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Magnetic resonance elastography plus Fibrosis-4 versus FibroScan–aspartate aminotransferase in detection of candidates for pharmacological treatment of NASH-related fibrosis

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Abstract

Background and Aims: Patients with NAFLD with significant hepatic fibrosis (Stage ≥ 2) are at increased risk of liver-related morbidity and are candidates for pharmacologic therapies. In this

study, we compared the diagnostic accuracy of MEFIB (the combination of magnetic resonance elastography [MRE] and Fibrosis-4 [FIB-4]) and FAST (FibroScan–aspartate aminotransferase; combined liver stiffness measurement by vibration-controlled transient elastography, controlled attenuation parameter, and aspartate aminotransferase) for detecting significant fibrosis.

Approach and Results: This prospective cohort study included 234 consecutive patients with NAFLD who underwent liver biopsy, MRE, and FibroScan at the University of California San Diego (UCSD cohort) and an independent cohort ($N = 314$) from Yokohama City University, Japan. The primary outcome was diagnostic accuracy for significant fibrosis (Stage ≥ 2). The proportions of significant fibrosis in the UCSD and Yokohama cohorts were 29.5% and 66.2%, respectively. Area under the receiver operating characteristic curve (95% CI) of MEFIB (0.860 [0.81–0.91]) was significantly higher than that of FAST (0.757 [0.69–0.82]) in the UCSD cohort ($p = 0.005$), with consistent results in the Yokohama cohort (AUROC, 0.899 [MEFIB] versus 0.724 [FAST]; $p < 0.001$). When used as the rule-in criteria (MEFIB, MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6; FAST ≥ 0.67), the positive predictive value for significant fibrosis was 91.2%–96.0% for MEFIB and 74.2%–89.2% for FAST. When used as the rule-out criteria (MEFIB, MRE < 3.3 kPa and FIB-4 < 1.6; FAST ≤ 0.35), the negative predictive value for significant fibrosis was 85.6%–92.8% for MEFIB and 57.8%–88.3% for FAST.

Conclusions: MEFIB has higher diagnostic accuracy than FAST for significant fibrosis in NAFLD, and our results support the utility of a two-step strategy for detecting significant fibrosis in NAFLD.

INTRODUCTION

NAFLD is one of the main causes of chronic liver disease, and > 25% of the general population is affected by NAFLD worldwide.[1,2] Due to the increase of patients with diabetes mellitus and metabolic syndrome, the number of patients with NAFLD has been rising, resulting in NAFLD emerging as a major health problem.[3–5] A subset of patients with NAFLD has the progressive form called NASH, which may lead to cirrhosis, HCC, and liver failure. Therefore, the identification of patients with NAFLD with a high risk of disease progression is an unmet need in clinical practice.

Recent studies have demonstrated that liver fibrosis is the most important prognostic feature in NAFLD.[6,7] Liver biopsy is a gold standard method for diagnosing liver fibrosis, but liver biopsy has several limitations including its invasiveness, sampling error, and interobserver and intraobserver reproducibility.[8,9] As a result of the limitations of liver biopsy, several noninvasive methods have been developed and are in use in clinical practice. Noninvasive assessment for predicting hepatic fibrosis in NAFLD includes serum-based fibrosis markers, ultrasound-based methods, and MRI-based methods.[10,11]

Treatment for high-risk patients with NAFLD is in high demand; but there is no drug approved by the US Food and Drug Administration currently, and many clinical trials are ongoing. Patients with significant fibrosis (Stage ≥ 2) are candidates for clinical trial participation given the risk for poor prognosis. However, a high screening failure rate is a major problem of NASH clinical trials, and a non-invasive method for detecting candidates for clinical trials and reducing unnecessary liver biopsy is needed. The FibroScan–aspartate

