



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 Cholestatische 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*

Scoring

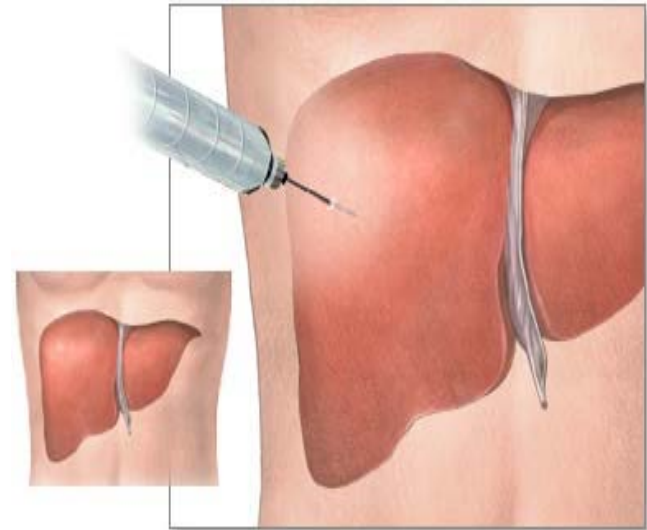
- In general, the histological staging systems for liver fibrosis currently used derive from the initial Knodell fibrosis score, and consist of either a five or seven tier rating. The higher the number, the more advanced the liver disease. The five tier rating system is most common, where the fibrosis score ranges from 0 to 4:
 - 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®

Erasmus MC
Erasmus



FibroScan®

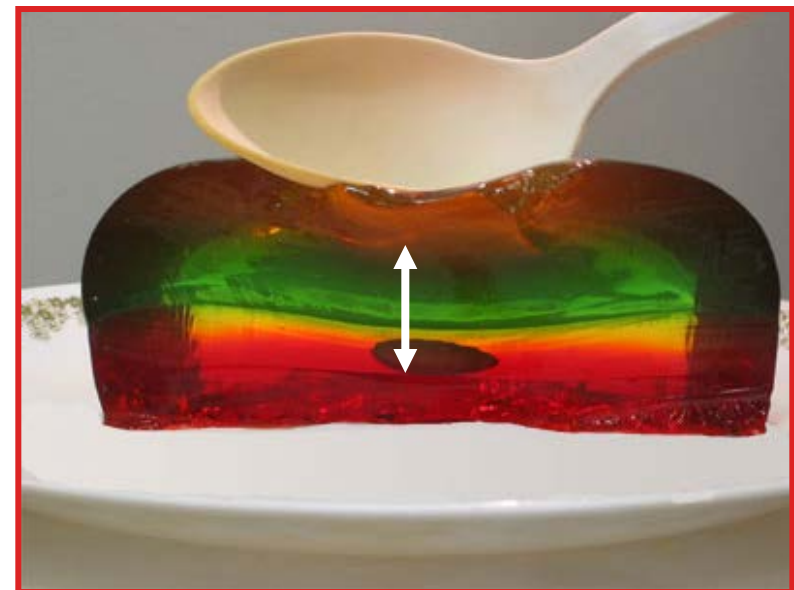
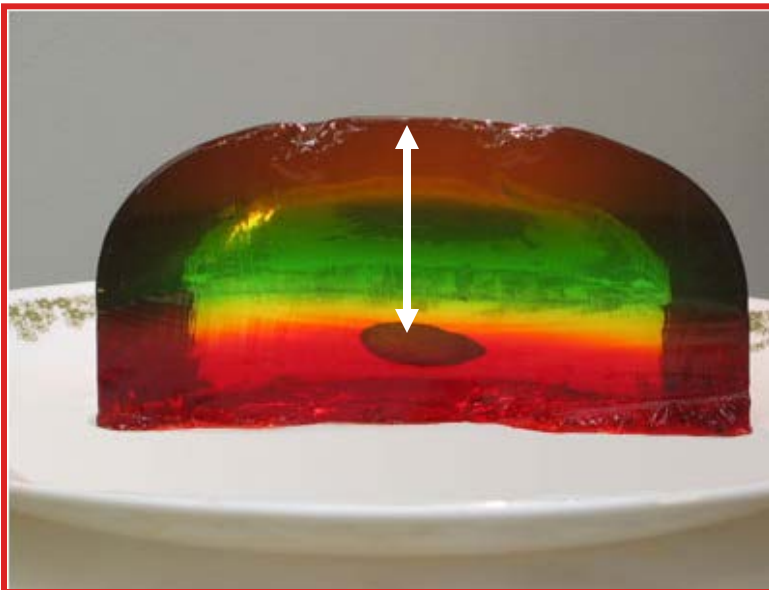
Ultrasound Elastography

