Hepatotoxicidad: actualización 2023

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University Hospital of Málaga
Spain

Agenda

- Análisis proteómico de biomarcadores
- Amoxicilina-clavulánico: epidemiología y variantes genéticas
- Metrotexato y riesgo de fibrosis hepática
- DILI autoinmune
- Corticoides en el tratamiento del DILI

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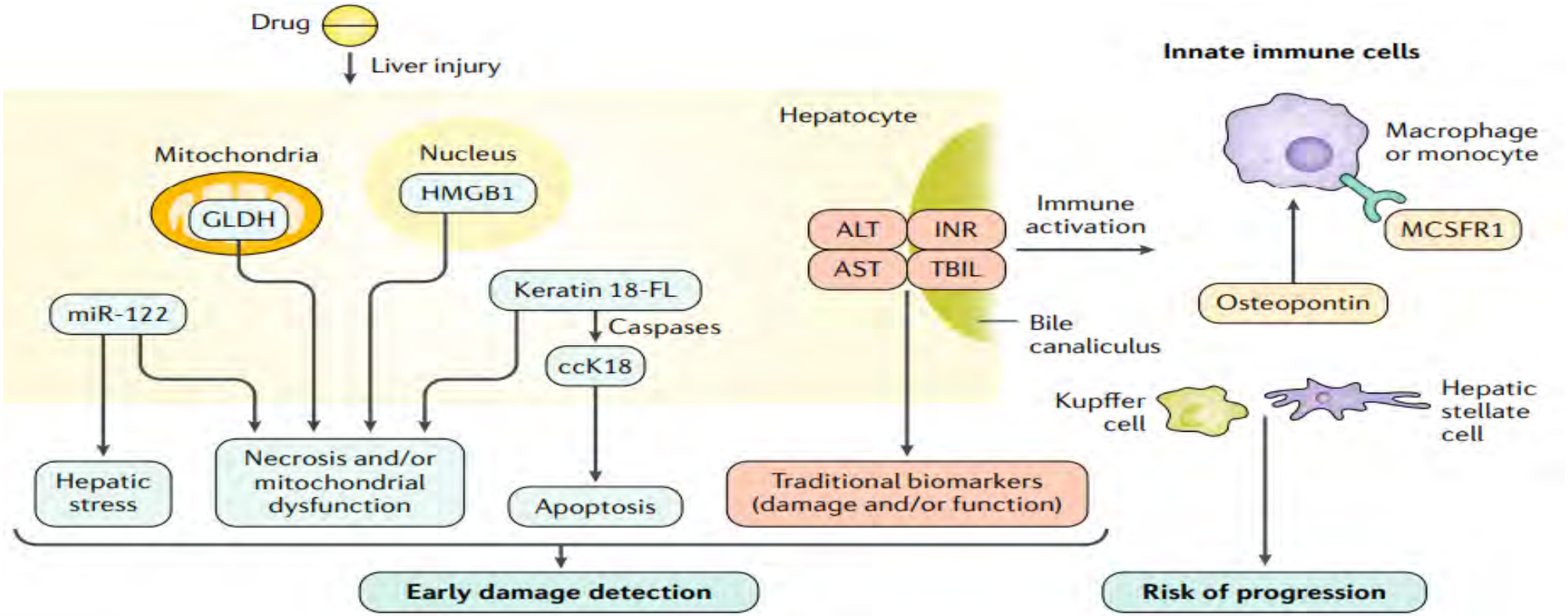
Nuevos biomarcadores en DILI



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

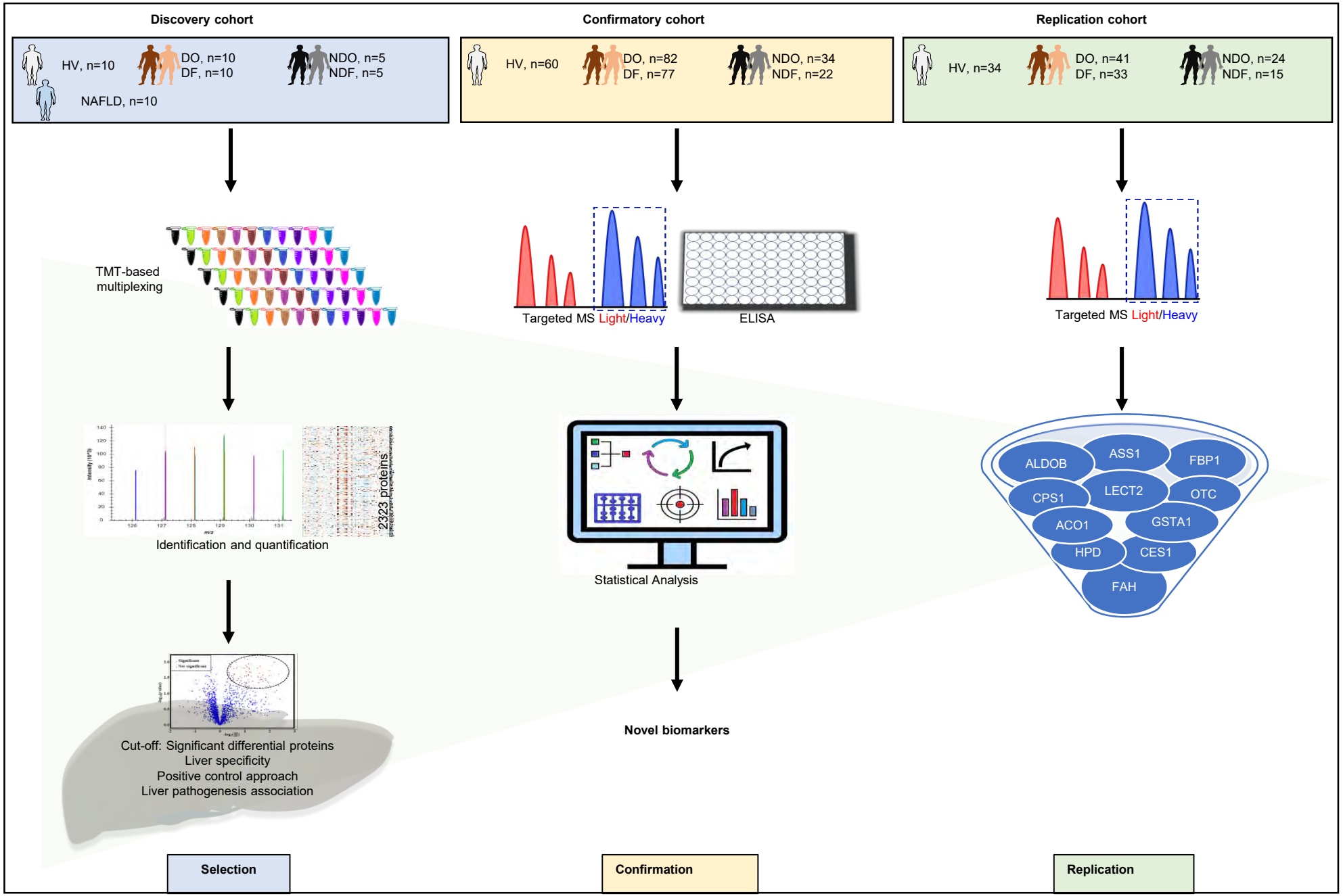
Received: 2 June 2022

Accepted: 16 February 2023

Published online: 03 March 2023

Check for updates

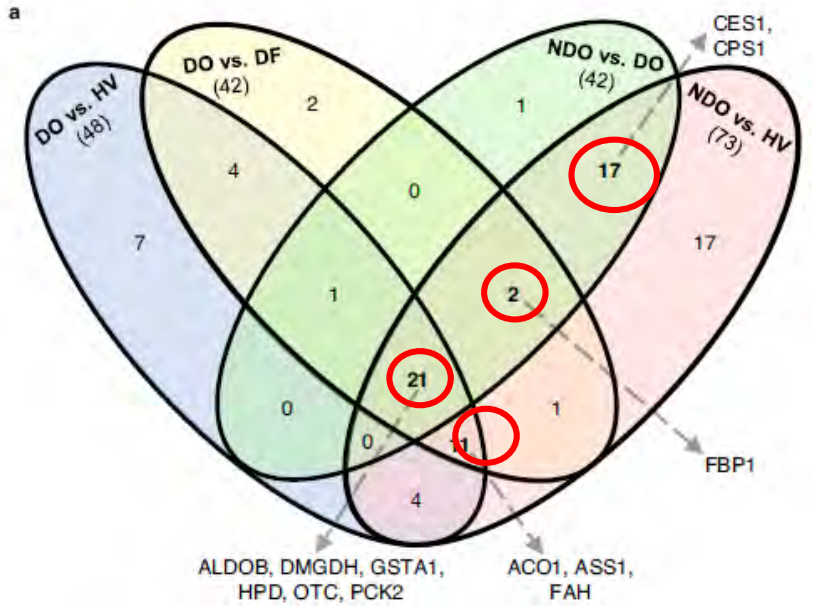
Kodihalli C. Ravindra[1,18], Vishal S. Vaidya[1,18,19] ✉, Zhenyu Wang[1], Joel D. Federspiel[1], Richard Virgen-Slane[1], Robert A. Everley[1], Jane I. Grove[2,3], Camilla Stephens[4,5], Mireia F. Ocana[1], Mercedes Robles-Díaz[4,5], M. Isabel Lucena[4,5], Raul J. Andrade[4,5], Edmond Atallah[2,3], Alexander 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

