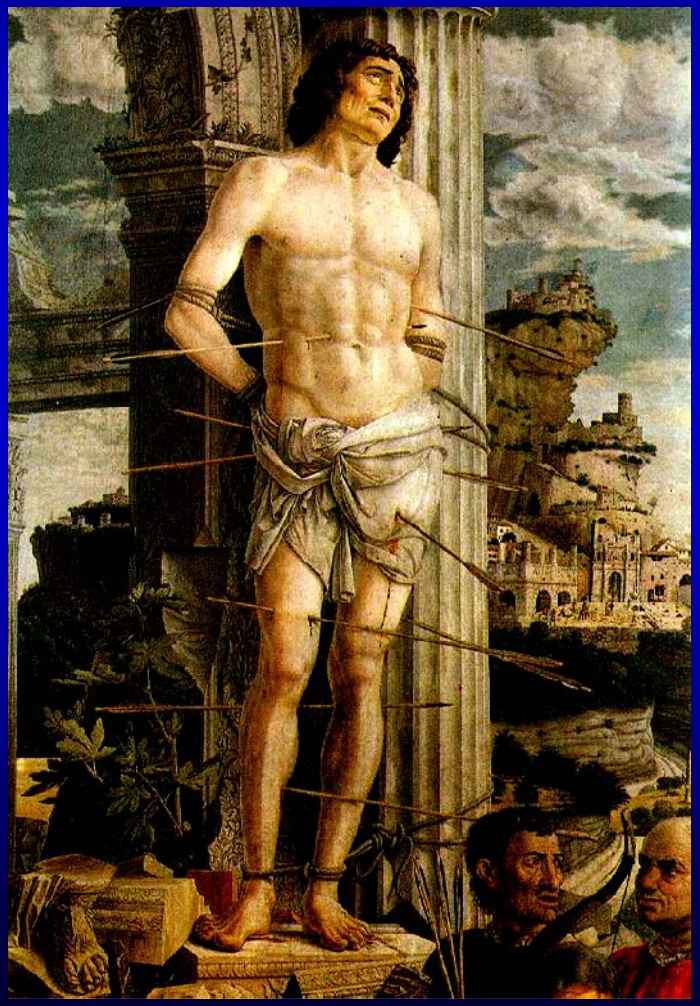
How to assess liver fibrosis Serum markers or FibroScan vs. liver biopsy ?

Laurent CASTERA & Pierre BEDOSSA

Hôpital Beaujon, AP-HP, Clichy
Université Paris-VII
France

4th Paris Hepatitis Conference, Paris, january 17-18 2011

Limitations of liver biopsy



- Invasive
- Sampling error
- Interobserver variability
- Nondynamic evaluation of fibrosis

Regev et al. Am J Gastroenterol 2002; 97:2614-8
Bedossa et al. Hepatology 2003;38: 1449-57
Rousselet et al. Hepatology 2005; 41: 257-64.

Limitations of liver biopsy

The patient perspective

Non-invasive assessment of liver fibrosis: are we ready?

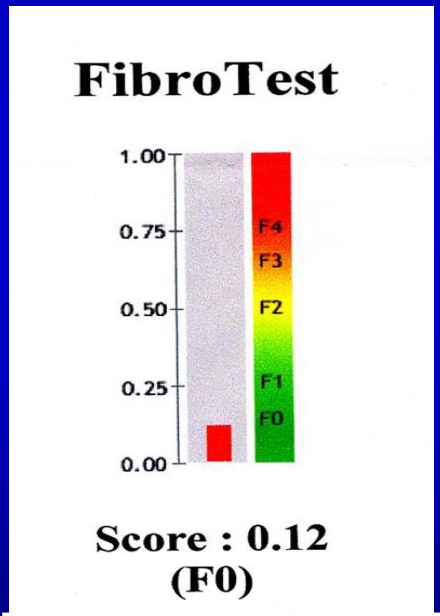
Laurent Castera, Massimo Pinzani

www.thelancet.com Vol 375 April 24, 2010

Available non invasives methods

2 different but *complementary* approaches

« Biological » approach



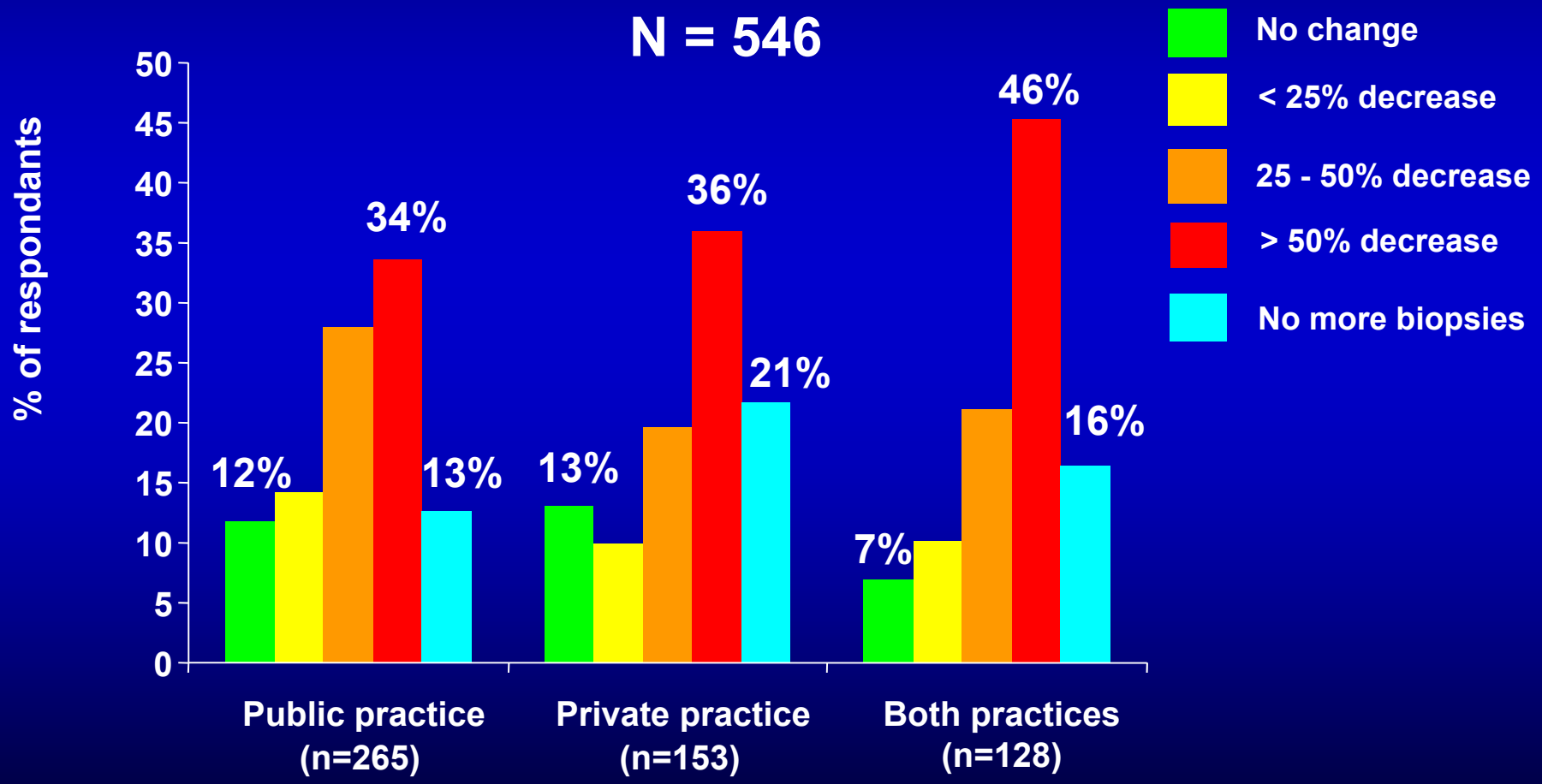
$$APRI = \frac{AST \times 100}{Platelet}$$

Serum markers

« Physical » approach

Transient elastography

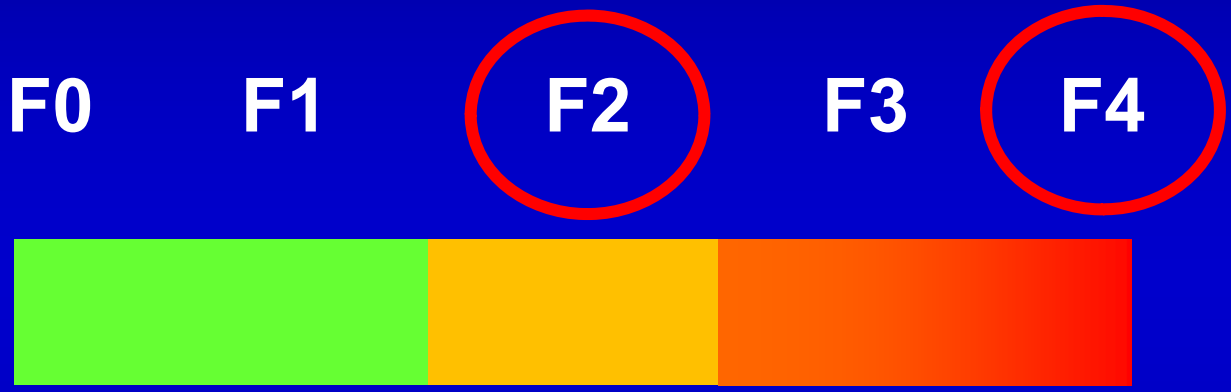
Impact of the use of non invasive markers on the need for liver biopsy in CHC in France



Castera et al. J Hepatol 2007; 46: 528-9

What are the diagnostic performances of non invasive methods?

