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How to Diagnose Cirrhosis

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Disclosures

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Disclosures

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Consultant: AbbVie, Clinical Area- Hepatitis C
Consultant: Fuji-Film Wako, Clinical Area- HCC
Consultant: Gilead, Clinical Area- Hepatitis B, Hepatitis C, NASH
Consultant: Intercept, Clinical Area- PBC, NASH
Cirrhosis Is the Final Pathway for Most Chronic Liver Diseases

Accumulation of collagen deposition = fibrosis → cirrhosis


### Cirrhosis
**A Pathophysiological Classification**

<table>
<thead>
<tr>
<th>Histological</th>
<th>Clinical</th>
<th>Symptoms</th>
<th>Sub-stage</th>
<th>Hemodynamic</th>
<th>Biological</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1-F3</td>
<td>Non-cirrhotic</td>
<td>None</td>
<td>-</td>
<td>Fibrosis and Angiogenesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compensated</td>
<td>None (no varices)</td>
<td>Stage 1</td>
<td>Scar and Cross-linking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compensated</td>
<td>None (varices)</td>
<td>Stage 2</td>
<td>Thick (acellular) scar and nodules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decompensated</td>
<td>Ascites, Hemorrhage, Encephalopathy</td>
<td>Stages 3 and 4</td>
<td>Insoluble scar</td>
<td></td>
</tr>
</tbody>
</table>

So… How Do We Diagnose Cirrhosis?
Invasive vs Non-Invasive

- Invasive
  - Liver biopsy

- Non-invasive
  - Serum markers and calculations
  - Elastography
  - Clinical findings
Invasive-Liver Biopsy

Current standard

According to the AASLD guidelines, liver biopsy remains the most reliable tool to identify steatohepatitis and fibrosis but it presents many challenges\(^1\)

Liver biopsy evaluates histology

Biopsy allows evaluation of the defining histological features of NASH (steatosis, inflammation, cellular ballooning) and also evaluation of fibrosis stage

- The procedure can cost from $1k to $3k\(^2\)
- Mis-staging fibrosis in up to 41% of cases\(^3\)
- 0.35% risk of serious bleeding and 0.14% risk of death\(^4\)

2. Franciscus A. Hepatitis C Support Project 2014;
## Liver Staging

<table>
<thead>
<tr>
<th>Score</th>
<th>Metavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Periportal fibrotic expansion</td>
</tr>
<tr>
<td>2</td>
<td>Periportal septae (&gt; 1 septum)</td>
</tr>
<tr>
<td>3</td>
<td>Pericentral septae</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
Non-Invasive – Serum Markers

Fibrotest

**Fibrosis stage**

- **F0**
- **F1**
- **F2**
- **F3**
- **F4**

**B**

- 5-marker index
- 0.0
- 0.1
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6
- 0.7
- 0.8
- 0.9
- 1.0

**Fibrotest Results**

- FT > 0.80
  - Spec 97%
  - PPV 92%

- FT ≤ 0.20
  - Sens 92%
  - NPV 87%

**Indeterminate**

- 54%

**n=134**

- F2-F4 fibrosis: 45%

Non-Invasive – Calculations

FIB-4 = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}

APRI = \frac{\text{AST Level}}{\text{Platelet Count (10}^9/\text{L})} \times 100

- < 1.45 excludes severe fibrosis (F3-F4) with high negative predictive value
- > 3.25 has high predictive value for significant (F3-F4 fibrosis)
- Calculator available on internet

- Estimate for predicting severe fibrosis or cirrhosis
- Most laboratories use an AST upper limit of 40 IU/mL
- Best use: APRI<0.5 will rule out cirrhosis
- Calculator available on internet

# Performance of Non-Invasive Fibrosis Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>AUC</th>
<th>Cut-off</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT ratio</td>
<td>0.83 (0.74-0.91)</td>
<td>0.8</td>
<td>74</td>
<td>78</td>
<td>44</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>52</td>
<td>90</td>
<td>55</td>
<td>89</td>
</tr>
<tr>
<td>APRI</td>
<td>0.67 (0.54-0.8)</td>
<td>1</td>
<td>27</td>
<td>89</td>
<td>37</td>
<td>84</td>
</tr>
<tr>
<td>BARD score</td>
<td>0.77 (0.68-0.87)</td>
<td>2</td>
<td>89</td>
<td>44</td>
<td>27</td>
<td>95</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>0.86 (0.78-0.94)</td>
<td>1.30</td>
<td>85</td>
<td>65</td>
<td>36</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.25</td>
<td>26</td>
<td>98</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>NAFLD fibrosis score</td>
<td>0.81 (0.71-0.91)</td>
<td>-1.455</td>
<td>78</td>
<td>58</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.676</td>
<td>33</td>
<td>98</td>
<td>79</td>
<td>86</td>
</tr>
</tbody>
</table>

Non-Invasive – Transient Elastography

- Measures velocity of a low-frequency (50 Hz) elastic shear wave\(^1\).
- Liver stiffness expressed in kPa which correlates to liver fibrosis stage\(^2\).
- Volume of tissue is 100 times bigger than biopsy\(^4\).
- False positives: recent meals, acute hepatitis, extrahepatic cholestasis, and congestion\(^1\).
- Issues: obesity, ascites, operator inexperience\(^1\).

The velocity of the sound wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface.

- Reliable LSMs: 10 valid measurements and interquartile range ≤ 30% of the median.
- Median LSMs for patients without and with F3–F4 (advanced) fibrosis were 6.6 kPa (5.3–8.9) and 14.4 kPa (12.1–24.3), respectively.
- **Optimal LSM cutoff for advanced fibrosis was 9.9 kPA (sensitivity 95% and specificity 77%).**
- All patients with LSM<7.9 kPA did not have advanced fibrosis.
- Detection of F3–F4 in patients with reliable VCTE has AUROC 0.93 (95% CI: 0.86–0.96).

Implementing a Non-Invasive Approach to Clinical Staging of Liver Disease

To determine whether patient has advanced liver disease
Perform elastography or serologic test for fibrosis with high negative likelihood ratio
If not low risk, perform second test, combining elastography and serologic test

Test results are concordant
Low risk
Disease-specific follow-up and management
High risk
Disease-specific follow-up and indicated surveillance procedures for patients with cirrhosis
Indeterminate risk
Consider liver biopsy

Test results are discordant or elastography fails
Recheck test results or perform MRE

Test results are still discordant
Advanced fibrosis (F3 or F4)
Mild fibrosis (F0 – F2)

If low risk, cirrhosis is unlikely and disease-specific follow-up management should be arranged

Correlation Between LSM & Fibrosis Stage

Non-Invasive – Clinical Findings

- **Asymptomatic (compensated)**
  - Subtle clues may be overlooked
    - Thrombocytopenia
    - Muscle wasting
    - AST>ALT without alcohol consumption
    - Liver enzymes may not be abnormal
    - Albumin < 3.5 mg/dL
    - Bili > 1.0-1.2
    - Nodular appearing liver on imaging
    - Splenomegaly

- ** Decompensated (Symptomatic)**
  - Portal hypertension: ascites, overt hepatic encephalopathy, variceal bleeding
  - Hepatic failure: jaundice, coagulopathy

In Conclusion

• Liver biopsy still the standard.
• Multiple other modalities available that are non-invasive.
• Be aware of clinical signs and symptoms. DO NOT miss them!