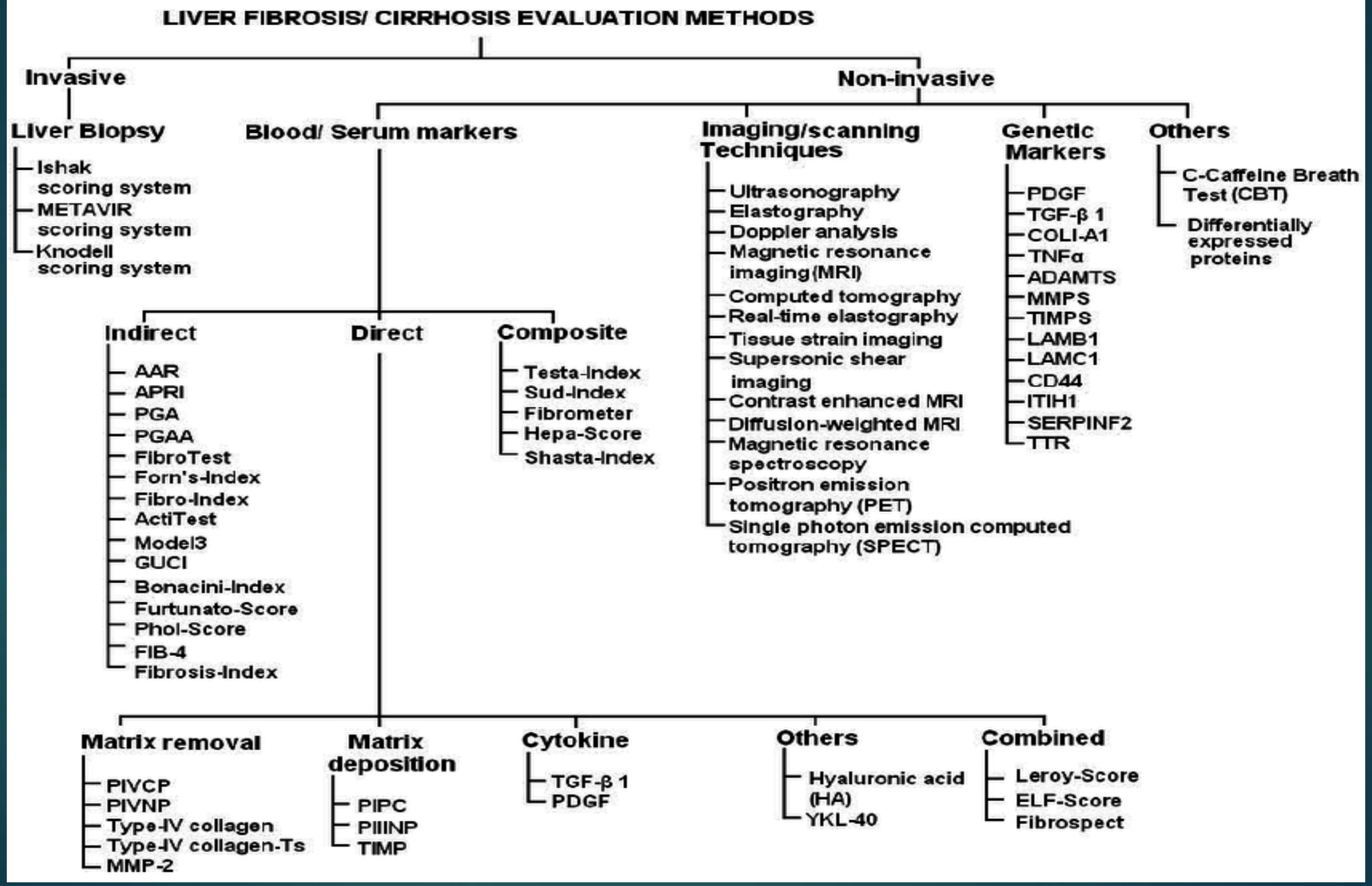
Hepatic fibrosis noninvasive diagnostic methods

BY:FATEMEH SAFI _MD


LIVER FIBROSIS/ CIRRHOSIS EVALUATION METHODS
Invasive
Non-invasive
Liver Biopsy
Ishak scoring system
METAVIR scoring system
Knodell scoring system
Blood/ Serum markers
Indirect
AAR
APRI
PGA
PGAA
FibroTest
Forn's-Index
Fibro-Index
ActiTest
Model3
GUCI
Bonacini-Index
Furtunato-Score
Phol-Score
FIB-4
Fibrosis-Index
Direct
Composite
Testa-Index
Sud-Index
Fibrometer
Hepa-Score
Shasta-Index
Matrix removal
PIVCP
PIVNP
Type-IV collagen
Type-IV collagen-Ts
MMP-2
Matrix deposition
PIPC
PIIINP
TIMP
Cytokine
TGF-β 1
PDGF
Others
Hyaluronic acid (HA)
YKL-40
Combined
Leroy-Score
ELF-Score
Fibrospect
Imaging/scanning Techniques
Ultrasonography
Elastography
Doppler analysis
Magnetic resonance imaging (MRI)
Computed tomography
Real-time elastography
Tissue strain imaging
Supersonic shear imaging
Contrast enhanced MRI
Diffusion-weighted MRI
Magnetic resonance spectroscopy
Positron emission tomography (PET)
Single photon emission computed tomography (SPECT)
Genetic Markers
PDGF
TGF-β 1
COLI-A1
TNFα
ADAMTS
MMPS
TIMPS
LAMB1
LAMC1
CD44
ITIH1
SERPINF2
TTR
Others
C-Caffeine Breath Test (CBT)
Differentially expressed proteins

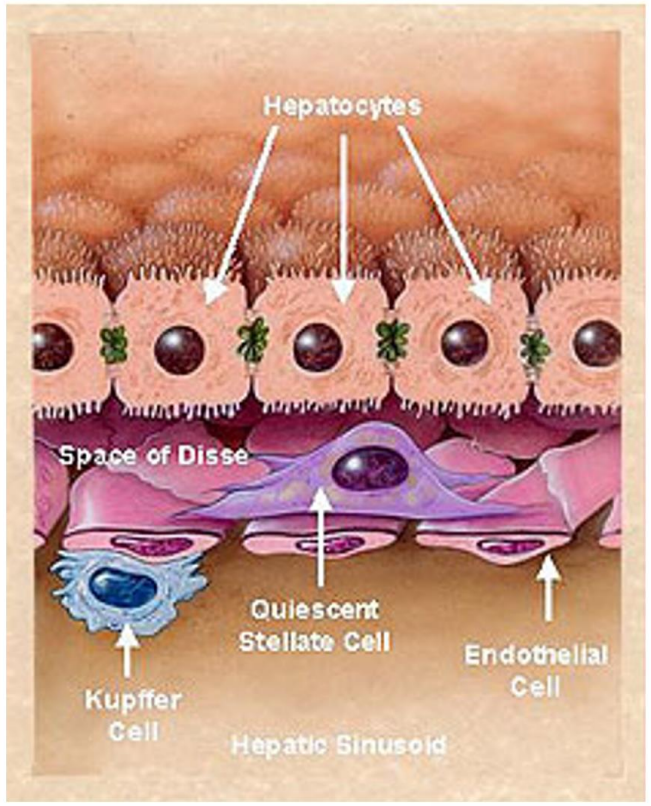
Causes of liver fibrosis

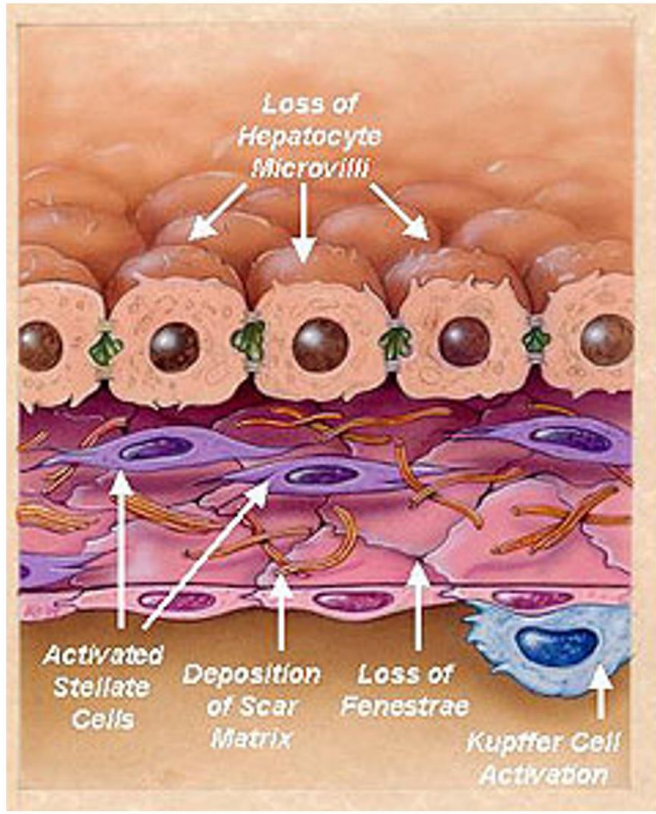
- Fibrosis corresponds to the formation of scar tissue in the liver. Generally speaking, inflammation is the precursor to fibrosis. Scaring occurs as the liver tries to repair damaged tissue.

- Causes of chronic liver disease:
  - Viral hepatitis (HBV, HCV)
  - Alcoholic and non alcoholic fatty liver diseases
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Autoimmune hepatitis
  - Excessive intake of vitamins (A)
  - Hemochromatosis
  - Budd-Chiari syndrome
  - Congestive heart failure
  - Etc.…

Fibrosis development

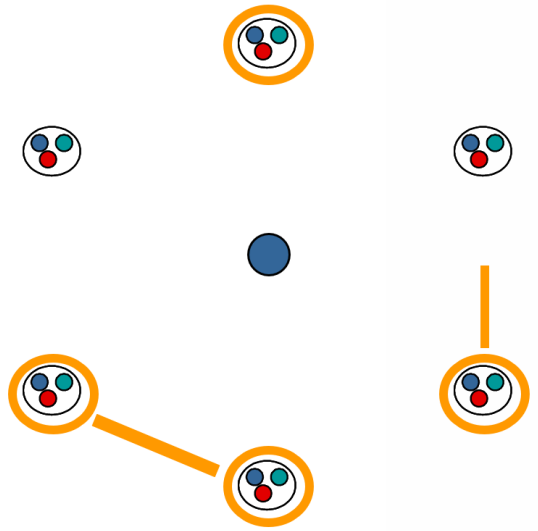
- Fibrosis is an accumulation of fibrous tissue.
- As liver cells structures change, the function of the liver is altered.





