Assessment of Liver Fibrosis

Pablo Barreiro
Hospital Carlos III- La Paz. Madrid, Spain
Growing Need to Target the Liver in Chronic Hepatitis

- Rising prevalence of advanced liver disease
  - Ageing (progression of fibrosis)
  - Obesity (steatosis)
  - HIV coinfection
    - Accelerated course of viral hepatitis

- Prioritization of therapeutic options
  - Direct Acting Antivirals
  - Oral drugs for hepatitis B

- Prognostic and therapeutic implications
  - Fibrosis
  - Steatosis
# EASL HCV Treatment Indications in 2015

<table>
<thead>
<tr>
<th>Priority</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated</td>
<td>- All HCV chronically infected</td>
</tr>
<tr>
<td>Prioritized</td>
<td>- Stage F3, F4A, F4B, F4C</td>
</tr>
<tr>
<td></td>
<td>- HIV and/or HBV coinfection</td>
</tr>
<tr>
<td></td>
<td>- Prior to or after OLT</td>
</tr>
<tr>
<td></td>
<td>- Extrahepatic disease of fatigue</td>
</tr>
<tr>
<td></td>
<td>- Risk of transmission</td>
</tr>
<tr>
<td>Delayable</td>
<td>- Stage F0-F1</td>
</tr>
</tbody>
</table>
ASLD HBV Treatment Criteria in 2015

INTRODUCTION

HBV-DNA (IU/mL)
- <20,000 (eAg pos)
- <2,000 (eAg neg)
- >20,000 (eAg pos)
- >2,000 (eAg neg)

ALT
- <2 ULN
- ≥2 ULN

Liver fibrosis
- mild
- significant

No Tx

Tx
Stage of Fibrosis in Chronic Hepatitis

- Portal
- Periportal
- Septal
- Cirrhosis
Technical Limitations of Liver Biopsy

Microscopic error: <3 cm LB underestimate fibrosis

Macroscopic error: ≥1 F-stage difference between lobes in 30%

Colloredo, J Hepatol 2003; Regev Am J Gastro 2002
Interpretation Issues with Liver Biopsy

![Bar chart showing percentage of discordant and concordant biopsy scores](image)

Colloredo, J Hepatol 2003; Regev Am J Gastro 2002
# Liver Fibrosis at Biopsy: Staging ≠ Measuring

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Ishak stage: Categorical description</th>
<th>Ishak stage: Categorical assignment</th>
<th>Fibrosis measurement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis (normal)</td>
<td></td>
<td>0</td>
<td>1.9%</td>
</tr>
<tr>
<td>Fibrous expansion of some portal areas ± short fibrous septa</td>
<td></td>
<td>1</td>
<td>3.0%</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas ± short fibrous septa</td>
<td></td>
<td>2</td>
<td>3.6%</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging</td>
<td></td>
<td>3</td>
<td>6.5%</td>
</tr>
<tr>
<td>Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C))</td>
<td></td>
<td>4</td>
<td>13.7%</td>
</tr>
<tr>
<td>Marked bridging (P-P and/or P-C), with occasional nodules (incomplete cirrhosis)</td>
<td></td>
<td>5</td>
<td>24.8%</td>
</tr>
<tr>
<td>Cirrhosis, probable or definite</td>
<td></td>
<td>6</td>
<td>27.8%</td>
</tr>
</tbody>
</table>

Standish R et al. Gut 2006
Clinical Utility of Liver Biopsy

Pros
- Different types of liver damage
  - Fibrosis
  - Steatosis
  - Inflammation
  - Necrosis
- Other liver conditions
  - Alcohol liver disease
  - Granulomatosis
  - Storage disease
  - Mitochondrial damage
  - Portal fibrosis
  - Nodular hyperplasia
- Objective assessment

Cons
- Invasive and costly
  - Morbidity and mortality
  - Aggressive for follow-up
  - Not well accepted
- Needs expertise
  - Infectologist / Hepatologist
  - Radiologist
  - Pathologist
- Microscopic error
  - Size of biopsy (>25 mm)
- Macroscopic error
  - Heterogeneity of liver damage
- Subjective and qualitative staging
The Hepatic Fibrogenic Process

