AASLD Nov. 4-8, 2022

The Liver Meeting®

WASHINGTON D.C.

The Best of The Liver Meeting®

NAFLD/NASH

About the program:

Best of The Liver Meeting 2022 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

Use of these slides:

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Prognostic value of non-invasive tests in patients with NAFLD

Aim

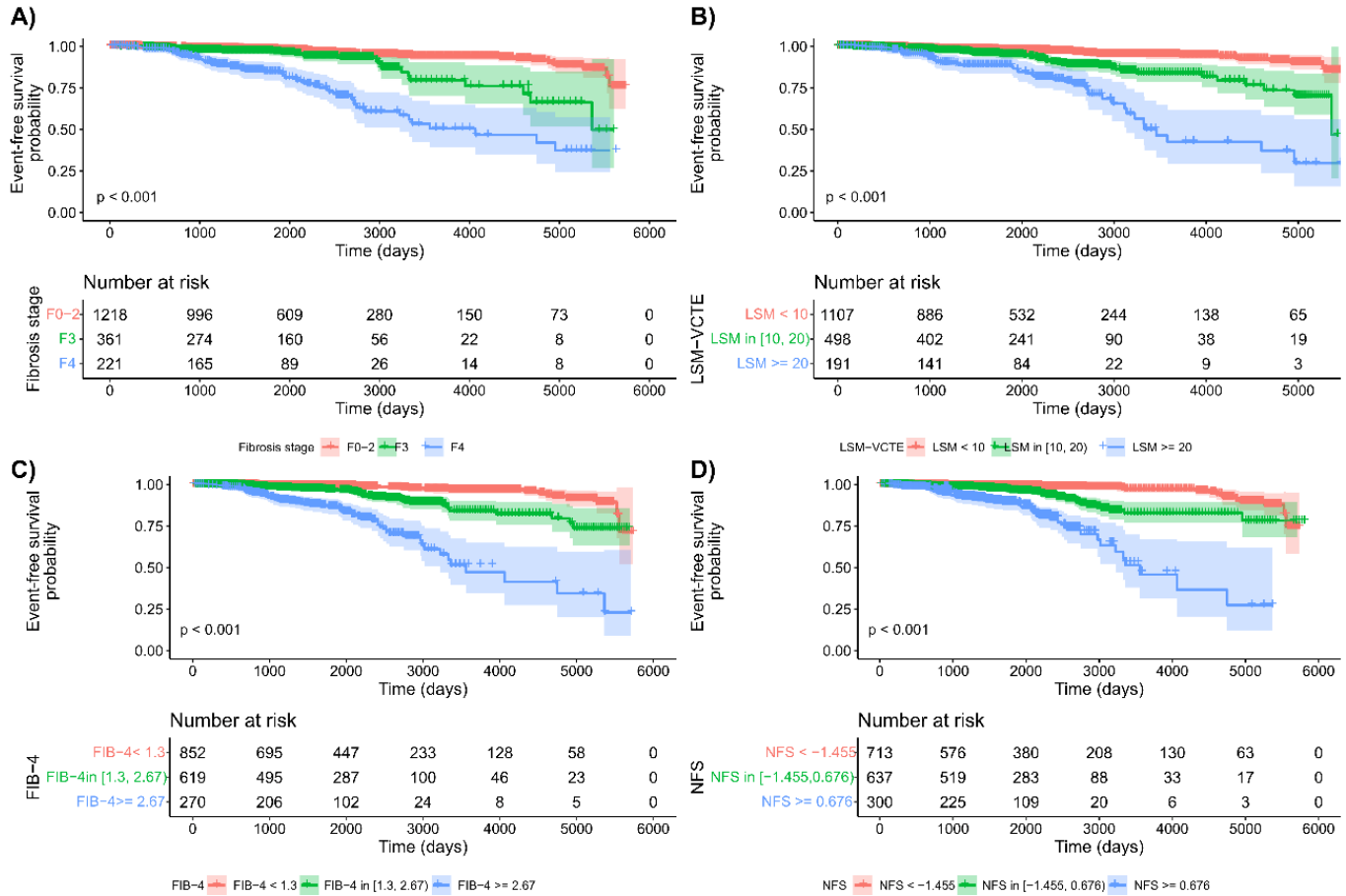
To evaluate the prognostic value of histologically assessed liver fibrosis, liver stiffness measurements (LSM) by FibroScan, FIB-4, and NFS scores.

Methods

- Individual participant data meta-analysis of studies with baseline FibroScan-LSM, FIB-4, NFS, and liver histology within 6 months and at least one year of follow-up.
- Primary endpoint
  - Liver-related events or all-cause mortality
- Kaplan-Meier curve analysis for:
  - Fibrosis: F0-2 vs F3 vs F4
  - LSM: < 10 kPa vs 10 – 20 kPa vs ≥ 20 kPa
  - FIB4 < 1.3 vs 1.3 – 2.67 vs ≥ 2.67
  - NFS < -1.455 vs -1.455 – 0.676 vs ≥ 0.676

Conclusions

Fibrosis biomarkers have similar prognostic performance to histology, supporting their adoption as surrogate endpoints in clinical trials.



Mozes F, et al., Abstract 9.

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Fibrosis progression rate among diabetic versus non-diabetic patients with biopsy-proven non-alcoholic fatty liver disease: A multicenter prospective study

Objective

- There are limited data regarding the *fibrosis progression rate* among diabetic versus non-diabetic patients with biopsy-proven non-alcoholic fatty liver disease (NAFLD).
- We assessed the *fibrosis progression rate* of diabetic versus non-diabetic participants in a large, multicenter, prospective study of participants with NAFLD who had paired liver biopsies.

Methods

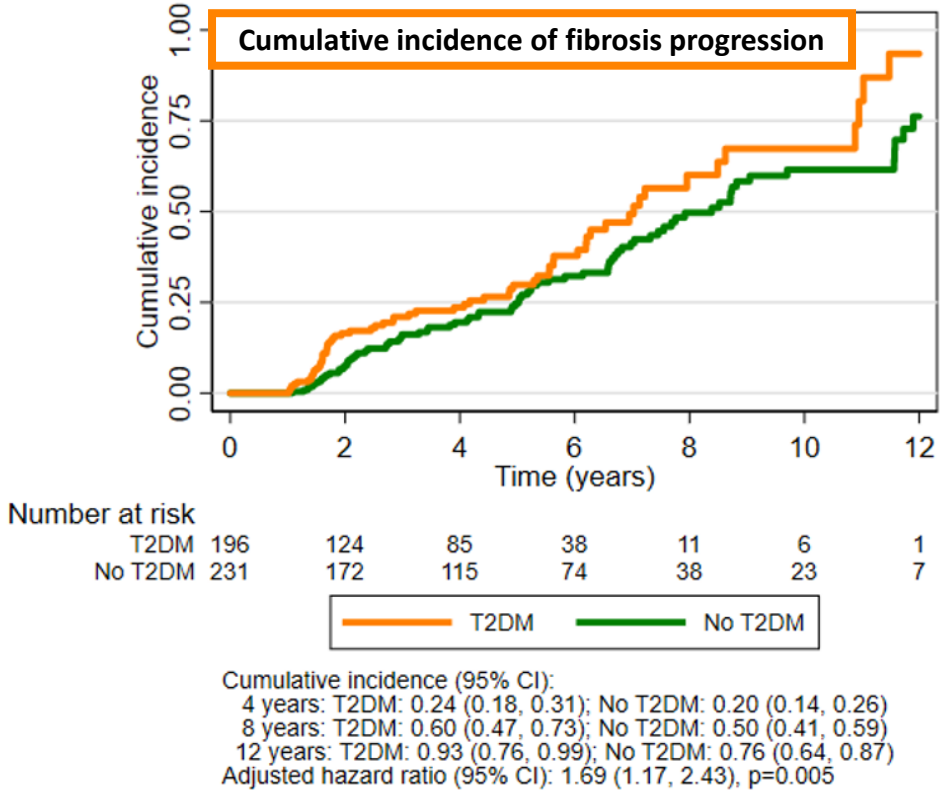
- This prospective study included 447 adult participants (64% female) with NAFLD who had paired liver biopsies >1 year apart.
- The primary outcome was the *fibrosis progression rate*, defined as the increase in fibrosis stage over time between biopsies (years) and compared using linear regression between diabetic versus non-diabetic participants at baseline.

