

Elastography in viral hepatitis related liver disease

Prof. Ioan Sporea, MD, PhD

Head of Dept. of Gastroenterology and Hepatology,

University of Medicine and Pharmacy

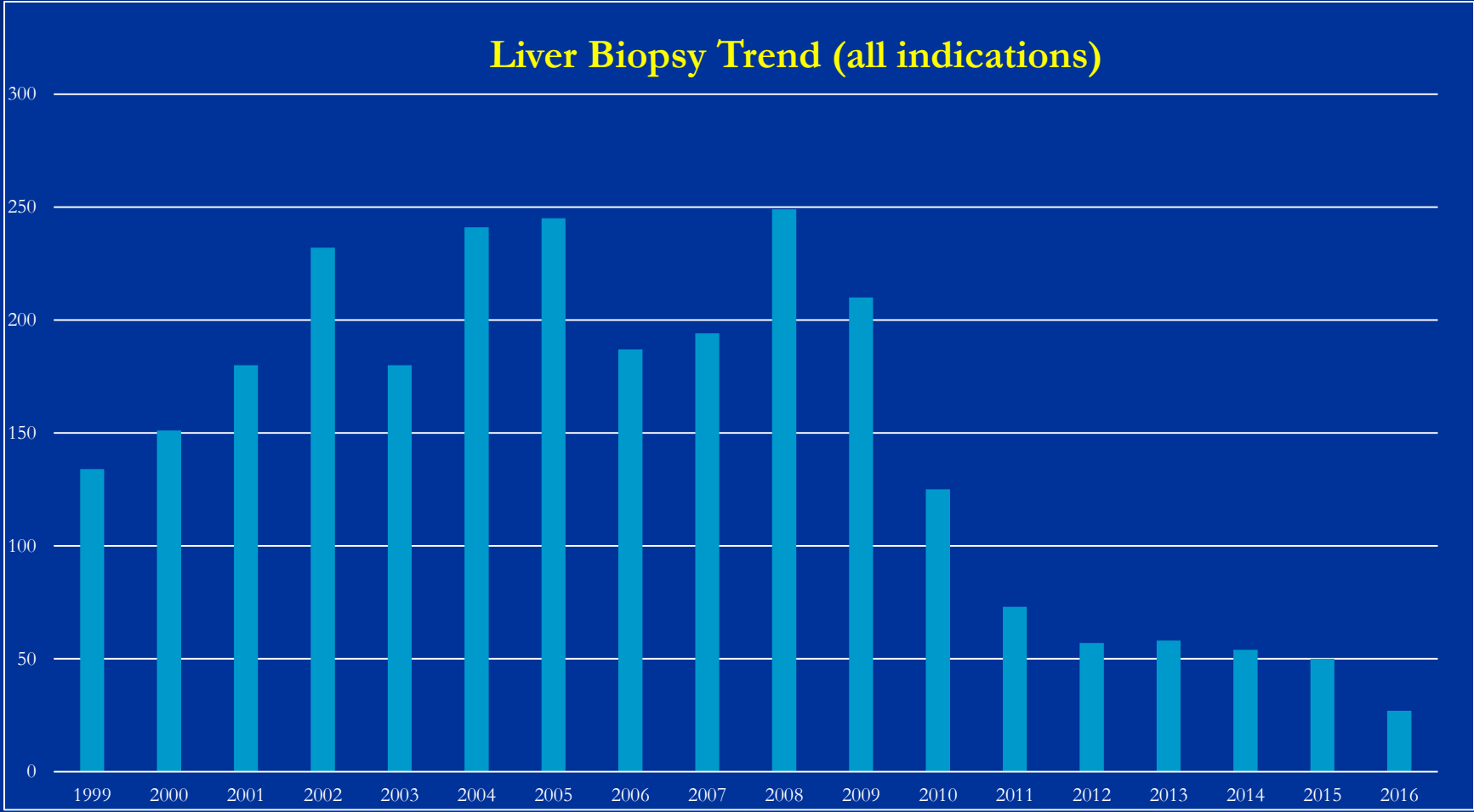
WFUMB Center of Education

EFSUMB Ultrasound Learning Center

Timișoara, Romania

- *Chronic liver diseases are frequent in daily hepatological practice* (HCV, HBV, NAFLD/NASH, ASH, autoimmune, others).
- Assessment of chronic liver diseases severity can be performed **invasively (by liver biopsy)** or **non-invasively (biological tests and elastographic methods)**.

