MASSACHUSETTS GENERAL HOSPITAL

Quantitative Imaging Biomarkers Alliance

RSNA

RSNA-QIBA SWS Profile – What the Clinical Workflow Would look like and a Review of Biological Confounders

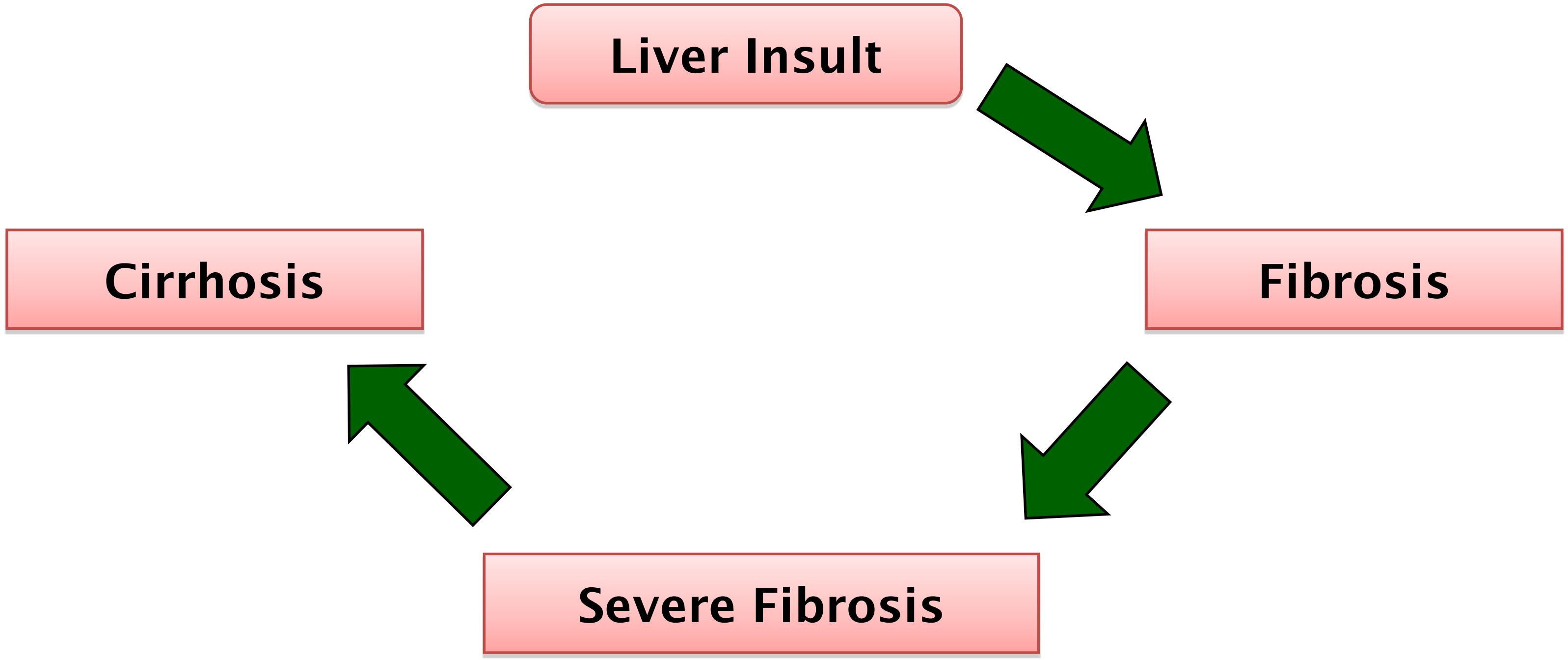
Manish Dhyani, MD

Anthony Samir, MD MPH

HARVARD MEDICAL SCHOOL

Background

- Liver fibrosis is the final common pathway for many different liver insults
- In the context of diffuse liver disease, liver fibrosis staging is essential for prognostication and treatment selection.



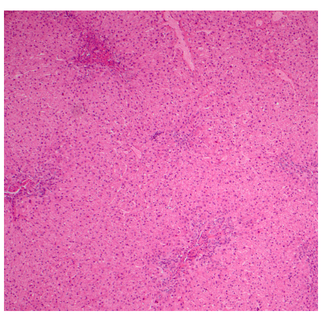
Goal of Management

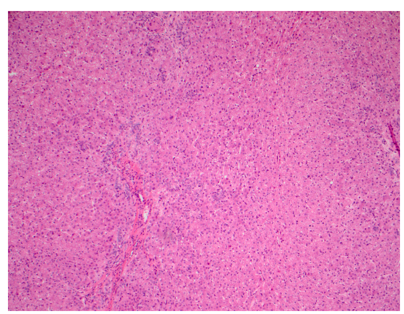
HCV, HBV, NAFLD (Liver Insult)

