Comorbidities in NAFLD – metabolic syndromes and beyond, REPAIR study insights

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Disclosures

- Research support: Janssen, Abbvie, Merck Sharp & Dohme, Abbott, Sanofi, Promed.cs.Praha, Adamed
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NAFLD-associated comorbidities

Metabolism[1,2]

- Obesity
- Dyslipidemia

Pancreas/ endocrine[1,2]

- IR, T2DM

Vessels[2]

- Arterial hypertension

IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

1. Lonardo H and Targher G. Int J Mol Sci 2017;18:1955; 2. Rosato V et al. Int J Environ Res Public Health 2019;16:3415.

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NAFLD-associated comorbidities

Metabolism[1,2]

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Pancreas/ endocrine[1,2]

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Vessels[2]

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= Metabolic syndrome

AHA/NHLBI criteria, 2005[3]

≥3 of the following:

- Elevated WC
- Elevated TG
- Reduced HDL
- Elevated BP
- Elevated FPG

IDF criteria, 2005[4]

Central obesity (based on race- and gender-specific WC cut-offs) **+ ≥2 of the following:**

- Elevated TG
- Reduced HDL
- Elevated BP
- Elevated FPG

Japanese criteria, 2005[5]

Central obesity (WC at umbilical level: men, ≥85 cm; women, ≥90 cm) **+ ≥2 of the following:**

- Elevated TG and/or reduced HDL
- Elevated BP
- Elevated FPG

Harmonized criteria (IDF, NHLBI, AHA, WHF, IAS, IASO), 2009[6]

≥3 of the following:

- Elevated WC
- Elevated TG
- Reduced HDL
- Elevated BP
- Elevated FPG

BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference. 1. Lonardo H and Targher G. Int J Mol Sci 2017;18:1955; 2. Rosato V et al. Int J Environ Res Public Health 2019;16:3415; 3. Grundy SM et al. Circulation 2005;112:2735–52; 4. Alberti KGMM et al. Diabetic Med 2005;23:469–80; 5. Yamagishi K and Hiroyasu I. Epidemiology and Health 2017;39:e2017003; 6. Alberti KGMM et al. Circulation 2009;120:1640–5.

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NAFLD-associated comorbidities

Metabolism[1,2]

- Obesity
- Dyslipidemia

Pancreas/ endocrine[1,2]

- IR, T2DM

Vessels[2]

- Arterial hypertension

Heart[1,2]

- IHD
- Arrythmia
- AS
- Diastolic disfunction
- Heart failure

Brain[2]

- Ischemic stroke
- Fatigue

Lungs[1,2]

- Obstructive sleep apnea

Kidneys[1,2,3]

- CKD
- Albuminuria
- Urolithiasis

GI[2]

- Periodontitis

Skin[1,2]

- Psoriasis

Tumors[1]

- HCC
- CRC
- Breast cancer

AS, aortic stenosis; CKD, chronic kidney disease; CRC, colorectal cancer; GI, gastrointestinal; HCC, hepatocellular carcinoma; IHD, ischemic heart disease; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

1. Lonardo H and Targher G. Int J Mol Sci 2017;18:1955; 2. Rosato V et al. Int J Environ Res Public Health 2019;16:3415; 3. Eugene Han, YH. Diabetes Metab J 2017 Dec; 41(6):430–7.

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NAFLD-associated comorbidities

GI, gastrointestinal. NAFLD, non-alcoholic fatty liver disease.

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NAFLD and metabolic syndrome

Meta-analysis of 20 trials[1]

N=117,020

Observation period (mean): 5 (3–14.7) years

NAFLD was associated with an **increased risk** of:

- **Metabolic syndrome**
  - OR (95% CI) 1.80 (1.72; 1.89)
- **T2DM**
  - OR (95% CI) 1.97 (1.80; 2.15)

Non-alcoholic fatty liver disease → **Metabolic-associated** fatty liver disease

Redefining non-alcoholic fatty liver disease: what's in a name? [2]

Disease names have difficult and often underappreciated roles. They must be specific, and clearly describe conditions without stigmatising the patients who live with them. Improved understanding of a disease and changing social attitudes mean that some names become inappropriate and need to be updated. A notable example from the field of hepatology is primary biliary cirrhosis, which was renamed to primary biliary cholangitis in 2015. This name change was instigated and embraced for several reasons: it better reflects the disease natural history (most patients do not have cirrhosis at diagnosis), avoids the potentially stigmatising term "cirrhosis", and retains the "PBC" abbreviation, easing adoption. Now, an international consensus panel of 31 leading researchers have proposed that the nomenclature for non-alcoholic fatty liver disease (NAFLD) is similarly re-examined.

The terms NAFLD and non-alcoholic steatohepatitis were first used in 1980 to describe a condition bearing the histological features of alcoholic liver disease in the absence of clinically significant alcohol consumption or other liver disease. Interest in NAFLD has since risen dramatically, driven by its markedly increasing global prevalence and subsequent research into its pathophysiology and clinical and socioeconomic burdens. Today, the disease is recognised as highly heterogeneous, with variable rates of progression and important factor underlying the poor performance of NAFLD pharmacotherapies in trials.

Further, the exclusionary disease definition is challenging in patients with co-occurring liver pathology, such as viral hepatitis or alcohol-related liver disease. Explicit reference to alcohol intake in both the name and diagnostic criteria for NAFLD has provoked debate on appropriate consumption thresholds and the extent of synergistic interactions between alcohol intake and liver disease associated with metabolic dysfunction. In the clinic, diagnoses of alcohol-related liver disease and NAFLD can overlap, and questions of how best to assess alcohol intake are unavoidable. In addition, the reference to alcohol has potentially stigmatising associations with alcohol use disorder and alcoholic liver disease; the European Liver Patients' Association made changing NAFLD nomenclature a key target in 2018.

