Acute liver injury after SARS-CoV-2 vaccination

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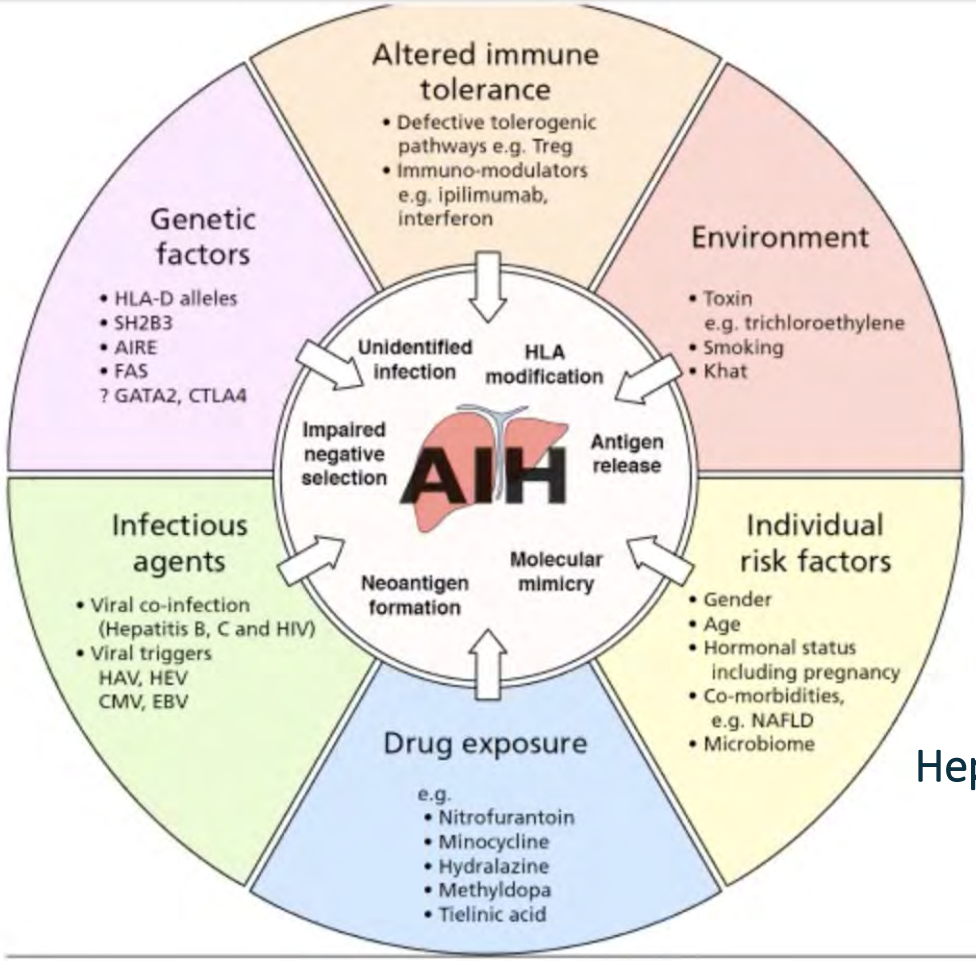
AIH is a heterogeneous condition

18 year old female
ALT 200 U/l
Anti-LKM positive
Interface hepatitis

Liver biopsy:
consistent with
AIH



18 year old female
ALT 200 U/l
Anti-LKM positive
Interface hepatitis

Liver biopsy:
consistent with
AIH

Hepatitis C PCR positive

- Although COVID-19 vaccines have show effectiveness in preventing severe and fatal courses of COVID-19, they have been associated with a range of side effects

- During the immunization of billions of people, an increasing number of cases of acute hepatitis following vaccination have been reported.

Bril F. et Al., J Hepatol 2021; Tun GS et Al. , J Hepatol 2021; Ghielmetti M. et Al. , Journal of Autoimmunity 2021

- Most of the cases showed a phenotype resembling autoimmune hepatitis, with:
  - ✓ Positive autoantibodies
  - ✓ Elevated IgG levels
  - ✓ Interface hepatitis in liver histology

Efe C. et Al. , Hepatology 2022

Liver injury after SARS-CoV-2 vaccination: Features of immune-mediated hepatitis, role of corticosteroid therapy and outcome

- Retrospective report of 87 patients from all over the world
- 12 with pre-existing liver disease
- 73 hepatocellular pattern
- 45 had IgG > ULN and/or positive autoantibodies
- 46 treated with corticosteroids
- Favorable outcome in all but one, requiring LT

Efe et al, Hepatol 2023

Our index case

63-year old man with pre-existing mild diabetes (metformin) and coronary heart disease (aspirin, rosuvastatin)

Presented with jaundice and fatigue 7 days after the first mRNA-1273 dose

Abdominal US: normal liver parenchyma, no ascites, spleen 11 cm

Laboratory results:
INR 1.16
ASAT 1127 U/l (ULN 35 U/l)
ALAT 1038 U/l (ULN 55 U/l)
GGT 536 U/l (ULN 55 U/l)
ALP 192 U/l (40–150 U/l)
total bilirubin 204.8 µmol/l (ULN 20.4 µmol/l)
PCR HBV, HCV and HEV and anti-HAV IgM negative

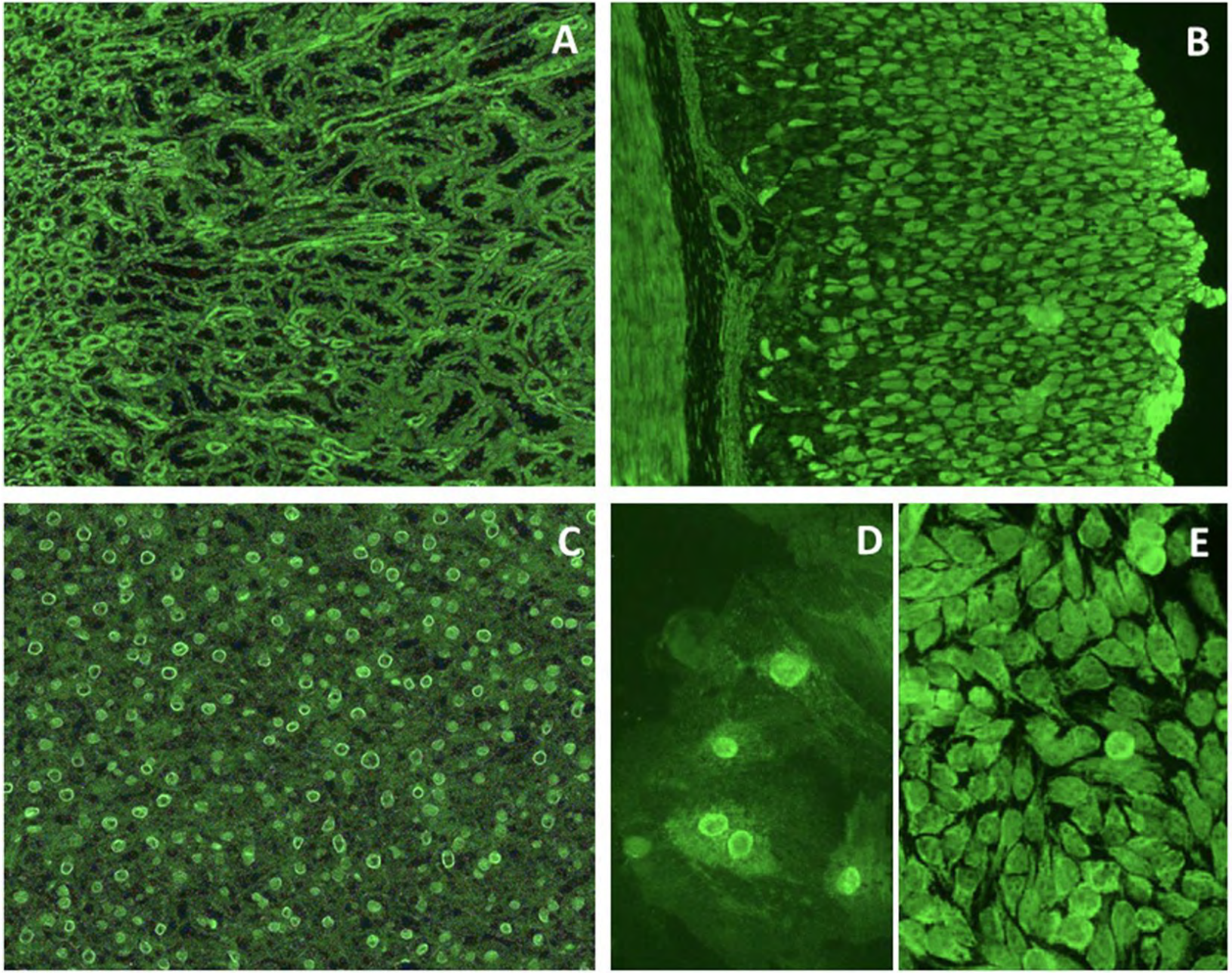
IgG 19.7 g/l (normal range: 5.4–18.2 g/l)