Strain Imaging

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

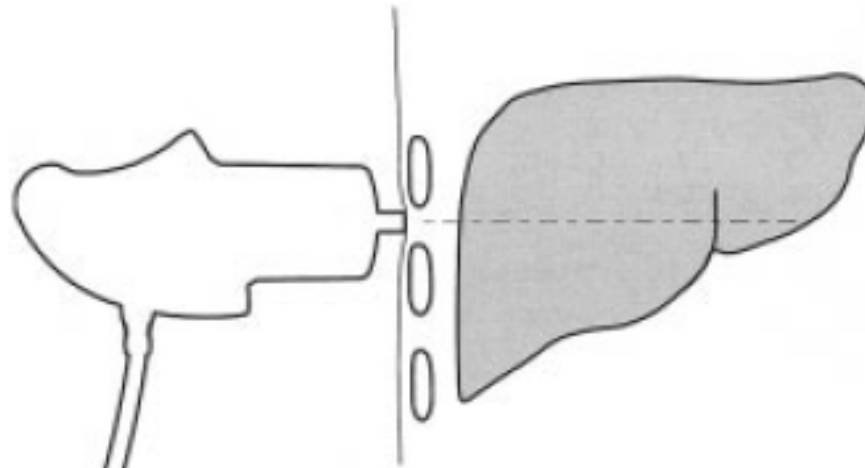
$$\text{Strain} = d/L$$

- 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

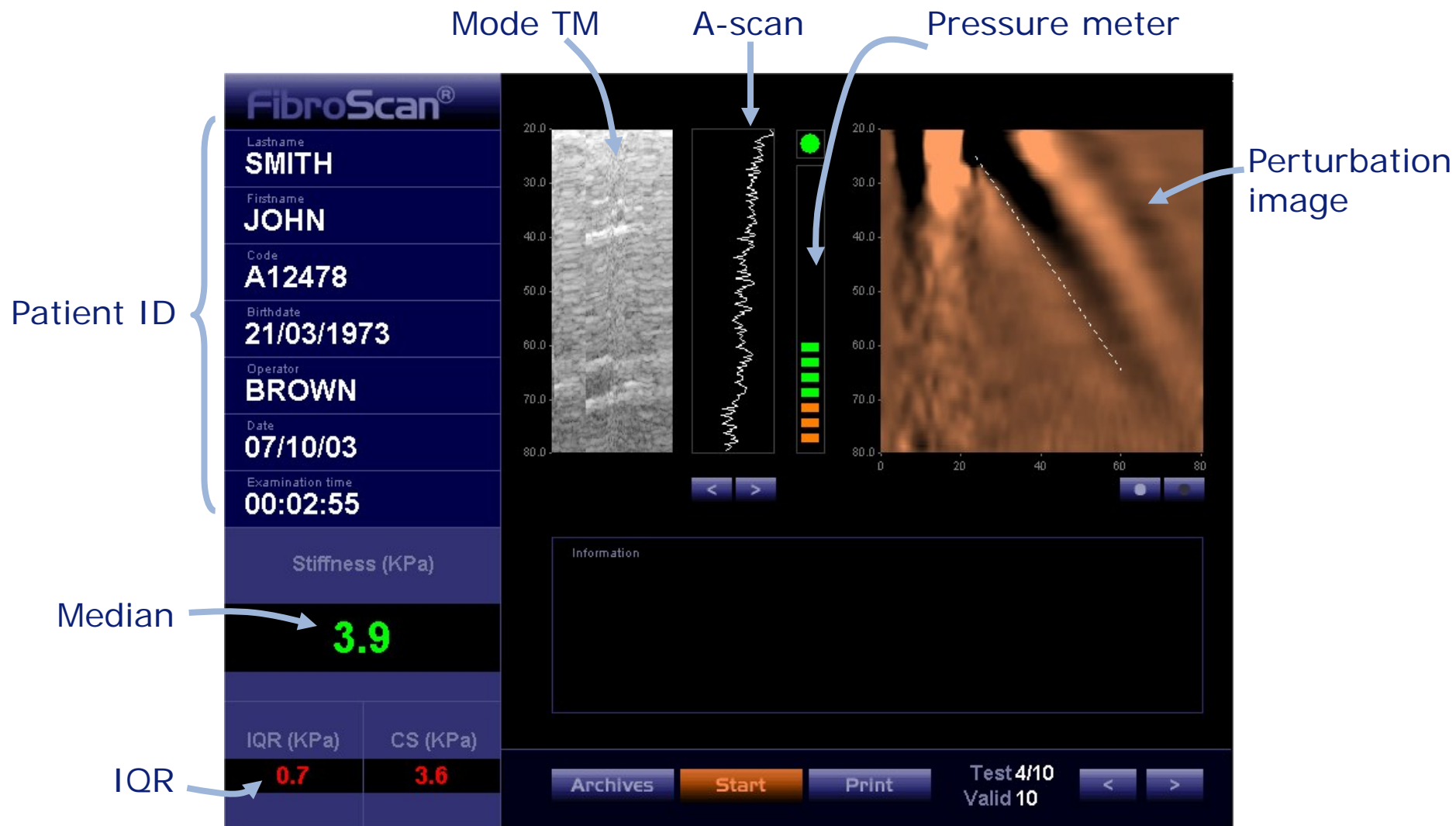


Fibroscan

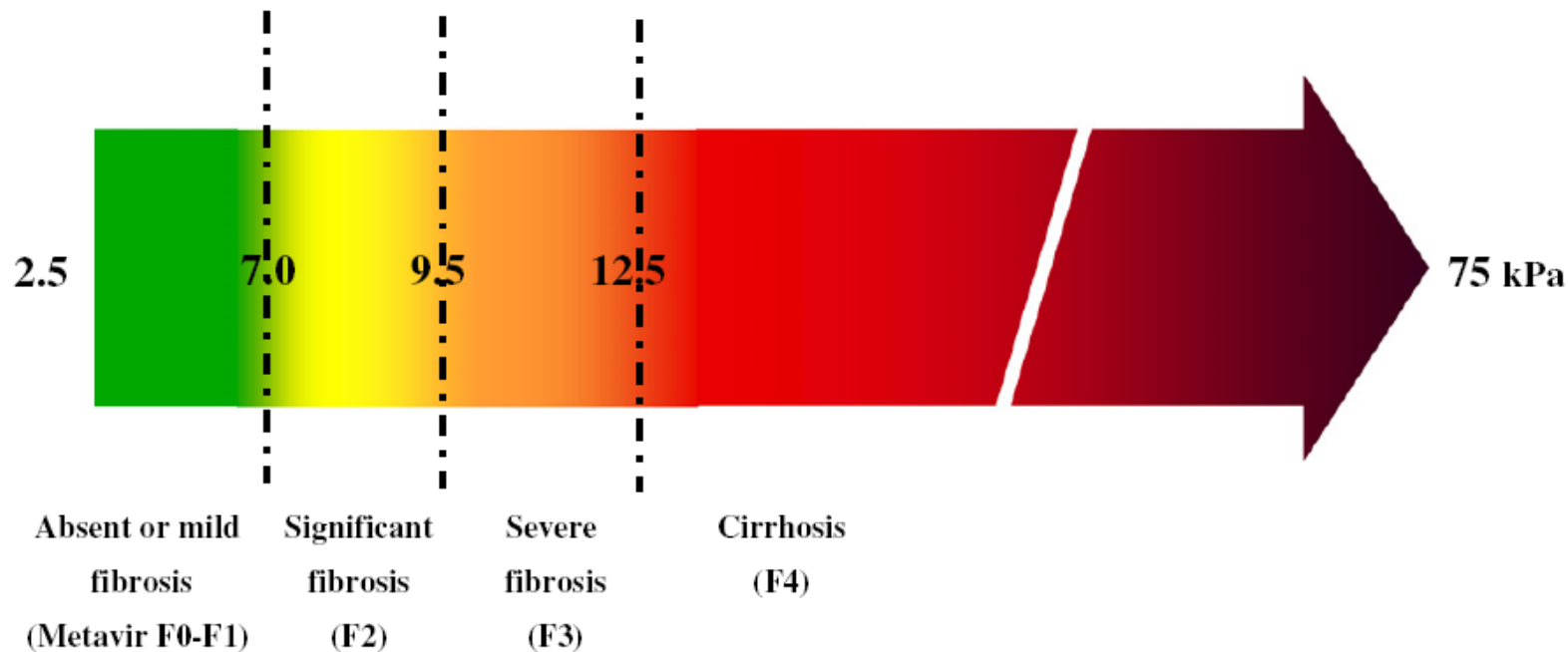
- Elasticity:
 - Pressure wave (kPa) - vibration
 - Velocity of transmission ~ liver stiffness
- Information about cylinder 1-4 cm
 - 100x bigger than median liver biopsy
 - More representative?
- Most studies performed in patients with Hep C



The software

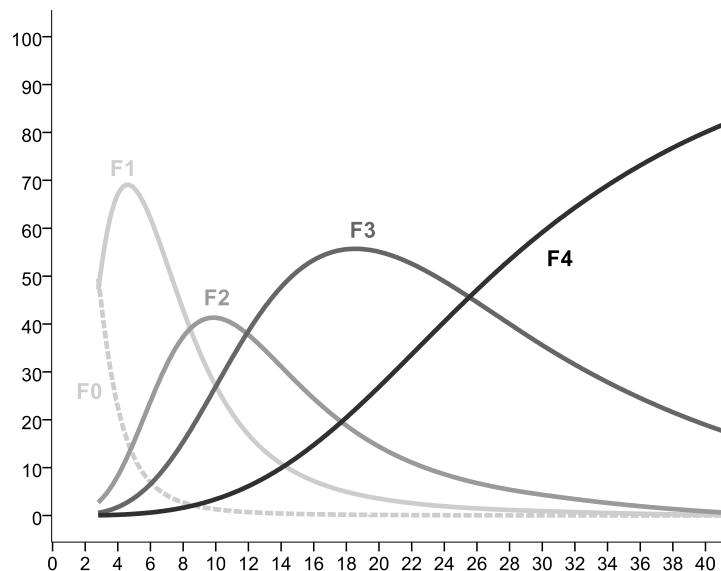


Ranges for stiffness with fibroscan

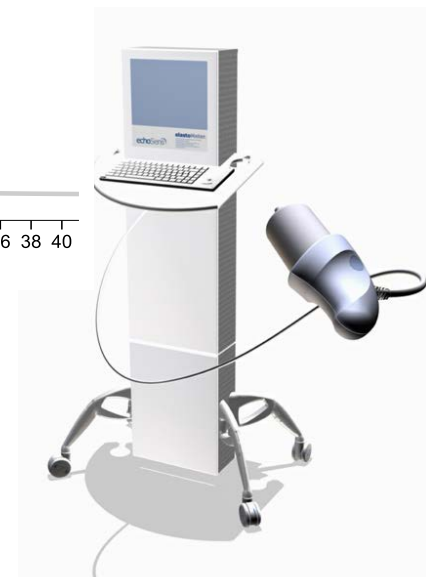
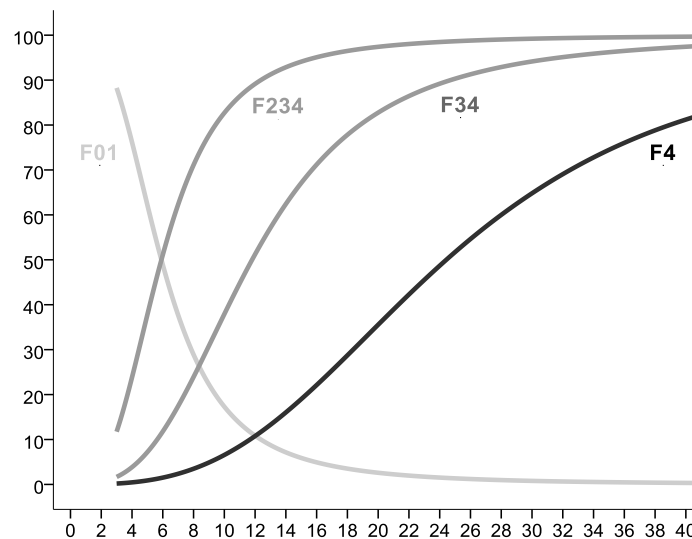