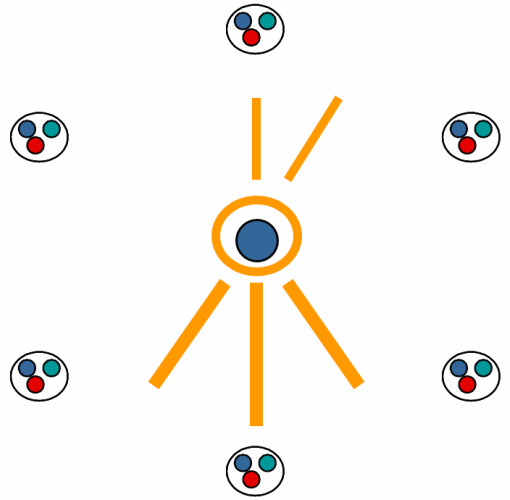
Fibrosis types

- **Portal fibrosis**



- Viral hepatitis (HBV, HCV)
- METAVIR scoring system

- **Sinusoidal fibrosis**



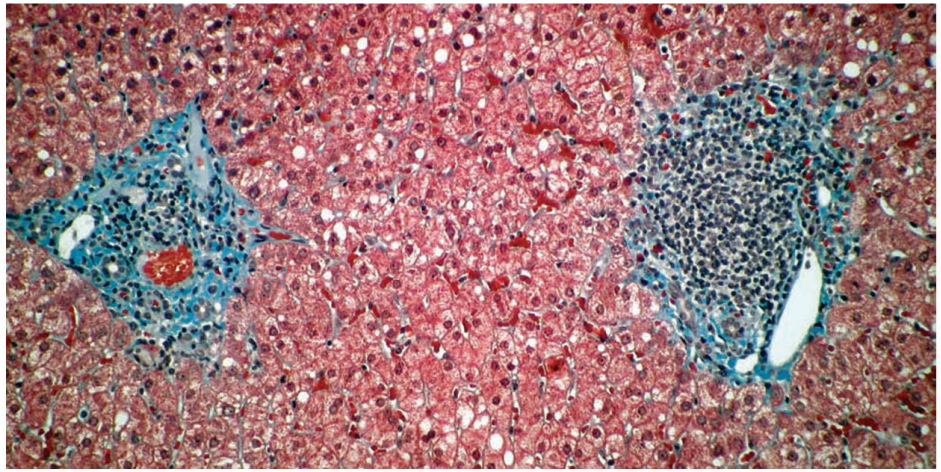
- Alcohol, NASH…
- Brunt scoring system

Fibrosis scoring system

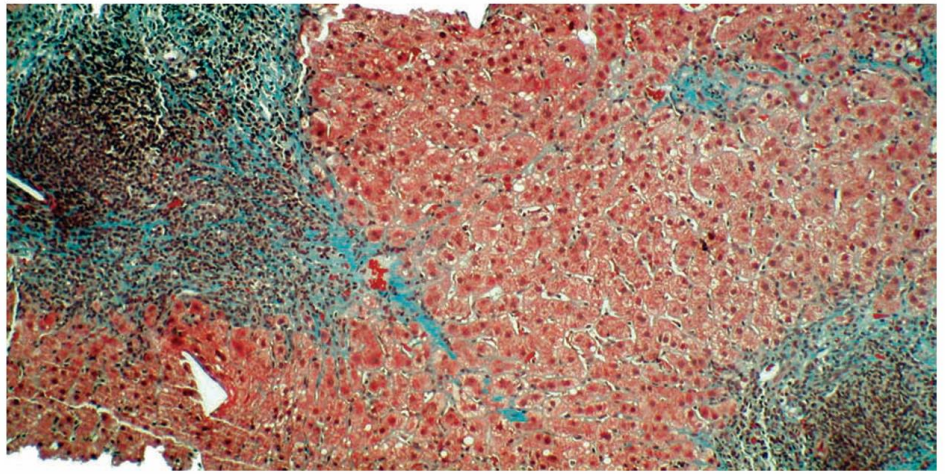
- There are several fibrosis scoring system depending on fibrosis type thus etiology
  - ➔ **Chronic hepatitis C and B:**
    METAVIR, Ishak or Knodell scores
  - ➔ **Alcoholic and non alcoholic steato hepatitis:**
    Brunt score
  - ➔ **Biliary diseases:**
    Ludwig score
  - ➔ **All types:**
    Le Chevalier score

Fibrosis Metavir stage

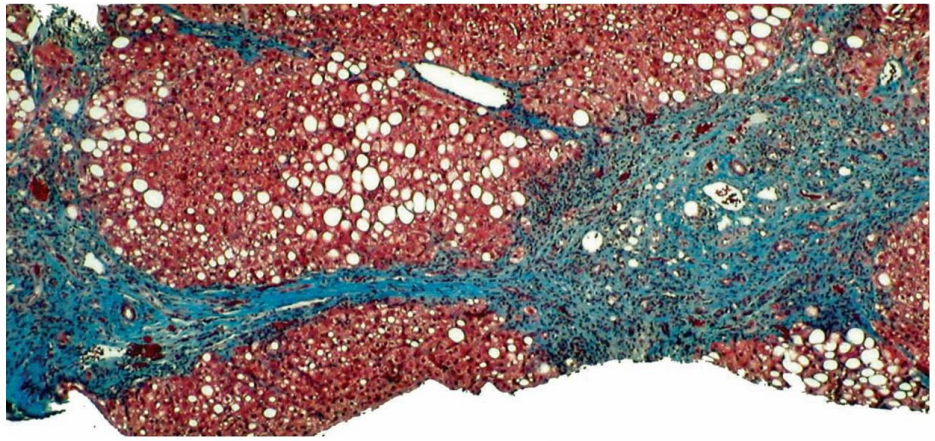
F1



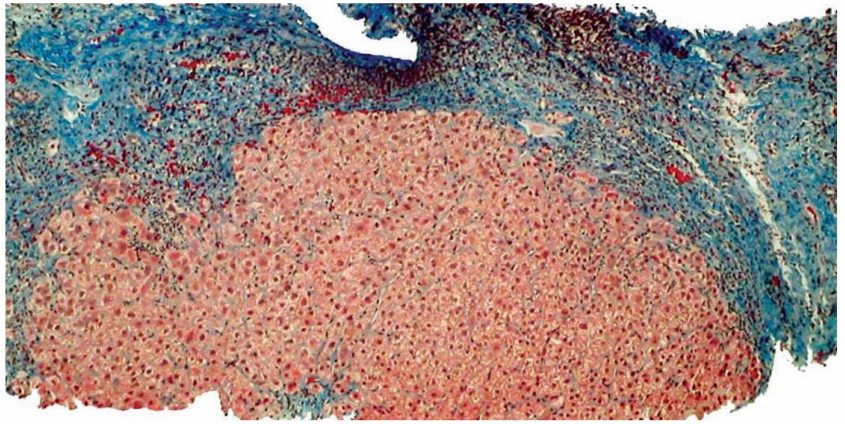
F2



F3

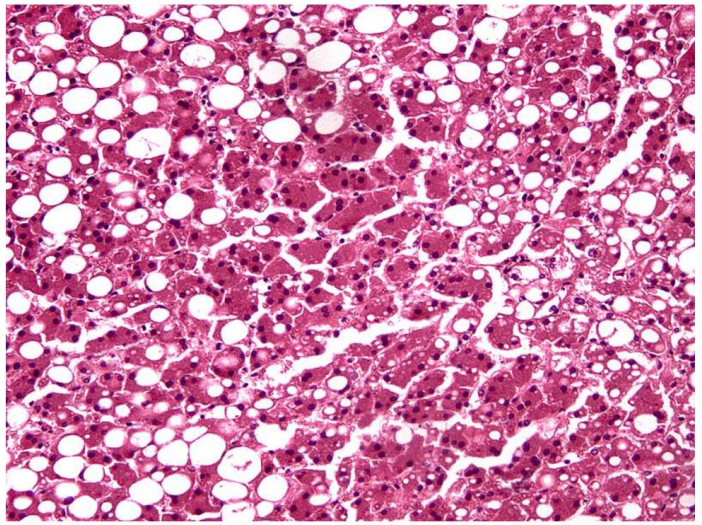


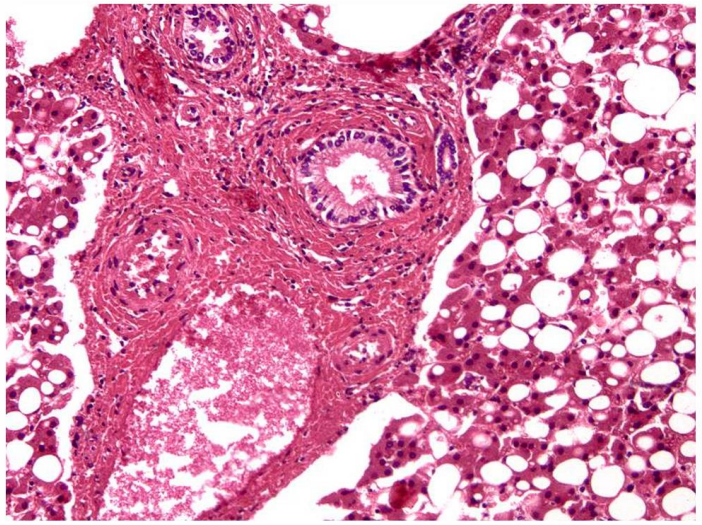
F4



Steatosis

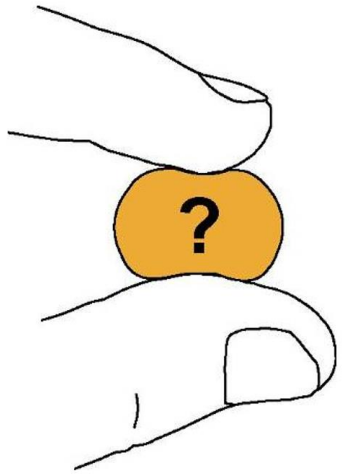
- Deposition of fatty vacuole within hepatocytes
- Usually scored using percentages of hepatocytes with fatty vacuoles
  - → 0: 0%
  - → 1: 1-10%
  - → 2: 11-30%
  - → 3: 31-60%
  - → 4: 61-100%

