



Non-invasieve diagnostiek voor leverziekten



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Disclosures

Honoraria for consulting or speaking (last 5 years):

AbbVie, BMS, Gilead, Janssen-Cilag, Medtronic,
Merck/Schering-Plough, Norgine, Roche

Research grants (last 5 years):

BMS, Gilead, Janssen Cilag, Medtronic, Philips, Roche

Patiënt: man, 45 jaar, eerste bezoek hepatitis C

- Laboratorium onderzoek
 - ALAT 56, ASAT 45, bilirubine 16
 - Genotype 1b
- Wat zijn de volgende stappen?
 - 1 Is een abdominale echo zinvol ? JA of NEE
 - 2 Is een Fibroscan-meting zinvol ? JA of NEE

Grading and staging in de hepatologie

- Oorzaak-Ziekte-Toxine etc.



- Hepatitis



- Fibrose



- Cirrose

- Gedecompenseerde cirrose
- HCC

Leverziekten zijn reversibel

- Alcoholische leverziekten
- Niet-alcoholische leverziekten, NAFLD/NASH
- Metabole leverziekten
 - Hemochromatose, M. Wilson, Cystic Fibrosis
- Auto-immuun ziekten en Cholestatiche leverziekten
 - Autoimmuun hepatitis, Primair Scleroserende Cholangitis, Primair Biliaire Cholangitis
- Virale hepatitis
 - Hepatitis B, C, Delta en E
- Stoppen met C2
- Liraglutide, SGLT2, FXR etc.
- Chelatie, enzym-agonisten
- Steroiden, UDCA, FXR
- Antivirale middelen

Grading and staging in de hepatologie

*Graad
(inflammatie) en
stadium (fibrose)
leverziekte*

*Bepalen de
indicatie voor
therapie*

*En de urgentie
voor therapie*

Metavir Scoring

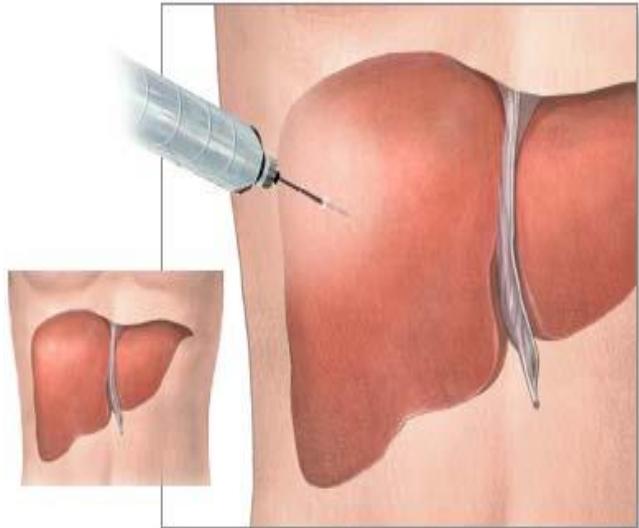
- 0 = no signs of fibrosis
- 1 = mild fibrosis
- 2 = moderate fibrosis
- 3 = severe fibrosis; fibrosis has spread and has connected to other areas on the liver
- 4 = cirrhosis

Liver biopsy

- A liver biopsy is a medical procedure used to remove a small piece of liver tissue so doctors can examine the sample under a microscope. This enables them to:
- diagnose liver disease
- determine a score for fibrosis
- detect cancer and/or infections (although liver cancer is typically diagnosed via CT scan or MRI)

Limitations of liver biopsy

- Invasive
- Morbidity and mortality
 - 20-30% pain
 - 0.6 % severe complications
 - Mortality 1- 3/10,000
- Sampling error
- Intra- and interobserver variability
- Costs € 500



Advantages of non-invasive liver fibrosis tests

- Liver biopsy is not the only way to evaluate liver tissue. Non-invasive methods are widely available, and their advantages include:
- The absence of contraindications and dangerous complications.
- Their reproducibility.
- The ability to evaluate fibrosis extent in the whole organ – not just the sampled section.
- Their potential ability to identify and differentiate between advanced fibrosis stages.
- Their high specificity and sensitivity to diagnose cirrhosis.
- Their easy application.

Categories for non-invasive liver fibrosis tests

- There are three basic categories for non-invasive liver fibrosis tests:
- *Serologic Panels*
- *Combined Scores and Algorithms*
- *Imaging Techniques*

Examples

- **APRI – AST to Platelet Ratio Index** This test is good for predicting severe fibrosis/cirrhosis or low risk of significant fibrosis, but does not accurately differentiate intermediate fibrosis from mild or severe fibrosis.
- **FIB-4 – Age x AST : Platelets x V-ALT** This test is easy-to-use, quick and inexpensive, and is good at excluding or confirming cirrhosis. However, mid-range values do not fully discriminate fibrosis and need an additional method to predict liver fibrosis.
- **Forns Index – Age, platelets, cholesterol, GGT** This algorithm has good predictive value in selecting those with low risk of significant fibrosis, but does not reliably predict more advanced fibrosis or cirrhosis.
- **HepaScore – GGT, total bilirubin, hyaluronic acid, alpha-2-macroglobulin**, Also known as FibroScore, this method is good at excluding significant fibrosis but not as good at predicting cirrhosis.
- **TE – Transient elastography**, also known as FibroScan®, helps with detecting advanced fibrosis and cirrhosis. However, liver inflammation, obesity, ascites and high central venous pressure can interfere with TE results. Most clinicians use FibroScan® in combination with other types of liver fibrosis tests.
- **MRE –** This imaging test has similar limitations to TE, although its high sensitivity and specificity results are proving to be clinically valuable. Unfortunately, this test is costly.

FibroScan®



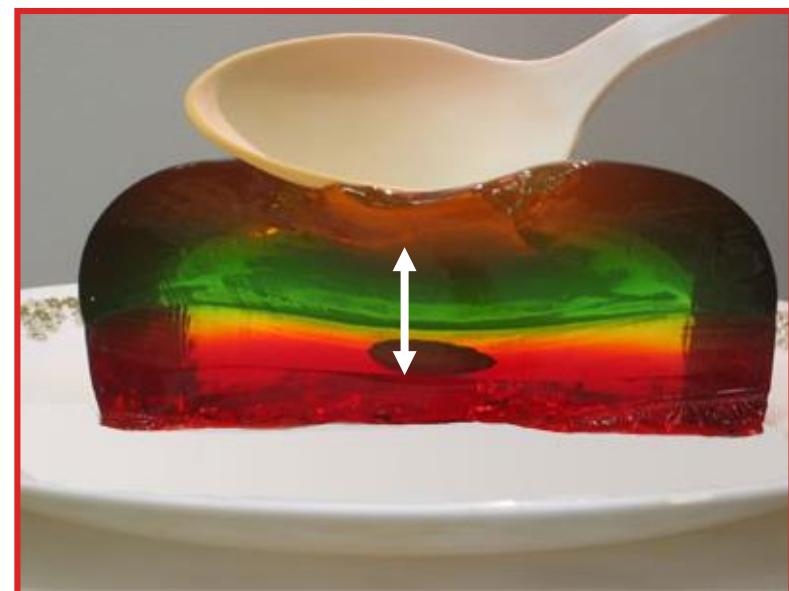
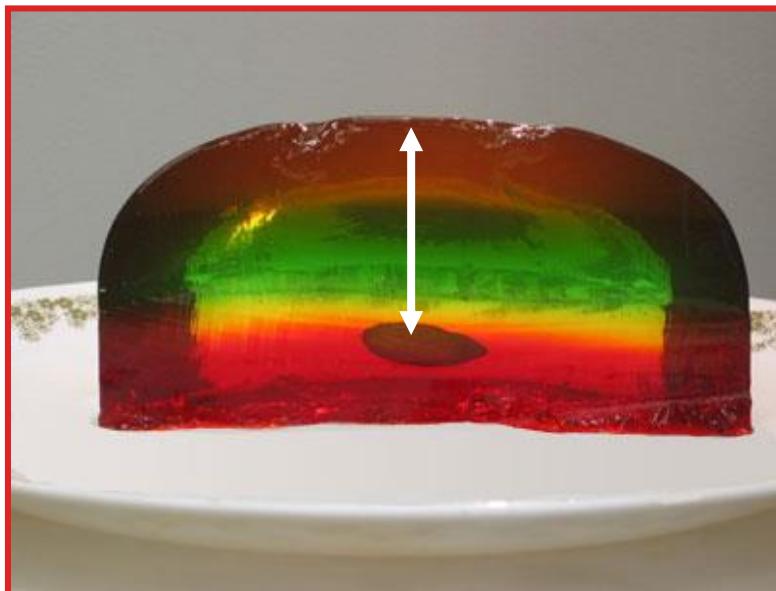
Ultrasound Elastography

