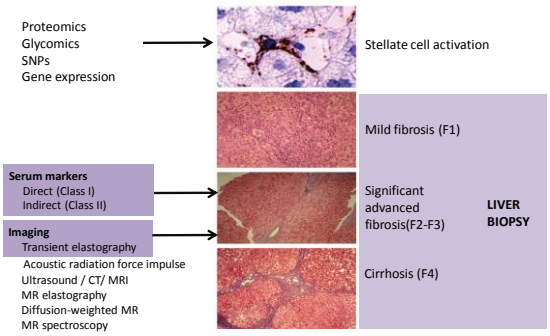
Assessment of Liver Fibrosis

Shruti H. Mehta, PhD MPH
Associate Professor
Johns Hopkins Bloomberg School of Public Health
April 27. 2011

Fibrosis staging in chronic HCV Infection: *Why?*

1. **Identify persons with cirrhosis (Metavir F4)**
   - Screening for hepatocellular carcinoma and gastroesophageal varices
2. **Identify persons with significant fibrosis (> Metavir F2)**
   - Determine treatment need
   - Identify persons who can safely wait for treatment
3. **Identify of persons at risk for disease progression**
4. **Characterize response to therapy**

Fibrosis staging in chronic HCV infection: *How?*



Martinez 2011

Liver biopsy: *A flawed gold standard*

Strengths

- History / dogma
- Established semi-quantitative fibrosis staging systems: Knodell, Scheuer, Metavir, Ishak modified HAI
- Provides simultaneous evaluation of necroinflammation, steatosis, steatohepatitis, iron overload etc.

Weaknesses

- Expensive
- Invasive
- Sampling error
  - 1/50,000 of the liver
  - Adequate size: >15 mm with > 5 portal tracts
- Intraobserver and interobserver variation
- Morbidity
  - pain in 20%
  - Major complications in 0.5%
- Patient reluctance

Froehlich 1993; Perrault 1978; Bedossa 2003; Holund 1980

Serum markers

Direct (class I)

- Intended to detect extracellular matrix (ECM) turnover and/or fibrogenic cell changes

Collagen fragments
N-terminal procollagen pepties I/II
7S-type IV collagen
Type VI collagen
Urine hydroxylysyl pyridinolines

Glycoproteins
Tenascin
Laminin
Fibronectin
YKL-40
Vitronectin

Glycosaminoglycans
Hyaluronic Acid

Cellular adhesion
ICAM-1
VCAM-1

ECM-associated enzymes
TIMP -1,2
MMP-2
Prolyl hydroxylase
Lysl oxidase
Collagen peptidase

Indirect (class II)

- Reflect functional alterations in liver function
- Do not necessarily reflect ECM turnover or fibrogenic cell changes

ALT	Total cholesterol
AST	LDL cholesterol
GGT	Bilirubin
Prothrombin time	Albumin
Platelets	Immunoglobulins
Apolipoproteins	Macroglobulin
Ferritin	C-reactive protein
Urea	Insulin resistance

Serum markers have been tested in A LOT of combinations!!!

Year	Author	Panel	Markers in Panel	N	AUROC
1988	Williams	AAR	AAR	177	N/A
1997	Bonacini	CDS index	PLT,AAR,PT	75	N/A
1997	Poynard	AP index	Age,PLT	620	0.76-0.69
2001	Fortunato	Fortunato	Fibronectin, prothrombin,ALT,PCHE,Mn-SOD,β-NAG	103	N/A
2001	Pohl	Pohl	AAR,PLT	211	N/A
2001	Imbert-Bismut	Fibrotest	A2M,Hpt,GGT,APoA1,bilirubin	339	0.84-0.87
2002	Kaul	Kaul	PLT,AST,sex,spider nevi	264	N/A
2003	Wai	APRI	AST,PLT	270	0.80-0.88
2004	Rosenberg	ELF-score	Age,HA,PIINP,TIMP-1	1021	0.80
2004	Patel	FIBROSpect II	HA,TIMP-1,A2M	696	0.82-0.83
2004	Sud	FPI	Age,AST,TC,Homa-IR,alcohol	302	0.77-0.84
2004	Leroy	MP3	PIINP,MMP-1	194	0.82
2005	Lok	HALT-C	PLT,AAR,INR	1141	0.78-0.81
2005	Adams	Hepascore	Bilirubin,GGT,HA,A2M,age,sex	2210	0.82-0.85
2005	Cales	Fibrometer	PLT,PI,AST,A2M,HA,urea,age	383	0.88-0.89
2005	Kelleher	SHASTA	HA,AST,albumin	95	0.88
2006	Sterling	FIB-4	Age,AST,ALT,PLT	832	0.77
2006	Fontana	Virahep-C	Age,AST,ALP,PLT	399	0.84-0.85
2007	Koda	FibroIndex	PLT,AST,γ-globulin	402	0.83-0.84
2007	Alsatie	Alsatie	Diabetes,PLT,AST,INR,bilirubin	286	0.75-0.79
2007	Esmat	Esmat	HA,age	220	0.84
2010	Ho	Ho	A2M,Vit D binding protein,ApoA1	61	N/A
2011	Macias	Macias	AST,Platelet count, MMP-2	90	0.76-0.88

