Importance of RWE in understanding the current disease landscape: MANPOWER results put into perspective

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Disclosures

- As a Vice-president of the Russian Scientific Liver Society, I received direct funding from Sanofi for work related to the DIREG 02 study, which is an observational study examining the prevalence of non-alcoholic fatty liver disease in Russia. Also I was invited by Sanofi, Russia, through the Russian Liver Scientific Society, to deliver clinical lectures on epidemiology, pathogenesis, diagnostic options, and treatment of non-alcoholic fatty liver disease

Learning objectives

1. Explore the clinical links between COVID-19 and liver disease
2. Assess various diagnostic tools available for NAFLD
3. Review the mechanism of action of EPL in steatosis, as well as recent clinical evidence of their use in NAFLD and in an intravenous form
4. Present highlights from the MANPOWER real-world study of EPL treatment in NAFLD patients with cardiometabolic comorbidities

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease

«I’ve observed 30 cases in my clinic. And what do you think? Patients who do not read papers feel good.»

«Those, who I forced to read “The Truth", — lost weight. […] Moreover, they were characterized with decreased patellar reflex, loss of appetite, depressed state of mind.»

COVID-19 and liver disease

COVID-19 in people with pre-existing liver disease: International registries

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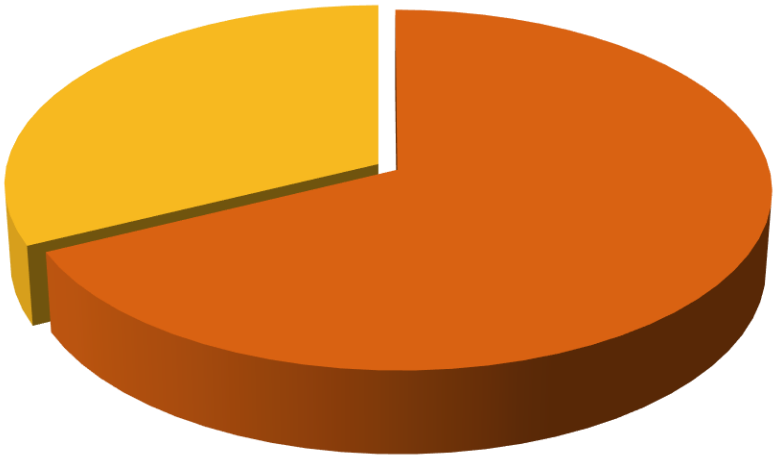
Registry of people with liver disease

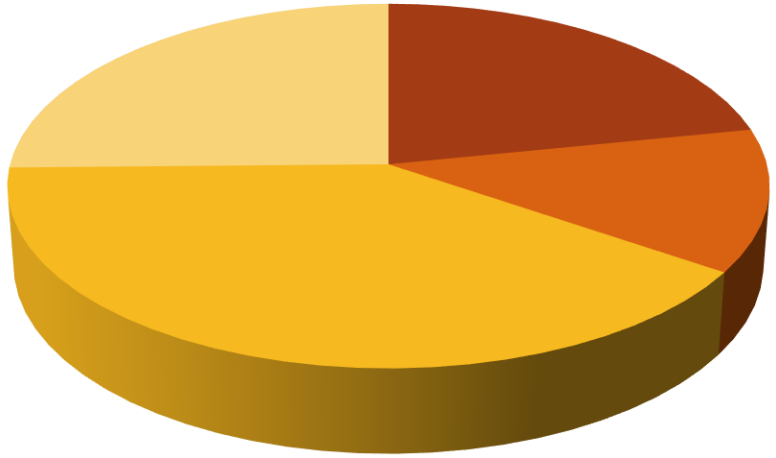
- From 25 March 2020 to 20 April 2020 (COVID-Hep.net and COVIDCirrhosis.org)
- 152 people (21 countries) – 95% of which were hospitalized

Structure of liver disease



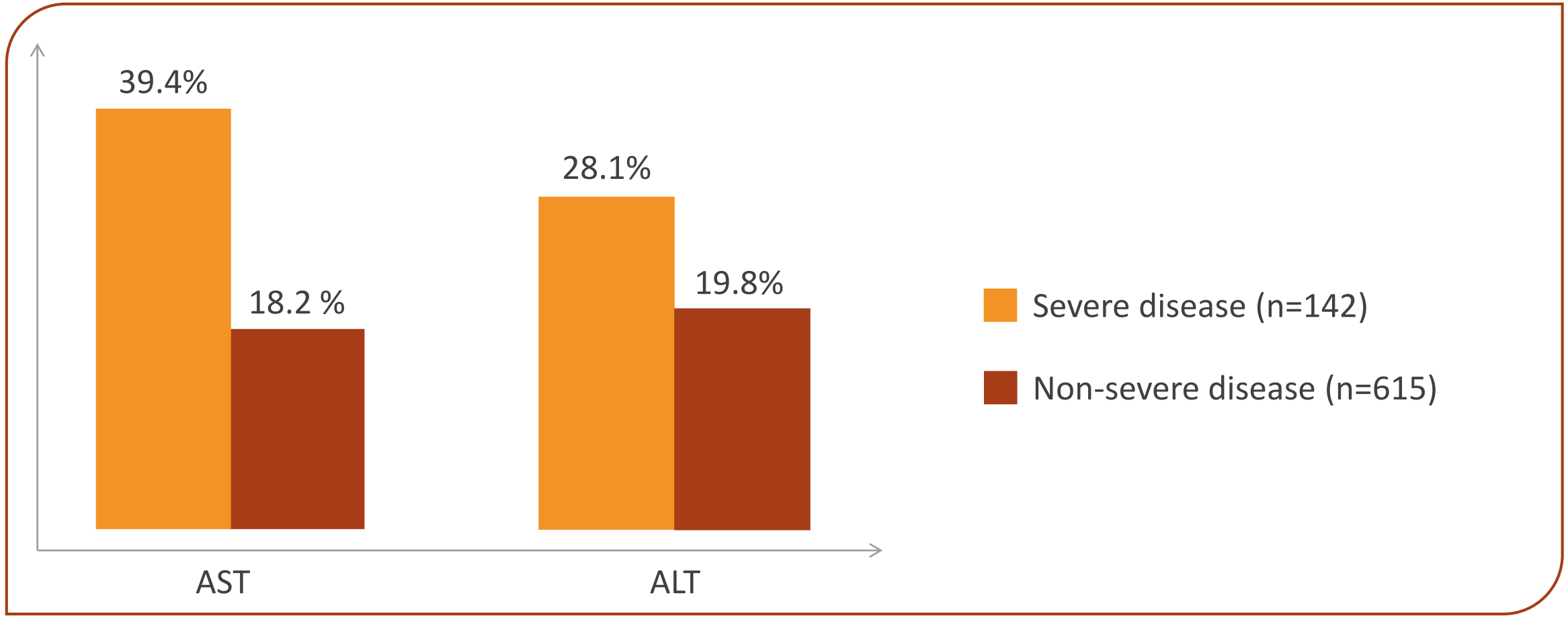
Liver cirrhosis Chronic liver disease

Aetiology of patients



HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease. Moon AM, et al. J Hepatol 2020;73:705–8

Incidence of AST and ALT abnormal levels in patients with COVID-19

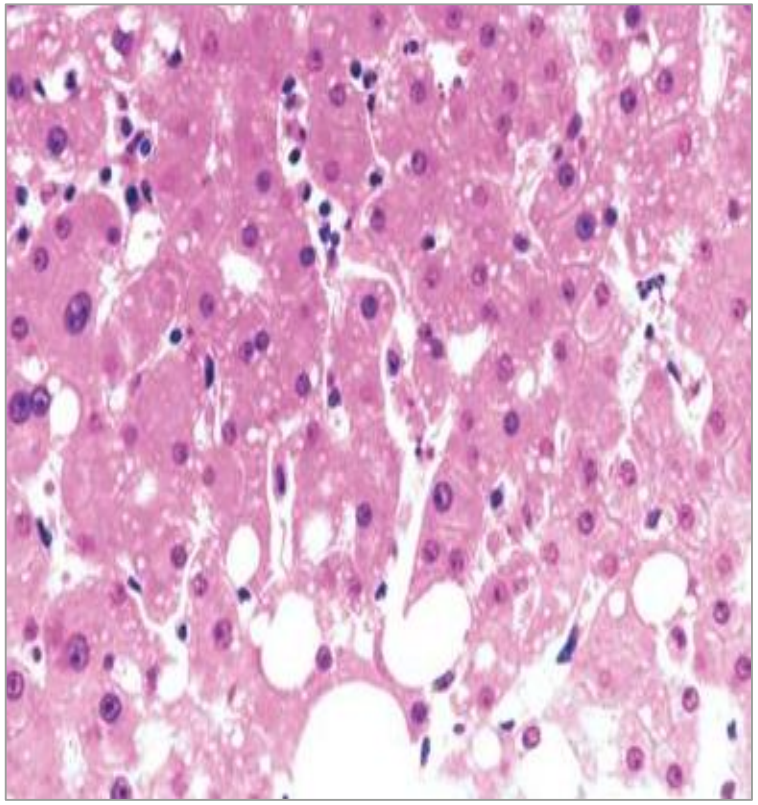


Data from a large cohort of 1099 patients from 552 hospitals in 31 provinces or provincial municipalities
ALT, alanine aminotransferase; AST, aspartate aminotransferase
Zhang C, et al. Lancet Gastroenterol Hepatol 2020;5:428–30