Liver Biopsy in our Dept. of Hepato/Gastroenterology Timisoara during the time



Ultrasound based Liver Elastography can be divided:

1. Shear Waves Elastography:

a) **Transient Elastography-TE** (FibroScan)

b) **Point Shear wave- pSWE** [using **Acoustic Radiation Force Impulse Quantification (ARFI): VTQ** (Siemens), **Elast PQ** (Phillips), Hitachi]

c) **Real Time Shear Wave Elastography- 2D SWE** [**SuperSonic Imaging Elastography (SSI)** (Aixplorer) GE, Toshiba, Philips]

2. Strain Elastography (RTE)

Transient Elastography (FibroScan)

- *TE is used for more than 10 years in clinical practice and many meta-analyses showed its good value for liver fibrosis evaluation, considering liver biopsy as the reference method.*
- *The correlation between TE measurements and fibrosis severity on liver biopsy increases with the severity of fibrosis.*

Transient Elastography (FibroScan)

- Is easy to be used (*in some countries like France, is manipulated mainly by nurses*);
- Is a semi-blind method (the liver is not seen during the examination);
- Have different probes: M, XL or pediatric probes, for different patients;
- The probes must be calibrated periodically and this cost!
- More than 1500 published papers on this method!

Transient Elastography (FibroScan)

- The results of TE are **good in patients with chronic hepatitis C, chronic hepatitis B, non-alcoholic fatty liver disease (NAFLD), colestatic liver diseases and others.**
- TE is now **a validated method for liver fibrosis evaluation and many guidelines (such as the EASL Guidelines)** and introduced this method in their diagnostic and therapeutical algorithm (1,2).

- 1. EASL Recommendations on Treatment of Hepatitis C 2015
- 2. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis

FibroScan- advantages

- *Painless, well accepted by patients;*
- Rapid method of evaluation (**less than 5 min. for 10 valid measurements**); **Immediate results (in kPa).**
- **But: Valid measurements in approx. 85% of the cases (with IQR and SR)(1) or less (2) for standard probe (M probe).**
- *Using M and XL probes valid measurements can be obtained in 93,5% of cases (3).*

1. Castera L, Foucher J, Bernard PH, et al. Pitfalls of Liver Stiffness Measurement: A 5-Year Prospective Study of 13,369 Examinations. Hepatology 2010; 51: 828-835.

2. Sirlı R, Sporea I, Bota S et al: Factor sinfluencing reliability of liver stiffness measurement using transient Elastography (M probe-monocentric experience). Eur J Radiol. 2013;82(8):e313-6

3. Sporea I, Şırlı R, Mare R, Popescet al.. Feasibility of Transient Elastography with M and XL probes in real life. Med Ultrason. 2016 Mar;18(1):7-10

Practical value of TE

- For **clinical decision** in hepatology, the results **must be reproducible and with high accuracy**, specially *for the confirmation* of liver cirrhosis (and to exclude this disease) and **significant fibrosis (F \geq 2 Metavir)**.
- *Results from large multicenter prospective studies, meta-analyses are in favor of this method.*
- Transient Elastography is a validated method for liver stiffness assessment [being proposed too by **EASL Guidelines (1,2)**].
- **M and XL probes must be used!**

1. EASL Recommendations on Treatment of Hepatitis C 2015

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

TE: Meta-analysis HCV patients

- For significant fibrosis ($F \geq 2$ Metavir):
 - In the **Friedrich-Rust meta-analysis**, based on 50 studies [1], the **mean AUROC was 0.84, with a suggested optimal cut-off of 7.6 kPa.**
 - In the **Tsochatzis meta-analysis**, the pooled cut-off for **$F \geq 2$ Metavir** was also **7.6 kPa, with 0.78 pooled sensitivity and 0.89 pooled specificity [2].**

1. Friedrich-Rust M et al: Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008; 134(4): 960-74

2. Tsochatzis EA et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol. 2011;54(4):650-6

Liver stiffness for the diagnosis of cirrhosis

- LS measurement by means of FibroScan is a **reliable method for the diagnosis of cirrhosis, with 87% sensitivity** (95%CI: 84-90%), **91% specificity** (95%CI: 89-92 as shown in a **meta-analysis**(1).
- **Meta-analysis: for F 4 optimal cut-off: 13 kPa with AUROC : 0.94 (0.93-0.95) (2).**
- In the Tsochatzis **meta-analysis, for HCV patients, proposed cut-off: 12 kPa (3).**