To address these concerns, the consensus panel propose a more appropriate nomenclature. Following a survey and Delphi process, the term "metabolic associated fatty liver disease" (MAFLD) was selected to replace NAFLD. Similar terms have previously been suggested, and the projected benefits of a revised nomenclature are comparable to those in earlier proposals. First, the shift towards inclusionary diagnostic criteria—ie, the presence of metabolic dysfunction, rather than the absence of

CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; T2DM, type 2 diabetes mellitus.

1. Ballestri S, et al. J Gastroenterol Hepatol 2016;31:936–44. 2. Editorial. Lancet Gastroenterol Hepatol 2020;5:419.

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NAFLD and obesity

Increased BMI and waist circumference:

- ✓ Are associated with IR and NAFLD
- ✓ Predict advanced disease, particularly in the elderly
- ✓ Warrant screening for NAFLD

Most people with NAFLD who are lean display:

- ✓ IR
- ✓ Altered body fat distribution

BMI, body mass index; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease.
EASL–EASD–EASO. J Hepatol 2016;64:1388–402.

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NAFLD in lean patients

In a meta-analysis, lean patients with NAFLD:

15 studies

N=23,877

Had **increased FPG**:
- 6.43 (SE: 1.12) mg/dL
- $P=10^{-10}$

Had **increased total cholesterol**:
- 7.04 (SE: 3.80) mg/dL
- $P=4.2 \times 10^{-7}$

Had **increased** systolic and diastolic **blood pressure**:
- Systolic: 5.64 (SE: 0.67) mmHg
  - $P=10^{-10}$
- Diastolic (3.37 (SE: 0.90) mmHg
  - $P=10^{-10}$

Had **increased HOMA-IR**:
- 0.52 (SE: 0.094) units
- $P=10^{-10}$

Had **increased triglycerides**:
- 48.37 (SE: 3.66)
- $P=10^{-10}$

Had **greater BMI**:
- 1.24 (SE: 0.26) cm
- $P=10^{-10}$

Had **greater waist circumference**:
- 5.88 (SE: 0.4) cm
- $P=10^{-10}$

BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment for insulin resistance; NAFLD, non-alcoholic fatty liver disease; SE, standard error.

Sookoian, S and Pirola, CJ. Aliment Pharmacol Ther 2017;46:85–9.

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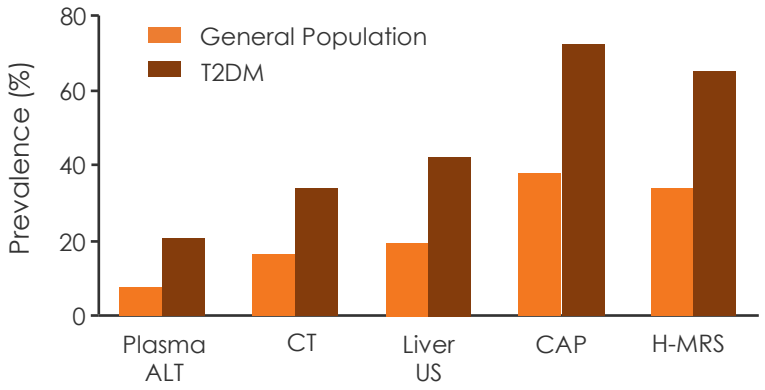
NAFLD and IR/T2DM

IR and T2DM correlates with fatty infiltration in the liver and are strongly associated with:[1,2]

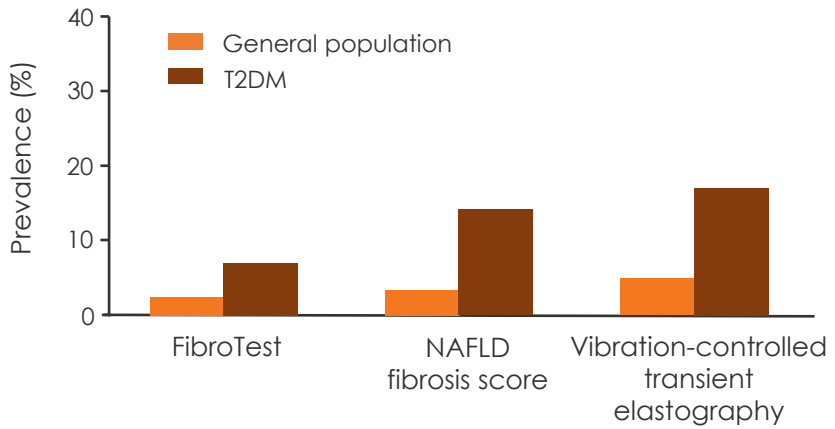
- ✓ Increased NAFLD severity
- ✓ Progression to NASH
- ✓ HCC risk

The presence of T2DM significantly increases the prevalence of both NAFLD and advanced fibrosis

Prevalence of NAFLD using different diagnostic tools[2]



Overall prevalence of advanced fibrosis[2]



ALT, alanine aminotransferase; CAP, controlled attenuation parameters; CT, computed tomography; H-MRS, proton magnetic resonance spectroscopy; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; US, ultrasound. 1. Donadon V, et al. Liver Int 2010;30:750–8. 2. Brill F and Kenneth C. Diabetes Care 2017;40:419–30.

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NAFLD and dyslipidemia

NAFLD is strongly associated with:

- ✓ Atherogenic dyslipidemia
- ✓ Postprandial lipemia
- ✓ HDL dysfunction
- ✓ Increased risk for both liver and CVD morbidity and mortality

CVD, cardiovascular disease; HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease.
Katsiki N, et al. Metabolism 2016;65:1109–23.

