Utility of FIB-4 Thresholds 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)

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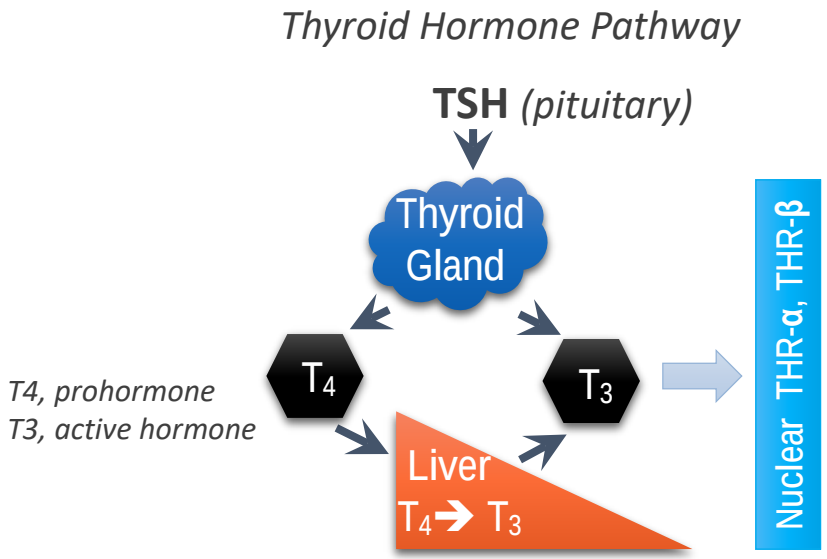
Mechanism of Action: The Importance of Liver THR-β in NASH



In humans, THR-β agonism:

- Lowers LDL-C
- Lowers TG
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

Resmetirom (MGL-3196)

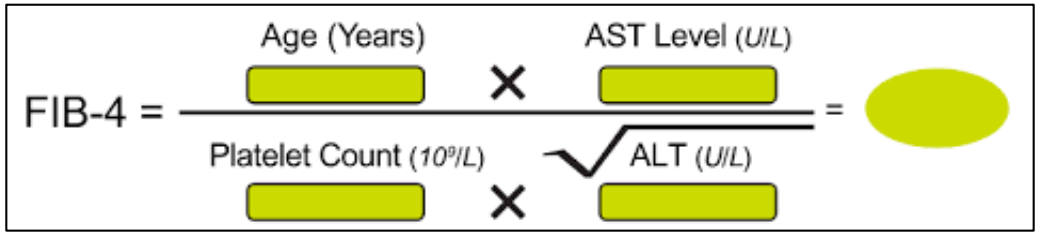
- Liver-targeted, oral, once-daily selective THR-β agonist with established safety & efficacy in >1000 patients
  - No exposure in tissues outside the liver or activity at the systemic THR-α receptor
- Pleiotropic effects in the liver with potential for addressing the underlying metabolic syndrome & hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly & indirectly)

LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; TG, triglycerides; THR, thyroid hormone receptor; TSH, thyroid-stimulating hormone.

1. Sinha RA, Yen PM. *Cell Biosci.* 2016;6:46. 2. Sinha RA, et al. *Autophagy*. 2015;11(8):1341-1357.

MAESTRO-NASH

- MAESTRO-NASH (NCT03900429) is an ongoing 52-week, randomized, double-blind, placebo-controlled Phase 3 trial to evaluate the efficacy & safety of resmetirom in >1000 patients with NASH (NAS ≥4, all components) & significant liver fibrosis (F2/F3)[1]
- FIB-4 is frequently used to identify individuals at-risk for NASH:
  - FIB-4 ≥1.3 is considered indeterminant risk; FIB-4 ≥2.67 indicates probable liver disease
  - FIB-4 <1.3 is considered low risk



