

NON INVASIVE EVALUATION OF DISEASE PROGRESSION IN CHRONIC LIVER DISEASES

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[**www.ucl.ac.uk/medicine/liver-and-digestive-health**](http://www.ucl.ac.uk/medicine/liver-and-digestive-health)

Search for early predictor of decompensation and ACLF

Search for early predictor of HCC

Search for predictors of
progression rate to cirrhosis

Spleen-related Noninvasive Indexes & Algorithms

Spleen Stiffness Measurement

Liver Stiffness Measurement

Serum Markers: Direct/Indirect

Serum Markers: predictors of liver related outcomes

Liver Biopsy (PC or TJ) : Quantitative staging with CPA

Early to Advanced Liver Fibrosis

Cirrhosis without Clinical
Manifestations

Cirrhosis with Clinical
Manifestations

Liver Failure

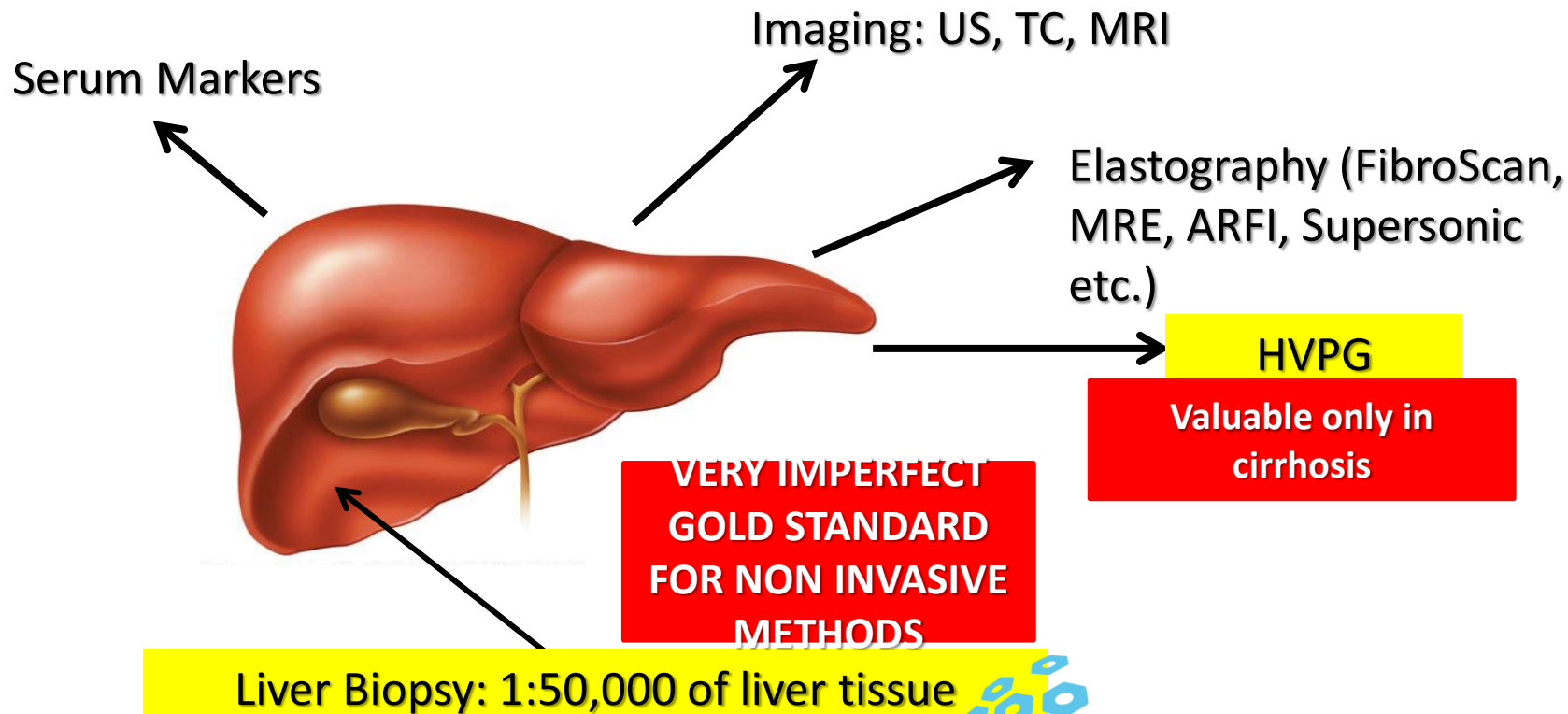
HVPG < 5 mm Hg

HVPG 5-10 mm Hg

HVPG > 10-12 mm Hg

Advanced Chronic Liver Disease

Non Invasive Evaluation of Liver Tissue Fibrosis (Staging)



End-Points in Fibrogenic CLDs

S0

K/F0

S1&2

K/F1

S3

K/F2

S4-S5

K/F3

S6

K/F4



F: METAVIR
S: ISHAK's
K: KLEINER

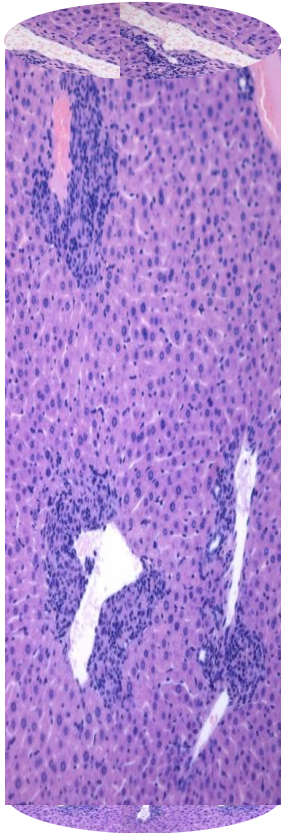


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Screening for
Oesophageal
Varices