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NAFLD and cardiac comorbidities

Study type	Patients (N)	Key findings
Austrian cohort study[1]	1965 asymptomatic patients	Patients with NAFLD had **higher CV risk (FRS)** compared with those without: 8.7% (6.4) vs 5.4% (5.2); *P*<0.001. NFS correlated with FRS (*r* = 0.29; P<0.001)
Sub-study from the Framingham Study[2]	808 patients with NAFLD	Increasing liver fat over 6 years was associated with **progression of CV risk factors**, even after accounting for BMI changes
Meta-analysis of 6 studies[3]	25,837 patients with NAFLD	CV events* (14.9% vs 6.3%**), CAD (7.5% vs 1.4%**) and CV mortality (higher vs lower**) were **higher in patients with NALFD versus without**, respectively
Korean cohort study[4]	308,578 healthy participants	FLI was significantly associated with **increased risk of new-onset HF**, regardless of baseline characteristics
Subgroup analysis of a retrospective cross-sectional study[5]	8,705 patients with fatty liver screening and CAC assessment	**A significant association** between NAFLD and CAC was observed in male participants without obesity - OR, 1.36 (95% CI: 1.07; 1.75)
Prospective observational study[6]	1,307 patients aged 30–60 years without DM	**Increased IMT, CHD risk, and reduced insulin sensitivity are associated with high FLI values**
Prospective study[7]	958 hypertensive patients and control	Multiple Cox regression analysis: **NAFLD is an independent predictor of AF** – OR, 1.88 (95% CI 1.03; 3.45)
Retrospective single center study[8]	416 patients with NAFLD and CVD	Despite a high prevalence of AF among Caucasian patients, **liver fibrosis was more relevant for Asian individuals with AF**

*Definition of CVE varied between studies; **P<0.001. ALT, alanine aminotransferase; AST, aspartate transaminase; CAC, coronary artery calcification; CAD, coronary artery disease; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FLI, Fatty Liver Index; FRS, Framingham Risk Score; GGT, amma-glutamyltransferase; HF, heart failure; IMT, intima media thickness; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD Fibrosis Score; OR, odds ratio; US, ultrasound. 1. Niederseer D, et al. J Clin Med 2020;9:1065; 2. Brunner KT, et al. Liver Int 2020;40:1339–43; 3. Haddad TM, et al. Diabetes and Metab Syndr: Clin Res Rev, 2016;11:S209–16; 4. Roh JH, et al. BMC Cardiovasc Disord 2020;20:204; 5. Kim SH, et al. Sci Rep 2020;10:1025; 6. Gastaldelli A, et al. Hepatology. 2009;49:1537–44; 7. Käräjämäki J, et al. PLoS ONE 2015;10:e0142937; 8. Nersesov A, et al. Hepatol Int 2020;14:S358

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NAFLD and CKD

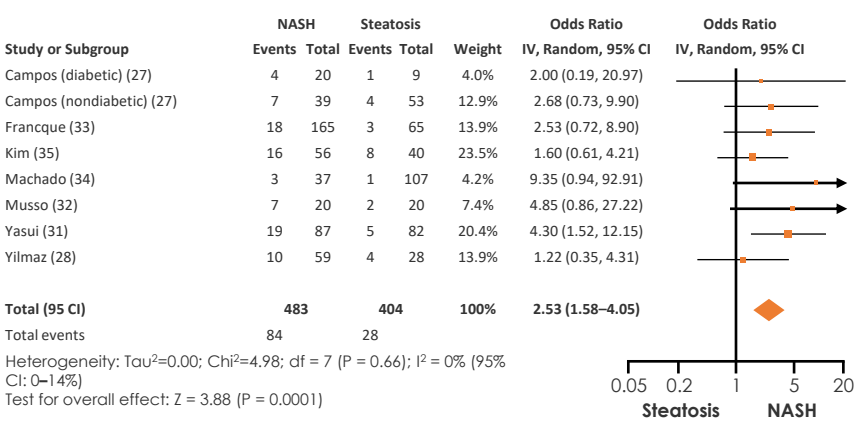
The prevalence of CKD in NAFLD is 20%–50%

- **NAFLD may accelerate the development and progression of CKD**

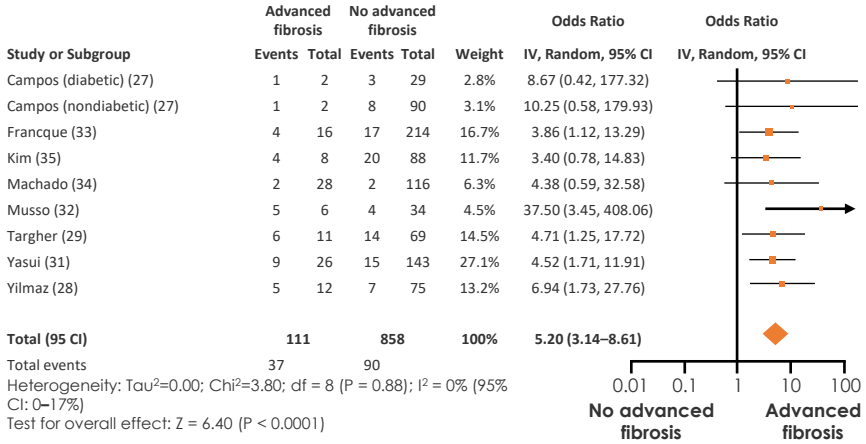
In a meta-analysis of 23 studies (N=63,902), **the severity of NAFLD was directly associated with CKD**

	NAFLD (presence vs absence)	NASH (presence vs simple steatosis)
Prevalence of CKD, OR (95% CI)	2.12 (1.69; 2.66)	2.53 (1.58; 4.05)
Incidence of CKD, HR (95% CI)	1.79 (1.65; 1.95)	2.12 (1.42; 3.17)

CKD prevalence: NASH vs no NASH



CKD prevalence: advanced fibrosis vs no advanced fibrosis



CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio.
Musso G, et al. PLoS Med. 2014;11:e1001680.