End points in viral hepatitis



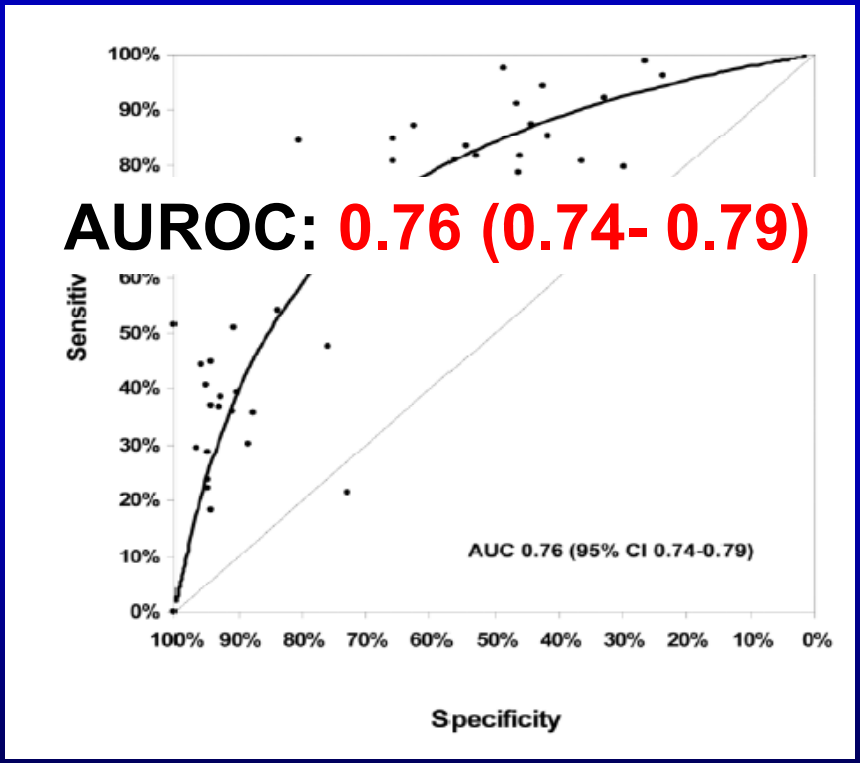
Indication for antiviral treatment

Screening for Eosophageal varices

Screening for Hepatocellular carcinoma

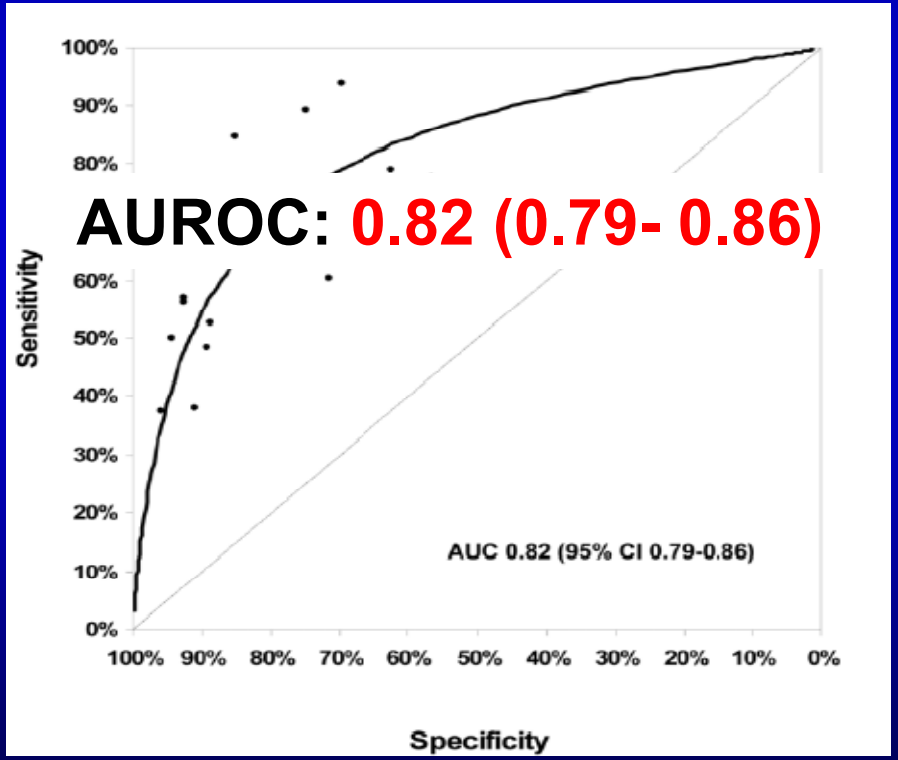
APRI
meta-analysis

Significant fibrosis



19 studies; N= 3778 patients; F2F3F4 47%

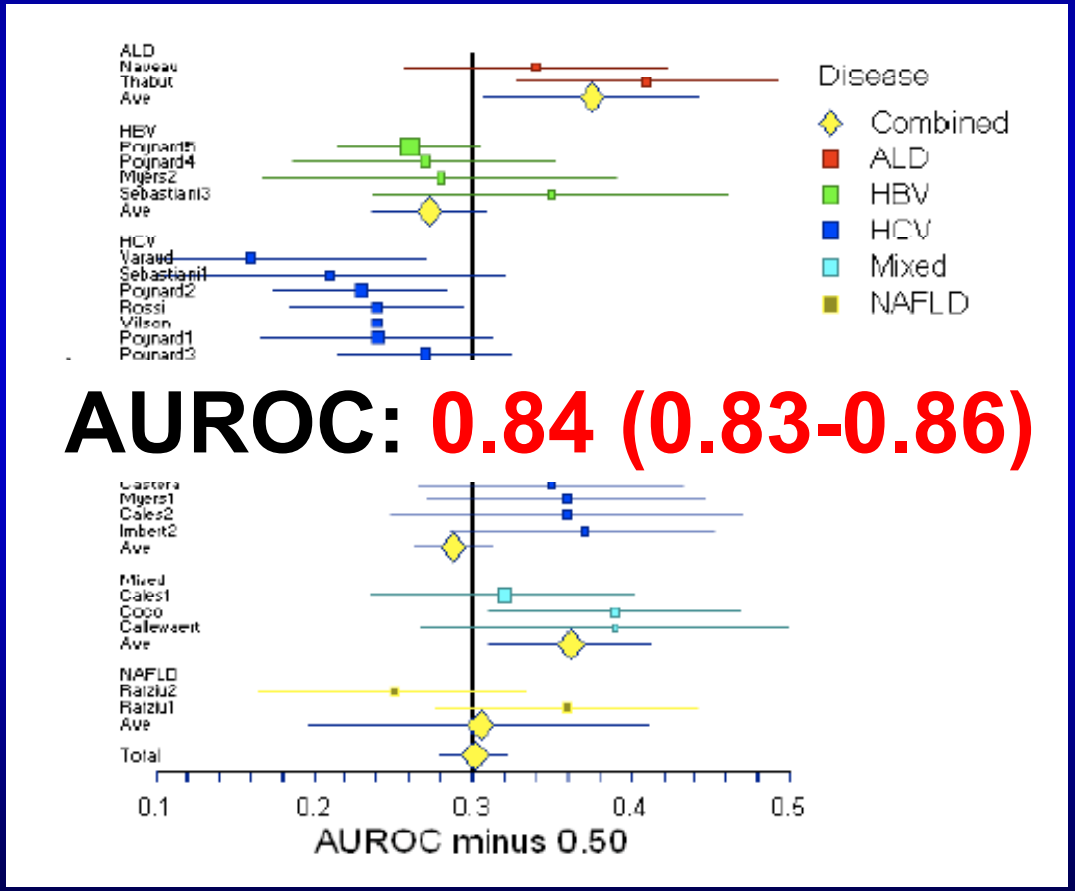
Cirrhosis



Shaheen et al. Hepatology 2008; 46: 912-21

FibroTest®

meta-analysis F≥2



AUROC: 0.84 (0.83-0.86)

30 studies; N= 6378 patients

Poynard et al. BMC Gastroenterol 2007; 7-40

Other available serum markers

- Forns Index
- FibroSpect®
- MP3
- ELF score®
- Fibrosis Probability Index
- Hepascore®
- FibroMeter®
- Fibroindex
- Virahep-C model

