¿Cómo afecta la enfermedad hepática crónica al riesgo y el curso de DILI?

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Drug-Induced Liver Injury

- **In drug development**
  - Main cause of clinical trial termination (33%)
  - Leading cause of post-marketing withdrawals
  - DILI accounted for 30% of warnings of 197 novel agents FDA approved 2012-2017
- Drug-induced liver injury (DILI) is **relatively uncommon**
  - 14 to 19 per 100,000 inhabitants (general population)
  - ≈ 34 per 100,000 patients (healthcare setting)
- DILI can have **serious clinical outcomes**
  - Overall cases:
    - 56% symptomatic
    - 12% to 17% hospitalized
  - Clinically significant cases: ≈10% liver transplant or death
- **Challenge to diagnose and study**
  - Lacks predictive biomarkers
  - Can mimic other hepatic diseases
  - Presents with diverse clinical phenotypes

Sgro C et al *Hepatology* 2002;*36:451-455;* Andrade RJ, *et al. Gastroenterology* 2005;129:512–521; *Bjornsson ES , et al Gastroenterology* 2013;144:1419–1425; Robles-Díaz M, et al. *Gastroenterology* 2014; 147:96–108; Stephens C et al. *J Hepatol* 2021;

A new mechanistic clasification of DILI

DIRECT (INTRINSIC)	Dose - related Predictable Short latency Reproducible Acetaminophen
IDIOSYNCRATIC	Threshold dose. Dose > 50-100mg and extensive hepatic metabolism are associated with liver failure, death and liver transplant Unpredictable, host dependent. Delayed onset, variable latency No reproducible in animal models Amoxicilline clavulanic, diclofenac, macrolides
INDIRECT	Unintended effects of drug actions on the liver Increased drug-induced immune autoreactivity Reactivation/worsening of an underlying hepatic disease (viral hepatitis B/ fatty liver) ICIs, rituximab, corticosteroids

Lammert C, *Hepatology* 2008; Chen M, *Hepatology* 2013; Hoofnagle JH, Björnsson ES. *New Eng J Med* 2019.

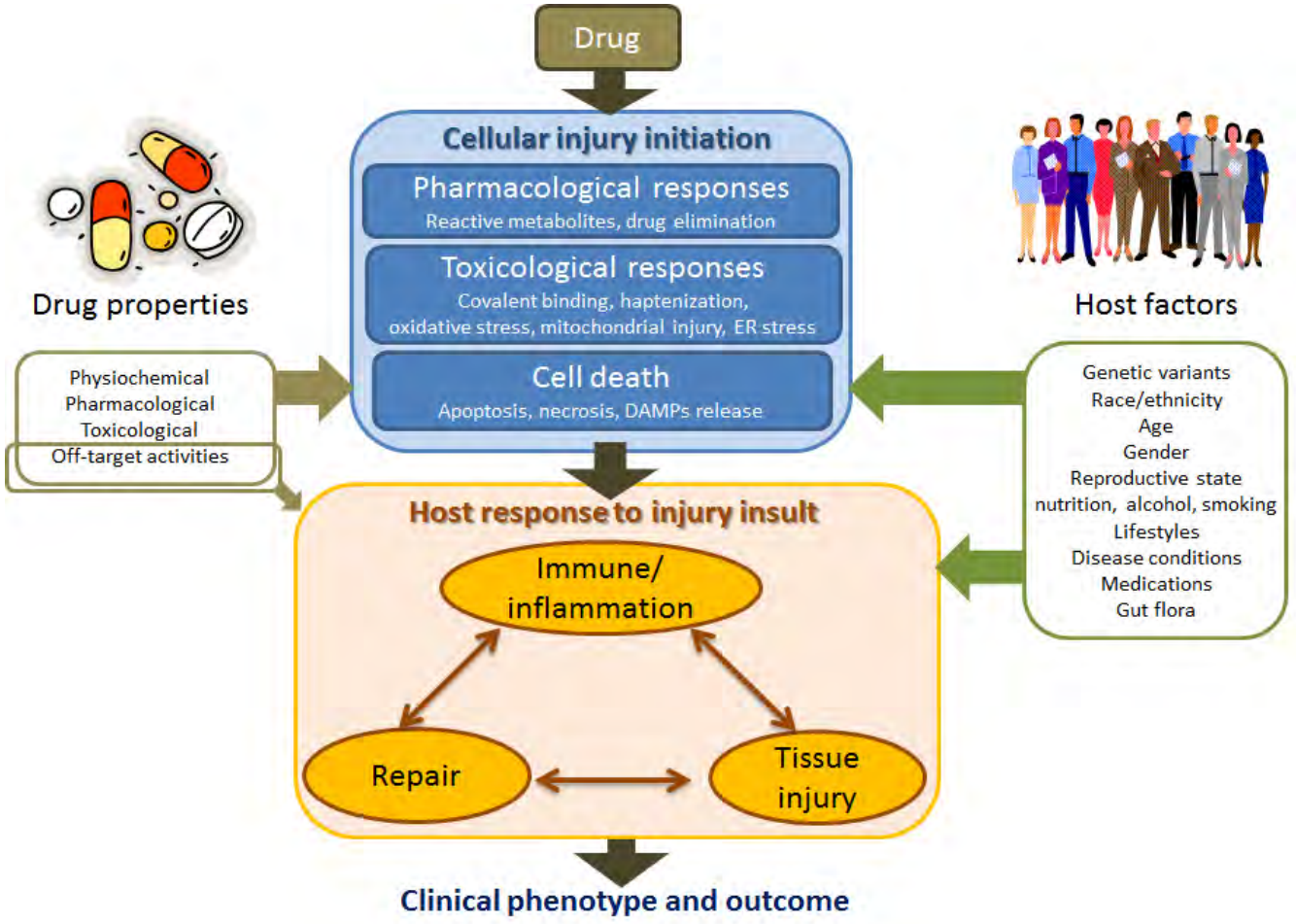
Examples of drugs causing DILI when doses were increased

- Fluconazole (several case reports)
- Atorvastatin
- Azathioprine
- Atomoxetine
- Duloxetine

Bronsterin JA, et al. CID 1997; 27:1266-1267; Wells C, et al. J Infect 1992; 24: 111-2;
Crearar-Gilbert A, et al, Anes Intensive Care 1999; 27:650-652; Carrascosa M, et al. J Hepatol 2015;62(3):751-2

Drug Induced Liver Injury (DILI)
Interplay between drug properties and host factors

- Although not fully understood, the pathogenesis of iDILI is based on the interplay between drug characteristics, environmental and host factors.
- The genetic background and the immune system have a significant role.



Chen M…, Andrade RJ. *J Hepatol,* 2015, 63(2): 503

DILI in patients with chronic liver disease: Key points

- Are individuals with chronic liver disease more susceptible to idiosyncratic DILI?
- Is DILI associated with worse outcomes in individuals with chronic liver disease?
- Does pre-existing chronic liver disease confound causality assessment in DILI ?

Mechanisms behind altered pharmacokinetics in cirrhosis

Mechanism

1. Reduced Intrinsic Capacity
   -Decreased enzymes
   -Decreased activity
2. Reduction in blood Flow
3. Shunts
4. Changes in protein binding
5. Reduced delivery of oxigen
6. Altered transport expression and function
7. Gut CYP activity

Comment

There may be etiology specific variability in different CYPs. Alcohol and infection can affect some CYPs selectively

Intrahepatic shunts in the fibrous bands – may account for up to 65% of hepatic blood flow. Spontaneous portasystemic shunts and TIPS can significantly modify

Oxygen is important for CYP activity

Hepatocyte uptake as well as efflux into biliary canaliculi can be affected

TIPS significantly reduces small bowel CYP3A activity

DAAs & DILI

- Viekera Pak is a fixed-dose combined package of ombitasvir, paritaprevir, and ritonavir and a tablet of dasabuvir.

- Liver failure, including liver transplantation or death, have occurred in association with Viekera Pak in individuals with hepatic impairment.

- Significant relationship between exposure to paritaprevir and DILI risk was evident. In Child's B, the exposure to paritaprevir was increased by 62% but in severe hepatic impairment, it was increased by 945%.

- Similar phenomenon was evident with Zepatier (elbasvir and grazoprevir). Severe hepatic impairment was associated with ~ 12 fold increase in exposure to grazoprevir. GZR- associated hepatotoxicity is exposure dependent.

Mishra P & Chen M. *Gastroenterology* 2017; 154: 1270-1274

Acute Drug-Related Hepatic Decompensation in Patients with Preexisting Chronic Hepatitis C

Dig Dis Sci (2015) 60:1031–1035
DOI 10.1007/s10620-014-3422-x

CrossMark

ORIGINAL ARTICLE

Hepatic Decompensation Likely Attributable to Simeprevir in Patients with Advanced Cirrhosis

Jonathan G. Stine · Nicolas Intagliata · Neeral L. Shah · Curtis K. Argo · Stephen H. Caldwell · James H. Lewis · Patrick G. Northup

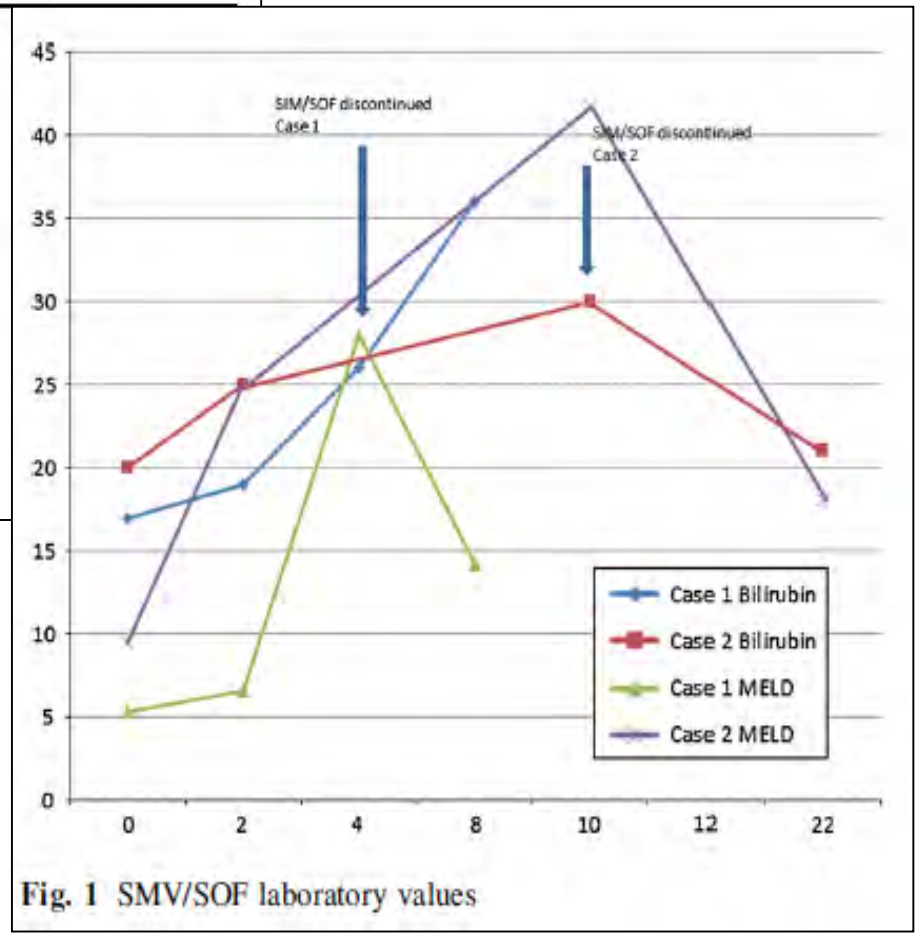


Fig. 1 SMV/SOF laboratory values

- Undetectable HCV viral load in both cases
- ALT 90 U/L in case 1 and WNL in case 2
- Contraindications to the use of protease-inhibitor-containing regimens in HCV patients with advance liver disease

Obeticholic acid: Post-marketing experience

- Since marketing approval in May 2016 for PBC, the FDA Adverse Event Reporting System received reports of 19 deaths and 11 cases of serious liver injury in patients taking OCA.

