# **Detecting steatosis in clinical practice** – insights from the EPOCH RWD analysis

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*President of Scientific Society of Russian Gastroenterologists*

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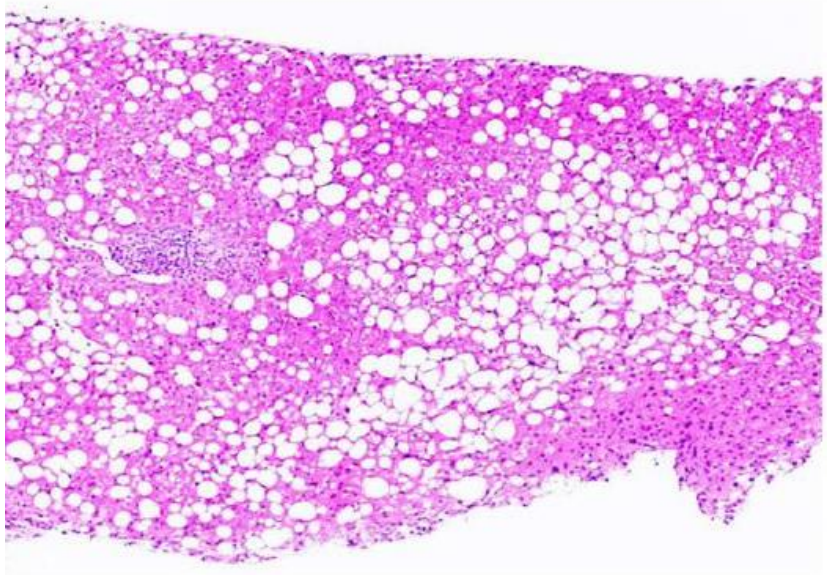
# NAFLD phenomenon and clinical point of view

## NAFLD *PER SE*



>5% hepatocytes with fatty droplets

## CLINICAL MANIFESTATION

- **Asthenic** syndrome — fatigue, sleep disorders[1,2]
- **Dyspepsia** syndrome — bloating, nausea, stool disorders[1]
- Pain syndrome — dull pain/**heaviness** in the right upper abdomen[1,2]
- **Hepatomegaly** and/or splenomegaly[2,3]

So, almost nobody has biopsy performed and NAFLD is considered as a silent disease

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*NAFLD, non-alcoholic fatty liver disease*
*1. Khoonsari M et al. Iran J Pathol. 2017;12:99–105;*
*2. Basaranoglu M and Neuschwander-Tetri BA. Gastroenterol Hepatol (N Y) 2006;2:282–91;*
*3. Malnick SDH et al. QMJ 2003;96:2003*

*Francque 2019*

# Why don't we treat liver steatosis as dangerous as obesity?

**Is simple steatosis a harmless adaptive reaction to the kcal overload?**

> Interestingly, the dogma that isolated steatosis is (almost) harmless and NASH is the culprit has recently been challenged by paired biopsy studies showing that patients with isolated steatosis also exhibit progressive fibrosis[1]

**TODAY, STEATOSIS IS NOT CONSIDERED HARMLESS ANYMORE – THANKS TO THE 'MAFLD' CONCEPT TOO**

In paired biopsy studies, **STEATOSIS PROGRESSED TO FIBROSIS**

STEATOSIS is ASSOCIATED WITH **x3 TIMES** CARDIOVASCULAR DEATH INCREASE

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*MAFLD, metabolic associated fatty liver disease; NASH, non-alcoholic steatohepatitis*

*1. Francque S et al. Adv Ther 2019;36:1052–74; 2. Zhou YJ et al. Dig Dis 2012;13:153–60*

# MAFLD (NAFLD) and severe COVID-19

Digestive and Liver Disease 53 (2021) 153–157

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

## Metabolic associated fatty liver disease increases the severity of COVID-19: A meta-analysis

Lu Pan[a], Pan Huang[b,*], Xia Xie[c,*], Jiachen Xu[d], Dawei Guo[e], Yuan Jiang[f]

*Meta-analysis of 6 studies, N=1,293*

MAFLD is associated with increased risk of severe COVID-19 – Odds ratio (OR) = **2.93** (95%CI 1.87, 4.60)

Young patients (!)