Pathological findings of COVID-19

- Moderate microvesicular steatosis, and mild lobular and portal activity
- No obvious intranuclear or intracytoplasmic viral inclusions
- Damage can be due to immune interactions involving intrahepatic cytotoxic T cells and Kupffer cells without viral replication

Pathological manifestations in the liver tissue of a patient with severe pneumonia cased by COVID-19



Xu Z, et al. Lancet Respir Med 2020;8:420–2

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1st GLOBAL LIVER HEALTH FORUM

Diagnostic tools for NAFLD

Steatosis, surrogate markers and the St-index

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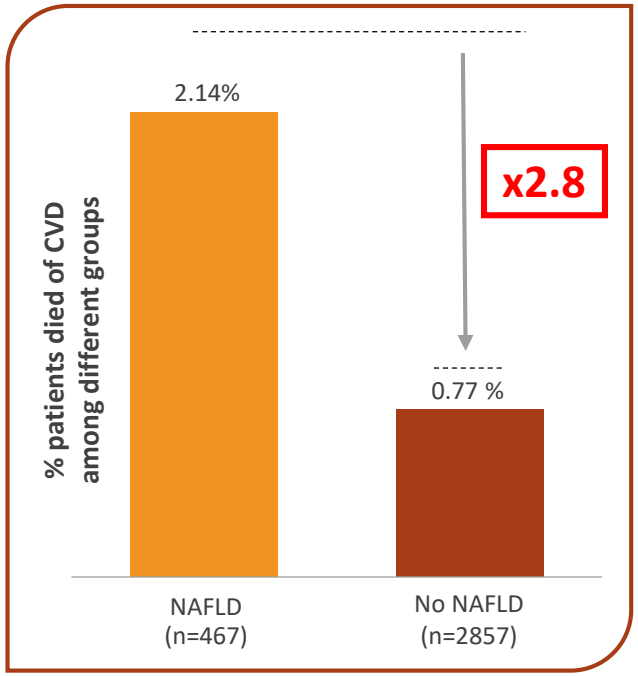
Which of these tools does your clinic currently use to assess NAFLD?

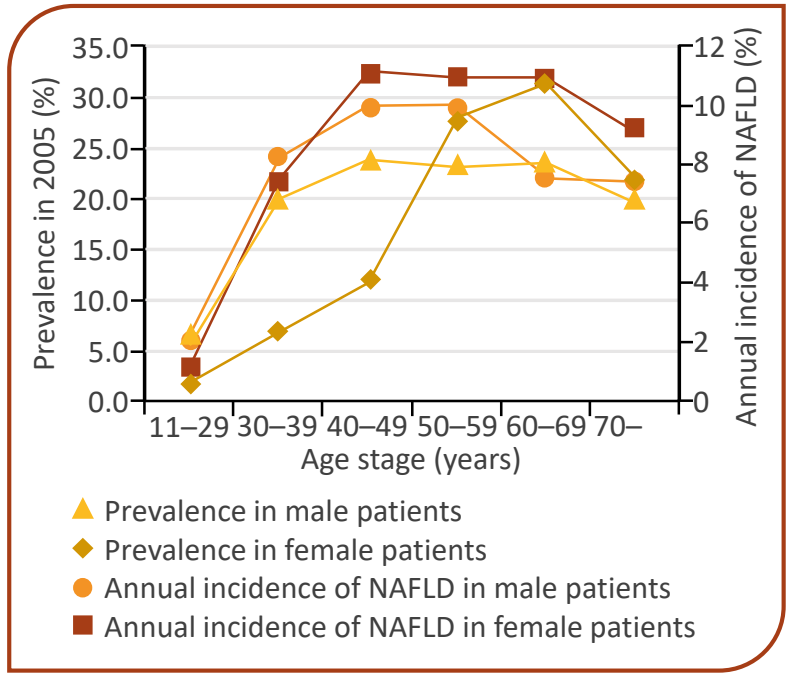
1. ALT and AST biomarkers
2. Histology
3. Ultrasound
4. St-Index
5. Transient elastography
6. FibroMax
7. Others

ALT, alanine aminotransferase; AST, aspartate transaminase; NAFLD, non-alcoholic fatty liver disease

Should we pay attention to liver steatosis at ultrasound?

4-year cardiovascular mortality in a large prospective cohort study of patients with and without NAFLD based on ultrasound* (n=3324)





Cardiovascular death risk may be higher in steatosis patients diagnosed with ultrasound

*Ultrasound examination was performed by two blinded, experienced physicians
CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease
Zhou YJ, et al. J Dig Dis 2012;13:153–60

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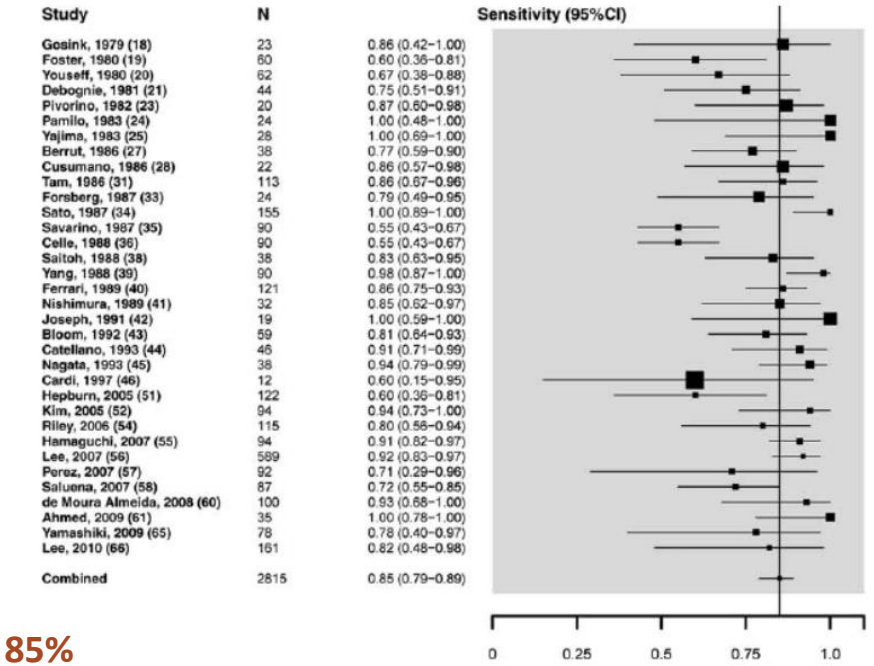
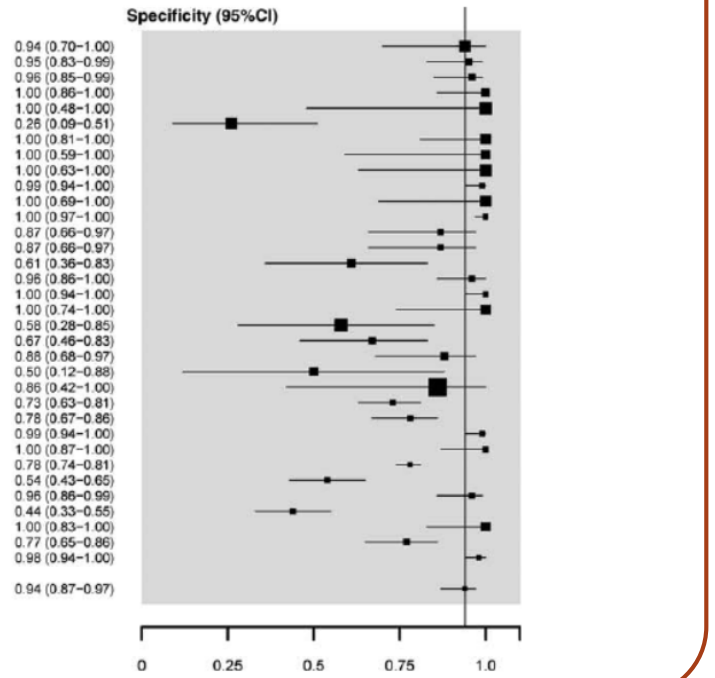
Let’s compare ultrasound to histology