1. Talwalkar JA. et al: Clin Gastroenterol Hepatol. 2007; 5: 1214-20.

2. Friedrich-Rust et al : Gastroenterology 2008;134:960-974

3. Tsochatzis EA et al.. J Hepatol. 2011;54(4):650-6

Diagnostic performance for $F \geq 2$ in HBV patients

■ HBV: Cut off 7 kPa AUROC 0.81

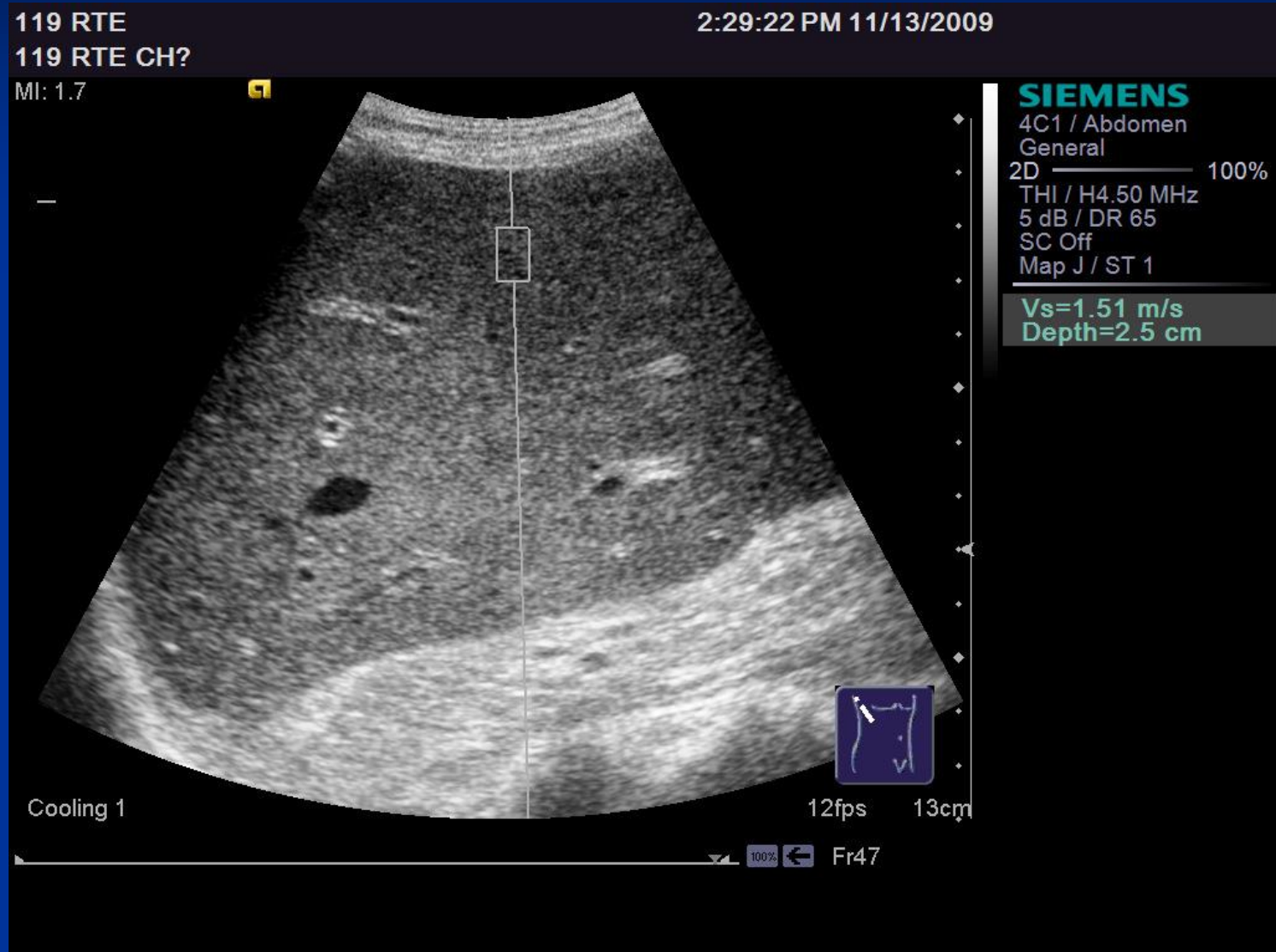
Acoustic Radiation Force Impulse (ARFI) techniques

- These techniques are *based on the generation of shear waves by the push-pulse of the ultrasound beam.*
- Are **implemented in ultrasound machine!**
- Can be used in patients with ascites.
- **This techniques are devided in :**
 - a) Point SWE (very simple)
 - b) 2D-SWE (seem to be more precise!)

a) Point SWE

- Point SWE is integrated into standard ultrasound machines and *is a simple method* for liver fibrosis evaluation.
- It *can also be performed in patients with ascites, like 2D-SWE* and this is an advantage as compared to TE.
- Virtual Touch Quantification (VTQ) was the **first** point SWE method introduced in clinical practice.
- *Several meta-analyses shown its good value as compared to liver biopsy or TE.*

