How to diagnose NASH?

Prof. Nicolas Lanthier, MD, PhD
BASL Winter Meeting
Saturday December 2 2017
The answer is simple

- Non-alcoholic steatohepatitis
  - Histological diagnosis: coexistence of all 3 criteria
    - Steatosis
    - Hepatocyte ballooning
    - Lobular inflammation
  - Additional information: degree of fibrosis

- A liver biopsy is mandatory
Liver biopsy

Percutaneous
- Major complications: 1-3% (hemobilia, intraperitoneal bleeding)
- Death 0.01%
  - ↓ by US guidance, experience operator, small number of passes
  - ↓ elective cases
- Pain 20%
- Anxiety >30%

Transvenous
- Safer and better tolerated
- Possible if ascites or coagulation disorder
- Complications
  - Minor: 6.5%
  - Major: 0.56% (mortality 0.09%: hemorrhage 0.06%, ventricular arrhythmia 0.03%)
- No added complications if several passes
- Value of hepato-venous pressure gradient

Biopsy advantages

- Qualitative diagnosis (confirmation)
  - Exclusion of other chronic liver diseases
    - Alpha1-antitrypsin deficiency
    - Wilson disease
    - Auto-immune hepatitis
    - ...

- Quantitative diagnosis (precise disease staging)
  - NASH scoring system
  - Beaujon score
NAFLD activity score (NAS)

**Steatosis**

0 : < 5%
1 : 5-33%
2 : 34-66%
3 : > 66%

**Lobular inflammation**

0 : absence
1 : < 2 foci/field 20x
2 : 2-4 foci/field 20x
3 : > 4 foci/field 20x

**Hepatocyte ballooning**

0 : absence
1 : few
2 : many - prominent

→ **NAS : 0-8** (Not NASH 0-2, borderline 3-4, NASH 5-8)

**Fibrosis**

0 : absence
1a : mild zone 3 perisinusoidal fibrosis, requiring Masson trichrome
1b : moderate perisinusoidal fibrosis appreciated on H&E
1c : protal fibrosis only
2 : zone 3 perisinusoidal fibrosis and periportal fibrosis
3 : bridging fibrosis
4 : cirrhosis

Beaujon score or SAF score

<table>
<thead>
<tr>
<th>Steatosis</th>
<th>Ballooning</th>
<th>Lobular inflammation</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0, 1, 2, 3)</td>
<td>(0, 1, 2)</td>
<td>(0, 1, 2)</td>
<td>No NAFLD</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0, 1, 2</td>
<td>NAFLD</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>NAFLD</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2</td>
<td>NAFLD</td>
</tr>
<tr>
<td>1, 2, 3</td>
<td>1</td>
<td>0</td>
<td>NAFLD</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>NASH</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>NASH</td>
</tr>
<tr>
<td>1, 2, 3</td>
<td>1</td>
<td>2</td>
<td>NASH</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>NAFLD</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>NASH</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>NASH</td>
</tr>
</tbody>
</table>
Biopsy advantages: quantitative: morphometry and more

- Collagen proportionate area
- Better scoring with digital imaging analysis

Evaluation of the portal tract inflammation

- Chemical-molecular pathways
  - Metabolomics

Liver biopsy problems

- Small ++++ (1/50000 part of the liver)
  - Sampling variability if two liver biopsies performed on the same patient

- Invasive method with complications, not easily reproducible

- Needs a good quality specimen

- Intra-observer and inter-observer variability
  - Despite length of 25 mm (25% rate of discordance for fibrosis staging)
  - Cf patients included in clinical trials (confrontation with local pathologists)
  - Cf other stories

Transvenous liver biopsy

- Male patients with diabetes
- Low platelet count
- Liver biopsy in 2014: NASH cirrhosis, HVPG:
- New liver biopsy for inclusion in a clinical trial, MELD 11 pts, HVPG:

Masson trichrome

- Histology: fibrosis F0!
Other markers are needed

- Steatosis
- Steatohepatitis
- Fibrosis
Steatosis

- Important for confirming our clinical suspicion

- Detection
  - Ultrasound: simple but vague (> 25% fatty hepatocytes)
  - Computed tomography (CT): > 25% fatty hepatocytes and ionizing

- Scores
  - Fatty liver index (FLI): 4 variables, compared with US
  - SteatoTest \(®\): 12 variables, patented, low positive predictive value
  - NAFLD liver fat score: 5 variables.