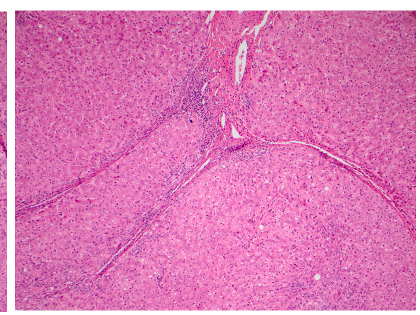
Fibrosis | Severe Fibrosis | Cirrhosis

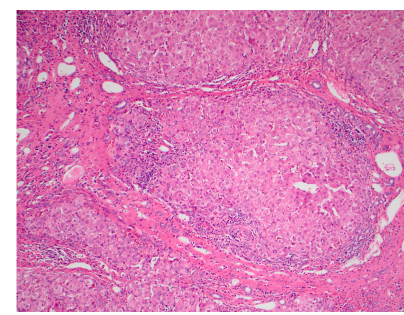
F0 → F1 → F2 → F3 → F4

No Fibrosis









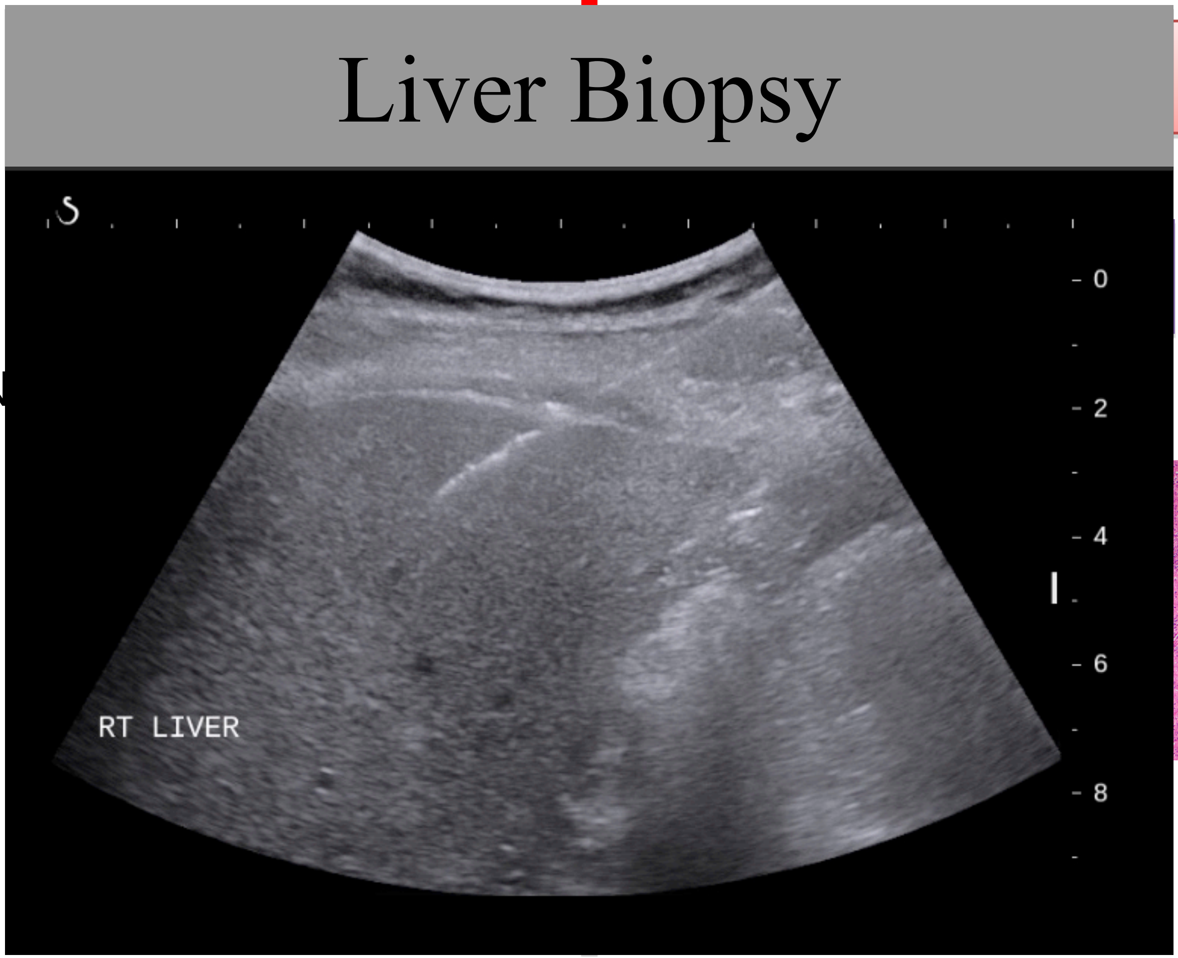
Current Gold Standard for Estimation of Fibrosis Grade

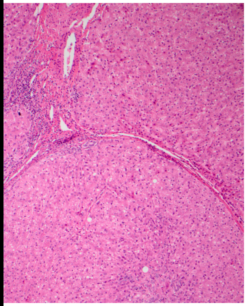
HCV, HBV, NAFLD (Liver Insult)

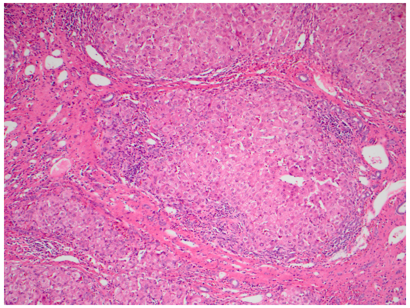
Cirrhosis

F4

N







Liver Biopsy is Imperfect

Limitations:

1. Invasive:
    a) Transient pain, anxiety and discomfort (30%)
    b) Bleeding in 0.3%, mortality in 0.01%
2. Inaccurate:
    a) Sampling error (1/50,000th of the liver sampled)
    b) Intra- and inter-observer variability (pathologist expertise)
3. Expensive.