Performance of select serum marker panels to assess liver fibrosis/cirrhosis in chronic HCV

Class	Score	Markers	N	% ≥ F2	AUC ≥ F2	% F4	AUC F4
II	FibroTest	GGT, haptoglobulin, bilirubin, apolipoprotein A1, alpha-2-macroglobulin	2342	33-74	0.74-0.89	15-20	0.76-0.87
II	APRI	AST, platelets	3160	27-74	0.69-0.88	3-25	0.61-0.94
II	FIB-4	Age, ALT, AST, platelets	1778	21-36	0.74-0.85	7	0.91
II	Forns	Age, GGT, cholesterol platelets	1982	32-59	0.75-0.91	3-20	-
I	ELF	N-terminal peptide of collagen type III, HA, TIMP-1, age	1346	27-64	0.77-0.87	12-16	0.87-0.90
I / II	Hepascore	Age, sex, alpha-2 macroglobulin, hyaluronate, bilirubin, GGT	1660	39-79	0.74-0.86	6-34	0.80-0.94
I / II	Fibrometer	Platelets, prothrombin time, macroglobulin, AST, hyaluronate, age, urea	1039	41-56	0.78-0.89	4-15	0.94

- 13 biomarkers with at least two published validations in patients with chronic HCV (5 patented)
- ELF, Fibrotest, Fibrometer and Hepascore are patented

Martinez 2011

APRI vs. FibroTest

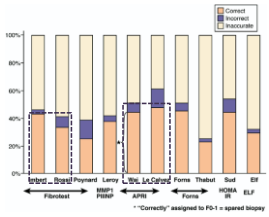
Class	Score	Markers	N	% ≥ F2	AUC ≥ F2	% F4	AUC F4
II	FibroTest	GGT, haptoglobulin, bilirubin, apolipoprotein A1, alpha-2-macroglobulin	2342	33-74	0.74-0.89	15-20	0.76-0.87
II	APRI	AST, platelets	3160	27-74	0.69-0.88	3-25	0.61-0.94

	APRI	FibroTest
Ease of performance/ cost	Routinely performed inexpensive markers	More expensive / less widely available markers
Liver specific	Platelet count reflects other injury (e.g., HIV)	More so than APRI
External validation	Lower accuracy in validation studies than original report	Performance less variable but little validation outside Europe
Ability to distinguish between different stages of fibrosis	Primary strengths: -Exclusion of fibrosis in low/average prevalence settings -Exclusion of cirrhosis in high prevalence settings	Better than APRI but still has lower diagnostic value to discriminate between two adjacent stages

Martinez 2011; Shaheen 2007; Poynard 2007; Manning 2008

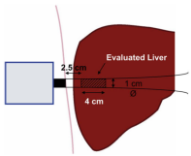
Serum markers of fibrosis: *Are we there yet?*

- **Strengths**
  - Easy to handle
  - Highly reproducible
- **Limitations**
  - Direct markers are not generally available in hospital laboratories
  - Some are non-specific (e.g., affected by renal function, HIV)
  - **Difficulty in distinguishing between mild/moderate disease**
  - Correlation with clinical outcomes?
  - Intraindividual changes not examined



Manning 2008; Parkes 2006

Transient elastography (Fibroscan)



