Management of Liver Diseases: A Nonhepatologist's Viewpoint

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the need to ascertain fibrosis state
- Counsel patients regarding advanced fibrosis
- State pros and cons for various fibrosis measurements

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Overview

- Why is the ascertainment of fibrosis important?
- What are key counseling points for those with advanced fibrosis?
- How does one diagnosis cirrhosis?
- How do I choose between various approaches?

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Determination of cirrhosis is important

- It is important to ascertain the fibrosis state in those with chronic HCV:
  - Future prognosis
    - Determines urgency for treatment to prevent complications
  - Counseling points
  - Insurance approval for treatment
- Fibrosis is variable and while duration of infection, HIV, alcohol, obesity may correlate one cannot predict with confidence
  - HCV RNA and ALT are imperfect markers

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Diagnosing cirrhosis




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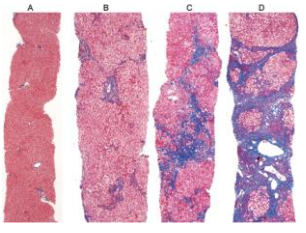
Cirrhosis is a histologic diagnosis

Normal

Cirrhotic



Ishak	0	1	2	3	4	5	6
	0 No Fibrosis						
Metavir	0	1	Mild Fibrosis 2	3	Bridging Fibrosis 3	4	Cirrhosis 4

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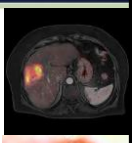
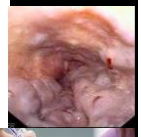
Cirrhosis affects management

- Screening for hepatocellular carcinoma
  - Ultrasound or other imaging every 6 months
- Endoscopic screening for varices
  - Prevention of hemorrhage via banding and beta-blockers
- Hepatotoxicity
- Vaccinations - pneumococcal
- Treatment: depends on regimen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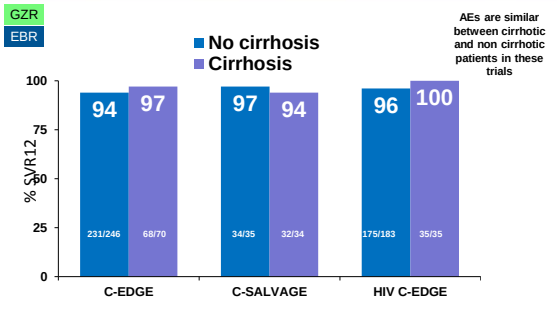
Cirrhosis impact on SVR rates for 12 weeks of EBR/GZR



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Zeuzem et al. Ann Intern Med 2015; Rockstroh et al. Lancet HIV 2015; Buti et al. CID 2016; Jacobson et al. AASLD 2015

The simplication of first-line therapy

Drug	FDA-Approved Indication
Preferred Products	
Epclusa (sofosbuvir/ velpatasvir)	Adults with chronic HCV genotype 1-6 infection without cirrhosis or with cirrhosis (compensated or decompensated)
Harvoni (ledipasvir/ sofosbuvir)	• Adults with chronic HCV infection o Genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis o Genotype 1 with decompensated cirrhosis o Genotype 1 or 4 who are liver transplant recipients without cirrhosis or with compensated cirrhosis • Pediatrics with chronic HCV infection o Genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis
Mavyret (glecaprevir/ pibrentasvir)	• Adult patients with genotype 1, 2, 3, 4, 5, or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis • Adult patients with genotype 1 chronic HCV infection who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

For naive patients:
sofosbuvir/velpatasvir 12 weeks regardless
ledipasvir/sofosbuvir (GT1): 8 weeks if noncirrhotic + HCV RNA < 6,000,000 IU/mL
glecaprevir/pibrentasvir is 8 weeks if noncirrhotic, extended to 12 weeks if cirrhotic

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Tufts Health Plan, preferred HCV formulary as of January 2018; http://hcvguidelines.org

Case 1

A 59 y/o man with compensated cirrhosis and chronic HCV
Few spider angiomata, no edema
MELD 7, bilirubin 0.8 SGOT 95 SGPT 80 platelets 133K
Ultrasound shows mild splenomegaly

ARS Question 1: Of the following, what is the most likely cause of death?

1. Hepatocellular carcinoma
2. Variceal bleeding
3. Cardiovascular disease
4. Hepatic encephalopathy
5. Other

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Modulation of the natural history of advanced fibrosis / cirrhosis

- Prevention of other co-factors
  - Prevent HIV (risk reduction, PREP)
  - Prevent HBV (vaccination)
  - Steatosis / weight gain
  - Alcohol

When can I have my next drink, doc?

