3rd GLOBAL LIVER HEALTH FORUM

sanofi

MAFLD and COVID-19

An interplay leading to poor clinical outcomes

Jose D Sollano, MD
Professor of Medicine
Faculty of Medicine & Surgery
University of Santo Tomas
Manila, Philippines

MAT-GLB-2201297-v-1.0
Date of approval: 26 April 2022

Disclosures

- Speaker Bureau of Abbott, A. Menarini, Eisai, Ferring, J&J, Sanofi, Takeda
- Research grant from Cristcot

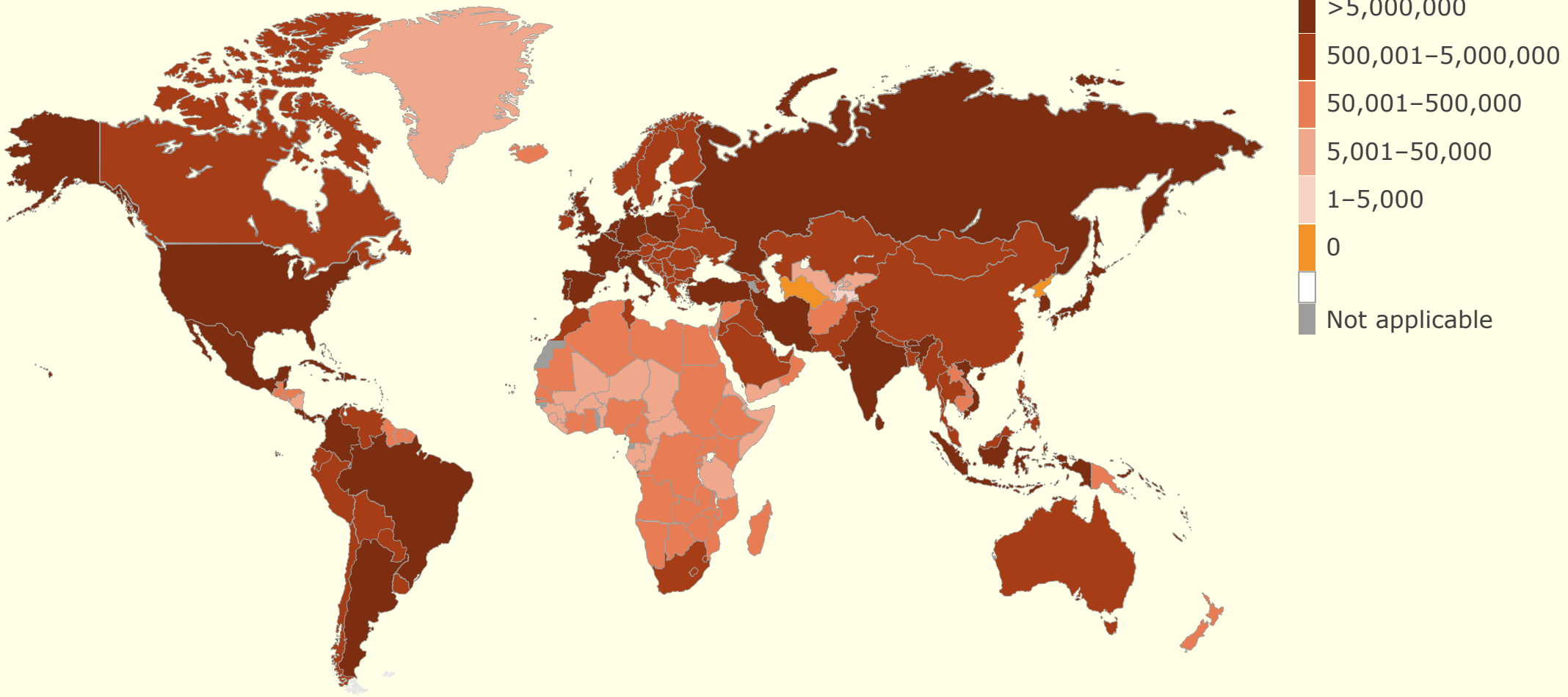
Overview

1. What is COVID-19?
2. The interplay between COVID-19 and MAFLD impacts clinical outcomes
3. What mechanisms are responsible for the poor clinical outcomes seen in patients with MAFLD and COVID-19?
4. Could essential phospholipids improve clinical outcomes for patients with MAFLD?
5. Summary

COVID-19, coronavirus disease 2019; EPL, essential phospholipids; MAFLD, metabolic associated fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus

What is COVID-19?