**Table 1**
The characteristics of the included studies.

| Study | Region | Age | Sample | Study design | Male | MAFLD% | NOS score |
|---|---|---|---|---|---|---|---|
| Zhou Y(a) 2020 | China | – | 327 | cross-sectional study | – | 28.4% | 9 |
| Zhou YJ(b) 2020 | China | 42.1 ± 11.4 | 101 | case-control study | 0.745 | – | 8 |
| Targher G 2020 | China | 47 | 310 | cross-sectional study | 0.481 | 30.3% | 8 |
| Ji D 2020 | China | 44.5(34.8–54.1) | 202 | cross-sectional study | 0.559 | 37.6% | 9 |
| Zheng K 2020 | China | 47 | 214 | cross-sectional study | 0.258 | 30.8% | 8 |
| Gao F 2020 | China | 46.0 ± 13.0 | 130 | case-control study | 0.631 | – | 9 |

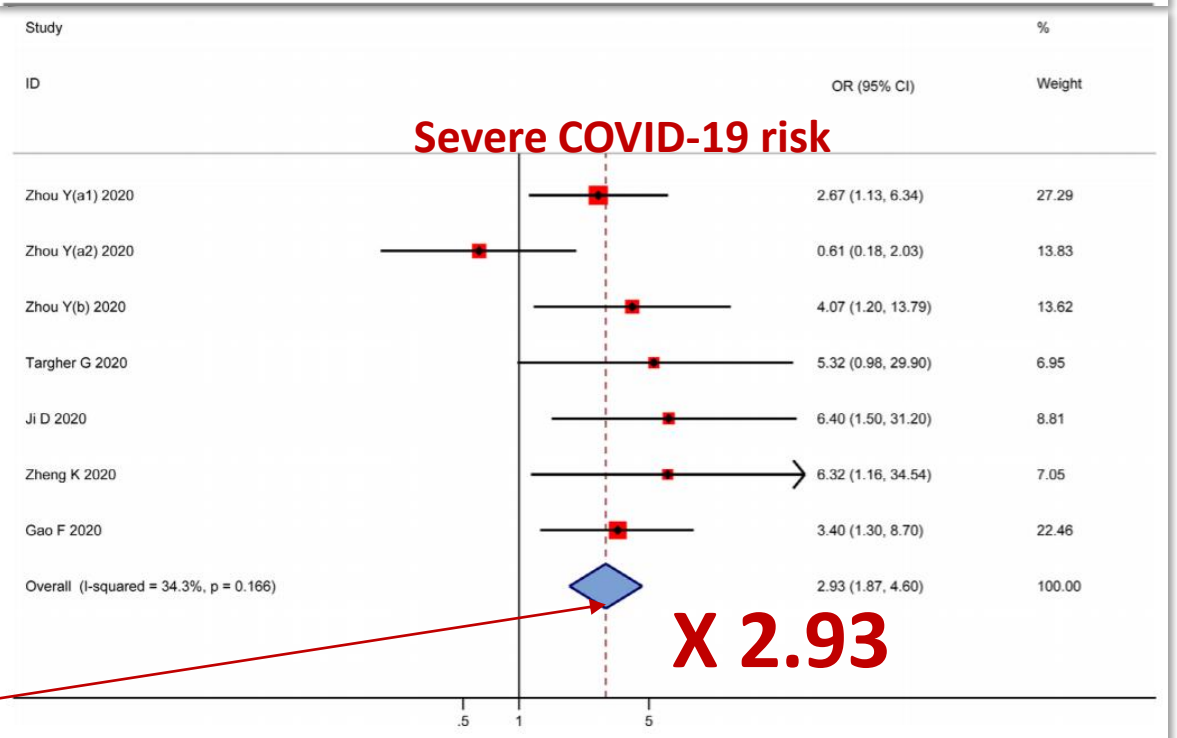


Fig. 3. The association of MAFLD with disease severity among patients with COVID-19.

*CI, confidence interval; MAFLD, metabolic associated fatty liver disease; NOS, Newcastle-Ottawa Scale; OR, odds ratio*

*1. Pan Lu, et al. Dig Liver Dis 2021;53:153–7*

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# NAFLD or MAFLD?