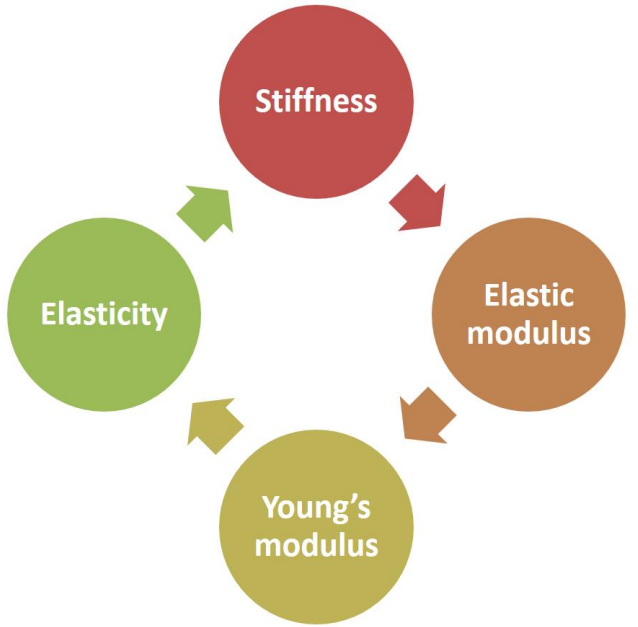




What is stiffness ?

- Quantifies the ability of a medium not to get out of shape when under **mechanical stress**
- **Stiffness** and **Elastic modulus** and **Young's modulus** are expressed in Pascal (Pa)

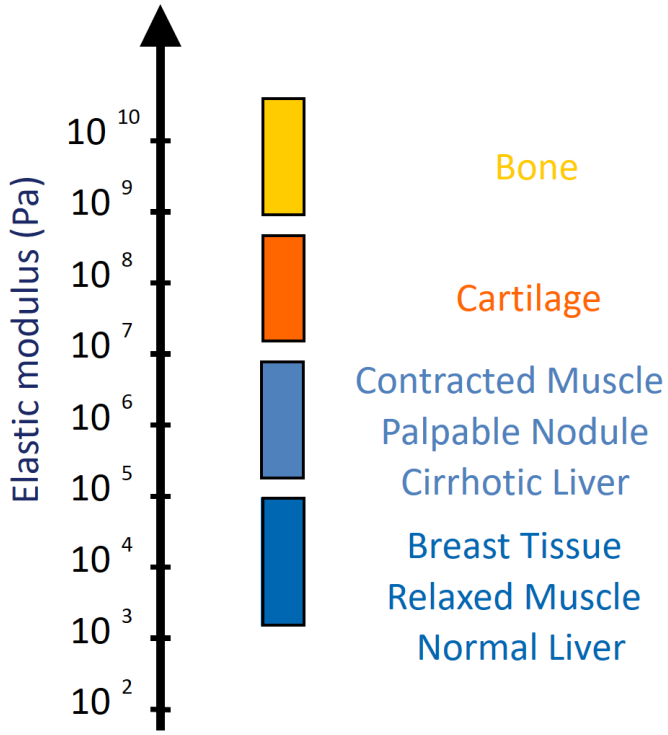




Identical terms !

Why measure stiffness ?

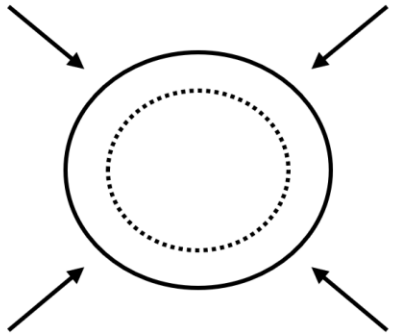
- Stiffness is a **key parameter** depending on the pathological state of soft tissues
- For centuries, physicians have used liver palpation



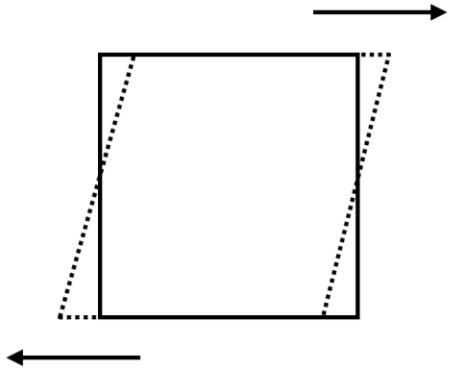
Examples of elastic modulus

2 types of stiffness

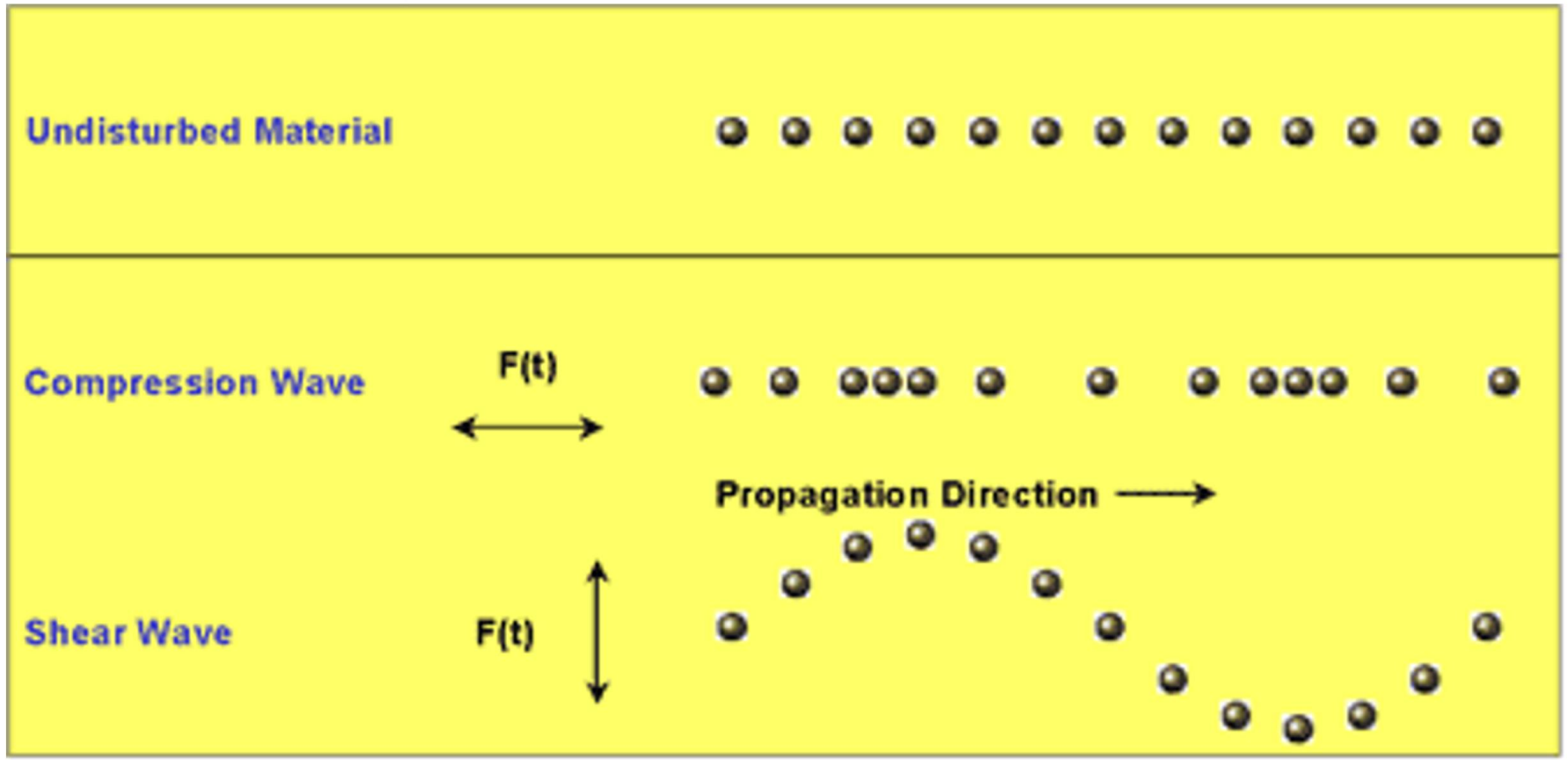
- Elastic compression modulus
  - Ability to resist to streching with change of volume



- Elastic shear modulus
  - Ability to resist to streching without change of volume



2 types of stiffness (2)



Ultrasonic waves

Definition:

- Ultrasonic waves refer to sound waves whose frequency is above 20 kHz and not audible by human ear
- Ultrasonic frequency commonly used is from 0.5 to 100 MHz

Characteristics of ultrasonic waves:

- Frequency: Operate on FibroScan® at 2.5, 3.5 or 5 Mhz according to the probe used.
- Velocity: around 1500 m/s in soft tissues
- Other properties:
  - Sensitive to compression properties (λ) of the medium but not to shear properties.
  - Freely propagates through liquids and soft tissues but not through bones and gases.
  - Reflect any density change interface.