- Liver stiffness measured by ultrasound (Fibroscan®, Echosens, France)
- Evaluates the velocity of propagation of a shock wave within liver tissue
- Velocity of wave relates to tissue stiffness
  - Harder tissue → faster propagation
  - Normal liver is viscous: not favorable to wave propagation
  - Fibrosis hardens tissue: favors more rapid propagation

Denzer 2009

Transient elastography (Fibroscan)

Class	Score	Method	N	% ≥ F2	AUC ≥ F2	% F4	AUC F4
I	Fibroscan	Transient elastography	2052	37-74	0.72-0.91	8-25	0.87-0.98

Strengths

- Ease of use: quick, noninvasive, inexpensive, high patient acceptance, reproducibility
- Reduced sampling error (volume assessed is 100x the liver biopsy)
- Wide range of values for cirrhosis

Limitations

- Unreliable in morbid obesity
- Acute inflammation, cholestasis and steatosis have been shown to elevate liver stiffness values
- Lack of standardized cutpoints
  - Recent meta-analysis of 50 studies (23 HCV-infected)
  - Cutpoints of 4.5 – 11.2 for ≥ F2 fibrosis and 10.1-19 for cirrhosis

Martinez 2011; Friedrich-Rust 2008

Non-invasive diagnosis: *Where do we stand?*

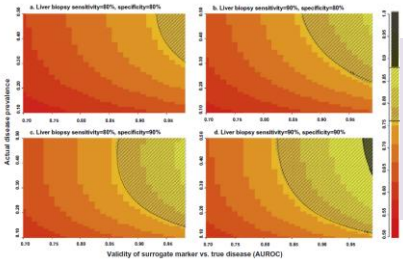
- **AASLD practice guidelines (2009)**
  - A liver biopsy should be considered in patients with chronic HCV if the patient and health care provider wish information regarding fibrosis stage for prognostic purposes or to make a decision regarding treatment
  - Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic hepatitis C infection, but should not replace the liver biopsy in routine clinical practice
- **EASL practice guidelines (2011)**
  - Liver biopsy is still regarded as the reference method to assess the grade of inflammation and the stage of fibrosis
  - Transient elastography (TE) can be used to asses liver fibrosis in patients with chronic hepatitis C
  - Non-invasive serum markers can be recommended for the detection of significant fibrosis (METAVIR F2-F4)
  - The combination of blood tests or the combination of TE and a blood test improve accuracy and reduce the necessity of using liver biopsy to resolve uncertainty

http://www.has-sante.fr; Ghany et al, Hepatology 2009; EASL J Hepatol 2011

How do we move forward?

1. Recognize that liver biopsy is not an ideal gold standard

Liver biopsy is not an ideal gold standard



Best case scenario:

- Prevalence of significant fibrosis: 40%
- Sensitivity/specificity of biopsy: 90%
- True accuracy of surrogate: 99%
- Estimated accuracy of surrogate: 90%

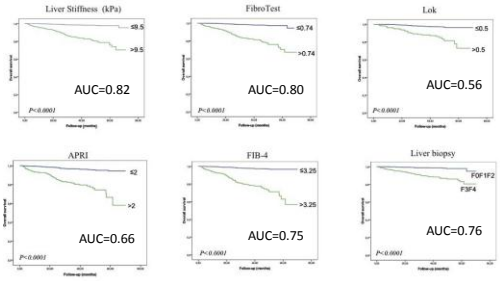
- Because of the limitations of the biopsy, a perfect surrogate cannot be distinguished from a less valid surrogate
- We may already have the perfect surrogate!

Mehta SH et al, *J Hepatology* 2009

How do we move forward?

1. Recognize that liver biopsy is not an ideal gold standard
   - No more new surrogates!!
   - Focus on external validation of existing surrogates
   - Validate existing surrogates against clinical outcomes

Validation against clinical outcomes (survival)



- Liver stiffness and FibroTest performed <u>better</u> than the liver biopsy in predicting survival

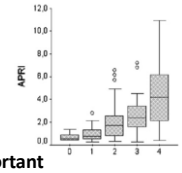
Vergnio, Gastroenterology 2011

How do we move forward?

