Hepatic steatosis in MAFLD – importance of early intervention

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Disclosures

- I received funding from Sanofi for work related to the DIREG 02 study, which is an observational study examining the prevalence of NAFLD in Russia. Also, I was invited by Sanofi, Russia, to deliver clinical lectures on epidemiology, pathogenesis, diagnostic options, and treatment of NAFLD

NAFLD, non-alcoholic fatty liver disease

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Learning objectives

1. Prognostic scenarios of steatosis in MAFLD
2. DTA of tools available for diagnosis of MAFLD
3. Lifestyle modifications for non-alcohol-related fatty liver disease
4. Indications for EPL administration in steatosis and clinical evidence of their use in MAFLD

DTA, diagnostic test accuracy; EPL, essential phospholipid; MAFLD, metabolic-associated fatty liver disease

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Prognostic scenarios of steatosis in MAFLD

MAFLD, metabolic associated fatty liver disease

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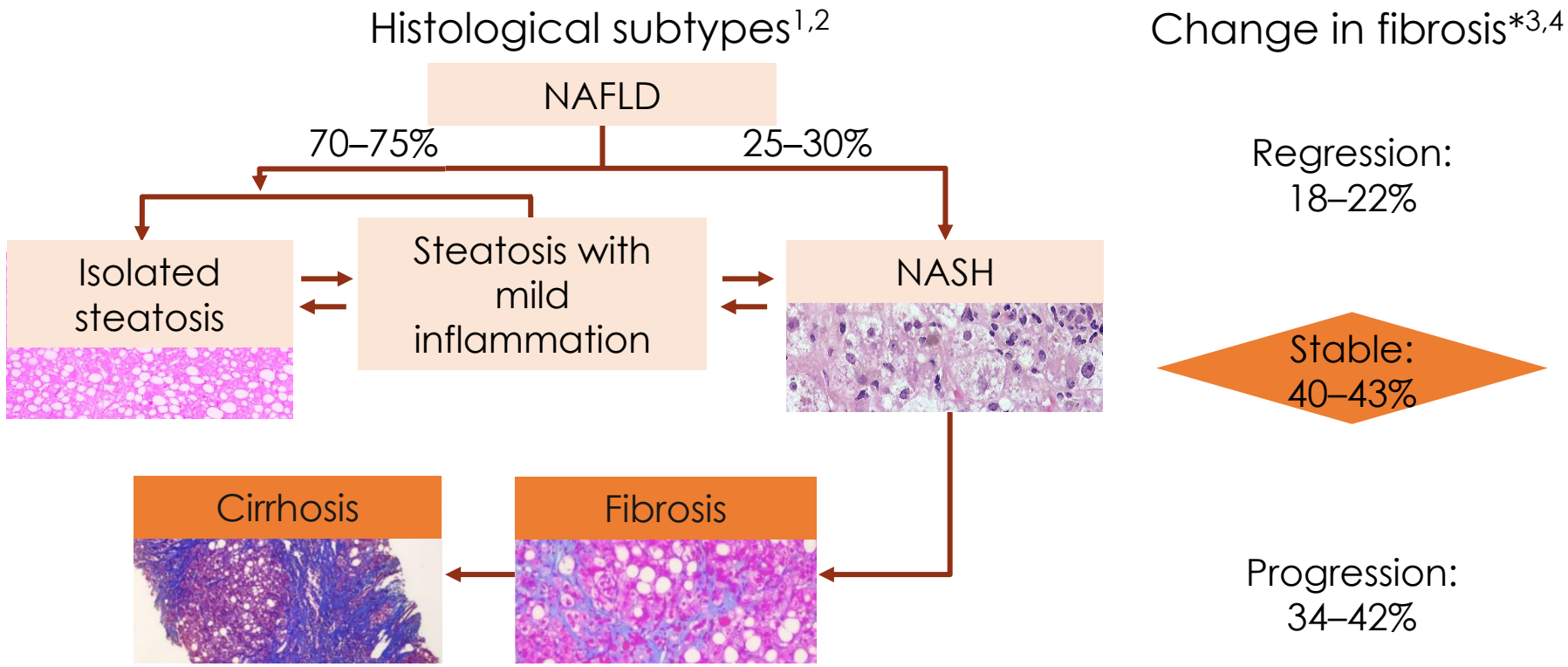
MAFLD disease progression



*N=108 patients with NAFLD/NASH and median 6.6 years follow-up (data from serial biopsies)
MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
1. Ludwig J, et al. Mayo Clin Proc 1980;55:434–8; 2. Kleiner DE, et al. Hepatology 2015;41:1313–21; 3. McPherson S, et al. J Hepatol 2015;62:1148–55;
4. Singh S, et al. Clin Gastroenterol Hepatol 2015;13:643–54

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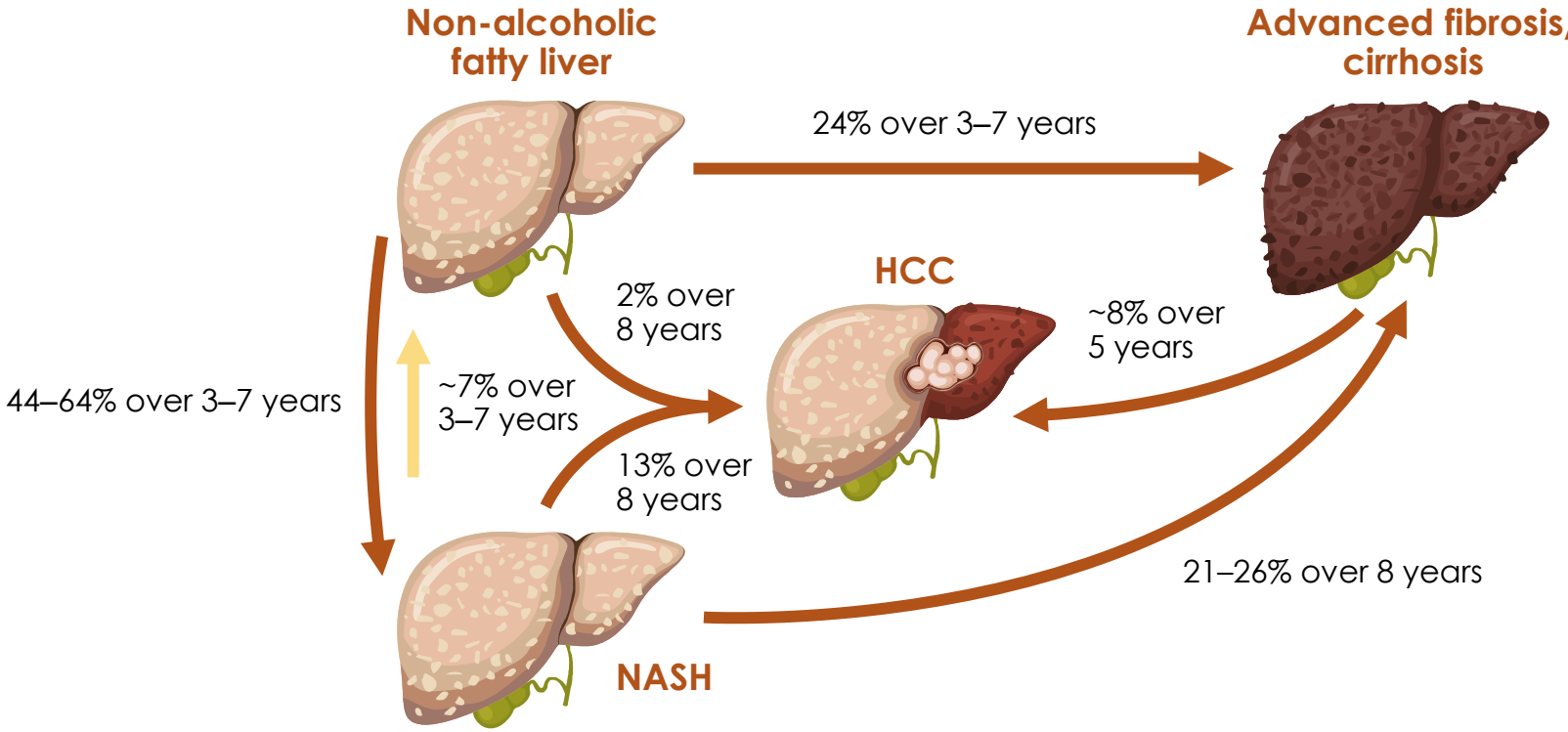
MAFLD progression from simple steatosis to NASH and HCC