- **NAFLD – officially recognized disease in WHO disease classification (ICD-10/11)[1,2]**

- **MAFLD – as a new working consensus concept for different disease phenotypes and accepting decisions concerning treatment approach[3]**

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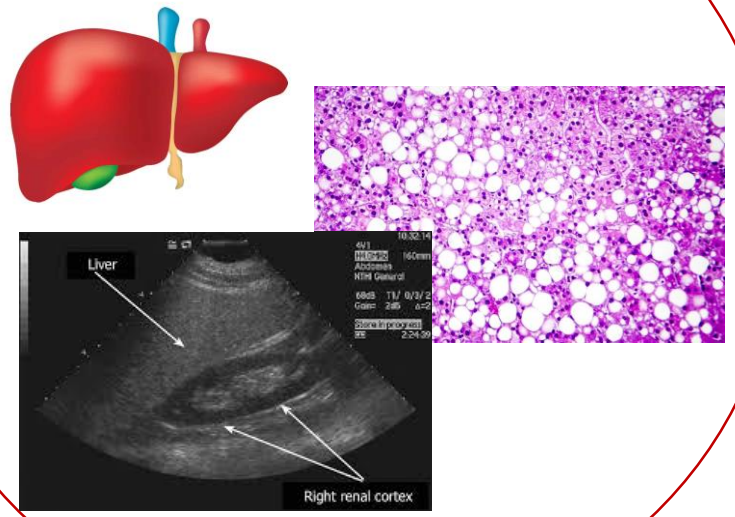
*ICD, international classification of disease; MAFLD, metabolic fatty liver disease; NALFD, non-alcoholic fatty liver disease*

*1. WHO ICD-10 Version: 2016. Available from: https://icd.who.int/browse10/2016/en Accessed June 2021;*
*2. WHO ICD-11 for mortality and morbidity statistics. Available from: https://icd.who.int/browse11/l-m/en Accessed June 2021;*
*3. Eslam M et al. J Hepatol 2020;73:202–9*

# 7 reasons to start liver steatosis treatment right away (!!!)

↑x16 **Hepatocellular carcinoma** risk[1]

↑x3 **Cardiovascular death** risk increase[3]




↑x2 **Breast cancer** risk in women[1]

↑x4 **Drug induced liver injury** risk[2]

↑x2 **Colorectal cancer** risk in men[1]

45% **Erectile dysfunction** in men[4]

↑x3 Risk of severe **COVID-19**[5]

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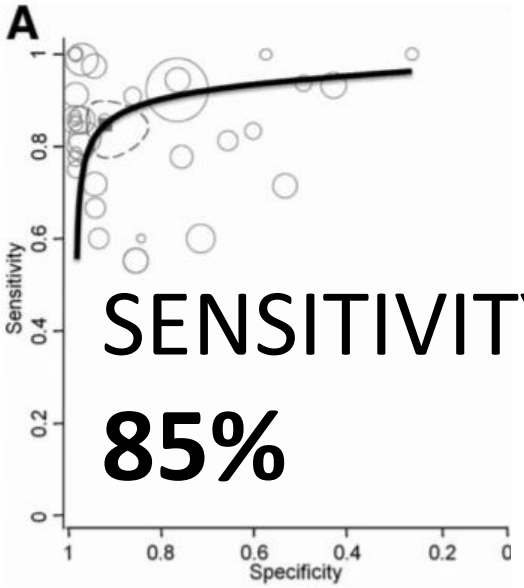
*1. Kim GA, et al. 2017 J Hepatol. 2017;32294–8; 2. Tarantino G, et al. Hepatology Research 2007;37:410–415; 3. YJ Zhou, et al. J Dig Dis 2012;13;153–160; 4. Hasanain AFA, et al. Arab J Gastroenterol 2017;17:21–24; 5. Pan Lu, et al. Dig Liver Dis 2021;53:153–7.*

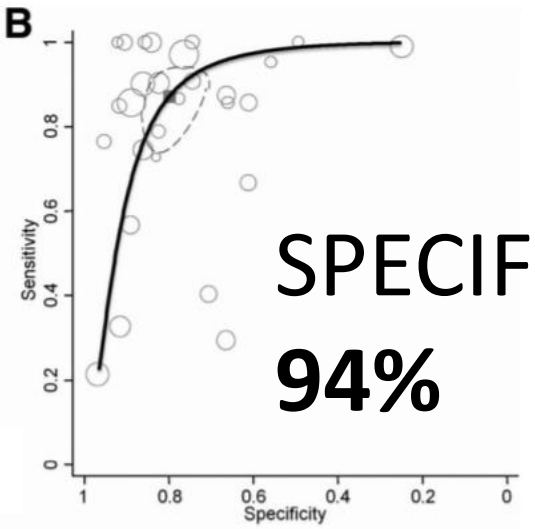
# Ultrasound is an excellent screening tool to detect liver steatosis