Screening for HCC

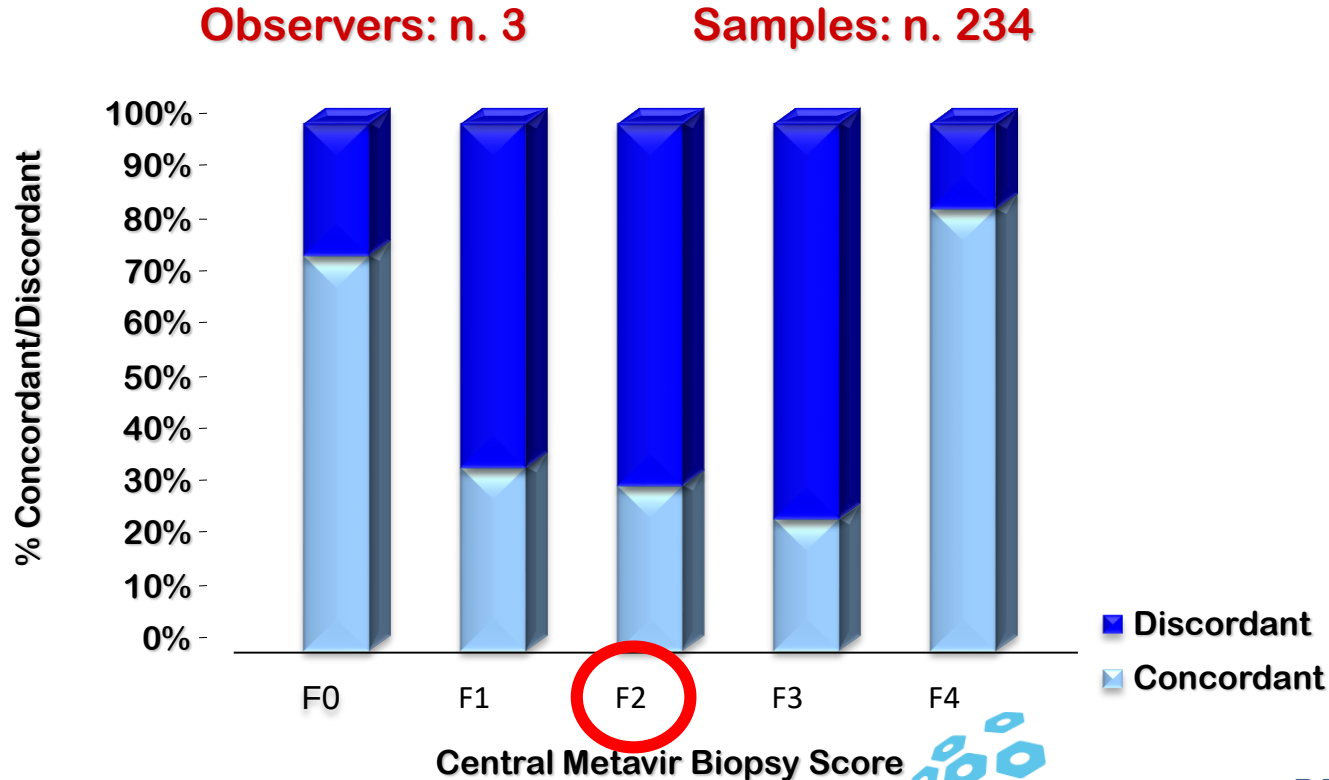
Liver Biopsy



1. - Provides clues about etiology and co-factors
2. - Allows immunohistochemical, biochemical biomolecular, genetic and epigenetic investigations
3. - Allows assessment of iron/copper content
4. - Is employed for grading (ACTIVITY) and staging (FIBROSIS), but

**is a very imperfect GOLD STANDARD
for non invasive methods**

Liver Biopsy: Inter-Observer Diagnostic Accuracy



Established and Candidate Serum Biomarkers of Liver Fibrosis

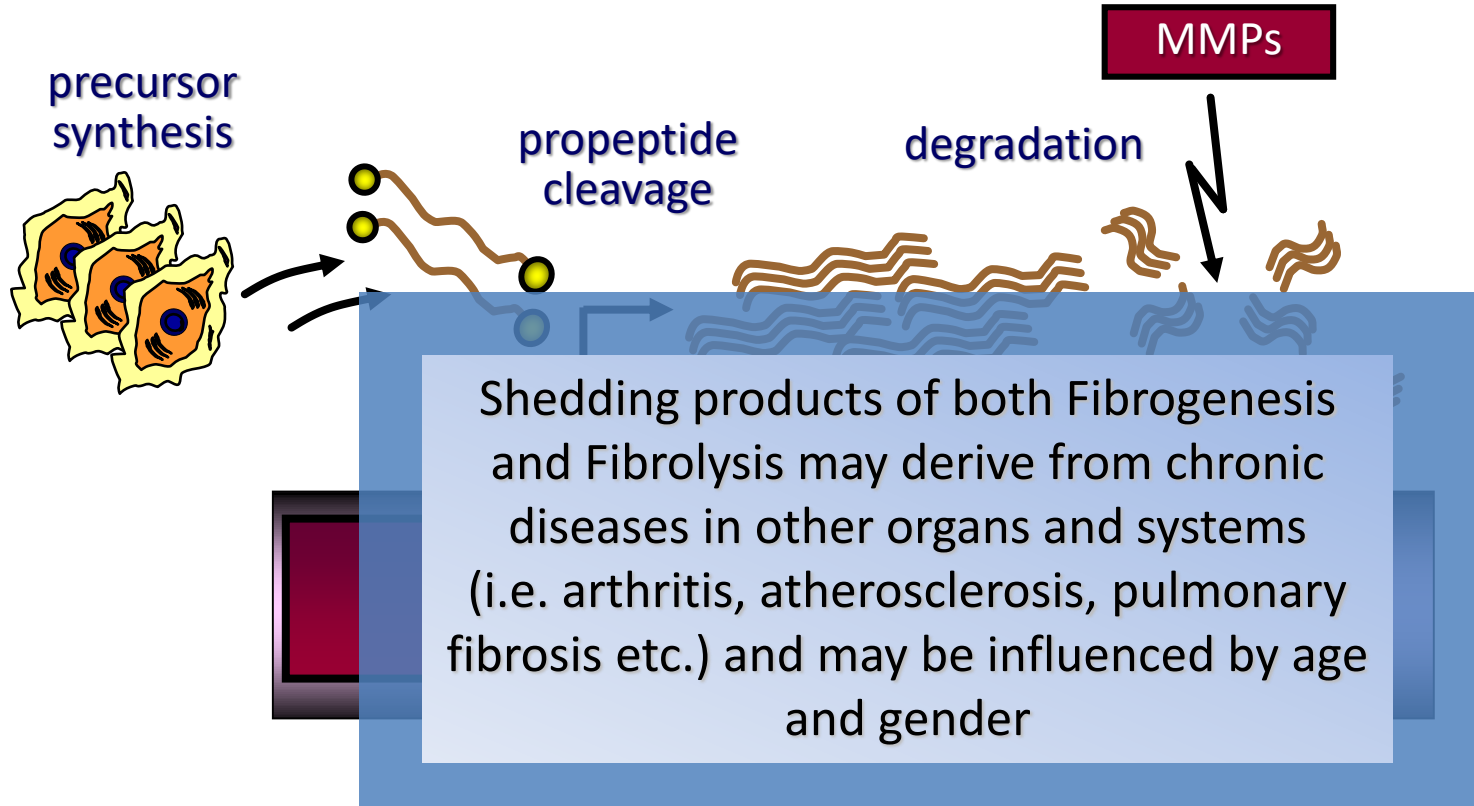
- **“Indirect”:** *Not related to Fibrogenesis*
 - AST, ALT, gGT, Apolipoprotein A1, bilirubin, a2-macroglobulin, haptoglobin, cholesterol
 - HOMA-IR, HOGIS
 - Platelets, INR/PT
- **“Direct”:** *ECM components and enzymes*
 - HA, PIIINP, Collagen IV, Collagen VI, TIMP-1, Laminin, YKL-40, Tenascin, Undulin, MMP-1, MMP-2



