A comparison of magnetic resonance elastography (MRE) to biomarker testing for staging fibrosis in non-alcoholic fatty liver disease (NAFLD)

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Background: Non-alcoholic fatty liver disease (NAFLD) is the world's most prevalent chronic liver disease. In advanced stages, it is associated with significant morbidity and mortality. Magnetic resonance elastography (MRE) and scoring panels Fibrosis-4 (FIB-4) and NAFLD Fibrosis Score (NFS) are useful noninvasive alternatives to liver biopsy for fibrosis staging. Our study aimed to determine how well MRE corresponds with both FIB-4 and NFS at different stages of fibrosis.

Methods: We performed a retrospective chart review of patients age ≥18 with NAFLD as their only known liver disease who underwent MRE within six months of a lab draw. MRE stratified patients into fibrosis stages using kPa values. FIB-4 categorized patients as Advanced Fibrosis Excluded, Further Investigation Needed or Advanced Fibrosis Likely. NFS categorized them as F0-2, Indeterminate or F3-4. MRE fibrosis staging was compared to FIB-4 and NFS for both ruling out advanced fibrosis and identifying advanced fibrosis/cirrhosis.

Results: Overall, 193 patients met inclusion criteria. Our statistical analysis included calculating positive predictive values (PPVs) and negative predictive values (NPVs), which are the proportions of positive and negative fibrosis screening results that correspond to positive and negative MRE results respectively. NPV for FIB-4 (0.84) and NFS (0.89) in the 'rule out advanced fibrosis' category signify that 84% and 89% of respective biomarker scores correspond to MRE in early stage disease. The PPV for FIB-4 and NFS in the 'identify advanced fibrosis/cirrhosis' category signify 63% and 72% of respective biomarker scores correspond to MRE in late stage disease.

Conclusions: FIB-4 and NFS scores indicating little to no fibrosis correspond extremely well with MRE, while scores suggesting advanced fibrosis/cirrhosis correspond less convincingly. MRE shows promise as an effective alternative to liver biopsy, however our study suggests FIB-4 and NFS alone may be sufficient for fibrosis staging, particularly in early stage NAFLD.

Keywords: Biomarkers; fibrosis; cirrhosis; non-alcoholic fatty liver disease (NAFLD); magnetic resonance elastography (MRE)

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the world's most prevalent form of chronic liver disease. It affects up to 30% of the US population and is associated with increasing morbidity and mortality (1,2). Obesity, dyslipidemia and diabetes mellitus are known predisposing risk factors for the development and progression of this condition (3). Their rising incidence is believed by many to be of epidemic proportions (4). This has led to predictions that NAFLD will soon become the leading indication for liver transplantation (5,6). NAFLD is a slowly progressive disease with a calculated fibrosis progression rate of 7.7 years per each stage of fibrosis (7). Fibrosis can be divided into different stages to show progression of liver disease from no fibrosis to cirrhosis. Staging is based on histological scoring models such as the Knodell, Metavir, and Ishak systems (8-10).

NAFLD can lead to progressively worsening liver fibrosis and in some individuals eventually results in cirrhosis. This puts these individuals at risk for known complications of advanced liver disease such as hepatocellular carcinoma (HCC) and esophageal varices. The strongest association between NAFLD and HCC is the development of non-alcoholic steatohepatitis (NASH) and NASH associated cirrhosis (11-13). HCC is a serious consequence of NASH cirrhosis and as a result screening and surveillance are crucial (14). The incidence of HCC in patients with cirrhosis in the setting of NAFLD has been noted to range from 2.4% to 12.8% over a 3.2- to 7.2-year period (15). When it comes to treating NAFLD, lifestyle modifications and treatment of underlying metabolic syndromes such as obesity, hyperlipidemia and diabetes are believed to be the main beneficial options (16). There are no FDA approved medications specifically for NAFLD or NASH with or without cirrhosis, however this continues to be a field where advancements are actively being made (17,18). As a result, it is imperative that accurate NAFLD fibrosis staging be obtained in order to predict patient outcomes and ensure proper screening for conditions such as HCC and esophageal varices is performed (19).

Currently, there are several methods used for NAFLD fibrosis staging (20,21). Liver biopsy has historically been considered the gold standard despite being random, invasive, costly and timely (22). Reliability is compromised given biopsy is associated with great tissue sampling variability (23). Fibrosis staging, as determined by pathologists, has been shown to vary by as much as 20% in one study, while another reported a paired biopsy discordance of one or more fibrosis stage in 41% of cases (24,25). In addition, biopsy requires expertise and harbors risk with some patients being either unable or unwilling to undergo this invasive procedure (26). Other than biopsy, ultrasound based testing such as transient elastography (TE), radiographic testing such as magnetic resonance elastography (MRE) and biomarker testing using calculations such as Fibrosis-4 (FIB-4), NAFLD Fibrosis Score (NFS) and AST to Platelet Ratio Index (APRI) are additional clinical staging options.

