MR Elastography of Liver: Fibrosis and Beyond

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Learning Objectives

I. **Understand the principle and technique of MRE liver**

II. **Learn about current clinical applications**
- Liver fibrosis detection and staging

III. **Learn about applications beyond liver fibrosis**
- Differentiate NAFL from NASH
- Prediction of clinically significant esophageal varices
- Prediction of hepatic decompensation
- Differentiate fibrosis from inflammation and congestion
- Other diffuse infiltrative liver disease

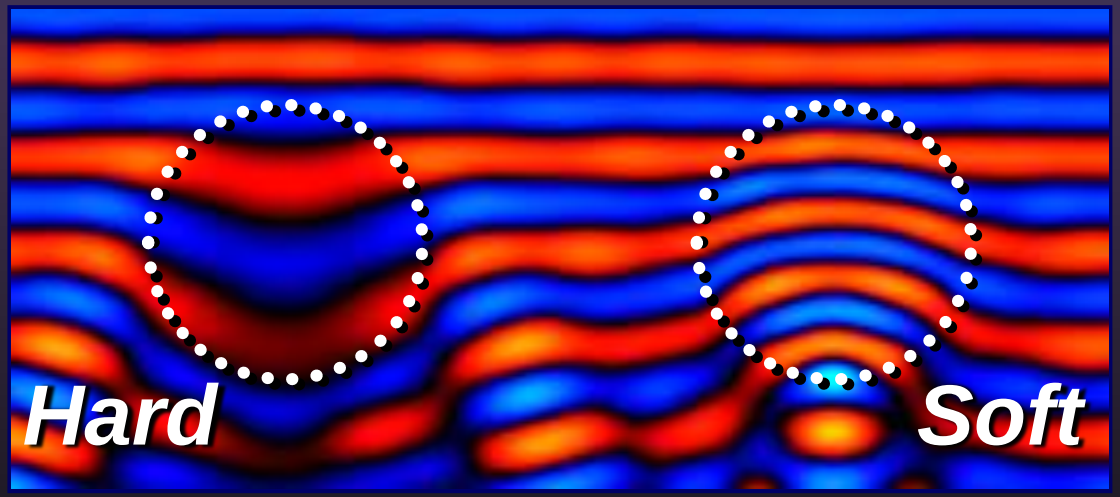
IV. **Learn about emerging applications**
- Differentiate non cirrhotic portal hypertension (NCPH) from cirrhosis
- Stiffness distribution may predict etiology of chronic liver disease
- Differentiate benign and malignant focal liver lesions
- Prediction of grade, vascular invasion and recurrence of HCC

Background

- MR elastography is a non-invasive technique that measures tissue stiffness.
- Liver stiffness (LS) measured with MRE is an excellent biomarker for both detection and staging of liver fibrosis.
- Recent innovations in MRE has expanded the utility of MRE in evaluation of diffuse liver diseases and focal liver lesions.
- This presentation illustrates with examples the current and emerging uses of MRE of Liver.

Principle of MRE

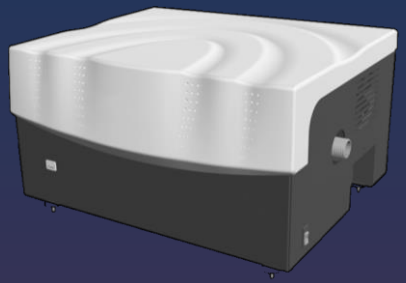
- **Tissues can be differentiated based on their viscoelastic property- stiffness**
- **Shear waves travel faster in hard (stiffer) than soft tissues**



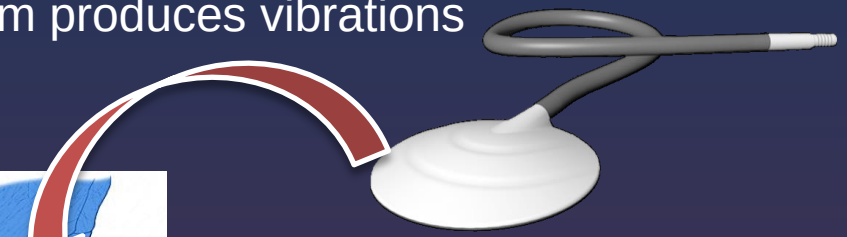
MRE image showing shear waves propagating in a gel phantom with ***hard*** and ***soft*** inclusions.
The shear waves ***travel faster*** and with ***longer wavelength*** in the hard inclusion compared to the soft inclusion

- *An inversion algorithm converts shear velocity information into shear stiffness*
- *Shear stiffness is measured in kilopascals (kPa) depicted on a stiffness map*

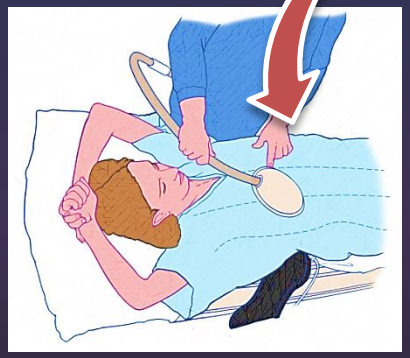
Clinical Liver MRE Technique



A pneumatic **mechanical wave generator** placed outside the MRI scanner room produces vibrations

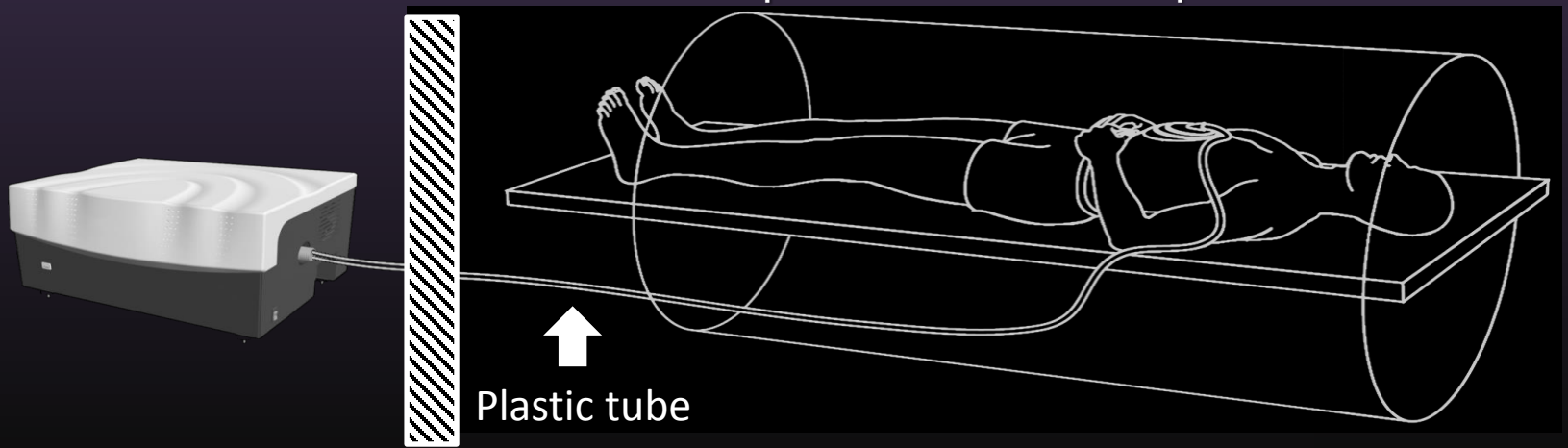


Passive driver placed over the right chest wall /upper abdomen at the level of xiphisternum in right mid clavicular line.



The passive driver is applied to the abdomen and held in place with an elastic belt.

A hollow plastic tube (25ft) connects the generator to the passive driver, allowing transmission of mechanical vibrations into the patient's tissues via passive driver.

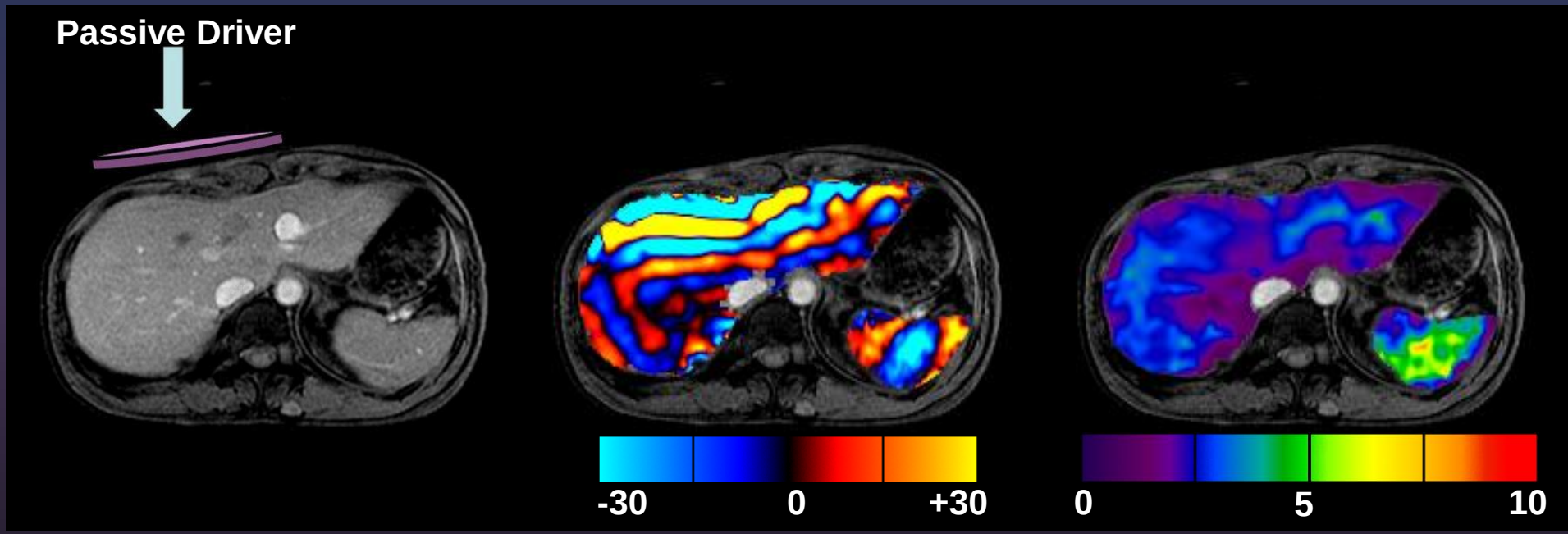


Three steps in Liver MRE

Propagate shear waves through liver (60Hz)

Image the shear waves with MRE sequence

Inversion algorithm* process wave information



Conventional MR Image

Displacement (μm)

Wave image

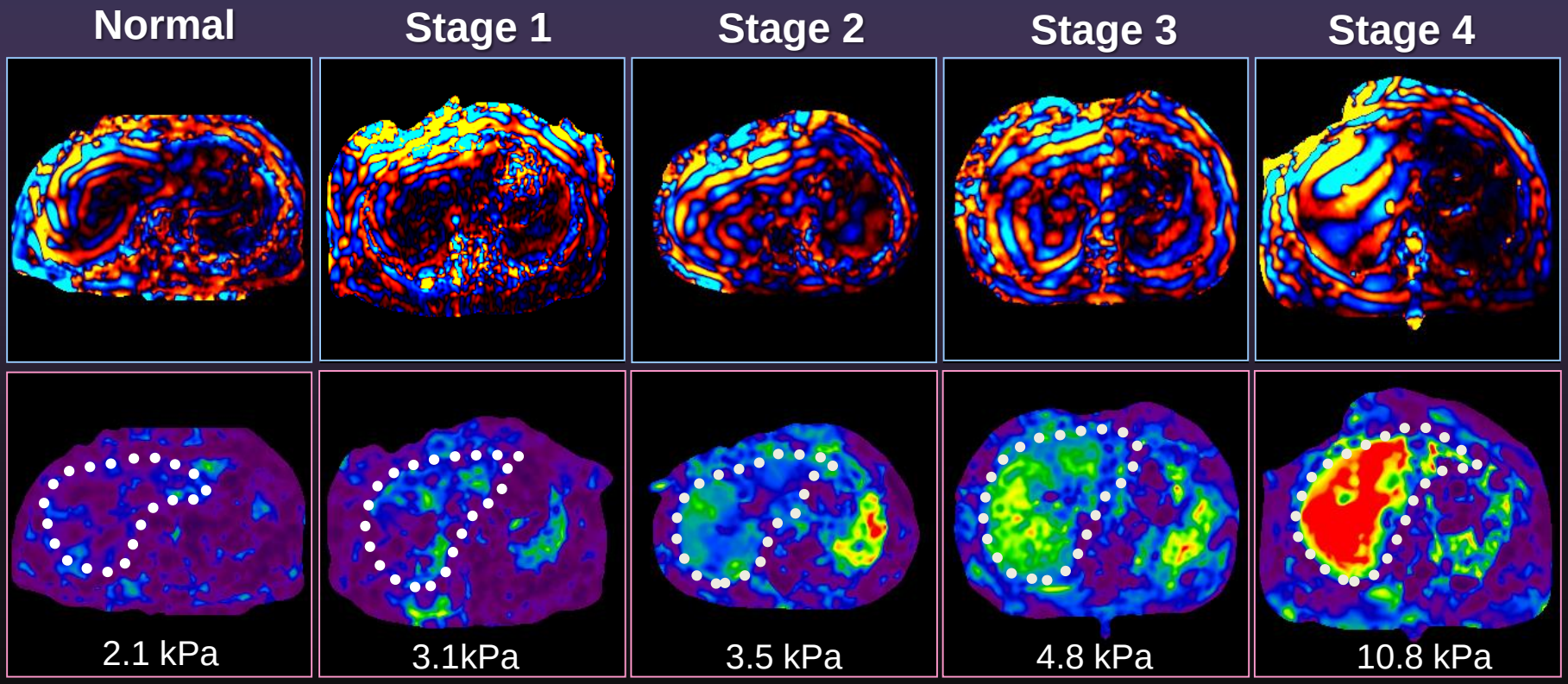
Shear stiffness (kPa)