Ultrasound and histology comparison in terms of liver steatosis diagnostic specificity and sensitivity



Sensitivity **85%**



Specificity **94%**

ROC = 0.93, meaning high prognostic value of ultrasound in steatosis verification
Ultrasound is accurate and reliable method to detect steatosis 2–3 grade comparing to histology

Meta-analysis of 34 studies, N=2815. CI, confidence interval; ROC, receiver operating characteristics
Hernaez R, et al. Hepatology 2011;54:1082–90

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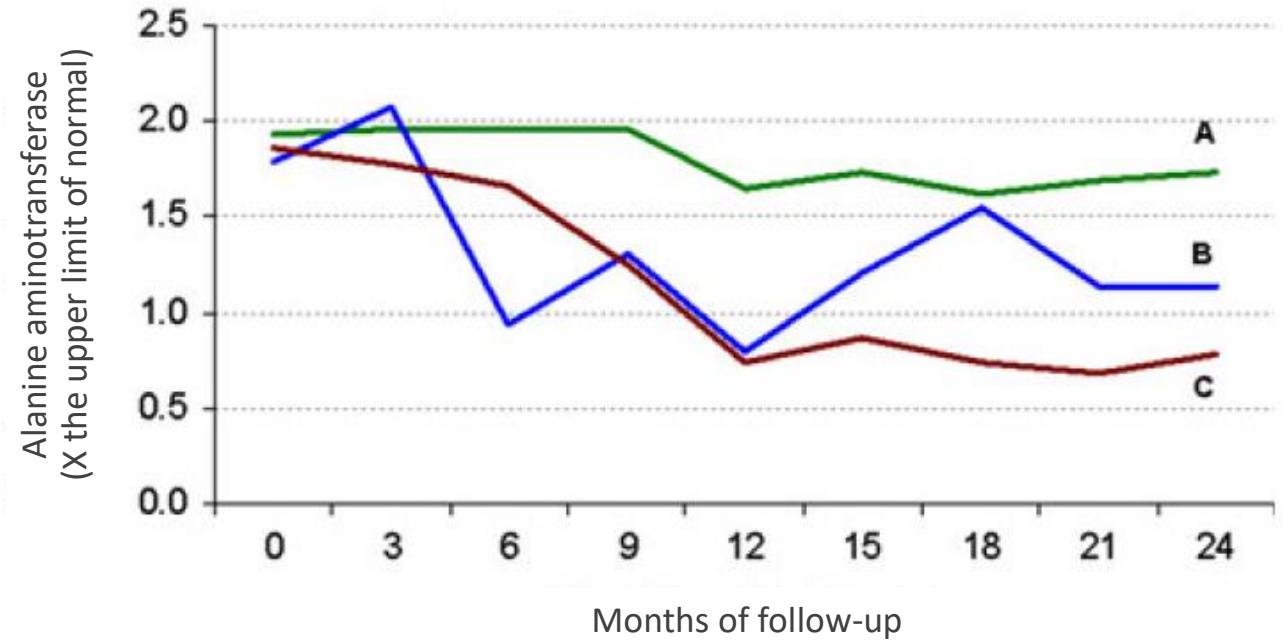
ALT and AST markers of inflammation: Are they valuable in diagnosing NAFLD?

- ALT and AST are a practical tool to monitor liver disease; however, they may fluctuate, normalize spontaneously, and **do not reflect steatosis, dynamic changes of fibrosis, or correlate with histological inflammation activity in NAFLD/NASH**
- Spontaneous course of ALT in untreated NASH patients during 2 years (n=73):
  - Constantly increased in **68% of patients**
  - Spontaneously **fluctuated between normal and elevated in 22% of patient**
  - Spontaneously **normalized in 10% of patients**



ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatisis

Charatcharoenwitthaya P, et al. Dig Dis Sci 2012;57:1925–31

St-index: A new, non-invasive screening tool to detect steatosis based on real-world data

Real-world data → Real-world evidence → Real-world solution

St-index – new non-invasive tool for doctors and patients suspecting NAFLD (you only need a ruler)

- Data we need:
  - Age
  - T2DM Y/N
  - Waist-to-height ratio

$$Y = -3.5856 + 0.0141*age + 0.4711*T2D + 4.4373*WCHR$$

NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; WCHR, waist-to-height ratio
Data on file

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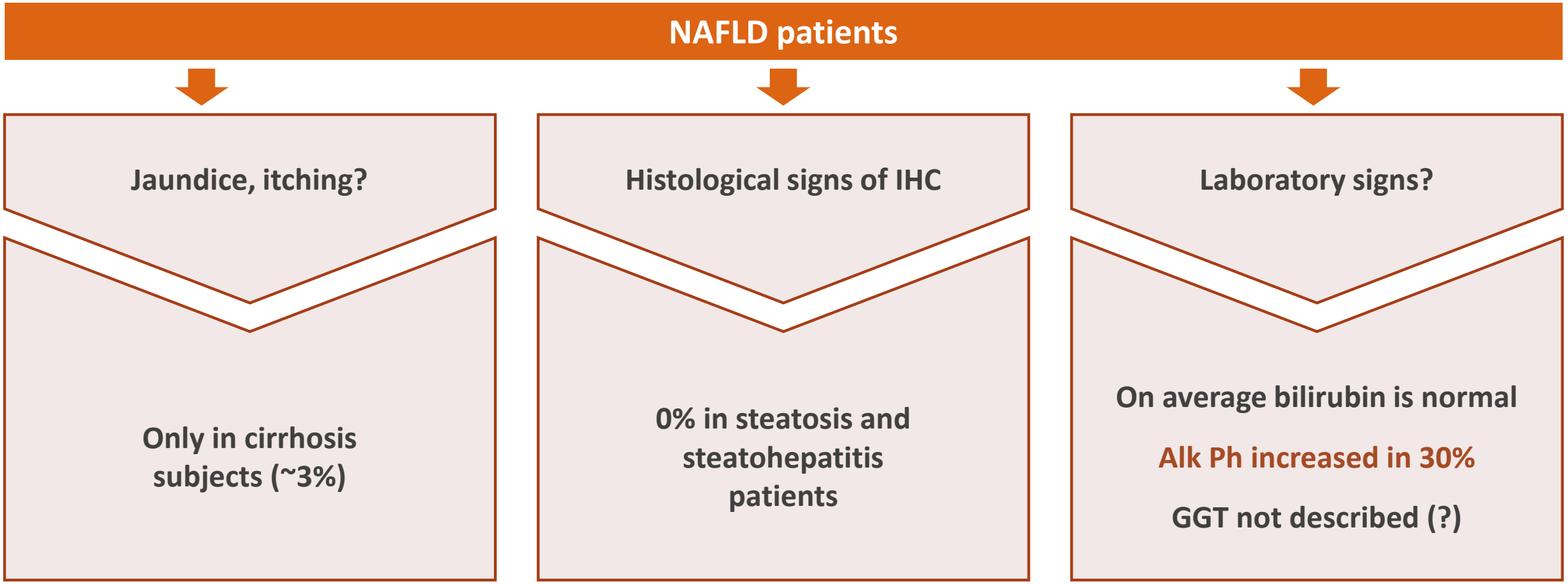
Is intrahepatic cholestasis common in NAFLD?

