

Sorting Out The Diagnostics

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Dignity HealthTM

St. Joseph's Hospital and
Medical Center

Goals and Objectives

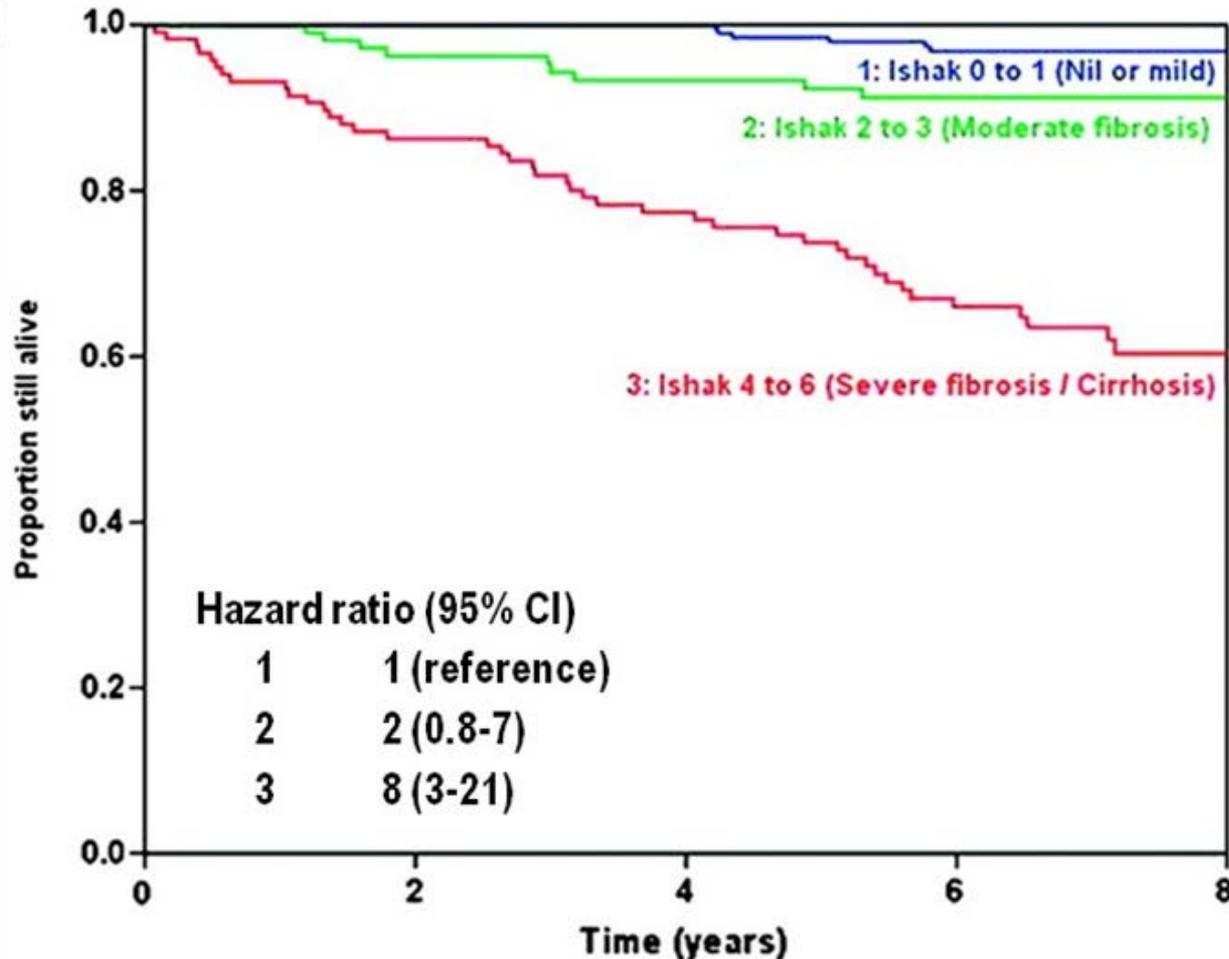
- Describe different techniques to measure liver fibrosis
- Identify the advantages and disadvantages of each technique

I have no financial disclosures relevant to the content of this presentation.

Why do we need to assess liver fibrosis?

- Assessment of prognosis
- Decision-making in medical treatment
- Guiding response to treatment

Fibrosis stage as a predictor of long-term liver-related morbidity/mortality



N=457

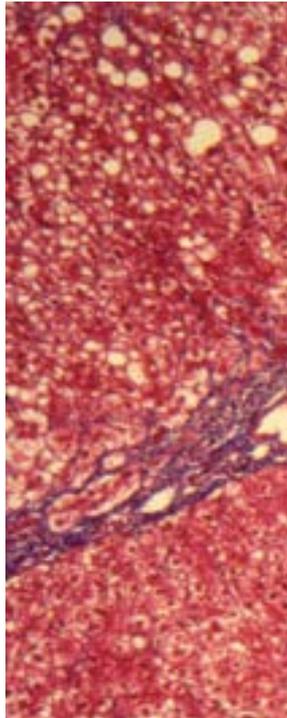
Median follow-up: 7yrs

Fibrosis associated with:

- Portal HTN
- Risk of HCC
- Liver decompensation
- Need for OLTx

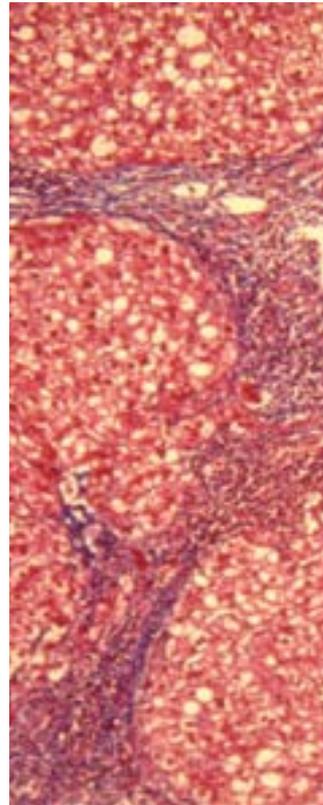


Liver Biopsy Staging of Fibrosis

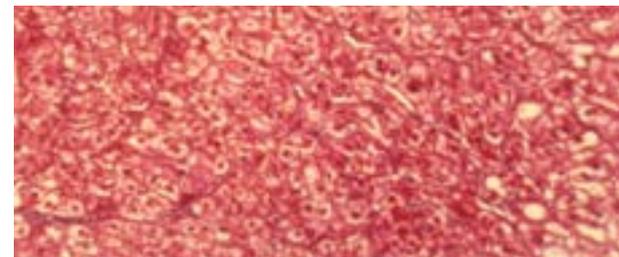


Fibrosis present, suggestion of a bridge?