Prediction of liver cirrhosis by fibrosis score

CHB- prediction of fibrosis score by kPa



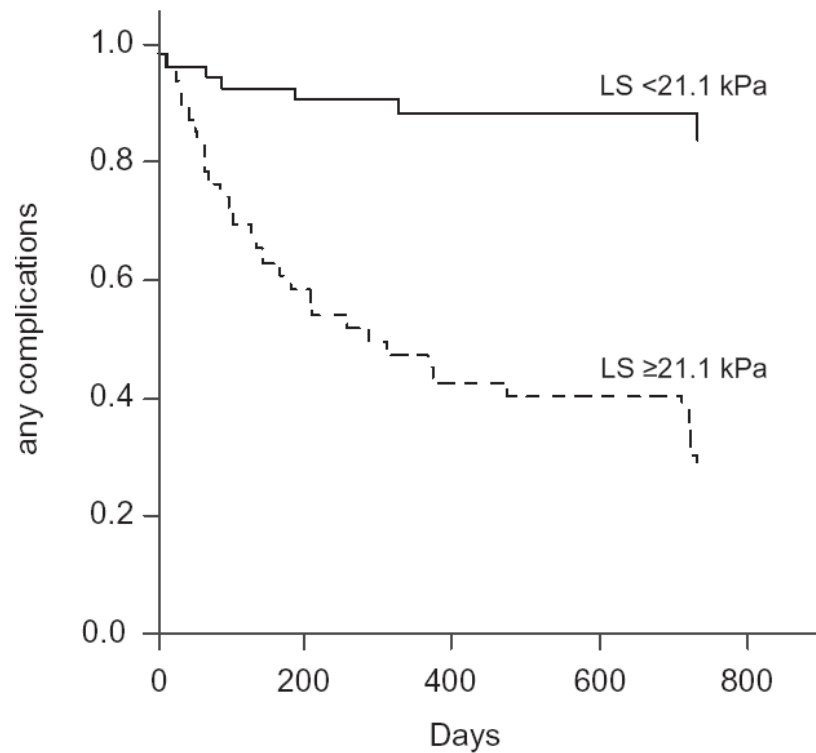
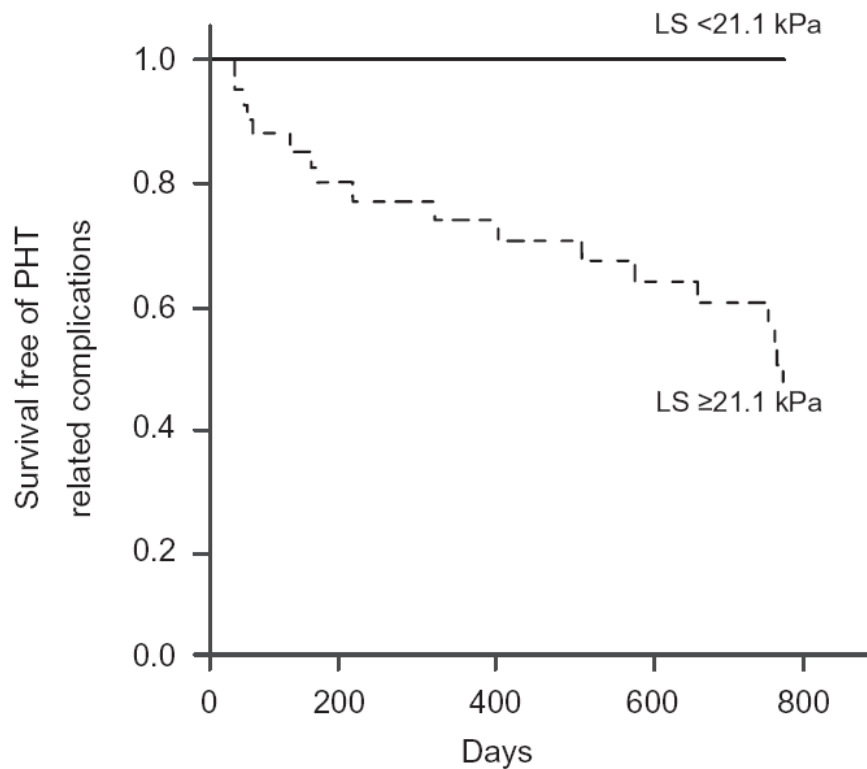
CHC- prediction of fibrosis score by kPa



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

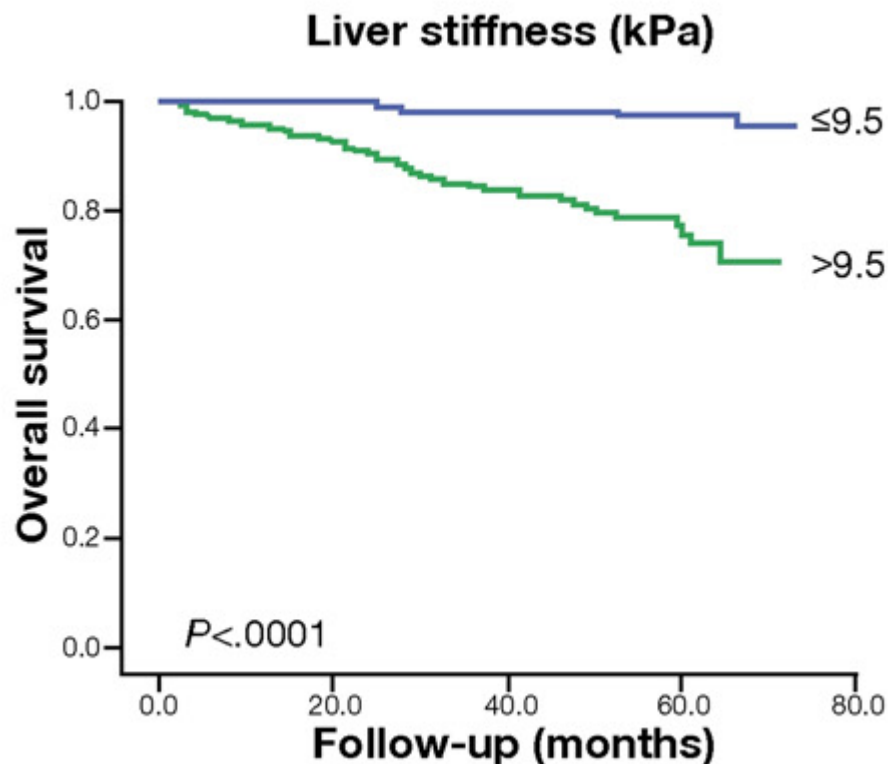
Marie Angèle Robic^{1,†}, Bogdan Procopet^{1,2,†}, Sophie Métivier¹, Jean Marie Péron^{1,3}, Janick Selves^{3,4},
Jean Pierre Vinel^{1,3}, Christophe Bureau^{1,3,*}



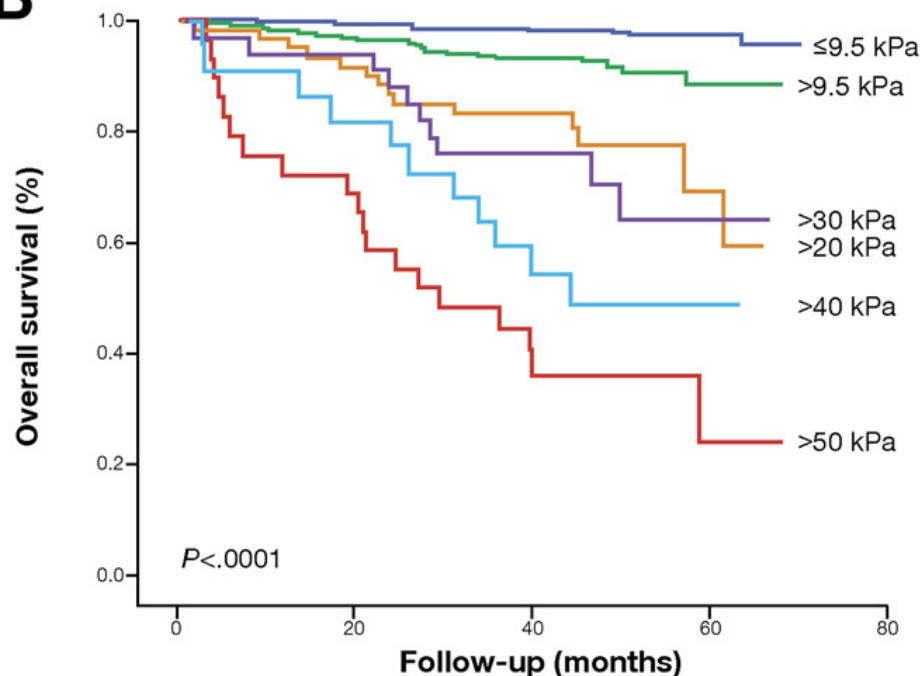
Noninvasive Tests for Fibrosis and Liver Stiffness Predict 5-Year Outcomes of Patients With Chronic Hepatitis C