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Should we recommend coffee for those at risk for fibrosis progression?

Reference	Year	Design	Cohort*		Country	Findings
Corrao et al.	1994	Case-Control	Cases	115	Italy	Protective effect of coffee on alcohol cirrhosis
			Controls	167		
Corrao et al.	2001	Case-Control	Cases	274	Italy	Coffee, but not other caffeine containing beverages, may prevent alcohol cirrhosis
			Controls	458		
Gallus et al.	2002	Case-Control	Cases	101	Italy	Inverse association between coffee and cirrhosis
			Controls	1538		
Tverdal & Skurtveit	2003	Retrospective Cohort		51,308	Norway	Inverse association between coffee and cirrhosis
Klatsky et al.†	2006	Retrospective Cohort		125,580	USA	Coffee protects against cirrhosis, particularly alcoholic cirrhosis
Ruhl et al.	2005	Retrospective Cohort		9846	USA	Coffee and tea decrease risk of chronic liver disease among patients at increased risk of liver disease

Saab et al. Liver International 2014;34(4):495-504.
Corrao et al. Eur J Epidemiol 1994; Corrao et al. Ann Epidemiol 2001; Gallus et al. Ann Epidemiol 2002, Tverdal Ann Epidemiol 2003; Klatsky et al. Arch Intern Med 2006; Ruhl et al. Gastroenterology 2005

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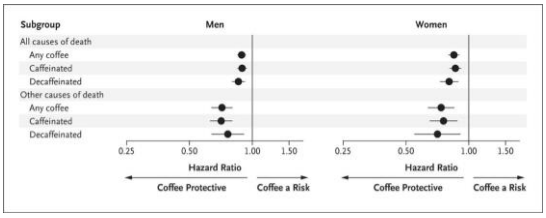
Should we recommend coffee for those with cirrhosis?



n=617,000, Follow-up 5,149,000 person years
Overall Hazards ratio = 0.88 (95% CI, 0.84 to 0.93) P<0.001

Freedman ND et al. N Engl J Med 2012;366:1891-1904

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Coffee tied to lower mortality in French HIV/HCV coinfected patients

- French ANRS HEPAVIH cohort
- n=1035 followed for median 5 years
  - deaths (N=77)
    - HCV-related causes 42.8%
    - non-AIDS, non-HCC cancer 11.7%
    - AIDS 10.4%
  - aHR for death:
    - Unstable housing 3.7
    - CD4 =< 200 3.2
    - HCV cured 0.2
    - female gender 0.6
    - 1 or fewer EtOH drinks 0.5
    - **3 or more coffee 0.5**

Carrieri et al. J Hepatology 2017

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Case 1

A 65 y/o man with compensated cirrhosis and chronic HCV
Few spider angiomata
MELD 7, bilirubin 0.8 SGOT 95 SGPT 80

ARS Question 2: What additional staging is medically indicated?
1. No further staging
2. Routine ultrasound
3. FibroTest
4. Transient elastography
5. Liver biopsy
6. Other

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Case 2

A 23 y/o woman with a 5-year history of intravenous drug use, tested 2 years earlier, now anti-HCV positive

HCV RNA 125,000 IU/mL, genotype 1a

BMI 19, SGPT 26 SGOT 24 bilirubin 0.5 platelets 285K

No significant alcohol use

ARS Question 3: What additional staging is medically indicated?

1. No further staging
2. Routine ultrasound
3. FibroTest
4. Transient elastography
5. Liver biopsy
6. Other

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AASLD HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C IDSA Infectious Diseases Society of America

Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening).

Rating: Class I, Level B

- Almost all patients should have staging by more than labs
  - Required by many payers
  - Some incorrectly require biopsy as prerequisite
  - Cirrhosis may be obvious by physical exam, routine labs and imaging

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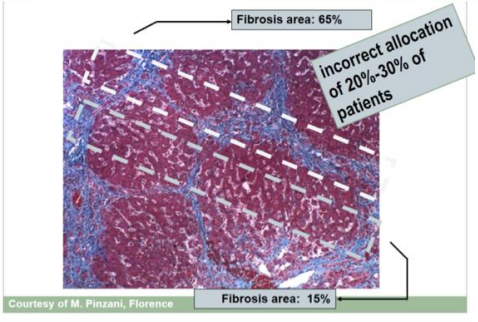
Liver biopsies are not a “gold standard”



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Pros and cons of liver biopsy for staging