Main Findings

The annual *fibrosis progression rate* was significantly higher in diabetic (n=208) versus non-diabetic participants (n=239) (0.17 stages/year versus 0.13 stages/year, *P*=0.02). *Fibrosis regression rate* between diabetics and non-diabetics were similar.

Conclusions

Diabetic patients with NAFLD have a significantly higher *fibrosis progression rate* compared with non-diabetic patients. These data have important implications for clinical practice and trial design.



Huang DQ, et al., Abstract 10.

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Liver stiffness by transient elastography to predict clinical events in patients with Nonalcoholic Fatty Liver Disease: A multicenter study of 995 biopsy-proven cases

Aim

To examine the utility of liver stiffness measurement (LSM) in predicting clinical events in patients with NAFLD.

Methods

A multicenter, retrospective study to collect long-term clinical events on 995 patients with biopsy-proven NAFLD who received LSM by transient elastography (TE: FibroScan®).

Main Findings

- LSM was an independent factor contributing to HCC development and liver failure, but not to cardiovascular disease (CVD) and all-cause mortality.
- The annual incidence of HCC and liver failure were significantly higher in patients with higher LSM.

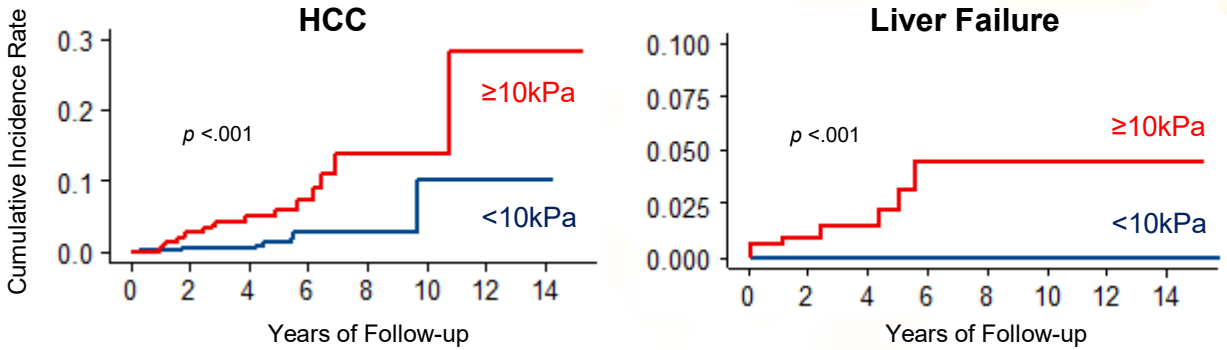
Conclusions

LSM is useful for risk stratification of liver-related events in patients with NAFLD.

Cox Regression Analysis (multivariate)

	HCC		Failure		CVD		Death	
Variable	HR	*P*	HR	*P*	HR	*P*	HR	*P*
LSM by TE (log)	**2.55**	**.006**	**11.5**	**.002**	-	-	1.02	.96
Age (per year)	**1.08**	**.003**	-	-	**1.13**	**.001**	1.04	.11
Male	0.76	.54	-	-	0.44	0.21	-	-
BMI (kg/m^2)	-	-	**0.78**	**.02**	-	-	**1.13**	**.03**
Albumin (g/L)	-	-	0.12	.06	0.44	0.23	0.42	.22
Platelet count (x10^9/μL)	**0.91**	**.03**	0.88	.13	0.99	0895	0.91	.08

*Covariates were chosen based on their significance in univariate analysis (*P* <.10)



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Nakatsuka T, et al., Abstract 91.

Development of a clinical prediction rule for moderate to severe fibrosis in children with non-alcoholic fatty liver disease

Aims

- Evaluate existing pediatric and adult fibrosis prediction models.
- Develop a clinical prediction rule for identifying moderate to severe fibrosis in children with NAFLD.

Methods

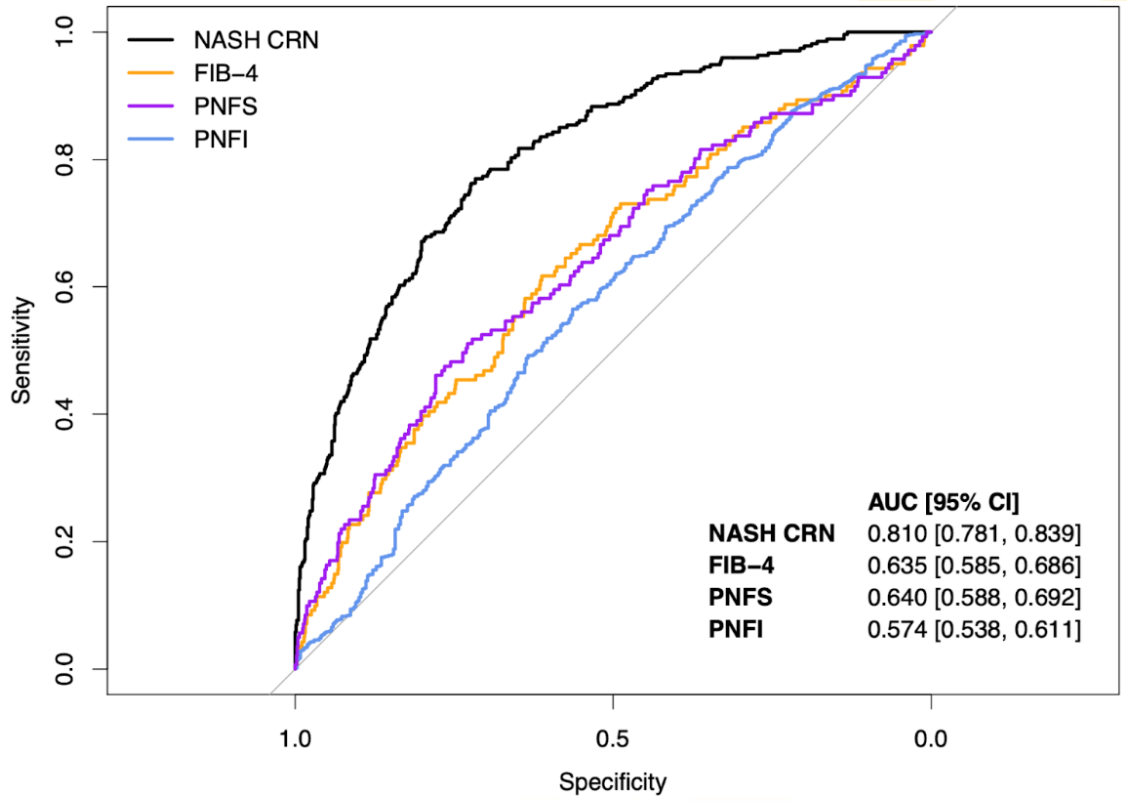
1055 children with biopsy proven NAFLD reviewed by NASH CRN Pathology Committee and contemporaneous demographic and clinical data used to test, develop, validate existing and a newly developed model for stage 2-4 fibrosis.

