Non-invasive fibrosis markers do not replace liver biopsy

University of Illinois at Chicago
Mrudula V. Kumar, MD
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Role of Liver Biopsy

To assess fibrosis AND inflammatory activity
To evaluate for co-etiologies (ex. HCV and NASH)
To help determine the need for treatment in hepatitis C infection (mild vs. moderate vs. severe fibrosis)

UIC: 53% of 593 biopsies done in the last 3 years were for staging of HCV
French study 54% (Hepatology 2000)
Advantages of Liver Biopsy

Provides a direct, quantitative assessment of fibrosis
Allows fibrosis to be measured using a standardized system
Can be used to assess progression of disease/fibrosis over time
Provides additional information regarding:
  - Degree of inflammation
  - Distribution of fibrosis
  - Co-existing pathology
Risk of a serious adverse event is rare (<0.2%)

Limitations of Liver Biopsy: Size Matters

Specimen length:

1.5 cm
  - Fails to recognize cirrhosis in 15-40%
  - Even so, NPV 93% (as good or better than most non-invasive tests)
3.0 cm
  - PPV and NPV 100%
  - Diagnostic accuracy 100%

Ideal Characteristics of Non-invasive Fibrosis Markers

Liver Specific
Reflect fibrosis irrespective of the cause
Simple
Readily available
Inexpensive
Sensitive enough to distinguish between different stages of fibrosis
***No tests that are currently available meet all of these criteria

<table>
<thead>
<tr>
<th>Name</th>
<th>Components</th>
<th>Sens/Spec</th>
<th>PPV/NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT</td>
<td>AST/ALT ratio</td>
<td>53%/100%</td>
<td>100%/81%</td>
</tr>
<tr>
<td>APRI</td>
<td>AST, plts</td>
<td>41%/95%</td>
<td>88%/64%</td>
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<tr>
<td>Fibrotest</td>
<td>GGT, bilirubin, apolipoprotein A</td>
<td>87%/59%</td>
<td>63%/85%</td>
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<tr>
<td></td>
<td>Hyaluronic acid, TIMP-1, alpha-2-</td>
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<td></td>
<td>macroglobulin</td>
<td></td>
<td></td>
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<tr>
<td>Fibrospect</td>
<td></td>
<td>83%/66%</td>
<td>72%/78%</td>
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</tbody>
</table>

Limitations of Non-invasive Fibrosis Markers

Indirect measure
Can predict mild (F0/1) or severe (F3/4) fibrosis, not intermediate stages
Either have poor sensitivity and NPV or poor specificity and PPV
Only few of these non-invasive markers have been compared in head-to-head trials
Little evidence is available on patients with non-HCV liver disease

Elastography

Measures mean hepatic tissue stiffness which is indirectly related to the degree of fibrosis using pulse-echo technology
The velocity of the vibration wave as it passes through the liver correlates directly with tissue stiffness
The stiffer the tissue, the faster the shear wave
Elastography Limitations

Signal propagation (25-65mm) limited in:
- Obese patients
- Patients with ascites
- Patients with narrow intercostal space
- No established optimal cutoff for what is abnormal
- Cannot differentiate between fibrosis and steatosis
- Cannot track changes in fibrosis as a result of treatment

Elastography (≥ F2 Fibrosis)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>AUC</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>Ziol et al</td>
<td>327</td>
<td>0.79</td>
<td>0.56</td>
<td>0.91</td>
<td>0.88</td>
<td>0.56</td>
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<tr>
<td>Castera et al</td>
<td>183</td>
<td>0.83</td>
<td>0.67</td>
<td>0.89</td>
<td>0.95</td>
<td>0.48</td>
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<tr>
<td>Colletta et al</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</table>

*Fibrosis scores are rated by the METAVIR score
## Summary

Liver biopsy has been the gold standard for fibrosis assessment because it is a **direct** measure. Biopsy enables an accurate 3-level staging of fibrosis when there is an adequate sample length. Non-invasive markers assess the extremes of fibrosis, not the clinically relevant intermediate stages. Non-invasive markers have either a low specificity or sensitivity, circumventing the need for liver biopsy in only a minority of patients. Many non-invasive markers are not readily available or standardized.

## Conclusions

Liver biopsy remains the most accurate means to directly measure different stages of liver fibrosis. There is no convincing evidence that non-invasive markers have the precision that is necessary to track disease progression or response to therapy. While non-invasive markers may prove useful in their ability to assess the extremes of fibrosis, their low specificity and/or sensitivity abolish the need for liver biopsy in only a minority of patients. Future non-invasive markers need to be able to detect intermediate stages of fibrosis with more sensitivity and specificity before they are ready for routine clinical use.