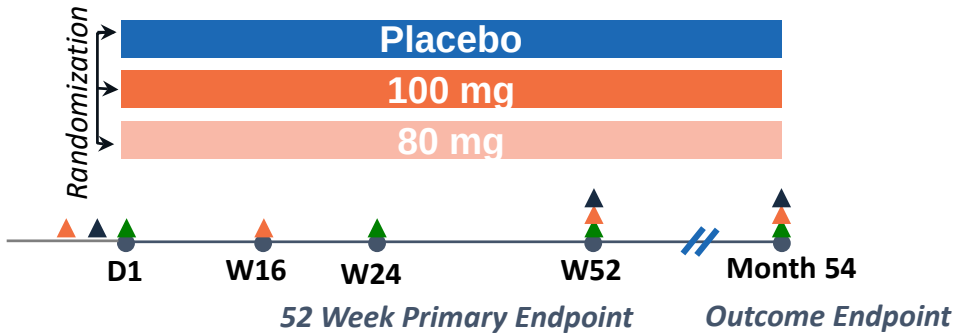
- MAESTRO-NASH did not use liver enzymes or FIB-4 as prescreening criteria for study eligibility
  - >2000 screened patients evaluated in this analysis had screening liver biopsies

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; THR, thyroid hormone receptor.

1. ClinicalTrials.gov (NCT03900429): https://clinicaltrials.gov/ct2/show/NCT03900429

Phase 3 MAESTRO-NASH Study Design: Randomized, Double-Blind, Placebo-Controlled Serial Liver Biopsy Study

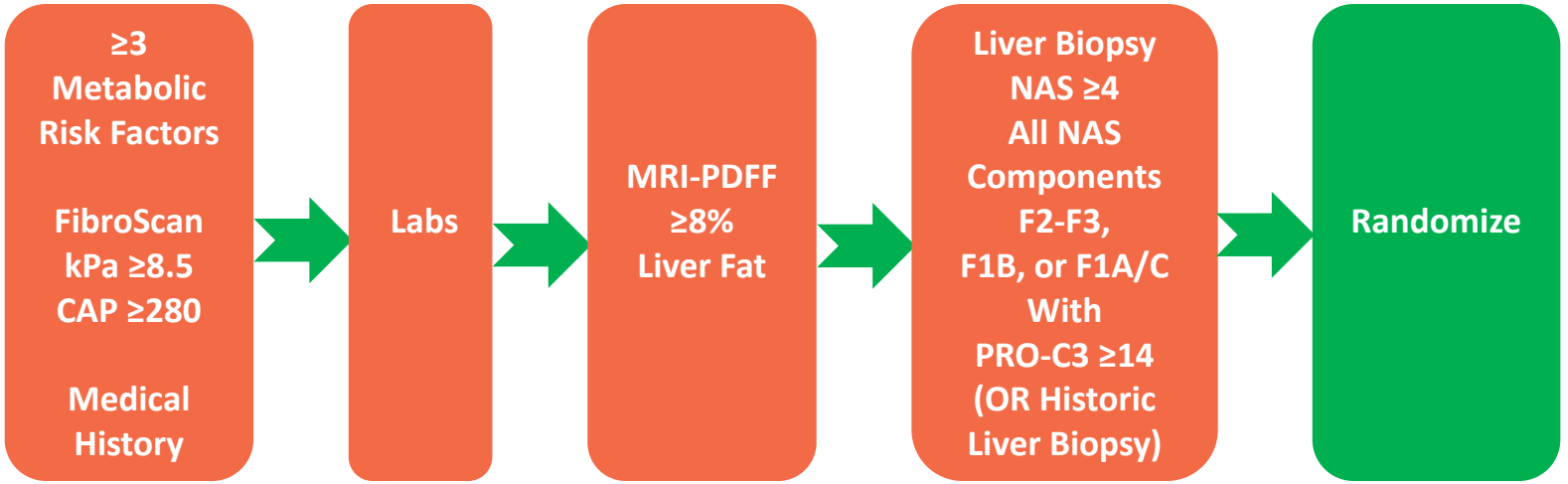
▲ MRI-PDFF
▲ Liver Biopsy
▲ LDL-C



Risk Factors of Significant Fibrosis?

- Age >50 years
- BMI >30 kg/m^2
- Elevated liver enzymes (AST >20 U/L, AST/ALT ≥1)
- T2D
- Hypertension
- Dyslipidemia
- Metabolic Syndrome components (obesity, insulin resistance)
- Historical FibroScan >8.5 kPa, CAP >280 dB/M (Ideally 300)

MAESTRO-NASH 8-Week Screening Process



Screening paradigm led to ~80% of screening biopsies showing at-risk NASH (F2-F4 NAS ≥3) of which 65-70% met all eligibility criteria

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PRO-C3, N-terminal type III collagen propeptide; T2D, type 2 diabetes.