Main Findings

- PFNS, PFNI, FIB-4 had AUC ranging from 0.57 to 0.64.
- NASH CRN model based on commonly available variables had an AUC of 0.81 (95% CI: 0.78 to 0.84).

Conclusions

New model offers improved performance characteristics to identify moderate to severe fibrosis in children with NAFLD.



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Wang A, et al., Abstract 93.

Prevalence of NAFLD, advanced fibrosis, cirrhosis, and hepatocellular carcinoma in patients with type II diabetes: A prospective study

Aim

To evaluate the prevalence of advanced fibrosis and cirrhosis in a prospectively recruited cohort of adults with type II diabetes mellitus (T2DM).

Methods

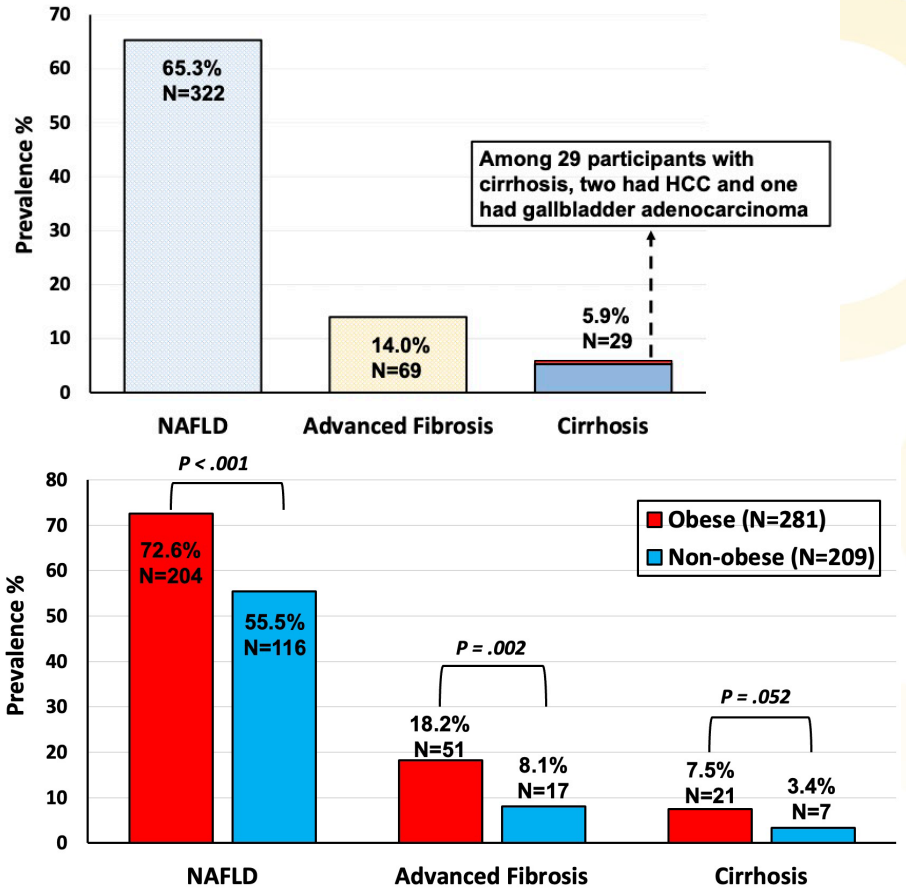
Adults age ≥ 50 years with T2DM recruited from primary care or endocrinology clinics underwent a standardized clinical research visit with MRI-PDFF, MRE, VCTE, and CAP.

Main Findings

- The prevalence of NAFLD, advanced fibrosis, and cirrhosis was 65%, 14% and 6%, respectively.
- In multivariable adjusted models, adjusted for age and sex, obesity and insulin use were associated with increased odds of advanced fibrosis OR=2.50 (95% CI: 1.38-4.54, p=0.003) and OR=2.71 (95% CI: 1.33-5.50, p=0.006), respectively.

Conclusions

The high disease burden in adults with T2DM provide new data to support systematic screening to identify advanced fibrosis or cirrhosis in adults ≥ 50 years with T2DM.



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Ajmera V, et al., Abstract 95.

Higher mortality among lean versus non-lean patients with non-alcoholic fatty liver disease despite lower incidence of cirrhosis and cardiovascular disease

Hypothesis/Aim/Objective

We compared mortality and incidence of cirrhosis, cardiovascular disease (CVD), diabetes mellitus (DM), and cancer between lean versus non-lean persons with NAFLD.