Strain Imaging

$$E = \frac{\text{Stress}}{\text{Strain}}$$

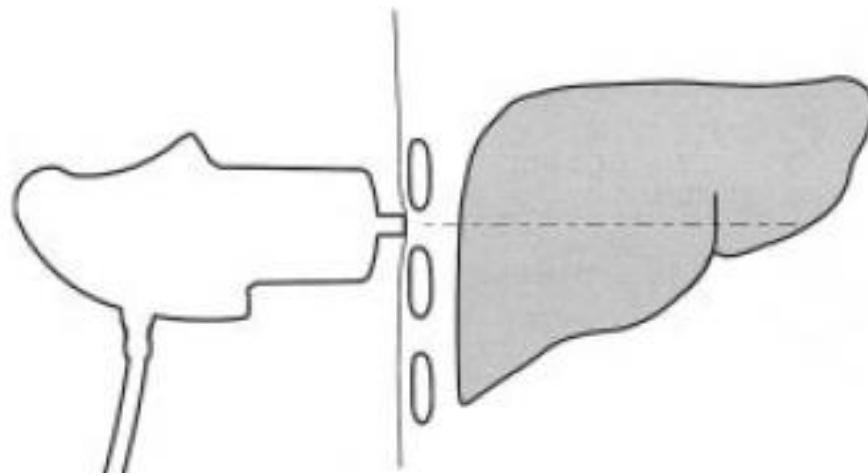
$$\text{Strain} = d/L$$

- Strain represents the deformation of tissue.
- Relative stiffness of tissue compared to normal tissue
- Strain is the magnitude of deformation of tissue calculated as the change in distance between two points divided by the initial length

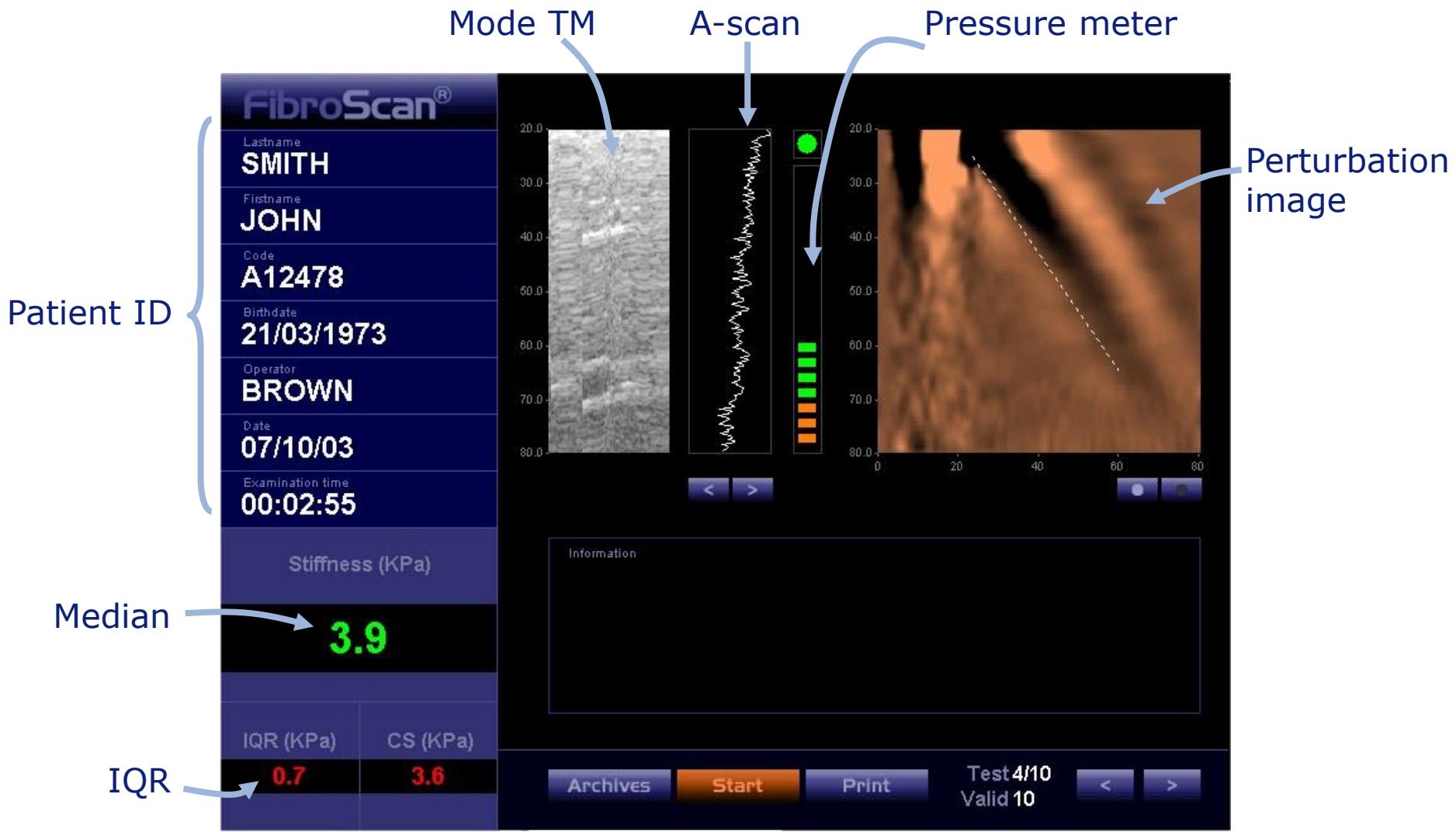


Fibroscan

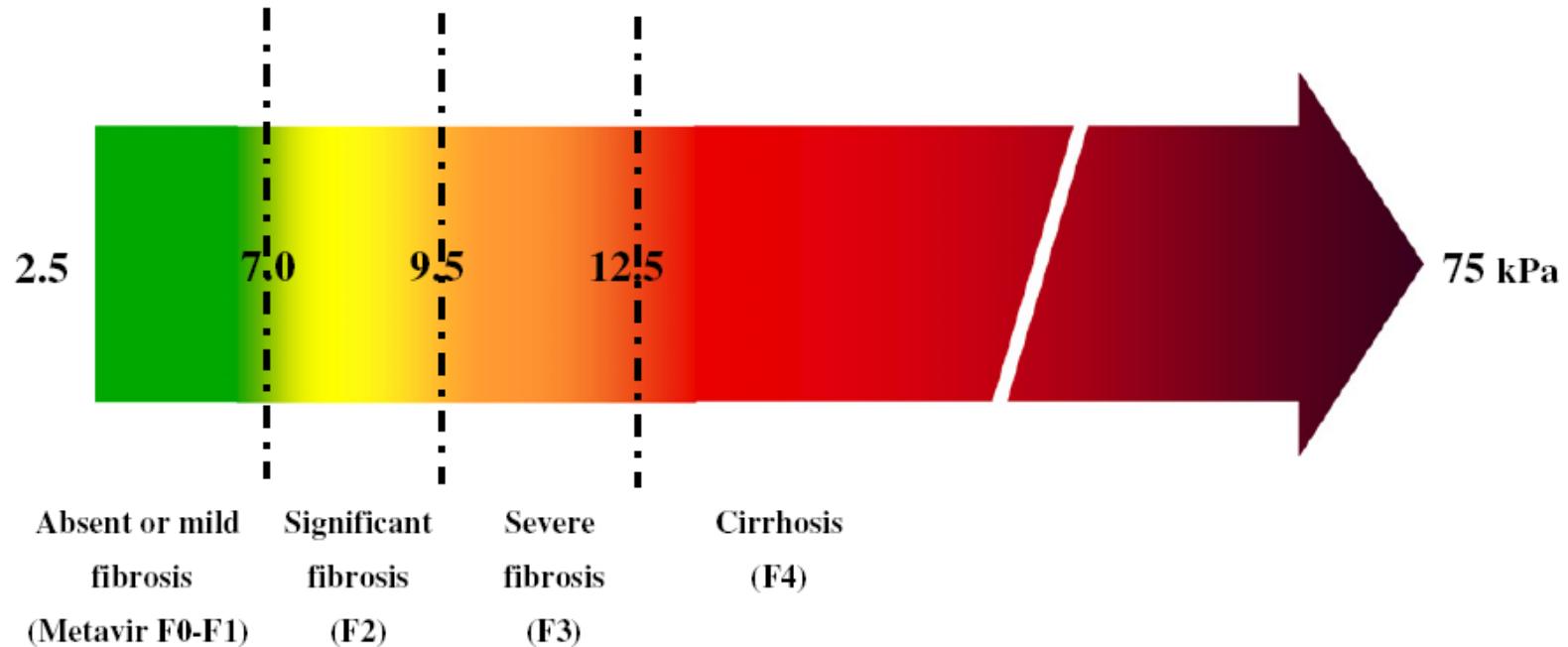
- Elasticity:
 - Pressure wave (kPa) - vibration
 - Velocity of transmission ~ liver stiffness
- Information about cylinder 1-4 cm
 - 100x bigger than median liver biopsy
 - More representative?
- Most studies performed in patients with Hep C



