AETC AIDS Education & Training Center Program Mountain West

Noninvasive Fibrosis Testing for Liver Disease

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echo

Disclosures

In the last year, I have served on a data adjudication cmte for Novartis on a non-Hep C and non-HIV medication.
I serve on the AASLD guideline cmte and my talk today does not represent that cmte.
Dr. Maggie Shuhart shared slides on FibroTest.

Objectives

- To list the commonly used non-invasive tests for liver disease and their relative pros/cons
- To describe how to resolve discrepancies in fibrosis scores

Case

- You are seeing a 45 yo man with well-controlled HIV and untreated hep C. He has GT 1a, VL 800,000 IU/ml, plt count of 160, ALT of 45, AST 40 and otherwise nl liver panel. His only risk factor for Hep C is MSM intercourse and he tested positive for Hep C 10 yrs ago at time of HIV dx.
- His APRI calculates to 0.625. His Fibrosure shows F4 fibrosis.

Case

What would you do next?

A) Take the highest score and use that for treatment and long term HCC surveillance decisions

B) Obtain a Fibroscan or liver biopsy

C) Obtain an ultrasound

D) Obtain an EGD

Overall Principles

- Noninvasive tests perform best at extremes (F0, F4)
- Most accurate when combined, especially with a different method
- Be aware of limitations, including concurrent medications, conditions
- Consider the clinical picture, such as duration of infection, synthetic labs, cytopenias, splenomegaly, physical exam
- Fibroscan > Fibrosure > APRI
- Look at the raw data!

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

Seeff LB , et al. Clin Gastroenterol Hepatol . 2010;8:877–883.
The French METAVIR Cooperative Study Group . Hepatology . 1994;20:15-20.

Benefits of Noninvasive Tests

- Ease of administration
- Lower cost (1/10th)
- Assessment of degree of fibrosis
- Assist with decision to treat or wait
- Can be repeated over time to monitor progression of liver disease, need for long term HCC surveillance
- May predict clinical outcomes better than liver biopsy

Indirect Markers of Fibrosis and Accuracy

Biomarkers	Cut-offs	Sensitivity	Specificity	Fibrosis
APRI	**>0.7** **>1.0**	**77%** **61-76%**	**72%** **64-72%**	**≥ F2** **F3 or F4**
FIB-4	<1.45 >3.25	74%	80% 98%	≤F2 F4
Fibroindex	≥ 2.25	36%	97%	F2 or F3
Fibrosure	**<0.31** **>0.72**	**NPV 91%** **PPV76%**		**<F2** **≥F2**

- For complete information Castera, L., Gastroenterology 2012;142: 1293-1302.

HCV Fibrosure/Fibrotest

- Proprietary algorithm
- Alpha 2 macroglobulin, GGT, haptoglobin, ALT, bilirubin, age, gender
- 4 approved US labs: Quest, LabCorp, Mayo and BioReference
- Data submitted online to BioPredictive servers which vet for outliers, FP/FNs

Factors Which Affect Fibrosure Interpretation

Component	Impact of liver disease	Caveats
Alpha-2-Macroglobulin	Increased	• Increased in patients w/nephrotic syndrome, diabetes; low in acute pancreatitis, sepsis, severe hepatic insufficiency, and after major surgery,
Haptoglobin	Decreased synthesis	• Decreased in hemolysis, regular strenuous exercise, and anhaptoglobinemia (West Africans) • Increased in acute inflammation (acute phase), nephrotic syndrome
Apolipoprotein A-1	Decreased synthesis	• Decreased in severe malnutrition, uncontrolled diabetes, chronic renal failure, and w/some drugs (androgens, beta blockers, diuretics) • Increased in lipemic serum, and w/some drugs (estrogens, niacin and statins)
Bilirubin, Total	Increased	• Increased in hemolysis, cholestasis, Gilbert's, & w/HIV PIs
GGT	Increased	• Increased in alcohol use; increased synthesis by phenytoin, phenobarbital, carbamazepine; increased levels with other drugs (next slide) • Decreased with estrogen use
ALT (ActiTest only)	Increased	• Increased in acute hepatitis