**Ultrasonography vs histology**




SENSITIVITY

**85%**




SPECIFICITY

**94%**

HEPATOLOGY AASLD

Review | Free Access

Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis†‡

Ruben Hernaez, Mariana Lazo, Susanne Bonekamp, Ihab Kamel, Frederick L. Brancati, Eliseo Guallar, Jeanne M. Clark

First published: 26 May 2011 | https://doi.org/10.1002/hep.24452 | Citations: 565

**Meta-analysis, 34 studies, N=2,815 (Hernaez, 2011)**

**Ultrasound** is an **accurate and reliable** method to detect steatosis 2–3 grade comparing to histology with high prognostic value – ROC = 0.93

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*ROC, receiver-operating curve*

*Hernaez R, et al. Hepatology 2011;54:1082–90*

# The question is can we detect liver steatosis, NAFLD/MAFLD and NASH without ultrasound, MRI or histology?

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*MAFLD, metabolic associated fatty liver disease; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis*

# What's wrong with all of these "non-invasive" tools?

**Steatosis**

- FLI
- HIS
- SteatoTest
- LAP
- ION
- NAFLD-LFS

**Fibrosis**

- APRI
- FIB-4
- FibroTest
- Fibrometer NAFLD
- ELF
- Hepacore
- BARD score
- NFS

Actually, all of them are invasive *(need lab markers or diagnostic procedures)*

So, the question is:
Can we develop fully non-invasive steatosis screening tool?

**EPOCH real-world data project has given the answer**

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***APRI, aspartate aminotransferase to platelet ratio; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; FLI, fatty liver index; HIS, hepatic steatosis index; ION, index of non-alcoholic steatohepatitis; LAP, lipid accumulation product; NAFLD-LFS, non-alcoholic fatty liver disease liver fat score; NFS, non-alcoholic fatty liver disease fibrosis score***

# EPOCH 1 design

**Database: (Russian epidemiology study – DIREG2)**

EPOCH-1

50 000 subjects

Liver Ultrasound
available


\+ Other data related to subjects

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*Maev IV et al. Adv Ther 2020;4627–40*

# St-index – steatosis index, new and the first fully non-invasive approach to liver steatosis screening

EPOCH-1

**Just 3 questions:**

- Age (full years)
- T2DM Yes (1) / No (0)
- Waist (cm)-to-height(см) ratio (WHR)

Publication in Advances in Therapy journal - 16 Sep 2020


IF = 3.9

So, you need only a ruler, fasting sugar analyzer and good memory of the patient's birthday




St-index = -3.6 + 0.014*Age + 0.5*T2DM + 4.44*WHR

*IF, impact factor; T2DM, type 2 diabetes mellitus*

*Maev IV et al. Adv Ther 2020;4627–40*

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# St-index – what do figures mean?

EPOCH-1

Adv Ther (2020) 37:4627–4640
https://doi.org/10.1007/s12325-020-01493-w

ORIGINAL RESEARCH

**A New, Non-Invasive Scale for Steatosis Developed Using Real-World Data From Russian Outpatients to Aid in the Diagnosis of Non-Alcoholic Fatty Liver Disease**

| | Novel test: St-index | |
|---|---|---|
| Cutoff | – 0.847 | |
| AUROC | 0.6527 | |
| Sensitivity (%) | 93.8 | 18.7 |
| Specificity ( %) | 23.1 | 91.4 |
| LR+ | 1.22 | 2.17 |
| LR– | 0.27 | 0.89 |

*Sensitivity=**93.8%***
***NO***
*Liver Steatosis*
**St < -0.85**

*Indefinite zone*
*ULTRASOUND required*

*Specificity=**91.4%***
**St > 0.4**
***YES***
*Liver Steatosis*

St-index

**St-index value** -0.85 0.4



*AUROC, area under the receiver operating characteristic curve; LR, likelihood ratio*
*Maev IV, et al. Adv Ther 2020;37:4627–40*

# At first glance, how do you find the practical validity of the St-index?

1. Very good
2. Good
3. Neutral
4. Not good


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# Russian NAFLD guidelines 2021

*MAFLD concept has been taken into account*

экспериментальная и клиническая гастроэнтерология | № 185 (1) 2021 experimental & clinical gastroenterology | № 185 (1) 2021



https://doi.org/10.31146/1682-8658-ecg-185-1-...-...