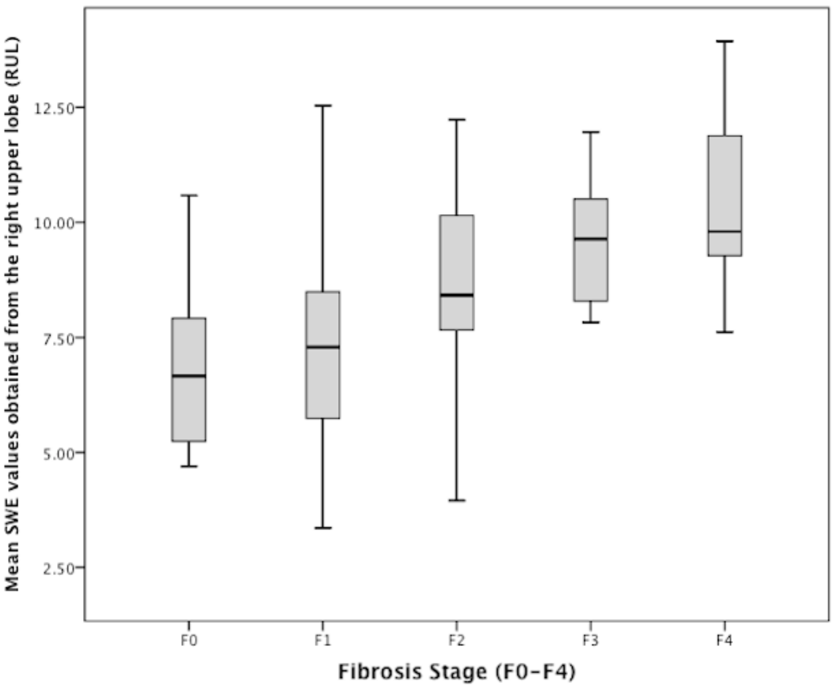
AUROC for F0-1 vs F2-4

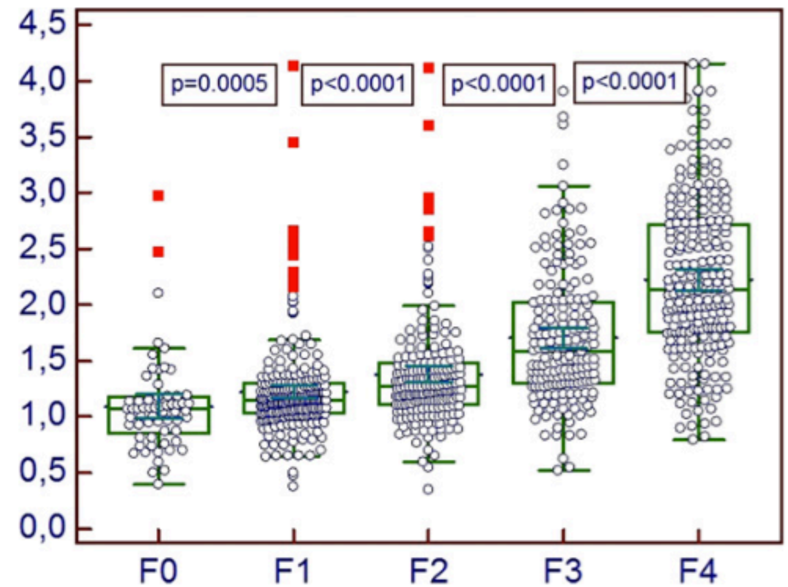
Modality	Study	Test	Study	Patients	AUROC
Serum Bio-marker	Halfon et al.	FibroTest	Meta-Analysis (38 studies)	7985	0.84
USE	Friedrich-Rust et al.	TE	Meta-Analysis (50 studies)	-	0.84
	Friedrich-Rust et al.	ARFI	Meta-Analysis (8 studies)	518	0.87
	Samir et al. (MGH)*	SWE	Prospective study	136	0.77
	Ferraioli et al.	SWE	Prospective study	121	0.92
MRE	Wang et al.	MRE	Meta-Analysis	-	0.94

- *Halfon P, Munteanu M, Poynard T: FibroTest-ActiTest as a non- invasive marker of liver fibrosis. Gastroenterol Clin Biol 32:22-39, 2008*
- *Friedrich-Rust M, Ong MF, Martens S, et al: Performance of transient elastography for the staging of liver fibrosis: A meta- analysis. Gastroenterology 134:960-974, 2008*
- *Friedrich-Rust M, Nierhoff J, Lupsor M, et al: Performance of acoustic radiation force impulse imaging for the staging of liver fibrosis: A pooled meta-analysis. J Viral Hepat 19:e212-e219, 2012*
- *Wang QB, Zhu H, Liu HL, et al: Performance of magnetic resonance elastography and diffusion-weighted imaging for the staging of hepatic fibrosis: A meta-analysis. Hepatology 56:239-247, 2012*
- *Ferraioli et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012 Dec;56(6):2125–33.*

Variability in the Assessment of Liver Fibrosis using SWE

Variability in the Assessment of Liver Fibrosis using SWE





Samir AE, Dhyani M, Vij A, Bhan AK, Halpern EF, Mendez-navarro J, et al. Shear-wave Elastography for the Estimation of Liver Fibrosis in Chronic Liver Disease: Determining Accuracy and Ideal Site for Measurement. Radiology Nov 2014.

Sporea, I. et al., 2012. European journal of radiology, 81(12), pp.4112–4118.

Sources of Variability: QIBA effort

Literature review to identify sources of variability

- 1548 manuscripts using search broad terms were identified.
- Abstracts were reviewed to identify papers that studies ARFI/SWS
- 102 papers that studied liver fibrosis assessment using ARFI/SWS were studied in detail to identify clinical and patient related sources of variability

Quantitative Imaging Biomarkers Alliance RSNA

Sources of Variability

1. Equipment sources
2. Patient sources
3. Technique sources

Variability in the Assessment of Liver Fibrosis using SWE

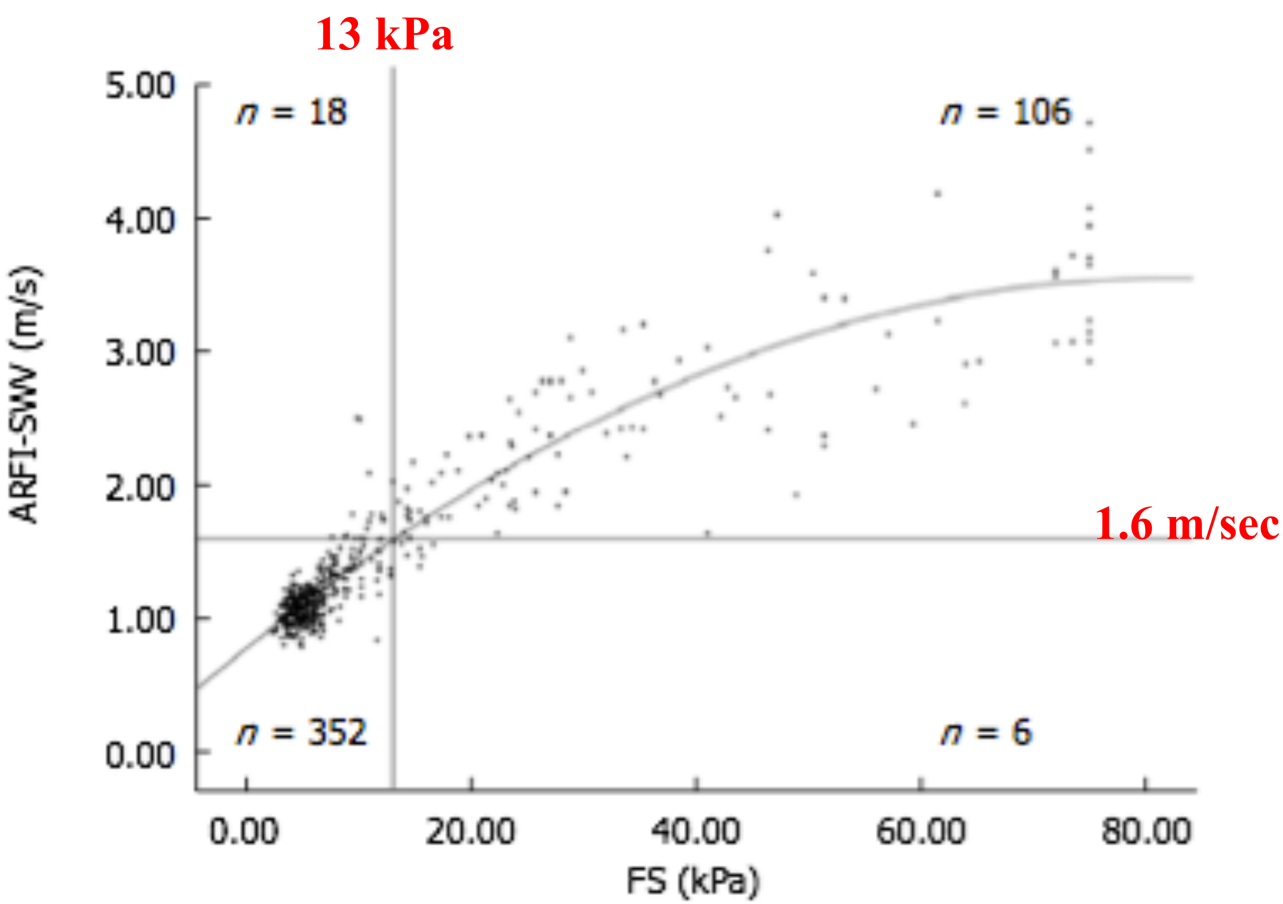
	TE	ARFI	ElastPQ	2D-SWE	RT-E
Patient position	Supine	Supine	Supine	Supine	Supine
Confounding factors	-non-fasting condition -high AT levels -CHF -obstructive jaundice -contradictory data on steatosis	-non-fasting condition -high AT levels -CHF	-no clear available information	-non-fasting condition -no others information available	-no available information
Healthy volunteers values	4.6-5.5 kPa	1.07-1.19 m/s	~3.5 kPa	~ 5.7 kPa	-no available information
HCV cut-offs	-F≥1: 4.9-5.3 kPa -F≥2: 6.8-7.4 kPa -F≥3: 8.6-9.1 kPa -F=4:11.8-13.6 kPa	-F≥1:1.18-1.19 m/s -F≥2: 1.21-1.34m/s -F≥3: 1.54-1.61 m/s -F=4: 1.81-2 m/s	No available data	-F≥1: No data -F≥2: 7.1 kPa -F≥3: 8.7 kPa -F=4:10.4 kPa	ER: -F≥1: No data -F≥2: 2.73 -F≥3: 3.25 -F=4: 3.93 LFI: -F≥1: No data -F≥2: 2.05 -F≥3: 2.28 -F=4: 2.36
HBV cut-offs	-F≥1: No clear data -F≥2: 7-7.9 kPa -F≥3: 8.2-8.8 kPa -F=4:11.3-11.7 kPa	Similar mean LS values for chronic hepatitis B and C patients	-F≥1: No data -F≥2:6.99 kPa -F≥3:No data -F=4: 9 kPa	-F≥1: 6.5 kPa -F≥2: 7.1 kPa -F≥3: 7.9 kPa -F=4:10.1 kPa	Elasticity index: -F≥1: 20.94 -F≥2: 55.33 -F≥3: 80.71 -F=4: 90.31
NAFLD cut-offs	-F≥1: 5.3 kPa -F≥2: 6.8 kPa -F≥3: 10.4 kPa -F=4: 11.5 kPa	-F≥1: 1.10 m/s -F≥2: 1.16 m/s -F≥3: 1.48 m/s -F=4: 1.63 m/s	No available data	No available data	No clear available data