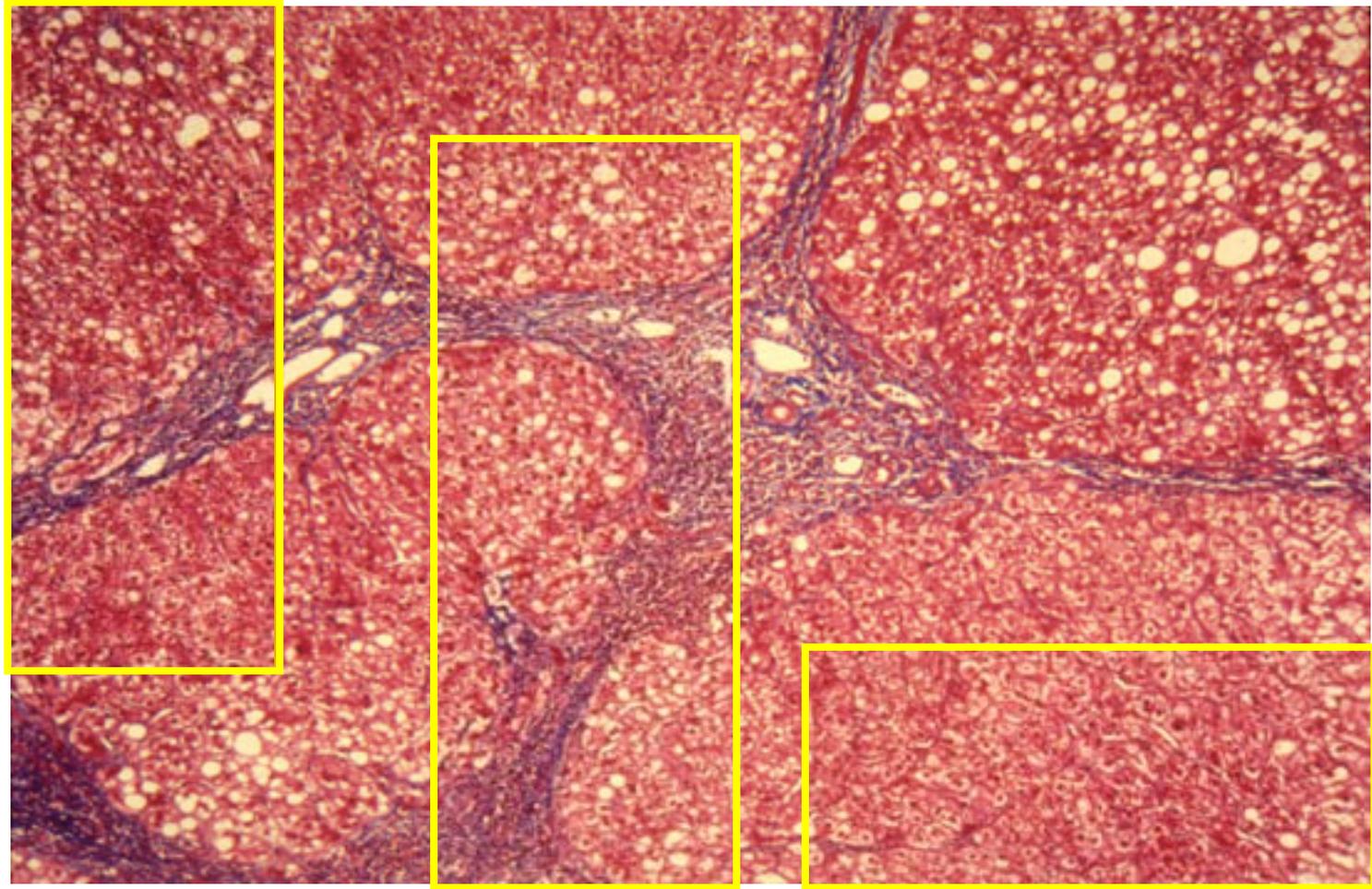
F4- bridging present with nodule formation