**PATHOGENESIS**

**Biomarkers of liver cell injury**
- ALT / AST
- α2-Mglobulin

**Biomarkers of inflammation**
- Hyaluronic acid

**Biomarkers of fibrogenesis**
- Fibrogenic cytokines, CTGF, circulating fibrocytes, CSF, chemokines

**Biomarkers of fibrosis and ECM-turnover**

**Liver cell injury**
- Parasites
- Alcohol, ASH
- Cryptogenic
- Drugs, toxins
- Obesitas, NAFLD
- Venous obstruction
- Metabolic diseases

**Inflammation**
- IGF-I
- PDGF
- TGF-β
- ET-1
- ROS

**Mediators**
- Activation of HSC
- Expansion of MFB-Pool

**Fibrosis**
- Collagen ↑
- Elastin ↑
- Glycoproteins ↑
- Proteoglycans ↑
- Hyaluronan ↑

**Cirrhosis**
- Primary liver cell carcinoma (PHC)

**Recruitment of (myo-)fibroblasts**

# Main Fibrosis Scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Parameters</th>
<th>Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroMeter</td>
<td>Urea, AST, ALT, GGT, platelets, prothrombin, α2-macroglobulin, hyaluronic acid</td>
<td>No</td>
</tr>
<tr>
<td>FibroTest</td>
<td>Age, gender, α2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, GGT</td>
<td>No</td>
</tr>
<tr>
<td>ELF</td>
<td>Age, hyaluronic acid, procollagen III, TIMP-1</td>
<td>No</td>
</tr>
<tr>
<td>HepaScore</td>
<td>Age, gender, bilirubin, GGT, α2-macroglobulin, hyaluronic acid</td>
<td>No</td>
</tr>
<tr>
<td>FibroSpect</td>
<td>Platelets, cholesterol, GGT, α2-macroglobulin</td>
<td>No</td>
</tr>
<tr>
<td>SHASTA</td>
<td>Hyaluronic acid, ALT, albumin</td>
<td>No</td>
</tr>
<tr>
<td>APRI</td>
<td>AST, platelets</td>
<td>Yes</td>
</tr>
<tr>
<td>Forns</td>
<td>Age, GGT, cholesterol, platelets</td>
<td>Yes</td>
</tr>
<tr>
<td>FIB-4</td>
<td>Age, platelets, AST, ALT</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Performances of FibroScores in HCV
AUROC for Metavir F2, F3 & F4

1,056 HCV infected patients

AUROC

<table>
<thead>
<tr>
<th>Test</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroMeter</td>
<td>0.853</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>0.811</td>
</tr>
<tr>
<td>Fib-4</td>
<td>0.799</td>
</tr>
<tr>
<td>Hepascore</td>
<td>0.784</td>
</tr>
<tr>
<td>APRI</td>
<td>0.786</td>
</tr>
</tbody>
</table>

Performances of FibroScores in HIV/HCV

➔ 272 patients (Study Fibrovic-ANRS HC02)

*BLOOD MARKERS*

(*with DANA adjustment*)

![Graph showing AUROC values for different fibrosis scores (Fibrometer, Hepascore, Fibrotest, Fib-4, SHASTA, APRI, Forn's index) across different fibrosis stages (F2, F3, F4). The graph indicates the accuracy of these scores in predicting fibrosis stages.*

*Cacoub et al. J Hepatol 2008*
FibroScores in Non Viral Chronic Hepatitis

Alcoholic Liver Disease

FM, FibroMeter; FT, FibroTest; HS, HepaScore

Clinical Utility of FibroScores

Pros
- No observer bias
- No sampling error
- No technical issues
- Valid for follow-up

Cons
- Best scores need non-routine tests ($\alpha_2$-MG, HA)
- More accurate for F3-F4
- Affected by HIV infection?
  - AST/ALT
  - Cholesterol
  - Platelets
Liver Stiffness Measurement