Globally, there have been over 497 million cases of SARS-CoV-2

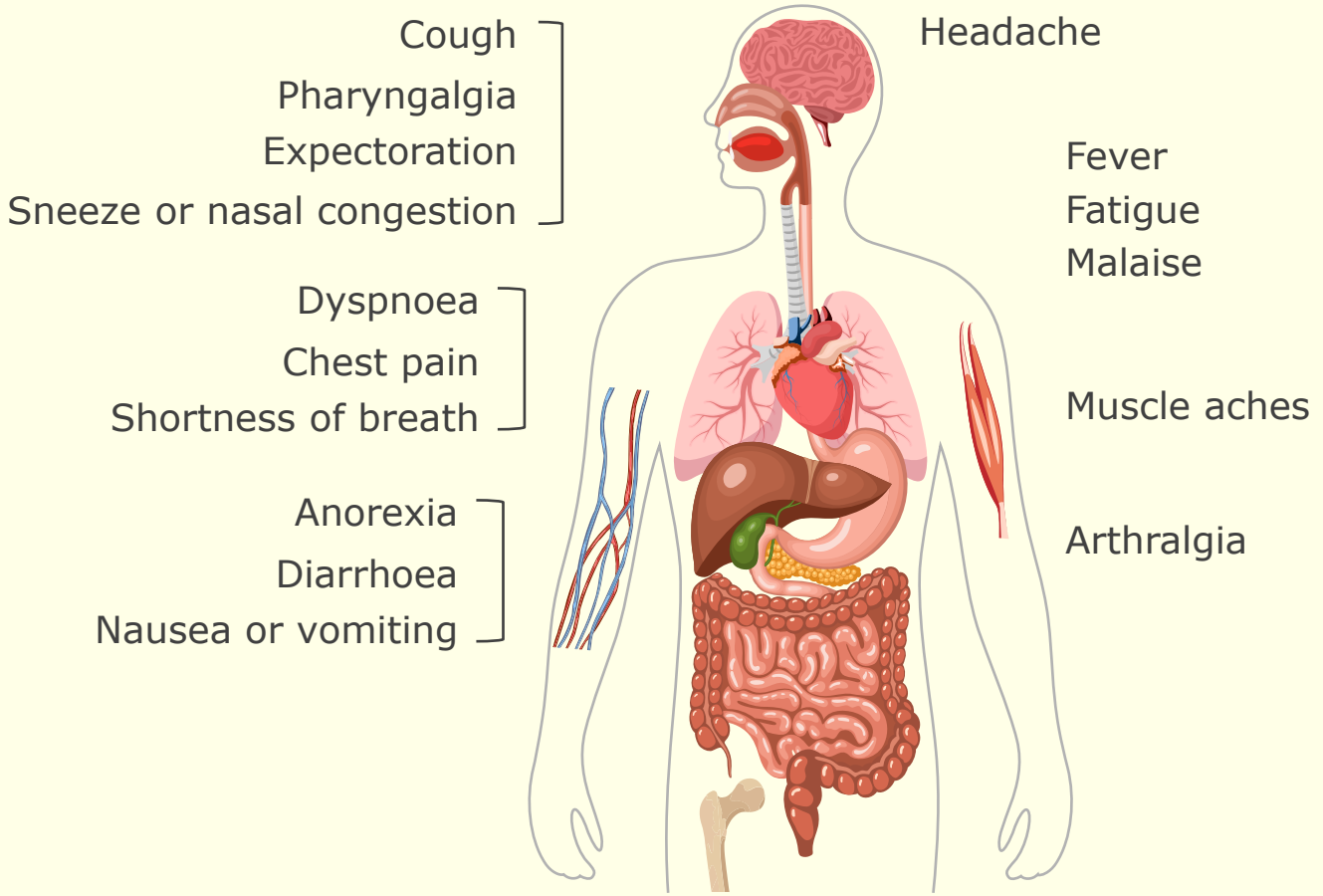


SARS-CoV-2, severe acute respiratory syndrome coronavirus
WHO Coronavirus Dashboard, available at: https://covid19.who.int/; accessed on 12/04/2022.

SARS-CoV-2 causes COVID-19 and its numerous systemic symptoms

- SARS-CoV-2 has a 5–15 day incubation period where there is minimal host immune response[1]
- This allows SARS-CoV-2 to replicate before an innate immune response is triggered[2]

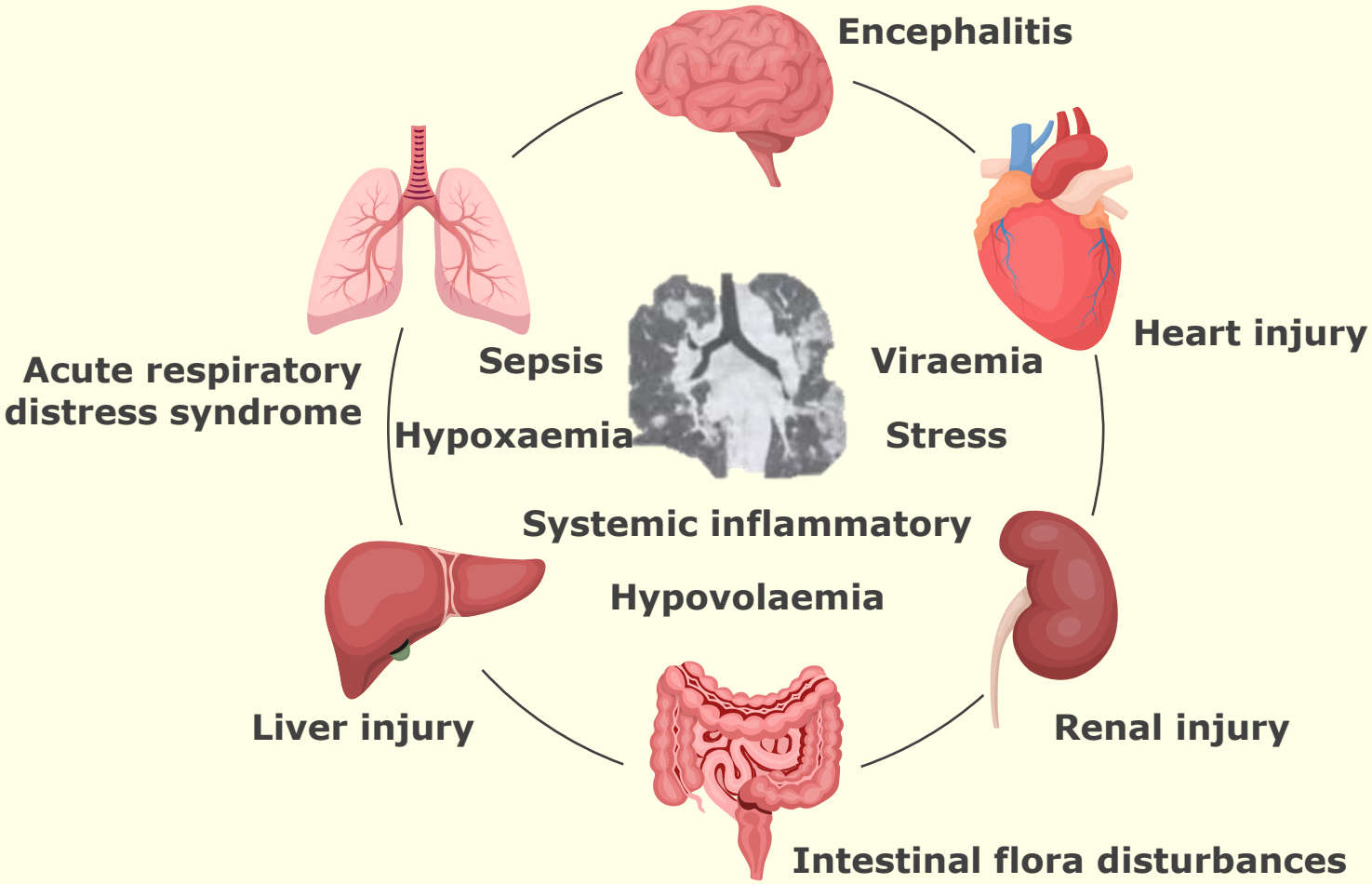
Systemic symptoms of COVID-19:[3]



COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus

1. Alipoor SD, et al. Front Cell Infect Microbiol 2021;11.; 2. Mason RJ, et al. Eur Respir J 2020;55(4):2000607.; 3. Li J, et al. J Clin Transl Hepatol 2020;8(1):13–17

COVID-19 can lead to multi-organ complications



Although commonly known to infect the respiratory system, COVID-19 impacts the function of multiple organs, meaning unexpected conditions may exacerbate symptoms and worsen clinical outcomes

COVID-19, coronavirus disease 2019
Li J, et al. J Clin Transl Hepatol 2020;8(1):13–17