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



B



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}

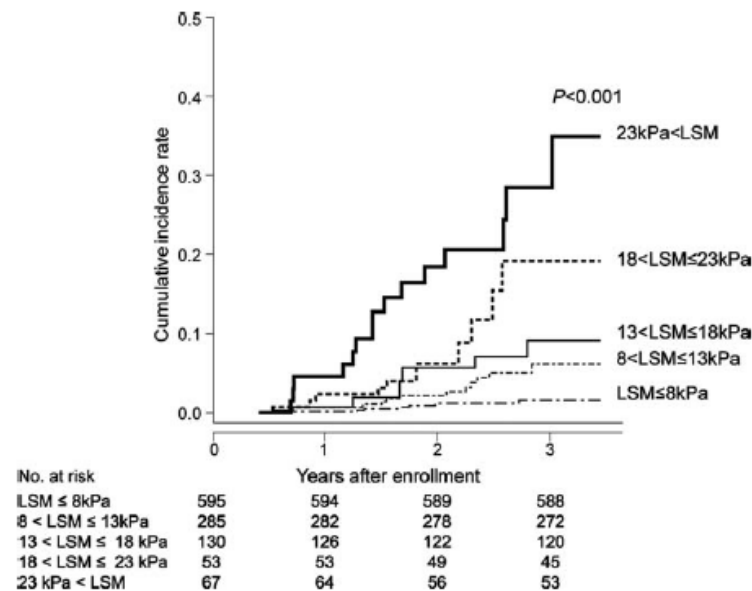
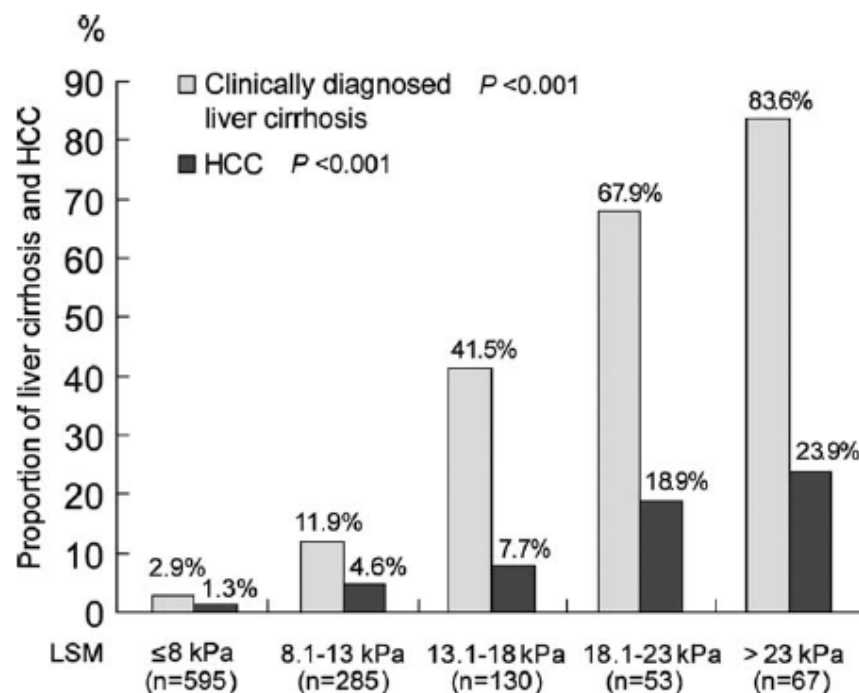
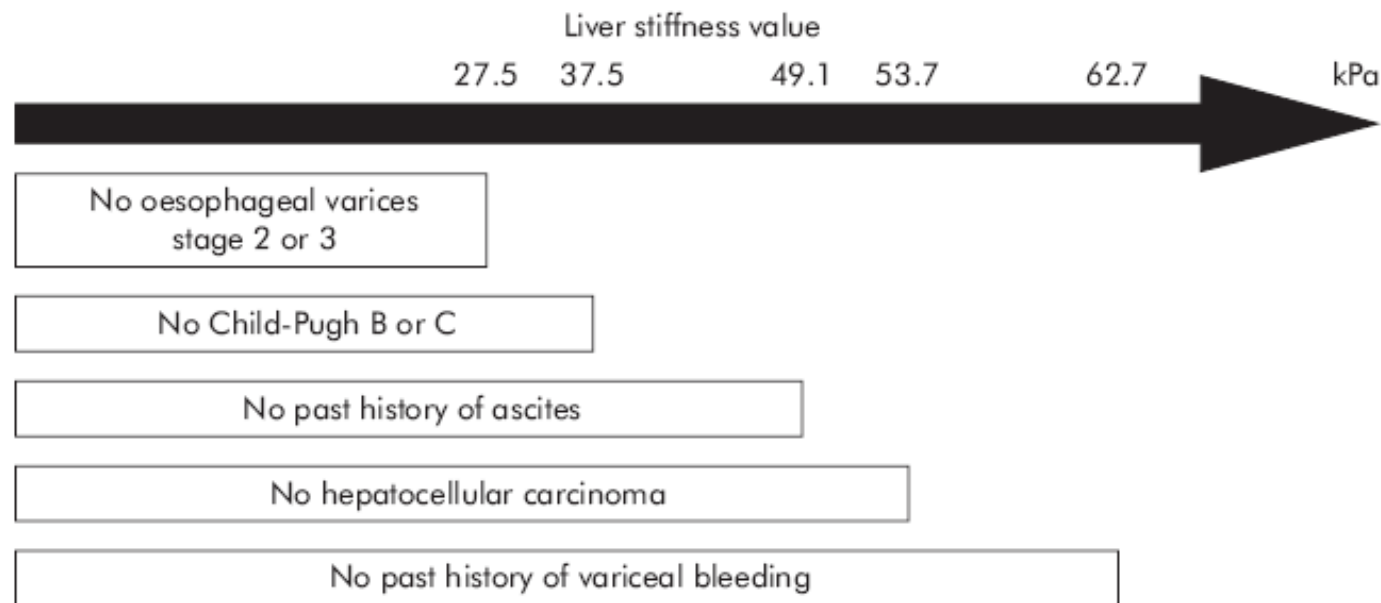


Fig. 3. Cumulative incidence rates of HCC based on stratified LSM (Kaplan-Meier plot). The cumulative incidence rates increased significantly in association with higher LSM (log-rank test, $P < 0.001$).

