Non-invasive Monitoring of Liver Disease

Hin Hin Ko

Giada Sebastiani

Feb 29, 2016

This program was co-developed with CAG/Merck and was planned to achieve scientific integrity, objectivity and balance

Accreditation

This event is an accredited (Section 1) group learning activity as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada (RCPSC). The program was produced under the RCPSC guidelines for the development of co-developed educational activities between the Canadian Association of Gastroenterology (CAG) and Merck Canada Inc.

Name: Dr. Hin Hin Ko, Dr. Giada Sebastiani

Financial Interest Disclosure

(over the past 24 months)

Dr. Sebastiani: speaker for Merck, Abbvie, Gilead, ViiV; advisory board member for Merck, BMS; she received unrestricted research funding from Merck, ViiV

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Learning Objectives

At the end of this session, participants will be able to:

- Recognize the clinical importance of staging fibrosis for management and prognosis in chronic liver diseases
- Identify and describe the different non-invasive modalities to diagnose and monitor liver disease
- Compare and contrast the benefits and limitations of the non-invasive monitoring modalities, such as Fibroscan, Fibrotest, Fib-4 and APRI

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Non-invasive monitoring of liver disease

CanMEDS Roles Covered:

✔	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
✔	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
✔	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
✔	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
✔	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
✔	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

EASL-ALEH Clinical Practice Guidelines:

Non-invasive tests for evaluation of liver disease severity and prognosis

Journal of Hepatology
Volume 63, Issue 1, Pages 237-264 (July 2015)
DOI: 10.1016/j.jhep.2015.04.006

WHY IS IT IMPORTANT TO STAGE LIVER FIBROSIS?

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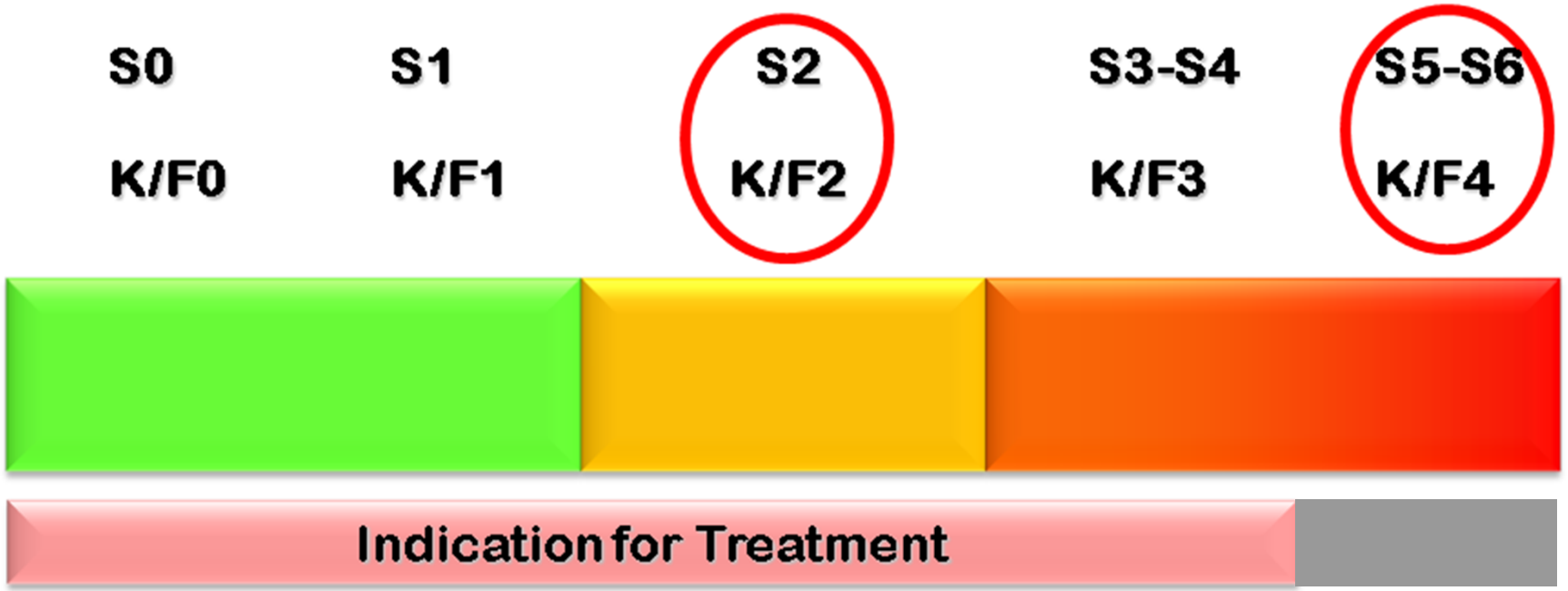
PINZANI M- 2010

End-Points in Fibrogenic CLDs



F: METAVIR
S: ISHAK's
K: KLEINER

Screening for Oesophageal Varices

Screening for HCC

WHY FIBROSIS STAGE is PIVOTAL in CHRONIC LIVER DISEASES?

- **Management**
  - definitive indication to antiviral therapy in HCV and HBV and to interventions on metabolic risk factors/vitamin E therapy in NAFLD/NASH when ≥F2 by METAVIR/Kleiner
  - Screening for HCC and esophageal varices when F4

- **Prognosis**
  - The more the liver disease is advanced, the less time it takes to develop cirrhosis and end-stage complications

STAGING of FIBROSIS: HOW ?

- Liver biopsy (gold standard)
  - Advantages: direct information on fibrosis, inflammation, steatosis, comorbidities
  - Limits: semiquantitative, invasive, costly, prone to sampling errors
- Blood tests (biomarkers)
- Fibroscan (transient elastography)

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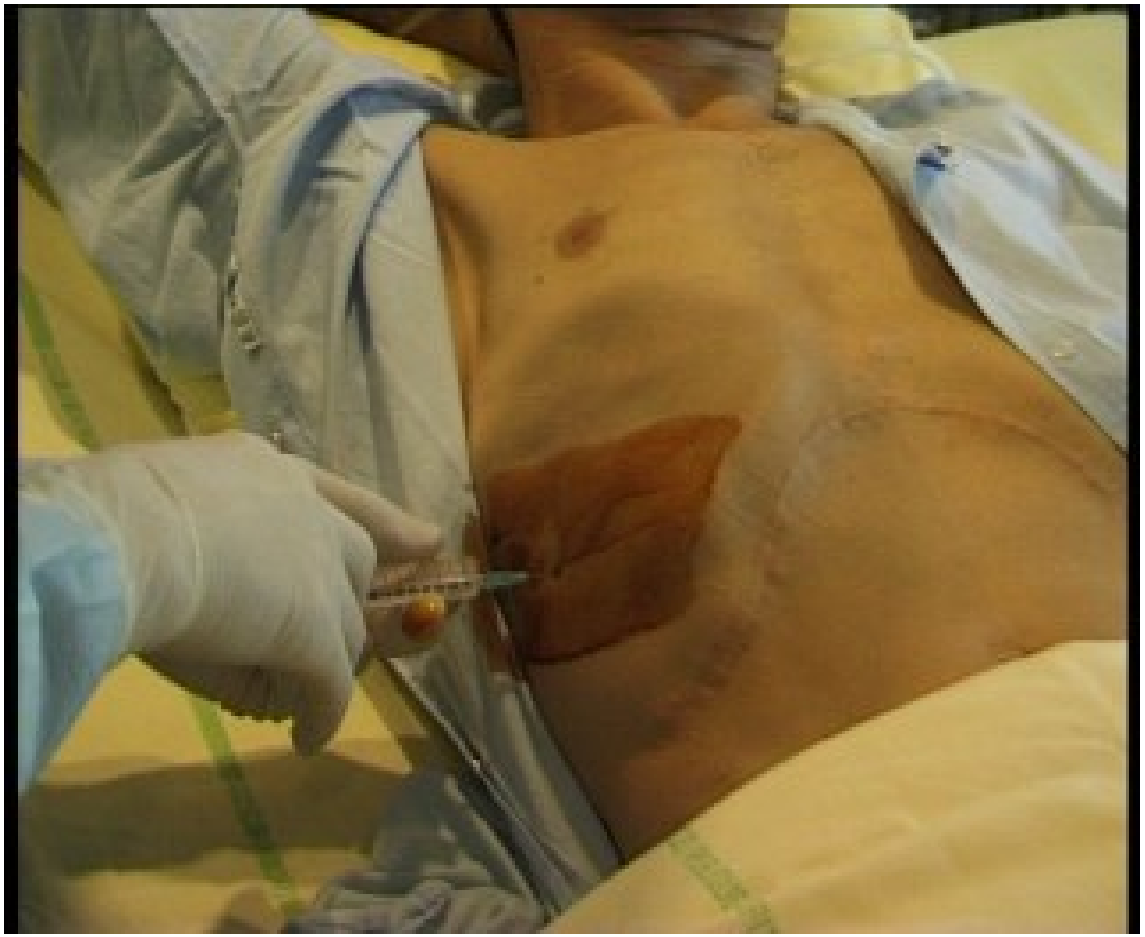
LIVER BIOPSY IS AN INVASIVE PROCEDURE!



