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How to Diagnose Cirrhosis

Patrick M. Horne, MSN, APRN-FNP, AF-AASLD
University of Florida-UF Health
Gainesville, FL

Disclosures

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Disclosures

Patrick M. Horne, MSN, APRN, FNP, AF-AASLD

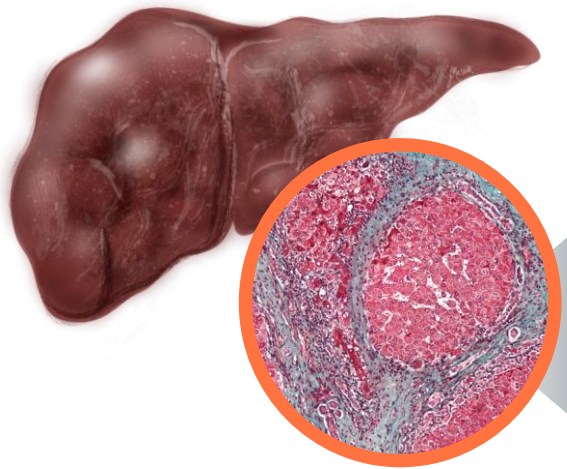
Consultant: AbbVie, Clinical Area- Hepatitis C

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



Decompensation/ liver failure

Hepatocellular carcinoma

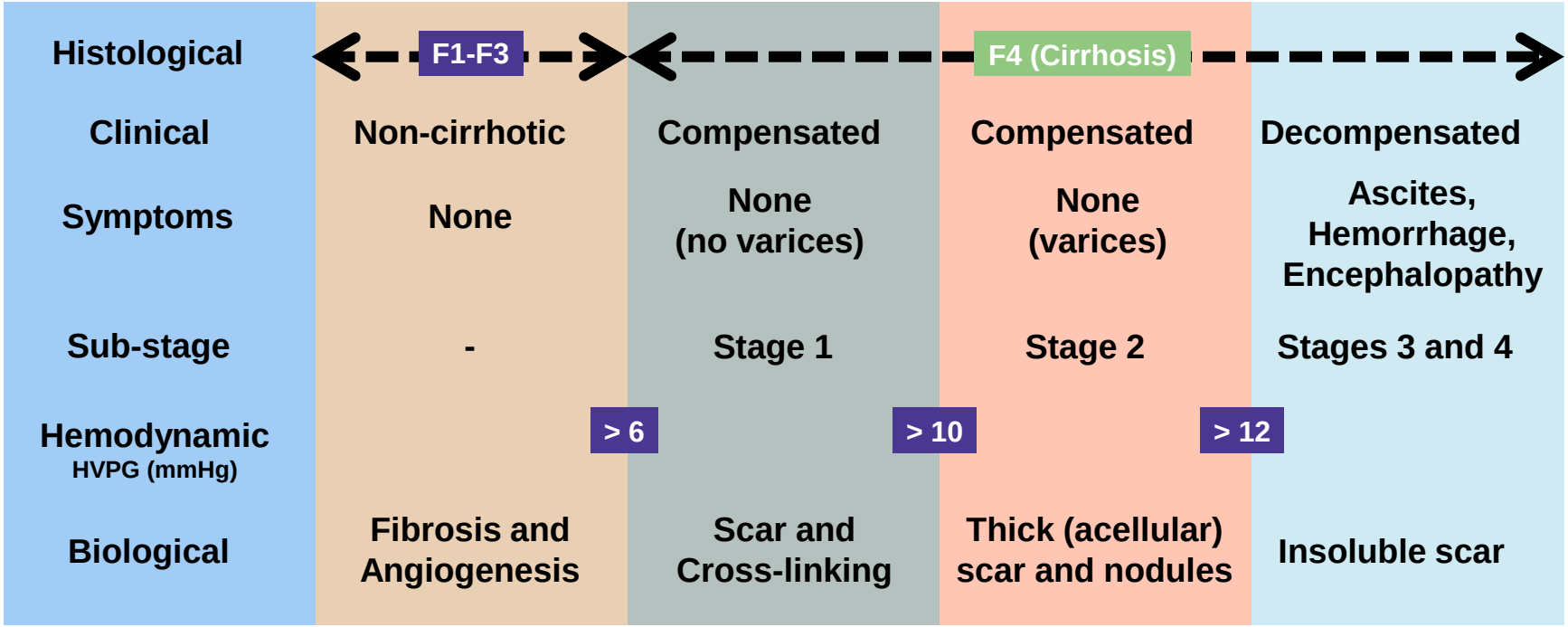
Liver transplantation

Accumulation of collagen deposition = fibrosis → cirrhosis

Histology image obtained from http://en.wikipedia.org/wiki/Cirrhosis. Accessed March 26, 2018.