- It has highly striking that much higher than recommended doses were prescribed to patients with moderate to severe hepatic impairment (5 mg once daily instead of 10 mg twice weekly)

- Primary pattern of liver injury is cholestatic jaundice – illustrating the significance of even cholestatic liver injury in individuals with hepatic impairment

https://www.fda.gov/Drugs/DrugSafety/ucm576656.htm
https://livertox.nih.gov/ObeticholicAcid.htm

Underlying HBV & DILI due to anti-TB drugs

	Anti-TB therapy (N=319)		HBV controls not on ATT (N=86)
	HBV carriers (n=43)	**Non-HBV carriers (n=276)**	
BMI (kg/m2)	20.6 ± 4.9	22 ± 5.9	21.4 ± 6.0
HBeAg/anti-HBe	9/34	-	17/69
Elevated baseline ALT (%)	23	18	17
Suspected DILI (%)	**34.9¶**	**9.4**	**8.1**
Bilirubin > 3 ULN	3	7	0

¶p<0.001 compared to other two groups

Definition of DILI: ALT > 1.5 X ULN at least 2 consecutive occasions within 4 weeks.
Most of the episodes of ALT elevation were associated with an increase in HBV-DNA levels irrespective of HBeAg status

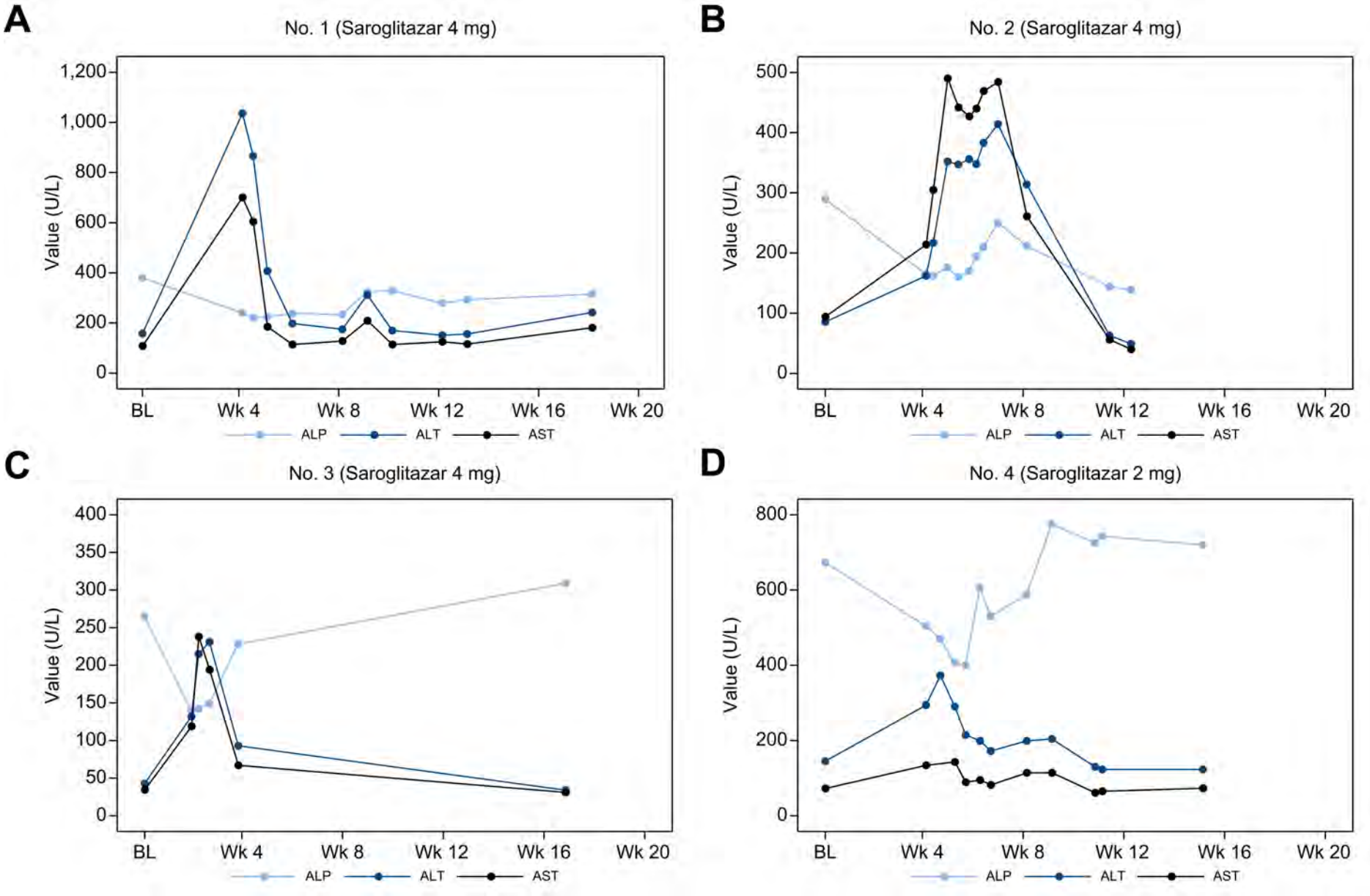
Wong WM et al. *Hepatology* 2000; 31: 201-206

Underlying viral hepatitis & HAART hepatotoxicity

- Chronic hepatitis C was associated with 2-5 fold increase in the risk for severe HAART hepatotoxicity
- Chronic hepatitis B was associated with ~ 9 fold increase in the risk for grade IV liver toxicity
- However, immune reconstitution and reactivation of underlying viral infection is an important confounder.

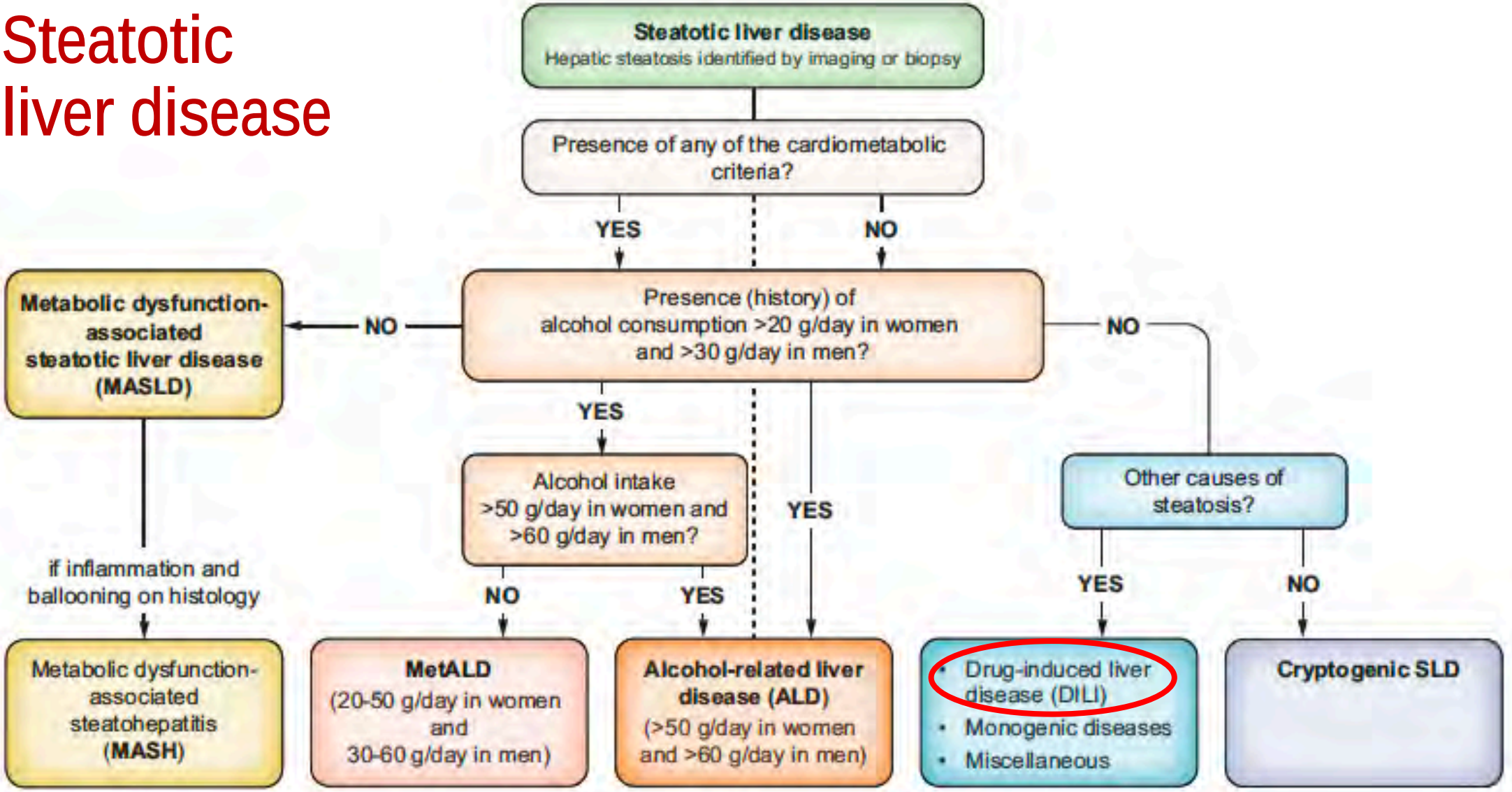
Sulkowski M, et al. *Hepatology* 2002; 31: 201-206*;* Nunez M, et al. *J AIDS* 2001; 27: 426-431*;* Servoss JC*, et al. J AIDS 2006;* 43: 320-323; Wir FWNM, et al. *JID* 2002; 186; 23-31

DILI associated with saroglitazar in PBC (but not in MASLD



Vuppalanchi et al. *J Hepatol* 2022 Jan;76(1):75-85.