Elastogram

**Inversion algorithm is installed in the MR scanner and the process is automated. The stiffness maps are automatically generated within minutes after MRE sequence is completed.*

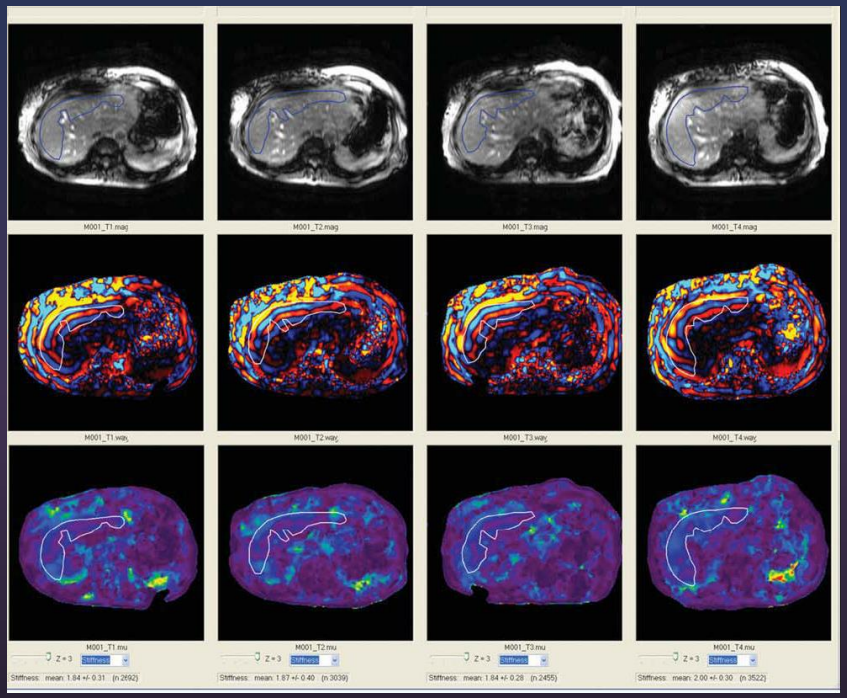
Liver stiffness increases with increasing fibrosis stage

Increase in liver stiffness is incremental in early stages but exponential in later stages



MRE is repeatable and reproducible
High interobserver correlation

Normal healthy volunteer

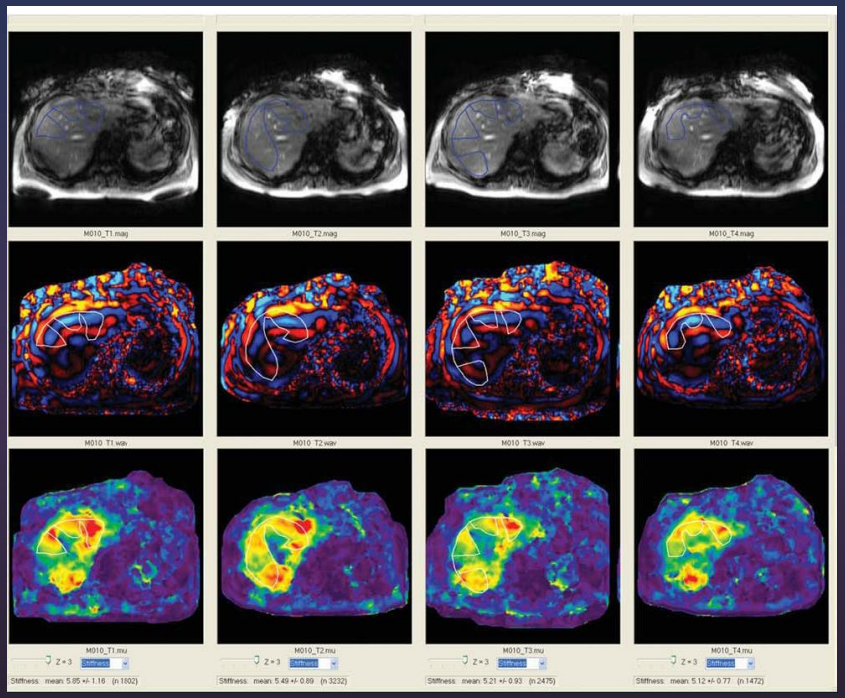


0 — 10 min — 0 min — 10 min

First Visit — 7-14 days — Second Visit

ICC 0.93

Chronic Hepatitis C patient



0 — 10 min — 0 min — 10 min

First Visit — 7-14 days — Second Visit

ICC 0.94

A measured change in hepatic stiffness of >20 % or greater, at the same site and with use of the same equipment and acquisition sequence, indicates that a true change in stiffness has occurred with 95% confidence.

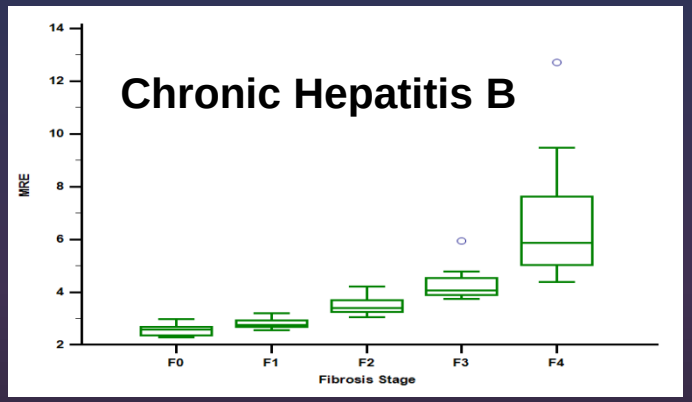
Quantitative Imaging Biomarkers Alliance MR elastography claim, RSNA 2017

Staging of liver fibrosis

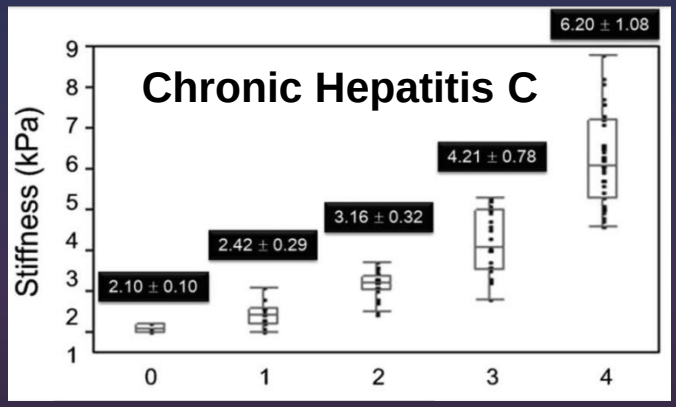
All chronic liver diseases show similar small (incremental) changes in liver stiffness in early stages and large (exponential) changes in later stages of fibrosis. This has important implications on clinical use of MRE and all elastography techniques.

The difference in stiffness between stages 0 and 4 is many times higher than difference between stages 0 and 1.

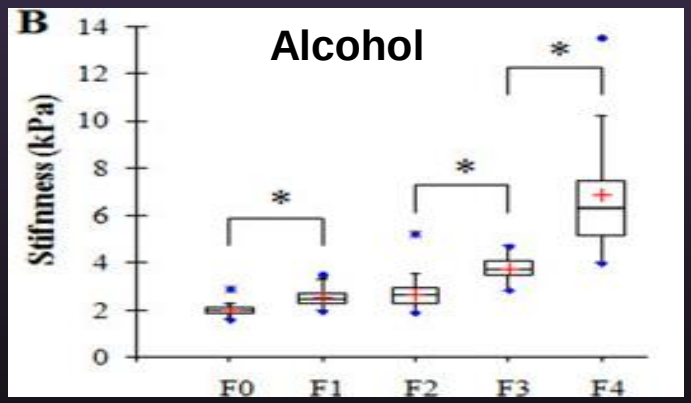
Accuracy for differentiating early stages of fibrosis (stage 0 vs. 1, 1 vs. 2 etc.,) is lower than that differentiating advanced stages (stage 3 vs. 4).



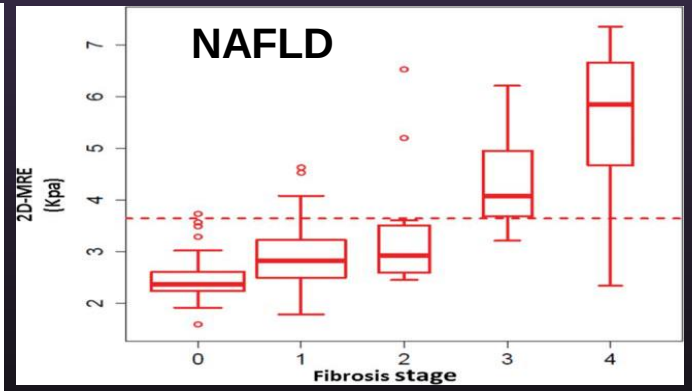
Venkatesh SK et al. Eur Radiol 2014;24:70-8



Ichikawa S et al. MRM 2012; 11(4): 798-98



Bensamoun et al. Alcoholism: Clin Exp Res 2012



Loomba R et al. Hepatology 2015

Accuracy of MRE in detection and staging of liver fibrosis

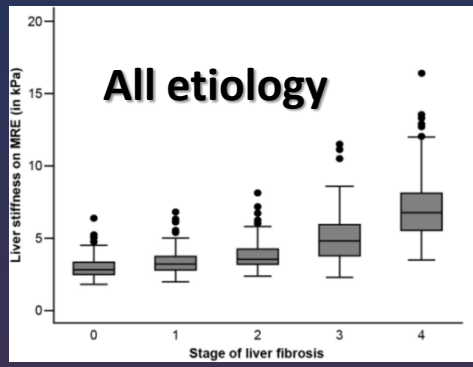


Table 2. Pooled Analysis of the Diagnostic Performance of Magnetic Resonance Elastography for Diagnosis and Staging of Liver Fibrosis, Based on 697 Patients From 12 Studies

Fibrosis stage	Optimal cut-off value, *kPa*	AUROC (95% CI)	Sensitivity	Specificity	Positive LR	Negative LR
Any fibrosis (≥stage 1)	3.45	0.84 (0.76–0.92)	0.73	0.79	3.48	0.34
Significant fibrosis (≥stage 2)	3.66	0.88 (0.84–0.91)	0.79	0.81	4.16	0.26
Advanced fibrosis (≥stage 3)	4.11	0.93 (0.90–0.95)	0.85	0.85	5.67	0.18
Cirrhosis (stage 4)	4.71	0.92 (0.90–0.94)	0.91	0.81	4.79	0.11

CI, confidence interval.

Singh S, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. Clinical Gastroenterology and Hepatology 2015; 13:440-451

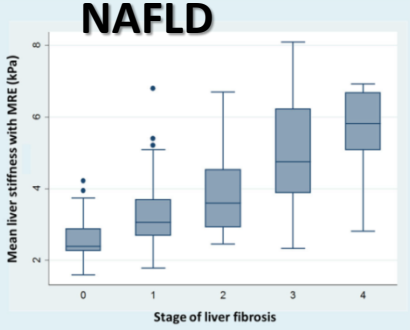


Table 2 Pooled analysis of the diagnostic performance of magnetic resonance elastography for diagnosis and staging of liver fibrosis, based on 232 patients from nine studies (six independent cohorts)

Fibrosis stage	Optimal cut-off (kPa)	AUROC (95 % CI)	Sensitivity (95 % CI)	Specificity (95 % CI)	Positive LR	Negative LR
Any fibrosis (≥stage 1)	2.88	0.86 (0.82–0.90)	0.75 (0.68–0.87)	0.77 (0.65–0.88)	3.24	0.33
Significant fibrosis (≥stage 2)	3.54	0.87 (0.82–0.93)	0.79 (0.76–0.90)	0.81 (0.72–0.91)	4.14	0.27
Advanced fibrosis (≥stage 3)	3.77	0.90 (0.84–0.94)	0.83 (0.53–0.90)	0.86 (0.81–0.96)	5.93	0.19
Cirrhosis (stage 4)	4.09	0.91 (0.76–0.95)	0.88 (0.82–1.00)	0.87 (0.77–0.97)	6.50	0.14

AUROC Area under receiver-operating curve, *CI* Confidence interval, *LR* likelihood ratio

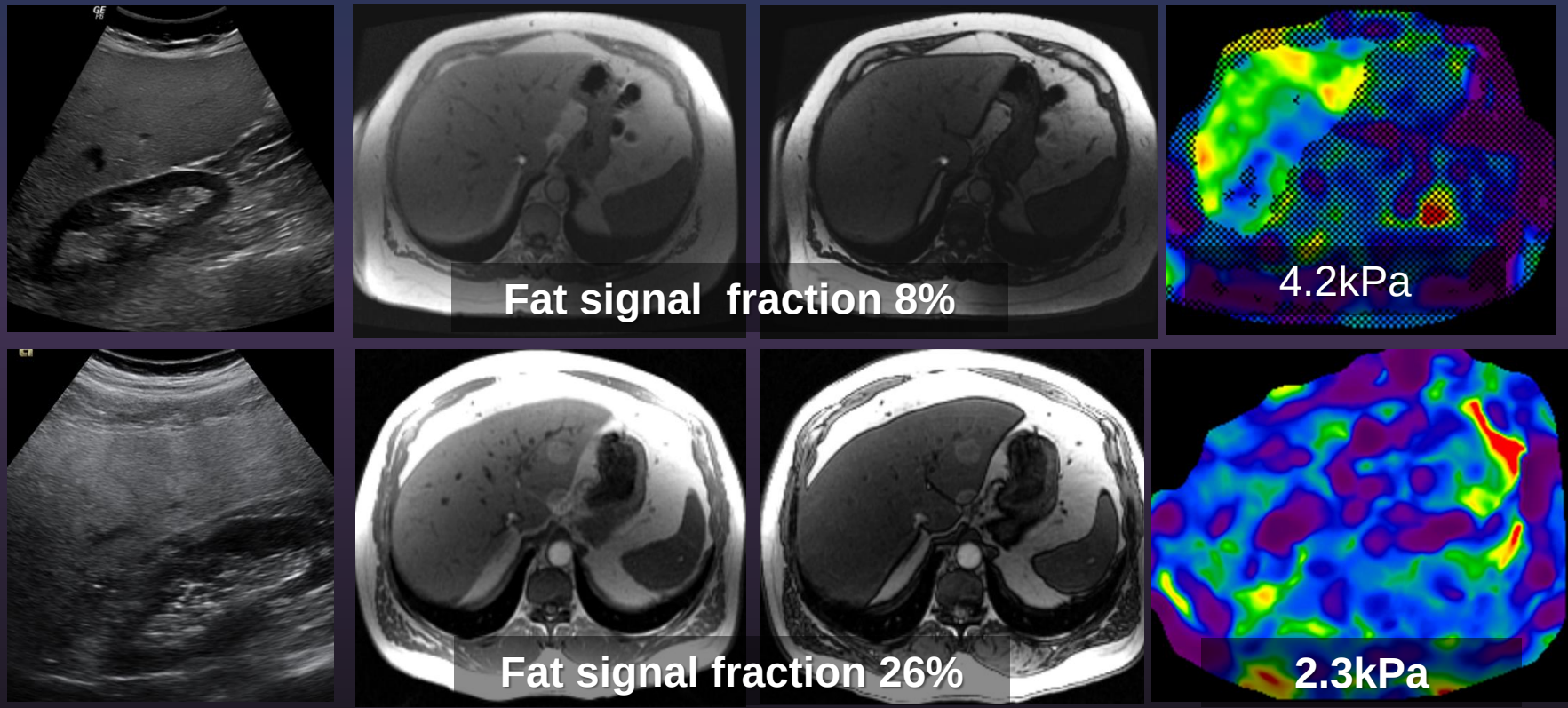
Singh S, et al. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. European Radiology 2016; 26:1431-40

Stage	Stage ≥1	Stage ≥2	Stage ≥3	Stage =4
Accuracy	0.93	0.95	0.94	0.92

26 studies and 3,200 patients

Kim YS et al. Comparison of gradient-recalled echo and spin-echo echo-planar imaging MR elastography in staging liver fibrosis: a meta-analysis. Eur Radiol 2018;28(4):1709-18

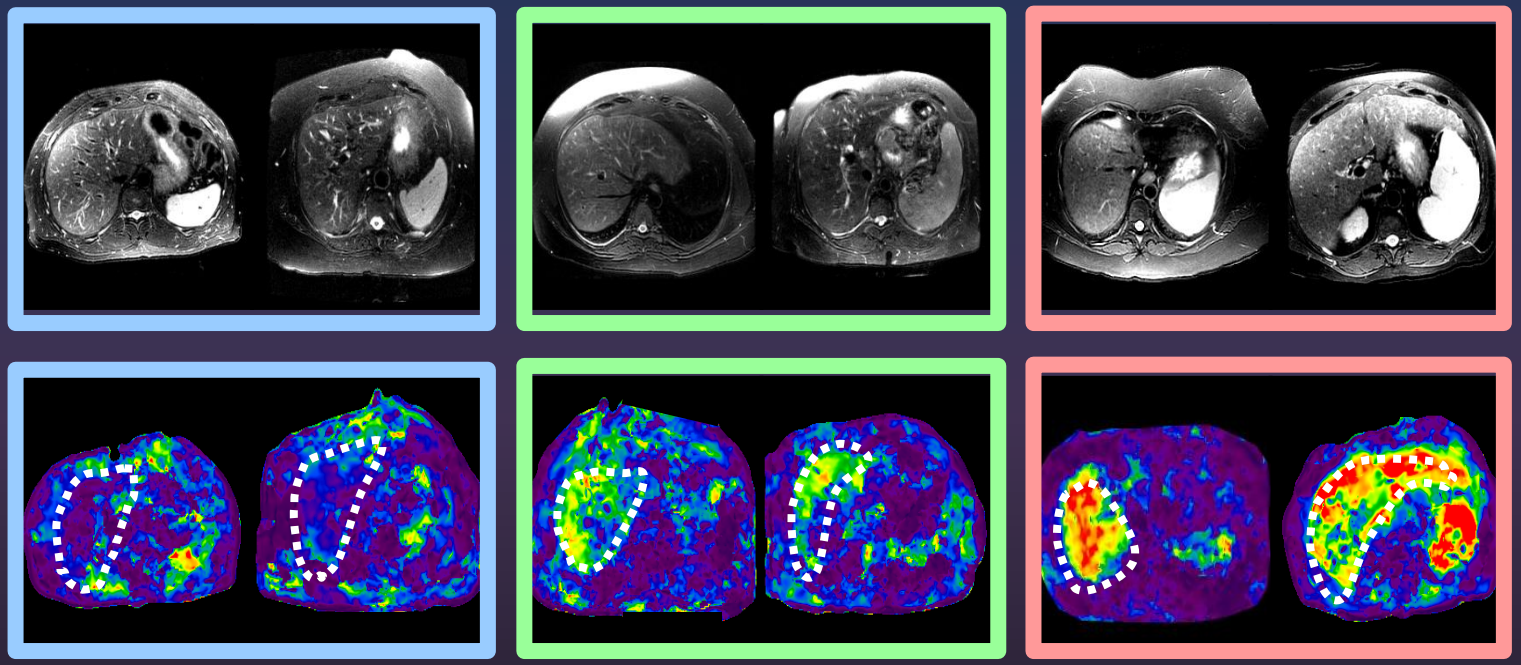
Differentiate Simple Steatosis (NAFL) from Steatohepatitis (NASH)



NAFL - Non alcoholic fatty liver
NASH - Non alcoholic steatohepatitis

MRE measured liver stiffness is not affected by presence of fatty change (steatosis)

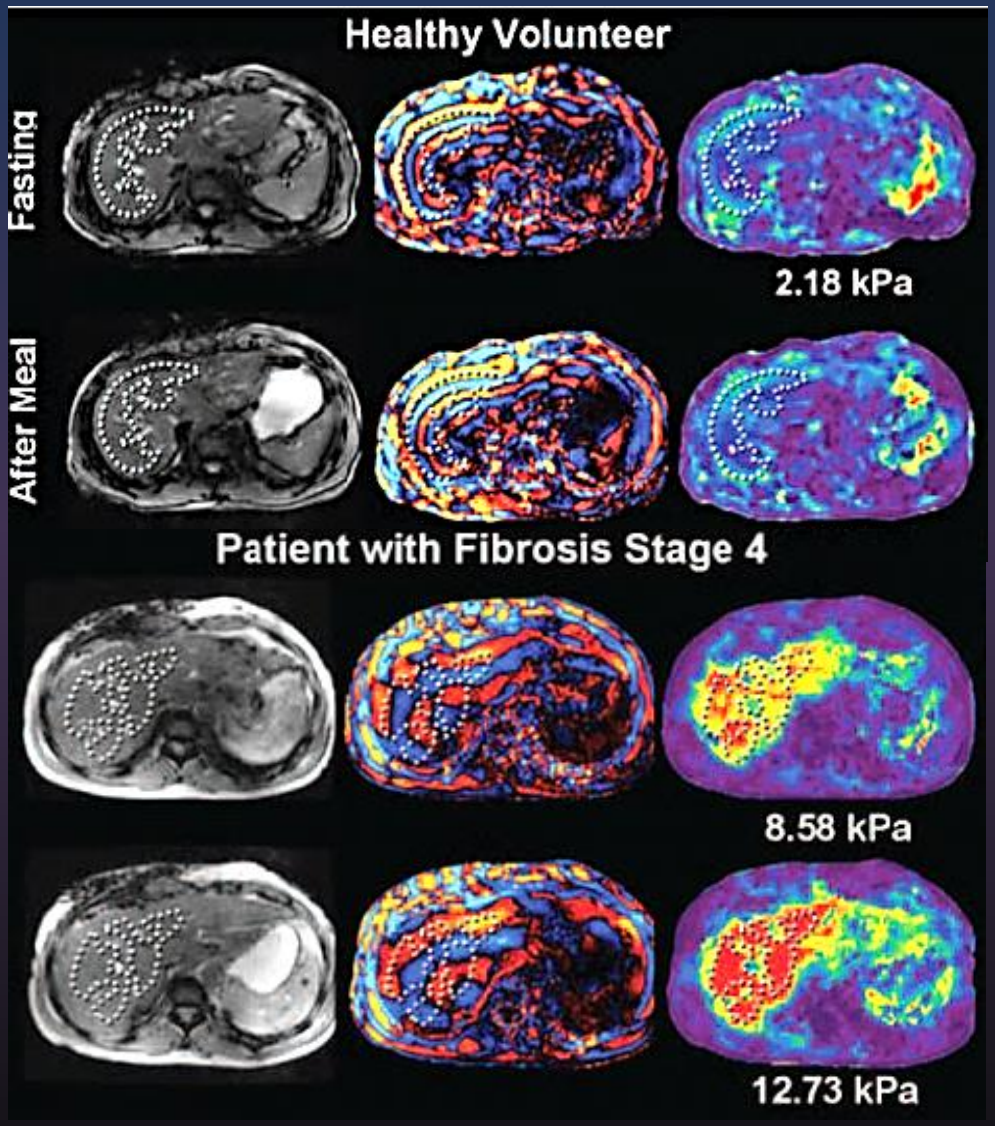
MRE can detect inflammation in NAFLD before fibrosis onset



Chen J, et al. Radiology 2011 259:749-56

Liver Stiffness	2.02	2.05	4.38	3.59	10.24	7.52
Fibrosis Stage	0	0	0	0	4	4
Inflammation Grade	0	0	1	1	2	1

Liver Stiffness in fibrosis is Dynamic



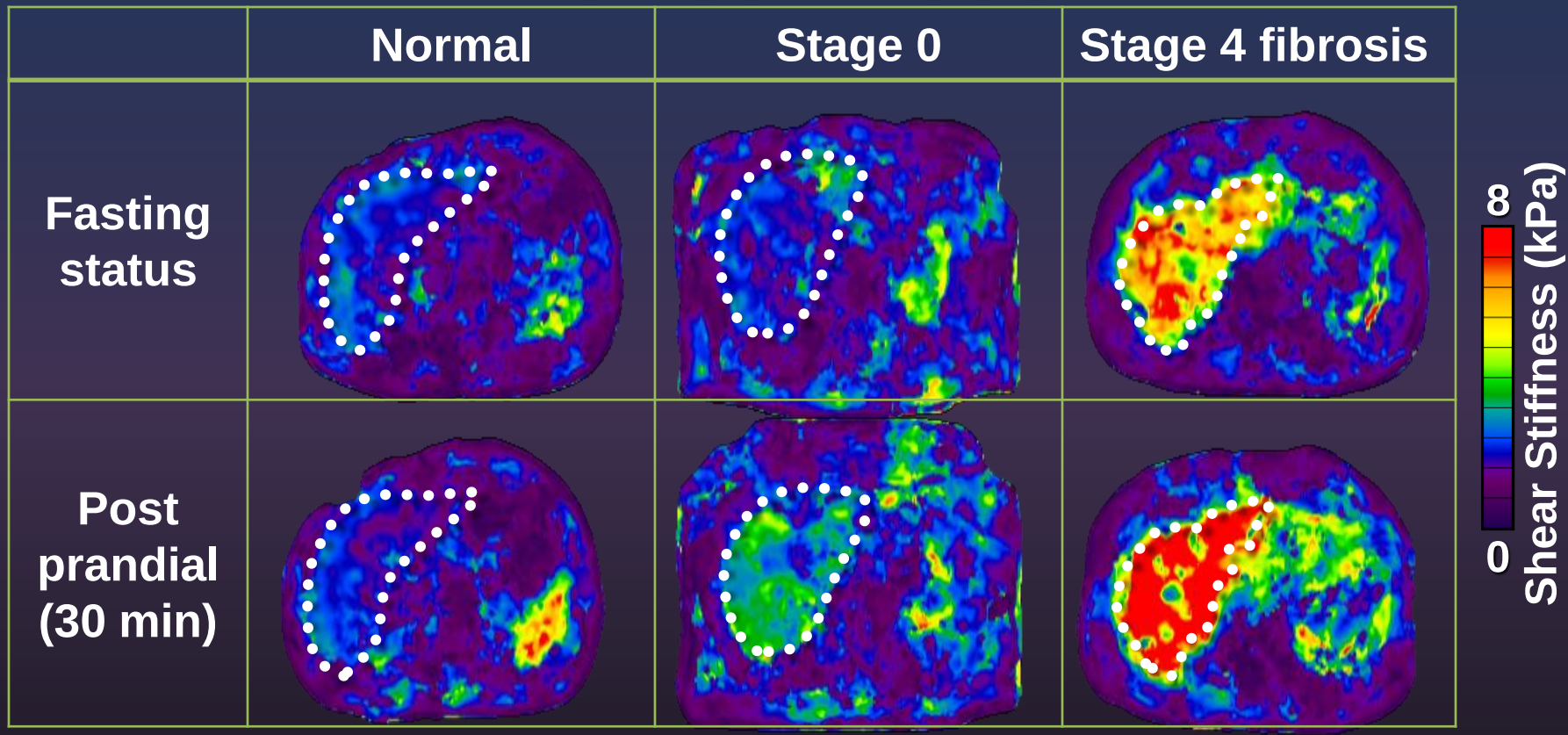
Two components of stiffness in fibrotic livers

Static component
reflecting structural change or fibrosis

Dynamic component
reflecting portal pressure that can increase after a meal.

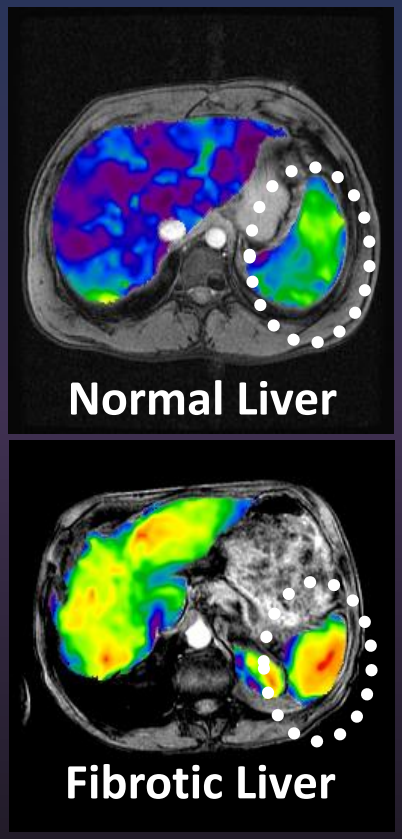
Yin M et al AJR 2011. Dynamic Postprandial Hepatic Stiffness Augmentation Assessed With MR Elastography in Patients With Chronic Liver Disease

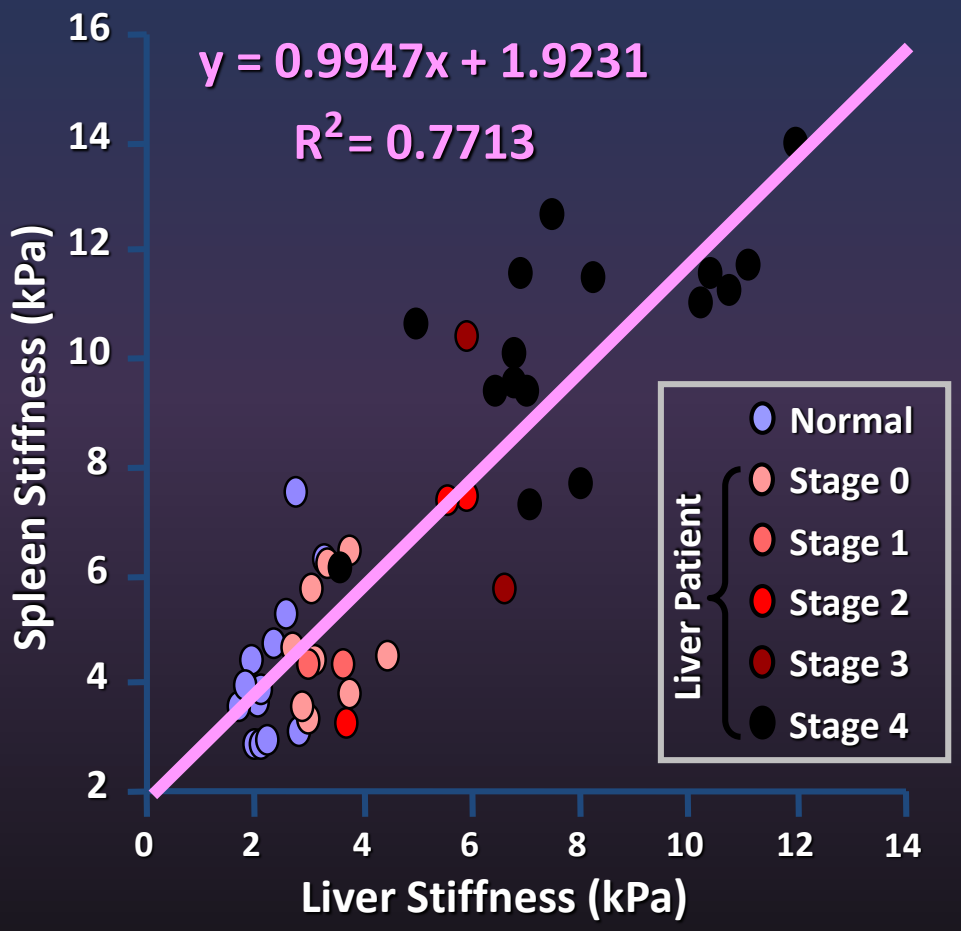
Portal hypertension increases liver stiffness



Increased portal flow causes no or minimal change in stiffness of normal liver as increased flow is accommodated without increase in portal pressure. In fibrotic livers, reduced capacitance leads to increased liver stiffness and this increase in stiffness is more in advanced fibrosis stage.

Liver and Spleen stiffness correlation in chronic liver disease





Good correlation between liver and spleen stiffness in chronic liver disease when splenoportal axis is patent

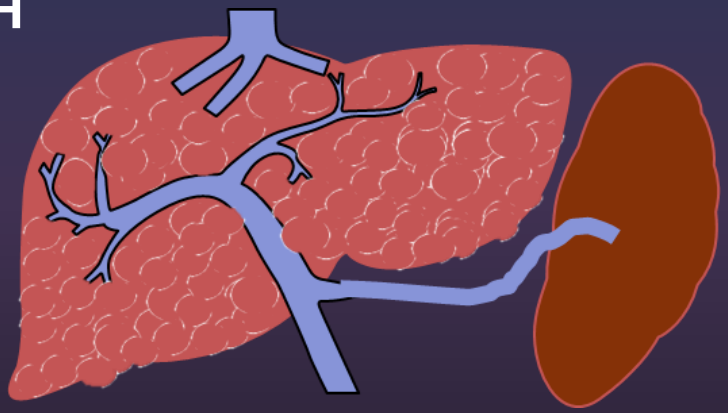
Splenic stiffness >10.5kPa is predictive of clinically significant esophageal varices

Talwalkar JA et al., AJR 2009

Non Cirrhotic Portal Hypertension (NCPH) vs. Cirrhosis

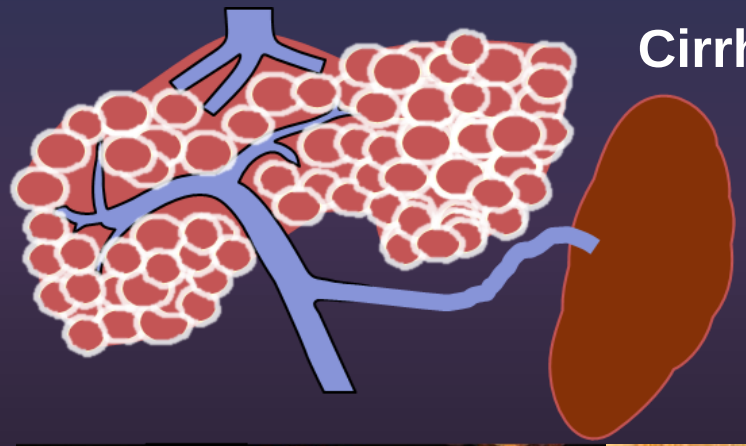
NCPH can result from various causes including portal thrombosis, portal sclerosis and nodular regenerative hyperplasia (NRH). In NRH, there is no fibrosis or minimal fibrosis in the liver → liver stiffness would be either normal or mildly increased.

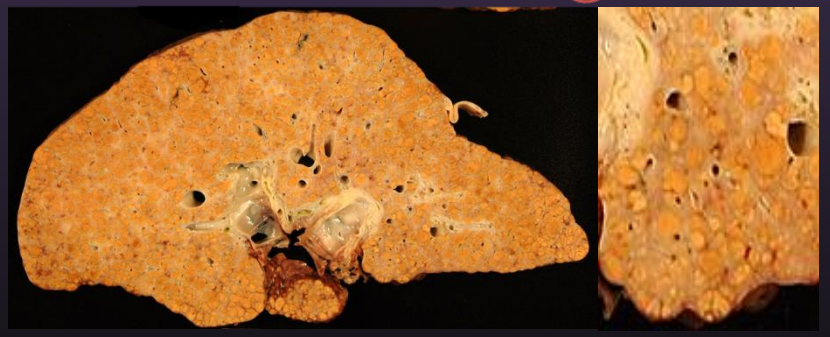
NCPH



Liver stiffness ↑/↔
Spleen stiffness ↑↑

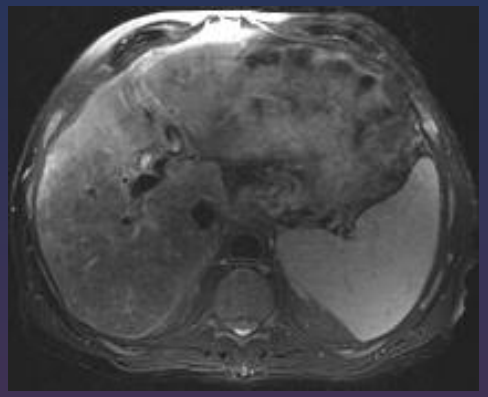
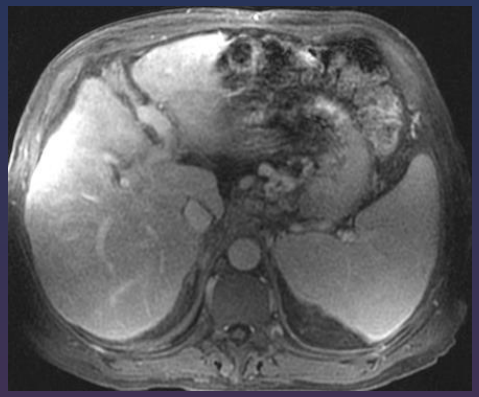
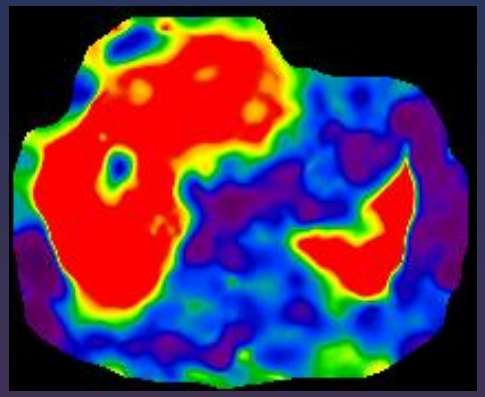
Cirrhosis





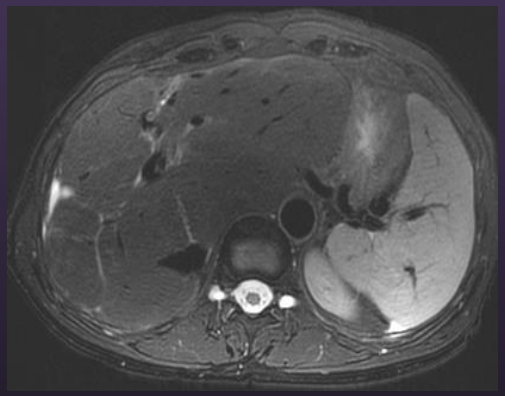
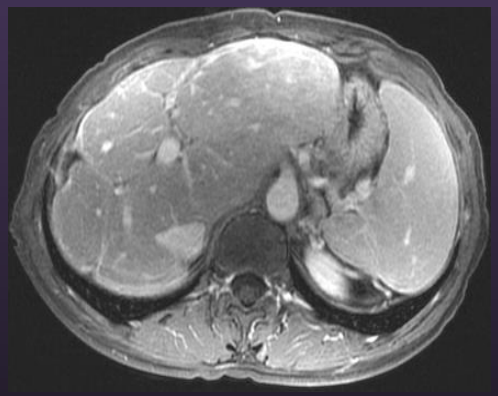
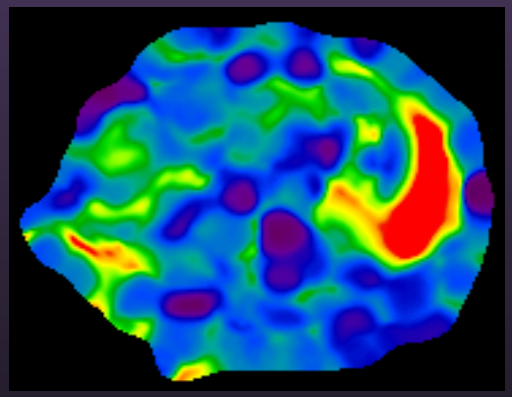
Liver stiffness ↑↑
Spleen stiffness ↑↑

MRE is useful to differentiate NCPH from Cirrhosis:

Cirrhosis

LSM = 10.3 kPa,
SSM = 10.2 kPa,
SSM:LSM = 1.0

Nodular Regenerative Hyperplasia

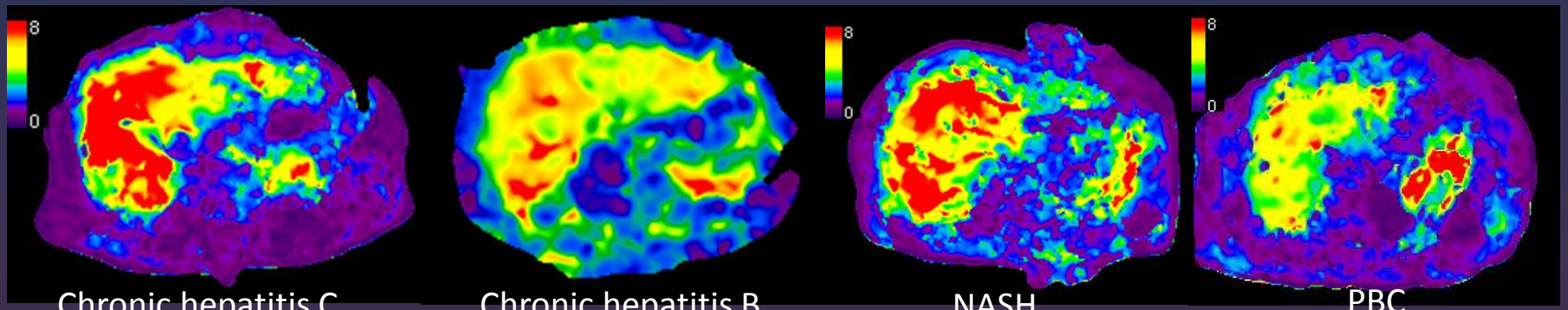
LSM = 3.9 kPa,
SSM = 8.8 kPa,
SSM : LSM = 2.3

Conventional T2W and portal venous phase T1W images in two patients with alcoholic cirrhosis (top row) and NRH (bottom row) demonstrating features of portal hypertension with nodular hepatic morphology. MRE shows increased liver and spleen stiffness in alcoholic cirrhosis, however spleen stiffness in increased much higher than liver in NCPH.

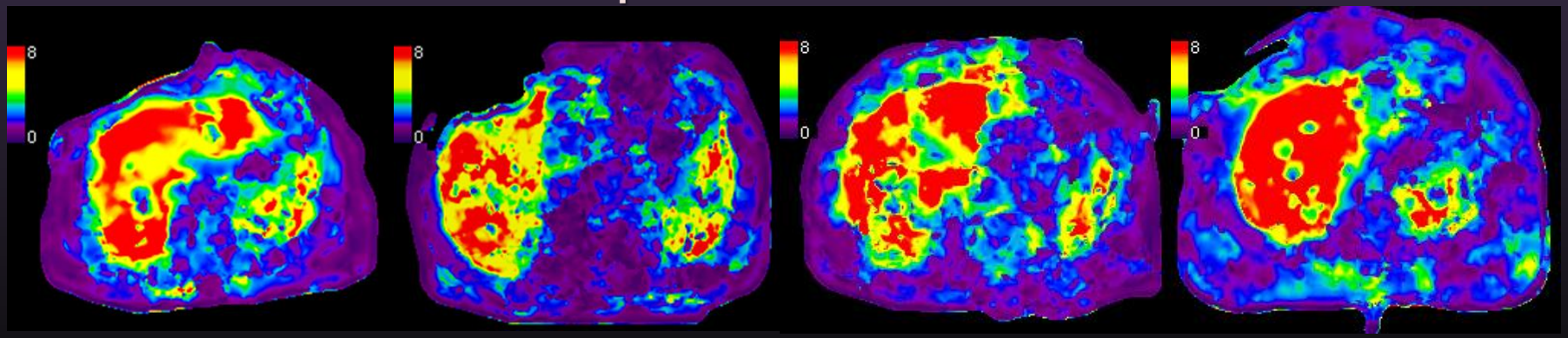
Navin PJ, et al. Hepatology 2019

Stiffness maps show distribution of fibrosis/inflammation

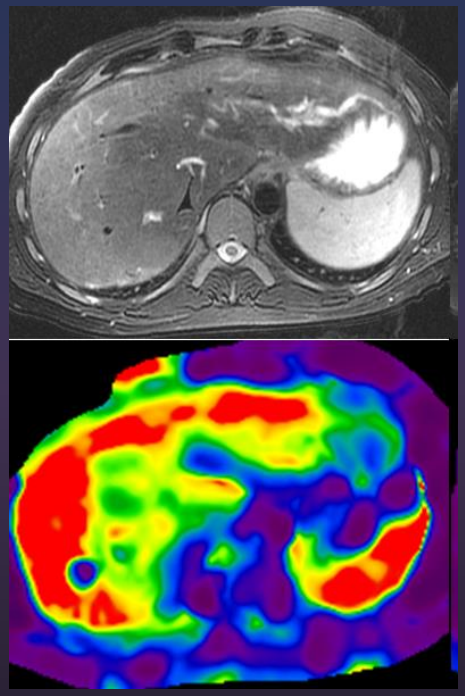
Stiffness is heterogeneous especially in advanced fibrosis stage



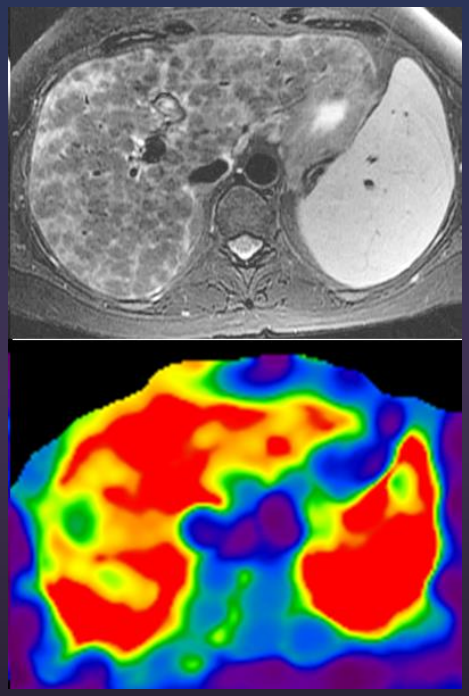
Stiffness distribution is different for same fibrosis stage as illustrated with 4 cases of chronic hepatitis C with cirrhosis below



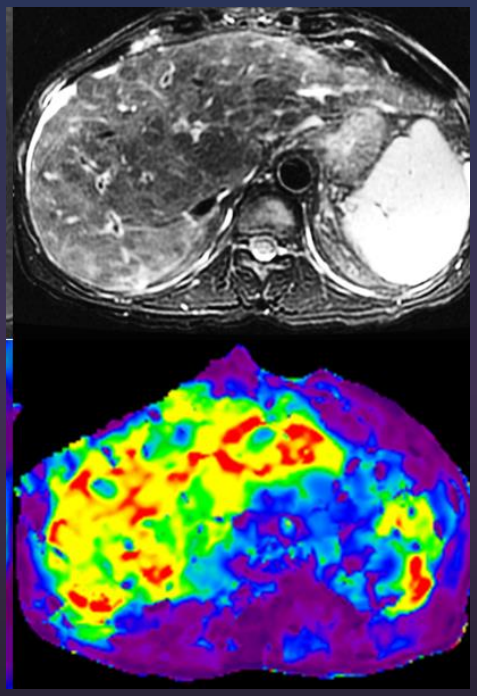
Pattern of Stiffness Distribution may suggest etiology



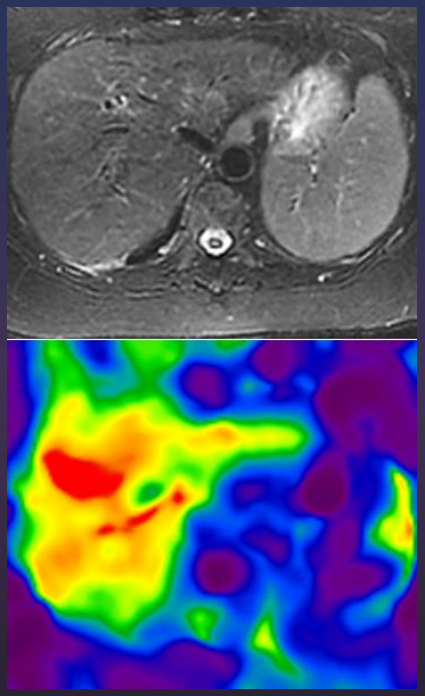
Primary sclerosing cholangitis



Alcoholic cirrhosis



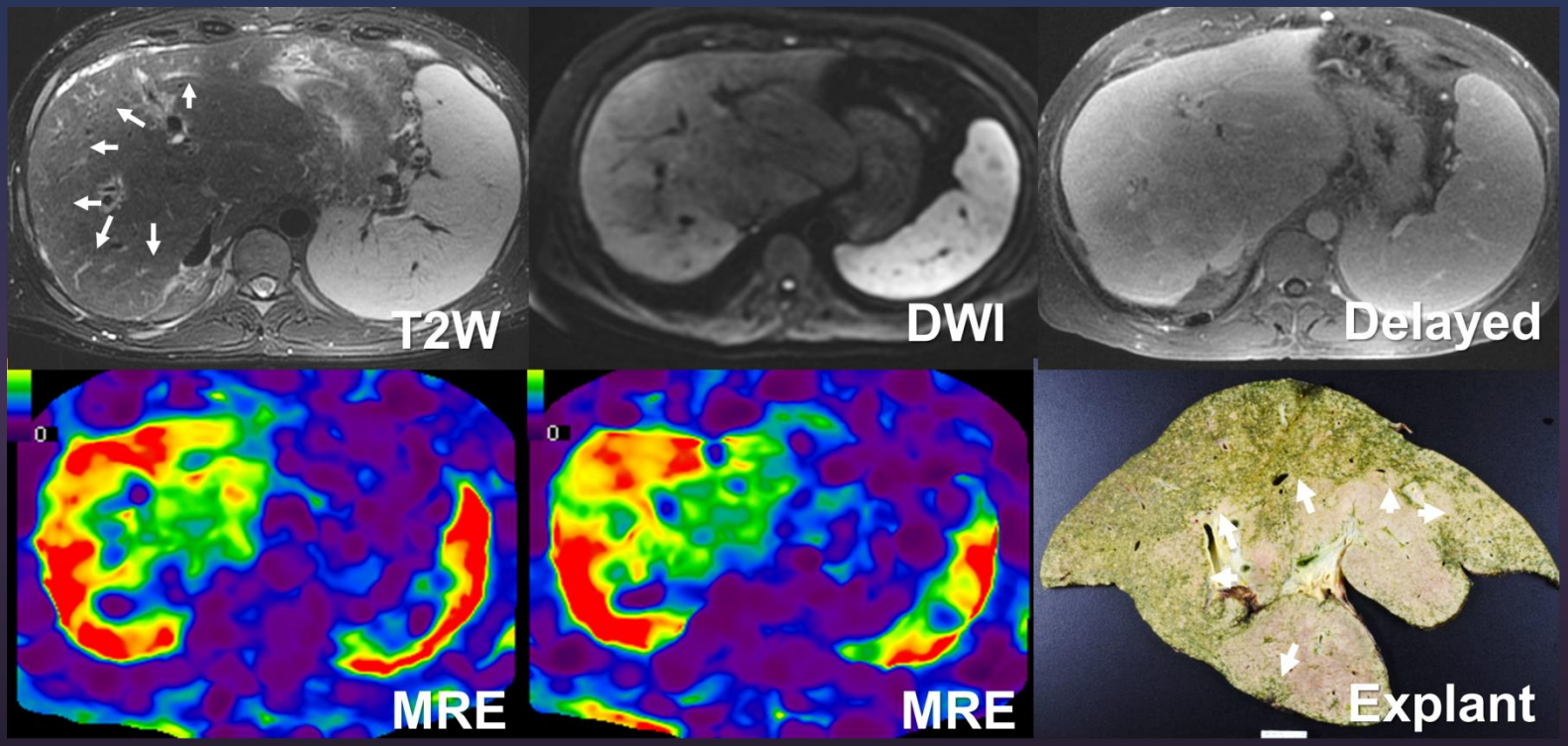
Autoimmune hepatitis



Chronic hepatitis C

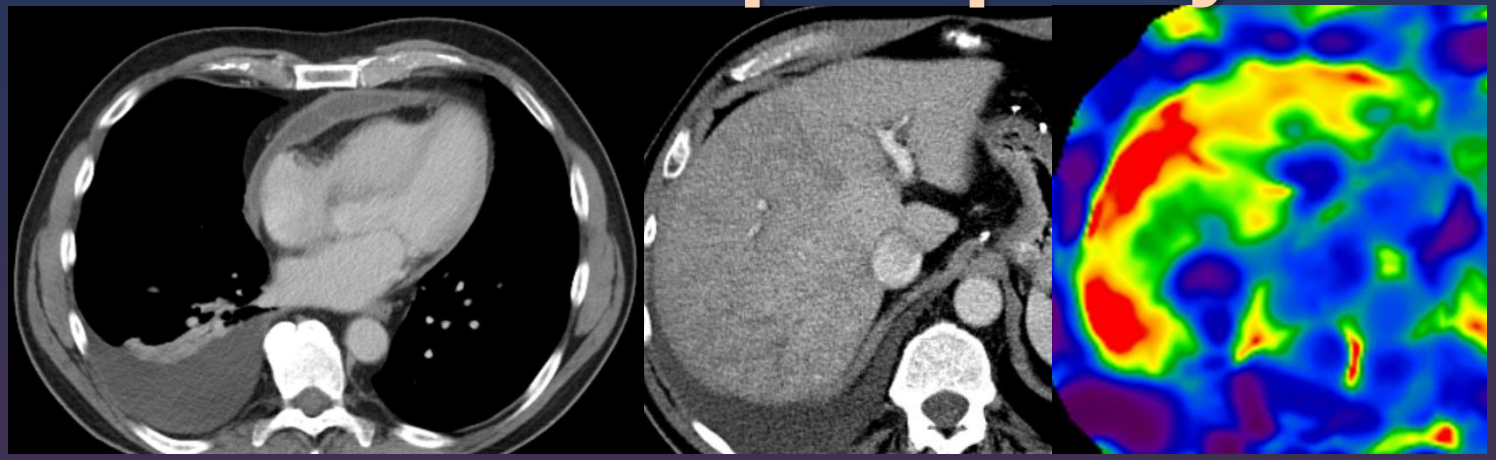
Primary sclerosing cholangitis shows peripheral rim like or segmental regions of increased stiffness in early stages of the disease with central large regenerative parenchyma that correspond to lower stiffness region

Increased Peripheral Stiffness in Primary Sclerosing Cholangitis

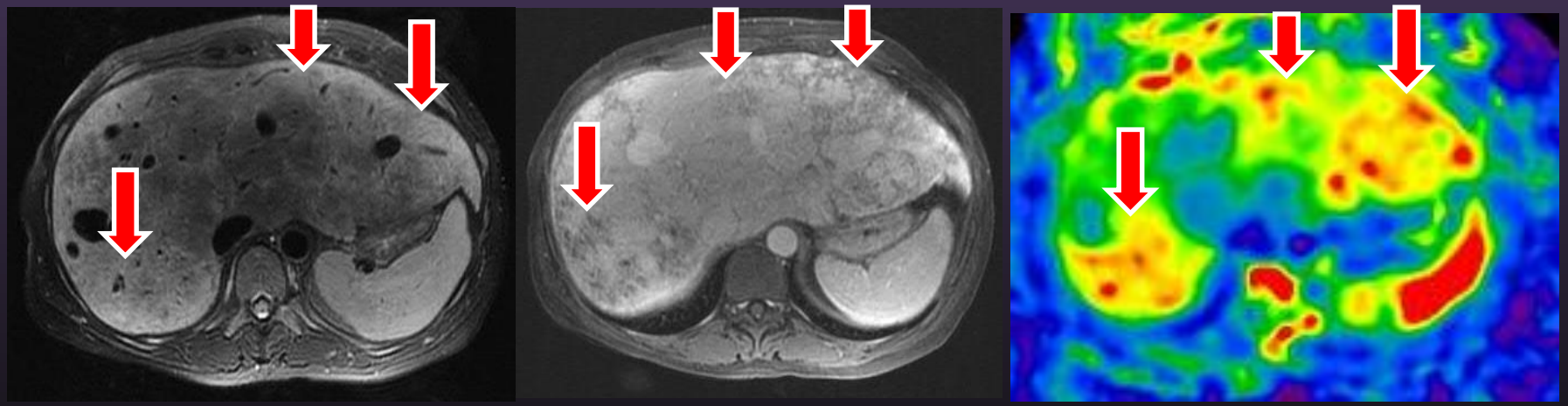


Peripheral fibrotic changes (arrows) with subtle increased T2 signal, diffusion restriction and delayed enhancement, with sparing and hypertrophy of the central liver consistent with central regeneration termed as macroregenerative nodule. MRE demonstrates markedly increased hepatic stiffness peripherally and mild to moderately increased stiffness in the central region. Explant showing corresponding advanced fibrosis and cholestasis in the periphery (arrows) with central regenerative changes.

Stiffness distribution in Congestive Hepatopathy



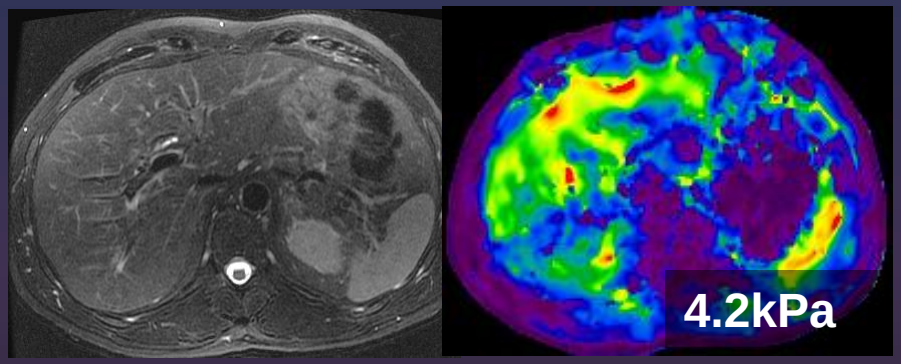
A 65 year old with constrictive pericarditis and congestive hepatopathy showing increased stiffness more so in the periphery of the right lobe.

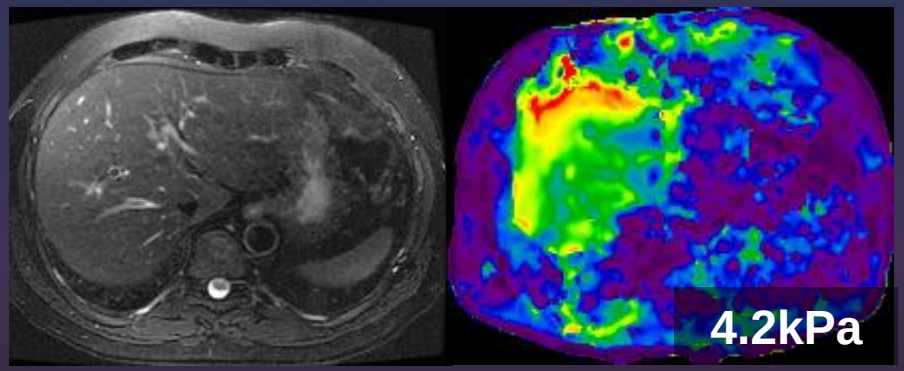


20 year old post heart transplant and chronic congestive hepatopathy. Note close association between of peripheral poor perfusion (arrows) and increased stiffness in the congested liver.

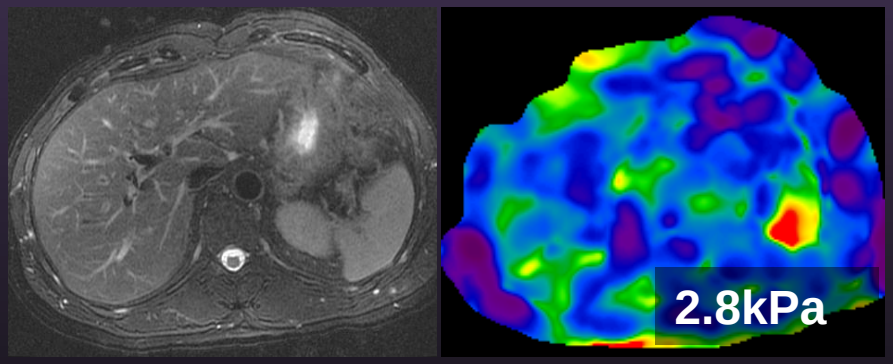
Clinical application of MRE-1 Assessment of Treatment Response

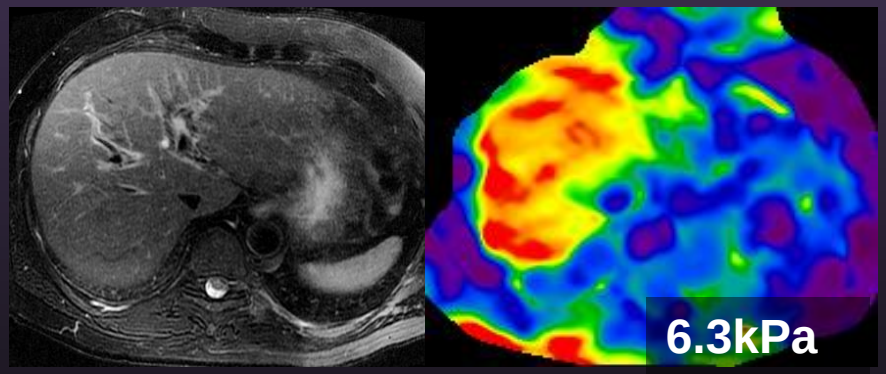
Two patients with Chronic Hepatitis C and on antiviral treatment





3 years

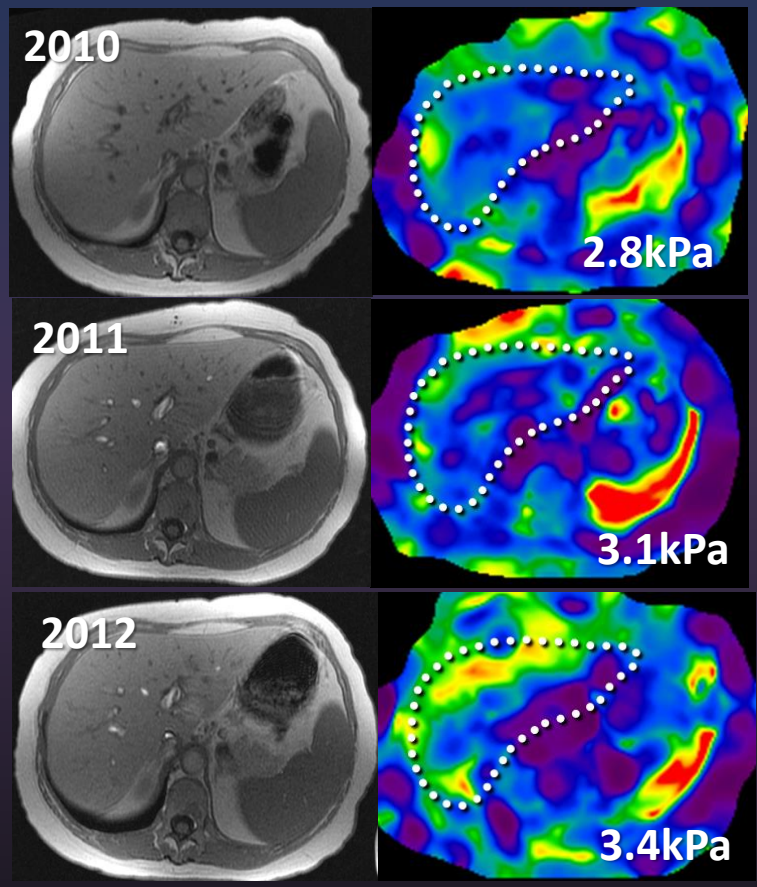




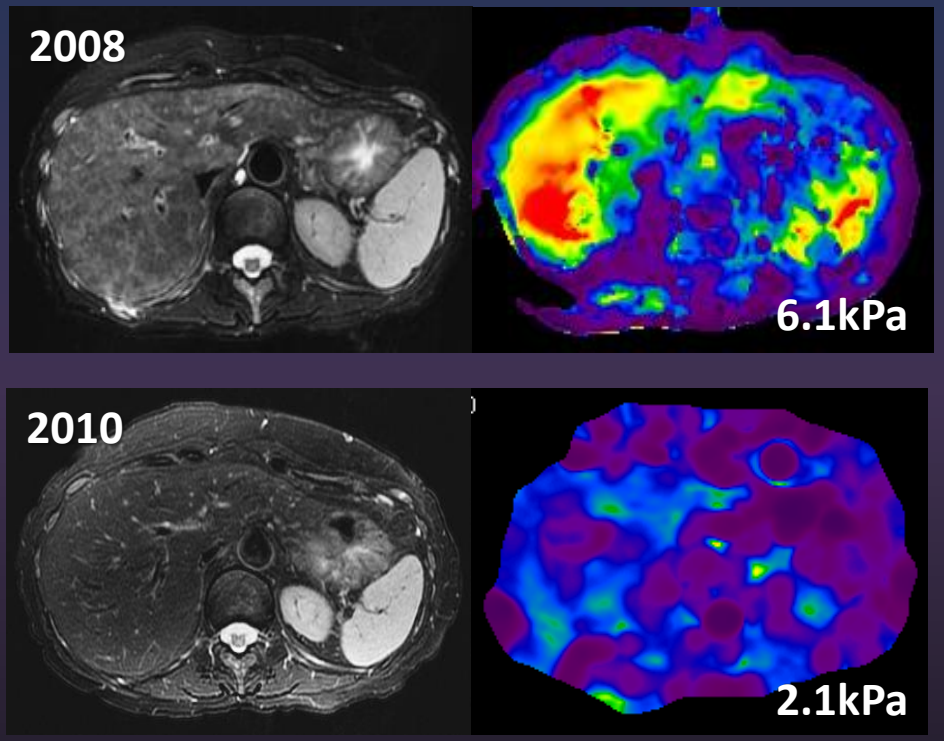
Improvement

Progression

Clinical application of MRE-2
Longitudinal clinical follow up



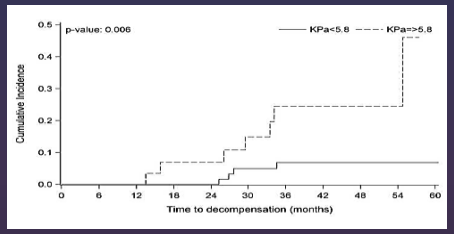
A 54-year-old female with primary biliary cholangitis. MRE at baseline (2010) showed mildly elevated stiffness and gradual increase in stiffness to 3.4kPa in two yeas. Note no change in morphology over time



A 73-year-old female with autoimmune hepatitis. MRE at presentation (2008) showed elevated stiffness and a liver biopsy performed at the same time showed stage 3-4 fibrosis and grade 3 inflammation. Patient was put on prednisone therapy and maintained on azathioprine. Four years later MRE shows near normal stiffness and note the resolution of hyperintensity in the liver on the T2W image.

Clinical application of Liver MRE-2

- **Predict hepatic decompensation**
  - The hazard of hepatic decompensation is 4.96 (95% CI 1.4-17.0, p=0.019) for a subject with compensated disease and mean LSM⩾5.8kPa as compared to an individual with compensated disease and lower mean LSM. *Asrani S et al . J Hepatol. 2014 May;60(5):934-9.*

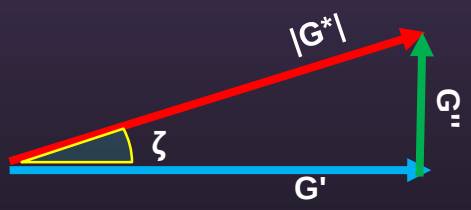


- **Predict major complications following liver resection**
  - A cut off value of 4.3 to 5.3kPa was a significant predictor of major complications following liver resection *Abe H, et al. Surgery. 2017;162:248–255; Sato N et al. Br J Surg 2018; 105:1192-99*
- **Predict radiation induced liver disease in patients receiving radiotherapy** *Ichikawa S, et al. Hepatology. 2017;66:664–665.*
  - The mean LSM of patients with RILD was significantly higher (8.3kPa) than that of patients without RILD (5kPa)

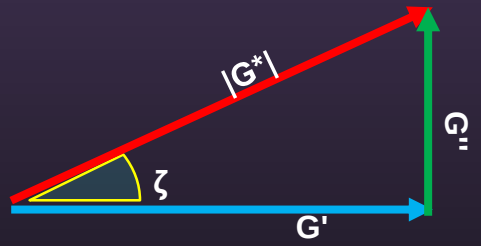
Advances in MRE

Before we learn advances lets recap a bit of physics

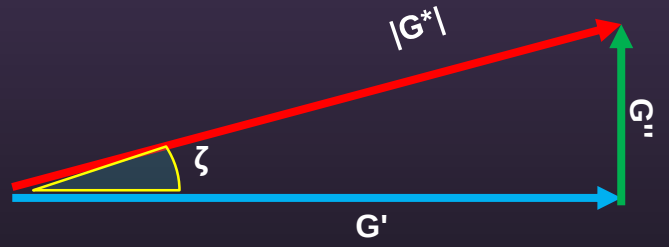
- The stiffness measured with MRE is **"Magnitude of the complex shear modulus" (G*).**
- Using linear viscoelasticity principles
  - G*= G′ + G″, where G′ is shear storage modulus (real part) and G″ is the shear loss modulus (imaginary part)
  - G″ and G′ are related; the ratio G″/ G′ is known as damping ratio (in simple words- how much of energy is lost)



Normal



Inflammation

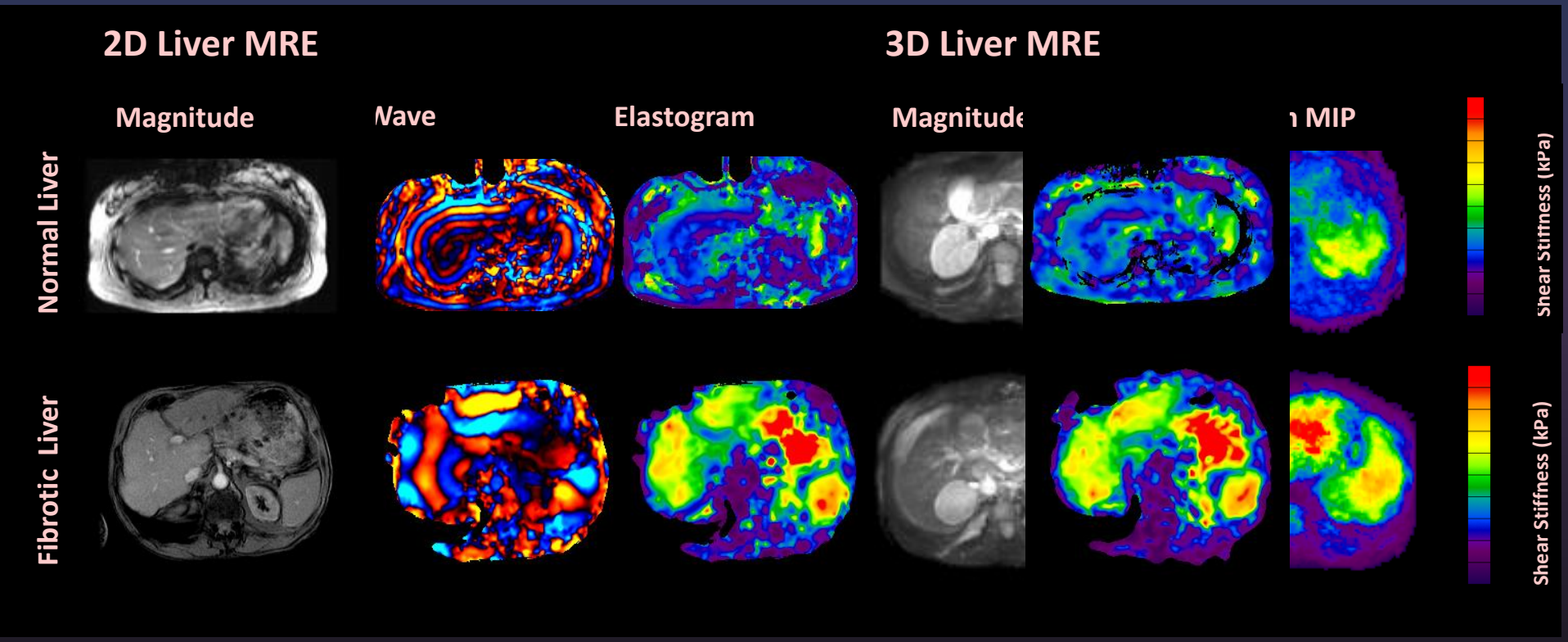


Fibrosis

It is possible to differentiate inflammation from fibrosis by deriving the shear modulus and loss modulus and damping ratio. This can be obtained by performing a three-dimensional (3D) MRE and at multiple frequencies (typically 30, 40 and 60Hz)

3D Liver MR Elastography

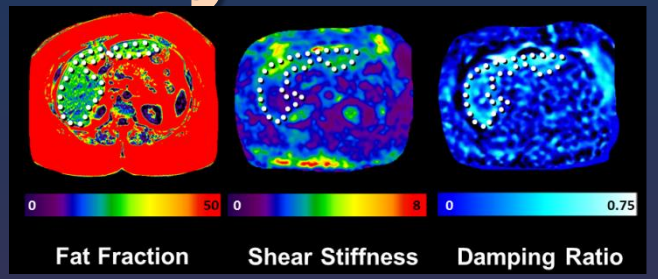
The current clinical standard MRE is a 2D GRE based MRE. The 3D MRE acquires a larger volume of liver by stacking multiple 2D slices (28-40 slices). The 3D method reduces the bias from oblique non planar waves that can occur with 2D acquisition

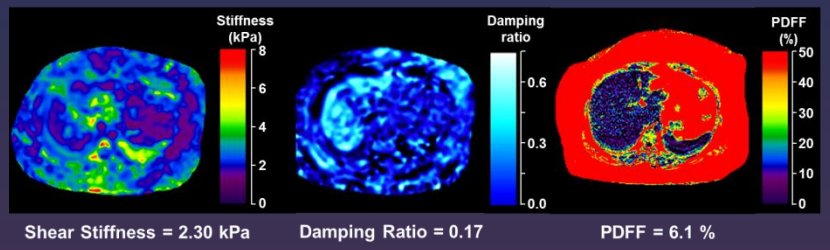


- 3D method is potentially more accurate method of estimation of viscoelastic properties of irregular shaped organs including liver, spleen, pancreas and kidneys.
- 3D MRE is very useful for evaluation of focal lesions like tumors within the liver.

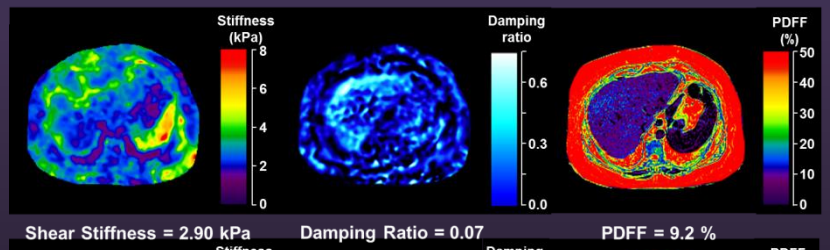
3D MRE for NAFLD Activity Score

It is possible to combine fat fraction score, shear stiffness and damping ratio to predict the NAFLD activity score (NAS)

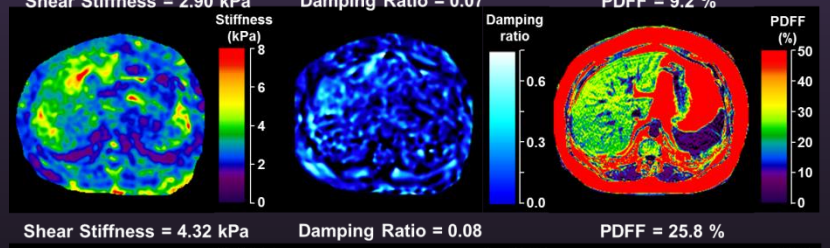




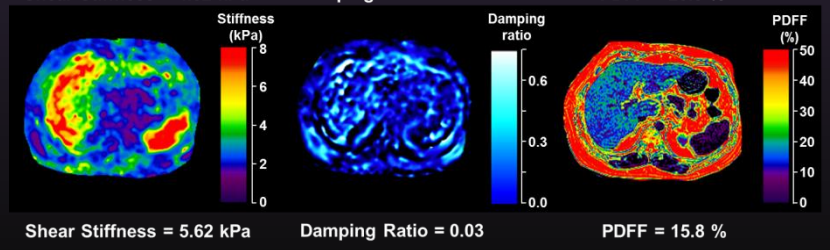
Probability of NASH=0.15
Histology showed no NASH



Probability of NASH=0.54
Histology showed no NASH



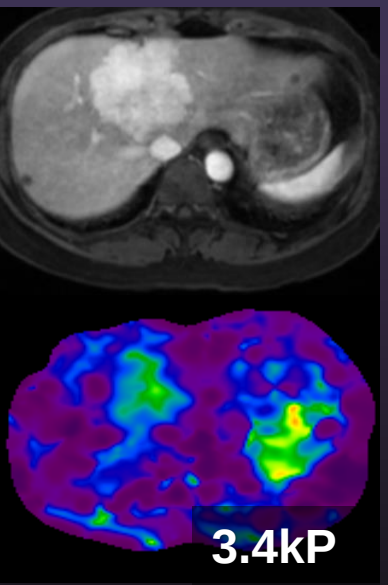
Probability of NASH=0.98
Histology showed NASH



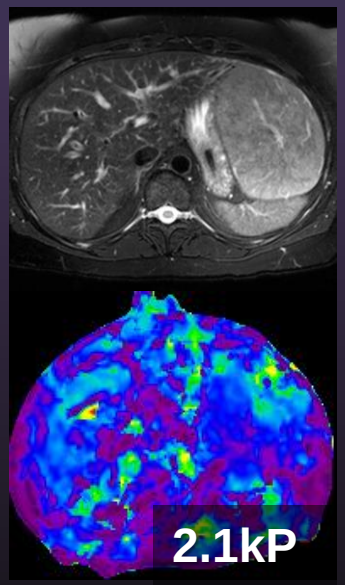
Probability of NASH=0.99
Histology showed NASH

Differentiate benign and malignant focal liver lesions

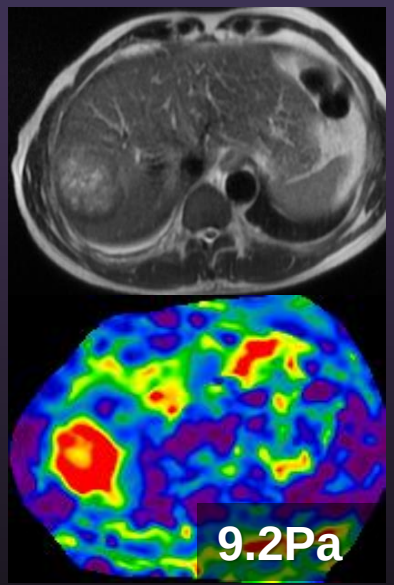
- Malignant tumors are stiffer than benign tumors
  - Increased extracellular matrix
  - Higher interstitial pressure



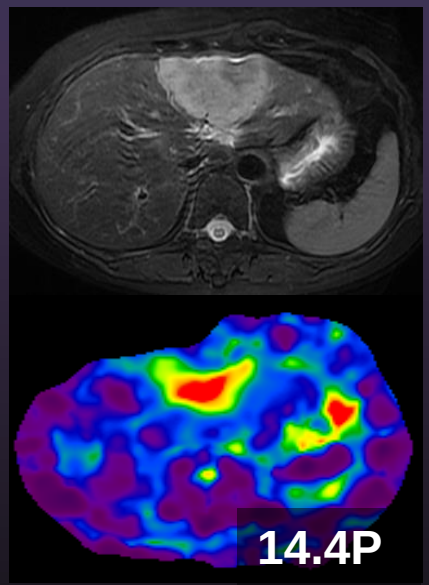
Focal Nodular Hyperplasia



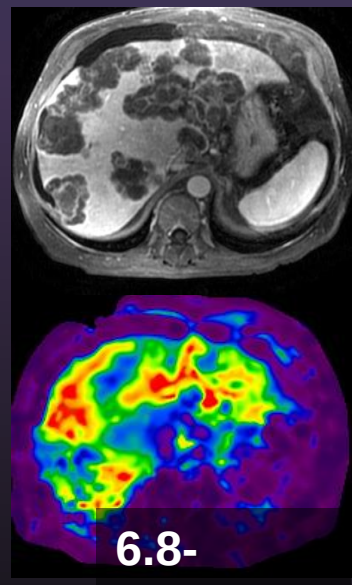
Hepatic adenoma



Hepatocellular carcinoma

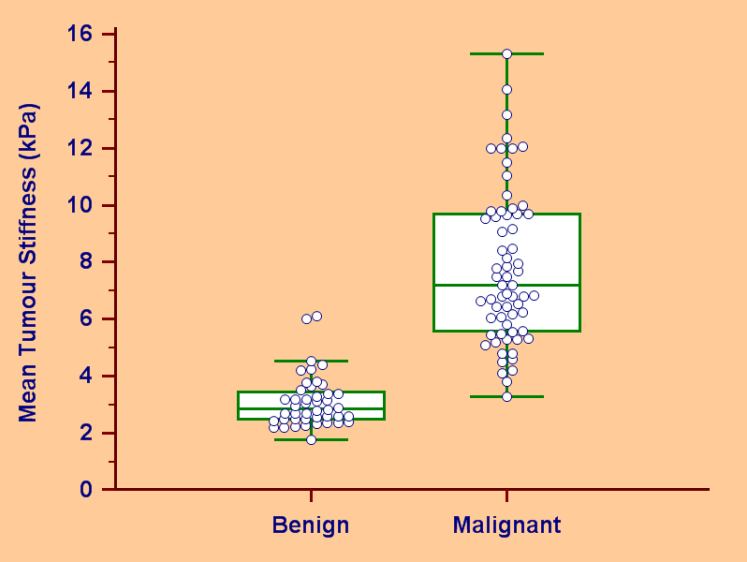


Cholangio-carcinoma



Colorectal mets

Differentiate benign and malignant focal liver lesions



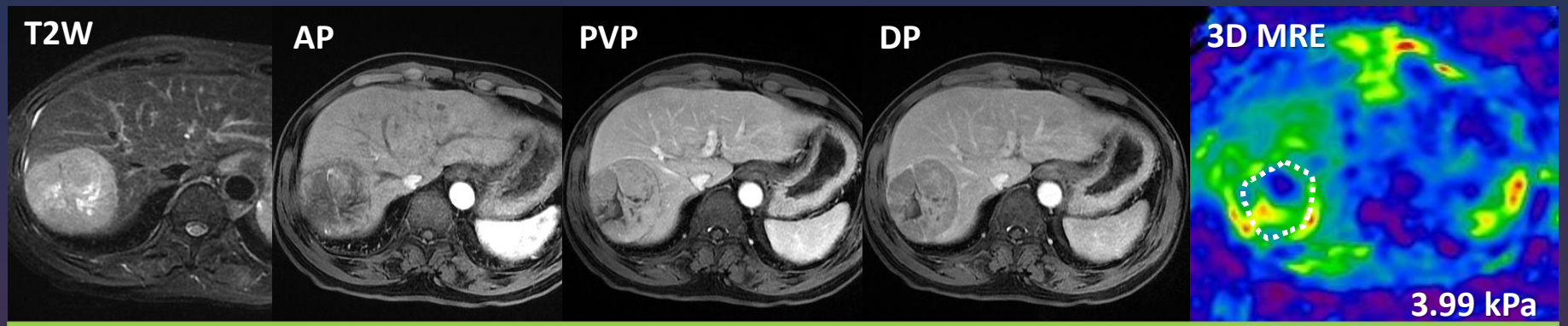
Lesion	Mean stiffness	Different from (p<0.001)
Hemangioma (HEM)	3.1 kPa	HCC, CCA, MET
Hepatic adenoma (HCA)	2.7 kPa	HCC, CCA, MET
Focal nodular hyperplasia (FNH)	3.5 kPa	HCC, CCA, MET
Hepatocellular carcinoma (HCC)	7.7 kPa	HEM, HCA, FNH
Cholangiocarcinoma (CCA)	8.7 kPa	HEM, HCA, FNH
Metastases (MET)	8.2 kPa	HEM, HCA, FNH

Tumour	Mean ± SD	95% CI
Benign	3.11± 0.91	2.83-3.40
Malignant	7.8 ± 2.71	7.13-8.5

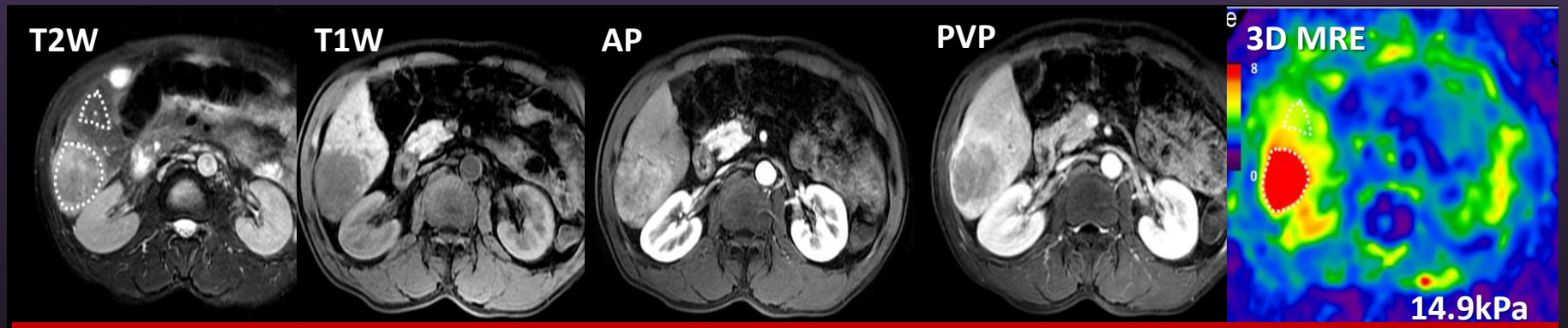
Cut off value	Accuracy	Sensitivity	Specificity	PPV	NPV
4.54 kPa	0.987	92.3	95.5	96.8	95.9

Hennedige T, et al . Eur Radiol. 2016 Feb;26(2):398-406.

Stiffness of HCC Predicts Histological Grade* and Capsule



Well to moderately differentiated HCC with capsule and no vascular invasion



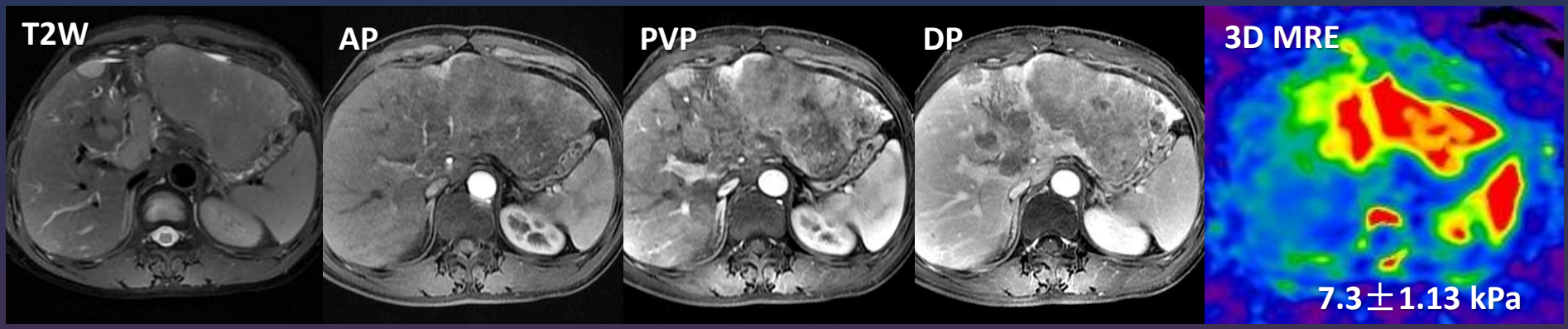
Poorly differentiated HCC with no tumor capsule and with vascular invasion

Stiffness <5.7kPa predicts capsule with 0.71 accuracy

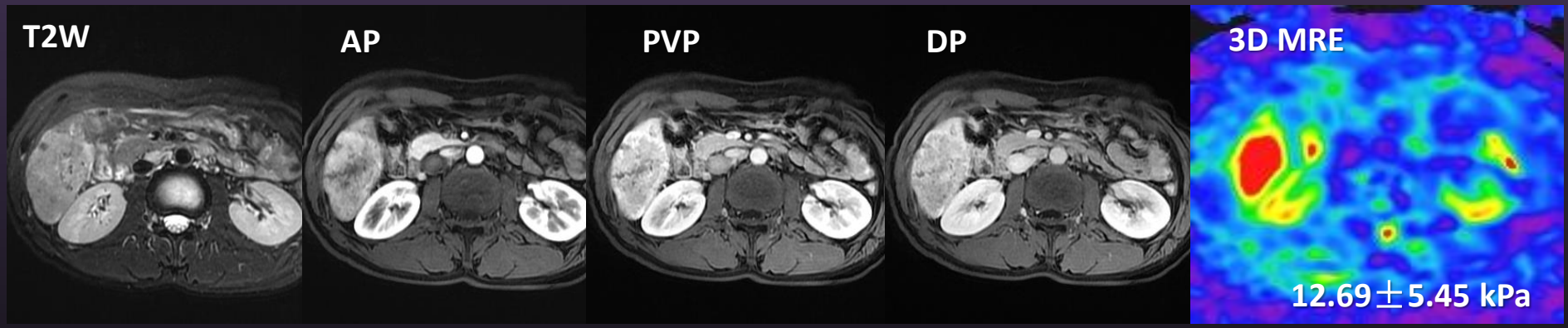
Wang J, et al JMRI 2019; 49(3):719-730

*In another study increased stiffness was found in well –moderately differentiated HCC compared to poorly differentiated HCC. Thompson SM et al. MRI 2017 ;37:41-45.

Increased Stiffness of HCC is Associated with Vascular Invasion



Moderately differentiated HCC with no capsule and macrovascular invasion



Moderately differentiated HCC with no capsule and microvascular invasion at pathology

Increased Stiffness of HCC is Associated with Recurrence

- **A recent study showed 5 risk factors for early HCC recurrence following surgery**
  - **Tumor stiffness** [HR=1.2 (95%CI,1.0-1.3) p< 0.001]
  - **Tumor size** [HR=2.6 (95%CI, 1.2-5.8) p=0.017]
  - **Histological grade** [HR=2.5 (95%CI,1.1-5.8) p=0.03]
  - **Vascular invasion** [HR=3.7 (95%CI, 1.4-9.7) p=0.008]
  - **Capsule** [HR=3.1 (95%CI, 1.5-6.4) p=0.003]
- **Multivariate analysis showed only two factors**
  - **Tumor stiffness** [HR=1.2 (95% CI,1.0-1.3) p= 0.002)
    - **Each 1kPa increase = 16.3% increase in risk for tumor recurrence**
  - **Vascular invasion** [HR=2.9 (95% CI, 1.1- 7.9) p=0.035)

Limitations of MRE

- Increased liver iron overload may cause technical failure with 2D GRE MRE sequence
  - An spin echo or echo planar based MRE may be useful in mild to moderate iron overload
- Increased stiffness is not specific for liver fibrosis
  - Acute inflammation, biliary obstruction, passive congestion, diffuse infiltrative disorders can cause increased stiffness
  - Advances in MRE will address separating these processes from liver fibrosis
- Susceptibility to motion artifacts
  - Breath hold artifacts, un cooperative patients
- Cost of MRE is more than ultrasound elastography

Advantages of MRE

- Comprehensive assessment with standard liver MRI study
  - Liver fat, iron and fibrosis
  - Focal liver lesions
  - vasculature
- Not affected by BMI (as long as patient can fit into the scanner) and hepatic steatosis
- Low technical failure compared to other elastography techniques

Conclusions

- **MR Elastography of Liver is a robust, reproducible, repeatable and accurate technique for detection and staging of liver fibrosis**
- **Advances in MRE is useful for staging NASH; distinguish diffuse processes that cause increase stiffness**
- **MRE can differentiate benign and malignant liver lesions and may be useful in non invasive prediction of HCC grade, vascular invasion and recurrence**

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