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NAFLD and Vitamin D deficiency

Patients with NAFLD, particularly those with obesity, have a high risk of vitamin D deficiency[1]

- Vitamin D receptors are highly expressed by hepatic stellate cells
  - The association with fibrogenesis is under investigation
- Screening for 25-OHD vitamin D is recommended if BMI is ≥30 kg/m^2
  - Supplementation is recommended if < 20 ng/mL

RCT of vitamin D supplementation in women with PCOS[2]

Parameter, mean (SD)	Vitamin D group (N=18)			Placebo group (N=19)			% Change		
	Baseline	3 months	P-value*	Baseline	3 months	P-value*	Vitamin D	Placebo	P-value*
25-OHD (nmol/L)	25.6 (11.4)	90.4 (19.5)	<0.001	30.9 (11.1)	47.6 (20.5)	<0.001	319 (214)	59.5 (56.7)	<0.001
ALT (IU/L)	27.0 (12.2)	22.1 (11.5)	0.042	24.9 (14.9)	28.2 (14.4)	0.039	−16.7 (25.7)	18.6 (28.6)	0.001

*P-values for comparisons within group. 25-OHD, 25-hydroxyvitamin D; ALT, alanine aminotransferase; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial. 1. Holick MF. J Clin Endocrinol Metab. 2011;96:1911; 2. Javed. Z Nutrients. 2019;11:118

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NAFLD and HCC

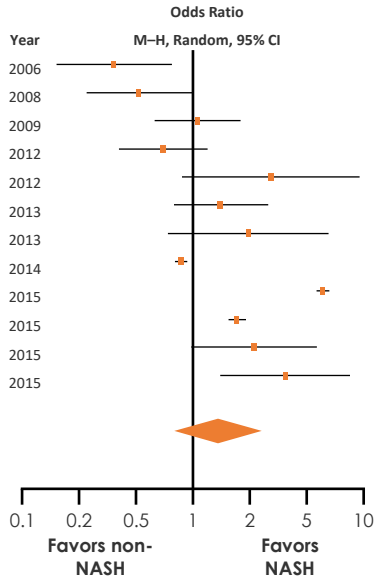
- From a meta-analysis of 19 trials (N=168,571)
- **Patients with NASH without LC have greater risk of HCC than patients with other liver diseases**
  - OR=2.61(95% CI: 1.27; 5.35), P=0.009

%	NASH	Other liver diseases	P-value
HCC prevalence in patients without cirrhosis	38.0	14.2	<0.001

Pooled measure of effects for NASH and HCC in all patients (with or without cirrhosis)

(A)	NASH		Non-NASH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Random, 95% CI	Year
Sanayal et al	10	152	25	150	8.1%	0.35 (0.16–0.76)	2006
Yatsuji et al	21	68	33	69	8.3%	0.49 (0.24–0.98)	2008
Malik et al	17	98	96	588	8.6%	1.08 (0.61–1.90)	2009
Hernandez-Alejandro et al	17	102	64	283	8.6%	0.68 (0.38–1.24)	2012
Jain et al	8	47	5	75	6.9%	2.87 (0.88–9.38)	2012
Amarapukar et al	15	105	49	480	8.5%	1.47 (0.79–2.73)	2013
Kodama et al	10	72	6	85	7.3%	2.12 (0.73–6.16)	2013
Wong et al	807	7100	7066	54768	9.3%	0.87 (0.80–0.94)	2014
Beste et al	1271	3036	6399	57479	9.3%	5.75 (5.32–6.21)	2015
Younossi et al	701	1944	4228	17922	9.3%	1.83 (1.65–2.02)	2015
Pais et al	14	47	15	96	7.9%	2.29 (1.00–5.27)	2015
Hsiang et al	9	122	14	624	7.9%	3.47 (1.47–8.21)	2015
Total (95 CI)	**12893**		**132619**		**100.0%**	**1.43 (0.77–2.65)**	
Total events	2900		18000				

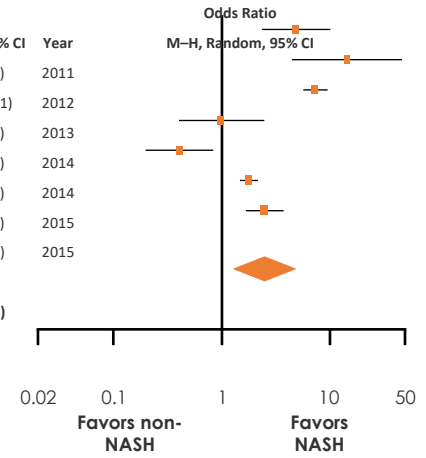
Heterogeneity: τ^2=1.06; χ^2=1267.84; *df* = 11 (P < 0.0001); I^2 = 99%
Test for overall effect: Z = 1.14 (P = 0.25)



Pooled measure of effects of NASH and HCC in patients without cirrhosis

(B)	NASH		Non-NASH			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Random, 95% CI	Year
Ertle et al	31	59	19	103	14.0%	4.89 (2.40, 9.99)	2011
Reddy et al	14	52	4	162	11.4%	14.55 (4.53, 46.71)	2012
Tokushige et al	111	292	1092	14238	16.0%	7.38 (5.78, 9.42)	2013
Schutte et al	6	43	87	621	13.0%	1.00 (0.41, 2.43)	2014
Rim et al	12	35	406	724	14.0%	0.41 (0.20, 0.83)	2014
Tateshi et al	228	590	1201	4640	16.1%	1.80 (1.51, 2.16)	2015
Mittal et al	50	120	306	1380	15.5%	2.51 (1.71, 3.68)	2015
Total (95 CI)	**1191**		**21868**		**100.0%**	**2.61 (1.27–5.35)**	
Total events	452		3115				

Heterogeneity: τ^2=0.83; χ^2=130.68; *df* = 6 (P < 0.0001); I^2 = 95%
Test for overall effect: Z = 2.61 (P = 0.009)



CI, confidence interval; HCC, hepatocellular carcinoma; LC, liver cancer; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio.
Stine JG et al. Aliment Pharmacol Ther, 2018;48(7):696-703.