ClinicalTrials.gov (NCT03900429): https://clinicaltrials.gov/ct2/show/NCT03900429

Demographic & Baseline Characteristics in MAESTRO-NASH

	Randomized Patients	Percent F3 54%	Percent F2 31%	Percent F1B 11%	Percent F1A/C 5%
Age, mean (SD), years	56.8 (11.0)	58.4	54.8	56.0	54.1
Sex, male, %	44%	44%	43%	44%	45%
Sex, female, %	56%	56%	57%	56%	55%
Ethnicity, Hispanic/Latino, %	20%	18%	21%	18%	29%
Body weight, mean (SD), kg	100.3 (22.7)	99.0	102.9	99.0	102.0
BMI, mean (SD), kg/m^2	35.6 (6.8)	35.2	36.3	35.0	36.3
Hypertension, %	74%	77%	70%	68%	69%
Hypothyroid, %	14%	14%	14%	11%	15%
T2D, %	60%	66%	55%	53%	40%
Years since T2D diagnosis, mean (SD)	9.7 (7.5)	9.7	9.2	11.2	9.7
ASCVD score, mean (SD)	14.8% (12.4%)	15.6%	13.9%	14.8%	8.6%
FibroScan TE, mean (SD), kPa	13.2 (6.4)	14.5	11.9	11.1	10.0
FibroScan CAP, mean (SD)	347 (37.8)	346	347	352	326
MRI-PDFF, mean (SD), %FF	17.9% (6.9%)	16.7%	19.2%	18.7%	18.7%
MRE, mean (SD), kPa	3.48 (1.0)	3.91	3.14	2.90	2.01
PRO-C3, mean (SD), ng/ml	19.2 (8.5)	20.4	18.3	15.9	19.2
ELF, mean (SD)	9.7 (0.9)	10.0	9.5	9.3	9.5
HbA1c, mean (SD), %	8.6 (1.1)	6.6	6.5	6.3	6.4
HOMA-IR, mean (SD)	11.2 (11.8)	12.0	10.2	9.5	11.5
Liver biopsy length, mean (SD), mm	24.2 (11.5)	24.6	24.0	23.4	21.9
NAS, mean (SD)	5.51 (1.1)	5.64	5.54	5.03	4.87
Statin use, %	44.5%	50%	38%	43%	36%

- Demographics include:
  - Mean age 56.8 years
  - Female 56%,
  - BMI 35.6 kg/m^2
  - Hypertension 74%
  - Hypothyroid 14%
  - T2D 60%
  - Mean ASCVD score 14.8%
- FibroScan (kPa 13.2), MRI-PDFF (17.9%), MRE (kPa 3.48) represent this NASH population

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; HOMA-IR, homeostatic model assessment for insulin resistance; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PRO-C3, N-terminal type III collagen propeptide; T2D, type 2 diabetes.

Baseline Laboratory Parameters in MAESTRO-NASH

Mean (SD)	Randomized Patients	Percent F3 54%	Percent F2 31%	Percent F1B 11%	Percent F1A/C 5%
MELD	7.4 (1.7)	7.5	7.3	7.1	6.8
NAFLD fibrosis score	-0.63 (1.7)	-0.40	-0.92	-0.90	-0.67
FIB-4	1.41 (0.70)	1.57	1.23	1.20	1.26
TC, mg/dL	179.6 (47.2)	174.0	184.5	182.0	201.8
TG, mg/dL	187.9 (129.1)	181.3	194.6	182.9	226.8
Lp(a), nmol/L	43.6 (60.9)	42.1	44.3	47.3	47.4
ApoB, mg/dL	97.9 (29.6)	94.8	100.5	97.6	115.3
LDL-C, mg/dL	106.3 (39.1)	101.8	110.5	107.2	124.0
HDL-C, mg/dL	43.8 (12.9)	44.1	43.5	45.2	39.5
ALT, IU/L	54.6 (33.85)	53.9	56.2	45.4	71.2
AST, IU/L	40.1 (23.3)	41.5	39.7	32.8	43.1
GGT, IU/L	80.0 (93.9)	87.7	73.3	60.8	79.3
CK (IU/L)	138.0 (165.3)	129.0	154.0	121.4	169.6
ALP, IU/L	84.1 (27.7)	85.1	82.8	81.7	86.1
Total bilirubin, mg/dL	0.64 (0.29)	0.66	0.64	0.59	0.63
Direct bilirubin, mg/dL	0.13 (0.06)	0.14	0.12	0.12	0.12
Platelet count	233 (62)	224	248	238	226
Albumin, g/dL	4.4 (0.3)	4.4	4.4	4.4	4.4
INR	1.1 (0.2)	1.1	1.1	1.1	1.0
CDT, %	1.69 (0.46)	1.67	1.68	1.76	1.83