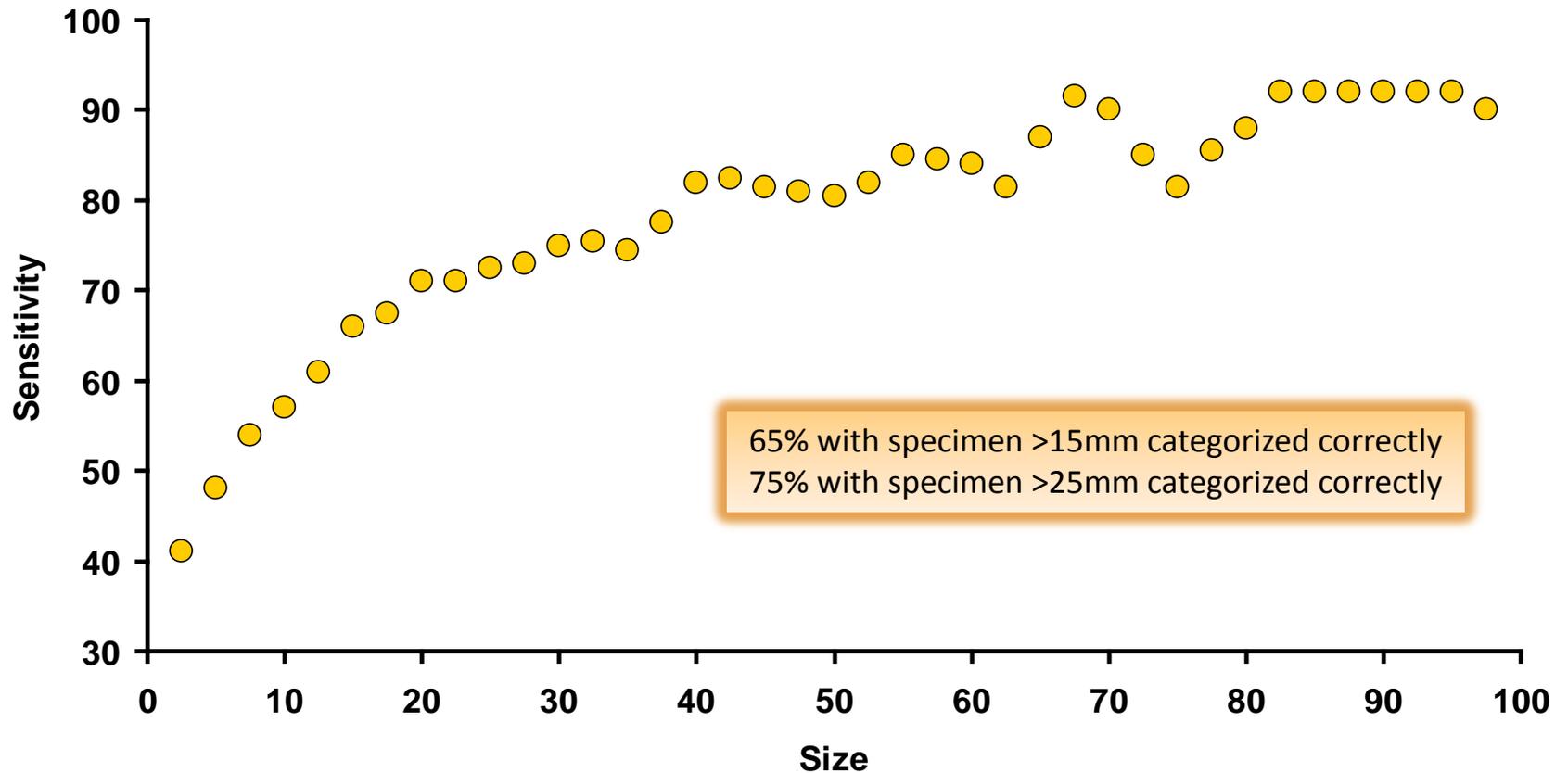
F0 – no fibrosis seen, no portal tracts



Liver Biopsy Staging of Fibrosis



Sampling variability of fibrosis in HCV



Complications of Liver Biopsy

Complication	Percent (%)
Pain at the right hypochondrium, shoulder	0.056-83%
Hemorrhagic complications	Subcapsular hematoma: 0.05% Intrahepatic hematoma: 0.05% Intraperitoneal bleeding: 0.03% Hemobilia: 0.05%
Bacteremia	0.08%
Death	0.001-0.0001%
Bile peritonitis	0.03-0.22%
Pneumothorax, hemothorax	0.08-0.28%
Subcutaneous emphysema	0.014%
Break of the biopsy needle	0.02%
Biopsy of other organs	Lungs-0.001% Bile-0.003% Colon-0.003% Kidneys-0.09%

Liver biopsy

- Advantages:
 - Diagnostic uses beyond staging alone
 - Still considered by many to be the “gold standard”**
- Disadvantages:
 - Risks to patient (complications)
 - Cost
 - Biopsy specimen only captures 1/50,000th of the liver
 - Sampling variation (can underestimate degree of fibrosis in 20-30%)
 - Interobserver variability
 - Sample adequacy

Serum fibrosis tests

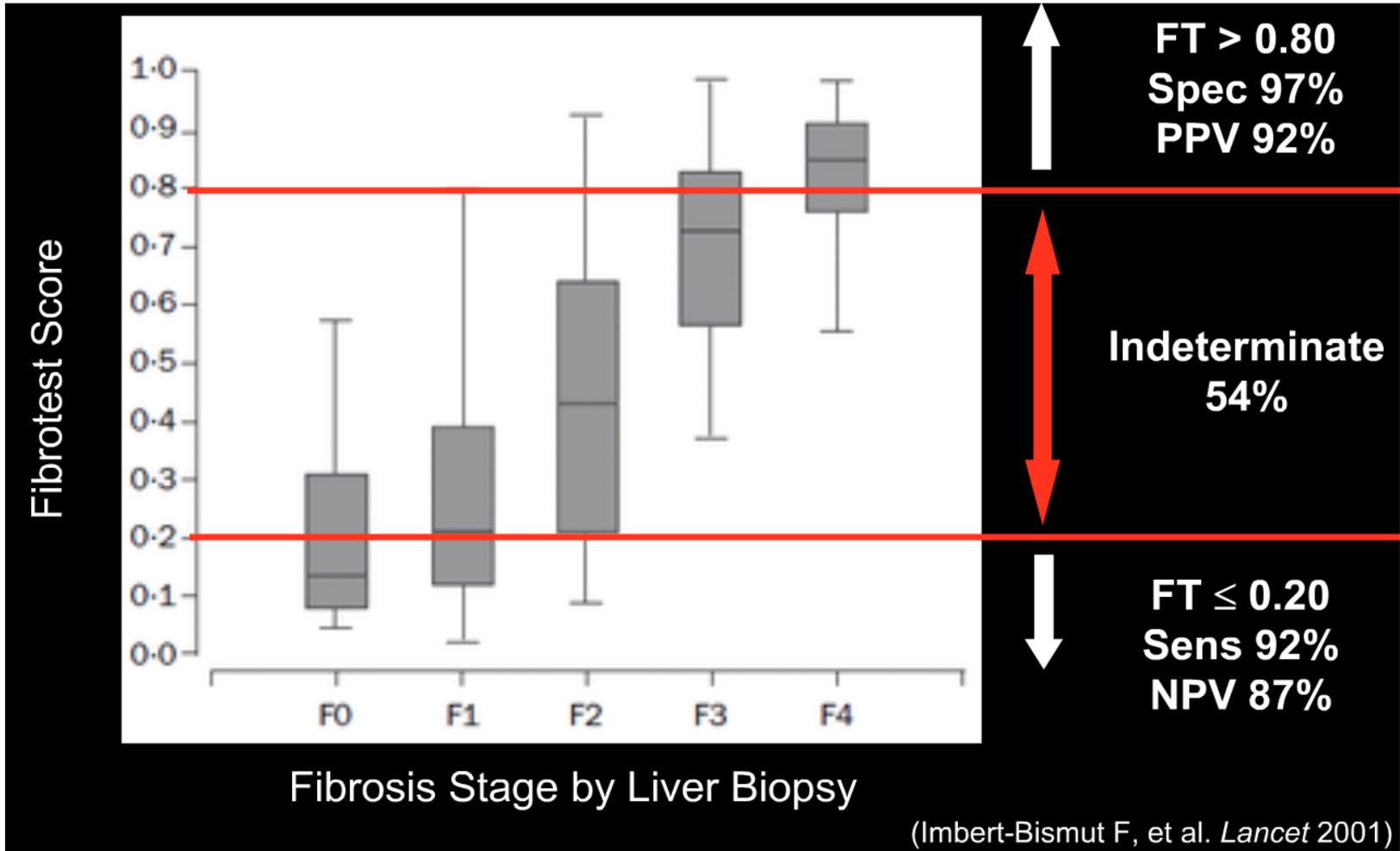
- Several commercially available fibrosis tests/panels:
 - FibroTest® (Biopredictive, Paris, France)
 - Fibrosure® (LabCorp, Burlington, NC, USA)
 - FibroSpect® (Prometheus Labs, San Diego, CA, USA)
 - HepaScore® (PathWest, Melbourne, Australia – licensed to Quest)
- Direct tests: markers related to the deposition of scar tissue and fibrosis within the liver (e.g. hyaluronic acid, MMPs, TIMP1, etc.)
- Indirect tests: markers related to liver function and metabolism (e.g. albumin, platelets, INR, bilirubin, ALT, etc.)