Ghielmetti et al, J Autoimmun 2021

Atypical AMA

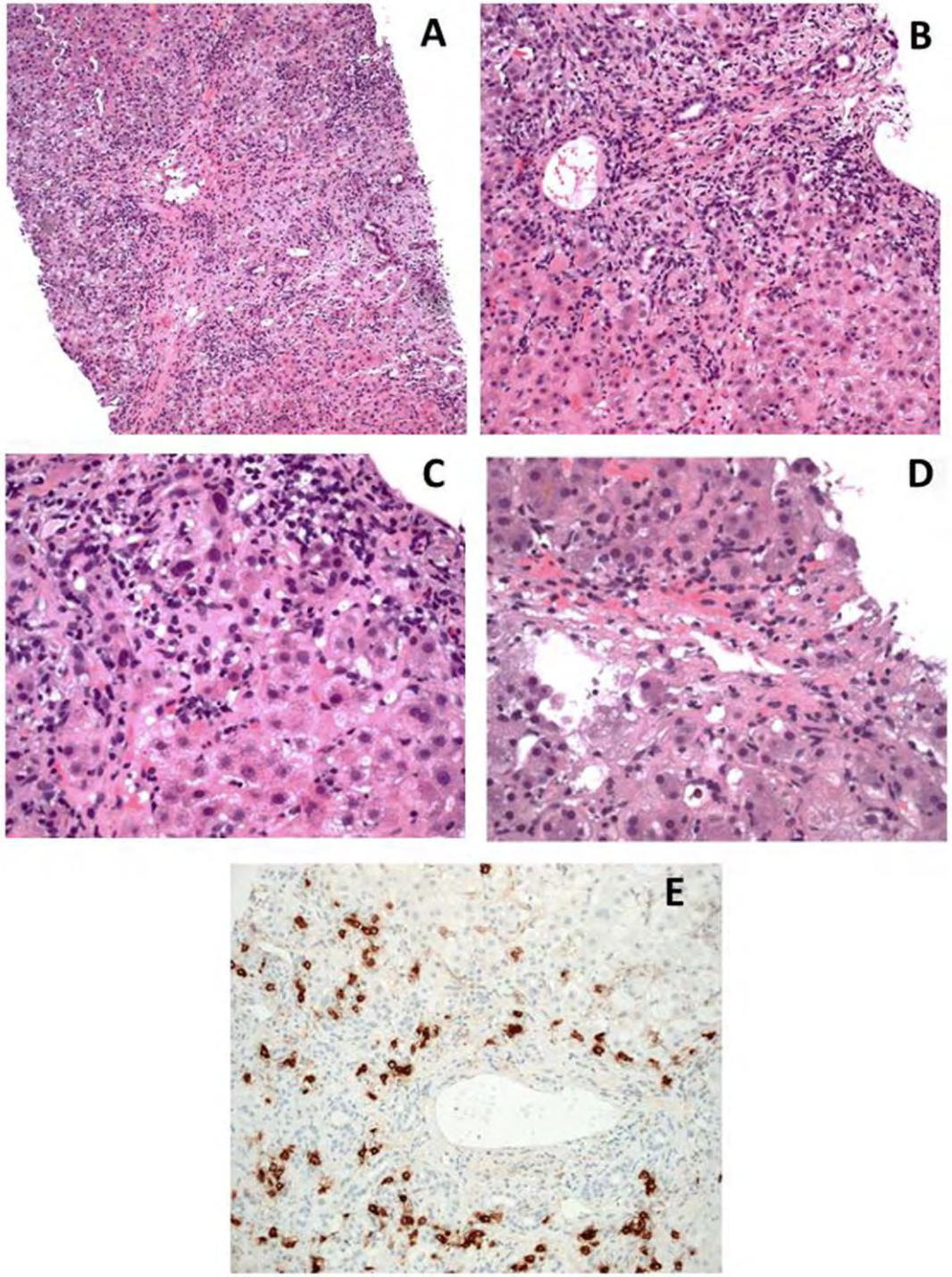
ANA
Speckled
Rim-like

Efe had 5
AMA+ patients
in his cohort



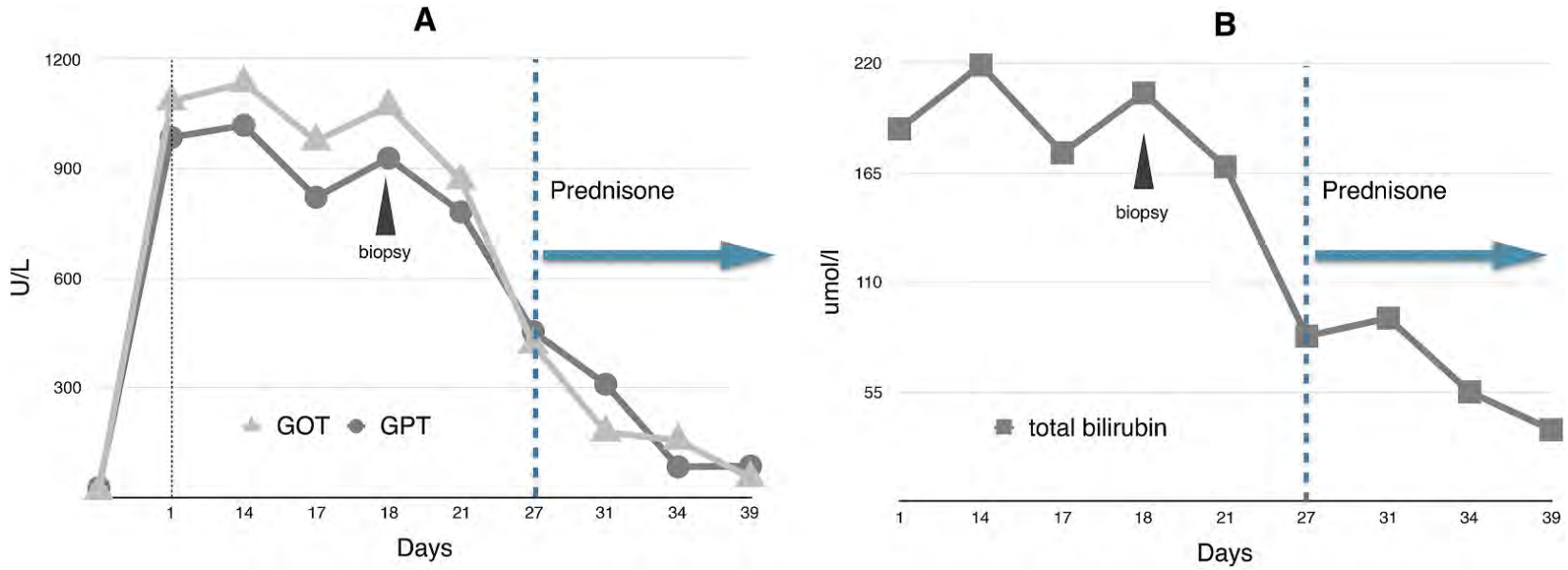
Ghielmetti et al, JAUT 2021

inflammatory portal infiltrate with interface hepatitis, lobular and centrilobular inflammation with centrilobular necrosis, in absence of fibrosis and steatosis



Ghielmetti et al, JAUT 2021

Treatment: prednisone 40 mg/ d with rapid tapering



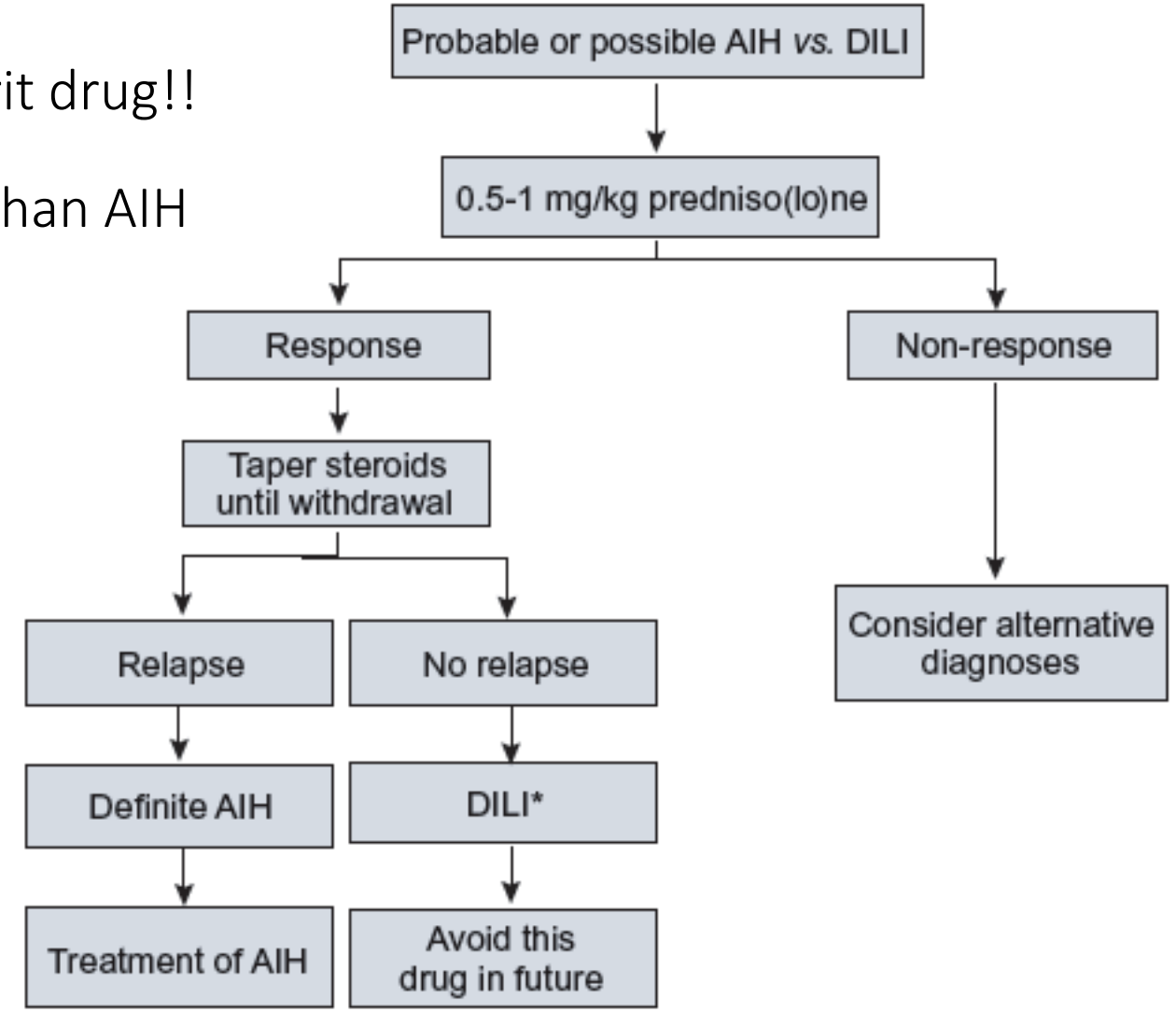
Prednisone withdrawal after 6 months without repalse after 3 years of follow-up

Ghielmetti et al, JAUT 2021

Drug-induced autoimmune-like hepatitis

Discontinue culprit drug!!

Response faster than AIH



EASL clinical practice guidelines 2015
Andrade et al, JHEP 2023

Background and aim

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,#,*]

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October 2022: large international cohort of 59 adults with acute liver injury within 3 months from vaccination against SARS-CoV-2

Liver biopsy, serological values and circulating autoantibodies were collected.