- **What is stiffness?**
  - Ability of a medium to preserve shape under mechanical stress
  - Stiffness is expressed in kiloPascal (kPa)

- **How is stiffness measured?**
  - Dedicated probe placed in the intercostal spaces above the right lobe of the liver
  - Real time US plus repetitive pulses from the tip of the probe
  - At least 10 valid measures make up for the median liver stiffness

→ **The more fibrosis in the liver, the higher stiffness will be**

*Friedrich Rust et al. Gastroenterology 2008 (meta-analysis)*
Validation of LSM for Liver Fibrosis Assessment in CHC

LIVER STIFFNESS

AUROC against Liver Biopsy
Staging Liver Fibrosis in CHB

199 patients with CHB
Paired LB and LS:

<table>
<thead>
<tr>
<th>Metavir</th>
<th>Marcellin et al. Liver Int 2009</th>
<th>AUROC</th>
<th>Chan et al. JVH 2009</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥F2</td>
<td>7.2 kPa</td>
<td>0.81</td>
<td>6.0 kPa</td>
<td>0.80</td>
</tr>
<tr>
<td>≥F3</td>
<td>8.0 kPa</td>
<td>0.93</td>
<td>8.4 kPa</td>
<td>0.87</td>
</tr>
<tr>
<td>F4</td>
<td>11.0 kPa</td>
<td>0.93</td>
<td>9.0 kPa</td>
<td>0.93</td>
</tr>
</tbody>
</table>
## FibroScan in Non Viral Chronic Hepatitis

### Alcoholic Liver Disease

<table>
<thead>
<tr>
<th>Metavir</th>
<th>Best cut-off</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.9 kPa</td>
<td>0.84 (0.73-0.95)</td>
</tr>
<tr>
<td>F2</td>
<td>7.8 kPa</td>
<td>0.91 (0.85-0.97)</td>
</tr>
<tr>
<td>F3</td>
<td>11.6 kPa</td>
<td>0.94 (0.90-0.97)</td>
</tr>
<tr>
<td>F4</td>
<td>28.5 kPa</td>
<td>0.97 (0.93-1.00)</td>
</tr>
</tbody>
</table>

*Better performance with AST <100 IU/L


FibroScan in Non Viral Chronic Hepatitis

Primary Biliary Cirrhosis

<table>
<thead>
<tr>
<th>Metavir</th>
<th>Best cut-off (kPa)</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.1 (5.9-7.5)</td>
<td>0.80 (0.69-0.88)</td>
</tr>
<tr>
<td>F2</td>
<td>8.7 (7.3-9.8)</td>
<td>0.91 (0.85-0.96)</td>
</tr>
<tr>
<td>F3</td>
<td>10.9 (10.7-11.5)</td>
<td>0.99 (0.90-0.98)</td>
</tr>
<tr>
<td>F4</td>
<td>16.1 (14.4-17.8)</td>
<td>0.99 (0.97-1.00)</td>
</tr>
</tbody>
</table>

Staging Liver Fibrosis in HCV Recurrence after OLT

Accuracy of FibroScan for monitoring of liver fibrosis by recurrent HCV infection after OLT

Adebajo et al. Liver Transplantation 2012
## Cut-Offs for LS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Source</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHC</td>
<td><em>Castera L et al. J Hepatol 2008</em></td>
<td>7.0 kPa</td>
<td>9.5 kPa</td>
<td>12.5 kPa</td>
<td>14.5 kPa</td>
<td></td>
</tr>
<tr>
<td>CHB (&gt;ALT)</td>
<td><em>Wong G L Gastroenterol Rep. 2013</em></td>
<td>7.0 kPa</td>
<td>12.5 kPa</td>
<td>14.5 kPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBC</td>
<td><em>Corpechot C, et al. Hepatology 2012;56:198-208.</em></td>
<td>7.1 kPa</td>
<td>8.7 kPa</td>
<td>10.9 kPa</td>
<td>16.1 kPa</td>
<td></td>
</tr>
<tr>
<td>CHB (NALT)</td>
<td><em>Wong G L Gastroenterol Rep. 2013</em></td>
<td>6.0 kPa</td>
<td>9.0 kPa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD</td>
<td><em>Janssens F, et al. J Clin Gastroenterol 2010; 44:S75–82</em></td>
<td>5.9 kPa</td>
<td>7.8 kPa</td>
<td>11.6 kPa</td>
<td>28.5 kPa</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis of Portal Hypertension (PHT)