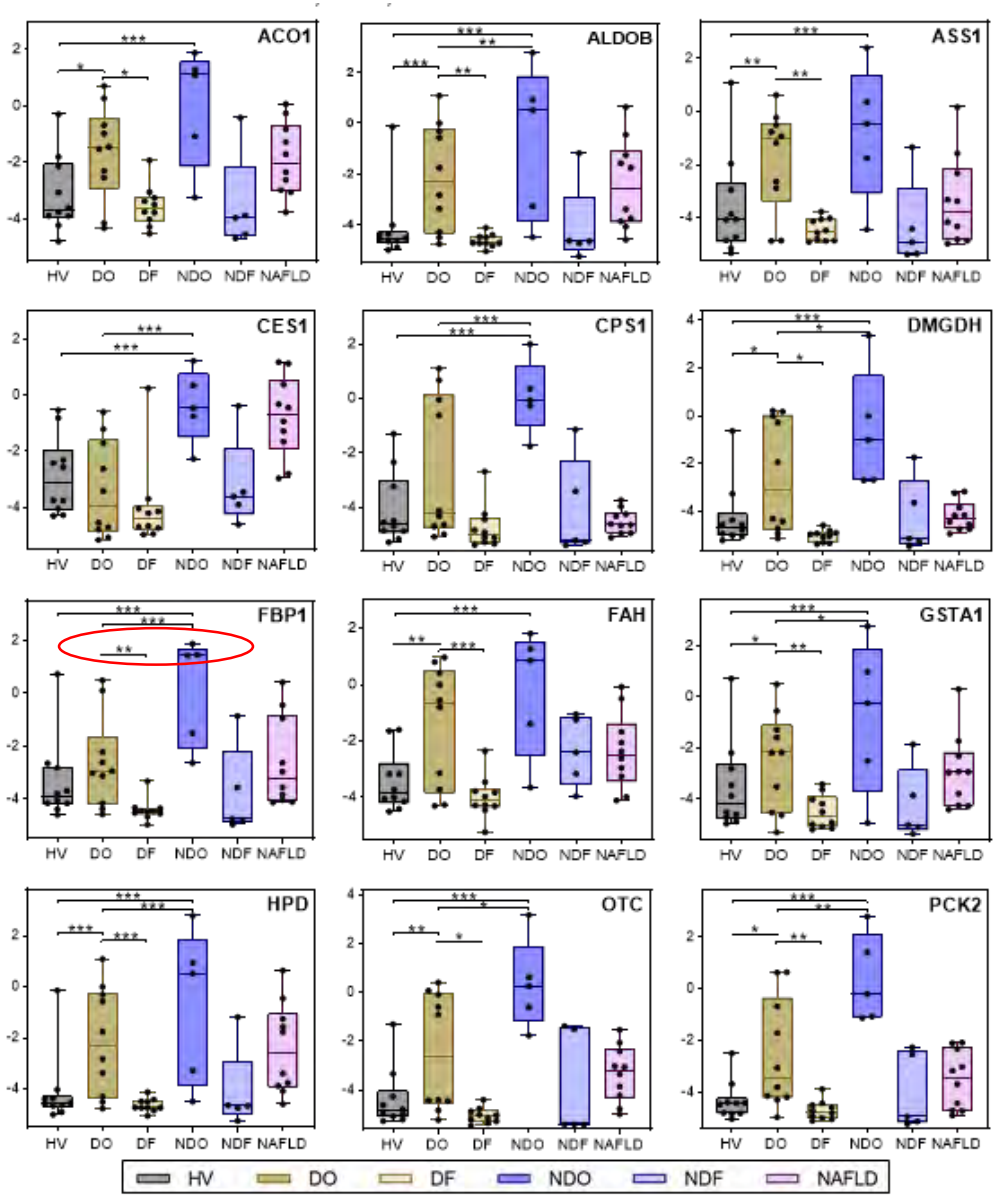
- 2323 proteínas identificados en la cohorte de descubrimiento
- 89 proteínas expresadas diferencialmente (DO vs HV, DO vs DF, NDO vs DO, NDO vs HV
- 51 presentes en al menos dos comparaciones



- 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

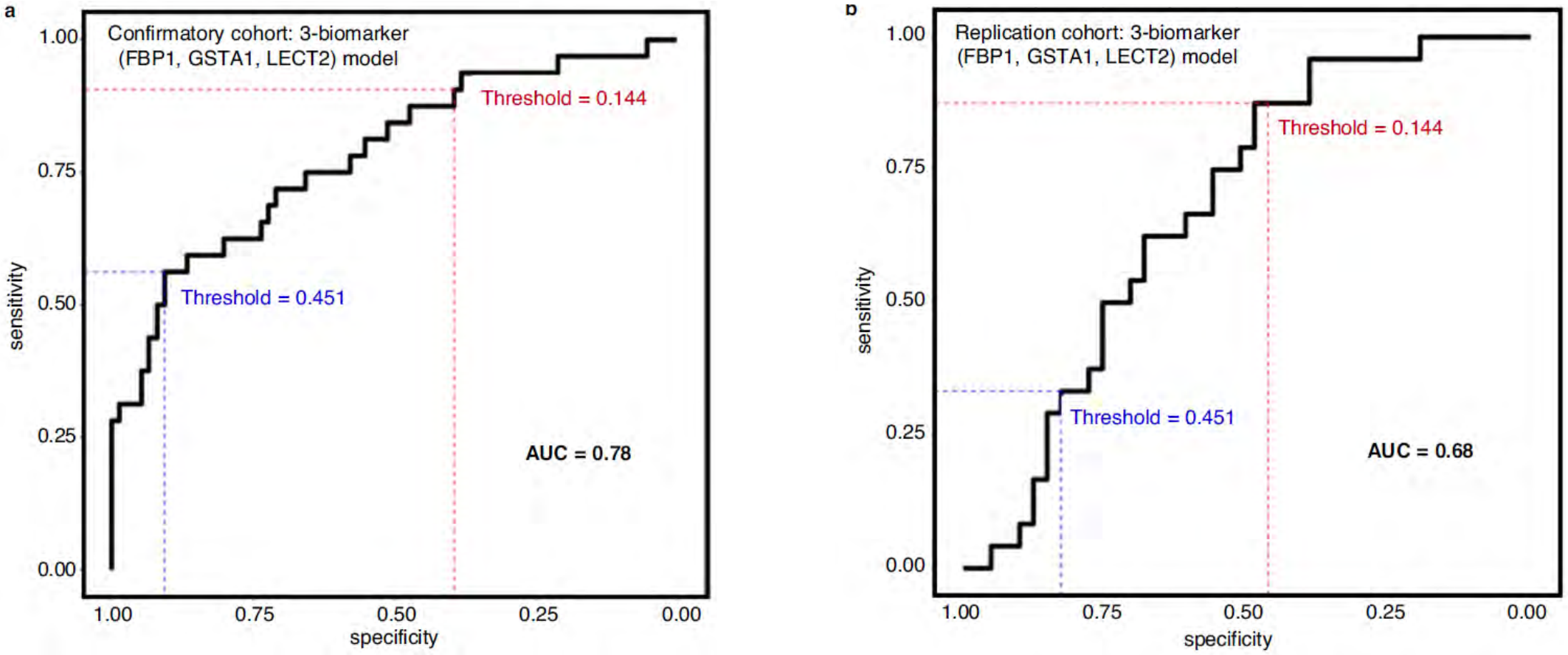
Ravindra K,.. Andrade RJ,…Nat Commun. 2023;14:1215. doi: 10.1038/s41467-023-36858-6.

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.

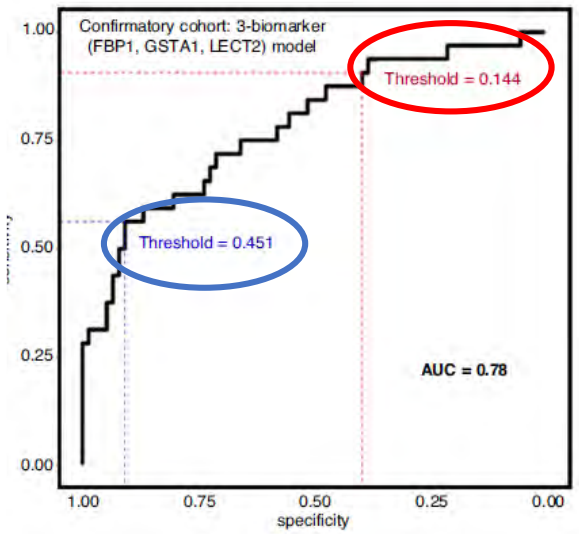
Aplicación clínica

“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.

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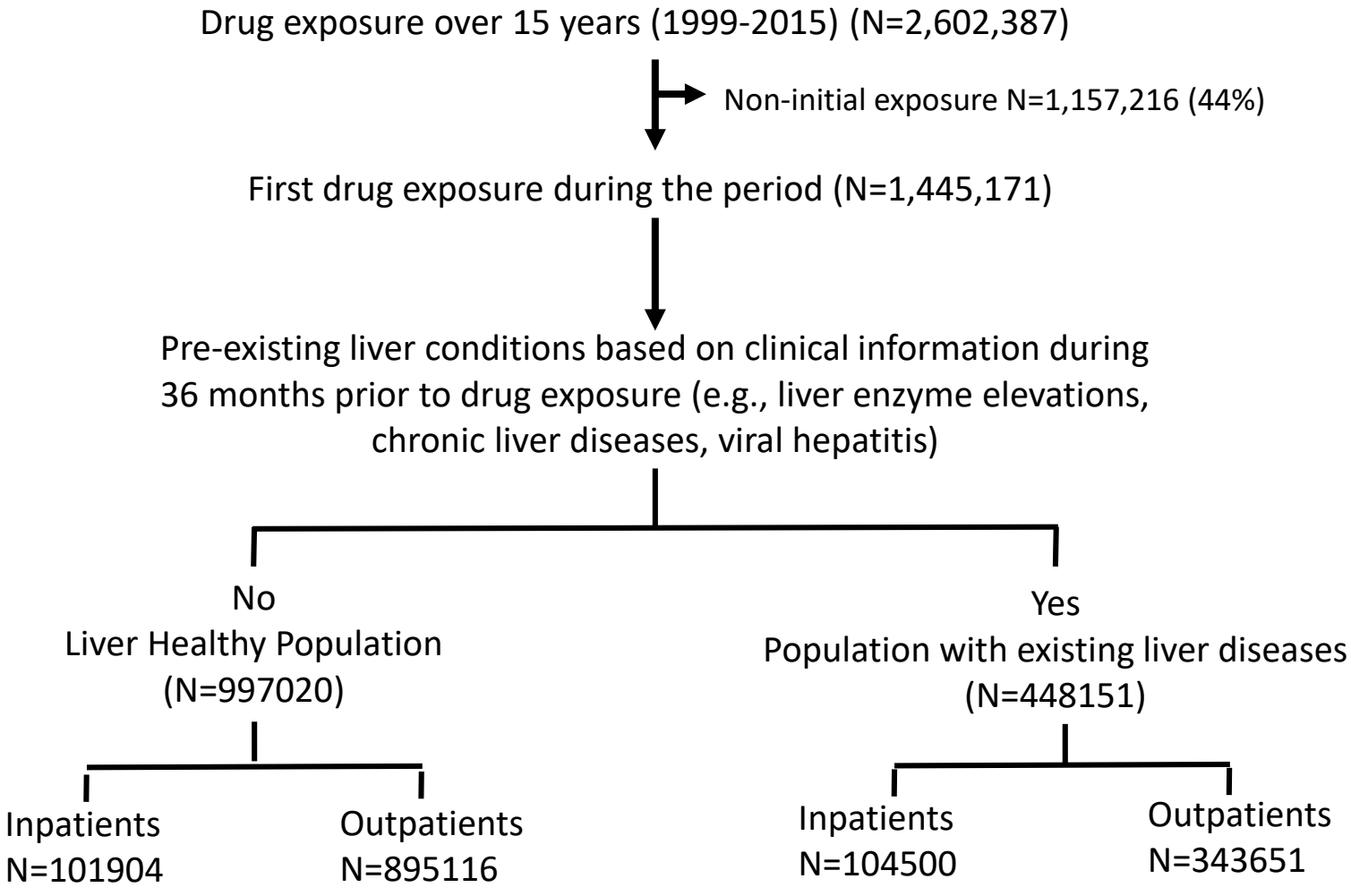
Drug Safety