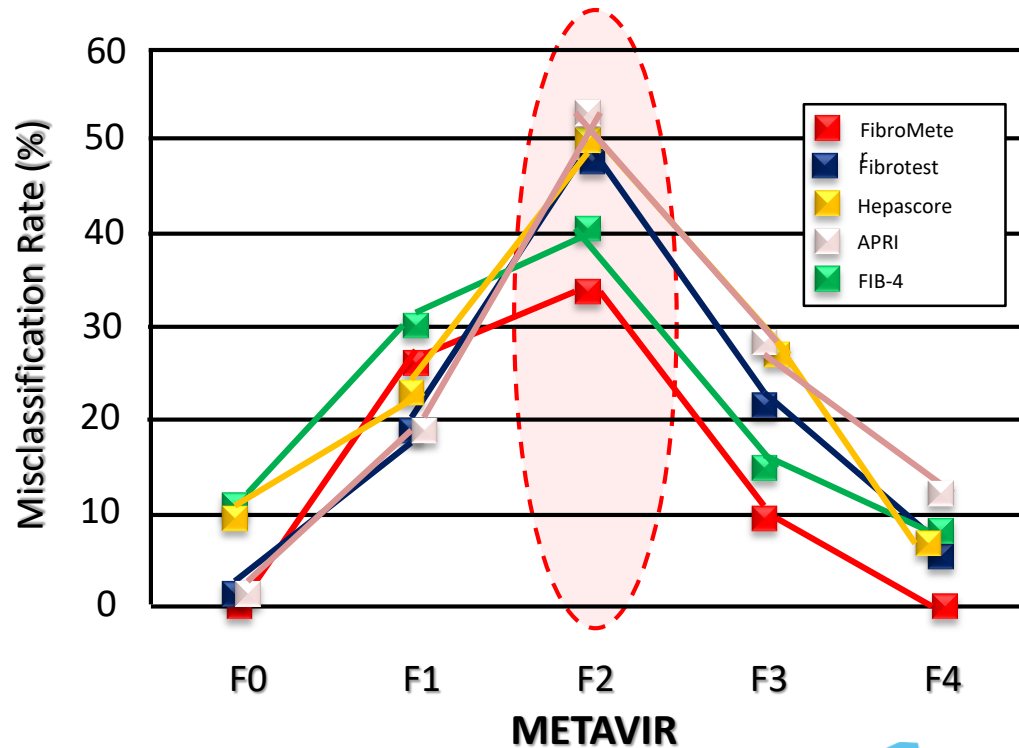
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Circulating Matrix Proteins Related to Fibrogenesis and Fibrolysis

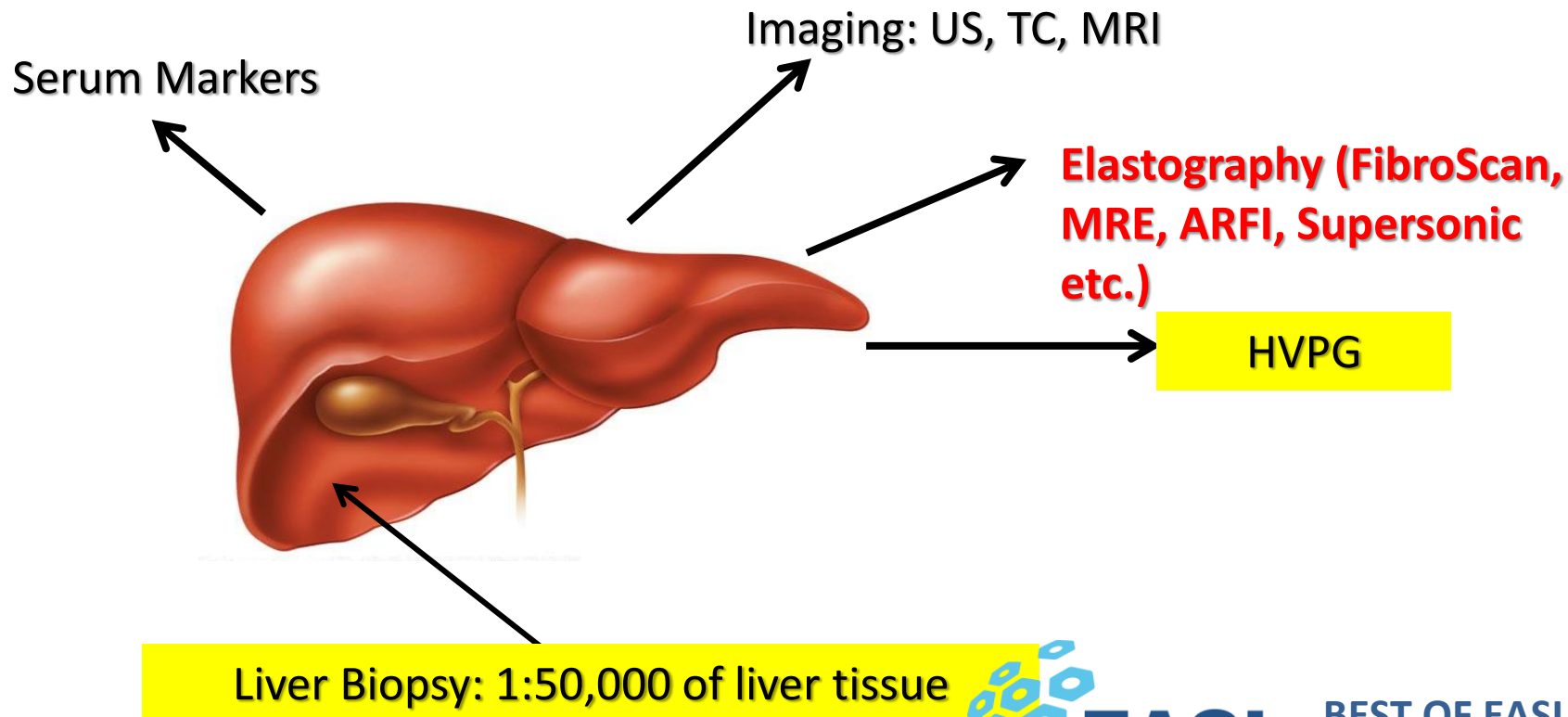


Misclassification Rate of Some Commonly Used Serum Markers

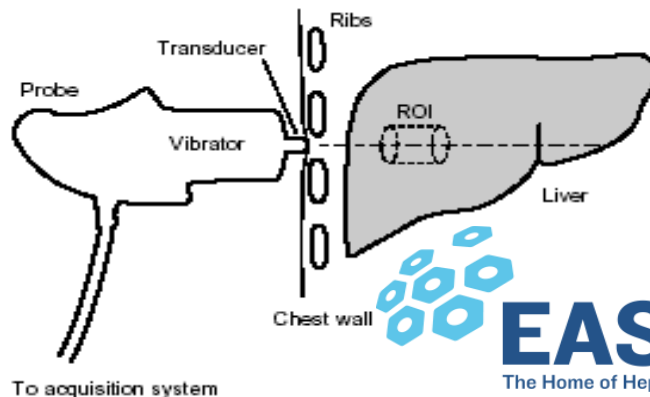


N= 1056 HCV patients
Cales P. et al. Liver Int 2009

Non Invasive Evaluation of Liver Tissue Fibrosis (Staging)