Source: Mayo Medical Labs

Medications that Increase GGT

Medication	Fold Increase (up to)
Acetaminophen	2x
Carbamazepine	2x
Cimetidine	2x
Coumadin	2x
Furosemide	2x
Heparin	2x
Isotretinoin	2x
Methotrexate	2x
Phenobarbital	2x
Phenytoin	5x
Testosterone	2x
Tricyclic antidepressants	2x
Valproic acid	2x

Also:
Abx
NSAIDS
Antifungals
Anti-depressants

FibroTest: Other Considerations

- No need to fast!
- Not accurate in acute hepatitis, hemolysis, extrahepatic cholestasis, acute inflammation (false neg)
- Validated in renal txp patients, “acceptable” performance in ESRD pts
- “As a general rule, extreme values in one of the 6 components should signal caution in interpretation
  - Haptoglobin < 12 mg/dl (43-212)
  - ALT >622 U/L
  - Bili >1.8 AND GGT < 50
  - Alpha 2 macroglobulin >590 mg/dL

Risk of False Positive Negative (RFPN)

- RFPN: Percentage of patients with abnormal component value for whom the switch to the component's median value would induce a variation of Fibrotest result by at least 0.30 (=1.5 histological fibrosis stage)

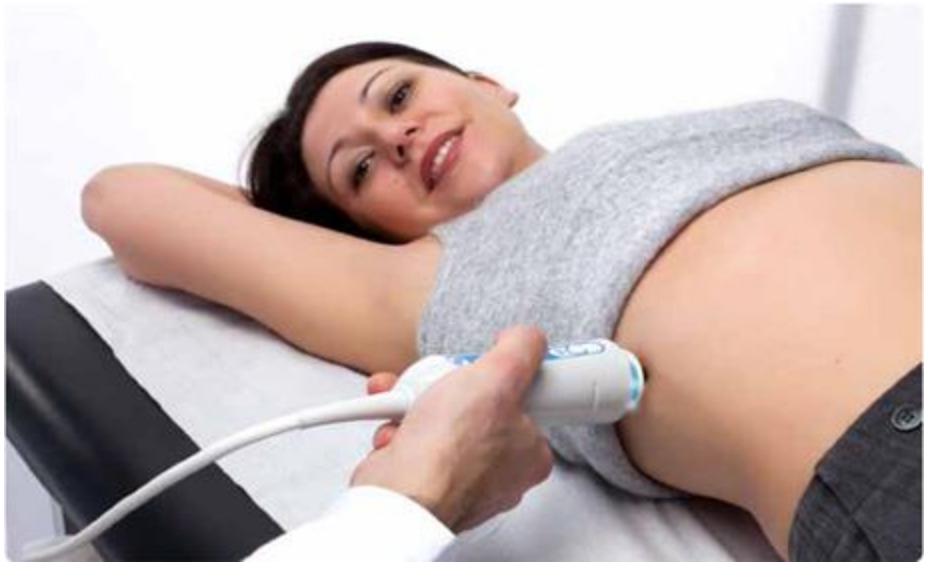
Population	N	RFPN (%)
Blood donors	954	0.52
Healthy volunteers	7494	0.51
Consecutive worldwide serum samples	345,695	0.97
Serum samples at tertiary care centers	24,872	1.97
Low haptoglobin		1.3
Low apolipoprotein A1		0.1
High apolipoprotein A1		0.23
Low alpha-2 macroglobulin		0.22
High alpha-2 macroglobulin		0.10
High GGT		0.03

