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Routinely Available Noninvasive Tests Perform Well in Identifying Patients with Advanced Fibrosis Due to NASH: Data from the TARGET-NASH Observational Cohort

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INTRODUCTION

- Histologic assessment is the current reference standard for liver fibrosis staging, but is an invasive procedure with several potentially serious complications.
- There is an unmet need for accurate, readily available, noninvasive tests (NITs) to identify patients with advanced fibrosis due to nonalcoholic steatohepatitis (NASH).
- Biopsy sampling error and observer variability limit the ability to accurately assess the performance of NITs.
- While NITs have been shown to accurately identify patients with advanced fibrosis due to NASH in clinical trials, real world-data are lacking.

OBJECTIVE

- The aim of this study is to describe the performance characteristics of NITs in identifying advanced fibrosis among intermediate/indeterminate and high-risk patients using real-world data from the TARGET-NASH observational cohort.

METHODS

- TARGET-NASH, a longitudinal observational study of participants at 59 sites (44 academic/15 community) in the United States, includes patients with NAFLD defined by biopsy and/or standard pragmatic case definitions.
- NITs, including the fibrosis-4 (FIB-4) index, the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS), and liver stiffness assessed by vibration-controlled transient elastography (VCTE), that were performed within 6 months of liver biopsies were analyzed.
- Using locally interpreted liver biopsies as the reference standard, the performance of these tests to discriminate advanced (F3-F4) fibrosis among intermediate/indeterminate and high-risk patients was evaluated. Thresholds for F3-F4 fibrosis were selected based on the literature.
- Sensitivity, specificity, and AUROC curves were calculated. NIT performance was also evaluated according to patient demographics and clinical variables.

RESULTS

- A total of 859 adult patients with at least one liver biopsy and at least one NIT available within 6 months were included for a total of 1905 biopsy-NIT comparisons (Tables 1 and 2).
- The distribution of NITs among participants with and without advanced fibrosis is presented in Figure 1.
- AUROCs to discriminate advanced fibrosis were 0.72 (95% CI 0.69, 0.75) for FIB-4, 0.66 (95% CI 0.64, 0.69) for NFS, and 0.67 (95% CI 0.61, 0.72) for Vibration-Controlled Transient Elastography (VCTE) for the lower cut-offs presented in Table 3.

RESULTS (CONTINUED)

Table 1: Patient Characteristics

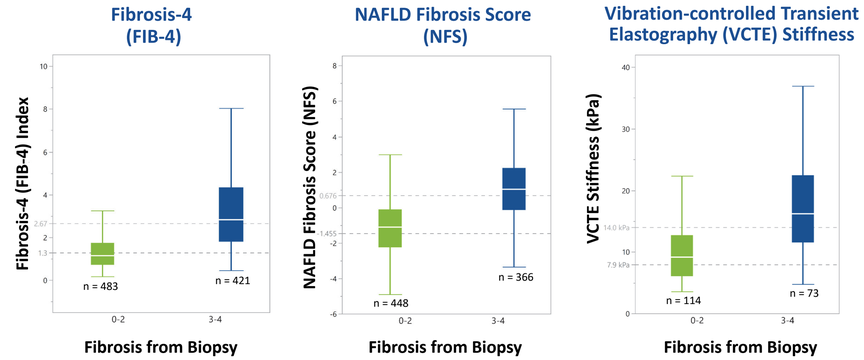
Characteristic	Patients without Advanced Fibrosis (F0-2) on Any Biopsy (N = 453)	Patients with Advanced Fibrosis (F3-4) on ≥ 1 Biopsy (N = 406)
Age at Study Entry (years)		
Median (n)	54.0 (453)	60.0 (406)
Q1 - Q3 (IQR)	44.0 - 62.0 (18.0)	53.0 - 66.0 (13.0)
Gender, n (%)		
Female	270 (59.6)	265 (65.3)
Race, n (%)		
Caucasian	357 (82.1)	367 (92.7)
Ethnicity, n (%)	**N = 442**	**N = 397**
Hispanic or Latino	62 (14.0)	53 (13.4)
Not Hispanic or Latino	377 (85.3)	343 (86.4)
Other	3 (0.7)	1 (0.3)
Not Available	11	9
BMI at Enrollment (kg/m²)		
Median (n)	33.0 (446)	33.0 (400)
Q1 - Q3 (IQR)	28.0 - 38.0 (10.0)	29.0 - 39.0 (10.0)
Diabetes, n (%)	216 (47.7)	296 (72.9)