Steatotic liver disease



European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO); European Association for the Study of the Liver (EASL). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Sep;81(3):492-542.

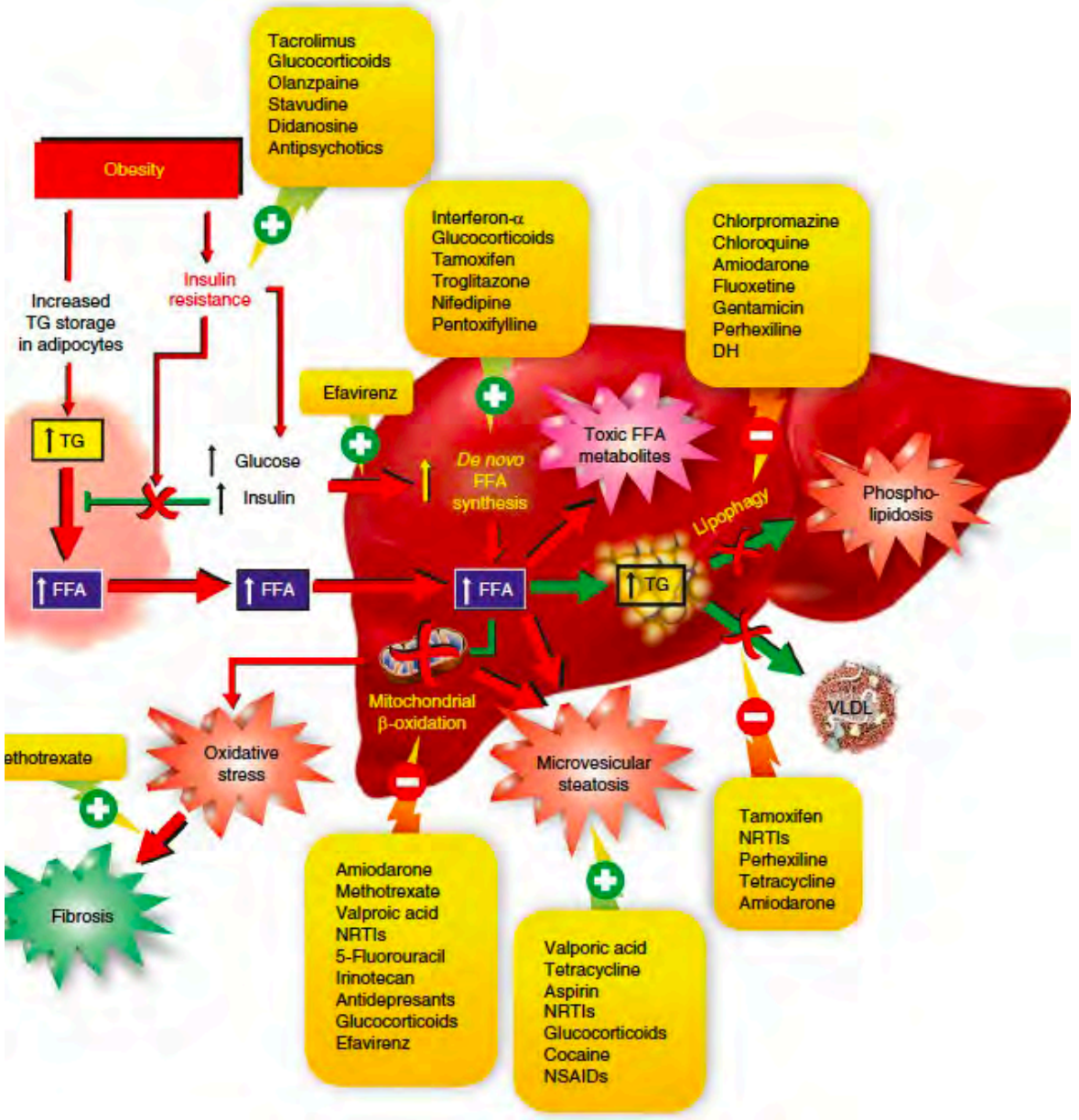
Mechanisms of DIS

1. Drugs can induce macrovesicular steatosis by mimicking MASLD pathogenic factors:

- **"First hit"**: insulin resistance and enhancement of lipid synthesis or free fatty acid hepatic uptake.
- **"Second hit"**: Worsen pre-existing MASLD
  - impairment of lipid degradation via lipophagy (leading to phospholipidosis)
  - Impairment of lipid exportation via VLDL

2. Mitochondrial dysfunction

3. Exacerbate the oxidative stress-dependent activation of hepatic stellate cells, leading to enhanced fibrosis.



Bessone F, *et al. AP&T* 2018.

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

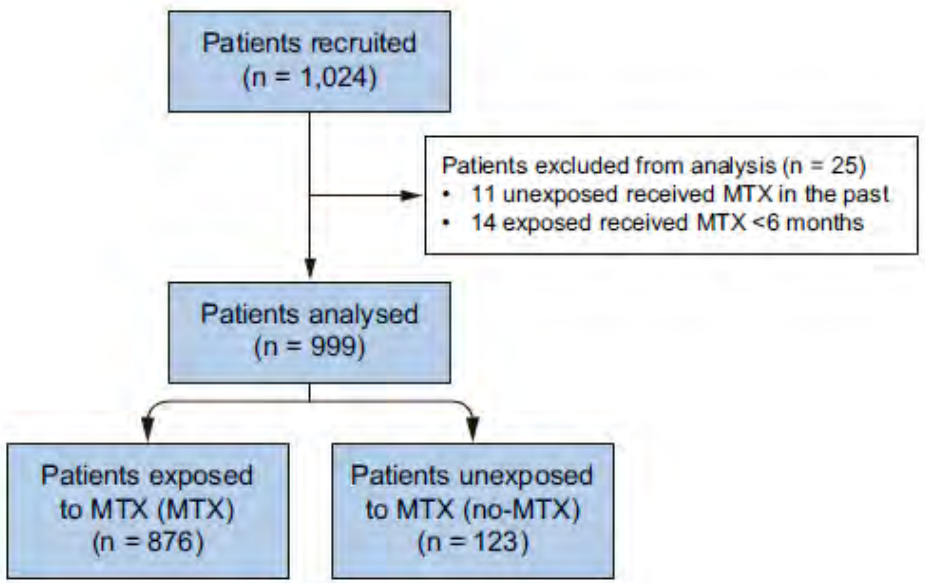
JOURNAL
OF HEPATOLOGY

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
5.5%	≥11.5 kPa ($p = 0.01$)	11.6%
9.32	(n.s.)	9.28
2.9%	≥11.3 (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 metrotrexate a matter of coexisting risk factors?

News & views

Hepatotoxicity

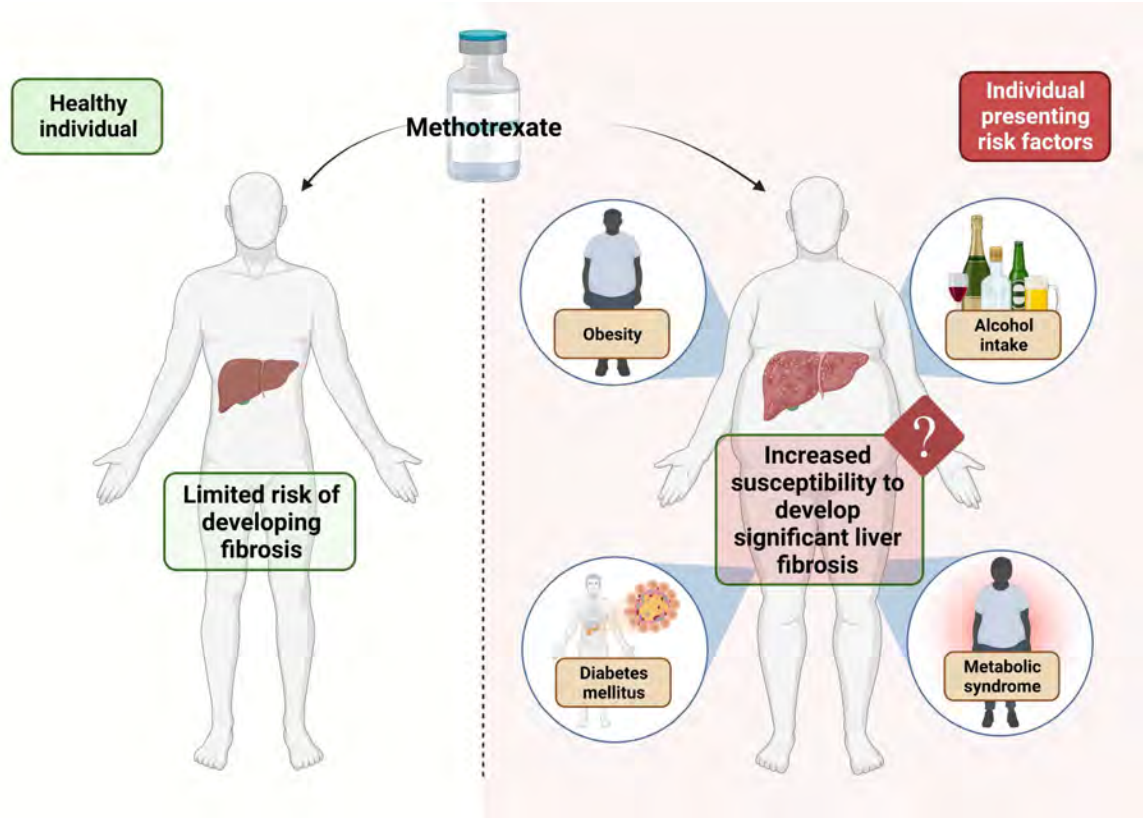
https://doi.org/10.1038/s41575-023-00782-3