Poynard T. BMC Gastro 2011; 11:39

Ultrasound

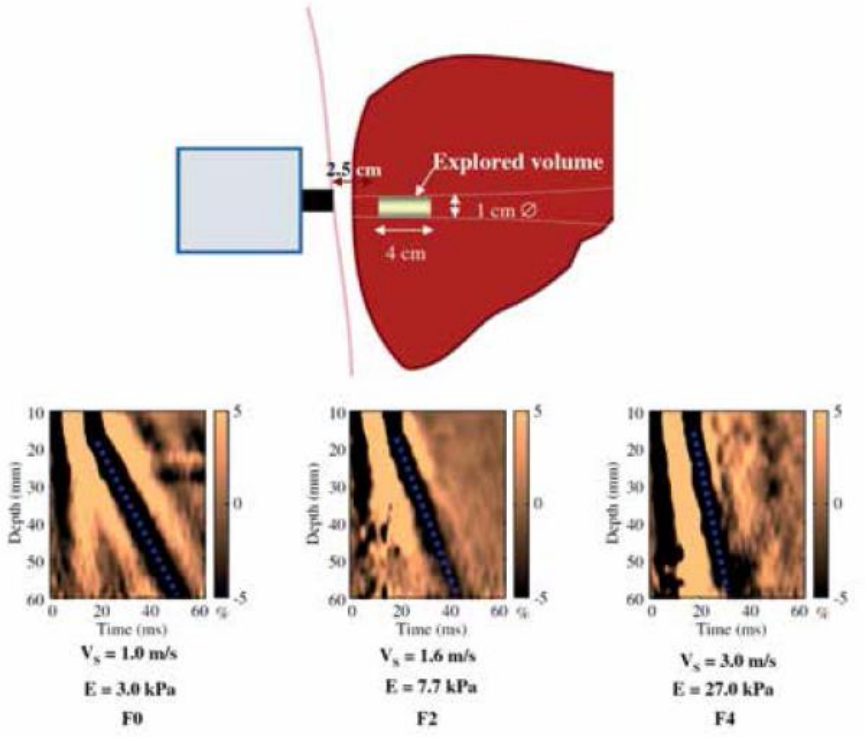
- Can assess for nodularity of the liver surface
  - If present, >80% PPV
- Coarseness of the parenchyma
- Size of lymph nodes around the hepatic artery, patency and flow of veins and arteries, spleen size, hepatocellular carcinoma, and small volume ascites.
- The use of high-frequency ultrasound transducers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

Fibroscan: How it Works



Fibroscan: Methods

- 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 shoots sound wave toward hepatic tissue, the vibrations are followed by pulse echo and their velocities are measured, which is related directly to liver stiffness.
- Patient should be fasting for at least 2 hrs.
- Results limited in those with ascites, elevated central venous pressure, and obesity, as fluid and adipose tissue attenuate the echo waves.



Source: Castera L, et al. J Hepatol 2008; 48:835-47.