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2010–2011

Screening for NAFLD and the prevalence of risk factors in patients treated by urban polyclinic primary physicians in Central Asia (Kazakhstan, Kyrgyzstan)

NAFLD, non-alcoholic fatty liver disease.
Isatullayev EA et al. Meditsina 2011;4:2–7.

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NAFLD spectrum

Patients applied to primary physicians (N=702)

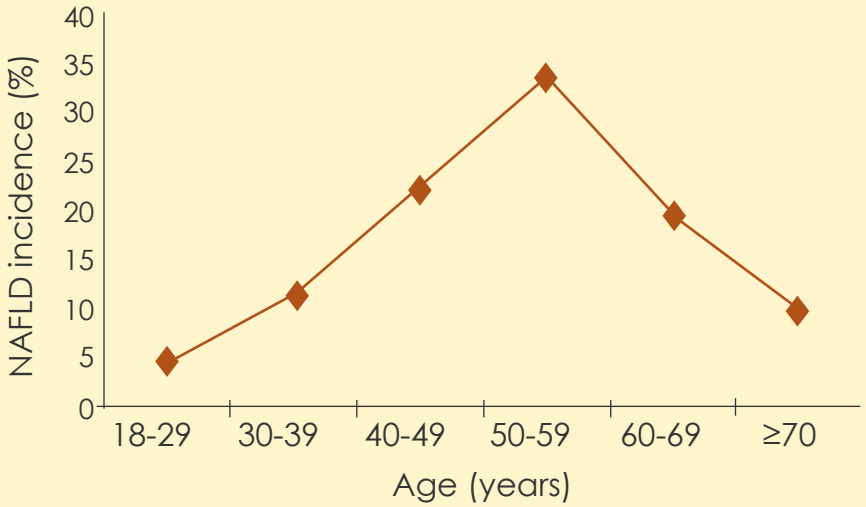
≥3 risk factors (obesity, AH, dyslipidemia, T2DM) 72.0%

NAFLD 40.9%

- Steatosis 76.5%
- NASH 19.5%
- LC 4.0%

Risk factors, N (%)	Incidence (N=702)
Arterial hypertension	547 (77.9)
Dyslipidemia	405 (57.7)
Obesity (BMI ≥30)	401 (57.1)
Hypercholesterolemia	397 (56.5)
Overweight/obesity BMI ≥25 to <30	379 (54.0)
Hypertriglyceridemia	192 (27.3)
T2DM	147 (20.9)

Most (62.4%) patients were female



The most **vulnerable** age was 50–59 years

AH, arterial hypertension; BMI, body mass index; LC, liver cancer; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

Isatullayev EA et al. Meditsina 2011;4:2–7.

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2018

Metabolic syndrome and NAFLD risk evaluation (Almaty office workers screening results)