Shear waves

Definition:

- Low frequency and amplitude waves
  - Can be observed in jelly cakes…

Characteristics of shear waves:

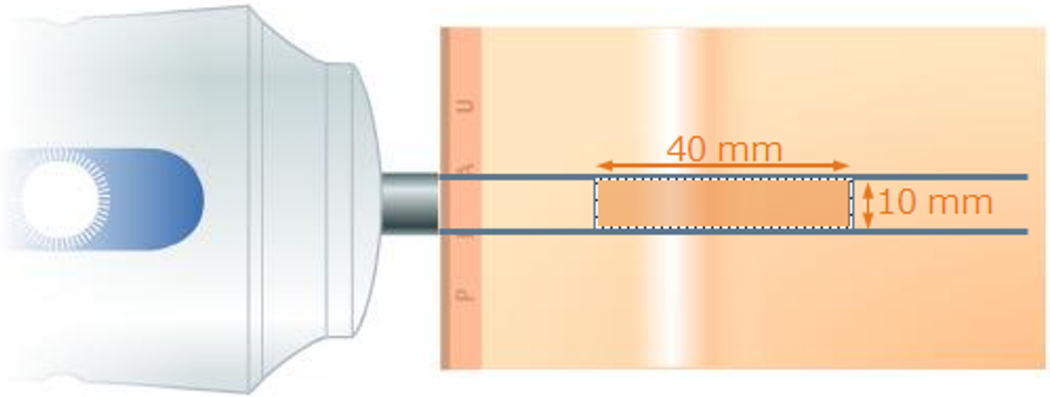
- Frequency: 50 Hz for FibroScan wih VCTE™ technology (Controlled frequency) for all probes.
- Velocity: propagate around 1 m/s in soft tissues
- Other properties:
  - sensitive to shear properties (μ) of the medium and not to the compression properties
  - freely propagates through soft tissues but no through liquids

Imaging techniques

- Quantitative techniques
  - Vibration controlled transient elastography (VCTE™)
  - Radiation force based elastography
  - Magnetic Resonance Elastography
- Qualitatives techniques
  - Real-Time Elastography

VCTE™(1)

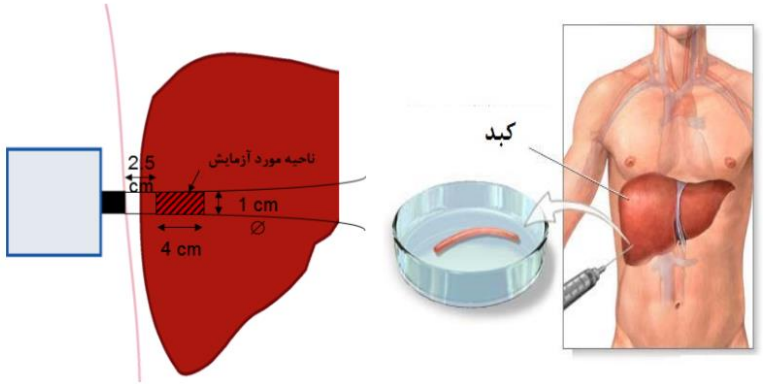
- FibroScan® is based on VCTE™ (**V**ibration **C**ontrolled **T**ransient **E**lastography)
  - Quantitative stiffness measurement in a 10 mm x 40 mm region of interest
  - The shear wave is generated by an external vibrator applying a mechanical pulse to the surface of the patient's skin.
  - Result expressed in kPa




350
5.6
Fibro

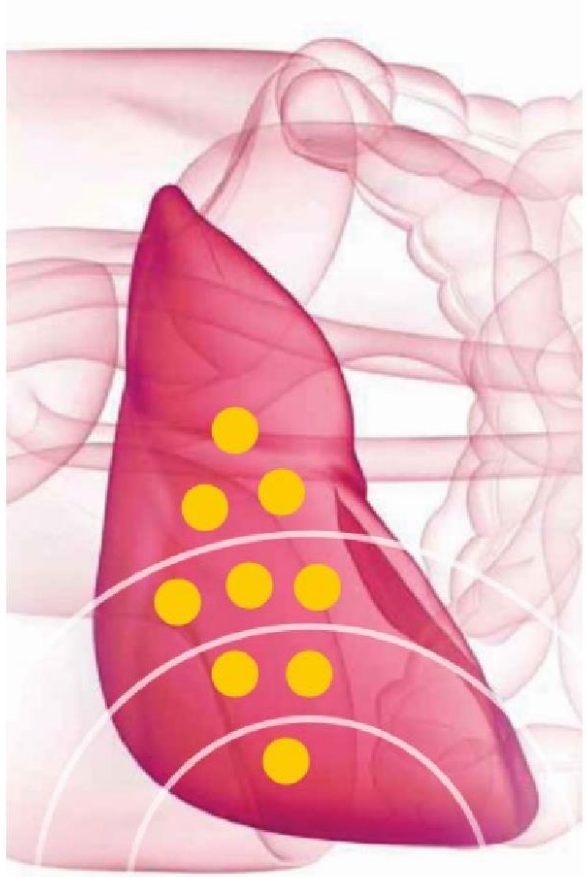
FibroScan

مقایسه فایبرواسکن با بیوپسی کبد



بیوپسی کبد	تست فایبرواسکن
تهاجمی بودن	غیر تهاجمی بودن
محدوده ی کوچک مورد بررسی	محدوده ی وسیع مورد بررسی (۲۵۰ برابر بزرگتر)
نیاز به بی حسی	عدم نیاز به بی حسی
نیاز به آمادگی قبلی	عدم نیاز به آمادگی قبلی
وجود ریسک بالا در تکرار بیوپسی	تکرار پذیری تست بدون ایجاد خطر
احتمال بستری شدن	عدم وجود احتمال بستری شدن
وجود درد و ناراحتی در حین و پس از انجام عمل	عدم وجود هر گونه درد و ناراحتی در حین و پس از انجام تست
استرس و ترس و دلهره قبل از عمل	آرامش و خونسردی قبل از انجام تست
زمانبر بودن انجام عمل و آماده شدن جواب آن	مدت زمان کوتاه انجام تست و آماده شدن جواب آن (۵ دقیقه)
هزینه بالا	هزینه پایین (تقریبا نصف هزینه ی انجام بیوپسی)
نیاز به وجود همراه بیمار	عدم نیاز به وجود همراه بیمار

FibroScan



N·I·S NikanTebSasan

فایبرواسکن touch

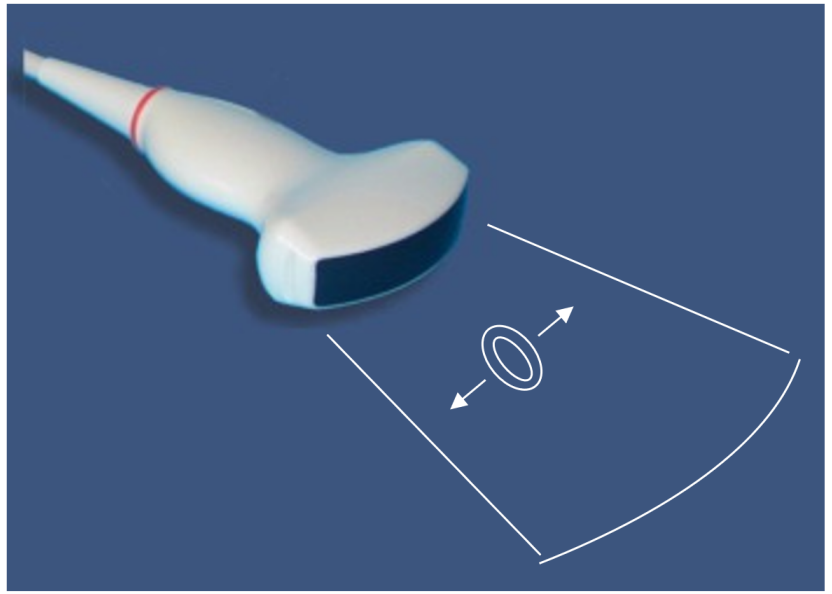
FibroScan 502

Radiation force elastography

- Quantitative stiffness assessment of deep tissues
- Shear waves are generated using radiation pressure by a high-power focused ultrasound beam

No control of the shear wave frequency !!

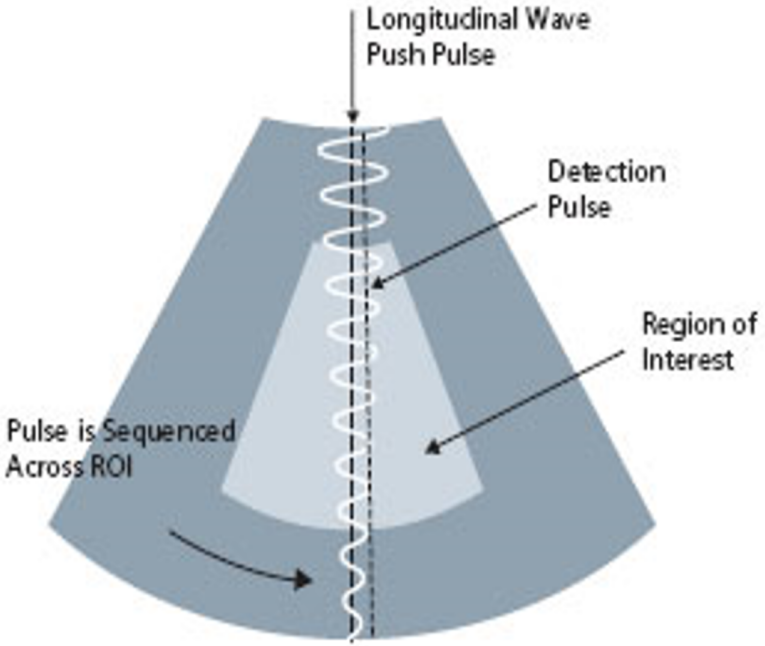
- High Power Ultrasound delivered



Radiation force elastography (1)