The software

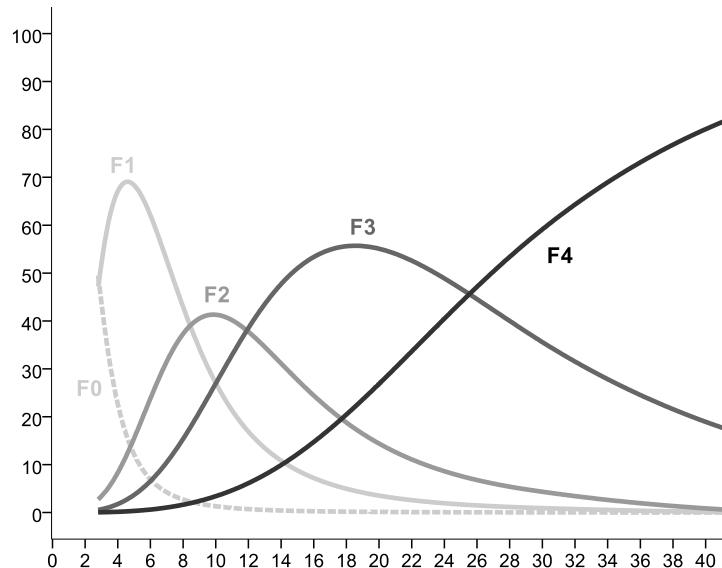


Ranges for stiffness with fibroscan

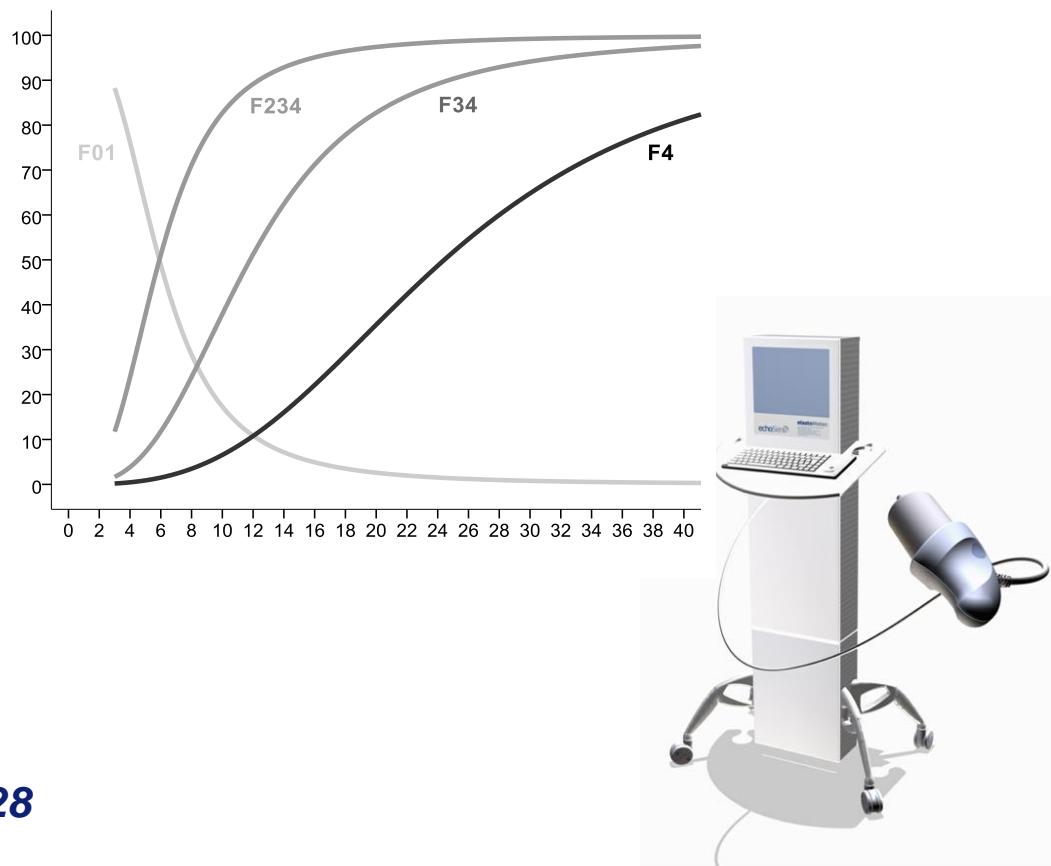


Prediction of liver cirrhosis by fibrosis score

CHB- prediction of fibrosis score by kPa



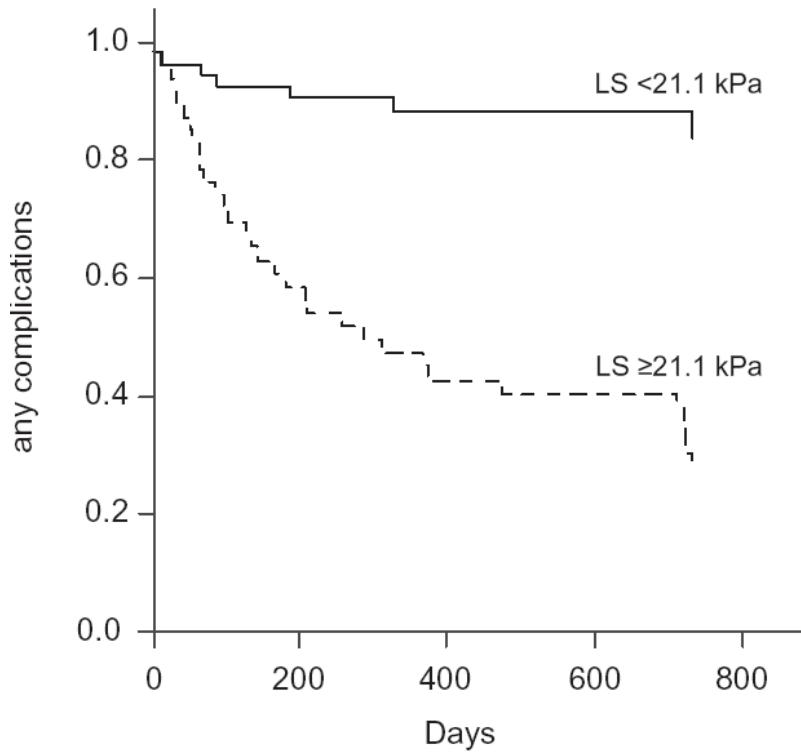
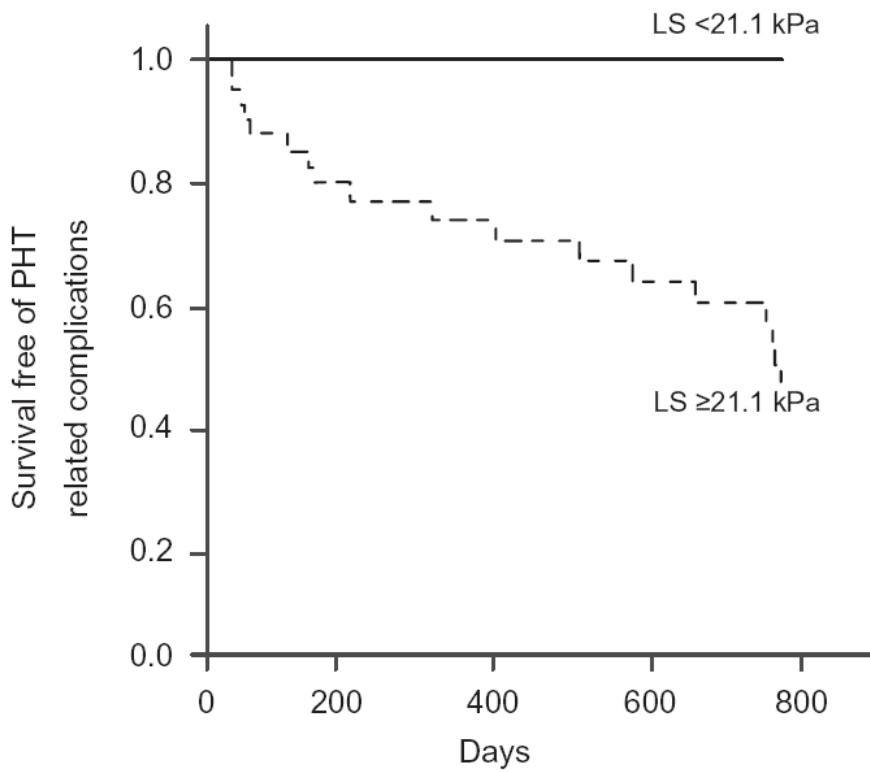
CHC- prediction of fibrosis score by kPa



