Non-Invasive Testing for Liver Fibrosis

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Conflicts of Interest

• In the past year, I have served on Advisory Boards for Gilead, given one talk for Jannsen, and serve on the DSMB for Tacere Therapeutics.

• My institution has received funding for clinical trials that I participate in from AbbVie, Gilead, Genentech, Merck, and BMS.
Objectives

- To understand the advantages and disadvantages of non-invasive tests
- To demonstrate a logical testing sequence for assessing liver fibrosis
AASLD Guidelines for Hep C Treatment

✓ All patients should be treated
✓ Highest priority for F3-F4, extrahepatic disease, pre and post-txp pts
✓ High priority is F2, HIV or HBV coinfection, other liver dz, PCT, DM, and severe fatigue

Liver Biopsy is an Unreliable Gold Standard!

- Sampling error leads to misinterpretation in 10-15% of cases
  - Need at least 2 cm sample, >10 portal triads
  - Beware fracturing! Tipoff to cirrhosis
- Can miss the diagnosis of cirrhosis
- Invasive procedure with complications
- Expensive ($2500)
- Poor patient acceptance
- Interpretation has significant inter observer variability

Blood Tests: Indirect Markers

- Uses commonly obtained laboratory values to estimate fibrosis and establish overt cirrhosis.
  - Prothrombin index
  - Platelet Count
  - Aspartate aminotransferase
  - Alanine aminotransferase
Calculating APRI

\[
\text{APRI} = \frac{\text{AST level} (/\text{ULN})}{\text{Platelet count} (10^9/L)} \times 100
\]
Fibrosure

- Includes: age, gender, alpha-2-macroglobulin, haptoglobin, GGT, apolipoprotein A1, total bilirubin, & ALT.

- Contraindications for use of the FibroTest method for fibrosis staging include Gilbert’s disease, acute hemolysis, extrahepatic cholestasis, post transplantation, or renal insufficiency, all of which may lead to inaccurate quantitative predictions.

- Indeterminate in middle fibrotic ranges
Direct Markers of Fibrosis

- These include the markers that demonstrate deposition or removal of extracellular matrix in the liver.
  
  Glycoproteins-hyaluronic laminin, procollagen III,IV, matrix metalloproteases(inhibitors), tissue metallopreotease -1
<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Etiologies</th>
<th>Year</th>
<th>Patients (n)</th>
<th>F ≥2 (%)</th>
<th>F4 (%)</th>
<th>Cut-offs</th>
<th>AUROC</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>CC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroTest</td>
<td>HCV</td>
<td>2001</td>
<td>339</td>
<td>80</td>
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<td>&gt;0.48</td>
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<td>30-94</td>
<td>51-95</td>
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<td>75-93</td>
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<td>ELF</td>
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<td>1021/496&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>12</td>
<td>0.102</td>
<td>0.78</td>
<td>87</td>
<td>51</td>
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<tr>
<td>FPI</td>
<td>HCV</td>
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<td>302</td>
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<td>≤0.2 ≥0.8</td>
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<td>42-85</td>
<td>48-98</td>
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<td>Hepascore</td>
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<td>211</td>
<td>57</td>
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<td>≥0.5</td>
<td>0.82</td>
<td>63</td>
<td>89</td>
<td>92</td>
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<tr>
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<td>598/503&lt;sup&gt;b&lt;/sup&gt;</td>
<td>56</td>
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<td>84</td>
<td>82</td>
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<td>HCV</td>
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<td>12</td>
<td></td>
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<td>54-90</td>
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<td>HCV</td>
<td>2007</td>
<td>847</td>
<td>17&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>0.85</td>
<td>38-74</td>
<td>81-98</td>
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<tr>
<td>HALT-C model</td>
<td>HCV</td>
<td>2008</td>
<td>512</td>
<td>38</td>
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<td>&lt;0.2 ≥0.5</td>
<td>0.81</td>
<td>47-88</td>
<td>45-92</td>
<td>48</td>
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<tr>
<td>Hui Score</td>
<td>HBV</td>
<td>2005</td>
<td>235</td>
<td>25</td>
<td></td>
<td>≤0.15 &gt; 0.5</td>
<td>0.79</td>
<td>37-88</td>
<td>50-88</td>
<td>49</td>
</tr>
<tr>
<td>Zeng score</td>
<td>HBV</td>
<td>2005</td>
<td>372</td>
<td>58</td>
<td></td>
<td>&lt;3.0 &gt; 8.7</td>
<td>0.77</td>
<td>40-98</td>
<td>28-90</td>
<td>35</td>
</tr>
</tbody>
</table>

AUROC, area under ROC curve; CC, correctly classified; true positive and negative; HBV, chronic hepatitis B; HCV, chronic hepatitis C; NA, not available; Se, sensitivity; Sp specificity.

<sup>a</sup>Number of HCV patients.

<sup>b</sup>Number of patients with viral hepatitis.