Point SWE (VTQ) – very simple



Meta-analysis: 13 studies, 1163 patients

Predicting significant fibrosis ($F \geq 2$)

- For **ARFI (VTQ)** elastography the summary Se was **0.74** (95% CI: 0.66-0.80), the summary Sp was **0.83** (95%CI: 0.75-0.89).
- For **TE**, the summary Se was **0.78** (95%CI: 0.72-0.83), the summary Sp was **0.84** (95%CI:0.75-0.90).
- The diagnostic odds ratio of **ARFI (VTQ)** and **TE** did not differ significantly [mean difference in rDOR =0.27 (95%CI -0.69 to 0.14)].

Meta-analysis

Predicting Liver cirrhosis (F=4)

- For ARFI (VTQ) elastography, the summary Se was **0.87** (95%CI: 0.79-0.92), the summary Sp was **0.87** (0.81-0.91).
- For TE, the summary Se was **0.89** (95%CI: 0.80-0.94), the summary Sp was **0.87** (95%CI: 0.82-0.91).
- The diagnostic odds ratio of ARFI (VTQ) and TE did not differ significantly [mean difference in rDOR =0.12 (95%CI -0.29 to 0.52)].

VTQ- Meta-analysis

- 36 studies with 3951 patients (1):
- The mean diagnostic accuracy of ARFI (VTQ) expressed as the AUROC were:
 - a) 0.84 for the diagnosis of significant fibrosis ($F \geq 2$),
 - b) 0.89 for the diagnosis of severe fibrosis ($F \geq 3$) and
 - c) 0.91 for the diagnosis of liver cirrhosis ($F = 4$).

pSWE from Philips – Elast PQ



Elast PQ: paper published last year

- **228 consecutive subjects with chronic viral hepatopathies** (1) (26% **HBV**, 74% **HCV**), from whom 51% had liver cirrhosis. *Liver stiffness (LS) was evaluated in the same session by means of 2 elastographic methods: TE (FibroScan, EchoSens) and ElastPQ (Affinity, Philips) techniques.*
- The **AUROC**s were calculated considering TE as the reference method: 0.94 for significant fibrosis ($F \geq 2$), 0.97 for severe fibrosis ($F \geq 3$) and 0.97 for cirrhosis ($F = 4$).
- *A strong correlation between measurements obtained by Transient Elastography and ElastPQ ($r = 0.85$, $p < 0.001$).*

Point SWE from Hitachi

YOUR APPLICATION

ARIETTA 85

Shear Wave Measurement (SWM)

Median values of liver stiffness

Study based on 445 patients

Reliability index VsN > 50% improves diagnostic performance of SWM

Fibrosis Stage	SWM, kPa (interquartile range)		Ruling-in F \geq 2 (95% CI)	Ruling-out F \geq 2 (95% CI)	Ruling-in F=4 (95% CI)	Ruling-out F=4 (95% CI)
Mild/No fibrosis (F0-F1)	4.8 (4.0-5.7)					
Significant fibrosis (F2)	7.2 (5.7-9.0)	Cutoff, KPa	6.78	5.55	9.15	8.41
Advanced fibrosis (F3)	8.5 (6.7-9.5)	Sensitivity	76.9	90.6	83.3	90.6
Liver cirrhosis (F4)	14.0 (11-17)	Specificity	90.3	72.2	90.1	82.2

Ferraioli et al., J Gastrointestin Liver Dis, 2017



b) 2D-SWE (real time SWE)