Methods

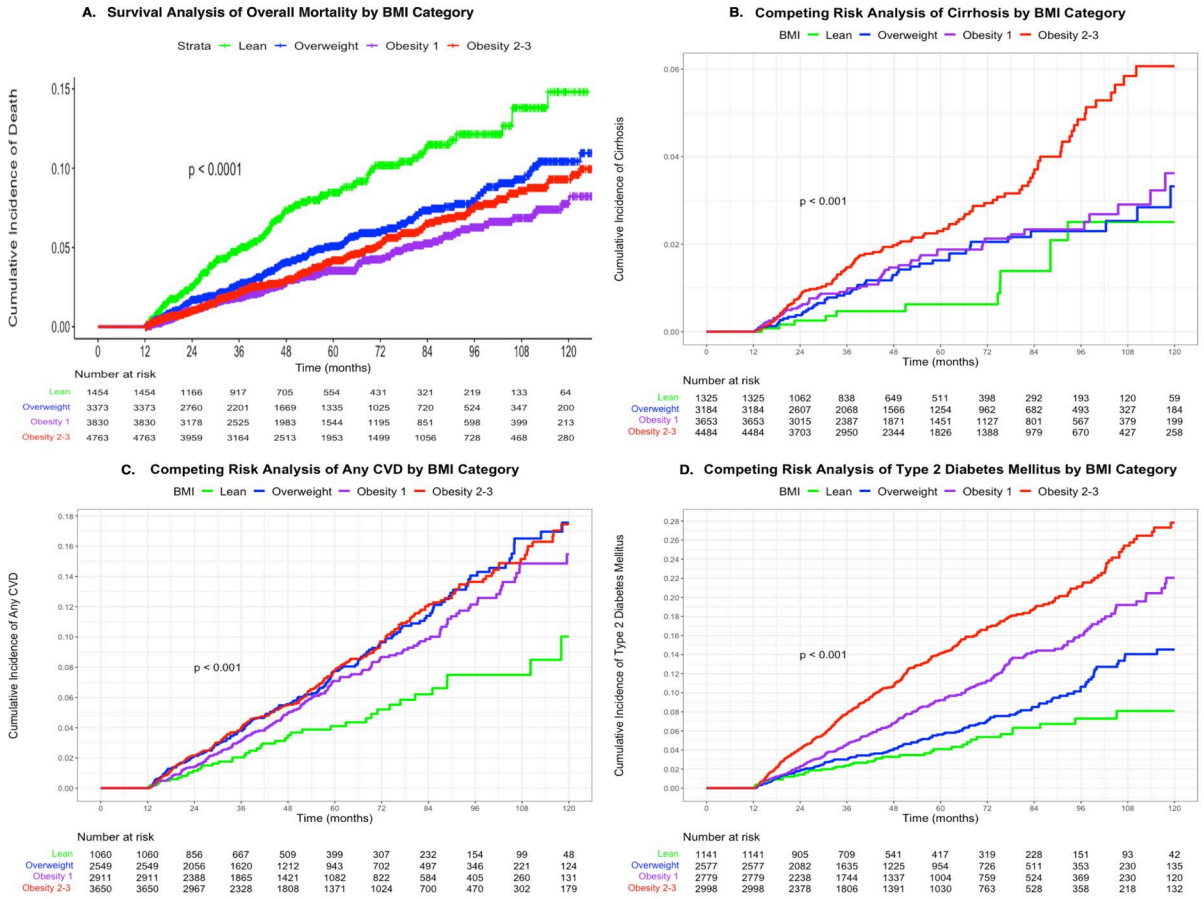
We conducted a single-center retrospective analysis of adults with NAFLD identified from 2012 to 2021, with mortality compared using Cox proportional hazards and incident disease using competing risk statistics.

Main Findings

Lean patients with NAFLD had higher mortality than non-lean patients with NAFLD despite lower incidence of cirrhosis, DM, and CVD.

Conclusions

NAFLD in lean individuals confers greater mortality than obese individuals, and optimal control of medical comorbidities and diet/lifestyle intervention to combat sarcopenia/malnutrition may mitigate this difference in mortality.



Wijarnpreecha K, et al., Abstract 96.

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The Agile 3+ and 4 scores most accurately predict major adverse liver outcomes and death compared to LSM and FAST score

Aim

Compare the Agile 3+ and 4 scores' performances in predicting adverse events to LSM alone and the Fibroscan-AST (FAST) score by VCTE

Methods

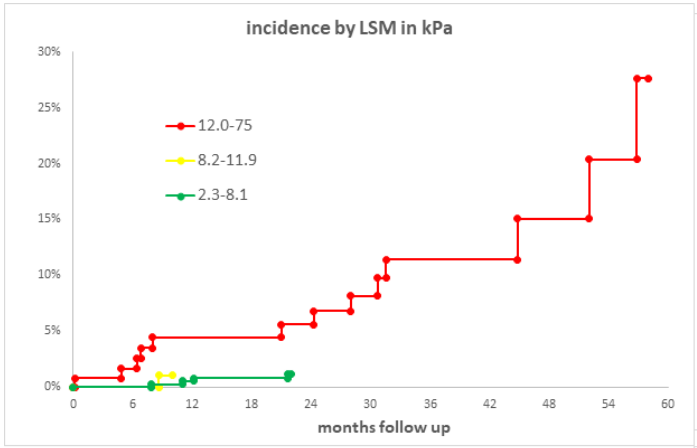
Retrospective analysis of NAFLD patients with VCTE and lab data from a tertiary care center (2013-2022)

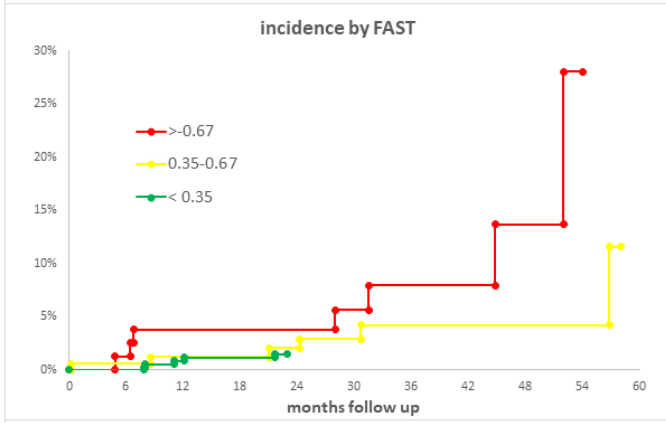
Main Findings

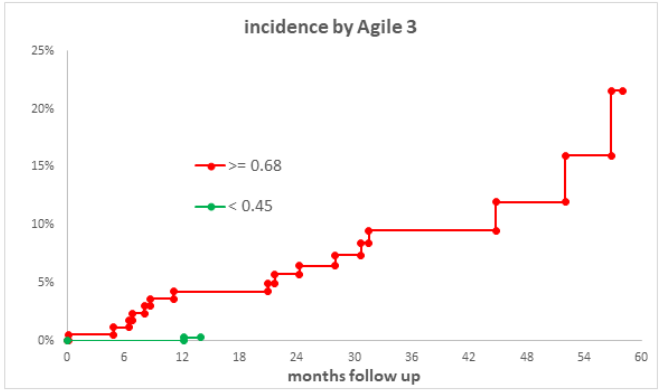
Using Harrel Concordance statistic (C stat), Agile 3+ and 4, respectively, had the highest C stat of **0.872** (C stat SE 0.069) and **0.852** (C stat SE 0.050) compared to LSM via VCTE (C stat 0.817, C stat SE 0.052) or FAST (C stat 0.697, C stat SE 0.069).

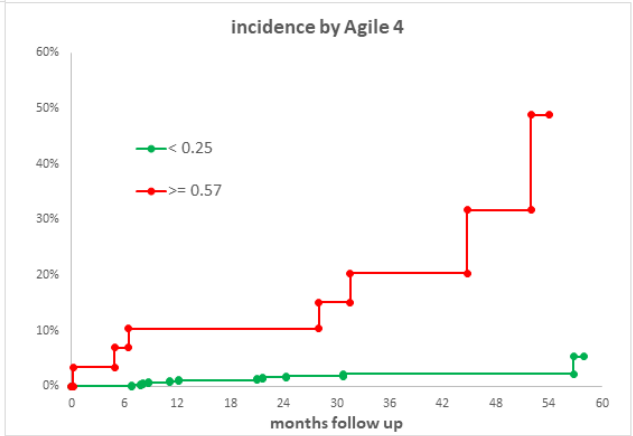
Conclusions

The Agile 3+ and 4 scores had the highest likelihood of accurately predicting adverse outcomes including MALO and death compared to LSM via VCTE or FAST score.