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

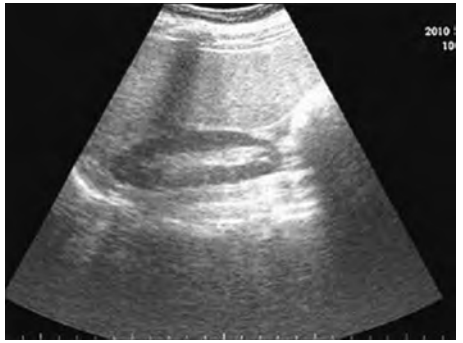


Andrade RJ and Bjornssön ES. *Nat Rev Gastroenterol Hepatol* 2023

Clinical vignette

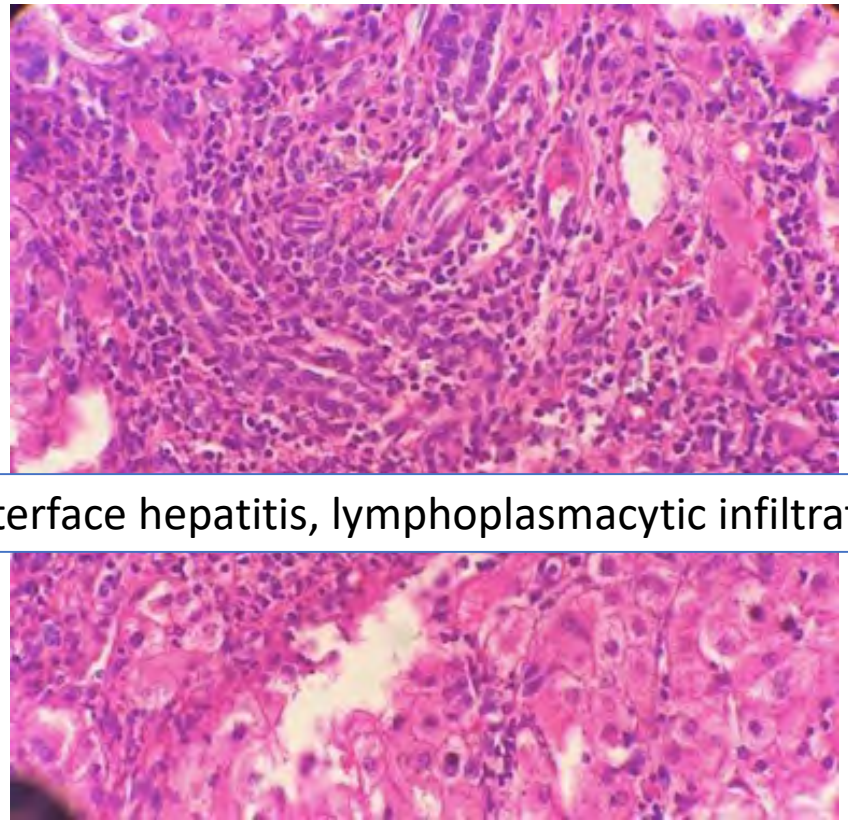
- 57 year-old Latino man, 30.3 BMI, and MS (type 2 DM and hypertension).
- Slightly raised and fluctuating ALT since 10 y before. In 2016 ALT 72 UI/L (N<56 UI/L)
- October 2018 liver test checked on a routine basis AST 155 UI/L and ALT 238 UI/L.
- **Lymecycline** for rosacea from August 2018
- ***Upon continuation of the drug*** on May 2019 AST was 296 UI/L, ALT 292 UI/L, GGT 155 UI/L (N<32 UI/L) and ALP 127 UI/L (N<126 UI/L). Total bilirubin and INR were normal.

- HAV, HBV, HCV, HEV, CMV, EBV, autoimmune serology and IgG negative/normal
- Abdominal ultrasound: steatosis

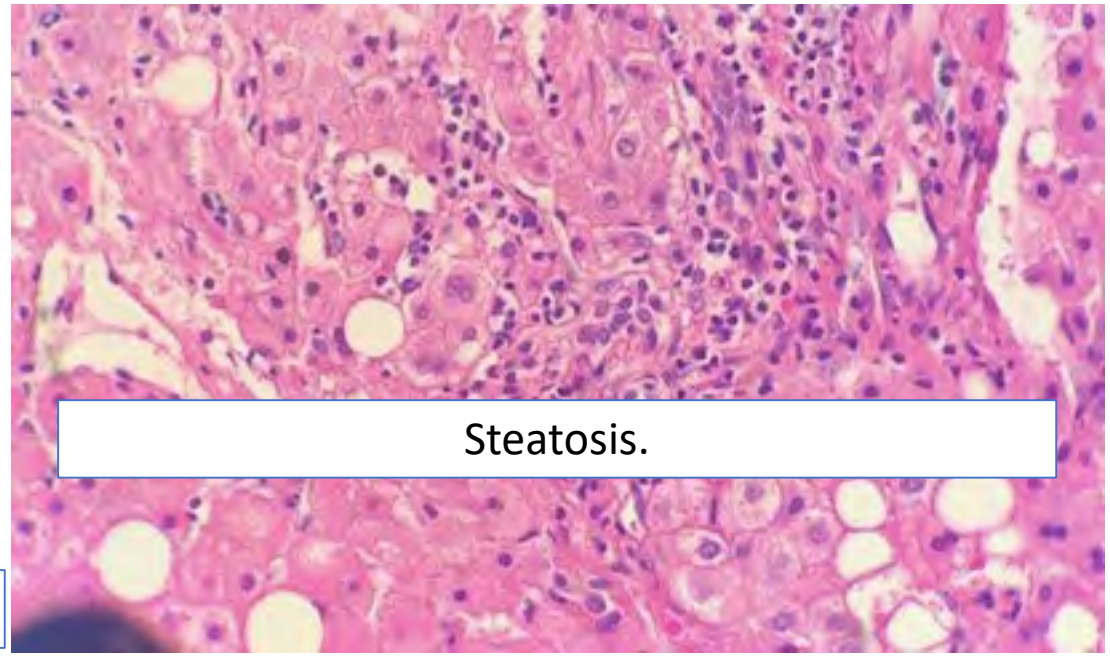


- A liver biopsy was performed.

Liver biopsy

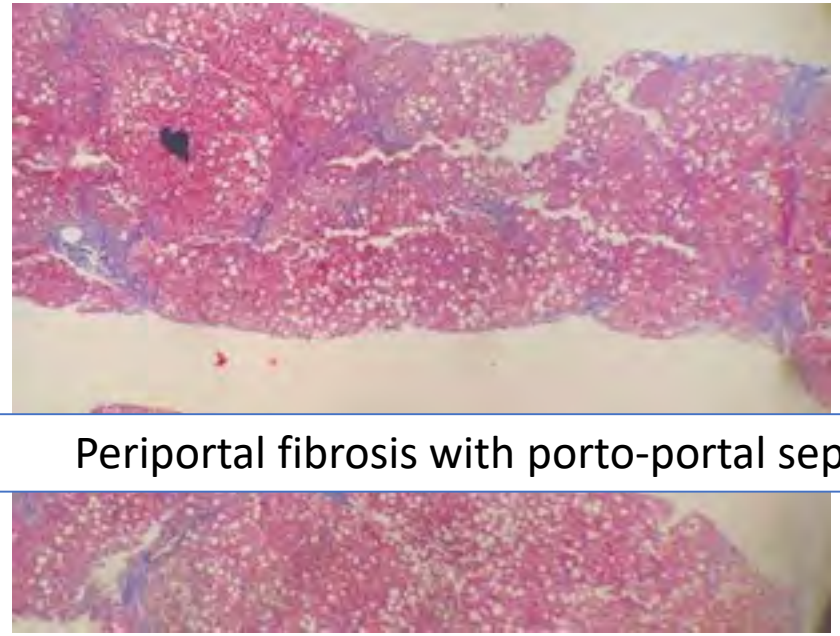


Interface hepatitis, lymphoplasmacytic infiltrate.



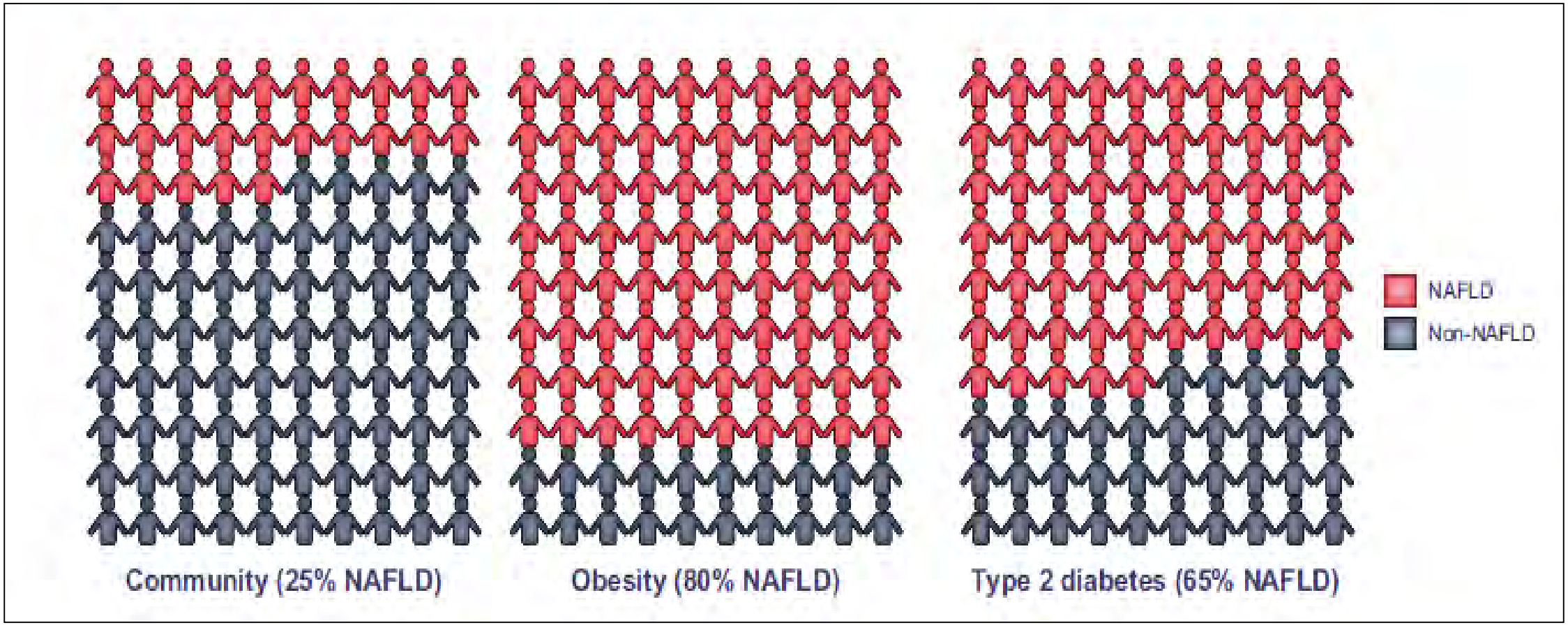
Steatosis.