- ✓PAIN
- ✓BLEEDING
- ✓COST
- ✓HOSPITALIZATION

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Complications

- HALT-C reported complications of liver biopsy in HCV patients with advanced liver disease
  - 1.1 % serious adverse events
  - 0.6% due to bleeding (most common)
    - More common if platelet <60,000
    - INR>1.3

- The mean cost in Canada for a complicates liver biopsy requiring hospitalization is $4,579

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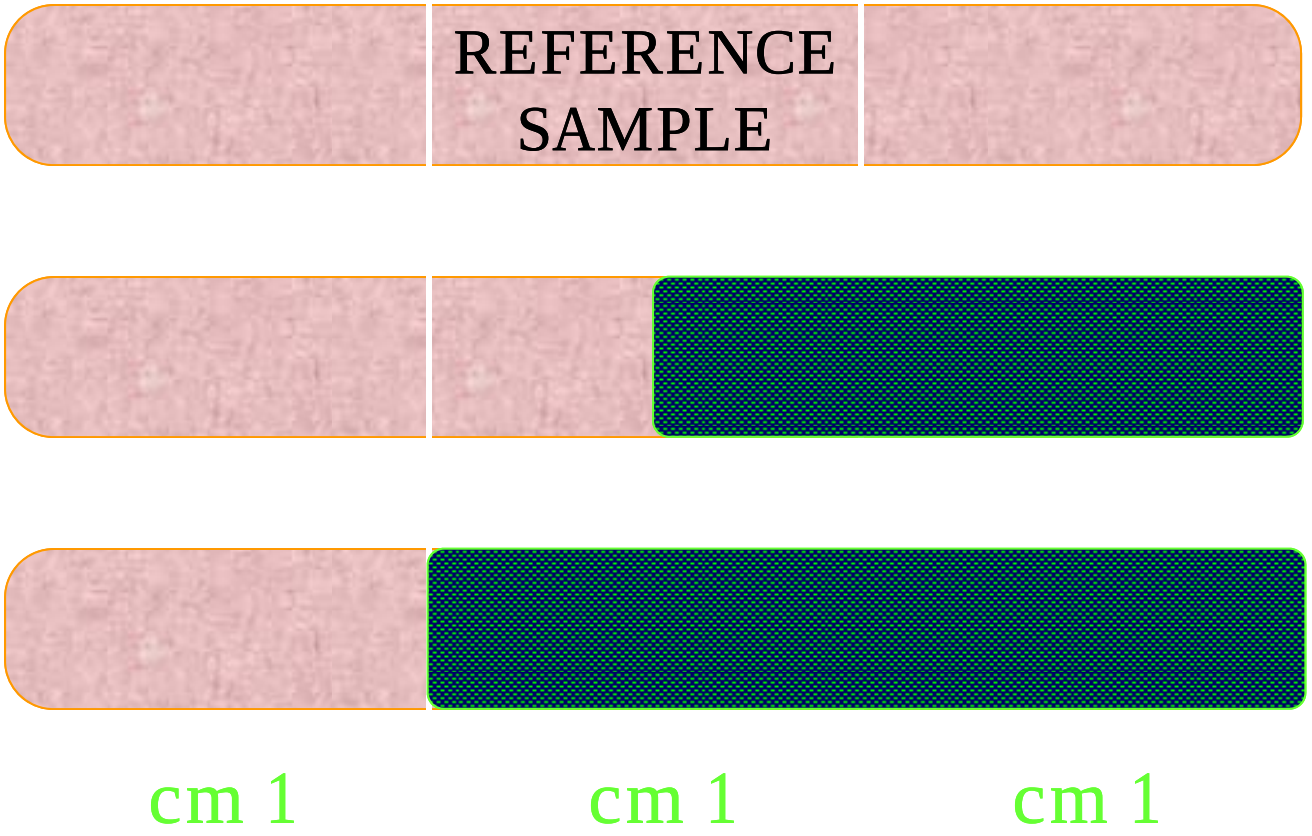
Seeff et al. *Clin Gastroentrol Hepatol 2010*; Myers et al, *Liv Internat* 2008

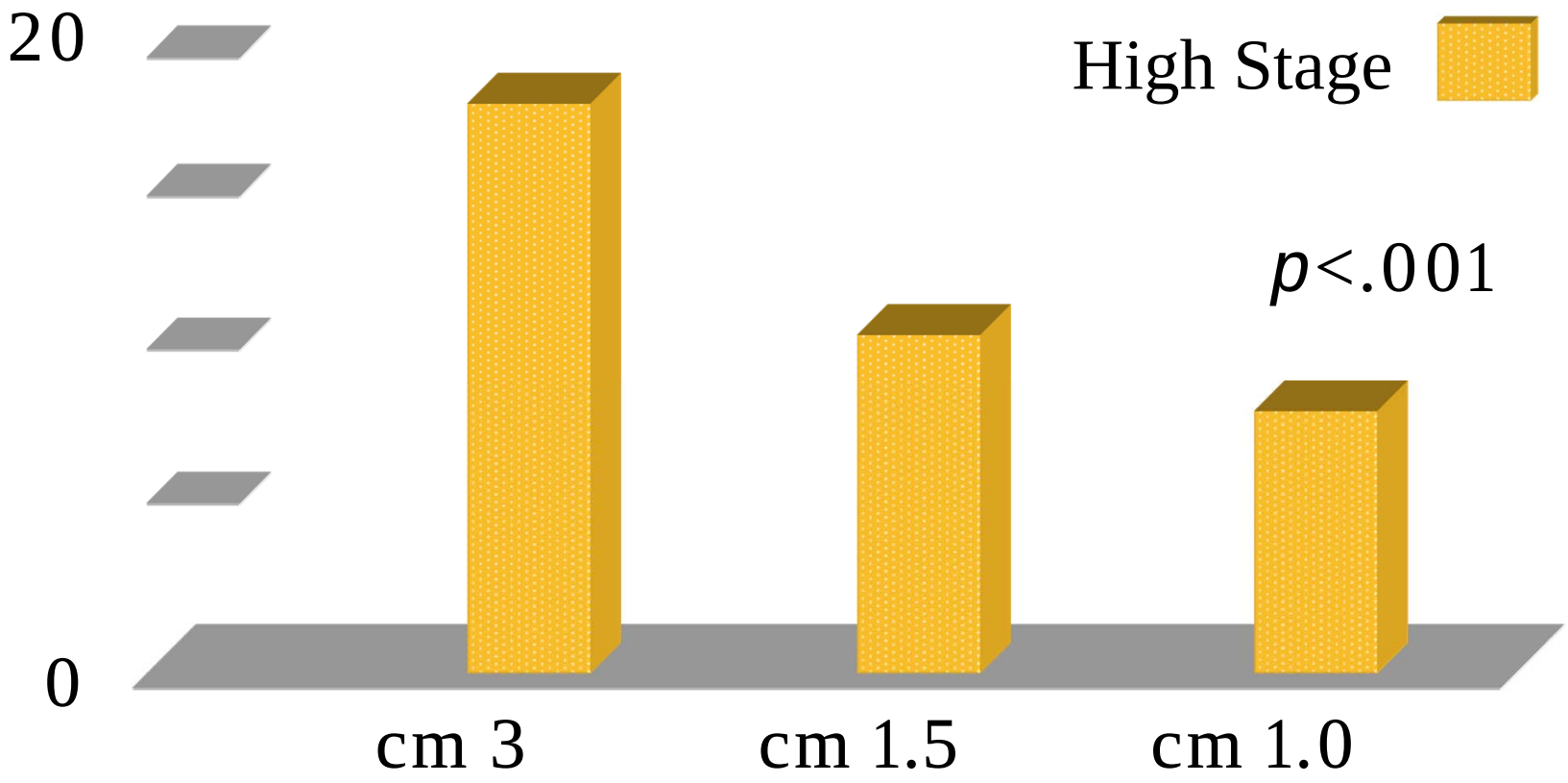
Interobserver variability –

THE SMALLER THE SAMPLE, THE MILDER THE DISEASE



Colloredo et al, J Hepatol 2003

THE LENGTH OF THE SAMPLE



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Colloredo et al, J Hepatol 2003

CONSENSUS AMONG PATHOLOGISTS ?

Author	Length (mm)	Portal tracts (n°)
Bedossa, Hepatology 2003	25	NA
Scheuer, Hepatology 2003	Bigger is better	NA
Guido, Sem Liv Dis 2004	20	11
AASLD, position paper on liver biopsy 2008	20	11
APASL, consensus conference on fibrosis 2009	15	10

Sebastiani G, WJG 2009

NON-INVASIVE METHODS

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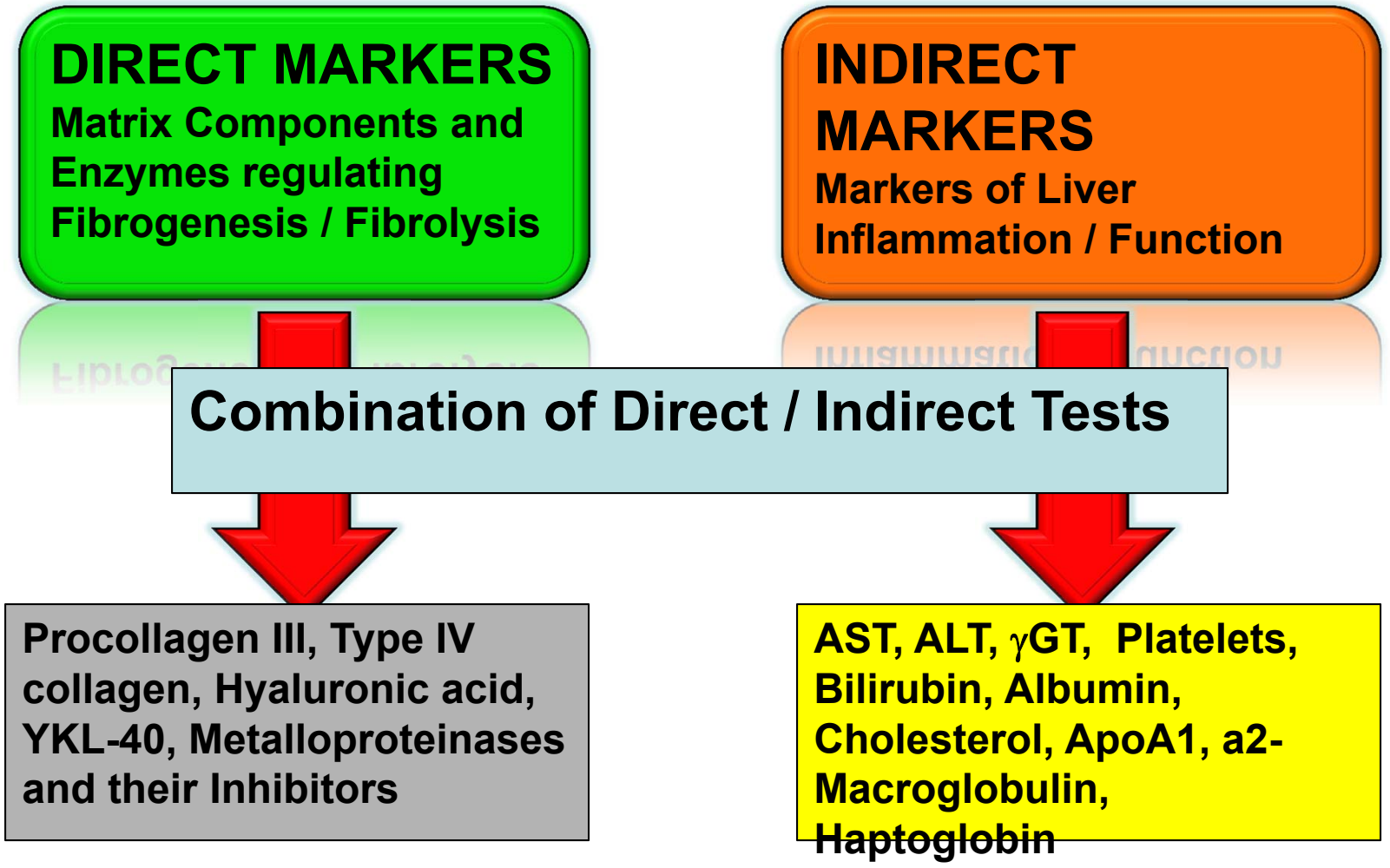
SERUM NON-INVASIVE MARKERS for LIVER FIBROSIS



