Liver Disease Assessment Among PWID: The Role of Transient Elastography

Peer Brehm Christensen, Professor
Department of Infectious Diseases
Odense University Hospital Denmark
Peer.christensen@dadlnet.dk
Disclosures

• I have received research grants from
  – Roche, Schering-Plough, Gilead, and Abbvie
  – Echosens have facilitated a Fibroscan device for my research
Why bother about liver fibrosis?

- Because:
  - As long as we cannot afford to treat everyone with hepatitis C, we should at least identify and treat the patients at risk of complications.
  - These patients are characterized by fibrosis of the liver.
Liver biopsy is the "gold" standard: Metavir fibrosis score

- F0/1
- F2
- F3
- F4 = Cirrhosis
Non-invasive diagnosis of liver fibrosis

- Clinical signs
- Image modalities (ultrasound)
- Blood test
- Liver stiffness measurement (LSM) (transient elastography)

<table>
<thead>
<tr>
<th></th>
<th>APRI (low cut-off)</th>
<th>APRI (high cut-off)</th>
<th>FIB-4 (low cut-off)</th>
<th>FIB-4 (high cut-off)</th>
<th>Transient elastography (FibroScan®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant fibrosis (METAVIR ≥F2)</td>
<td>0.5</td>
<td>1.5</td>
<td>1.45</td>
<td>3.25</td>
<td>7–8.5 kPa</td>
</tr>
<tr>
<td>Cirrhosis (METAVIR F4)</td>
<td>1.0</td>
<td>2.0</td>
<td>-</td>
<td>-</td>
<td>11–14 kPa</td>
</tr>
</tbody>
</table>

APRI: aminotransferase/platelet ratio index; kPa: kilopascal

WHO HCV guidelines 2016
LSM is the preferred test for fibrosis among PWID

Liver stiffness measurement
(Fibroscan®)
Liver stiffness varies with fibrosis

\[ V_S = 1.1 \text{ m/s} \]
\[ E \sim 3\text{kPa} \]

\[ V_S = 1.7 \text{ m/s} \]
\[ E \sim 9\text{kPa} \]

\[ V_S = 3.6 \text{ m/s} \]
\[ E \sim 40\text{kPa} \]

F0
F1
F2
F3
F4

Normal liver
Fibrosis
Cirrhosis
Problems with fibroscan

- **Overestimation**
  - Measurement near the liver capsule
  - Overweight
  - Narrow intercostal space
  - Post prandial examination
  - Heart failure (liver stasis)
  - Steatosis(?)
  - ALT elevation
  - Liver inflammation
  - ???

- Invalid measurements are not rare
  - In one out of 10 patients examination is difficult
  - With XL probe for obese patients and repeated measurement <1%

Criteria of a valid LSM (Fibrosocan) 2016

• 10 Measurements
• IQR/median <0,30 (if median> 7kPa)

• EASL guidelines
  – Fasting examination (2 hours)
  – XL probe if BMI >30 /skin capsule distance >25mm
  – ALT <5 xULN
  – No cholestase, heart failure / ”congestive liver”
  – No ongoing alcohol abuse

Boursier. Hepatology 2013:57;1182-91
EASL Non-invasive tests J.hepatol 2015; 63:237-64
Cut-offs for fibrosis (F2+) and cirrhosis (F4) among patients with hepatitis C by LSM

- 183 HCV patients with liver biopsy and LSM
- Male 57%, Mean age 51Y
- Metavir F1 26% F2 29% F3 20% F4 25%

<table>
<thead>
<tr>
<th>LSM Value</th>
<th>F ≥ 2</th>
<th>F ≥ 3</th>
<th>F = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal cut-off(^a) (kPa)</td>
<td>7.1</td>
<td>9.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>.67</td>
<td>.73</td>
<td>.87</td>
</tr>
<tr>
<td>Specificity</td>
<td>.89</td>
<td>.91</td>
<td>.91</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>.95</td>
<td>.87</td>
<td>.77</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>.48</td>
<td>.81</td>
<td>.95</td>
</tr>
</tbody>
</table>

\(^a\)The optimal cut-off values are those giving the highest sum of sensitivity + specificity.

USA LSM validation study

- Development cohort: 188 (95% HCV)
- Validation cohort: 560 (92% HCV)
- Development:
  - F0/1 56%
  - F2/3 24%
  - F4 20%
- Validation:
  - F0/1 33%
  - F2/3 52%
  - F4 15%

<table>
<thead>
<tr>
<th>METAVIR LSM cutoff (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>DA (%)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>F≥2</td>
<td>8.4</td>
<td>81.9</td>
<td>79.0</td>
<td>75.6</td>
<td>84.7</td>
<td>80.3</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>57.9</td>
<td>57.9</td>
<td>57.9</td>
<td>80.8</td>
<td>55.0</td>
<td>80.3</td>
<td>0.23</td>
</tr>
<tr>
<td>F≥3</td>
<td>9.6</td>
<td>88.3</td>
<td>81.9</td>
<td>68.8</td>
<td>93.7</td>
<td>83.5</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>71.8</td>
<td>71.8</td>
<td>71.8</td>
<td>88.6</td>
<td>77.0</td>
<td>71.8</td>
<td>0.14</td>
</tr>
<tr>
<td>F4</td>
<td>12.8</td>
<td>84.2</td>
<td>86.0</td>
<td>60.4</td>
<td>95.6</td>
<td>85.6</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>75.9</td>
<td>75.9</td>
<td>75.9</td>
<td>97.6</td>
<td>79.8</td>
<td>75.9</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Clinical evaluation of PWID with LSM $\geq 12$ kPa