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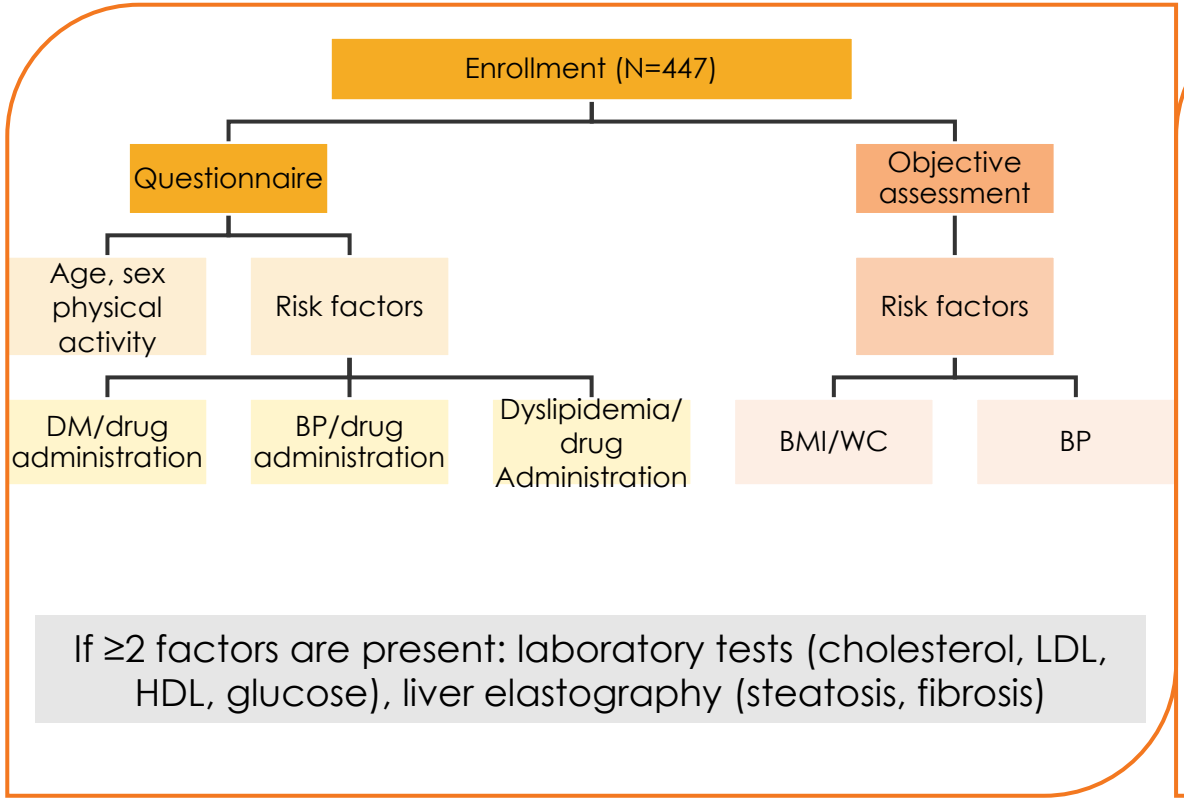
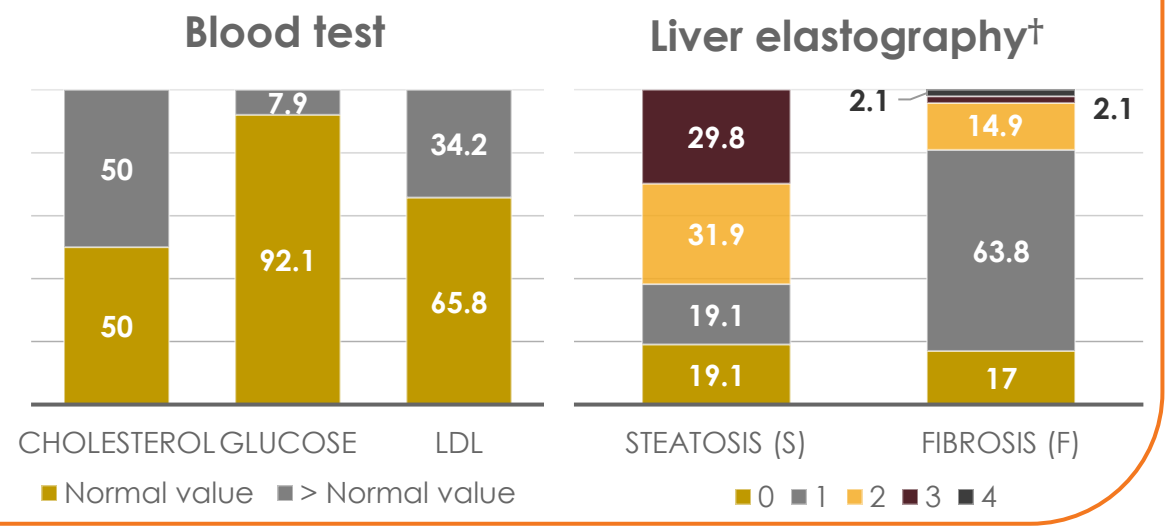
Study design and key results



If ≥2 factors are present: laboratory tests (cholesterol, LDL, HDL, glucose), liver elastography (steatosis, fibrosis)

Risk Factors (%)	
Yes	No
25.3	74.7

HDL (%)*	
<Normal	Normal
84.2	15.8



*n=38; †,n=47. BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference.
Personal communication from the presenter

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REPAIR (2015–2017)

Characteristics of outpatients with liver disorders (chronic viral hepatitis, liver steatosis, liver disorders due to T2DM, or obesity) treated with Essentiale® Forte N added to the standard of care in real-life clinical practice setting

T2DM, type 2 diabetes mellitus.

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REPAIR study – study design

The REPAIR study was a descriptive, cross-sectional, non-interventional, multicenter study conducted in **64 sites** across **5 cities** in the Republic of Kazakhstan

Participating physicians were randomly selected from a list of physicians with practical experience in managing liver disease

Outpatients aged 15–65 years with newly-diagnosed or previously diagnosed chronic viral hepatitis, hepatic steatosis, or diabetes- and obesity-related liver disease treated with EPL (physician decision) as an add-on to standard of care were recruited

Stage 1
A registry was created to assess the **profile of patients** treated with EPL, and study the **prescribing practice** of the drug

Stage 2
12 weeks after their first visit, patients attended a second visit, during which their **adherence, tolerance** and **satisfaction** with EPL treatment was assessed

EPL, essential phospholipids.
Nersesov AV, et al. Medicine (Almaty) 2016;9(171):35–50.

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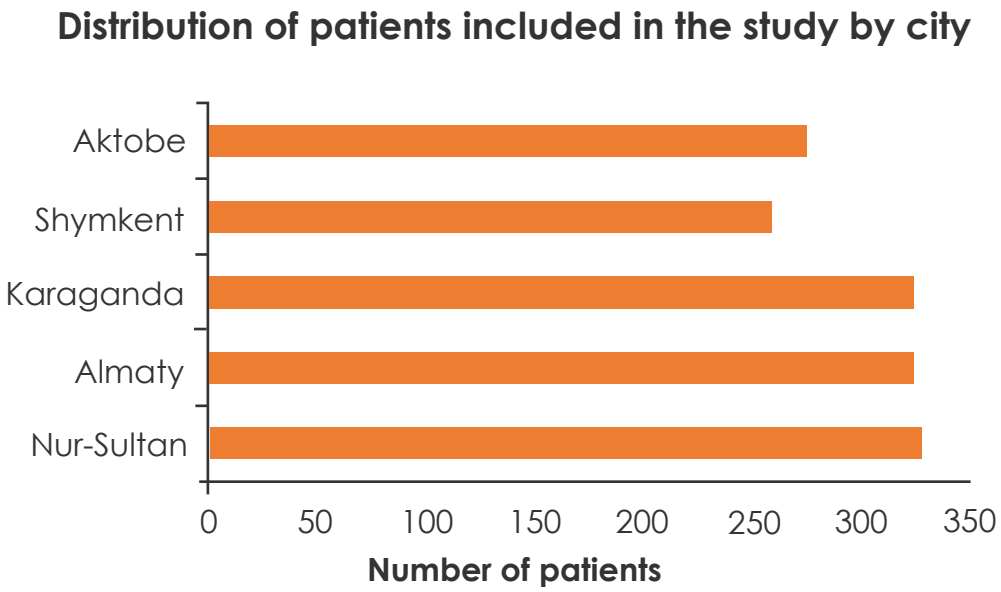
Baseline characteristics of participants included in the REPAIR study