Admission criteria

Inclusion criteria:

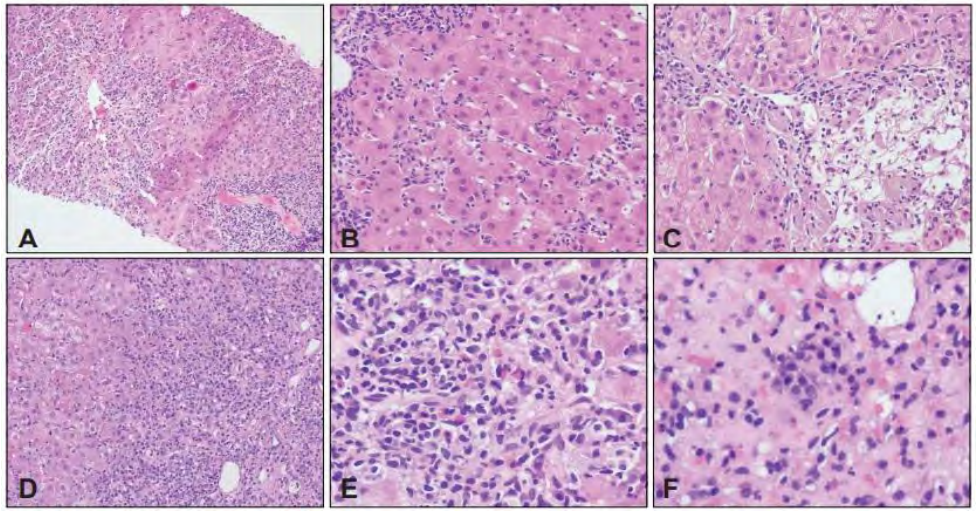
- Elevation of transaminase levels ≥ 5x ULN within 3 months from any vaccination against SARS-Cov-2
- Liver biopsy available
- Clinical follow up of at least 3 months or until liver transplantation/death from the diagnosis of acute liver injury

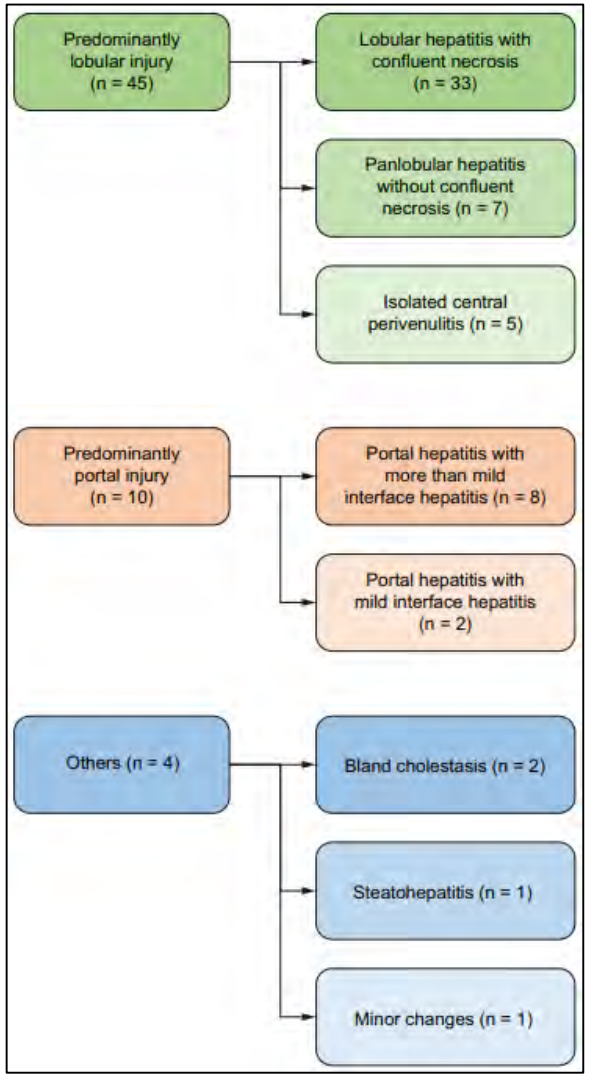
Exclusion criteria:

- Known history of autoimmune liver disease (AIH, PBC, PSC)
- Acute or chronic viral hepatitis including hepatitis A,B,C,D or E
- History of liver transplant

Histopathology

Liver biopsies were centrally reviewed by an experienced histopathologist, Prof. Dr. Yoh Zen





AIH vs DI-AILH

- Serological, biochemical and histopathological data were compatible with both AIH and DI-ALH in most cases

- The distinction between these two clinical entities remains a challenge in clinical practice, often being impossible at presentation.

Andrade RJ et Al., J Hepatol 2023;

- **The most reliable feature for reaching the correct diagnosis is considered the withdrawal of immunosuppression without hepatitis relapse**.

EASL Clinical Practice Guidelines: Autoimmune hepatitis, J Hepatol 2015;
Andrade RJ et Al. , J Hepatol 2023;

Scoring systems are not helpful in differentiating AIH from DI-AILH

Simplified IAIHG scoring system

82% of patients scored as ‘typical or ‘probable’ AIH

New ERN histology scoring system

92% of patients scored as ‘likely’ or ‘possible’ AIH

In particular, the new ERN histological criteria, which include the acute presentation of AIH characterized by lobular hepatitis, led to a more frequent rate of AIH likelihood (“likely”, 70%) compared to the IAIHG criteria (“typical”, 24%)

Codoni et al, JHEPR 2022
Hennes et al, Hepatol 2008
Lohse et al, Liv Int 2022

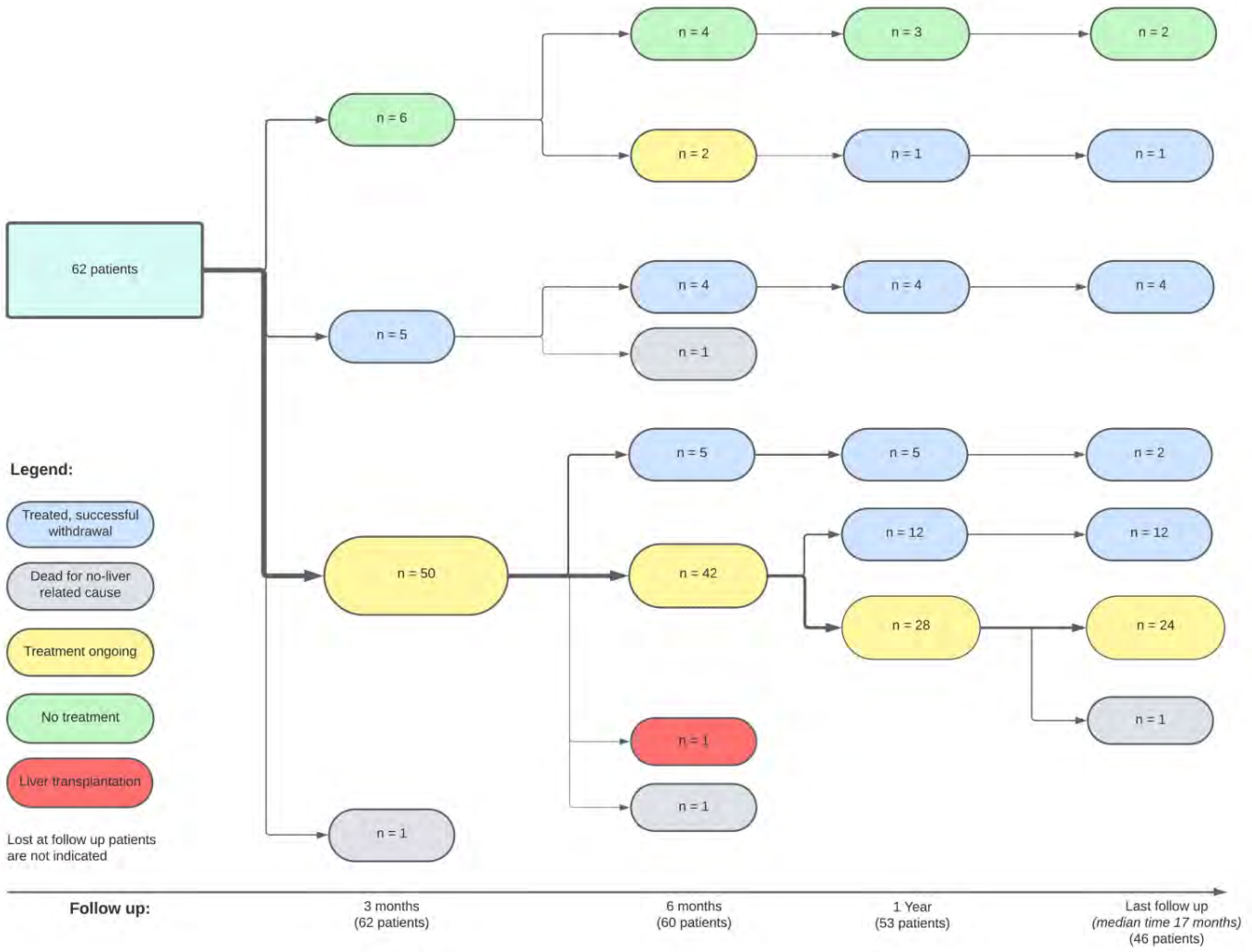
Follow up at 17 months

In the present study, we report the 17-month follow-up of our large international cohort, with the aim of understanding whether acute liver injury following COVID-19 vaccines follows a course like AIH or DI-AILH over time

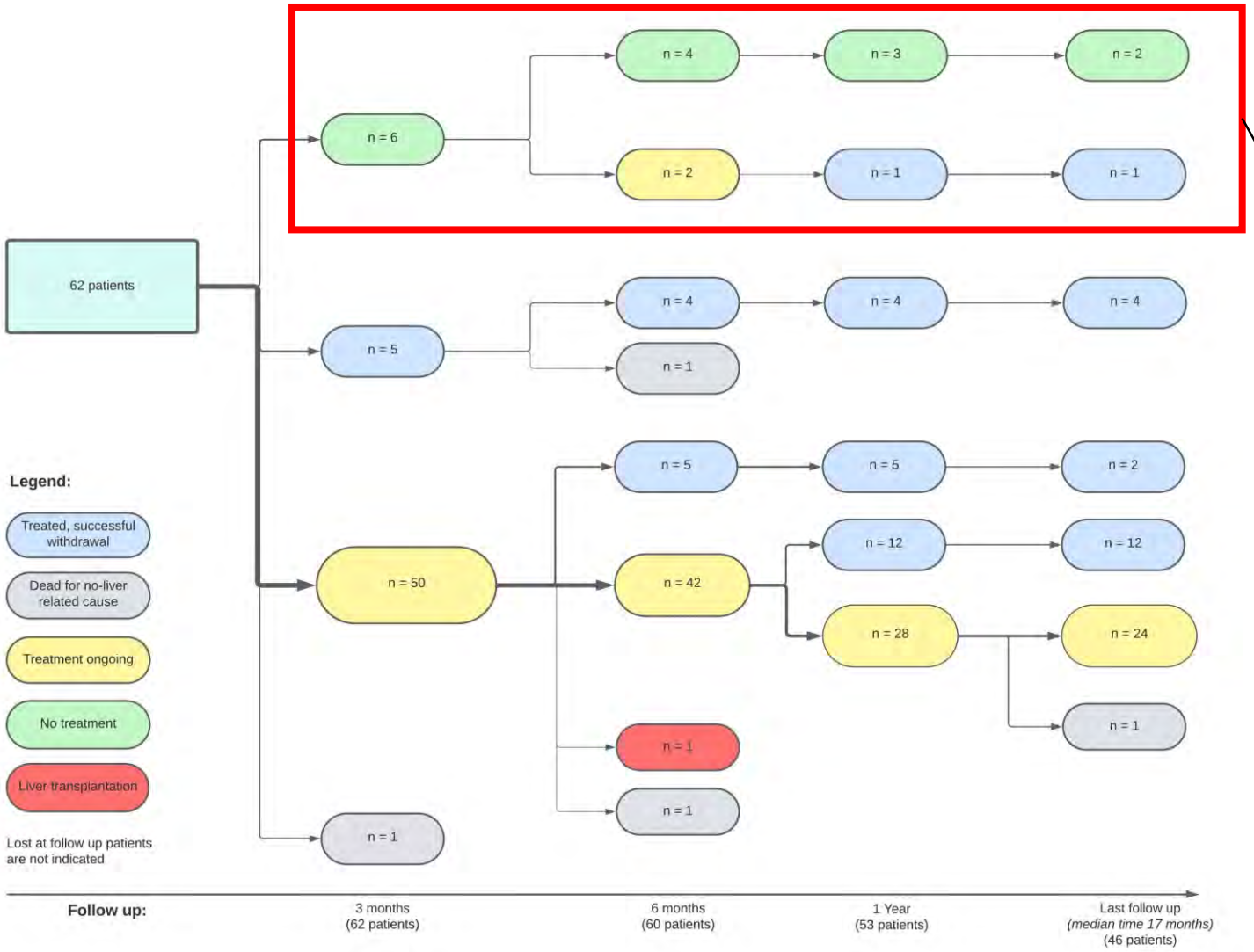
Study population:

- 62 patients
- 35 female (57%)
- Median age: 56.5 y (19-92)
- Follow-up data at 6-12 and last available follow up after hepatitis
- Median follow up time (months): 17.1 (4-24)
- Original inclusion/exclusion criteria were considered

Results: our cohort

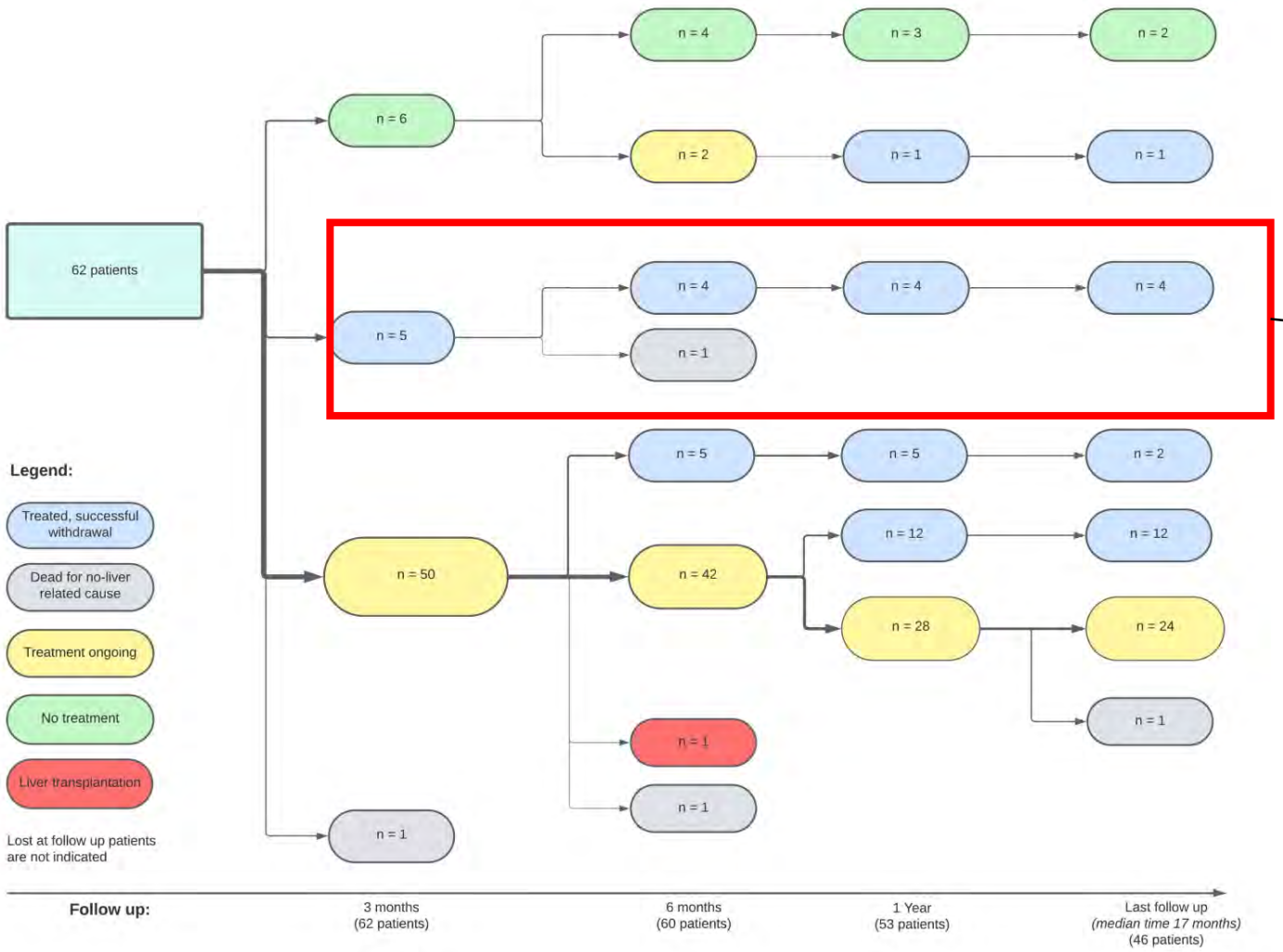


Results: our cohort



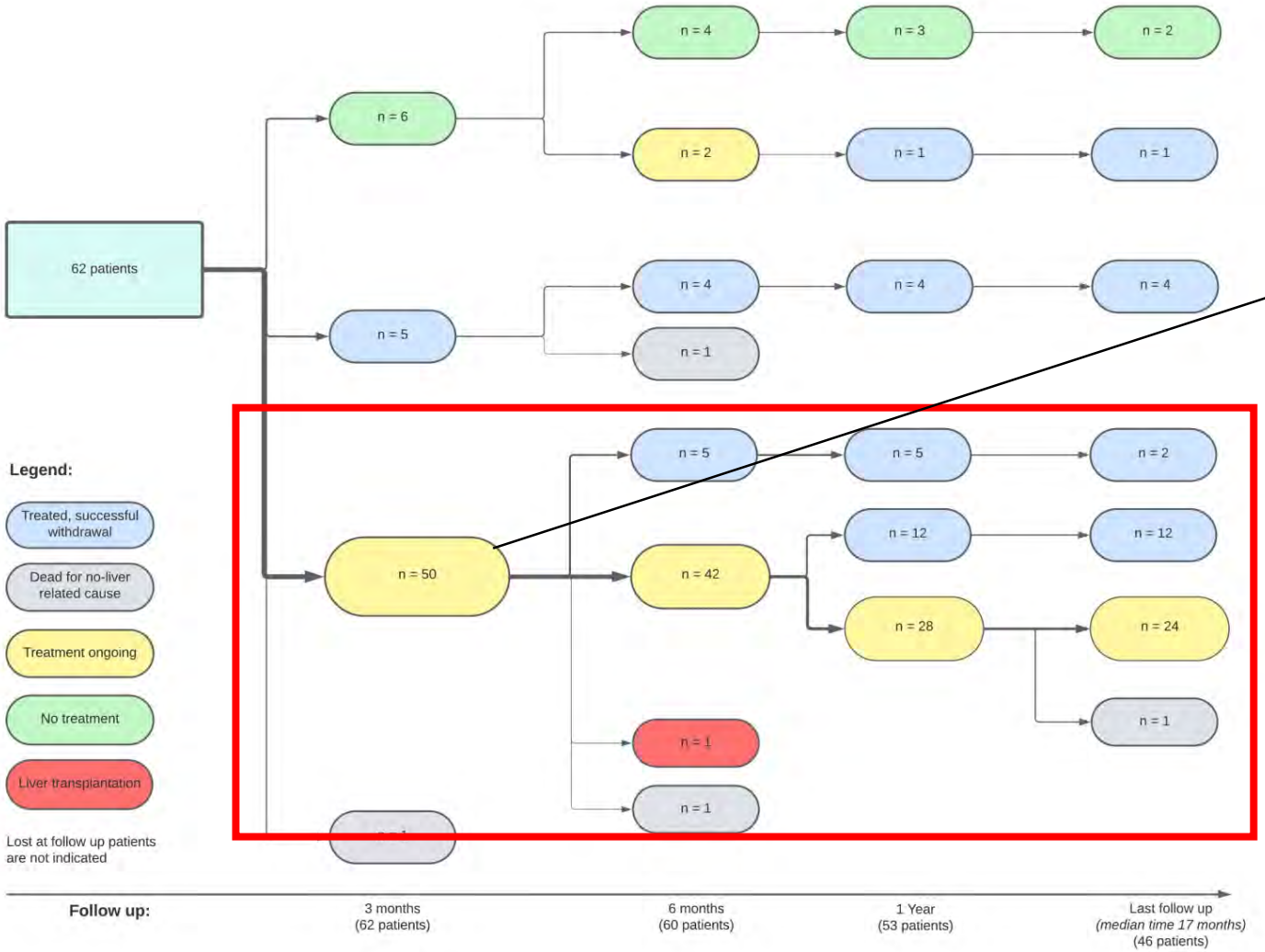
- 6 patients had spontaneous improvement at diagnosis
- 2 were treated lately with a successful treatment withdrawal

Results: our cohort



5 patients discontinued treatments at 3 months already

Results: our cohort



Among these 50 patients we had at 3 months:

- 21 patients who had normal ALT levels
- 29 patients had still ALT levels elevated

Results: 3 sub-groups

- DI-AILH-like course: 22 patients
  - ✓ALT normalization within 9 months (18)
  - ✓No relapse after treatment discontinuation (4)
- AIH-like course: 14 patients.
  - ✓Relapse after immunosuppression discontinuation (5)
  - ✓Liver transplant (1)
  - ✓Persistence of abnormal ALT levels >= 6 months of treatment duration (8)
- Non-definable course: 26 patients
  - ✓Persistence of normal ALT levels without a treatment discontinuation attempt (21)
  - ✓Lost to follow-up (2)
  - ✓Early treatment discontinuation (side-effects) (1)
  - ✓Death from non-liver-related causes within 3 months of diagnosis (1)

Results: 3 sub-groups

Factors linked to an AIH-like course

- Autoimmune comorbidities
- Higher IgG levels at diagnosis
- Advanced fibrosis
- Moderate-severe interface hepatitis