Indirect Biomarkers

	Cut-off	AUROC	Classified
APRI	0.5 / 1.5	0.69-0.88	51%
Forns' index	4.2 / 6.9	0.60-0.86	49%
Fib-4	1.45 / 3.25	0.82-0.89	72.8%
AST-to-ALT ratio	1	0.51-0.83	100%

APRI = AST, platelets

Forns' index = GGT, cholesterol, platelets, age

Fib-4 = platelets, AST, ALT, age

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Wai et al, Hepatology 2003; Forns et al, Hepatology 2002; Pichard et al, Hepatology 2004; Sebastiani et al, APT 2011

APRI: THE PROTOTYPE OF THE SIMPLE BIOMARKERS FOR LIVER FIBROSIS

APRI=[AST (/ULN) x 100] / Platelet (10^9/L)

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Wai et al, Hepatology 2003

Performance of the Aspartate Aminotransferase-to-Platelet Ratio Index for the Staging of Hepatitis C-Related Fibrosis: An Updated Meta-Analysis

Zhong-Hua Lin,[1,2]* Yong-Ning Xin,[2,3]* Quan-Jiang Dong,[2] Qing Wang,[2] Xiang-Jun Jiang,[2] Shu-Hui Zhan,[2] Ying Sun,[2] and Shi-Ying Xuan[2,3]

- 40 studies included, n=8,739
- APRI can be used in clinical practice as a good tool for the confirmation of severe fibrosis/cirrhosis when other clinical signs and examinations are nondecisive
- It is cheap and simple → reference test to be compared with the others

Although APRI shows less diagnostic accuracy than some other noninvasive methods, it is still the first choice for HCV patients to identify fibrosis in regions with limited healthcare resources

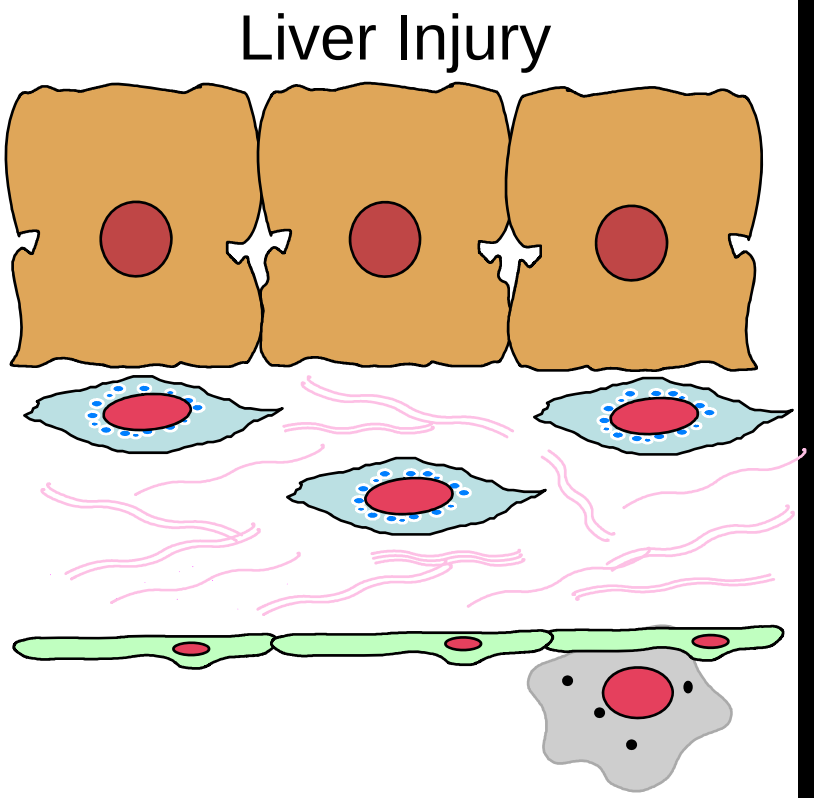
HEPATOLOGY, Vol. 53, No. 3, 2011

Direct Biomarkers and Combination Panels

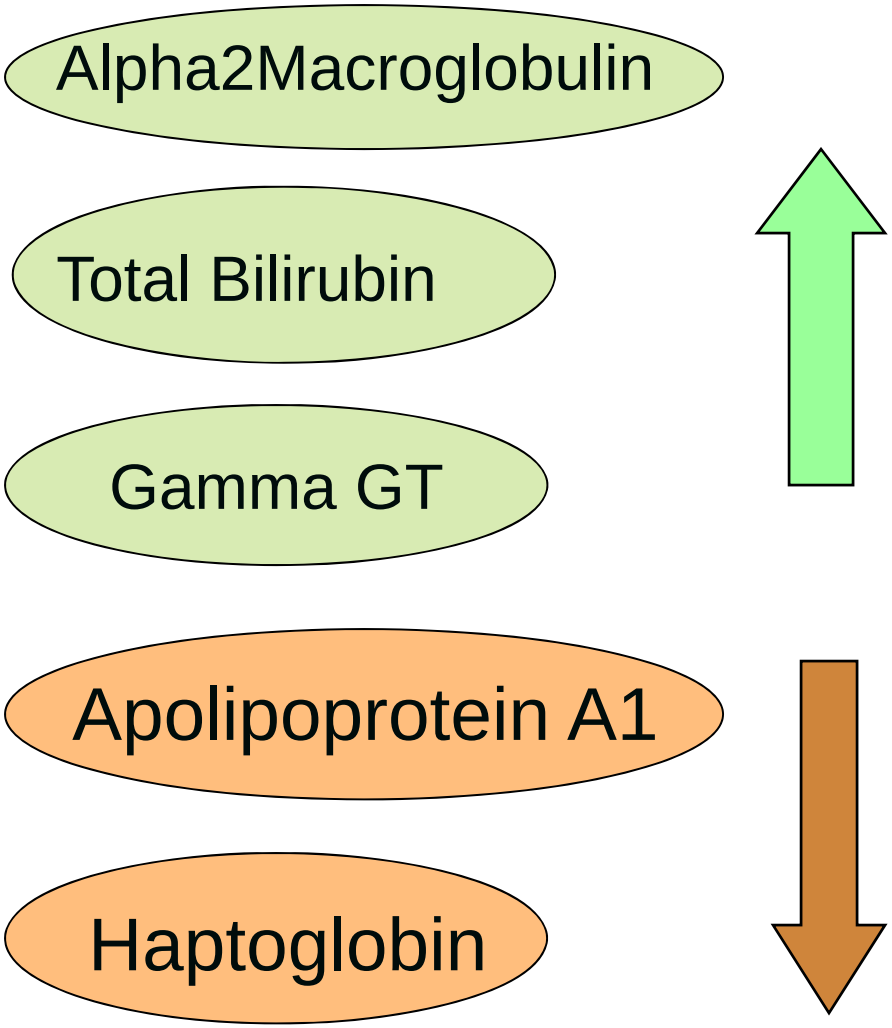
	Parameters	AUC for ≥F2	AUC for F4	Validation
Fibrotest®	γGT, bilirubin, haptoglobin, ApoA1, α2M	0.74-0.87	0.71-0.87	
Fibrospect®	Hyaluronan, TIMP1, α2M	0.82-0.87	-	
ELF®	Hyaluronan, PIIINP, TIMP1	0.80	0.95	
Fibrometer®	Platelets, PT, AST, α2M, hyaluronan, BUN	0.85-0.89	0.91	
Hepascore®	Hyaluronan, bilirubin, γGT, α2M	0.79-0.85	0.95-0.94	