- Laboratory parameters demonstrate statistically significant differences between low-risk F0 & high-risk F2/F3 patients:
  - ALT ($p<0.0001$)
  - AST ($p<0.0001$)
  - GGT ($p<0.0001$)
  - PRO-C3 ($p<0.0001$)
  - HbA1c ($p=0.0001$)
  - MRE ($p<0.0001$)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; apoB, apolipoproteinB; AST, aspartate aminotransferase; CDT, carbohydrate-deficient transferrin; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MELD, model for end-stage liver disease; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; PRO-C3, N-terminal type III collagen propeptide; TC, total cholesterol; TG, triglycerides.

Liver Enzymes in MAESTRO-NASH Patients Who Met Biopsy Criteria

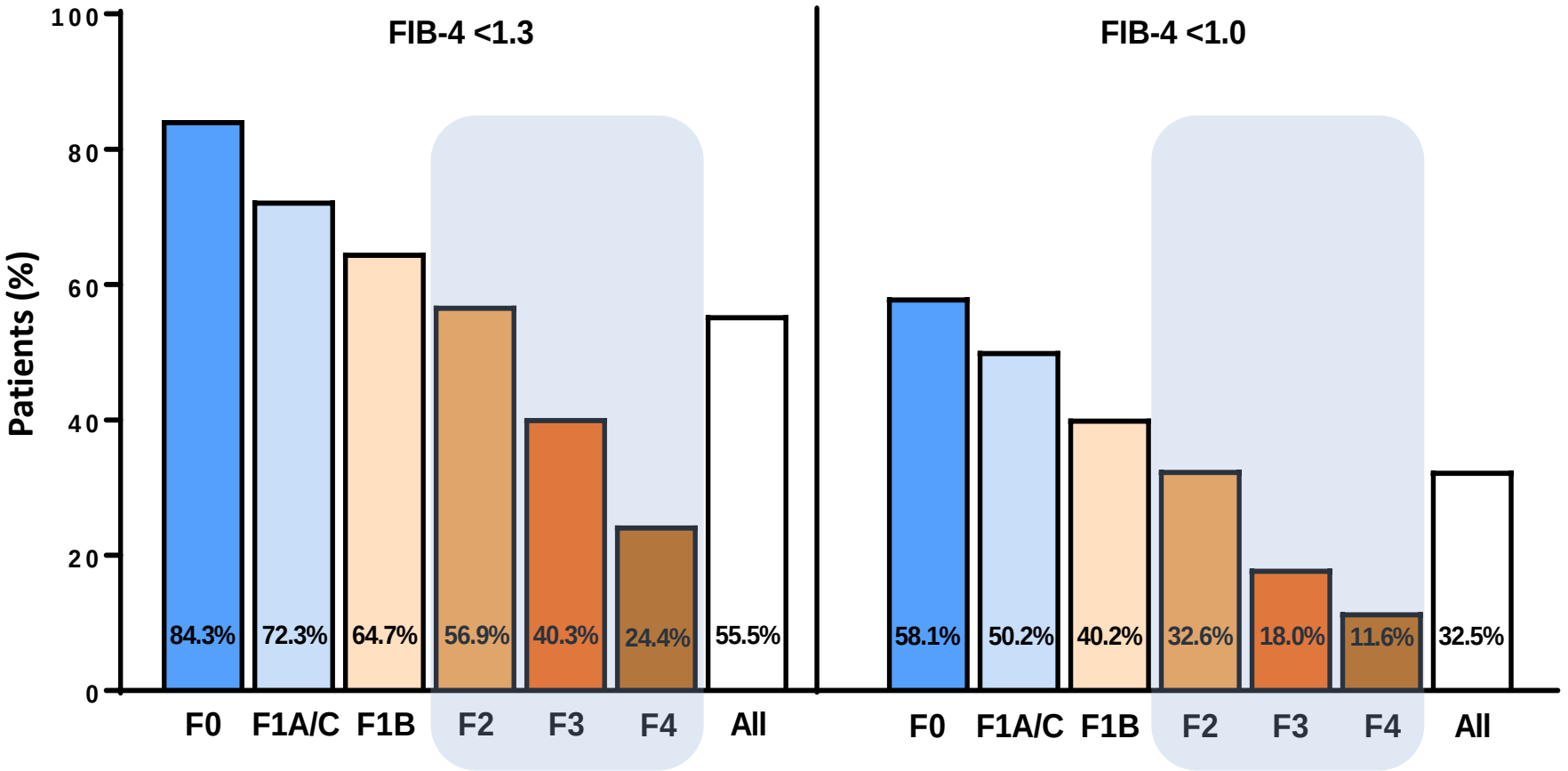
Patients With Eligible Biopsies for MAESTRO-NASH