TE has been proven effective, especially when diagnosing advanced fibrosis. As fibrosis increases, the sensitivity, specificity and NPV of TE improves in NAFLD patients (27). However, it is a test that only evaluates a limited portion of the liver and underlying medical conditions such as obesity, congestive hepatopathy, cholestasis and elevated liver enzymes are known confounders that result in testing inaccuracy (28). MRE, as compared to TE, has been shown to offer a higher degree of accuracy. This is of significant clinical importance given the ability to accurately predict adverse pathologic events related to increased liver stiffness (29-36). As a result, this new test has gained recognition as an important screening tool and is being used more frequently. Biomarker testing via calculations such as FIB-4, NFS and APRI is another important staging option (37). Although FIB-4 was originally created for use in viral hepatitis, it has seen been proven to accurately evaluate NAFLD as well (38,39). The FIB-4 calculator uses age, platelet count, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). AST and ALT are liver enzymes that are known to be elevated in the setting of liver damage. NFS uses the same values as FIB-4, in addition to Albumin, BMI and impaired fasting glucose/diabetes. These two tests are known to have good predictive value, most prominently when staging those with advanced fibrosis or cirrhosis (10,40,41). In addition, FIB-4 and NFS have been proven to correlate most accurately with other scoring algorithms when dealing with advanced fibrosis staging as well (42).

APRI, however, has been shown to perform poorly as compared to NFS when discriminating between different stages of fibrosis (43,44).

Given the rising incidence of both NAFLD and its associated morbidity and mortality, it is important to establish protocols for both diagnostic purposes and fibrosis progression monitoring. There have been many studies evaluating the efficacy and accuracy of MRE and TE in NAFLD fibrosis staging (45,46). However, to date no studies have specifically assessed the relationship and correlation between MR Elastography and biomarker tests FIB-4 and NFS at different stages of liver fibrosis in patients with NAFLD. Most studies tend to assess their accuracy as compared to biopsy, not as compared to each other. Here, we evaluate how well biomarker staging corresponds with MRE staging in NAFLD. There are many cases where patients may be either unable or unwilling to undergo biopsy and we hope that our study can help physicians determine what the best and necessary next steps might be in these situations. Biomarker testing alone may be a sufficient means for staging, either in certain subgroups or as a whole. Of note, we present this article in accordance with the STARD reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-27/rc).

Methods

We conducted an IRB approved (Northwell Health Protocol Registration # 19-0465) retrospective chart review of all patients evaluated within our hospital system who were diagnosed with NAFLD with age ≥18 years old and no history of other concurrent liver disease. We looked at all patients who obtained MR Elastography for fibrosis staging between 2015 and 2020. Patients were excluded if they did not have labs drawn within 6 months of MRE. They were also excluded if they had a separate medical condition that could result in lab abnormalities and thus inaccurate biomarker test staging; for example thrombocytopenia from a non-liver etiology. We reviewed medical records containing patient demographics, medical conditions, medications, laboratory testing and radiologic imaging. Informed consent was not obtained in accordance with our IRB approved protocol for this retrospective chart review. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Biomarker testing was completed using FIB-4, which categorized patients as advanced fibrosis excluded (score of <1.3 if aged 36–64 and <2.0 if aged 65+), further

investigation needed (1.3–2.67 if aged 36–64 and 2.0–2.67 if aged 65+), or advanced fibrosis likely (>2.67). Patients 35 years or younger were excluded from FIB-4 assessment. Biomarker testing using NFS categorized patients as F0-2 (score of <–1.455), Indeterminate (–1.455 to 0.675), or F3–F4 (>0.675).

Patients were stratified into six different fibrosis groups based on MRE kPa values. The six groups are: Normal, Normal or Inflammation, Stage ≥1 to ≤2, Stage >2 to <3, Stage ≥3 to <4, Stage ≥4. These six groups are designed to differentiate NAFLD based on the five fibrosis stages: F0, F1, F2, F3 and F4. F4 is considered to be cirrhosis. The MRE kPa value cutoffs used for our study to divide the groups are 2.5, 2.9, 3.5, 4 and 5 (30). These kPa values are the standard cutoffs adopted by Radiologists throughout our hospital system. A value ≤2.5 kPa represents normal liver tissue while >2.5 kPa indicates the presence of inflammatory liver changes. Based on this, the 'normal' group as seen in *Figure 1*, which represents fibrosis stage F0, consists of all MRE kPa ≤2.5. At 2.9 kPa the liver stiffness is deemed to have stage 1 fibrosis while 3.5 kPa is the value used to signify that liver fibrosis has reached stage 2. As a result, the 'normal or inflammation' group, which represents fibrosis staging > F0 to < F1, contains MRE from kPa >2.5 to <2.9 kPa while 'stage ≥1 to ≤2', which represents fibrosis stage ≥F1 to ≤ F2, consists of MRE kPa from ≥2.9 kPa to ≤3.5 kPa. At 4 kPa the liver is considered to have reached stage 3 fibrosis and a value of 5 kPa is the final cutoff signifying progression to stage 4 fibrosis. Therefore, the 'stage >2 to <3' group, which represents fibrosis staging > F2 to < F3, contains MRE kPa >3.5 kPa to <4 kPa while 'stage ≥3 to <4', which represents fibrosis staging ≥ F3 to < F4, consists of MRE kPa values ≥4 kPa to <5 kPa. The final group, 'stage ≥4', represents fibrosis stage F4 and consists of all kPa ≥5 kPa.