Fibroscan

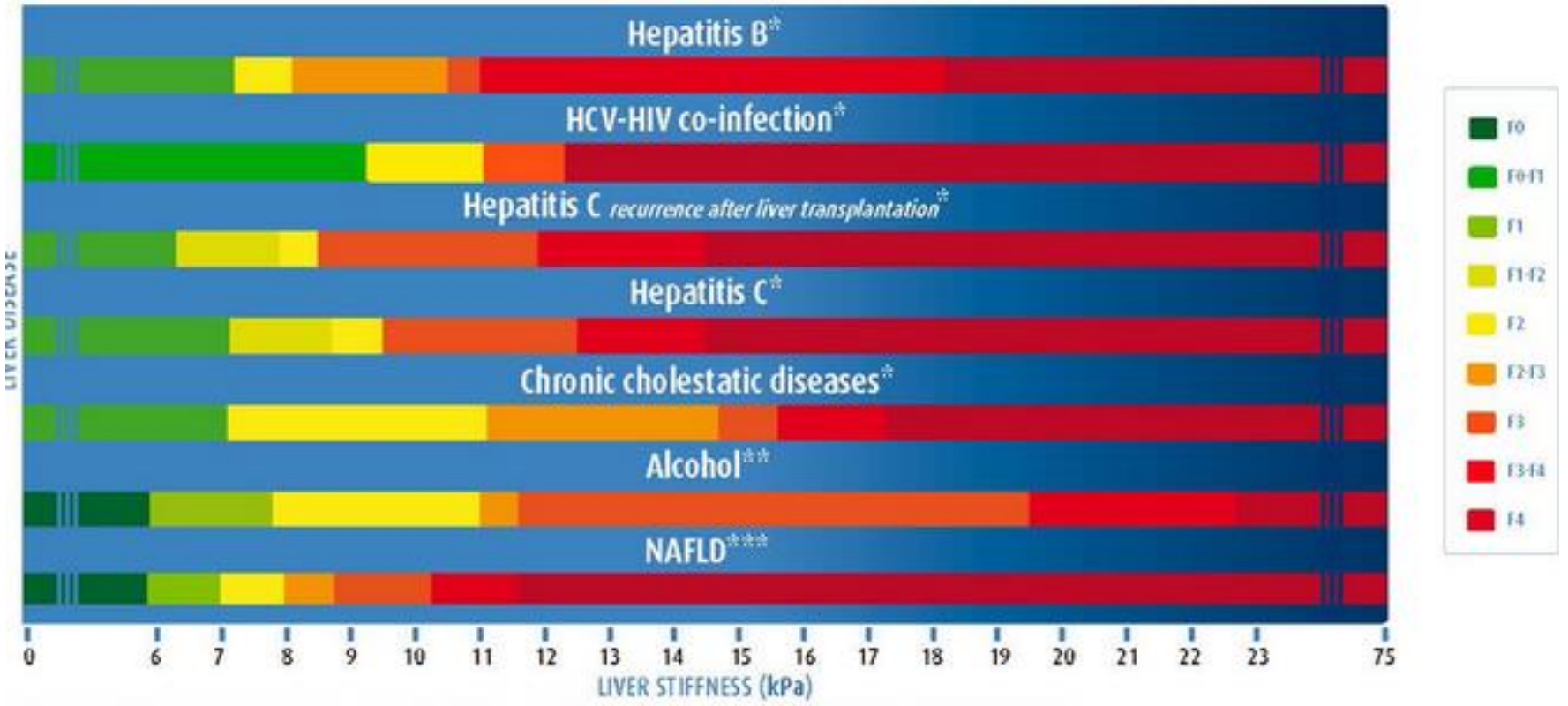
Results

Stiffness (kPa)
Median value of 10 shots
3.9 Kilo Pascals

❸ IQR * (kPa)
Interval around median
Contains 50% of valid shots
≤ 25% of median value

❶ At least 10 shots
❷ Success Rate: ≥ 60%

Different Cutoffs for Different Disease States



Transient Elastography Predicts 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

Outcomes with TE cutoff of 10.5 kPa, %	Sensitivity	Specificity	PPV	NPV
Overall population	95	63	19	99
Cirrhotics only	98	10	27	92

Klibansky DA, et al. J Viral Hepat . 2012;19:e184–e193.

Comparison of TE to Other Tests

AUROC for FS, FT, and APRI and Their Combinations, According to METAVIR Fibrosis Stages			
Method	**F ≥ 2**	**F ≥ 3**	**F = 4**
Fibroscan (FS)	0.83	0.90	0.95
Fibrotest (FT)	0.85	0.90	0.87
APRI	0.78	0.84	0.83
FS + APRI	0.84	0.91	0.95
FS + Fibrotest	0.88	0.95	0.95
FS + FT + APRI	0.88	0.95	0.95

Castera L, et al. Gastroenterology 2005; 128:343-50.

Fibroscan: Cost and Logistics

- CPT code 91200
- Medicare reimburses $134.80 per test
- HMC charges $250
- Machine costs over $100,000
- Available in most metropolitan areas now

References

- Afdhal NH. Fibroscan (transient elastography) for the measurement of liver fibrosis. Gastroenterol Hepatol (N Y). 2012;8:605-7.
- Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol. 2008;48:835-47.
- Castera L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005;128:343-50.
- Gara N, Zhao X, Kleiner DE, Liang TJ, Hoofnagle JH, Ghany MG. Discordance among transient elastography, aspartate aminotransferase to platelet ratio index, and histologic assessments of liver fibrosis in patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2013;11:303-8.
- Kirk GD, Astemborski J, Mehta SH, et al. Assessment of liver fibrosis by transient elastography in persons with hepatitis C virus infection or HIV-hepatitis C virus coinfection. Clin Infect Dis. 2009;48:963-72.