Sporea et al. Romanian national guidelines and practical recommendations on liver elastography. 2014 Jun;16(2):123–38.

Machine Sources of Variability

- Variability in technology (Kircheis et al.)
- Cirrhosis

($r = 0.920$; $P < 0.001$)

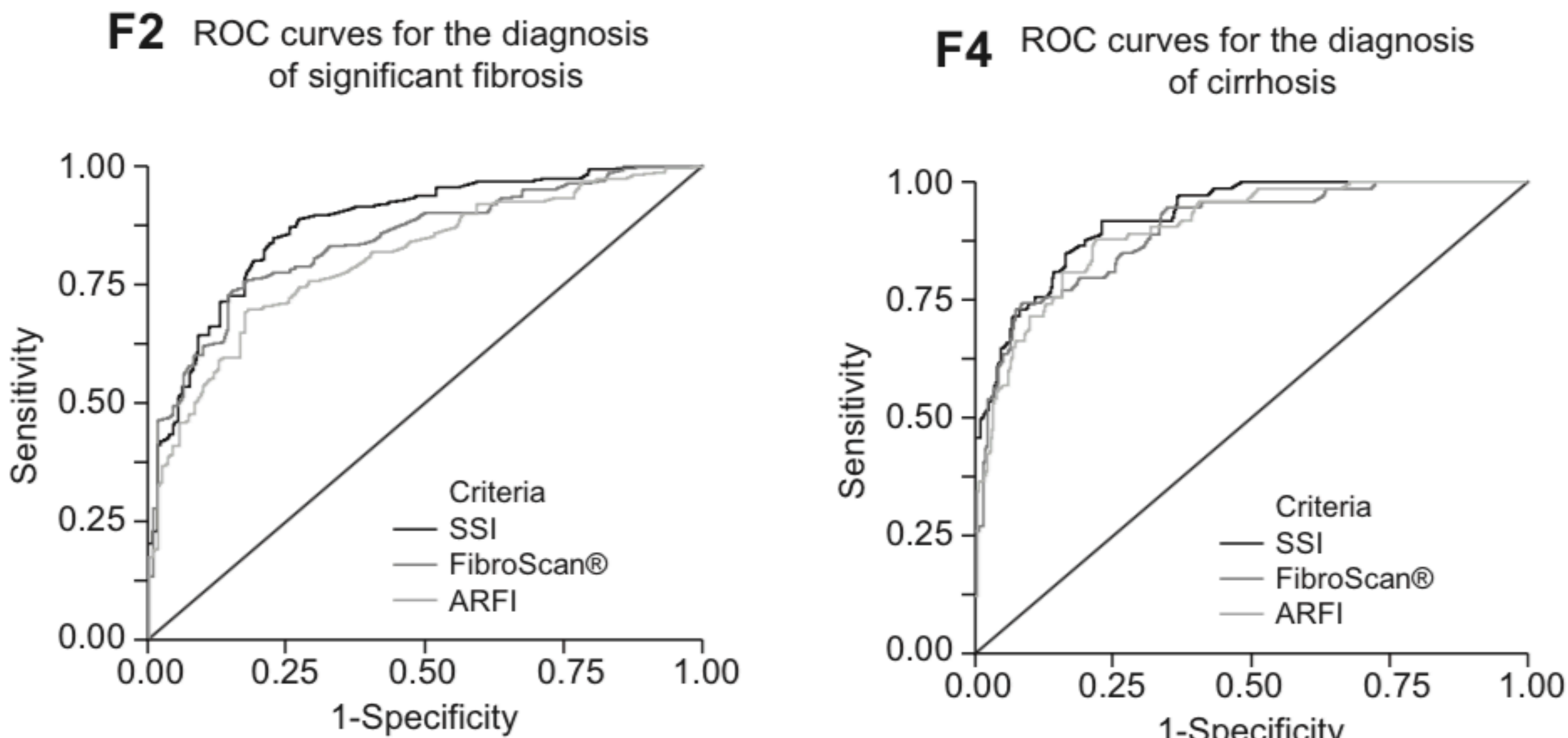


- *Kircheis G, Sagir A, Vogt C, Vom Dahl S, Kubitz R, H a ussinger D. Evaluation of acoustic radiation force impulse imaging for determination of liver stiffness using transient elastography as a reference. World J Gastroenterol [Internet]. 2012 ed. 2012 Mar;18(10):1077–84.*