aminotransferase (FAST) score is derived from combined noninvasive measures of liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), controlled attenuation parameter (CAP), and aspartate aminotransferase (AST); and the utility for detecting patients at risk of progressive NASH with significant activity and fibrosis has been reported.[12] Recently, we have demonstrated that the MEFIB index, combining Fibrosis-4 (FIB-4) as a serum-based marker and magnetic resonance elastography (MRE), may be used for noninvasive identification of patients with NAFLD and significant fibrosis.[13] To address these gaps in knowledge, we compared the diagnostic ability of MEFIB and FAST in a well-characterized cohort of adults with NAFLD and contemporaneous liver biopsy, LSM by MRE and VCTE, and CAP assessment at the University of California San Diego (UCSD). We then evaluated the diagnostic ability of MEFIB and FAST in a separate Yokohama (Japan) cohort.

PATIENTS AND METHODS

Study design

This is a prospective study that includes a well-characterized cohort with biopsy-proven NAFLD. This study includes 234 consecutive uniquely phenotyped adults who underwent liver biopsy with contemporaneous MRE, VCTE, and CAP assessment at the NAFLD Research Center, UCSD, from August 2014 through March 2021. Furthermore, a total of 314 consecutive patients with NAFLD who underwent liver biopsy with contemporaneous MRE, VCTE, and CAP assessment at Yokohama City University from March 2014 through April 2021 were also enrolled in the study as a geographically distinct cohort. All patients completed written informed consent prior to enrollment. The study was approved by the institutional review boards at both sites.

Inclusion and exclusion criteria

In the UCSD cohort, adults (≥ 18 years of age) with biopsy-proven NAFLD and written informed consent were included in the study. For this study, patients were included if LSM by MRE, LSM by VCTE, and CAP were measured contemporaneously with liver biopsy. Patients meeting any of the following criteria were excluded from the study: significant alcohol consumption (defined as ≥ 14 drinks/week for men or ≥ 7 drinks/week for women) within the previous 2-year period; underlying liver disease including hepatitis B, hepatitis C, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, glycogen storage disease, autoimmune hepatitis, and cholestatic or vascular liver disease; clinical or laboratory evidence of secondary causes or chronic conditions associated with hepatic steatosis including nutritional disorders, HIV infection, and use of steatogenic drugs such as amiodarone, glucocorticoids, methotrexate, l-asparaginase, and valproic acid; major systemic illnesses; decompensated liver disease (defined as Child-Pugh score > 7 points); contraindications to MRI including metallic implants, claustrophobia, and body circumference exceeding the imaging chamber capacity; pregnancy or attempting to become pregnant.

In the Yokohama cohort, adults (≥ 18 years of age) with biopsy-proven NAFLD and written informed consent were included in the study. For this study, patients were included if LSM

by MRE, LSM by VCTE, and CAP were measured contemporaneously with liver biopsy. Patients with a history of excessive alcohol consumption (> 10 drinks for male and > 5 drinks for women per week); other liver diseases such as chronic hepatitis; or using drugs that are associated with fatty liver, weight reduction, renal disease, or thyroid disease were excluded. All subjects provided written consent prior to examination.

Clinical and laboratory data

The patient's age, sex, height, weight, and alcohol in-take were recorded at entry into the study. Standard blood counts and biochemistry tests were obtained in all patients. The FIB-4 index was calculated according to the following formula: FIB-4 = age (years) × AST (IU/L)/ platelets (10^9/L) × alanine aminotransferase (IU/L)$^{1/2}$.[14]

Histological evaluation

All patients underwent a liver biopsy. An adequate liver specimen was defined as > 10 mm in length and/or having > 10 portal tracts in both sites. Histologic assessments of liver biopsies were systematically assessed by an experienced liver pathologist of each site blinded to clinical data. Biopsy results were scored using the NASH Clinical Research Network histologic scoring system.[15] Fibrosis was scored from 0 to 4, with stage 4 fibrosis defined as cirrhosis. Hepatic steatosis and lobular inflammation were scored from 0 to 3. Hepatocyte ballooning was scored from 0 to 2. Hepatic steatosis, lobular inflammation, and hepatocyte ballooning were combined to obtain the NAFLD activity score, ranging from 0 to 8. The median (interquartile range [IQR]) specimen length and number of portal tracts were 20 (16–25) mm and 14 (11–20), respectively, in the UCSD cohort and 17 (15–22) mm and 12 (10–17), respectively, in the Yokohama cohort.