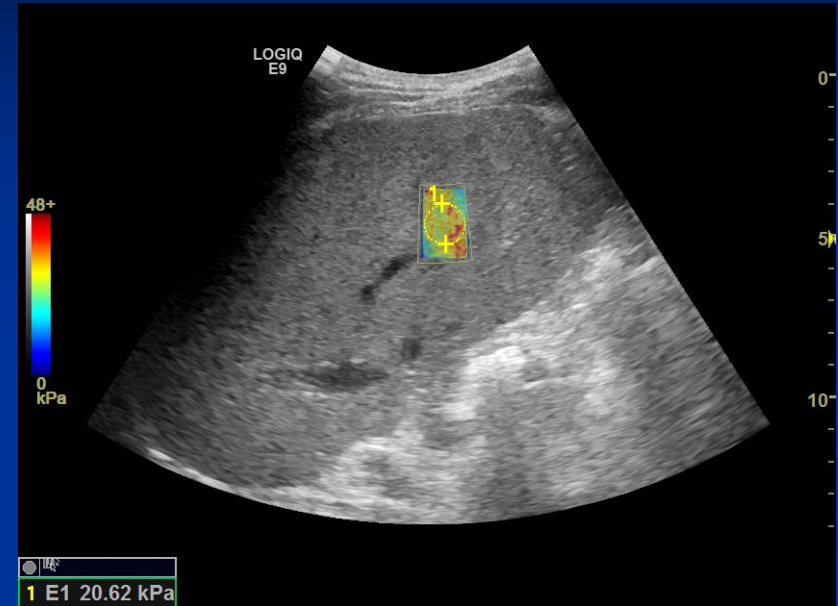
- 2D-SWE is an elastographic method integrated into a standard ultrasound machine, it *is a numeric and color coded method.*
- *Published papers revealing its good results for liver fibrosis assessment.*
- **Super Sonic Imagine (SSI)** (Aixplorer) was the first used in practice (1,2), followed by **2D-SWE.GE** and others [**Canon (Toshiba), Philips**].

1. Ferraioli G, *et al.*: Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: A pilot study. Hepatology 2012;56: 2125-2133

2. Ferraioli G, *et al.*: Reproducibility of real-time shear wave elastography in the evaluation of liver elasticity. Eur J Radiol 2012;81:3102-3106

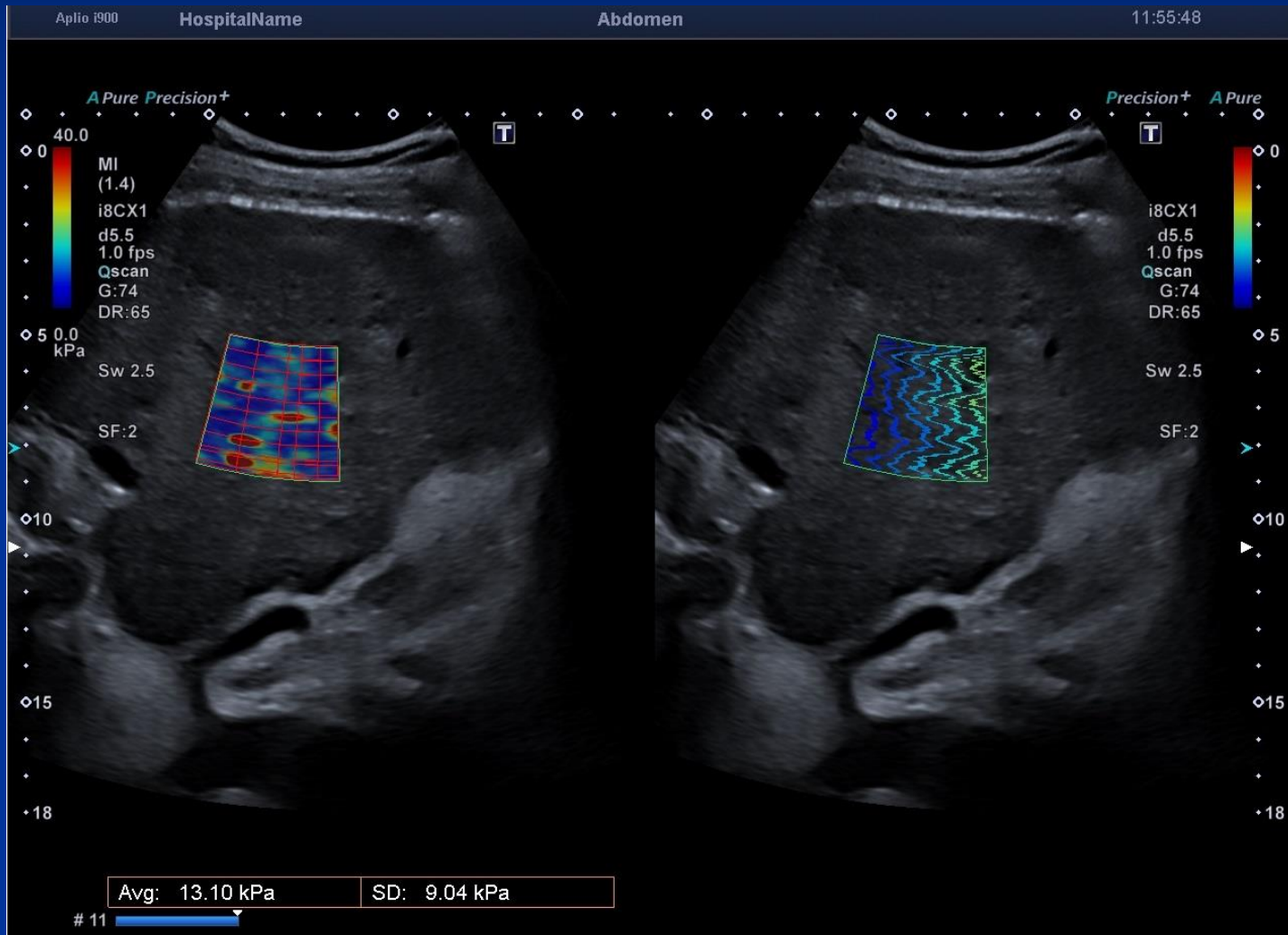
c) 2D-SWE (color coded and numeric values)

