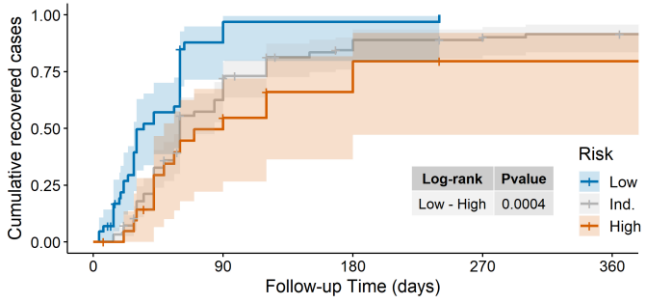


External Validations

Spanish DILI Cohort (N=257)



LiverTox Cohort (N=191)



Chen M,…, Andrade RJ,..,et al. *J Hepatol* 2021

Tratamiento

- Medidas generales **¡Interrumpir cualquier fármaco no esencial!**
- Pacientes **asintomáticos podrían no requerir ingreso hospitalario**: vigilancia estrecha
- Contactar de inmediato con un centro de trasplante si encefalopatía y/o INR > 1.5
- Ausencia de evidencia basada en estudios controlados
- Tratamiento específico para algunas situaciones: ***colestiramina*** *para la hepatotoxicidad por leflunomida y* ***carnitina*** *para el daño hepático por ácido valpróico*
- Tratamientos no-específicos indicados para el DILI

- **Colestiramina**: prurito
- **Esteroides**: manifestaciones de hipersensibilidad, evolución mas grave?
- **Ácido ursodeoxicólico** : Colestasis severa o prolongada
- **Molecular adsorbent recirculating system (MARS)**: usado anecdóticamente para la ictericia intensa y el prurito

EASL CPG DILI. *J Hepatol* 2019; 70:1222-61.

Systematic review and meta-analysis of RCT for DILI prevention and management

"drug-induced liver injury" OR "drug-induced hepatotoxicity" OR "acute liver failure" AND "preven*" OR "manag*" OR "treat*" OR "trial"

- Randomised clinical trials
- Use of pharmacological or herbal treatment on the prevention or management of DILI
- Explain the methodology of the trial

- PubMed
- MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Web of Science
- OpenGrey

Hao N,…, Andrade RJ. *Pharmacol Res* 2021; Feb;164:105404. doi: 10.1016/j.phrs.2020.105404

Challenges in clinical trials in drug-induced liver injury (DILI)

- Rarity of the condition
- Lack of specific diagnostic tests
- Different phenotypic presentations

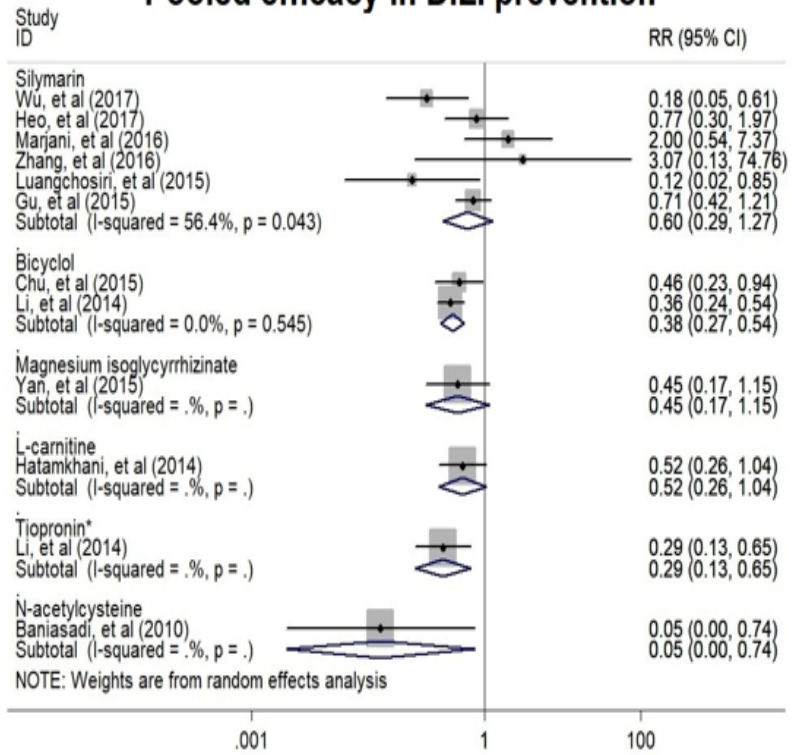
Literature search (2,268 records)