FAST=Fibroscan-AST. LSM=liver stiffness measurement.
VCTE=vibration-controlled transient elastography.

Noureddin M, et al., Abstract 98.

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Utility of FIB-4, MRE, MRI-PDFF, and FibroScan to identify patients with at-risk F2-F3 NASH based on screening data from a 2000 patient biopsy-confirmed cohort of resmetirom Phase 3 clinical trial (MAESTRO-NASH)

Objective

To evaluate the utility of various noninvasive tests & imaging modalities to identify patients with at-risk F2-F3 NASH in a large serial liver biopsy trial (MAESTRO-NASH).

Methods

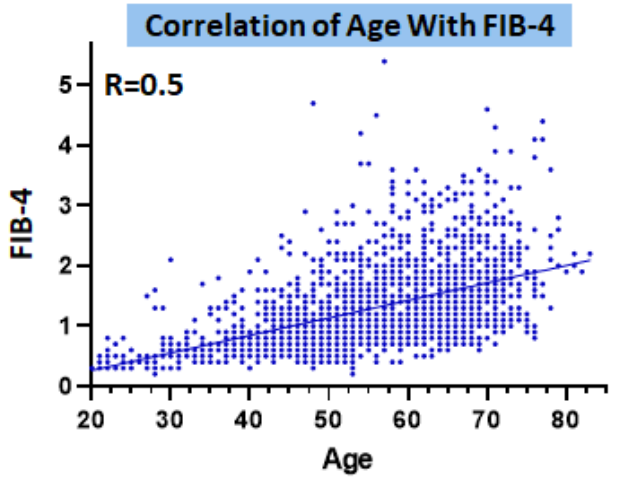
- This analysis used screening data from MAESTRO-NASH (NCT03900429), a randomized, double-blind, placebo-controlled Phase 3 trial evaluating resmetirom, a liver-targeted, oral thyroid hormone receptor-beta selective agonist, for treatment of NASH (NAS ≥4, all components) with significant liver fibrosis (F2/F3).
- Screening included requirement for ≥3 metabolic risk factors; FibroScan kPa ≥8.5; CAP ≥280; MRI-PDFF ≥8%.

Main Findings

- 56.9% F2 & 40.3% F3 biopsy-confirmed patients had FIB-4 <1.3 while 32.6% and 18.0%, respectively, had FIB-4 <1.0
- More low-risk NAFLD patients had FIB-4 <1.3 vs FIB-4 <1.0
- Younger age of 10 years in patients with at-risk NASH removed ~0.2 from FIB-4 suggesting a lower threshold (decreasing many to <1.3).

Conclusions

The influence of age on FIB-4 may require an adjustment (to ensure younger patients are not removed from consideration for treatment) and/or the need for additional noninvasive tests to improve at-risk patient identification.



Patients With Fibrosis (F2-F4)				
	AUROC	Sensitivity	Specificity	Optimal Value
FIB-4	0.68	61%	64%	1.1
FibroScan TE	0.66	NA	62%	10.6 kPa
FAST	0.72	70%	61%	0.52
MRE	0.79	70%	73%	2.9 kPa
MAST	0.79	70%	73%	0.10
MEFIB	0.78	33% (F3)	>90% (≥F2)	NA

Loomba R, et al., Abstract 102.

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The protection conferred by *HSD17B13* rs72613567 on hepatic fibrosis in NAFLD is mediated indirectly by lowering ballooning and portal inflammation

Hypothesis/Aim/Objective

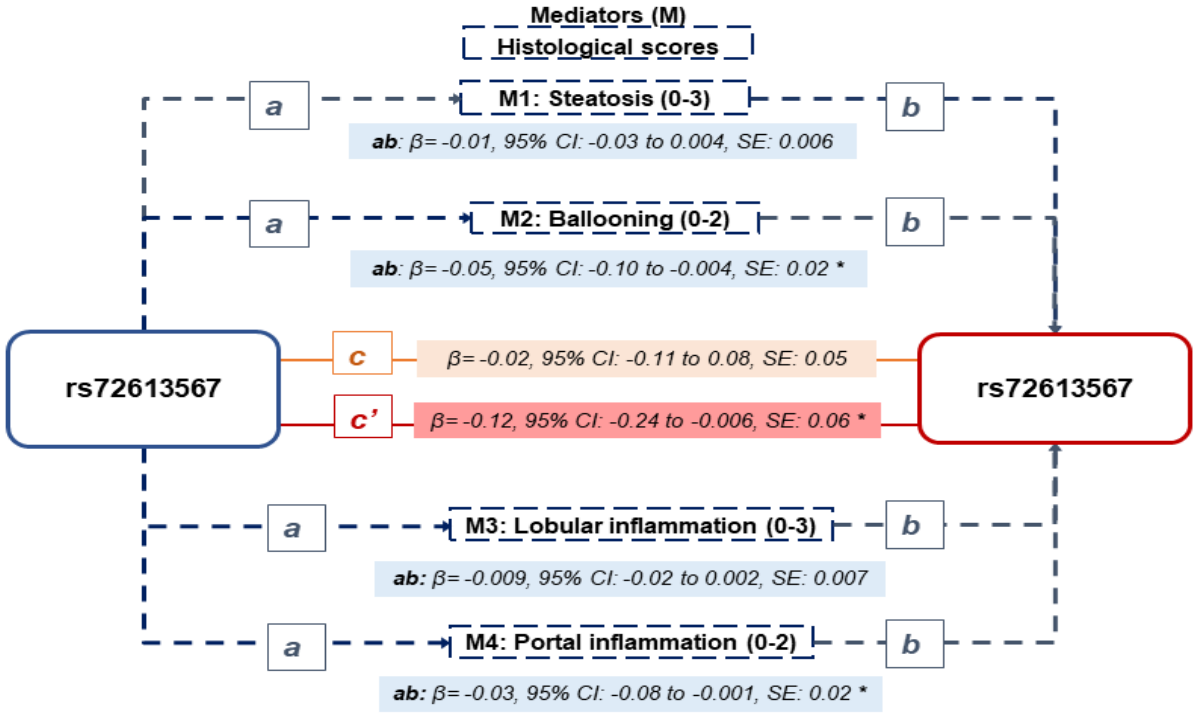
To investigate whether rs72613567 protects against fibrosis by reducing the severity of intermediate histological lesions and/or by a direct effect on fibrosis.

Methods

- 1153 non-Hispanic whites with biopsy-proven NAFLD from the NASH CRN.
- NASH CRN scoring system to assess the NAFLD histology severity.
- A causal parallel mediation analysis examined the effect of rs72613567 (additive genetic model: -/-, -/A, A/A) on overall fibrosis (0-4) explained (indirect effect) or unexplained (direct effect) by steatosis, lobular inflammation, or ballooning degeneration.