Ge PS, Runyon BA. *N Engl J Med*. 2016;375:767-777.

Cirrhosis
A Pathophysiological Classification



Garcia-Tsao G, et al. *Hepatology.* 2010; 51:1445-9.

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So…How Do We Diagnose Cirrhosis?

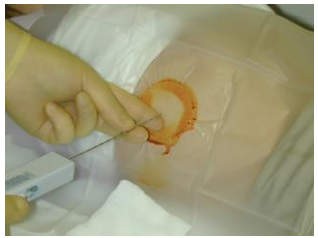
Invasive vs Non-Invasive

- 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

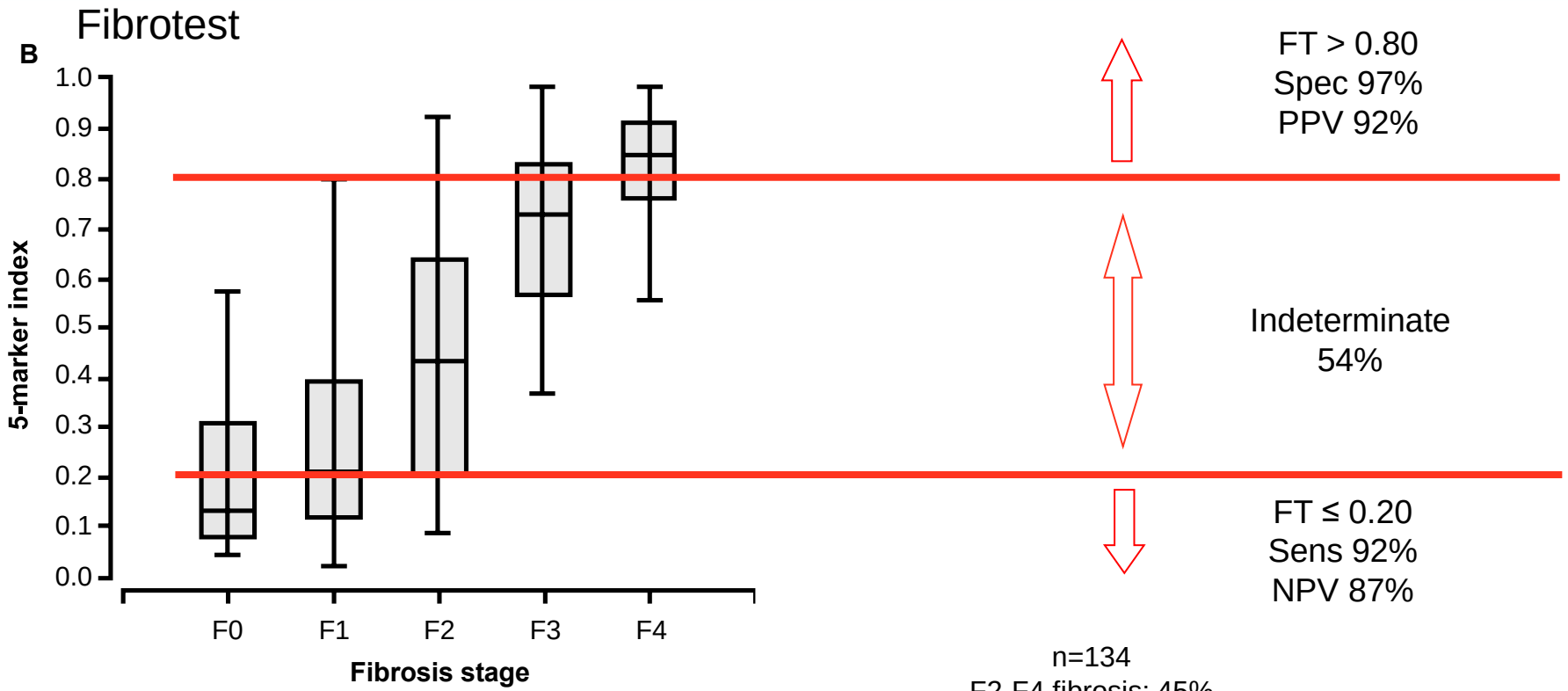
- The procedure can cost from $1k to $3k[2]
- Mis-staging fibrosis in up to 41% of cases[3]
- 0.35% risk of serious bleeding and 0.14% risk of death[4]

Sources: 1. Chalasani N, et al. *Hepatology*. 2017. doi:10.1002/hep.29367;
2. Franciscus A. Hepatitis C Support Project 2014; 3. Ratziu V, et al. *Gastroenterology.* 2005;128:1898-1906;
4. Myers RP, et al. *Liver Int.* 2008;28:705-712.