Machine Sources of Variability

- Variability in technology (Cassinotto et al.)

n=349



- *Cassinotto C, Lapuyade B, Mouries A, Hiriart J-B, Vergniol J, Gaye D, et al. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan®. J Hepatol. 2014 Sep;61(3):550–7.*

Patient sources of variability

- Inflammation
- Steatosis
- Cholestasis
- Right heart insufficiency

Inflammation

Clinical Confounder - Inflammation

- There is overwhelming evidence that inflammation and/or acute hepatitis increase SWE estimation of liver stiffness
  - *Bota 2013*
  - *Ebinuma 2011*
  - *Friedrich-Rust 2009*
  - *Lupsor 2009*
  - *Rifai 2011*
  - *Takahashi 2010*
  - *Chen 2012*
  - *Fierbinteanu-Braticevici, 2013*
  - *Guzmán-Aroca 2012*
  - *Potthoff 2013*
  - *Sporea 2012*
  - *Takaki 2014*
- However, to what extent this effect manifests, and how to correct for it – remains to be determined.

Liver Stiffness Measurement Using Acoustic Radiation Force Impulse (ARFI) Elastography and Effect of Necroinflammation

Ki Tae Yoon · Sun Min Lim · Jun Yong Park · Do Young Kim · Sang Hoon Ahn · Kwang-Hyub Han · Chae Yoon Chon · Mong Cho · Jun Woo Lee · Seung Up Kim

Table 4 Optimum cutoff values of ARFI elastography for each fibrosis stage and the effect of ALT level

	$F \geq 2$	$F = 4$
All patients ($n = 250$)		
Cut off	1.13	1.98
PPV	62.0	90.8
NPV	83.0	78.2
Sensitivity	58.1	81.4
Specificity	84.1	50.8
AUROC	0.74	0.79
95% CI	0.64–0.86	0.67–0.91
Patients with normal ALT ($n = 131$, 52%)		
Cut off	1.09	1.81
PPV	78.8	78.3
NPV	89.6	93.1
Sensitivity	83.9	81.8
Specificity	86.0	91.4
AUROC	0.88	0.92
95% CI	0.83–0.97	0.84–0.98
Patients with high ALT ($n = 119$, 48%)		
Cut off	1.16	2.23
PPV	85.7	93.0
NPV	66.6	78.4
Sensitivity	75.0	58.0
Specificity	67.0	85.0
AUROC	0.73	0.72
95% CI	0.63–0.85	0.62–0.83

- 250 subjects

Yoon KT, Lim SM, Park JY, Kim DY, Ahn SH, Han K-H, et al. Liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography and effect of necroinflammation. Dig Dis Sci. Springer US; 2012 Jun;57(6):1682–91.

Liver, Pancreas and Biliary Tract

The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: A retrospective multicentre study

Simona Bota[a,*], Ioan Sporea[a], Markus Peck-Radosavljevic[b], Roxana Sirli[a], Hironori Tanaka[c],

n = 1242

Fibrosis	ALT ≤ ULN*	ALT = 1.1–5× ULN#	ALT > 5× ULN¤	*p* value
F0	1.06 ± 0.33 (*n* = 52)	1.19 ± 0.49 (*n* = 31)	1.46 ± 0.30 (*n* = 7)	* vs. # 0.52 * vs. ¤ 0.001 # vs. ¤ 0.007
F1	1.16 ± 0.36 (*n* = 193)	1.26 ± 0.31 (*n* = 140)	1.44 ± 0.41 (*n* = 22)	* vs. # 0.001 * vs. ¤ 0.0005 # vs. ¤ 0.02
F2	1.23 ± 0.40 (*n* = 127)	1.42 ± 0.46 (*n* = 134)	1.55 ± 0.27 (*n* = 11)	* vs. # 0.002 * vs. ¤ 0.001 # vs. ¤ 0.06
F3	1.54 ± 0.50 (*n* = 89)	1.80 ± 0.68 (*n* = 147)	1.98 ± 0.67 (*n* = 9)	* vs. # 0.04 * vs. ¤ 0.005 # vs. ¤ 0.08
F4	2.09 ± 0.73 (*n* = 118)	2.33 ± 0.66 (*n* = 146)	2.47 ± 0.68 (*n* = 16)	* vs. # 0.01 * vs. ¤ 0.07 # vs. ¤ 0.39

Bota S, Sporea I, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H, et al. The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: a retrospective multicentre study. Dig Liver Dis. 2013 Sep;45(9):762–8.

Addressing increased value of Inflammation

Diagnostic performance of Acoustic Radiation Force Impulse Elastography according to alanine aminotransferase levels.

Fibrosis	ALT ≤ ULN	ALT = 1.1–5× ULN	ALT > 5× ULN
$F \geq 2$	Cut-off: >1.29 m/s Se: 63.6% Sp: 79.9% PPV: 81.2% NPV: 61.6% Accuracy: 70.4% AUROC: 0.766	Cut-off: >1.36 m/s Se: 75.3% Sp: 75.5% PPV: 88.4% NPV: 54.8% Accuracy: 75.2% AUROC: 0.802	Cut-off: >1.44 m/s Se: 81.5% Sp: 64.5% PPV: 74.3% NPV: 73.1% Accuracy: 73.8% AUROC: 0.767
$F = 4$	Cut-off: >1.59 m/s Se: 76.9% Sp: 84.9% PPV: 56.5% NPV: 93.5% Accuracy: 83.2% AUROC: 0.843	Cut-off: >1.57 m/s Se: 91.3% Sp: 72.7% PPV: 51.9% NPV: 96.1% Accuracy: 77.2% AUROC: 0.867	Cut-off: >1.75 m/s Se: 93.3% Sp: 72.2% PPV: 51.7% NPV: 97.2% Accuracy: 76.9% AUROC: 0.867

Abbreviations: F, fibrosis; ALT, alanine aminotransferase; ULN, upper limit of normal; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under receiver operating curve.

Bota S et al. The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: a retrospective multicentre study. Dig Liver Dis. 2013 Sep;45(9):762–8.