Pubmed, Web of Science, MEDLINE, Embase, CENTRAL, OpenGrey

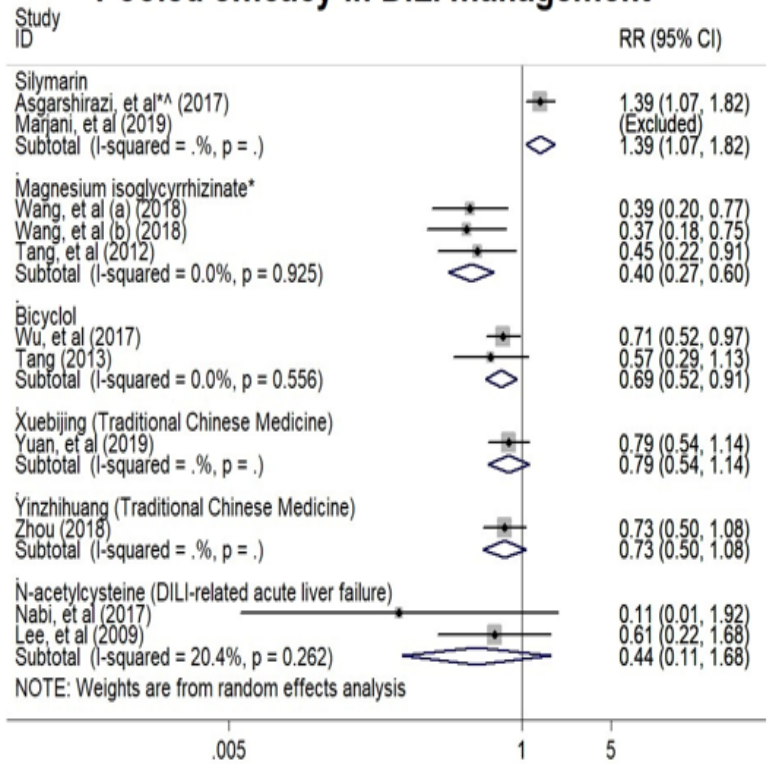
22 randomised clinical trials (RCT)

Characteristics	Trials (N)	Patients (N)
LOCATION		
Asian countries	21	3,223
United States of America	1	45
PHARMACOLOGICAL/HERBAL AGENTS		
Prevention	**12**	**2,471**
Silymarin	6	1,398
Bicyclol	2	531
Magnesium isoglycyrrhizinate	1	216
L-Carnitine	1	116
N-acetylcysteine	1	60
Tiopronin	1	150
Management	**10**	**797**
Silymarin	2	109
Bicyclol	2	209
Magnesium isoglycyrrhizinate	2	229
N-acetylcysteine	2	60
Traditional Chinese medicines	2	190