Liver Staging

Score	Metavir
0	No Fibrosis
1	Periportal fibrotic expansion
2	Periportal septae (> 1 septum)
3	Pericentral septae
4	Cirrhosis

Non-Invasive – Serum Markers



Imbert-Bismut. *Lancet*. 2001;357:1069-75.

Non-Invasive – Calculations

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

- < 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

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

- 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

Vallet-Pichard A, et al. *Hepatology*. 2007;46:32-6.

Performance of Non-Invasive Fibrosis Tests

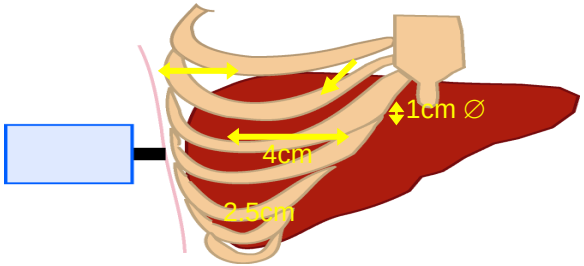
Test	AUC	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)
AST/ALT ratio	0.83 (0.74-0.91)	0.8 1	74 52	78 90	44 55	93 89
APRI	0.67 (0.54-0.8)	1	27	89	37	84
BARD score	0.77 (0.68-0.87)	2	89	44	27	95
FIB-4 score	0.86 (0.78-0.94)	1.30 3.25	85 26	65 98	36 75	95 85
NAFLD fibrosis score	0.81 (0.71-0.91)	-1.455 0.676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

McPherson, et al. *Gut*. 2010: 59(9) 1265.

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].

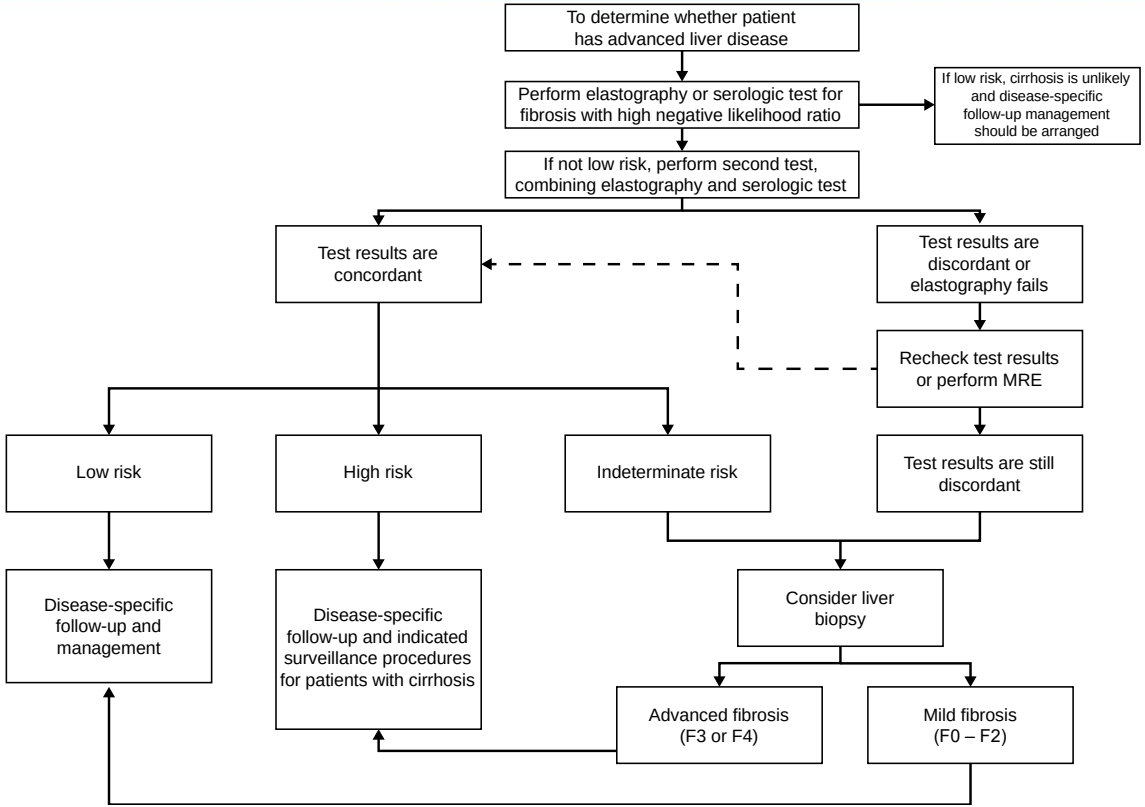
The velocity of the sound wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface



- 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).