Steatosis

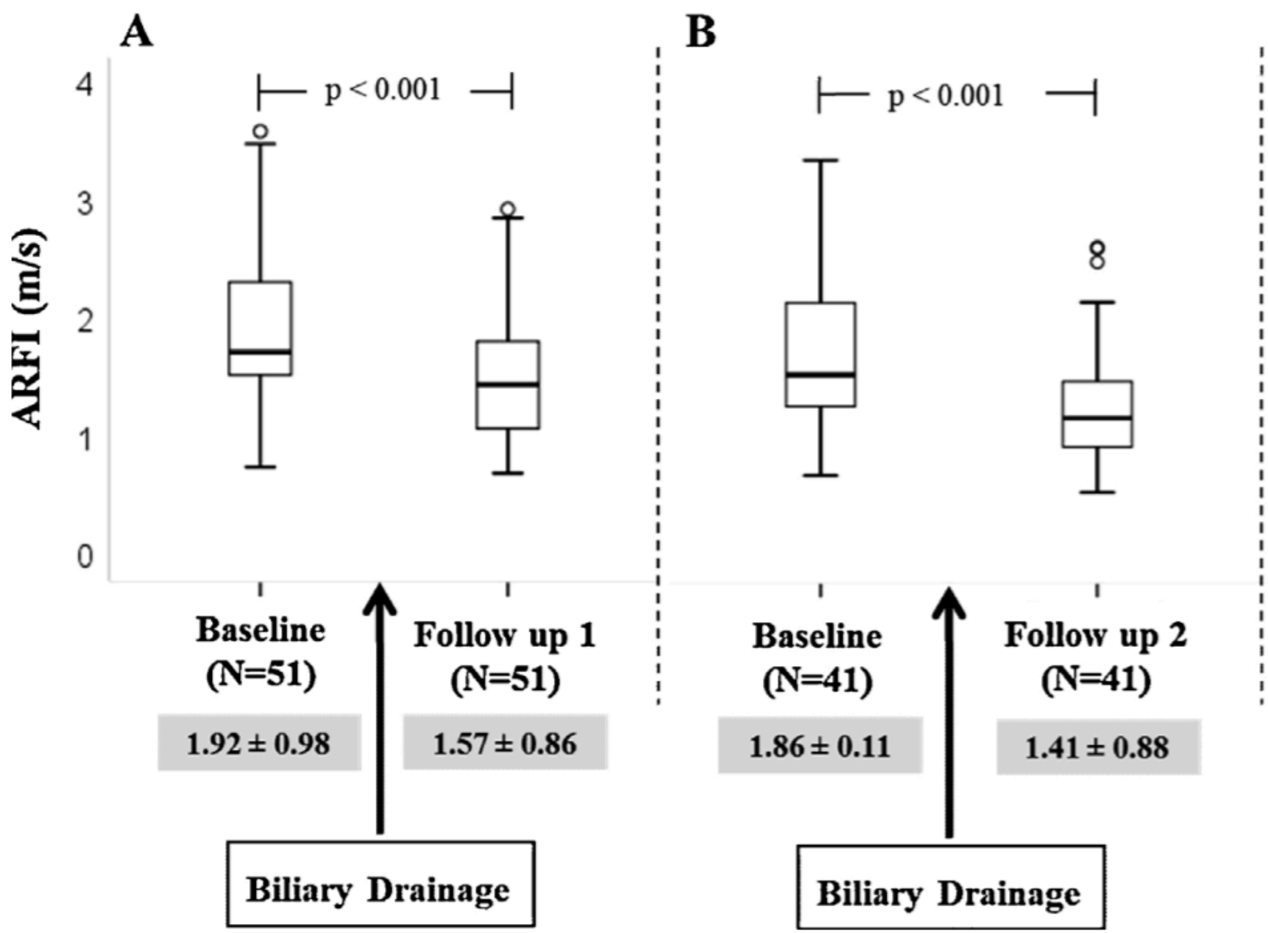
Clinical Confounder – Steatosis

- Several authors have reported that steatosis grade does not influence liver fibrosis staging with shear wave elastography (Yoneda 2008, Friedrich-Rust 2009, Lupsor 2009, Fierbinteanu-Braticevici 2009, Bota 2011, Rifai 2011).
- In two studies SWS was shown to decrease with increasing steatosis (Yoneda 2010, Fierbinteanu-Braticevici 2013).

Cholestasis

Changes in liver stiffness using acoustic radiation force impulse imaging in patients with obstructive cholestasis and cholangitis

Dina Attia[a,b], Sven Pischke[a], Ahmad A. Negm[a], Kinan Rifai[a], Michael P. Manns[a], Michael J. Gebel[a], Tim O. Lankisch[a], Andrej Potthoff[a,*]



Technique – As a sources of variability

Technique – As a sources of variability

- Fasting/Meals
- BMI
- Patient position
- Patient breathing
- Lobe of liver

Literature review - Fasting/Meals

- SWE values increase after food intake
  - Goertz et al. and Popescu et al. have shown that SWE values are increased post prandial and hence recommend assessment in a fasting state.
- Has no effect
  - Kaminuma et al. found that food consumption did not have a significant impact on SWE measurement. (? Meal size)

- *Goertz RS, Egger C, Neurath MF, Strobel D. Impact of food intake, ultrasound transducer, breathing maneuvers and body position on acoustic radiation force impulse (ARFI) elastometry of the liver. Ultraschall Med [Internet]. 2012 Aug;33(4):380–5.*
- *Popescu A, Bota S, Sporea I, Sirli R, Danila M, Racean S, et al. The Influence of Food Intake on Liver Stiffness Values Assessed by Acoustic Radiation Force Impulse Elastography-Preliminary Results. Ultrasound Med Biol [Internet]. 2013 Feb 13;39(2):211–25.*
- *Kaminuma C, Tsushima Y, Matsumoto N, Kurabayashi T, Taketomi-Takahashi A, Endo K. Reliable measurement procedure of virtual touch tissue quantification with acoustic radiation force impulse imaging. J Ultrasound Med. 2011 Jun;30(6):745–51.*

THE INFLUENCE OF FOOD INTAKE ON LIVER STIFFNESS VALUES ASSESSED BY ACOUSTIC RADIATION FORCE IMPULSE ELASTOGRAPHY—PRELIMINARY RESULTS

ALINA POPESCU, SIMONA BOTA, IOAN SPOREA, ROXANA SIRLI, MIRELA DANILA, SEBASTIAN RACEAN, DRAGOS SUSEANU, OANA GRADINARU, and CRISTIAN IVASCU SIEGFRIED
Department of Gastroenterology and Hepatology, University of Medicine and Pharmacy, Timişoara, Romania