Statistical analysis

Patient demographics, biomarker testing classifications and MRE categories were analyzed using descriptive statistics. All variables were considered as categorical and were described using frequency and percentage. They were compared using a Chi-Square Test or Fisher's Exact Test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of biomarker testing (FIB-4 and NFS) as compared to MRE was computed two different ways. First, to rule out the presence of advanced fibrosis/cirrhosis, FIB-4 testing was dichotomized as Advanced Fibrosis Excluded *vs.* other (which includes the
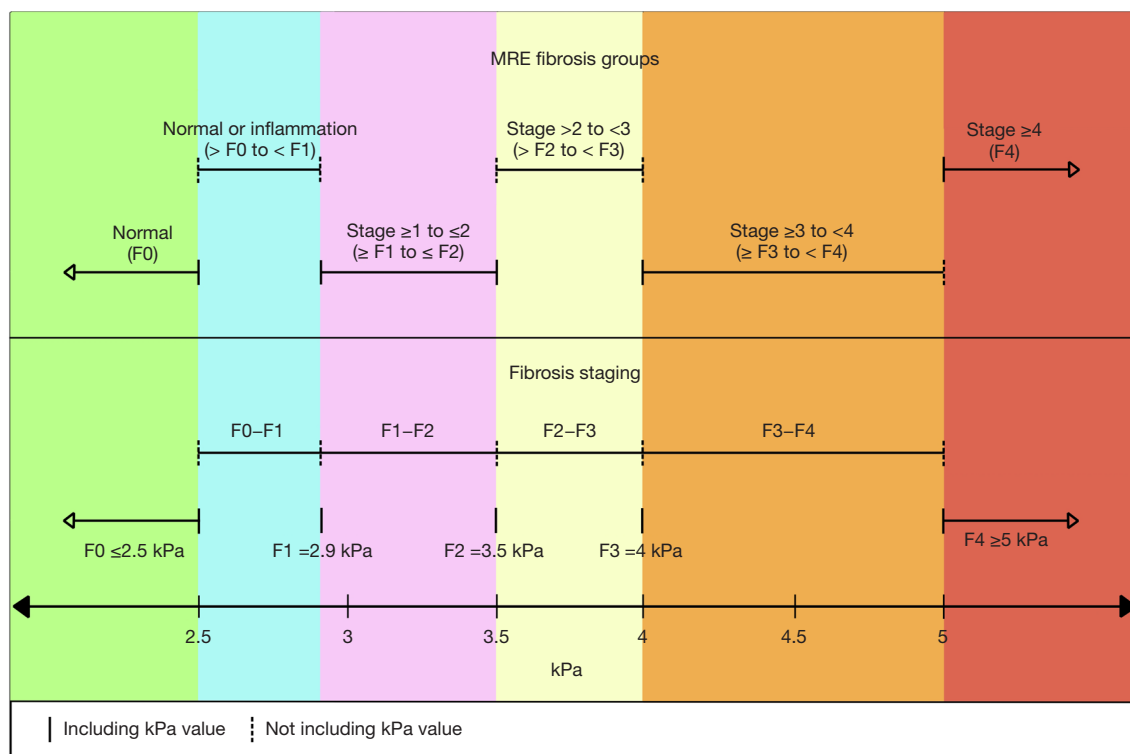
Figure 1 A value ≤2.5 kPa represents normal liver since 2.5 kPa serves as the transition point such that >2.5 kPa indicates the presence of inflammatory liver changes. Based on this, the 'normal' group, which represents fibrosis stage F0, consists of all MRE kPa ≤2.5. At 2.9 kPa the liver stiffness is deemed to have stage 1 fibrosis while 3.5 kPa is the value used to signify stage 2 fibrosis. As a result, the 'normal or inflammation' group, which represents fibrosis staging > F0 to < F1, contains MRE from kPa >2.5 to <2.9 kPa while 'stage ≥1 to ≤2', which represents fibrosis stage ≥ F1 to ≤ F2, consists of MRE kPa ranging from ≥2.9 kPa to ≤3.5 kPa. At 4 kPa the liver is considered to have reached stage 3 fibrosis and a value of 5 kPa is the final cutoff signifying progression to stage 4 fibrosis. Therefore, the 'stage >2 to <3' group, which represents fibrosis staging >F2 to <F3, contains MRE kPa ranging from >3.5 kPa to <4 kPa while 'stage ≥3 to <4', which represents fibrosis staging ≥ F3 to < F4, is made up of MRE kPa values ≥4 kPa to <5 kPa. The final group, 'stage ≥4', represents fibrosis stage F4 and consists of all kPa ≥5 kPa. MRE, magnetic resonance elastography.