45 detected

19 (42%) no further examination

26 (58%) examined

3 clinical cirrhosis

23 biopsy done

54% F4

(88% F2+)

Moessner et al: Addiction 2010: 970-76
The French multicenter study (FIBROSTIC)

- \( N = 1307 \) (70\% HCV)
- The diagnostic accuracy was high for cirrhosis, but poor for significant fibrosis (F2).
- A cut off of 17 kPa to rule in cirrhosis had a LR+ of 5.1 (and identified 72\% of patients with cirrhosis)

<table>
<thead>
<tr>
<th>METAVIR score</th>
<th>( = F4 )</th>
<th>(&lt; F4 )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elasticity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 12.9 \text{ kPa} )</td>
<td>127(54%)</td>
<td>111</td>
<td>238</td>
</tr>
<tr>
<td>(&lt; 12.9 \text{ kPa} )</td>
<td>54 (5%)</td>
<td>1015</td>
<td>1069</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>1126</td>
<td>1307</td>
</tr>
</tbody>
</table>
Baseline LSM and survival among patients with HCV

N = 1457
Males 53%
Age 51Y (mean)
F4 18%
HIV 10%

Overall mortality: 6.6% (93) ~ 1.6/100py
Liverrelated mortality 3.6% (53) ~ 0.9/100py

Liverrelated mortality 3.6% (53) ~ 0.9/100py

Vergniol: Gastroenterology: 2011; 1970-79
Mortality among HCV infected

- Crude mortality 2.4/100py (51/587)
  - Liver related 0.6/100py
  - Drug related causes. 0.5/100py

Overall mortality

Liver related death

- No liver related deaths below 17.6 kPa at first LSM
  (median 65 kPa, iqr 27-75)
LSM instead of gastroscopy can be used as screening for varices

Baveno VI recommendation

- If a patient with cirrhosis has LSM <20kPa and platelets >150
  - Gastroscopy is not indicated as the risk of significant varices is <2%
  - These patients can be screened by yearly LSM

De Franchis: J Hepatol 2015;63 j 743–752
Maurice: Jhepatol 2016 (early online)
LSM to rule in and rule out liver fibrosis

- 7 kPa is safe
- 10 kPa is trouble
- 17 kPa is cirrhosis

- But what about the grey zone (7-10 kPa)?
HCV 396 untreated during median 36 month of follow-up

Baseline distribution

<table>
<thead>
<tr>
<th>Range</th>
<th>Baseline</th>
<th>End of follow-up</th>
<th>End of FU distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 kPa</td>
<td>203 (100%)</td>
<td>214 (105%)</td>
<td>54%</td>
</tr>
<tr>
<td>7.0-9.9 kPa</td>
<td>75 (100%)</td>
<td>69 (92%)</td>
<td>17%</td>
</tr>
<tr>
<td>10.0-16.9 kPa</td>
<td>73 (100%)</td>
<td>70 (96%)</td>
<td>18%</td>
</tr>
<tr>
<td>&gt;=17 kPa</td>
<td>45 (100%)</td>
<td>43 (96%)</td>
<td>11%</td>
</tr>
</tbody>
</table>

HCV 396 untreated during median 36 month of follow-up

Baseline

<7 kPa
203 (100%)

7.0-9.9 kPa
75 (100%)

10.0-16.9 kPa
73 (100%)

>=17 kPa
45 (100%)

End of follow-up

<7 kPa
214 (105%)

7.0-9.9 kPa
69 (92%)

10.0-16.9 kPa
70 (96%)

>=17 kPa
43 (96.0%)

HCV 396 untreated during median 36 month of follow-up

Baseline

7.0-9.9 kPa
75 (100%)

End of follow-up

<7 kPa

60%

29%

11%

0%

7.0-9.9 kPa

10.0 -16.9 kPa

>=17 kPa

EASL HCV fibrose algoritme

Hepatitis C (HIV coinfection) Treatment-naïve

Combine Two non-invasive tests: TE + serum biomarker

Discordance
- Repeat exams and search for explanations
  - Discordance
    - Liver biopsy if results influence management

Concordance
- No severe fibrosis-cirrhosis
  - No liver biopsy follow-up or antiviral treatment (if extra-hepatic manifestations)
- Severe fibrosis-cirrhosis
  - No liver biopsy antiviral treatment screening for varices screening for HCC

EASL Non-invasive tests J.hepatol 2015; 63:237-64
Take home messages

- A LSM >7kPa should be repeated in the fasting state after (1)-3 months
- A LSM of 7-10 kPa is likely to decrease over time
- A repeated LSM > 10kPa indicates significant fibrosis
- A repeated LSM > 17 kPa indicates cirrhosis. It is associated with adverse outcome. These patients should enter a screening program for complications
Thanks to the OUH Fibrosis group:

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