MRE assessment and MEFIB criteria

LSM by MRE and a two-dimensional MRE protocol were performed using a 3.0T research scanner (GE Signa EXCITE HDxt; GE Healthcare, Waukesha, WI) as described at both sites.[16,17] The image analysts were blinded to all clinical and biochemical data. MEFIB was evaluated using MRE and FIB-4, and the rule-in and rule-out criteria for significant fibrosis were defined as follows: the rule-in criteria were MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6, and the rule-out criteria were MRE < 3.3 kPa and FIB-4 < 1.6, based on previous study.[13] The median (IQR) interval between liver biopsy and MRE assessment was 11 (−19 to 51) days in the UCSD cohort and 27 (−65 to 87) days in the Yokohama cohort.

FibroScan assessment and FAST score

LSM by VCTE and CAP were performed by a trained technician using the FibroScan 502 Touch model in the UCSD cohort and the FibroScan 502 Touch model or FibroScan 430 model in the Yokohama cohort (Echosens, Paris, France) according to described methods. [18] Technicians were blinded to clinical and histologic data. All patients were first scanned by applying the M probe (3.5 MHz), and rescanning using the XL probe (2.5 MHz) was performed only prompted by the automatic prove selection tool. At minimum, 10 measurements were made to obtain the median valid LSMs in kilopascals and the median valid CAP in decibels per meter. The FAST score was calculated according to the previous

study, and FAST scores of 0.67 and 0.35 were used as the rule-in and rule-out criteria, respectively.[12] The median (IQR) interval between liver biopsy and FibroScan assessment was 5 (−19 to 40) days in the UCSD cohort and 17 (−37 to 57) days in the Yokohama cohort.

Primary outcome

The primary outcome of the study was defined as the diagnostic accuracy for significant fibrosis (fibrosis stage 2).

Statistical analysis

Patient characteristic between the UCSD cohort and the Yokohama cohort were compared using Fisher's exact test or the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed for MRE, FIB-4, and FAST; and these factors were used in a continuous value. Similarly, ROC analyses were performed for MEFIB and FAST. MEFIB and FAST were examined using the rule-in and rule-out criteria. The Delong test was used to compare the area under the ROCs (AUROC). A two-tailed p 0.05 was considered statistically significant for all analyses. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan),[19] a graphical user interface for R, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 234 biopsy-confirmed patients with NAFLD were enrolled in the UCSD cohort, and 314 biopsy-confirmed patients with NAFLD were enrolled in the Yokohama cohort. The baseline patient characteristics are shown in Table 1. The median (IQR) ages of the UCSD and Yokohama cohorts were 54 (42–63) years and 61 (51–71) years, respectively. The proportions of patients with significant fibrosis (fibrosis stage 2) were 29.5% (69/234) in the UCSD cohort and 66.2% (208/314) in the Yokohama cohort. Median (IQR) MRE, FIB-4, and FAST scores were 2.47 (2.1–3.3) kPa, 1.19 (0.8–1.8), and 0.38 (0.23–0.57), respectively, in the UCSD cohort and 4.01 (2.6–5.4) kPa, 1.87 (1.1–3.2), and 0.46 (0.26–0.64), respectively, in the Yokohama cohort. The proportion of significant fibrosis was higher in the Yokohama cohort than the UCSD cohort.