Russian study (2018): Intrahepatic cholestasis in NAFLD patients (N=163; subjects with a full spectrum of NAFLD from simple steatosis to cirrhosis)



Alk Ph, alkaline phosphatase; GGT, gamma-glutamyl transferase; IHC, intrahepatic cholestasis; NAFLD, non-alcoholic fatty liver disease

Shipovskaya et al. Ther Archive 2018;02:69–74

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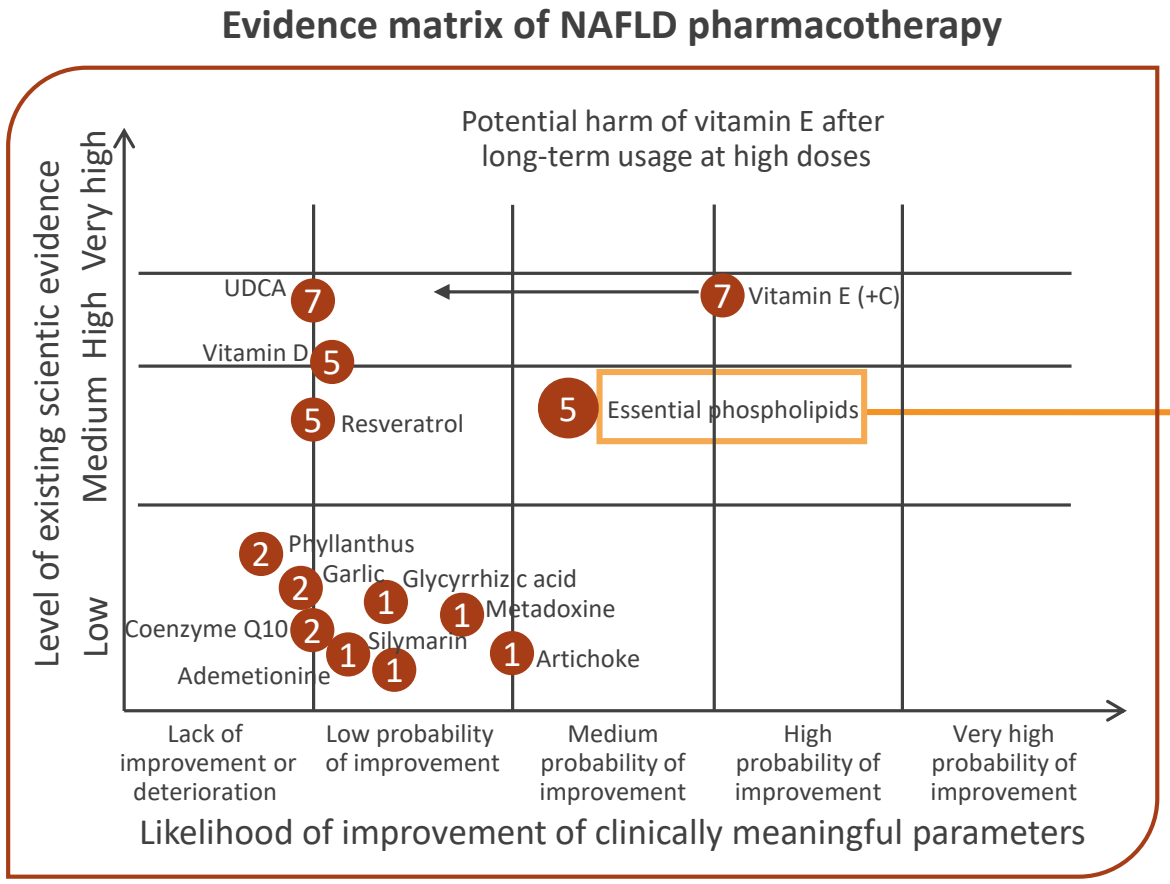
In your clinical practice, in addition to lifestyle changes, which adjunctive treatment would you consider for the management of mild steatosis in patients with NAFLD?

1. Pharmacological intervention
2. Hepatoprotectants
3. 1 + 2
4. I would not consider an adjunctive therapy

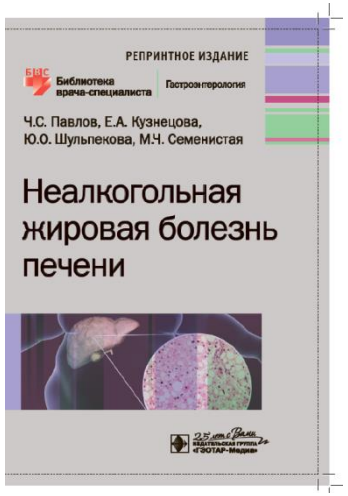
NAFLD, non-alcoholic fatty liver disease

Evidence for essential phospholipid use in NAFLD

Published analysis of the evidence base for NAFLD pharmacotherapy



EPL demonstrate effectiveness in steatosis in NAFLD (from 5 RCTs)



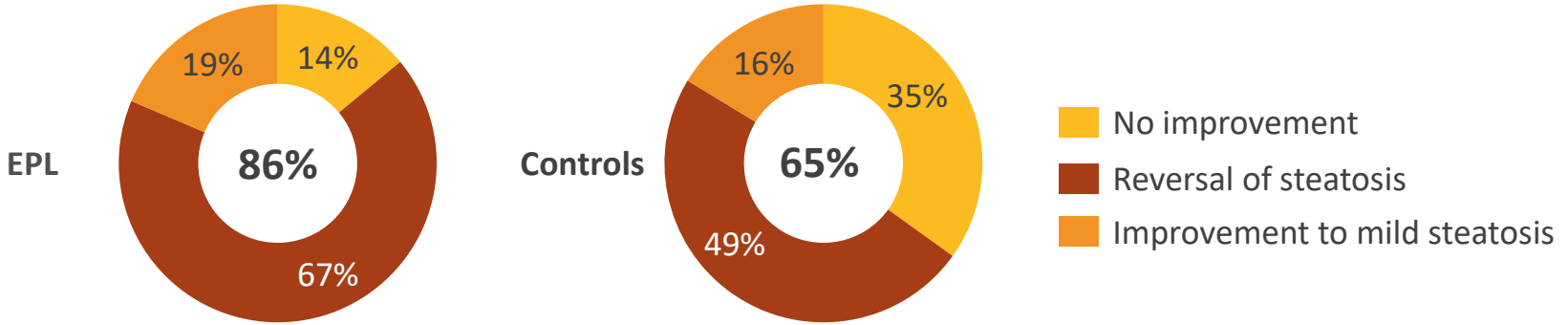
"Nonalcoholic liver disease" book – Pavlov Ch.S, E.A Kuznetsova, Yu.O Shulpekova, M.Ch Semenistaya (Moscow: GEOTAR-Media 2019)

At least one RCT with a placebo-controlled arm or no treatment arm, and N=50 in the group; or at least two RCTs with a placebo-controlled or no-treatment arm
EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; Q10, ubiquinone; RCTs, randomized controlled trials; UDCA, ursodeoxycholic acid; Vit, vitamin
Ч.С.Павлов и соавт. Неалкогольная жировая болезнь печени, М. Гэотар медиа, 2019

Clinical EPL effect in steatosis: Ultrasound in patients with T2DM

- 86 patients with NAFLD and T2DM (no significant statistical differences in gender, age, blood glucose level, lipid profile, US characteristics) were randomized into 2 groups:
  - Treatment group (n=43) received metformin and [ESSENTIALE® forte] 1800 mg/d
  - Control group (n=43) received metformin for 6 weeks
  - All the participants received diet and physical activity recommendations, and ultrasound was provided

Significant improvement of US characteristics (p<0.05)



Reversal of steatosis in NAFLD or an improvement in mild steatosis was shown in 86% patients (1.32 – fold higher than in controls)

International Nonproprietary Names or Trade Names are used only for scientific purposes and not to promote, raise awareness of, or focus on advantages of a pharmacy or a pharmaceutical company
EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; US, ultrasound
Zhiguo L, et al. Inner Mongolia Journal of Traditional Chinese Medicine, 2013 No. 31