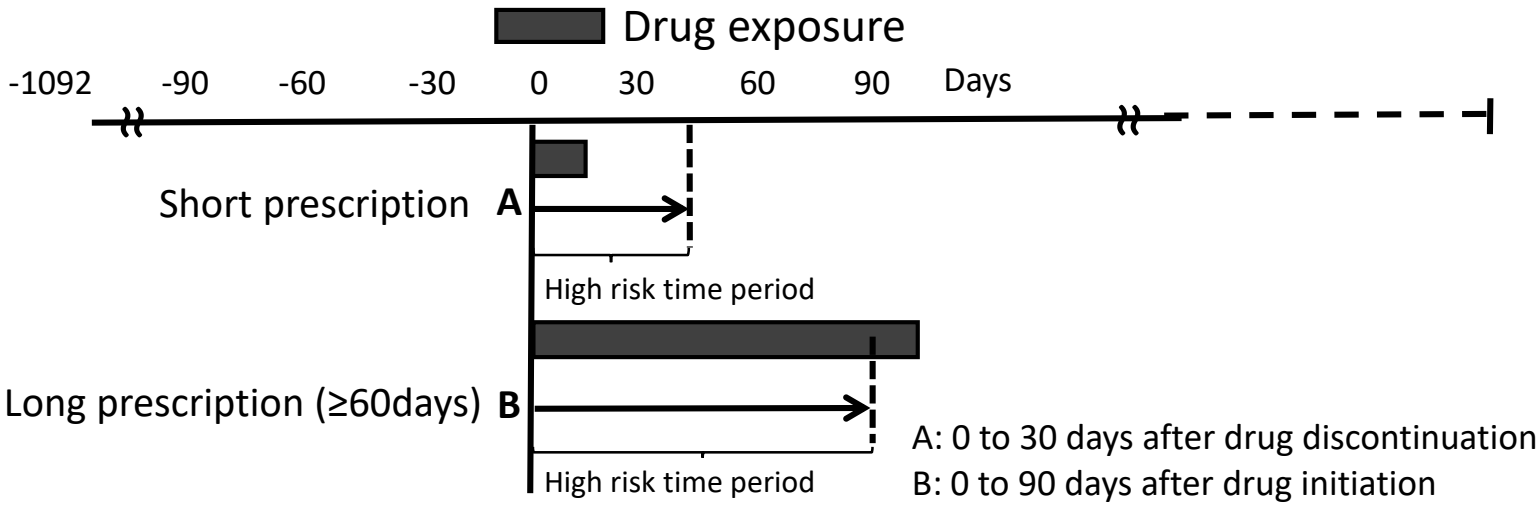
Assessment of the frequency, phenotypes, and outcomes of acute liver injury associated with amoxicillin/clavulanate in 1.4 million patients in the Veteran Health Administration

Ayako Suzuki, Hans Tillmann, James Williams, Ronald G. Hauser, Julie Frund, Mizuki Suzuki, Fred Prior, Guruprasad P. Aithal, M. Isabel Lucena, Raúl J. Andrade, Weida Tong, Christine M. Hunt



Suzuki, et al. *Drug Saf.* 2023;

Acute liver injury associated with amoxicillin/clavulanate in 1.4 million patients in the Veteran Health Administration



Baseline liver enzymes

- No test: use ULN
- Normal: use ULN
- Abnormal: median or mean values within 36 months, or ULN, whichever is higher

High risk period

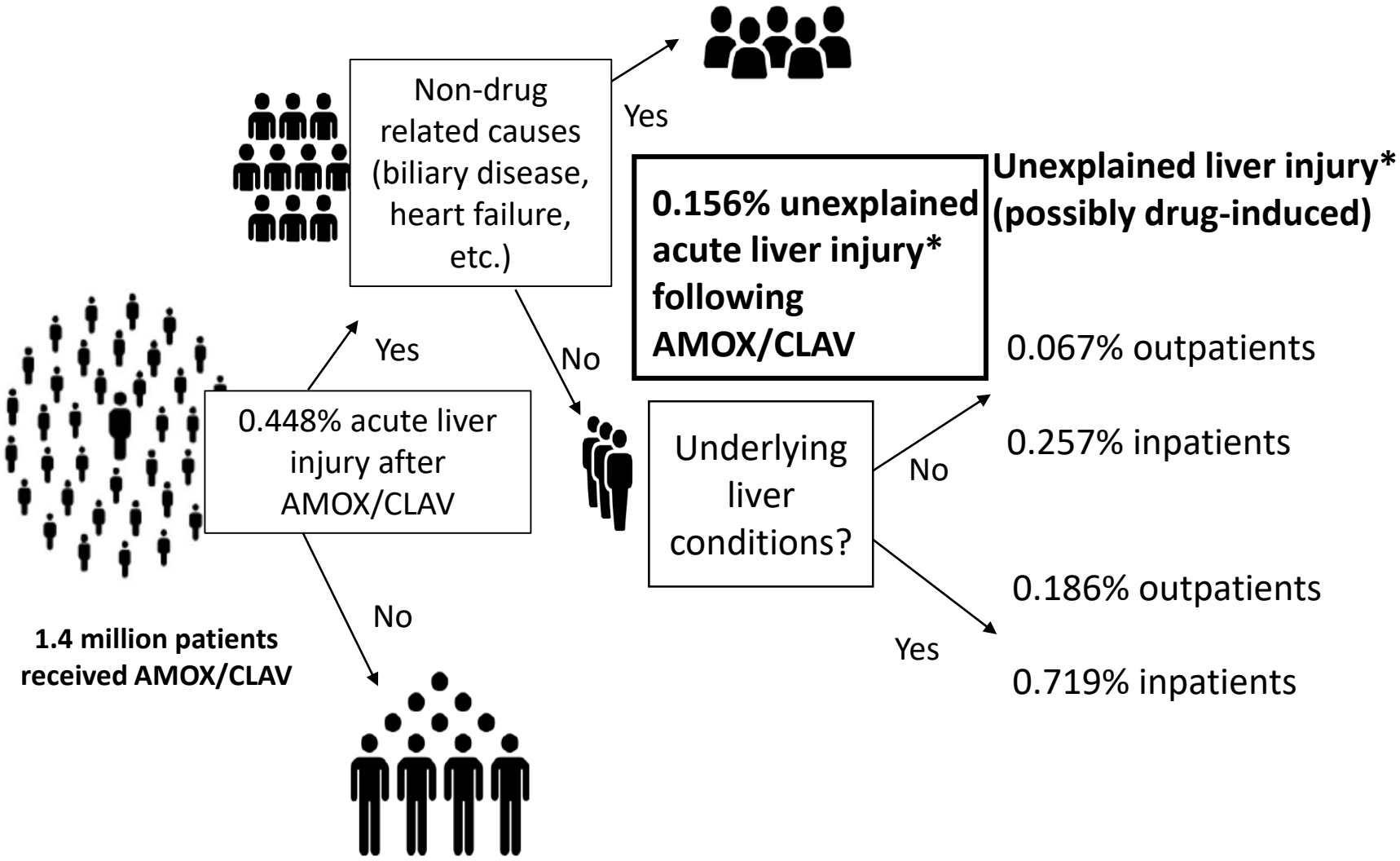
- Acute liver injury identification: ALT>5 ULN/BLM or ALP>2 ULN/BLM
- Exclude acute liver injury with competing causes within 90 days after liver event

2 year outcome follow-up

- 24 months after the event (cases) or after exposure (non-cases)
- Death (6, 12, 24 months)

Suzuki, et al. *Drug Saf.* 2023;46:129-143

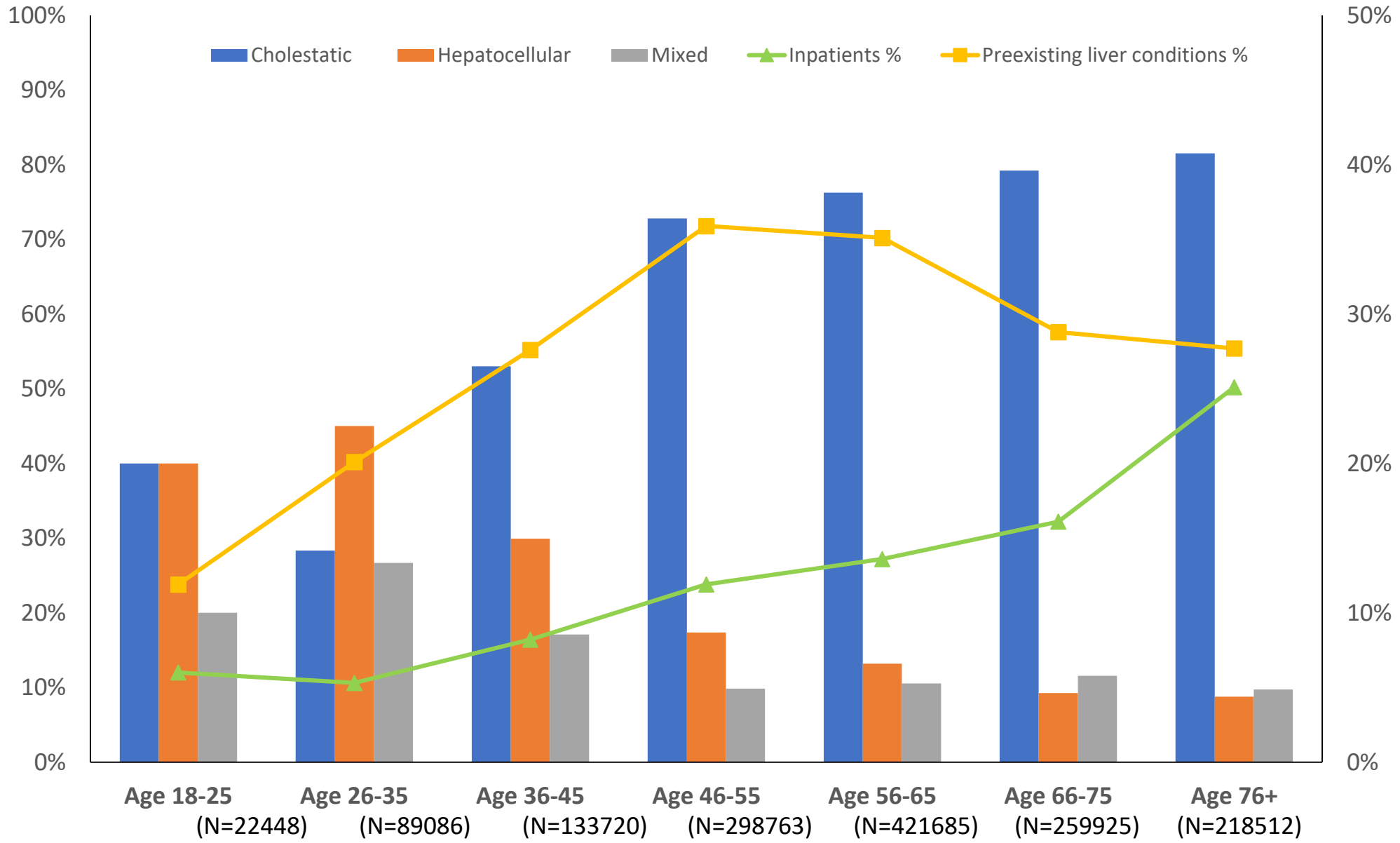
Acute liver injury associated with amoxicillin/clavulanate in 1.4 million patients in the VHA



*ALT≥5x upper limits normal (or baseline); or
alk phos≥2x upper limits normal (or baseline)

Suzuki, et al. *Drug Saf.* 2023;46:129-143

Acute liver injury associated with amoxicillin/clavulanate in 1.4 million patients in the VHA