Diagnostic accuracy of MRE, FIB-4, and FAST for significant fibrosis

Diagnostic accuracy of MRE, FIB-4, and FAST for detecting significant fibrosis (fibrosis stage 2) was compared as a continuous trait. In the UCSD cohort, AUROCs (95% CI) of MRE, FIB-4, and FAST were 0.937 (0.92–0.96), 0.818 (0.78–0.85), and 0.763 (0.72–0.80), respectively. The AUROC of MRE and FIB-4 was significantly higher than that of FAST ($p < 0.001$ for MRE, $p = 0.02$ for FIB-4; Figure 1A). Similarly, in the Yokohama cohort, AUROCs (95% CI) of MRE, FIB-4, and FAST were 0.923 (0.89–0.96), 0.828 (0.78–0.88), and 0.760 (0.70–0.82), respectively; and the AUROC of MRE and FIB-4 was also significantly higher than that of FAST ($p < 0.001$ for MRE and $p = 0.03$ for FIB-4; Figure 1B).

Diagnostic utility of the rule-in and rule-out criteria of MEFIB and FAST for significant fibrosis

MEFIB and FAST were divided into three categories using the rule-in and rule-out criteria for MEFIB and FAST as follows: the rule-in criteria (MEFIB, MRE 3.3 kPa and FIB-4 1.6; FAST, 0.67), the rule-out criteria (MEFIB, MRE < 3.3 kPa and FIB-4 < 1.6; FAST, 0.35).

The diagnostic utility of MEFIB and FAST for significant fibrosis (rule-in, rule-out, and indeterminate) was investigated. The AUROCs (95% CI) of MEFIB and FAST in the UCSD cohort were 0.860 (0.81–0.91) and 0.757 (0.69–0.82), respectively, and the AUROC of MEFIB was significantly higher than that of FAST ($p = 0.005$; Table 2). Similarly, the AUROCs (95% CI) of MEFIB and FAST in the Yokohama cohort were 0.899 (0.86–0.94) and 0.724 (0.67–0.78), respectively, and the AUROC of MEFIB was also significantly higher than that of FAST ($p < 0.001$; Table 2). Next, the diagnostic ability of the rule-in and out criteria for significant fibrosis was investigated. In the UCSD cohort, 34 patients (14.5%, 34/234) fulfilled the MEFIB rule-in criteria, and the positive predictive value (PPV) for significant fibrosis in these patients was 91.2% (31/34) (Table 2). Furthermore, 139 patients (59.4%, 139/234) fulfilled the MEFIB rule-out criteria, and the negative predictive value (NPV) for significant fibrosis (PPV for fibrosis stage 0 or 1) was 92.8% (129/139). On the other hand, the PPV of the FAST rule-in criteria for significant fibrosis was 74.2%, and the NPV of the FAST rule-out criteria was 88.3%. The PPV and the NPV of the MEFIB rule-in and rule-out criteria were superior than those of FAST. When the MEFIB criteria were used in the UCSD cohort, 73.9% (173/234) of patients fulfilled the rule-in or rule-out criteria, and the PPV among these patients was 92.5% (160/173).

In the Yokohama cohort, 149 (47.5%, 149/314) patients fulfilled the MEFIB rule-in criteria, and the PPV for significant fibrosis in these patients was 96.0% (143/149). For the MEFIB rule-out criteria, 90 (28.7%, 90/314) patients fulfilled the MEFIB rule-out criteria, and the NPV for significant fibrosis was 85.6% (77/90). The PPV and the NPV of the MEFIB rule-in and rule-out criteria were superior than those of FAST (PPV of the rule-in criteria, 89.2%; NPV of the rule-out criteria, 57.8%). When the MEFIB criteria were used in the Yokohama cohort, 76.1% (239/314) of patients fulfilled the MEFIB rule-in or rule-out criteria, and the PPV among these patients was 92.1% (220/239).

In the combined cohort, 33.4% of patients fulfilled the rule-in criteria (MRE 3.3 kPa and FIB-4 1.6), and the PPV for significant fibrosis among these patients was 95.1%. Furthermore, 41.8% of patients fulfilled the rule-out criteria (MRE < 3.3 kPa and FIB-4 < 1.6), and the NPV for significant fibrosis (PPV for fibrosis stage 0 or 1) was 90.0%. Indeterminate patients by the MEFIB and FAST criteria were 24.8% and 40.3%, respectively.