Further Investigation Needed and Advanced Fibrosis Likely groups) and NFS testing was dichotomized as F0-2 vs. other (which includes the Indeterminate and F3–F4 groups). These were compared to MRE, which was dichotomized as 'stage ≥1 to ≤2' fibrosis or lower vs. 'stage >2 to <3' fibrosis or higher. Second, to identify the presence of advanced fibrosis/cirrhosis, FIB-4 testing was dichotomized as Advanced Fibrosis Likely vs. other (which includes the Further Investigation Needed and Advanced Fibrosis Excluded groups) and NFS testing dichotomized as F3-4 vs. other (which includes the Indeterminate and F0-F2 groups). These were compared to MRE, which was dichotomized as 'stage ≥3 to <4' fibrosis or higher vs. 'stage >2 to <3' fibrosis or lower. Subsequently, the correlation between each dichotomized biomarker test was compared with the corresponding dichotomized MRE staging using Pearson Correlation Coefficients. For FIB-4 testing, correlations were additionally stratified by age category for those >35 years old. All statistical analysis was done using SAS (9.4) with $P<0.05$ considered statistically significant.

Results

Among 193 total patients, 22 (11.40%) did not receive a FIB-4 score as they were ≤35 years old. In terms of categorization, 100 (51.81%) were Advanced Fibrosis Excluded using FIB-4 while 39 (20.21%) were Further Investigation Needed and 32 (16.58%) were Advanced Fibrosis Likely. Among the same population, 98 (50.78%) patients were considered F0-2 using NFS, 63 (32.64%)

Table 1 An analysis of demographic characteristics and biomarker fibrosis staging for each fibrosis stage as determined via MRE

Demographics and biomarker scoring	Fibrosis stage based on MRE						P value
	Normal	Normal or inflammation	Stage ≥1 to ≤2	Stage >2 to <3	Stage ≥3 to <4	Stage ≥4	
Age (years)							0.0323
≤35	12 (15.00)	5 (12.82)	2 (8.70)	0 (0.00)	2 (9.52)	1 (4.76)	
36–64	55 (68.75)	21 (53.85)	13 (56.52)	4 (44.44)	9 (42.86)	9 (42.86)	
≥65	13 (16.25)	13 (33.33)	8 (34.78)	5 (55.56)	10 (47.62)	11 (52.38)	
Sex							0.7371
Male	34 (42.50)	18 (46.15)	13 (56.52)	5 (55.56)	12 (57.14)	11 (52.38)	
Female	46 (57.50)	21 (53.85)	10 (43.48)	4 (44.44)	9 (42.86)	10 (47.62)	
FIB-4 score							<0.0001
No score (≤35 years)	12 (15.00)	5 (12.82)	2 (8.70)	0 (0.00)	2 (9.52)	1 (4.76)	
Advanced fibrosis excluded	56 (70.00)	19 (48.72)	9 (39.13)	5 (55.56)	9 (42.86)	2 (9.52)	
Further investigation needed	8 (10.00)	12 (30.77)	9 (39.13)	2 (22.22)	6 (28.57)	2 (9.52)	
Advanced fibrosis likely	4 (5.00)	3 (7.69)	3 (13.04)	2 (22.22)	4 (19.05)	16 (76.19)	
NFS score							<0.0001
F0-F2	61 (76.25)	18 (46.15)	8 (34.78)	3 (33.33)	7 (33.33)	1 (4.76)	
Indeterminate	16 (20.00)	20 (51.28)	11 (47.83)	5 (55.56)	7 (33.33)	4 (19.05)	
F3-F4	3 (3.75)	1 (2.56)	4 (17.39)	1 (11.11)	7 (33.33)	16 (76.19)	

The numbers in parentheses represent the percentage with regards to the column within each subcategory. P value for sex using Chi-Square test, others using Fisher's Exact test since cross tabulations had >25% of cells with counts <5. MRE, magnetic resonance elastography; FIB-4, Fibrosis-4; NFS, NAFLD Fibrosis Score; NAFLD, non-alcoholic fatty liver disease.