ALT <ULN	ALT ≥ULN	AST <ULN	AST ≥ULN	ALT <2X ULN	ALT ≥2X ULN	AST <2X ULN	AST ≥2X ULN
35.7%	64.3%	45.8%	54.2%	80.5%	19.5%	87.8%	12.2%

- Based on >1000 biopsies in screened patients with paired MRE, MRI-PDFF, & FAST (of which >700 biopsies met criteria for eligibility)
- Unlike many NAFLD patients who are referred for GI/Hepatology consultation based on liver enzyme elevations, patients screened for MAESTRO-NASH did not have required thresholds for screening values on liver enzyme tests or elevated FIB-4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ULN, upper limit of normal.

Poor Performance of FIB-4 to Identify At-Risk Patients in MAESTRO-NASH



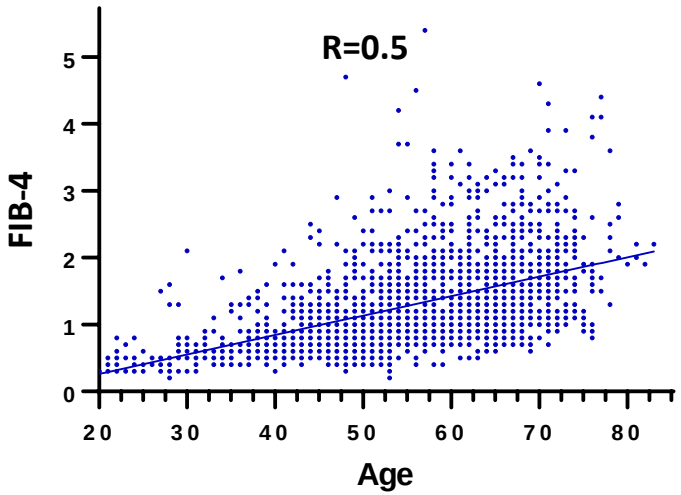
- 56.9% F2, 40.3% F3, & 24.4% F4 biopsy-confirmed patients had FIB-4 <1.3
- 46.4% of patients with active NASH (NAS ≥4) F2/F3 fibrosis had FIB-4 <1.3
- 32.6% F2 & 18.0% F3 patients had FIB-4 <1.0
- In patients with active NASH (NAS ≥4), 41.7% F2 & 17.3% F3 patients had FIB-4 <1.0
- More low-risk NAFLD patients (F0, F1A/C) had FIB-4 <1.3 than FIB-4 <1.0 (F0: 84.3% vs 58.1%, respectively)

