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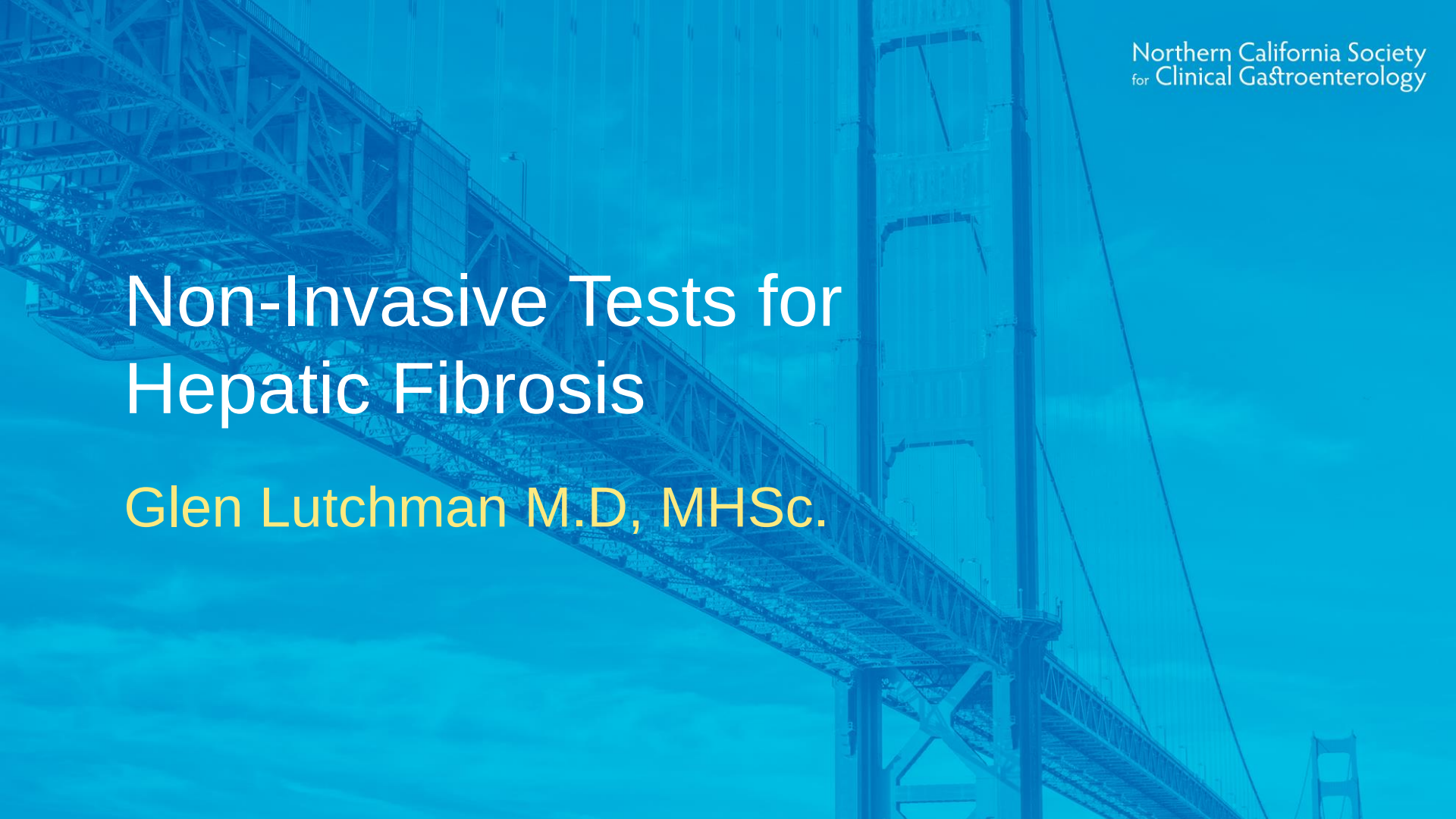


Northern California Society for Clinical Gastroenterology

Non-Invasive Tests for Hepatic Fibrosis

Glen Lutchman M.D, MHSc.

Patient R.G

- 50 year old Hispanic woman
- Chronic hepatitis C genotype 1a diagnosed in 2001
- No co-morbidities
- Declined IFN based treatment due to concern for side effects
- AST 61, ALT 92, platelets 185
- Requests all oral DAA therapy for her HCV
- Patients insurance provider requests confirmation of advanced fibrosis (F3-F4) before approving therapy
- Patient does not wish to undergo liver biopsy due to concerns over invasive nature of procedure

Modalities for the Diagnosis of Hepatic Fibrosis

- Gold Standard: Liver Biopsy
- Standard Lab investigations
- Standard Lab investigations + Clinical Markers of Fibrosis
- Serum Markers of Hepatic Fibrosis
- Fibrosis Panels
- Transient Elastography
- Acoustic Radiation Force Impulse Imaging
- Magnetic Resonance Elastography
- New Technology

Standard Lab Investigations and Fibrosis

- Aminotransferase levels > 2 x ULN
  - Inconsistent association
- AST/ALT > 1
  - Angulo P et al(1999)-47% NASH patients with advanced fibrosis
- AST-to-platelet ratio (APRI)
  - Kruger FC et al (2011)-AUROC of 0.85 for advanced fibrosis
  - Cutoff of 0.98 –NPV 93%, PPV 54%

Standard Labs + Clinical Markers of Fibrosis

Reference	n	Risk Factors	Odds Ratio (95% CI)
Angulo P, et al, 2007	733	Age (years)	1.04(1.01,1.07)
		BMI (kg/m2)	1.10(1.04,1.16)
		IGF/diabetes	3.12(1.77,5.51)
		AST/ALT	2.70(1.33,5.62)
		Platelet count (x 10 9/L)	0.987(0.98,0.99)
		Albumin (g/dl)	0.51(0.25,1.05)
Harrison S, et al	827	BMI ≥28	2.4(1.2,4.8)
		AST/ALT ≥0.8	9.3(6.3,13.6)
		Diabetes	4.0(2.8,5.7)

Composite Scores for Advanced Fibrosis (F3-4)

Predictive Score	n	Formula	AUROC (95% CI)	Cutoff	PPV (%)	NPV(%)
NAFLD Fibrosis Score	733	-1.675 + 0.037 x age + 0.094 x BMI + 1.13 x IGF/diabetes (1=yes, 0=no) + 0.99 x AST/ALT – 0.013 x platelet count – 0.66 x albumin	0.88 (0.85, 0.92)	≤ -1.455 ≥ 0.676	56 90	93 85
FIB-4 Score	541	(Age x AST)/(platelet count x ALT)	0.80 (0.75, 0.85)	≤ 1.30 ≥ 2.67	43 80	90 83

Angulo P, et al 2007. Shah AG, et al 2009.

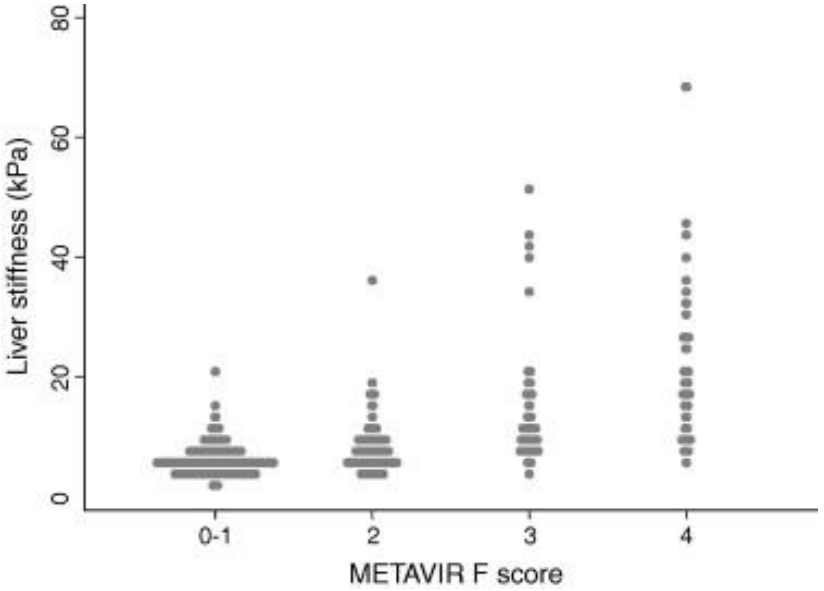
Serum Markers of Advanced Hepatic Fibrosis (F3-4)

Reference	n	Serum Marker	AUROC	Sensitivity	Specificity
Sukugaya et al, 2005	112	Hyaluronic acid ≥ 50 ng/ml Type 4 collagen 7S ≥ 5 ng/ml	0.80 0.82	68.8 81.3	82.8 71.4
Kaneda et al, 2006	148	Hyaluronic acid > 42 ng/ml		100.0	89.0
Santos et al, 2005	30	Hyaluronic acid > 24.6 ng/ml Type 4 collage > 145 ng/ml Laminin > 282 ng/ml	0.73 0.80 0.87	82.0 64.0 82.0	68.0 89.0 89.0