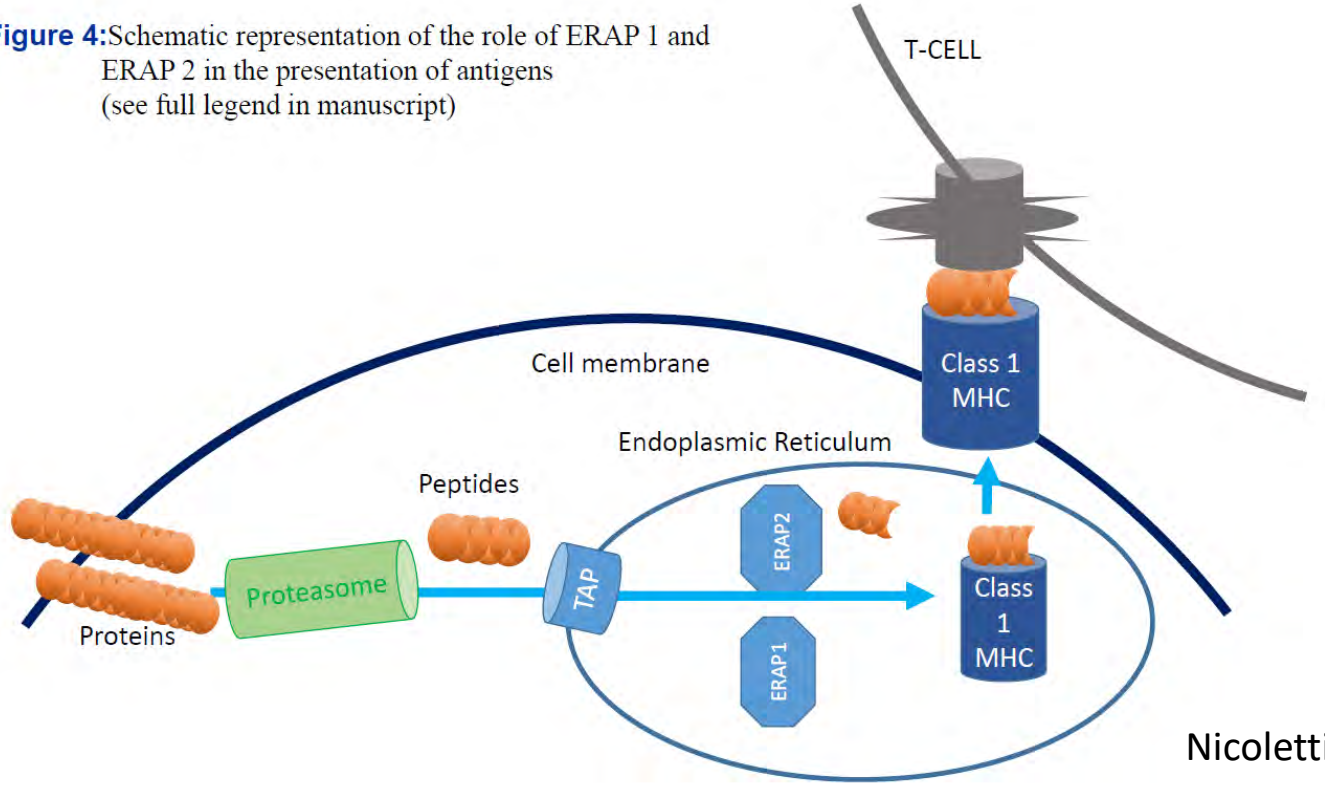


Suzuki, et al. *Drug Saf.* 2023;46:129-143

Identification of Reduced ERAP2 Expression and a Novel HLA Allele as Components of a Risk Score for Susceptibility to Liver Injury Due to Amoxicillin-Clavulanate

Paola Nicoletti,[1,§] Andrew Dellinger,[2] Yi Ju Li,[2,3] Huiman X. Barnhart,[2,3] Naga Chalasani,[4] Robert J. Fontana,[5] Joseph A. Odin,[6] Jose Serrano,[7] Andrew Stolz,[8] Amy S. Etheridge,[9] Federico Innocenti,[9] Olivier Govaere,[10] Jane I. Grove,[11,12] Camilla Stephens,[13,14,15] Guruprasad P. Aithal,[11,12] Raul J. Andrade,[13,14,15] Einar S. Bjornsson,[16,17] Ann K. Daly,[10] M. Isabel Lucena,[13,14,15] and Paul B. Watkins,[9,18,§] on behalf of Drug-Induced Liver Injury Network (DILIN), International Drug-Induced Liver Injury Consortium (iDILIC), Prospective European Drug-Induced Liver Injury (Pro-Euro DILI) Investigators

Figure 4: Schematic representation of the role of ERAP 1 and ERAP 2 in the presentation of antigens (see full legend in manuscript)



Nicoletti P…. Andrade RJ,…, Watkins PB. Gastroenterology 2023

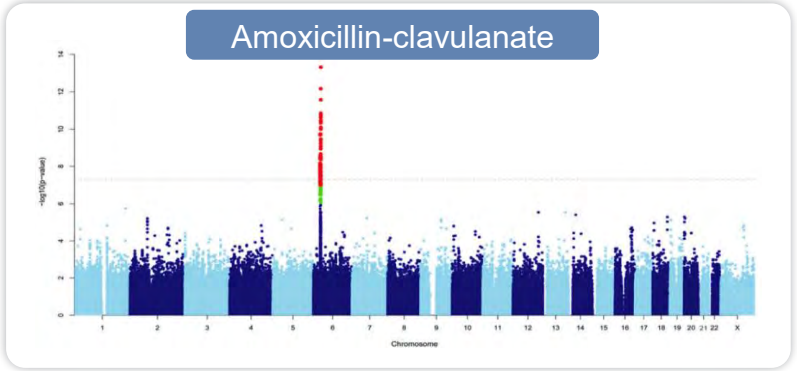
GENETIC BIOMARKERS (GWAS)

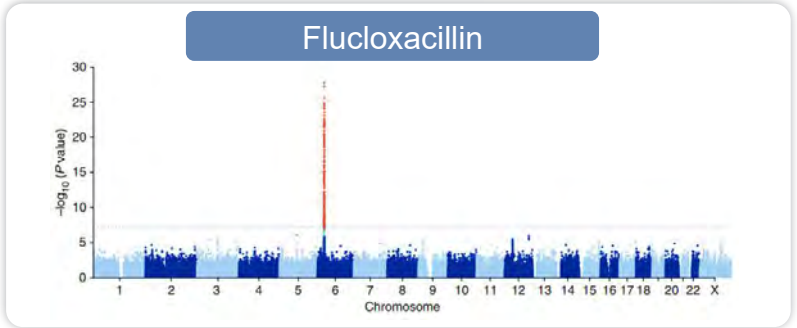
HLA

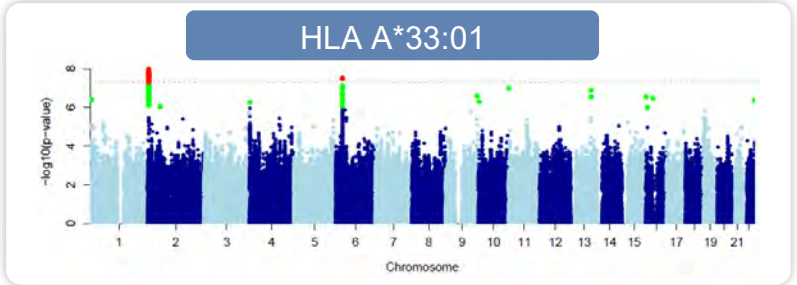
Test: HLA type	% positive in DILI cases	% + in 'normal' population
*DRB1*15:01 B* 1801, A* 0201*	57%-67% (Amoxicillin-clavulanate)	15%-20%
*B*57:01*	84%-87% (Flucloxacillin)	6%
*A*31:01*	17% (Carbamazepine)	2%
*DRB1*16:01-DQB1*05:02*	25% (Flupirtine)	1%
*A*33:01*	80% (Ticlopidine) 50% (Methyldopa) 50% (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*

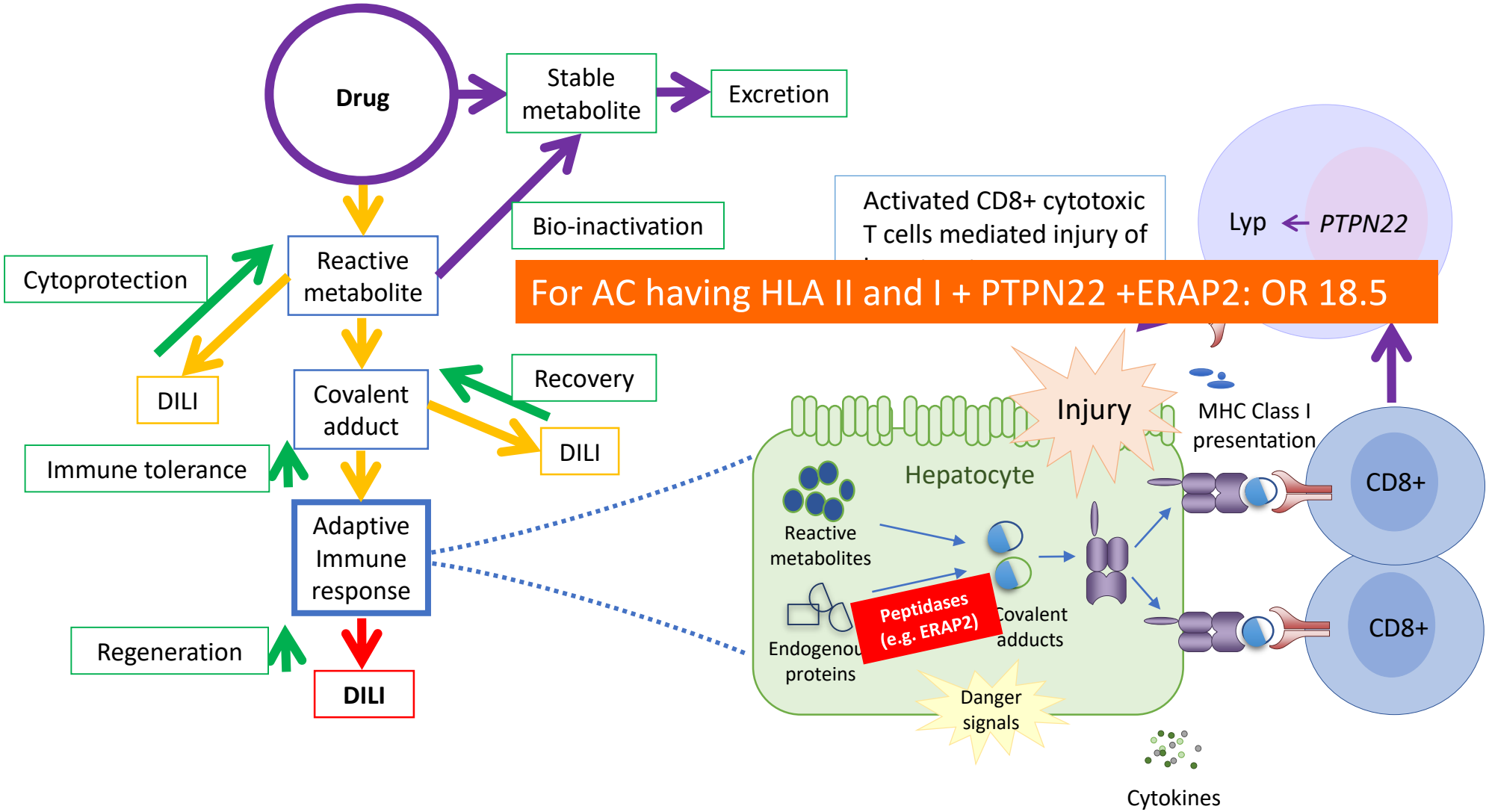






Lucena MI et al, *Gastroenterology* 2011; Daly A et al, *Nat Genet* 2009; Nicoletti P et al., *Gastroenterology* 2017;
Cirulli et al, *Gastroenterology* 2019: Li C et al *Hepatology* 2019; Hoofnagle JH, et al *Hepatology* 2021; EASL CPG DILI. *J Hepatol* 2019;