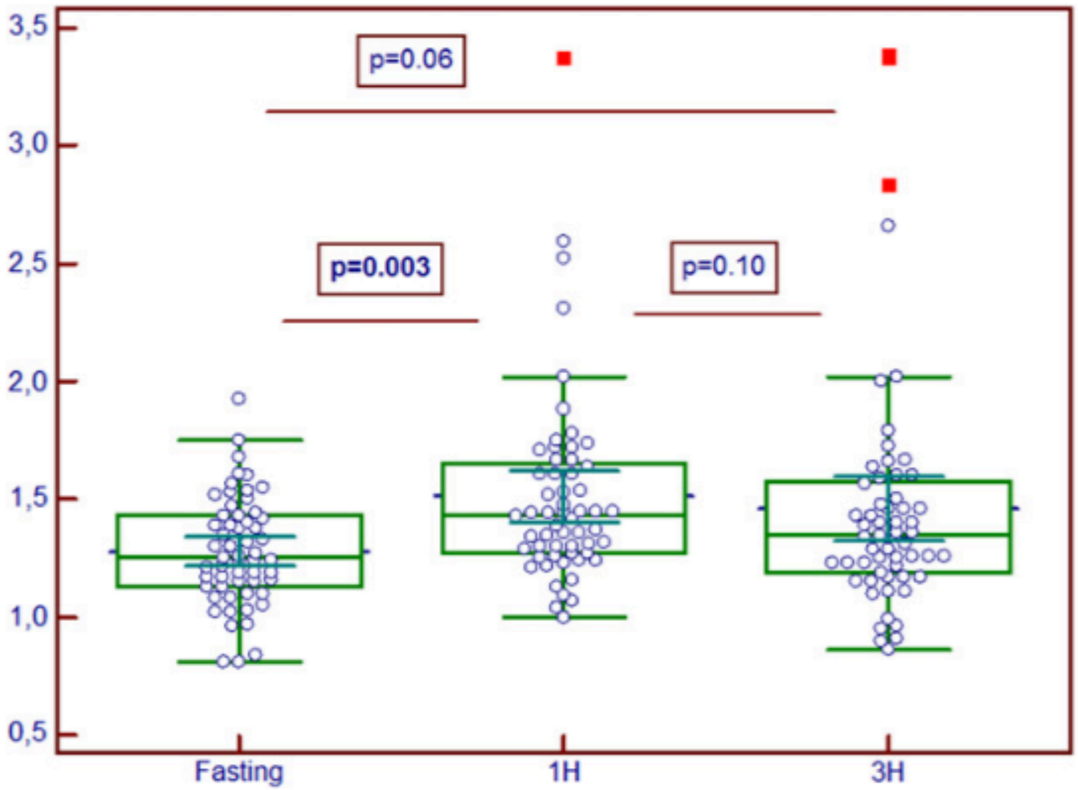


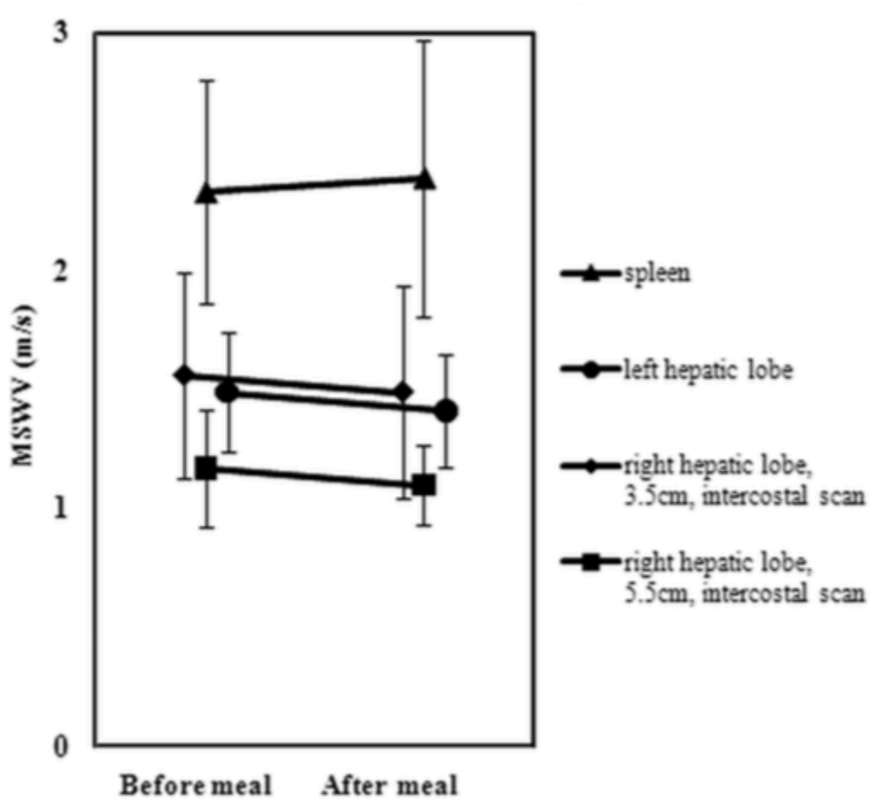
Fig. 2. The mean ARFI values at the study group according to the food intake.

n = 73

200-g ham and cheese sandwich and 500 mL still water (mineral water without gas).

Reliable Measurement Procedure of Virtual Touch Tissue Quantification With Acoustic Radiation Force Impulse Imaging

Chie Kaminuma, MD, Yoshito Tsushima, MD, Noriko Matsumoto, MD, Takemi Kurabayashi, MD, Ayako Taketomi-Takahashi, MD, Keigo Endo, MD



n = 20

Post lunch

?Meal

Kaminuma C, Tsushima Y, Matsumoto N, Kurabayashi T, Taketomi-Takahashi A, Endo K. Reliable measurement procedure of virtual touch tissue quantification with acoustic radiation force impulse imaging. J Ultrasound Med. 2011 Jun;30(6):745–51.

Position – Overwhelming evidence that measurements from the left lobe are not reliable

	Fibrosis		
Site	*P* Value	*r*	95% CI
Left lobe	.061	0.16	−0.01, 0.32
Upper right lobe	<.001	0.41	0.26, 0.54
Lower right lobe	<.001	0.35	0.19, 0.49
Biopsy site	.009	0.23	0.06, 0.38

Original Research

Ultrasonography

Shear-Wave Elastography for the Estimation of Liver Fibrosis in Chronic Liver Disease: Determining Accuracy and Ideal Site for Measurement

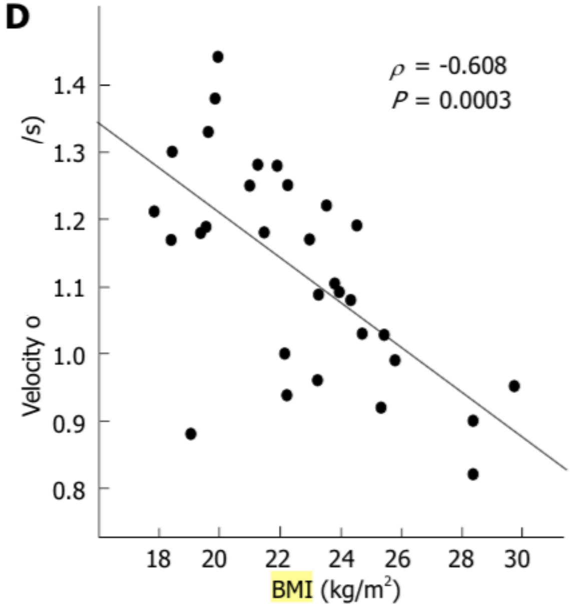
Anthony E. Samir, MD, MPH, Manish Dhyani, MBBS, Abhinav Vij, MBBS, MPH, Atul K. Bhan, MBBS, MD, Elkan F. Halpern, PhD, Jorge Méndez-

BMI

- Increasing evidence that discordance in measurements correlates with high BMI
- There is also a high degree of measurement failure in patients with BMI > 30

Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C

n = 108



Nishikawa T, Hashimoto S, Kawabe N, Harata M, Nitta Y, Murao M, et al. Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C. World J Gastroenterol. 2014 Feb 7;20(5):1289–97.