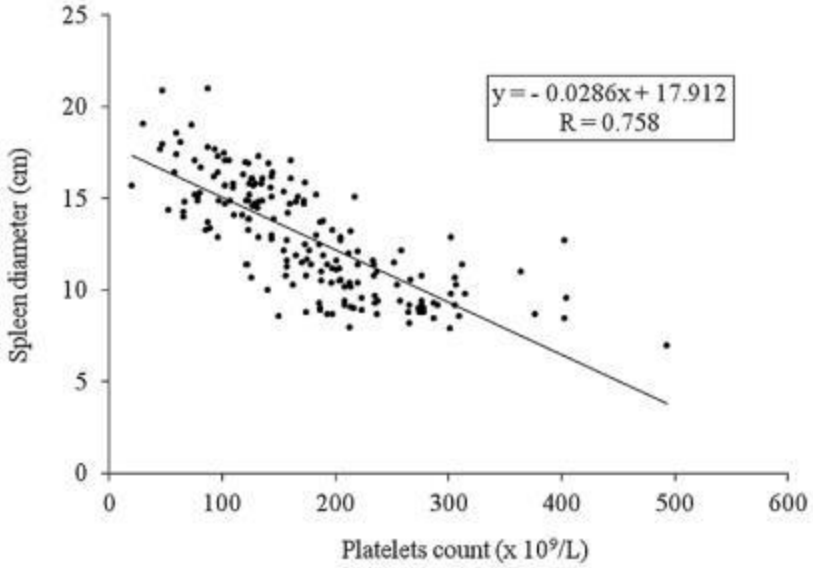
Fibrosis Panel Predictors of Advanced Fibrosis In NAFLD

Reference	n	Serum Marker	AUROC	Sensitivity	Specificity
Ratziu et al, 2006	267	Fibrotest 0.30 Fibrotest 0.70	0.88 0.88	92.0 25.0	71.0 97.0
Guha et al, 2008	192	ELF Score= -7.412 + (ln(HA)*0.681) + (ln(P3NP)*0.775) + (ln(TIMP1)*0.494) ELF = 0.3576	0.93	80	90

The Problem with the Gold Standard



Comparing a Continuous and Categorical Variable



Comparing two continuous variables

QUANTITATIVE ASSESSMENT OF LIVER FIBROSIS BY DIGITAL IMAGE ANALYSIS: RELATIONSHIP TO ISHAK STAGING AND ELASTICITY BY SHEAR-WAVE ELASTOGRAPHY

2016712

Ender G. Yegin[1], Korkut Yegin[2], Faruk Erdem Kombak[1], Emrah Karatay[1], Davut Tuney[1], Cigdem Ataizi Celikel[1], Osman C. Ozdogan[1]

[1]Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Ege University, Electrical and Electronics Engineering, Izmir, Turkey

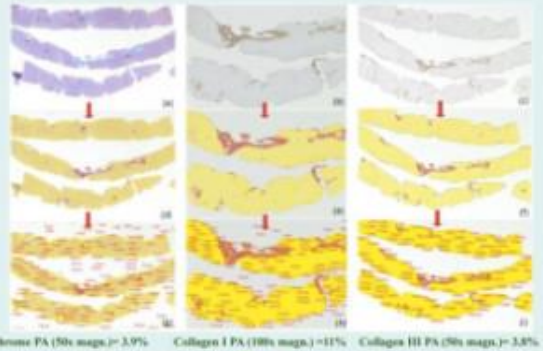


Figure 1- Digital image analyses procedure. Three digital images are presented for trichrome, collagen I and collagen III stained liver biopsy sections magnified by 50x, 100x and 50x, respectively, of a chronic hepatitis B patient staged as Ishak F4 (a, b, c). After the manual thresholding, the software marked the pixels to be measured and turned the original image into red (fibrosis) and yellow (parenchyma) colored overlay (d, e, f). The software next automatically calculated the areas of fibrosis and parenchyma by direct pixel counting (g, h, i).

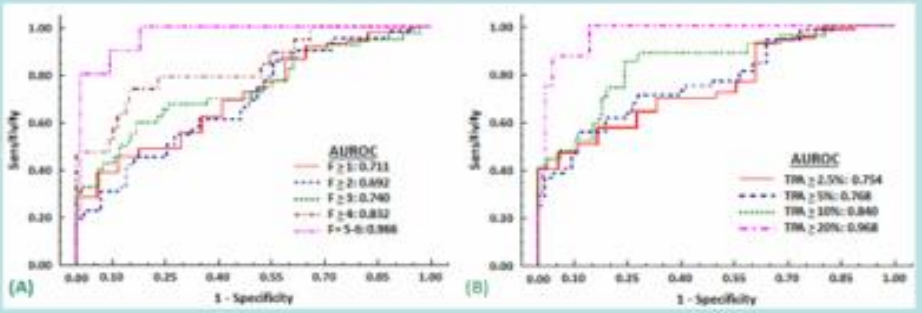


Figure 2- ROC curves illustrating the performance of SWE on differentiating qualitative stages of Ishak (A), and quantitative TPA (50x magn) thresholds of morphometry. Diagnostic performance of SWE increased gradually with progressing levels of fibrosis either as stages (A) or PA thresholds (B) which was indicated by the increases in AUROC values.

Abbreviations: AUROC, area under the ROC curve; ROC, receiver-operating characteristic; TPA, trichrome proportionate area

Conclusions:

DIA may serve as a reproducible quantitative reference standard for surrogate tests. We believe it is a better histological standard compared to histopathological staging systems for evaluating the true performances of non-invasive surrogates of fibrosis. SWE's performance and correlation with fibrosis amount were better for advanced levels of fibrosis, but less satisfactory for milder fibrosis levels.

#1490. Non-invasive Markers of Liver Fibrosis: Which One to Pick From a Myriad of Them! A Study of 1602 Liver Biopsies in Patients With Hepatitis C. Ragesh B Et. Al. Qatar.

- Aim:
  - Compare multiple non-invasive scores of liver fibrosis in patients with HCV
- Methods:
  - 1602 patients with liver biopsy (10/04-10/13).
  - F0=1.9%, F1=32.9%, F2=39.5%, F3=19%, F4=6.6%
  - Study derived score: albumin, AST, platelet count

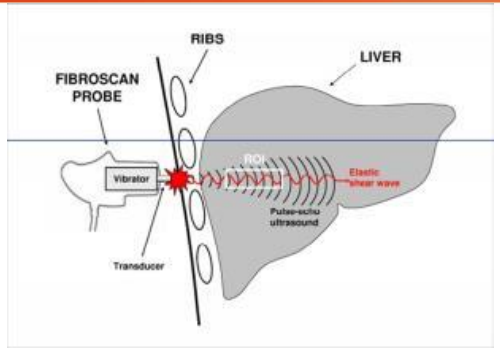
	Score	AUROC for predicting Cirrhosis (95% CI)
1	APRI	0.909 (0.853-0.965)
2	FIB-4	0.904 (0.861-0.946)
3	Lok score	0.847 (0.769-0.924)
4	GUCI score	0.910 (0.853-0.967)
5	Fibro-alpha	0.866 (0.807-0.926)
6	Forns' score	0.855 (0.793-0.917)
7	King score	0.908 (0.857-0.958)
8	AAR	0.691 (0.593-0.790)
9	Fibrosis index	0.894 (0.839-0.948)
10	Pohl score	0.618 (0.503-0.732)
11	Fibro-Q score	0.845 (0.774-0.916)
12	Fibrosis Cirrhosis Index	0.841(0.768-0.914)
13	Study score	0.868 (0.833-0.904)

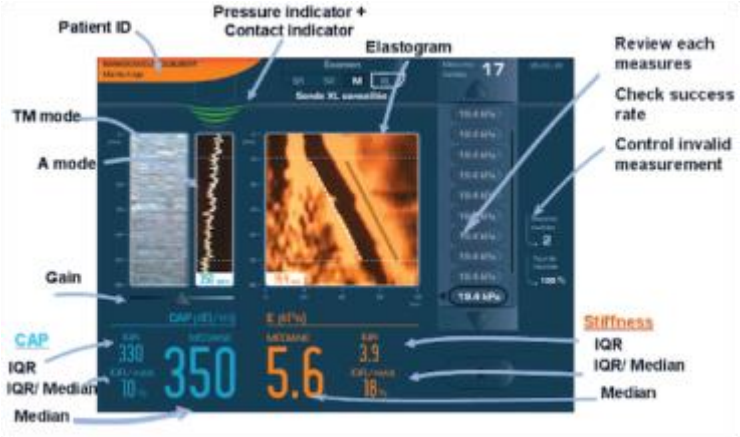
Results

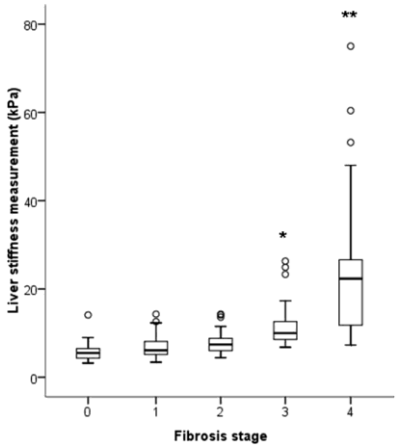
Conclusion:

- Excluding Pohl score and AAR, all the non-invasive scores showed high predictive accuracy for cirrhosis

Transient Elastography (FibroScan)







#13. Factors Associated with and Prevalence of Liver Fibrosis in a General Elderly Population: Results from the Rotterdam Study. Plompen E.P et. al. Erasmus University, Rotterdam

- Fibrosis assessed using TE
- LS ≥ 8.0 kPa cutoff for clinically relevant fibrosis
- 3417 participants
- Age 66.0 ± 7.6 yrs.
- BMI 27.3± 4.0
- Median LS 4.7 kPa (3.8-5.8)
- LS ≥ 8.0 kPa 169 (5.8%)

	OR	CI
Age	1.1	1.0 – 1.1
Diabetes	2.5	1.6 – 3.9
ALT	1.02	1.0 – 1.0
HBsAg/anti HCV	5.3	1.6 – 17.7
Steatosis	2.0	1.3 – 2.9
Spleen size	1.3	1.1 – 1.4

Factors associated with clinically relevant fibrosis

	LS ≥ 8.0 kPa	
50 – 60 yrs.	2.1%	1.5 – 3.5
80 – 90 yrs.	7.3%	4.4 – 12.6

Effect of age

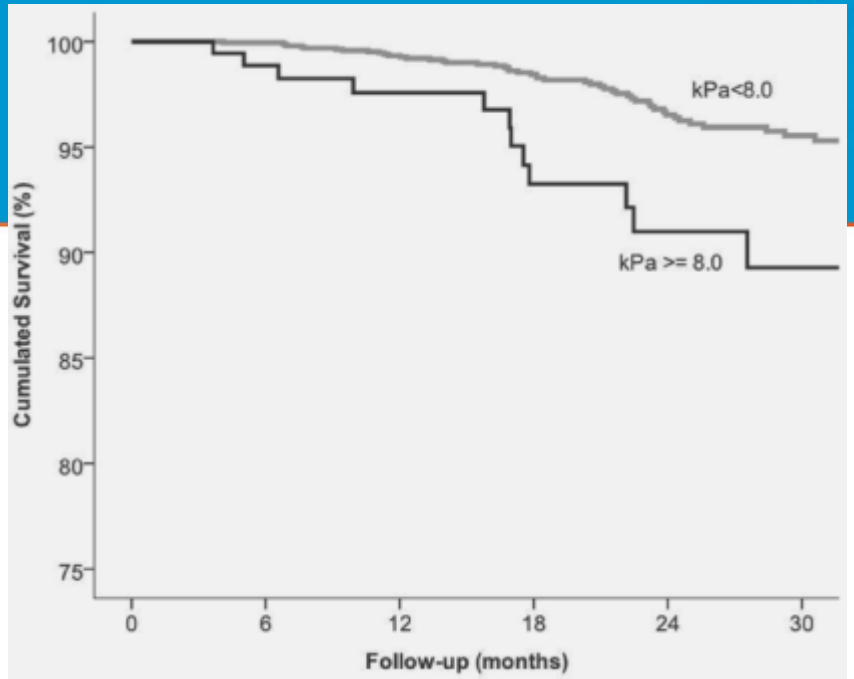
	Steatosis	No Steatosis
50 – 60 yrs.	4.2% (3.0 – 6.7)	1.7% (1.3 – 2.4)
80 – 90 yrs.	13.5% (10.0 – 22.1)	6.8% (4.1 – 11.1)

Effect of steatosis by age group

- Conclusion
  - 5.6% of patients had clinically relevant fibrosis, LS ≥ 8.0 kPa, on TE
  - Probability of fibrosis increased with age and steatosis

#14. Increased Liver Stiffness is Associated With Higher All-cause Mortality in Older Adults: Results From a Population Based Study. Koehler E.M Et. At. Erasmus University, Rotterdam.

- Cohort of Rotterdam study
- Mortality monitored via medical record linkage
- Association between LS ≥ 8.0 kPa and all-cause mortality by Cox regression analysis
- 2456 participants
- Age 71 ± 6.9 yrs
- Median follow up 18 months



- Conclusions
  - LS ≥ 8.0 associated with all cause mortality after adjusting for age and sex
  - HR 2.44 (1.35-4.42)

FEASABILITY OF TRANSIENT ELASTOGRAPHY USING M AND XL PROBES FOR ASSESING LIVER STIFI
A PRACTICE AUDIT OF 3235 EXAMINATIONS ON A MULTI-ETIOLOGY COHORT

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Department of Gastroenterology and Hepatology,"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

1. BACKGROUND

Liver Stiffness Measurements (LSMs) using Transient Elastography (TE) is widely used in the management of patients with chronic liver disease.

2. OBJECTIVES

To examine the feasibility and reliability of liver stiffness measurements by Transient Elastography and to assess the benefit of using both M and XL probes, in a large cohort of patients.

3. MATERIALS & METHODS I

- We studied retrospectively a group of 3235 patients with chronic liver disease (chronic hepatitis HCV, HBV, ASH, NASH, Primary biliary cirrhosis, autoimmune hepatitis) referred to our Department to assess liver fibrosis by TE.
- TE measurements were performed with a FibroScan® device (EchoSens, Paris, France).

3. MATERIALS & METHODS II

- We used the M Probe (standard probe – transducer frequency 3.5 MHz) and XL Probe (transducer frequency 2.5 MHz) in overweight and obese patients.
- In all patients the M probe was used first, and if the results were unreliable we used the XL probe.
- Reliable measurements were defined as the median of 10 valid measurements with a success rate ≥ 60% and an interquartile range < 30%.
- Results of liver elasticity were expressed in kiloPascals (kPa).

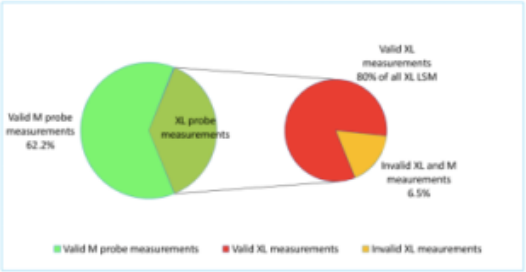


Fig.1. LS measurements by M and XL probes

4. RESULTS

- The studied group included 3235 patients with an average BMI of 28 kg/m².
- Valid measurements were obtained by M probe in 62.2% (2015/3235) patients, with an average BMI of 26.1 kg/m² (Fig.1).
- The average BMI of the patients evaluated with XL probe was 31.3 kg/m², higher than in patients who could be evaluated by M probe.
- Of the 1220 patients with unreliable results with M probe, valid measurements were obtained with XL probe in 80% (1011) patients (Fig.1).
- Only in 209 cases we did not obtain valid measurements with either probe, finally we obtained valid measurements by TE in 93.5% of cases.

5. CONCLUSIONS

- In our Dept., the feasibility of M probe was 62.2 %
- Reliable measurements using both M or XL probes allowed LS evaluation in 93.5% of cases.
- The use of XL probe, especially in patients with BMI> 30 kg/m² increases the feasibility of non-invasive diagnosis of liver fibrosis by TE.

6. Disclosures

No potential conflict of interest to disclose regarding this poster presentation

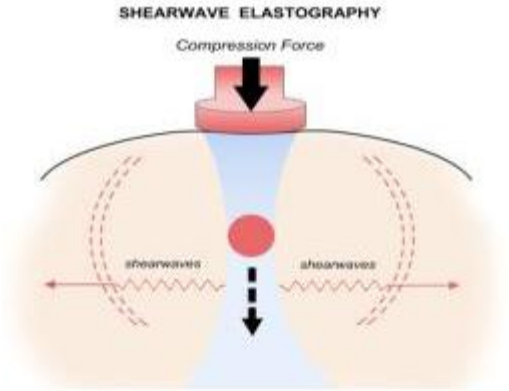
#211. The Severity of Steatosis Overestimates Liver Fibrosis Diagnosis by Liver Stiffness Measurement in Patients with NAFLD.
Petta S, et. at. University of Palermo, Italy.

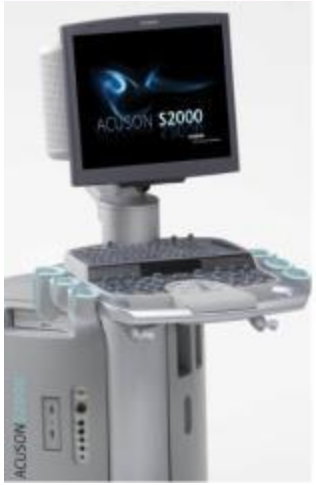
- Aim: To evaluate the effect of steatosis on LSM as measured by TE
- Methods: 253 patients with biopsy proven NAFLD. Fibrosis staged using METAVIR, Kleiner scoring of steatosis. TE performed with the M probe for LSM

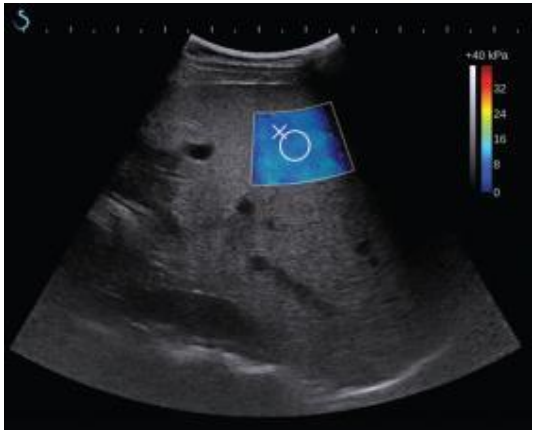
METAVIR Stage	≥ 66% Steatosis	< 66% Steatosis	P
F0-F2	8.0±3.1	6.5±2.6	0.002
F3-F4	-	-	NS

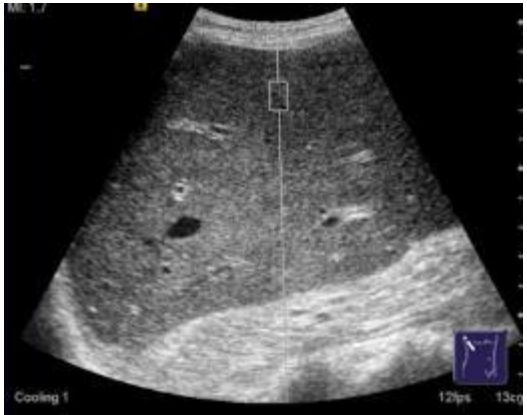
- Conclusions:
  - In patients with NAFLD, the presence of severe steatosis leads to an overestimation of liver fibrosis by LSM

Shear **W**ave **E**lastography (Airexplorer)
Acoustic **R**adiation **F**orce **I**mpulse Imaging









#15. Supersonic Shear Wave Elastography Versus Transient Elastography for the Diagnosis of Alcoholic Liver Fibrosis: A Biopsy Controlled Prospective Study. Thiele M, Et, Al. University Of Bonn, Germany

- Aim:
  - Evaluate SWE vs TE in diagnosis of alcoholic liver fibrosis
- Methods:
  - 140 patients
  - Alcohol overuse : women >16 g and men > 24 g/day
  - Liver biopsy, SWE and TE done on same day
  - ROC curve statistics comparing SWE and TE

Baseline Characteristics	N=140
Male	104
F0	30
F1	34
F2	19
F3	9
F4	48

	SWE	TE	P
F ≥ 2 Cutoff	8.0 kPa	8.7 kPa	
F4 Cutoff	12.1 kPa	16.2 kPa	
AUROC ≥ F2	0.90 (0.84-0.96)	0.90 (0.85-0.96)	NS
AUROC≥F4	0.94 (0.89-0.99)	0.95 (0.91-0.99)	NS
Failure	7%	9%	NS

- Conclusions:
  - TE has higher cutoff for cirrhosis than SWE
  - SWE not superior to TE in diagnostic accuracy or failure rate

SUPERSONIC SHEAR IMAGING PREDICTS CIRRHOSIS AND ADVANCED FIBROSIS IN CHRONIC HEPATITIS C PATIENTS

SHIH-JER HSU[1], YU-LIN TAN[2], DING-SHINN CHEN[3,4], JIA-HORNG KAO[3,4]

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Background

Staging hepatic fibrosis is important in the management of chronic hepatitis C. The elastic modulus of liver has been shown to correlates well with histologic fibrosis stage. Supersonic shear imaging (SSI) is based on the acoustic radiation force imaging technique to generate shear waves in liver tissue and is able to quantify the elastic modulus of liver. Thus SSI seems promising for the quantification of liver stiffness.

Methods

Chronic hepatitis C patients naïve to anti-viral therapy were enrolled. Liver stiffness, expressed in kPa, was measured with SSI using a SuperSonic Imagine Aixplorer diagnostic ultrasound scanner. Liver stiffness measurement with Fibroscan system was performed simultaneously for comparison. Liver histological examinations performed within 2 years were evaluated for the correlation of liver stiffness with METAVIR fibrosis stage.

Results

A total of 191 chronic hepatitis C patients (97 men and 94 women; mean age, 63.1 years) were enrolled. Liver stiffness values measured by SSI and Fibroscan had a good correlation (r = 0.8653, P<0.0001). Seventy patients had received liver histological examination within 2 years. The mean±SD of SSI liver stiffness for each fibrosis stage was 6.9±1.9 (F1), 10.3±2.4 (F2), 12.7±2.7 (F3), and 21.6±6.9 (F4), respectively. Using 13.6kPa as cut-off value, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SSI in discriminating advanced fibrosis (≥F3) was 81.6%, 95.7%, 93.9.%, and 75.0%, respectively. With a cut-off value of 15.6kPa the sensitivity, specificity, PPV, and NPV of SSI in predicting cirrhosis is 88.9%, 97.1%, 96.0%, and 91.7%, respectively.

Patient characteristic	
Gender (M/F)	97/94
Age, years (±SD)	63.1 (11.2)
BMI (±SD)	25.3 (3.4)
AST, IU/mL (±SD)	89 (64)
ALT, IU/mL (±SD)	121 (96)
ALP, IU/mL (±SD)	159 (59)
γ-GT, IU/mL (±SD)	58 (78)
Total bilirubin, mg/dL (±SD)	1.0 (0.4)
Albumin, mg/dL (±SD)	4.2 (0.3)
Platelet count, K/μL (±SD)	167 (56)
METAVIR fibrosis score, N*	
F1	8
F2	16
F3	12
F4	34

*Liver biopsy results were available in 70 patients.

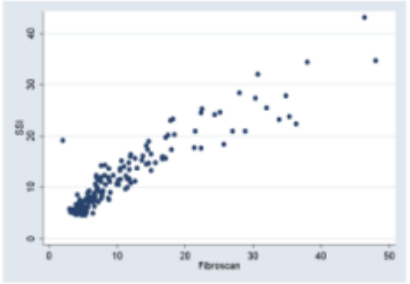

Figure 1. Scatter plot of liver stiffness measurement (kPa) by Fibroscan and SSI (N=191).

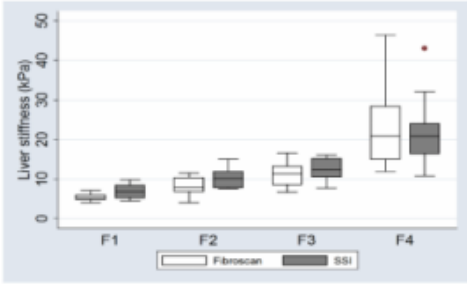

Figure 2. Box plot of Fibroscan and SSI values for each METAVIR fibrosis stage (N=70).

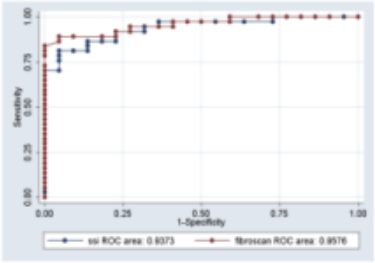

Figure 3. ROC curves of Fibroscan and SSI for fibrosis stage

Figure 4. ROC curves of Fibroscan and SSI for fibrosis stage

Conclusions

The liver stiffness measurement in chronic hepatitis C patients is comparable between SSI and Fibroscan systems. SSI appears to be a promising noninvasive method for liver fibrosis evaluation.

Disclosures

Ding-Shinn Chen - Consulting: BMS, GSK, Gilead, Roche, Merck
The following people have nothing to disclosure: Shih-Jer Hsu, Yu-Lin Tan, Jia-Horng Kao

Diagnostic Accuracy and Reliability of Supersonic Shear Imaging in Comparison with Transient Elastography for Assessment of Liver Fibrosis in Patients with Chronic Liver Disease.

University of Miami Miller School of Medicine, Schiff Center for Liver Diseases
Masato Yoneda, Emmanuel Thomas, Seth N. Sclair, Eugene R Schiff

Introduction and Premise

Staging of liver fibrosis is essential in determining the prognosis and optimal treatment for patients with chronic liver disease and also to guide surveillance for the development of hepatocellular carcinoma (HCC). Liver biopsy is recommended as the reference standard method for the diagnosis and staging of fibrosis in chronic liver disease. This procedure, however, is invasive with associated risks of complications, high cost and it is time consuming both for providers and patients with a lag time before results are reported. Therefore, there is great need for a rapid, quantitative and noninvasive method for detecting fibrosis.

Aims

The aim of this study was to compare elastography measurements of liver fibrosis using the Supersonic Shear Imaging (SSI) and Fibroscan® in patients with chronic liver disease.

Methods

This was a prospective study of 445 patients (mean age: 56.8 ± 12.0; BMI 26.5 ± 4.7) in which liver stiffness was assessed using Fibroscan® (M probe or XL probe) and SSI during the same clinic visit. In total, 205 out of 445 patients had histologic determination of fibrosis stage.

FibroScan® (Transient Elastography)

Probe including an ultrasonic transducer

Liver stiffness measurement (LSM) was assessed using FibroScan® with the M probe. The XL probe was used when the M probe was unreliable for obtaining measurement in obese patients.

Reliable LSMs were obtained as the median of 10 valid measurements with a success rate (SR = ratio of the number of acquisitions) of ≥ 60% and an interquartile range (IQR = the range of the middle 50% of the data) of <30%.

Aixplorer® (Supersonic Shear Imaging)

SSI, also named ShearWave™ elastography, is based on the measurement of the velocity of a local shear wave through soft tissue. SSI can be integrated into a conventional ultrasound system using conventional probes.

We used IQR and SR to assess the quality of SSI measurements with the same criteria for determination of unreliable LSM used for FibroScan®.

Noninvasive Clinical Scoring Systems

The FIB-4 index: age x AST (IU/L) / platelet count (x 10^9/L) / √ALT (IU/L).
AST to ALT ratio (AAR): AST/ALT.
AST to platelet ratio index (APRI): AST (/ ULN) / Platelet counts (x 10^9/L) x 100.

Results

Table 1. Underlying Liver Conditions Observed in This Study

Hepatitis C virus infection (HCV)	263
Hepatitis B virus infection (HBV)	28
HBV/HCV	3
HCV/HIV (Human Immunodeficiency Virus)	1
HBV/HIV	13
Autoimmune Hepatitis (AIH)	9
Primary Biliary Cirrhosis (PBC)	14
Primary sclerosing cholangitis (PSC)	16
Nonalcoholic fatty liver disease (NAFLD)	43
Alcoholic liver disease	4
α1-antitrypsin deficiency	4
Elevated liver enzymes from unknown origin	47

Figure 1. Relationship Between BMI and the Probe Utilized for FibroScan®

Table 2. LSM Failure (Unreliable LSM Rate)

Aixplorer® (Supersonic shear Imagining)	9.5%
FibroScan® (M + XL probe)	2.5%

Figure 2. Correlation Between LSM Obtained Using SSI Fibroscan

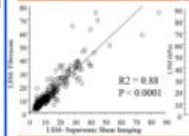

Figure 3. LSM Obtained Using SSI for Each Stage of Fibrosis

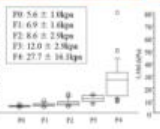

Figure 4. LSM Obtained Using FibroScan® for Each Stage of Fibrosis

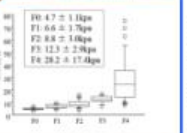

Figure 5. Receiver-Operating Characteristic (ROC) Curves for Detecting Stage ≥ 3 Fibrosis.

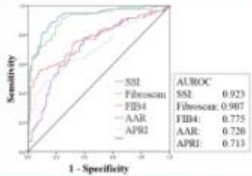

Figure 6. Receiver-Operating Characteristic (ROC) Curves for Detecting Liver Cirrhosis.

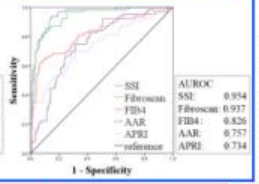

Table 3. Optimal Cutoff and Diagnostic Accuracy of SSI and Fibroscan for Detecting Each Fibrosis Stage

Elastography	Fibrosis stage	Cutoff value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
SSI	F ≥ 1	6.5 Kpa	65.3%	91.3%	98.3%	25.5%
	F ≥ 2	7.7 Kpa	78.2%	83.3%	90.4%	65.5%
	F ≥ 3	9.7 Kpa	84.9%	86.8%	84.9%	86.8%
	F = 4	11.4 Kpa	94.4%	87.4%	80.6%	96.5%
Fibroscan	F ≥ 1	5.4KPa	87.4%	56.5%	93.8%	37.1%
	F ≥ 2	7.8KPa	79.4%	74.2%	86.0%	64.5%
	F ≥ 3	8SKPa	91.1%	74.8%	75.2%	90.9%
	F = 4	12.6KPa	85.5%	90.6%	83.1%	92.1%

Discussion

FibroScan®, the first developed ultrasound-based elastography method, was recently included in the European Association for the Study of the Liver (EASL) Guidelines for fibrosis assessment for chronic hepatitis B and C infection. Furthermore, FibroScan® received approval from the U.S. Food and Drug Administration (FDA) on April 5th, 2013 and it is expected that its use will subsequently increase in not only Europe but also the U.S.

We evaluated the diagnostic accuracy and reliability of LSMs using SSI and the FibroScan® for the assessment of liver fibrosis in patients with chronic liver disease. The percentage of reliable SSI and TE were 90.5% and 92.5%, respectively.

We showed that SSI and FibroScan® are valuable diagnostic tools for the diagnosis of advanced fibrosis (F3-F4) and liver cirrhosis (F4) with AUROCs greater than 0.9. Furthermore, both types of elastography demonstrated higher accuracy than clinical scoring systems in the diagnosis of advanced fibrosis (F3-F4) and liver cirrhosis (F4).

The major advantages of FibroScan® and SSI, as compared with liver biopsy, are that these techniques are painless, rapid, and have no associated complications, and are universally accepted by patients. Moreover, SSI can be integrated into a conventional ultrasound system using conventional probes and therefore can be performed during standard examinations of the liver that are routinely performed in patients with chronic liver diseases for HCC surveillance.

Conclusion

In conclusion, SSI and FibroScan® were similarly accurate in diagnosing liver fibrosis in patients with chronic liver disease. Furthermore, both types of elastography methods demonstrated higher accuracy than scoring systems utilizing clinical parameters. This is the first study, to our knowledge, to compare SSI and FibroScan® from U.S. investigators that also includes patients from within the U.S. population.

Masato Yoneda
University of Miami Miller School of Medicine Schiff Center for Liver Diseases
I have no financial relationships to disclose within the past 12 months relevant to my presentation
AND
My presentation does not include discussion of off-label or investigational use medications.

THE USEFULNESS OF SPLEEN STIFFNESS EVALUATED BY ACOUSTIC RADIATION FORCE IMPULSE (ARFI) ELASTOGRAPHY FOR ASSESSING LIVER FIBROSIS

Simona Bota, Ioan Sporea, Oana Grădinaru-Taşcău, Alina Popescu, Roxana Şirli, Mirela Dănilă
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1. BACKGROUND

Recently, spleen stiffness (SS) assessed by various elastographic methods was evaluated for predicting liver fibrosis. Very good results were published for liver fibrosis assessment using SS by Acoustic Radiation Force Impulse (ARFI) elastography (1).

2. OBJECTIVES

The aim of this study was to try to validate these cut-offs in an independent cohort of patients chronic hepatitis B and C, considering liver biopsy (LB) as "gold-standard" method for liver fibrosis evaluation.

3. MATERIALS & METHODS

- Our retrospective study included 71 patients evaluated in the same session by LB and SS by ARFI elastography.
- The mean age of the patients was 46.3 ± 12.6 years, 39.4% having chronic hepatitis B and 60.6% chronic hepatitis C.
- Performed in all patients with a Siemens Acuson S2000™ ultrasound system in fasting condition
- Scanning was performed in supine position by intercostal approach in the midle part of the spleen, 1-2 cm under the splenn capsule (Fig.1) with minimal scan pressure applied by the operator
- We aimed for 10 valid measurements in every patient and a median value was calculated, the result being measured in meters/second (m/s).
- Reliable SS measurements was considered the median of 10 valid SS measurements with an interquartile range interval (IQR) <30%.
- For SS the following cut-offs were analyzed (1): F≥2: 2.74 m/s, F≥3: 3.14 m/s and F=4: 3.32 m/s.

4. RESULTS

Table 1.-

Fibrosis	SS Cut-off (m/s)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)
F≥2	>2.74	43.3	90.9	95.8	32.2	51.1
F≥3	>3.14	15	77.2	23.1	66.6	57.8
F=4	>3.32	40	89.8	25	94.6	85.9

Table.1. Predictive value of SS evaluated by ARFI elastography for predicting various stage of liver fibrosis

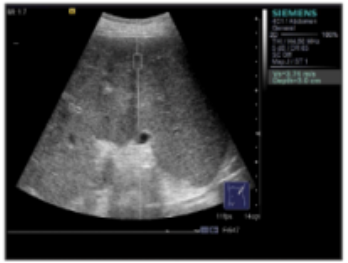

Fig.1. SS assessment by ARFI elastography

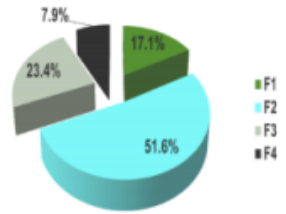

Fig.2. The distribution of liver fibrosis on liver biopsy

- Reliable SS measurements were obtained in only 64/71 patients (90.1%), which were included in the final analysis.
- The distribution of liver fibrosis on LB at this cohort of patients was: F0-0%, F1-17.2%, F2-51.6%, F3-23.4% and F4-7.9% (Fig.2).
- According to the pre-specified cut-off values, the performance of SS by ARFI elastography for predicting diferent stages of liver fibrosis is presented in Table 1.

5. CONCLUSIONS

In our patient cohort, SS by ARFI elastography had not the same very good accuracy for predicting different stages of liver fibrosis like in the paper of Chen et al (1). Because of the very good positive predictive value for predicting the presence of significant fibrosis and very good negative predictive value for excluding the presence of liver cirrhosis, SS by ARFI elastography might be use as supplementary diagnosistic tool in some patients with chronic viral hepatitis.

6. REFERENCES

1.Chan SH et al. J Viral Hepat 2012; 19: 654-663

7. Disclosures

Nothing to disclose regarding this poster presentation

NON-INVASIVE EVALUATION OF PORTAL HYPERTENSION BY SPLEEN ELASTOGRAPHY.

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Background / Aims

Severity of portal hypertension is a crucial prognostic factor in patients with liver cirrhosis. Invasive measurement of hepatic venous pressure gradient (HVPG) is a standard method used for the evaluation of portal hypertension. Although generally safe and well tolerated, this invasive procedure is not routinely available in all hospitals and it does not particulary enable long-term monitoring. Recently many non-invasive approaches have been studied for evaluation of portal hypertension in patients with liver cirrhosis.

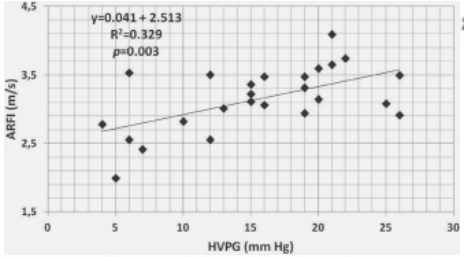
The aim was to assess usefulness of spleen elastography in the evaluation of portal hypertension in patients with liver cirrhosis

1. *Classical HVPG measurement using wedged balloon technique*
2. *Spleen elastography using ARFI (Siemens Acuson S2000)*

Methods

We examined 25 consecutive patients (18 men, 7 women), with average age 56,7 years with liver cirrhosis of various ethiology (13 alcoholic, 5 viral hepatitis, 5 NAFLD, 2 other). Diagnosis of cirrhosis was confirmed either with liver biopsy or with presence of portal hypertension. A control group consisted of 20 age-matched healthy individuals.

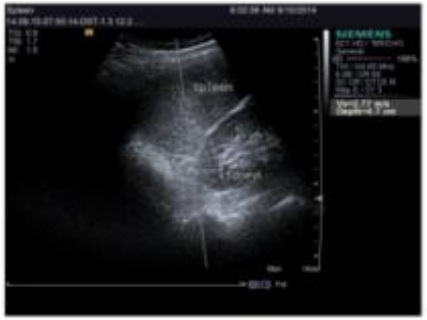
Every patient underwent standard biochemistry and blood count, abdominal ultrasound and elastography of liver and spleen (median of ten measurements) using ARFI (Acoustic Radiation Force Impulse) measurement with ultrasound system Siemens Acuson S2000. HVPG was afterwards measured in every patient.



Results

Clinicaly significant portal hypertension (HVPG>12mmHg) was diagnosed in 20 patients. The HVPG values were (mmHg; median, IQ range) 16,0 (4-26), ARFI of liver (m/s; median, IQ range) 2,817, ARFI of spleen (m/s; median, IQ range) 3,14.

The value of spleen stiffness significantly correlated with HVPG (p=0,003), liver stiffness did not (p=0,163). Another parameter which correlated with HVPG was the length of the spleen (p=0,033).



Conclusion

Spleen elastography using ARFI is simple, reproducible and easy to repeat non-invasive method for evaluation of portal hypertension in cirrhotic patients.

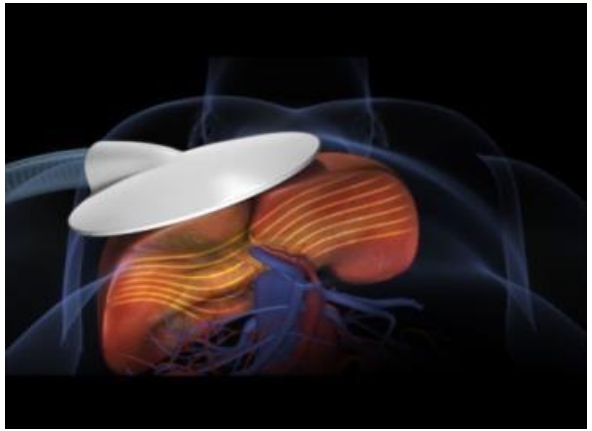
References

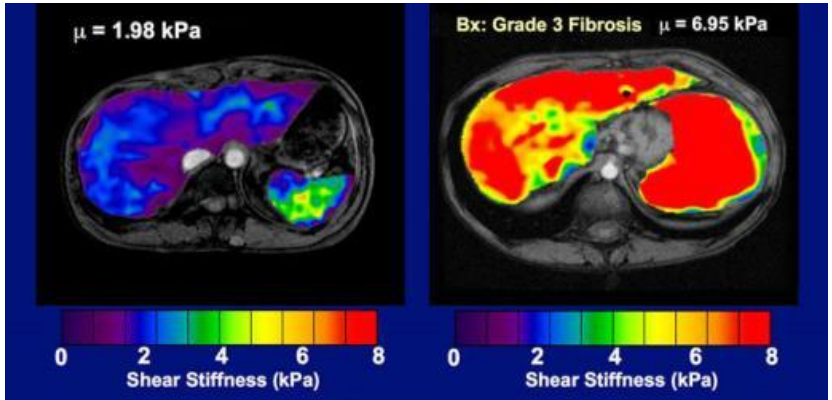
1. *de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2010 Oct;53(4):762-8*
2. *Castera L et al. Non invasive evaluation of portal hypertension using transient elastography. J Hepatol. 2012;56(3):696-703*
3. *Kim MY et al. Invasive and non-invasive diagnosis of liver cirrhosis and portal hypertension. World J Gastroenterol 2014;20(15):4300-4315*

Supported by IGA MZCR NT 12290/4 and SVV 260032-2014.

Contact: Dr. Karel Dvorak; k2dvorak@gmail.com
Disclosures: none

Magnetic Resonance Elastography





Magnetic resonance elastography is useful as non-invasive diagnostic method for predicting liver fibrosis in nonalcoholic fatty liver disease

I do not have any relevant financial or other relationship with a commercial organization that could influence the content of my presentation.

Kento Imajo, Takaomi Kessoku, Yasushi Honda, Wataru Tomeno, Yuji Ogawa, Hironori Mawatari, Koji Fujita, Masato Yoneda, Satoru Saito, Atsushi Nakajima

Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Japan.

BACKGROUND/AIMS

- Assessment of the severity of liver fibrosis is important in the evaluation of the stage of NAFLD.
- Although a liver biopsy is presently recognized as the only reliable method of liver fibrosis, this procedure is generally very invasive, expensive, and may result in a sampling error.
- Transient elastography (Fibroscan, EchoSens, Paris, France) is a useful technique that allows rapid and no -invasive measurement of the mean tissue stiffness (Yoneda M, et al. Dig Liver Dis. 2008).
- While recent clinical studies using the FibroScan system have appeared in the literature that have demonstrated increasing liver stiffness with advanced fibrosis in patients with NAFLD, body mass indices (BMI) >28 kg/m2 have been identified as an independent risk factor for failure to obtain a measure of liver elastography. Therefore, another modality is required for diagnosis of liver fibrosis in a morbid obese patients with NAFLD.
- MR elastography (MRE) is an MR imaging-based method for quantitatively imaging tissue stiffness.
- To investigate the clinical usefulness of MRE in patients with a diagnosis of nonalcoholic fatty liver disease (NAFLD) and compare MRE results with transient elastography and serum fibrosis marker test results.

Methods

- Patients diagnosed as not having fibrosis (n=7; stage 0) or having fibrosis (n=119; stage 1/2/3/4: 46/31/32/10) based on a liver biopsy were enrolled.
- All patients with NAFLD underwent MRE, transient elastography, and serum liver fibrosis marker testing (hyaluronic acids, type IV collagen 7s, and scoring systems).

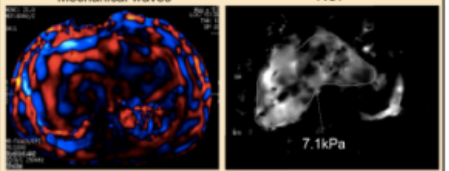
Agenda:
✓Comparison of the diagnostic accuracy for fibrosis staging in patients with NAFLD among MRE, transient elastography, and serum fibrosis marker testing.

Liver stiffness measurement using by MRE:
✓MRE was performed with a 3.0-T whole-body imager (Signa; GE Medical System, Milwaukee, Wis) by using a transmit-receiver coil.

✓Continuous longitudinal mechanical waves at 60 Hz were generated by using an acoustic preon the anterior chest ssure waves–transmitted driver device wall (see below).

✓The mean liver stiffness was reported from the region obtained by pooling the regions of interest drawn on all of the sections (see below).

Mechanical waves ROI



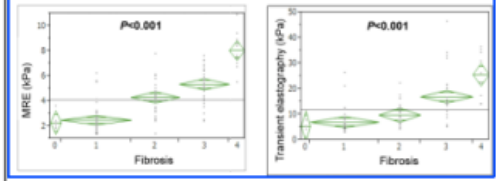
Conclusion

- There is a significant positive correlation between liver stiffness measured at MRE or transient elastography and severity of liver fibrosis in patients with NAFLD.
- The results of MRE were not inferior to those of transient elastography. In addition, we found that liver stiffness using by transient elastography was not measured in 12 patients with NAFLD with a morbid obesity (BMI>28). In contrast, we could evaluate the liver stiffness using by MRE in all patients with NAFLD.
- We recommend MRE as an useful method for diagnosis of liver fibrosis in NAFLD patients with a morbid obesity. In addition, MRE has usefulness for evaluating the stiffness of whole lobe in liver.

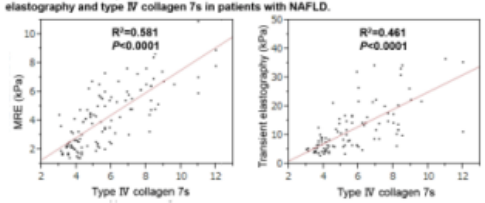
Result 1. Characteristics of NAFLD patients in this study.

	Stage 0 (n=7)	Stage 1 (n=46)	Stage 2 (n=31)	Stage 3 (n=32)	Stage 4 (n=10)
Age (years)	41.9±8.1	50.4±12.4	52.1±10.1	61.1±9.12	66.4±11.2
BMI (kg/m^2)	26.2±4.6	27.9±3.7	28.6±5.1	28.0±4.0	27±4.8
Plts (10^4 /μl)	27.4±7.2	24.7±6.6	22.2±6.2	15.6±6.2	11.7±4.4
Alb (g/dl)	4.62±0.31	4.56±0.28	4.44±0.32	4.23±0.49	3.84±0.42
AST (IU/L)	36.3±10.3	45.2±21.1	50.4±28.9	49.8±18.1	51.9±33.7
ALT (IU/L)	62.0±18.1	57.8±30.2	48.9±38.1	43..2±28.5	55.2±22.9
Type Ⅳ collagen 7s (ng/ml)	3.98±0.86	4.23±0.76	5.83±1.90	6.80±1.77	9.02±1.81
Hyaluronic acid (ng/ml)	39.7±45.9	31.7±28.8	71.6±60.1	171.1±216.0	263.2±158.9

Result 2. Liver stiffness measured at MRE or Transient elastography in each fibrosis stage in patients with NAFLD.



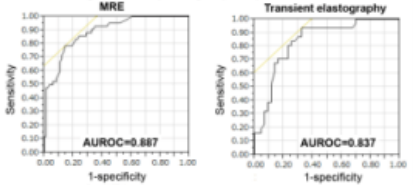
Result 3. Relationship between the liver stiffness measured at MRE or Transient elastography and type Ⅳ collagen 7s in patients with NAFLD.



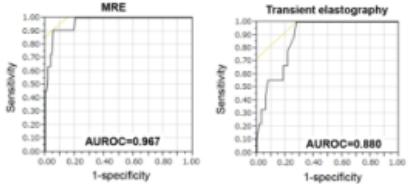
Results

- A steady stepwise increase of liver stiffness measured at MRE or transient elastography was observed with increasing severity of liver fibrosis (Result 2).
- Liver stiffness measured at MRE or transient elastography was markedly correlated with type Ⅳ collagen 7s (Result 3).
- When comparing MRE or transient elastography results with liver biopsy results, the best cutoff for apparent fibrosis (stage 3-4) and liver cirrhosis (stage 4) was 4.8kPa (AUROC=0.887) and 6.7kPa (AUROC=0.967) or 9.2kPa (AUROC=0.837) and 14kPa (AUROC=0.880) (Result 4).
- Of the noninvasive tests, the NAFLD fibrosis score performed the best. MRE was superior to other tests including NAFLD fibrosis score (Result 5).

Result 4. Diagnostic accuracy of MRE or Transient elastography by detecting liver fibrosis stage 3-4 (above) or stage 4 (below).



	Cutoff value	Se (%)	Sp (%)	PPV (%)	NPV (%)
Stage 0-2 vs Stage 3-4	4.8kPa	81.2	85.5	70.1	87.7
Stage 0-2 vs Stage 3-4	9.2kPa	83.9	74.4	70.3	86.5



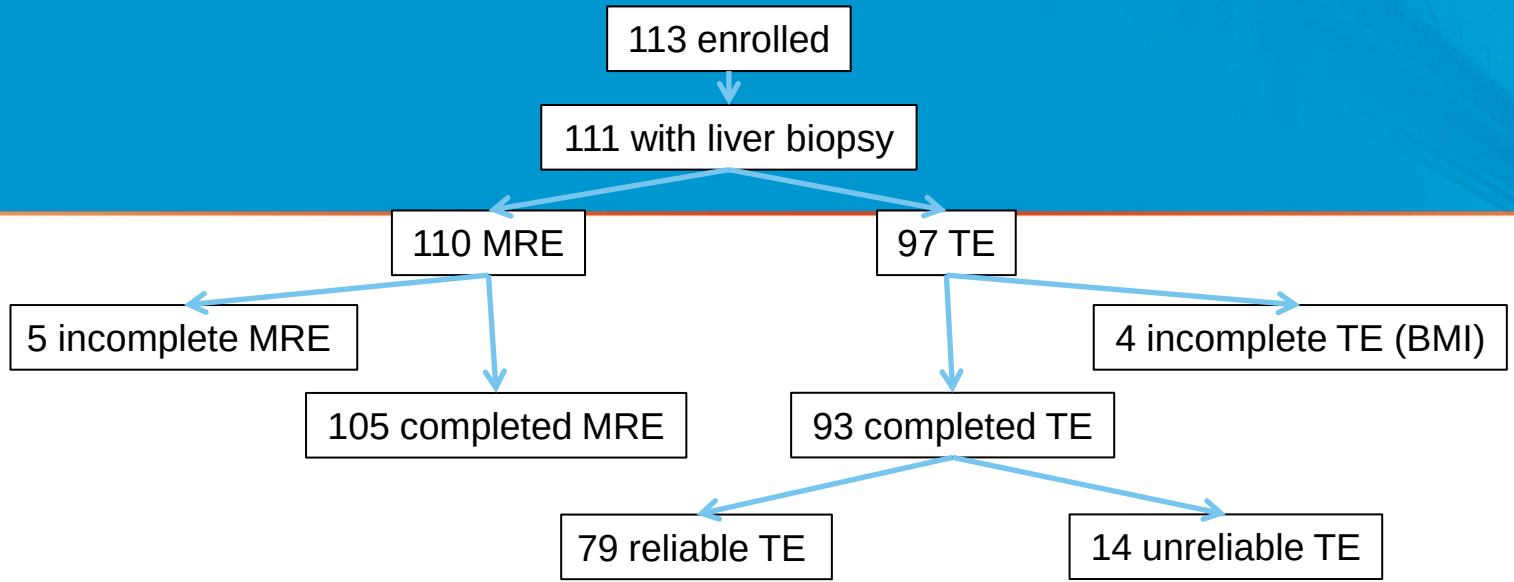
	Cutoff value	Se (%)	Sp (%)	PPV (%)	NPV (%)
Stage 0-3 vs Stage 4	6.7kPa	90.9	94.7	71.4	99.0
Stage 0-3 vs Stage 4	14kPa	93.2	72.3	66.7	98.0

Result 5. Diagnostic accuracy of scoring system for detecting liver fibrosis stage 3-4.

	AUROC	P value	Relationship with liver stiffness (MRE) R^2
Fib4 index	0.822	<0.0001	0.342
NAFLD fibrosis score	0.839	<0.0001	0.438
AST/ALT ratio	0.704	0.0020	0.112
BARD scrore	0.687	0.0078	0.082
APRI	0.662	0.0072	0.079

#16. Assessment of Clinical Effectiveness of MR Elastography and Vibration-Controlled Transient Elastography for Detecting Hepatic Fibrosis. Chen J et. al. Mayo Clinic

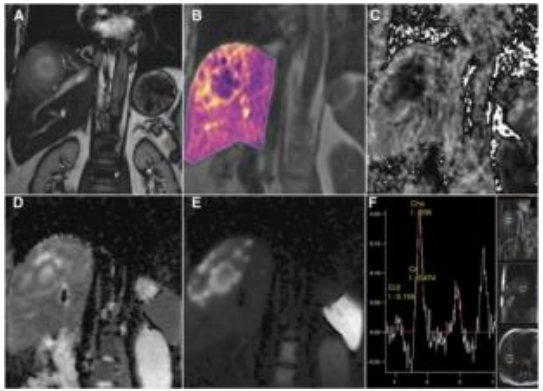
- Aim:
  - Prospectively evaluate MRE vs. TE
- Methods:
  - 2D MRE and TE (XL or M probe) within 1-month of biopsy
  - Operators and pathologist (single) blinded
  - Comparison of AUROC
- Results:
  - 65% female
  - BMI 40 (39,42)
  - NAFLD 83%, HCV 14%,

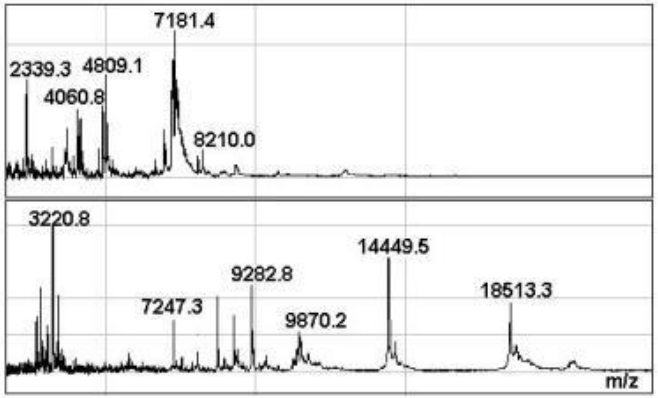


	MRE AUROC (CI) (3.12 kPa)	TE AUROC (CI) (6.10 kPa)	TE AUROC (CI) (6.10 kPa)
N	105	93	79
F ≥ 2	0.895 (0.811-0.944)	0.792 (0.686-0.869)	0.852 (0.748-0.918)

- Conclusion:
  - Significant difference between performance of MRE and TE (p=0.022)
  - AUROC of TE improved if unreliable exams excluded

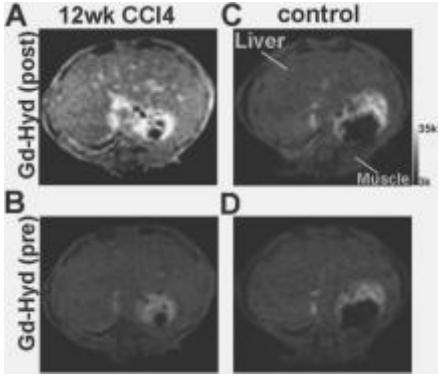
New Technology





#17. Quantitative Molecular MRI of Lysyl-oxidase – Mediated Collagen Crosslinking During Liver Fibrosis. Chen HH Et. Al. Harvard Medical School

- Liver fibrosis➡ Collagen deposition
- Collagen crosslinked by lysyl oxidase
- Gadolinium based MRI probe (Gd-Hyd) targets lysyl oxidase reaction
- CCl4 treated mice imaged
- Gd-Hyd resulted in increased liver MR signal in CCl4 mice but not in control
- Conclusion: Liver fibrosis can be staged quantitatively using a novel Gd probe



#441. Exhaled Breath Analysis Reveals New Biomarkers to Diagnose Advanced Fibrosis in Patients with Chronic Liver Disease. Yaseen ME et. al. Cleveland Clinic, OH

- Aim:
  - Utility of volatile organic compounds measured by mass spectrometry to diagnose advanced fibrosis
- Methods:
  - Liver biopsy read by single pathologist. F3-F4=advanced fibrosis
  - Exhaled breath collected and analyzed with mass spectrometry same day as liver biopsy
- Results:
  - 49 patients, 38% HCV, 35% NAFLD
  - Lower levels of isoprene, trimethyl-amine, ethane, acrylonitrile, pentane and 1-heptene in advanced fibrosis ($p < 0.05$ for all)
  - AUROC for Isoprene 0.765
- Conclusion:
  - Promising technology, further validation required

A 6-Gene Score Associated With Advanced Stages of Presymptomatic HBV Related Fibrosis

Mingyi Xu*, Ying Qu, Qingqing Zhang, Lungen Lu
Department of Gastroenterology, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine

Premise

1. To characterize the molecular genomic activity linked to histological stages of liver fibrosis, microarray were performed .
2. A set of 18 predictor genes were found correlating with HBV related liver fibrosis (HRLF) by Genome data analysis .
3. Validation study supported 6 genes were associated with advanced HRLF.

Background

HRLF has been shown to involve complex interactions in genomics. We utilized microarray to reveal it.

Methods

1. 143 patients were divided into 3 subgroups including control, Fibrosis and HCC.
2. Affymetrix GeneChip was used. Genome data analysis was obtained by GeneSpring GX software, Significant Analysis of Microarray (SAM) and Prediction Analysis of Microarray (PAM).
3. qRT-PCR and AUROC analysis were used to verify predictor genes.

Results

1. The expression pattern of 678 significant genes identified by SAM showed different feature in significant HRLF (≥S2). A subset of 18 predictor genes, which were identified by PAM, was defined to have "Fibrotic Risk" signature of HRLF. Six novel predictor genes were differentially expressed among S4, S1-S3 and S0 group (Figure 1).

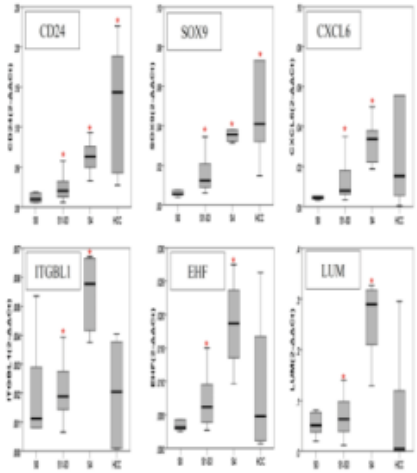
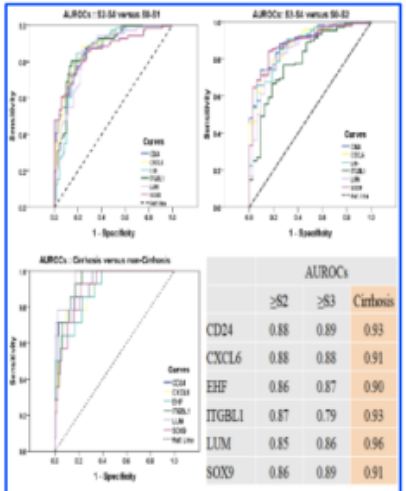


Figure 1 qRT-PCR of 6 predictor genes
(* Means compar ing to S0, p<0.05)



AUROCs

	≥S2	≥S3	Cirrhosis
CD24	0.88	0.89	0.93
CXCL6	0.88	0.88	0.91
EHF	0.86	0.87	0.90
ITGBL1	0.87	0.79	0.93
LUM	0.85	0.86	0.96
SOX9	0.86	0.89	0.91

Figure 2 AUROCs of 6 predictor genes diagnosing fibrosis and cirrhosis

2. AUROCs of 6 genes were 0.85-0.88 in diagnosing significant HRLF (≥S2). Total 6 predictor genes including CD24, CXCL6, EHF, ITGBL1, LUM and SOX9 were found to have AUROCs among 0.90-0.96 in discriminating cirrhosis (Figure 2). Univariate logistic regression analysis also identified their expression in liver tissue associated with cirrhosis.

Conclusion

1. The genomic expression profiles of 143 enrolled patients (Control, n=7; S0-S4, n=126; HCC, n=10) represented the entire spectrum of chronic hepatitis B.
2. Our study provide a molecular portrait of genomes in HRLF.
3. A set of 6 "Fibrotic Risk" genes (CD24, CXCL6, EHF, ITGBL1, LUM and SOX9) are promising predictors for diagnosis of advanced stages of presymptomatic HBV related fibrosis, especially cirrhosis.
4. Moreover, the correlation of 6-genes markers with cirrhosis suggested that understanding the mechanisms in liver fibrosis may facilitate the design of new therapeutic approaches.

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Key Words

Hepatitis B Virus; Liver Fibrosis; Microarray Analysis

Multi-parametric MRI predicts clinical outcomes in unselected patients with liver disease – a non-invasive test that meets the AASLD criteria for clinical trials?

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BACKGROUND

There is currently no approved non-invasive biomarker of liver disease which predicts clinical outcomes in a general liver patient population. The American Association for the Study of Liver Disease and the US Food and Drug Administration agency have prioritised this as a pressing need. A multi-parametric magnetic resonance (MR) protocol developed in our centre has shown excellent correlation with histology in an unselected patient population undergoing clinically indicated liver biopsy for evaluation of fibrosis[1]. The aim of this study was to determine if this quantitative MR technique could predict clinical outcomes in the same patients.

METHODS

Patients scheduled for a clinically indicated liver biopsy at 2 UK centres (Oxford and Reading) were prospectively recruited between April 2011 and May 2013. All patients had a quantitative MRI as previously described[1]. Patients were followed up for a minimum of 12 months. Liver-related events, defined as any index episode of ascites, hepatic encephalopathy (HE), variceal bleed, hepatocellular carcinoma (HCC) or liver related death, were captured for analysis. Kaplan Meier survival analysis was performed and differences between the curves were compared using the log-rank test (GraphPad Prism 6).

MR image processing

Quantitative MR data for fat, iron and T1 relaxation times were acquired from a clinical 3T Siemens scanner. Images were analysed using *LiverMultiScan*. (Perspectum Diagnostics, Oxford, UK) to calculate the Liver Inflammation and Fibrosis (LIF) score. The reporting operator was blinded to the clinical and histological data. Disease severity was stratified according to pre-set cut-offs on a continuous scale (0-4), as normal (<1), mild (1-<2), moderate (2-<3) and severe (≥3). Examples of scans are shown in figure 1.

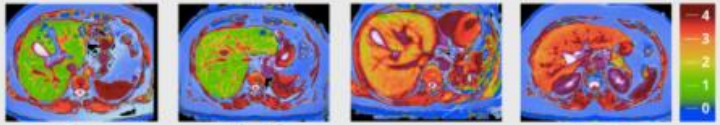

Figure 1. Examples of MR data. The images show representative scans (LIF maps) from patients in each LIF severity category. These maps can be used to measure LIF in any part of the liver parenchyma away from vascular and billary structures. The measured LIF score for each patient is shown under each scan. The predefined colour scale used to generate these maps is also shown. **LIF:** Liver Inflammation and Fibrosis score.

Results

92 patients were recruited and 87 (64 male) were followed up for a median of 28 months. Five patients were lost to follow up. The median age was 49.5 years and median BMI 26.8 kg/m². Liver biopsy was performed in 78 (90%) patients. In the patients that had liver biopsies, the main diagnoses were Non-Alcoholic Fatty Liver Disease (n=31; NAFLD), and chronic viral hepatitis (n=28). Histological fibrosis was mild (Ishak F0-2) in 48 (56%), moderate (Ishak F3-4) in 13 (15%) and severe (Ishak F5-6) in 17 (20%) patients.

Seven patients (8%) suffered at least one liver-related clinical event and five patients (6%) died in the follow up period. Table 1 below summarises the clinical features of the patients who suffered clinical events.

There were no clinical events in the patients with LIF<2 (negative predictive value 100%). Overall, 7 out of 39 (18%) patients with LIF 2-4 had clinical events (2 patients with LIF 2-<3 and 5 patients with LIF≥3). On Kaplan Meier analysis, patients with LIF≥3 had a greater cumulative risk of clinical events compared to those with LIF 0-<1 (p=0.028) or LIF 1-<2 (p=0.031; Figure 2).

References

1. Banerjee R, Pavlides M, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol. 2014 Jan;60(1):69-77.

TABLE 1. CLINICAL FEATURES OF PATIENTS WHO SUFFERED LIVER RELATED EVENTS DURING THE FOLLOW UP PERIOD

Study ID	LIF score	Ishak stage	CPT	Diagnosis	Index event (months from scan)	Patient mortality (months from scan)
RIAL 6	2.5	6	B	NAFLD	Encephalopathy (15)	Yes (24)
RIAL 30	3.0	6	A	HCV	Encephalopathy (7)	No
RIAL 43	2.7	6	A	HCV	HCC (11)	Yes (19)
RIAL 22	3.5	5	A	ASH	Liver related death (3)	Yes (3)
RIAL 37	3.5	6	A	NAFLD	Ascites (22)	No
RIAL 93	3.8	6	B	NAFLD	Liver related death (7)	Yes (7)
RIAL 24	3.8	Refused Bx	A	ASH*	Ascites (7)	Yes (10)

Abbreviations: LIF: Liver Inflammation and Fibrosis, CPT: Child Pugh Turcotte class, NAFLD: Non- Alcoholic Fatty Liver Disease, HCV: Hepatitis C Virus, HCC: Hepatocellular Carcinoma, ASH: Alcoholic steatohepatitis

*This patient took part in the imaging study, but refused his biopsy. Excessive alcohol use suggested a working diagnosis of ASH

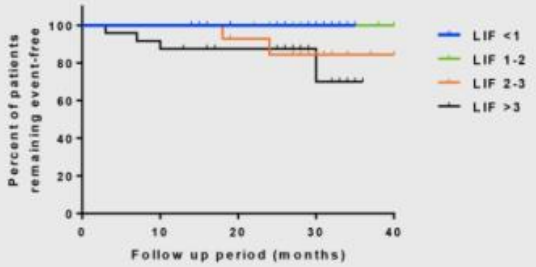

Figure 2. Kaplan Meier curves. The cumulative risk of liver related events was significantly higher in patients with LIF≥3 compared to patients with LIF<1 (0.028) log rang test) or LIF 1-<2 (p = 0.031 log-rank test)

CONCLUSION

The non-invasive and standardised MR method we have developed can predict clinical outcomes in an unselected population of liver patients. This technique is therefore very attractive for risk stratification of patients in clinical practice, and as a surrogate end-point in clinical trials.

Financial Disclosures

MP and EB are shareholders in Perspectum Diagnostics. RB, MDR and SN are on the board of directors and shareholders in Perspectum Diagnostics. RB and CK are employed by Perspectum Diagnostics. JS, JB, and JC have no financial disclosures.

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OCMR

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Royal Berkshire NHS Foundation Trust

Summary

- Evolving area in Hepatology (42 abstracts at AASLD 2014)
- APRI and FIB-4 are accurate predictors of cirrhosis
- TE, SWE and MRE are superior to biochemical/serological fibrosis panels but all have limitations
- MRE appears to be better than TE for evaluation of liver fibrosis in patients with NAFLD
- Newer technologies are on the horizon