Serum fibrosis tests

- Several commercially available fibrosis tests/panels:
 - FibroTest[®] (Biopredictive, Paris, France)
 - GGT, total bilirubin, a2-macroglobulins, apolipoprotein A-1, haptoglobin
 - Fibrosure[®] (LabCorp, Burlington, NC, USA) – *for HCV*
 - ALT, GGT, total bilirubin, a2-macroglobulins, apolipoprotein A-1, haptoglobin
 - FibroSpect[®] (Prometheus Labs, San Diego, CA, USA)
 - Hyaluronic acid, tissue inhibitor of metalloproteinase (TIMP1), and a2-macroglobulins
 - HepaScore[®] (PathWest, Melbourne, Australia – licensed to Quest)
 - GGT, total bilirubin, hyaluronic acid, a2-macroglobulins

Fibrosis panels and degree of uncertainty



AST to Platelet Ratio Index (APRI) Calculator

This is an **AST to Platelet Ratio Index** calculator tool. Enter the required values to calculate the APRI value. The APRI Score will appear in the oval on the far right (highlighted in yellow). Most laboratories use 40 IU/L as the value for the AST upper limit of normal.

$$\text{APRI} = \frac{\text{AST Level (IU/L)}}{\text{AST (Upper Limit of Normal) (IU/L)}} \times \frac{\text{Platelet Count (10}^9\text{/L)}}{125} = 1.260$$

The calculation uses the following values:

- AST Level (IU/L): 63
- AST (Upper Limit of Normal) (IU/L): 40
- Platelet Count (10⁹/L): 125

Interpretation:

In a meta-analysis of 40 studies, investigators concluded that an APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. In addition, they concluded that APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.

Source: Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology*. 2011;53:726-36.

Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = 3.31$$

Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Source: Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. *Hepatology* 2006;43:1317-1325.

Performance of serum markers

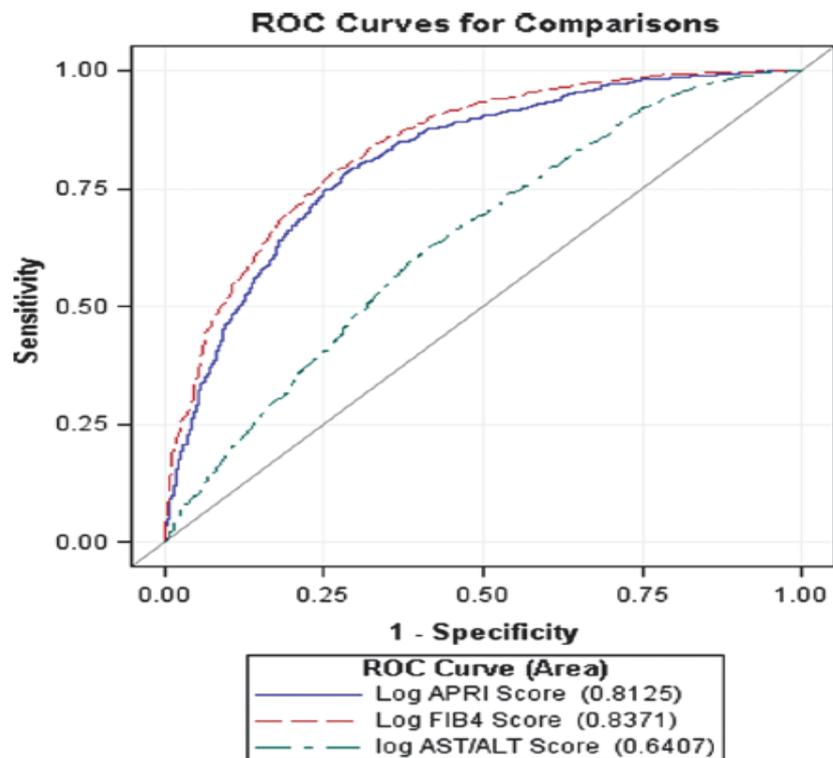


Figure 1. The predictive ability of 3 noninvasive methods for severe fibrosis. The areas under the receiver operating characteristic curve analysis in distinguishing severe fibrosis (stages F3 and F4) from mild-to-moderate fibrosis (stages F0–F2) were 0.80 (95% confidence interval [CI], .78–.82) for APRI, 0.83 (95% confidence interval [CI], .81–.85) for FIB-4, and 0.64 (95% CI, .61–.66) for aspartate aminotransferase/alanine aminotransferase ratio. Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; FIB-4, an index from serum fibrosis markers; ROC, receiver operating characteristic.