HCC, hepatocellular carcinoma; MAFLD, metabolic associated fatty liver disease; NASH, non-alcoholic steatohepatitis
Perumpail BJ, et al. World J Gastroenterol 2017;23:8263–76

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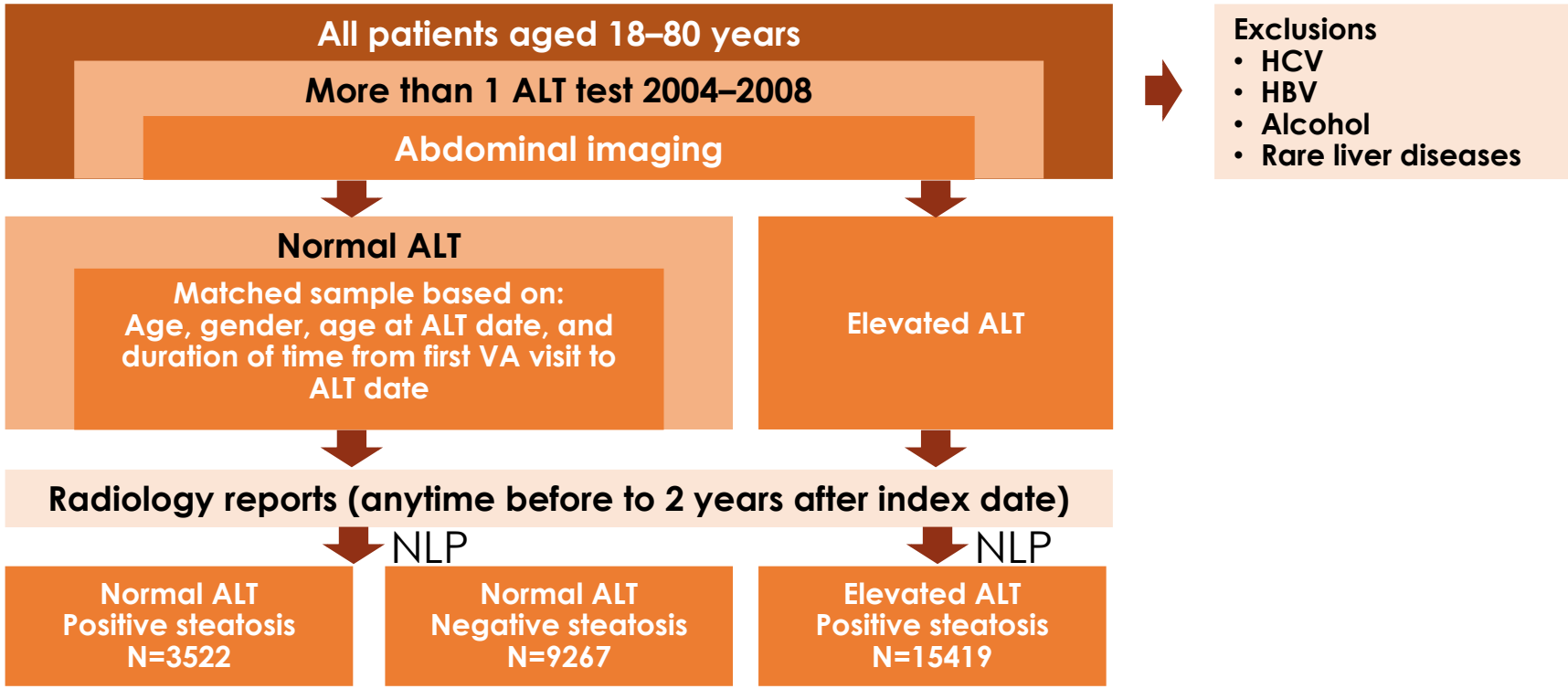
Risk of developing cirrhosis and HCC in patients with hepatic steatosis and normal ALT levels



ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NLP, natural language processing; VA, veterans Affairs
Natarajan Y, et al. Hepatology 2020;72:1242–52

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Risk of developing cirrhosis and HCC in patients with hepatic steatosis and normal ALT levels

Incidences per 1000 person-years (95% CI)	No steatosis, normal ALT	Steatosis, normal ALT	Steatosis, elevated ALT
Cirrhosis	0.97 (0.74–1.24)	1.22 (0.83–1.74)	3.85 (3.50–4.23)
HCC	0.06 (0.02–0.16)	0.20 (0.06–0.46)	0.37 (0.26–0.49)

ALT, alanine aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma
Natarajan Y, et al. Hepatology 2020;72:1242–52

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DTA of tools available for diagnosis of MAFLD

DTA, diagnostic test accuracy; MAFLD, metabolic associated fatty liver disease

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Tools for diagnosis of MAFLD

Method	Sensitivity (%)	Specificity (%)	Comments
Liver enzymes			
GGT[1]	63	65	Not reliable for diagnosis
Ultrasound[2]	85	94	Inexpensive and accessible, but cannot distinguish fibrosis/steatosis
Any degree[3]	61	100	
Cut-off ≥20%[3]	100	90	
CT without contrast[4]			Better in morbid obesity, but affected by iron, fibrosis, and less accurate with less steatosis
Cut-off >30%	79	97	
MRI[5]			Detects mild steatosis, quantifies hepatic fat most accurately
Cut-off PDFF 6.4%, grade ≥1	86	83	
Cut-off PDFF 17.4%, grade ≥2	64	96	
MRS[6]			
Cut-off ≥5%	90–96	87–100	
Cut-off >33%	92–100	92–97	
Liver biopsy[7]			Gold standard, but invasive and subject to sampling error