Sebastiani et al, CCLM 2011

In Situ

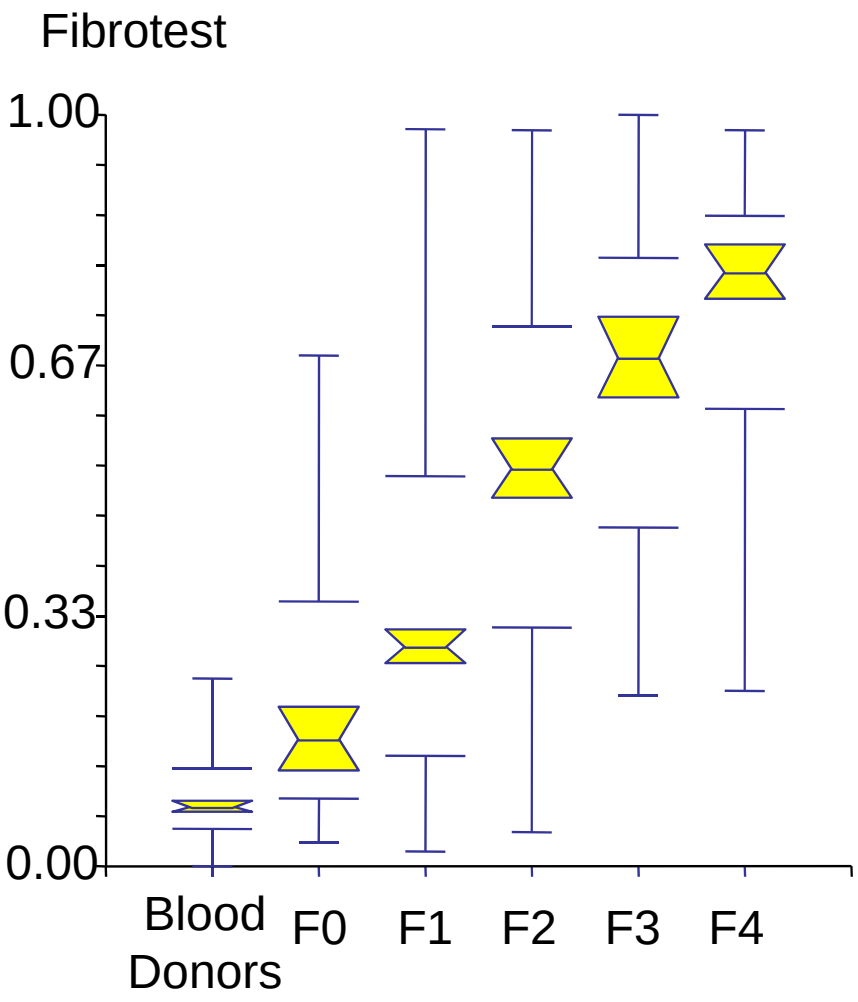


In Serum: FibroTest



Imbert-Bismut et al, Lancet 2001

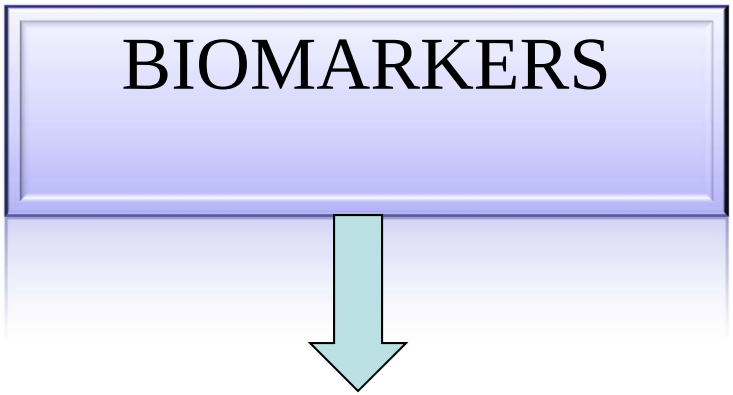
FIBROTEST IN HEPATITIS C



FibroTest	Estimate of fibrosis stage
0.75-1.00	**F4**
0.73-0.74	**F3-F4**
0.59-0.72	**F3**
0.49-0.58	**F2**
0.32-0.48	**F1-F2**
0.28-0.31	**F1**
0.22-0.27	**F0-F1**
0.00-0.21	**F0**

Imbert-Bismut et al, Lancet 2001

SERUM BIOMARKERS : PITFALLS



Risk factors for biomarkers

- hemolysis (Fibrotest)
- Gilbert (Fibrotest)
- systemic inflammation (Fibrotest)
- extra-hepatic cholestasis (Fibrotest)
- thrombocytopenia not liver-related (APRI)

Liver stiffness

- Assessed by US (FibroScan®) & more recently by MRI
- Evaluates velocity of propagation of a shock wave within liver tissue (examines a physical parameter of liver tissue which is related to its elasticity)
- Rationale
  - Normal liver is viscous
  - Not favorable to wave propagation
  - Fibrosis increases hardness of tissue
  - Favors more rapid propagation

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Bedossa P. Liver Int 2009 ; 29 (s1): 19 – 22.

FibroScan

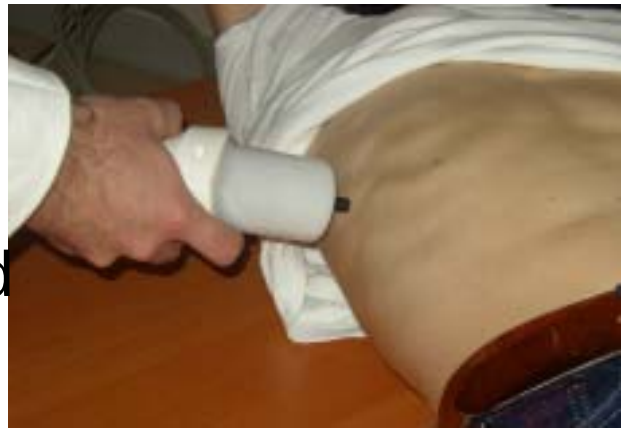
Painless

Rapid (5 min)

Bedside/Outpatient

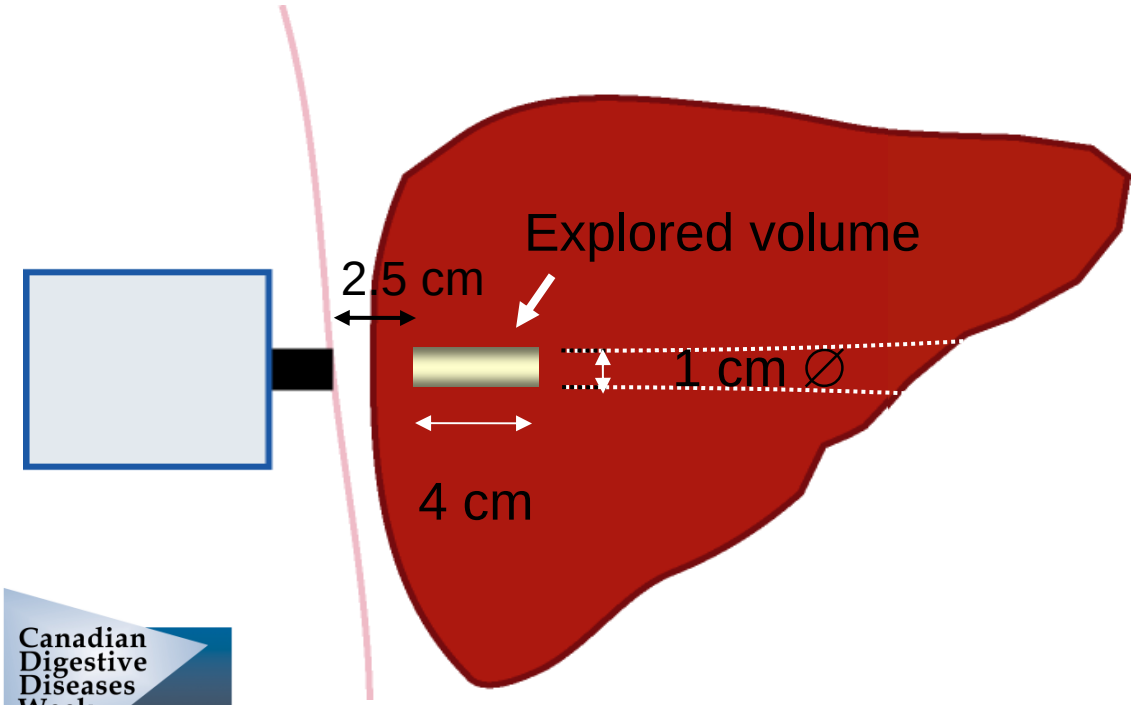
Immediate results (3 - 75 kPa)

>1500 peer-reviewed studies



Position of probe & explored volume

« The stiffer the liver, the faster the shear wave propagates »



Cylinder of 1 cm wide & 4 cm long

From 25 mm to 65 mm below skin surface

This volume is at least **100 times** bigger than a biopsy sample

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Results

Stiffness (kPa)
Median value of 10 shots

❸ IQR * (kPa)
Interval around median
Contains 50% of valid shots
≤ 30% of median value