1. **Recognize that liver biopsy is not an <u>ideal gold standard</u>**
   - No more new surrogates!!
   - Focus on external validation of existing surrogates
   - Validate existing surrogates against <u>clinical</u> outcomes
   - Incorporate metrics of calibration (assesses the ability of the marker to distinguish between different fibrosis stages)

Are we using the right metrics for validation?

- **Most validation has been based on <u>discrimination</u> statistics**
  - Test most commonly used (AUC) implies a dichotomous comparison
    - Significant vs. non-significant fibrosis
    - Cirrhosis vs. no cirrhosis
- **<u>Calibration</u> is also important**
  - Comparison of predicted stage vs. actual stage
- **Recalibration is potentially <u>more</u> important**
  - Use when a score systematically over or underestimates risk when applied to a new population
  - Account for differences in mean values of markers in different populations

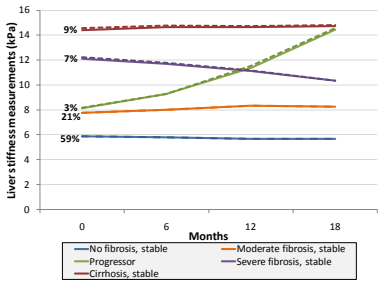


Leroy J Hepatology 2007

How do we move forward?

1. **Recognize that liver biopsy is not an ideal gold standard**
   - No more new surrogates!!
   - Focus on external validation of existing surrogates
   - Validate existing surrogates against clinical outcomes
   - Incorporate metrics of calibration (assesses the ability of the marker to distinguish between different fibrosis stages)
2. **Assess reliability of the measurements**

Multiple measurements may improve accuracy



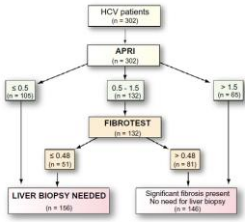
- 591 persons with four semi-annual LSM assessments
- LSM were stable in the majority
- A single measurement ≥ 12.3 kPa appears valid for identifying cirrhosis
- Requirement of two measurements <8kPa significantly improves accuracy for ruling out significant fibrosis

Mehta SH et al, *CROI* 2011

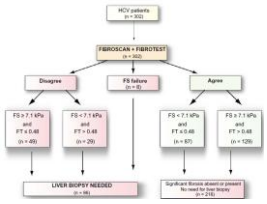
How do we move forward?

1. **Recognize that liver biopsy is not an ideal gold standard**
   - No more new surrogates!!
   - Focus on external validation of existing surrogates
   - Validate existing surrogates against clinical outcomes
   - Incorporate metrics of calibration (assesses the ability of the marker to distinguish between different fibrosis stages)
2. **Assess reliability of the measurements**
3. **Consider combination algorithms**

Combination algorithms improve accuracy
(vs. biopsy)



SAFE biopsy (Sebastiani)



Castera algorithm (Castera)

- **Reduction in need for biopsy:**
  - FIBROSIS: Castera: 72%; SAFE: 48%
  - CIRRHOSIS: Castera: 78%; SAFE: 74%

Castera, Sebastiani et al, J Hepatol 2010

Combination algorithms improve accuracy
(vs *clinical outcomes)*

	Hazard ratio	95% CI	P value
LSM	3.1	1.5-6.1	0.002
Fibro Test	55	4.1-736	0.003
Acti Test	0.07	0.01-0.47	0.006
HCV treatment	0.19	0.09-0.39	0.14
Age	1.03	0.99-1.06	0.14
AUC of combination	**0.91**	**0.83-0.95**	

- **Also considered as predictors:** Liver biopsy, APRI, FIB-4

Vergnio, Gastroenterology 2011

Conclusions

- **Even with the anticipated FDA approval of Boceprevir and Telaprevir, liver disease staging <u>remains</u> important**
  - Some may want to <u>wait</u> for interferon-free regimens
  - Not everyone may be <u>ready</u> for treatment
  - Treating everyone is not the reality for the <u>developing</u> world
- **Liver biopsy <u>remains</u> the gold standard for staging**
- ***BUT, the tide is <u>changing</u>…..***
  - Validation against clinical outcomes may improve acceptability of surrogate markers
  - Fibroscan and FibroTest are the most promising candidates
  - The final word will likely involve some combination of surrogates and the biopsy