Transient Elastography: Liver Stiffness Measurement: Fibroscan[®]



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- 1.- The probe induces an elastic wave through the liver
- 2.- The velocity of the wave is evaluated in a region located from 2,5 to 6,5 cm below the skin surface
- 3.- **The velocity of the wave is related to liver stiffness and to fibrosis**
- 4.- Liver biopsy 1/50.000 of the liver; Fibroscan[®] 1/500 of the liver

Fibroscan Limitations and Confounding Factors



- 1.- BMI > 30 and obesity
- 2.- Presence of ascites
- 3.- Flares of necroinflammation, hepatocyte swelling and steatosis (ETOH)
- 4.- Cholestasis
- 5.- High liver tissue iron content
- 6.- Fasting < 2 hours

Fibroscan's Challengers

PROS & CONS



ARFI

• PROS

- Can be implemented on a

Very high intra- and inter-observer variability
Need US skills and experience

- Performance equal to TE

• CONS

- Results on meter/sec
- Narrow range of values
- **Quality criteria not defined**

SWE

• PROS

- Can be implemented on a

- Performance higher than TE !

• CONS

- Further validation needed
- **Quality criteria not defined**

Fibroscan Applications in Liver Diseases

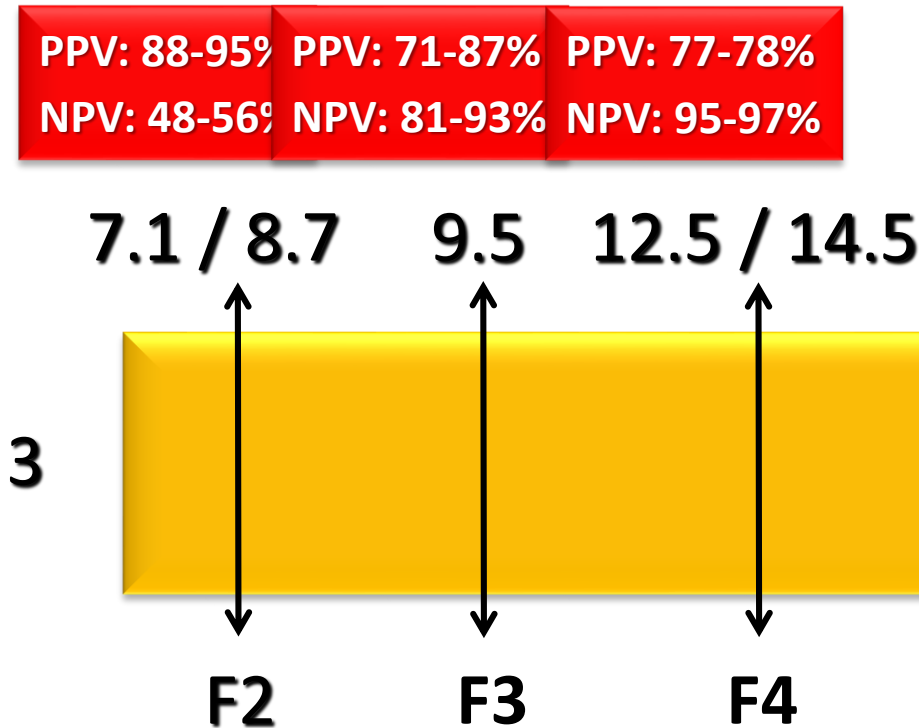


- 1.- Chronic Viral Hepatitis (cross-sectional)
- 2.- Chronic Viral Hepatitis (longitudinal and prognostic)
- 3.- Alcoholic Hepatitis
- 4.- NAFLD & NASH
- 5.- Cirrhosis and Portal Hypertension
- 6.- Liver Involvement in Systemic Diseases (Storage, Amyloidosis, Hemathology etc)

Hepatitis C: cut-offs



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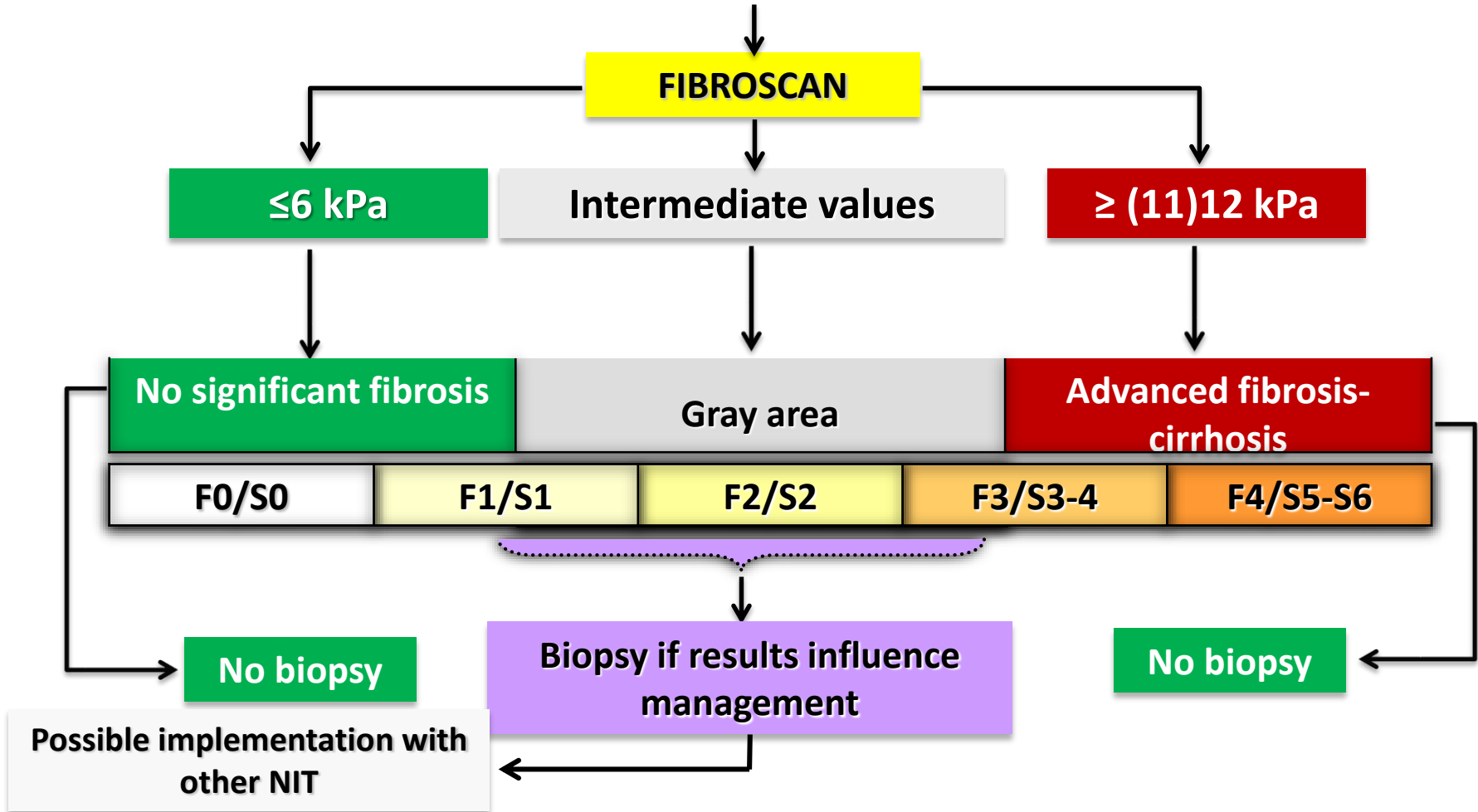