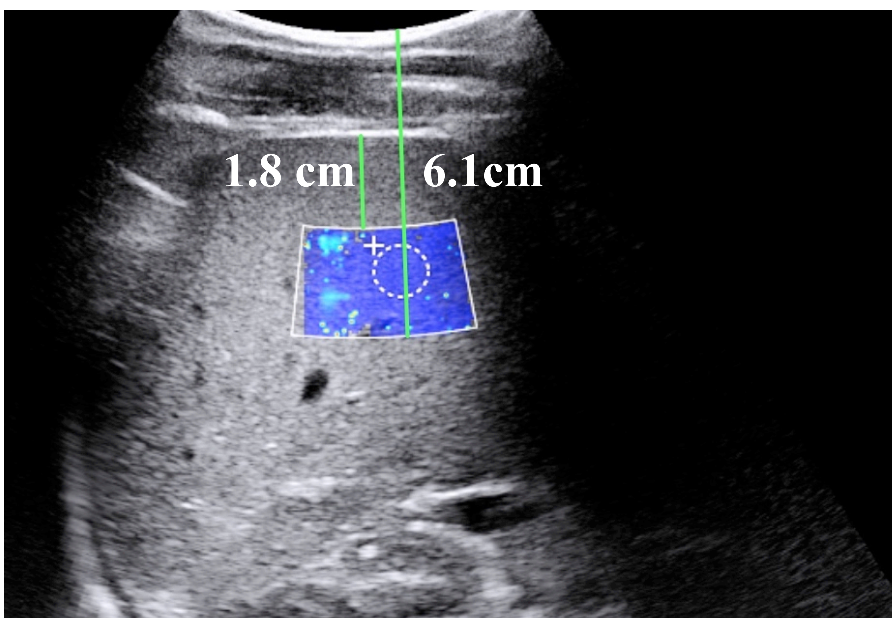
QIBA Profile

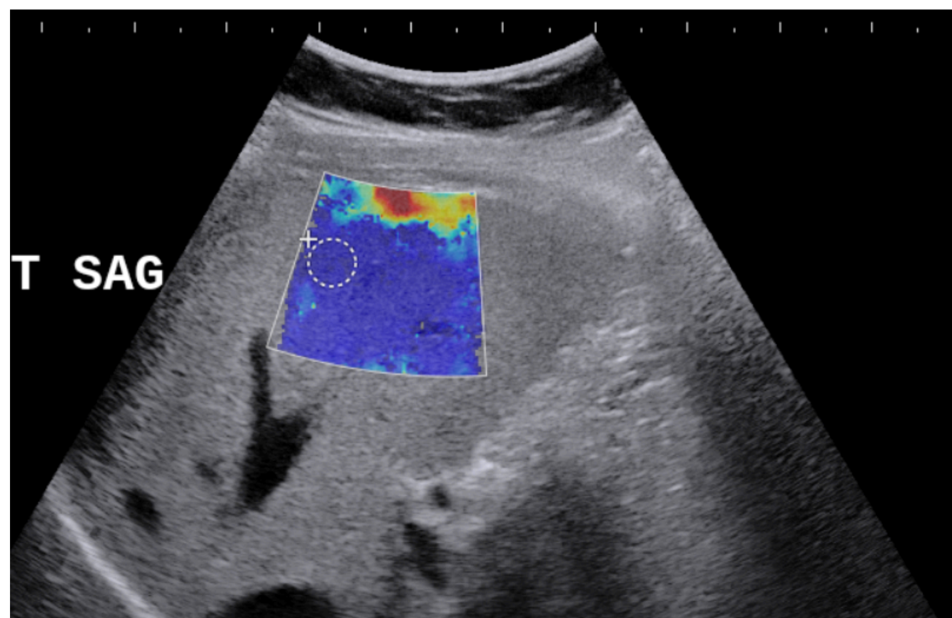
Scanning Protocol

- Patient Position – supine or oblique left decubitus
- Fasting – 4 hours
- Breathing – suspended tidal respiration
- Acquisitions – Intercostal approach

Depth

Parameter	Actor	Specification
Region of Interest (ROI) Placement	Technologist or Radiologist	• Shall position the ROI at least 2cm deep to the liver capsule and less than 6.5 cm from the transducer face. • Shall position the ROI away from discrete structures such as liver margin, nodules, portal triads or hepatic veins for acquisition of SWS estimates • Shall position the ROI near the center of the image in the lateral direction and away from the right or left image margins. • A standard ROI size as per MFR specifications that is a default for their system. The standard for each MFR should conform to a minimum size of 10mm X 10mm or diameter of 10mm. • Should try to place the ROI at a constant depth for all acquisitions, but especially for follow up acquisitions in the same patient or subject.





QIBA RSNA Profile

https://www.rsna.org/QIBA-Profiles-and-Protocols/

- Feedback once the document is released for public comment.

Thank you!!

QIBA – Participating Sites

- Duke University, Durham, NC
- Echosens, Paris, France
- Hôpitaux Universitaires Paris-Sud, Paris, France
- Institut Langevin, Paris, France
- CIRS, Norfolk, VA
- Massachusetts General Hospital, Boston, MA
- Mayo Clinic, Rochester, MN
- Michigan Technological University, Houghton, MI
- Philips Ultrasound, Bothell, WA
- Rheolution, Inc, Montreal, Canada
- Royal Marsden Hospital, London, UK
- Siemens Ultrasound, Issaquah, WA
- Southwoods Imaging Center, Youngstown, OH
- Supersonic Imagine (SSI), Aix-en-Provence, France
- Toshiba Medical Research Institute, USA
- University of California at San Diego
- University of Michigan, Ann Arbor, MI
- University of Rochester, Rochester, NY
- University of Wisconsin, Madison, WI
- Food and Drug Administration, USA