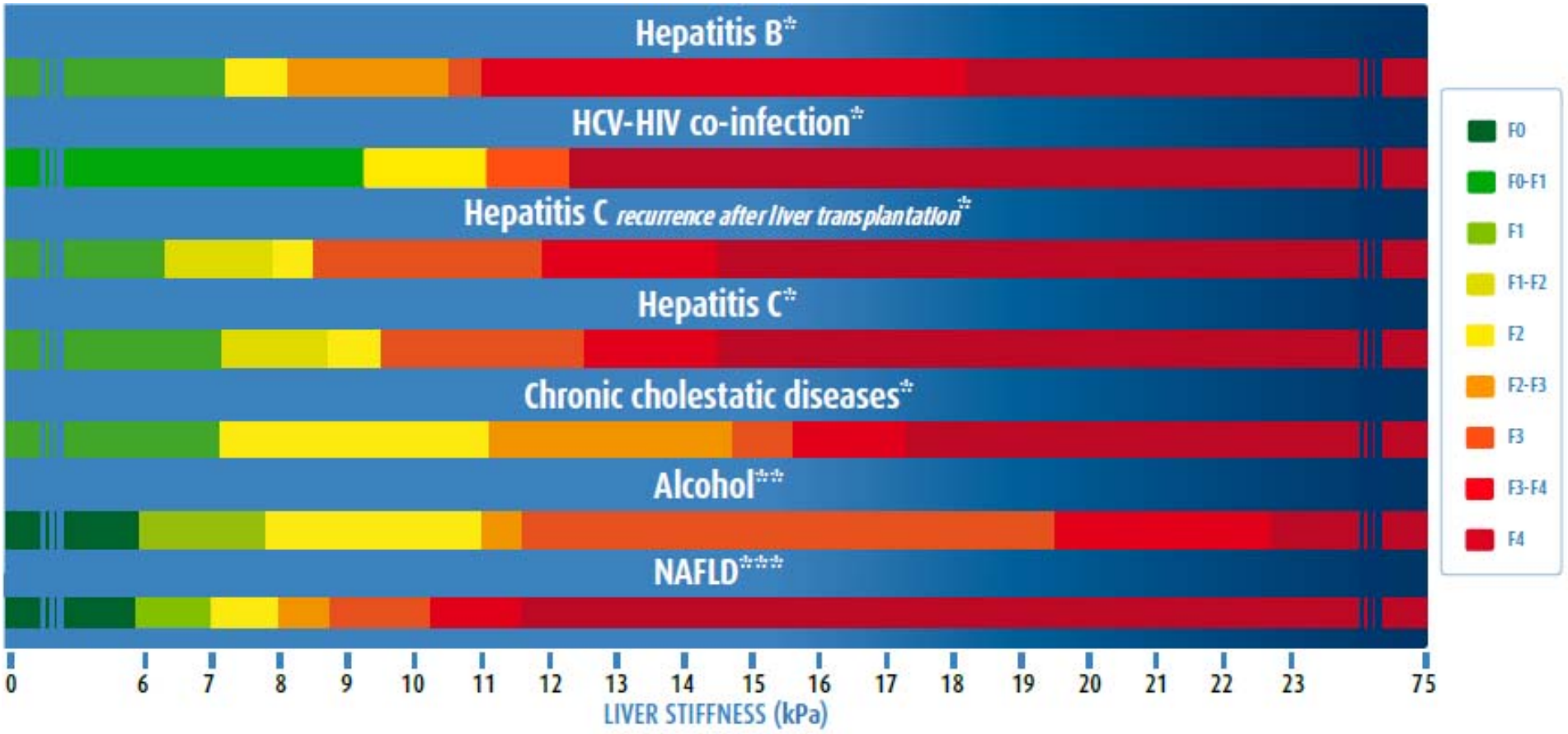
❶At least 10 shots
❶Success rate ≥60%

Accuracy in Hepatitis C

Reference	Cut-off for ≥F2	AUC for ≥F2	Cut-off for F4	AUC for F4	N of patients
Degos 2010	5.2	0.75	12.9	0.90	913
Kettaneh 2007	6.8	0.79	17.6	0.91	935
Castera 2005	7.1	0.83	12.5	0.95	183
Sandrin 2003	7.6	0.88	14.4	0.99	106
Arena 2008	7.8	0.91	14.8	0.98	150
Ziol 2005	8.7	0.79	14.5	0.97	327
Cross 2010	8.9	0.89	10.1	0.97	187

Sebastiani & Alberti J Vir Hepat 2012

Correlation between LSM & fibrosis stage ?



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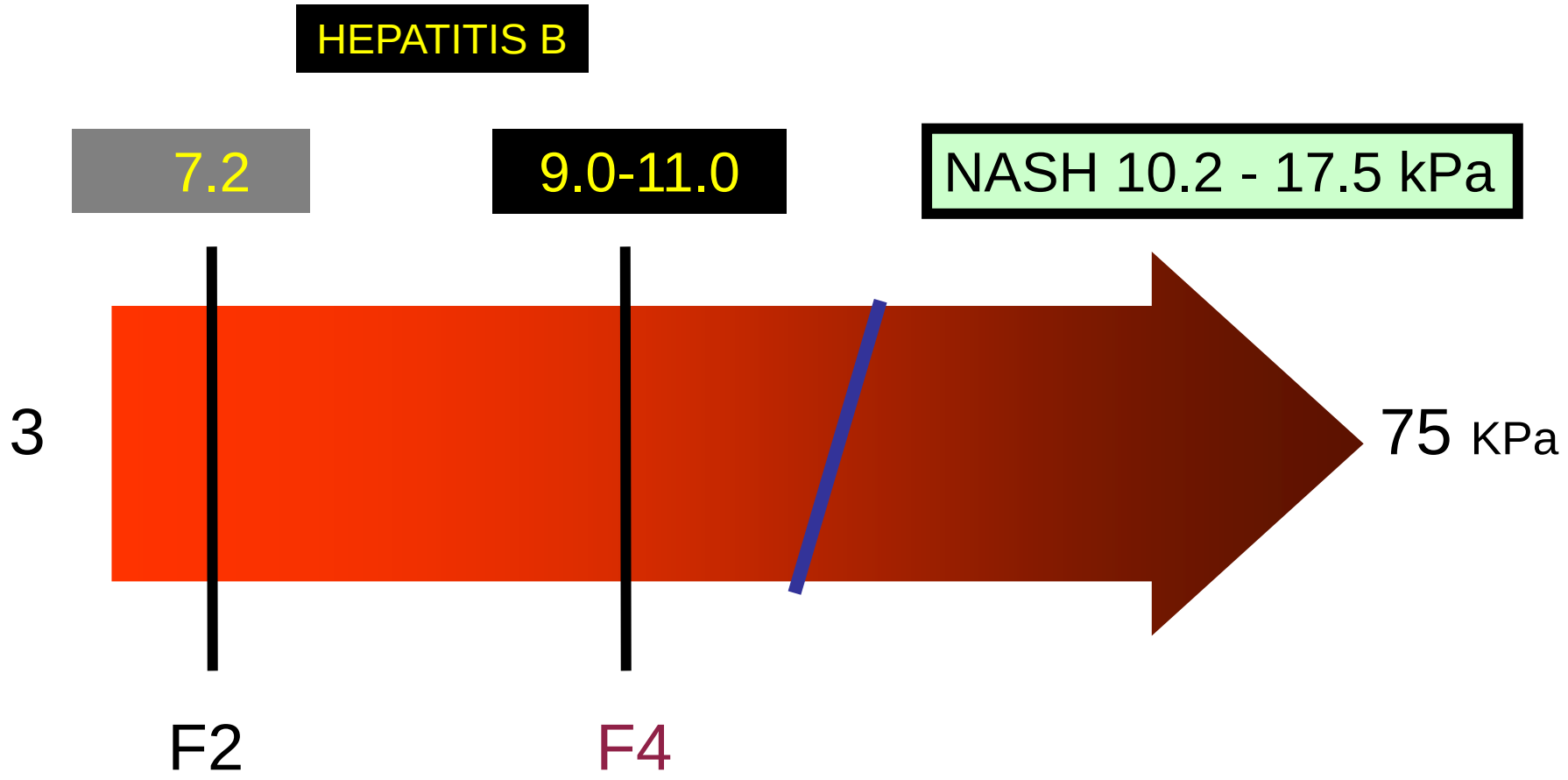
* Gastroentérol Clin Biol 2008;32,58-67.
** J Hepatol 2009;49:1062-68, Aliment Pharmacol Ther 2008;28:1188-98.
*** Hepatology 2010;51:454-62. Gastroentérol Clin Biol 2008;32:58-67.

THE CLINICAL USE OF CUT-OFF



Fibrosis Stage

Marcellin P et al., *Liver Int.* 2009; 28 (2) :242-7.
Chan HLY et al., *J Viral Hepat.* 2009; 16 (I), 36-44.

Ziol et al, Hepatology 2005
Castera et al, Gastroenterology 2005

APPLICABILITY of FIBROSCAN in CLINICAL PRACTICE

- RISK FACTORS OF FAILURE → Obesity, Ascites, narrow intercostal spaces
- RISK FACTORS OF POOR QUALITY → N measurements, IQR
- RISK FACTORS OF FALSE POSITIVITY → ALT flares, extra-hepatic cholestasis, hepatic congestion, meal effect

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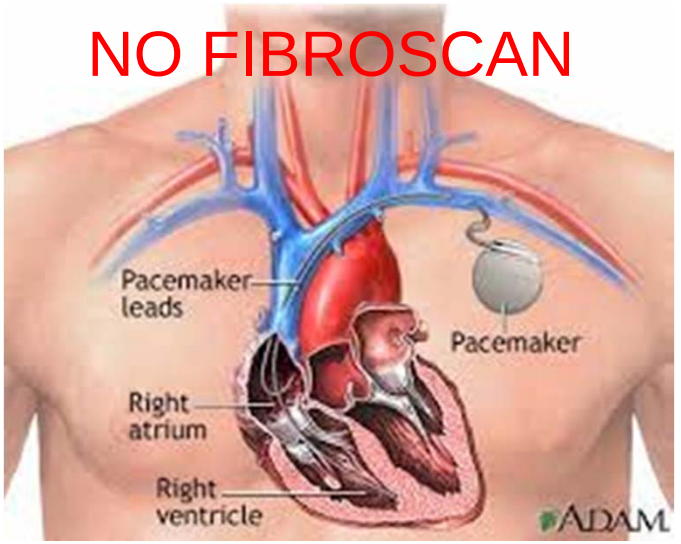
CONTRAINDICATIONS TO FIBROSCAN
(as per manufacturer recommendations)

- Pregnancy

- Pacemaker



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FIBROSCAN FAILURE

n=2114

Wong et al: 25.5% if BMI > 30,
2.6% if BMI < 30

Reliable results with the XL probe were obtained in 61% of patients in whom the M probe was unreliable