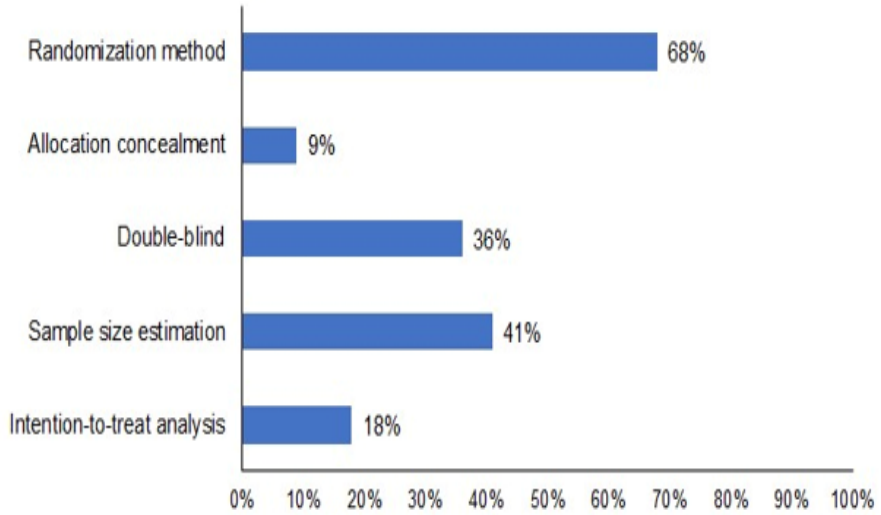
Pooled efficacy in DILI prevention



Pooled efficacy in DILI management



Methodology assessment of the included clinical trials



- Heterogeneity in DILI case qualification confounded by low thresholds.
- Heterogeneous and not clinically robust endpoints and methodological flaws
- The analysed clinical trials demonstrated limited efficacy of specific interventions
- To establish a framework on RCTs design and therapeutic endpoints international research networks are essential

Hao N,…, Andrade RJ. *Pharmacol Res* 2021; Feb;164

Tratamiento empírico de pacientes con DILI: datos del Spanish DILI Registry

	Steroids (N=66)	UDCA (n=50)	MARS (n=12)	No treatment (n=497)	p value
Age (years), mean±SD (range)	53±20 (16-88)	55±18 (17-91)	41±18 (20-73)	54±18 (11-90)	0.170
Jaundice, %	89	88	100	65	**<0.001**
Hospitalization, %	91	67	100	46	**<0.001**
Hypersensitivity features, %	48	51	83	40	**0.010**
Total bilirubin	15±11	17±12	30±17	8±9	**<0.001**
Alanine aminotrasferase	24±30	21±25	12±9	21±24	0.824
Aspartate aminotransferase	21±23	20±31	11±15	18±25	0.317
Alkaline phosphatase	2.8±3.0	3.3±3.4	2.8±2.3	2.2±2.1	**0.001**
Outcome					
Liver-related death, n (%)	4 (6.1)	3 (6.0)	1 (8.3)	9 (1.8)	**0.011**
Liver transplantation, n (%)	2 (3.0)	1 (2.0)	1 (8.3)	1 (0.2)	**0.011**

Stephens C,.. Andrade RJ. *J Hepatol* 2021; S0168-8278(21)00043-X. doi: 10.1016/j.jhep.2021.01.029.

Corticosteroids in DILI: a propensity score matching

Corticosteroid therapy (n=106)

No treatment (n=618)

In the univariate comparison, patients treated with corticosteroids had:

- ↑ AST values
- ↑ Total bilirubin values
- ↑ Positive autoantibodies

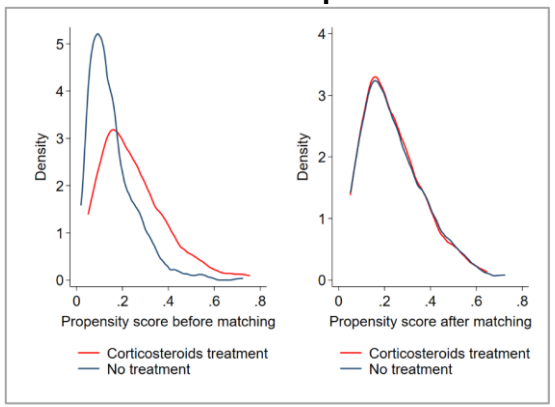
In the univariate analysis, corticosteroids were associated with higher frequency of ALF
OR = 3.05; 95% CI 1.20 – 7.75;
p = 0.019