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

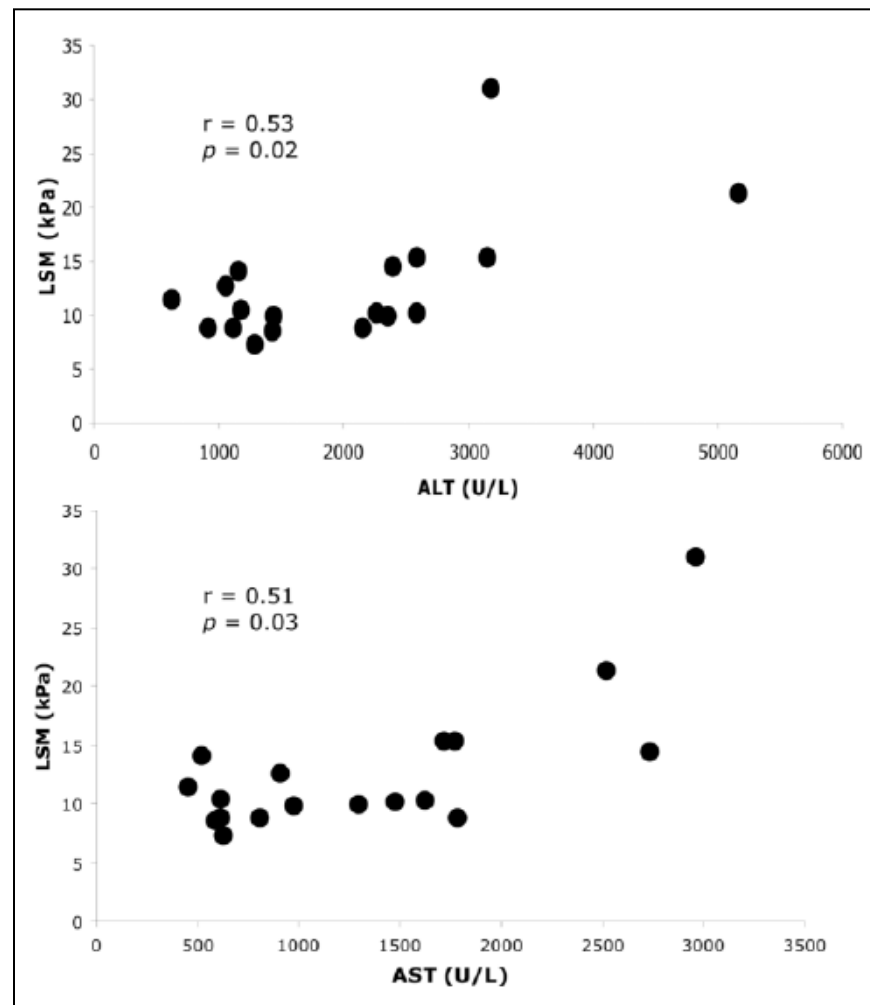
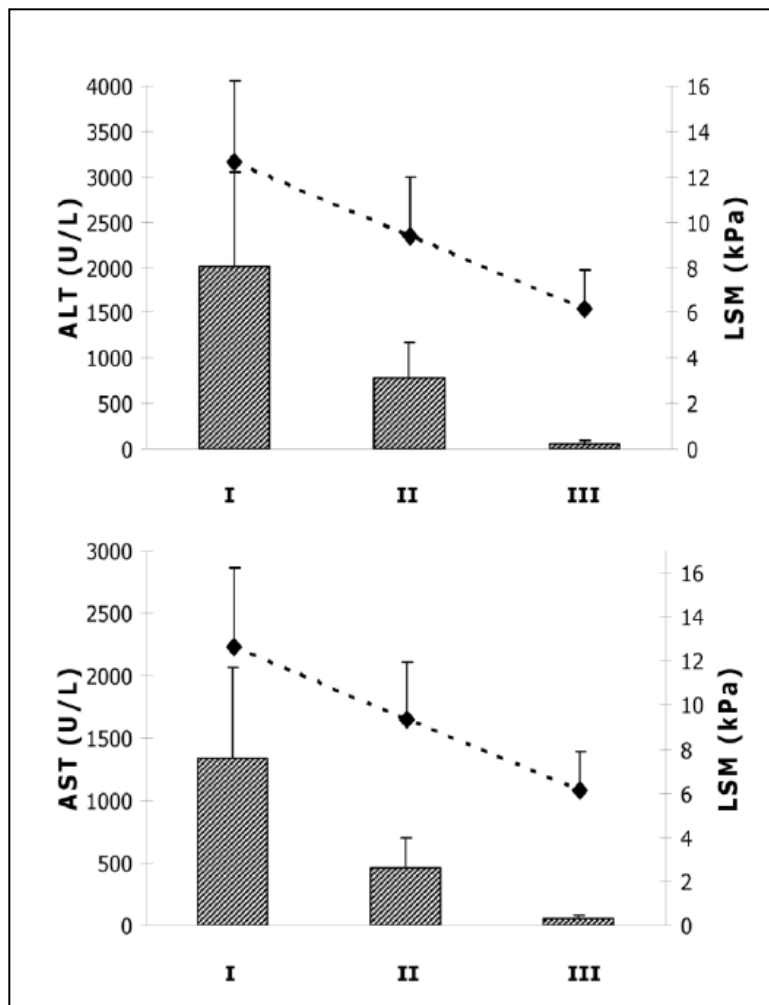
J Foucher, E Chanteloup, J Vergniol, L Castéra, B Le Bail, X Adhoute, J Bertet, P Couzigou, V de Lédinghen

Gut 2006;**55**:403–408.

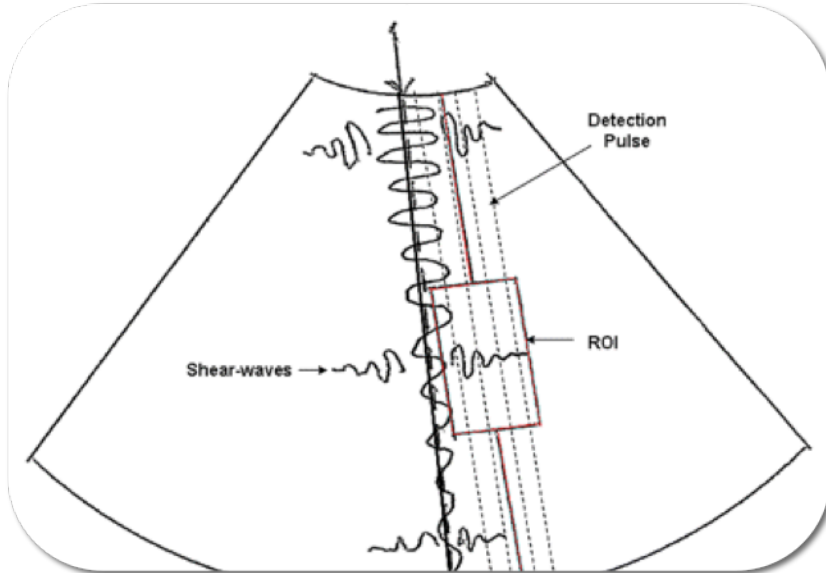


Influence of hepatitis on liver stiffness

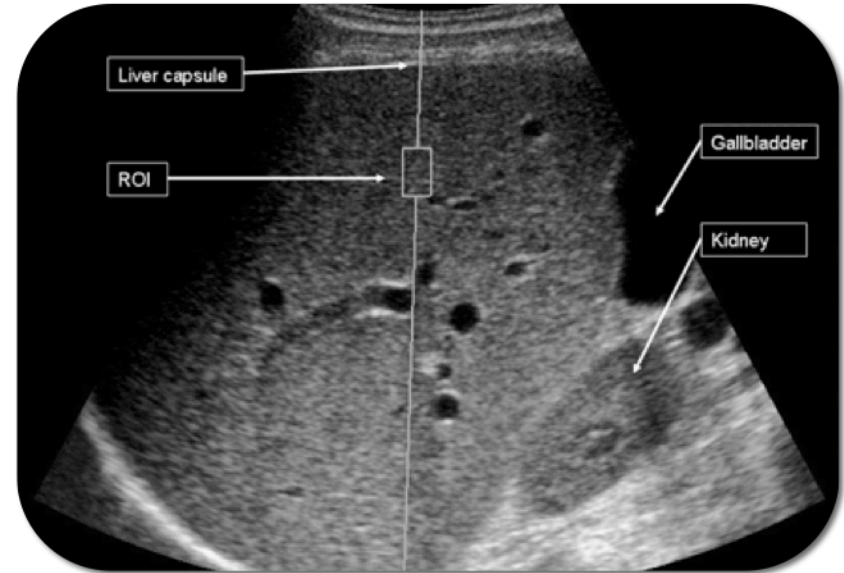
- not all that's stiff is a fibrosis



ARFI (Siemens)