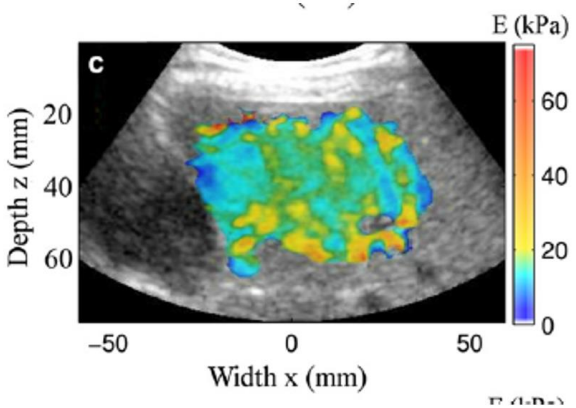
- The ARFI system (Siemens®)
  - Implemented on an ultrasound device (Acuson S2000)
  - Measurement principle:

- Shear waves generated using radiation pressure (high intensity accoustic beams)
- Quantitative measurement of the shear wave velocity in a region of interest (ROI, 1 x 0.5 cm) chosen by the practitioner
- Results expressed in m/s

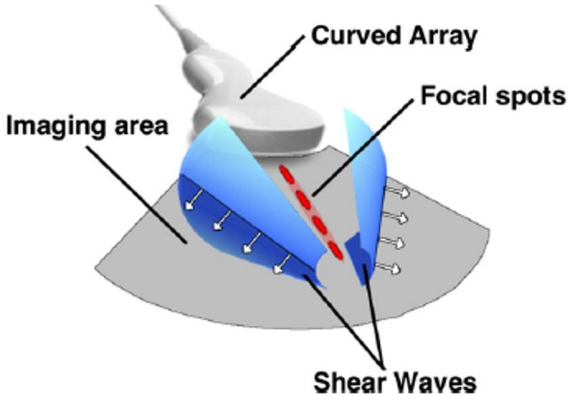


Radiation force elastography (2)

- The Aixplorer system (Super Sonic Imagine®)
  - Also implemented on an ultrasound device
  - Measurement principle:
    - Generation of « pushing beams » (radiation force) at increased depths in the liver tissue to generate a shear wave
    - Large bandwidth of shear wave frequency (60-600 Hz)
    - Calculation of the shear wave velocity using high frame rate ultrasound signal
    - Final stiffness result expressed in kPa



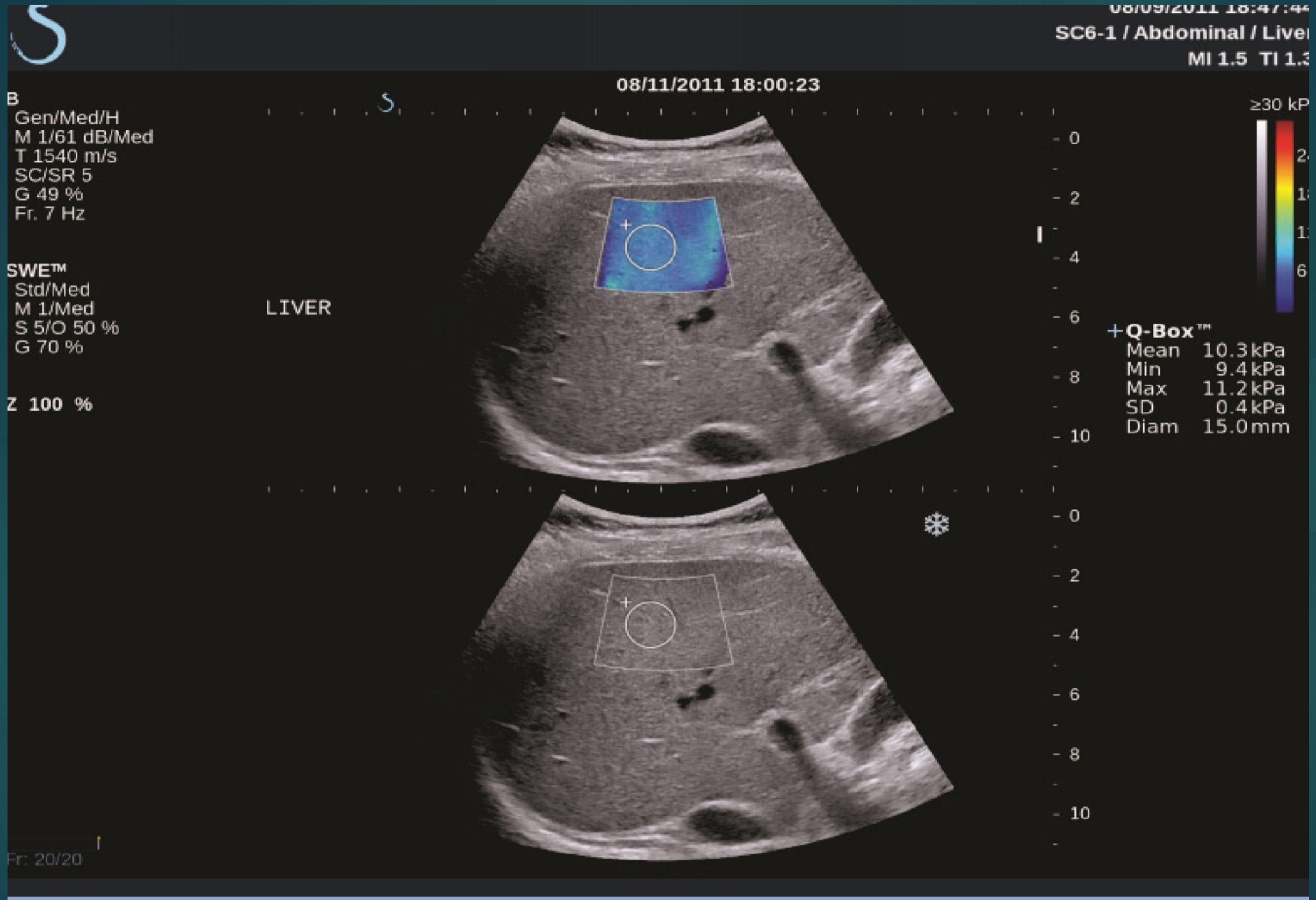
Bidimensional elasticity map assessed using SSI system



Generation of shear wave from pushing beams at increasing depths

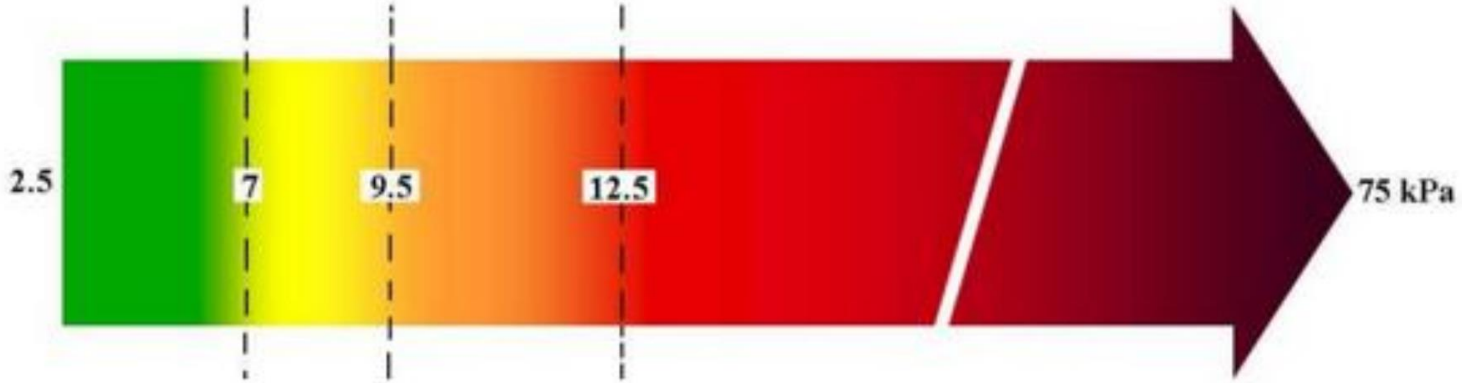
Radiation force elastography (3)

- Advantages
  - *Implemented on an ultrasound device ➡ image available*
  - *Technology already used in other organs (breast…)*
  - *Allows stiffness assessment in tumors*
  - *Allows assessing fibrosis heterogeneity in the liver*
  - *Possibility of performing measurements on patients with ascites and on the left lobe of the liver*



شکل ۲: اسکن کبد با رعایت قوانین ذکر شده

Liver stiffness cut-offs in chronic liver diseases

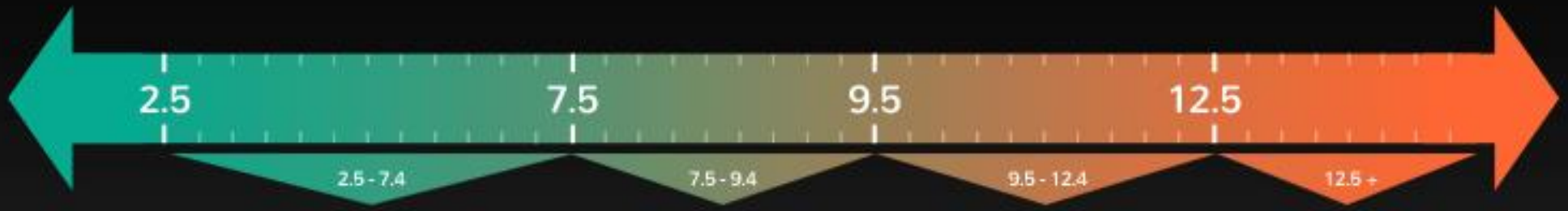


Matavir	F0-F1	F2	F3	F4
Fibrosis	Mild	Sign	Severe	Cirrhosis

Castéra L et al. J Hepatol 2008 ; 48 : 835 – 847.