Ziol et al. Hepatology 2005; 41: 48-54

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

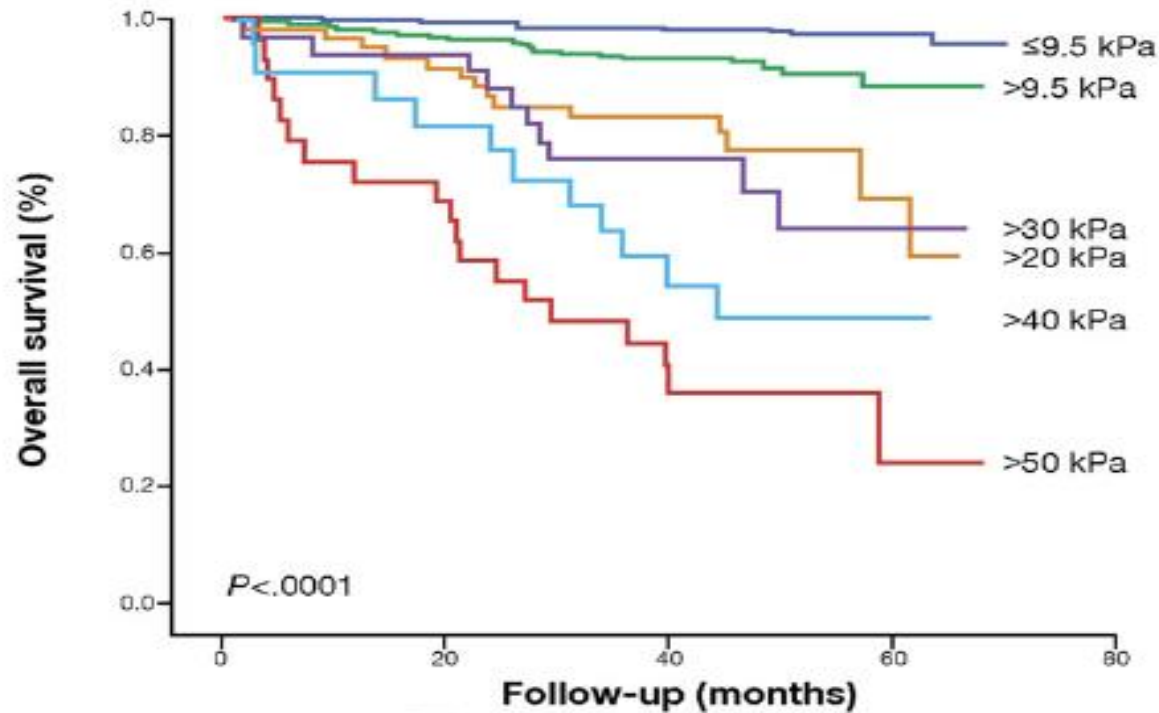
TE for Fast Patient Allocation

Suspected Chronic HCV/HBV Hepatitis



Noninvasive Tests for Fibrosis and Liver Stiffness Predict 5-Year Outcomes of Patients with Chronic Hepatitis C

JULIEN VERGNIOL,* JULIETTE FOUCHER,*[‡] ERIC TERREBONNE,* PIERRE-HENRI BERNARD,[‡] BRIGITTE LE BAIL^{S,||}
WASSIL MERROUCHE,* PATRICE COUZIGOU,* and VICTOR DE LEDINGHEN*^{||}



Non Invasive Measures Including Spleen Parameters

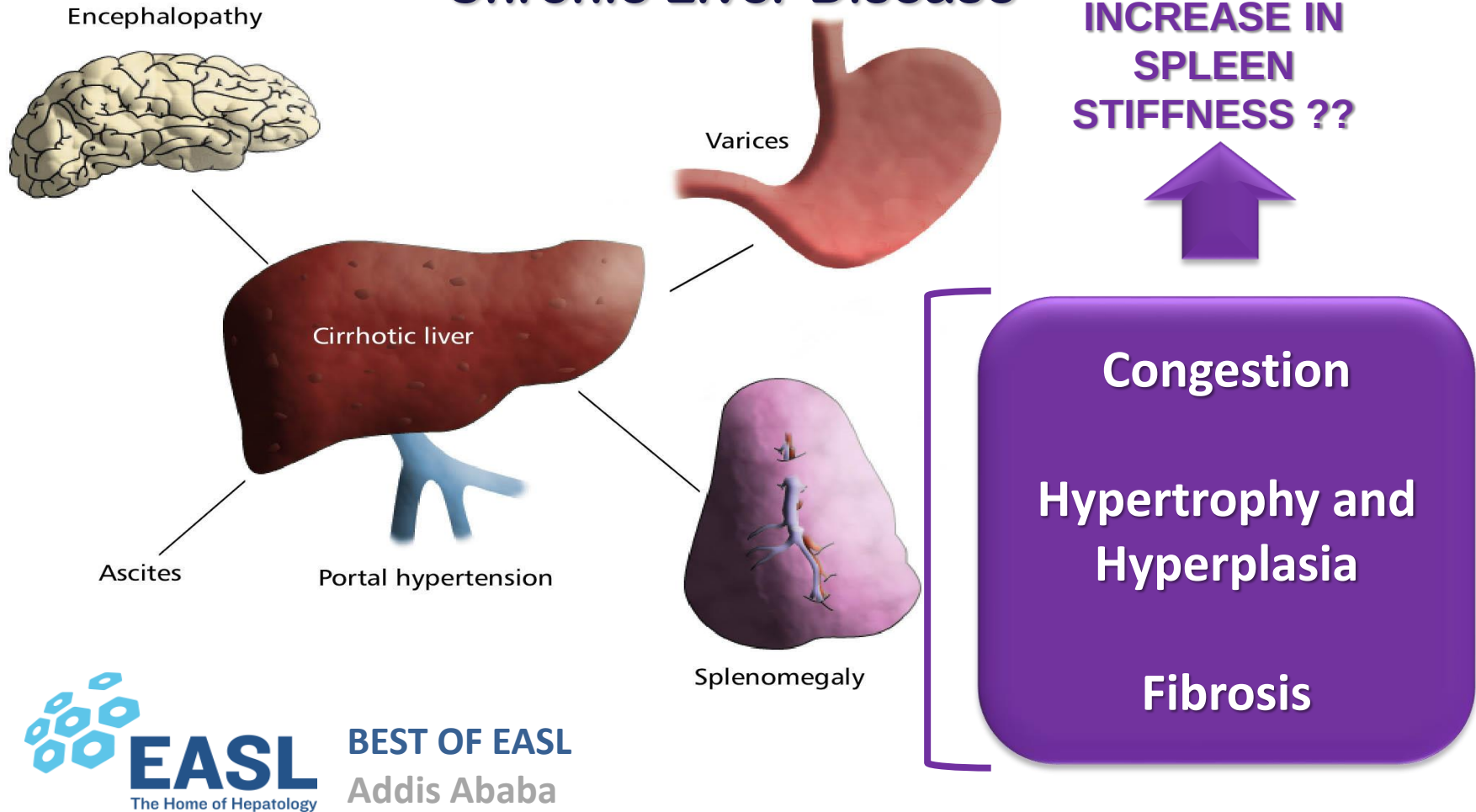
Platelet count/spleen diameter ratio (Plt/Spl)

Giannini E. et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut 2003;52: 1200-1205.

