Identifying at-risk NASH patients

**FAST™ Score Target**

<table>
<thead>
<tr>
<th>NAFL</th>
<th>NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Steatosis</td>
<td>Ballooning Inflammation</td>
</tr>
</tbody>
</table>

**FAST™ Score Construction**

**FAST™ score Performance**

**ORAL AASLD 2018**

### DERIVATION COHORT

<table>
<thead>
<tr>
<th>Development population</th>
<th>Bootstrap validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>335</td>
</tr>
<tr>
<td>Prevalence of NASH+NAS≥4+F≥2</td>
<td>166 (50%) (44%-55%)*</td>
</tr>
<tr>
<td>FAST™ score AUROC (95%CI)</td>
<td>0.83 (0.78-0.87)</td>
</tr>
</tbody>
</table>

### EXTERNAL VALIDATION COHORTS

<table>
<thead>
<tr>
<th>Malaysian NAFLD cohort</th>
<th>US screening cohort</th>
<th>French bariatric surgery cohort</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>335</td>
<td>193</td>
<td>110</td>
</tr>
<tr>
<td>Prevalence of NASH+NAS≥4+F≥2</td>
<td>53 (23%)</td>
<td>24 (12%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>FAST™ score AUROC (95%CI)</td>
<td>0.85 (0.80-0.91)</td>
<td>0.91 (0.86-0.96)</td>
<td>0.93 (0.89-0.98)</td>
</tr>
</tbody>
</table>

* 95% confidence interval for prevalence

- Good to excellent performance in derivation cohort as well as in external validation cohorts from different clinical settings (NAFLD tertiary care unit, screening, bariatric surgery) and geographical origins (USA, Europe, Asia)
- Formula is public with a free web-based calculator available on myFibroScan app

**References:**

- Sasso M. et al., Comparison of FS3 with different liver biomarkers to identify patients with active NASH (NAS≥4) and advanced fibrosis (F≥2). EASL-NAFLD Summit 2018.
- Sasso M. et. al, Fibroscan-Based Score (FS3) to Identify Nash Patients with NAS≥4 and F≥2: Development in a NAFLD UK Cohort - External Validation in a Malaysian NAFLD Cohort, a US Screening Cohort and a French Bariatric Surgery Cohort. Hepatology 2018;68(S1):87A.
- Harrison S. et al, Fibroscan-Based Score (FAST) to Identify Nash Patients with NAS≥4 and F≥2: Development in a NAFLD UK Cohort - External Validation in a Malaysian NAFLD Cohort, a US Screening Cohort and a French Bariatric Surgery Cohort. NAST-TAG Conference 2019.
- Wong V. et al., External validation in Asian non-alcoholic fatty liver disease (NAFLD) patients of the FibroScan-based FAST™ score to identify at risk non-alcoholic steato-hepatitis (NASH) patients. Hepatology International 2019;13(S1):S137.
- 1 oral presentation and two posters at EASL 2019 (see abstract at the back)

The FAST™ product is an in vitro diagnostic medical device as defined by Directive 98/79/EC. FAST™ is an algorithm intended to calculate a score from Aspartate Aminotransferase (AST) blood parameter, Liver Stiffness and CAP™ (Controlled attenuation parameter) measurements obtained from VCTE™-based FibroScan® devices, useful for identifying at risk NASH patients (patients with NAS≥4 and Fibrosis stage≥2) in patients with suspicion with NAFLD.

Products in the FibroScan® range are Class IIa medical devices as defined by Directive 93/42/EEC (EC 0459). These devices are designed for use in a medical practice in order to measure liver stiffness and ultrasound attenuation in patients with liver disease. Examinations with FibroScan® device shall be performed by an operator who has been certified by the manufacturer or its approved local representative. Operators are expressly recommended to carefully read the instructions given in the user manual and on the labeling of these products. Check cost defrayal conditions with paying bodies. FAST™ and FibroScan® are registered trademarks of Echosens.

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Identifying at-risk NASH patients
EASL 2019

Oral presentation PS-201 - Sunday 14 April 2019 9:00 am – Strauss 1-2
External validation in NAFLD cohorts of the FibroScan-based FAST score combining liver stiffness, controlled attenuation parameter and AST to identify patients with active NASH (NAS>4) and significant fibrosis (F≥2) - Boursier et al.

BACKGROUND AND AIMS: Given the recent need to identify NASH patients with fibrosis in drug development, Echosens has developed a score to identify patients with active NASH (NAS≥4) and significant fibrosis (F≥2) combining FibroScan liver stiffness measurement (LSM), controlled attenuation parameter (CAP) and AST. The objective was to perform an external validation of this score in several independent cohorts of biopsy-proven NAFLD patients.

METHOD: Patients from three centers (Angers, Wenzhou, Hong-Kong) who underwent FibroScan (LSM and CAP) and a clinically indicated liver biopsy (LB) for suspected NAFLD were included. In each cohort, all LB were read by a single expert pathologist using the NASH CRN scoring system and the FLIP definition for NASH. FibroScan-based score performance to identify NASH+NAS≥4+F≥2 was assessed using area under the receiver operating characteristics (AUC). Diagnostic performance in each cohort were calculated using cutoffs determined in the score’s derivation cohort: 0.40 for a sensitivity (Se)≥0.90 and 0.76 for a specificity (Sp)≥0.90.