Haffar

FIBROSCAN SCORE



F0/F1
NO, OR MILD FIBROSIS

Indicates no or minimal liver fibrosis and no evidence of progressive liver disease

F2
MODERATE FIBROSIS

Indicates significant liver fibrosis and evidence of progressive liver disease

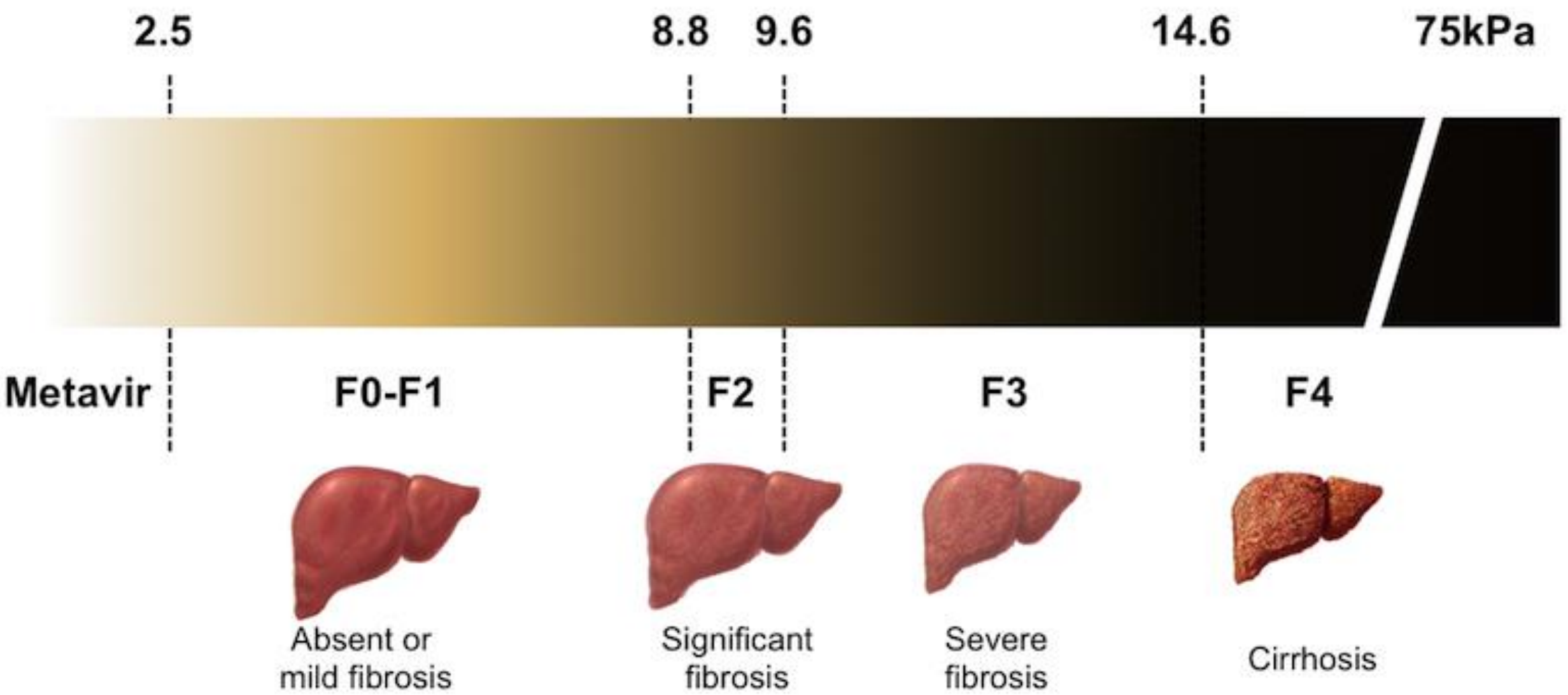
F3
SEVERE FIBROSIS

Indicates severe liver fibrosis and high risk progression to cirrhosis

F4
CIRRHOSIS

Indicates extensive liver fibrosis consistent with cirrhosis

Ziol Transient Elastography Breakpoints



	3	18/06/2018

Q-Box Liver

1

	Depth	Diam	Stability Index	Elasticity				Velocity			
				Min	Max	Mean	SD	Min	Max	Mean	SD
Q-Box 1	3.8 cm	16.60 mm	93 %	5.2 kPa	15.0 kPa	7.1 kPa	1.7 kPa	1.3 m/s	2.2 m/s	1.5 m/s	0.2 m/s
Mean	3.8 cm	16.6 mm		5.2 kPa	15.0 kPa	7.1 kPa	1.7 kPa	1.3 m/s	2.2 m/s	1.5 m/s	0.2 m/s

5

Mean	7.1 kPa	1.5 m/s
Median	7.1 kPa	1.5 m/s
IQR	0.0 kPa	0.0 m/s
SD	0.0 kPa	0.0 m/s

2

Reference

4

Samir A, Radiology. 2015, Mixed etiologies ▼

Fibrosis METAVIR stage	Stiffness range	AUROC (95% CI)	Cut-off value criterion	Cut-off value (kPa)
F0-F1	3.4-12.5			
F2	4.0-12.2	0.77 (0.68-0.86)	N/A	7.3 (Sens: 91.4% | Spec: 52.5%)
F3	7.8-12.0	0.82 (0.75-0.91)	N/A	8.9 (Sens: 76.5% | Spec: 76.5%)
F4	7.6-13.9	0.82 (0.70-0.95)	N/A	9.6 (Sens: 71.4% | Spec: 82.2%)

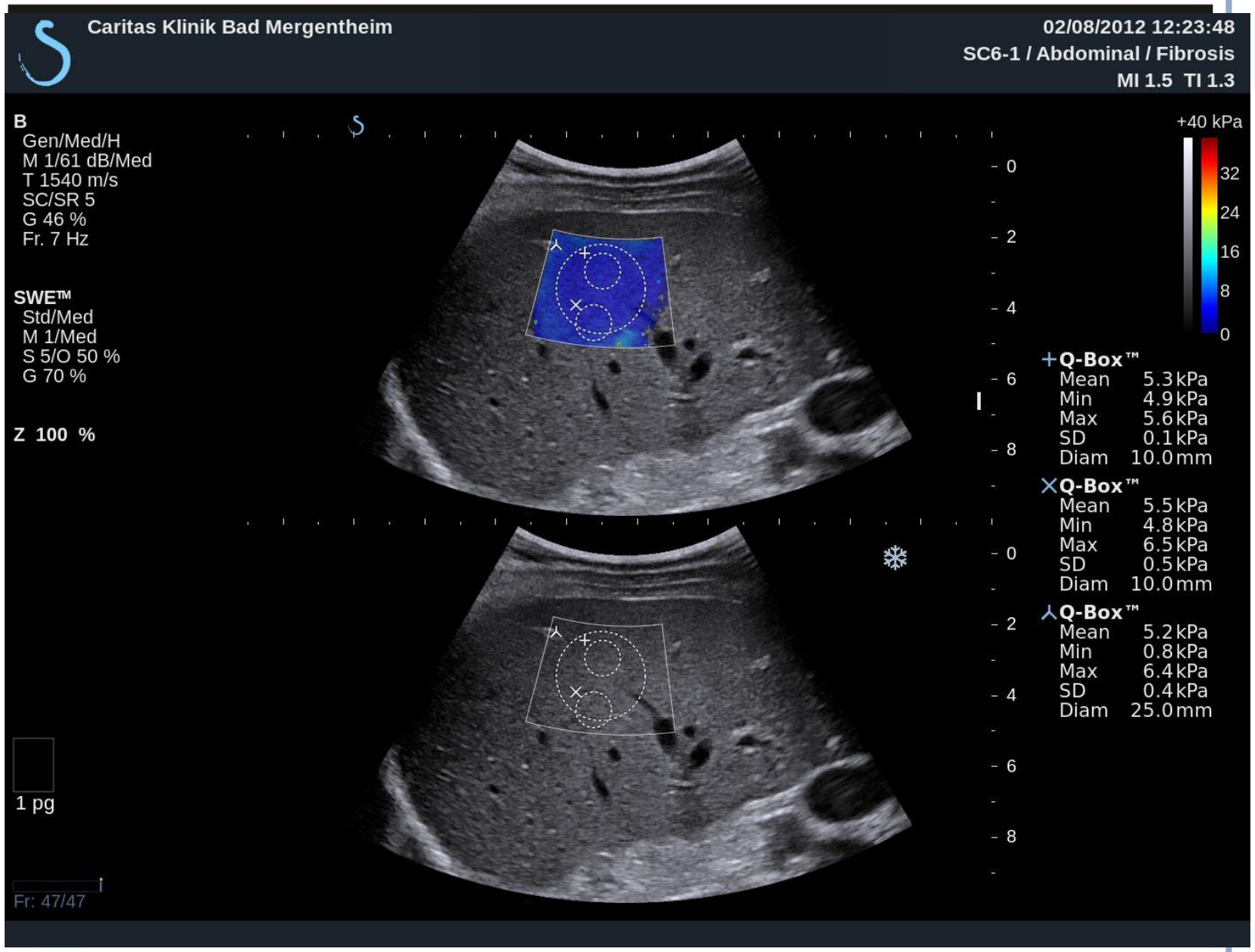
Samir AE, Dhyani M, Vij A, Bhan AK, Halpern EF, Méndez-Navarro J, Corey KE, Chung RT. Shear-wave elastography for the estimation of liver fibrosis in chronic liver disease:

cotm_dec2016-fig1a.jpg

شکل ۱۶: هیستولوژی : F_0 در سیستم **Metavir**

تصویر مد **B**: پنجره ی اکوستیکی مناسب علی رغم وجود **shadow** های جانبی، ناحیه ی خالی از عروق