	DI-ALH-like (22 patients)	AIH-like (14 patients)	P value
Gender: Male/Female	13 / 18	7 / 7	p = 0.7
Age > 50 y	9	10	p = 0.0967
Last vaccine before hepatitis was mRNA	17	10	p = 0.7115
Time from vaccine to hepatitis (median of days)	18	24.5	p = 0.7317
Number of vaccine doses before hepatitis (median)	2	2	p = 0.726
Autoimmune comorbidities	3	7	p = 0.0262
ALT (U/l) at three months, median	30	123	p = 0.0005
IgG (g/dl) at diagnosis, median	16.4	20	p = 0.016
Hy's law	11	8	p = 1
ANA > 1:160 titer	12	11	p = 0.175
ASMA positive	3	6	p = 0.122
AMA positive	2	1	p = 0.5076
Predominant histology: lobular/portal pattern	18 / 2	8 / 4	p = 0.1651
Advance fibrosis	0	3	p = 0.051
AIH possible or likely according to new histological criteria	20	12	p = 0.4847
Confluent necrosis	13	7	p = 0.773
Panlobular necrosis	2	1	p = 1
> mild interface hepatitis	0	3	p = 0.051
AIH simplified score ≥ 6	10	8	p = 0.49

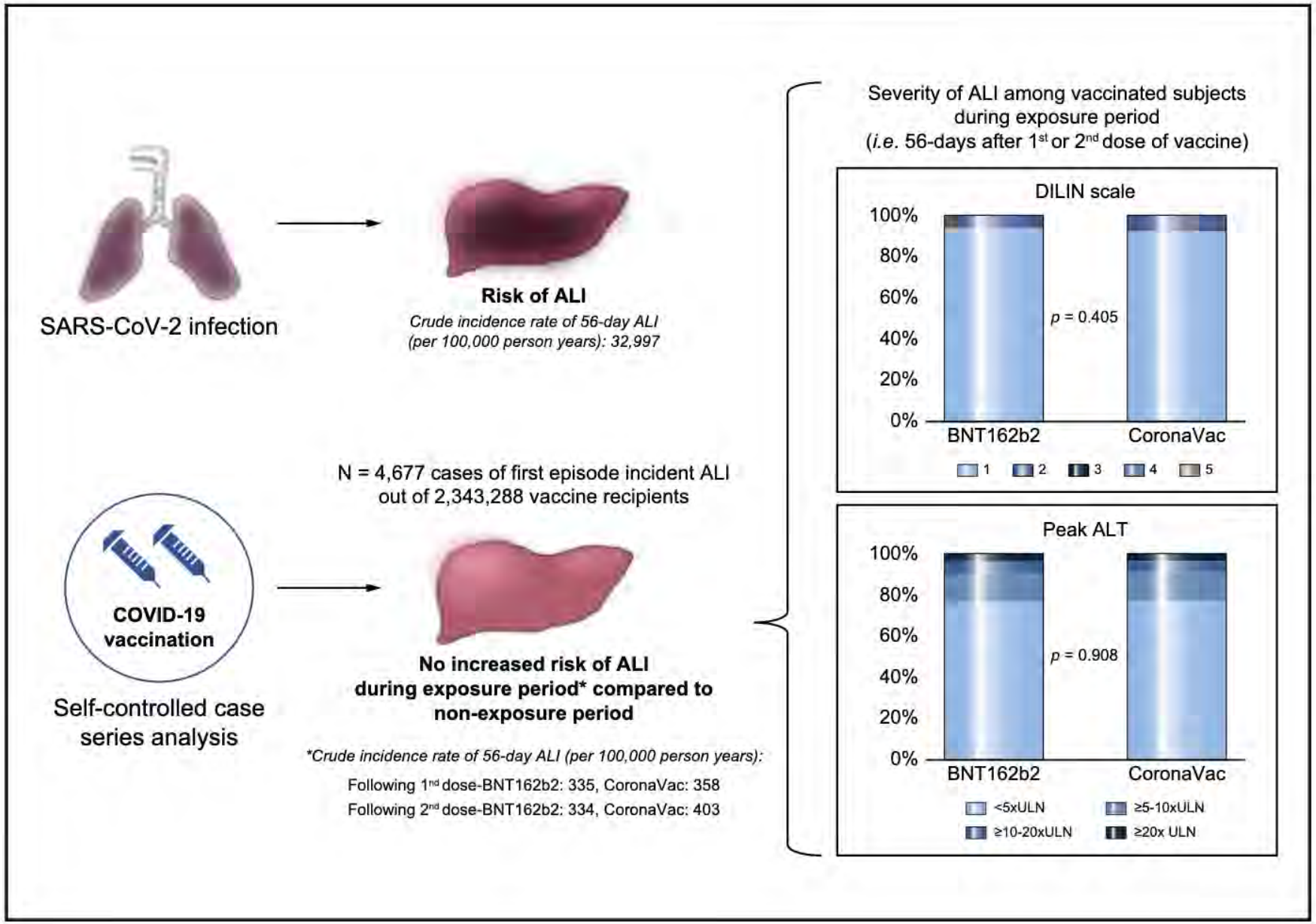
Conclusions

- The course of acute liver injury after COVID-19 vaccine is heterogeneous, mainly favorable
- A small fraction had a more aggressive course resembling AIH
- A longer follow-up is required to determine whether these patients have developed AIH triggered by the COVID-19 vaccine

Of note, the majority of patients
presented after the second vaccine dose, suggesting that repeated
exposure increases the risk of liver injury with autoimmune features

Three patients had mild hepatitis after the first dose of vaccine but a more severe liver injury after a second dose of the same vaccine