Verveer et al., Liver Int 2012;32:622-628

Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: A prospective study

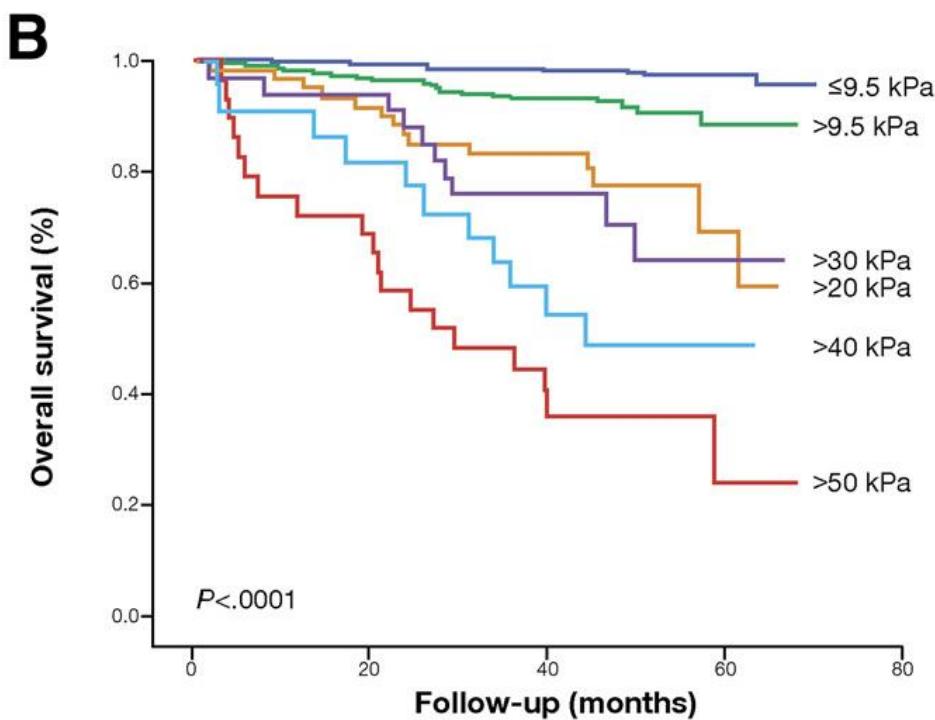
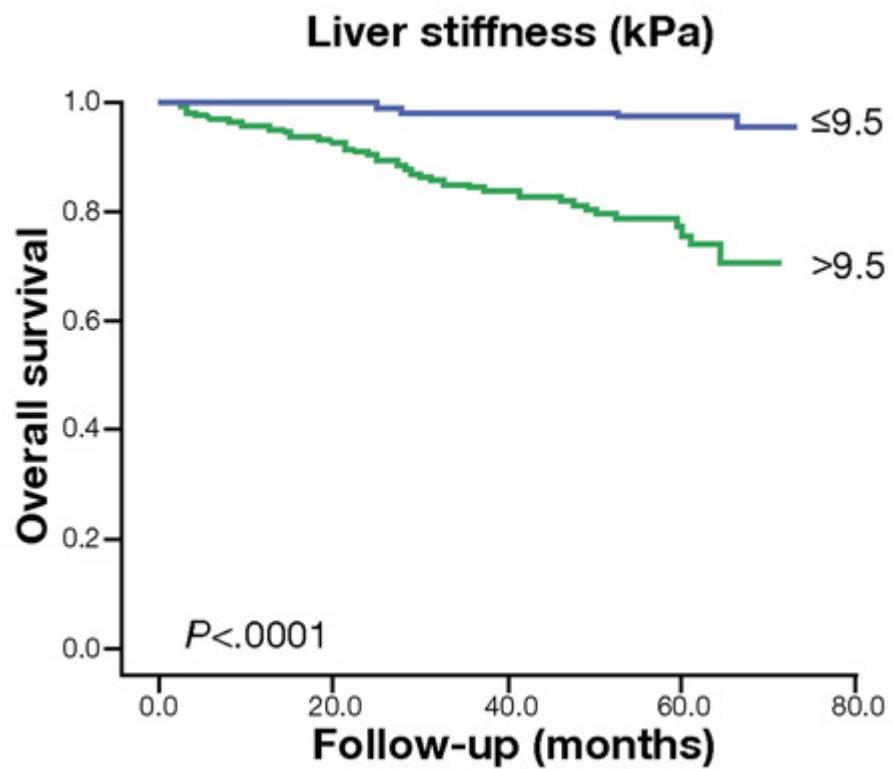
Marie Angèle Robic^{1,†}, Bogdan Procopet^{1,2,†}, Sophie Métivier¹, Jean Marie Péron^{1,3}, Janick Selves^{3,4},
Jean Pierre Vinel^{1,3}, Christophe Bureau^{1,3,*}



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*,||

GASTROENTEROLOGY 2011;140:1970–1979



Risk Assessment of Hepatitis B Virus–Related Hepatocellular Carcinoma Development Using Liver Stiffness Measurement (FibroScan)

Kyu Sik Jung,^{1,*} Seung Up Kim,^{1,*} Sang Hoon Ahn,^{1,2,5,6} Young Nyun Park,³ Do Young Kim,^{1,2,5}
Jun Yong Park,^{1,2,5} Chae Yoon Chon,^{1,2,5} Eun Hee Choi,⁴ and Kwang-Hyub Han^{1,2,5,6}

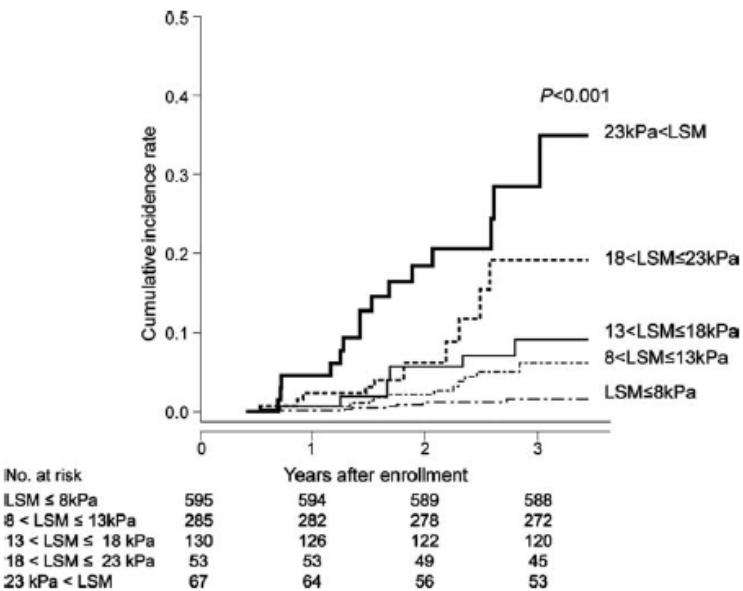
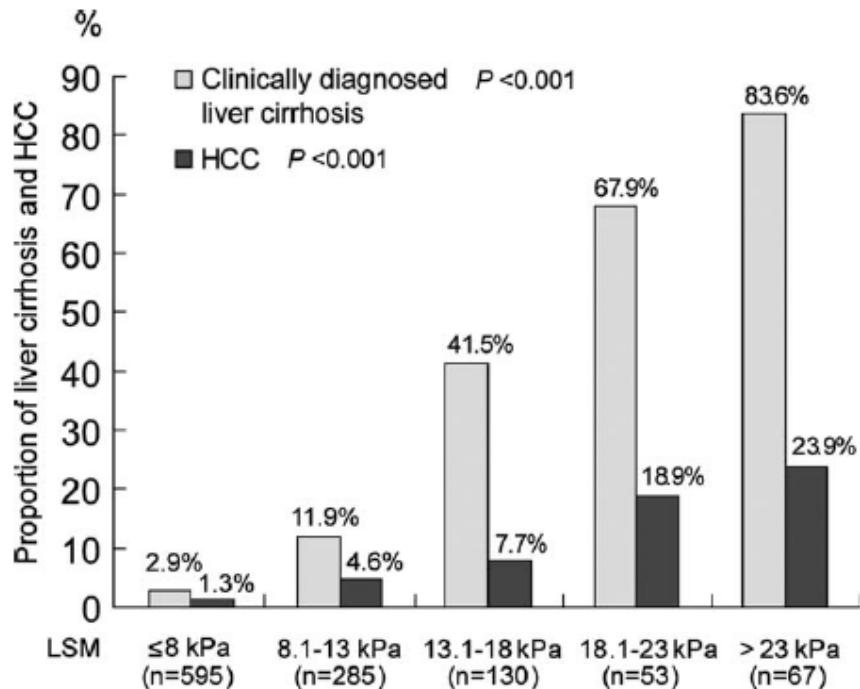
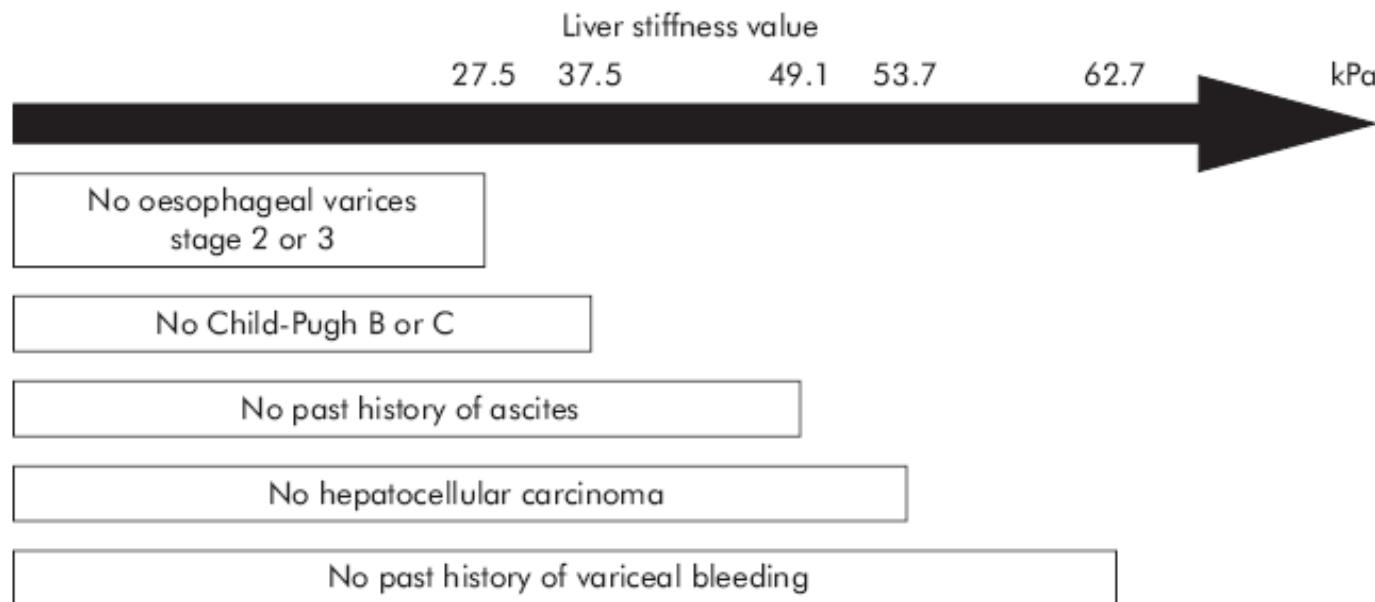