CT, computed tomography; GGT, gamma-glutamyl transferase; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MAFLD, metabolic associated fatty liver disease; PDFF, proton density fat fraction

1. Alam S, et al. BSMMU J 2015;8:61–7; 2. Hernaez R, et al. Hepatology 2011;54:1082–90; 3. Dasarathy S, et al. J Hepatol 2009;51:1061–7; 4. Rogier J, et al. Liver Transpl 2015;21:690–5; 5. Tang A, et al. Radiology 2015;274:416–25; 6. McPherson S, et al. J Hepatol 2009;51:389–97; 7. Sumida Y, et al World J Gastroenterol 2014;20:475–85

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Diagnostic accuracy of TE for fibrosis in patients with MAFLD: a systematic review and meta-analysis

	Studies, n (patients; n)	Prevalence (%; 95% CI)	Cut-off range	sAUC (95% CI)	sSe (%; 95% CI)	sSp (%,95% CI)
VCTE (kPa) F≥1	14 (1064)	67 (23–94)	5.3–8.2	0.82 (0.78–0.85)	78 (73–82)	72 (65–79)
F≥2	37 (2763)	45 (5–77)	3.8–10.2	0.83 (0.80–0.87)	80 (76–83)	73 (68–77)
F≥3	44 (4219)	25 (5–54)	6.8–12.9	0.85 (0.83–0.87)	80 (77–83)	77 (74–80)
F=4	22 (337)	9 (3–31)	6.9–19.4	0.89 (0.84–0.93)	76 (70–82)	88 (85–91)

MAFLD, metabolic associated fatty liver disease; CI, confidence interval; sAUC, specificity and area under the curve; sSe, summary sensitivity; sSp, summary specificity; TE, transient elastography; VCTE, vibration-controlled transient elastography
Selvaraj EA, et al. J Hepatol 2021;75:770–85

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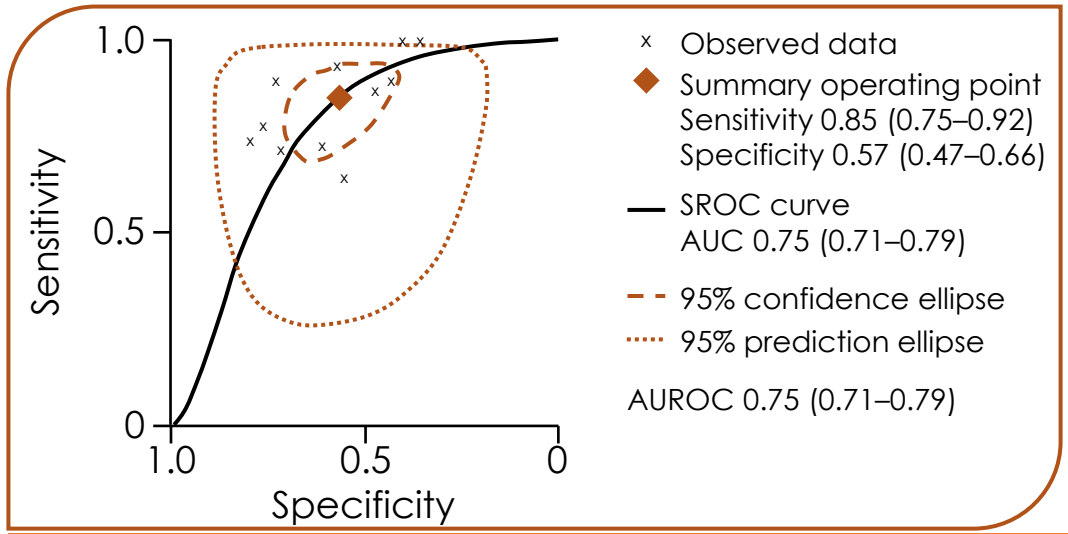
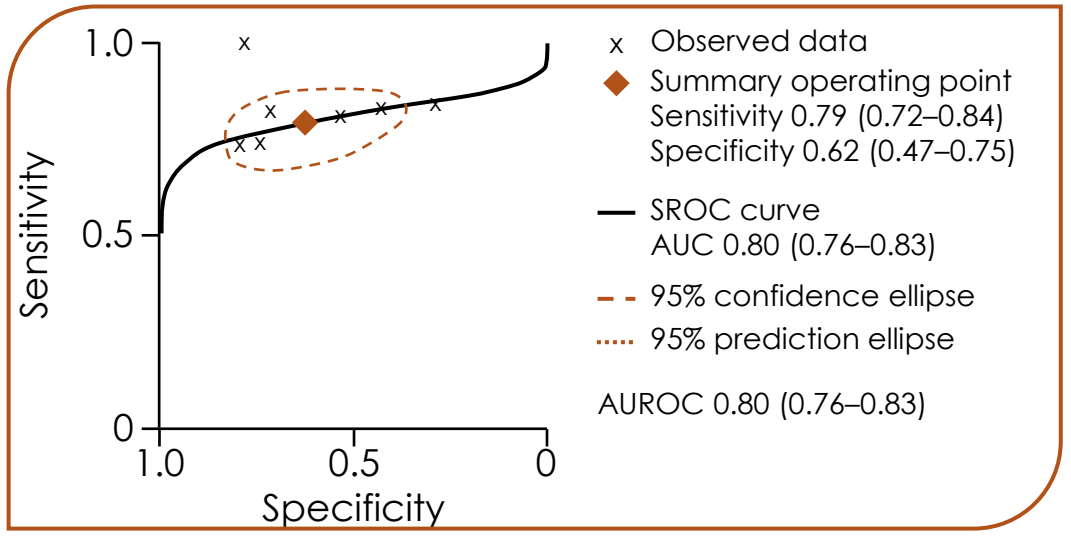
Quantitative assessment of liver fat by TE with CAP (FibroScan®)

TE-CAP: S0–2 vs S3

HRSROC with confidence and predictive ellipses





- TE with CAP had the **highest diagnostic accuracy** for detecting the stage of steatosis ≥S1, with a total sensitivity of 0.82 (95% CI: 0.79–0.84), specificity 0.83 (0.80–0.86) and HSROC 0.85

- The diagnostic accuracy was **relatively low** for S3 detection, with an overall sensitivity of 0.79 (0.77–0.81), a specificity of 0.56 (0.53–0.58), and an HSROC 0.79

AUC, area under the curve; AUROC, area under the receiver operating curve; CAP, controlled attenuation parameter; CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic curves; TE, transient elastography