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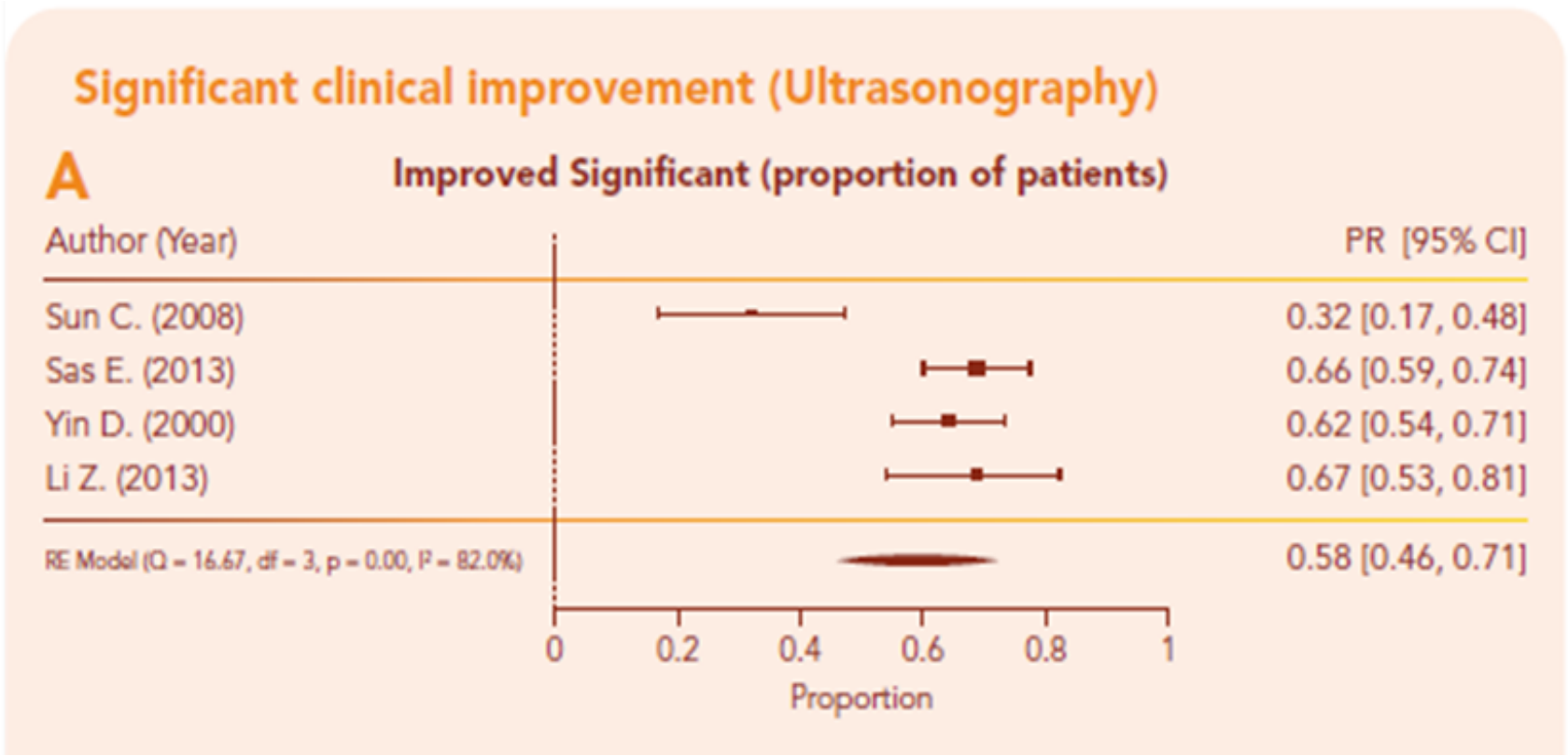
EPL in NAFLD: Meta-analysis presented at APASL 2020

Confirmed EPL effectiveness in steatosis in RCTs



EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease
Dajani AI & Popovic B. Poster presented at APASL 2020; PO-7-84

Antisteatotic effect of phosphatidylcholine: Mechanism of action

- NAFLD presence relates to decreasing amount of phosphotidylcholine[1] and follows functional disorders in the liver:
  1. Excessive fatty acids and triglycerides synthesis
  2. Insufficient fatty acid oxidation (β-oxidation in mitochondria)
  3. Defective very low-density lipoproteins secretion and evacuation

1 Inhibition of triglyceride synthesis in liver cells

EPL[2–4] - - - - → ***STOP PRODUCTION OF TRIGLYCERIDES IN THE LIVER CELLS[3,4]***

2 Improvement of fatty acid β-oxidation in liver cells

EPL[5–7] - - - - → ***ELIMINATION OF TRIGLYCIRIDES FROM HEPATOCYTES[8]***

3 Normalization of lipoprotein evacuation

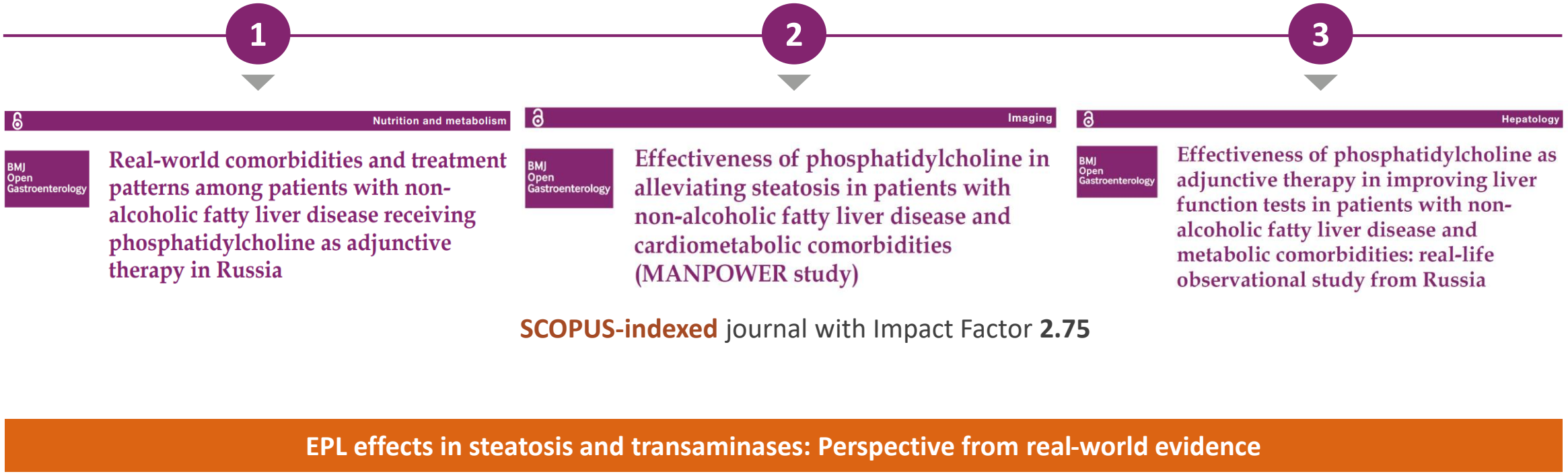
EPL[5–7] - - - - → ***NORMALIZATION OF LIPOPROTEIN EVACUATION FROM HEPATOCYTES[7]***

*NAFLD, non-alcoholic fatty liver disease; PC, phosphotidylcholine. 1. Puri P, et al. Hepatology 2007;46:1081–90; 2. Walker AK, et al. Cell 2011;147:840–52; 3. Matías Caviglia J, et al. J Lipid Res 2004;45:1500–9; 4. Takeuchi K, et al. Am J Physiol Endocrinol Metab 2009;296:E1195–E1209; 5. Chakravarthy MV, et al. Cell 2009;138:476–88; 6. Mehedint MG, et al. Curr Opin Clin Nutr Metab Care 2013;16:339–45; 7. Mello T, et al. PPAR Research 2016, Article ID 7403230; 8. Choi SH, et al. Trends Endocrinol Metab 2011;22:353–63

RWE: Highlights from the MANPOWER study

Three MANPOWER publications in BMJ Open Gastroenterology (2019–2020)

Published data of observational multicenter study MANPOWER:
EPL treatment in NAFLD patients with cardiometabolic comorbidities for 24 weeks



SCOPUS-indexed journal with Impact Factor **2.75**

EPL effects in steatosis and transaminases: Perspective from real-world evidence

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease

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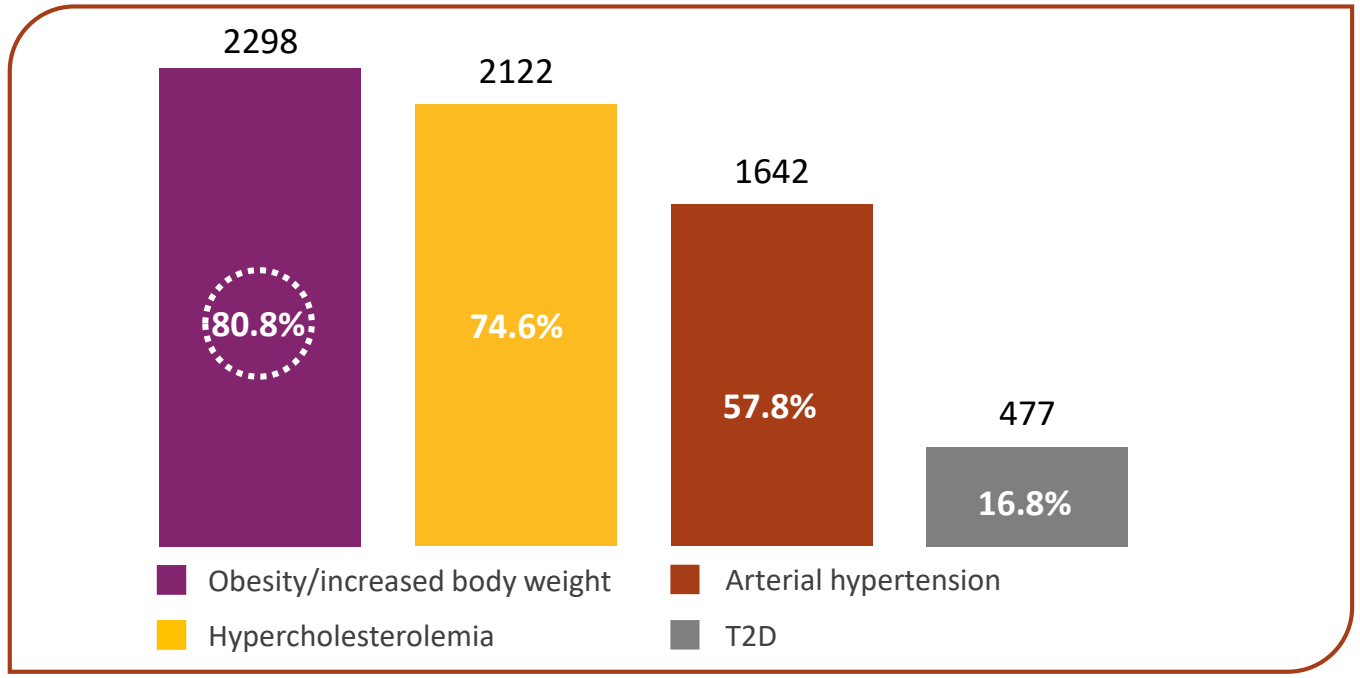
MANPOWER: Descriptive data and adherence to adjunctive EPL treatment