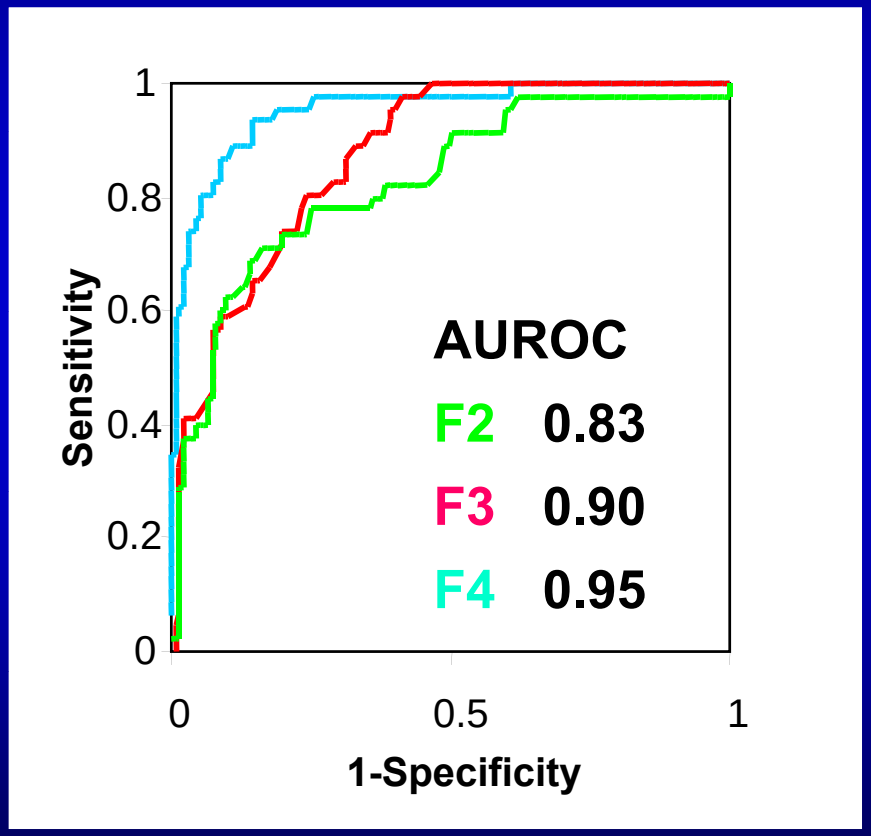
Comparative performance
serum biomarkers

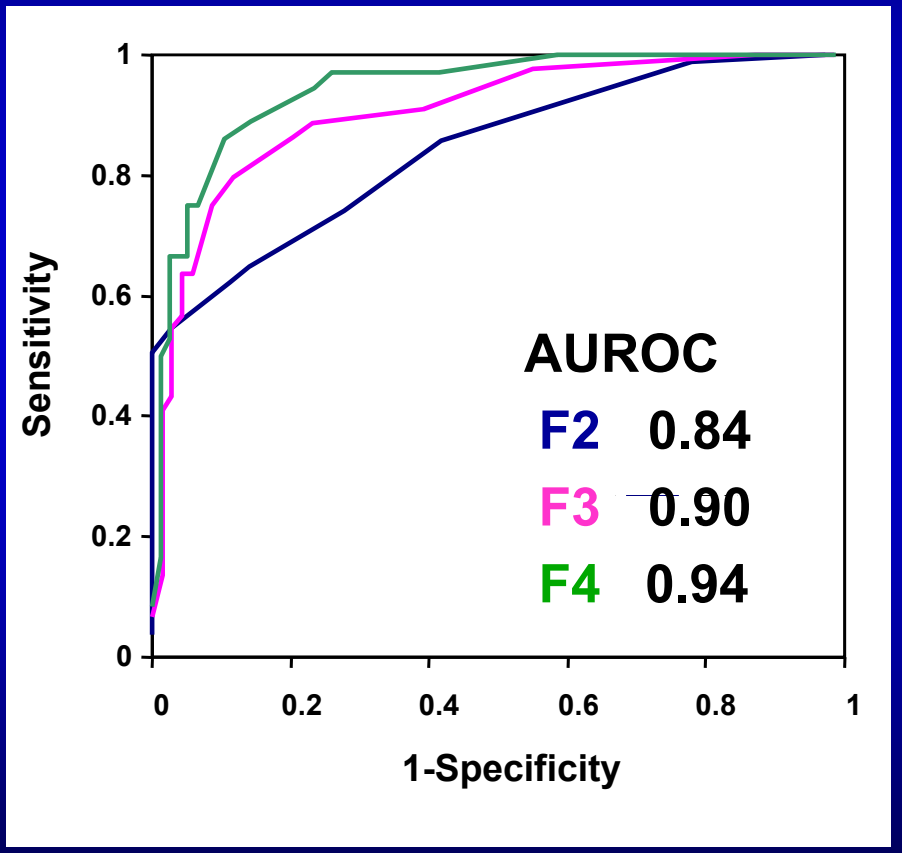
	Number of patients	Significant Fibrosis Cut-off	Significant Fibrosis AUC	Cirrhosis Cut-off	Cirrhosis AUC
Biomarkers[†‡]					
Fibrotest®	1197	0.48	0.78 (0.75-0.81)	0.74	0.82 (0.79-0.85)[†]
Fibrometre®	1204		P=NS		P=NS
APRI	1272	0.5	0.72 (0.69-0.75)	2.0	0.77 (0.73-0.81)[†]
Hepascore	1238	0.5	0.78 (0.75-0.80)	0.84	0.86 (0.83-0.88)[‡]

N= 1307 patients; F2: 57%; F4: 14%

Degos et al. J Hepatol 2010; 53: 1013-21

Transient elastography
Diagnostic performance



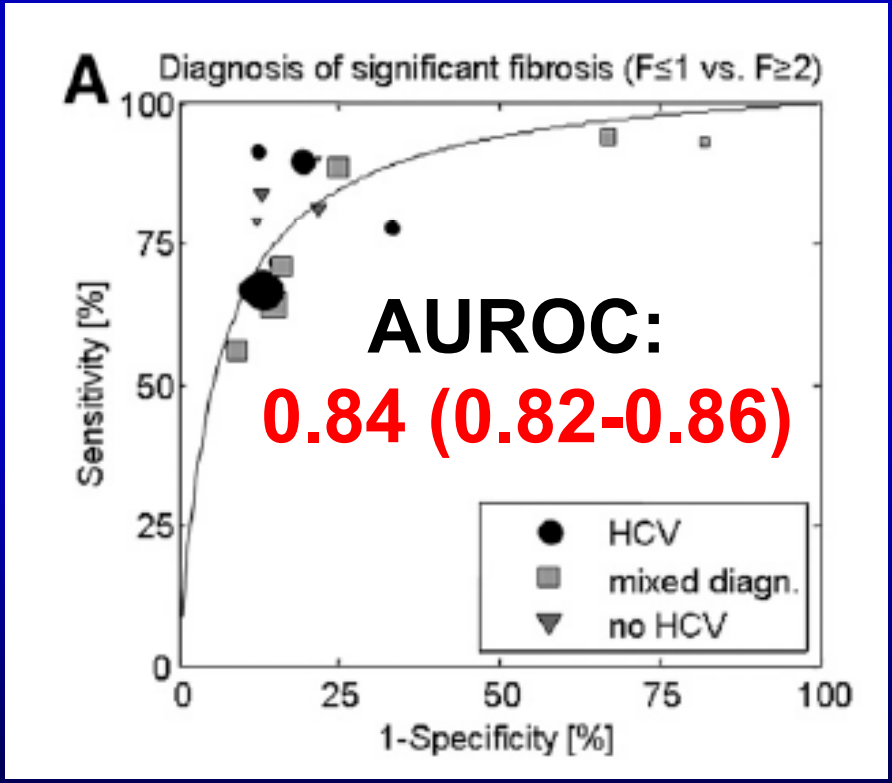


Ziol et al. Hepatology 2005; 41: 48-54

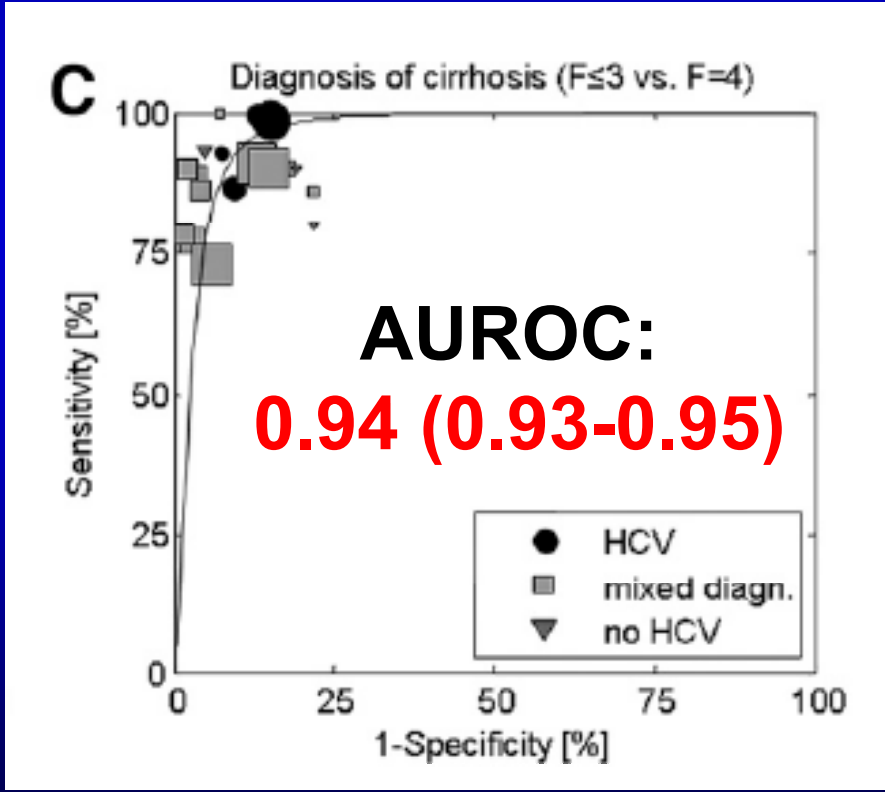
Castera et al. Gastroenterology 2005; 128: 343-50.