Conclusions

rs72613567 may indirectly reduce fibrosis severity through improvements in ballooning degeneration and portal inflammation.



ab: The effect of rs72613567 on the fibrosis score, operating through mediators.
c: The direct effect of rs72613567 on the fibrosis score, not operating through mediators.
c': the total effect of rs72613567.
β indicates bootstrap coefficients.
The star symbol (*) represents statistically significant paths.

Vilar-Gomez E, et al., Abstract 104.

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MEFIB-Index and MAST-Score assessment of incident hepatic decompensation in nonalcoholic fatty liver disease (NAFLD): An individual patient data meta-analysis

Aim

To examine the longitudinal association between MEFIB-Index versus MAST-Score in predicting hepatic decompensation in NAFLD patients

Methods

Longitudinal, retrospective analysis of NAFLD patients' cohorts from United States, Japan, and Turkey who underwent a baseline MRE and MRI-PDFF and were followed for hepatic decompensation (ascites, hepatic encephalopathy, and varices needing treatment). Cox-proportional hazard analyses were used. Positive MEFIB-Index defined as MRE ≥ 3.3kPa and FIB-4 ≥ 1.6, whereas positive MAST-Score defined as MAST > .242.

Main Findings

- Among 297 patients with a median (IQR) of 4.2 (5.0) years of follow-up, total of 25 incident cases with hepatic decompensation.
- A positive MEFIB-Index and MAST-Score were statistically significant predictors of the incident hepatic decompensation [HR=49.22 (95%CI: 6.23-388.64, p<0.001)] and [HR=3.86 (95%CI: 1.46-10.17, p<0.001)], respectively (Figure 1).
- MEFIB-Index (c-statistic: 0.89, standard error(se)=0.02) was statistically superior to the MAST-Score (c-statistic: 0.81, se=0.03) (p<.0001) in predicting hepatic decompensation (Figure 2).

Conclusions

A combination of MRI-based biomarker and blood tests such as MEFIB-Index and MAST-Score predict future risk of hepatic decompensation.

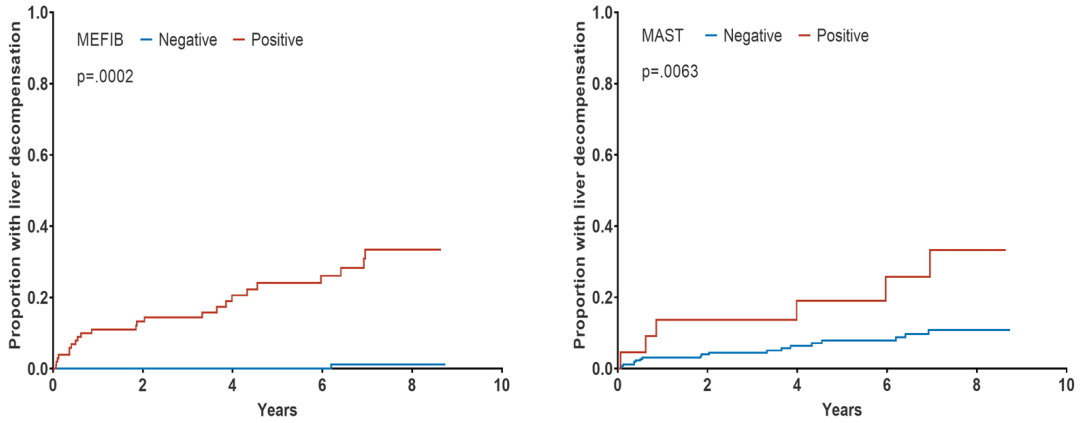
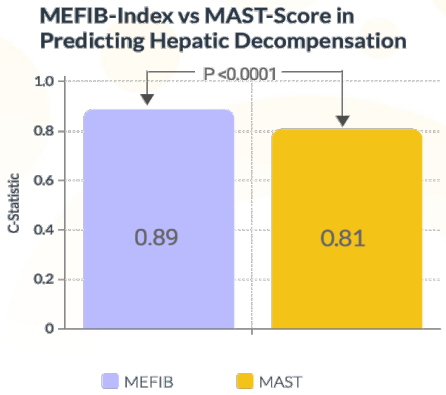


Figure 1: Cumulative incidence plots for the primary outcome for MEFIB-Index and MAST-Score.

Figure 2: C-Statistics Comparison Between MEFIB-Index and MAST-Score



Loomba R, et al., Abstract 107.

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Pediatric non-alcoholic fatty liver disease: Residing in low resource neighborhoods may increase risk

Hypothesis

The prevalence of NAFLD will be higher in low resource neighborhoods within large, metropolitan areas with significant socioeconomic disparity.

Methods

Mapped 200 pediatric patients with NAFLD to their census tract and assessed an aggregate marker of community deprivation (CDI) compared to national and NYC data.

Main Findings

NAFLD cohort mean CDI 0.50 compared to 0.39 in NYC and 0.35 nationally (see Figure 1).

Conclusions

Children with NAFLD are co-located with increased neighborhood deprivation; more attention should be focused on under-resourced neighborhoods to understand the underlying causality.

Figure 1: Distribution of Non-Alcoholic Fatty Liver Cases in Relation to the Community Deprivation Index

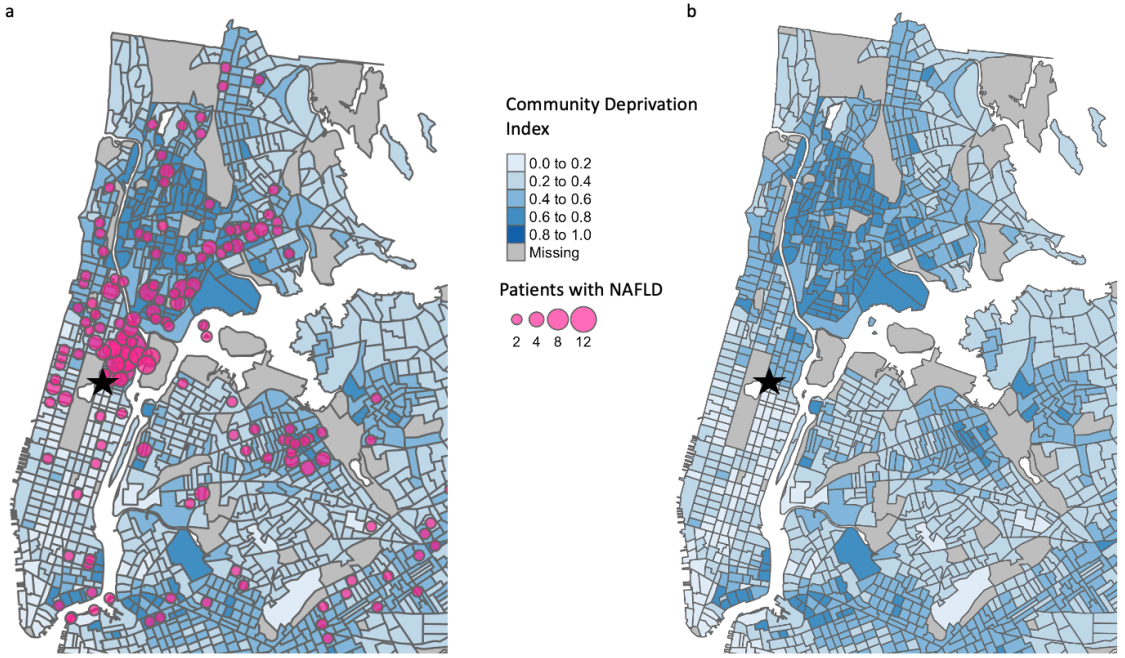

Figure 1a shows New York City[1] divided by census tract with more heavily shaded tracts indicating a higher community deprivation index (CDI). The overlaid magenta circles indicate the number of patients with NAFLD in each census tract with a larger circle indicating greater patient density. Mount Sinai is located at the black star. The overlay of NAFLD patient density is removed in figure 1b for comparison.