- Pros
  - Acceptable
    - >80% of prev bx recipients willing to do 2nd*
  - Rules out other etiologies
  - Rules out co-factors
    - Steatosis
    - Iron deposition
- Some can perform morphometric analysis

- Cons
  - Acceptability compared to other options
  - Pain, complications
  - Difficult to repeat
  - It is a "bronze standard"
    - Requires at least 2.5 cm
    - 1:50,000th of liver
    - Discrepancy R/L lobe
    - Intra- and inter- observer variability

Kan et al. Can J Gastroenterol Hepatol 2015
Amorosa et al. J Clin Gastroenterol 2013

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Serum Markers for Fibrosis Staging

- APRI: AST and platelet count
- FIB-4: AST, ALT platelet count and age
- Forns index: GGT, cholesterol, platelet, age
- Fibrotest:
  - Alpha-2-macroglobulin, GGT, Apo A1, total bilirubin, haptoglobin, adjusted for age and gender
- Hepascore:
  - HA, alpha2 macroglobulin, GGT and T bili (adjusted for age and gender)
- Fibrospect II
  - HA, TIMP and alpha2 macroglobulin

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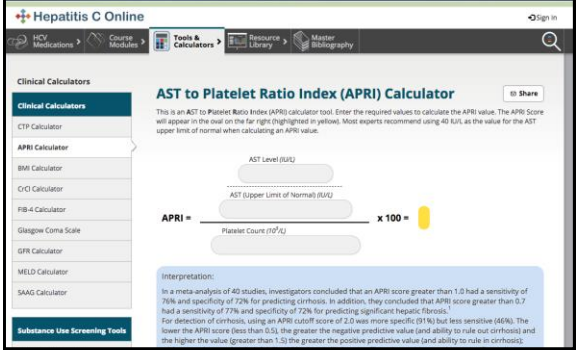
University of Washington HCV website https://www.hepatitisc.uw.edu/



Example of Fibrosure

General Comments & Additional Information
Clinical Info: NORMAL REPORT
Ordered Items
HCV FibroSure

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
HCV FibroSure					
HCV FibroSURE Results:					01
Fibrosis Score	0.12			0.00 - 0.21	01
Fibrosis Stage					01
	F0 - No fibrosis				
Necroinflammat Activity Score					
	0.25	**High**		0.00 - 0.17	01
Necroinflammat Activity Grade					
	A0-A1				01
.					01
Analysis:					01
Alpha 2-Macroglobulins, Qn	**405**	**High**	mg/dL	110 - 276	01
Haptoglobin	**206**	**High**	mg/dL	34 - 200	01
Apolipoprotein A-1	145		mg/dL	116 - 209	01
Bilirubin, Total	0.3		mg/dL	0.0 - 1.2	01
GGT	12		IU/L	0 - 60	01
ALT (SGPT) P5P	**53**	**High**	IU/L	0 - 40	01
.					01
Interpretations:					01
Quantitative results of 6 biochemical tests are analyzed using a computational algorithm to provide a quantitative surrogate marker (0.0-1.0) for liver fibrosis (METAVIR F0-F4) and for necroinflammatory activity (METAVIR A0-A3).					
Fibrosis Scoring:					01
<0.21 = Stage F0 - No fibrosis					
0.21 - 0.27 = Stage F0 - F1					
0.27 - 0.31 = Stage F1 - Portal fibrosis					
0.31 - 0.48 = Stage F1 - F2					
0.48 - 0.58 = Stage F2 - Bridging fibrosis with few septa					
0.58 - 0.72 = Stage F3 - Bridging fibrosis with many septa					
0.72 - 0.74 = Stage F3 - F4					
>0.74 = Stage F4 - Cirrhosis					
Necroinflamm Activity Scoring:					01
<0.17 = Grade A0 - No Activity					

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Pros and cons of serum markers

- Pros
  - Acceptable
  - Available
    - APRI, FIB-4 no added cost over routine labs
  - Non-invasive
  - Validated
- Cons
  - Not liver specific
  - Some components may be confounded
    - e.g. bilirubin
  - Do not perform well in the “middle” - intermediate fibrosis
  - For certain tests, cost

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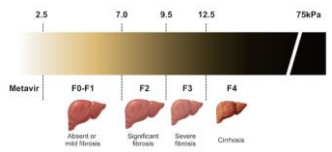
Transient Elastography (TE)

- FDA-approved
- Expanding availability
- Most accurate at extremes
  - 12.5 kPa cutoff for cirrhosis
- XL probe for higher BMI
- CAP for steatosis