- Quantification by imaging
  - Controlled attenuation parameter
  - Magnetic resonance imaging with proton density fraction
Evaluation of steatosis grade

- **Fibroscan (M or XL probe)**
  - **CAP**
    - For a sensitivity \( \geq 90\% \), cut-offs
      - \( 215 \text{ dB/m} \) for S \( \geq 1 \)
      - \( 252 \text{ dB/m} \) for S \( \geq 2 \)
      - \( 296 \text{ dB/m} \) for S3
    - \( \geq 310 \text{ dB/m} \) for S2-S3 steatosis grade (sensitivity 79\%, specificity 71\%)

---

MRI-PDFF versus CAP

Permut APT 2012.
The detection of NASH is more important

**Rationale**
- Identify the risk of NAFLD
- Identify patients with worse prognosis
- Link with fibrosis evolution

---

Non-invasive NASH screening

- Disappointing results
  - Liver transaminases
    - AUROC 0.6
    - Use low values (25 U/L 33 U/L)
  - Imaging methods
    - No
  - Serum markers
    - Cytokertain 18

EASL. J Hepatol. 2016.
Cusi K et al. J Hepatol. 2014.

ROC curve for NASH

Caspase-3–generated CK-18 fragments
Wait until fibrosis progression...

- Numerous methods
  - Indirect serum markers
  - Direct serum markers
  - Serum indices
  - Imaging techniques evaluating liver stiffness
  - « Minimally invasive » techniques
Classification

1. Serum tests
   1. AST-ALT
   2. AST/ALT
   3. γGT
   4. Hyaluronic acid
   5. Others: Pentraxin-3, type IV collagen 7S, Laminin, Procollagen, Metalloproteinases (MMP-1 and MMP-2), Tissue inhibitors of the metalloproteinases (TIMPs), Transforming growth factor-β1 (TGF-β1)...

2. Scores
   1. BAAT (age, BMI, triglycerides, ALT)
   2. Enhanced Liver Fibrosis (ELF)
   3. FibroTest (age, α2macroglobulin, bilirubin, GGT, apolipoprotein A1)
   4. NAFLD fibrosis score
   5. BARD
   6. FIB-4
   7. Fibrometer (glucose, platelet count, aminotransferases, ferritin, body weight, age)
   8. NAFLD Diagnostic panel (DM, triglycerides, TIMP-1, AST)

3. Liver stiffness
   1. Transient elastography (FibroScan®, Echosens)
   2. Acoustic Radiation Force Impulse (ARFI) sonoelsatography (Siemens)
   3. MR elastography
   4. Supersonic shear imaging (SSI) or Shear WaveTM elastography (Supersonic Imagine)
   5. Real-time elastography
Other classification

1. Direct serum markers
   • Hyaluronic acid

2. Indirect serum markers/panels
   • Transaminases
   • APRI

3. Patented serum panels
   • Fibrotest®

4. Imaging modalities
   • Transient elastography (FibroScan®, Echosens)
   • Acoustic Radiation Force Impulse (ARFI) sonoelsatography
   • MR elastography
   • Supersonic shear imaging (SSI) or Shear WaveTM elastography
Simple indirect indices NFS and FIB-4

- Based on routinely available parameters
  - NAFLD Fibrosis score (age, BG, BMI, platelets, albumin, AST/ALT) AUROC 0.84
  - FIB-4 (age, ALT, AST, platelets) AUROC 0.8
  - ELF (HA, TIMP1, PIIINP): AUROC 0.9

- Both rule-in and rule-out significant fibrosis
  - NFS < -1.455; FIB-4 < 1.30: new evaluation in 2 years
  - NFS > 0.67; FIB-4 > 2.67: refer to hepatologist
  - Attention if < 35 years and > 65 years

- Excessive number of specialist referrals and unjustified increase in health costs?