Gu Q et al. Eur J Clin Invest 2021;51:e13446

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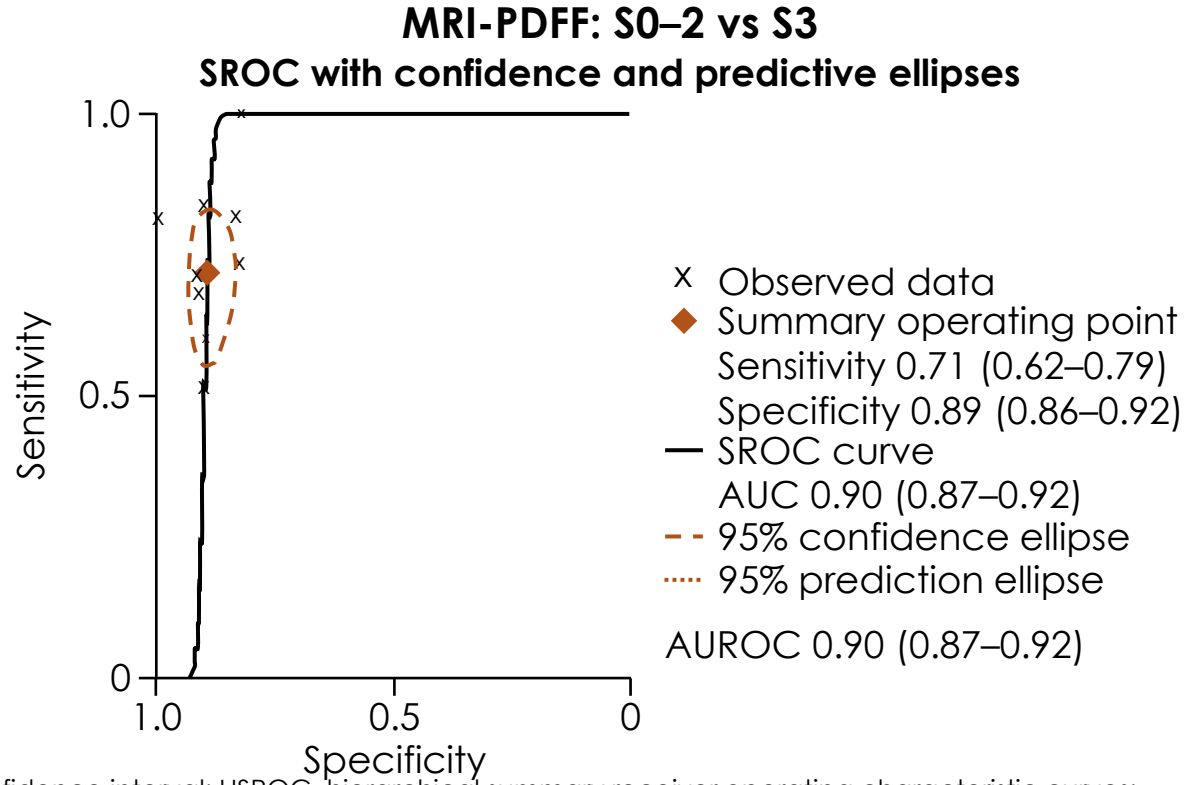
Quantitative assessment of liver fat by MRI-PDFF (imaging-derived proton density fat fraction)

- MRI-PDFF had the highest diagnostic accuracy for stage 1 detection, with an overall **sensitivity of 0.91** (95% CI: 0.80–0.97), a **specificity of 0.93** (0.90–0.96), and HSROC 0.97

- The diagnostic accuracy was the same for detecting ≥**S2 and ≥S3 with HSROC values of 0.93 and 0.91**, respectively



AUC, area under the curve; AUROC, area under the receiver operating curve; CI, confidence interval; HSROC, hierarchical summary receiver operating characteristic curves; MRI-PDFF, magnetic resonance imaging-proton density fat fraction

Gu Q, et al. Eur J Clin Invest 2021;51:e13446

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NAFLD: implementing complete automated diagnosis and staging – a systematic review

All methods were associated with significant automated diagnosis of NAFLD (AUC >0.7)

Deep-learning index demonstrated the best diagnostic ability to distinguish between moderate and severe NAFLD (AUC 0.958)

Extreme learning machine – diagnostic accuracy, 96.75%, AUC 0.97

Support vector machines – diagnostic accuracy, 89.01%, AUC 0.91

AUC, area under the curve; NAFLD, non-alcoholic fatty liver disease
Popa SL et al. Diagnostics 2021;11:1078

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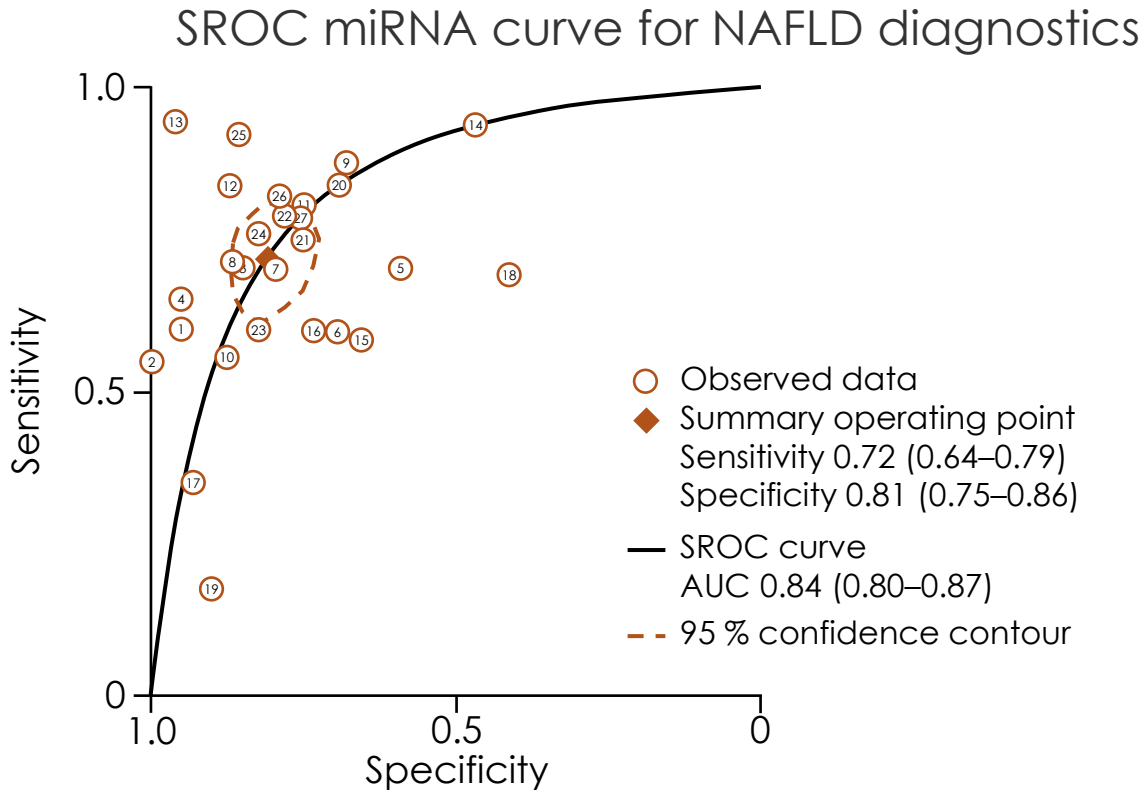
Efficacy of serum miRNA test as non-invasive method to diagnose NASH: a systematic review and meta-analysis