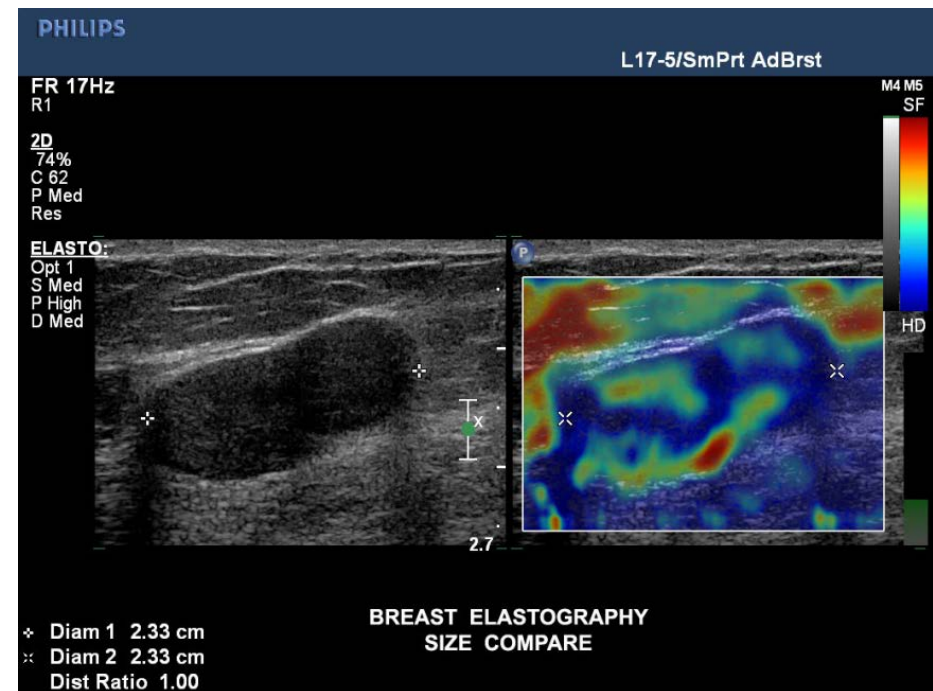
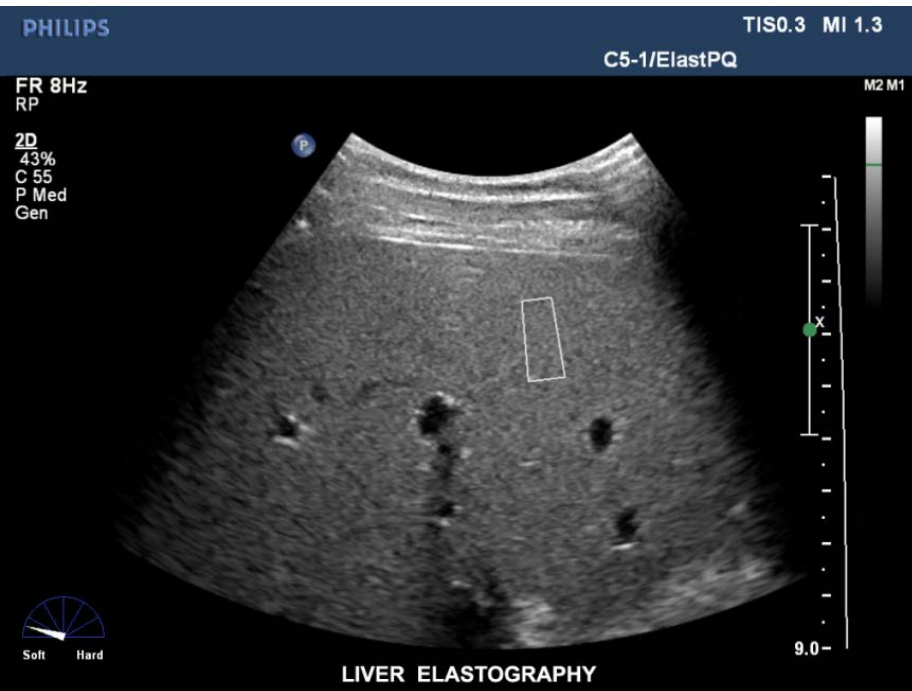
Acoustic radiation force
impulse imaging
elastography



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

ElastPQ® Shear Wave Elastography (Philips)

Philips iU22



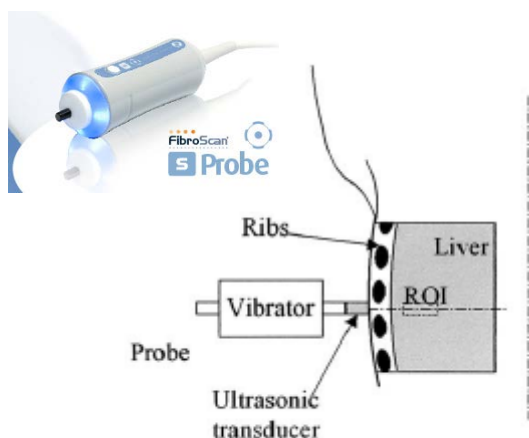
Ling: European Journal Radiology 2013

Ferraioli: EASL 2013

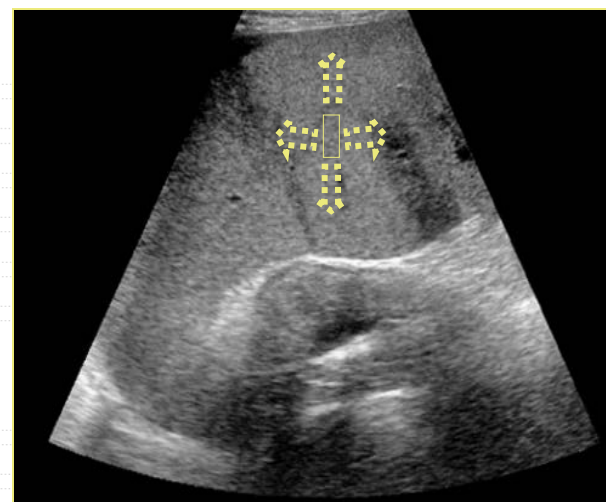
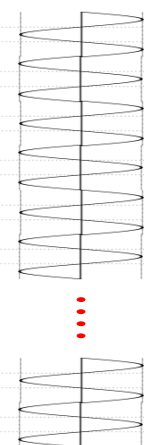
Ultrasound Elastography

Shearwave Point Quantification

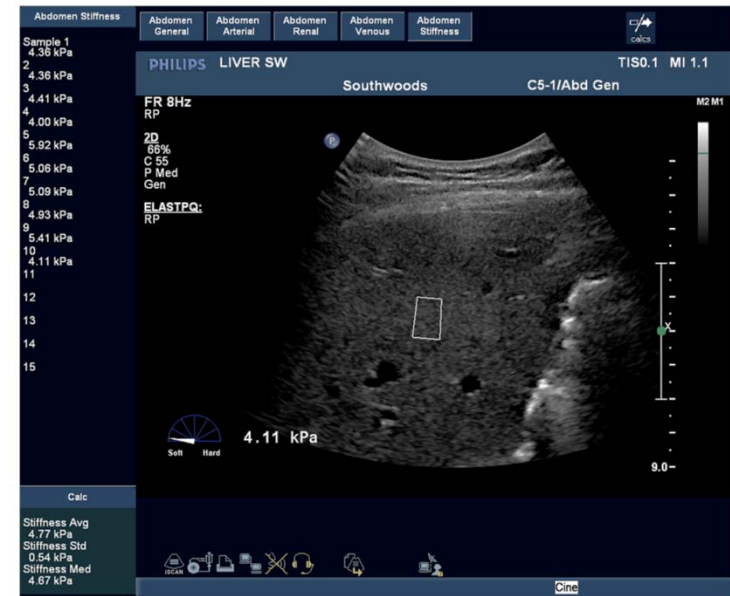
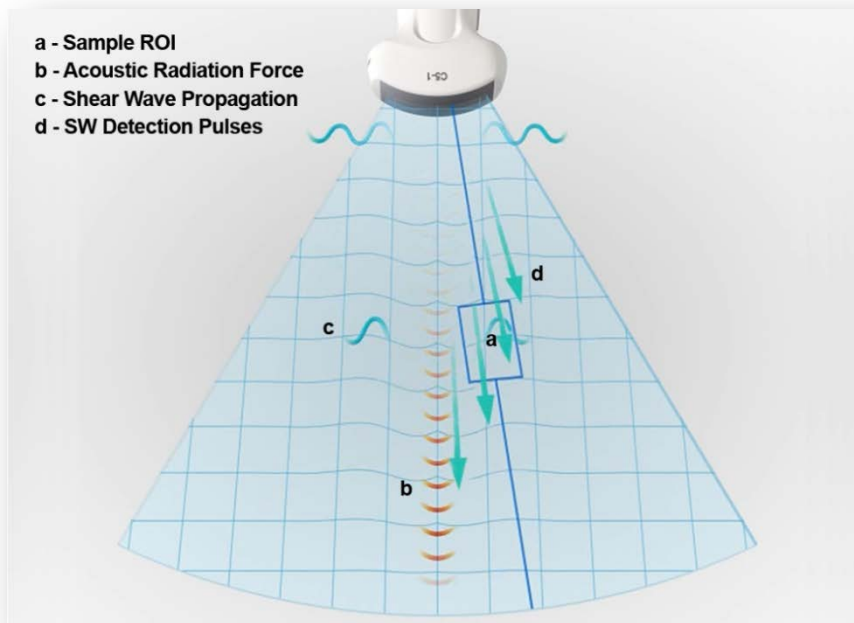
- Induces shear waves perpendicular to the ultrasound beam
- Velocity of the shear wave is proportional to stiffness
- PW-like sample volume quantification: Reporting a single number of shear wave velocity
- Clinical studies primarily targeting liver fibrosis assessment
- Force on tissues can again come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