There is a trend between COVID-19 and liver injury

- A systematic review found the **incidence of liver injury after COVID-19** to be **14.8–53%**[1]
  - Patients with liver injury caused by COVID-19 had higher levels of ALT, AST and total bilirubin and lower serum albumin than patients without liver injury
  - It has been reported liver injury diagnosed by elevated aminotransferases and/or cholestatic enzyme activity may be as high as 50% at hospital admission and >75% during hospitalisation[2]

- Another systematic review found a median of **24.5% of patients with COVID-19 had hepatic injury**, while only 2% of patients with a pre-existing liver disease[3]

- In an observational study, **20% of patients with COVID-19 had liver injury** without underlying liver disease[2]
  - **18%** of patients with COVID-19 and liver injury **died during hospitalisation**
  - Liver injury symptoms resolved at the end of hospitalisation in 20% of patients with COVID-19 and liver injury

- The exact cause of liver injury in patients with CVOID-19 is still unclear[4]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019

1. Velarde-Ruiz Velasco JA, et al. Ver Gastroenterol Mex (Engl Ed) 2020:85(3):303–11; 2. Pazgan-Simon M, et al. J Clin Med 2022;11:308.;
3. Debes JD, et al. Dig Liver Dis 2020:52(9):953–5; 4. Yu D, et al. Virol J 2021;18:121.

The interplay between COVID-19 and MAFLD impacts clinical outcomes

How familiar are you with the clinical evidence suggesting there is a link between MAFLD and COVID-19 outcomes?

1. I am fully up to date with the latest data on MAFLD and COVID-19
2. I am aware of some data on the interplay between MAFLD and COVID-19
3. I am aware of data for other comorbidities of COVID-19, but not for MAFLD
4. I am not aware of data supporting an interplay between MAFLD and COVID-19

COVID-19, coronavirus disease 2019; MAFLD, metabolic associated fatty liver disease

Liver diseases may confer poorer outcomes in patients with COVID-19

In a real-time network analysis of 2780 patients with COVID-19:

The **hospitalisation rate** with COVID-19 was **higher** for patients with **liver disease** (n=250) vs those without (n=2530)

52.0% of patients **with liver disease**

30.0% of patients **without liver disease**

Patient mortality with COVID-19 was **higher** for patients **with liver disease** (n=250) vs those without (n=2530)

12.0% of patients **with liver disease**

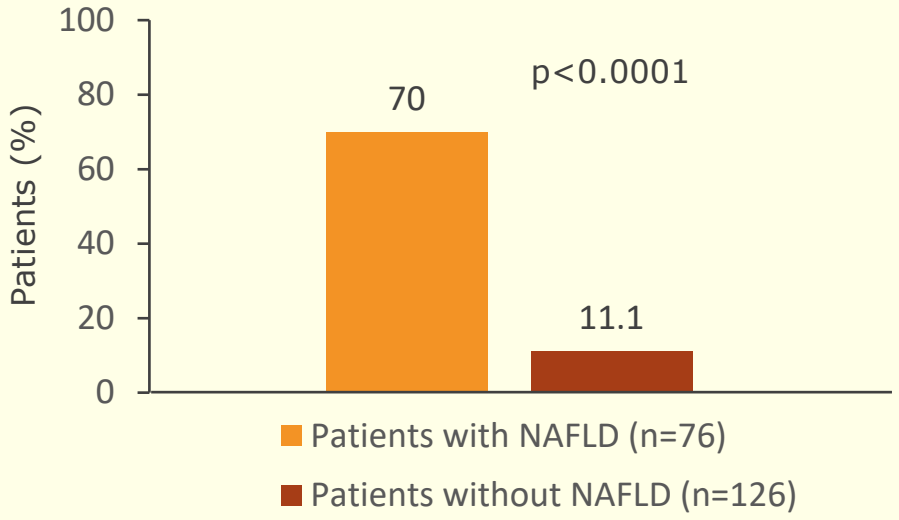
4.3% of patients **without liver disease**

COVID-19 diagnosed using COVID-19-specific diagnosis and terminology recommended by the World Health Organization and Centers for Disease Control and Prevention. Patients were defined as with liver disease if they had a diagnosis of chronic liver disease, cirrhosis, or related complications at the time of diagnosis of COVID-19, or any time before that
COVID-19, coronavirus disease 2019
Singh S, et al. Gastroenterolgy 2020;159(2):768–71.e3

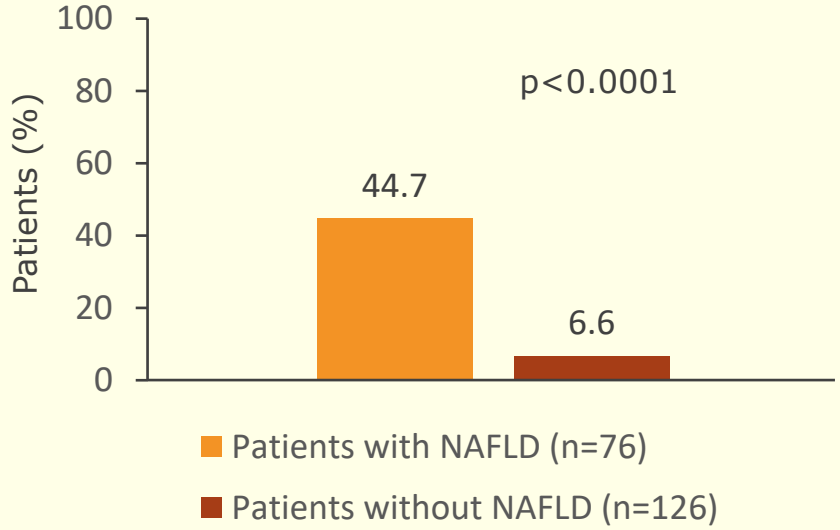
Patients with NAFLD have poorer outcomes with COVID-19 compared with patients without NAFLD

In a retrospective study of 202 patients with COVID-19 and information on NAFLD status:

Patients with NAFLD were more likely to have **abnormal liver function** with COVID-19 vs patients without NAFLD



Patients with NAFLD were more likely to have **COVID-19 disease progression** vs patients without NAFLD



Patients with NAFLD had **prolonged viral shedding** vs patients without NAFLD (p<0.001)

