NON-INVASIVE TESTING TO RULE-IN MODERATE TO SEVERE FIBROSIS WHILE RULING OUT CIRRHOSIS FOR THERAPEUTIC INTERVENTION IN METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS

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Introduction

- Metabolic dysfunction-associated steatohepatitis (MASH) affects up to 25 million adults in the United States and can cause liver cirrhosis and liver cancer.[1]
- Recently, therapeutic agents have been approved for the treatment of MASH in patients with fibrosis stages F2/F3.[2]
- Liver biopsy remains the "gold standard" for diagnosing and staging of hepatic fibrosis in patients with MASH.[3]
- A non-invasive, blood-based diagnostic test is required to enable population-level screening and accurately identify patients with MASH at therapy-eligible fibrosis stages.
- A serum-based, multi-analyte test (FIBRO*Spect*® MASH, Prometheus Laboratories) has been developed to distinguish patients with moderate to advanced fibrosis (Brunt stages F2/F3) from those with mild fibrosis (F0/F1) or cirrhosis (F4). The test quantifies three biomarkers, alpha2-macroglobulin (A2M), hyaluronic acid (HA) and tissue inhibitor of metalloproteinase-1 (TIMP-1), which are further integrated into an algorithm to generate a score ranging from 0 to 100.

Aim

To validate the non-invasive FIBRO*Spect* test's ability to stage MASH patients and establish clinically actionable index intervals using sensitivity, specificity, and interval likelihood ratios that guide rule-in and rule-out decisions across fibrosis stages.

Methods

- This study utilized 1,036 biopsy-proven MASH serum samples archived from patients treated at two geographically distinct tertiary care centers.
- Cohort 1 (N=792, Duke University) samples were collected on the day of liver biopsy.
- Cohort 2 (N=244, University of California, San Diego) were collected within a median of 11 days from biopsy.
- Cohort 1 was randomly and evenly assigned to training and validation sets. Cohort 2 provided additional validation samples.
- Following algorithm training (10,000 bootstrap iterations and 10-fold cross-validation), a logistic regression model was derived and validated.

Conclusions

- The FIBRO*Spect* MASH algorithm has been validated in an independent cohort of well characterized, biopsy-proven MASH patients. The algorithm exhibited robust performance in both the training and validation studies to differentiate F2/F3s from F0/F1s and F4s.
- Interval likelihood ratios (LRs) provide more granular diagnostic information than simply dichotomizing a continuous test at a cutoff, better reflecting how clinicians intuitively interpret test results across ranges.
- Overall, interval-based interpretation of the index improves non-invasive fibrosis staging and may guide treatment selection and monitoring in patients with MASH.