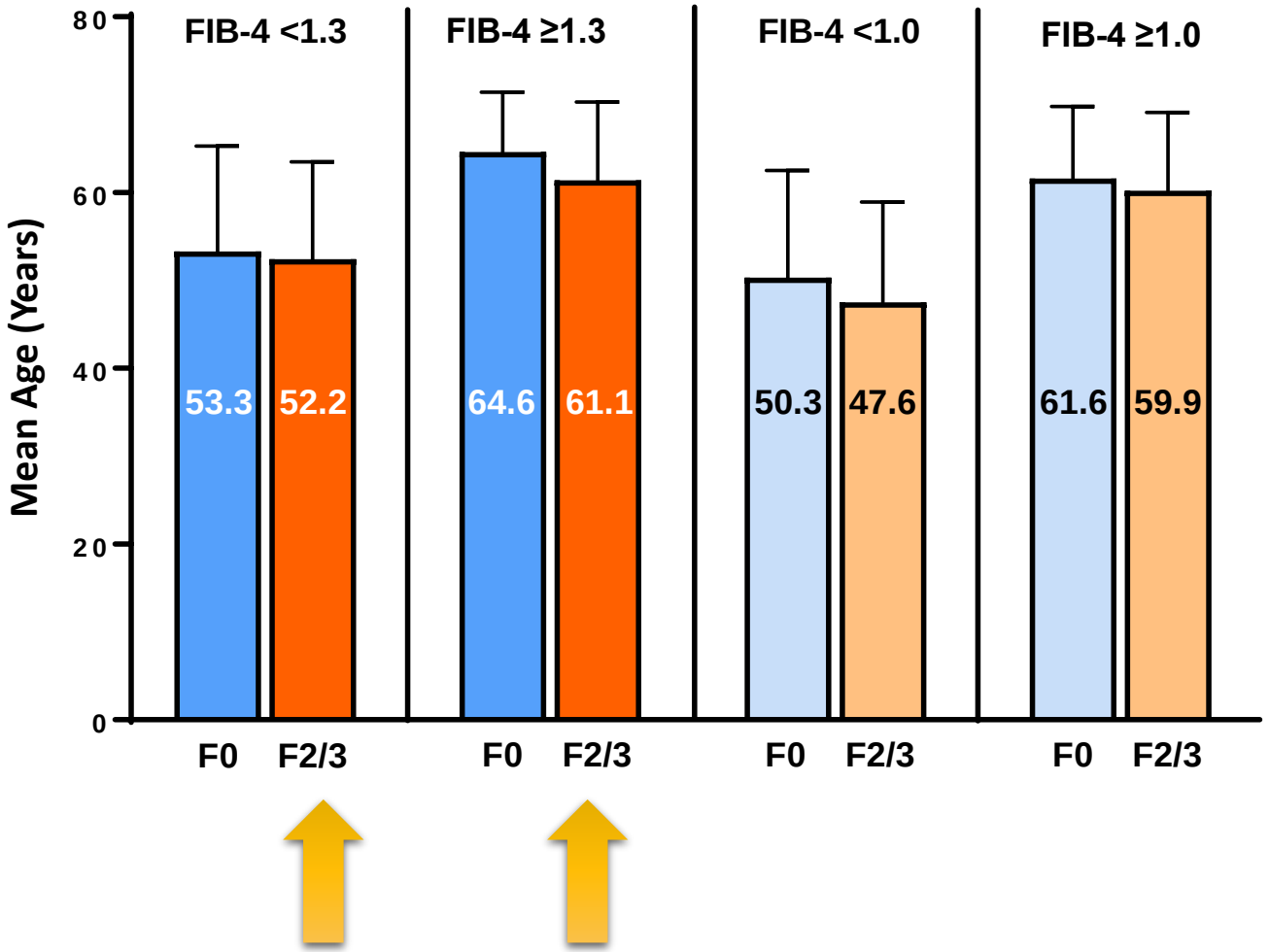
FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.

Influence of Age on FIB-4

- NAS ≥4 F2/F3 patients with FIB-4 ≥1.3 had mean age 61.1 years while NAS ≥4 F2/F3 patients with FIB-4 <1.3 had mean age 52.2 years (p<0.001)
- NAS ≥4 F2/F3 patients with FIB-4 ≥1.0 had mean age 59.9 years while NAS ≥4 F2/F3 patients with FIB-4 <1.0 had mean age 47.6 years (p<0.001)
- Younger age of 10 years in patients with at-risk NASH removed ~0.2 from the FIB-4 suggesting a lower threshold (decreasing many to <1.3)