SuperSonic Imagine (SSI)
(Aixplorer): kPa or m/s



2D SWE.GE: kPa or m/s

2D-SWE with propagation map (Toshiba)



Results of 2D-SWE.SSI- paper just published

- **Meta-analysis** : Data on both **2D-SWE** and **liver biopsy** was available in **1134 patients** from 13 sites, as well as on successful *transient elastography (TE) in 665 patients*. (1).

Main etiologies: Most patients had chronic hepatitis C (HCV, n = 379) and hepatitis B (HBV, n = 400).

Histology: *40.8% of the patients had minimal or no fibrosis, 19.3% had significant fibrosis, 14.0% had severe fibrosis and 26.0% had cirrhosis.*

Results of the study

- **AUROC**s of **2D-SWE** in patients with **HCV** and **HBV** were:
 - 86.3% and 90.6% for diagnosing **significant fibrosis** ($F \geq 2$),
 - 92.9% and 95.5% for diagnosing **cirrhosis**, respectively.
- **CONCLUSION:** *2D-SWE has good to excellent performance for the non-invasive staging of liver fibrosis.*

Meta-analysis for 2D-SWE (SSI)

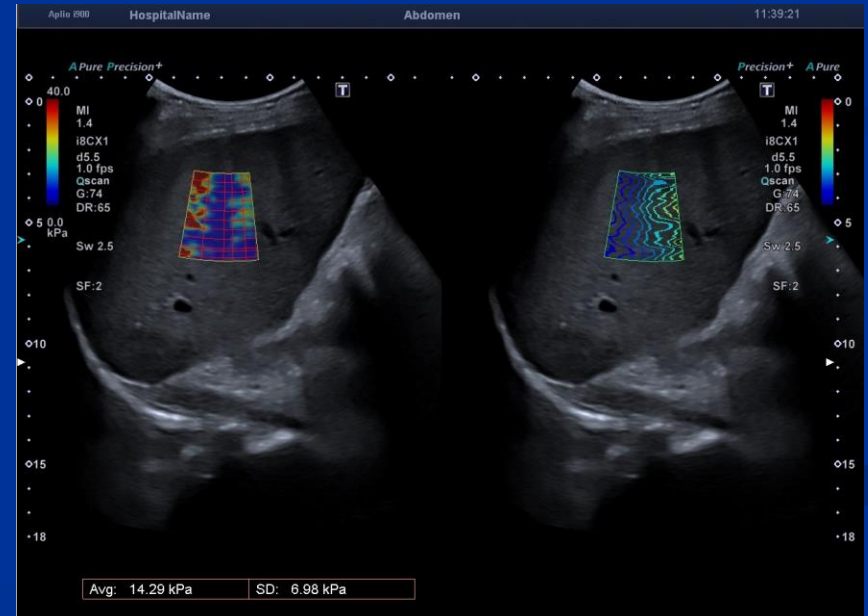
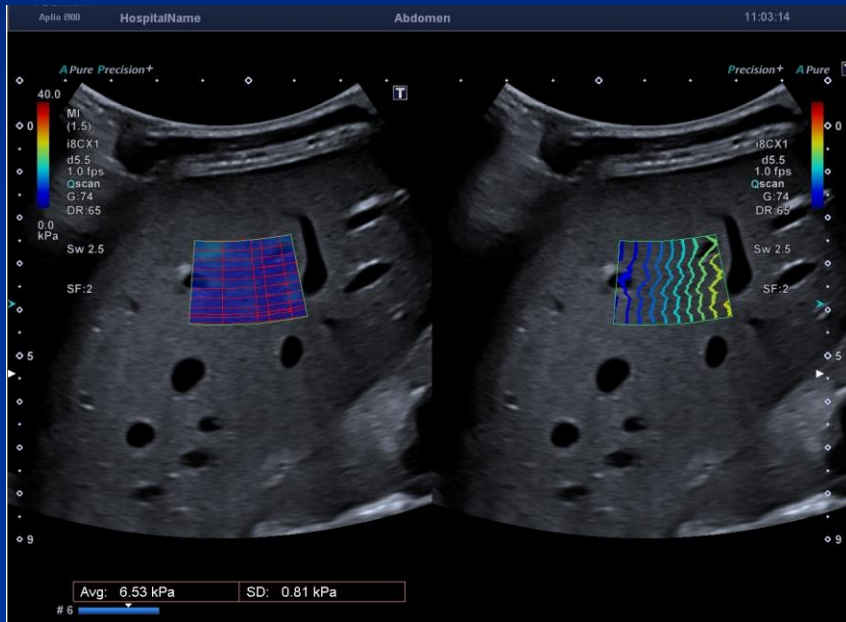
(3 published)