Fig. 3. Cumulative incidence rates of HCC based on stratified LSM (Kaplan-Meier plot). The cumulative incidence rates increased significantly in association with higher LSM (log-rank test, $P < 0.001$).

Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study

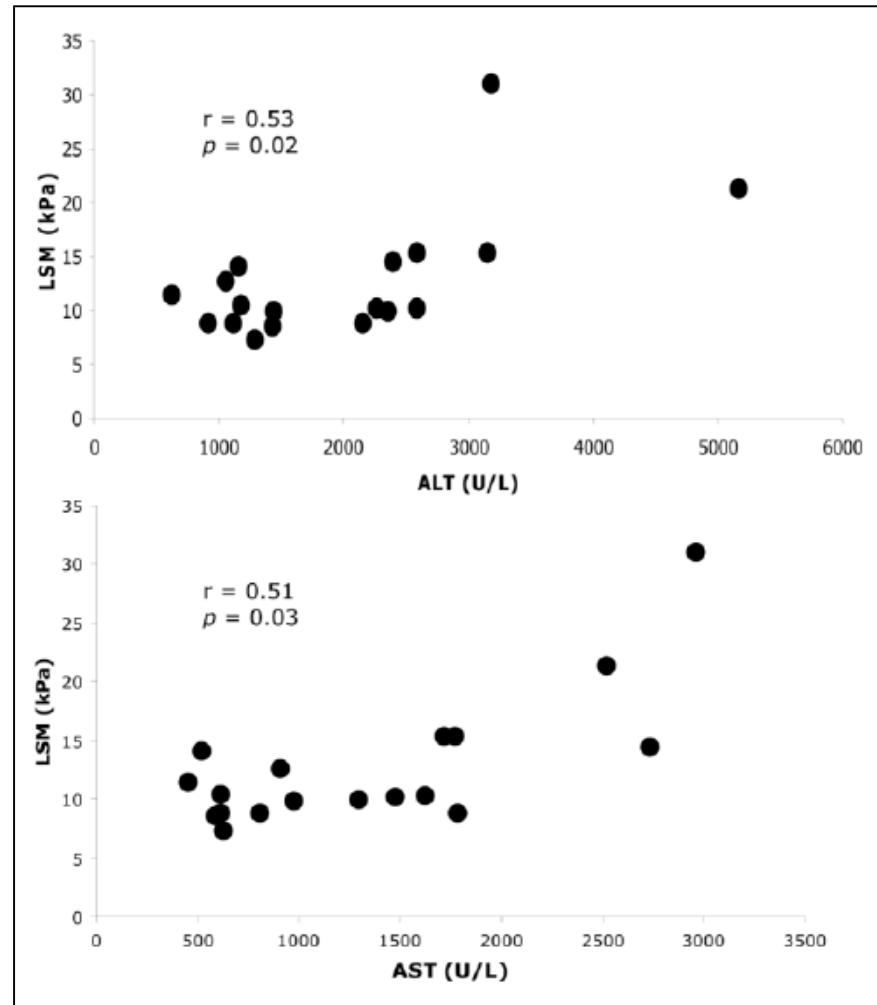
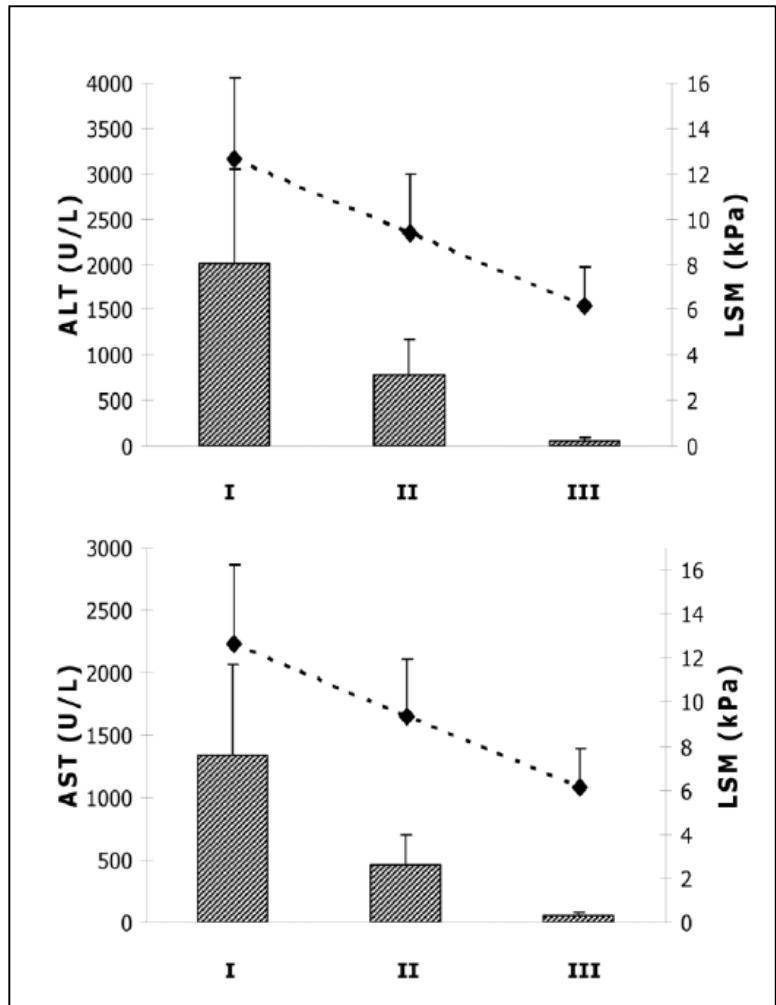
J Foucher, E Chanteloup, J Vergniol, L Castéra, B Le Bail, X Adhoute, J Bertet,
P Couzigou, V de Lédinghen

Gut 2006;55:403–408.