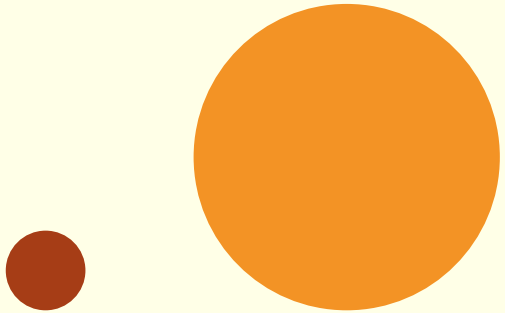
COVID-19 diagnosed in accordance with The Chinese National Health Commission practice guidelines and diagnosis was confirmed by the detection of severe acute respiratory syndrome coronavirus 2 in the throat by reverse transcription PCR. NAFLD was defined as HSI (HSI = 8 × [ALT/AST] + BMI [+ 2 if type 2 diabetes yes, + 2 if female]) >36 points and/or by abdominal ultrasound examination

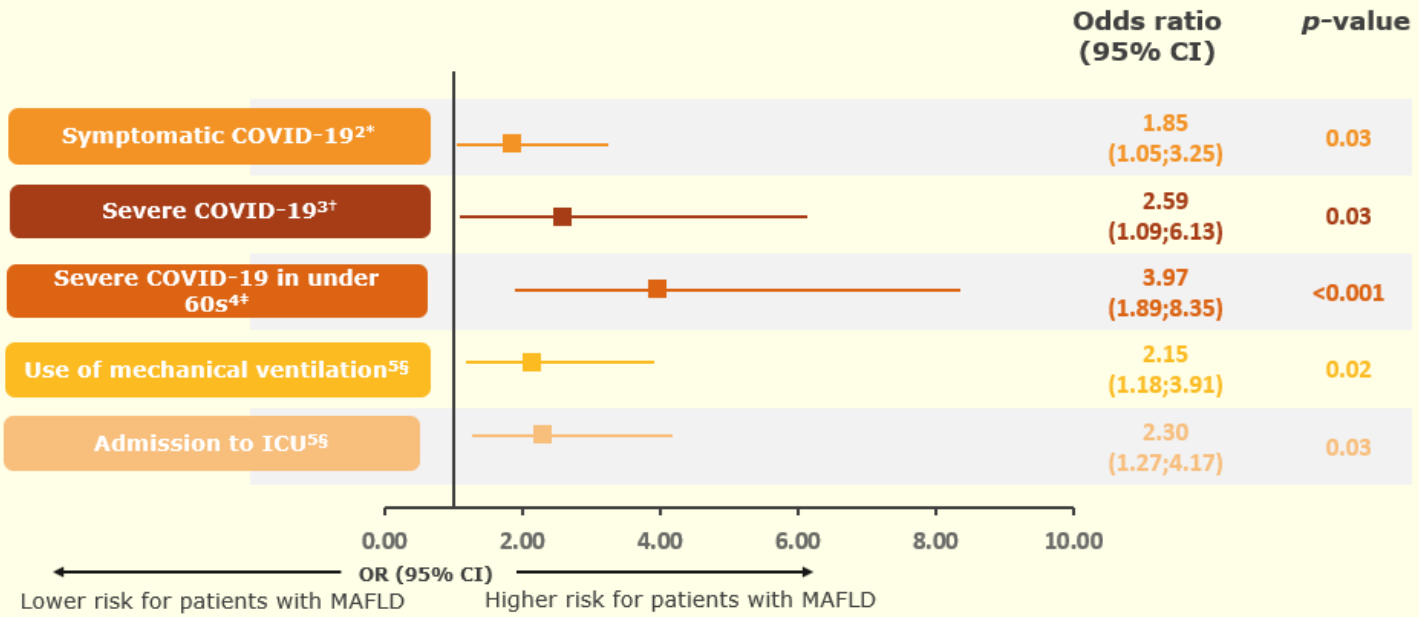
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; HSI, hepatic steatosis index; NAFLD, non-alcoholic fatty liver disease; PCR, polymerase chain reaction

Ji D, et al. J Hepatol 2020;73(2):451–3

Patients with MAFLD have poorer outcomes with COVID-19 compared with patients without MAFLD

In a retrospective study there was a **4-fold increased risk of severe COVID-19** in non-diabetic patients **with MAFLD** compared with patients without MAFLD, OR 4.22[1] (n=130)





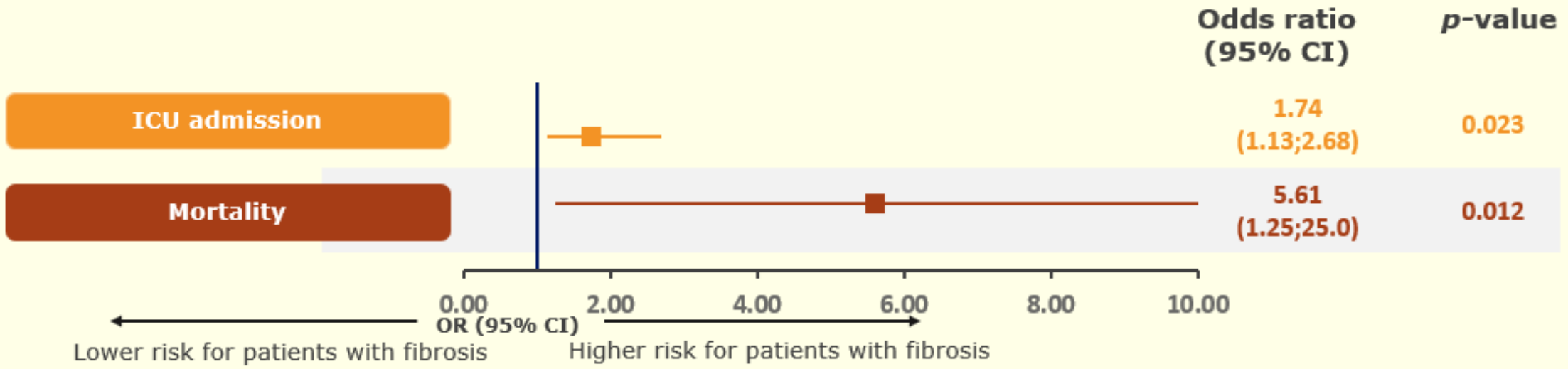
*n=79; COVID-19 was defined as a positive COVID-19 test within the UK Biobank; MAFLD defined as increased (≥) liver fat; †n=310; this study included patients with NAFLD; COVID-19 and NAFLD were not defined; ‡n=327; COVID-19 was diagnosed by high-throughput sequencing or reverse-transcriptase PCR of oropharyngeal swab specimens; MAFLD was diagnosed according to the MAFLD consensus criteria; §n=363; study included patients with NAFLD; COVID-19 was defined a positive SARS-CoV-2 infection via PCR nasopharyngeal swab or tracheal aspirate; NAFLD was defined by the presence of diffuse hepatic steatosis on any prior imaging studies or liver histology in the absence of secondary causes of hepatic fat accumulation including significant alcohol use, long-term use of steatogenic medications or hereditary disorders

CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; PCR, polymerase chain reaction

1. Gao F, et al. J Gastroenterol Hepatol 2020:36(1):204–7; 2. Roca-Fernández A, et al. medRxic 2020:06.04.20122457; 3. Targer G, et al. Gut 2020;69(8):1545–7
4. Zhou YJ, et al. J Hepatol 2020:73(3):719–21; 5. Hashemi N, et al. Liver Int 2020:40(10):2515–21

Liver fibrosis results in poorer outcomes with COVID-19 vs patients without liver fibrosis

In a retrospective study, **patients with liver fibrosis** had a **higher risk of ICU admission and mortality with COVID-19** compared with patients without liver fibrosis (n=155)

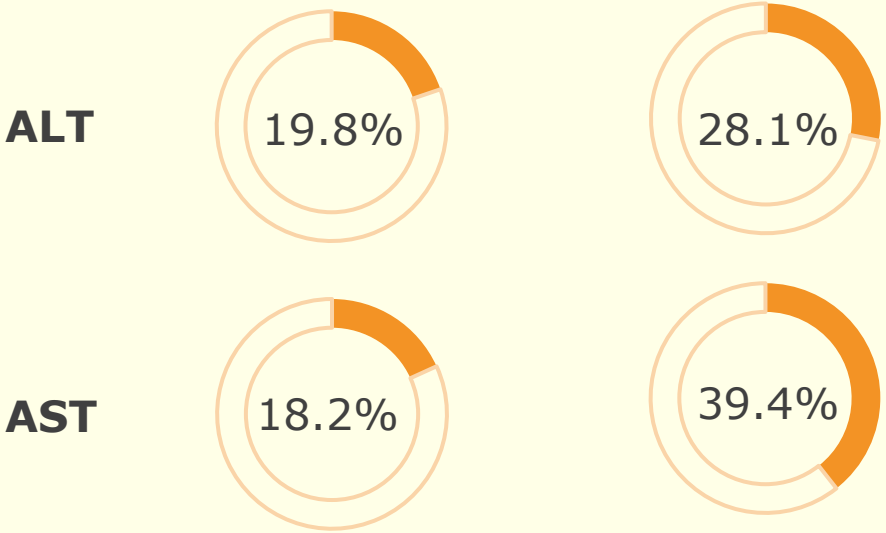


COVID-19 was diagnosed by a positive RT-PCR-SARS-CoV-2 test in nasopharyngeal swab on patient's medical records, followed by a lateral flow test determination in the first 48 hours after admission. Fibrosis was assessed by three predictive scores for advanced fibrosis: AST to Platelet Ratio Index (APRI), NAFLD Fibrosis Score and Fibrosis-4 index (FIB4)
*Fibrosis assessed by FIB4, a non-invasive scoring system based on several laboratory tests as an index for liver fibrosis; †Fibrosis assessed by any method
AST, aspartate transaminase; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NAFLD, non-alcoholic fatty liver disease
Lopez-Mendez I, et al. Ann Hepatol 2021;20:100271

What mechanisms are responsible for the poor clinical outcomes seen in patients with MAFLD and COVID-19?

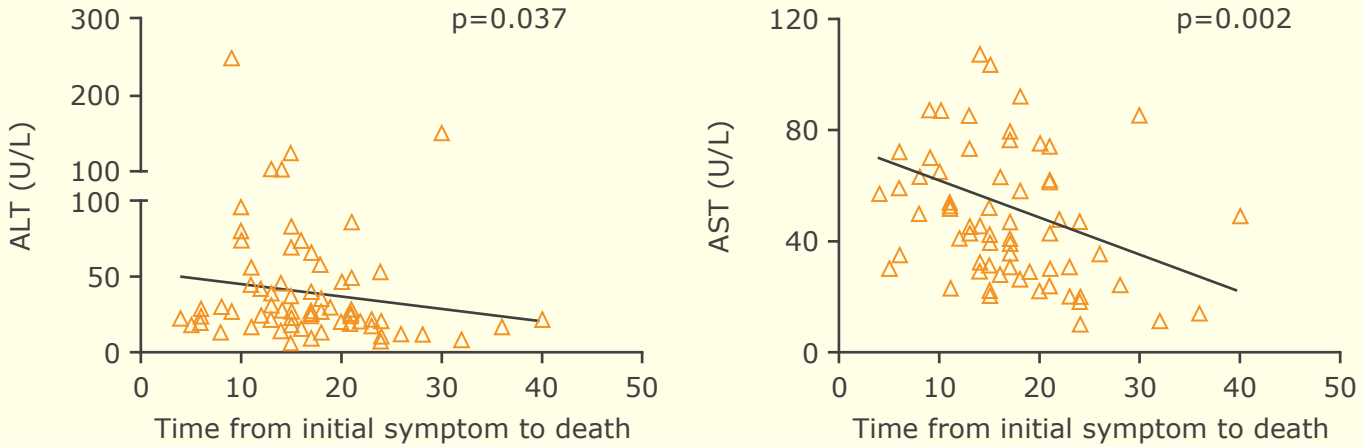
ALT and AST are raised in patients with COVID-19 and result in poorer outcomes

Percentage of patients with ALT or AST >40 U/L[1]



Raised ALT and AST result in poorer outcomes with COVID-19[2]

(N=82)