- **NASH F3/autoimmune hepatitis**



Periportal fibrosis with porto-portal septa

MASLD / metabolic syndrome and DILI - a likely link



Francque SM et al, EASL, *J Hepatol*, 2021

Does MASLD/MASH confer a greater DILI risk?

- Scanty data in the literature
- Population-based studies did not mention on metabolic syndrome, obesity or other risk factors[1,2]
- Large DILI Registries failed to find a greater DILI risk [3,4]
  - No appropriate to test that hypothesis because of the selection bias
  - MASLD is often diagnosed by imaging/raised liver tests in patients with obesity or other components of metabolic syndrome

1.Sgro *et al Hepatology* 2002,
2.Bjornsson *et al Gastroenterology* 2013
3. Andrade *et al Gastroenterology* 2005
4.Chalasani et al *Gastroenterology* 2015

Does pre-existing MASLD increase the risk of DILI?

Experimental data support a higher susceptibility to DILI

- Physiologic doses of lipopolysaccharide induce a higher increase in aminotransferase levels and higher mortality in rodents with fatty liver.
- Steatotic liver is sensitized to apoptotic liver injury.
- Steatotic liver is more susceptible to bile acid–induced hepatotoxicity.

Effect of MASLD on drug metabolism

- Cytochrome P450 activity
- Transporters

Presence and stage of Advanced chronic liver disease (cirrhosis)

- Altered phamacokinetics and pharmacodynamics

Metabolic syndrome

Yang S, et al. *Am J Physiol Gastrointest Liver Physiol* 2001;281:G382–92.

Feldstein AE, et al. *Hepatology* 2004;40:185–94.

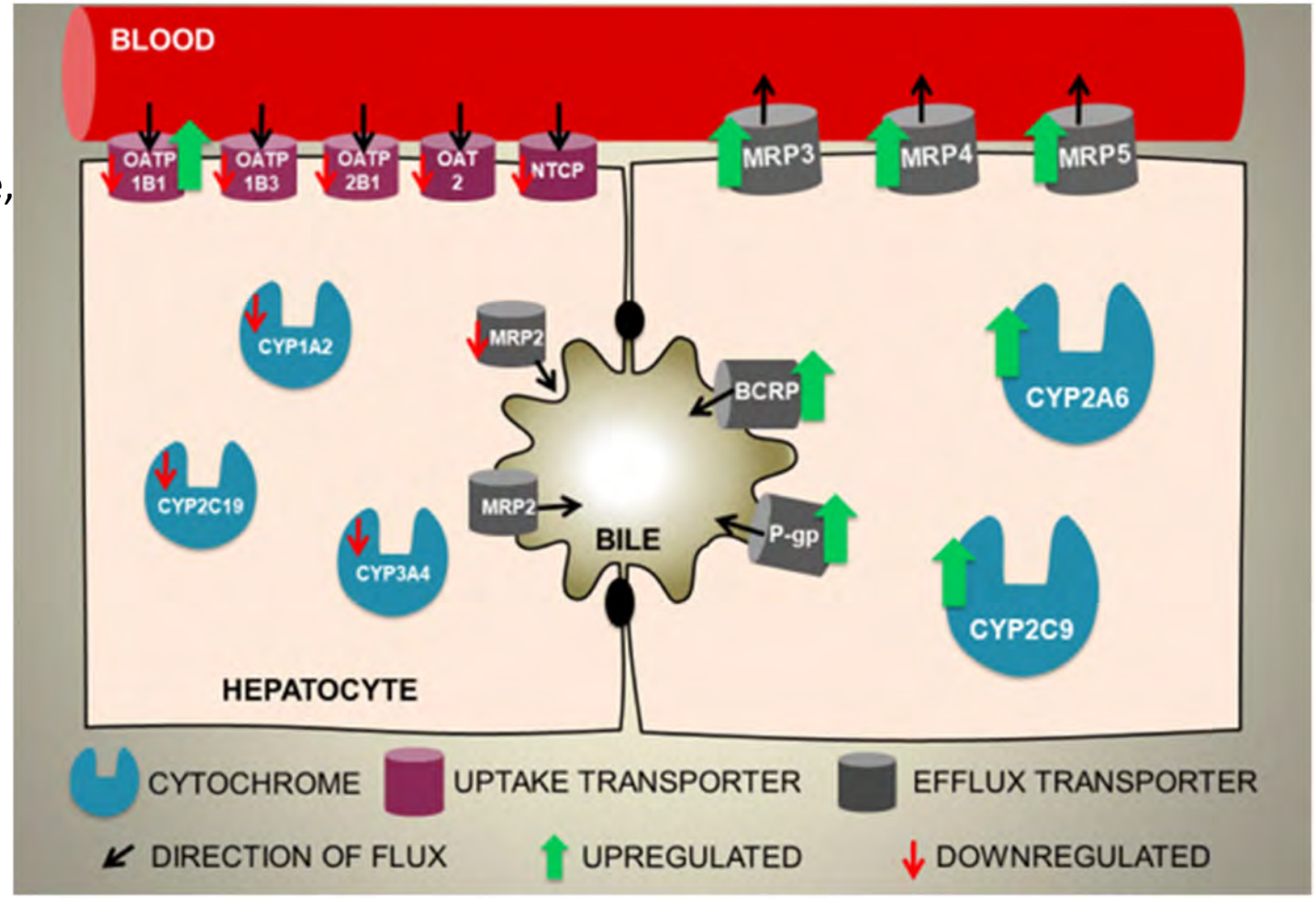
Soden JS, et al. *Hepatology* 2007;46:485–95.

Does pre-existing MASLD increase the risk of DILI?

Predicting disruptions to drug pharmacokinetics and the risk of adverse drug reactions in non-alcoholic steatohepatitis patients

Bibliografic research identified 71 drugs with reported ADRs in patients with liver disease, mainly non-alcoholic fatty liver disease (NAFLD), 54 of which are known substrates of transporters and/or metabolizing enzymes

Alterations on absorption, distribution, metabolism, and excretion processes, including a decrease in protein expression of basolateral uptake transporters, an increase in efflux transporters, and modifications to enzyme activity.



Marie S, et al. *Acta Pharm Sin B*. 2023 Jan;13(1):1-28.

Does pre-existing MASLD increase the risk of DILI?

Association Between Nonalcoholic Hepatic Steatosis and Hepatic Cytochrome P-450 3A Activity

49 human liver samples from the cadaveric solid organ donation process

Table 2. Selected Characteristics of Normal Liver and Fatty Liver Groups

	Normal group (n = 25)	Fatty liver group (n = 24)
Age (*y*)	43 ± 20 (18–69)	47 ± 11 (14–69)
Male/female (%)	15/10	16/8
Race	11 white/3 black/1 Asian	18 white/1 Hispanic/1 Asian
% Receiving medications with potential for interaction with CYP3A	28	29
CYP3A4 mRNA[a]	5063 ± 1565 (23–24,162)	3071 ± 803 (9–12,886)
CYP3A5 wt mRNA[a]	390 ± 134 (2–2515)	171 ± 66 (9–1467)
CYP3A5 SV1 mRNA[a]	45 ± 7.5 (7–113)	49.5 ± 15 (2–319)
PXR mRNA[a]	5.5 ± 1.6 (0.3–37)	5.3 ± 2.9 (0.2–66)
CYP3A4 protein content (*pmol/mg* protein)	8.5 ± 2.2 (0.2–33.9)	6 ± 1.3 (0.5–25.7)
CYP3A activity ($pmol \cdot min^{-1} \cdot mg^{-1}$ of protein)	4287 ± 659 (1337–14,397)	1978 ± 299 (278–6676)[b]

NOTE. Data are represented as mean ± standard error with ranges in parentheses unless indicated otherwise.
[a]mRNA values are in attograms/attograms after normalization to 18S RNA as a housekeeping gene.
[b]$P = .003$.

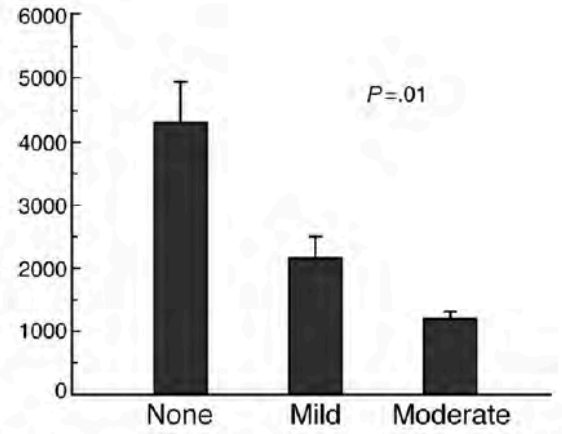


Figure 2. Relationship between hepatic CYP3A activity and severity of steatosis. Steatosis was categorized into none (n = 25), mild (≥5%–33% steatosis) (n = 20) or moderate steatosis (>33%) (n = 4). Data are shown as mean ± standard error.