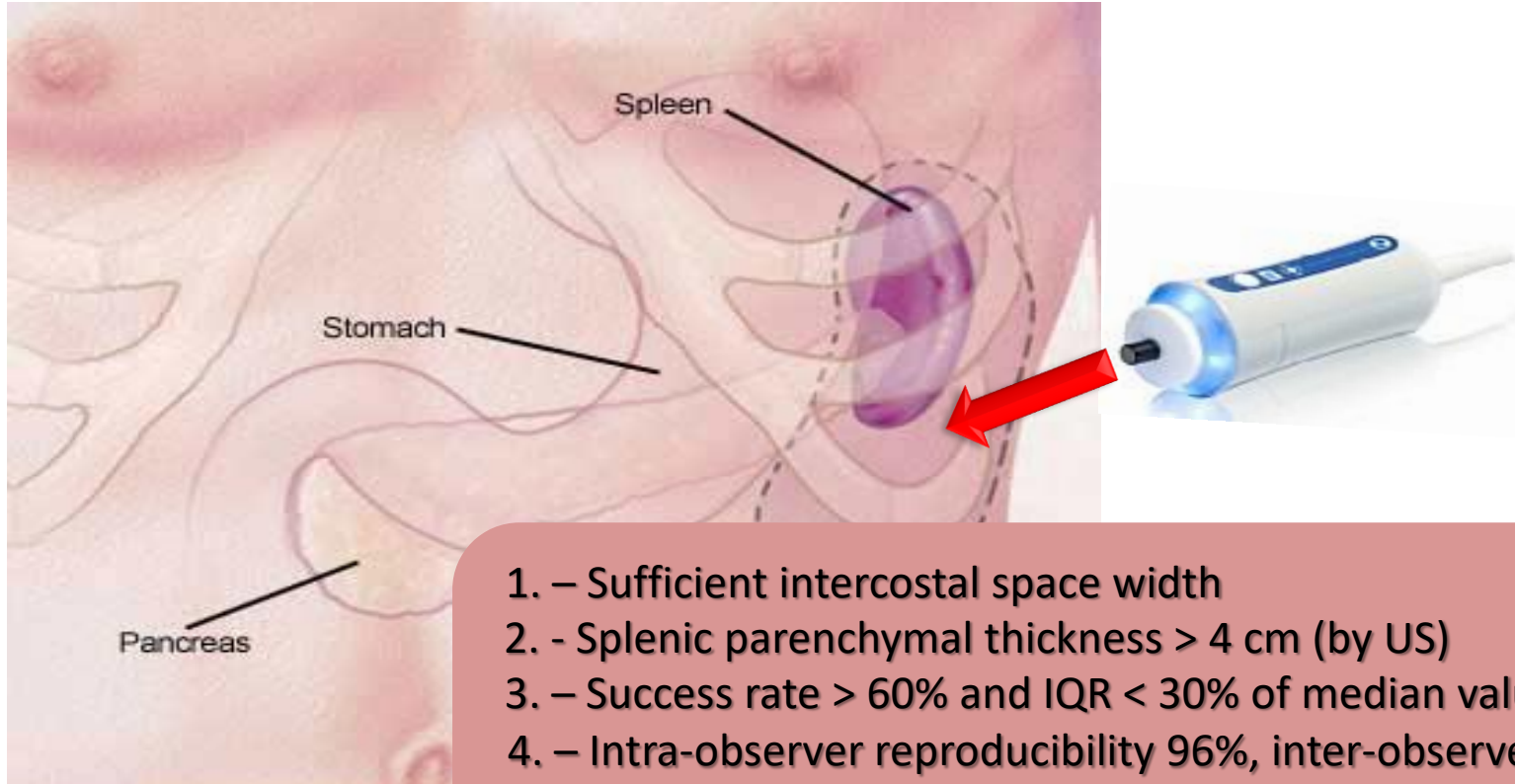
Liver stiffness x spleen diameter/platelet count (LSPS)

Kim BK et al. A Liver Stiffness Measurement-Based, Noninvasive Prediction Model for High-Risk Esophageal Varices in B-Viral Liver Cirrhosis. Am J Gastroenterol 2010; 105: 1382-1390.

The Spleen in the Assessment of Advanced Chronic Liver Disease



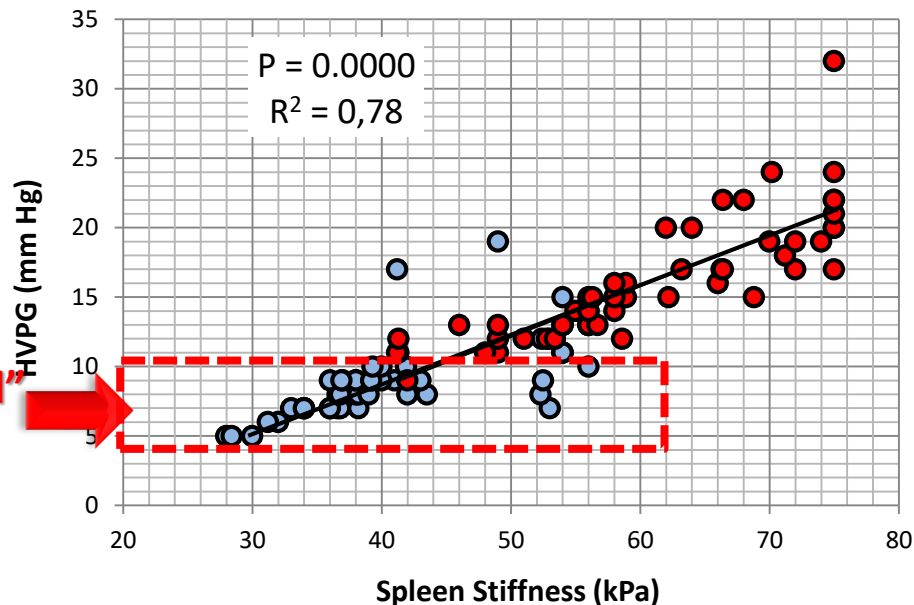
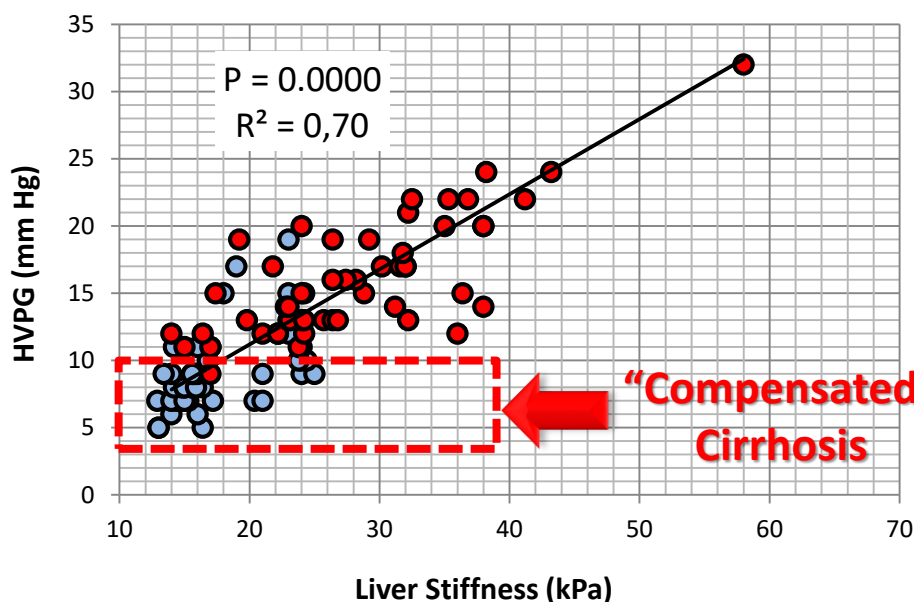
Measurement of Spleen Stiffness by Fibroscan