Non-alcoholic fatty liver disease in adults: clinic, diagnostics, treatment.
Guidelines for therapists, third version

- Для выявления групп риска стеатоза печени **рекомендуется расчитать индекс стеатоза (St-index)** – (как неинвазивный скрининговый метод оценки риска стеатоза печени).
  **Уровень убедительности рекомендаций В (уровень достоверности доказательств 2)**

**St-index – liver steatosis screening (B2)**


- Скрининговым методом выявления стеатоза печени при подозрении на НАЖБП является УЗИ. Наличие признаков стеатоза печени по данным УЗИ после исключения других причин его развития позволяет установить диагноз НАЖБП
  **Уровень убедительности рекомендаций А (уровень достоверности доказательств 2)**

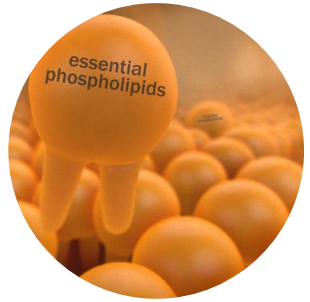
  **Комментарии:** *Среди визуальных методов диагностики НАЖБП наибольшее распространение в виду своей доступности получило УЗИ, дающее возможность с высокой чувствительностью и специфичностью выявить стеатоз в печени и оценивать изменения в динамике.*

**Ultrasound as a routine liver steatosis diagnostic tool (A2)**

- Постепенное снижение веса и увеличение физической нагрузки является ведущими факторами в лечении НАЖБП, потеря веса при использовании гипокалорийной диеты или ее сочетание с повышенной физической активностью способствует уменьшению проявлений стеатоза.
  **Уровень убедительности рекомендаций А (уровень достоверности доказательств 1)**

**Basic therapy:**

- **Weight reduction (A1)**
- **Physical activity (A1)**
- **Essential phospholipids (A1)**




- #ЭФЛ рекомендуются для лечения пациентов с признаками стеатоза печени вне зависимости от стадии заболевания (НАЖБП/НАСГ).
  **Уровень убедительности рекомендаций А (уровень достоверности доказательств 1)**

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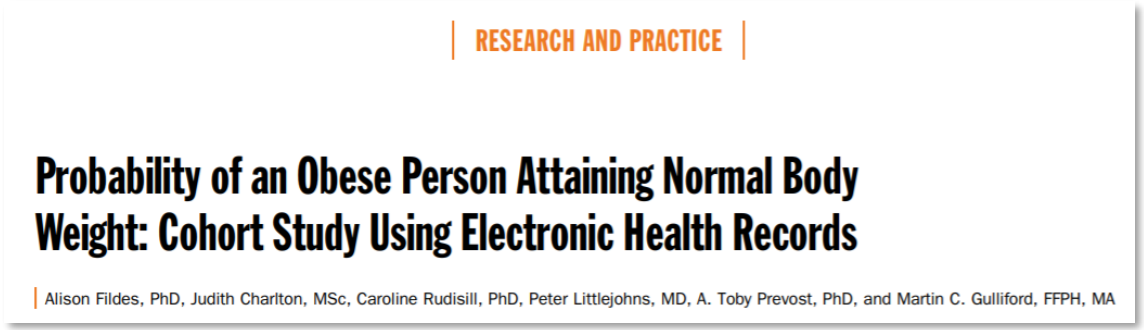
***Lazebnik LB, et al. Gastroenterology 2021;1:4–52 (In Russ.)***

# Well, we diagnosed steatosis. Do we need pharmacotherapy?

*Real world data*

**According to the recent analysis, the probability of achieving normal mass in a person with obesity is <2%**

Wide-scale cohort study:
N = **176,495**; M, n=76,704; W, n=99,791;
**Follow-up = up to 9 years**, CPRD database



RESEARCH AND PRACTICE

Probability of an Obese Person Attaining Normal Body Weight: Cohort Study Using Electronic Health Records