Table 2 SE, SP, PPV, and NPV for ruling out the presence of advanced fibrosis/cirrhosis

Biomarker test and classification	MRE fibrosis stage ('stage ≥1 to ≤2' fibrosis or lower *vs.* 'stage >2 to <3' fibrosis or higher)			
	SE	SP	PPV	NPV
FIB-4 (advanced fibrosis excluded *vs.* other)	0.67 (0.53, 0.80)	0.68 (0.60, 0.77)	0.45 (0.34, 0.57)	0.84 (0.77, 0.91)
NFS (F0-2 *vs.* other)	0.78 (0.67, 0.90)	0.61 (0.53, 0.69)	0.42 (0.32, 0.52)	0.89 (0.83, 0.95)

Confidence intervals are listed in parentheses. SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; FIB-4, Fibrosis-4; NFS, NAFLD Fibrosis Score; NAFLD, non-alcoholic fatty liver disease.

were considered indeterminate and 32 (16.58%) were F3-4. There were 80 (41.45%) patients considered 'Normal' using MRE, 39 (20.21%) 'Normal or Inflammation', 23 (11.92%) 'stage ≥1 to ≤2', 9 (4.66%) 'stage >2 to <3' fibrosis, 21 (10.88%) 'stage ≥3 to <4' fibrosis, and 21 (10.88%) 'stage ≥4' fibrosis/cirrhosis. Demographic characteristics, FIB-4 and NFS scores were summarized for each MRE fibrosis stage (*Table 1*).

The sensitivity, specificity, PPV and NPV for each dichotomized measure is presented in *Tables 2,3* while the correlations between the dichotomized biomarker and MRE results are presented in *Table 4*. *Table 2* shows the data for ruling out the presence of advanced fibrosis/cirrhosis while the data for identifying the presence of advanced fibrosis/cirrhosis is seen in *Table 3*. The raw data for these calculations can be seen in *Tables 5-8*. Most notably, for ruling out advanced fibrosis/cirrhosis, the NPV for FIB-4 (Advanced Fibrosis Excluded *vs.* other) when compared to

Table 3 SE, SP, PPV, and NPV for identifying the presence of advanced fibrosis/cirrhosis

Biomarker test and classification	MRE fibrosis stage ('stage ≥3 to <4' fibrosis or higher *vs.* 'stage >2 to <3' fibrosis or lower)			
	SE	SP	PPV	NPV
FIB-4 (advanced fibrosis likely *vs.* other)	0.51 (0.36, 0.67)	0.91 (0.86, 0.96)	0.63 (0.46, 0.79)	0.86 (0.81, 0.92)
NFS (F3-4 *vs.* other)	0.55 (0.40, 0.70)	0.94 (0.90, 0.98)	0.72 (0.56, 0.87)	0.88 (0.83, 0.93)

Confidence intervals are listed in parentheses. SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; FIB-4, Fibrosis-4; NFS, NAFLD Fibrosis Score; NAFLD, non-alcoholic fatty liver disease.

Table 4 Correlation values

Biomarker test classification	MRE fibrosis stage	
	'Stage ≥1 to ≤2' fibrosis or lower *vs.* 'Stage >2 to <3' fibrosis or higher	'Stage ≥3 to <4' fibrosis or higher *vs.* 'Stage >2 to <3' fibrosis or lower
FIB-4 (ages 36+, N=171)		
Advanced fibrosis excluded *vs.* other	0.32	–
Advanced fibrosis likely *vs.* other	–	0.45
FIB-4 (ages 36–64, N=111)		
Advanced fibrosis excluded *vs.* other	0.43	–
Advanced fibrosis likely *vs.* other	–	0.52
FIB-4 (ages 65+, N=60)		
Advanced fibrosis excluded *vs.* other	0.11	–
Advanced fibrosis likely *vs.* other	–	0.33
NFS (overall, N=193)		
F0-2 *vs.* other	0.35	–
F3-4 *vs.* other	–	0.54

Pearson correlation coefficients presented. FIB-4, Fibrosis-4; NFS, NAFLD Fibrosis Score; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease.

Table 5 FIB-4 data for identifying advanced fibrosis

MRE classification	Fibrosis category	
	Advanced fibrosis likely	Further investigation needed and advanced fibrosis excluded
'Stage ≥3 to <4' fibrosis or higher	20	19
'Stage >2 to <3' fibrosis or lower	12	120

FIB-4, Fibrosis-4; MRE, magnetic resonance elastography.

MRE fibrosis staging was found to be 0.84 (95% CI: 0.77, 0.91) and the NPV for NFS (F0-2 *vs.* other) was found to be 0.89 (95% CI: 0.83, 0.95). For identifying the presence of advanced fibrosis/cirrhosis, the PPV for FIB-4 (Advanced Fibrosis Likely *vs.* other) was found to be 0.63 (95% CI: 0.46, 0.79), and the PPV for NFS (F3-4 *vs.* other) was found to be 0.72 (95% CI: 0.56, 0.87).