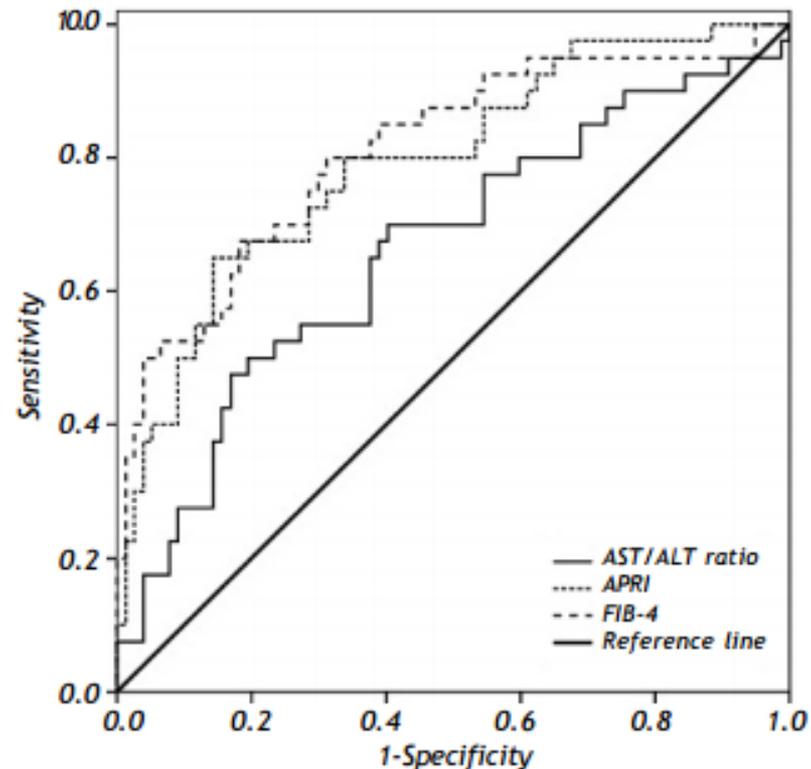
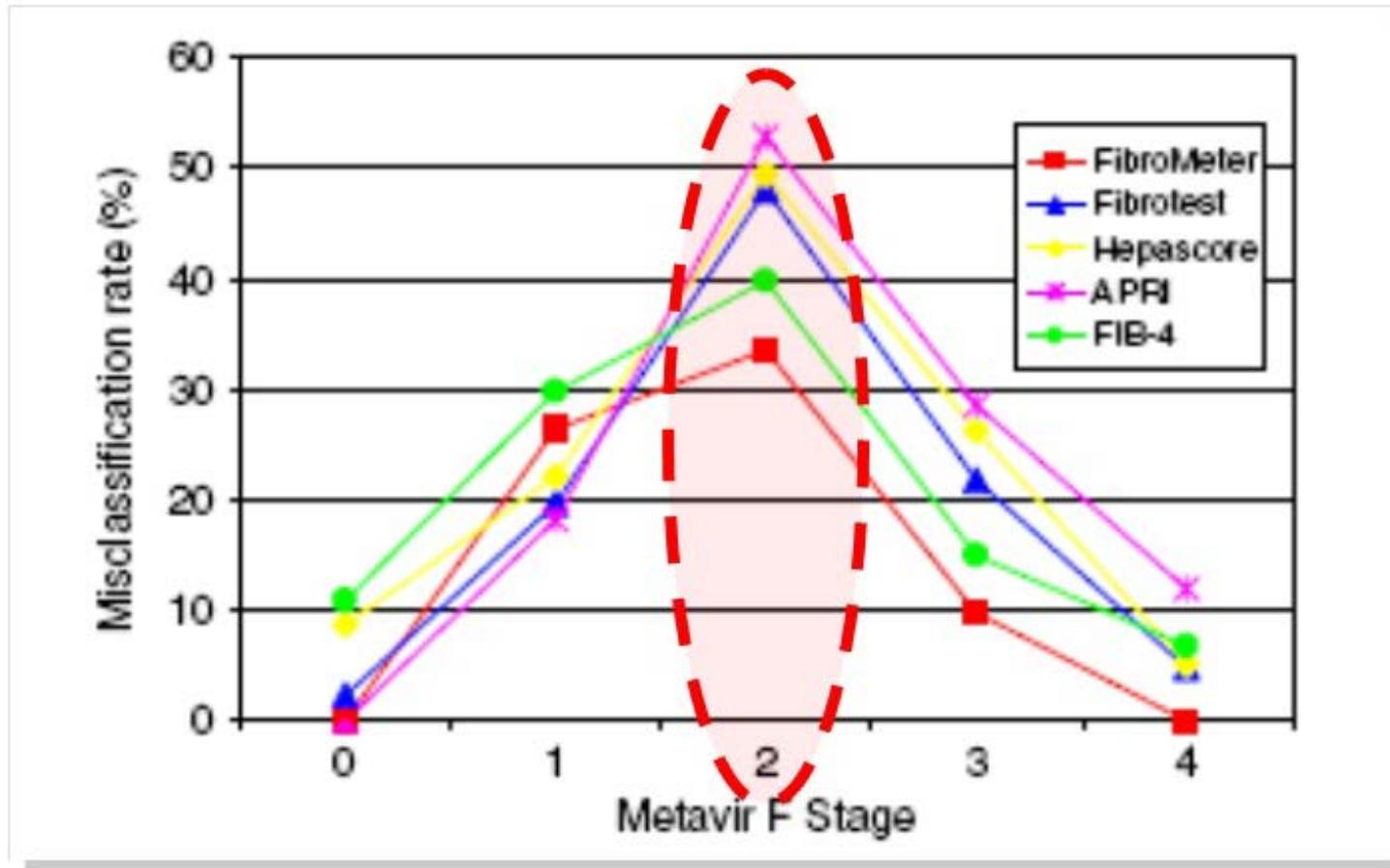


Figure 3. ROC curves of AST/ALT ratio, APRI and FIB-4 in distinguishing significant liver fibrosis (F2-F3-F4) from non-significant liver fibrosis (F0-F1). Comparison of AUROCs showed superior diagnostic accuracy of FIB-4 ($P = 0.014$) and a trend toward higher AUROC for APRI ($P = 0.054$) when compared to the AST/ALT ratio.