Diagnostic ability for fibrosis stages 2 and 3 (except fibrosis stage 4)

Diagnostic accuracy of MEFIB, FAST, MRE, and VCTE for fibrosis stages 2–3 (versus fibrosis stages 0–1) after excepting patients with fibrosis stage 4 was investigated in the combined cohort ($n = 486$, 44.2% [215/486] of patients were fibrosis stages 2 and 3).

MEFIB and FAST were divided into three categories using the rule-in and rule-out criteria for MEFIB and FAST. MRE and VCTE were dichotomized using thresholds of 3.34 kPa and 7.8 kPa determined by the Youden index. AUROCs (95% CI) of MEFIB, FAST, MRE, and VCTE for fibrosis stage 2–3 were 0.880 (0.85–0.91), 0.715 (0.67–0.76), 0.863 (0.83–0.89), and 0.771 (0.73–0.81), respectively (Figure 2 and Table 3); and the AUROC of MEFIB was significantly higher than those of FAST ($p < 0.001$) and VCTE ($p < 0.001$). When using the rule-in criteria of MEFIB and FAST and thresholds of MRE 3.34 kPa and VCTE 7.8 kPa, the PPVs for fibrosis stages 2–3 were 93.0% in MEFIB, 78.7% in FAST, 89.6% in MRE, and 71.9% in VCTE; and the PPV was higher in MEFIB (Table 3). The sensitivity of MEFIB was 55.3% (119/215), and a false negative was observed in 96 patients with significant fibrosis. Among these false-negative patients, 54, 20, and 22 patients were misdiagnosed by FIB-4 < 1.6, MRE < 3.3 kPa, and both FIB-4 < 1.6 and MRE < 3.3 kPa, respectively.

DISCUSSION

Main findings

In this study, we demonstrated that the diagnostic accuracy of MEFIB for significant fibrosis (fibrosis stage 2) was higher than that of FAST, and these remained statistically and clinically significant in an independent racially and geographically diverse validation cohort from Japan. Using the MEFIB rule-in criteria (MRE 3.3 kPa and FIB-4 1.6), the PPV for significant fibrosis was 95.1%. Furthermore, using the MEFIB rule-out criteria, the NPV for significant fibrosis (PPV for fibrosis stage 0 or 1) was 90.0%. Because patients with significant fibrosis are at high risk of poor prognosis and are candidates for NASH treatment clinical trials, MEFIB is useful for detecting these high-risk patients and may be used as a noninvasive screening method.

Context with published literature

Liver fibrosis is the most important prognostic factor in NAFLD, and mortality risk increases for patients with significant fibrosis (fibrosis stage 2).[6] Therefore, detecting patients with significant fibrosis is an unmet clinical need. Because liver biopsy has several limitations, several noninvasive methods including serum markers, ultrasound-based modalities, and MRI-based modalities have been developed; and such noninvasive methods have been reported to detect these high-risk patients.[8,9,11]

FibroScan is the first approved ultrasound-based modality, and LSM and CAP by FibroScan are associated with fibrosis stage and steatosis grade.[20] To further improve the diagnostic accuracy for liver fibrosis, one strategy is to combine noninvasive markers. The FAST score is a marker combining LSM by VCTE, CAP, and AST; and high diagnostic accuracy for NASH with significant activity and fibrosis was reported. The diagnostic accuracy increased by combining these factors compared to using each factor alone. Furthermore, the FAST score is not affected by probe selection and has high reproducibility.[21,22] Therefore, FAST may be a suitable method for screening patients with NAFLD who are candidates for NASH treatment clinical trials.