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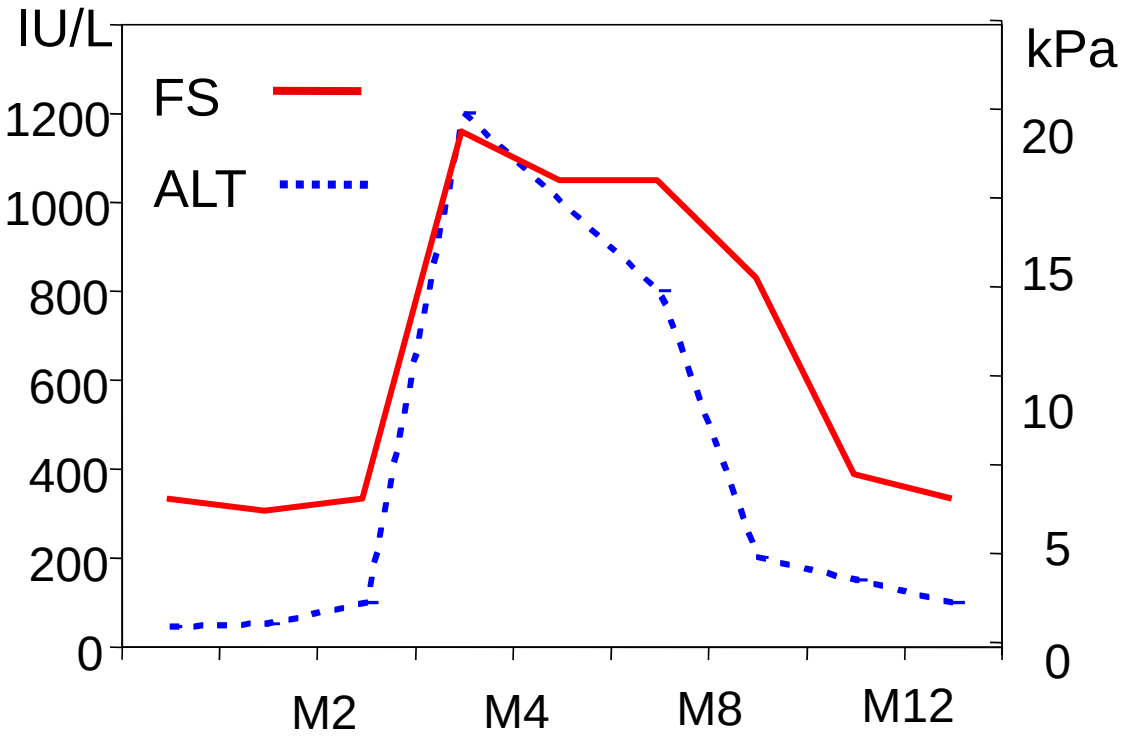
Foucher et al. Eur J Gastroenterol Hepatol 2006; Wong et al, Hepatology 2010; Myers et al, Hepatology 2012

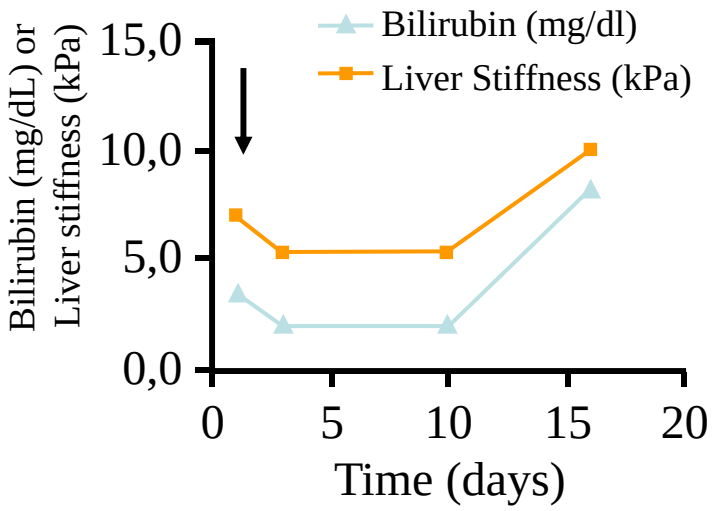
FALSE POSITIVE : ALT FLARES



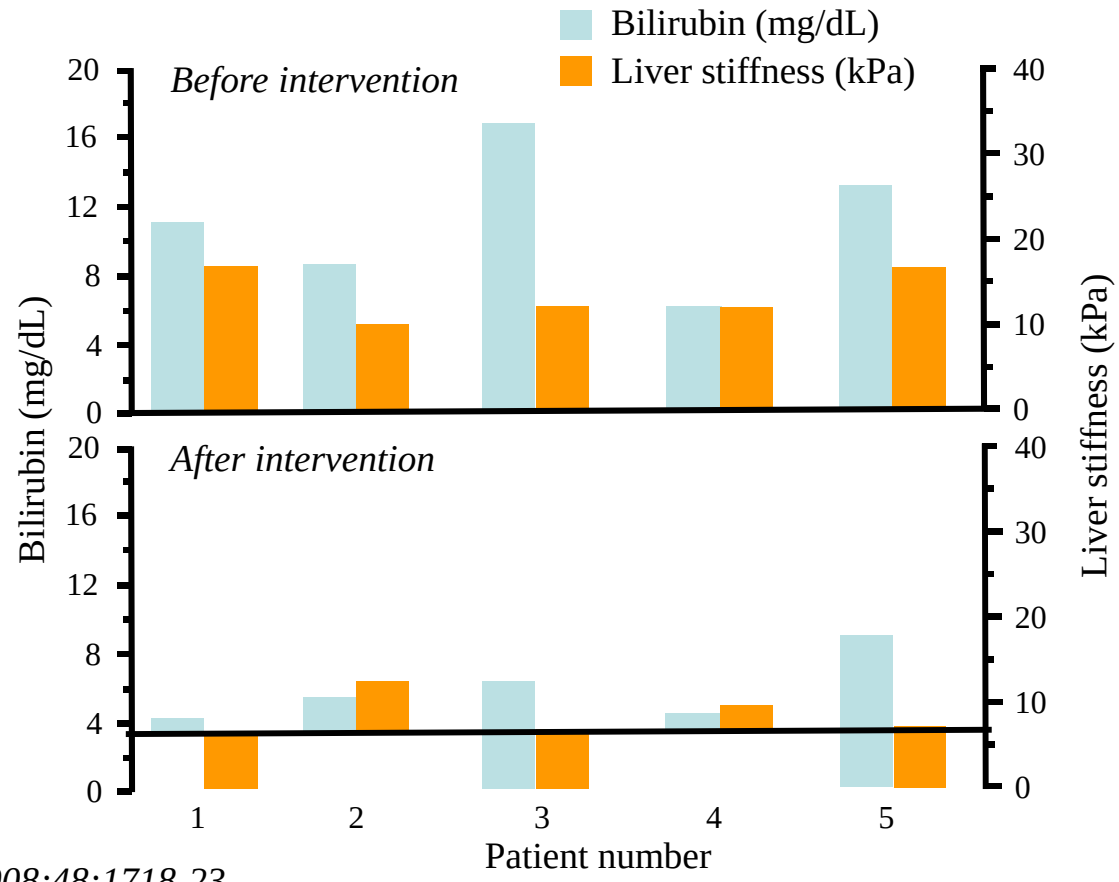
Arena U, et al., Hepatology 2008; 47: 380-4. 2. Sagir A, et al., Hepatology 2008; 47: 592-5. 3. Coco B, et al., J Viral Hepat. 2007;14: 360-9.

FALSE POSITIVE : CHOLESTASIS

- Liver stiffness significantly correlated with bilirubin levels in patients with extra-hepatic cholestasis ($r=0.67$, $p<0.05$)



- Liver stiffness reduction following successful bilirubin drainage



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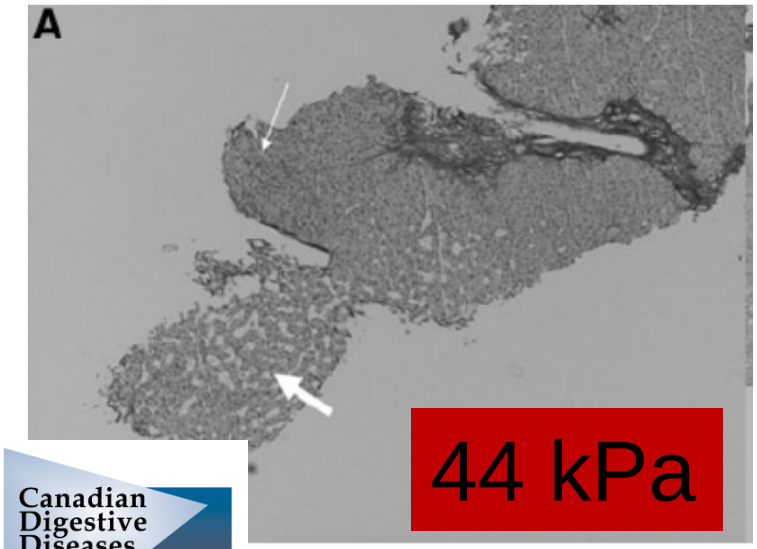
Millonig G, et al., Hepatology 2008;48:1718-23

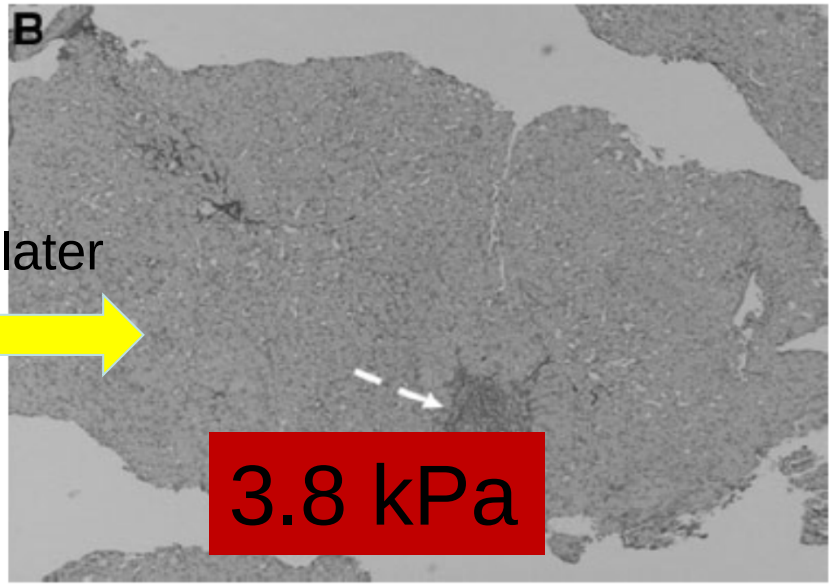
False positive TE measurements cardiac insufficiency: A case study

- Liver biopsy showed:
  - Major sinusoidal dilation, perisinusoidal fibrosis and nodular hepatic regeneration, compatible with cardiac hepatopathy – no cirrhosis
  - Mild necrotic and inflammatory activity (A1F2)

- Upon correction of cardiovascular dysfunction, liver biopsy showed:
  - No visible sinusoidal dilation and nodular hepatic regeneration
  - Mild necrotic and inflammatory activity (A1F1)