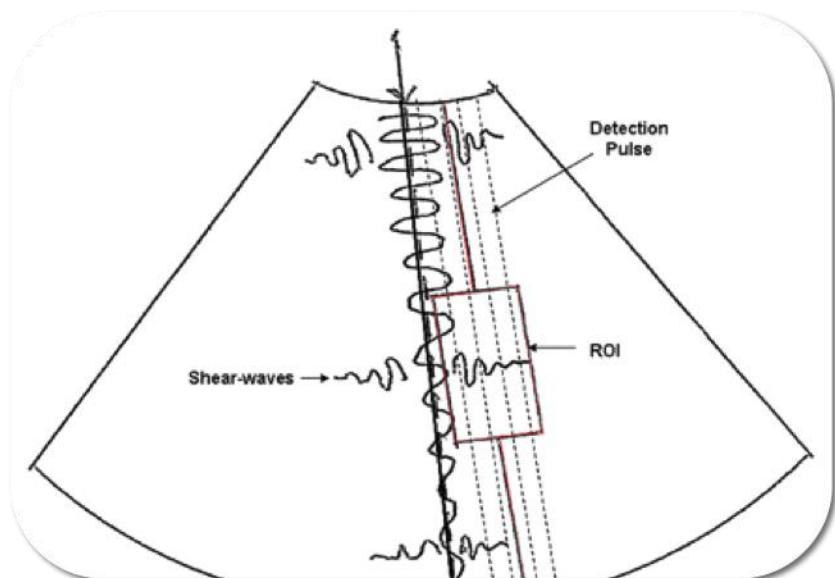


Influence of hepatitis on liver stiffness

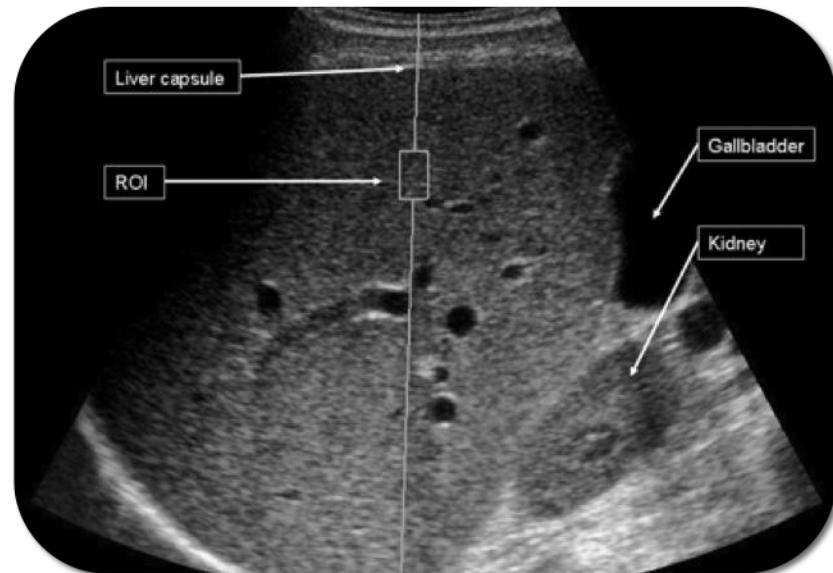
- not all that's stiff is a fibrosis



ARFI (Siemens)



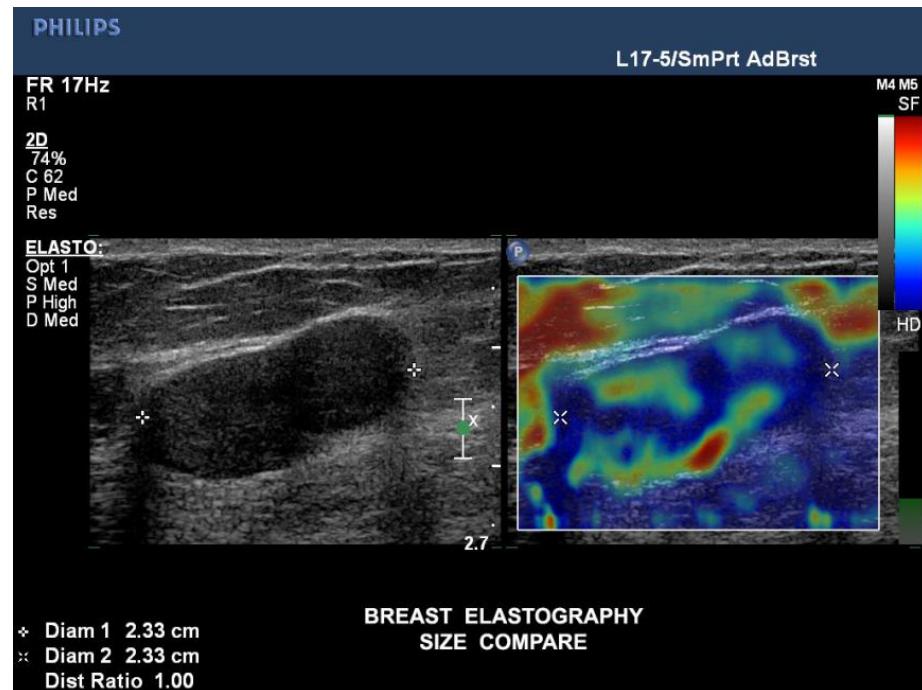
Acoustic radiation force
impulse imaging
elastography



Single step examination
Integrated in conventional US system
Results comparable with Fibroscan

Elast(P)Q® Shear Wave Elastography (Philips)

Philips iU22



Ling: European Journal Radiology 2013
Ferraioli: EASL 2013

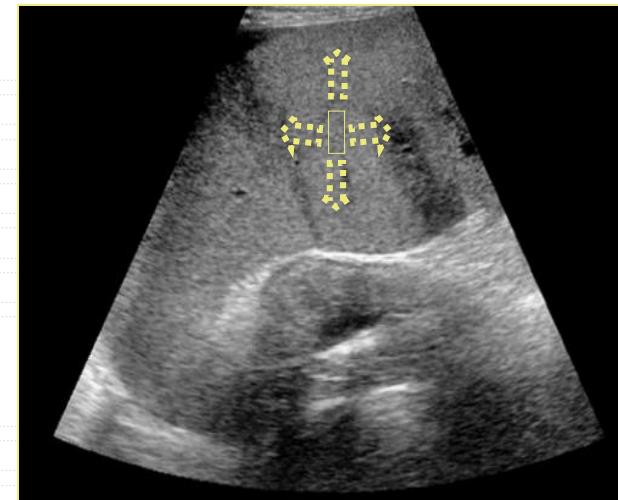
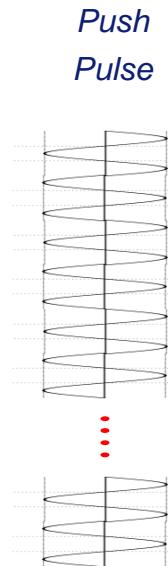
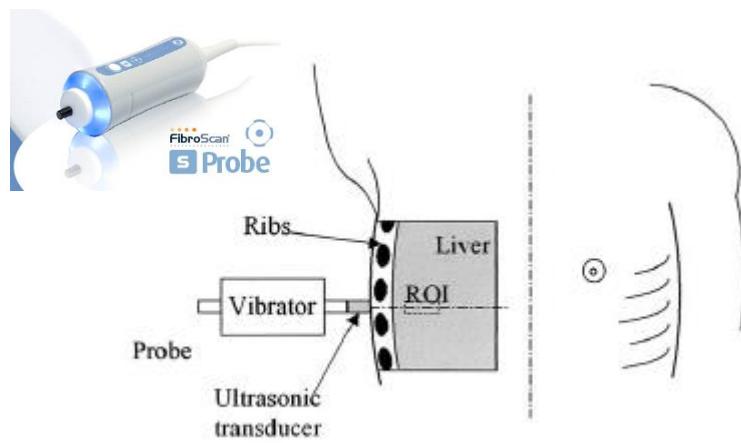
Ultrasound Elastography

Shearwave Point Quantification

- Induces shear waves perpendicular to the ultrasound beam
- Velocity of the shear wave is proportional to stiffness
- PW-like sample volume quantification: Reporting a single number of shear wave velocity
- Clinical studies primarily targeting liver fibrosis assessment
- Force on tissues can again come from various sources:

External probe motion

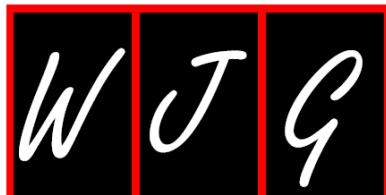
Acoustic Radiation Force



ARFI Shear wave

Assessment of liver tissue stiffness in Chronic Hep C infections

Liver Fibrosis Staging	Metavir Score	kPa	m/s
Normal	F0	2.0 – 4.5	.81 – 1.22
Normal – Mild	F0 – F1	4.5 – 5.7	1.22 – 1.37
Mild – Moderate	F2 – F3	5.7 – 12.0	1.37 – 2.00
Moderate - Severe	F3 – F4	12.0 – 21.0+	2.00 – 2.64+



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 bpgoffice@wjgnet.com
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OBSERVATIONAL STUDY

Point shear wave elastography method for assessing liver stiffness

5.7 kPa/1.37m/s appears to be the crossover from normal/insignificant/mild to significant Fibrotic changes in chronic Hep C patients.