- For NAFLD compared with NASH, it was found that the combined:
  - Sensitivity is 0.71 versus 0.74
  - Specificity is 0.76 versus 0.85
  - AUROC is 0.80 versus 0.86

- Serum miRNA had a high accuracy to differentiate NASH from simple steatosis, with an AUROC of 0.91

- Among the most commonly studied serum microRNA the miRNA-34a showed moderate diagnostic accuracy in NAFLD and the lowest heterogeneity, AUROC = 0.85



AUC, area under the curve; AUROC, area under the receiver operator curve; miRNA, microribonucleic acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SROC, summary receiver operating characteristics

Xin S et al. BMC Gastroenterol 2020;20:186 doi: 10.1186/s12876-020-01334-8

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Lifestyle modifications for non-alcohol-related fatty liver disease: a network meta-analysis

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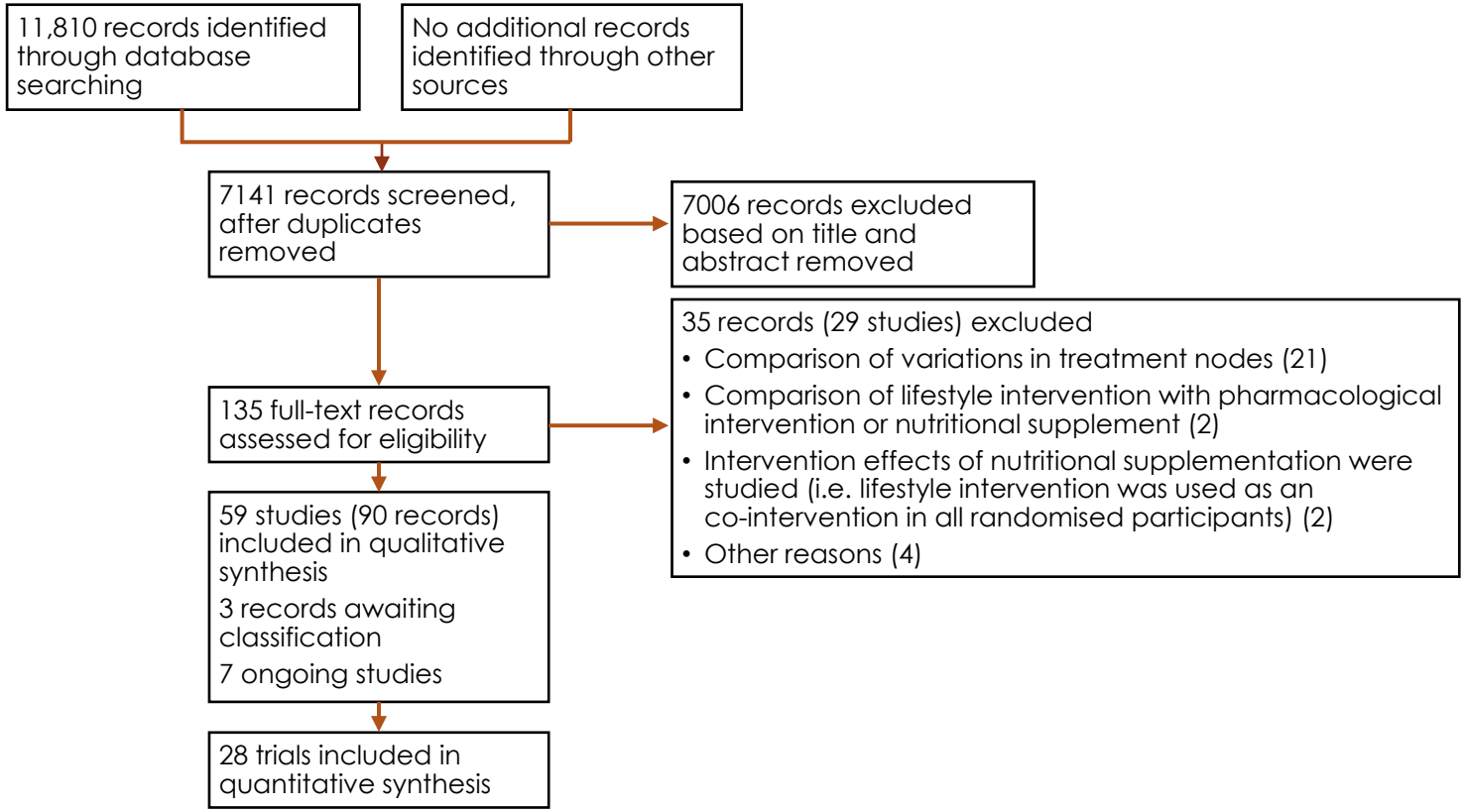
Meta-analysis: study design

Objectives: to assess the comparative **benefits and harms of different lifestyle interventions** in the treatment of NAFLD through a network meta-analysis, and to **generate rankings of the different lifestyle interventions** according to their safety and efficacy



NAFLD, non-alcoholic fatty liver disease

Buzzetti E, et al Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD013156. DOI: 10.1002/14651858.CD013156.pub2

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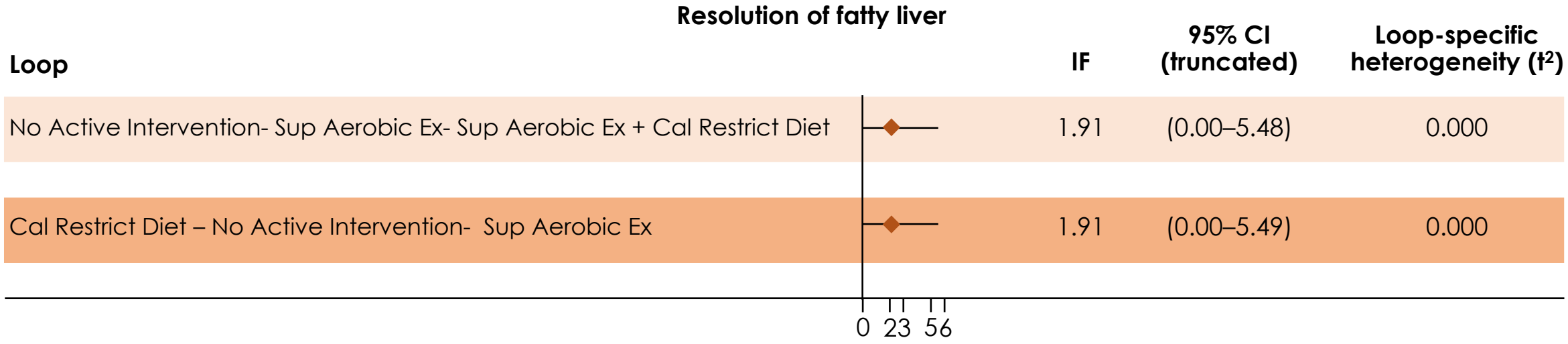
Meta-analysis: results