Metanalysis in 3,644 patients

- LIVER STIFFNESS

<table>
<thead>
<tr>
<th></th>
<th>PHT</th>
<th>EOV</th>
<th>LOEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC</td>
<td>0.93</td>
<td>0.84</td>
<td>0.78</td>
</tr>
<tr>
<td>Sens</td>
<td>0.90</td>
<td>0.87</td>
<td>0.86</td>
</tr>
<tr>
<td>Spec</td>
<td>0.79</td>
<td>0.53</td>
<td>0.59</td>
</tr>
<tr>
<td>PPV</td>
<td>0.88</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>NPV</td>
<td>0.88</td>
<td>0.64</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Shi et al. Liver Int 2012

- LS correlated with advanced stages of PHT, but less accurate for suspicion of large EOV

PHT: HVPG ≥10 mmHg
EOV: Any grade
LOEV: Grade II/III
Prognostic Value: Survival Rate

- 1,457 patients with HCV
- Correlation with survival (OR [95% CI]):
  - LS: 44 [15-127]
  - FibroTest: 90 [15-549]
  - APRI: 2.8 [1.6-4.7]
  - FIB-4: 4.1 [2.3-7.3]
  - METAVIR: 2.6 [1.8-3.8]

- Fibroscan and FibroTest better predictors of survival than LB

Liver Stiffness Predicts Risk of LEE

Advanced liver fibrosis (liver elasticity $\geq 9.5$ kPa)

- Yes
- No

Log Rank: 6.48 (p=0.01)
Confounding Factors for Estimation of Fibrosis

- Cholestasis
- Sinusoidal fibrosis
- Portal blood flow
- Inflammation
- Fasting

Portal fibrosis

- Centrilobular fibrosis
- Steatosis

ALT / AST correction
CAP correction
BLR / gGT correction

Diagnosis of Steatosis with CAP

- 261 patients with NAFLD

Grade 2/3 steatosis
Cut-off >310 dB/m
AUROC: 0.80 (0.73–0.86)
Sensitivity: 79%
Specificity: 71%

US Shear Wave Elastography

Longitudinal waves

Shear waves

Acoustic Radiation Force Impulse (ARFI) Elastography

Frulio N, et al. BMC Infectious Diseases 2014; 14:405
TE vs ARFI vs SWE in Chronic Hepatitis

TE vs ARFI vs SWE in NAFLD

Cut off values

<table>
<thead>
<tr>
<th></th>
<th>≥F2</th>
<th>≥F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity ≥90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWE</td>
<td>6.3</td>
<td>8.3</td>
<td>10.5</td>
</tr>
<tr>
<td>TE</td>
<td>6.2</td>
<td>8.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Specificity ≥90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWE</td>
<td>8.7</td>
<td>10.7</td>
<td>14.4</td>
</tr>
<tr>
<td>TE</td>
<td>9.8</td>
<td>12.5</td>
<td>16.1</td>
</tr>
</tbody>
</table>

Clinical Utility of Liver Elastrometry

**Pros**
- Easy and non-invasive
- Reproducible
- Bed-side diagnosis
  - Fibrosis (LSM)
  - Steatosis (CAP)
- Internal control
  - 10 valid measurements
  - IQR/Median <30%
- Validated for different types of liver disease
- Adapted probes (patients with low/high BMI)

**Cons**
- Influenced by other parameters independent of fibrosis:
  - liver edema
  - inflammation
  - cholestasis
  - large vessels
  - granuloma
Magnetic Resonance Elastography

Magnetic Resonance Elastography

Magnetic Resonance Elastography

AUROC
0.9502
0.9663
0.9644
0.9768