Correlation of Age With FIB-4



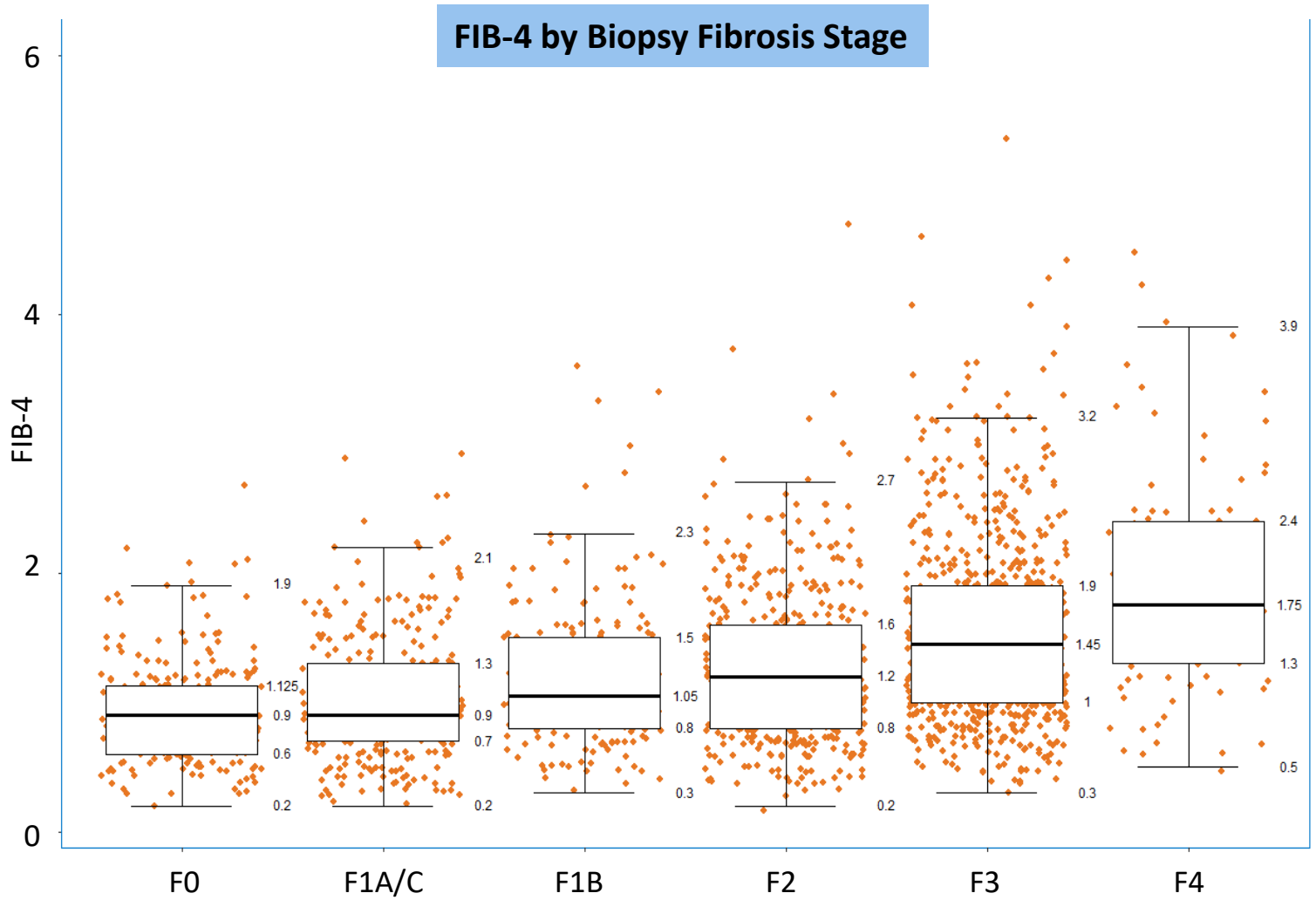


FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.

Comparison of Diagnostic Accuracy of Noninvasive Imaging in NASH

Noninvasive Imaging	Patient Groups	AUROC for ≥F2 Fibrosis
FIB-4	F0-F4	0.68
FibroScan TE	F0-F4	0.66
FAST	F0-F4	0.72
MAST	F0-F4	0.79
MRE	F0-F4	0.79