In *Table 4* we see correlation values comparing the dichotomized biomarker results to MRE results. For ruling out the presence of advanced fibrosis/cirrhosis using FIB-4, the overall correlation between FIB-4 (Advanced Fibrosis Excluded *vs.* other) and MRE ('stage ≥1 to ≤2' fibrosis or

lower *vs.* 'stage >2 to <3' fibrosis or higher) showed a low positive correlation (r=0.32). After stratifying by age it was even lower for those who are 65 and older (r=0.11), while slightly higher for those who are 36–64 (r=0.43). For ruling out the presence of advanced fibrosis/cirrhosis using NFS, there was also a low positive correlation (r=0.35) found between NFS (F0-2 *vs.* other) and MRE fibrosis stage ('stage ≥1 to ≤2' fibrosis or lower *vs.* 'stage >2 to <3' fibrosis or higher).

For identifying the presence of advanced fibrosis/cirrhosis using FIB-4, moderate positive correlation (r=0.45) was found between FIB-4 (Advanced Fibrosis Likely *vs.* other) and MRE fibrosis stage ('stage ≥3 to <4' fibrosis or higher *vs.* 'stage >2 to <3' fibrosis or lower). It was again higher for those 36–64 (r=0.52) and lower for those 65 and older (r=0.33). For identifying the presence of advanced fibrosis/cirrhosis using NFS, there was a moderate correlation (r=0.54) between NFS (F3-4 *vs.* other) and MRE fibrosis stage ('stage ≥3 to <4' fibrosis or higher *vs.* 'stage >2 to <3' fibrosis or lower).

Discussion

The main implication for NAFLD fibrosis staging is to assess for advanced liver disease. Staging stratifies patients with varying degrees of fibrosis to identify those who benefit from proper screening for complications such as HCC and esophageal varices. Noninvasive imaging

techniques such as MRE have become widely used, however accessibility remains limited and cost effectiveness is unclear (47,48). It is important to note that liver biopsy remains the gold standard for fibrosis staging, however in patients who are either unable or unwilling to undergo biopsy, MRE and biomarker testing are well known and frequently used alternatives. The purpose of our study is not to imply that biopsy should be replaced by these other options but instead to determine whether or not patients who are planning to undergo MRE truly require it in all cases. Correlating NAFLD fibrosis staging via MRE to biomarker testing may prove MRE excessive in some situations (49). A study that were to show biomarker testing alone is sufficient for staging in certain cases would be of significant clinical importance, especially for those with financial constraints or those unable to undergo MRE. Our analysis suggested that some patients with NAFLD may only require biomarker testing to classify their fibrosis. We hope our results can help pave the way for cost-effective, standardized guidance to be used when staging fibrosis and recommending appropriate screening for NAFLD.

Our results showed positive correlations for all of the subgroups analyzed in comparing MRE fibrosis staging to that of either FIB-4 or NFS. For ruling out advanced fibrosis, the lower correlation coefficients obtained for FIB-4 (r=0.32) and NFS (r=0.35) suggest that early stage NAFLD is certainly associated with some variability with regards to the exact stage of fibrosis determined via MRE as compared to FIB-4 or NFS. As NAFLD progresses to late stage disease, the higher correlation coefficients obtained for advanced fibrosis show that fibrosis staging as determined by FIB-4 (r=0.45) and NFS (r=0.54) corresponds more closely to the stage identified via MRE. These correlation coefficients suggest a higher probability of MRE characterizing liver fibrosis to be the same stage that either FIB-4 or NFS does in advanced disease. This supports the previously discussed and known general consensus that both MRE and the biomarker scoring methods tend to be more accurate in late stage disease (50-52).

Table 6 NFS data for identifying advanced fibrosis

MRE classification	Fibrosis category	
	F3–F4	Indeterminate and F0–F2
'Stage ≥3 to <4' fibrosis or higher	23	19
'Stage >2 to <3' fibrosis or lower	9	142

NFS, NAFLD Fibrosis Score; NAFLD, non-alcoholic fatty liver disease; MRE, magnetic resonance elastography.

Table 7 FIB-4 data for ruling out advanced fibrosis

MRE classification	Fibrosis category	
	Advanced fibrosis likely and further investigation needed	Advanced fibrosis excluded
'Stage >2 to <3' fibrosis or higher	32	16
'Stage ≥1 to ≤2' fibrosis or lower	39	84

FIB-4, Fibrosis-4; MRE, magnetic resonance elastography.