- *Twelve studies* were included in this meta-analysis and reported on *1635 patients* (liver biopsy as the reference, mixed etiologies) (1).
- The pooled *sensitivity and specificity* were 0.78 and 0.95 respectively, for fibrosis stages $F \geq 1$, *0.84* and *0.81* for $F \geq 2$, *0.89* and *0.84* for $F \geq 3$, and *0.88* and *0.86* for $F=4$.
- The AUROC' were *0.87* for $F \geq 1$, *0.85* for $F \geq 2$, *0.93* for $F \geq 3$, and *0.93* for $F=4$.
- **Conclusion of the study:** “2D-SWE could be used for staging of liver fibrosis. Especially, it has *high diagnostic accuracy for severe fibrosis and cirrhosis.*”

Results with 2D-SWE.GE

- **331 consecutive subjects with or without chronic hepatopathies** (1) in whom LS was evaluated **in the same session** by means of 2 elastographic techniques: **TE** (FibroScan, EchoSens)(M or XL probes) and **2D-SWE.GE** (LOGIQ E 9 XD clear 2.0, GE Healthcare).
- **Reliable LS measurements were obtained in 95.8% subjects by 2D-SWE.GE and 94.2% by TE (p=0.44).**
- **A very strong correlation was found between the LS values obtained by the 2 methods: $r=0.83$, $p<0.0001$.**
- **The best cut-off value for $F\geq 2$, $F\geq 3$ and for $F=4$ were 6.7 kPa, 8.2 kPa and 9.3 kPa.**

2D-SWE with a propagation map



2D-SWE with a propagation map

- 115 consecutive patients underwent 2D-SWE by two different operators and TE by sonographers on the same day (1).
- The correlation coefficient of the **intra-class correlation** test between an experienced radiologist and a third-year radiology resident was **0.878**.
- There was a moderate correlation between SWE and TE ($r = 0.511$) in the diagnosis of hepatic fibrosis.
- The *best cutoff values predicting significant hepatic fibrosis and liver cirrhosis by 2D-SWE were >1.78 m/s (AUROC = 0.777) and >2.24 m/s (AUROC = 0.935), respectively.*
- Conclusion of the study: “2D-SWE with a propagation map is a reliable method for predicting hepatic fibrosis, regardless of operator experience”.

2D-SWE with a propagation map – our experience

- **142 subjects** with or without chronic liver disease, in which LS was evaluated in the **same session by means of TE** (Fibroscan, EchoSens) and a **2D-SWE technique with vibration control** from Canon (Toshiba) (implemented on the Aplio I900 system).
- ***For classification we used the TE as a reference method.***
- **Results:** 124 subjects with both methods had reliable LS measurements.
- The ***mean LS values obtained by 2D-SWE were significantly lower than those obtained by TE.***
- **A direct, significant correlation ($r=0.65$), was obtained between LS values assessed by means of 2D-SWE and TE ($p<0.001$).**
- The **cut-off values for 2D-SWE for diagnosing significant fibrosis, $F\geq 2$ were >6.4 kPa (AUROC=0.85), for $F4$ was >10.6 kPa (AUROC=0.95).**

Comparative study : TE, ARFI (VTQ) and SSI in chronic liver diseases

- A total of 349 consecutive patients with chronic liver diseases who underwent liver biopsy.
- For each patient, liver stiffness was assessed by SSI, ARFI (VTQ), FibroScan (*M and XL probes*).
- *SSI, Fibroscan, and ARFI correlated significantly with histological fibrosis score ($r=0.79$, $p<.00001$; $r=0.70$, $p<.00001$; $r=0.64$, $p<.00001$, respectively).*
- **Conclusion:** *No significant difference between methods was observed for the diagnosis of mild fibrosis and cirrhosis.*

Have in mind in liver Elasto!

- Different elastographic systems give different values for the same degree of liver fibrosis!
Than the cut-off values must be known for the system with which we work!
- There are some **confounding factors in liver elastography: fasting or not** (liver elastography must be performed in fasting conditions), **increases aminotranpherasis** (confident values < 100 iu/ml), **obstructive jaundice, right hearth failure** (*all increasing elastographic values*), others.

One or more elastographic methods for liver fibrosis assessment? (1)

- **Transient Elastography is a validated method for liver stiffness assessment** [being proposed too by EASL Guidelines (2,3)].
- But, in this moment, *in my opinion*, the body of evidence for others methods (**like point or 2D-SWE**) is enough strong (meta-analyses or large multicenter studies) for the introduction of this techniques in clinical practice in hepatology!

1. Sporea I. One or more elastographic methods for liver fibrosis assessment? Med Ultrason. 2015 Jun;17(2):137-138

2. EASL Recommendations on Treatment of Hepatitis C 2015

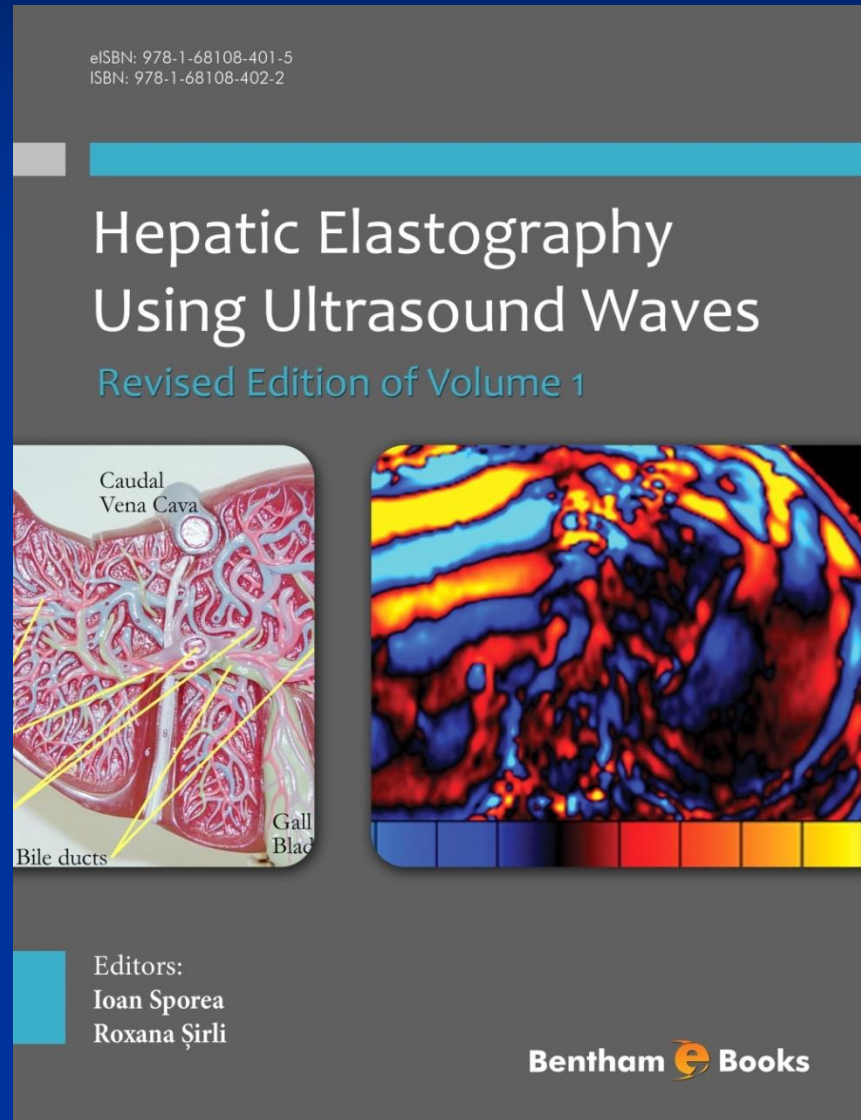
3. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis

CONCLUSIONS

- *Body of evidence regarding the value of ultrasound based elastographic methods for liver fibrosis evaluation is large enough to enable their use in daily hepatological activity.*
- **The new EFSUMB Guidelines on Liver Elastography 2017 (1), that was recently published support this reality.**
- *In real life, in many cases, in clinical situations, Liver Elastography replaced Liver Biopsy!*

E-book on Liver Elastography, revised Edition, was published recently (free download):

<http://ebooks.benthamscience.com/book/9781681084015>



Elastography Group Timișoara