Putative mechanism: individual to the general

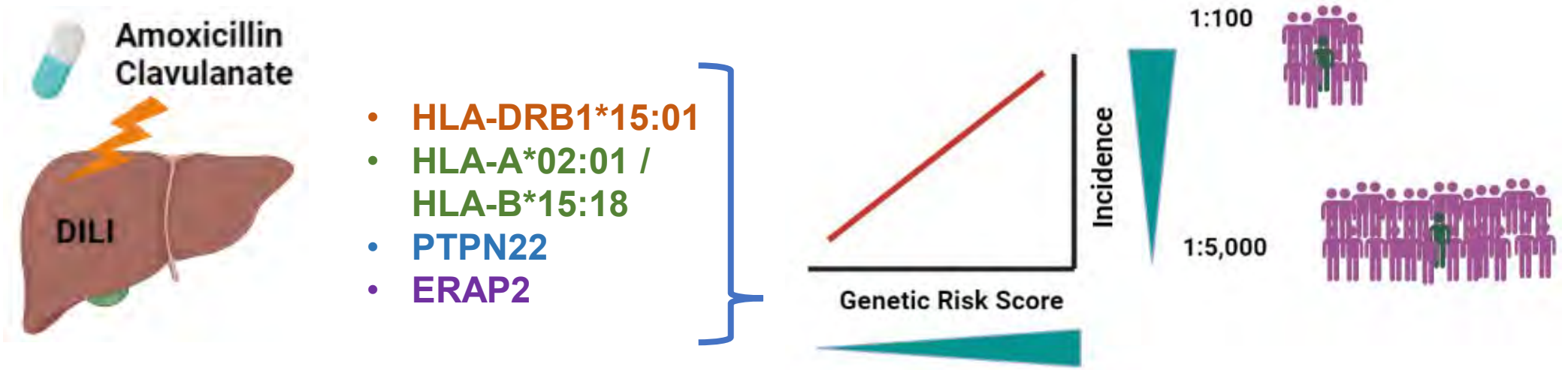


Aithal GP. *Hepatology* 2019

Nicoletti P,.., Andrade RJ.., Watkins PB. *Gastroenterology* 2022

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,…, Watkins P. Gastroenterology 2023

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Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

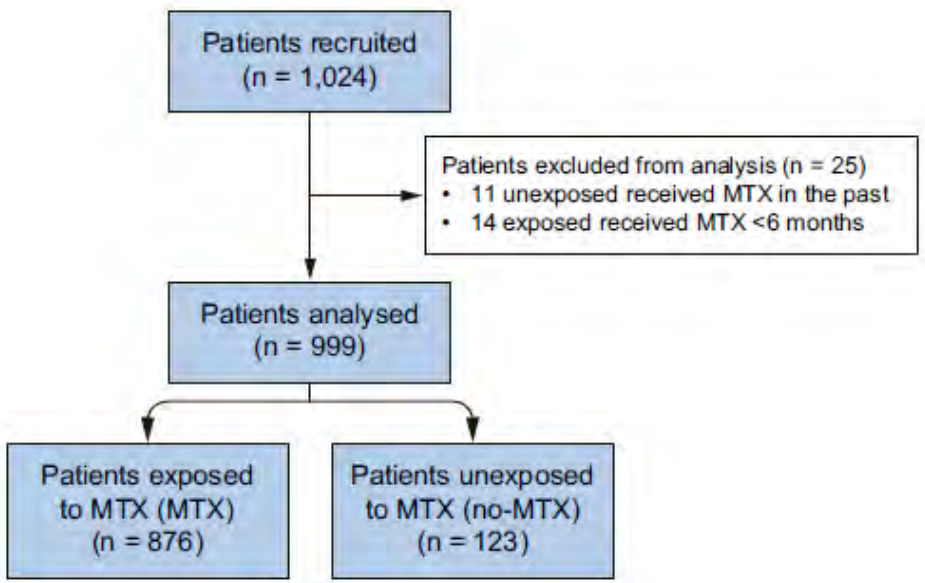
JOURNAL
OF HEPATOLOGY

Risk of liver fibrosis associated with long-term methotrexate therapy may be overestimated

Edmond Atallah[1,2,†], **Jane I. Grove**[1,2,†], Colin Crooks[1,2], Esther Burden-Teh[3], Abhishek Abhishek[4], Sulleman Moreea[5], Kelsey M. Jordan[6], Aftab Ala[7,8,9], David Hutchinson[10], Richard J. Aspinall[11], Ruth Murphy[12], Guruprasad P. Aithal[1,2,*]

Journal of Hepatology **2023**. vol. 78 | 989–997

See Editorial, pages 896–897



Non-invasive markers of liver fibrosis for monitoring of long-term methotrexate therapy: A multi-centre longitudinal cohort study

Patients and setting

6 centres, 2014 - 2021

RA or psoriasis (n = 999)

- Exposed to MTX (n = 876)
- Unexposed to MTX (n = 123)

Cumulative
- 4.8 g
- 6 years

Non-invasive markers

Liver stiffness

Enhanced liver fibrosis score (ELF)

Results

Exposed	vs.	Unexposed
4.9 kPa	($p = 0.049$)	5.3 kPa
≥11.5 kPa		
5.5%	($p = 0.01$)	11.6%
9.32	(n.s.)	9.28
≥11.3		
2.9%	(n.s.)	2.9%

Neither MTX cumulative dose nor duration was associated with elevated liver stiffness.
Type 2 diabetes and BMI were significantly associated with elevated liver stiffness.

Atallah et al *J Hepatol* 2023

Is the development of liver fibrosis in patients receiving methotrexate a matter of coexisting risk factors?

News & views

Hepatotoxicity

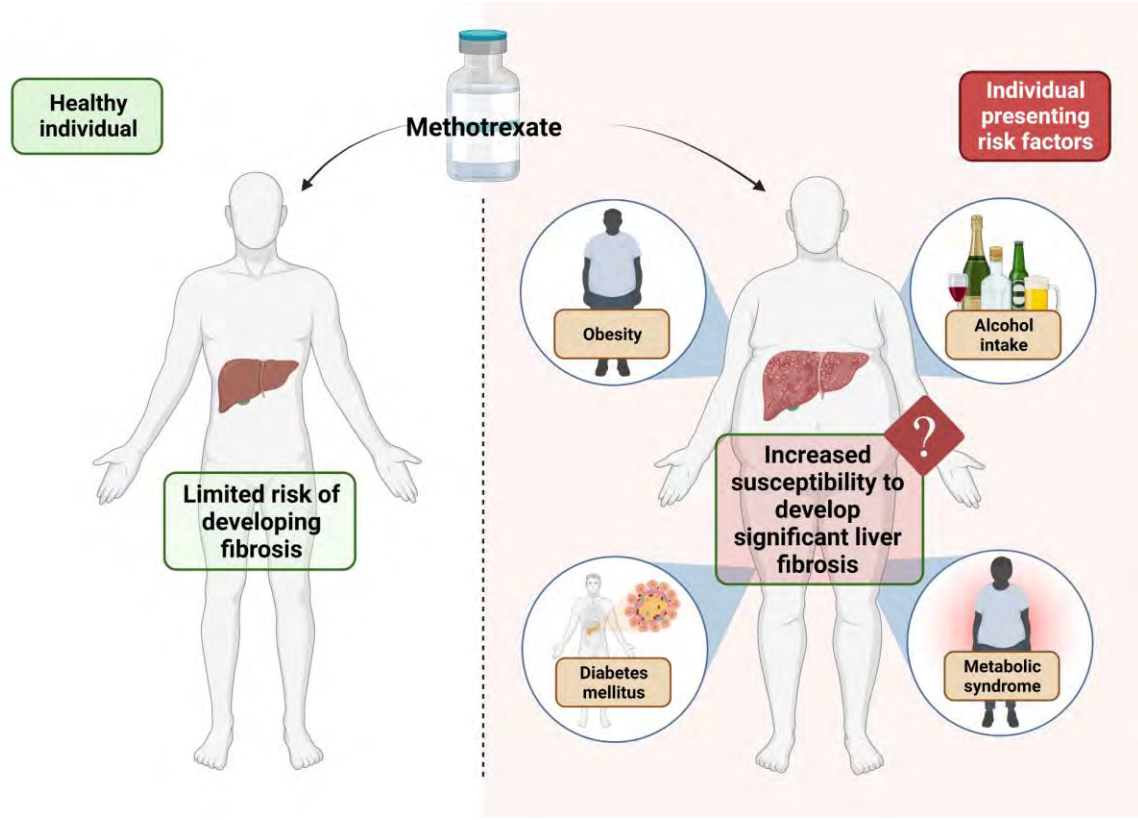
https://doi.org/10.1038/s41575-023-00782-3

Liver fibrosis with methotrexate — an overestimated risk?

Raul J. Andrade & Einar S. Björnsson

A prospective study suggests that the risk of liver fibrosis with methotrexate treatment has been overestimated. The findings suggest the need to reconsider the intensive strategies and the screening tools that are recommended for monitoring liver fibrosis in patients receiving methotrexate.

received methotrexate than among those who had, and ELF markers did not differ between the two groups overall. Neither the cumulative dose of methotrexate nor the duration of therapy with methotrexate was associated with liver stiffness. The cumulative dose of methotrexate was associated with increased ELF markers, but sensitivity analysis revealed that this association was only seen among patients with rheumatoid arthritis. Among these patients, regular use of non-steroidal anti-inflammatory drugs (NSAIDs) — which was considered to be a marker of disease activity — was more strongly associated with an increased ELF score. Given that inflammatory arthritis increases collagen turnover, disease activity increases levels of amino-terminal



Andrade RJ and Bjornssön ES. *Nat Rev Gastroenterol Hepatol* 2023

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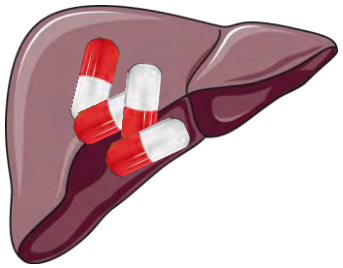


Drug induced liver injury

- Acute hepatitis
- Cholestatic and mixed hepatitis
- Peliosis hepatis
- Acute hepatic necrosis
- Hypersensitivity syndrome
- Hepatic steatosis
- Sinusoidal obstruction syndrome (SOS)
- Secondary sclerosing cholangitis
- Granulomatous hepatitis
- Acute fatty liver
- Vanishing bile duct syndrome
- Nodular regenerative hyperplasia (NRH)
- Drug-induced autoimmune-like hepatitis **(DI-AILH)**

Drug withdrawal
+/- immunosuppression

- **Self limiting** → **NO RELAPSE**
- **Chronic self perpetuating** → **RELAPSE**

IDIOPATHIC AUTOIMMUNE HEPATITIS (AIH) ← ?