Table 8 NFS data for ruling out advanced fibrosis

MRE classification	Fibrosis category	
	F3–F4 and indeterminate	F0–F2
'Stage >2 to <3' fibrosis or higher	40	11
'Stage ≥1 to ≤2' fibrosis or lower	55	87

NFS, NAFLD Fibrosis Score; NAFLD, non-alcoholic fatty liver disease; MRE, magnetic resonance elastography.

The NPV and PPV values obtained suggest that, when grouping patients together as either early stage NAFLD (rule out advanced fibrosis) or late stage NAFLD (identify advanced fibrosis/cirrhosis), MRE corresponds well with FIB-4 and NFS in identifying late stage disease while having an even stronger association in those with early stage disease. For early stage disease, NPV values for FIB-4 (0.84) and NFS (0.89) in the 'rule out advanced fibrosis' category signify that 84% and 89% of respective biomarker scores ('Advanced Fibrosis Excluded *vs.* other' for FIB-4 and 'F0-2 *vs.* other' for NFS) correspond to MRE categories 'stage ≥1 to ≤2' fibrosis or lower. For late stage disease, PPV values for FIB-4 (0.63) and NFS (0.72) in the 'identify advanced fibrosis/cirrhosis' category signify that 63% and 72% of respective biomarker scores ('Advanced Fibrosis Likely *vs.* other' for FIB-4 and 'F3-4 *vs.* other' for NFS) correspond to MRE categories 'stage ≥3 to <4' fibrosis or higher. This has significant clinical implications as it suggests that those deemed to have early stage NAFLD using FIB-4 and NFS were also found to have early stage NAFLD using MRE 84% and 89% of the time respectively. MRE, NFS and FIB-4 are known to be accurate fibrosis staging options which are widely believed to perform better in late stage NAFLD. This enables them to effectively differentiate early from late stage disease. Early stage NAFLD may only require lifestyle modifications and risk reduction to prevent progression of disease, whereas late stage disease requires more regimented screening for serious complications. Our data suggested that patients with early stage disease on biomarker testing are very likely to show early stage disease on MRE as well. In our study, 100 individuals fell into the advanced fibrosis excluded category using FIB-4, suggesting early stage disease. Out of these, MRE provided contradictory results in 11 cases where MRE staging suggested advanced fibrosis/cirrhosis. With regards to NFS, 98 individuals were in the F0-2 range showing early stage disease. However, 8 of those 98 showed advanced fibrosis/cirrhosis on MRE. We were unable to determine whether biomarker testing or MRE was more accurate in these instances of contradictory results without liver biopsy.

There are several different components of MRE that must be performed with technical proficiency in order to ensure proper and accurate results (53). When done correctly, MRE is known to be very accurate with impressive interobserver agreement when head-to-head comparisons were performed to confirm appropriate fibrosis staging and reproducibility (54-57). One notable pitfall is that the MRE kPa cutoff values used in our study [2.5, 2.9, 3.5, 4, 5] were not universally used. The greatest uncertainty and variability involves the cutoff used for differentiating normal liver from inflammation in the setting of early fibrosis (58,59).

Based on our aforementioned results, MRE seemed to be excessive in a large majority of patients given it provided the same information obtained using FIB-4 or NFS. These findings pose a question as to whether or not patients with FIB-4 and NFS scores in the 'rule out advanced fibrosis' category truly benefit from MRE testing as well. Our study showed that FIB-4 and NFS scores indicating little to no fibrosis correspond quite well with respective 'normal, normal or inflammation and stage ≥1 to ≤2' MRE staging, while scores suggesting advanced fibrosis/cirrhosis do correspond with respective 'stage ≥3 to <4 and stage ≥4' MRE staging but less convincingly. Although the clinical implication of MRE as an alternative to liver biopsy has recently gained recognition, our study suggested that FIB-4 and NFS remain very effective and sufficient in assessing fibrosis for those with FIB-4 scores indicating Advanced Fibrosis Excluded and NFS scores indicating F0-2. A large majority of cases may fare well with monitoring simply via biomarker testing. MRE could be more useful when biomarker staging indicates progression of disease since MRE has proven most accurate when staging advanced fibrosis/cirrhosis (59). We provide a proposed fibrosis screening algorithm based upon this in *Figure 2*.