Giovanna Ferraioli, Carmine Tinelli, Raffaella Lissandrini, Mabel Zicchetti, Barbara Dal Bello, Gaetano Filice, Carlo Filice

Temp ID-20130927111142 O111120130927

09/27/2013 11:19:27 AM

Live

Calc List

Abdominal > Abdomen General

- Application: Abdominal
- Abdomen General
 - Abdomen Arterial
 - Abdomen Renal
 - Abdomen Venous
 - Abdomen Stiffness

Measurements

- Bladder Dimensions
 - Bladder L
 - Bladder H
 - Bladder W
 - IV Bladder L
 - IV Bladder II
 - IV Bladder W

- Organ Dimensions
 - Liver Length
 - Gt Wall Diam
 - CBD Ulam
 - Ao Pnx Diam
 - Ao Mid Diam
 - An Dist Diam

Calculations

- Bladder Vol
- IV Bladder Vol
- Spleen Vol

Abd Gen

C5-1

22Hz

RP

2D

69%

Dyn R 55

P Med

Gen

Elasto

Opt 1

RP

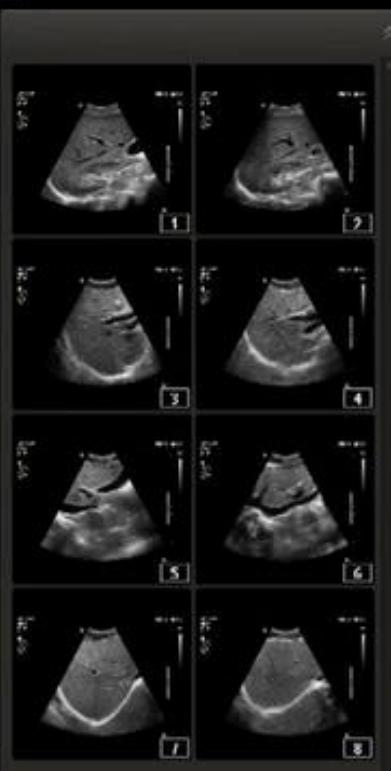
71Hz

TIS0.2 MI 1.2

M3 M1

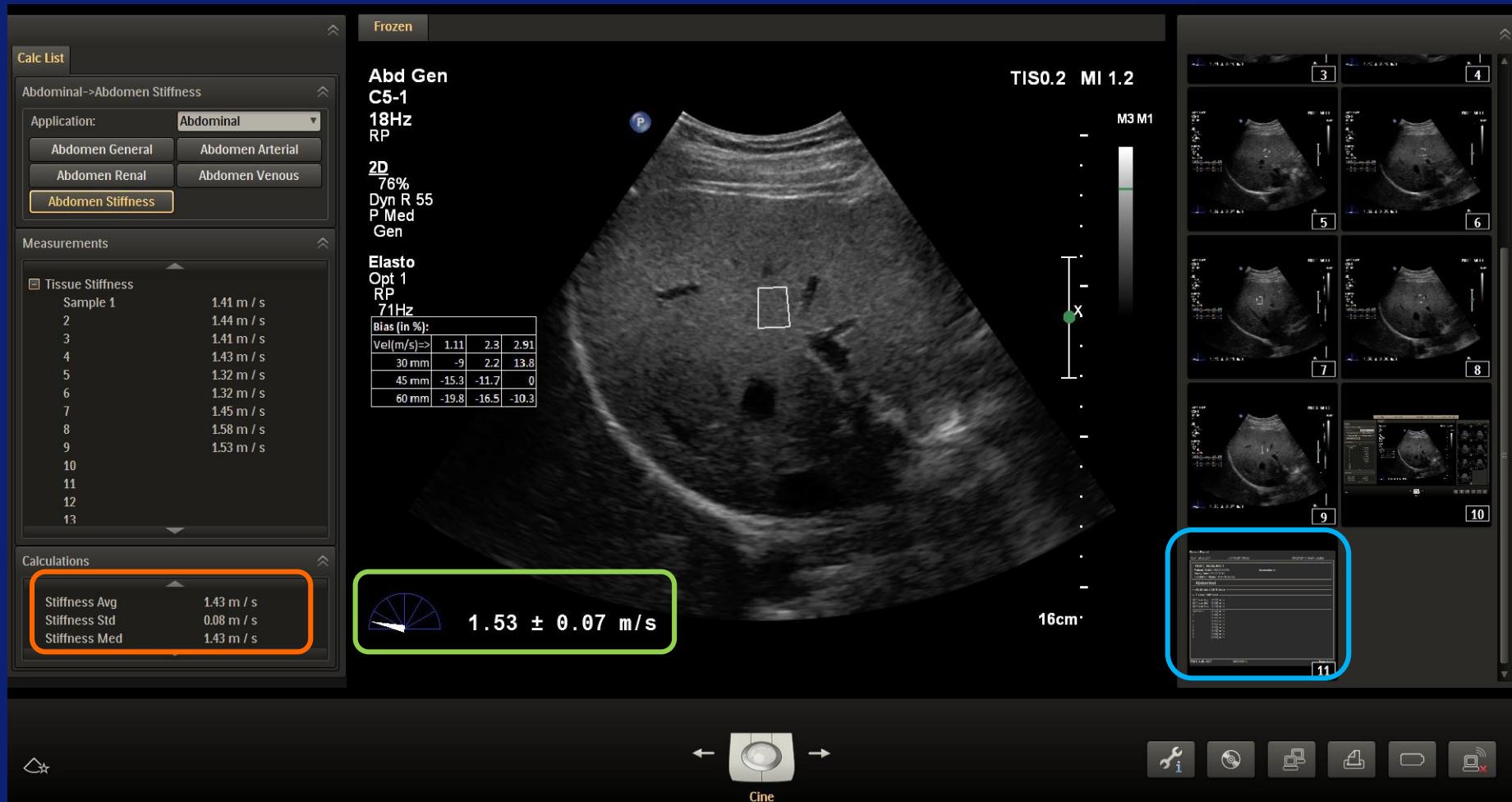


11cm



Move Elastography ROI 2D Position





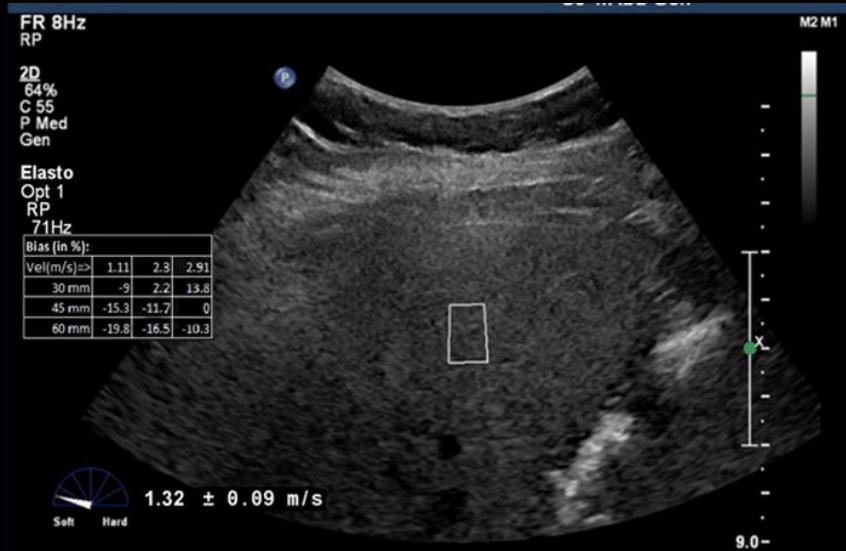
Real time Stiffness Statistics

Selectable Units: m/s or kPa
(m/s only for U.S. market)

Stiffness report

Ultrasound Elastography

Liver



Variables that will affect shear wave sampling

- Acute on chronic conditions (inflammatory)
- Multiple disease etiology
- Post prandial may have higher readings – especially in men
- Sampling on or near vessels / biliary structures
- Samples too deep or shallow
- Samples too close to edge of sector
- Sampling near rib shadows
- Sampling in areas of than segment 7 or 8
- Patient motion – respiration or cardiac
- User motion during sampling



Take into account:

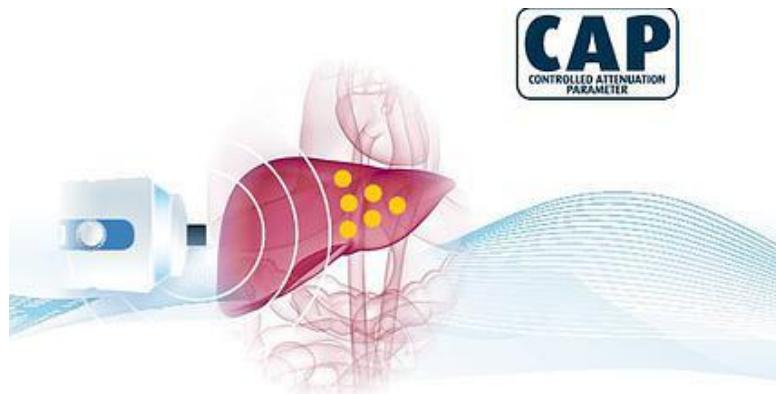
- At this time the technique and interpretation of elastography images varies with each manufacturer
- The use of Elastography is improving and more validations are needed
- It may play a significant role in breast, liver and will expand in the future
- Elastography in other organs is just beginning

