Biomarcadores e imagen en NASH: ¿pueden sustituir a la biopsia?

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UCM Digestive Diseases and Ciberehd. Virgen del Rocío University Hospital. SeLiver Group. IBIS. University of Seville, Sevilla, Spain.

Imaging Biomarkers

- Accumulation **of iron and fat** in hepatocytes contributes to **chronic liver inflammation**, a key driver for **fibrosis progression.**
- **There is a need for new biomarkers** that allow the detection and quantification of liver diseases supported on the measurement of **fat, iron, fibrosis, inflammation.**

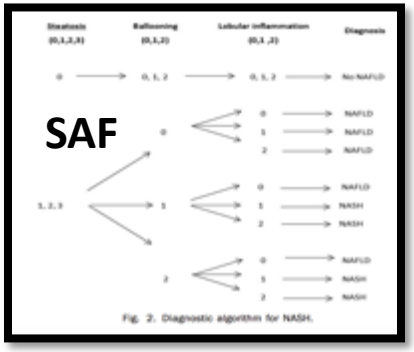
- **Current Gold Standard: Liver biopsy: Histology vs. Clinical outcomes:**
  1. **Liver-related: Cirrhosis >> HCC >> decompensation >> OLT**
  2. **Extrahepatic: CV events >> Extrahepatic neoplasms**
  3. **Survival**

Limitations of liver biopsy as gold standard:

a) Diagnostic criteria for steatohepatitis

NASH diagnosis	Yes	No

NAScore	Steatosis	Ballooning	Inflammation
0	< 5%	No	No
1	5%-33%	Few	<2 foci
2	33%-66%	prominent	2-4 foci
3	>66%		> 4 foci



b) Overlap between inflammatory activity and fibrosis stage

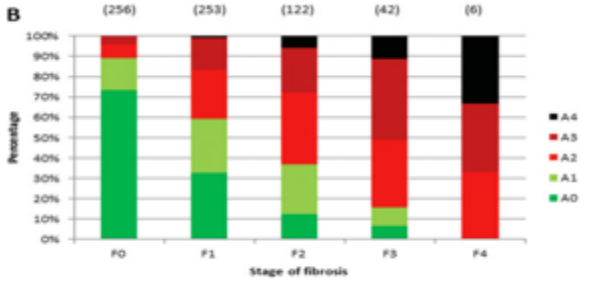
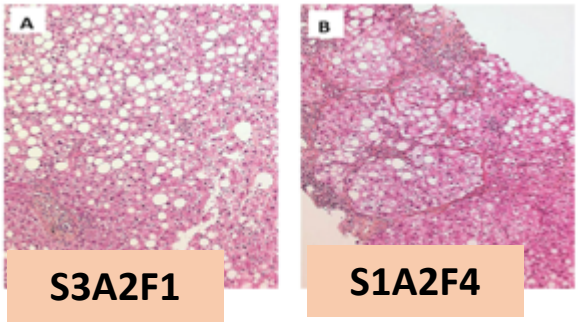


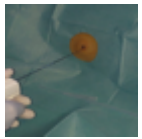
Fig. 6. (A) Correlation between activity grade and fibrosis stage. (B) Between fibrosis stage and activity grade.



Bedossa P et al. Hepatology 2012;56:1751

Histological features in liver biopsy as gold standard:

Steatosis >> Steatohepatitis >> Fibrosis



c) Sampling variability[1]

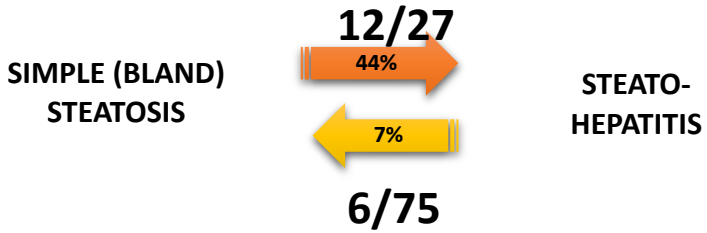
Diagnostic accuracy of 2nd biopsy:
NASH: 0.81 (0.65–0.90)
F3-F4: 0.87 (0.7–0.95)
Ballooning: 0.66 (0.57–0.73)

N=51 NAFLD (2 samples of liver biopsy)

NPV NASH: 74%
≥1 Fibrosis stage: 41%
Bridging fibrosis in just 1 biopsy 35%

d) Progression over time[2]

Evidence of NAFLD progression from steatosis to fibrosis-steatohepatitis…
N=108 mean follow-up 6.6 years



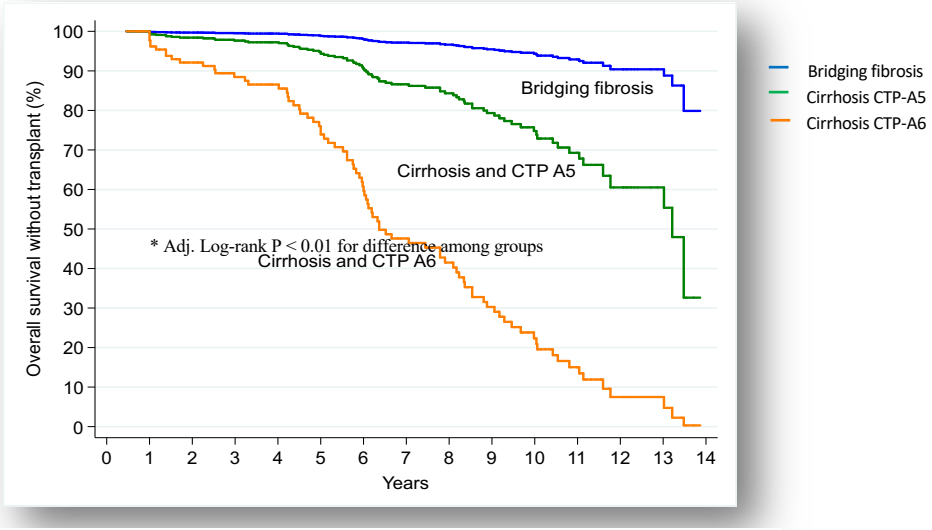
1. *Ratziu V, et al. Gastroenterology 2005;128:1898*
2. *McPherson S, et al. J Hepatol 2015;62:1148*

The Long-Term Clinical Course of Histologically Advanced NAFLD. Impact of Fibrosis Severity on Major Clinical Outcomes.

N=458

Transplant-Free Survival

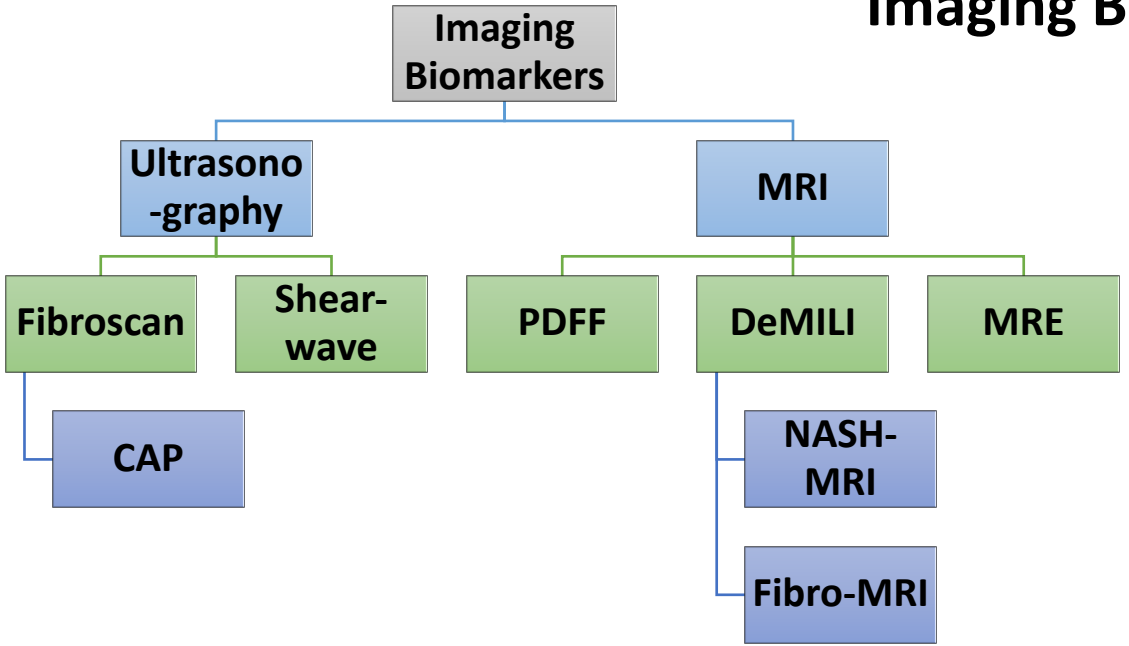
Stratified analysis by fibrosis and CTP classes

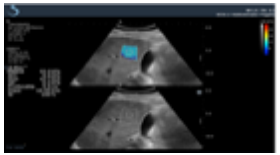


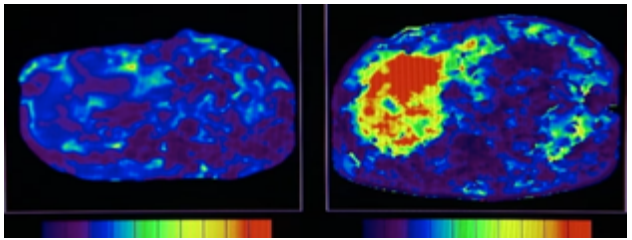
(Adjusted analysis by center, race/ethnicity, age and gender*)

Vilar-Gómez et al. Gastroenterology 2018

Imaging Biomarkers







Liver Ultrasonography

Liver ultrasonography

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Recommendations

- US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information (**A1**)

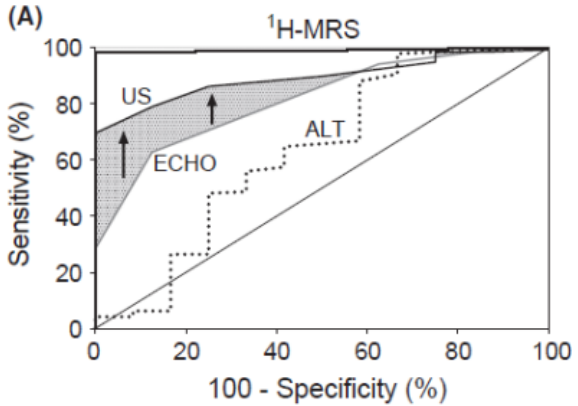
Clinical value of liver ultrasound for the diagnosis of non-alcoholic fatty liver disease in overweight and obese patients. Brill F et al. Liver Int 2015;35:2139-2146

N=146

Parenchymal echogenicity	Far gain attenuation	GB wall blurring	Portal vein blurring	Hepatic vein blurring

AUROC
0,96
0,89
0,82

Threshold for steatosis detection: 12.5%

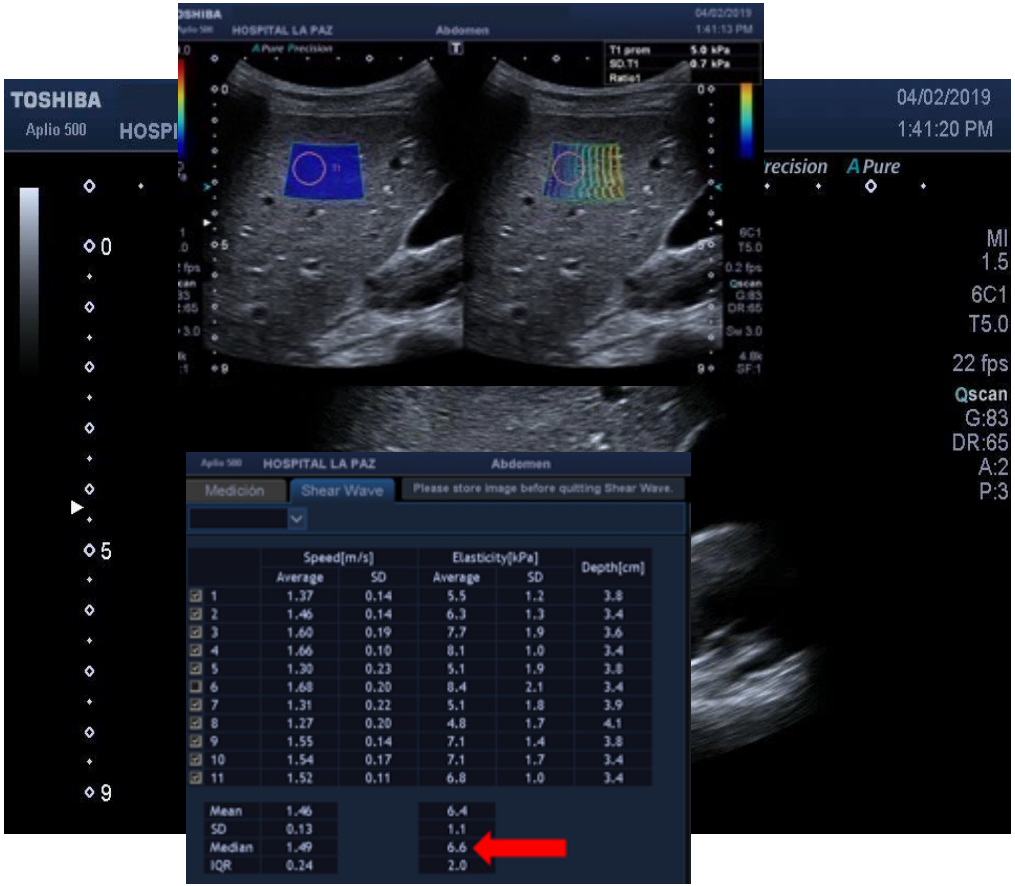


Ultrasonography limitations:

- Not able to segregate steatohepatitis from steatosis.
- Liver hyper-ecogenicity do not correlate with hepatic injury
- Brilliant liver requires differential diagnosis
- Steatosis detected by ultrasonography when higher than **12.5%**

J Hepatol 2016

shear-wave elastography

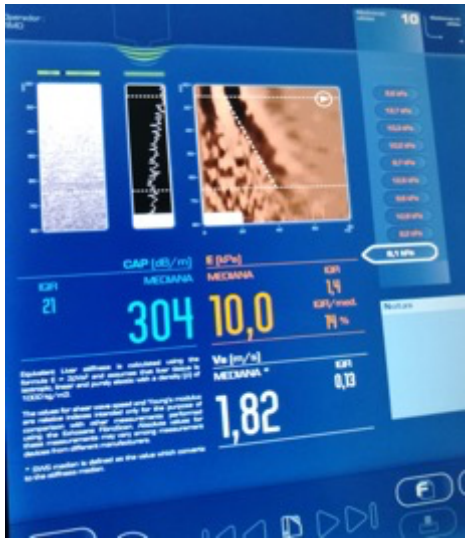


N=2735

Individual patient data metaanalysis CAP detecting steatosis

NAFLD (n=537); HepC (n=997); HepB (n=1003); Others (n=198)

F0: 304 (11%); F1: 970 (36%); F2: 725 (27%); F3:334 (12%; F4: 350 (13%)



Transient Elastography CAP (dB/m)

Etiology – Diabetes – BMI

CAP values dB/m

- **NAFLD/NASH** Deduct 10 dB/m
- **Diabetes** Deduct 10 dB/m
- **BMI** (20-30 Kg/m²) Deduct 4.4 dB/m for each Unit>25 Add 4.4 for each Unit below 25

Recalculated CAP value

>S0	>S1	>S2
248 (237 to 261)	**268** (257 to 284)	**280** (268 to 294)

	AUROC
S0 vs. S1-S3	0.82 (0.81-0.84)
S0-S1 vs. S2-S3	0.87 (0.85-0.88)
S0-S1-S2 vs. S3	0.88 (0.86-0.91)

Karlas et al. J Hepatol 2017;66:1022-1030
Romero-Gómez M, Cortez-Pinto H. J Hepatol 2017

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

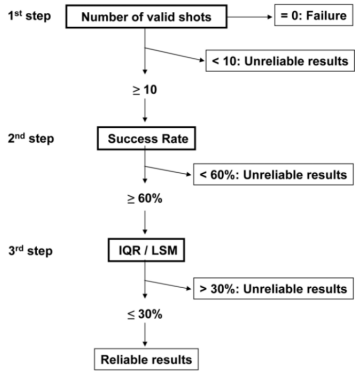
EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis

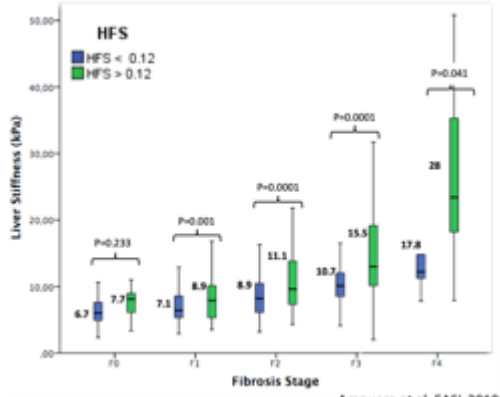
Correct interpretation of TE results in clinical practice must consider the following parameters:

- IQR/ median value (<30%),
- Serum aminotransferases levels (<5 x ULN),
- BMI (use XL probe above 30 kg/m^2 or if skin-to-capsule distance is >25 mm),
- Absence of extra-hepatic cholestasis,
- Absence of right heart failure, or other causes of congestive liver
- Absence of ongoing excessive alcohol intake

J Hepatol 2015

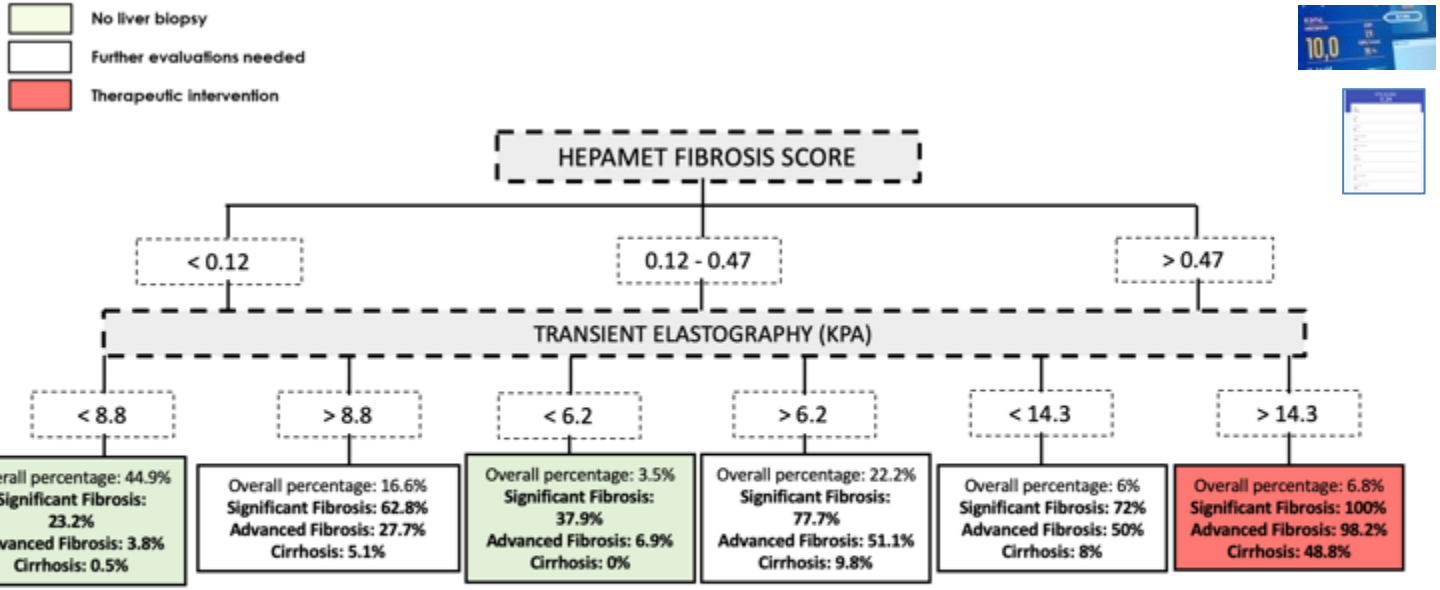
Castera L. Hepatology 2010; Boursier J Hepatol 2016





Ampuero et al. EASL 2019

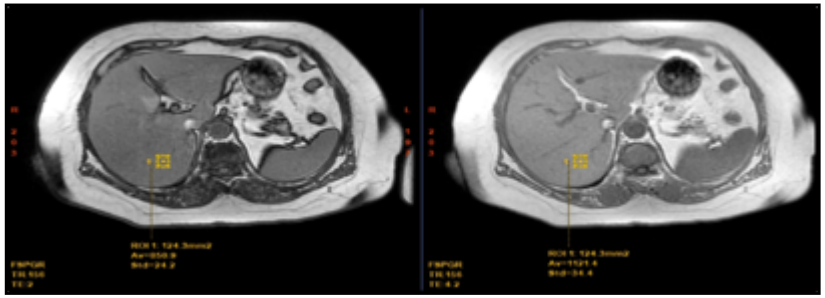
Interpretation of kPa according to metabolic derangement of the liver

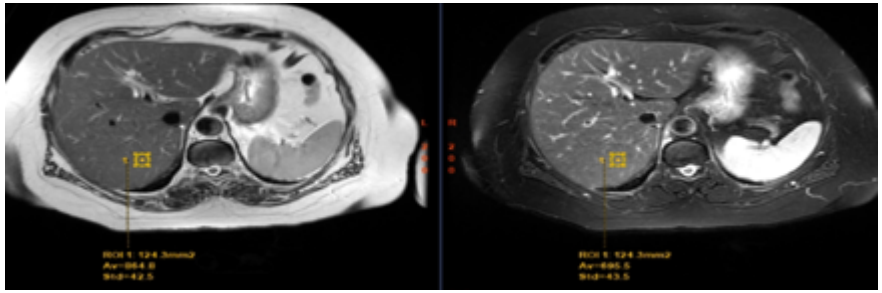


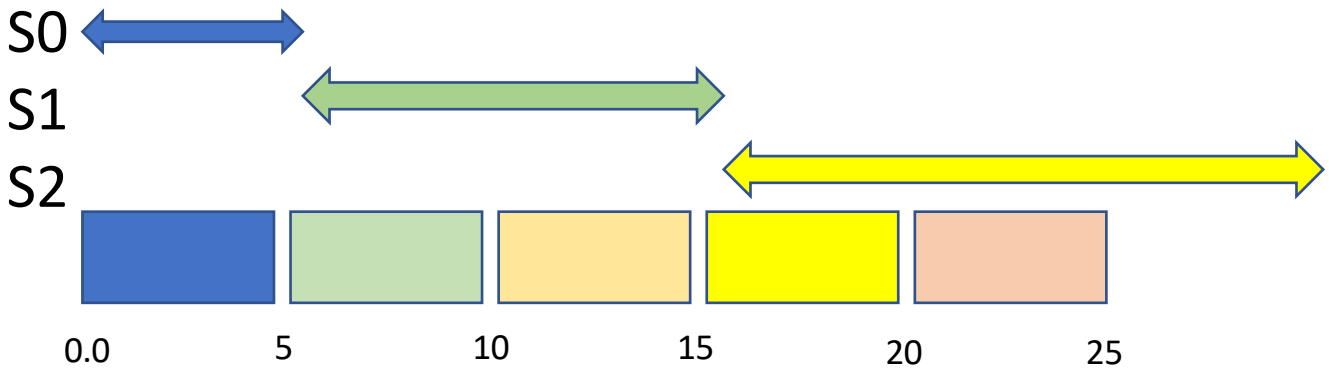
No Liver Biopsy required	**44.9% + 3.5% + 6.8%**	**55.2%**
MR studies	16.6% + 22.2% + 6%	44.8%

Magnetic Resonance on the diagnosis of MAFLD

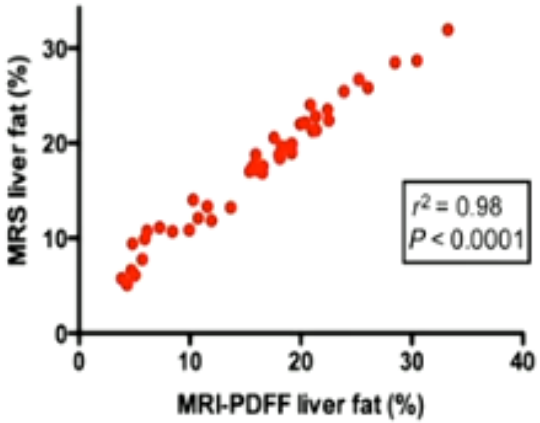
PDFF a gold estándar for Fat Infiltration

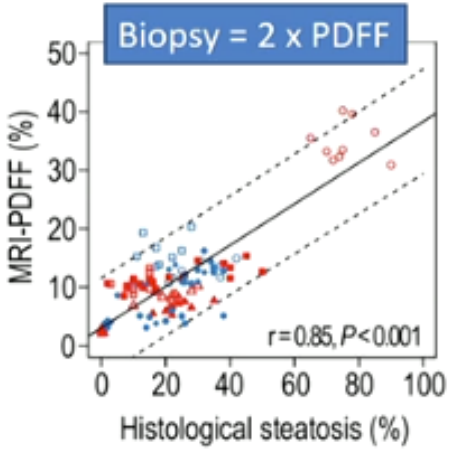






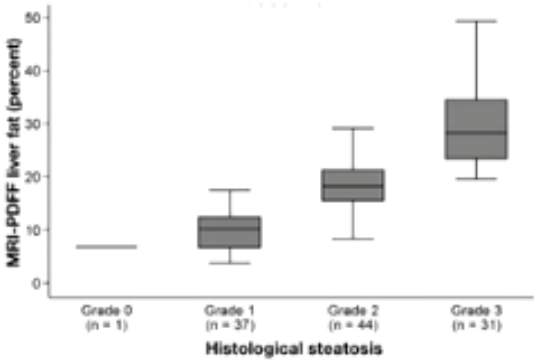
Liver Fat Comparison
PDFF vs. MRS vs. LB





MRI-PDFF as the Gold Standard for the Detection of Hepatic Steatosis

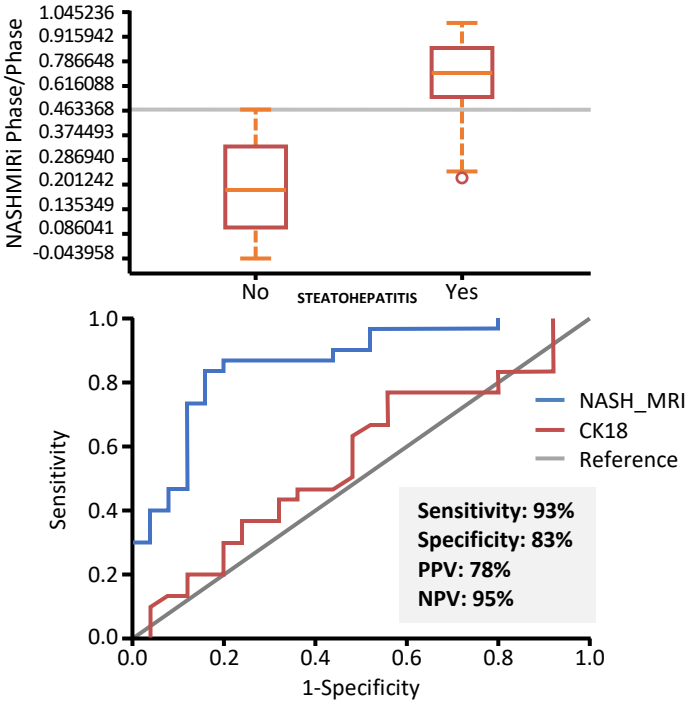
Cynthia Cooper,[1,2] Mouah H. Akpinish,[1] Phirum Nguyen,[1] Carolyn Hernandez,[1] Sandra Cepin,[1] Lynda E. Forney,[1] Veeral Ajmera,[1,2] Ricki Bettencourt,[1] Sumeer Collier,[1] Jonathan Hooker,[4] Ethan Sy,[4] Emily Rios,[1] Lisa Richards,[1] Claude B. Sirlin,[4] and Rohit Loomba[1,2,3]

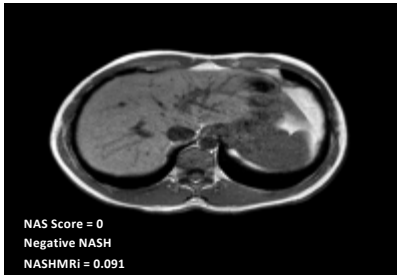


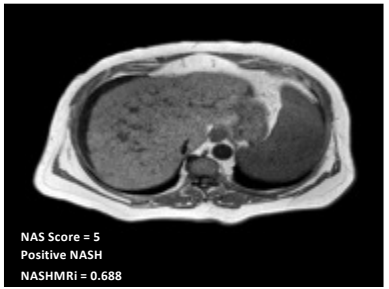
grade 0–1 vs 2–3 AUROC of 0.95
grade 0–2 vs grade 3 AUROC of 0.96

Bannas et al. Hepatology 2015; O'Regan et al. Radiology 2008; Noureddin et al. Hepatology 2013

DeMILI: NASHMRi



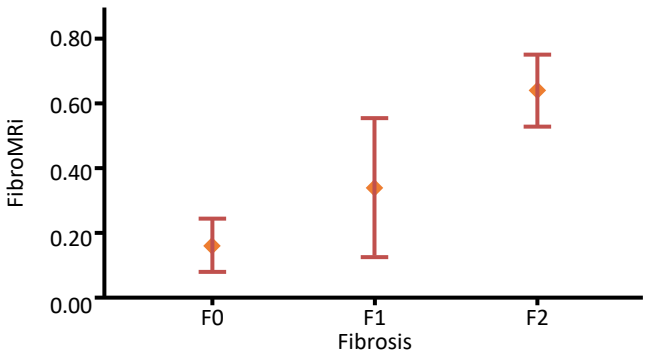


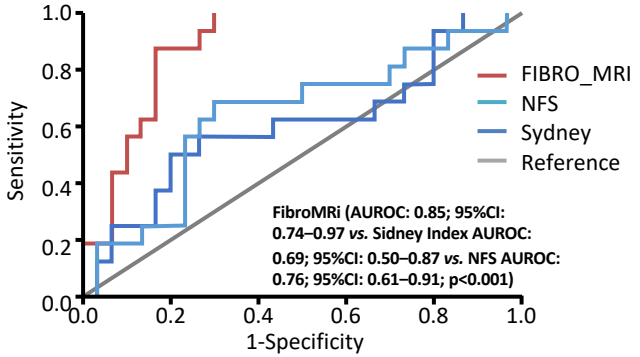


NASHMRI vs. CK-18 (AUROC: 0.86; 95%CI: 0.76–0.96 *vs.* AUROC: 0.44; 95%CI: 0.29–0.60, respectively; p<0.0001).

Gallego Durán R, et al. Sci Rep 2016;6:31421

FibroMRi & significant fibrosis

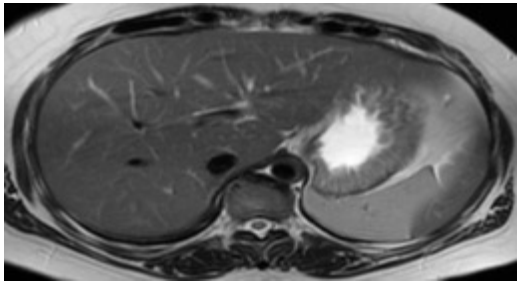




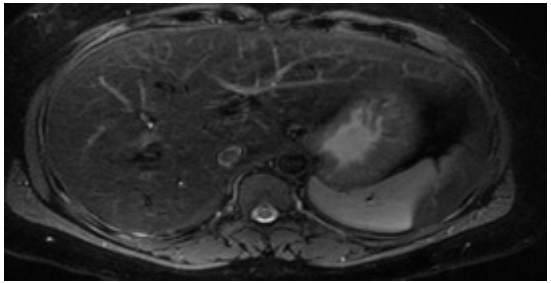
PROTOCOL	ESTIMATOR	NAME
SSFSE-T2	E3	Harmonic mean
DYNAMIC	E57	Second order contrast
FAST-STIR	E73	Weighted mean curvature
SSFSE-T2	E22	Pearson's asymmetry coefficient
DYNAMIC	E6	Mode
DYNAMIC	E31	Column's mean of multi-oriented co-occurrence matrix
DYNAMIC	**E75**	Maximum of main curvatures

Gallego Durán R, et al. Sci Rep 2016;6:31421

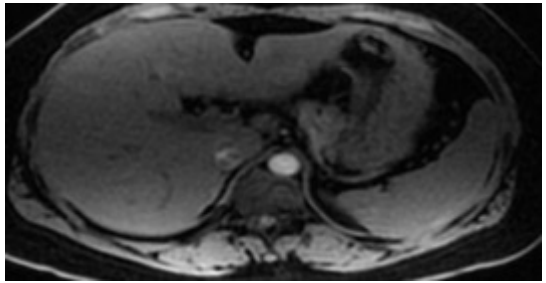
NASH-MRI the only one imaging biomarker to detect steatohepatitis



SSFE-T2 BH

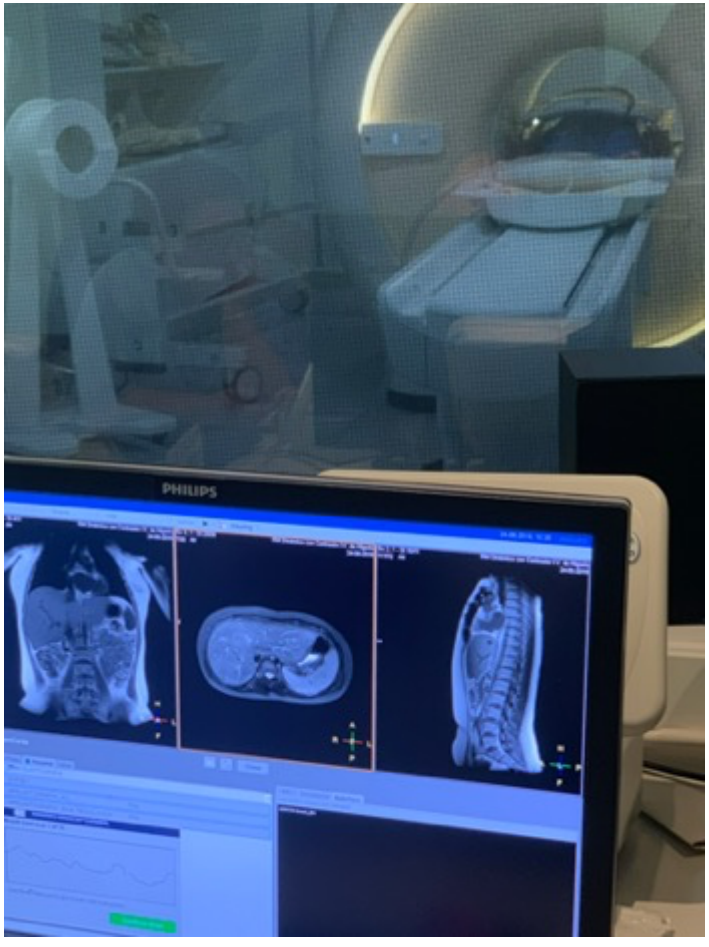


FAST-STIR



2D-FFE-T1

Dermili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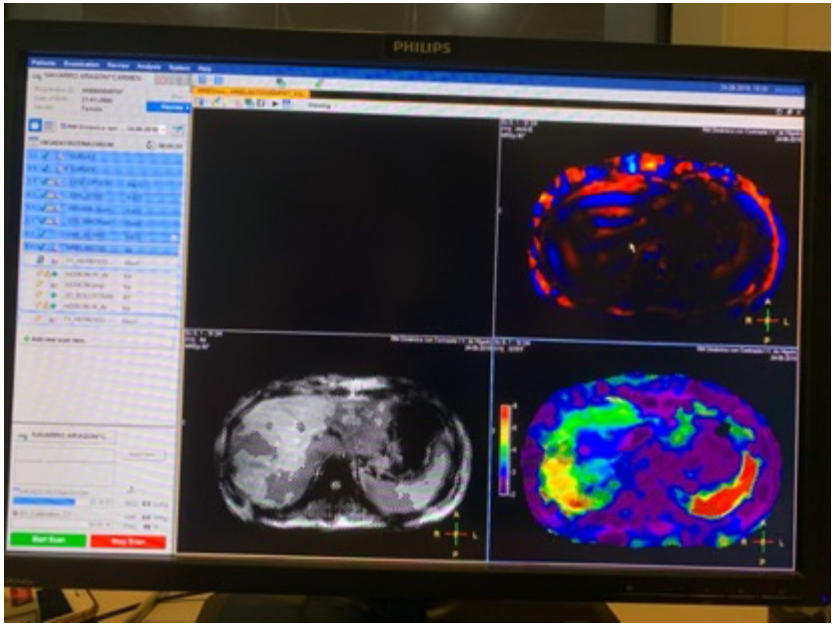
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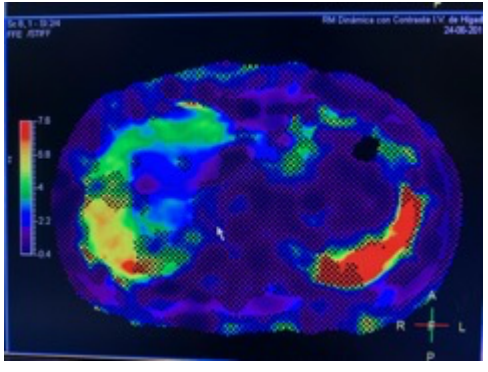
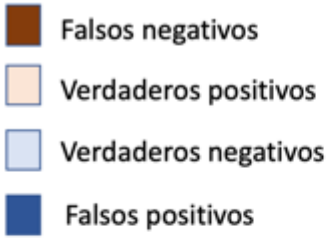
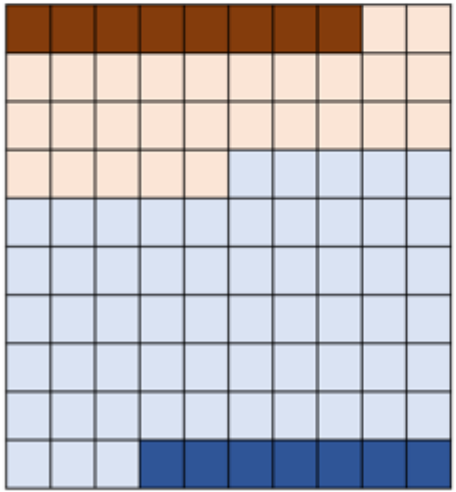


Diagnostic accuracy of elastography, and magnetic resonance imaging in patients with NAFLD: a systematic review and meta-analysis

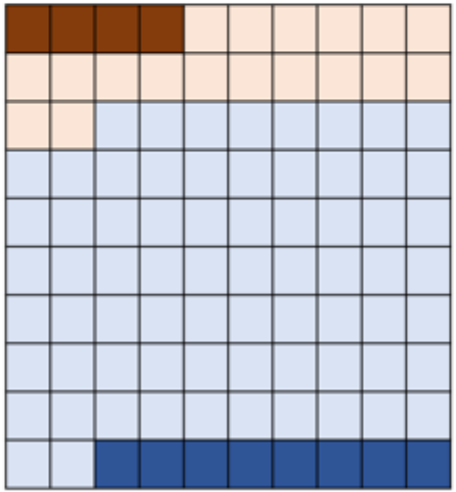


	Estadio	Prev	FN	VN	VP	FP	AUROC
Elastografía RM	Fibrosis significativa	35%	FN= 8/35	VN=27/35	VP=58/65	FP=7/65	85%
	Fibrosis avanzada	22%	FN= 4/22	VN=18/22	VP=70/78	FP: 8/78	88%
	Cirrosis hepática	8%	FN=2/8	VN=83/92	VP=6/8	FP=9/92	89%

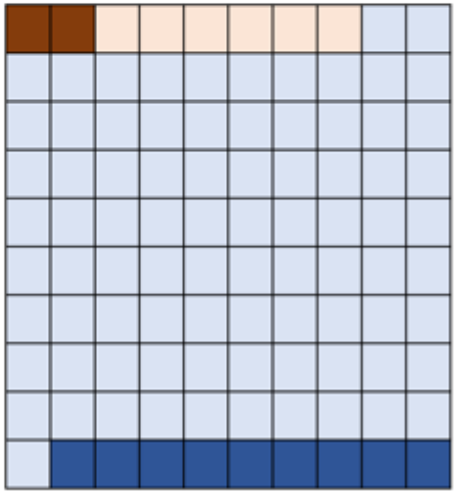
F2: [Se 76% - Esp: 90%]



F3: Se 82% - Esp: 89%

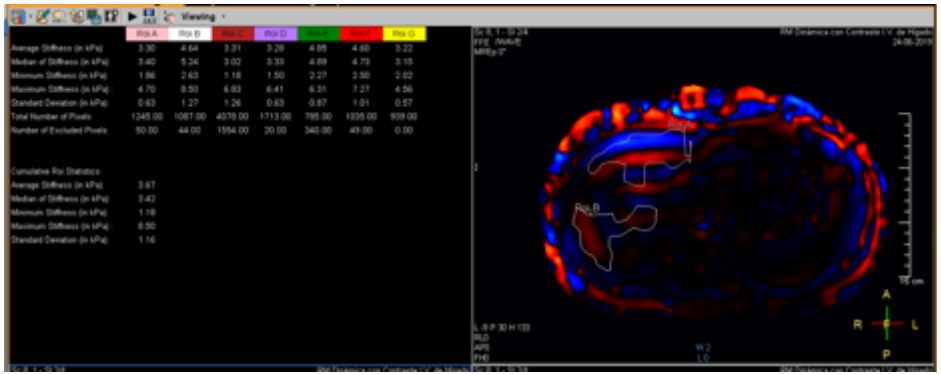


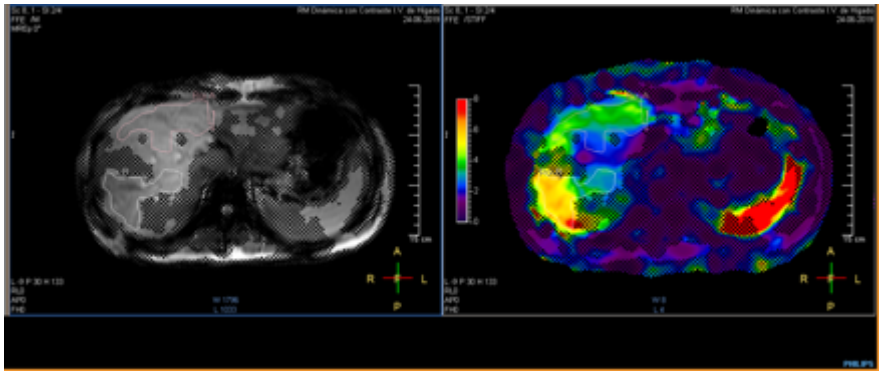
F4: Se 81% - Esp: 90%

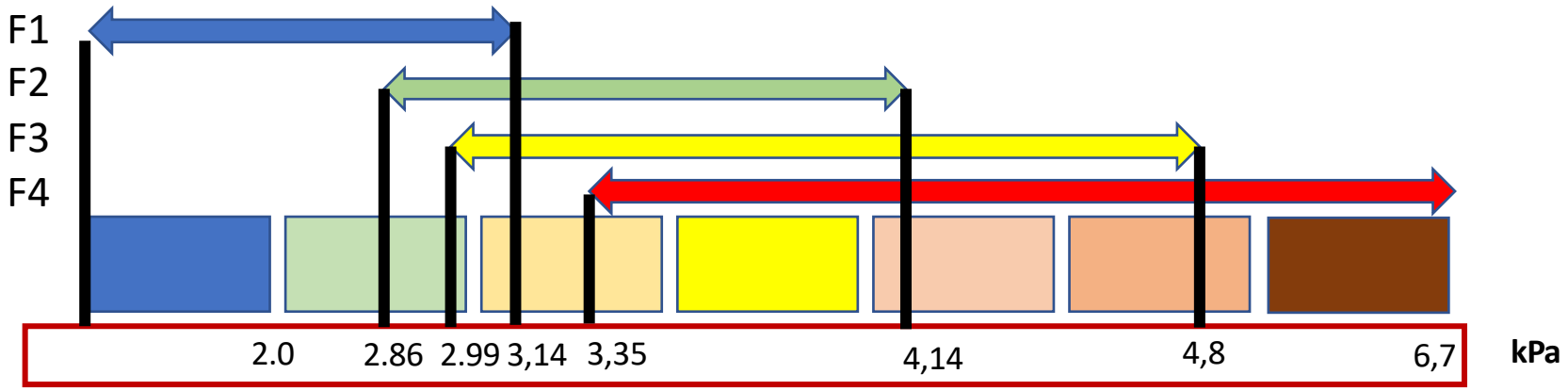


Selvaraj et al. JHep 2020 (submitted)

Magnetic Resonance Elastography to detect liver fibrosis in MAFLD





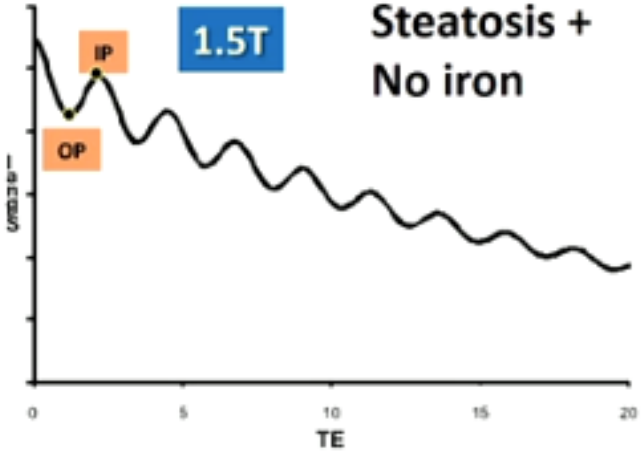


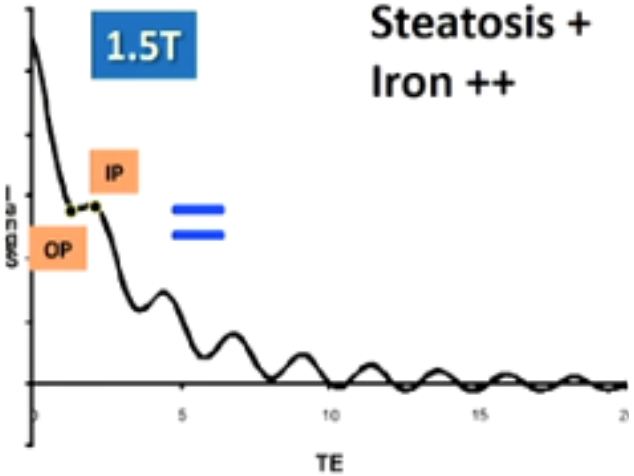
Liver Fat Quantification with MRI

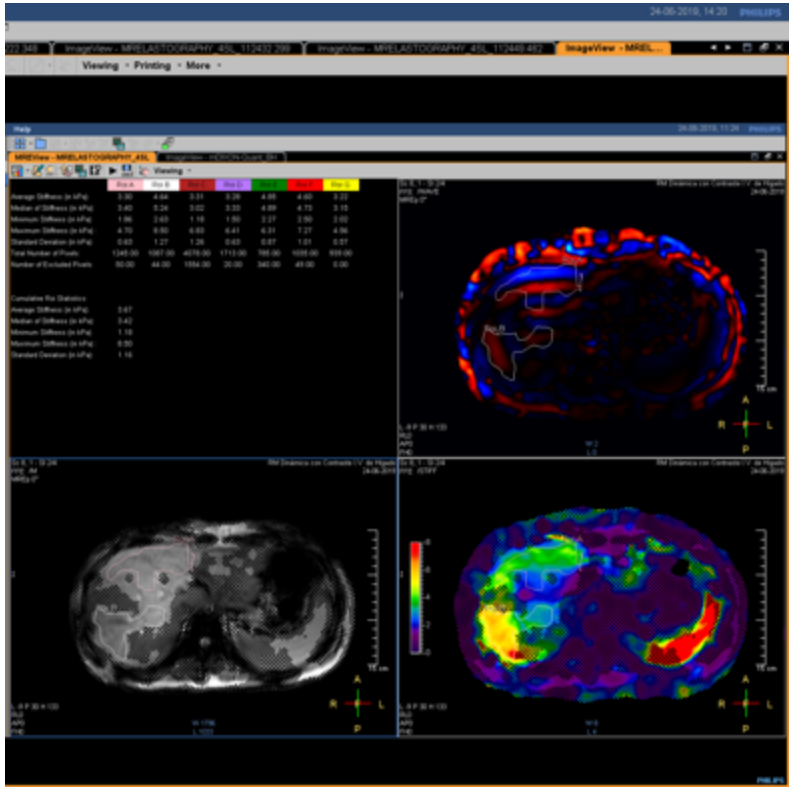
Basic chemical shift imaging

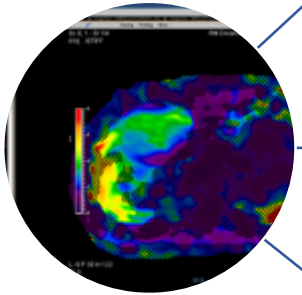
Numerous theoretical biases

T1 effect
Flip angle
T2* decay effect
Spectral complexity of liver fat









T1 mapping
STIR

- Inflammation

mDixon-Quant
R2*

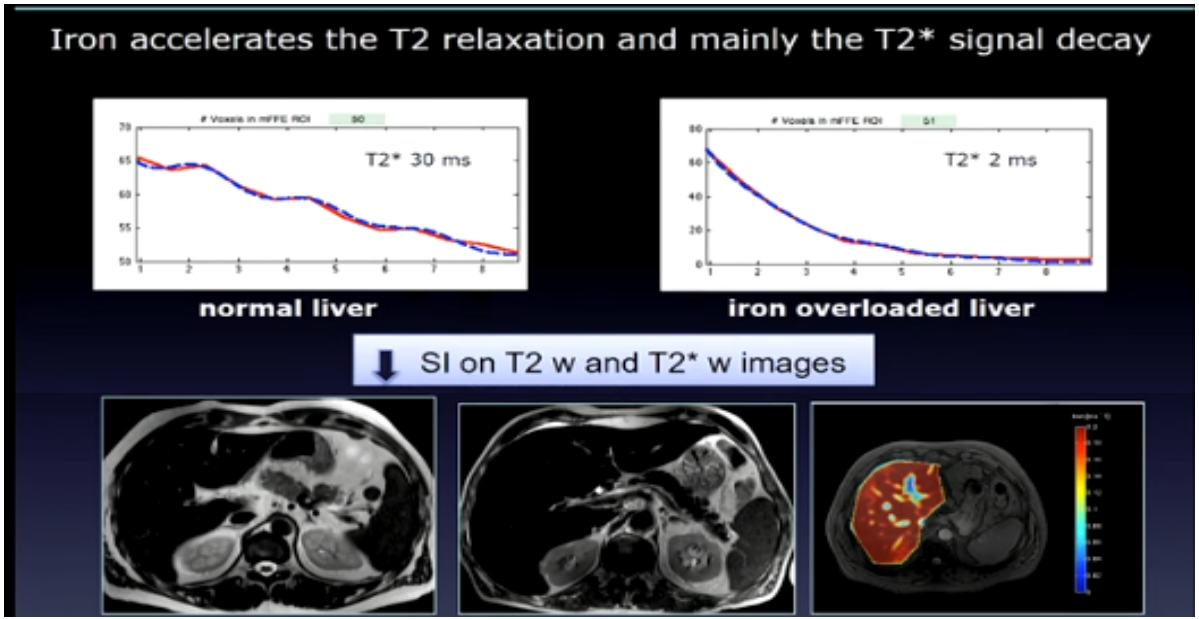
- Iron overload

Colestasis
Stasis
Breathing

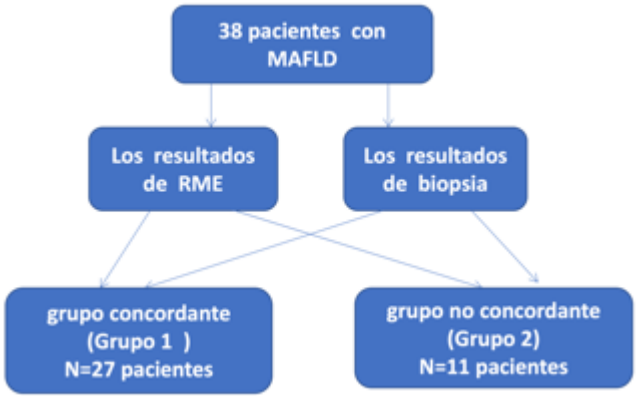
N=9108

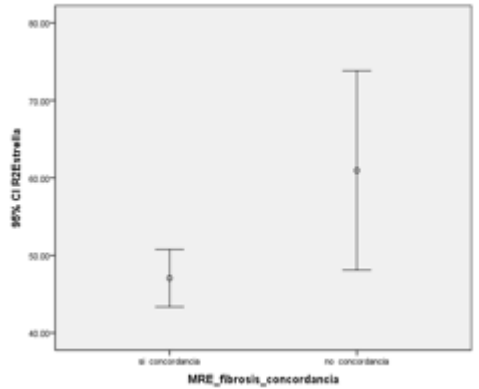
Prevalence of liver iron overload in general population

Elevated Liver Iron Concentration (> 1.8 mg/g)
(444/9108; **4,87%)**



Análisis de factores que afectan la seguridad diagnóstica de la elastografía por resonancia magnética (ERM) en pacientes con MAFLD.

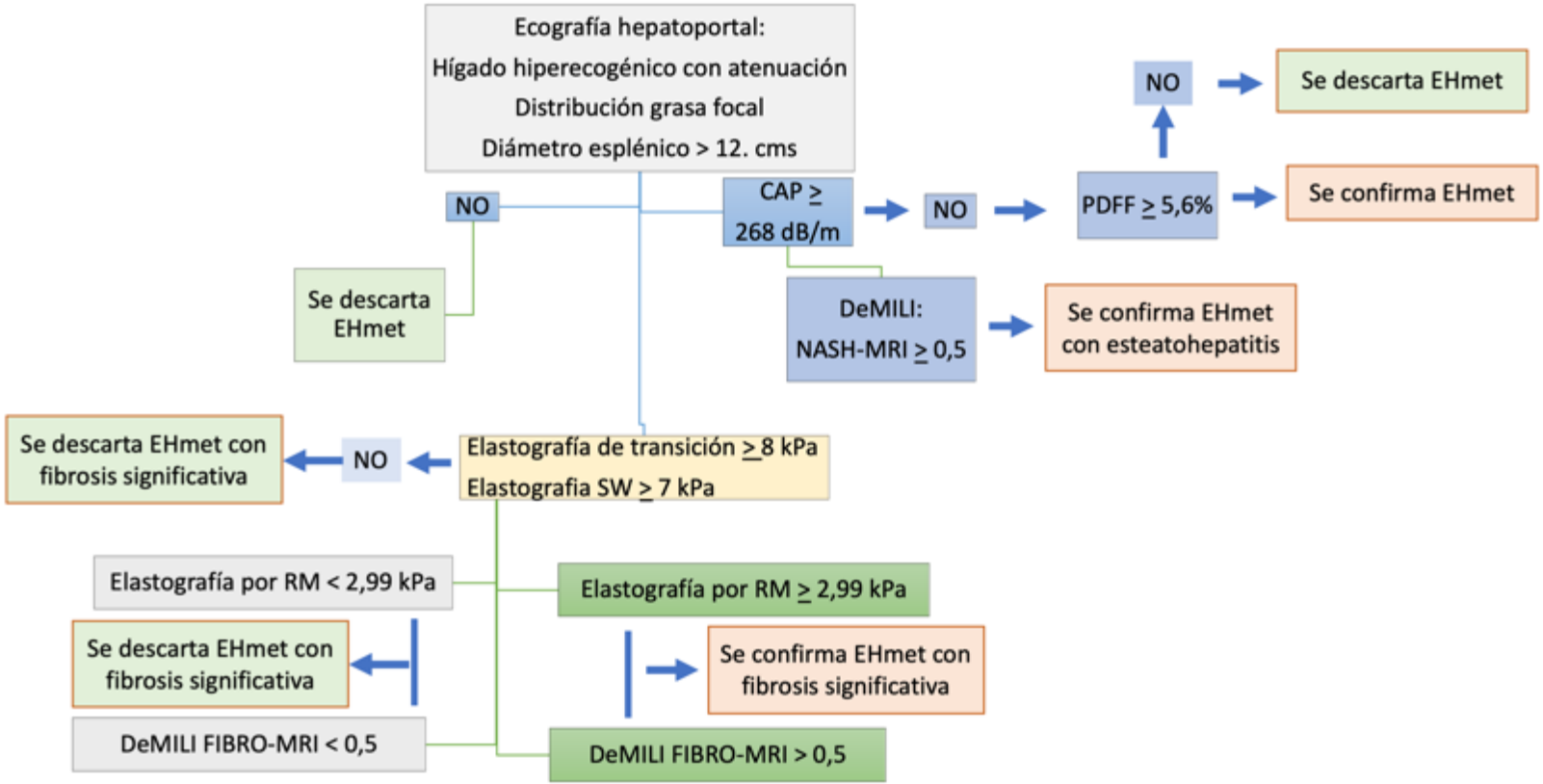




	β	S.E	Wals	P value	OR	OR 95% C.I.	
R2*	0.306	0.150	4.139	0.042	1.358	1.011	1.823
IMC	0.054	0.199	0.074	0.786	1.056	0.714	1.560
grosor del panículo adiposo	-0.398	0.237	2.831	0.092	0.672	0.423	1.068
Diametro de bazo	0.268	0.389	0.475	0.491	1.307	0.610	2.799
esteatohepatitis	0.777	1.720	0.204	0.652	2.174	0.075	63.300
Ferritina	-0.011	0.007	2.761	0.097	0.989	0.977	1.002
TG	0.005	0.006	0.855	0.355	1.005	0.994	1.016

Liang X et al. SAPD 2020

Algoritmo diagnostico de enfermedad hepática metabólica basado en biomarcadores de imagen



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Take home messages

Imaging biomarkers (transient elastography and shear-wave) plus MRI techniques allow assessment of liver damage in NAFLD with high diagnostic accuracy:

1. **Transient Elastography should add metabolic status of the liver to the interpretation of stiffness.**
2. **MR Elastography** correctly classify across fibrosis stages
3. **Proton-Density Fat Fraction** accurately quantify fat accumulation in the liver
4. **DeMILI** showed the best diagnostic accuracy for NASH

"tunnel of MRI-based NASH & Fibrosis diagnosis"
PDFF >> MRI (LMS + DeMILI) >> MRE