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Pros and cons of Transient Elastography

- Pros
  - Widely used in Europe and validated
  - Reproducible
  - Excellent for cirrhosis
  - Range of values may be useful for prognosis
- Cons
  - Dedicated machine - $130K
  - Intermediate stages
  - Confounded by obesity, ascites, acute hepatitis, food intake
  - Operator experience important

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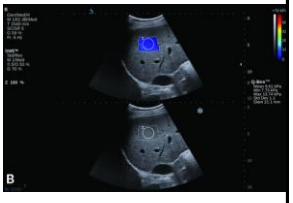
Shear Wave Elastography (SWE) and Acoustic Radiation Force Impulse (ARFI)

- Integrated into high-end ultrasound systems
- Shear waves generated within the liver from focused ultrasound beam
- Not limited by ascites
- SWE:
  - 7.1 kPa for F ≥ 2
  - 8.7 kPa for F ≥ 3
  - 10.4 kPa for F = 4



Samir et al. Radiology 2015
Frulio and Trillaud, Diagnostic and Interventional Imaging 2013

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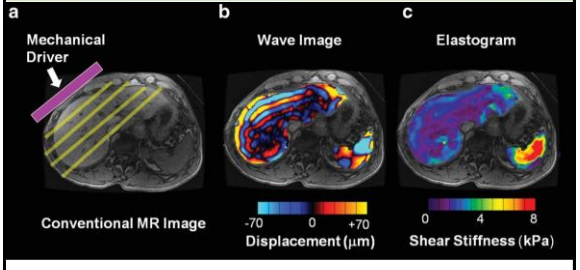
MR Elastography (MRE)



- Requires equipment in addition to MRI
- Gives fuller picture of the liver - whole organ
- Potential disadvantage: cost

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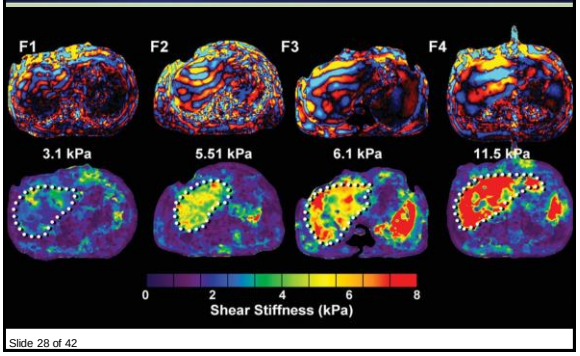
MR Elastography (MRE)



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Pros and cons of MR Elastography

- Pros
  - Whole liver
  - Uses MRI machine
  - Not confounded by obesity, ascites
  - Excellent for cirrhosis
  - Good for prognosis
- Cons
  - Iron overload
  - Requires MRI
    - More time than TE
  - Cost

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Diagnostic accuracy of noninvasive techniques Each are pretty good!

Advanced fibrosis

Test	AUROC	Sens	Spec
Fibrotest	0.74-0.89	72-91%	72-91%
Fibroscan	0.79-0.91	56-83%	82-91%
ARFI	0.81	72%	81%
SSI	0.89	83%	82%
MRE	0.97	98%	51%

Cirrhosis

Test	AUROC	Sens	Spec
Fibrotest	0.71-0.92	70-93%	70-93%
Fibroscan	0.90-0.97	86-97%	83-92%
ARFI	0.84	79%	81%
SSI	0.92	85%	83%
MRE	0.96	97%	80%

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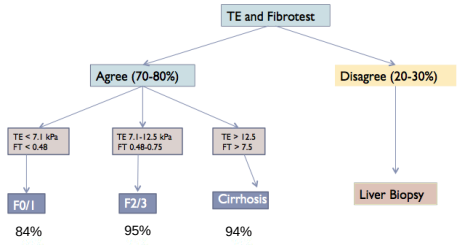
Original Slide D. Nunes, BMC

Use of two noninvasive tests when concordant can confidently get close to the truth

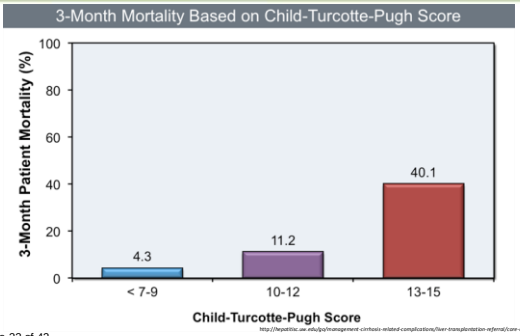


Boursier et al. Alimentary Pharm Ther 2014

Child-Turcotte-Pugh Staging of Cirrhosis

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged *or* International normalized ratio	<4 <1.7	4-6 1.7-2.3	>6 >2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