---

EASL. J Hepatol. 2016.
Other complex scores, algorithms or indices

Freely available and dedicated to NAFLD

**BAAT** (age, BMI, triglycerides, ALT)

**NAFLD Fibrosis Score** (age, glycemia, BMI, platelets, albumin, AST/ALT)

**NAFLD diagnostic panel** (diabetes, triglycerides, TIMP-1, AST)

**BARD** (BMI, AST/ALT, presence of diabetes)
Fibrotest®

HBV

Fibromax®

NAFLD suspicion

http://www.biopredictive.com
Fibrotest®, Fibromax® and NAFLD

Parameters:
• $\alpha_2$-macroglobulin
• haptoglobin
• apolipoprotein A1
• $\gamma$GT
• bilirubin
• ALAT
• ASAT
• total cholesterol
• triglycerides
• blood glucose

AUROC for significant fibrosis: 0.75-0.86
Unable to distinguish mild from moderate fibrosis

Gilbert syndrome, cholestasis, acute inflammation, abnormal lipoprotein A1

Direct markers: hyaluronic acid and NAFLD

79 patients with histologically confirmed NAFLD

AUROC:

0.67 (any levels of fibrosis);
0.87 (≥ moderate fibrosis);
0.89 (≥ severe fibrosis);
0.92 (cirrhosis).

Cut-off of 46.1 µg/l
best for severe fibrosis (sens. 85%, spec. 80%)
VPP 51%, VPN 96%

New circulating markers

- Procollagen III

- Metabolomics

Conclusion:
Complex non-invasive fibrosis models versus simple models

Trial on NAFLD patients

N= 242

For significant fibrosis: modest accuracy of models (AUROC 0,7)

For advanced fibrosis: complex models more accurate than simple (AUROC 0,8 versus 0,7)

Novel Pro-C3 « FIB-C3 Score »

- Plasma procollagen III
  - Correlated with NASH and fibrosis
  - Similar performance to the FIB-4 score for detection of ≥ F3 fibrosis (AUROC 0.76)

- FIB-C3
  - Age, BMI, T2DM, platelets and pro-C3
  - Optimal threshold for ≥ F3 fibrosis: -0.28

<table>
<thead>
<tr>
<th>Test</th>
<th>Cohort</th>
<th>Sensitivity % (95%CI)</th>
<th>Specificity % (95%CI)</th>
<th>PPV % (95%CI)</th>
<th>NPV % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIB4 (≥2.67)</td>
<td>Discovery (N=320)</td>
<td>25.2 (17.9-33.7)</td>
<td>91.1 (86.3-94.7)</td>
<td>64.0 (51.0-75.2)</td>
<td>66.1 (63.6-68.5)</td>
</tr>
<tr>
<td>FIB-C3 (≥ -0.28)</td>
<td></td>
<td>77.0 (68.7-84.0)</td>
<td>80.4 (74.1-85.8)</td>
<td>71.8 (65.4-77.5)</td>
<td>84.3 (79.5-88.2)</td>
</tr>
</tbody>
</table>

Measurement of liver stiffness

Transient elastography (Fibroscan®)  
Acoustic Radiation Force Impulse (ARFI) sonoelastography  
Supersonic shear imaging (SSI) or ShearWave™ elastography  
Magnetic resonance (MR) elastography
Transient elastography

First tool developed to quantify liver fibrosis

Measurement of mechanical shear wave propagation through the hepatic parenchyma
  Vibration of mild amplitude and low frequency transmitted by the transduced
  Induction of an elastic shear wave that propagates within the liver
  Pulse-echo ultrasonic acquisition performed to follow the shear wave and measure its speed

Liver volume evaluated: 4x1 cm (>100 times bigger than a liver biopsy)

Painless, rapid (5 min)

Speed directly related to the tissue stiffness
  Fast shear propagation if harder tissue

Results in kPa (median value of ten validated measurements)


More accurate than serum biomarkers

$V_s$: shear velocity

$E$ (elastic modulus) = $3\rho V^2$

$\rho$: mass density (constant for tissues)

Transient elastography: limitations

- Acute liver injury
- Congestive heart failure
- Postprandial measurements
- Degree of liver inflammation
- Degree of steatosis
- Obesity
- Narrow intercostal spaces
- Ascites

⇒ Overestimation of the measured liver stiffness

⇒ Difficult

⇒ Impossible

Transient elastography: criteria for reliable results

1. Number of valid shots ≥ 10

2. Interquartile range (IQR) < 30% of the median value

3. Successful measurements ≥ 60% of the total number of acquisitions

4. Fasting patient

5. Avoid situations of overestimated liver stiffness (high transaminases, congestive heart failure...)


### Fibroscan (M or XL probe)

<table>
<thead>
<tr>
<th></th>
<th>M Probe</th>
<th>XL Probe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff (kPa)</td>
<td>Sensitivity % (95% CI)</td>
</tr>
<tr>
<td>F2-4 vs. F0-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0-1 fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>≥7.8</td>
<td>82 (72-90)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>≥6.5</td>
<td>96 (85-99)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>≥7.8</td>
<td>84 (67-95)</td>
</tr>
<tr>
<td>F4 vs. F0-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0-3 fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>≥21.5</td>
<td>84 (60-97)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>≥14.0</td>
<td>92 (62-100)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>≥22.3</td>
<td>80 (28-99)</td>
</tr>
</tbody>
</table>