Misclassification Rate



N= 1056 HCV patients

Cales P. et al. Liver Int 2009

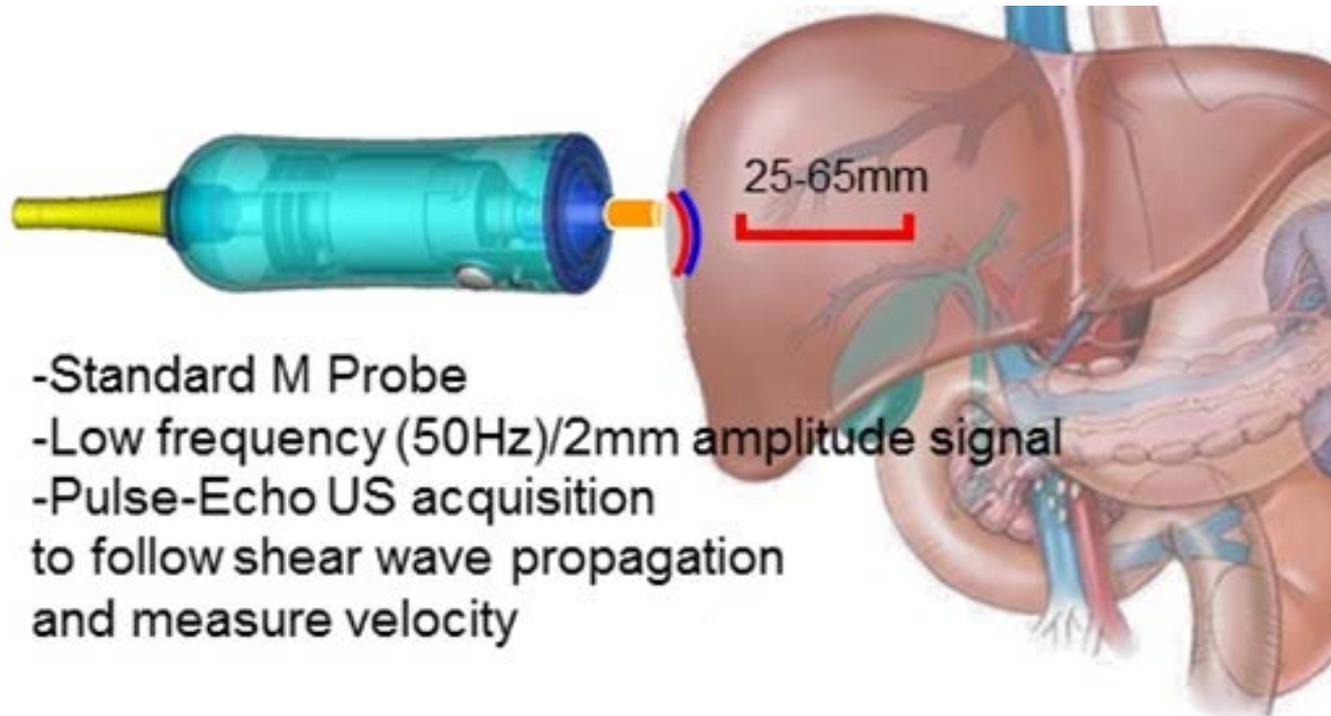
Ultrasound-based Elastography

- FibroScan

- Transient elastography utilizing single-frequency ultrasound waves
- Rapid examination—takes approx. 10 minutes.
- FDA-approved with own CPT code
- No real-time imaging or dopplers
- High acquisition cost (>\$100,000)
- Limited by obesity, fatty liver, CHF, skin thickness, narrow ribs, ascites, inflammation, technique (operator experience), other technical factors



FibroScan



- Standard M Probe
- Low frequency (50Hz)/2mm amplitude signal
- Pulse-Echo US acquisition to follow shear wave propagation and measure velocity

Overall failure rate of LS measurement:

25% for BMI 30-35 kg/m²

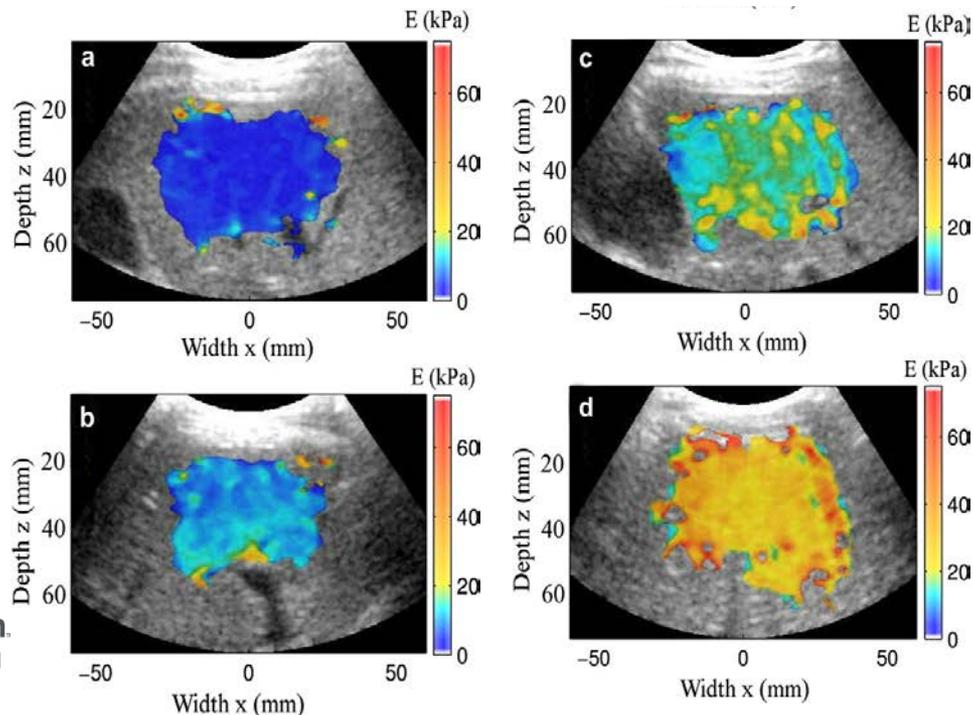
41% for BMI 35-40 kg/m²

88% for BMI > 40 kg/m²

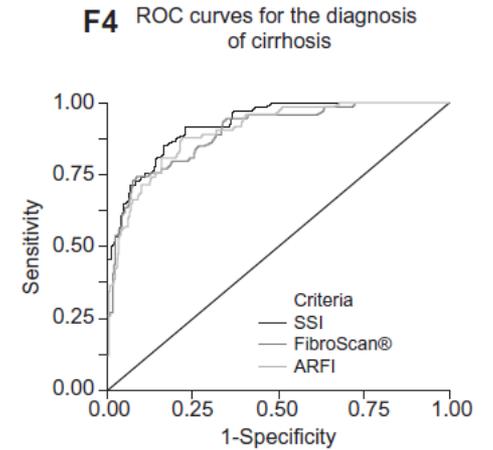
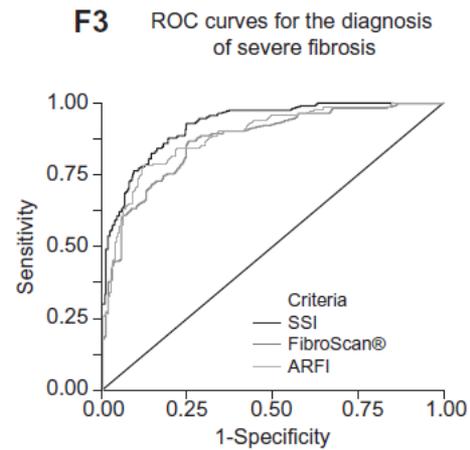
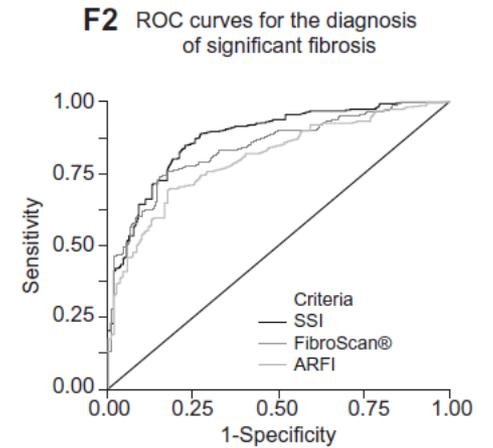
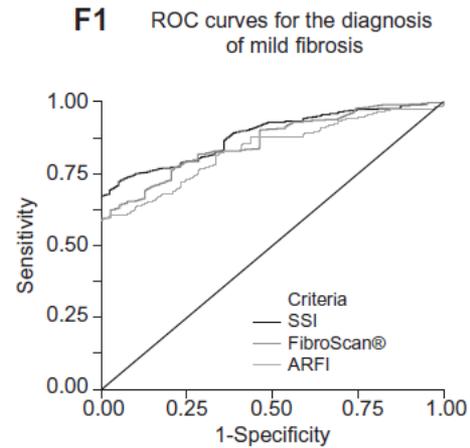
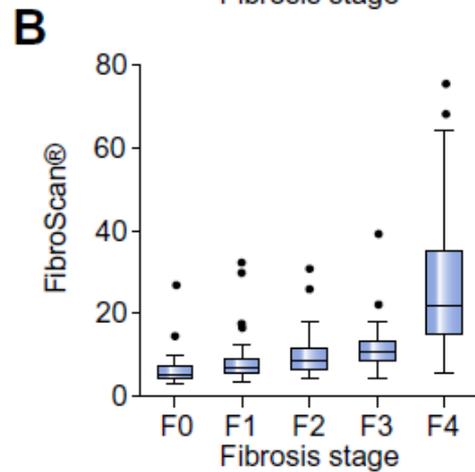
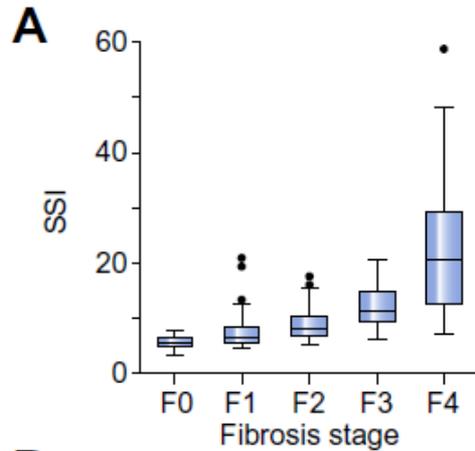
Ultrasound-based Elastography

- Aixplorer

- Supersonic shear imaging (ShearWave)
- Multiple wave fronts with frequencies ranging from 60-600 Hz
- Real-time imaging available to target area of interest