The plot shows the inconsistency factors for the only outcome (resolution of fatty liver) where direct and indirect evidence were available for one or more comparisons



The evidence indicates considerable uncertainty about the effects of the lifestyle interventions compared with no additional intervention (to general public health advice) on any of the clinical outcomes after a short follow-up period of 2 months to 24 months in people with NAFLD

***Loop(s) [CalRestrictDiet-NoActiveIntervention-SupAerobicEx+CalRestrictDiet] [CalRestrictDiet-SupAerobicEx-SupAerobicEx]
CI, confidence interval; IF, impact factor; NAFLD, non-alcoholic fatty liver disease
Buzzetti E, et al. Lifestyle modifications for nonalcohol-related fatty liver disease: a network meta-analysis. Cochrane Database of Systematic Reviews 2021, Issue 6. Art. No.: CD013156. DOI: 10.1002/14651858.CD013156.pub2

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Indications for EPL administration in steatosis and clinical evidence of their use in MAFLD

EPL, essential phospholipid; MAFLD, metabolic-associated fatty liver disease

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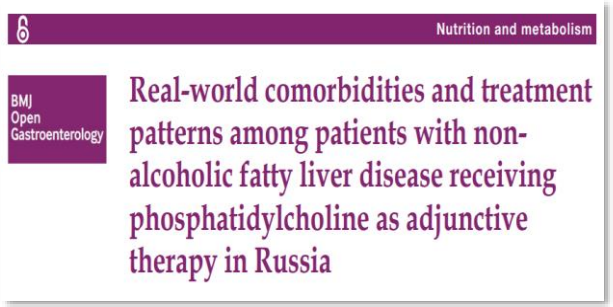
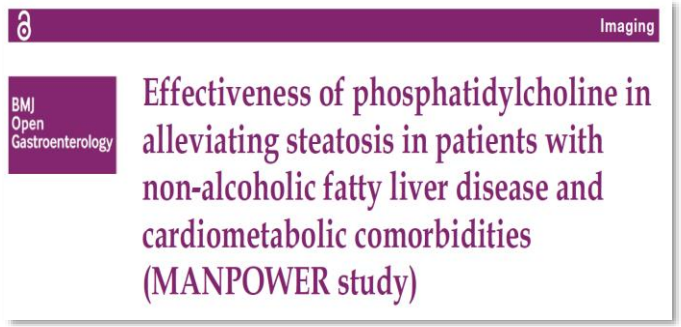
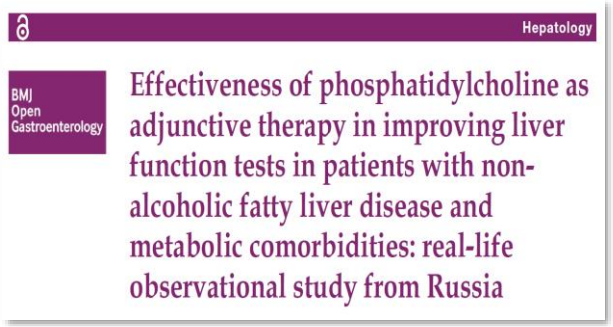
MANPOWER publications in *BMJ Open Gastroenterology* (2019–2020)

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

1. 

2. 

3. 

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

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

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

1. Maev IV, et al. BMJ Open Gastro 2019;6:e000307; 2. Maev IV.et al. BMJ Open Gastro 2020;7:e000341; 3. Maev IV, et al. BMJ Open Gastro 2020;7:e000368

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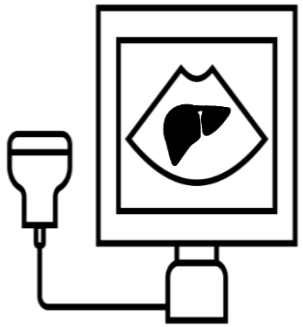
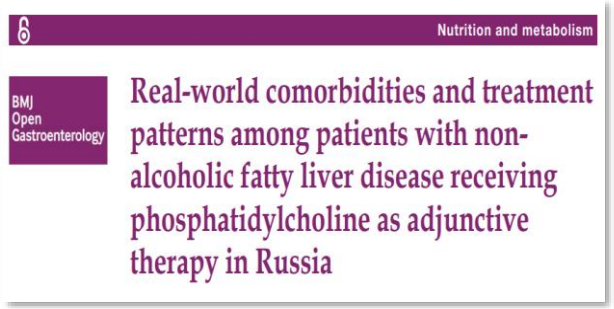
MANPOWER: NAFLD spectrum and adherence to lifestyle changes



As per available data **SIMPLE STEATOSIS was reported in 74.9%** of the 2843 patients included in this study



Diet and physical activities

Of **2827** patients **only**

13.8%

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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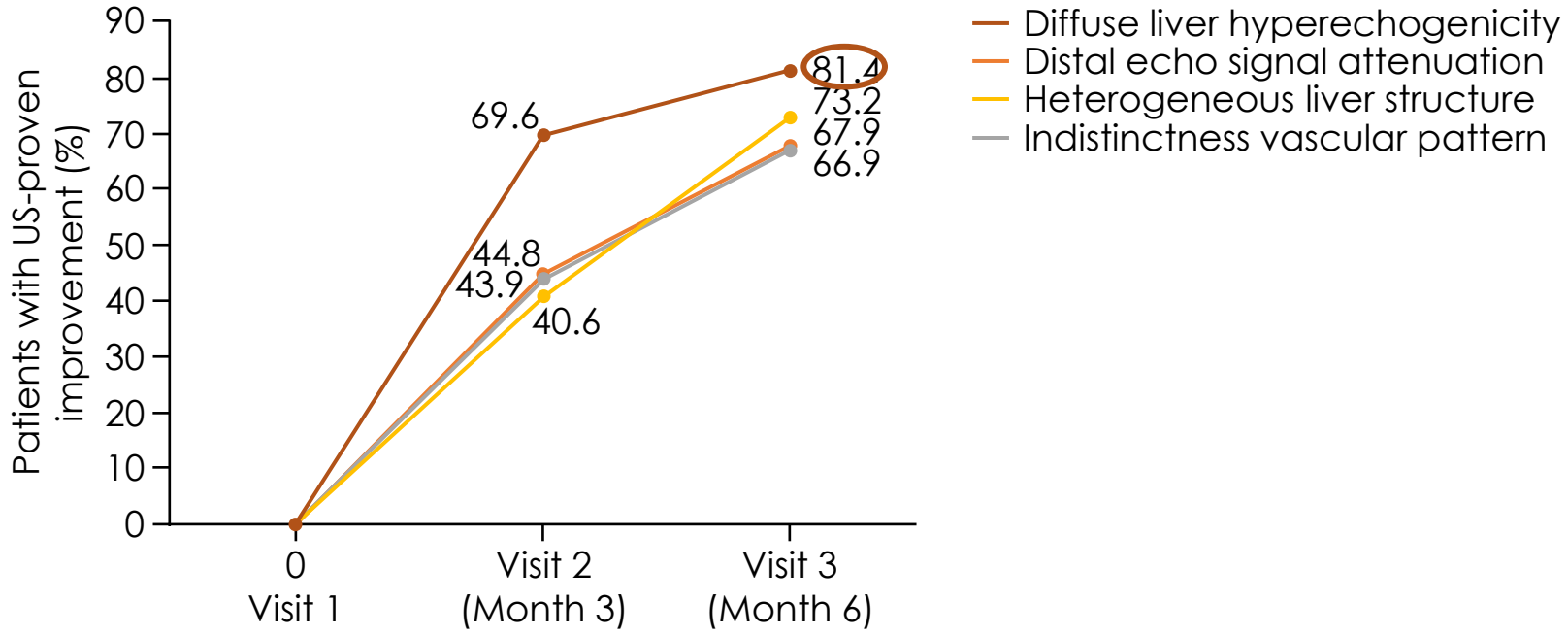
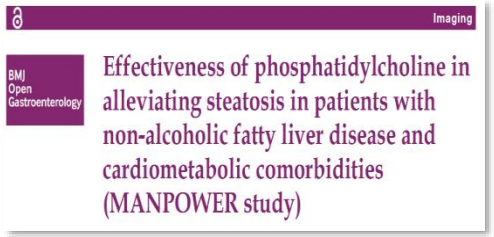
MANPOWER: EPL effect on steatosis