Acoustic Radiation Force Impulse (ARFI) elastography

Elastography system directly integrated on a standard ultrasonography device (Acuson S2000, Siemens)

Short-duration (262 µs) acoustic pulses localized, allowing selection of the site of measurement by the operator on a real-time B-mode ultrasound image

Volume of liver explored: 10 mm x 6 mm (smaller than Fibroscan)

Since 2009

Advantages:
- Possibility to choose the representative area
- No case of invalid measurements
- No influence of liver steatosis

Acoustic Radiation Force Impulse (ARFI) elastography

Proposed cut-offs for NAFLD

$\geq$ F3  1,77  m/sec  
F4   1,9  m/sec
Supersonic shear imaging (SSI) elastography or ShearWave™ elastography

Since 2011

As ARFI, based on the measurement of the velocity of a local shear wave through soft tissues built on a ultrasound device (Aixplorer, Supersonic Imagine, France)
no external vibrator needed to produce shear wave

But,
emission of a plurality of pulse wave beams at increasing depths using a wide frequency band ranging from 60 to 600 Hz

(Transient elastography and ARFI: single shear wave emitted temporarily at a single frequency for each measurement)

⇒ Generation of a real-time color mapping of the elasticity

⇒ Placing a region of interest (ROI)
⇒ Calculated value (average of many values within the ROI)
Proposed cut-offs for NAFLD (90% specificity)

≥ F2  8,7  kPa
≥ F3  10,7 kPa
F4  14,4 kPa

Bavu E et al. EASL. 2010.
Supersonic shear imaging elastography: F1
Supersonic shear imaging elastography: F4 + ascites
Supersonic shear imaging elastography: real-life
Supersonic shear imaging elastography: trial

Characteristics of the 349 included patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>NASH (n=145)</th>
<th>HCV (n=79)</th>
<th>HBV (n=33)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex - Male: n (%)</td>
<td>112 (78)</td>
<td>42 (53)</td>
<td>13 (40)</td>
<td>20 (54)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.4 ± 14.1</td>
<td>57.8 ± 14.2</td>
<td>53.2 ± 14.6</td>
<td>53.9 ± 14.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>28 (19.3)</td>
<td>14 (17.9)</td>
<td>9 (27.2)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>25 to 29.9</td>
<td>66 (45.8)</td>
<td>34 (43.0)</td>
<td>22 (66.7)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>≥30</td>
<td>51 (35.8)</td>
<td>31 (39.2)</td>
<td>6 (18.2)</td>
<td>16 (42.5)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97.4 ± 17.3</td>
<td>97.4 ± 17.3</td>
<td>100 ± 17.3</td>
<td>98 ± 17.3</td>
</tr>
<tr>
<td>Diabetes: n (%)</td>
<td>67 (46.5)</td>
<td>26 (32.9)</td>
<td>13 (39.4)</td>
<td>23 (59.0)</td>
</tr>
<tr>
<td>Hypertension: n (%)</td>
<td>74 (51.4)</td>
<td>41 (52.8)</td>
<td>15 (45.5)</td>
<td>22 (57.1)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>102 ± 183</td>
<td>103 ± 183</td>
<td>107 ± 183</td>
<td>105 ± 183</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>116 ± 170</td>
<td>117 ± 170</td>
<td>123 ± 170</td>
<td>121 ± 170</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>197 ± 253</td>
<td>198 ± 253</td>
<td>204 ± 253</td>
<td>200 ± 253</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>29.3 ± 59</td>
<td>29.4 ± 59</td>
<td>30.2 ± 59</td>
<td>29.5 ± 59</td>
</tr>
<tr>
<td>Platelet count (x10⁹/L)</td>
<td>185 ± 86</td>
<td>184 ± 86</td>
<td>191 ± 86</td>
<td>189 ± 86</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>96 ± 20</td>
<td>96 ± 20</td>
<td>98 ± 20</td>
<td>97 ± 20</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>115 ± 96</td>
<td>116 ± 96</td>
<td>118 ± 96</td>
<td>117 ± 96</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>40.5 ± 5</td>
<td>40.6 ± 5</td>
<td>41.0 ± 5</td>
<td>40.7 ± 5</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.3 ± 3.3</td>
<td>5.3 ± 3.3</td>
<td>5.5 ± 3.3</td>
<td>5.4 ± 3.3</td>
</tr>
<tr>
<td>Histologic fibrosis stage n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0</td>
<td>17 (11.7)</td>
<td>13 (16.5)</td>
<td>6 (18.2)</td>
<td>18 (46.2)</td>
</tr>
<tr>
<td>F1</td>
<td>60 (41.7)</td>
<td>34 (43.0)</td>
<td>16 (48.5)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>F2</td>
<td>49 (34.3)</td>
<td>22 (27.8)</td>
<td>11 (33.3)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>F3</td>
<td>12 (8.5)</td>
<td>5 (6.4)</td>
<td>4 (12.1)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>F4</td>
<td>6 (4.2)</td>
<td>3 (3.8)</td>
<td>2 (6.1)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Activity grade n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (7.0)</td>
<td>7 (8.9)</td>
<td>4 (12.1)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>1</td>
<td>58 (40.0)</td>
<td>36 (45.4)</td>
<td>18 (54.5)</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td>2</td>
<td>69 (47.0)</td>
<td>25 (31.6)</td>
<td>11 (33.3)</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td>3</td>
<td>2 (1.4)</td>
<td>2 (2.5)</td>
<td>1 (3.1)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Steatosis grade n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0 (&lt;5%)</td>
<td>102 (71.4)</td>
<td>71 (90.1)</td>
<td>24 (72.7)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>S1 (5-33%)</td>
<td>128 (89.3)</td>
<td>82 (103.9)</td>
<td>30 (90.9)</td>
<td>16 (42.1)</td>
</tr>
<tr>
<td>S2 (34-66%)</td>
<td>64 (44.8)</td>
<td>48 (60.8)</td>
<td>16 (48.5)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>S3 (&gt;66%)</td>
<td>56 (39.2)</td>
<td>42 (53.8)</td>
<td>15 (45.5)</td>
<td>19 (50.0)</td>
</tr>
</tbody>
</table>