Transient elastography
Meta-analysis

Significant fibrosis



cirrhosis



Friedrich-Rust et al. Gastroenterology 2008; 134: 960-74

How do serum markers

&

FibroScan compare ?

Comparative performance
significant fibrosis

	Number of patients	Preva-lence	Cut-off	AUC
FibroScan®*	1307	57.1	7.1	0.76 (0.74-0.79)
Fibrotest®			0.48	0.78 (0.75-0.81)
Fibrometre®			0.41	0.79 (0.76-0.81)
APRI	1272	57.1	0.5	0.72 (0.69-0.75)
Hepascore	1238	57.1	0.5	0.78 (0.75-0.80)

P=NS

N= 1307 patients; F2: 56%

Degos et al. J Hepatol 2010; 53: 1013-21

Comparative performance
cirrhosis

	Number of patients	Prevalence	Cut-off	AUC
FibroScan®*	1307	13.8	12.5	0.90 (0.87-0.92)
Fibrotest®				0.82 (0.79-0.85)
Fibrometre®	1204	13.6	0.44	0.86 (0.83-0.89)
APRI	1272	13.9	2.0	0.77 (0.73-0.81)
Hepascore	1238	14.0	0.84	0.86 (0.83-0.88)

P<0.0001

N= 1307 patients; F4: 14%

Degos et al. J Hepatol 2010; 53: 1013-21

What about combining serum markers & FibroScan?

Combining methods increases diagnostic accuracy

Serum markers

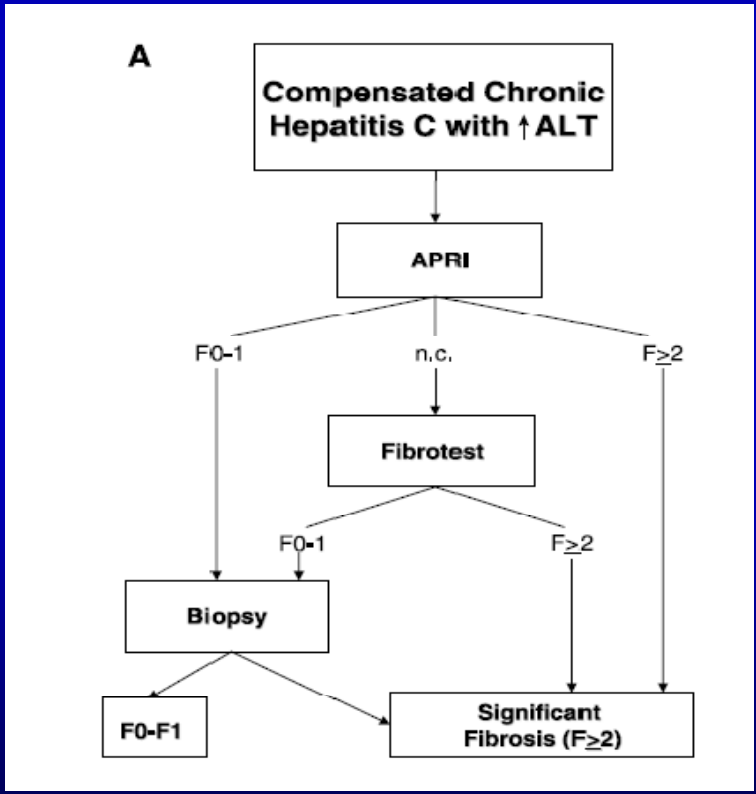
Correctly classified for F≥2: 75%

Transient elastography

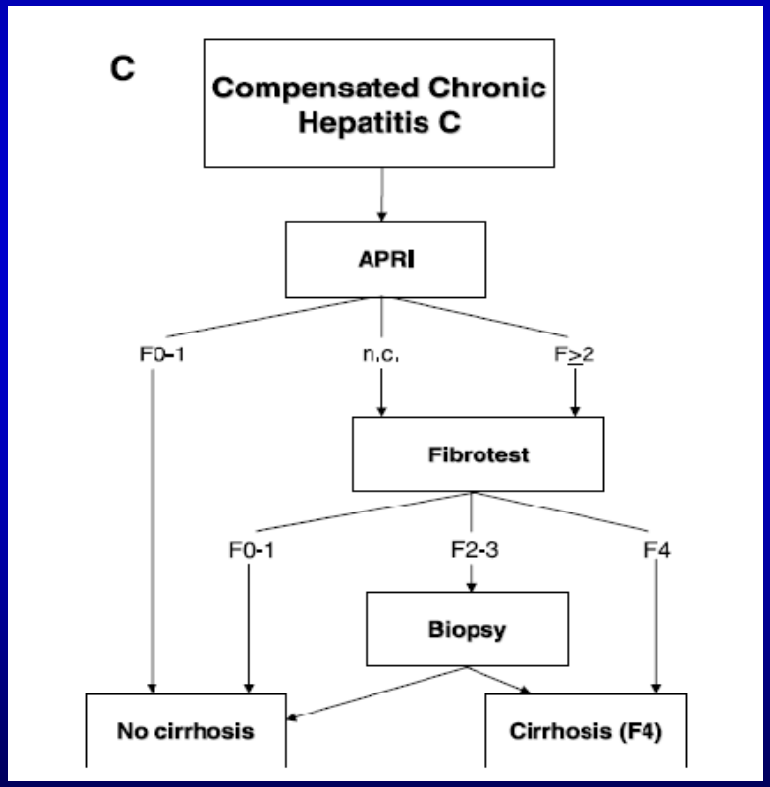
Castera et al. Gastroenterology 2005; 128: 343-50.

Combining sequentially APRI & FibroTest the SAFE Biopsy algorithm

Significant fibrosis



Cirrhosis



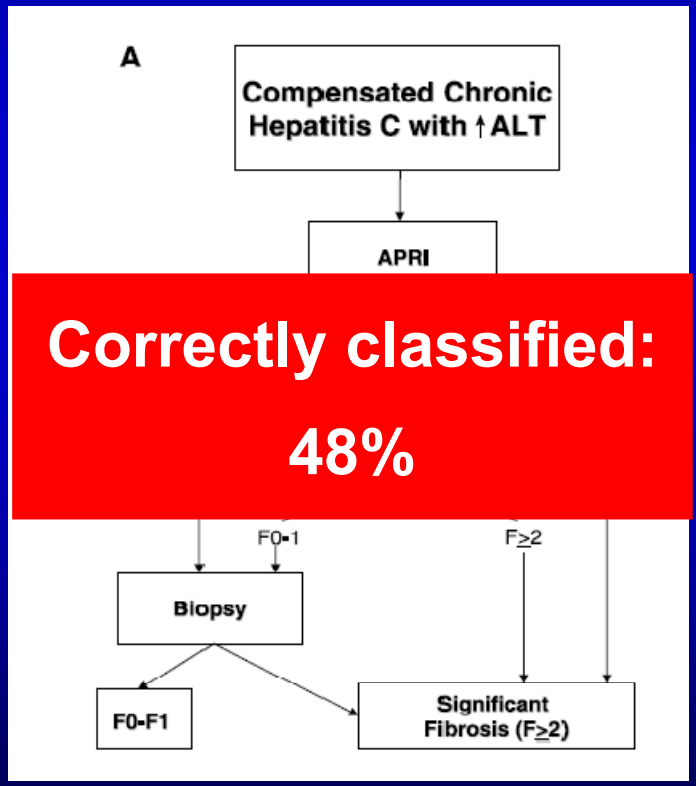
Sebastiani et al. J Hepatol 2006; 44: 686-93.