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

EPL, essential phospholipid; US, ultrasound
Maev IV, et al. BMJ Open Gastro 2020;7:e000341

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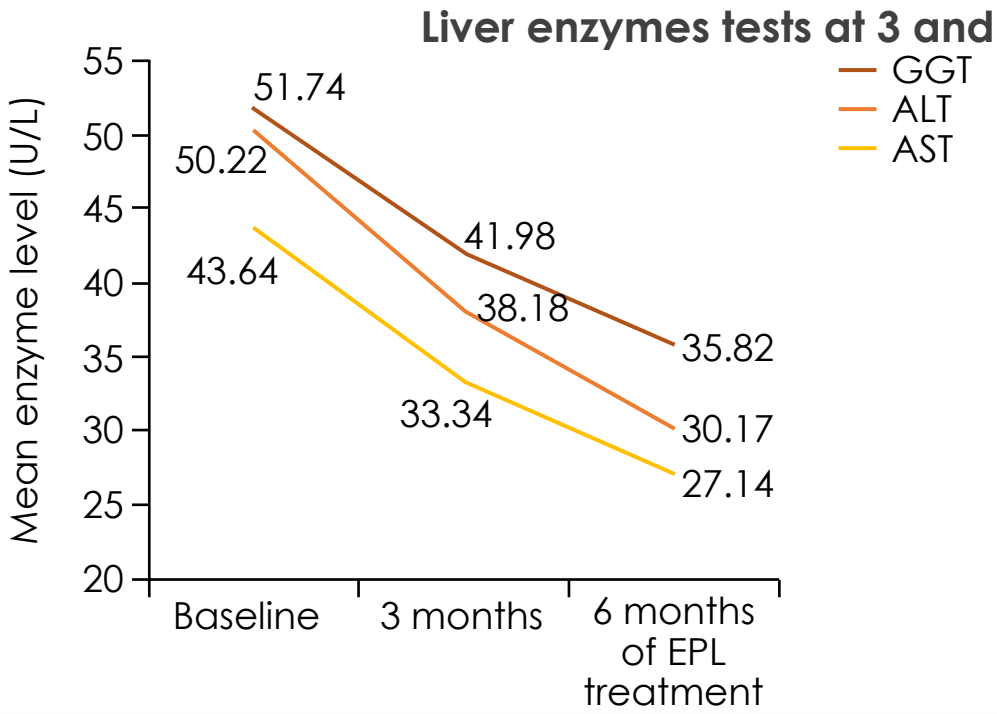
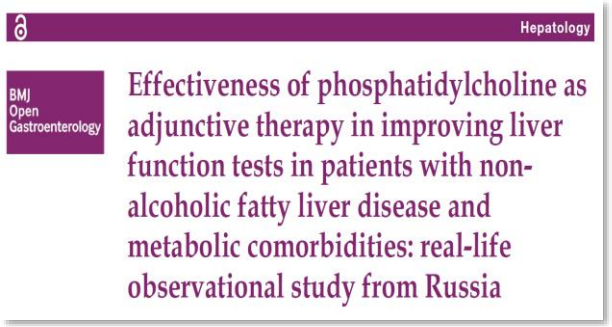
MANPOWER: liver enzymes kinetics





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 phospholipid; GGT, gamma-glutamyl transferase
Maev IV, et al. BMJ Open Gastro 2020;7:e000368