Figure 1: Interval Likelihood Ratios by FIBRO*Spect*® MASH and Intervals

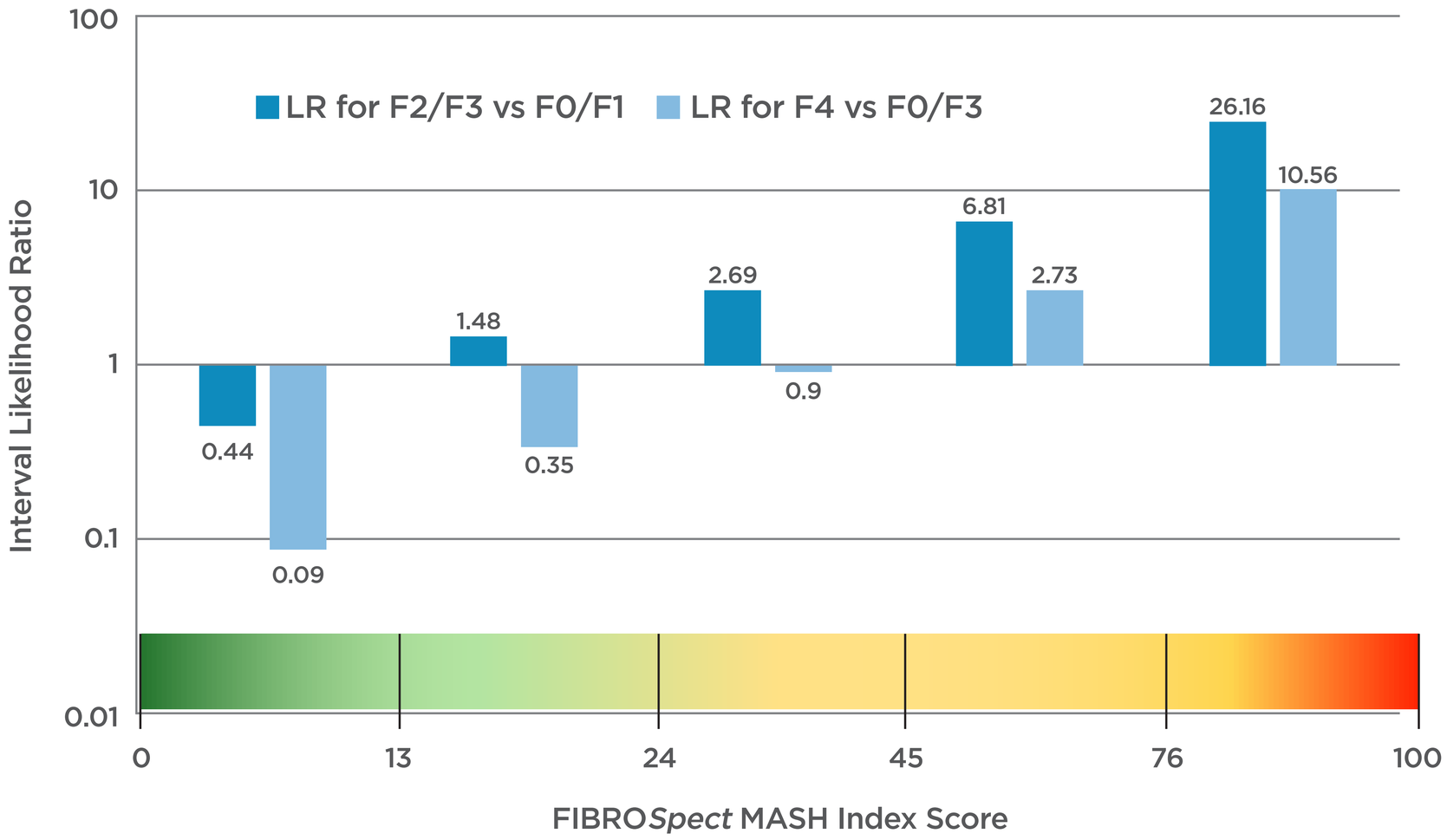

Table 1: Decision Framework and Fibrosis Staging and Treatment using FIBRO*Spect* MASH

Index Interval	LR (F2/F3 vs F0/F1)	LR (F4 vs F0/F3)	Sensitivity/ Specificity	Interpretation	Clinical Action
0–13	0.44	0.09	**F2/F3 vs F0/F1:** Sensitivity: 66% Specificity: 77%	Strong rule-out for F2/F3 and F4	Surveillance
13–24	1.48	0.35		Marginal rule-in for F2/F3; rule-out F4	Consider approved treatments
24–45	2.69	0.90	**F2/F3 vs F0/F1:** Sensitivity: 47% Specificity: 90%	Intermediate rule-in for F2/F3; F4 unlikely	Consider approved treatments
45–76	6.81	2.73	**F4 vs F0/F3:** Sensitivity: 78% Specificity: 88%	Moderate rule-in for F2/F3; F4 still unlikely	Consider approved treatments
76–100	26.16	10.56	**F4 vs F0/F3:** Sensitivity: 61% Specificity: 94%	Strong rule-in for F2/F3; F4 likely	Evaluate for cirrhosis

Results

- Fibrosis stages 0, 1, 2, 3, and 4 were represented in the validation cohort by 209 (33%), 168 (26%), 130 (20%), 115 (18%), and 18 (3%) patients, respectively. The resulting F2/F3 prevalence of 38% is comparable to, and marginally above, that described in published studies of biopsy-confirmed MASH.[4]
- An index >13 yields 66% sensitivity and 77% specificity in detecting F2/F3 while an index >76 yields 61% sensitivity and 94% specificity in detecting F4.
- Interval likelihood ratios (LRs) show that rising index scores strongly increase the probability of F2/F3 while keeping F4 unlikely across the mid-range: F2/F3 LRs progress from strong rule-out (<13; LR = 0.4) to moderate (24–45; LR = 2.7) and strong rule-in evidence (>76; LR = 26.2), whereas F4 LRs remain low through 24–45 (LR = 0.9) and rise only above 45, defining a treatment-eligible window (13–76) where F2/F3 is favored and cirrhosis risk remains minimal.
- The FIBRO*Spect* MASH test demonstrates discrimination for ruling in F2/F3 (AUC 0.794 vs 0.747 for FIB-4 [p=0.034] and 0.641 for NAFLD fibrosis score [p<0.01]) and ruling out F4 (AUC 0.904 vs 0.844 for FIB-4 [p<0.01], and 0.744 for NAFLD fibrosis score [p<0.01]).

References

[1]Le P et al. Estimated Burden of Metabolic Dysfunction-Associated Steatotic Liver Disease in US Adults, 2020 to 2050. *JAMA Netw Open*. 2025 Jan;8(1):e2454707.
[2]Newsome PN & Loomba R. Therapeutic horizons in metabolic dysfunction-associated steatohepatitis. *J Clin Invest*. 2025 Jul;135(13):e186425.
[3]Noureddin M & Loomba R. Nonalcoholic fatty liver disease: Indications for liver biopsy and noninvasive biomarkers. *Clin Liver Dis*. 2012 Sept;1(4):104-107.
[4]Mózes FE et al. Diagnostic accuracy of non-invasive tests to screen for at-risk MASH-An individual participant data meta-analysis. *Liver Int*. 2024 Aug;44(8):1872-1885.

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