Table 2: Clinical Characteristics

Characteristic	Biopsies without advanced fibrosis (F0-2) (N = 547)	Biopsies with advanced fibrosis (F3-4) (N = 453)
Laboratory Measurements[1]		
ALT (IU/L)		
Median (n)	52.0 (492)	44.0 (423)
Q1 - Q3 (IQR)	33.0 - 87.0 (54.0)	29.0 - 73.0 (44.0)
AST (IU/L)		
Median (n)	34.0 (493)	47.0 (423)
Q1 - Q3 (IQR)	25.0 - 56.0 (31.0)	32.0 - 72.0 (40.0)
Platelets (10^3/uL)		
Median (n)	236.0 (484)	152.0 (423)
Q1 - Q3 (IQR)	191.0 - 283.0 (92.0)	107.0 - 209.0 (102.0)
Albumin (g/dL)		
Median (n)	4.30 (486)	4.00 (409)
Q1 - Q3 (IQR)	4.00 - 4.50 (0.50)	3.50 - 4.30 (0.80)
Markers of Fibrosis		
FIB-4		
Median (n)	1.14 (483)	2.84 (421)
Q1 - Q3 (IQR)	0.73 - 1.75 (1.02)	1.82 - 4.30 (2.48)
Stiffness (kPa)		
Median (n)	9.2 (114)	16.2 (73)
Q1 - Q3 (IQR)	6.1 - 12.7 (6.6)	11.7 - 22.0 (10.3)
NFS		
Median (n)	-1.10 (448)	1.04 (366)
Q1 - Q3 (IQR)	-2.23 - -0.13 (2.10)	-0.16 - 2.23 (2.39)

IQR = interquartile range
[1]Laboratory measurements within 6 months of biopsy

Figure 1. Distribution of NITs With and Without Advanced Fibrosis



NAFLD = nonalcoholic fatty liver disease; VCTE = vibration-controlled transient elastography
Box plots show median, 1st and 3rd quartiles (white line, lower and upper edges of box, respectively). Whisker length is 1.5 times the interquartile range (distance from 1st and 3rd quartiles).
The dotted line indicates the cut-off used for each test and the green and blue colored boxes indicate fibrosis stage 0-2 and 3-4, respectively.

Table 3: Performance of NITs to Predict Advanced Fibrosis

Test	AUROC (std. error)	95% Confidence Interval	Cut-off	% Sensitivity	% Specificity	PPV (%)	NPV (%)
FIB-4	0.72 (0.01)	0.69, 0.75	1.3	86	58	64	83
	0.73 (0.01)	0.70, 0.75	2.67	53	92	85	69
NFS	0.66 (0.01)	0.64, 0.69	-1.455	92	41	56	86
	0.73 (0.01)	0.70, 0.76	0.676	57	89	81	72
Transient Elastography	0.67 (0.03)	0.61, 0.72	7.9	92	42	50	89
	0.72 (0.03)	0.65, 0.79	14	63	81	68	77

AUROC: area under the receiver-operating characteristic curve; NPV: negative predictive value; PPV: positive predictive value
Model assumed exchangeable within-patient correlation.

CONCLUSIONS

- Real-world data from TARGET-NASH are similar to studies performed in well-controlled clinical trial populations and support the use of currently available NITs.
- NIT performance was similar across gender, race, BMI, and ethnicity subgroups (data not shown).
- FIB-4, NFS, and transient elastography can be used in daily practice to accurately identify patients at risk of having advanced fibrosis due to NASH.
- There is a need for tests with better specificity without losing sensitivity.

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