- Of 1,514 patients recruited to the study, **1,505 (99.4%) met the inclusion criteria** and were included in the analysis
- 1,446 patients (**96.1%**) **completed the study** according to the protocol
- **300** (19.9%) **patients** were selected for Stage 2 of the study, of which **59 (19.7%) either changed treatment or discontinued treatment** with EPL
- 56.5% female, 43.5% male
- Mean **age**: 49.9 ± 11.1 years
- Mean **BMI**:
  - Women: 30.6 ± 5.6 kg/m^2
  - Men: 29.9 ± 4.5 kg/m^2



BMI, body mass index; EPL, essential phospholipids.
Nersesov AV, et al. Medicine (Almaty) 2016;9(171):35–50.

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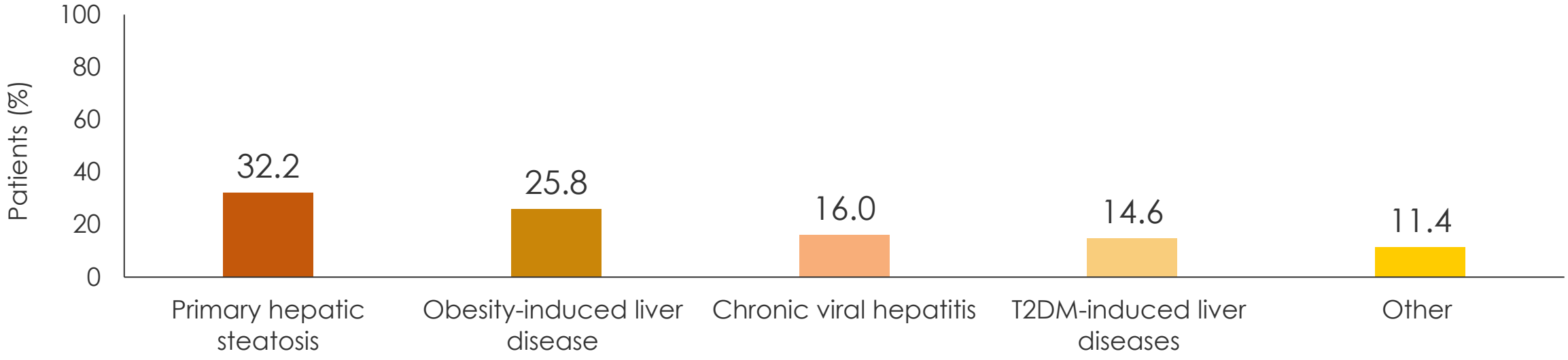
Patient profile – prevalence of chronic liver diseases in patients receiving treatment with EPL

Of the **51 patients who underwent liver biopsy, 87.8%** of patients **had pathological signs of NAFLD**

Most common chronic liver diseases in patients receiving treatment with EPL



EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.
Nersesov AV, et al. Medicine (Almaty) 2016;9(171):35–50.

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Which of the below was the most common chronic liver disease reported in the REPAIR study?

1. Chronic viral hepatitis
2. T2DM-induced liver disease
3. Primary hepatic steatosis
4. Obesity-induced liver disease

Type 2 diabetes mellitus.

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Patient profile: comorbidities