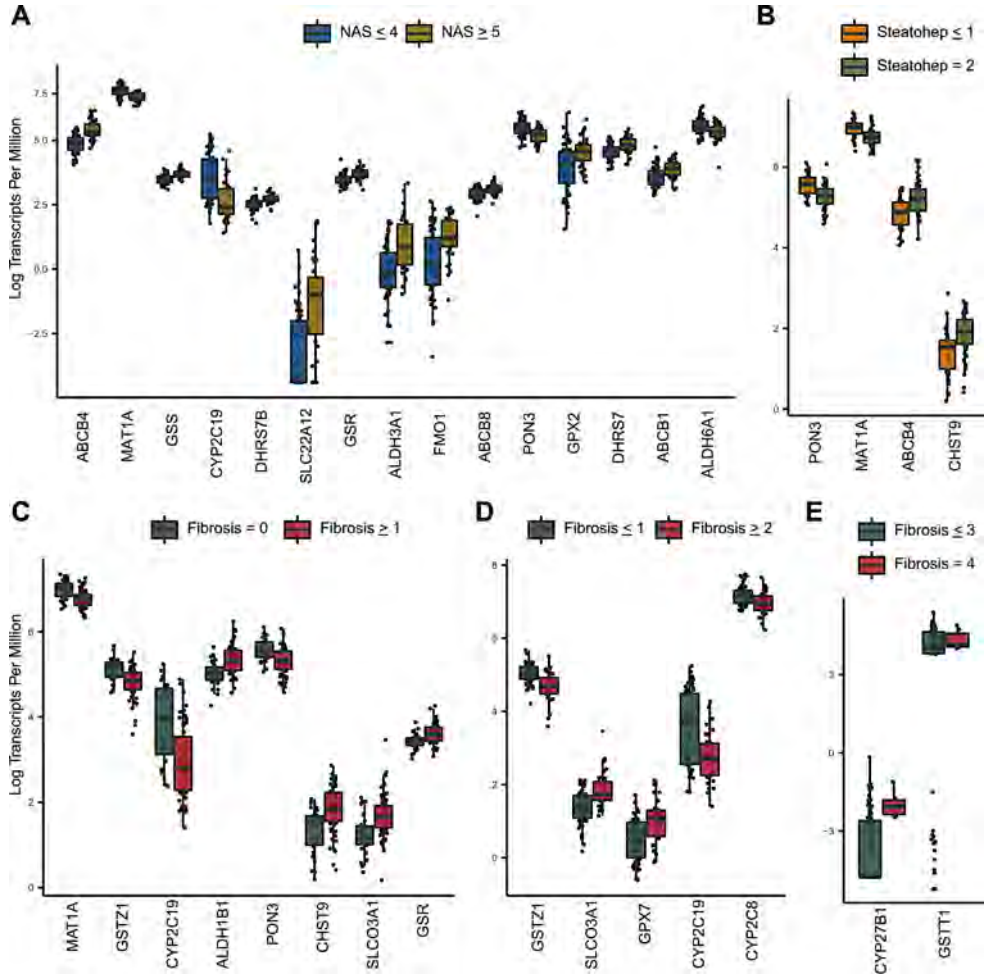
Hepatic steatosis is associated with decreased hepatic CYP3A activity in humans via post-translational mechanism.

Kolwankar D, et al. *Clin Gastroenterol Hepatol* 2007;5:388–393.

Clinically important alterations in pharmacogene expression in histologically severe MASLD

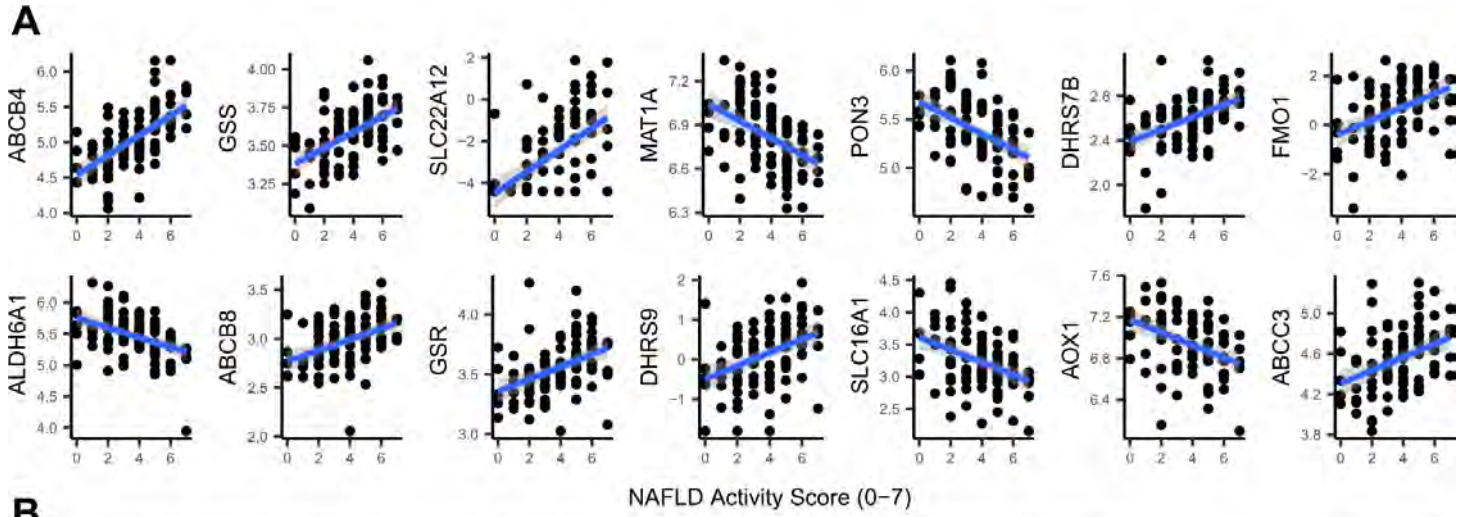
- RNA-seq for 93 liver biopsies histologically staged.
- Identification of 37 significant pharmacogene-MASLD severity associations.

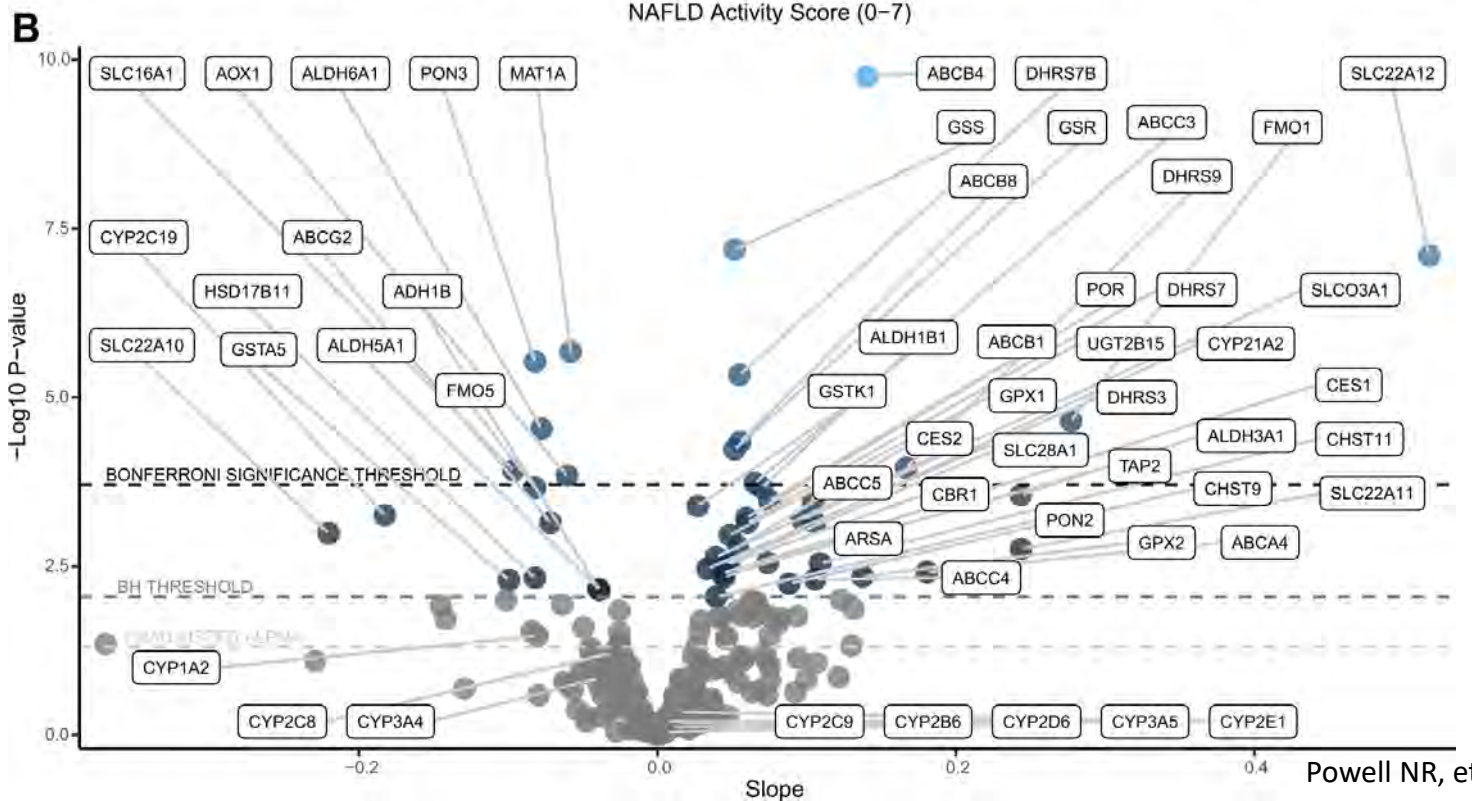
- Downregulation of *CYP2C19* in MASLD.
- Meta-analysis of 16 independent studies demonstrate that ***CYP2C19* is significantly downregulated to:**
  - **46% in NASH**
  - **43% in severe fibrosis**.



Powell NR, et al. *Nat Commun*. 2023; 17;14:1474.

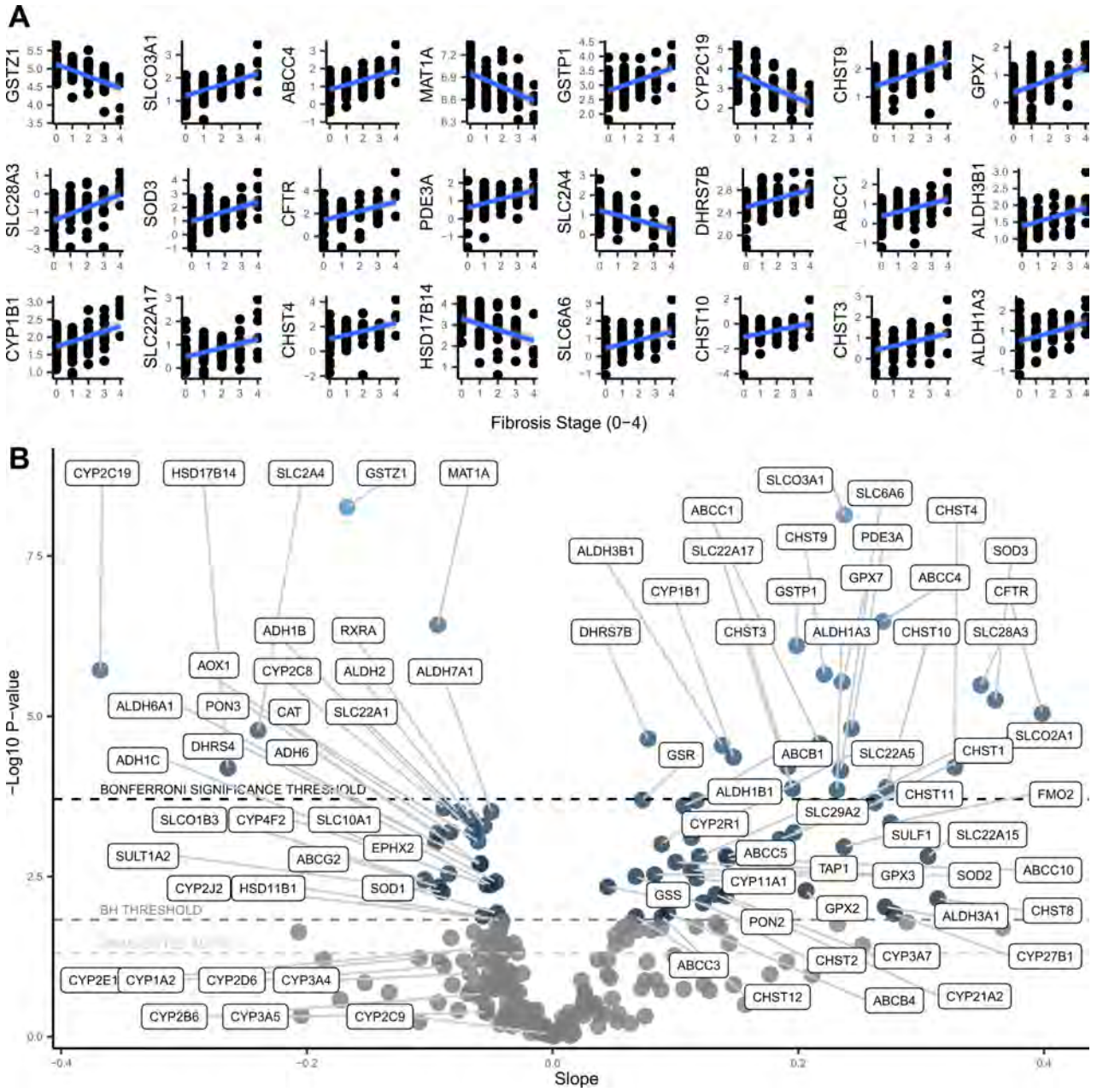
MASLD activity score correlates with decrease pharmacogene expression