Metabolic comorbidities in NAFLD patients (N=2843)



Nutrition and metabolism

BMJ Open Gastroenterology

Real-world comorbidities and treatment patterns among patients with non-alcoholic fatty liver disease receiving phosphatidylcholine as adjunctive therapy in Russia

Obesity and increased body weight are the most frequent comorbidities in **NAFLD** patients

1800 mg/day EPL were prescribed for 6 months
Adherence to treatment constituted 90.5%

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes
Maev IV, et al. BMJ Open Gastro 2019;6:e000307

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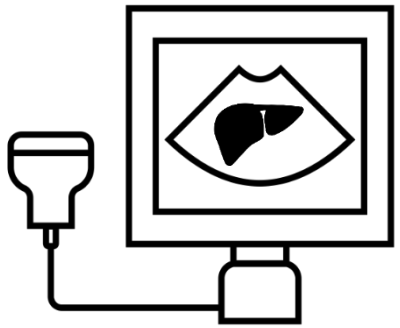
MANPOWER: NAFLD spectrum and adherence to lifestyle changes



As per available data **SIMPLE STEATOSIS was revealed in 74.9%**

Nutrition and metabolism

BMJ Open Gastroenterology

Real-world comorbidities and treatment patterns among patients with non-alcoholic fatty liver disease receiving phosphatidylcholine as adjunctive therapy in Russia

Of **2827** patients **only 13.8%**

Diet and physical activities

Followed diet

Which is the first step to NAFLD treatment

NAFLD, non-alcoholic fatty liver disease
Maev IV, et al. BMJ Open Gastro 2019;**6:**e000307

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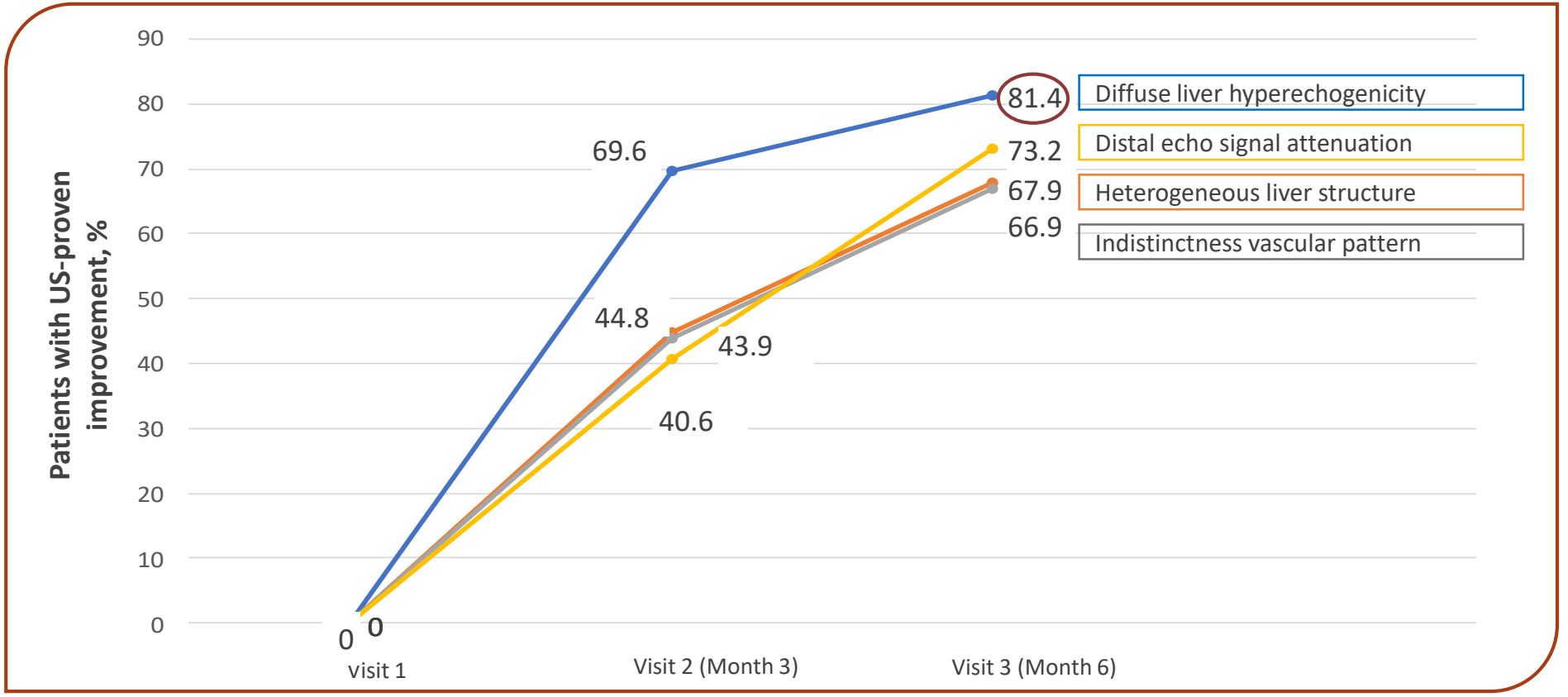
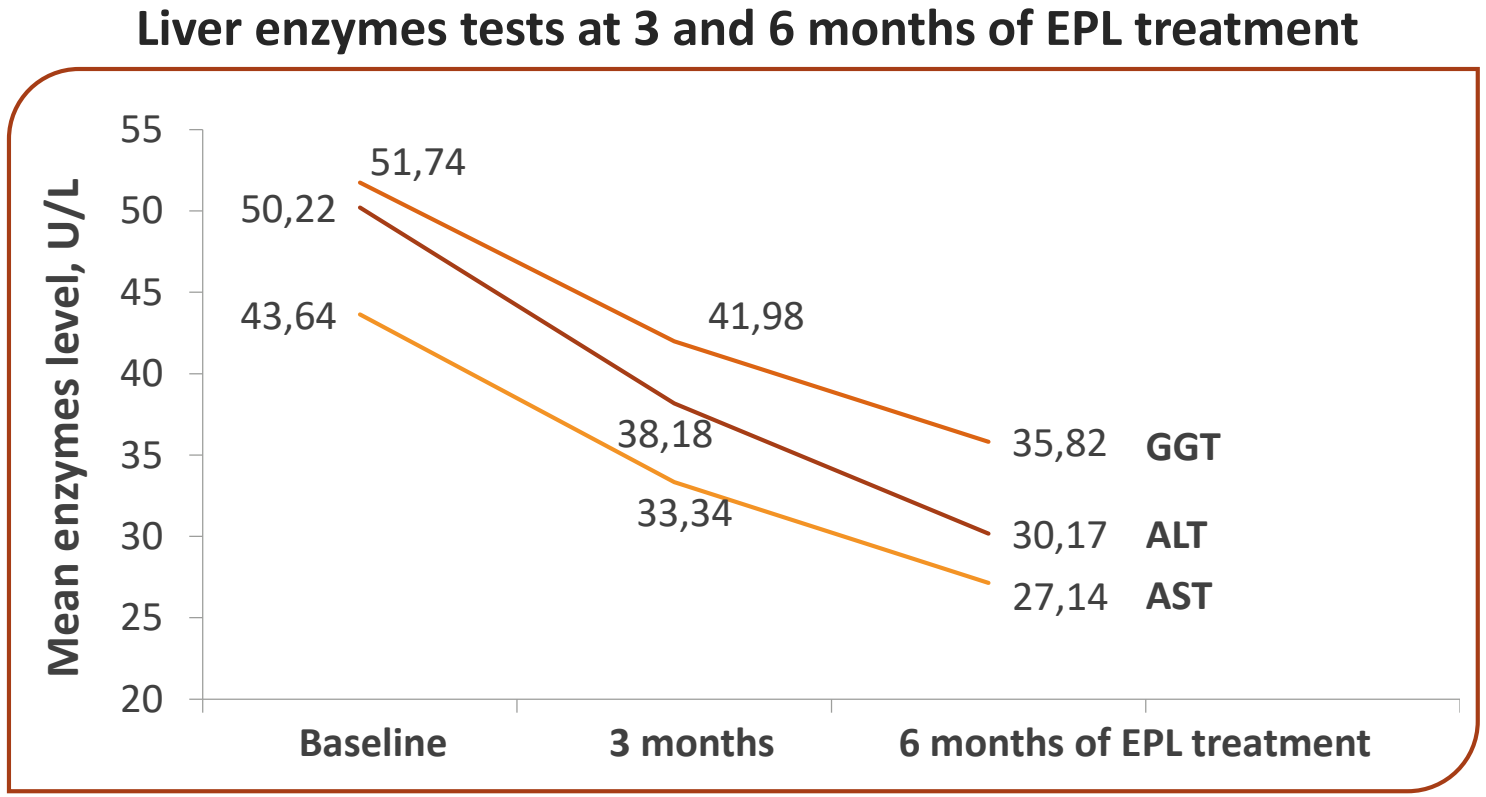
MANPOWER: EPL effect on steatosis