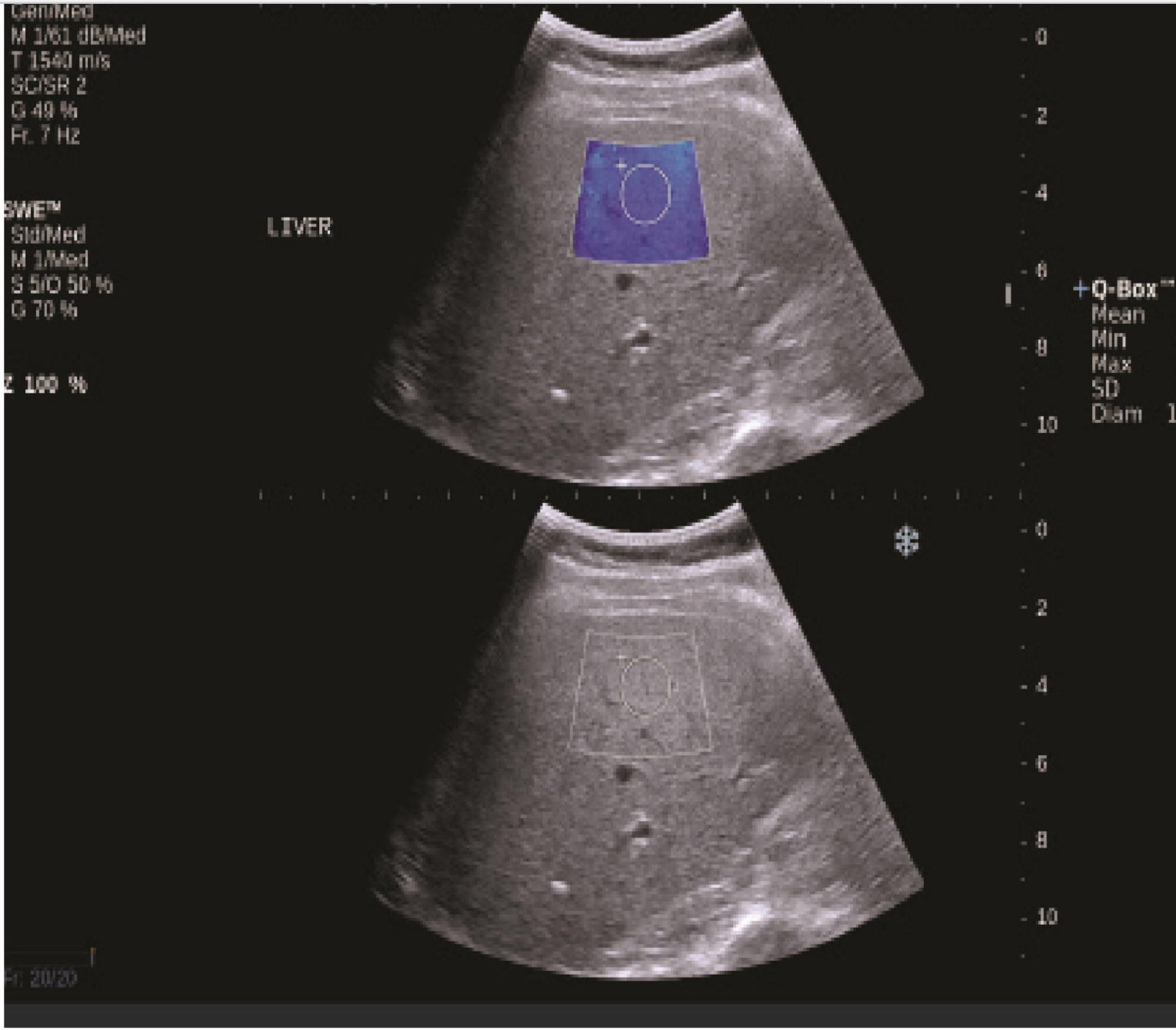
مد **SWE™**: باکس کاملا پر شده است. رنگ باکس آبی یکدست است.



شکل۱۷: هیستولوژی F_1 در سیستم Metavir

تصویر مد B: پنجره ی اکوستیکی مناسب ناحیه ی خالی از رگ

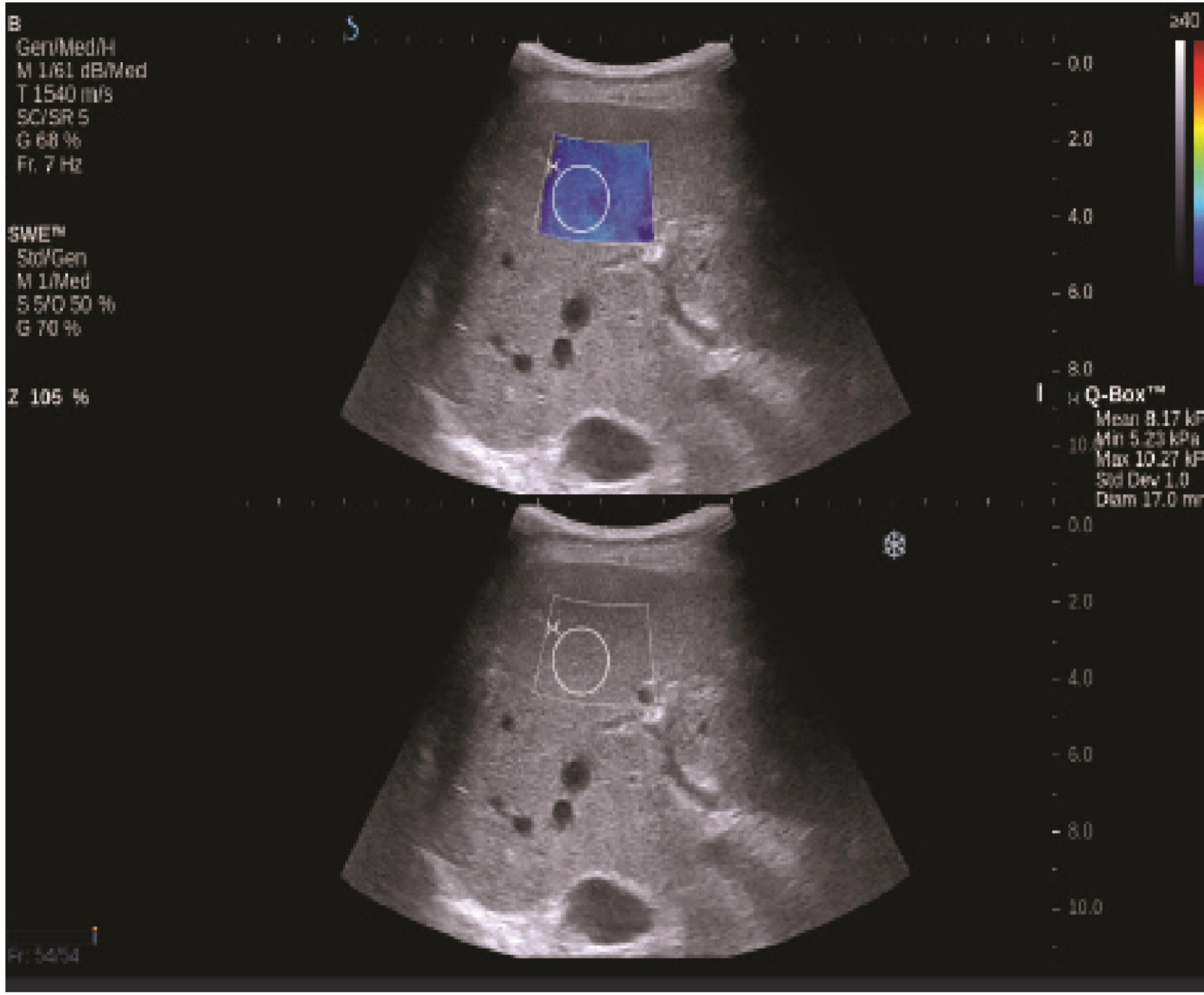
تصویر مد SWE^{TM}: باکس کاملا پر شده است. رنگ باکس آبی یکدست است.



شکل ۱۸: هیستولوژی F_2 در سیستم Metavir

تصویر مد B: پنجره ی اکوستیکی مناسب ناحیه ی خالی از رگ

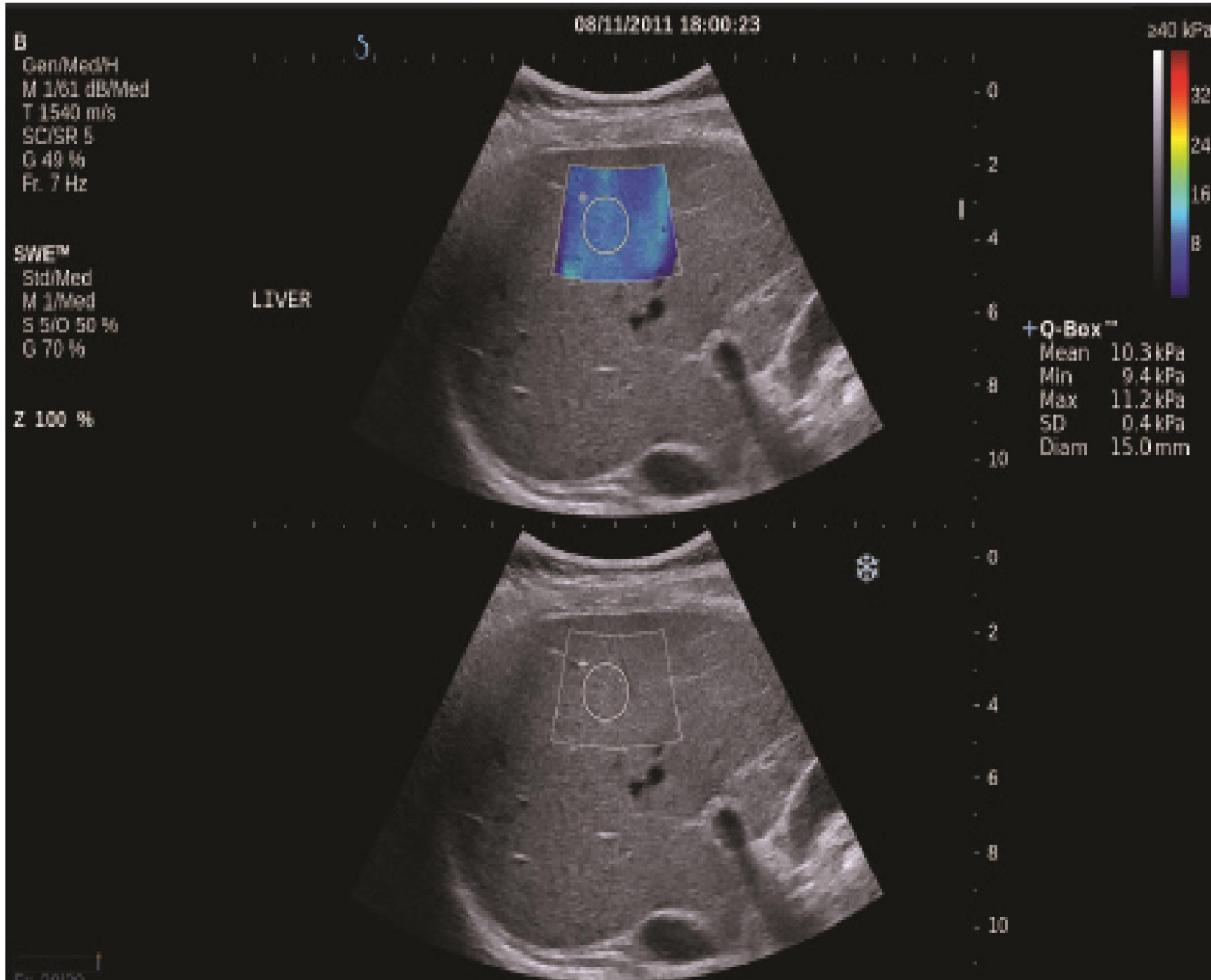
تصویر مد SWE™: باکس کاملا پر و طیف های متفاوت از رنگ آبی



شکل ۱۵: هیستولوژی F_3 در سیستم **Metavir**

تصویر مد **B**: پنجره ی اکوستیکی مناسب ناحیه ی خالی از رگ

تصویر مد **SWE™**: باکس کاملا پر و طیف های مختلف آبی دیده میشود.