Patients with liver biopsy (n = 416) from November 2011 to October 2013

Excluded patients, n = 67:
- Biopsy length under 10 mm, n = 13
- Ascite, n = 4
- Congestive hepatopathy or regenerative nodular hyperplasia, n = 23
- Graft-versus-host disease, n = 7
- Acute alcoholic hepatitis, n = 6
- Acute/infectious liver disease, n = 10
- Lymphomatous infiltration, n = 2
- Uncommon chronic liver disease
  - Glycogenosis, n = 1
  - Congenital hepatic fibrosis, n = 1

Patients included, n = 349
- Alcoholic/NASH disorders, n = 145
- Viral hepatitis, n = 127
- Other chronic liver diseases, n = 46
- Unexplained chronic cytolysis, n = 31

SSI, n = 336
(missing SSI, n = 13)

FibroScan®, n = 341
(missing FibroScan®, n = 8)

ARFI, n = 337
(missing ARFI, n = 12)
Idem
AUROC 0.89; 0.86; 0.84

SSI better than ARFI
AUROC 0.88; 0.84; 0.81

Idem
AUROC 0.93; 0.90; 0.90

SSI better than Fibroscan
AUROC 0.93; 0.87; 0.89

No discussion about measurement failures:
10.4% of cases (35/336) with SSI (more in obese patients)
2.6% of cases (9/341) with Fibroscan
6/235 with M probe
Study conclusion

However:

- No difference for F1, F2 and F4 when compared to Fibroscan
- No discussion about measurement failures:
  10.4% of cases (35/336) with SSI (more in obese patients)
  2.6% of cases (9/341) with Fibroscan
    6/235 with M probe
    3/106 with XL probe
  none with ARFI

Unreliable results:

5.9% of cases with Fibroscan

20/341 patients

9/235 M Probe

Application of elastography to MRI using a modified phase-contrast method to evaluate the propagation of the shear waves within the liver

Advantages:
- Evaluation throughout the whole liver parenchyma
- Applicability for patients with obesity or ascites
Magnetic resonance (MR) elastography

5 sagittal sections through the right liver (4 mm thick)

Longitudinal mechanical waves 65Hz (transducer at the back)