One notable limitation in our study is the possibility of confounding medical conditions that may have unexpectedly affected biochemical results leading to inaccurate biomarker testing scores. We excluded patients from our study that had obvious conditions that could impact our results, however undiagnosed diseases could always be playing a role. With regards to MRE, patients are told to fast at least 4 hours prior to imaging to ensure the most accurate results. Unknown patient adherence was another aspect that we could not control and could have impacted our results. In addition, our limited sample size poses another
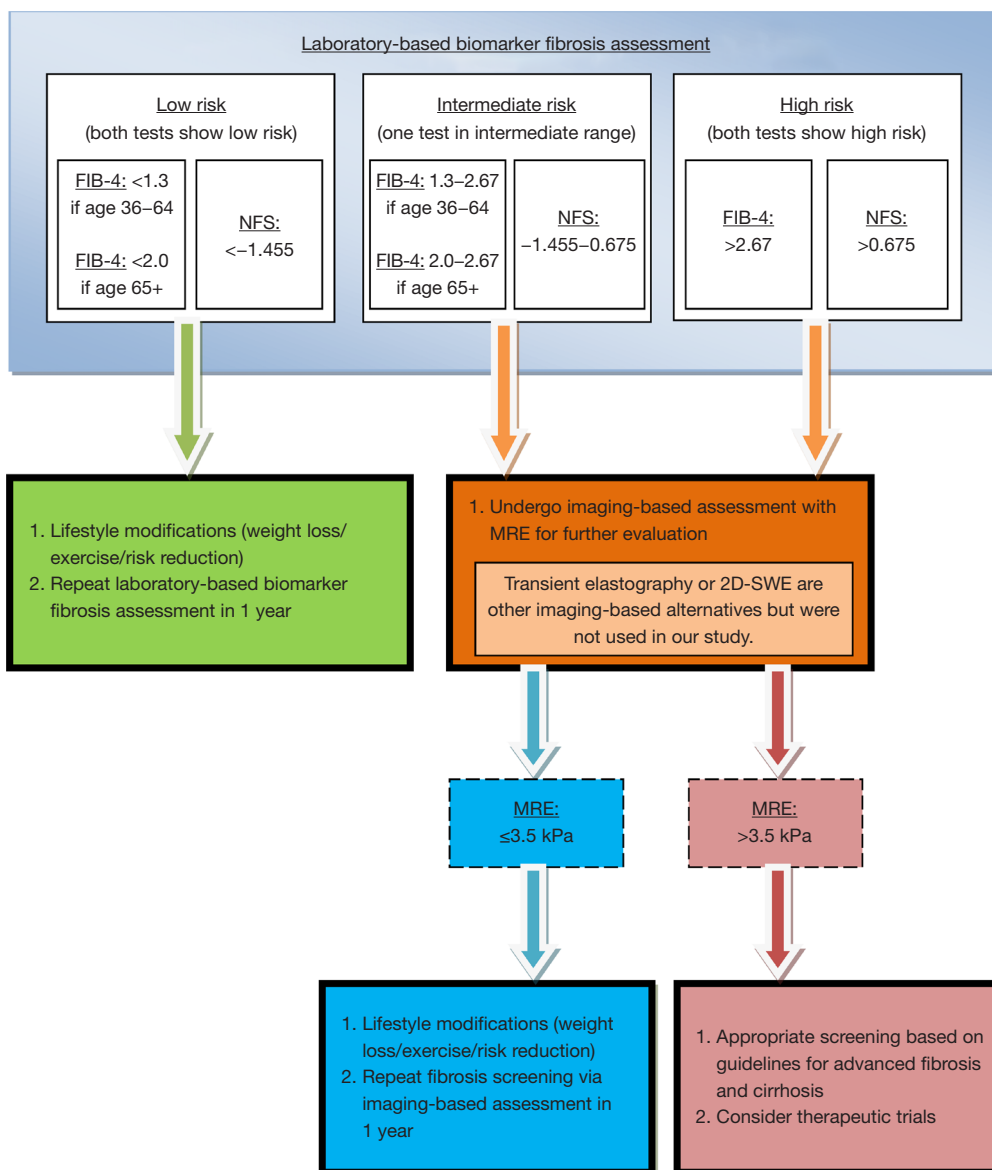
Figure 2 Non-invasive fibrosis assessment algorithm for patients with presumed NAFLD in clinical practice. FIB-4, Fibrosis-4; NFS, NAFLD Fibrosis Score; 2D-SWE, two-dimensional shear wave elastography; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease.

limitation while the retrospective nature of the study also contributes to further constraints. Future prospective large series studies are warranted to further investigate the relationship between MRE and biomarker testing with regards to NAFLD fibrosis staging. As MRE continues to be utilized more often and data supporting its accuracy as compared to biopsy becomes more readily available, it is possible that it may become a noninvasive gold standard for

NAFLD fibrosis staging and monitoring (60-62). However, there is a need for further universal guidance to standardize the kPa cutoff values of MRE for NAFLD, most notably in differentiating normal liver from mild fibrosis. We have noted cases where biomarker testing and MRE give conflicting results and it would be beneficial to further investigate these instances in an attempt to uncover the reasons for discrepancy in such cases.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-27/rc

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-27/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-22-27/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by our ethics committee (Northwell Health Protocol Registration # 19-0465). Informed consent was not obtained in accordance with our IRB approved protocol for this retrospective chart review. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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