Non-invasive tests as a prediction tool to assess MASH resolution score

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Introduction

- Liver biopsy is the reference standard for diagnosing metabolic dysfunction-associated steatohepatitis (MASH), but there are limitations to conducting biopsies for diagnosing and monitoring disease
- Non-invasive tests (NITs) were developed to assess liver fibrosis and steatosis; however, test sequences of commonly used biomarker and imaging NIT's have not been studied extensively related to MASH resolution apart from fibrosis
- There are limited data correlating NIT scores to non-alcoholic fatty liver disease (NAFLD) activity score (NAS) and fibrosis scores from biopsies
- Previous studies have shown MRI-PDFF and serum ALT can predict NAS derived MASH resolution however, MRI-PDFF is not widely used in clinical practice in the US. Biomarkers and imaging NITs have also predicted MASH resolution
- Understanding the correlation between NIT scores and NAS from biopsies may help improve the role and utilization of NITs (i.e. vibration-controlled transient elastography (VCTE), AST to Platelet Ratio Index (APRI), NAFLD fibrosis scores (NFS), or Fibrosis-4 (FIB-4)) to diagnose and monitor patients with MASH and rule out low-risk MASH (sequencing NITs could be used rather than using NITs independently)

Objective

- The purpose of the study was to assess use of NITs compared to NAS score obtained from biopsy to evaluate the presence of MASH in the context of routine clinical practice

Methods

- Adults ($\geq$18 years old) diagnosed with MASH enrolled in the ongoing, longitudinal observational TARGET-NASH study, receiving care in the United States (US) with at least one available biopsy and NAS score were included
- NAS derived MASH resolution (i.e., presence of MASH) was defined as no ballooning or inflammation
- This was an independent measure analysis (as opposed to repeated measures) with the use of a single biopsy and clustered NITs around the time of the biopsy
- Fisher's exact test and Kruskal-Wallis were used to assess the univariate association between demographic and clinical measures and the presence/absence of MASH resolution
- All NITs were calculated from data available $\pm$3 months of the biopsy date and previously established cutoffs were utilized
- All logistic models controlled for age, sex, history of use of vitamin E, fibrosis stage, and body mass index
- Sequential algorithms consisting of two or three NITs were investigated following a stepwise approach
- The first NIT was applied to the full training dataset; subsequent algorithms were applied to the indeterminate data from the previous algorithm

Figure 1. Study Population

TARGET-NASH
N=6,591

↓

Adults (18$\geq$years)
N=5,745

↓

Cirrhotic or non-cirrhotic MASH with 1+ biopsies
N=1,481

↓

Biopsy with ballooning and inflammation
N=812

↓

VCTE (N=156)
FIB-4 (N=765)
APRI (N=765)
NSF (N=568)
FAST (N=135)

Results

- 812 biopsy confirmed MASH adults enrolled in TARGET-NASH were included in this analysis (Figure 1)
- Approximately half of the cohort had MASH resolution (54.7%) were classified as Fibrosis stage 0 or 1, while those without MASH resolution were in Fibrosis Stage 3 or 4 (50.8%) ($p<0.0001$)
- Overall, patients without MASH resolution have higher baseline median FIB-4 (1.7 vs. 1.4, $p<0.003$), APRI (0.7 vs. 0.5, $p<0.0001$) and VCTE (12.5 vs. 8.4, $p=0.0054$)
- The use of sequential NITs reduced the percentage of indeterminates, sometimes by half (i.e. FIB-4 alone indeterminates=35.6% vs. FIB-4 to NFS indeterminates=17.4%)
- Starting with FIB-4 or NFS followed by VCTE appeared to produce a larger reduction in the number of indeterminates
- The sequence of FIB-4, NFS, and then VCTE achieved a larger indeterminate reduction while maintaining moderate to high levels of accuracy (PPV=67%, NPV=83%, specificity=95%, AUC=0.73)

Conclusions

In an evaluation of NITs, FAST, VCTE, and APRI demonstrated a strong prediction for absence of MASH, particularly with the use of sequencing, and a better ability to assess MASH resolution providing a reliable alternative in the absence of a liver biopsy. These findings provide a possible alternative for the diagnosis and monitoring of MASH that may be both effective and reliable.

Table 1: Non-invasive tests for the prediction of MASH resolution

NIT Test Sequencing	PPV	NPV	Sensitivity	Specificity	LR+	LR-	AUROC	Indeterminates
FIB-4 → APRI	0.6	0.84	0.30	0.95	5.85	0.74	0.66 (0.65-0.75)	27.36%
FIB-4 → NFS	0.62	0.83	0.35	0.93	5.4	0.76	0.74 (0.64-0.74)	17.42%
FIB-4 → VCTE	0.69	0.83	0.29	0.96	8.13	0.74	0.74 (0.64-0.74)	3.94%
NFS → VCTE	0.60	0.79	0.32	0.92	4.12	0.74	0.74 (0.6-0.72)	6.61%
NFS → APRI	0.62	0.82	0.33	0.94	5.44	0.71	0.76 (0.66-0.76)	32.31%
APRI → VCTE	0.89	0.82	0.27	0.99	27.47	0.74	0.74 (0.6-0.71)	6.08%
FIB-4 → APRI → VCTE	0.69	0.83	0.30	0.97	8.39	0.74	0.74 (0.64-0.74)	30.68%
FIB-4 → NFS → APRI	0.63	0.83	0.32	0.95	5.40	0.74	0.73 (0.64-0.73)	15.91%
FIB-4 → NFS → VCTE	0.67	0.83	0.32	0.95	6.79	0.72	0.73 (0.63-0.73)	2.14%
FIB-4 → VCTE → APRI	0.69	0.83	0.29	0.96	8.2	0.74	0.74 (0.63-0.74)	2.86%
NFS → VCTE → APRI	0.56	0.79	0.32	0.91	3.58	0.75	0.72 (0.6-0.72)	4.03%
APRI → NFS → VCTE	0.67	0.81	0.26	0.96	6.63	0.77	0.69 (0.59-0.69)	2.53%

Note: All logistic models include the NIT test and the following control variables: age + sex + history of vitamin E + BMI; PPV – positive predictive value, NPV – negative predictive value, LR+ - positive likelihood ratio, LR- = negative likelihood ratio, AUROC = area under the receiver operating characteristic

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