Fibrometer-VCTE-Light provides highest discrimination over other Fibrometer-derived biomarkers and outperforms FIB-4 for stratification of fibrosis across a spectrum of fibrosis stages.

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Performance of fibrometer-derived biomarker panels for assessment of fibrosis stage in NAFLD: NIMBLE stage 1 and the NASH CRN collaborative Study

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NIMBLE
Non-Invasive BioMarkers of MetaBolic Liver DiseasE

NASH CRN

1 Introduction

- The intent of the current collaborative study between Non-invasive Biomarkers of Metabolic Liver Disease (NIMBLE) and the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) was to further evaluate the performance of Fibrometer-based biomarker panels, including those developed for non-alcoholic fatty liver disease (NAFLD) or other liver diseases, with and without vibration-controlled transient elastography (VCTE) for identification of fibrosis strata in those with NAFLD.

2 Aim

- To evaluate the diagnostic-test performance characteristics of four Fibrometer-based biomarker panels for assessing fibrosis in a well-characterized cohort of patients with biopsy-confirmed NAFLD with description of sensitivity and specificity at Youden's cutoff for their intended diagnostic use in a large, multi-center US cohort of patients with NAFLD/NASH.

3 Methods

- The performance of Fibrometer Virus (FM-VIRUS), Cirrhometer Virus (CM-VIRUS), Fibrometer NAFLD (FM-NAFLD) and Fibrometer VCTE-Light (FM-VCTE-Light) was evaluated for the assessment of fibrosis.
- Blood-based parameters were tested from aliquots of the same blood sample from each patient obtained within 90 days of a liver biopsy demonstrating NAFLD of varying activity and stages (Stages 0-4). VCTE measurements were performed in a subgroup of trial participants within this time window.
- In order to minimize spectrum bias, the cohort was selected a priori to have a similar distribution of fibrosis stages across its entire range.
- The primary hypothesis was that the AUROC for each panel for its intended use was numerically > 0.7 and significantly superior to 0.5. The secondary hypothesis was that the AUROC for each panel for fibrosis was significantly greater than that for FIB-4 (as the common reference).

Parameters	FIB-4	FM-VIRUS	CM-VIRUS	FM-NAFLD	FM-VCTE-Light
	Age, ALT, AST, PLT	Age, sex, A2M, AST, BUN, GGT, INR, PLT	Age, sex, A2M, AST, BUN, GGT, INR, PLT	Age, weight, AST, ALT, FER, GLU, PLT	Age, sex, A2M, AST, GGT, LSM, PLT

A2M: alpha-2-macroglobulin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; FER: ferritin; GGT: gamma-glutamyl transferase; GLU: fasting glucose; INR: international normalized ratio; LSM: liver stiffness by VCTE; PLT: platelet count.

4 Results

- 1073 patients with biopsy-proven NAFLD including NAFL (n = 220) and NASH (n = 853) were evaluated.
- The number of patients with fibrosis stages 0, 1, 2, 3 and 4 were 222, 114, 262, 277 and 198, respectively.
- The dataset for Fibrometer VCTE-Light was smaller as VCTE data were available in only 393 patients.
- The AUROCs, Youden's cutoff with its sensitivity/specificity are provided below: All 4 panels met criteria for intended use for diagnosis of fibrosis stage ≥2, advanced fibrosis, and cirrhosis.
- Compared to FIB-4, FM-VIRUS and FM-NAFLD met criteria for diagnosis of advanced fibrosis but not for fibrosis stage ≥2 or cirrhosis, while CM-VIRUS was not superior to FIB-4 for any of the intended uses.
- In contrast, FM-VCTE-Light was significantly superior to FIB-4 for all three intended uses.

Table: Diagnostic test characteristics of various Fibrometer-derived panels for detection of fibrosis in NAFLD

Diagnostic test characteristics	FIB-4	FM-VIRUS	CM-VIRUS	FM-NAFLD	FM-VCTE-Light
	AUROC (Youden cut-off value) [Sensitivity, Specificity]				
F stage ≥ 2	0.80 (1.4) [65.4, 80.8]	0.80 (0.4) [69.2, 77.4]	0.72 (0.0) [65.2, 69.9]	0.81 (0.4) [67.7, 80.0]	0.84** (0.4) [71.6, 81.1]
F stage ≥ 3	0.79 (1.4) [75.1, 68.6]	0.81* (0.4) [76.4, 69.9]	0.76 (0.0) [76.2, 63.0]	0.80* (0.4) [77.9, 67.0]	0.85 (0.4) [89.9, 65.3]
F stage 4	0.81 (1.5) [85, 63.4]	0.83 (0.6) [75.0, 73.2]	0.82 (0.1) [65.6, 81.5]	0.80 (0.5) [76.7, 68.0]	0.90* (0.7) [94.2, 74.7]

*p<0.05 for comparison with FIB-4 for their intended use
**p<0.001 for comparison with FIB-4 for their intended use
All AUROCs are statistically significant and superior to AUROC=0.5 (p<0.001)

5 Conclusions

- FM-VCTE-Light consistently outperformed FIB-4 for stratification of fibrosis across a spectrum of fibrosis stages. FM-VIRUS and FM-NAFLD appear to be better than FIB-4 for detecting advanced fibrosis but not for other fibrosis stages.
- These data will be helpful in informing trial design for future studies using these Fibrometer-based non-invasive tools across various intended use populations.

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