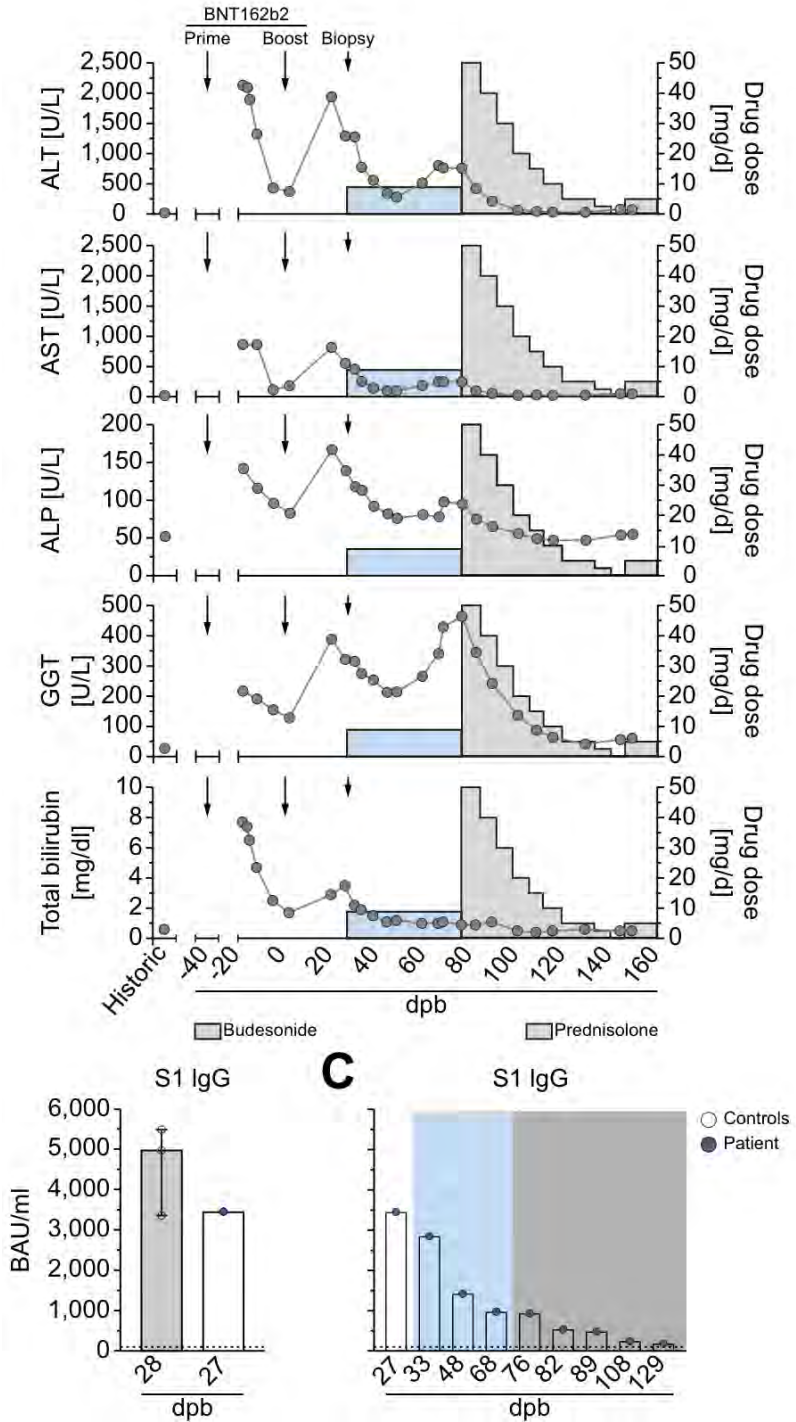
Codoni, JHEPR 2021
Efe, Hepatol 202



Wong et al, JHEP 2022

Pathophysiology

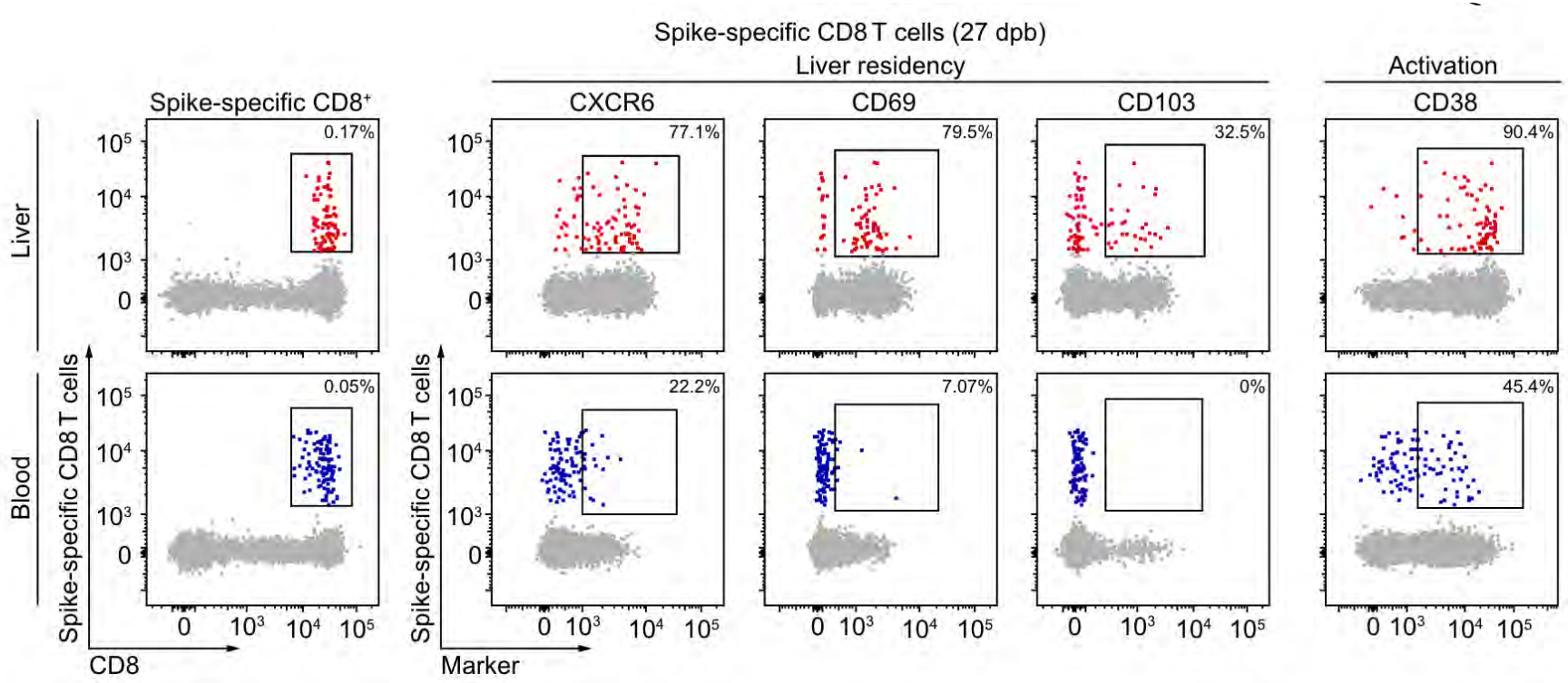
52-year-old male presenting with acute mixed hepatocellular/cholestatic hepatitis after the first dose of BNT162b2 mRNA vaccine and severe hepatitis after the second dose



Liver biopsy:
Interface hepatitis with moderate degree of lymphoplasmacytic infiltrate and foci of lobular necrosis and apoptosis. Eosinophilic granulocytes were not present. Neither relevant perisinusoidal nor portal fibrosis were observed.

Boettler et al, JHEP 2022

Anti-spike specific CD8 T cells in the liver and in the blood



Is the liver injury related to the spike protein rather than to the vaccine type?

Boettler et al, JHEP 2022

Morphologic and molecular analysis of liver injury after SARS-CoV-2 vaccination reveals distinct characteristics

Patient ID	Age	Sex	Symptoms	Symptoms after vaccination	Drugs at time of vaccination	Therapy (prednisone)*	Follow-up (months)	Remission
VILI1	48	F	Fatigue, abdominal pain	2 days after 2nd vaccination	Multivitamins	40 mg/d for 3 months	18	Yes
VILI2	85	M	Nausea, dark urine	5 days after 1st vaccination	None	None	18	Yes
VILI3	21	F	Fatigue, jaundice, nausea	21 days after 2nd vaccination	Oral contraceptive	60 mg/d for 3 months	15	Yes
VILI4	53	M	Fatigue, jaundice, nausea	7 days after 2nd vaccination	None	40 mg/d for 3 months	18	Yes
VILI5	63	M	Fatigue, jaundice, weight loss	10 days after 1st vaccination	Aspirin, rosuvastatin, metformin	40 mg/d for 11 months	18	Yes
VILI6	78	M	None	28 days after 1st vaccination†	Lercanidipine, telmisartan	40 mg/d for 5 months	12	Yes

New histological AIH criteria:

VILI
Likely AIH 5/6
Possible AIH 1/6

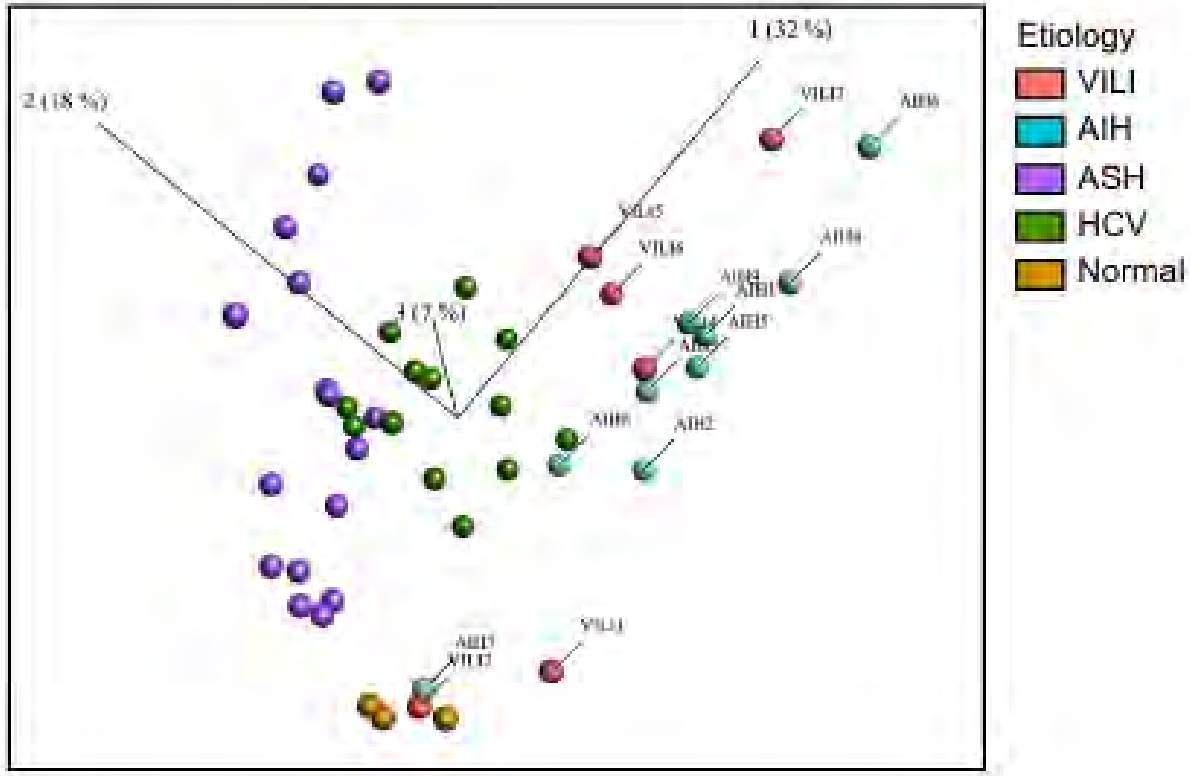
AIH
Likely 9/9

	VILI (n = 6)	AIH (n = 9)	p value VILI vs AIH
Age, median years (range)	58 (21-85)	61(49-78)	n.s. (0.76)
Gender (female), n (%)	2 (33%)	8 (89%)	
AST/ULN, mean	38.3	18.0	ns (0.08)
ALT/ULN, mean	44.1	27.7	ns (0.30)
GGT/ULN, mean	5.3	7.6	ns (0.33)
ALP/ULN,mean	1.2	1.5	ns (0.43)
R-value, mean	44.0	19.2	ns (0.11)
Bilirubin/ULN, mean	9.2	4.0	ns (0.13)
Pattern of injury			
• Hepatocytic % (n)	100% (n = 6)	88.9% (n = 8)	
• Mixed	0	11.1% (n = 1)	
• Cholestatic	0	0	
elevated ANA and/or ASMA/AAA, % (n)	67% (4)	100% (9)	
anti-SLA, anti-LKM1, or anti-LC1	0	0	
AMA	1*	0	
ANCA	0	2	
Increased IgG, n/totally measured (%)	2/5 (40%)	4/8 (50%)	
Ishak Grading, score, mean	12.2	10.2	ns (0.34)
• Piecemeal necrosis	2.3	2.9	ns (0.39)
• Focal lytic necrosis/apoptosis/inflammation	3.5	3.4	ns (0.92)
• Portal inflammation	2.3	3.2	ns (0.12)
• Confluent necrosis	3.8	1	0.0025
Fibrosis			
• F0	6 (100%)	5 (55.5%)	
• F1	0	4 (44.4%)	
Eosinophils portal tract (mean/HPF)	30.0	57.8	ns (0.21)
Eosinophils lobular (mean/HPF)	11.8	12.1	ns (0.96)
Simplified AIH score ≥ 6	60% (3/5)	100 % (9/9)	

Uzun et al, JHEP 2023

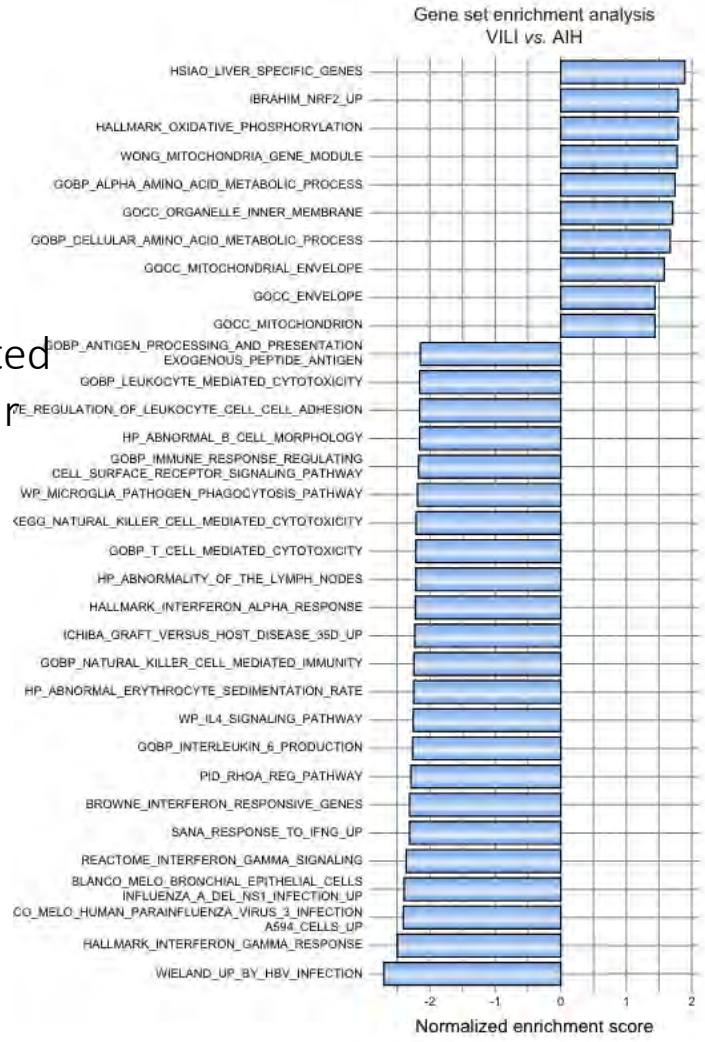
Whole transcriptome profiling with bulk RNA, isolated from FFPE liver biopsies of patients with VILI and AIH