Andrade RJ et al., *J Hepatol.* 2023: in press

Cases included in the Spanish and LatinAmerica DILI Registries	DILI without autoimmune features (n=1,393)	DILI with autoimmune features (n=33)	AIH (n=71)	*p* value
Female sex, %	53	58	75	0.001
Age (y), mean±SD	52±18	53±20	53±15	0.971
Pattern of liver injury, %				0.005
Hepatocellular	63	84	81	
Cholestatic	21	6.5	2.3	
Mixed	16	9.7	16	
Jaundice, %	66	58	41	<0.001
Treatment duration (d), median (IQR)	29 (9-68)	92 (40-312)	NA	<0.001
Time to onset (d), median (IQR)	25 (10-62)	94 (42-255)	NA	<0.001
Liver profile at recognition (x ULN), median (IQR)				
Total bilirubin	4.6 (1.1-10)	2.9 (1.5-6.6)	1.1 (0.5-5.0)	<0.001
Aspartate aminotransferase (AST)	6.2 (2.9-18)	20 (11-29)	9.7 (2.5-22)	<0.001
Alanine aminotransferase (ALT)	9.2 (4.6-23)	22 (13-34)	9.2 (3.4-26)	<0.001
Immunoglobulin G (peak; g/L), mean±SD	13±7.0	23±11	21±12	<0.001
Positive autoantibodies titres, %	18	100	92	<0.001
ANA	14	91	81	<0.001
ASMA	10	34	70	<0.001
AMA	2.0	3.1	2.8	0.466
Anti-LKM1	1.1	4.0	19	<0.001
Immunosuppressive treatment, %	6.9	63	93	<0.001
Corticosteroids only	6.9	15	37	
Corticosteroids and azathioprine	0	48	56	
Liver-related death, n (%)	33 (2.4)	0 (0)	NA	1.000
Liver transplant, n (%)	24 (1.7)	1 (3.0)	NA	0.446
Normalization time (d), median (IQR)	93 (48-182)	162 (90-260)	NA	0.004

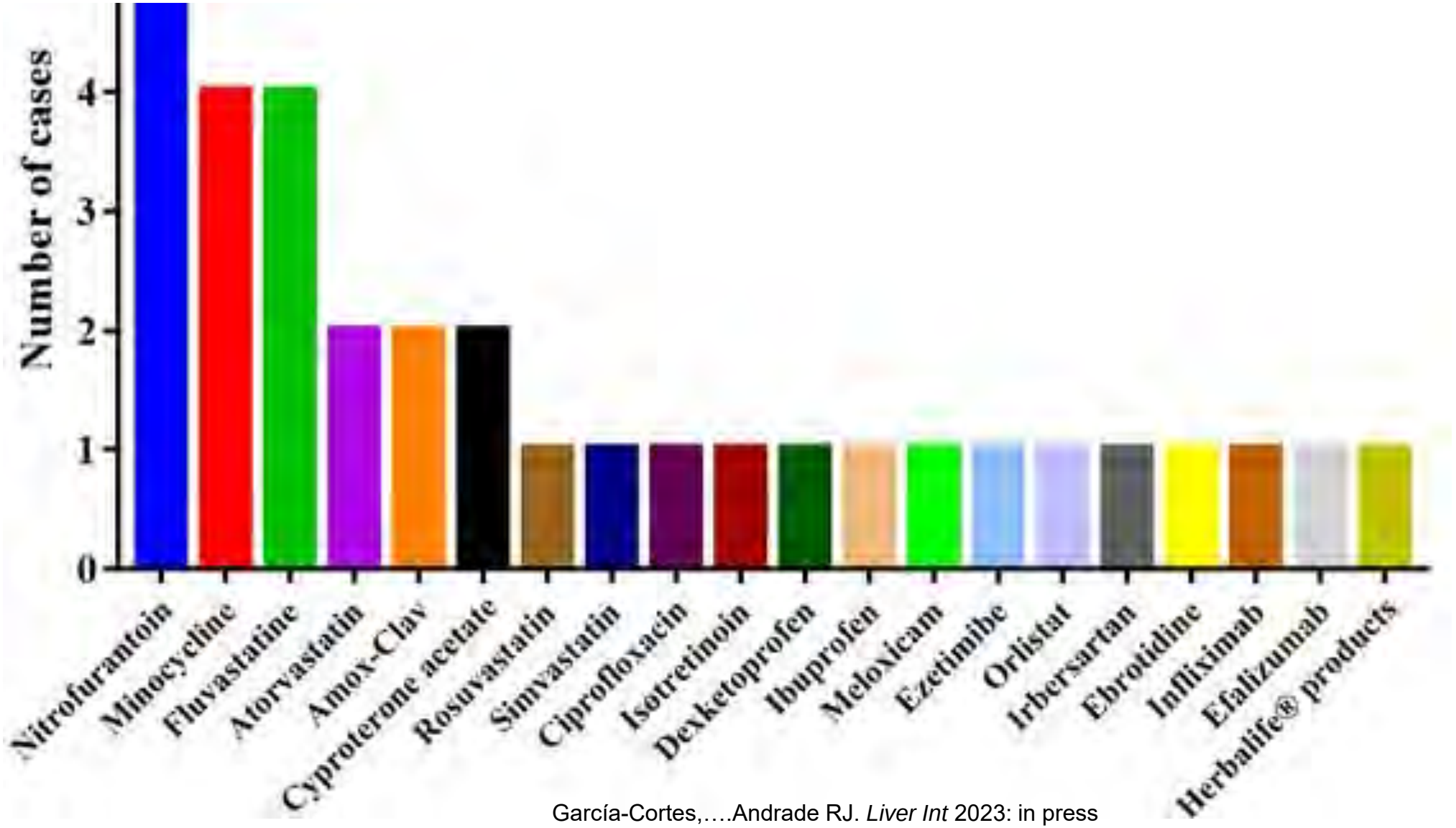
García-Cortes,….Andrade RJ. *Liver Int* 2023: in press

Cases included in the Spanish and LatinAmerica DILI Registries

Histological features, %	DILI with autoimmune features (n=23)	AIH patients (n=65)	p value
Lymphoplasmacytic and eosinophilic infiltrate	70	91	0.034
Monocytic infiltrate	22	15	0.525
Inflammation	43	91	<0.001
Fibrosis stage			
F0	26	14	0.205
F1	30	32	1.000
F2	17	25	0.573
F2-F3	8.7	1.5	0.166
F3	8.7	25	0.138
F4	8.7	3.1	0.279
Interface hepatitis	61	62	1.000
Focal necrosis	26	46	0.138
Rosettes	13	20	0.546
Ballooned hepatocytes	8.7	4.6	0.603

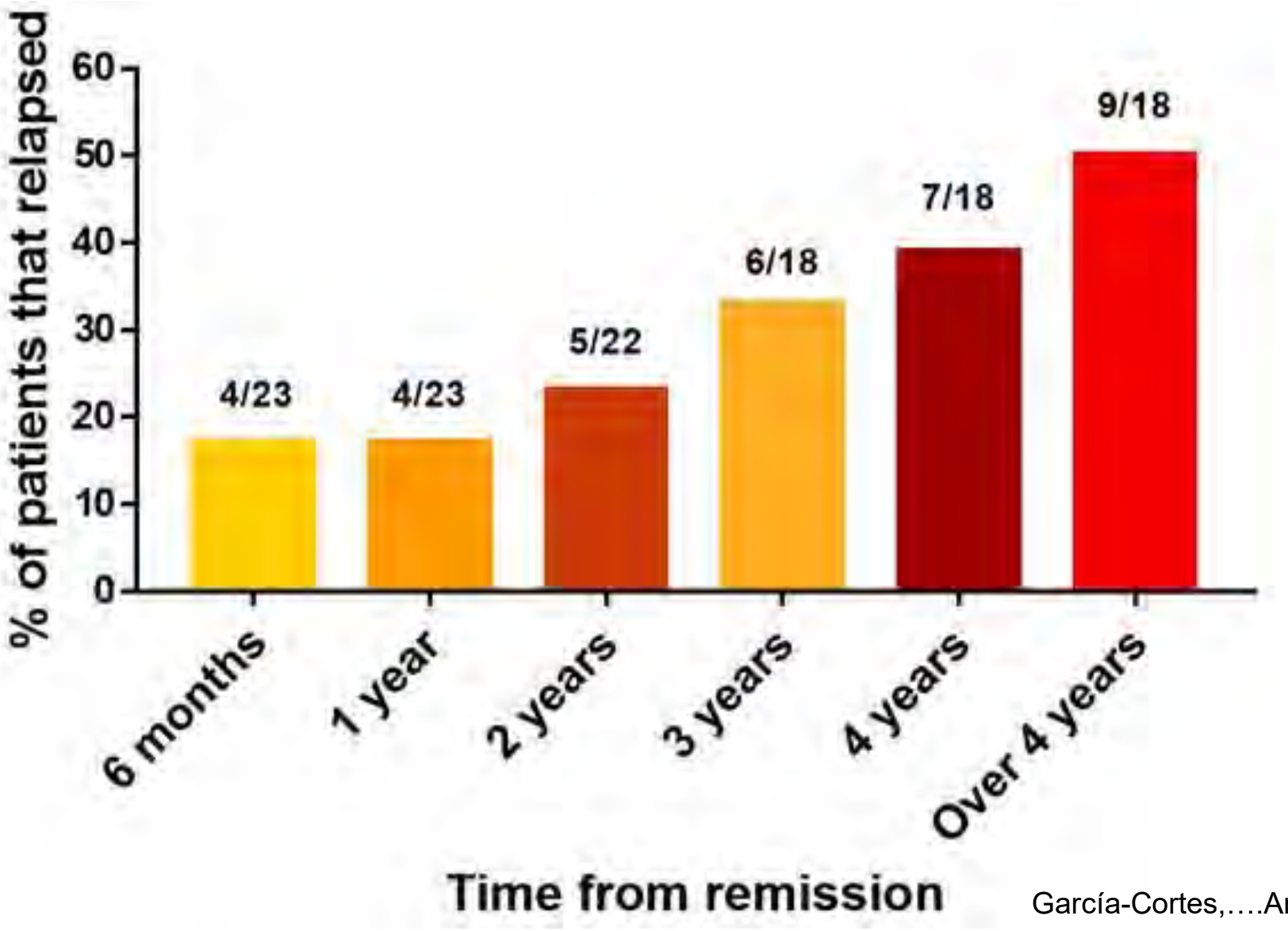
García-Cortes,….Andrade RJ. *Liver Int* 2023: in press

Most frequent culprit drugs in drug-induced autoimmune-like hepatitis cases in the Spanish DILI Registry and the LATINDILI Network