1. – Sufficient intercostal space width
2. – Splenic parenchymal thickness > 4 cm (by US)
3. – Success rate $> 60\%$ and IQR $< 30\%$ of median value
4. – Intra-observer reproducibility 96%, inter-observer reproducibility 94%
5. – Probe upper limit 75 kPa

Spleen Stiffness (SS), a Promising Diagnostic Parameter in Cirrhosis

Colecchia A. et al., Gastroenterology 2012 ; 143(3):646-54



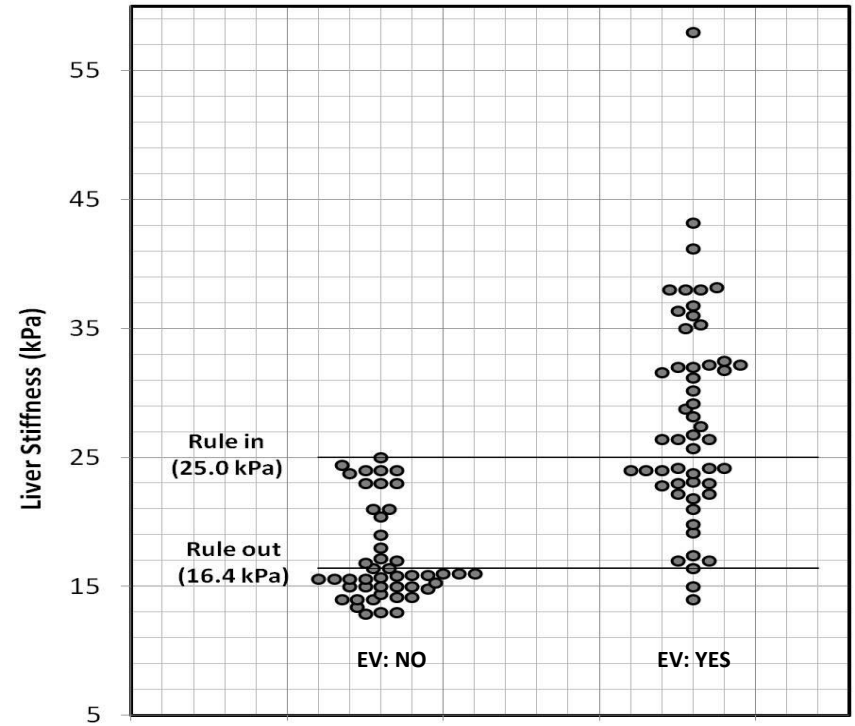
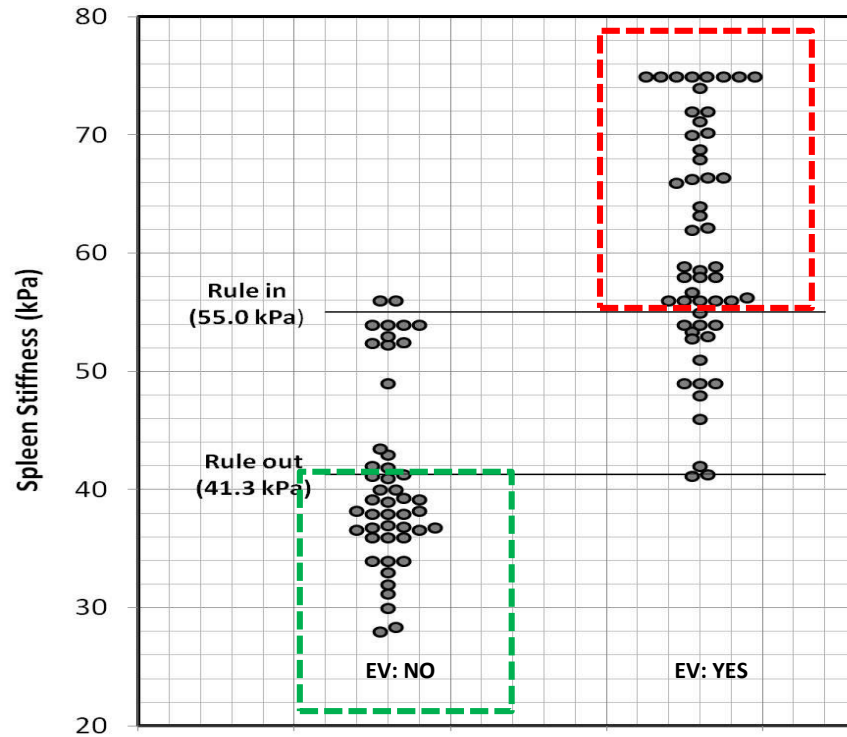
Esophageal Varices: NO