Patients with VILI and AIH had different transcriptome profiles but were close to each other and significantly different from patients with chronic HCV infection or ASH

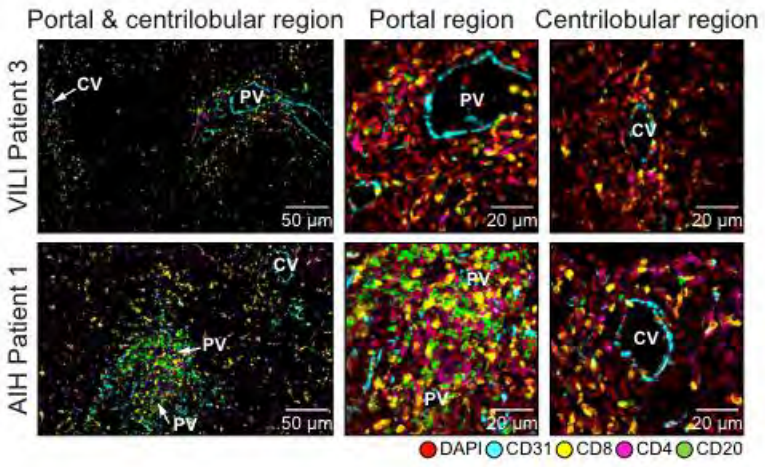


Pathways related to immune response were overrepresented in the AIH cohort, in particular gene sets associated with interferon response.

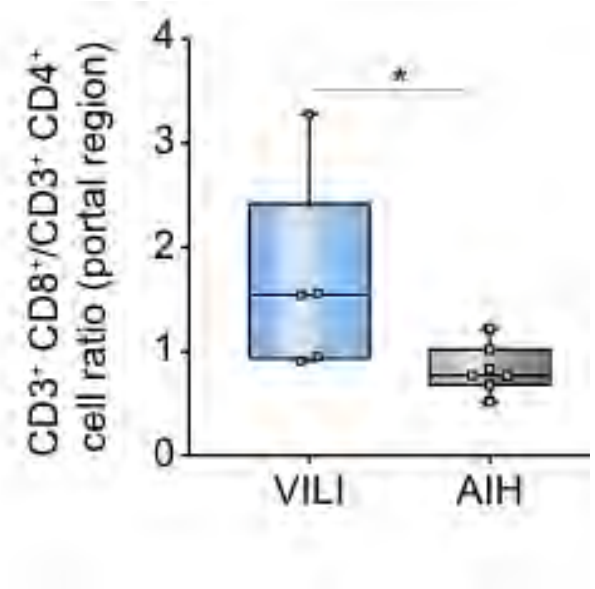
In contrast, mitochondrial metabolism and oxidative stressrelated pathways were overrepresented in the VILI cohort.



Characterization of the immune infiltrates in the biopsy tissue

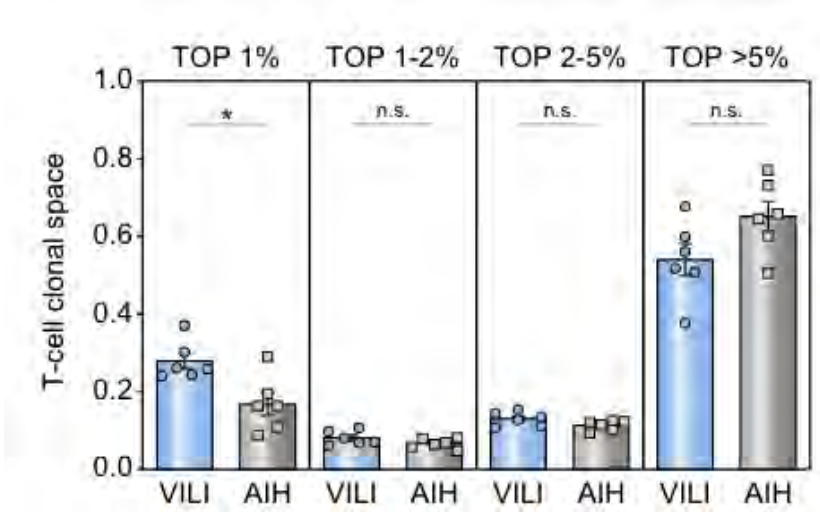


More CD20+ cells in AIH



The proportion of CD3+ CD8+ effector T cells in patients with VILI was significantly higher than in patients with AIH

Clonal distribution of the adaptive immune infiltrate in patients with VILI and AIH

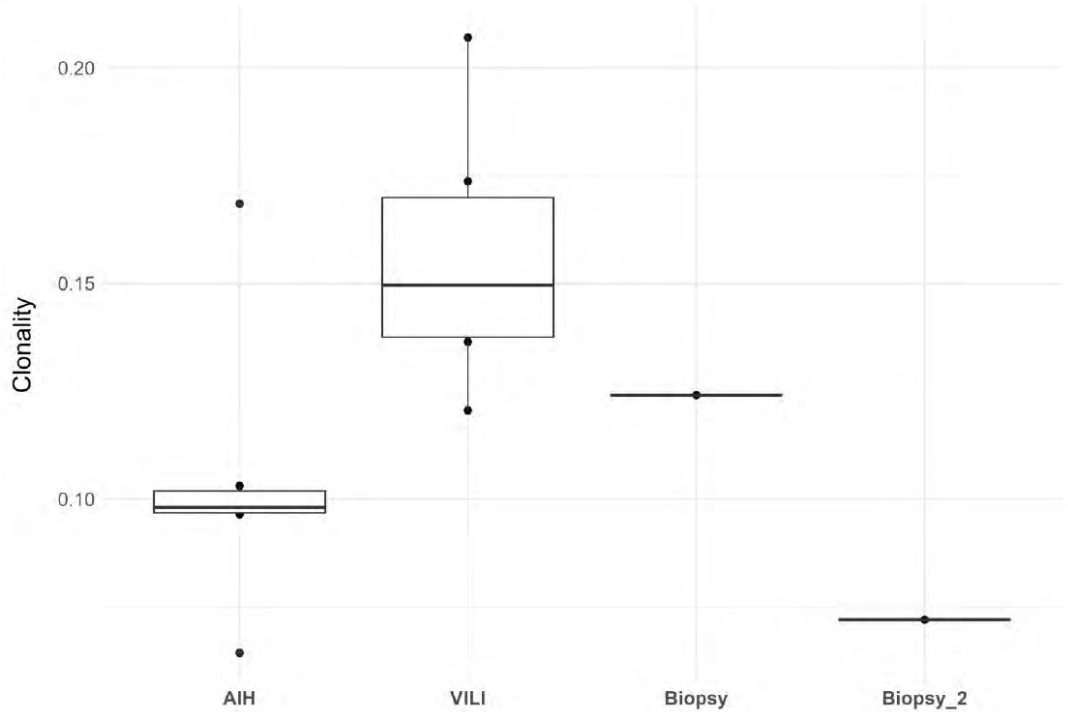


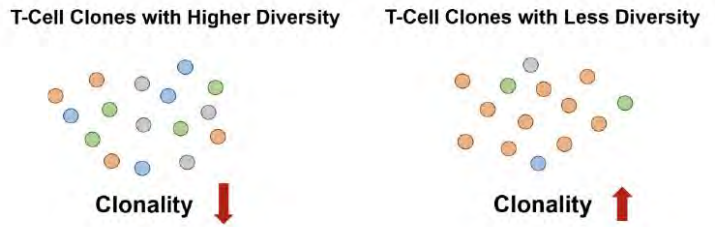
VILI had more expanded clones in T and B cell architecture in comparison with AIH

As expected from the difference in evenness, we found that the T cell clones in the top 1% group of the VILI cohort had a significantly larger clonal space compared to the AIH cohort

Although we cannot exclude that some VILI represent activation of latent AIH, our results suggest that in many individuals, VILI represents a separate disease entity, which is distinct from AIH, but more closely related to DI-AILH. Therefore, there is a good chance that many patients with VILI will recover completely and not develop long-term AIH

Clonality Assesment of Biopsy Samples





Data of AIH and VILI samples are from our original study

Biopsy samples of this patient present lower clonality which is similar to AIH

Courtesy of Sharp Uzun

Similar phenotype of acute liver injury after mRNA or vectorial vaccines

	Pfizer-Biontech (*n* = 51)	Oxford-AstraZeneca (*n* = 20)	Moderna (*n* = 16)	*p* value
Age, median years (range)	46 (18–71)	47 (20–76)	57 (21–79)	0.157
Sex, female, *n* (%)	32 (62.7)	10 (50)	13 (81.3)	0.154
Pre-existing liver disease, *n* (%)	7 (13.7)	2 (10)	3 (18.8)	0.751
Peak ALT × ULN	16.7 (3.1–203)	11.7 (3.2–63.8)	21.7 (5–66.4)	0.519
Peak AST × ULN	14.9 (1.8–250)	14 (2.6–169)	21.4 (3.4–55)	0.608
Peak ALP × ULN	1.3 (0.6–6.5)	1.2 (0.7–2.2)	1.3 (0.4–5.6)	0.970
Peak total bilirubin × ULN	2.6 (0.5–19.5)	5.4 (0.5–22.1)	1.1 (0.3–23.2)	0.210
INR	1.1 (0.7–3.6)	1.3 (0.6–3.8)	1 (0.6–2.7)	0.289
Pattern of injury, *n* (%)				
Hepatocellular	43 (84.3)	17 (85)	13 (81.3)	0.948
Mixed	5 (9.8)	2 (10)	2 (12.5)	0.952
Cholestatic	3 (5.9)	1 (5)	1 (6.3)	0.985
ANA positivity, *n* (%)	31 (63.3)	15 (75)	10 (71.4)	0.603
SMA positivity, *n* (%)	8 (16.3)	5 (25)	2 (14.2)	0.643
IgG × UNL	1.12 (0.41–2.61)	1.05 (0.5–2.71)	1.08 (0.60–1.84)	0.833
Immune-mediated phenotype, *n* (%)	28 (59.6)	10 (55.6)	7 (50)	0.810
Grade 3-4 liver injury, *n* (%)	9 (17.6)	6 (30)	3 (18.8)	0.501
Liver transplant, *n* (%)	1 (2)	-	-	0.700
Corticosteroid therapy, *n* (%)	24 (47.1)	12 (60)	10 (62.5)	0.429