Push
Pulse



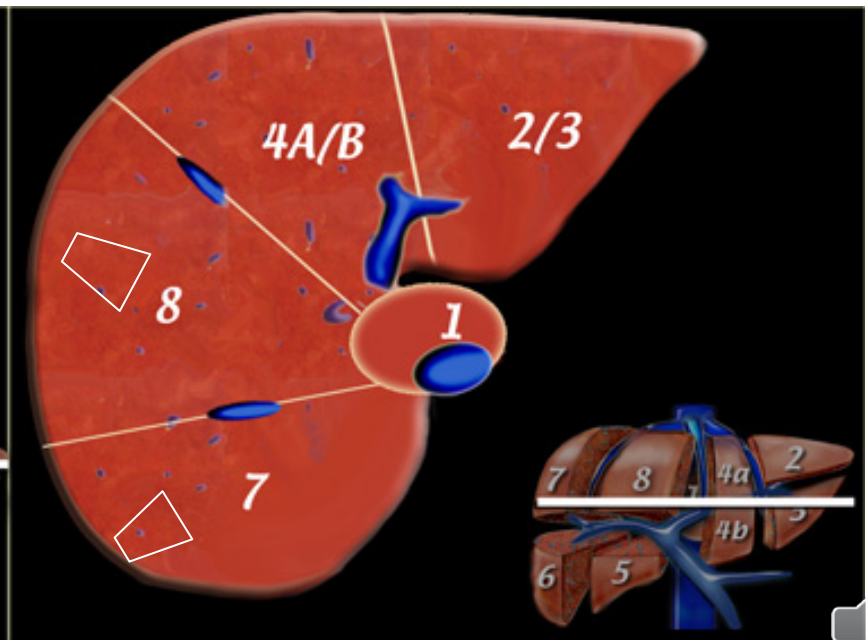
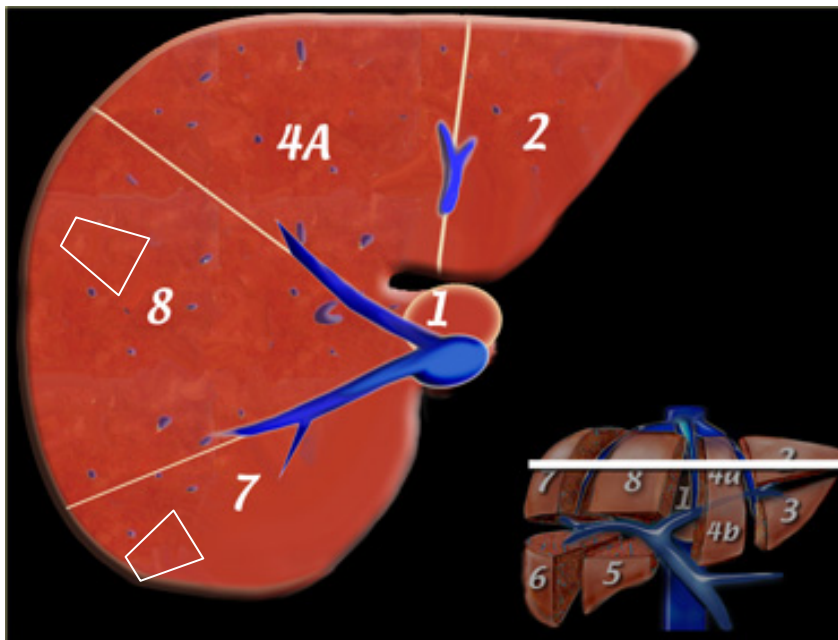
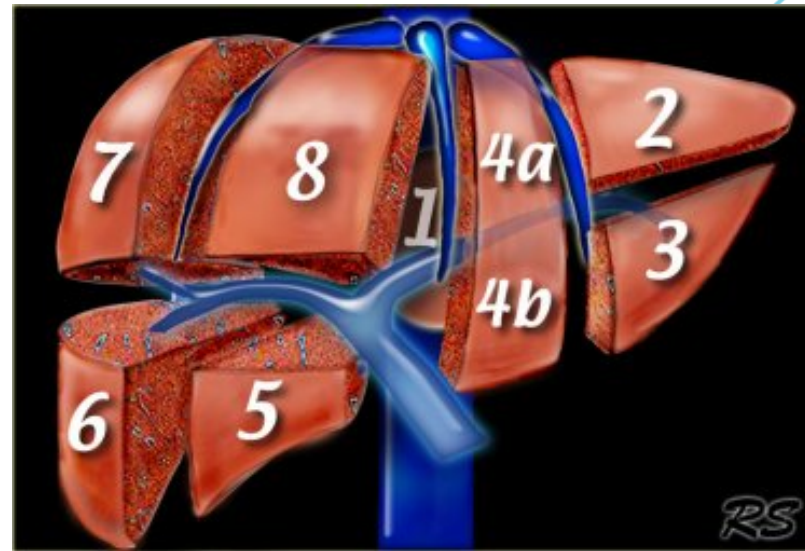
ARFI based shear wave elastography



- Absolute tissue stiffness measurement (m/s or kPa)
- Requires special pulsing sequence and beamformer voltage control
- Shear wave generation is depth limited
- Shear waves will attenuate quickly in stiff tissues
- Sensitive to tissue motion

Recommended ElastPQ liver sampling sites

- Segments 7 & 8
- Intercostal approach
- Avoid biliary, portal venous and hepatic venous structures



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+



Online Submissions: <http://www.wjgnet.com/esps/>
 bpjoffice@wjgnet.com
 doi:10.3748/wjg.v20.i16.4787

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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 Lissandrin, Mabel Zicchetti, Barbara Dal Bello, Gaetano Filice,
 Carlo Filice