Powell NR, et al. *Nat Commun*. 2023; 17;14:1474.

MASLD-fibrosis stage correlates with decrease pharmacogene expression



Powell NR, et al. *Nat Commun*. 2023; 17;14:1474.

Original Article

A prospective study of acute drug-induced liver injury in patients suffering from non-alcoholic fatty liver disease

Giovanni Tarantino,[1] Paolo Conca,[1] Vincenzo Basile,[2] Antonio Gentile,[2] Domenico Capone,[2] Giuliano Polichetti[2] and Emilio Leo[2]

[1]*Department of Clinical and Experimental Medicine and* [2]*Unit of Clinical Pharmacology, Department of Neurosciences, Federico II University Medical School of Naples, Naples, Italy*

Aim: Liver damage due to facultative hepatotoxins is scarcely foreseeable. We evaluated the prevalence of acute drug-induced liver injury (DILI) in a specific setting, assessing eventual interactions with pre-existing hepatic illnesses.

Methods: The research was carried out in an Italian tertiary care hospital, by analyzing 248 patients with non-advanced liver disease, divided into two well-matched groups: 174 patients (median age 53, 94 females) with hepatitis C virus-related chronic hepatitis; and 74 (median age 55, 39 females) with non-alcoholic fatty liver disease (NAFLD).

Results: Six patients (2.4% of the whole population) belonging to the NAFLD group (χ^2-test, $P = 0.004$) suffered from acute hepatoxicity related to the following drugs, that is anti-hypertensive, acting on platelet aggregation, antimicrobial, non-steroidal anti-inflammatory and proton pump inhibitor. The NAFLD presence was an independent risk factor in determining drug-related acute hepatitis, with an odds ratio of 3.95 (95% confidence intervals: 11.48–1.35). Central obesity was relevant in every patient with acute toxicity. Alcohol consumption and drug association did not influence the acute drug-induced liver damage.

Conclusion: NAFLD conveys a nearly fourfold increase of DILI risk in obese middle-aged patients. NAFLD, characterized by mitochondrial dysfunction, could predispose to drug-induced hepatotoxicity that probably shares the same pathophysiological mechanism.

Key words: DILI, NAFLD, metabolic syndrome, ALT, gamma-GT

Tarantino et al *Hepatol Res* 2007

A prospective study of acute drug-induced liver injury in patients suffering from non-alcoholic fatty liver disease

Giovanni Tarantino,[1] Paolo Conca,[1] Vincenzo Basile,[2] Antonio Gentile,[2] Domenico Capone,[2] Giuliano Polichetti[2] and Emilio Leo[2]

Table 3 Acute DILI in NAFLD patients with their highest and basal liver tests, histological features and drug exposure

Patient (a)	WHR	Gender	Age (years)	Drug (exposure time)	Hepatic injury (recovery time)
1† Fatty liver	0.96	Male	57	Fosinopril (14 days)	Acute hepatitis Moderate cholestasis (28 days)
2‡ NASH	0.91	Female	57	Losartan (15 days)	Acute hepatitis Minimal cholestasis (13 days)
3 Fatty liver	1.01	Male	51	Piperacillin-tazobactam plus NSAIDs (5 days)	Acute hepatitis Light cholestasis (19 days)
4 NASH	0.98	Female	53	Ticlopidine (15 days)	Acute hepatitis Minimal cholestasis (18 days)
5 NASH	1.12	Male	54	Telithromycin (4 days)	Acute hepatitis Light cholestasis (13 days)
6 NASH	1.04	Male	41	Omeprazole (13 days)	Acute hepatitis (12 days)

OUR DATA PROVIDE clear evidence that NAFLD conveys a nearly fourfold increase of DILI risk in middle-aged patients, not necessarily during combined therapies. Visceral adiposity presence, one of the MS grassroots criteria, had a relevant presence among the patients who developed DILI.

The concern about obesity rises, representing a major health problem in many countries. This aspect deserves great attention by physicians when treating metabolic patients with comorbidities to avoid acute toxicity.

Tarantino et al *Hepatol Res* 2007

Underlying liver disease & increased risk for all-cause DILI

Hypothesis

Individuals with chronic liver disease are not at increased risk for DILI due to common hepatotoxic agents.

Methods

Using the Indiana Health Information Exchange, we compared the frequency of suspected DILI between individuals with likely chronic liver disease (CLD cohort) and two control groups with no biochemical evidence for liver disease over a 10 year period.

- **CLD cohort** had serum ALT > 45 U/L on at least two occasions occurring 6-24 months apart in the absence of positive anti-HCV antibody, hepatitis B surface antigen, heavy alcohol consumption, or hypotension (N=25,499).
- **Control group 1** had ALT ≤ 45 U/L (N=276,897) and **Control group 2** had ALT ≤ 31 U/L in men and ALT ≤ 19 U/L in women (N=212,809) on at least two occasions occurring 6-24 months apart.
- **Suspected DILI** was defined as ALT > 200 U/L and/or AP > 250 U/L and/or total bilirubin > 2.5 mg/dl on at least two consecutive occasions within 3 months after receiving a **prescription for one of 10 candidate prescription medications**, in the absence of positive anti-HCV antibody, hepatitis B surface antigen, heavy alcohol consumption, or hypotension.

Lammert C & Chalasani N. *Clin Gastroenterol Hepatol* 2019

Clinical Gastroenterology and Hepatology 2019;17:2814–2815

Patients With Chronic Liver Disease Suggestive of Nonalcoholic Fatty Liver Disease May Be at Higher Risk for Drug-Induced Liver Injury

Craig Lammert,* Timothy Imler,*,‡ Evgenia Teal,‡ and Naga Chalasani*

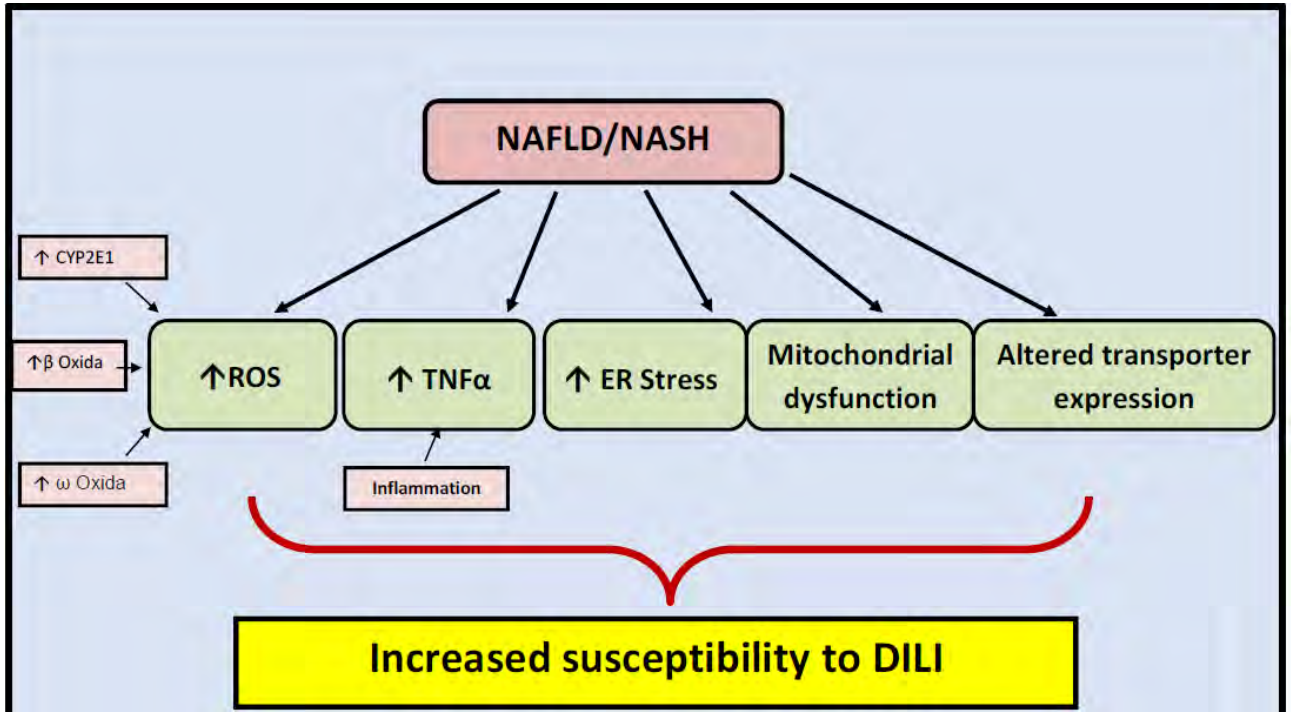
The 10 candidate medications *were as follows: amoxicillin-clavulanate,isoniazid, nitrofurantoin, minocycline, trimethoprim-sulfamethoxazole, ciprofloxacin,levofloxacin, azithromycin, cefazolin, and diclofenac.*