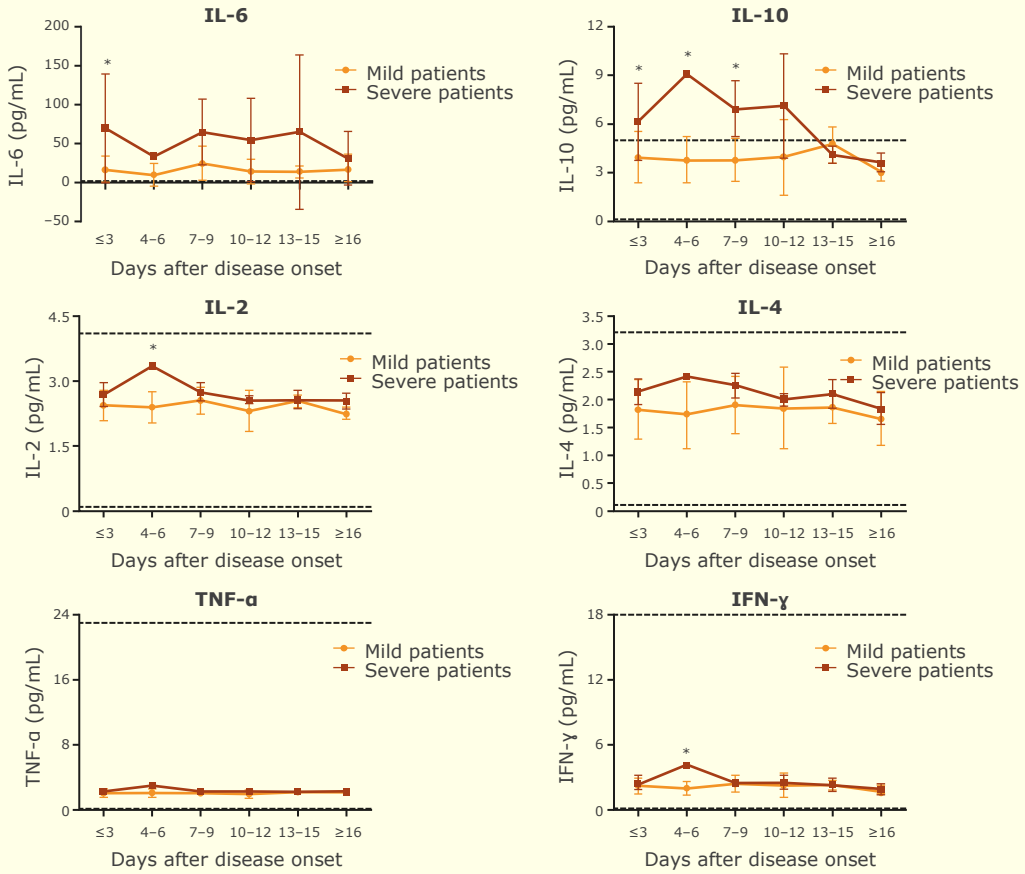
Patients with MAFLD commonly display elevated ALT and AST levels which is characteristic of hypoxic liver injury,[3] and may in part be an indicator of the increased mortality rates amongst patients with COVID-19 and MAFLD compared with patients with COVID-19 alone

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; MAFLD, metabolic dysfunction associated fatty liver disease

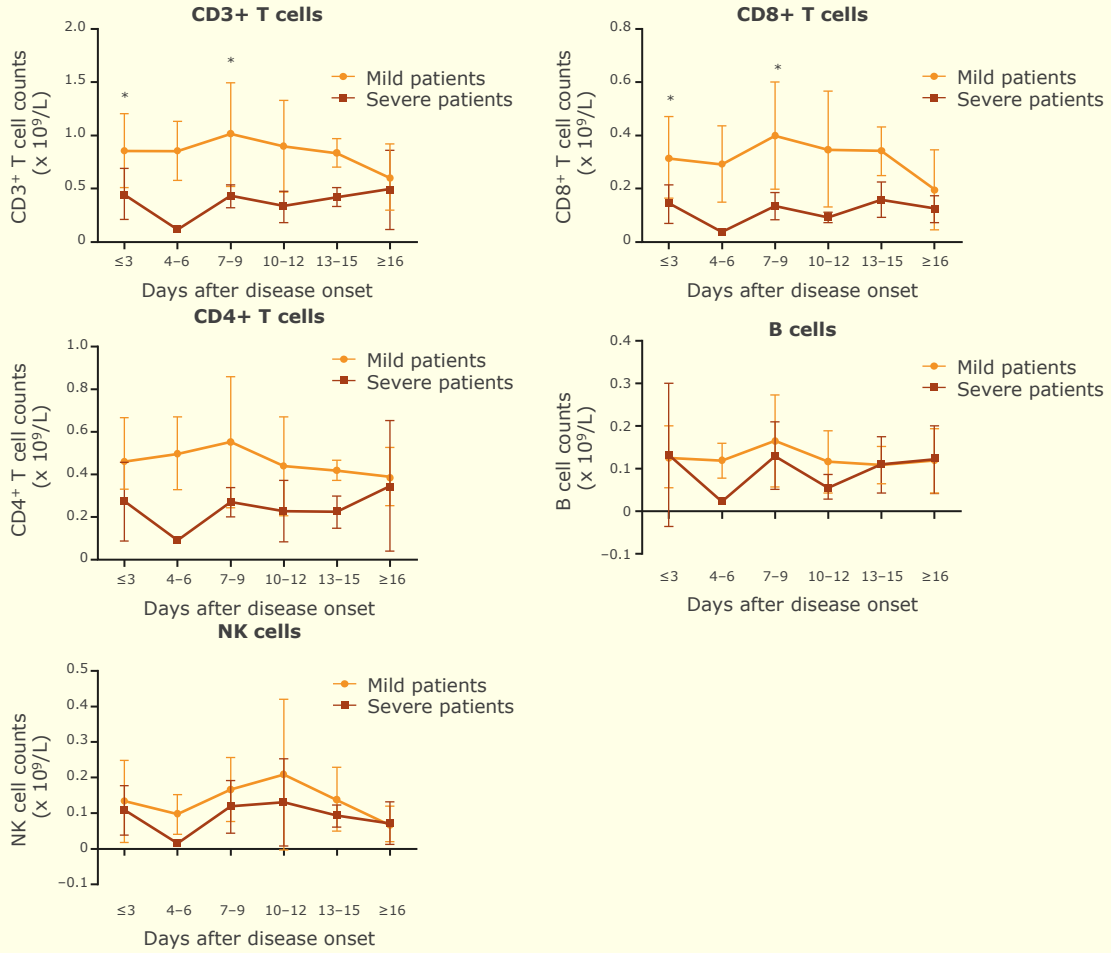
1. Guan WJ, et al. N Engl J Med 2020;382(18):1708–20; 2. Zhang B, et al. PLoS One 2020;15(7):e0235458; 3. Ebert EC. Mayo Clin Proc 2006;81(9):1232–6

Liver injury in COVID-19 may be the result of a cytokine storm

Patients with severe COVID-19 had **increased levels of pro-inflammatory cytokines**



Patients with severe COVID-19 had **decreased levels of anti-inflammatory immune cells**