Alison Fildes, PhD, Judith Charlton, MSc, Caroline Rudisill, PhD, Peter Littlejohns, MD, A. Toby Prevost, PhD, and Martin C. Gulliford, FFPH, MA

**~ 2% patients managed to reach normal body mass during observation:**

- **1.7% of men (n=1,283) and 2.2% of women (n=2,245)**

**So, liver steatosis requires pharmacotherapy (!)**

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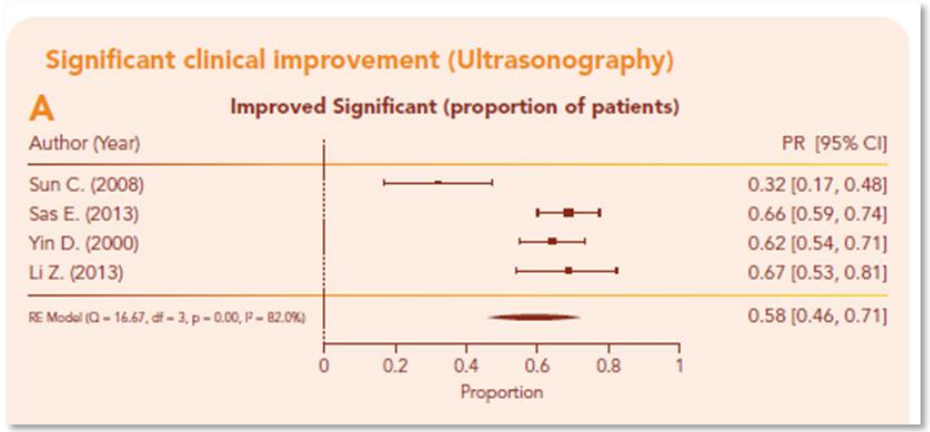
*CPRD, Clinical Practice Research Datalink; F, women; M, men*
*Fildes A, et al. Am J Public Health 2015;105:e54–9*

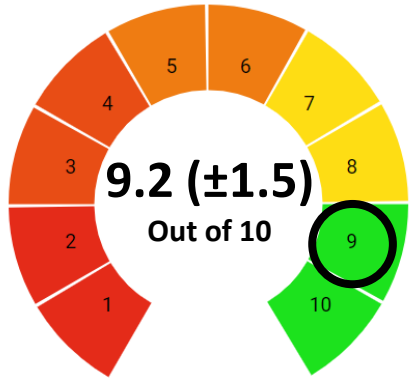
# There was another part of EPOCH analysis…

We already knew that EPLs cause **steatosis regression** from RCTs and a meta-analysis[1]




And we knew that EPLs are associated to **high subjective treatment satisfaction rate[2]**

**Mean Satisfaction score***




So, we asked a question whether **subjective treatment satisfaction correlates with objective liver structure and function improvement**

?

**EPOCH-2**

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**Data are mean (SD). CI, confidence interval; EPL, essential phospholipids; PR, prevalence ratio; RCT, randomized controlled trials; SD, standard deviation*

*1. Dajani A, et al. World J Clin Cases 2020;8:5235–49; 2. Sas YI, et al. Clin Prospects Gastroenterol Hepatol 2015;1:9–17*

# NAFLD treatment satisfaction can be associated with an improvement in clinical symptoms, true or false?

1. True
2. False

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# EPOCH-2: study design

**3 Real-World Russian studies:**
**MANPOWER, LIDER, LIDER-2 studies**

SpringerLink

Original Research Article | Open Access | Published: 15 May 2021

Correlation of Objective Endpoints and Subjective Patient-Reported Outcomes in NAFLD Treatment with Essential Phospholipids: Real-World Data Based on Pooled Analysis of Observational Studies

Vladimir T. Ivashkin, Marina V. Maevskaya, Elena N. Shirokova, Igor V. Maev, Alexey A. Samsonov, Evgeniy I. Sas, Liudmila K. Palgova & Kirill Starostin

*Drugs - Real World Outcomes* (2021) | Cite this article

146 Accesses | Metrics

*Drugs – Real world outcomes*
*Published: 15 May 2021*

EPOCH-2

**3,384 patients with NAFLD taking EPL therapy for 12/24 weeks**

**Pooled analysis**

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***Patients from the MANPOWER cohort; treated as non-adherent for the adherence estimation. EPL, essential phospholipids**