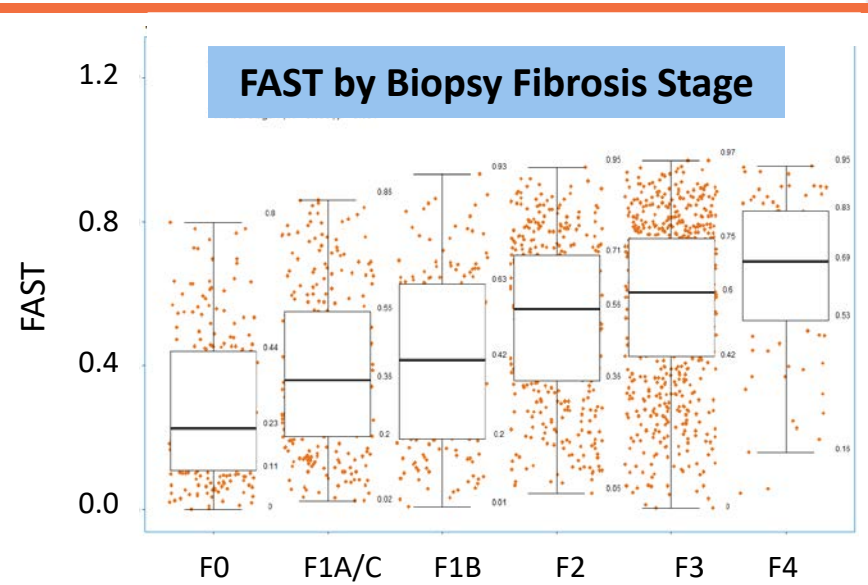
- FIB-4 AUROC was 0.68
- AUROC of MRE, MAST, FAST for fibrosis stage & NASH were >0.7

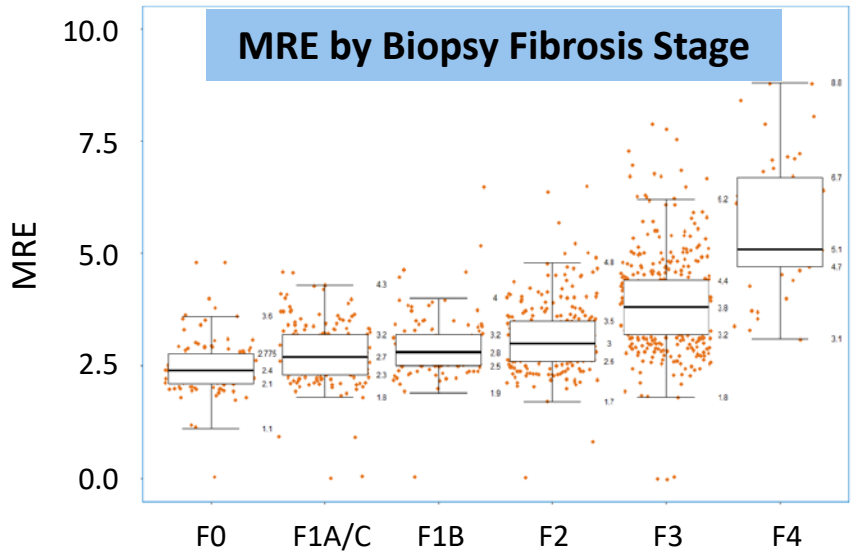


AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; MAST, magnetic resonance imaging-aspartate aminotransferase; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis.

Assessment of Imaging Modalities For Detecting ≥F2 Fibrosis in Liver Biopsy

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
Fibrosis (F1B-F3) plus NAS ≥4				
	AUROC	Sensitivity	Specificity	Optimal Value
FAST	0.74	70%	64%	0.44
MRE	0.75	72%	64%	2.9 kPa
MAST	0.77	72%	69%	0.10





AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4;
MAST, magnetic resonance imaging-aspartate aminotransferase; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score.

Conclusions

- Based on a large Phase 3 data set of biopsy-confirmed patients with NASH, FIB-4 ≥1.3 lacks the sensitivity to accurately identify patients with at-risk (F2/F3) fibrosis
- The influence of age on FIB-4 may require an adjustment to ensure younger patients are not removed from consideration for therapy
- Additional tests such as FAST or MAST may improve at-risk patient enrichment
- MAST & MRE showed the best sensitivity & specificity in this cohort
- Learnings from MAESTRO-NASH provide insight on the utility of FIB-4 & other noninvasive tests & imaging modalities for identification of at-risk NASH

FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; MAST, magnetic resonance imaging-aspartate aminotransferase; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis.