Proteomic markers of cardiovascular and metabolic health in at-risk NASH

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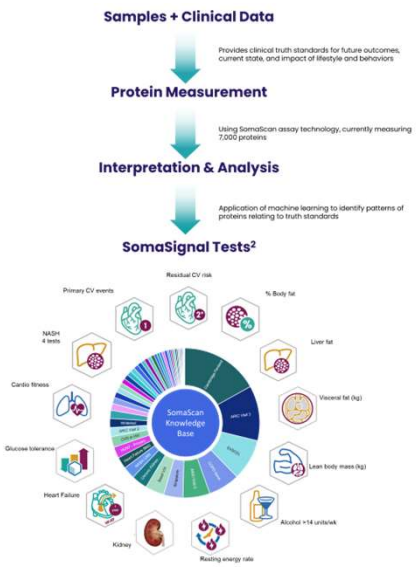
Background

- Non-alcoholic steatohepatitis (NASH) is a complex disease process that affects multiple organ systems.
- Assessing or monitoring patients holistically presents a unique challenge for patient care and in the clinical trial setting.
- Large-scale proteomic profiling using a novel aptamer-based technology has facilitated the development and validation of blood-based proteomic signatures for 11 different cardiometabolic SomaSignal Tests (SST) as well as the four biopsy components of NASH.
- We applied cardiometabolic blood tests to individuals with NAFLD and NASH to investigate the cardiometabolic proteomic phenotype of at-risk NASH in samples derived from the LITMUS Metacohort.

Methods

- The LITMUS Metacohort study is a retrospective collection of blood samples with accompanying histology and clinical data from participants diagnosed with NAFLD and NASH in the European NAFLD Registry, with the goal of identifying non-invasive biomarkers for the diagnosis, risk stratification, and monitoring of patients with NAFLD and NASH.[1]
- Plasma samples from 182 participants were analyzed with multiplexed modified aptamer-based proteomics (SomaScan assay) to measure ~5000 plasma proteins and to generate predictions for the previously validated metabolic health proteomic signatures.
- We used logistic regression to estimate odds ratios to compare log2 transformed proteomic cardiometabolic signatures for individuals with biopsy-identified "at-risk" NASH (NAS ≥ 4 and fibrosis ≥ F2) to participants with NAFLD or less severe NASH; p-values were corrected for multiple comparisons using false discovery rate.

SomaSignal™ tests



Results

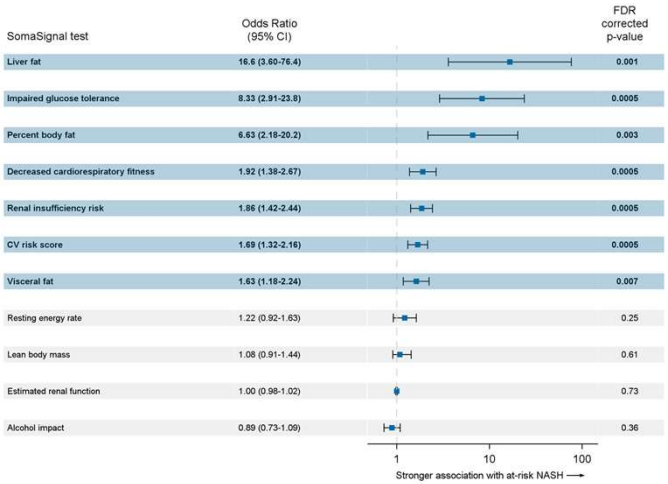


Figure 1. Logistic regression results showing the association between SST and at-risk NASH in the LITMUS Metacohort. Shaded SST are significantly associated with at-risk NASH

Table 1. Demographics and clinical characteristics of the LITMUS Metacohort

Characteristic	Biopsy identified **at-risk** NASH n = 92 (50.5%)	Biopsy identified **not** at-risk NASH n = 90 (49.5%)	p-value
Gender			
n(%) female	43 (46.7%)	29 (32.2%)	0.05
n(%) male	49 (53.3%)	61 (67.8%)	
Mean age (years), (SD, range)	56.5 (10.4, 22.0-76.0)	53.5 (11.8, 20.0-78.0)	0.08
Diabetes status			
n(%) Yes	71 (77.2%)	39 (43.3%)	<0.0001
n(%) No	21 (22.8%)	51 (56.7%)	
Hypertension status*			
n(%) Yes	74 (80.4%)	56 (62.2%)	0.0007
n(%) No	18 (19.6%)	34 (37.8%)	
Cirrhosis status			
n(%) Yes	15 (16.3%)	4 (4.4%)	0.01
n(%) No	77 (83.7%)	86 (95.6%)	
Mean eGFR(ml/min/1.73m^2), (SD, range)	88.4 (19.7, 41.3-137.5)	89.7 (18.0, 42.6-131.2)	0.64
Mean BMI (SD, range)	35.7 (5.9, 25.1-53.8)	31.2 (6.8, 17.8-58.8)	<0.0001
n(%) on lipid-lowering medications			
n(%) Yes	54 (58.7%)	38 (42.2%)	0.02
n(%) No	28 (30.4%)	43 (47.8%)	
Liver parameters			
Mean ALT (U/L), (SD, range)	67.2 (36.9, 17.0-231.0)	51.3 (28.4, 16.0-155.0)	0.001
Mean ALP (U/L), (SD, range)	88.3 (37.2, 33.0-227.0)	75.7 (28.5, 31.0-174.0)	0.02
Mean AST (U/L), (SD, range)	51.5 (23.6, 19.0-142.0)	34.9 (15.7, 12.0-107.0)	<0.0001
Mean GGT (U/L), (SD, range)	150.2 (173.2, 17.0-896.0)	89.1 (116.9, 5.0-620.0)	0.008
Mean platelet count (10^9/L), (SD, range)	224.5 (74.9, 82.0-626.0)	227.0 (60.9, 102.0-399.0)	0.81
Liver biopsy results			
n(%) ballooning	92 (100%)	67 (74.4%)	<0.0001
n(%) inflammation	50(54.4%)	11 (12.2%)	<0.0001
n(%) fibrosis	92 (100%)	17 (18.9%)	<0.0001
n(%) steatosis	92(100%)	90 (100%)	N/A

* n missing = 19 (10.4%)

Results

- **Figure 1** shows the associations between proteomic signatures and at-risk NASH:
  - Higher liver fat: every doubling of liver fat score is associated with a 15.6 times increased odds for at-risk NASH
  - Impaired glucose tolerance: every doubling of impaired glucose tolerance score is associated with a 7.3 times increased odds for at-risk NASH
  - Higher body fat: every doubling of body fat score is associated with a 5.6 times increased odds for at-risk NASH
  - Decreased cardiorespiratory fitness: every halving of cardiorespiratory fitness score is associated with 92% increased odds for at-risk NASH
  - Increased risk for renal insufficiency within four years: every doubling of renal insufficiency risk score is associated with 89% increased odds for at-risk NASH
  - Increased risk for a cardiovascular event within four years: every doubling of cardiovascular risk score is associated with 69% increased odds for at-risk NASH
  - Increased visceral fat predictions: every doubling of visceral fat score is associated with 63% increased odds for at-risk NASH
- Lean body mass, current renal function, and alcohol consumption predictions were not associated with at-risk NASH vs NAFLD.
- **Table 1** shows the demographic and clinical characteristics of the LITMUS Metacohort based on at-risk NASH status.
  - Participants with at-risk NASH are more likely to be female, have more diabetes and hypertension, have higher BMI, and worse liver parameters compared to participants that do not have at-risk NASH.

Conclusions

- These results demonstrate that participants with at-risk NASH have proteomic signatures that are consistent with decreased cardiometabolic health compared to participants with NAFLD.
- This study shows that SST can be used in multiple ways to better **know your patient**.
- Identifying proteomic phenotypes may be used to improve patient care and clinical trial screening and monitoring, and to identify the non-hepatic consequences of the progression of NASH.

Contact us

References

1. https://litmus-project.eu/publications/

2. Williams SA-O, Kivimaki MA-O, Langenberg CA-O, et al. Plasma protein patterns as comprehensive indicators of health.

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