Calc List

Abdominal > Abdomen General

Applications

Abdominal

Abdomen General

Abdomen Arterial

Abdomen Renal

Abdomen Venous

Abdomen Stiffness

Measurements

Bladder Dimensions

Bladder L

Bladder H

Bladder W

IV Bladder L

PV Bladder H

IV Bladder W

Organ Dimensions

Liver Length

GB Wall Diam

CBD Diam

Ao Prox Diam

Ao Mid Diam

Ao Dist Diam

Calculations

Bladder Vol

IV Bladder Vol

Spleen Vol

Live

Abd Gen

C5-1

22Hz

RP

2D

69%

Dyn R 55

P Med

Gen

Elasto

Opt 1

RP

71Hz

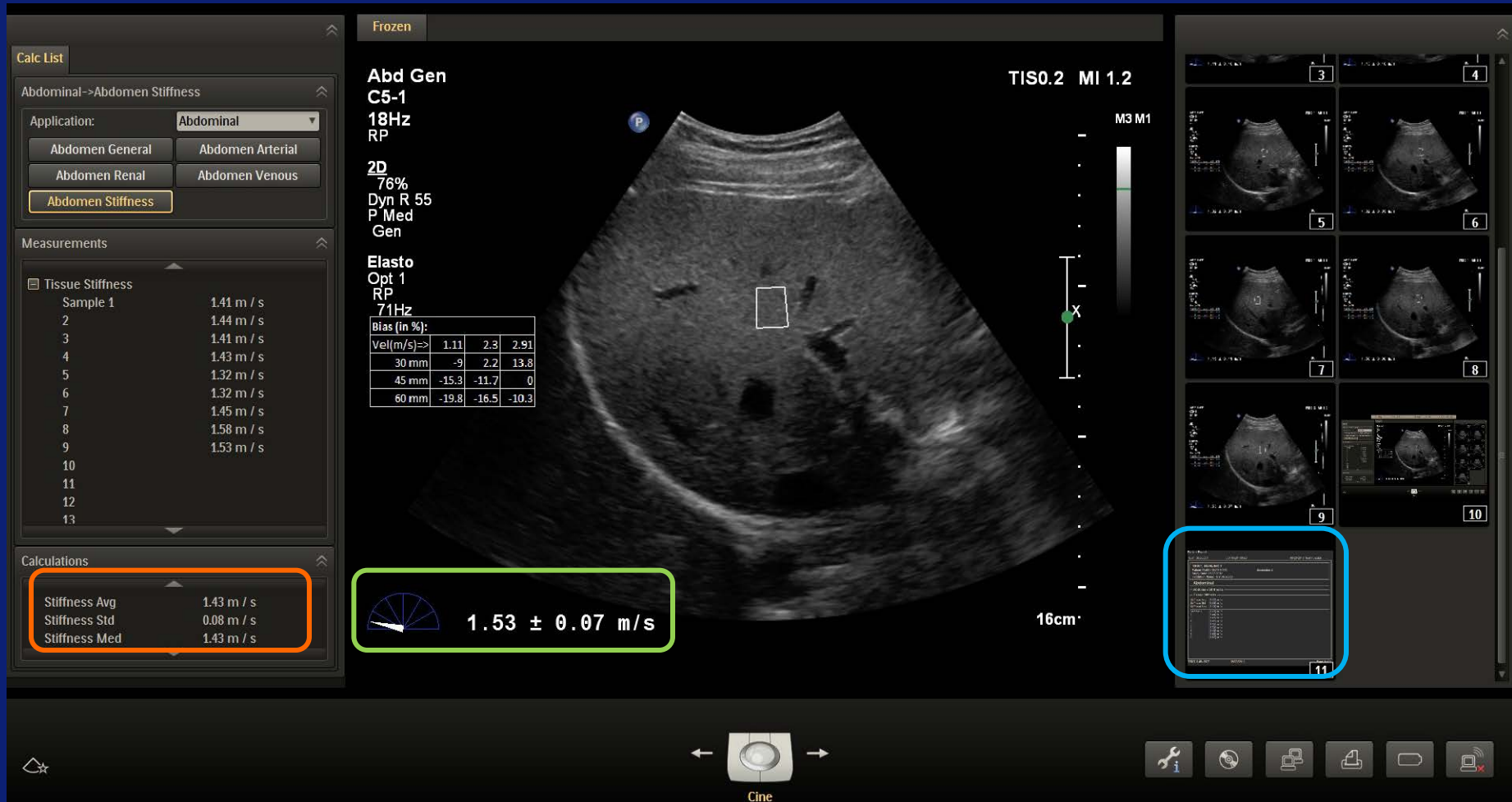
TIS0.2 MI 1.2

M3 M1



Move Elastography ROI 2D Position



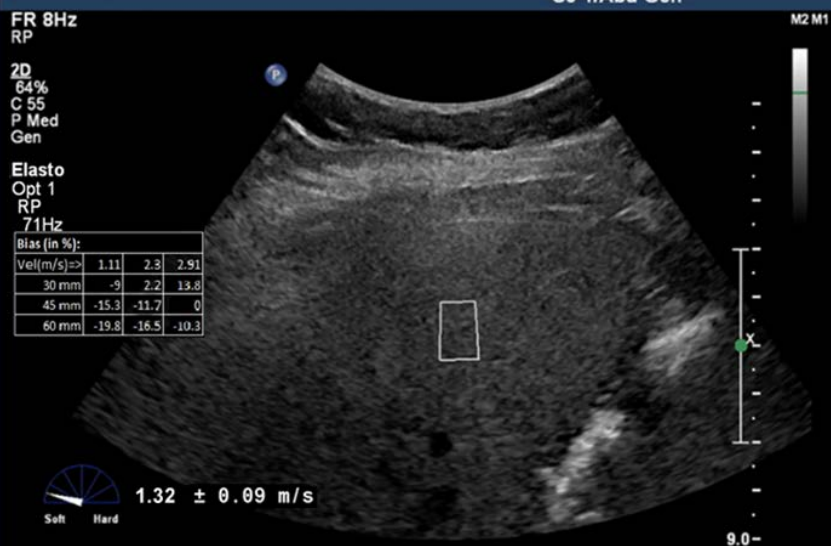


Real time Stiffness Statistics

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

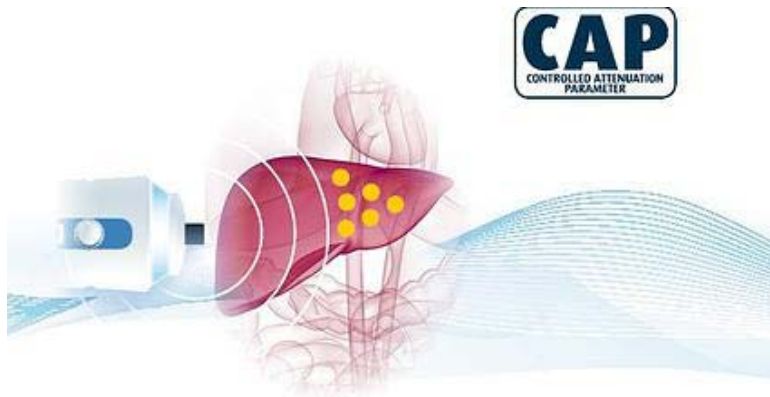


Take into account:

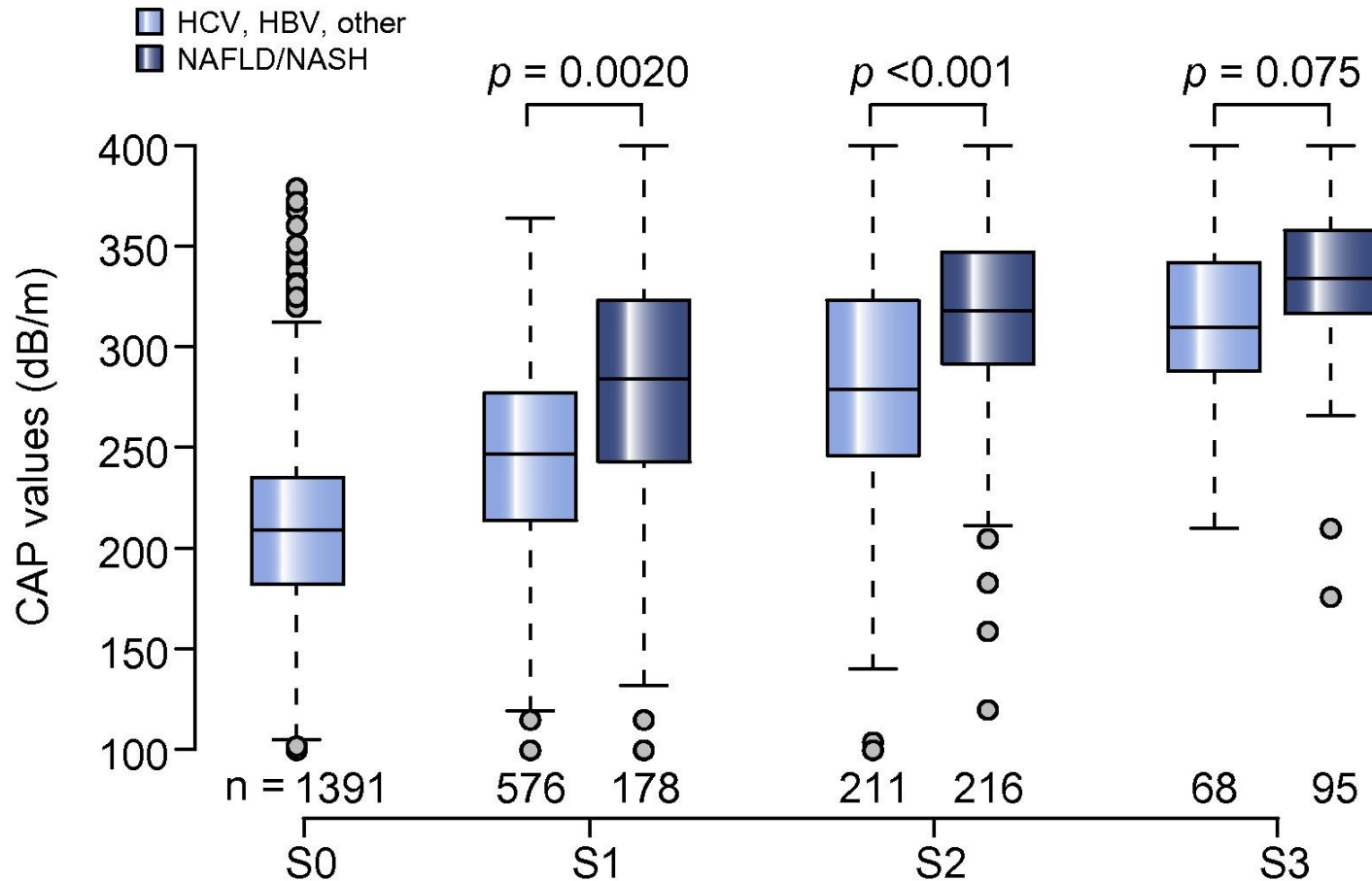
- At this time the technique and interpretation of elastography images varies with each manufacturer
- The use of Elastography is improving and more validations are needed
- It may play a significant role in breast, liver and will expand in the future
- Elastography in other organs is just beginning

- 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 Knegt¹¹, 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.



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 + galwegen + vasculatuur + vet
- Voor bepaling ernst en prognose van leverziekte; voor het vervolgen van therapie

Dank voor de aandacht !