However:

out of the 39 patients presenting with acute liver injury
after the second or third vaccine dose, only six received a vectorial vaccine (p = 0.006)

Efe et al, Hepatol 2023
Codoni et al, JHEPR 2023

Does the vaccine type matter?

mRNA vaccines		Vectorial vaccines
ALT 26.2 x ULN	p=0.008	ALT 14.0 x ULN
INR 1.3	p=0.012	INR 1.1

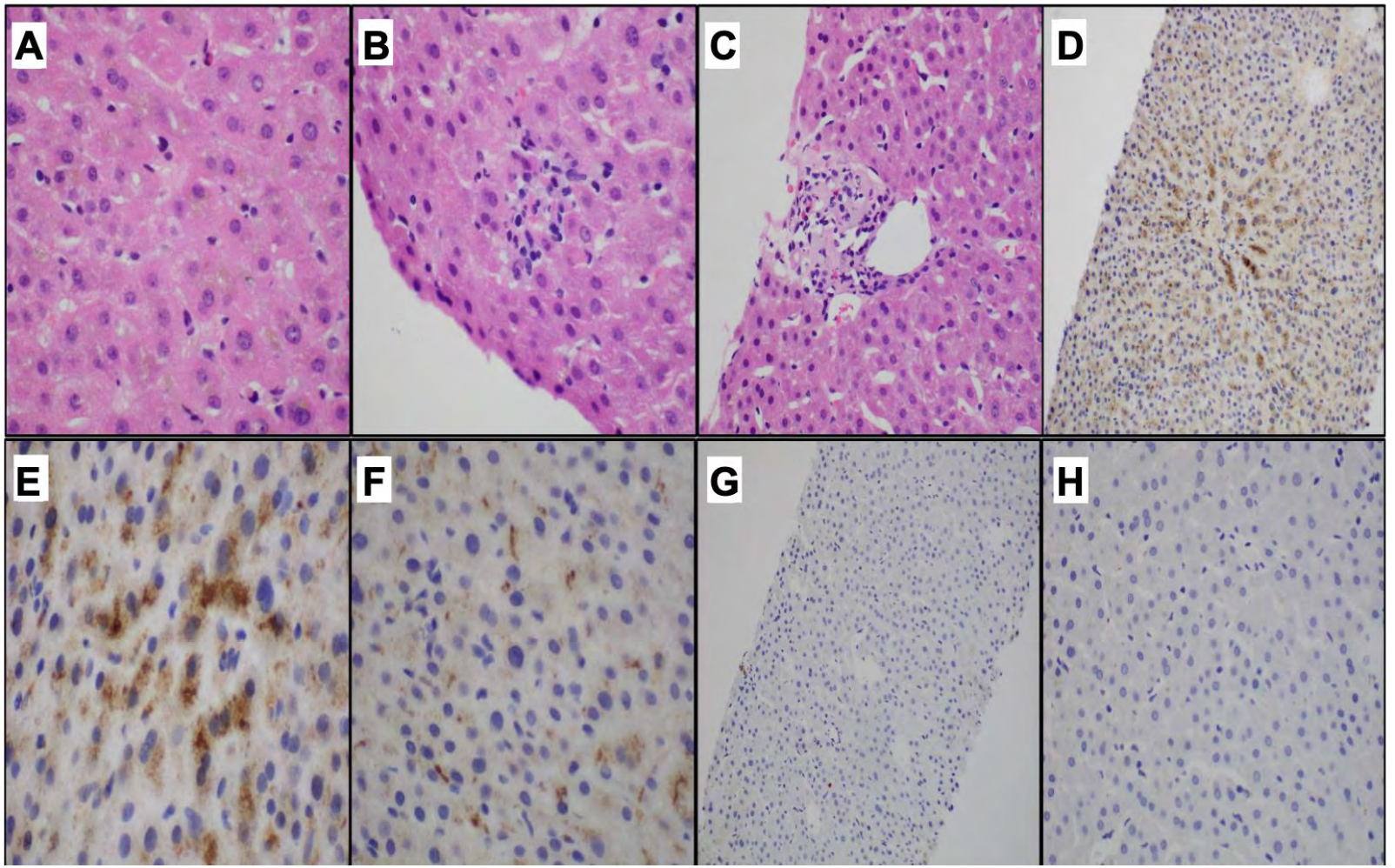
Treatment and treatment response were similar in both groups

mRNA-1273 (n=12)		BNT162b2 (n = 30)
Ishak 11	p=0.001	Ishak 9
SMA > 1:160 8/8	p=0.007	SMA > 1:160 2/8

Codoni et al, JHEPR 2023

Pathophysiology

Spike protein in hepatocytes in a patient with acute cholestatic liver injury after mRNA-1273 vaccine



Our patient tolerated the inactivated Sinovac vaccine suggesting the immunological processes may be unique to mRNA vaccination

Nyein et al, JHEP 2022

Conclusions

1. Acute liver injury after SARS-CoV-2 vaccines is rare

2. Autoimmune features are frequently observed, careful study of the autoantobodies would be helpful

3. The vast majority of the patients do well with or without immunosuppression

4. The pathophysiology is likely heterogeneous, with some patients resembling AIH and others resembling DI-AILH

5. Overtreatment should be avoided

6. Role of vaccine type still unknown

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Patients

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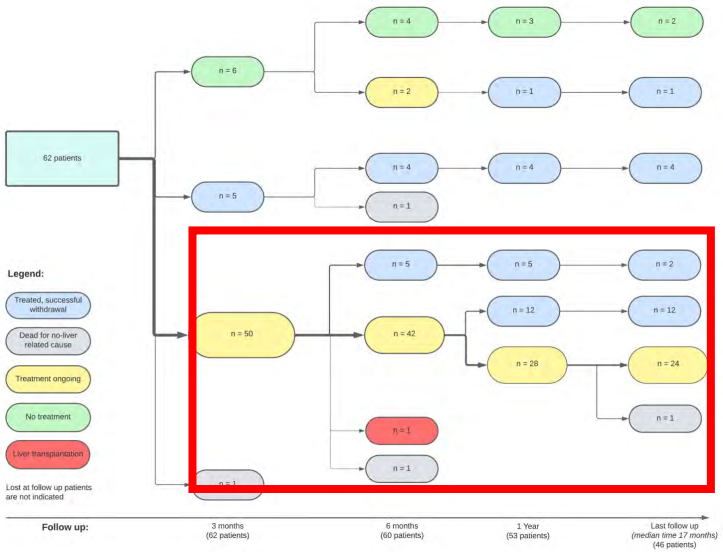
Prof Maria Isabel Lucena and Raul Andrade

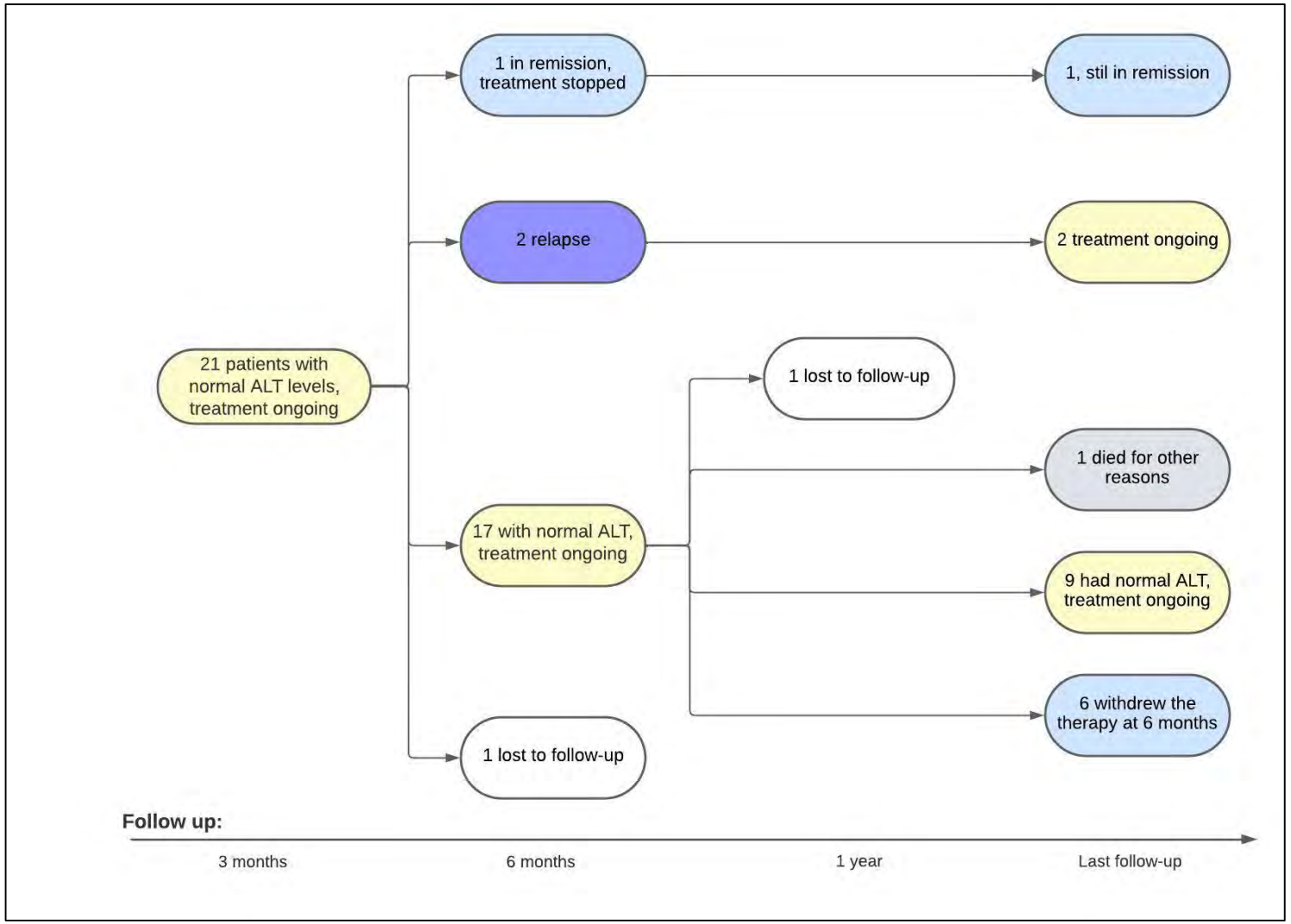
Fondazione Epatocentro Ticino

Prof Giorgina Mieli-Vergani and Prof Diego Vergani, my mentors

Thank you!

Results: our cohort





Results: our cohort