Sebastiani et al. Hepatology 2009; 49: 1821-7

Comparison between algorithms

significant fibrosis

APRI + FT

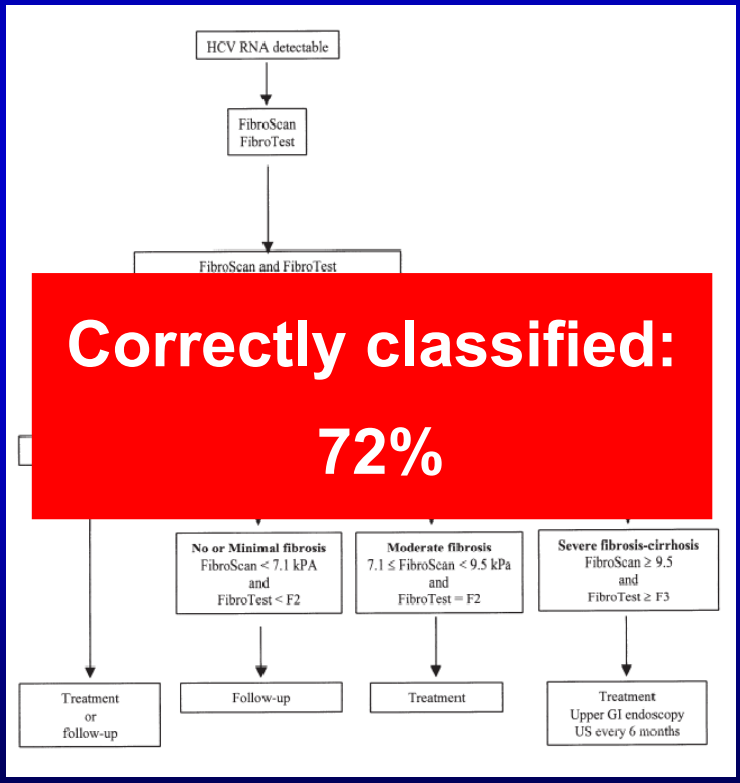


Correctly classified: 48%

P<0.001

<

FS + FT



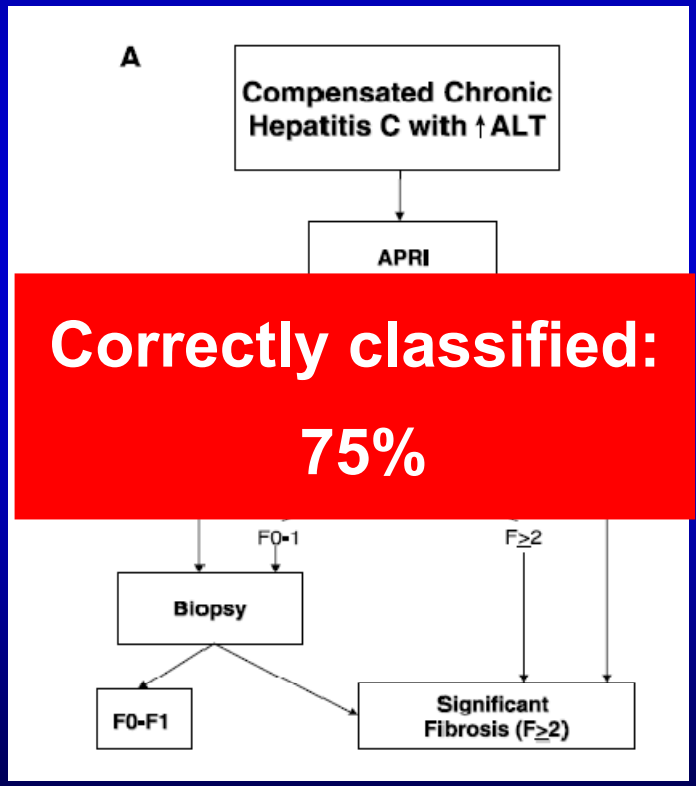
Correctly classified: 72%

N=302 HCV patients

Castéra et al. J Hepatol 2010; 52: 191-8.

Comparison between algorithms
cirrhosis

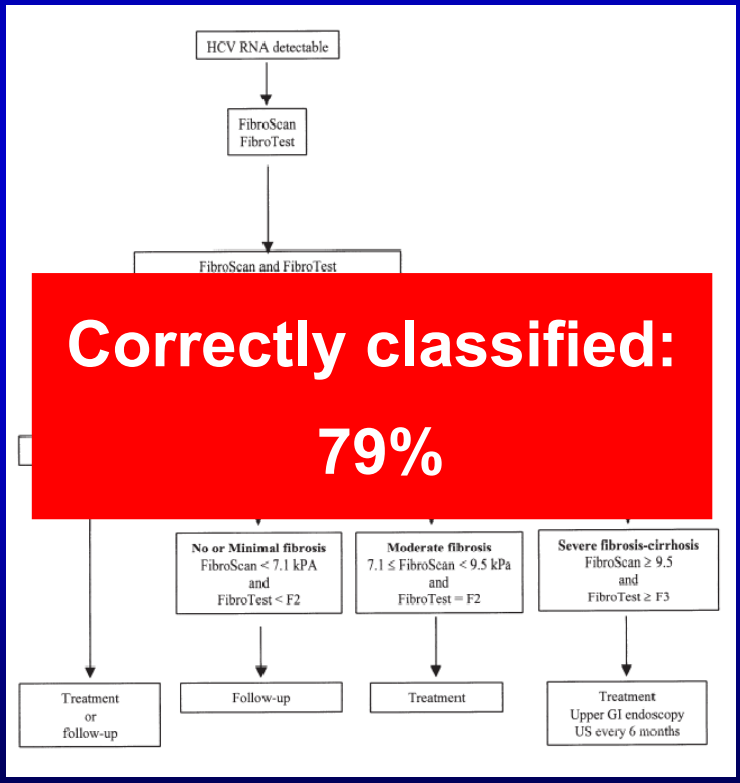
APRI + FT



Correctly classified: 75%

=

FS + FT



Correctly classified: 79%

N=302 HCV patients

Castéra et al. J Hepatol 2010; 52: 191-8.

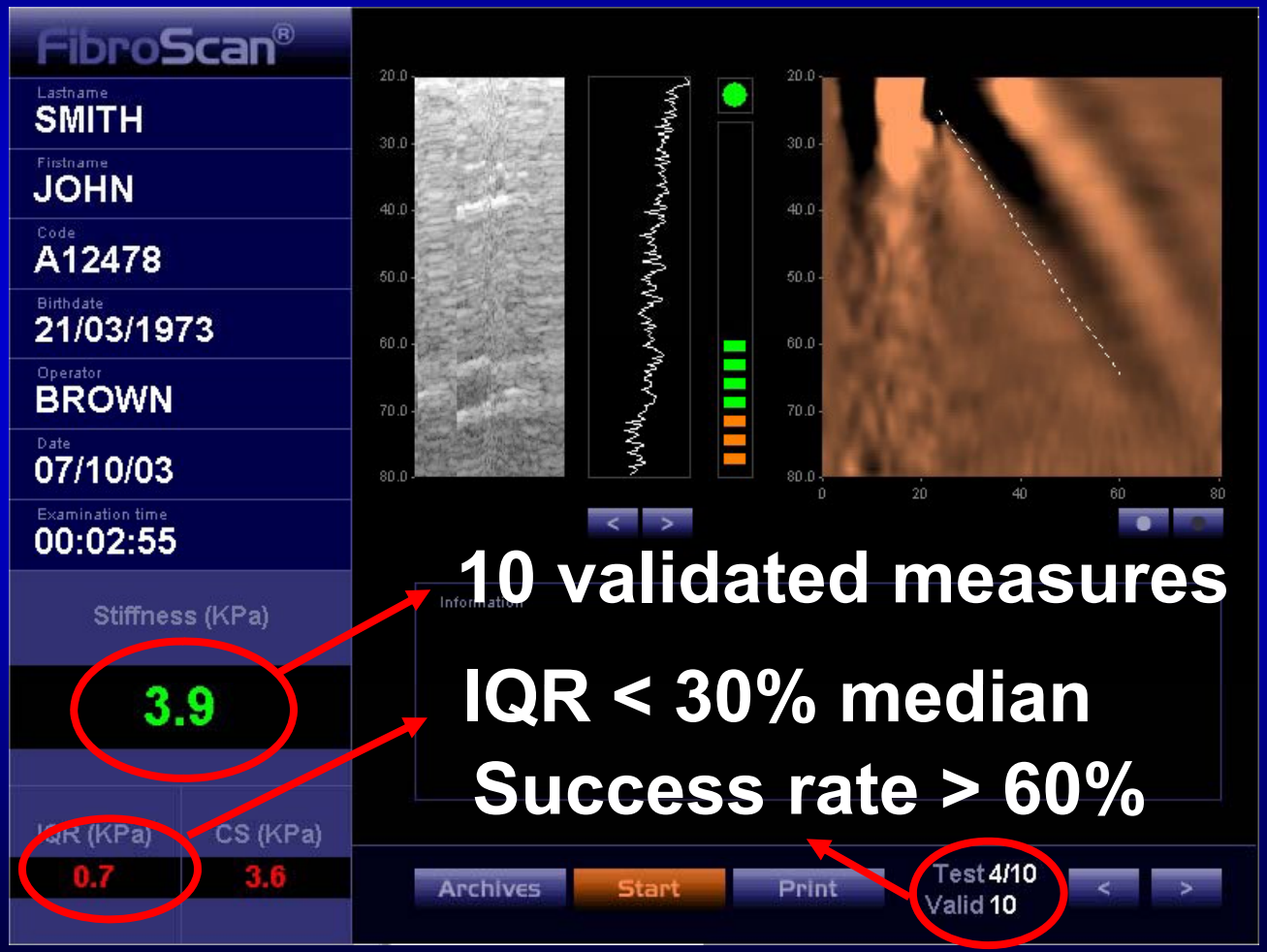
What are the limitations of non invasive methods?