[1]Image cropped to show detail; full image available in presentation

Smith R, et al., Abstract 116.

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Effects if advanced donor age on post-liver transplant prognosis of patients with nonalcoholic steatohepatitis (NASH): Analysis of UNOS database

Aim

The liver transplant (LT) UNOS registry was used to identify the post-transplant outcomes of recipients with NASH who received grafts from donors older than 50 years of age vs. younger donors.

Methods

- The UNOS-STAR database (2005-2019) was used to select LT patients with NASH (including cryptogenic liver disease).
- Living/multi-organ transplants and pediatric population excluded.
- Study sample was stratified into: quinquagenarians (QU), sexagenarians (SX), septuagenarians (SP), octogenarians (OC). Strata were then compared to the reference group (RG) of donors younger than 50 years of age.
- Cox regression iterations were performed and the cumulative risk curves were generated for each comparison using all-cause mortality (ACM) and graft failure (GF) as endpoints.

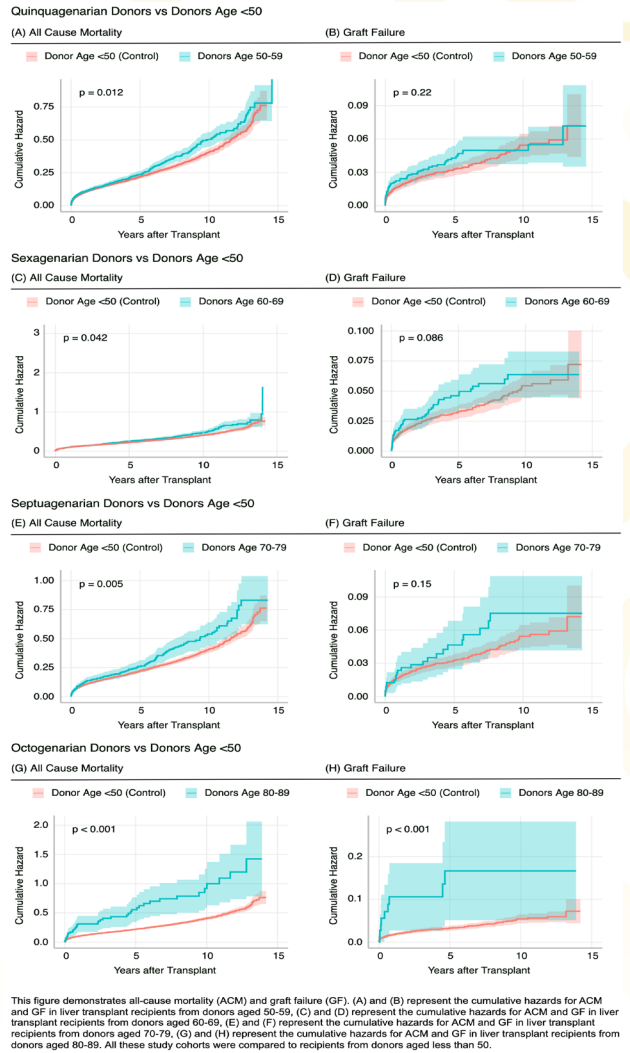
Main Findings

- Advanced-age categories had higher risks of ACM than the RG except the SX cohort (QU: aHR 1.13 [1.02-1.26]; SP: 1.20 [1.01-1.43]; OC: 2.04 [1.48-2.81]).
- All cohorts showed higher ACM incidence rates than the RG (expressed in per 1000 person-years; RG: 48.72, QU: 55.47, SX: 54.49, SP: 60.65, OC: 113.26).
- Advanced-age categories had higher risks of GF, except the QU and SP cohorts (QU: aHR 1.25 [0.95-1.65]; SX: 1.41 [1.04-1.92]; SP: 1.55 [1.00-2.42]; OC: 4.48 [2.24-9.00]).
- All cohorts showed higher GF incidence rates than the RG (in 1000 person-years; RG: 6.86, QU: 8.10, SX: 8.82, SP: 9.04, OC: 24.86).

Conclusions

Our work demonstrated that NASH-LT recipients receiving grafts from older age donors are at higher risk of all-cause mortality and graft failure.

Lee D, et al., Abstract 1515.



This figure demonstrates all-cause mortality (ACM) and graft failure (GF). (A) and (B) represent the cumulative hazards for ACM and GF in liver transplant recipients from donors aged 50-59, (C) and (D) represent the cumulative hazards for ACM and GF in liver transplant recipients from donors aged 60-69, (E) and (F) represent the cumulative hazards for ACM and GF in liver transplant recipients from donors aged 70-79, (G) and (H) represent the cumulative hazards for ACM and GF in liver transplant recipients from donors aged 80-89. All these study cohorts were compared to recipients from donors aged less than 50.

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Efruxifermin (EFX) in nonalcoholic steatohepatitis with fibrosis: Results from a randomized, double-blind, placebo-controlled, phase 2b trial (HARMONY)

Aim

To evaluate the efficacy and safety of efruxifermin (EFX), a long-acting, Fc-FGF21 fusion protein, compared to placebo in patients with fibrosis stage 2 or 3 due to biopsy-confirmed NASH.

Methods

Randomized, placebo-controlled trial evaluating once-weekly 28 mg (n=42) and 50 mg (n=43) EFX compared to placebo (n=43) after 24 weeks.

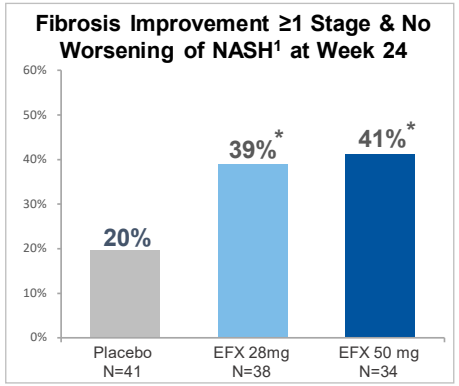
Main Findings

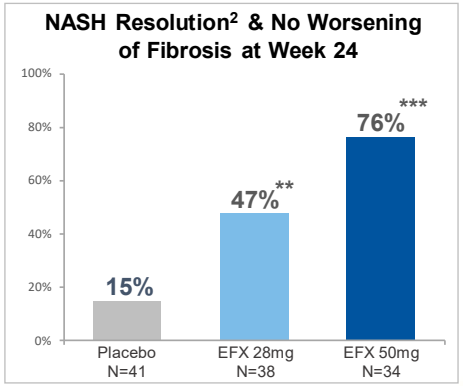
- EFX significantly reduced liver fibrosis and resolved NASH.
- EFX also improved markers of lipid and glucose metabolism.
- The high rates of NASH resolution correlated with normalization of liver fat.
- EFX was well tolerated with the most frequent treatment-emergent adverse events being gastrointestinal, mild-to-moderate in severity.