هیستولوژی: F_4 در سیستم Metavir

تصویر مد B: آسیت

تصویر مد SWE™: باکس SWE™ کاملا پر شده است. آسیت محدودیت SWE™ نیست.

Diagnostic performance of LSM for fibrosis

Adults

	Fibroscan TE *	ARFI**	sSWE***
Significant ≥ F2	0,84	0,87	0,88-0,92
Severe ≥ F3	0,89	0,91	0,93-0,98
Cirrhosis F4	0,94	0,93	0,98

- Good diagnostic performance for significant and severe liver fibrosis, and cirrhosis
- Very few reports on low stages of fibrosis: F1 and F2 /vs F0

- **TE can be used to assess liver fibrosis in chronic viral C hepatitis in adults (1)**
- No validation for other techniques

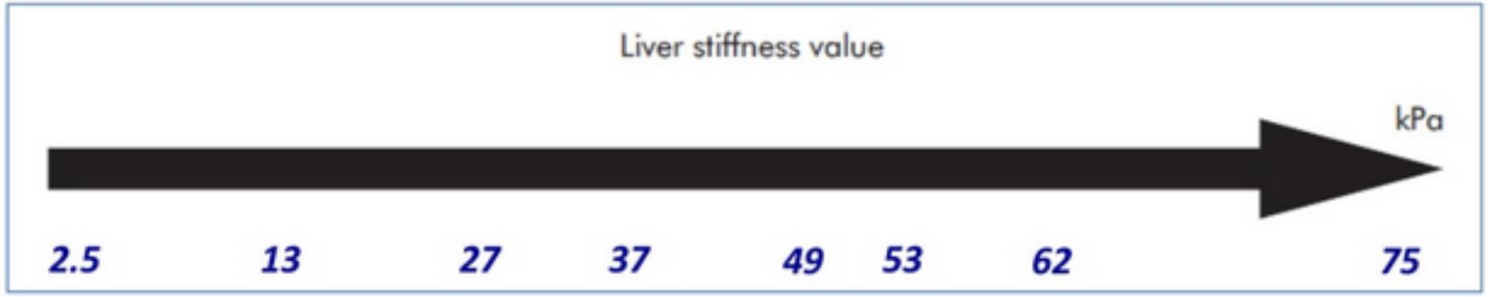
* Metanalysis 50 studies
** Friedrich-Rust, J Viral Hepatol 2012 (518 pts)
*** Ferraioli, Hepatology 2012, Leung Radiology 2013

(1) EASL clinical practice guidelines; managements hepatite C virus infection, J Hepatol 2011

Leung Radiology 2013; Chongsriwat BMC Gastrenterol 2011;

What about liver stiffness and prognosis?

- 1457 patient with chronic hepatitis C



TE > 9.5 kPa = reduced 5 year-survival

Vergniol, Gastroenterology 2011

Prediction of complications

- Correlation between fibroscan values & development of varices
- Higher elastograms predict a higher risk for HCC
- Liver elasticity falls in parallel with antiviral respons
- Increased stiffness in relapse

Other applications in liver

- Splenic stiffness > 9 kpa = portal hypertension
- To diagnose the stiffest biopsy site
- ……

limitations

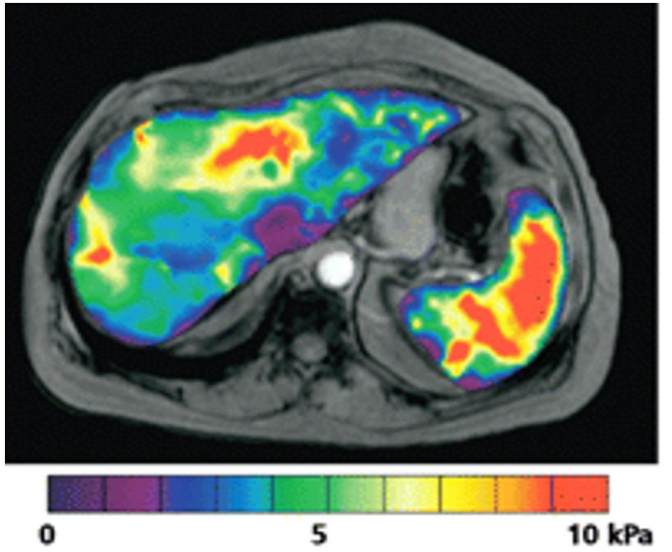
- Obesity
- Acute liver injury
- Extrahepatic cholestasis
- Increased CVP
- Narrow intercostal space

Magnetic Resonance Elastography

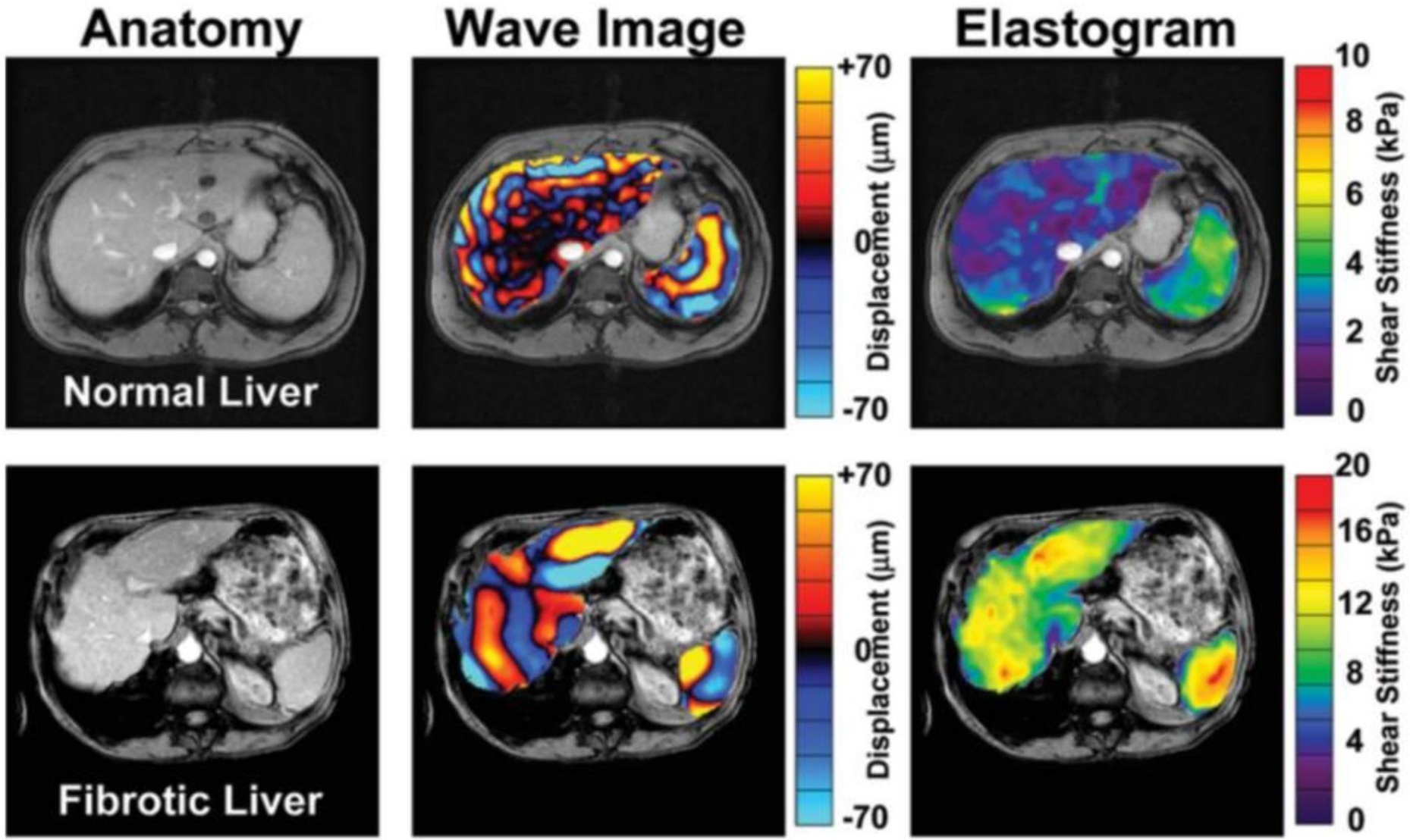
- Technique implemented to MRI device :
  - 1. Generation of accoustic waves (50-90 Hz) in the region of interest (Acquisition = 15 seconds)
  - 2. Analysis of tissues displacements that result from wave propagation
  - 3. Generation of maps of overall tissue stiffness

Semi quantitative method

- Range of colors
- Scale of stiffness values



« Map » of the global liver stiffness



Talwalkar, Yin et al. 2008