Ultraschall in der Medizin

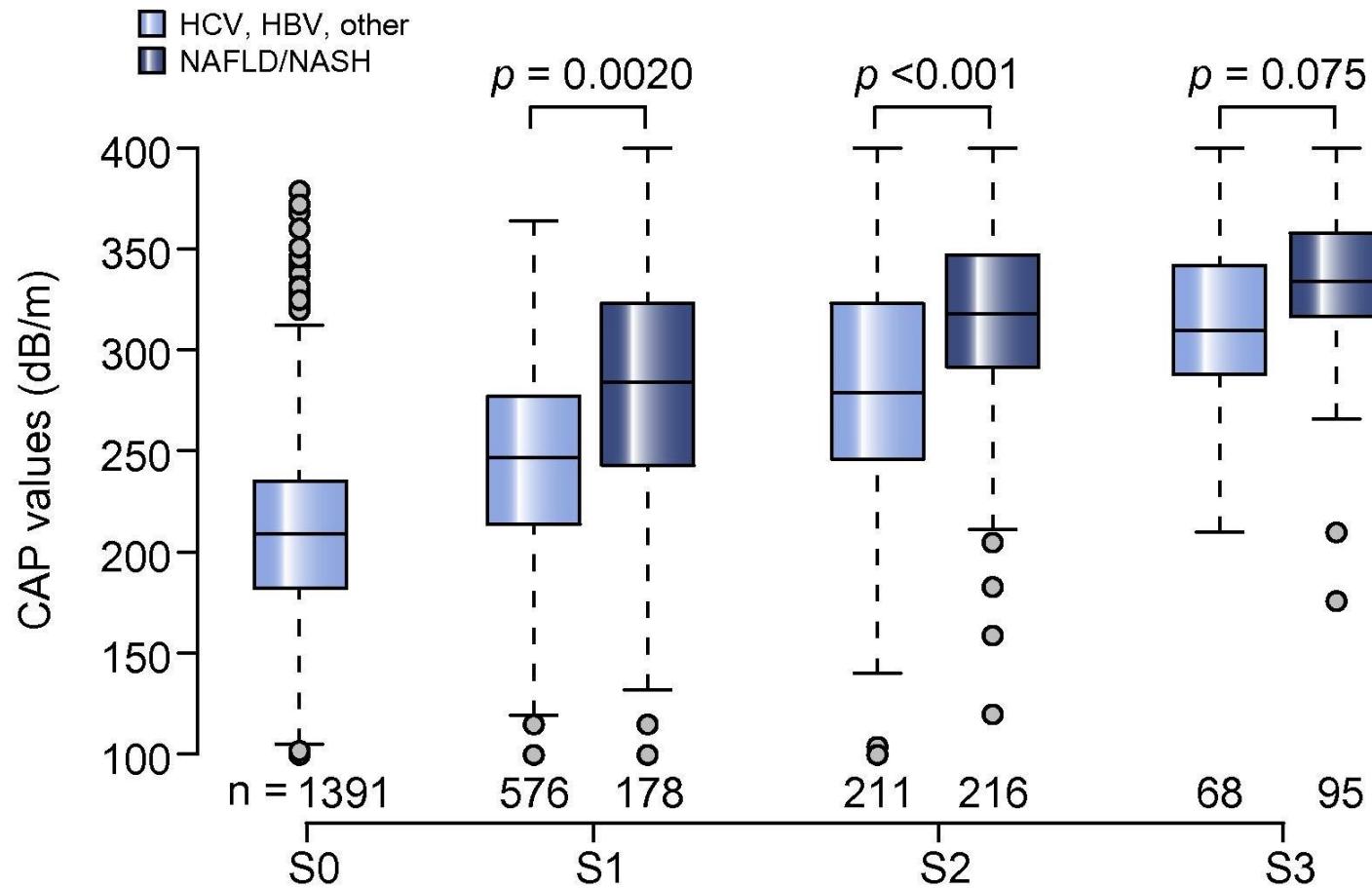
European Journal of Ultrasound

- EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017
- EFSUMB-Leitlinien und Empfehlungen zur klinischen Anwendung der Leberelastographie, Update 2017
- Authors
- Christoph F. Dietrich^{1, 2}, Jeffrey Bamber³, Annalisa Berzigotti⁴, Simona Bota⁵, Vito Cantisani⁶, Laurent Castera⁷, David Cosgrove⁸, Mireen Friedrich-Rust⁹, Victor de Ledinghen¹⁰, Robert de Knecht¹¹, Giovanna Ferraioli¹², Odd Helge Gilja¹³, Ruediger Stephan Goertz¹⁴, Thomas Karlas¹⁵, Fabio Piscaglia¹⁶, Bogdan Procopet¹⁷, Adrian Saftoiu¹⁸, Paul S. Sidhu¹⁹, Ioan Sporea²⁰, Maja Thiele²¹
- 2017, April 13

Quantitative fat measurement



Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis,
Karlas T et al., J Hepatol 2017; 66: 1022-1030.

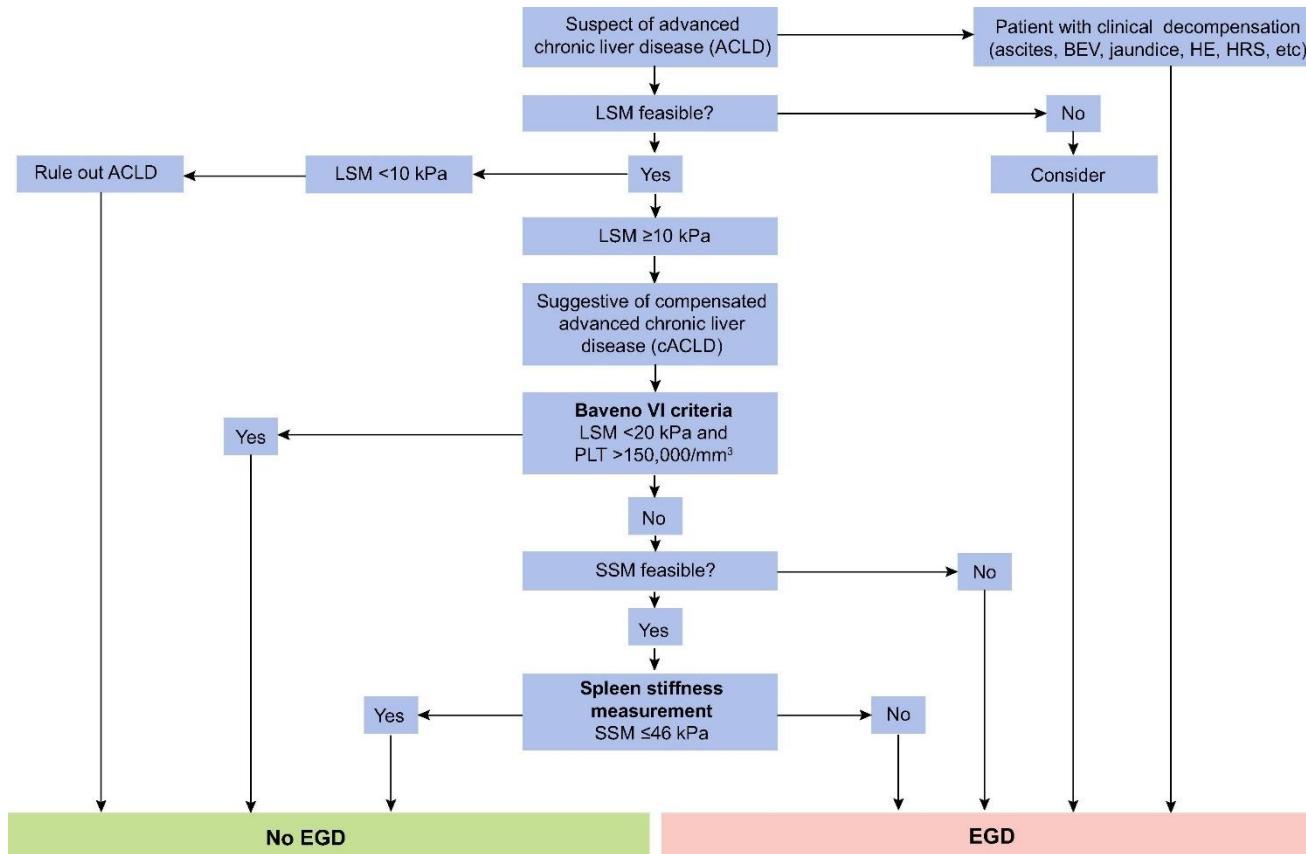


New development: spleen stiffness



The potential role of spleen stiffness measurement in the diagnostic work-up of liver disease patients.

Colecchia A et al., J Hepatol 2018, in press



Casus

- Young Asian girl (20 years old), recent diagnosis hep B
- High HBV DNA, HBeAg+, normal ASAT and ALAT
- Normal abdominal ultrasound, no signs of portal hypertension
- FS stiffness 4.2 kPa

Liver biopsy ? **YES** or **NO**

Casus 2

- Male 55Y, chronic hep C, high HCV RNA
- Elevated AST/ALT
- Abdominal ultrasound: nodular liver border
- Fibroscan stiffness: 25 kPa

Liver biopsy **YES** or **NO** ?

Elastografie - Conclusies

- Fibroscan, beste uitgezocht
- Andere vormen van elastografie, vooralsnog wees voorzichtig
- Elasticiteit
 - Wordt bepaald door fibrose + evt. oedeem + galwegen + vasculatuur + vet
- Voor bepaling ernst en prognose van leverziekte; voor het vervolgen van therapie
- CAP, voor het meten van vet (NAFLD), geeft geen informatie over evt. NASH
- Spleen stiffness, nieuw, eerste resultaten veelbelovend

Dank voor de aandacht !