Limitations of serum markers

Serum markers

- Standardization and reproducibility of dosage methods ?
  - AST/ALT, Platelets
- False positive with Fibrotest
  - Hemolysis, Gilbert syndrome

How to interpret FibroScan results
manufacturer's recommendations



Castera, Forns & Alberti. J Hepatol 2008; 48: 835-47

Limitations : LSM failure
n=13369

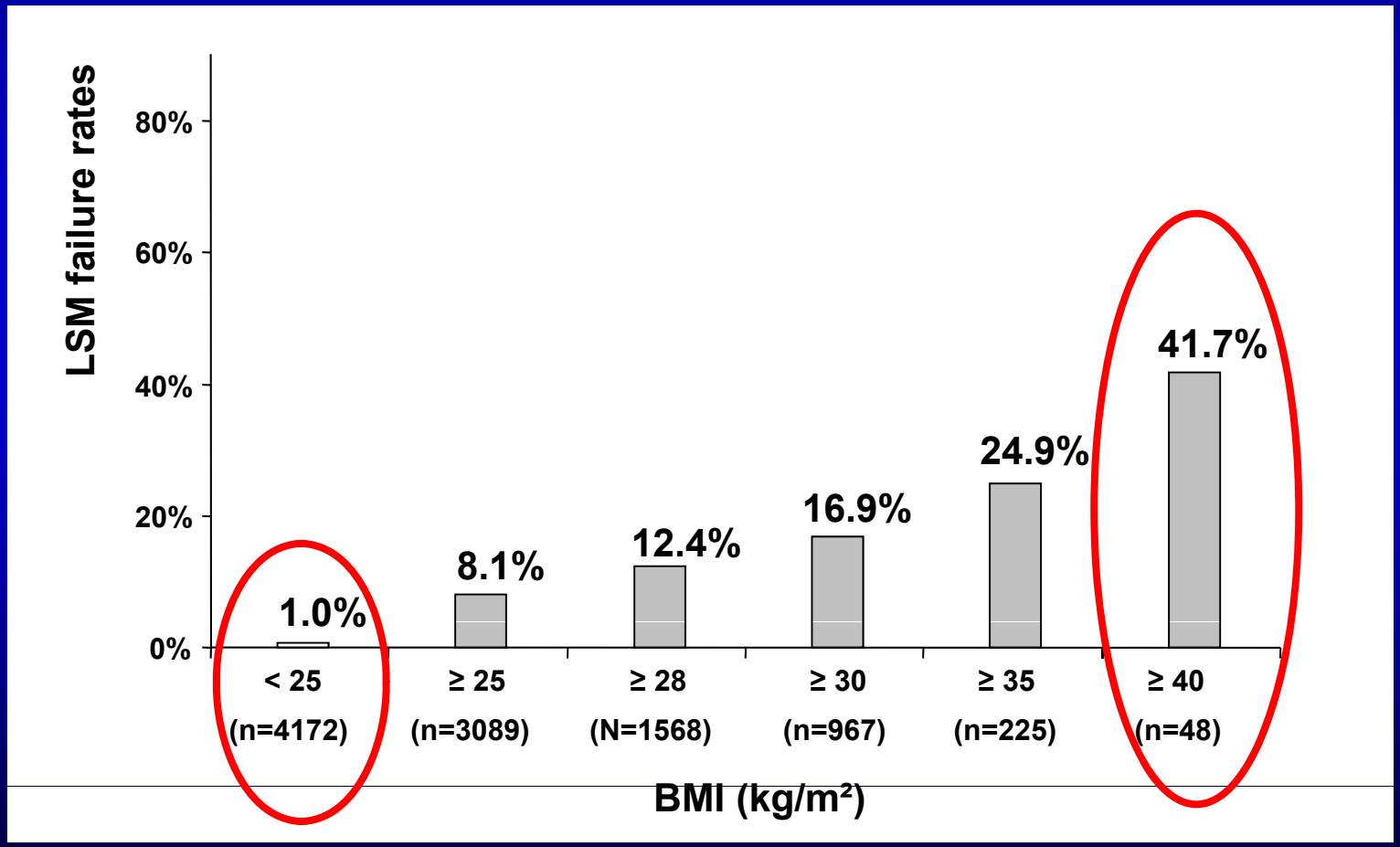
Failure : 3.1 %

- BMI > 30

- Operator Experience

Castéra et al. Hepatology 2010; 51: 828-35

Limitations : LSM failure
n=13369

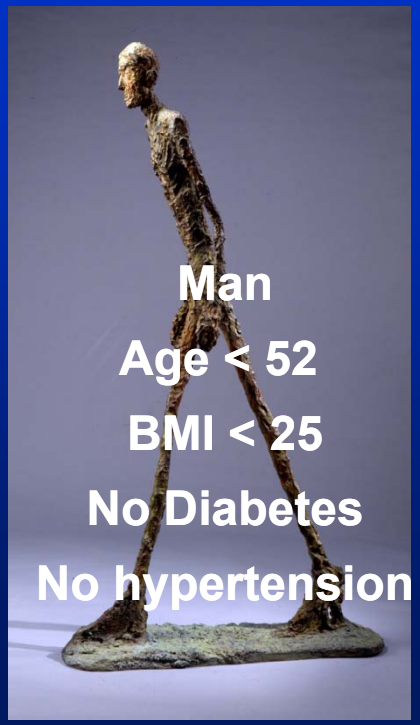


Castéra et al. Hepatology 2010; 51: 828-35

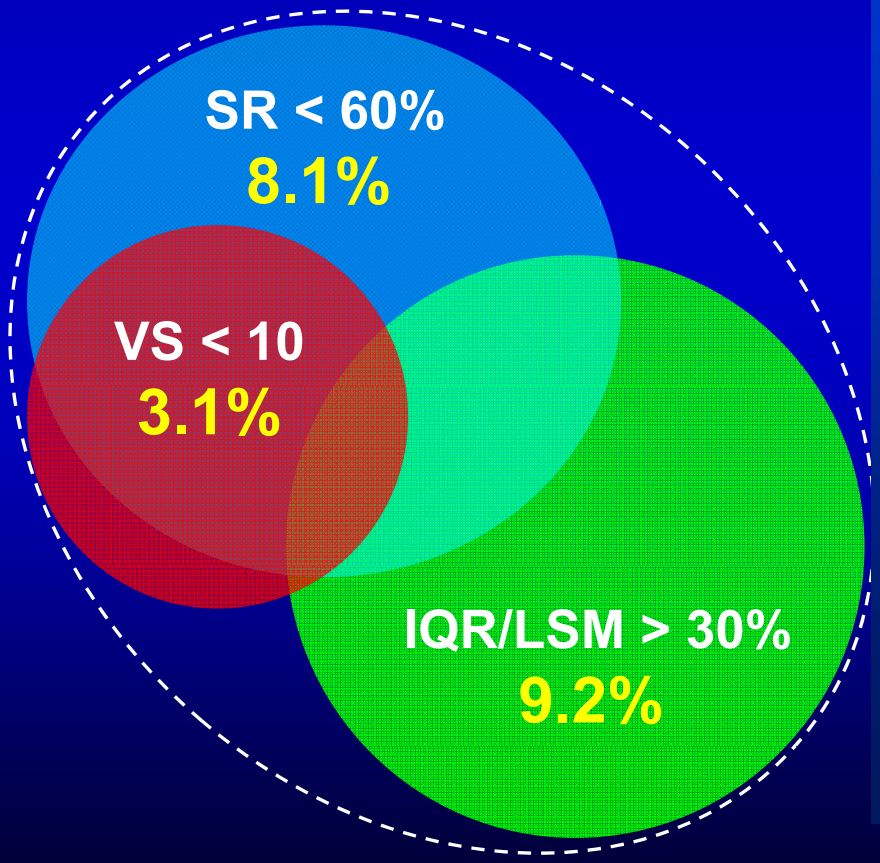
Limitations: unreliable LSM results

n=12 949

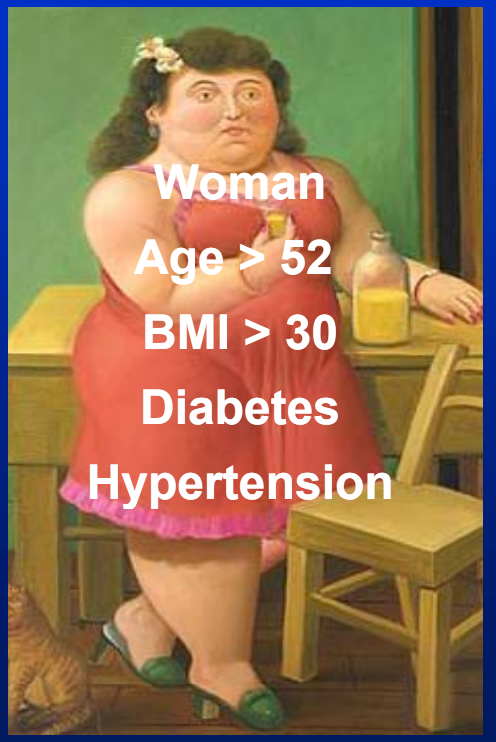
7.2%



15.8%

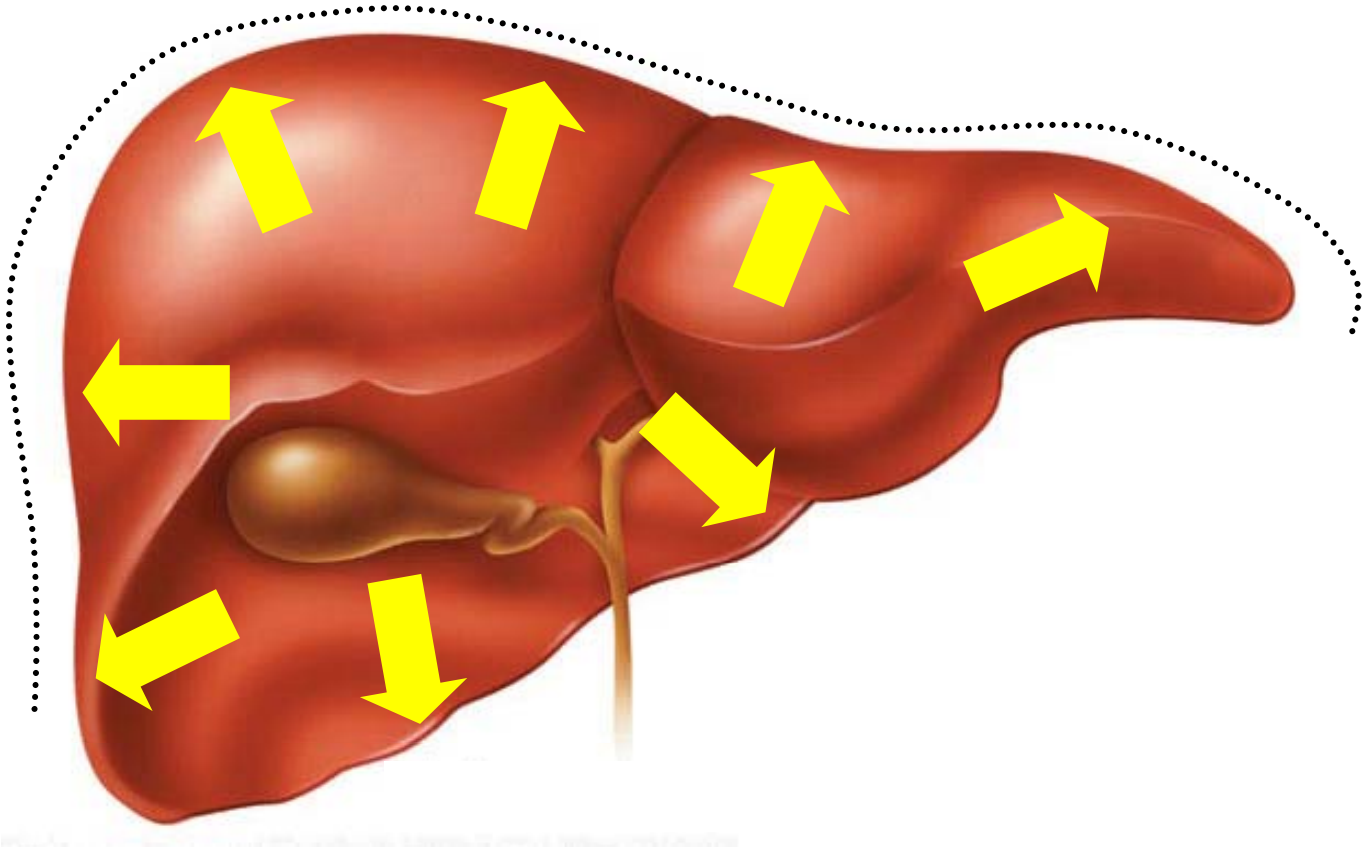


60.4%



Castéra et al. Hepatology 2010; 51: 828-35

Glisson's capsula:
a distensible but non elastic envelope



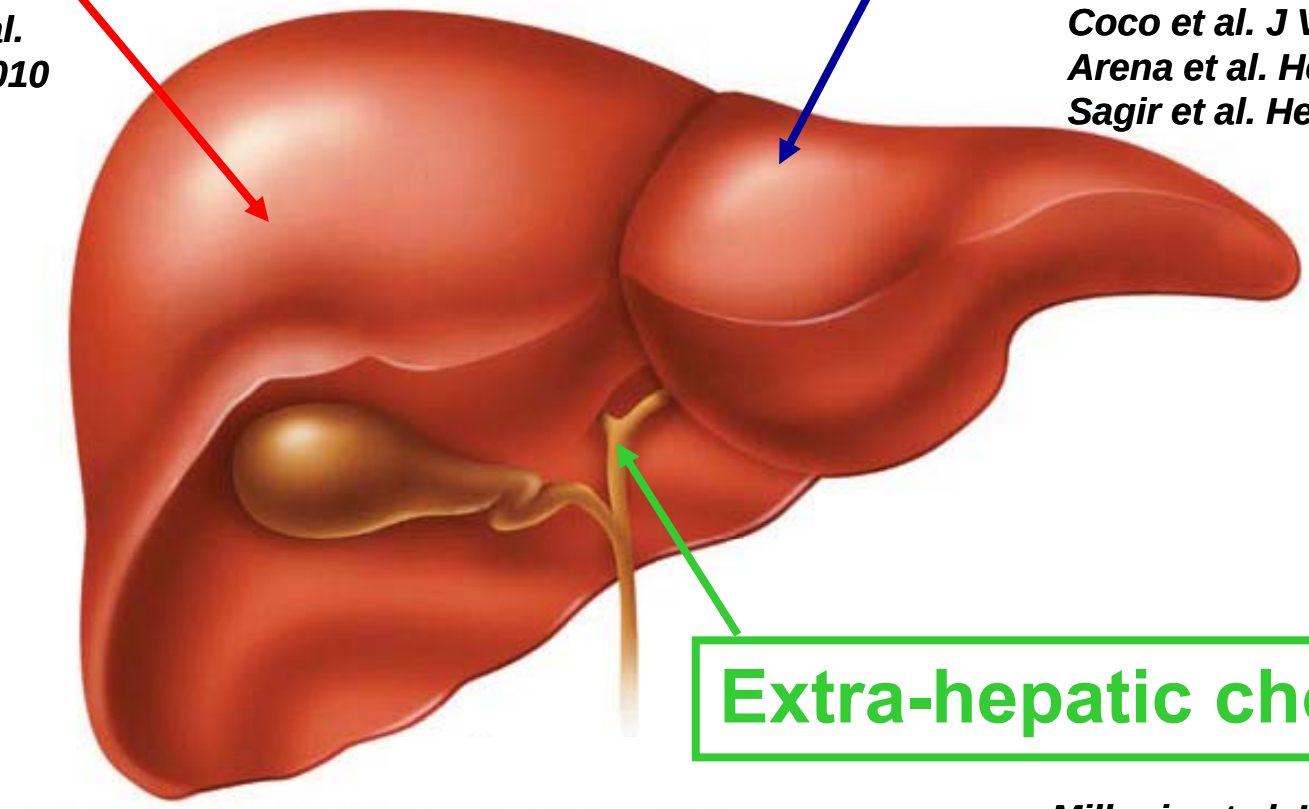
Confounding factors for liver stiffness

Liver congestion

Millonig et al.
J Hepatol 2010

Acute Inflammation

Coco et al. J Viral Hepat 2007
Arena et al. Hepatology 2008
Sagir et al. Hepatology 2008



Extra-hepatic cholestasis

Millonig et al. Hepatology 2008