MRE is another noninvasive modality for measuring liver stiffness. LSM by MRE is associated with fibrosis stage, and furthermore, LSM by MRE is also associated with HCC development, liver failure, and prognosis.[23–25] Although VCTE and MRE are used as noninvasive methods for LSM, MRE has higher diagnostic accuracy than VCTE for detecting liver fibrosis.[26,27] Based on these results, MRE is permitted for use in inclusion criteria and as an endpoint in early-phase clinical trials instead of liver biopsy.[17,28] FIB-4 is a serum-based fibrosis marker, and it is also associated with fibrosis and prognosis.[29–31] Recently, we demonstrated that the diagnostic accuracy for significant fibrosis increased by combining MRE and FIB-4 (MEFIB) versus MRE alone.[13]

Although MEFIB and FAST are thought to be effective methods for detecting patients with NAFLD and significant fibrosis, there is no head-to-head comparison between MEFIB and FAST in assessing the comparative utility of these noninvasive tests in clinical risk stratification in NAFLD. Because the diagnostic accuracy of MRE is higher than that of VCTE for detecting liver fibrosis, we hypothesized that MEFIB would have a higher diagnostic accuracy than the FAST score. In this study, we demonstrated that the diagnostic accuracy of MEFIB for significant fibrosis is higher than that of FAST, and more importantly it has superior PPV and NPV than FAST. This study provides evidence regarding MEFIB, and MEFIB may be suitable for detecting patients with significant fibrosis who are candidates for clinical trials when available.

Strengths and limitations

The strengths of the study are that it enrolled prospectively recruited well-characterized patients with NAFLD in two geographically distinct cohorts. Consecutive patients who underwent a liver biopsy, MRE, VCTE, and CAP were enrolled in the study. The proportions of patients with significant fibrosis were different between the two cohorts (29.5% in the UCSD cohort and 66.2% in the Yokohama cohort), and the utility of MEFIB for significant fibrosis was confirmed in both cohorts. This indicates that MEFIB could be used in another cohort, but the utility of MEFIB in a cohort with a low proportion of patients with significant fibrosis should be validated in a future study.

Future implication

In this study, we demonstrated that MEFIB (MRE + FIB-4) is useful for detecting patients with NAFLD and significant fibrosis (fibrosis stage ≥ 2), more so than FAST. Regarding enrollment in NASH clinical trials, a high screening failure rate is a major problem. To mitigate the failure rate, a two-step screening strategy is recommended.[32,33] In a primary care center, a readily and widely available blood-based test is suitable, and FIB-4 could be applied for the first screening. Because FIB-4 < 1.3 has a high NPV for significant fibrosis, patients with FIB-4 < 1.3 need no further examination, and patients with FIB-4 ≥ 1.3 may be referred for further assessment; this may be refined further by targeting especially those with a FIB-4 ≥ 1.6 who may need additional elastographic examination at a referral care center.[31] As a second step in those with a FIB-4 ≥ 1.6, MRE could be applied based on the present study results. Patients with the MEFIB rule-in criteria (MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6) have a high PPV for significant fibrosis, and they are likely good candidates for clinical trials. MRE alone also demonstrated high diagnostic accuracy for significant

fibrosis. However, PPV for significant fibrosis increased by combining MRE and FIB-4 rather than using MRE alone. Because a high screening failure rate is a major problem in the enrollment of NASH clinical trials, the two-step strategy (combining FIB-4 and MRE) may be more suitable than MRE alone to reduce the screening failure rate in NASH clinical trials that use MRI-based assessment. Furthermore, a recent study showed that a two-step strategy contributes to reducing health care costs,[34] and MEFIB may contribute to reducing health care costs by reducing excessive MRE examinations. Therefore, MEFIB, a combination of FIB-4 and MRE, appears to be a suitable tool for the two-step screening strategy for studies and centers that are using MRI-based assessment. For centers where MRE is not available, FAST may still be used and remains an important alternative, although it has a much lower PPV and NPV. The two-step screening strategy using MEFIB and the diagnostic ability of MEFIB for significant fibrosis are summarized in Figure 3.