Child-Turcotte-Pugh Staging Predicts Mortality



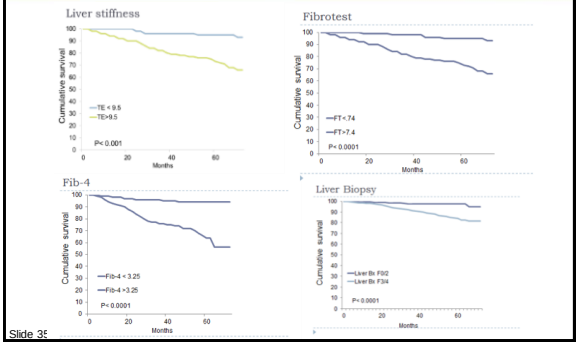
http://hepatitis.uw.edu/pg/management-cirrhosis-related-complications/liver-transplantation-referral/core-concept/ta

Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91-

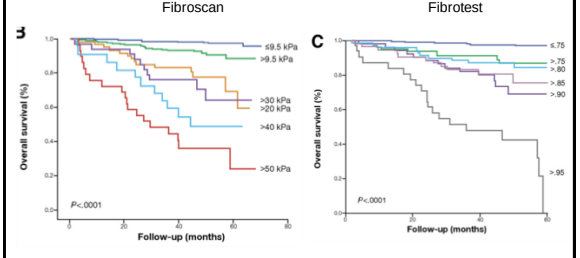
MELD Scores are prognostic

http://hepatitisc.uw.edu/go/management-cirrhosis-related-complications/liver-transplantation-referral/core-concept/all

Degrees of liver stiffness can prognosticate outcome in cirrhosis

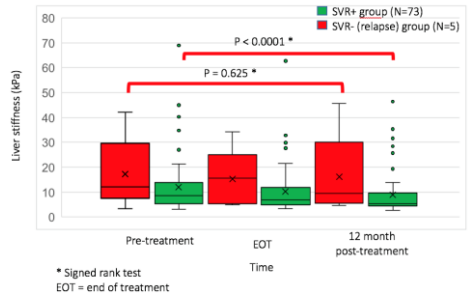


Degrees of liver stiffness can prognosticate outcome in cirrhosis



Vergniol et al., Gastroenterology 2011

What happens to liver stiffness after HCV cure?



Chan et al. Dig Dis Sci 2018

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Prevention and surveillance for hepatocellular carcinoma

- HCV: F3/F4
  - Older age, black race, lower platelet count
  - Increased with diabetes, dual infection HBV, possibly HIV and other liver diseases (eg alcohol, fatty liver)
  - SVR reduces risk substantially
  - Coffee consumption protective
  - Pending further data, continue if noninvasive testing results fall below F3
- Imaging every 6 months
  - Preferred modalities vary - but 6 months superior to 12 months
- Alfa-fetoprotein
  - Poor specificity and poor sensitivity, but has returned as an adjunct to recommendations

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My pragmatic approach-

- Duration of infection, AST/ALT ratio and platelet count
  - Formally determine FIB-4
- Fibrosure +/- Fibroscan
- Shear-wave elastography available along with full ultrasound (but reports do not give kPA value that distinguish F0-F2)
- Yet to order MRE because I can't get straight answer as to cost
- Very few liver biopsies
- q6m imaging, + AFP for those with poor adherence to imaging

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Take home points

- Ascertaining the fibrosis state in those with chronic HCV has value for patients and providers:
  - Diagnose cirrhosis for future prognosis and urgency of treatment
  - Counseling points
  - Insurance approval
- Non-invasive markers are more acceptable to patients
  - Specific choice depends on clinical context and availability
- Cirrhosis - multiple measures of prognosis
  - Referral for endoscopy to screen for varices (if portal hypertension)
  - Screening for HCC
  - Referral for decompensation
  - Prognosis through CTP, MELD, liver stiffness

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Acknowledgments

- Andrew Aronsohn, University of Chicago
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- Ray Chung, Massachusetts General Hospital
- David Nunes, Boston University / Boston Medical Center
- Ken Sherman, University of Cincinnatti
- David Thomas, Johns Hopkins

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Question-and-Answer

Remember to raise your hand and wait until you have the microphone before you ask your question—we are recording!

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