PANISH DILI REGISTRY

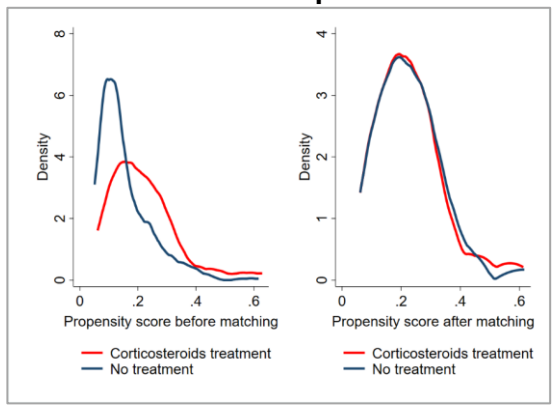
INDIANA UNIVERSITY SCHOOL OF MEDICINE

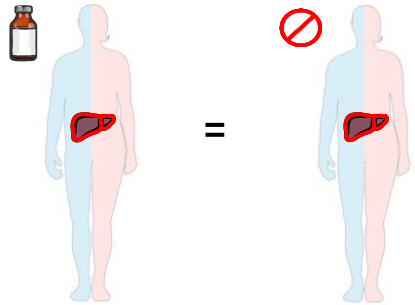
Propensity score matching

80 matched pairs



41 matched pairs





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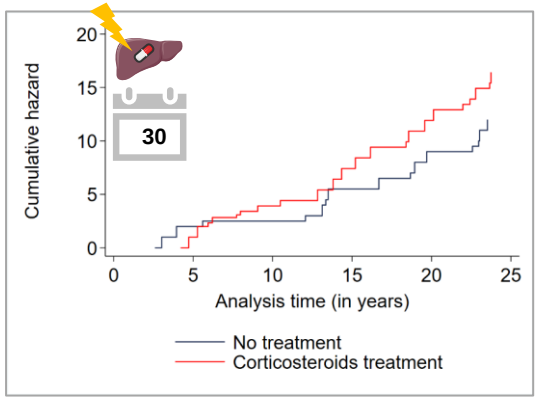
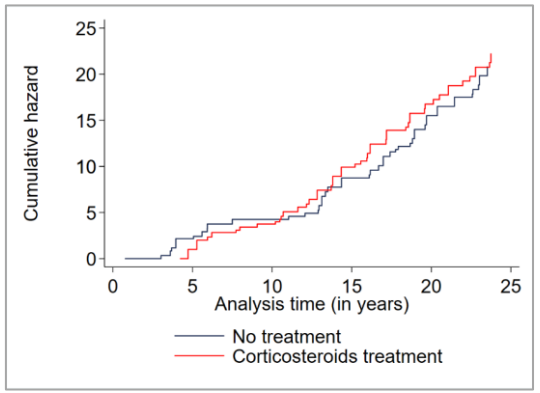
Corticosteroid therapy does not increase the risk of liver-related mortality
OR = 0.58; 95% CI 0.11 – 3.13; p = 0.527





Analysis time refers to origin of time-scale and starts when the first DILI patient was enrolled.

Corticosteroid use increase the normalization rate of liver enzymes
HR = 2.17; 95% CI 1.23 – 3.83;
p = 0.007

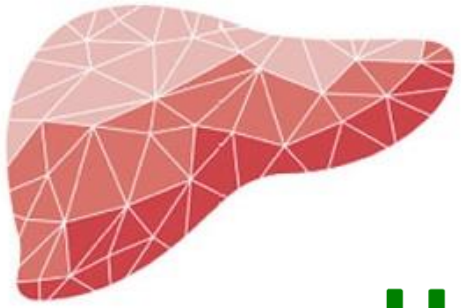
Benefit more evident in patients with severe injury (nR-based Hy's law) and no resolution ≤ 30 days
HR = 2.88; 95% CI 1.23 – 6.73;
p = 0.015

Niu H, Ma J, …,Alvarez-Alvarez I, Andrade RJ. *Alim Pharmacol Ther* 2023

Conclusiones

- La hepatotoxicidad es una enfermedad hepática de diagnóstico incierto y requiere de un abordaje sistemático y ordenado.
- Biomarcadores solubles en investigación y test genéticos pueden incrementar la certeza diagnóstica en casos específicos
- Diversos scores y variables clínicas y analíticas pueden refinar la predicción pronóstica del DILI
- Ningún tratamiento ha demostrado prevenir el DILI o reducir la mortalidad asociada, aunque los esteroides pueden ser útiles en casos graves.

MÁSTER EN HEPATOLOGÍA



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