Validation of the ADAPT Score for the Diagnosis of Clinically Significant Fibrosis in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)

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BACKGROUND

- Nonalcoholic fatty liver disease (NAFLD) is a widely prevalent condition but only a subset of patients with nonalcoholic steatohepatitis (NASH) and fibrosis stages 2 or higher are at greater risk of liver related outcomes and referred to as "at risk" NASH
- Many non-invasive tools (NIT) are in development to diagnose NASH with fibrosis and its sub-phenotypes
- There are however scientific gaps in the current literature on NITs that prevent their regulatory evaluation as diagnostic tests
- NIMBLE is a public-private initiative under the auspices of the Foundation-NIH (FNIH) whose goal is to fill these gaps
- We have previously reported on the utility of Pro-C3, a collagen fragment analyte linked to fibrogenesis and measured using an ELISA method for the detection of clinically significant fibrosis (*AASLD 2021 LB01*)
- This is a report on a post-hoc analysis of the ADAPT score, an algorithmic derivative of Pro-C3 from the same dataset for its performance for the context of use of detection of clinically significant fibrosis

AIM AND DESIGN

Collaboration between Circulating Biomarker Workstream of NIMBLE and NIDDK NASH Clinical Research Network.

AIM: To perform an assessment against histology of the performance of the ADAPT score, based on the analyte Pro-C3 and additional clinical parameters, selected for the intended use to detect hepatic fibrosis, by rigorously establishing the sensitivity/specificity at the Youden's cutoff in a cross-sectional analysis of a large multi-center US cohort of patients with NAFLD/NASH

DESIGN:

- All tests were run on different aliquots of the same blood sample obtained within 90 days of a liver biopsy.
- All biopsies read by the NASH CRN pathology committee using a pre-specified protocol and masked to any clinical data

Primary hypothesis: The ADAPT score will have a diagnostic accuracy defined by an AUROC of 0.7 or higher and be significantly superior to an AUROC of 0.5 for the detection of clinically significant fibrosis

Secondary hypothesis: The ADAPT score will be superior to FIB-4 for the detection of clinically significant fibrosis

MATERIAL & METHODS

Stage 1: Retrospective analysis of samples collected from patients with NAFLD

Inclusion criteria for sample collection:
- Age 18 years
- Histological evidence of NAFLD with data on presence of NASH (borderline or definite), NAS, fibrosis stage in a biopsy considered an evaluable biopsy section by NIDDK NASH CRN pathology committee
- Serum samples available within 90 days of the liver biopsy

Exclusion criteria for sample collection:
- No consent
- Pregnancy
- Other comorbid liver disease
- Drugs known to cause NAFLD
- Not enough serum available
- Bariatric surgery within past 3y
- Known biliary tract disease
- Hx of malignancy of liver
- Prior liver transplant

ADAPT score is an algorithmic derivative of the Pro-C3 analyte a collagen fragment linked to fibrogenesis

Biomarker and Specific Intended Use

	Clinically significant fibrosis (stage ≥ 2)	Advanced fibrosis (stage 3-4)	Cirrhosis
Pro-C3 (ELISA)	+	+	+
Pro-C3 (COBAS)	+	+	+
ADAPT	+	+	+

Pro-C3 (ELISA) (Nordic Biosciences): collagen fragments – *score µg/ml**
Pro-C3 (COBAS) (Nordic Biosciences): collagen fragments – *score µg/ml*
ADAPT (Nordic Biosciences): exp ($\log_{10}$ ((Age x Pro-C3)/(Vplatelets)) + Diabetes

RESULTS

TABLE 1

CLINICAL-LABORATORY-HISTOLOGICAL SPECTRUM OF THE POPULATION

		Stage 0 N= 222	Stage 1 N=114	Stage 2 N= 262	Stage 3 N= 277	Stage 4 N=198
Age (yrs)	Mean (SD)	47.8 (12.2)	48.1 (13.8)	51.7 (11.5)	54.4 (11.2)	56.2 (9.8)
Males	n (%)	99 (44.6%)	52 (45.6%)	102 (38.9%)	91 (32.9%)	60 (30.3%)
Caucasian	n (%)	158 (71.2%)	68 (59.6%)	199 (76.2%)	217 (78.9%)	169 (86.2%)
T2DM	n (%)	45 (20.3%)	41 (36.0%)	113 (43.1%)	162 (58.5%)	129 (65.2%)
BMI (kg/m2)	Mean (SD)	32.8 (6.6)	33.3 (6.1)	34.5 (6.3)	36.1 (6.6)	36.4 (7.3)
HbA1C (%)	Mean (SD)	5.8 (1.1)	6.0 (1.2)	6.4 (1.1)	6.7 (1.2)	6.7 (1.4)
AST (IU/l) ALT (IU/l) Alk phos (IU/l)	Mean (SD) Mean (SD) Mean (SD)	27.8 (13.3) 38.5 (25.4) 86.6 (30.5)	31.9 (17.7) 45.0 (34.6) 80.6 (28.2)	50.3 (29.3) 65.5 (43.1) 87.0 (28.0)	58.3 (39.8) 68.1 (47.8) 93.0 (33.2)	51.9 (28.9) 49.1 (34.5) 114.5 (53.2)
Bilirubin (mg/dl)	Mean (SD)	0.5 (0.3)	0.6 (0.5)	0.5 (0.3)	0.5 (0.4)	0.8 (0.8)
INR	Mean (SD)	1.0 (0.1)	1.0 (0.2)	1.0 (0.1)	1.1 (0.1)	2.8 (4.3)
LDL-Cholesterol (mg/dl)	Mean (SD)	117.5 (36.5)	105.9 (36.6)	112.0 (39.2)	106.1 (38.1)	100.7 (35.3)
NASH	n (%)	27 (12.2%)	91 (79.8%)	262 (100%)	277 (100%)	178 (89.9%)
NAS	Mean (SD)	2.5 (0.6)	2.5 (0.6)	4.8 (1.5)	5.2 (1.6)	4.2 (1.6)

TABLE 2

Pro-C3 (COBAS) - UTILITY FOR DIAGNOSIS OF CLINICALLY SIGNIFICANT FIBROSIS

TABLE 3

ADAPT - UTILITY FOR DIAGNOSIS OF CLINICALLY SIGNIFICANT FIBROSIS

Context of Use: to identify those with fibrosis in patients with NAFLD
Clinically significant fibrosis (stage 2 or higher), Advanced fibrosis (stage 3 or 4), Cirrhosis (stage 4)

Parameter	≥ Stage 2	Stage 3 or 4	Stage 4
AUROC (Pro-C3) (COBAS)	0.779	0.779	0.770
AUROC (FIB-4)	0.799	0.790	0.810
Is AUROC (Pro-C3) (COBAS) > 0.7 and superior to 0.5?	<0.001	<0.001	<0.001
Is AUROC superior to FIB-4?	0.900	0.700	0.900
Performance statistics for Pro-C3 (COBAS)			
Youden index cutoff	≥ 40.7	≥ 42.2	≥ 42.9
Sensitivity (%)	56.4	63.7	72.1
Specificity (%)	89.3	81.9	71.9

Parameter	≥ Stage 2	Stage 3 or 4	Stage 4
AUROC (ADAPT)	0.849	0.832	0.824
AUROC (FIB-4)	0.799	0.790	0.810
Is AUROC (ADAPT) > 0.7 and superior to 0.5?	<0.001	<0.001	<0.001
Is AUROC superior to FIB-4?	<0.001	<0.001	0.100
Performance statistics for ADAPT Score			
Youden index cutoff	≥ 6.2	≥ 6.9	≥ 7.1
Sensitivity	76.4	74.9	85.9
Specificity	76.8	78.7	68.1

CONCLUSIONS

- ***The ADAPT score was validated to diagnose clinically significant and advanced fibrosis in those with NAFLD and was superior to FIB4.***
- **Pro-C3** measured using the COBAS platform was superior to the unit line for the detection of clinically significant fibrosis
- **Pro-C3** measured using the COBAS platform was not superior to FIB-4 for the detection of clinically significant fibrosis
- **The ADAPT score** was superior to the unit line for the detection of clinically significant fibrosis
- **The ADAPT score** was superior to FIB-4 for the detection of clinically significant fibrosis and advanced fibrosis
- **FIB-4** had robust diagnostic characteristics for fibrosis related endpoints

ACKNOWLEDGEMENTS

NASH CRN:

Clinical Site Investigators: Anna Mae Diehl (Duke), Manal Abdelmalek (Duke), Mohammad Siddiqui (VCU), Velimir Luketic (VCU), Srinivasan Dasarathy (CCF), Arthur McCullough (CCF), Naga Chalasani (IU), Norah Terrault (USC), Bilal Hameed (UCSF)

Data Coordinating Center: Laura Wilson, Pat Belt, Laura Miriel, Mark Van Natta, Annette Wagoneer

NIDDK: Jay Hoofnagle, Edward Doo, Averell Sherker

NIMBLE Team:

FNIH: Joseph Menetski, Steve Hoffman, Tania Kamphaus, Helen Heymann, Biomarkers Consortium Metabolic Disorders Steering Committee and all FNIH Biomarkers Consortium staff supporting NIMBLE

Project Team: AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Echosens, GE Healthcare, Genentech, Inc., Gilead Sciences, Inc., Intercept Pharmaceuticals, Inc., Novo Nordisk A/S, Pfizer Inc, Takeda Development Center Americas Inc.

Key Lab collaborators: Genfit SA, Siemens Healthineers, One-Way Lipidomics, Nordic Biosciences, Echosens

U.S. FDA: Regulatory guidance and feedback through Biomarker Qualification Program

National Institute of Diabetes and Digestive and Kidney Diseases

BIOMARKERS CONSORTIUM IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH Foundation for the National Institutes of Health

NASH CRN

DOI: 10.3252/pso.au.ILC2022.2022

SAT–073

ILC2022