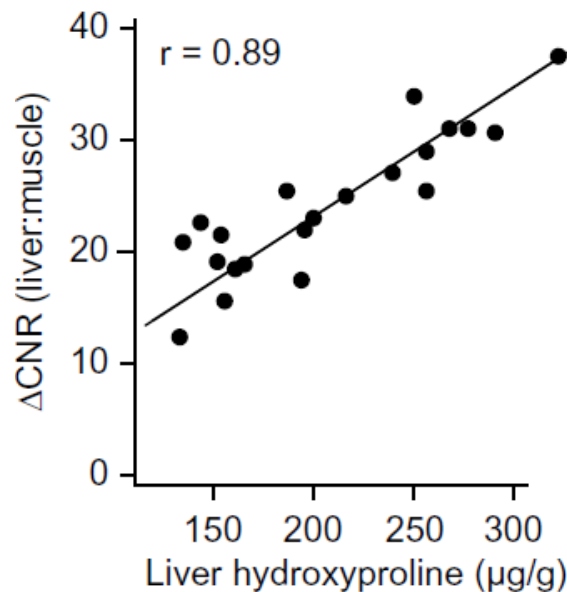
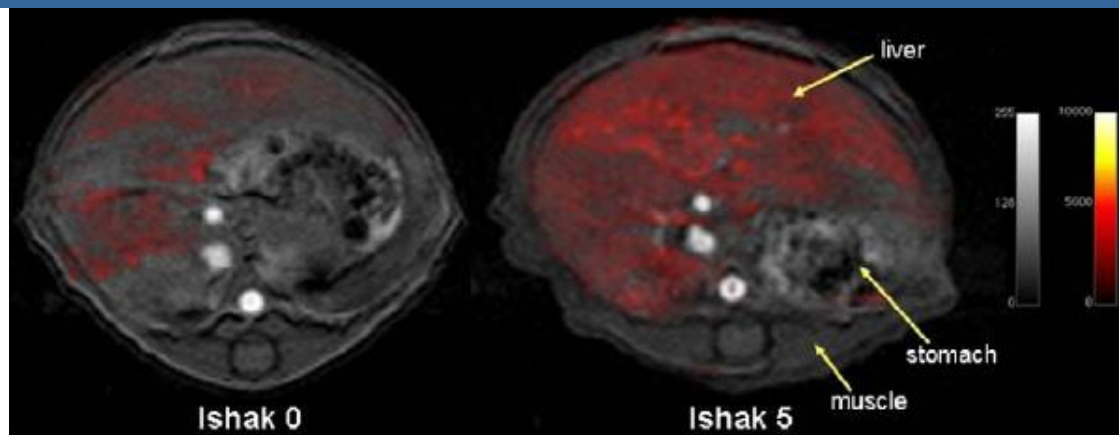
Esophageal Varices: YES

Liver and Spleen Stiffness for the Prediction of the Presence of Esophageal Varices

Colecchia A. et al., Gastroenterology 2012 ; 143(3):646-54



Molecular Imaging of Collagen



DEC-MRI with
EP-3533 contrast

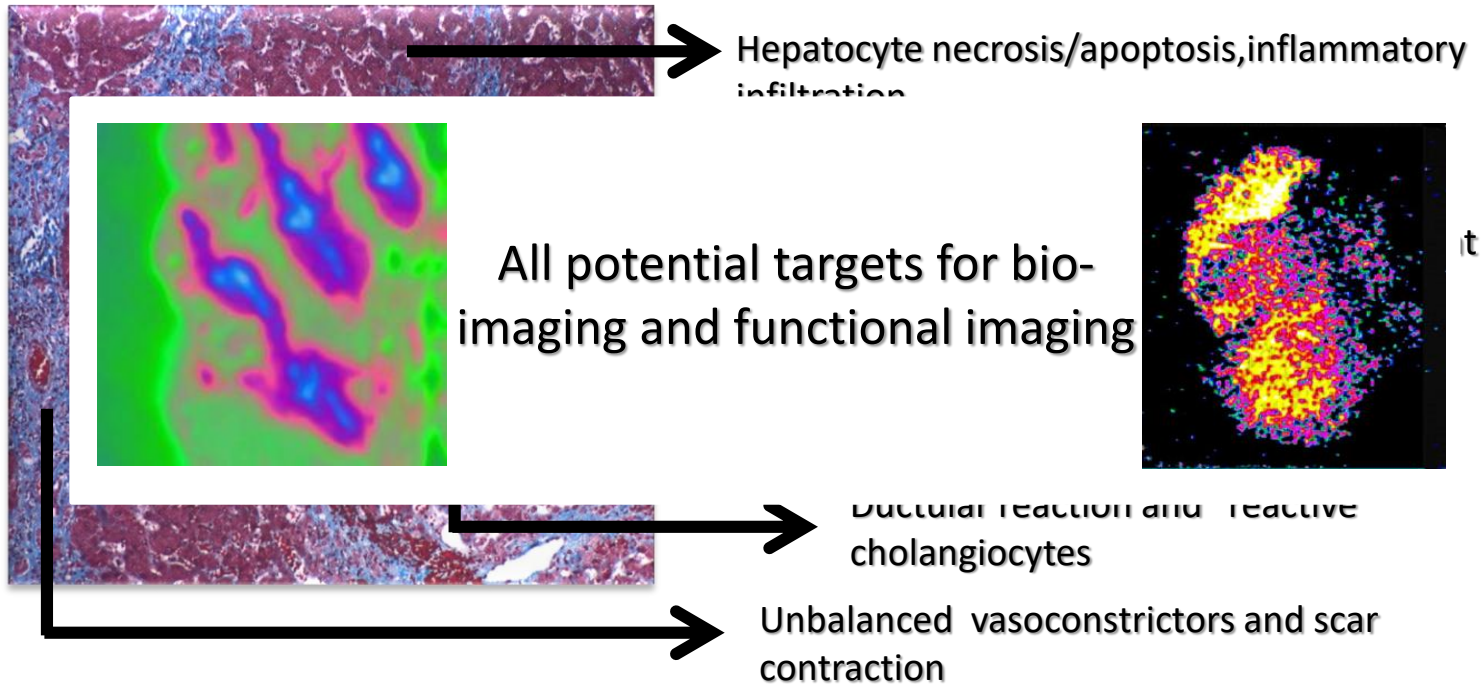


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Courtesy of Dr. Annalisa
Berzigotti, Hospital Clinic
Barcelona

Fuchs BC et al. J Hepatol 2013, in press

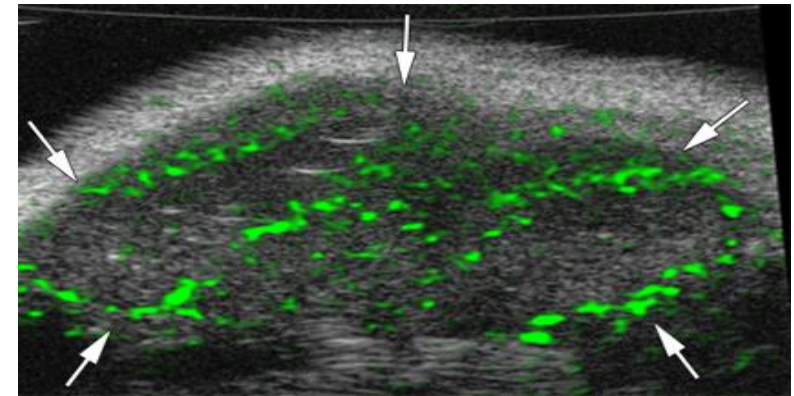
Measuring Collagen Content: What Are We Missing?



Possible molecular markers to be exploited:

Elastin, Collagen cross-linking: **IRREVERSIBILITY**

Immune markers: **REVERSIBILITY**



BR55: A lipopeptide-based VEGFR2-targeted US contrast agent for molecular imaging of angiogenesis

Pochon et al. Invest Radiol 2010

Willmann et al Radiology 2008

Binding is amplified by ARF

Frinking et al. Ultras Med Biol 2012



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