*p<0.05

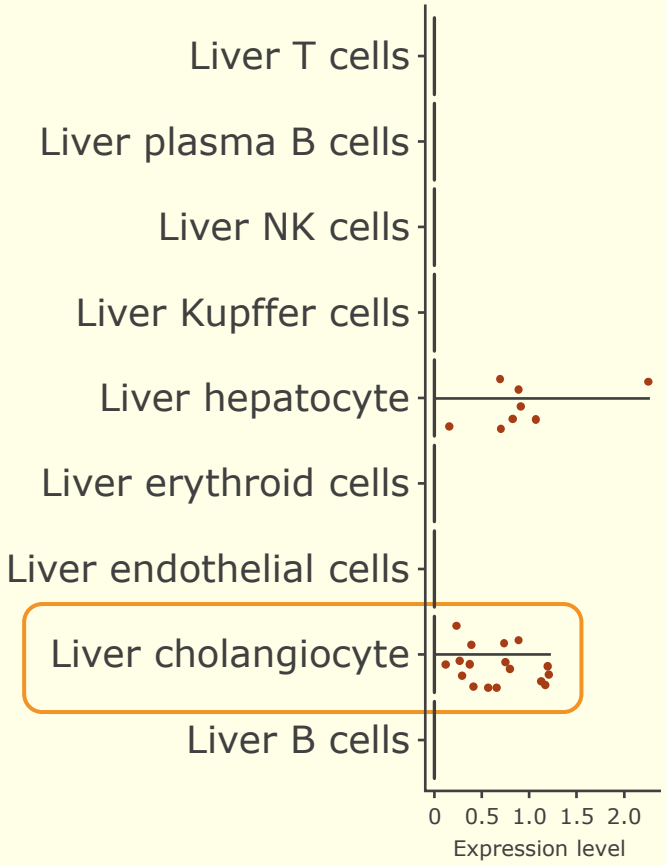
COVID-19, coronavirus disease 2019; IFN-γ, interferon-γ; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10;NK, natural killer; TNF-α, tumour necrosis factor-α

Liu J, et al. EBioMedicine 2020;55:102763

Liver injury in COVID-19 may be caused by direct cytotoxicity

- ACE-2, the cellular receptor SARS-CoV-2 binds to, is expressed in cholangiocytes[1]
- It is suggested that ACE-2 expression and viral entry into cholangiocytes may result in hepatocyte injury by viral replication, but this direct cytotoxicity has not been demonstrated[2]

Single cell RNA sequencing of liver tissue ACE-2 expression:[1]



ACE-2, angiotensin-converting enzyme-2; COVID-19, coronavirus disease 2019; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus

1. Qi F, et al. Biochem Biophys Res Commun 2020;526(1):135–40; 2. Sun J, et al. Liver Int 2020;40(6):1278–81

The risk of DILI in COVID-19 is increased for patients with MAFLD

Healthy individuals

- Normal liver function
- No concomitant drugs
- No metabolic disease
- Normal XME activity
- **No systemic inflammation**

Patients with MAFLD

- Fatty liver (possibly NASH)
- Weight-reduction drugs
- Obesity-linked diseases
- Altered XME activity
- **Mild-to-moderate systemic inflammation**

Patients with MAFLD and COVID-19

- Fatty liver (possibly NASH)
- Polypharmacy
- Obesity-linked diseases
- Altered XME activity
- **Severe systemic inflammation**

COVID-19, coronavirus disease 2019; DILI, drug induced liver injury; MAFLD, Metabolic associated fatty liver disease; NASH, non-alcoholic steatohepatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus; XME, xenobiotic-metabolising enzyme

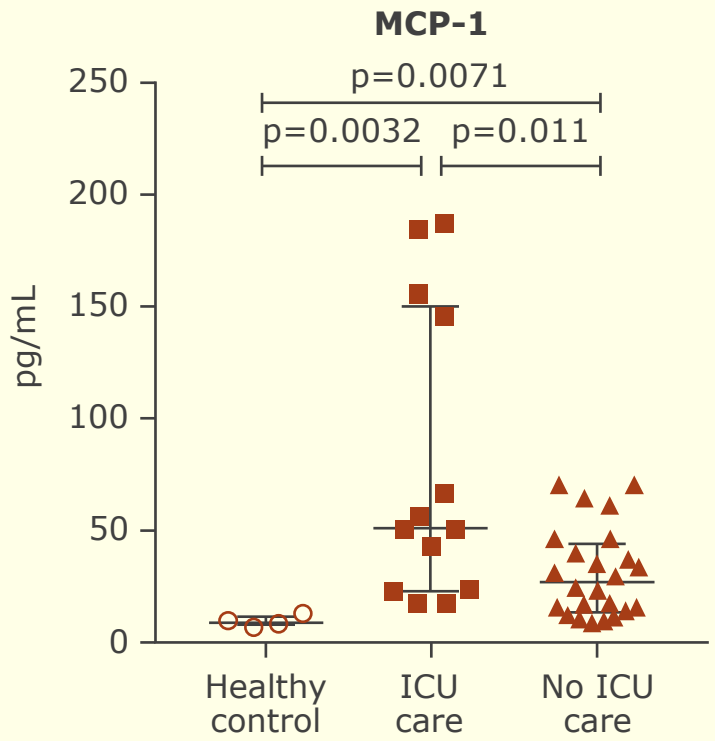
Ferron PJ, et al. Biochimie 2020;179:266e274

MCP-1 is raised in patients with severe COVID-19 and exacerbates steatohepatitis

- MCP-1 (a member of the C chemokine family) has been shown to exacerbate steatohepatitis[1]

Patients with severe (ICU care) and non-severe covid (no ICU care) had raised levels of MCP-1 compared to healthy individuals[2]

(N=41)