Metabolic comorbidities

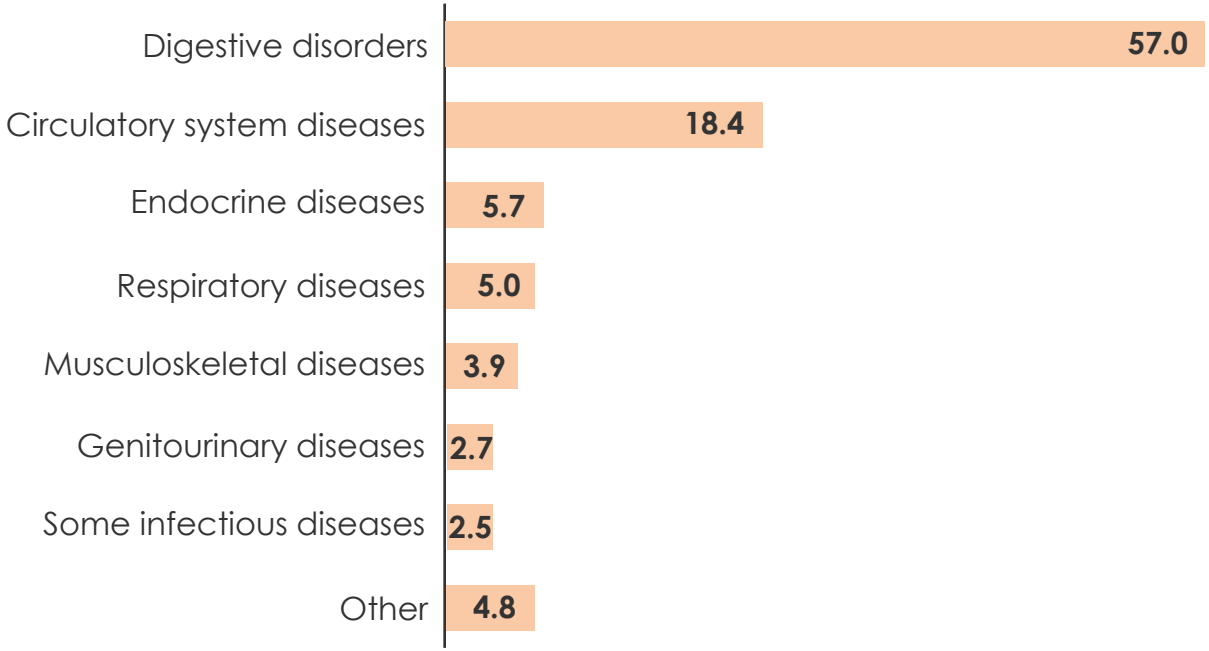
59.7% of patients were obese

58.8% of patients had hypertension

48.6% of patients had dyslipidemia

24.0% of patients had T2DM

Other comorbidities



T2DM, type 2 diabetes mellitus.
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EPL treatment: adherence and tolerance

Of the 300 patients invited to Stage 2 of the study, **80.3%** completed EPL treatment (median duration of 12 weeks)[1]

- Adherence was significantly different across cities (P=0.04); the highest was in Almaty (86.2%) and the lowest was in Karaganda (72.3%)[1]

59 patients (**19.7%**) did not finish treatment, most commonly due to financial difficulties (36.8%) and improvement in condition (31.6%)[1]

Three **mild AEs** were reported in two patients during the follow up period:[1]

- One patient reported **cholestasis** and **pruritus**; the patient recovered completely from both AEs
- One patient experienced **abdominal pain**

The results of the REPAIR study suggest good tolerability, patient adherence and safety of EPL treatment, consistent with previously published data[2,3]

AE, adverse event; EPL, essential phospholipids.

1. Nersesov AV, et al. Medicine (Almaty) 2016;9(171):35–50; 2. Gundermann KJ, et al. Pharmacol Rep 2011;63:643–59; 3. Gundermann KJ, et al. Clin Exp Gastroenterol 2016;9:10–7.

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Patient and physician satisfaction with the outcome of EPL treatment

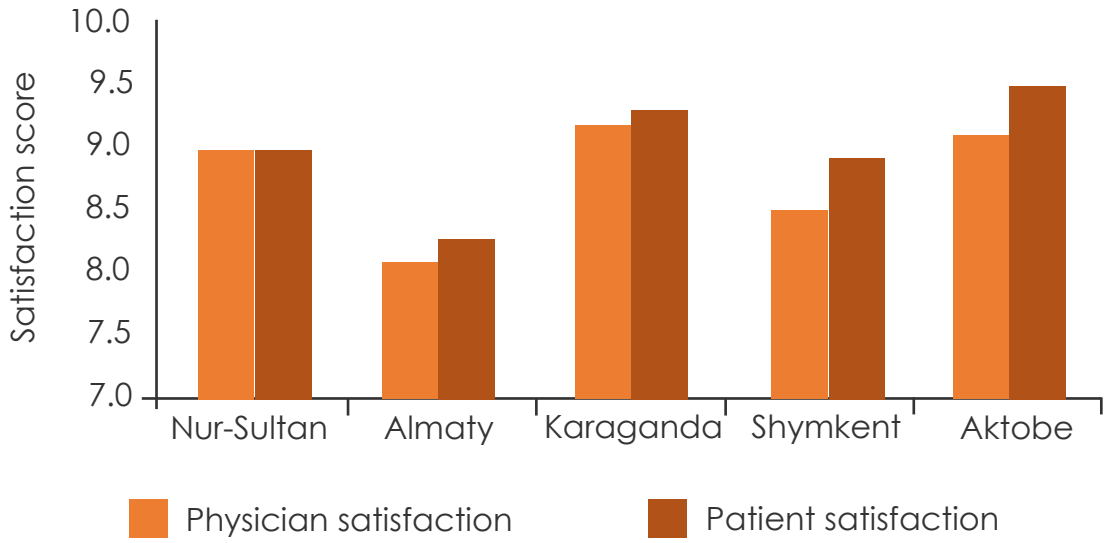
The mean value of physician satisfaction was **8.7 ± 1.7**[1]

The mean value of patient satisfaction was **9.0 ± 1.5**[1]

Of the 274 patients with known treatment outcomes:[1]

- **86 (31.4%)** recovered completely from their liver condition
- **164 (59.9%)** noted significant improvement in their liver condition

Mean physician and patient satisfaction scores with EPL treatment



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To conclude

1. In addition to the association between NAFLD and MS, there are other **established comorbidities,** including atherosclerosis, CVD (HF, dysrhythmia), CKD, obstructive sleep apnea, endocrinopathies, PCOS, and hypothyroidism

2. There are other extra-hepatic **emerging links**, including vitamin D deficiency, osteoporosis, male sexual dysfunction, CAC, carotid artery and aortic valve sclerosis, IHD, cardiomyopathy, ischemic stroke, fatigue, albuminuria, urolithiasis, periodontitis, psoriasis, and tumors (namely HCC, CRC and mammary cancer)

3. The REPAIR study, and other epidemiologic studies in Kazakhstan, have revealed the **prevalence of MS** components in line with wider trends in the Asian region

4. The results of the REPAIR study also suggest that **EPL treatment is highly effective and results in high patient and physician satisfaction**, consistent with previously published data

CAC, coronary artery calcification; CKD, chronic kidney disease; CRC, colorectal carcinoma; CVD, cardiovascular disease; EPL, essential phospholipids; HCC, hepatocellular carcinoma; HF, heart failure; IHD, ischemic heart disease; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome.

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