- *DILI in 4837 NAFLD cohort was* ***0.8%*** *(40 of 4837) significantly higher than in:*
  - *control group 1 (126 of 61,355 [0.2%];* ***odds ratio, 4.0****; 95% CI, 2.8–5.8; P <.001)*
  - *control group 2 (96 47,869 [0.2%];* ***odds ratio, 4.17****; 95% CI, 2.9–6.0; P < .001)*

	ALT<45 Control group 1 (n = 61,355)	Suspected NAFLD cohort (n = 4837)	ALT<31 Control group 2 (n = 47,869)
Age, *y*, means ± SD	55.8 ± 18	50.6 ±14.7	56.7 ±18
Females, %	65	48	60
Ethnicity, black/white, %	11/87	8.6/90	12/87
BMI, kg/m^2, means ± SD	31 ± 8.6	32.1 ± 8.7	30.4 ± 8.4
AST at baseline, *IU/L*, means ± SD	21.5 ± 11.5	56 ± 38	20 ± 11
ALT at baseline, *IU/L*, means ± SD	19 ± 8.2	69 ± 27	17 ± 5
Alk P at baseline, *IU/L*, means ± SD	74.5 ± 29	93 ± 41	73 ± 27
Total bilirubin at baseline, *mg/dL*, means ± SD	0.6 ± 0.5	0.7 ± 0.4	0.6 ± 0.34
Presence of type 2 diabetes, %[a]	24	34	24
Presence of hypertension, %[a]	50	56	51
Suspected DILI, %	0.2	0.8 *P* < .001	0.2 *P* < .001
Death or transplant within 6 months after suspected DILI onset, %	16.6	25 *P* = .2	13.5 *P* = .1

Mechanisms whereby MASH could increase the susceptibility of drug-induced acute liver injury.

- MASH is associated with increased CYP2E1 expression and activity, reduced MRC activity and inflammation.
- These events lead to ROS overproduction, reduced ATP synthesis and increased production of pro-inflammatory cytokines such as TNFα, which can favor the occurrence of DILI.



Massart J,et al. *J Clin Transl Res*. 2017 Feb;3(Suppl 1):212-232.

Does pre-existing CLD worsen outcomes of DILI?

- Patients with CLD and a superimposed DILI resulting in a new hepatic decompensation and possibly other organ failure would meet the definition of Acute on chronic liver failure (**ACLF)**.
- DILI accounts for a small proportion of ACLF: **1%–10% .**
- Geographic differences:
  - in underlying liver disease (a more common viral disease in the east)
  - In the class of implicated agents (antituberculosis, HDS, or complementary and alternative medicine in the east)
- Mortality rates are uniformly high ranging from 35% to 50%.

Ghabril M, Vuppaet al. *Liver Int*. 2025 Mar;45(3):e70019.

Does pre-existing CLD worsen outcomes of DILI?

Underlying liver disease	**Spanish DILI Registry 6,3%** Stephens 2021	**DILIN 10%** Chalasani 2015
Liver related death	7,5% vs 1,8% (p 0,0221)	9% vs 2,4 % (p 0,5)
Liver trasplant	0%	3,4% vs 4,1 (p1)
Mortality		16% vs 5,2% (p< .001)
Type of baseline liver injury	Viral Hepatitis Alcohol related liver disease	Viral Hepatitis MASLD
Drugs	Anti-tbc	Azitromicin

Stephens C, et al. *J Hepatol.* 2021 Jul;75(1):86-97.
Chalasani et al *Gastroenterology* 2015

World Journal of Hepatology

Submit a Manuscript: https://www.wjgnet.com World J Hepatol 2025 February 27; 17(2): 101741

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ORIGINAL ARTICLE

Retrospective Study

Clinical features and prognosis of drug-induced liver injury in patients with non-alcoholic fatty liver

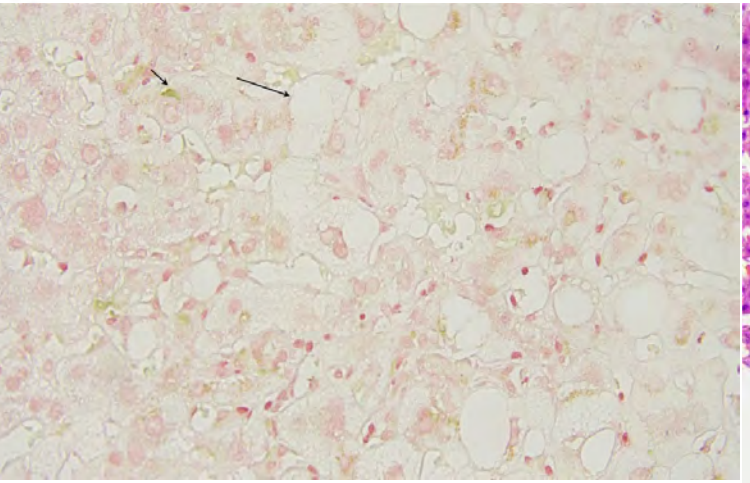
Ying Zhao, Jian-Zhou Li, Yong-Gang Liu, Yu-Jin Zhu, Yan Zhang, Wen-Wen Zheng, Lin Ma, Jia Li, Chun-Yan Wang

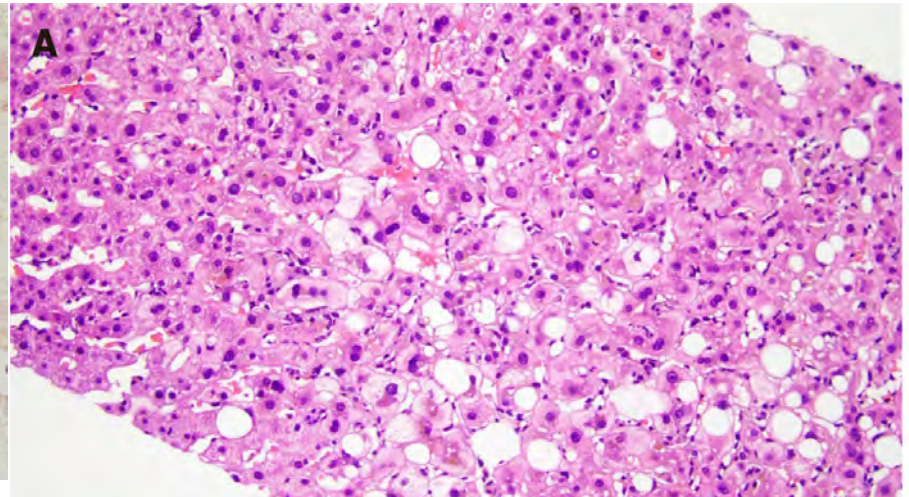
Table 6 Classification of severity of liver injury in the two groups

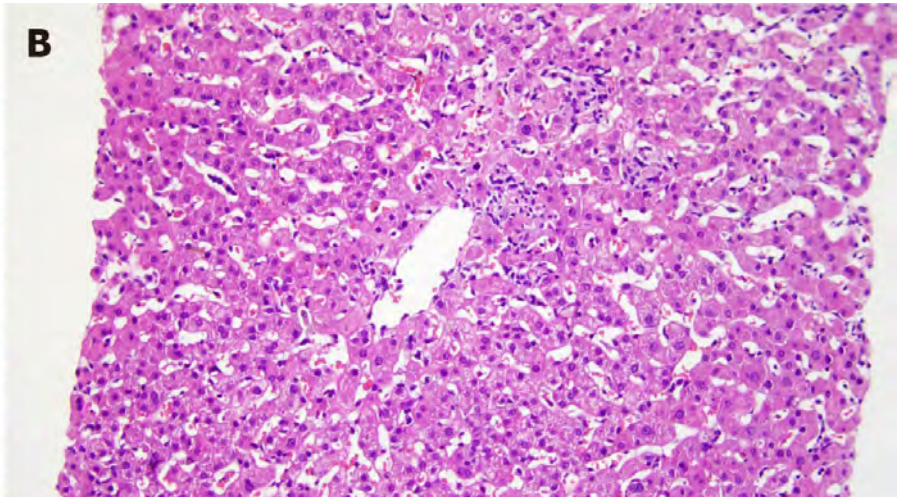
Grade	DILI (*n* = 89)	DILI + NAFL (*n* = 110)	*P* value
≤ grade 2	53 (59.55)	57 (51.82)	0.023
> grade 2 or above	36 (40.45)	53 (48.18)	

Table 5 Classification of liver injury in the two groups

Drug-induced liver injury types	DILI (*n* = 89)	DILI + NAFL (*n* = 110)	*P* value
Hepatocellular	79 (88.8)	77 (70)	0.001
Cholestatic types	4 (4.5)	18 (16.4)	0.008
Mixed	6 (6.7)	15 (13.6)	0.115







Does pre-existing MALD/MASH confound causality assessment in DILI ?

- Distinguishing DILI from MASLD/MASH in the hepatocellular pattern is challenging:
  - Suggest DILI if ALT levels exceed 5 times the ULN.
  - Alternatively, if there are concomitant increases in TB and symptoms such as nausea, vomiting and abdominal pain.
  - Other phenotypes (i.e. chol or mixed) are not consistent with the spontaneous progression of MASLD
- Chronic liver disease (cirrhosis) requires an individualized causality assessment
  - The criteria for case definition (i.e. ALT level > 5 x ULN) may be absent
  - The RUCAM scale is not suitable for use in this context

Causality in patients with underlying liver disease – DILIN experience

- In a prospective study of DILI cases, 10% had pre-existing liver disease (majority had MASLD). When assessed by expert opinion causality scores were different compared with patients without chronic liver disease

	Definite	Highly likley	Probable	P-value
Known pre-existing liver disease	17	49	34	0.009
No known chronic liver disease	27	52	21	

Chalasani *et al Gastroenterology* 2015

Mensajes finales

- La enfermedad hepatica condiciona **cambios farmacocinéticos y farmacodinámicos** cuya influencia en la susceptibilidad al DILI es incierta.
- El **tipo de enfermedad** hepatica condiciona **una mayor susceptibilidad** al DILI para algunos fármacos.
- Algunas enfermedades hepaticas, incluyendo **el MASLD/MASH podría incrementar el riesgo de aparición de DILI idiosincrásico**.
- El **efecto esteatogénico de diversos fármacos podría agravar el MASLD/MASH pre-existente**, aunque su influencia neta es difícil de estimar.
- En los pacientes con enfermedad hepática crónica, **el riesgo de evolución grave y muerte** durante un epidodio de DILI es mas elevado
- La enfermedad hepática **incrementa la dificultad en adjudicar** un evento hepático a un fármaco y constituye un desafío para la monitorización de la seguridad de fármacos en ensayos clínicos.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