Ultrasound – significant improvement after 3.6 months of treatment with EPL (p<0.05)

EPL, essential phospholipids. Maev IV, et al. BMJ Open Gastro 2020;**7:**e000341

MANPOWER: Liver enzymes dynamic



Significant decrease of ALT, AST and GGT (p<0.05) observed following 3 and 6 months of treatment with EPL

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; GGT, gamma-glutamyl transferase

Maev IV, et al. BMJ Open Gastro 2020;7:e000368

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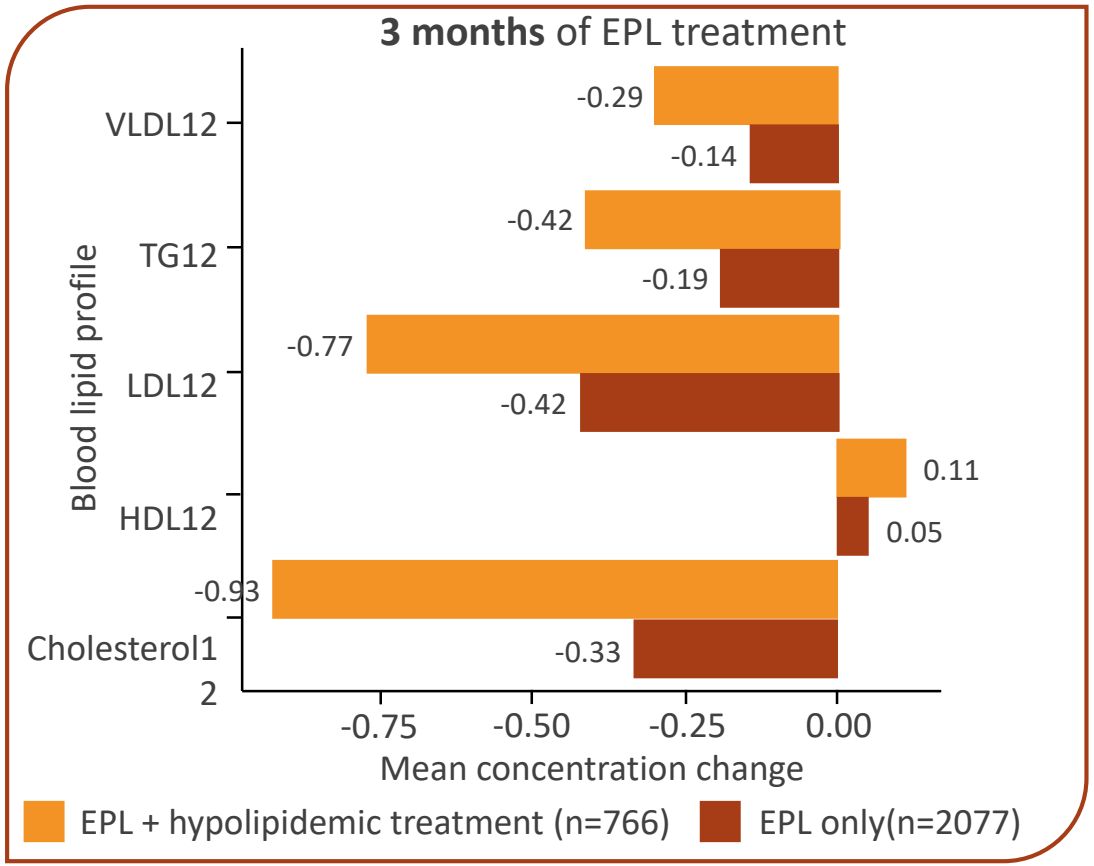
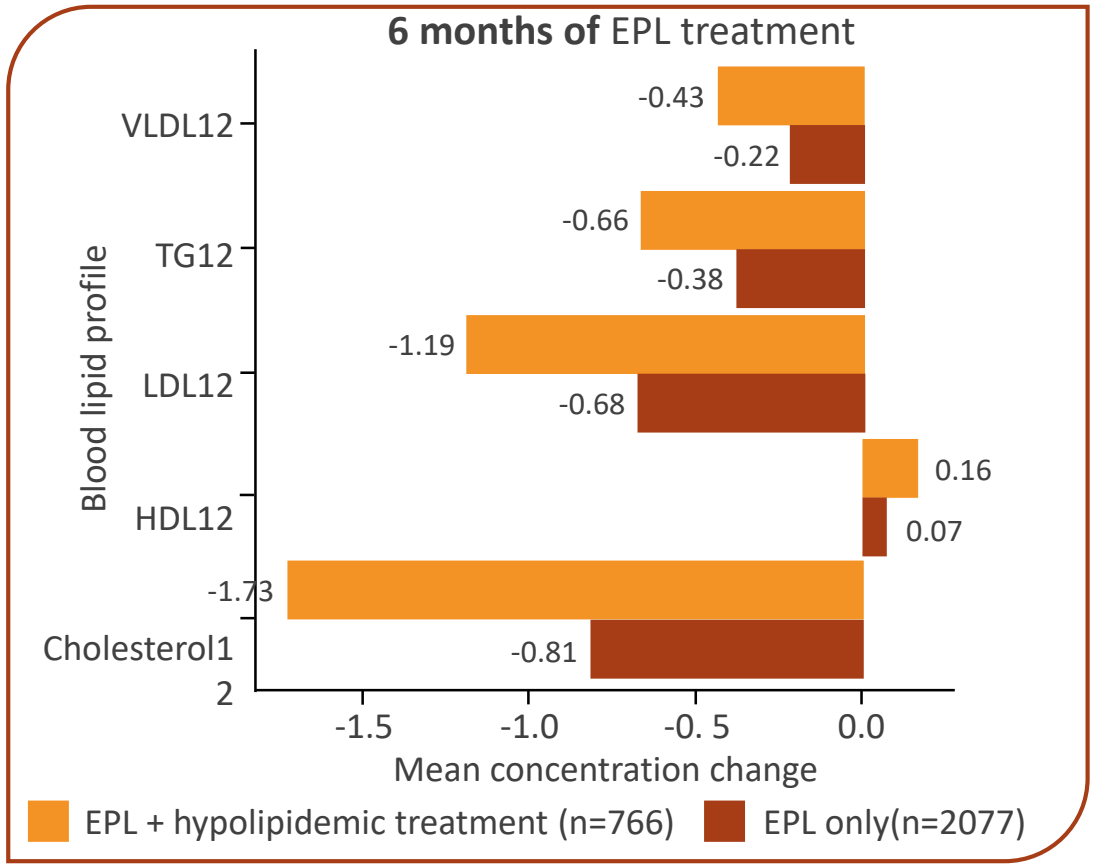
MANPOWER: Additional benefit of EPL on lipid profile





Significant improvement of lipid profile in both subgroups (p<0.05) after 3 months of treatment

EPL, essential phospholipids. Maev IV, et al. BMJ Open Gastro 2020;7:e000368

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Intravenous EPL

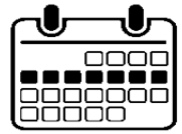
100% bioavailability

Clinical studies: Trials and real-world evidence

EPL – intravenous form (100% bioavailability)