In conclusion, MEFIB has higher diagnostic accuracy than FAST for patients with significant fibrosis who are at high risk of poor prognosis and candidates for clinical trials, and our results support the utility of a two-step strategy for detecting significant fibrosis in adults with NAFLD.

Funding information

CONFLICT OF INTEREST

Abbreviations:

|	
AST	aspartate aminotransferase
AUROC	area under the ROC
CAP	controlled attenuation parameter
FAST	FibroScan-AST
FIB-4	Fibrosis-4
IQR	interquartile range

| LSM | liver stiffness measurement |
MEFIB	FIB-4 combined with MRE
MRE	magnetic resonance elastography
NPV	negative predictive value
PPV	positive predictive value
ROC	receiver operating characteristic
UCSD	University of California San Diego
VCTE	vibration-controlled transient elastography

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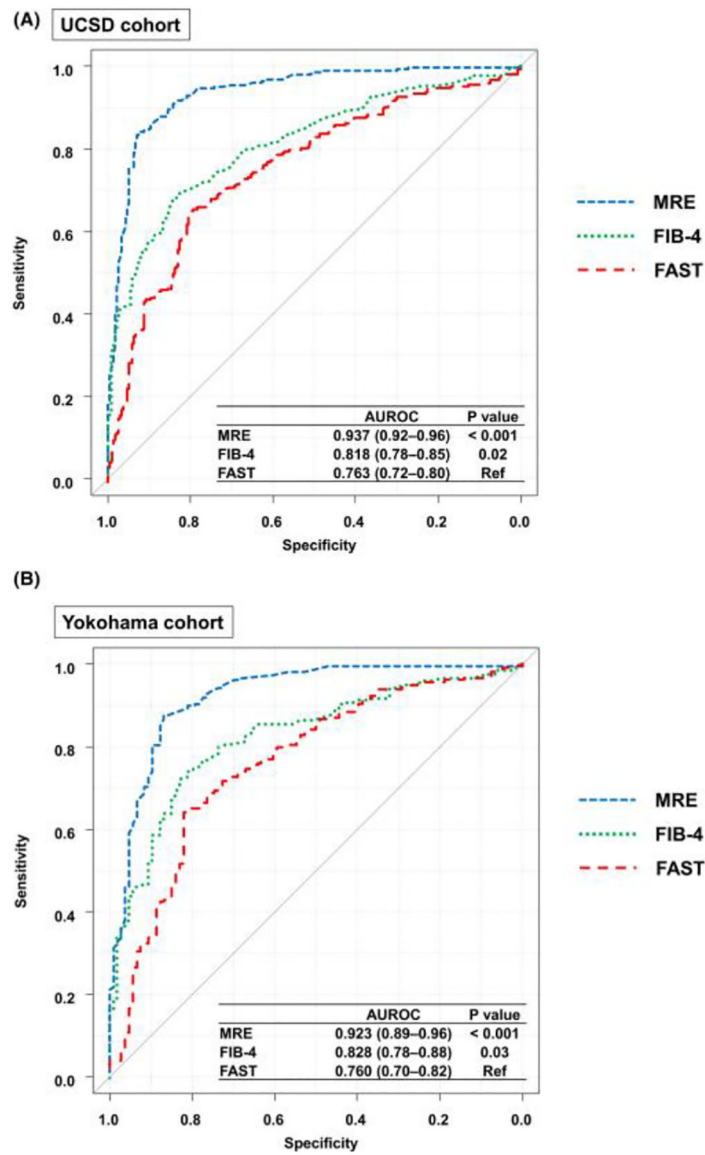
FIGURE 1.