1. Castera L, et al. *Nat Rev Gastroenterol Hepatol*. 2013;10:666-675; 2. Friedrich-Rust M, et al. *Gastroenterology*. 2008;134:960-974; 3. Sasso M, et al. *J Viral Hepat*. 2012;19:244-253; 4. Gómez-Domínguez E, et al. *Aliment Pharmacol Ther*. 2006;24:513-518; Tapper E, et al. *Am J of Gastro.* 2016.

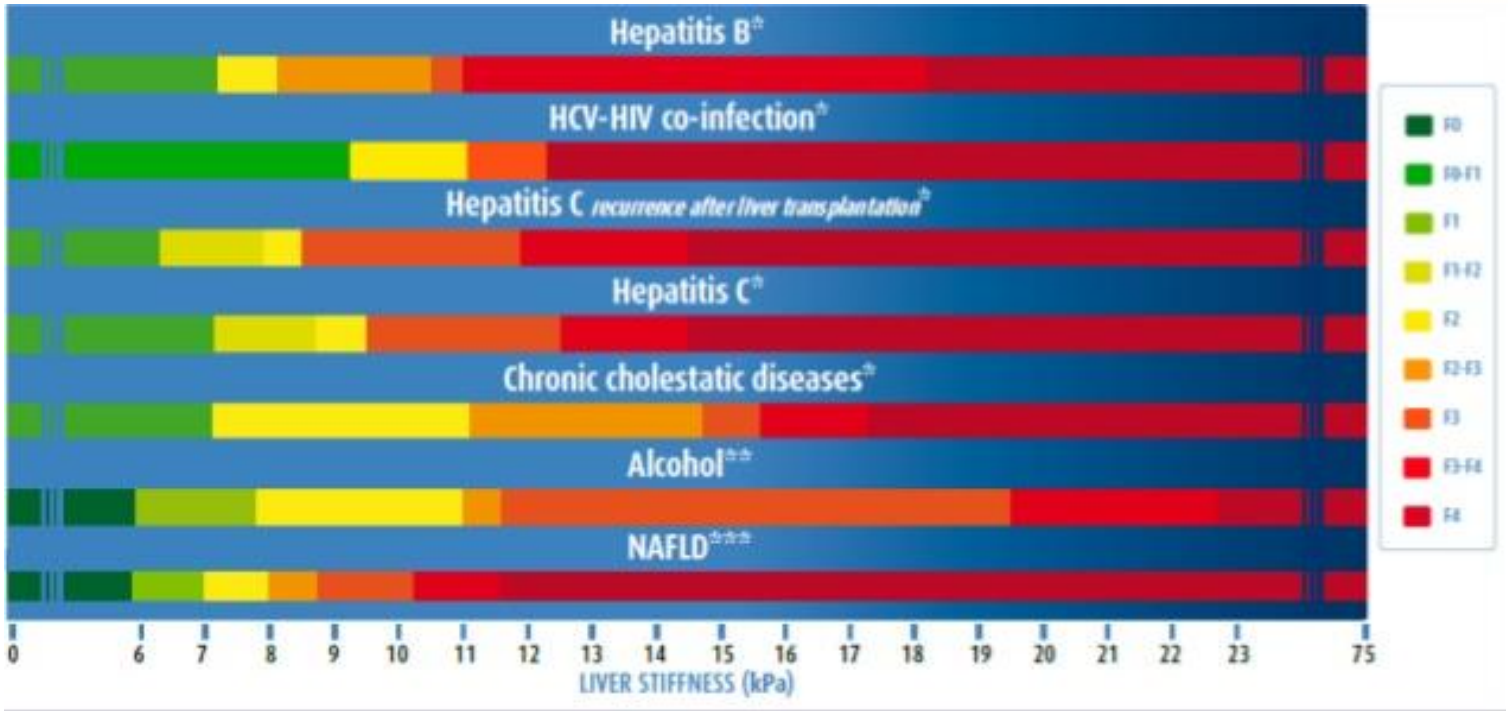
Implementing a Non-Invasive Approach to Clinical Staging of Liver Disease



The NEW ENGLAND JOURNAL of MEDICINE

Tapper EB, Lok AS-F. *N Engl J Med.* 2017;377:756-768.

Correlation Between LSM & Fibrosis Stage



Gastroentérol Clin Biol. 2008;32.58-67; ***J Hepatol*. 2009;49:1062-68; *Aliment Pharmacol Ther*. 2008;28:1188-98;
****Hepatology*. 2010;51:454-62; *Gastroentérol Clin Biol.* 2008;32:58-67.

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

From http://digestive.niddk.nih.gov/ddiseases/pubs/cirrhosis/. Accessed July 2015;
Trichrome stain micrograph from http://en.wikipedia.org/wiki/Cirrhosis. Accessed July 2015.

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!