García-Cortes,….Andrade RJ. *Liver Int* 2023: in press

Cumulative relapse rate of drug-induced autoimmune-like hepatitis cases

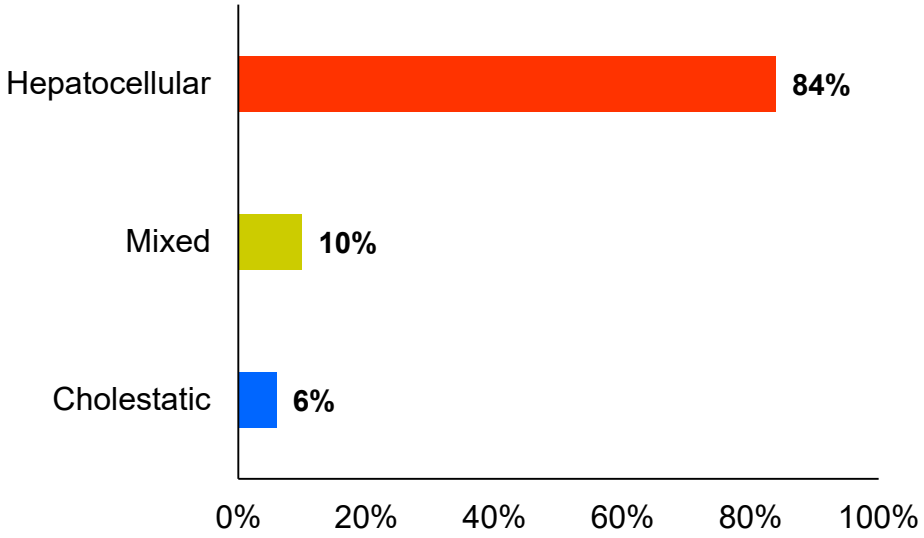


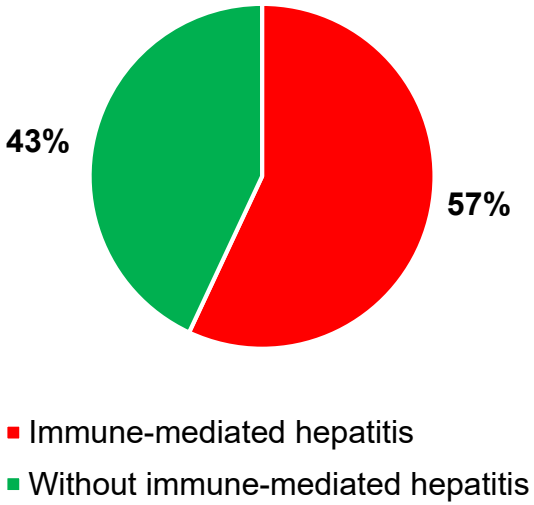
García-Cortes,….Andrade RJ. *Liver Int* 2023

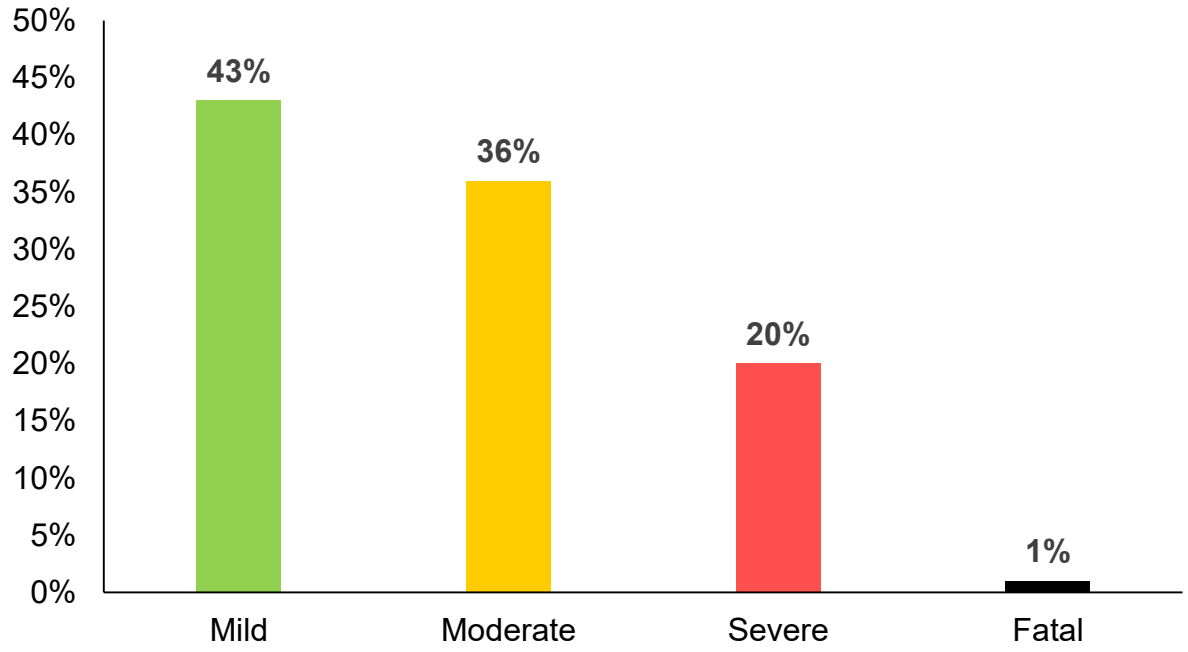
Cases included in the Spanish and LatinAmerica DILI Registries	No relapse (n=14)	Relapse (n=9)	p value
Female sex, %	50	89	0.086
Age (y), mean±SD	59±22	49±15	0.294
Pattern of liver injury, %			0.735
Hepatocellular	75	89	
Cholestatic	17	0	
Mixed	8.3	11	
Eosinophilia, %	43	0	0.048
Liver profile at DILI recognition (x ULN), median (IQR)			
Total bilirubin	1.5 (1.1-3.0)	7 (3.6-9.5)	0.008
Aspartate aminotransferase (AST)	13 (10-19)	29 (18-36)	0.029
Alanine aminotransferase (ALT)	12 (10-19)	31 (28-40)	0.038
Immunoglobulin G (peak value; g/L), mean±SD	21±11	19±5.6	0.858
Resolved, n (%)	14 (100)	9 (100)	-
Normalization time (d), median (IQR)	100 (90-202)	202 (176-395)	0.025

García-Cortes,….Andrade RJ. *Liver Int* 2023

DILI after SARS-CoV- 2 vaccination





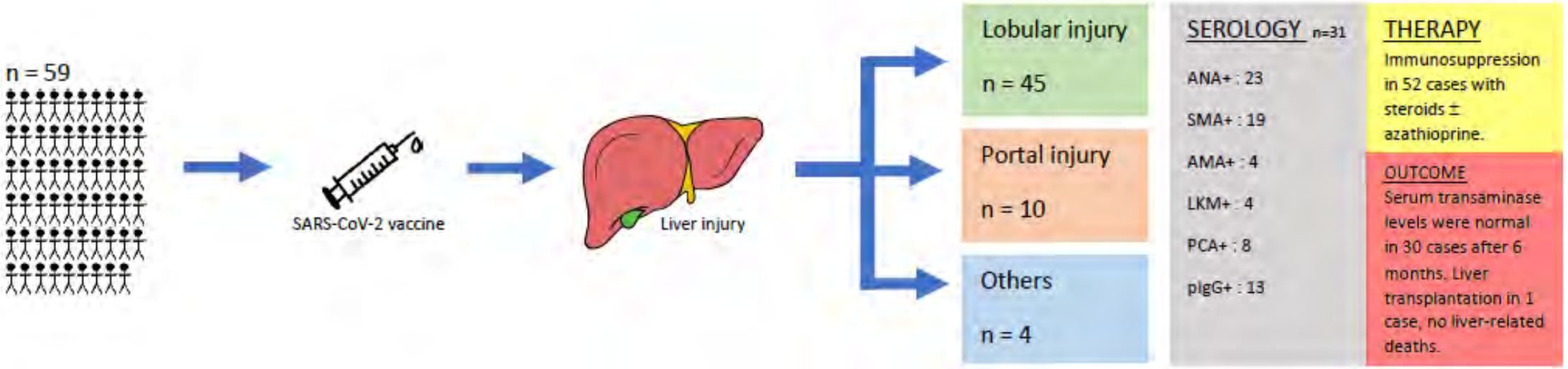


Efe et al., *Hepatology.* 2022 May 14:10.1002/hep.32572. doi: 10.1002/hep.32572. 2022

Research article JHEP|Reports

Histological and serological features of acute liver injury after SARS-CoV-2 vaccination

Greta Codoni,[1,†] Theresa Kirchner,[2,7,†] Bastian Engel,[2,7] Alejandra Maria Villamil,[3] Cumali Efe,[4] Albert Friedrich Stättermayer,[5] Jan Philipp Weltzsch,[6,7] Marcial Sebode,[6,7] Christine Bernsmeier,[8] Ana Lleo,[9,31] Tom JG. Gevers,[7,10] Limas Kupčinskas,[7,11] Agustin Castiella,[12] Jose Pinazo,[13] Eleonora De Martin,[14] Ingrid Bobis,[15] Thomas Damgaard Sandahl,[16] Federica Pedica,[17] Federica Invernizzi,[17] Paolo Del Poggio,[18] Tony Bruns,[7,19] Mirjam Kolev,[20] Nasser Semmo,[20] Fernando Bessone,[21] Baptiste Giguet,[22] Guido Poggi,[23] Masayuki Ueno,[24,32] Helena Jang,[25] Gülsüm Özlem Elpek,[26] Neşe Karadağ Soylu,[27] Andreas Cerny,[28] Heiner Wedemeyer,[2,7] Diego Vergani,[29] Giorgina Mieli-Vergani,[29] M. Isabel Lucena,[13,30] Raul J. Andrade,[13,30] Yoh Zen,[29] Richard Taubert,[2,7,#] Benedetta Terziroli Beretta-Piccoli[1,28,29,#,*]



Codoni et al JHEP Rep. 2022; 13;5(1):100605. doi: 10.1016/j.jhepr.2022.100605. eCollection 2023 Jan.

PRO-EURO DILI NETWORK
Prospective European Drug-induced Liver Injury Network

IAIHG
INTERNATIONAL AUTOIMMUNE HEPATITIS GROUP

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

COST is supported by the EU Framework Programme Horizon 2020

Consensus conference on Drug-Induced Autoinmune Hepatitis (DI-AIH). Parador de Nerja, Málaga (Spain).