***Ivashkin VT, et al. Drugs Real World Outcomes 2021;doi: 10.1007/s40801-021-00250-x [ePub ahead of print]***

# Patients not only feel improvement, these subjective feelings correlate with objective improvements

EPOCH-2

### Clinicians' satisfaction and laboratory improvements

| Median change from baseline | Low + very low | High + very high | p value† |
|---|---|---|---|
| **ALT, U/L** | **–8.00** | **–15.00** | **<0.001** |
| **AST, U/L** | **–7.00** | **–13.00** | **<0.001** |
| **GGT, U/L** | **–6.00** | **–10.00** | **<0.001** |
| HbA1c, % | –0.10 | –0.15 | 0.029 |
| Total cholesterol, mmol/L | –0.60 | –1.10 | <0.001 |
| **HDL, mmol/L** | **0.10** | **0.10** | **0.028** |
| **LDL, mmol/L** | **–0.40** | **–0.80** | **<0.001** |
| **VLDL, mmol/L** | **0.00** | **–0.20** | **<0.001** |
| **Triglycerides, mmol/L** | **–0.20** | **–0.40** | **<0.001** |
| ALP, U/L | –8.50 | –13.60 | <0.001 |
| Total bilirubin, µmol/L | –1.00 | –2.00 | <0.001 |

### Patients' satisfaction and liver structure improvements

| | Improvement | | p-value‡ |
|---|---|---|---|
| **Patient's satisfaction, %*** | Low + very low | High + very high | |
| Diffuse hyperechogenicity of the liver parenchyma on ultrasound | 65.3 | 84.6 | <0.001 |
| Heterogeneity of liver structure on ultrasound | 61.8 | 81.2 | <0.001 |
| Vascular blurring and/or underlined vascular pattern on ultrasound | 67.4 | 87.9 | <0.001 |
| Distal attenuation of the echo-signal | 51.8 | 77.8 | <0.001 |

**So, if patients feels objective improvement, NAFLD is probably not so silent?**

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**Clinicians' and patients' satisfaction with EPL treatment were assessed on a 10-point scale, where 1 is the lowest satisfaction and 10 is the highest satisfaction. †Wilcoxon signed-rank test. ‡chi squared test. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; GGT, Gamma-glutamyl transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoproteins; VLDL, very low-density lipids*

*Ivashkin VT et al. Drugs Real World Outcomes 2021 [in press].*

# Patients who experienced the largest changes from baseline in laboratory parameters after EPL treatment

EPOCH-2

**Like high-fat foods**
TB change >was in patients taking fat daily vs taking fat less often, p<0.001

**Smokers**
ALT, AST and GGT change > in smokers vs non-smokers, p<0.05

**Consuming alcohol**
GGT change > in patients consuming alcohol 1–3 times per week vs rarely or never, p<0.001

**Number of cardiovascular comorbidities**
ALT, AST, postcranial glucose, TChol, HDL, LDL, TG and ALP change > in patients with 4 comorbidities vs 1 comorbidity, p<0.001


**So, EPLs work even in case of unhealthy lifestyle and cardiometabolic comorbidities**

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*ALP, alkaline phosphatase, ALT, alanine aminotransferase, AST, aspartate aminotransferase, EPL, essential phospholipids; GGT, gamma-glutamyl transferase, HDL, high-density lipoprotein, LDL, low-density lipoprotein; TB, total bilirubin; Tchol, total cholesterol; TG, triglycerides*

*Ivashkin VT et al. Drugs Real World Outcomes 2021. doi: 10.1007/s40801-021-00250-x [ePub ahead of print]*

# EPOCH: summary of key findings


**St-index is a perfect first-line non-invasive screening tool to detect liver steatosis (NAFLD/MAFLD)[1]**

**EPL adherence and subjective treatment satisfaction are associated with objective improvements in liver enzymes, lipid levels and steatosis[2]**


**EPLs work even in subgroup of patients with comorbidities and unhealthy lifestyle which is important in real-world setting knowing that majority of patients have comorbidities and not adherent to lifestyle modification[2]**

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*EPL, essential phospholipid; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease*

*1. Maev IV, et al. Adv Ther 2020;37:4627–40; 2. Ivashkin VT et al. Drugs Real World Outcomes 2021. doi: 10.1007/s40801-021-00250-x [ePub ahead of print]*

# Disclosures

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