Summary

significant fibrosis

Serum markers

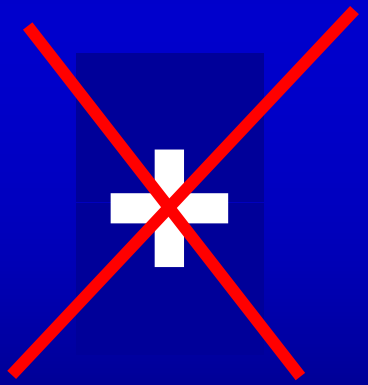
+

Transient elastography

Summary

Cirrhosis

Serum markers



Transient elastography

Let’s be serious, NOW !

THE LIVER BIOPSY

Liver Biopsy: Perfect or Gold standard ?

- **L.B not the perfect standard BUT :**
  - The gold standard for serum markers: any combination of serum marker is tuned up on histology
  - Liver stiffness is a physical criteria related to several different parameters (Fibrosis, inflammation, congestion, cholestasis….)

Liver Biopsy: When ?

1. Non-invasive tests not exploitable
2. Accurate staging of fibrosis necessary
3. Hepatitis C + Comorbidity
4. Any unclear situation

Liver Biopsy: When ?

1. Non-invasive tests not exploitable

- NI tests not available
- Predictable failure of NI tests :
  - Serum markers : specific restrictions
  - High BMI
  - ? Female, Age > 52, Diabetes…..*
- But some risk of failure are not predictable : inflammation, congestion discovered only at histology…….

** Castéra et al. Hepatology 2010; 51: 828-35*

Liver Biopsy: When ?

1. Non-invasive tests not exploitable
2. Accurate staging of fibrosis necessary

Liver Biopsy: When ?