1 year later



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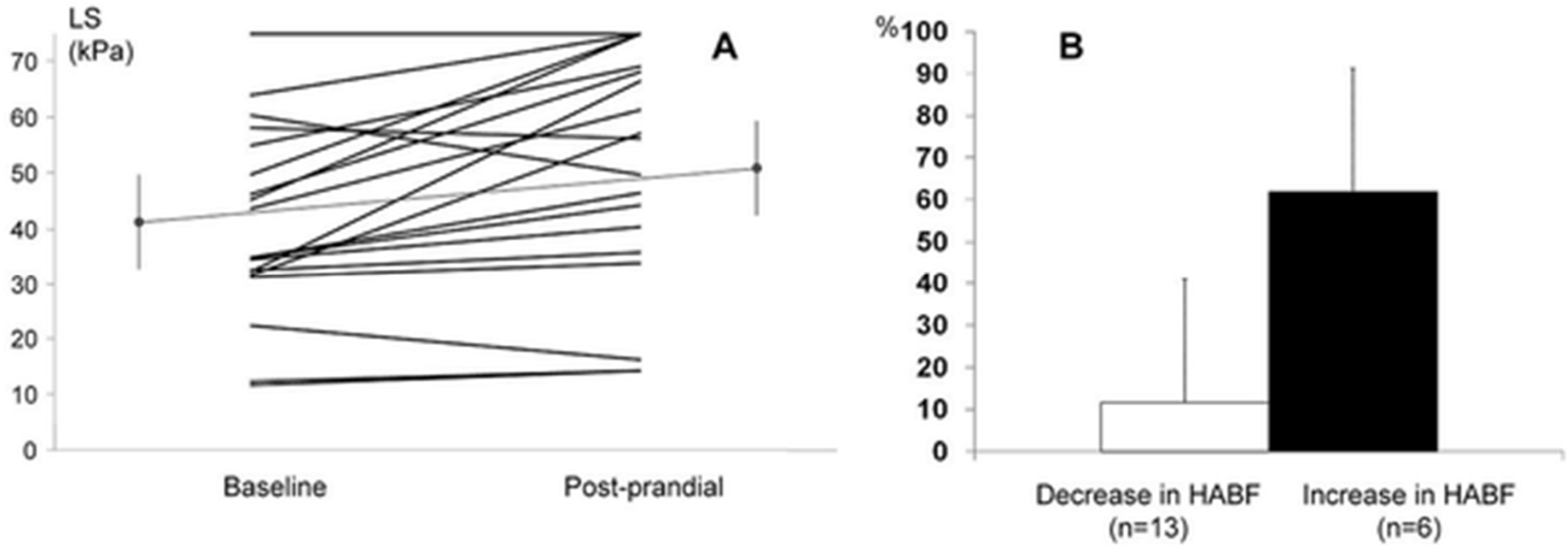
Lebray P, et al., *Hepatology* 2008;48:2090

Effect of ingestion of a meal on the elasticity of the liver in patients with cirrhosis and portal hypertension



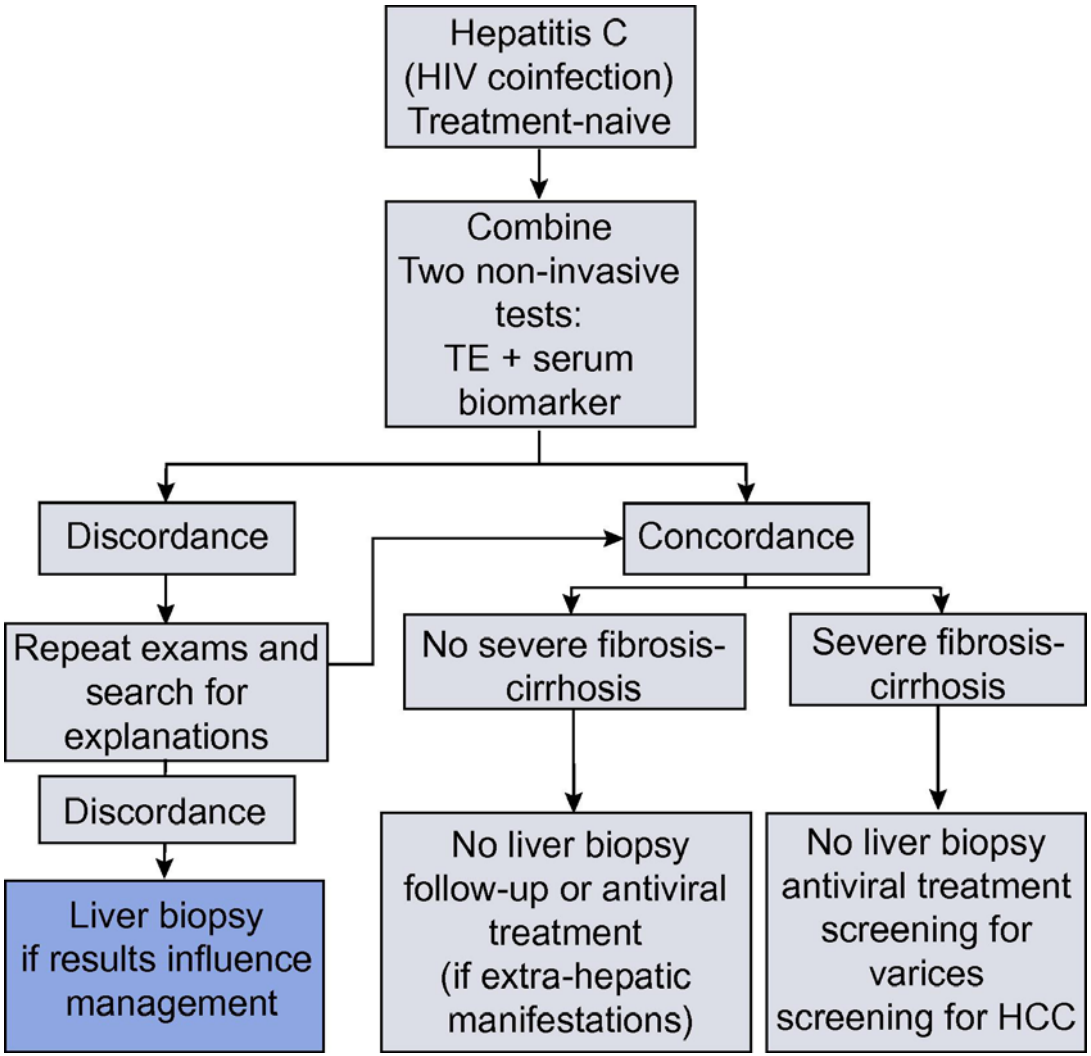
4 hours fasting required!!

Berzigotti et al, PLoSONE 2013

Serum biomarkers vs TE

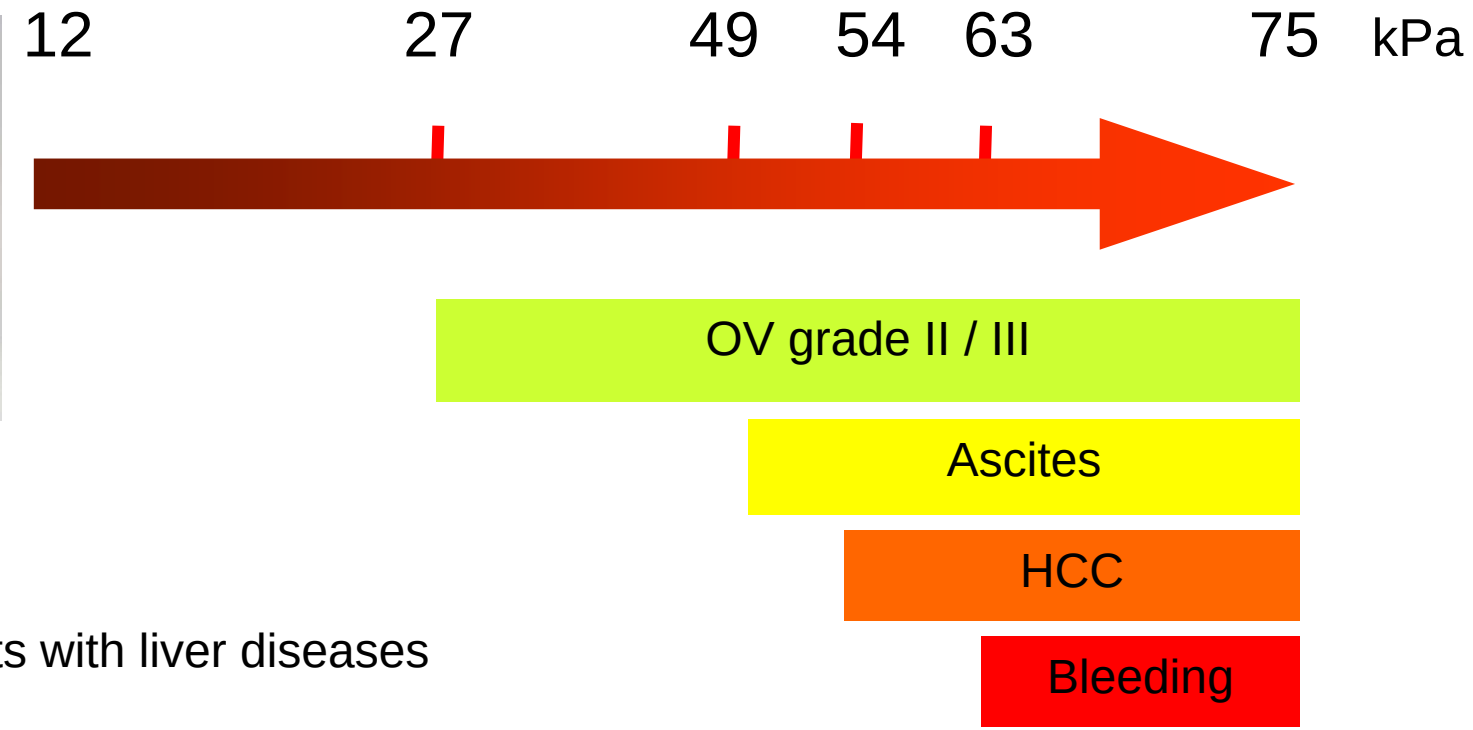
	Advantages	Disadvantages
Serum Biomarkers	• Good reproducibility • High applicability (90%) • Well validated • Can be performed in the outpatient clinic	• Non-specific of liver liver • Unable to disriminate between intermediate stages of fibrosis • Cost and limit availability
Transient elastography	• User-friendly • Good reproduciblity • High performed for cirrhosis (AUROC>0.90) • Most widely used and validated technique	• requires a dedicated machine • Applicability lower than serum markes (obesity, ascites) • Falsely elevated results in setting of acute hepatitis, liver congestion, food intake

EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis



Liver fibrosis stage is the single most important factor impacting on the prognosis of patients with liver disease

Monitoring of disease progression complications of cirrhosis



711 patients with liver diseases
F3F4 144

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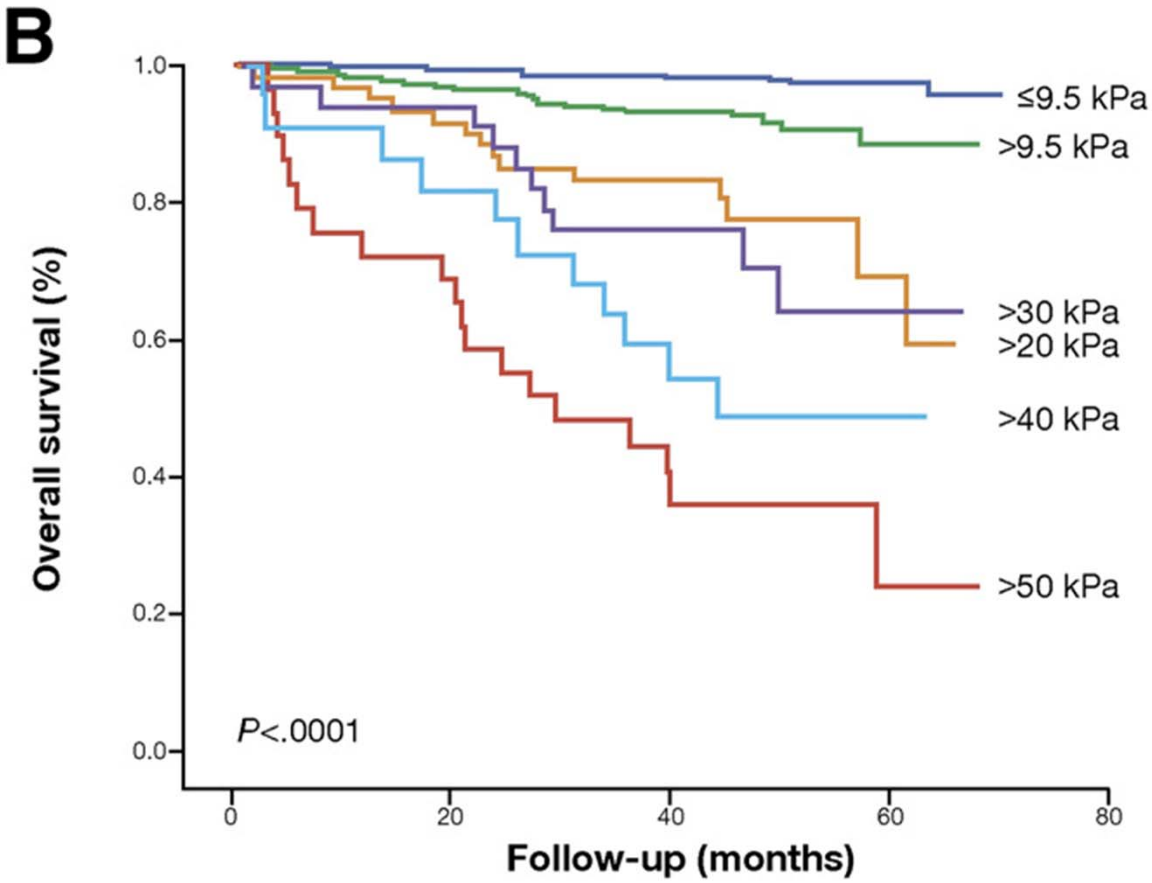
Noninvasive Tests for Fibrosis and Liver Stiffness Predict 5-Year Outcomes of Patients With Chronic Hepatitis C

JULIEN VERGNIOL,* JULIETTE FOUCHER,*,‡ ERIC TERREBONNE,* PIERRE-HENRI BERNARD,‡ BRIGITTE LE BAIL§,‖ WASSIL MERROUCHE,* PATRICE COUZIGOU,* and VICTOR DE LEDINGHEN*,‖

1457 patients with chronic hepatitis C

Outcomes defined as death
Or need for liver transplantation



GASTROENTEROLOGY 2011;140:1970-1979

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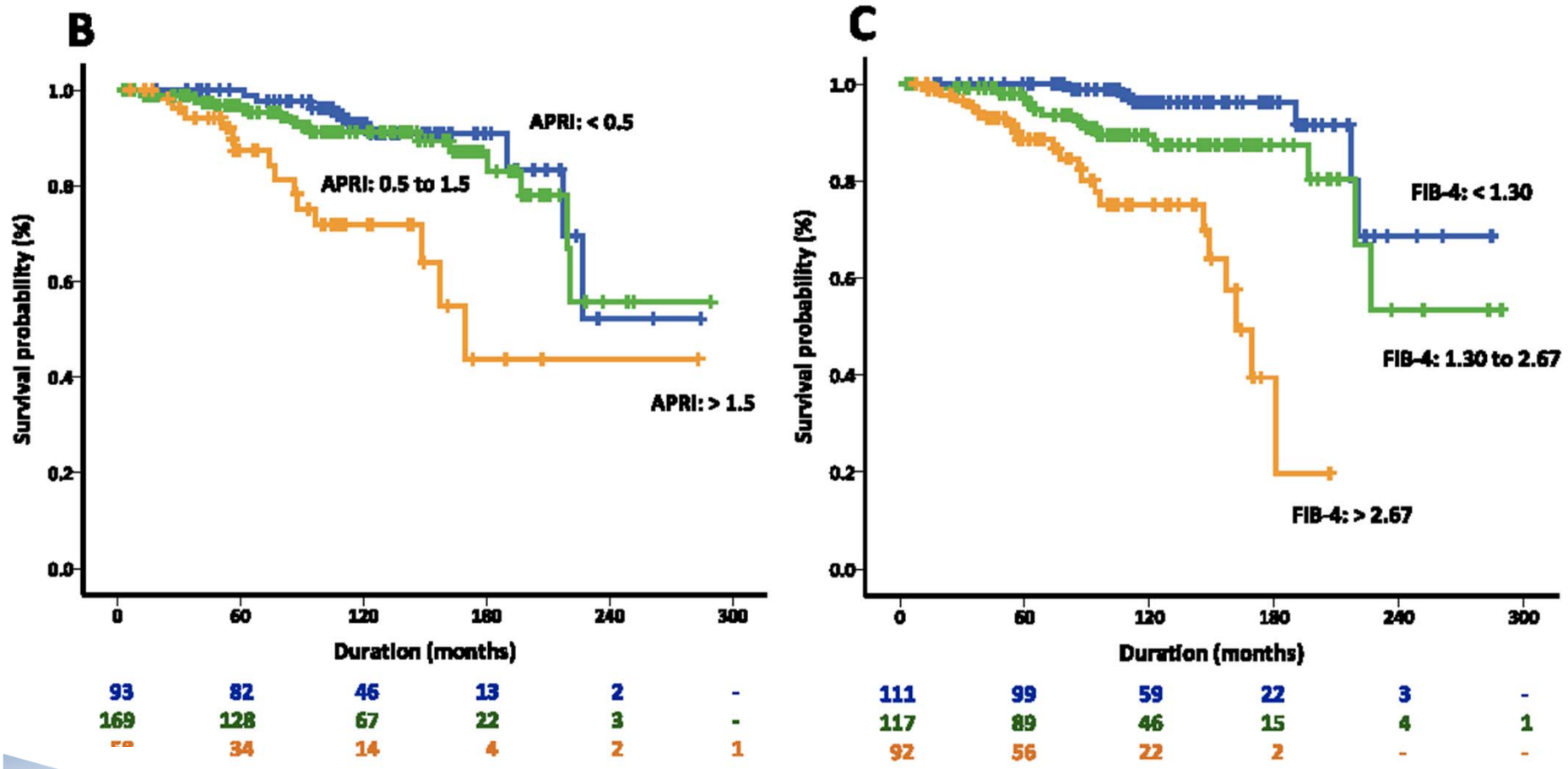
Simple Noninvasive Systems Predict Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

PAUL ANGULO,[1] ELISABETTA BUGIANESI,[2] EINAR S. BJORNSSON,[3] PHUNCHAI CHARATCHAROENWITTHAYA,[4] PETER R. MILLS,[5] FRANCISCO BARRERA,[6] SVANHILDUR HAFLIDADOTTIR,[3] CHRISTOPHER P. DAY,[7,§] and JACOB GEORGE[6,§]

320 with biopsy-proven NAFLD



GASTROENTEROLOGY 2013;■:1-8

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SUMMARY AND CLINICAL DIRECTIONS

- Liver fibrosis staging is pivotal for management of patients with chronic liver diseases
- Non-invasive tools for liver fibrosis diagnosis have high diagnostic and prognostic accuracy
- They can be used for risk stratification, prioritization for interventions such as antiviral/metabolic therapy, surveillance for HCC/varices and liver transplantation
- An optimal way to stage liver fibrosis in clinical practice is to combine two non-invasive tests and reserve liver biopsy to discordant cases or where an overlapping etiology is suspected

Thank you

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Evaluation and Certificate of Attendance

Please visit the CAG website at http://www.cag-acg.org/ to complete the session evaluation and to receive your certificate of attendance.

Or better yet, download the CDDW™ App from the CAG website!

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