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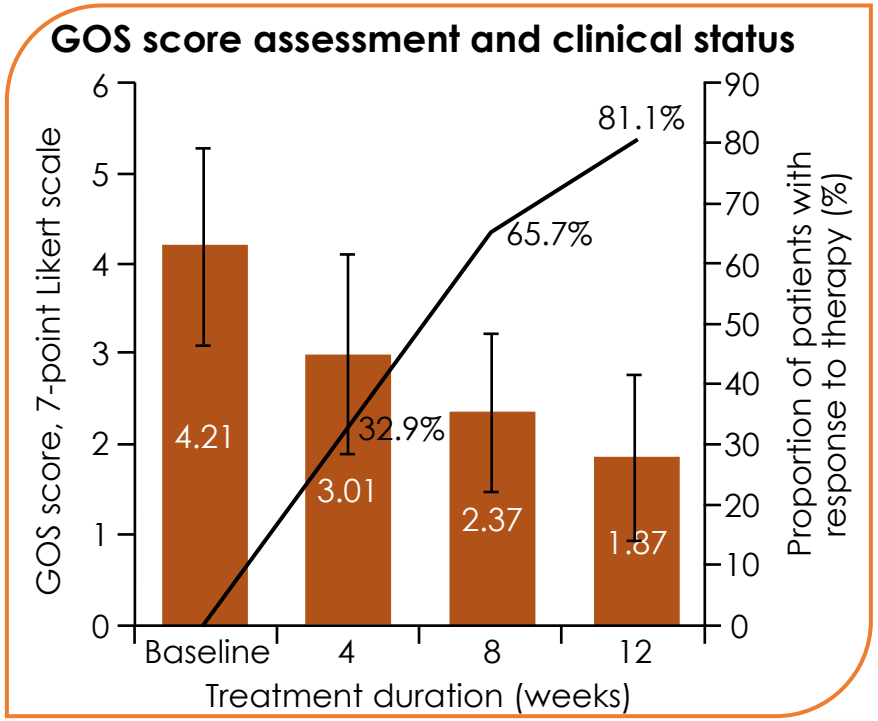
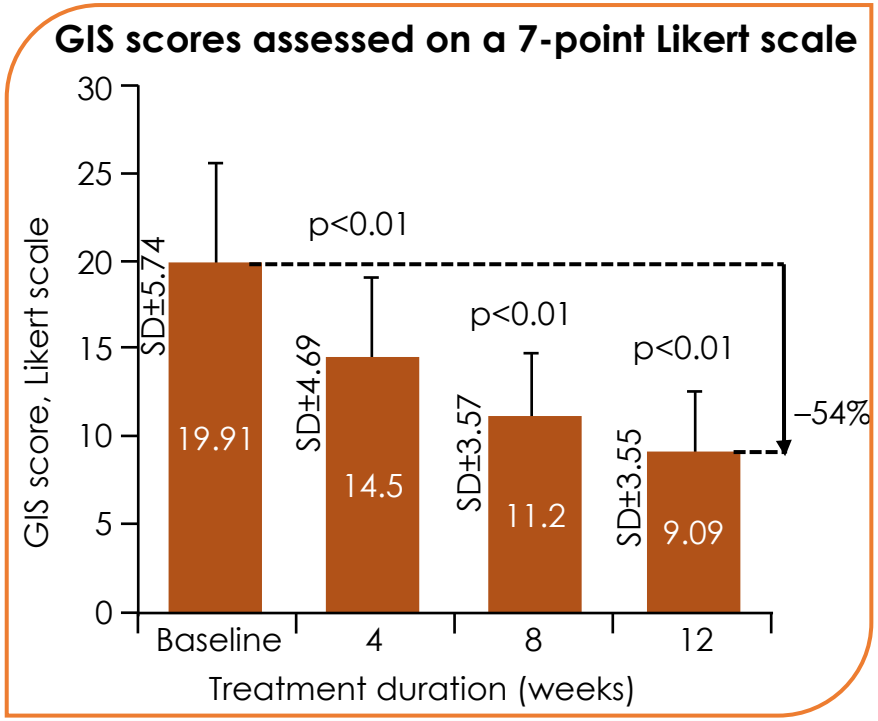
EPL in patients with NAFLD and HBV/HCV

147 patients:
NAFLD, n=107
Viral hepatitis, n=41*

Patients received EPL 600 mg TID for 12 weeks†

Patient-reported outcomes were recorded at Weeks 4, 8 and 12 using Likert scales





12 weeks of EPL paste 600 mg TID resulted in improvements in general and gastrointestinal symptoms in patients with NAFLD and/or viral hepatitis

*One patient had both NAFLD and viral hepatitis; †EPL paste was provided as one 600 mg sachet TID
HBV, hepatitis B virus; HCV, hepatitis C virus; GIS, gastrointestinal symptoms; GOS, global overall symptoms; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation; TID, three times a day
Ivashkin V, et al. Turk J Gastroenterol 2021;32:750–7

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Is the St index recommended for steatosis screening in NAFLD guidelines?

1. Yes
2. No

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Russian NAFLD guidelines 2021

MAFLD concept has been taken into account

Diagnostic tools: **Screening by St-index – liver steatosis (B2)**

Ultrasound as a routine liver steatosis diagnostic tool (A2)

Therapeutic options:
- **Weight reduction (A1)**
- **Physical activity (A1)**
- **EPLs (A1)**

EPL, essential phospholipid; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease
Lazebnik LB, et al. Experimental and Clinical Gastroenterology 2021;1:4–52 (In Russ.) https://doi.org/10.31146/1682-8658-ecg-185-1-4-52

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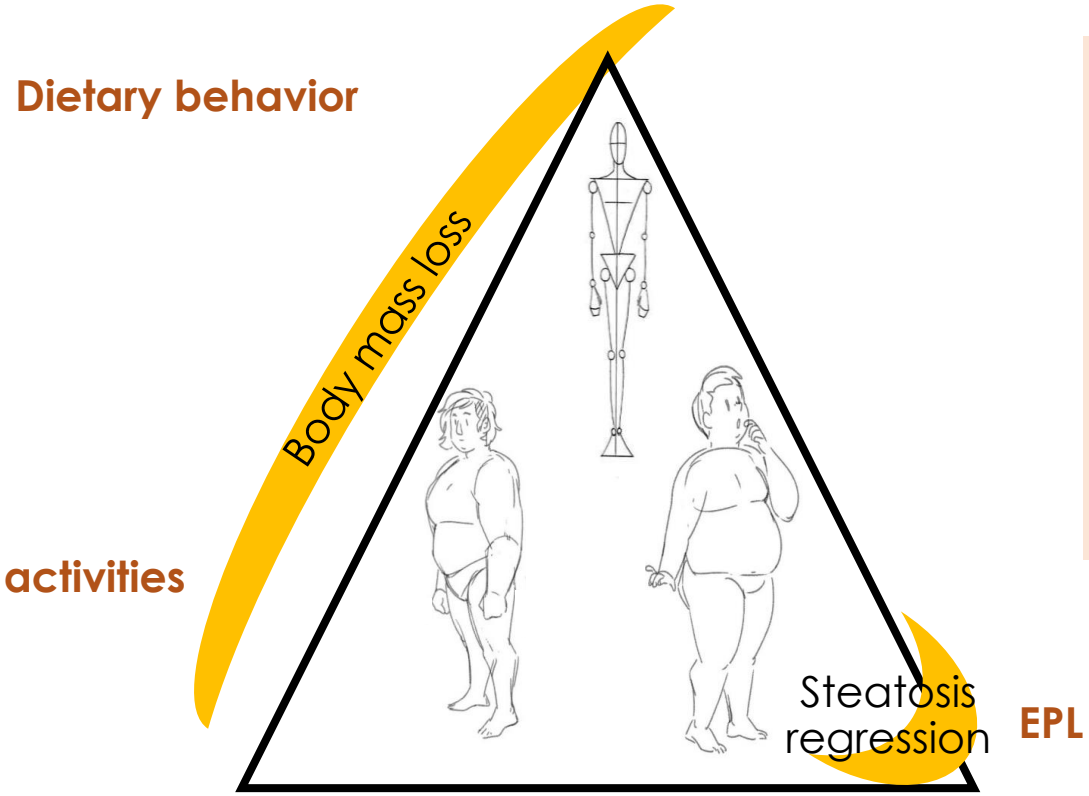
Take home messages



- Does the early intervention improve long-term outcome?
- Seems yes, but when to start intervention is still in debate
- The existing evidence tells us that rational MAFLD therapy should include lifestyle modification and EPLs

EPL, essential phospholipid; MAFLD, metabolic associated fatty liver disease
Lazebnik LB, et al. Experimental and Clinical Gastroenterology 2021;1:4–52 (In Russ.) https://doi.org/10.31146/1682-8658-ecg-185-1-4-52

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