2. Accurate staging of fibosis necessary

- NI tests validated for dichotomic evaluation only (Significant fibrosis : Yes / No)
- Major overlap for NI tests when adjacent stages are concerned (F1 vs F2, F2 vs F3…)

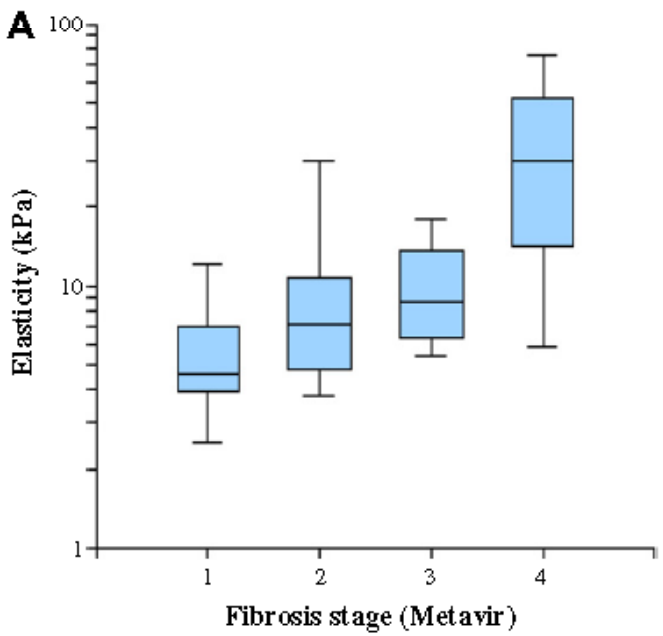
Stage by stage overlap for Fibrotest

	A.U.R.O.C.
F2 vs. F1(n = 2,055)	0.66 0.63–0.68
HCV (1,654)	0.66 0.63–0.69
HBV (155)	0.63 0.53–0.71
ALD (117)	0.65 0.53–0.74
NAFLD (129)	0.69 0.57–0.78
F3 vs. F2 (n = 1,059)	0.67 0.64–0.70
HCV (829)	0.66 0.62–0.69
HBV (99)	0.78 0.67–0.86
ALD (73)	0.66 0.50–0.77
NAFLD (58)	0.69 0.52–0.80
F4 vs F3 (817)	0.69 0.65–0.72
HCV (573)	0.66 0.61–0.70
HBV (81)*	0.54 0.40–0.65
ALD (127)*	0.82 0.69–0.90
NAFLD (36)	0.71 0.45–0.86

* P = 0.001 between HBV and ALD

Poynard *et al. BMC Gastroenterology* 2007 **7**:40 doi:10.1186/1471-230X-7-40

Stage by stage overlap for Fibroscan



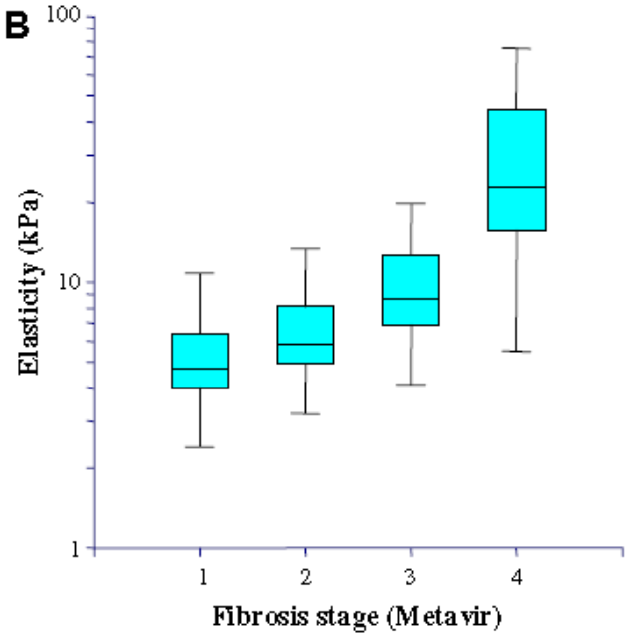


Fig. 3. Box-plots of liver stiffness values for each fibrosis stage (Metavir). Because of the wide range of FS values for *F*4, the vertical axis is in logarithmic scale. Adapted from (A) Ziol et al. [18] and (B) Castera et al. [17].

From Castera et al. J Hepatol 2008;833-847

Liver Biopsy: When ?

2. When accurate staging of fibrosis is necessary ?

- Patients difficult to treat or to manage
- Retreatment (no 1st biopsy)
- Any cases if hepatologist interested in :
  - F1 vs F2 ?
  - F3 vs F4 : prevention of variceal bleeding, screening program for HCC

Liver Biopsy: When ?

1. Non-invasive tests not exploitable
2. Accurate staging of fibosis necessary
3. Hepatitis C + Comorbidity

Liver Biopsy: When ?

3. Hepatitis C + Comorbidity

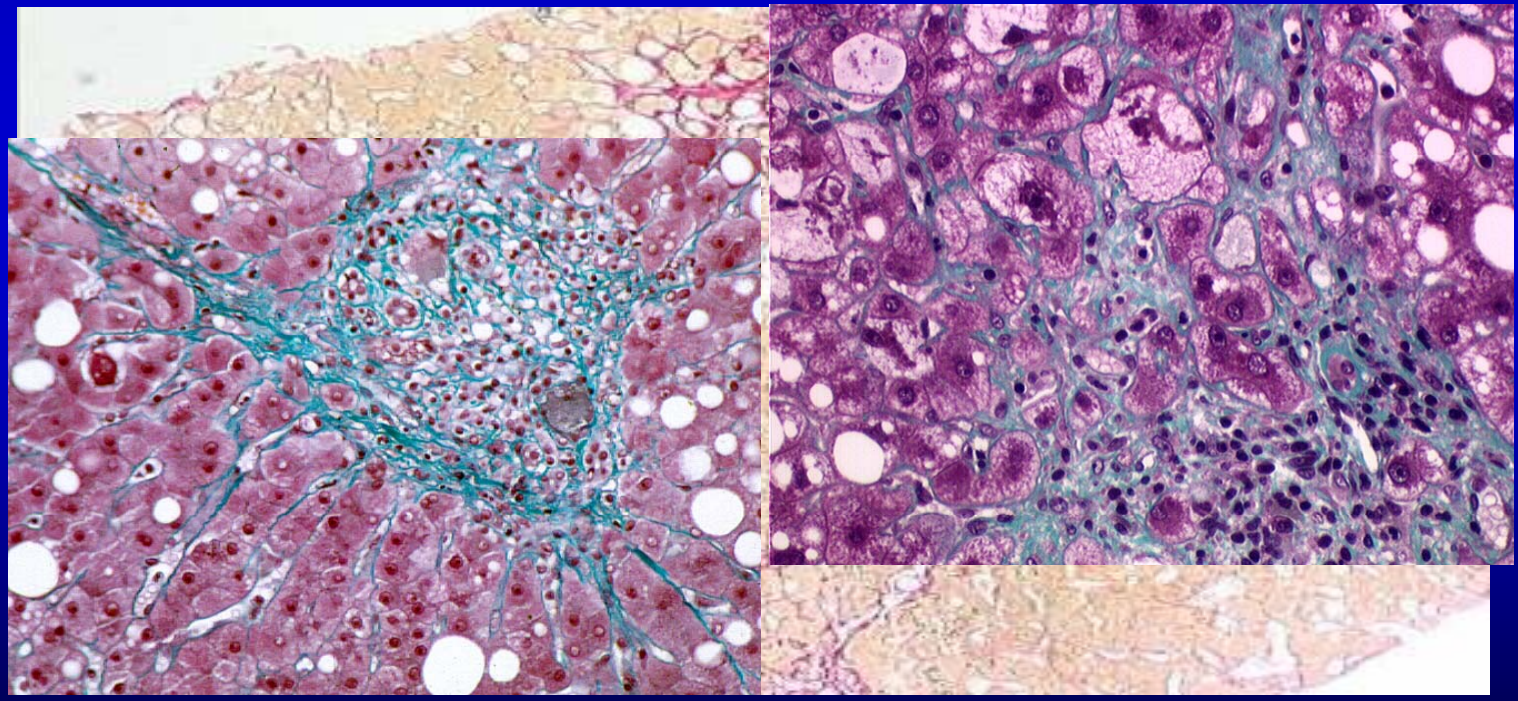
- Immune deficiency : HIV, post-transplant
- Alcohol consumption
- Metabolic syndrom

- HCV-associated Insulin resistance ???

Liver biopsy and comorbidity in Hepatitis C

Chronic hepatitis C (1b) + metabolic syndrom

Fibrotest = F4, Fibroscan = 11 kpA



L.B: STEATOHEPATITIS + Hep C Metavir A0F1

Liver Biopsy: When ?

4. Any unclear situation :

- In the context of the high burden of CLD, abnormal clinical symptoms or liver tests can be related to unsuspected disease
- Added diagnosis in CHC : 2.3% - 13.9 %*
  - Steatohepatitis
  - Auto-immunity
  - Iron overload
  - Granuloma

* Saadeh, Hepatology 2001, Spycher, BMC Gastro 2001

TAKE-HOME MESSAGES

- Non-invasive tests can be used as first line when crude evaluation of fibrosis is needed.
- All NI tests (as for liver biopsy) have limitations.
- Liver biopsy remains the best standard for liver fibrosis evaluation in HepC.
- LB has still a role in HepC for patient management.

Gut July 2010 Vol 59 No 7

Biopsy and non-invasive methods for the diagnosis of liver fibrosis: does it take two to tango?

Laurent Castera,[1] Massimo Pinzani[2]