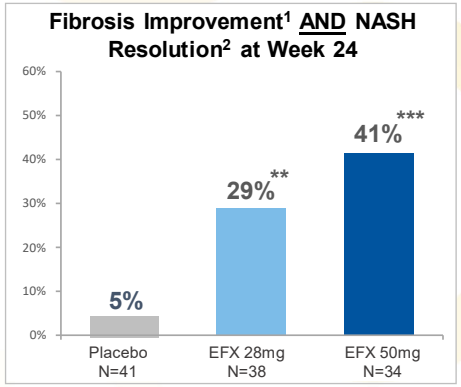
Conclusions

EFX has the potential to be a foundational monotherapy for treating NASH. It reverses fibrosis, resolves NASH, improves liver health, and restores whole body metabolism.

Harrison S, et al., Abstract LO6.







LS Mean Change from Baseline	Placebo (N=40-42)	EFX 28mg (N=35-38)	EFX 50mg (N=34-36)
LFC (%, Relative)	-6	-52***	-64***
% normalized LFC (≤5%)	2	34***	51***
ALT (U/L)	-3.0	-22.4***	-32.9***
Pro-C3 (µg/L)	0.1	-5.1***	-5.2***
ELF Score	0.1	-0.6***	-0.7***
HbA1c (%, Absolute), in T2D (N=82)	-0.0	-0.5*	-0.5*
Triglycerides (%)	+9	-25***	-29***
LDL Cholesterol (%)	+9	-8**	-8**
Body Weight (kg)	-0.6	-0.2	-2.9††
Odds Ratio [95%CI] of achieving NASH resolution	**All patients** (N=112)	**EFX-treated patients only** (N=71)	
LFC normalized (≤5% LFC)	9.3 [3.2, 23.8]****	4.3 [1.3, 11.7]*	

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. placebo; ††p<0.01 vs. baseline. [1]Improvement in liver fibrosis ≥ 1 stage without increase in NAS for ballooning, inflammation, or steatosis. [2] NAS score of 0 or 1 for lobular inflammation and 0 for ballooning

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PXL065 (Deuterium-stabilized *R*-enantiomer of Pioglitazone) reduces liver fat content and improves liver histology without PPARγ-mediated side effects in patients with NASH: 36-week placebo-controlled phase 2 trial

Objective

To evaluate the effect of 3 doses of PXL065 on liver fat content in a randomized, double-blind, placebo-controlled 36-week study.

Methods

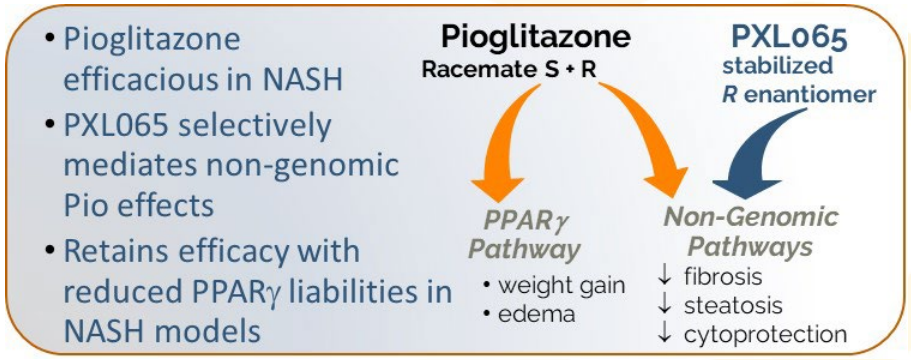
- 117 noncirrhotic NASH (F1-3) patients randomized: placebo vs PXL065 7.5, 15, 22.5 mg QD – 36-week treatment.
- Primary endpoint: liver fat content – LFC, MRI-PDFF.
- Secondary endpoints including paired liver biopsies.

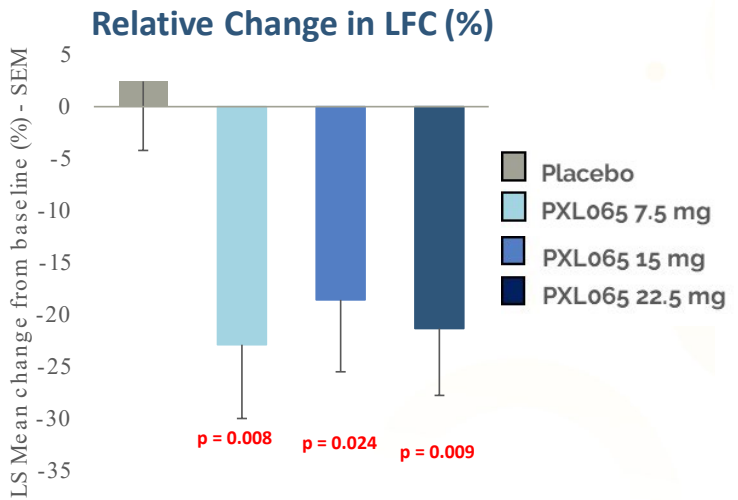
Main Findings

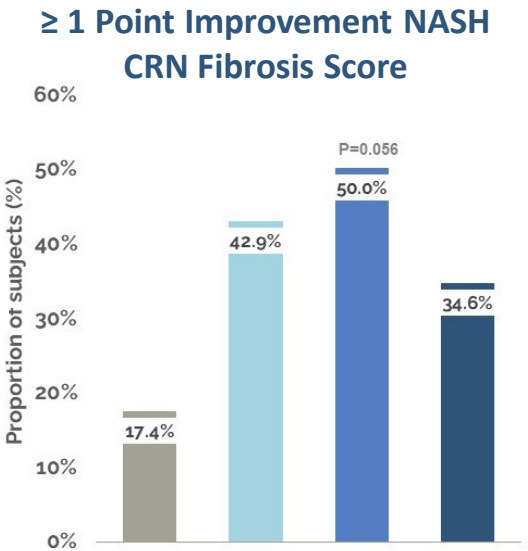
- ↓ LFC – all doses
- ↓ ALT (trend); fibrogenesis, fibrosis risk markers
- ↓ HbA1c; ↑ adiponectin
- Histology improvements (greatest for steatosis, fibrosis)
- No dose-related weight gain; no edema; favorable safety-tolerability
- PK confirms R > S-pioglitazone exposure in NASH patients vs Actos®.

Conclusions

Primary endpoint achieved all doses; improved histology; metabolic benefits; reduced potential for PPARγ side effects; pivotal trial planning ongoing.







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