Totally n=2501
EPL group n=982

23 clinical studies
1963–2018
15483 days of treatment



Treatment course:
7 days – 1 month

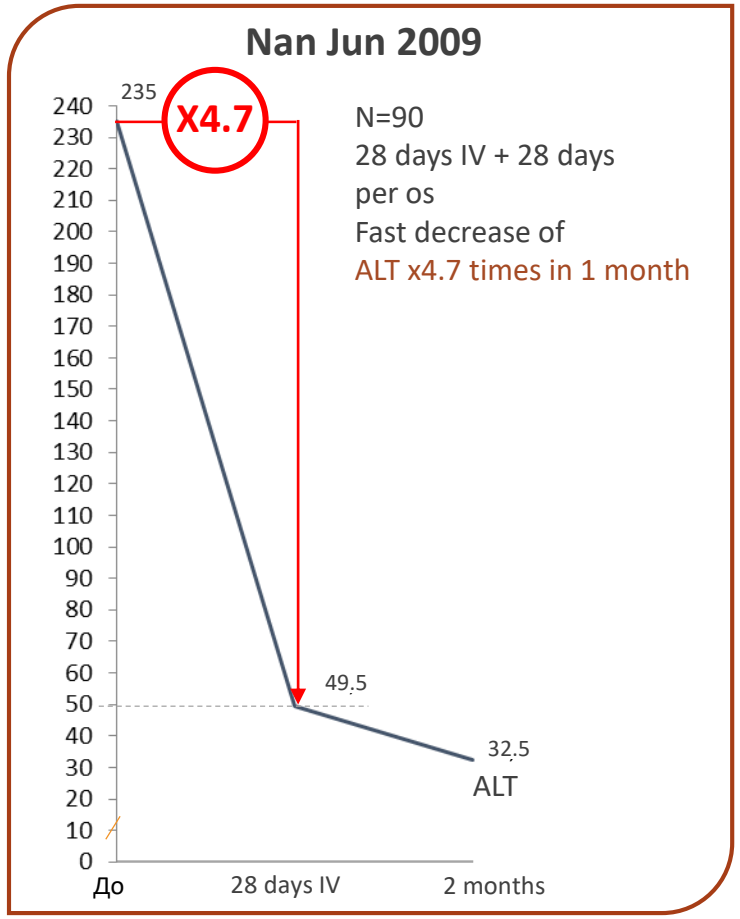
12 liver diseases of which
7 in NAFLD/NASH (2 in pregnant women)

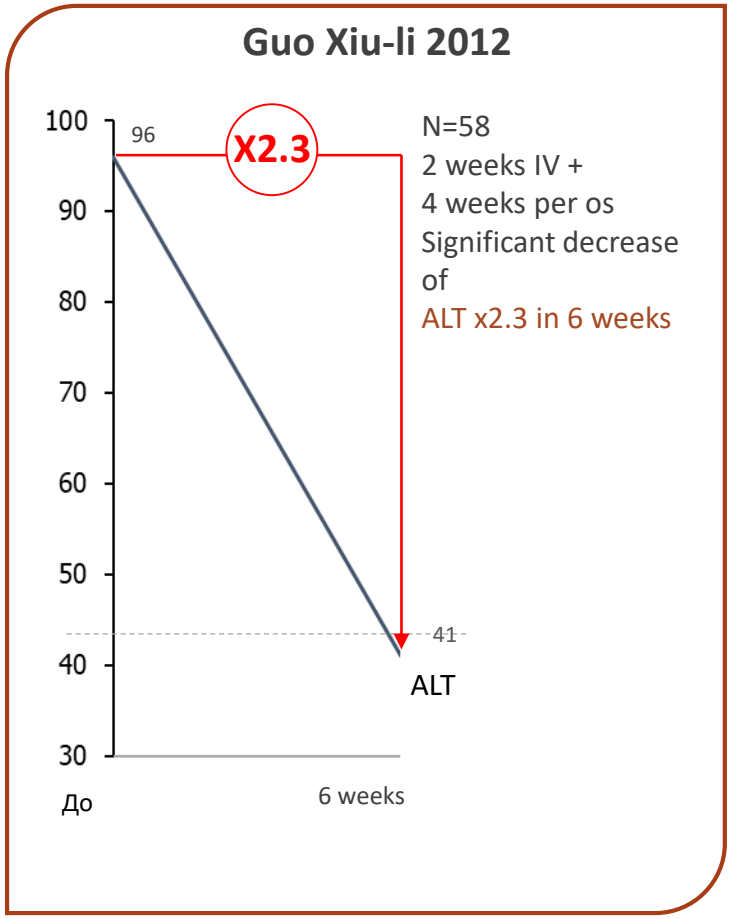
7 pregnancy toxicosis

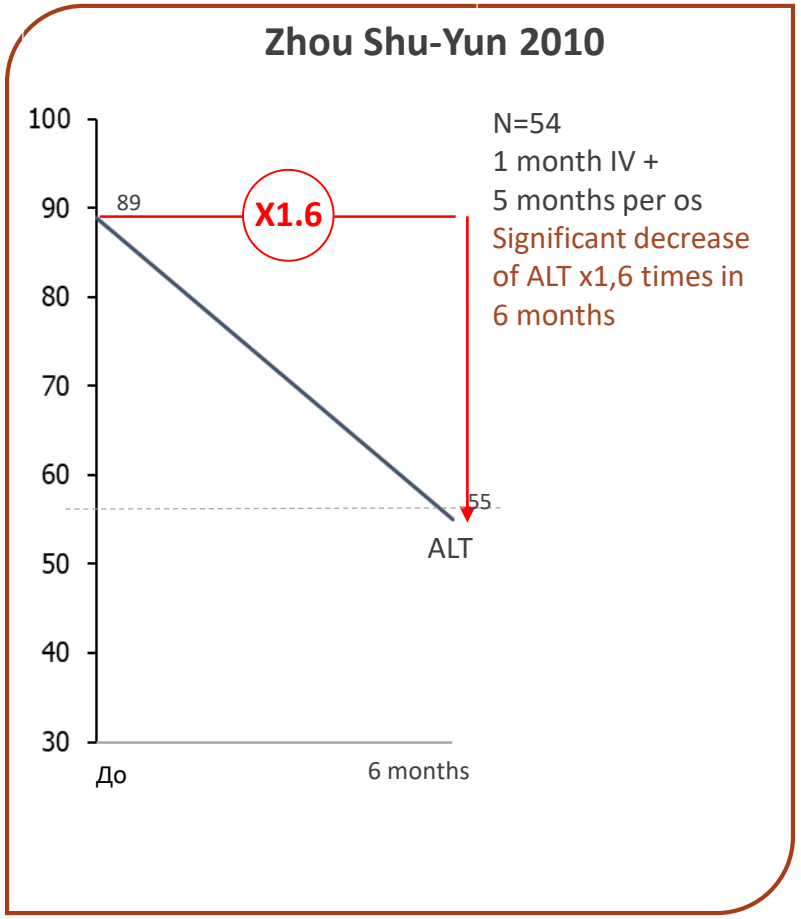
4 psoriasis

EPL, essential phospholipid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
Information from Sanofi internal literature review.

Liver function in EPL intravenous form cohorts: Changes in ALT







ALT, alanine aminotransferase; EPL, essential phospholipids; IV, intravenous

NAN Jun. Guide of China Medicine 2009;9:249–50; Guo X-L, et al. Chinese Journal of New Drugs 2012;21; Zhou S-Y, et al. J Clini Hepatol 2010;26

Conclusions

1. NAFLD and particularly steatosis are related to increased cardiovascular mortality, which can be detected by ultrasound imaging[1]
2. While ALT and AST levels are important indicators of cytolysis, they do not reflect steatosis or dynamic changes of fibrosis, and do not correlate with histological inflammation activity in NAFLD/NASH[2]
3. The st-index represents a new, non-invasive screening tool to detect steatosis, based on real-world data[3]
4. Recent RWE demonstrates a significant reduction in severity of steatosis with EPL treatment in >80% of patients with cardiometabolic comorbidities, due to their anti-steatotic mechanism of action[4,5]
5. There is also an IV form of EPL, with higher bioavailability, and clinical data shows that it may be beneficial in situations where steatosis is accompanied with increased liver enzymes[6–8]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; IV, intravenous; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RWE, real-world evidence

1. YJ Zhou YJ, et al. J Dig Dis 2012;13;153–60; 2. Cao X. et al. Zhonghua Gan Zang Bing Za Zhi 2015;23:569–73; 3. Maev IV, et al. Advances in Therapy 2020; Online ahead of print; 4. Maev IV, et al. BMJ Open Gastro 2019;6:e000307; 5. Maev IV, et al. BMJ Open Gastro 2020;7:e000368; 6. NAN Jun. Guide of China Medicine, 2009;9:249–50; 7. Guo X-L, et al. Chinese Journal of New Drugs 2012;21;
8. ZHOU Shu-Yun, SUN Zhe-Ying. J Clini Hepatol 2010;26