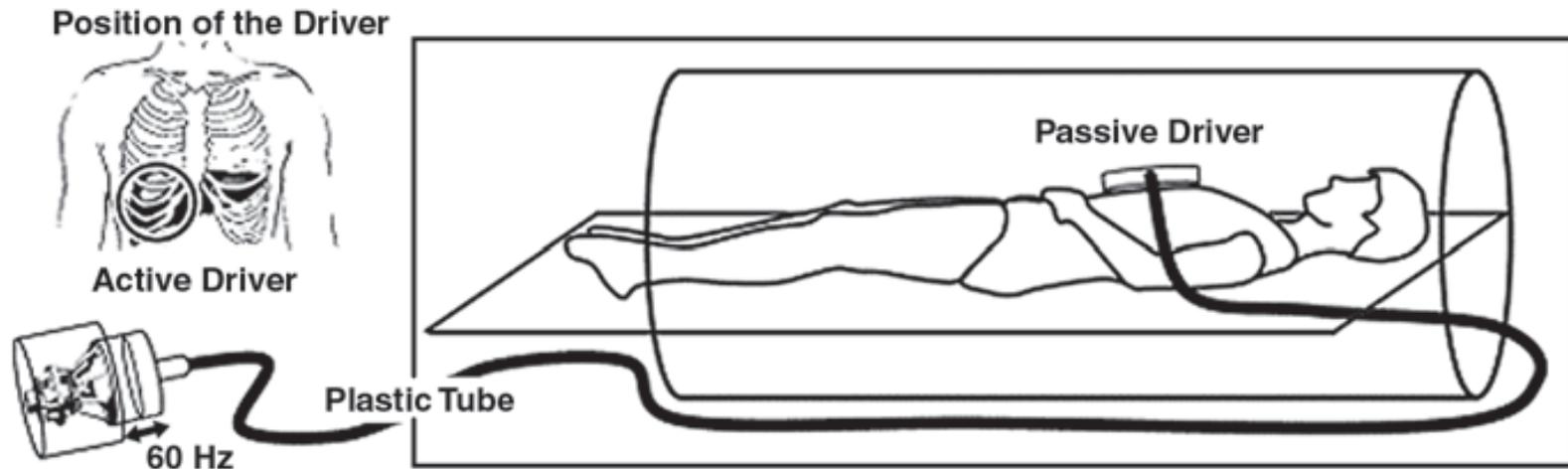


Ultrasound-based Elastography

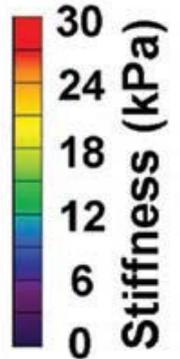
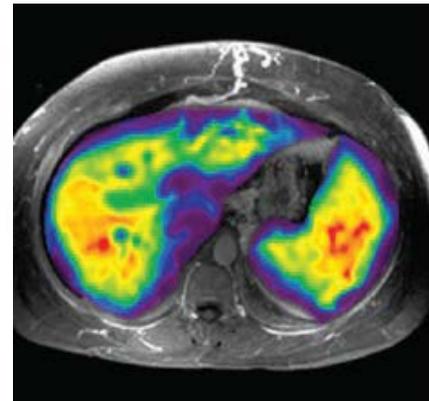
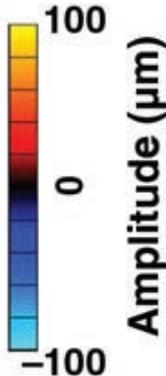
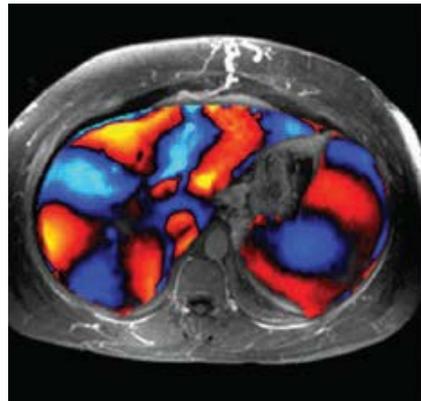
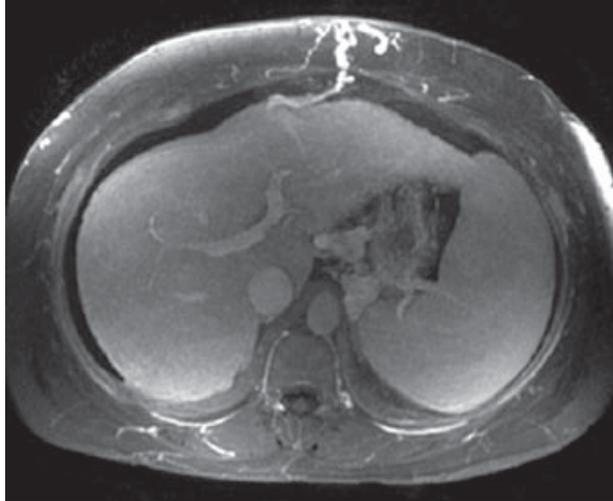
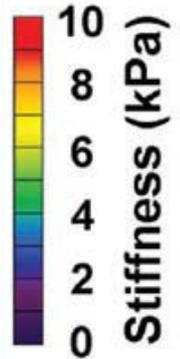
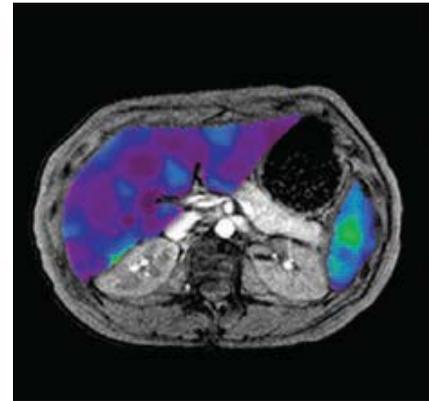
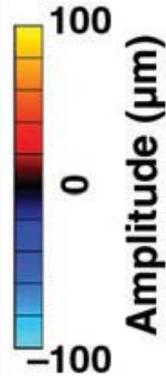
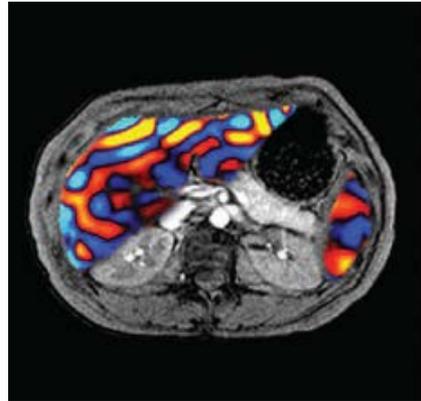
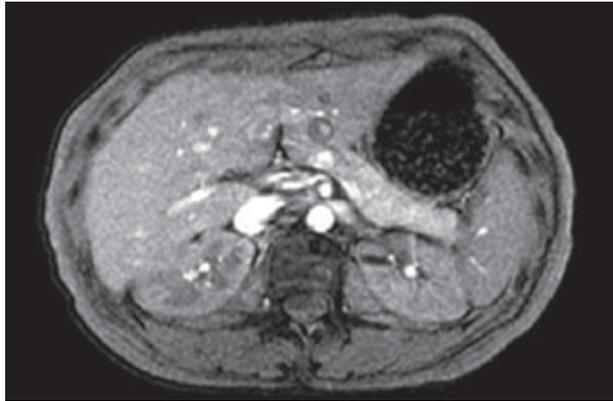


Elastography studies

- Magnetic-resonance elastography (MRE)
 - Continuous longitudinal vibrations at 60 Hz via the driver
 - 2D gradient-ECHO MRE sequence acquires images



Magnetic Resonance Elastography



Magnetic-resonance elastography (MRE)

- Advantages:

- Does not require full-sequence MRI or IV contrast
- Operator independent
- Measures stiffness of the entire liver
- Can be performed in obese subjects and in those with ascites

- Disadvantages:

- Expensive (requires software upgrade & hardware)
- Cannot be used in subjects with MRI-contraindication, claustrophobia, inability to breath hold, or iron overload (signal dropout—cannot see propagating waves)

Summary

- Fibrosis assessment is critical in patients with chronic liver disease
- Numerous methods of fibrosis assessment are available ranging from serological, to imaging-based, to invasive
- All methods of testing have unique advantages/disadvantages
- Use multiple tests to “stage” your patient
 - Physical examination, routine labs, APRI, Fib-4, elastography-based imaging studies, and/or fibrosis panels

Thank you

For questions:
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