Increased levels of MCP-1 during COVID-19 could drive NAFLD progression

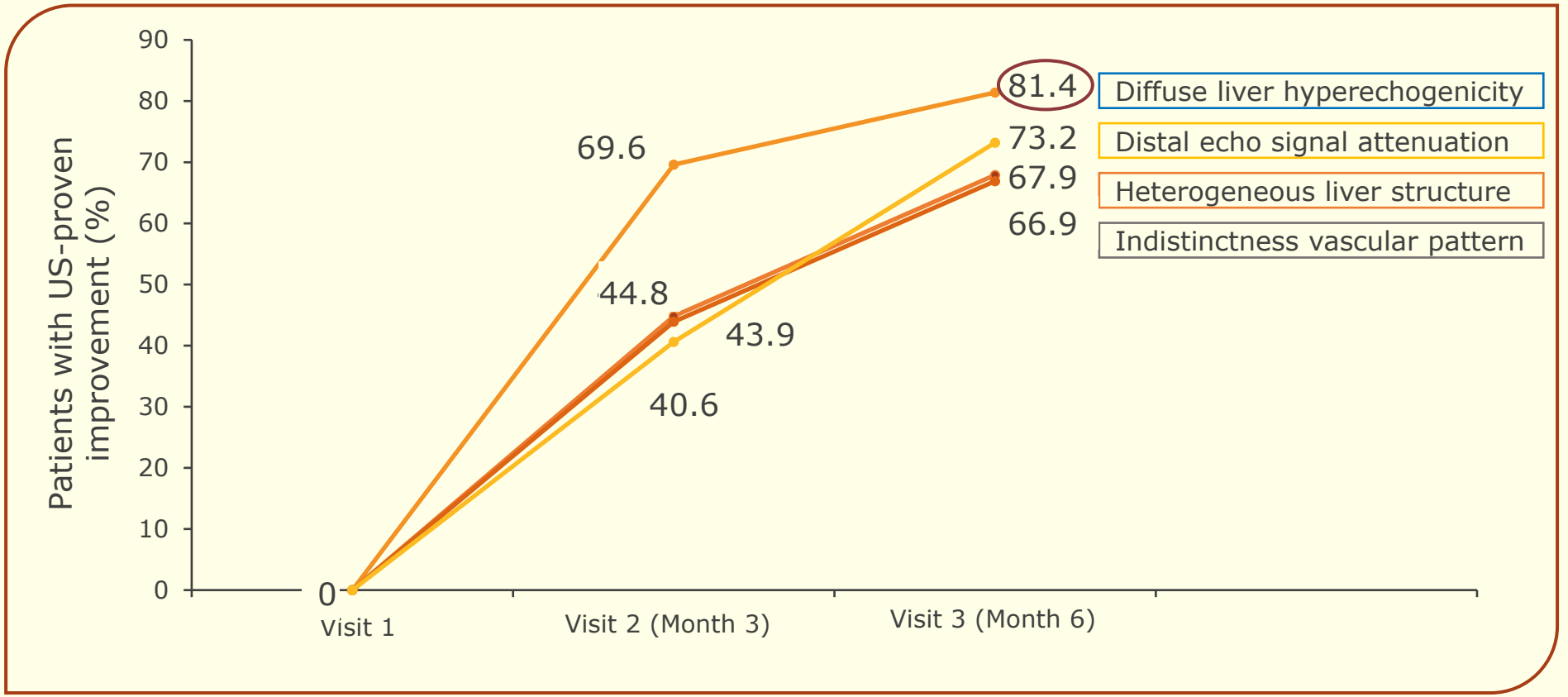
COVID-19, coronavirus disease 2019; ICU, intensive care unit; NAFLD, non-alcoholic fatty liver disease; MCP, monocyte chemoattractant protein

1. Gao B, et al. Gastroenterology 2016;150(8):1704–9; 2. Huang C, et al. Lancet 2020;395(10223):497–506. Suppl.

Could essential phospholipids improve clinical outcomes for patients with MAFLD?

Essential phospholipids have been shown to reduce steatosis in patients with MAFLD

MANPOWER study: N=2843 patients with NAFLD and cardiometabolic comorbidities*



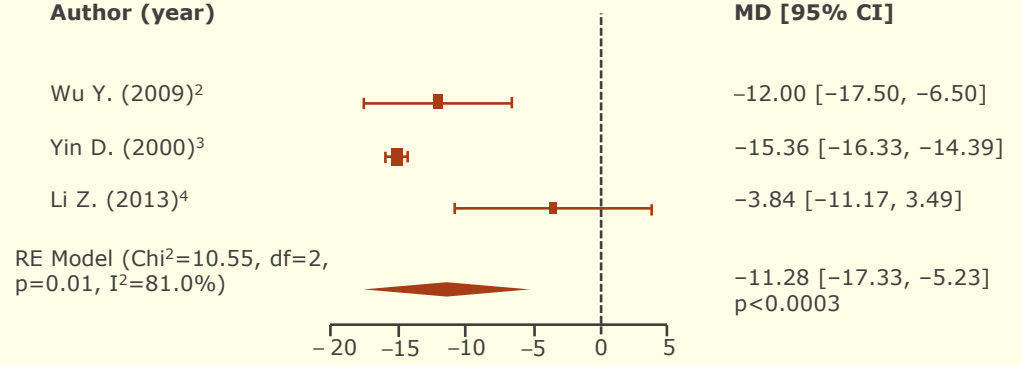
Significant improvement in ultrasound results after 3 and 6 months of treatment with EPL were seen ($p<0.05$)

*Cardiometabolic comorbidities included obesity, type 2 diabetes, hyperlipidaemia and hypertension
EPL, essential phospholipids; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; US, ultrasound
Maev IV, et al. BMJ Open Gastro 2020;7:e000341

Reduction in ALT and AST from baseline has been seen with EPL

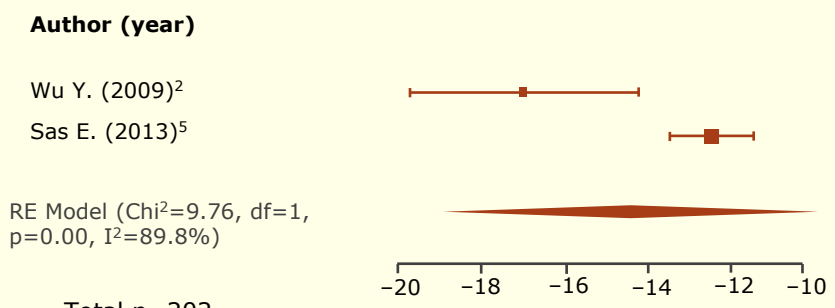
Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPL + AD vs AD alone[1]

Change in ALT (IU/L) levels from baseline*



Total n=371
Mean treatment duration: 1.97 months

Change in AST levels from baseline (U/L)



Total n=202
Mean treatment duration: 4.76 months

A significantly greater reduction in **ALT** levels was achieved with EPL + AD therapy compared with AD therapy alone

The pooled change from baseline in **AST** levels was −14.58 U/mL

*<0 favours EPL >0 favours control
AD, anti-diabetic treatment; ALT, alanine aminotransferase; CI, confidence interval; df, degrees of freedom; EPL, essential phospholipid; MD, mean difference; RCT, randomised controlled trial; RE, random effects

1. Dajani A, et al. World J Clin Cases 2020;8(21):5235–49; 2. Wu Y. J TCM Univ Hunan 2009;29:41–2; 3. Yin D, et al. Med JQ illu 2000;15:277–8;
4. Li Z. Inner Mongol J Tradit Chinese Med 2013;31:10–1; 5. Sas E, et al. J Hepatol Suppl. 2013;58(Suppl 1):S549

Summary

1. SARS-CoV-2 and the corresponding COVID-19 disease represent a serious and urgent global health concern
   - Although widely known to infect the respiratory system, COVID-19 has a negative impact on multiple organs

2. Pre-existing MAFLD in patients with COVID-19 is associated with increased morbidity and mortality. It is also a predictor of poor COVID-19 related outcomes in patients with SARS-CoV-2 infection

3. This relationship could be influenced by elevated ALT, AST and cytokine levels in patients with COVID-19 and MAFLD, but further investigations are needed

4. Essential phospholipids have been shown to improve steatosis, and triglyceride levels in patients with MAFLD, but further research is needed on their effect in patients with MAFLD and COVID-19

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; MAFLD, metabolic associated fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus