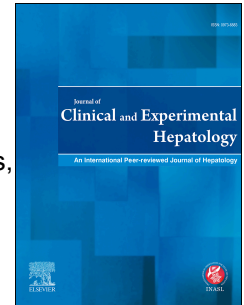# Journal Pre-proof

Magnetic resonance elastography for the clinical risk assessment of fibrosis, cirrhosis, and portal hypertension in patients with NAFLD

Yamini Natarajan, Rohit Loomba

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MAGNETIC RESONANCE ELASTOGRAPHY FOR THE CLINICAL RISK ASSESSMENT OF FIBROSIS, CIRRHOSIS, AND PORTAL HYPERTENSION IN PATIENTS WITH NAFLD

Authors: Yamini Natarajan[1-2], Rohit Loomba[3]

Institutional Affiliations: [1]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, [2]Clinical Epidemiology and Comparative Effectiveness Program, Section of Health Services Research (IQuESt), Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, Texas, USA; [3]NAFLD Research Center, Division of Gastroenterology, Department of Medicine, University of California at San Diego, La Jolla, CA, USA

Co-corresponding authors:
Yamini Natarajan, MD
2002 Holcombe Blvd (111-D), Houston, Texas 77030,
email: ynataraj@bcm.edu

or

Rohit Loomba, MD, MHSc
9500 Gilman Drive
ACTRI Building, 2W202
La Jolla, CA 92093-0887
Email: roloomba@ucsd.edu
Web: http://fattyliver.ucsd.edu

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Abstract:

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming one of the most common causes of liver disease. The progressive subtype of NAFLD, nonalcoholic steatohepatitis (NASH), leads to cirrhosis, hepatocellular carcinoma, and mortality. Fibrosis is the strongest predictor for complications. Due to the invasive nature of liver biopsy, non-invasive testing methods have emerged to detect fibrosis and predict outcomes. Of these modalities, magnetic resonance elastography (MRE) has demonstrated the highest accuracy to detect fibrosis.   In this review, we will focus on the emerging data regarding MRE and liver fibrosis, cirrhosis and portal hypertension in NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis on either imaging or histology in individuals who consume little or no alcohol and who do not have any secondary cause of hepatic steatosis such as medications, viral hepatitis, or human immunodeficiency virus infection.[1,2] NAFLD includes two subtypes: nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH). Steatosis, or increased fat content, is seen in both NAFL and NASH, but NASH also involves the presence of lobular inflammation and ballooning with or without peri-sinusoidal fibrosis.[3] Patients with NAFL are generally thought to have a benign course, but the NASH subtype is associated with increased risk of progression to cirrhosis, hepatocellular carcinoma (HCC), cardiovascular and liver related mortality.[1,4,5]

Paralleling the obesity epidemic, the clinical burden of NAFLD has increased steadily since the 1980s, currently affecting 25% of the global population. Even though a small percentage of patients with NAFLD have NASH, this population is burgeoning as well. It is estimated to affect 3-5% of the general population; this translates to over 30 million people worldwide.[6] The number of patients with NAFLD cirrhosis will likely double by the year 2030, leading to an estimated increase in 800,000 liver related deaths.[7] NASH has become the number one indication for liver transplantation in the US in women and patients older than 50.[8]

The presence of fibrosis strongly predicts mortality, rising dramatically with each stage greater than F2.[4] Liver biopsy is considered the gold standard to differentiate between NASH/NAFL as well as identify fibrosis. However, this procedure is limited by its invasive nature, risk of bleeding and other complications, and inter-observer

variability.[9,10] Non-invasive methods have been developed to detect fibrosis—these include serum calculators, genetic factors and imaging modalities such as elastography.[11,12]

Of these modalities, MRE has emerged as the superior test to evaluate fibrosis. MRE differs from traditional MRI by utilizing an acoustic driver and a two-dimensional pulse sequence to generate shear waves within the liver. Unlike vibration controlled transient elastography (VCTE), which evaluate shear waves at one location, MRE evaluates shear waves in 4 regional maps, called *elastograms*. These elastograms are interpreted in context of location of liver capsule, large blood vessels and artifact. Liver stiffness is calculated in each region; an average of all four regions to determine mean 2D liver stiffness measurement (LSM).[13] Of note, these measurements are not on the same scale as VCTE, even though both are measured in kilopascals (kPa). Three-dimensional MRE, which obtains elastograms in multiple dimensions, has also shown promise in evaluation of fibrosis.[14]

MRE has demonstrated superiority in diagnostic accuracy to other imaging modalities such as VCTE and 2-dimensional shear wave elastography (2D SWE) (Table 1).[16,17] While VCTE and 2D SWE can assess LSM at particular points, MRE can assess the stiffness of the entire liver. In addition, MRE performance is not affected by BMI, small ascites, and bowel gas. MRE is also less prone to operator error. Limitations of MRE include cost, access, and lack of portability. In this review, we will discuss MRE and its association with liver fibrosis, cirrhosis and portal hypertension in patients with NAFLD. We refer the readers to other reviews that cover other aspects of non-invasive assessment.[12,16,18]

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Technical Considerations

MRE can be performed on 1.5 Tesla to 7 Tesla MRI machines. Most patients are able to tolerate MRE, but they do need to be able to hold their breath for specific time periods. Liver stiffness is not affected by the presence of steatosis or increasing BMI. [19–21] Performance was similar in both male and female patients and does not vary with magnet strength.[20,22] Liver stiffness may be overestimated in patients with iron overload, large ascites, congestive hepatopathy or acute inflammation; MRE should be interpreted keeping the clinical context of use in mind especially in these patient populations.[23]

MRE for Assessment of Fibrosis

MRE has high diagnostic performance and low failure rate for assessment of fibrosis.[24] Interobserver variation is low and can be utilized on different types of MRI machines.[20] In a systematic review of 9 studies with 232 patients, MRE had a high AUROC for each stage of fibrosis: ≥F1 – 0.86 (cutoff: 2.88 kPa, sensitivity 0.75, specificity 0.77), ≥F2- 0.87 (cutoff: 3.54 kPa, sensitivity 0.79, specificity 0.81), ≥F3 – 0.90 (cutoff: 3.77 kPa; sensitivity 0.83, specificity 0.86), ≥F4 – 0.91 (cutoff: 4.09 kPa; sensitivity 0.88, specificity 0.87).[20] These findings were confirmed in a 2019 systematic review and meta-analysis, which demonstrated higher diagnostic accuracy of MRE vs VCTE at all stages of fibrosis.[22] There is a greater degree of discordance between VCTE and MRE measurements as BMI increases.[25] Three dimensional MRE at 40Hz has an even higher detection of advanced fibrosis in NAFLD compared to 2D MRE (AUROC 0.98 vs 0.92).[14] This modality is not yet widely available clinically.

Longitudinal Assessments of Fibrosis

Changes in liver stiffness over time may also provide prognostic value in NAFLD. A prospective study of 100 patients determined that a 15% increase in LSM is associated with a 3.4-fold increased risk of any progression of fibrosis stage, and 5-fold increased risk of progression to advanced fibrosis.[26] Similarly, Gidener et al, found that non-cirrhotic patients that had a 1 kilopascal increase in LSM were 3 fold more likely to develop cirrhosis. In addition, cirrhotic patients that had a 1 kilopascal increase in LSM were 5-fold increased risk of liver related decompensation or mortality within 5 years.[27] Alternatively, weight loss is associated with a decrease in liver stiffness. Patients who had a 5% decrease in BMI experienced ~16% decrease in liver stiffness.[13] A secondary analysis of phase II trial data for selonsertib showed that improvement in LSM measured by MRE was associated with improvement in fibrosis (48% positive predictive value, 79% negative predictive value). This study was limited by small sample size.[28] Further studies are needed to confirm these outcomes and determine optimal interval and cutoffs for changes in elastography.

In addition to elastography, changes proton density fat fraction (PDFF) may be used to evaluate prognosis. PDFF is the MRI signal intensity ratio of fat to the sum of fat and water, reported as percentage.[29] MRI-PDFF can assess regional variation of steatosis. Patients with high PDFF, defined as >15.7%, had a 6-7 fold increased risk of fibrosis progression on serial MRE (median time 1.4 years).[30] Conversely, improvements in PDFF are an independent predictor for fibrosis regression. Patients with a decrease of ≥ 30% PDFF are 7-fold more likely to have histologic improvement and 5.5 more likely to have resolution of NASH.[31] This marker also predicts > 1 stage

improvement in fibrosis.[32] These data will need to be validated in future studies.

Combining PDFF and MRE data may predict NASH (AUROC 0.87) and even estimate

granular data previously only found on biopsy, such as NAFLD Activity Score (AUROC

0.85). Use of automated algorithms demonstrated high fidelity compared to expert

radiologist interpretation.[33] These data are promising but need to be validated in larger

multicenter studies.

MRE can be combined with serum markers to increase predictive capability and

identify candidates for pharmacologic therapy. Using a FIB4 $\geq$ 1.6 and MRE liver

stiffness $\geq$ 3.3 kPa identified NAFLD patients with $\geq$F2 fibrosis with positive predictive

value (PPV) of 97.1% (p<0.02). This combination, known as MEFIB, were validated in a

separate international cohort.[34] Studies are ongoing to determine how performance

compares to Fibroscan-AST score (FAST).

MRE for Assessment of Compensated Cirrhosis

MRE can be used to distinguish lower levels of fibrosis and cirrhosis. Studies

evaluating the diagnostic performance of MRE for detection of cirrhosis have

determined cutoffs of 3.35-6.7 kPa (AUROC 0.8-0.97).[22,28,35–39] Difference in findings

can be accounted for by study population (single center vs multi-center, Japan vs

western population).   Based on pooled analysis of individual participant data by Hsu, et

al, we consider liver stiffness $\geq$ 4.67 to be indicative of cirrhosis. To increase ease of

use in clinical care, this can be rounded to 5 kPa.[22]

MRE for Assessment of Decompensated Cirrhosis and Portal Hypertension

Increased levels of liver stiffness may be predictive of decompensated cirrhosis,

portal hypertension and liver related outcomes. Baseline liver stiffness has been shown

to be predictive of decompensated disease in a cohort of all etiologies.[40] Within a NAFLD cohort, use of MRE to measure LSM with a cutoff of 6.48 kPa (AUROC 0.71) has been shown to differentiate between compensated and decompensated cirrhosis.[35] Evaluation of a NAFLD cohort at the Mayo demonstrated increasing LSM showed increased risk of decompensation; a cutoff of 8 kPa is associated with a 20% risk of decompensation.[27] As noted above, a 1 kilopascal increase in liver stiffness confers a 5-fold increased risk of mortality and liver related events.[27] Baseline LSM by MRE has been shown to predict HCC and death in a cohort of patients with all types of chronic liver disease; these findings need to be specifically evaluated in NAFLD.[41]

Similarly, MRE may be used to rule out portal hypertension, minimizing the need for screening upper endoscopy for varices. One cross-sectional study of 627 patients using MRE cutoff 4.2 kPa and platelets > 180,000 had a negative predictive value of 1.0.[42] This needs to be validated in prospective studies.   MRE can be used to assess splenic stiffness in addition to liver stiffness. A 2021 meta-analysis found that splenic stiffness assessed by MRE had a sensitivity, specificity, and AUC values for spleen stiffness on MRE were 79% (95% CI 61-90%), 90% (95% CI 80-95%), and 92% (95% CI 89-94%), respectively (PMID: 32282542).[43] When evaluating specific manifestations of portal hypertension such as varices and ascites, liver stiffness has been used alone or in combination with spleen stiffness/spleen size in small series to predict presence of esophageal varices.[44–48] These studies evaluated all types of liver disease and only included a small portion of NAFLD patients. In studies specifically evaluating NAFLD, the median LSM for patients with variceal bleeding was 10.15 kPa, however this was limited by small sample size.

There are limited data regarding the use MRE to predict the development of ascites and hepatic encephalopathy. NAFLD patients with ascites or hepatic encephalopathy have higher median liver stiffness than those who do not. Further studies need to be done to evaluate cutoffs and the role of MRE in predicting these events.[35]

The Big Picture

In patients with suspected NAFLD, we recommend a stepwise approach using FIB-4 score and MRE (Figure 1). For patients with FIB-4 < 1.3, no further assessment is needed; fibrosis can be assessed with serial FIB-score. For patients with FIB-4 score > 1.3, we recommend referral to a tertiary care center for MRE. Further management regarding biopsy, risk of of cirrhosis and decompensation is determined by LSM measurement.

Conclusion

The prevalence of NAFLD has grown considerably over the last two decades. Given the large burden of disease, development of noninvasive testing is essential to risk stratification and monitoring. Magnetic resonance elastography has emerged as comprehensive method to assess fibrosis throughout the liver. Longitudinal assessments may be predictive of disease progression or improvement. Additional studies are needed to determine the role of MRE in predicting liver related outcomes and reducing the need for liver biopsy in patients with NAFLD.

References:

1. Chalasani, N. *et al.* The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* (2017) doi:10.1002/hep.29367.
2. Loomba, R., Friedman, S. L. & Shulman, G. I. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell* **184**, 2537–2564 (2021).
3. Brunt, E. M. *et al.* NAFLD: Reporting Histologic Findings in Clinical Practice. *Hepatology* **73**, 2028–2038 (2021).
4. Dulai, P. S. *et al.* Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology* **65**, 1557–1565 (2017).
5. Huang, D. Q., El-Serag, H. B. & Loomba, R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 223–238 (2021).
6. Younossi, Z. M. Non-alcoholic fatty liver disease – A global public health perspective. *J. Hepatol.* **70**, 531–544 (2019).
7. Estes, C., Razavi, H., Loomba, R., Younossi, Z. & Sanyal, A. J. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* **67**, 123–133 (2018).
8. Noureddin, M. *et al.* NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. *Am. J. Gastroenterol.* **113**, 1649–1659 (2018).
9. Ratziu, V. *et al.* Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* **128**, 1898–906 (2005).
10. Merriman, R. B. *et al.* Correlation of paired liver biopsies in morbidly obese patients with suspected nonalcoholic fatty liver disease. *Hepatology* (2006) doi:10.1002/hep.21346.
11. Ajmera, V. *et al.* The impact of genetic risk on liver fibrosis in non-alcoholic fatty liver disease as assessed by magnetic resonance elastography. *Aliment. Pharmacol. Ther.* (2021) doi:10.1111/apt.16392.
12. Loomba, R. & Adams, L. A. Advances in non-invasive assessment of hepatic fibrosis. *Gut* **69**, 1343–1352 (2020).
13. Patel, N. S. *et al.* Weight Loss Decreases Magnetic Resonance Elastography Estimated Liver Stiffness in Nonalcoholic Fatty Liver Disease. *Clin. Gastroenterol. Hepatol.* **15**, 463–464 (2017).
14. Loomba, R. *et al.* Novel 3D Magnetic Resonance Elastography for the Noninvasive Diagnosis of Advanced Fibrosis in NAFLD: A Prospective Study. *Am. J. Gastroenterol.* **111**, 986–94 (2016).
15. Ajmera, V. & Loomba, R. Can Elastography Differentiate Isolated Fatty Liver from Nonalcoholic Steatohepatitis? *Semin. Liver Dis.* (2018) doi:10.1055/s-0037-1618587.
16. Long, M. T., Gandhi, S. & Loomba, R. Advances in non-invasive biomarkers for the diagnosis and monitoring of non-alcoholic fatty liver disease. *Metabolism.* **111S**, 154259 (2020).
17. Xiao, G. *et al.* Comparison of laboratory tests, ultrasound, or magnetic resonance

elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. *Hepatology* **66**, 1486–1501 (2017).

18. Ajmera, V. & Loomba, R. Imaging biomarkers of NAFLD, NASH, and fibrosis. *Mol. Metab.* 101167 (2021) doi:10.1016/j.molmet.2021.101167.

19. Venkatesh, S. K., Yin, M. & Ehman, R. L. Magnetic resonance elastography of liver: Technique, analysis, and clinical applications. *J. Magn. Reson. Imaging* **37**, 544–555 (2013).

20. 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. *Eur. Radiol.* **26**, 1431–40 (2016).

21. Chen, J. *et al.* Diagnostic Performance of MR Elastography and Vibration-controlled Transient Elastography in the Detection of Hepatic Fibrosis in Patients with Severe to Morbid Obesity. *Radiology* **283**, 418–428 (2017).

22. Hsu, C. *et al.* Magnetic Resonance vs Transient Elastography Analysis of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Pooled Analysis of Individual Participants. *Clin. Gastroenterol. Hepatol.* (2019) doi:10.1016/j.cgh.2018.05.059.

23. Wagner, M. *et al.* Technical Failure of MR Elastography Examinations of the Liver: Experience from a Large Single-Center Study. *Radiology* **284**, 401–412 (2017).

24. Singh, S. *et al.* Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: A systematic review and meta-analysis of individual participant data. *Clin. Gastroenterol. Hepatol.* (2015) doi:10.1016/j.cgh.2014.09.046.

25. Caussy, C. *et al.* Association Between Obesity and Discordance in Fibrosis Stage Determination by Magnetic Resonance vs Transient Elastography in Patients With Nonalcoholic Liver Disease. *Clin. Gastroenterol. Hepatol.* **16**, 1974-1982.e7 (2018).

26. Ajmera, V. H. *et al.* Clinical Utility of an Increase in Magnetic Resonance Elastography in Predicting Fibrosis Progression in Nonalcoholic Fatty Liver Disease. *Hepatology* **71**, 849–860 (2020).

27. Gidener, T. *et al.* Liver Stiffness by Magnetic Resonance Elastography Predicts Future Cirrhosis, Decompensation, and Death in NAFLD. *Clin. Gastroenterol. Hepatol.* (2020) doi:10.1016/j.cgh.2020.09.044.

28. Jayakumar, S. *et al.* Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib. *J. Hepatol.* (2019) doi:10.1016/j.jhep.2018.09.024.

29. Mashhood, A. *et al.* Reproducibility of hepatic fat fraction measurement by magnetic resonance imaging. *J. Magn. Reson. Imaging* **37**, 1359–1370 (2013).

30. Ajmera, V. *et al.* Magnetic Resonance Imaging Proton Density Fat Fraction Associates With Progression of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* **155**, 307-310.e2 (2018).

31. Stine, J. G. *et al.* Change in MRI-PDFF and Histologic Response in Patients With Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis. *Clin. Gastroenterol. Hepatol.* (2020) doi:10.1016/j.cgh.2020.08.061.

32. Tamaki, N. *et al.* Clinical utility of 30% relative decline in MRI-PDFF in predicting

fibrosis regression in non-alcoholic fatty liver disease. *Gut* (2021) doi:10.1136/gutjnl-2021-324264.

33. Dzyubak, B. *et al.* Automated Analysis of Multiparametric Magnetic Resonance Imaging/Magnetic Resonance Elastography Exams for Prediction of Nonalcoholic Steatohepatitis. *J. Magn. Reson. Imaging* (2021) doi:10.1002/jmri.27549.

34. Jung, J. *et al.* MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis. *Gut* gutjnl-2020-322976 (2020) doi:10.1136/gutjnl-2020-322976.

35. Han, M. A. T. *et al.* MR elastography-based liver fibrosis correlates with liver events in nonalcoholic fatty liver patients: A multicenter study. *Liver Int.* **40**, 2242–2251 (2020).

36. Loomba, R. *et al.* Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: A prospective study. *Hepatology* (2014) doi:10.1002/hep.27362.

37. Park, C. C. *et al.* Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease. *Gastroenterology* (2017) doi:10.1053/j.gastro.2016.10.026.

38. Wong, G. L. H. *et al.* A retrospective study on clinical features and prognostic factors of biopsy-proven primary biliary cirrhosis in Chinese patients. *Am. J. Gastroenterol.* **100**, 2205–2211 (2005).

39. Hui, J. M. *et al.* Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. *Hepatology* **38**, 420–427 (2003).

40. Asrani, S. K. *et al.* Role of magnetic resonance elastography in compensated and decompensated liver disease. *J. Hepatol.* **60**, 934–9 (2014).

41. Ichikawa, S., Motosugi, U., Enomoto, N. & Onishi, H. Magnetic resonance elastography can predict development of hepatocellular carcinoma with longitudinally acquired two-point data. *Eur. Radiol.* **29**, 1013–1021 (2019).

42. Matsui, N. *et al.* Magnetic resonance elastography increases usefulness and safety of non-invasive screening for esophageal varices. *J. Gastroenterol. Hepatol.* **33**, 2022–2028 (2018).

43. Singh, R. *et al.* Accuracy of liver and spleen stiffness on magnetic resonance elastography for detecting portal hypertension: a systematic review and meta-analysis. *Eur. J. Gastroenterol. Hepatol.* **32**, 237–245 (2021).

44. Sun, H. Y., Lee, J. M., Han, J. K. & Choi, B. I. Usefulness of MR elastography for predicting esophageal varices in cirrhotic patients. *J. Magn. Reson. Imaging* **39**, 559–66 (2014).

45. Abe, H. *et al.* Prediction of esophageal varices by liver and spleen MR elastography. *Eur. Radiol.* **29**, 6611–6619 (2019).

46. Hoffman, D. H. *et al.* MR elastography, T1 and T2 relaxometry of liver: role in noninvasive assessment of liver function and portal hypertension. *Abdom. Radiol. (New York)* **45**, 2680–2687 (2020).

47. Shin, S. U. *et al.* Prediction of esophageal varices in patients with cirrhosis: usefulness of three-dimensional MR elastography with echo-planar imaging technique. *Radiology* **272**, 143–53 (2014).

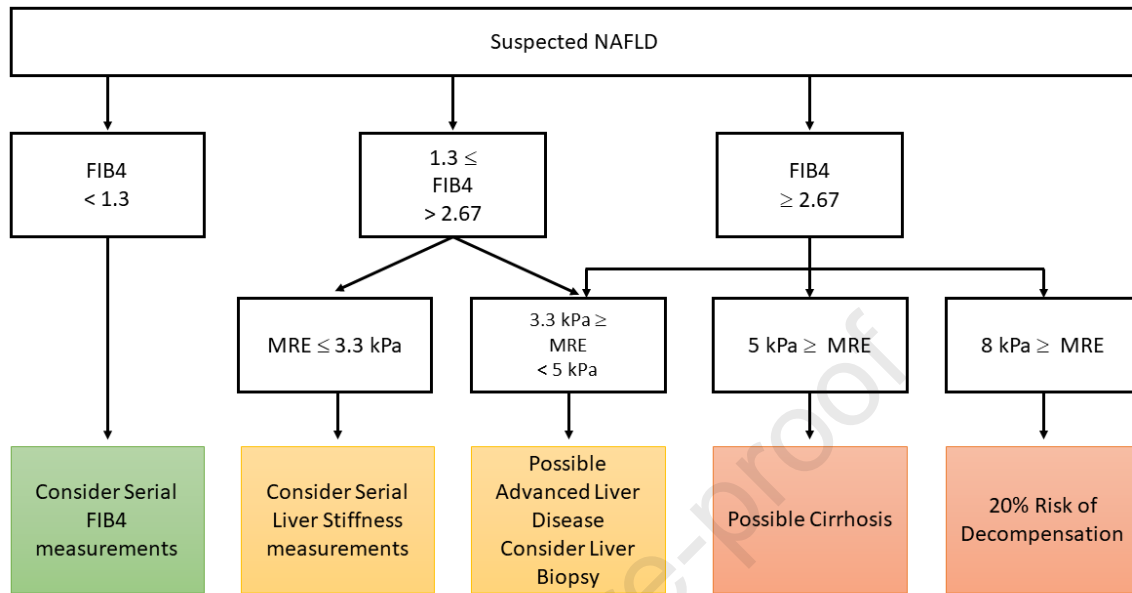48. Morisaka, H. *et al.* Association of splenic MR elastographic findings with

gastroesophageal varices in patients with chronic liver disease. *J. Magn. Reson. Imaging* **41**, 117–24 (2015).

Table 1. Diagnostic Accuracy, Advantages and Disadvantages of Noninvasive Measurements of Fibrosis

Testing Modality	Cutoffs	AUROC	Advantages	Disadvantages
MRE	≥F1 – 2.88 kPa ≥F2 – 3.54 kPa ≥F3 – 3.77 kPa ≥F4 – 4.09 kPa	0.86 0.87 0.90 0.91	-Overall best performance -Performs well at high BMI -Can be easily performed with techniques to quantify liver fat -Largest area of the liver assessed	-Performed in radiology -Performed at a limited number of centers -Quality control not integrated -Lack of portability -Cost
VCTE	≥F2 –4.8-8.2 (XL probe) ≥F3 –5.7-9.3 (M Probe) ≥F3 – 7.6-8 (M Probe)	0.80 0.88 0.85	-Performed in liver clinic -Simultaneously quantify fat (CAP) -Integrated quality control -Larger area of liver assessed -No prior experience with ultrasound required	-Failure if narrow rib spaces -Failure if large ascites -Only measures CAP and LSM -Less cost effective if also need ultrasound
2-Dimensional Shear Wave Elastography	≥F2 –2.67-9.4 ≥F3 –3.02-10.6	0.88 0.95	-Low failure rate for experienced operators -Uses ultrasound probe	-Failure/lower accuracy as BMI increases -Learning curve: higher interobserver variability with less experienced operators
NAFLD Fibrosis Score	≥F3 –0.67	0.84	-Easy to calculate -Clinical information for the score is often available	-Large number of individuals fall in the indeterminate range -Different cut-off values needed for younger or older participants -Limited usefulness in the general population
Fibrosis-4	≥F2 –0.37-3.25 ≥F3 –2.67	0.73 0.84	-Easy to calculate -Clinical information for the score is often available	-Large number of individuals fall in the indeterminate range -Various cut-offs used in studies -Limited usefulness in the general population
APRI	≥F2 –1.0 ≥F3 –1.5	0.76 0.77	-Easy to calculate -Clinical information for the score is often available	-Large number of individuals fall in the indeterminate range -Various cut-offs used in studies -Limited usefulness in the general population

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Figure 1. Risk Stratification of Patients with NAFLD using FIB4 and Magnetic Resonance Elastography

Abbreviations: NAFLD-Non-alcoholic Fatty liver disease; FIB4-Fibrosis-4 score; MRE-Magnetic Resonance Elastography; kPa-kilopascals

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┌─────────────────────────────────────────────────────────────────────────┐
│                            Suspected NAFLD                                │
└─────────────────────────────────────────────────────────────────────────┘
        │                        │                        │
        ▼                        ▼                        ▼
┌──────────────┐        ┌──────────────┐        ┌──────────────┐
│    FIB4      │        │    1.3 ≤      │        │    FIB4      │
│    < 1.3     │        │    FIB4      │        │    ≥ 2.67    │
│              │        │    > 2.67    │        │              │
└──────────────┘        └──────────────┘        └──────────────┘
        │              │              │        │              │
        │              ▼              ▼        ▼              ▼
        │        ┌──────────┐  ┌──────────┐  ┌──────────┐  ┌──────────┐
        │        │ MRE ≤    │  │ 3.3 kPa ≥│  │ 5 kPa ≥  │  │ 8 kPa ≥  │
        │        │ 3.3 kPa  │  │   MRE    │  │   MRE    │  │   MRE    │
        │        │          │  │  < 5 kPa │  │          │  │          │
        │        └──────────┘  └──────────┘  └──────────┘  └──────────┘
        ▼              ▼              ▼        ▼              ▼
┌──────────────┐ ┌──────────┐  ┌──────────┐  ┌──────────┐  ┌──────────┐
│Consider Serial│ │Consider  │  │ Possible │  │          │  │ 20% Risk │
│    FIB4      │ │Serial    │  │ Advanced │  │ Possible │  │    of    │
│ measurements │ │Liver     │  │  Liver   │  │ Cirrhosis│  │Decompensa-│
│              │ │Stiffness │  │ Disease  │  │          │  │  tion    │
│              │ │measure-  │  │ Consider │  │          │  │          │
│              │ │ments     │  │  Liver   │  │          │  │          │
│              │ │          │  │  Biopsy  │  │          │  │          │
└──────────────┘ └──────────┘  └──────────┘  └──────────┘  └──────────┘
```