<sup>c</sup>F3-F4 patients.
Radiologic Assessment of Fibrosis

- Ultrasound
- Transient Elastography/Fibroscan
- ARFI-Shear waves
- MRI elastography
Ultrasound

- Can assess for nodularity of the liver surface
  - If present, >80% PPV
- Coarseness of the parenchyma
- Size of lymph nodes around the hepatic artery, patency and flow of veins and arteries, spleen size, screen for hepatocellular carcinoma, and small volume ascites.
- The use of high-frequency ultrasound transducers is reported to be more reliable than low-frequency ultrasound in diagnosing cirrhosis.
FibroScan

- Transient elastography examines a large mass of liver tissue (1 cm diameter by 5 cm in length) and thus provides a more representative assessment of the entire hepatic parenchyma.
- Ultrasound transducer probe that is mounted on the axis of a vibrator. Vibration is transmitted toward hepatic tissue, the vibrations are followed by pulse echo and their velocities are measured which is related directly to liver stiffness.
- Sensitivities of 84 to 100% and specificities of 91 to 96%. Results limited in those with ascites, elevated central venous pressure, and obesity, as fluid and adipose tissue attenuate the echo waves.
ARFI: Acoustic Radiation Forced Impulse

- Acoustic radiation forced impulse (shear waves) measured in meters/sec
- Easily adaptable to ultrasound machines
- Does not have fluid or obesity limitations
- Better sensitivity than FibroScan, gives 3D picture
Transient Elastography Predicts Clinical Outcomes

- N = 667 patients (HCV, 67%; nonalcoholic steatohepatitis, 13%) with liver disease (n = 120 with cirrhosis)
- TE had an area under the receiver operating characteristic curve of 0.87 for predicting clinical outcome
- High negative predictive value with liver stiffness of 10.5 kPa for excluding a liver-related clinical outcome such as variceal bleeding, liver failure, or development of HCC over 2 yrs

<table>
<thead>
<tr>
<th>Outcomes with TE cutoff of 10.5 kPa, %</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>95</td>
<td>63</td>
<td>19</td>
<td>99</td>
</tr>
<tr>
<td>Cirrhotics only</td>
<td>98</td>
<td>10</td>
<td>27</td>
<td>92</td>
</tr>
</tbody>
</table>

Comparison of Blood Tests to Transient Elastography

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum biomarkers</td>
<td>• Good reproducibility</td>
<td>• Nonspecific of the liver</td>
</tr>
<tr>
<td></td>
<td>• High applicability (95%)</td>
<td>• Unable to discriminate between intermediate stages of fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Low cost (~$250) and wide availability (nonpatented)</td>
<td>• Performance not as good as TE for cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Well validated</td>
<td>• Results not immediately available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cost and limited availability (proprietary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Limitations (hemolysis, Gilbert syndrome, inflammation…) &lt; 5%</td>
</tr>
<tr>
<td>Transient elastography</td>
<td>• Liver stiffness is a genuine physical property of liver tissue</td>
<td>• Requires a dedicated device</td>
</tr>
<tr>
<td></td>
<td>• Good reproducibility</td>
<td>• Region of interest cannot be chosen</td>
</tr>
<tr>
<td></td>
<td>• Well validated</td>
<td>• Unable to discriminate between intermediate stages of fibrosis</td>
</tr>
<tr>
<td></td>
<td>• High performance for cirrhosis</td>
<td>• Low applicability (80%, obesity, ascites, limited operator experience)</td>
</tr>
<tr>
<td></td>
<td>• User friendly (rapid, results immediately available; short learning curve)</td>
<td>• False positive in case of acute hepatitis, extrahepatic cholestasis, and congestion</td>
</tr>
<tr>
<td></td>
<td>• Can be performed in the outpatient clinic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prognostic value in cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

Castera L. Gastroenterology. 2012;142:1293–1302
HCV Antibody Positive
(Test all Persons Born 1945-65 or persons with history IDU, Annual Test for Active IDU)

Check HCV RNA

Positive

Evaluate for Ongoing Alcohol Abuse & IDU

Significant Ongoing Alcohol Abuse or IDU

Patient Counseling on Transmission and Alcohol, Refer for Alcohol/Drug Treatment as Available, Vaccinate for HAV/HBV

Reevaluate Alcohol/Drug Use & Potential for Referral at Least Annually

No significant Ongoing Alcohol Abuse or IDU

Check HCV Genotype, LFTs & CBC
If APRI .5-1.5 Check Fibrosure or Fibroscan
Vaccinate for HBV/HAV, Counsel on Transmission Risks and to Avoid Alcohol

Evaluate for Treatment

Negative

No Active Infection
(Retest Persons with Ongoing Risk Reinfection Annually)

No significant Ongoing Alcohol Abuse or IDU
What is the role of the liver biopsy in 2014?

- Very useful when diagnosis is uncertain
  - eg, post liver transplant setting, autoimmune hepatitis, drug-induced hepatitis
- Diminishing role in most patients as noninvasive testing becomes more accurate and available
- Ultrasound transient elastography may be better test to predict clinical outcomes
- As treatment becomes less toxic and more effective, there is less need to stage the patient’s liver disease
Summary

• There is no perfect one test solution
• Serum markers good at ends but soft in middle
• More powerful if several tests used together such as 2 biomarker tests or one biomarker and elastography.
• Stay tuned for MRI elastography
Questions?