Rectangular region of interest and special MR sequence

Healthy volunteer

Cirrhotic patient

(b) elasticity

Magnetic resonance (MR) elastography

88 patients with chronic liver diseases (66 with HCV)

AUROC for elasticity
- 0.999 (≥ F2)
- 0.997 (≥ F3)
- 1.000 (F4)

Optimal cutoff values of elasticity:
- 2.5 kPa (≥ F2)
- 3.1 kPa (≥ F3)
- 4.3 kPa (F4)
Magnetic resonance (MR) elastography

96 patients with chronic liver diseases (60 with HCV)

AUROC for elasticity
- 0.994 (≥ F2)
- 0.985 (≥ F3)
- 0.998 (F4)

Better than APRI and transient elastography

Magnetic resonance elastography versus transient elastography

BMS-986036 (pegylated Fgf21)

- 16 weeks
- Improvement in hepatic fat fraction (MRI-PDFF)
- Improvement in liver stiffness (MRE)
- Reduction in serum pro-C3

### Conclusion

<table>
<thead>
<tr>
<th>Method</th>
<th>+</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient elastography</td>
<td>Validated (numerous studies)</td>
<td>Sometimes impossible</td>
</tr>
<tr>
<td></td>
<td>Efficiency</td>
<td>Not possible if ascites</td>
</tr>
<tr>
<td></td>
<td>Reproducibility</td>
<td>“False positive”</td>
</tr>
<tr>
<td></td>
<td>Different cut-offs among etiologies</td>
<td>No real-time technique</td>
</tr>
<tr>
<td>ARFI</td>
<td>No invalid measurements</td>
<td>No adequate detection of early stages of fibrosis</td>
</tr>
<tr>
<td></td>
<td>Real-time</td>
<td>Small liver portion</td>
</tr>
<tr>
<td></td>
<td>Possible if obesity, ascites…</td>
<td></td>
</tr>
<tr>
<td>MR elastography</td>
<td>Whole liver examination (3D)</td>
<td>Costs</td>
</tr>
<tr>
<td></td>
<td>Best results</td>
<td>Small population studied</td>
</tr>
<tr>
<td></td>
<td>Possible if obesity, ascites…</td>
<td>Availability/time-consuming</td>
</tr>
<tr>
<td>SSI elastography</td>
<td>Real-time</td>
<td>New</td>
</tr>
<tr>
<td></td>
<td>Large liver volume</td>
<td>Depend on the quality of the US image</td>
</tr>
<tr>
<td></td>
<td>Possible if obesity, ascites…</td>
<td>Experienced needed operator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Studies with mixed etiologies</td>
</tr>
</tbody>
</table>
« Minimally invasive » quantitative liver function test

1. Patient drinks 40 mg deuterated cholic acid (d4-CA) in juice at time 0.
2. A single peripheral blood sample at time 60 min is analyzed for d4-CA.

Recommendations

**Fibrosis**

- **Imaging**
  - No, not appropriated before the appearance of cirrhosis

- **Serum markers**
  - NAFLD fibrosis score (NFS)
  - Fibrosis 4 calculator (FIB-4)
  - Enhanced liver fibrosis (ELF)
  - FibroTest
  - FibroMeter

- **Elastography**
  - Transient elastography
  - Other techniques (acoustic radiation force impulse, ShearWave,...)

- **Combination**
  - FibroMeter with with vibration controlled transient elastography (VCTE)

EASL. J Hepatol. 2016.
Conclusion

- NASH is an histological diagnosis
  - Certainty diagnosis
  - Allows the evaluation of the severity
    - Fibrosis
    - SAF score, portal inflammation
  - Gold standard in clinical trials
- Problems
  - Invasive
  - Low accordance, need of a good quality sample

- « Non-invasive » techniques
  - Precise evaluation of steatosis and fibrosis
  - Simple NFS + FIB4 for general practitioners
  - Reproducible
  - MRI: future gold standard for clinical trial (with PDFF and elastography)?
  - New markers?
The current proposed algorithm

Identify the patient at risk

- Metabolic syndrome
- Increased transaminase level or \( \gamma \)GT
- Obesity, diabetes

Exclusion of frequent other chronic liver diseases

Non-invasive assessment
- Blood test for general practitioner
- Liver stiffness imaging for hepatologists

Low risk: nutritional counseling and follow-up
High risk: biopsy to confirm the diagnosis and severity + treat