RESULTS: A total of 395 patients were analyzed. Characteristics of each cohort and pooled patients are given in Table 1 together with the score performances. Performance was good in each cohort with AUC above 0.80. Pooled AUC was 0.82 (0.78-0.87).

CONCLUSION: The simple score based on FibroScan LSM, CAP and AST showed good performance in all NAFLD cohorts. It could be used in liver units to efficiently screen patients with active NASH (NAS≥4) and significant fibrosis (F≥2) for drugs trials as well as identifying patients eligible for treatment when drugs will be on the market.

Poster presentation SAT-292 - Saturday 13 April 2019 - Hall B
Effectively reducing screen failure rate in non-alcoholic fatty liver disease clinical trial using the FibroScan-based FAST score combining liver stiffness, controlled attenuation parameter and AST - Eddowes et al.

BACKGROUND AND AIMS: Identifying patients with active NASH (NAS≥4) and advanced fibrosis (F≥2) is a key priority for clinical trials yet current strategies are associated with high screen failure rates. We set out to evaluate the screen failure and missed case rate associated with a FibroScan-based score (TE/CAP/AST) in a UK setting.

METHOD: Patients were enrolled for undergo FibroScan examination within 2 weeks of a clinically indicated liver biopsy (LB) for suspected NAFLD. Recruitment took place (Mar 2014-Jan 2017) at seven UK centres. LB were scored by two expert pathologists in a blinded manner with consensus using the NASH CRN system and NASH using the FLIP definition. SFR was computed as being 1-positive predictive value for each value of the score. Similarly the missed case rate MCR was calculated as being 1-sensitivity. For each possible value of the score (ranging between 0 and 1), the corresponding SFR and MCR were plotted and used to define optimal cut-offs depending on the study objective. Cut-offs to reduce the SFR by a third and half were calculated as exploratory endpoints. For comparison SFR/MCR above the higher published cut-offs for FIB-4 (3.25) and NFS (0.67) were also calculated.

RESULTS: 335 patients were included in the analysis. AUROC of the FibroScan-based score to detect patients with NASH+NAS≥4+F≥2 was 0.83 (0.77-0.87). Prevalence of NASH+NAS≥4+F≥2 was 50% which would have been the SFR if no prior screening of patients was undertaken. Evolution of the SFR as a function of all endpoints. For each possible value of the score (ranging between 0 and 1), the corresponding SFR and MCR were plotted and used to define optimal cut-offs depending on the study objective. Cut-offs to reduce the SFR by a third and half were calculated as exploratory endpoints. For comparison SFR/MCR above the higher published cut-offs for FIB-4 (3.25) and NFS (0.67) were also calculated.

CONCLUSION: The Fibroscan-based score identified optimal cut-offs to significantly reduce SFR with an acceptable MCR.

Poster presentation SAT-301 - Saturday 13 April 2019 - Hall B
The FibroScan-based FAST score combining liver stiffness, controlled attenuation parameter and AST can efficiently screen for presence of at risk fibrotic NASH: Evaluation in an American cohort of patients screened for NAFLD - Harrison et al.

BACKGROUND & AIMS: Given the increased need to identify NASH patients with fibrosis in drug development, Echosens has developed a score to identify patients with NASH+NAS≥4+F≥2. The score combined the FibroScan liver stiffness measurement (LSM), controlled attenuation parameter (CAP) and AST. The objective was to assess its performance in a cohort of patients screened for NAFLD.

METHODS: Patients were screened for NAFLD in one American center. Patients with MRI-PDFF ≥5% or liver inflammation and fibrosis score (LIF) ≥2 or FibroScan LSM ≥7kPa or MRE ≥5kPa were advised to undergo a liver biopsy (LB). The performance of the score was assessed using area under the receiver operating characteristics (AUC).

RESULTS: 510 patients were included in the analysis: 240 with LB and 270 with no LB (all 4 liver imaging modalities “normal” (below the predefined cutoffs)). 50% of were female, median age was 56 (IQR=10) years and BMI was 30.3 (7.3) kg/m². At LB, 37 (15%) patients had at F≥2, 91 (38%) had NASH and 27 (11%) had a NASH+NAS≥4+F≥2. Of note, 7 (3%) had F≥2 but no NAS and 3 (1%) had F≥2 and NAS=3.

Cutoffs value for a sensitivity (Se) and specificity (Sp) ≥0.90 and associated diagnostic metrics are provided in Table 1. AUC for the score to detect NASH+NAS≥4+F≥2 was 0.88 (0.81-0.94) and significantly outperforming FibroScan LSM (0.77 (0.68-0.86), p<0.006), CAP (0.71 (0.63-0.80), p<10-3) and AST (0.76 (0.66-0.86), p=0.004) alone. Using the lower cutoff, 97 patients (19% of the population) would have been sent for referral. Among those patients, 26% were NASH+NAS≥4+F≥2, 69% weren’t and 5% had normal imaging modalities. Using the higher cutoff, 38 patients (7% of the population) would have been sent for referral. Among those patients 42% were NAS≥4+F≥2, 55% weren’t and 3% had normal imaging modalities. With the hypothesis that patients with normal imaging were not NASH+NAS≥4+F≥2, prevalence of NASH+NAS≥4+F≥2 would drop to 5%. Corresponding positive and negative value (PPV/NPV) of the score would be 0.26/99.5 for the lower cutoff and 0.42/97.7 for the higher cutoff.

CONCLUSION: A simple score based on FibroScan LSM, CAP and AST can be used to efficiently identify patients eligible for potential pharmacologic therapy.