02-03 March 2022

***Scientific Programme Committee*:** *RJ Andrade, GP Aithal, Einar S Björnsson, MI Lucena, G Mieli-Vergani, D Vergani, R Liberal, YS de Boer.*

AIMS: To to establish a consensus for standardized nomenclature in DI-ALH, best practices in management and identify key gaps in the diagnostic and mechanistic biomarkers

Minimal elements for assessment of a suspected case of DI-ALH

- **Demographic and clinical variables**, drug exposure history, temporal criteria, meet criteria for DILI qualification, exclusion of alternative causes
- **Biochemistry**
  - Liver tests at onset, on remission, when worsening, relapse
  - Autoantibodies, IgG
- **Histological features**: ***pattern of injury*** (portal or lobular based hepatitis), degree of necroinflammatory changes and fibrosis according to Ishak's grading and staging system, ***plasma cell infiltration or clusters***, ***documentation of other histological features of significance*** (hepatocellular or canalicular cholestasis, chronic cholestasis changes, eosinophils, confluent necrosis, steatosis, vascular injury), ***exclusion of other diseases*** (e.g., steatohepatitis, cholangiopathy), ***overall assessment based on the revised AIH scoring system, simplified criteria, and histological criteria***

Andrade RJ et al., *J Hepatol.* 2023: in press

Minimal elements for assessment of a suspected case of DI-ALH (II)

- **HLA data**: specific HLA for given drugs and general AIH related HLA
- **Severity:** International expert working group criteria (Aithal et al CPT 2011), nR based Hy's law
- **Treatment**: steroid therapy (when initiated), other immunosupressants, still on therapy?
- **Outcome**: remission achieved, worsening of the disease, relapse, liver-related death, liver transplant.
- **Follow-up**: 2-4 weeks, 1-3-6-12-18-24 months after diagnosis and once a year, thereafter for 5 years
- **Causality assessment tools**:
  - The RUCAM/CIOMS and its recently improved version RECAM.
  - the revised and the simplified AIH scoring systems issued by the International Autoimmune Hepatitis Group

Andrade RJ et al., *J Hepatol.* 2023: in press

Current gaps and future steps of research to improve the analysis and management of DI-ALH

- **Epidemiology**: based in correct diagnosis and dedicated prospective initiatives
- **Consensus definition:** will allow analyses of larger populations based on the same criteria, to define the different classes of drugs/agents that can cause DI-ALH
- **Improve liver histology evaluation**: to better characterize the patterns of DI-ALH
- **Systematic investigation of autoantibodies**: with comparison to AIH to determine their potential usefullness for diagnosis, prognosis and management.
- **Immunohistochemical and molecular techniques in liver biopsies**: may help identify immunohistochemical markers useful for the diagnosis of DI-ALH
- **Testing for carriage of particular HLA alleles**: in selected cases will assist in the diagnosis of DILI or AIH

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Current gaps and future steps of research to improve the analysis and management of DI-ALH (II)

- **Management**: which patients require immunosuppression, standardization in treatment regimens, and when to withdraw
- **Prospective assessment of predictors of positive rechallenge:** with the same or with a different drug and outcomes
- **Liver biopsies and conducting spatial profiling of gene signatures between DI-ALH and AIH**: would highlight the difference for future fine-tuning of nomenclature
- **Comparative analysis using distinct "omics" technologies**: may allow for categorizing DI-ALH cases to better predict their progression, spontaneous resolution, response to therapy and outcomes
- **Larger prospective studies with relevant follow-up information on immunosuppression**: to properly characterize the natural history of DI-ALH.
- **Referral of severe cases to specialized centers**: to better manage DI-ALH patients

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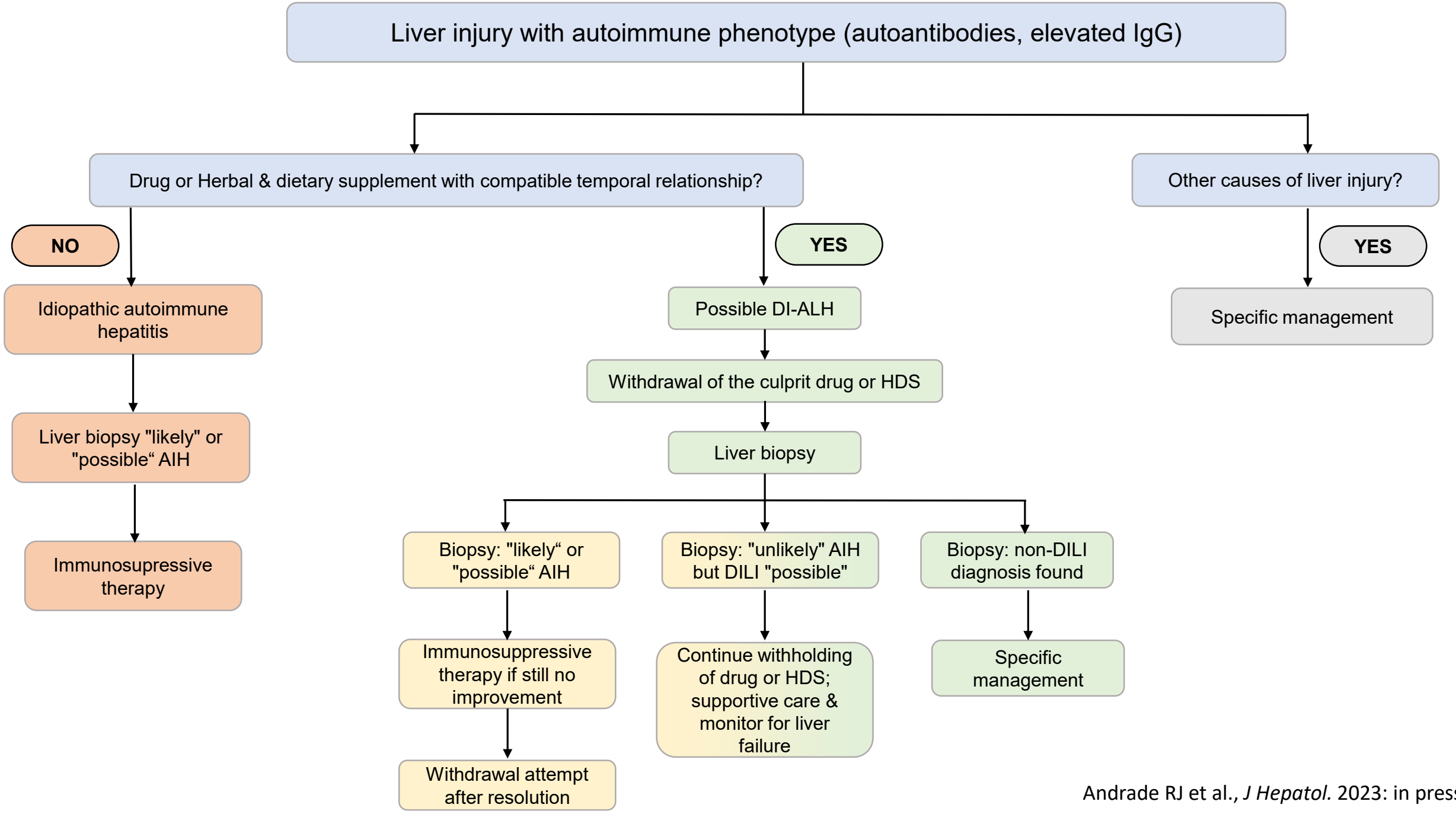


Andrade RJ et al., *J Hepatol.* 2023: in press

Agenda

- Análisis proteómico de biomarcadores
- Amoxicilina-clavulánico: epidemiología y variantes genéticas
- Metrotexato y riesgo de fibrosis hepática
- DILI autoinmune
- Corticoides en el tratamiento del DILI

Tratamiento

- No existe un tratamiento especifico en el DILI idiosincrásico que haya demostrado en estudios bien diseñados reducir el riesgo de evolución fulminante, muerte, o acortar el tiempo de resolución
- De forma empírica los corticoides se indican en casos de
  - presentación mas florida (ictericia, citólisis marcada)
  - que sugieren un componente alergico (fiebre, rash, eosinofilia)
  - fenotipo autoimmune
  - Toxicidad asociada al tratamiento con inmunoterapia
- Ausencia de evidencia basada en estudios controlados

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

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

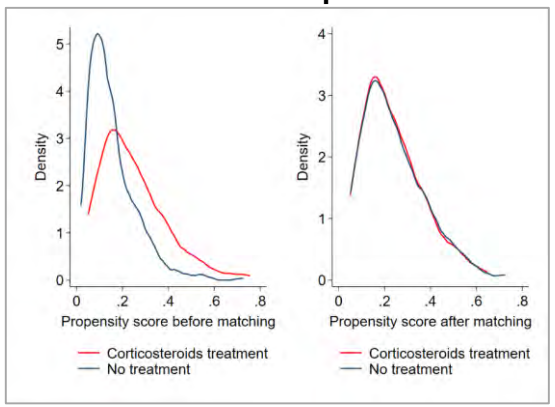
In the univariate analysis, corticosteroids were associated with higher frequency of ALF
OR = 3.05; 95% CI 1.20 – 7.75;
p = 0.019

PANISH DILI REGISTRY

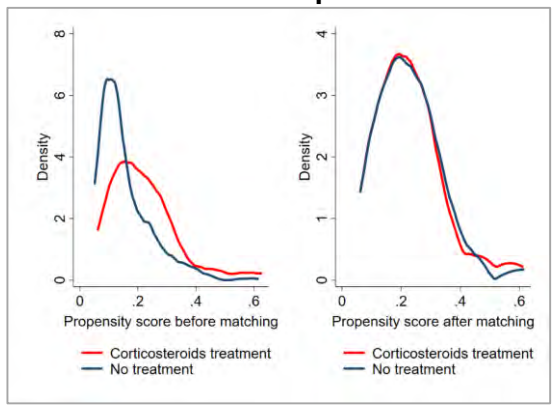
INDIANA UNIVERSITY SCHOOL OF MEDICINE

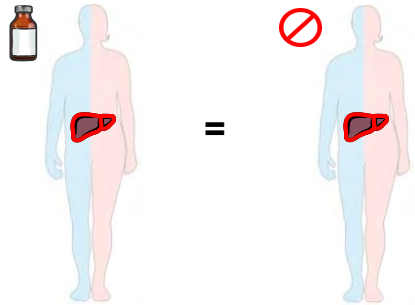
Propensity score matching

80 matched pairs



41 matched pairs





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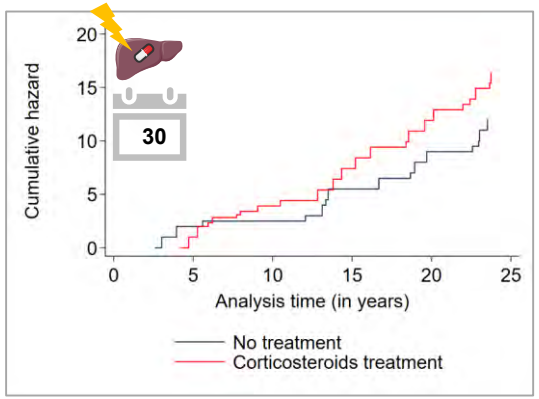
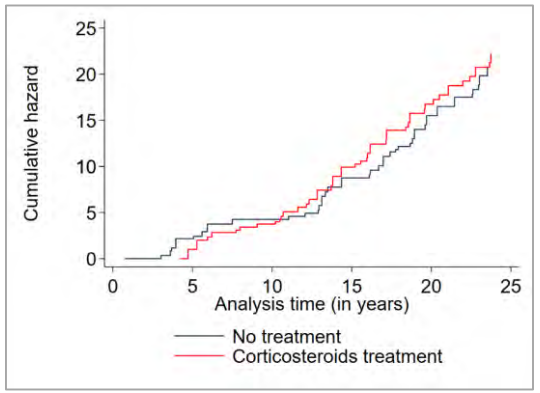
Corticosteroid therapy does not increase the risk of liver-related mortality
OR = 0.58; 95% CI 0.11 – 3.13; p = 0.527





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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