AUROCs of MRE, FIB-4, and FAST for significant fibrosis. (A) AUROCs of MRE, FIB-4, and FAST for significant fibrosis in the UCSD cohort. (B) AUROCs of MRE, FIB-4, and FAST for significant fibrosis in the Yokohama cohort
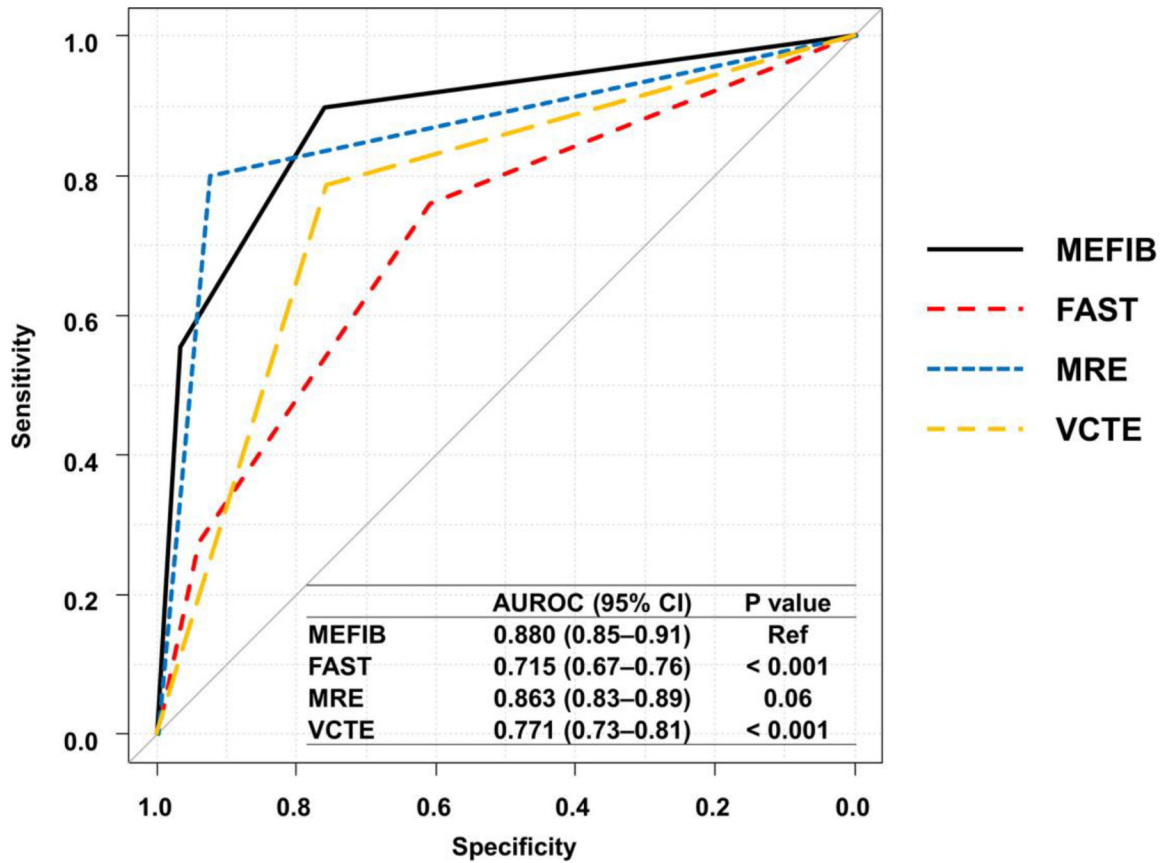
FIGURE 2.
AUROCs of MEFIB, FAST, MRE, and VCTE for fibrosis stages 2 and 3 (except patients
with fibrosis stage 4). Diagnostic accuracy of MEFIB, FAST, MRE, and VCTE for fibrosis
stages 2–3 (versus fibrosis stage 0–1) after excepting patients with fibrosis stage 4 was
investigated in the combined cohort. MEFIB and FAST were divided into three categories
using the rule-in criteria (MEFIB, MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6, FAST ≥ 0.67) and the
rule-out criteria (MEFIB, MRE < 3.3 kPa and FIB-4 < 1.6, FAST ≤ 0.35). MRE and VCTE
were dichotomized using thresholds of 3.34 and 7.8 kPa determined by the Youden index
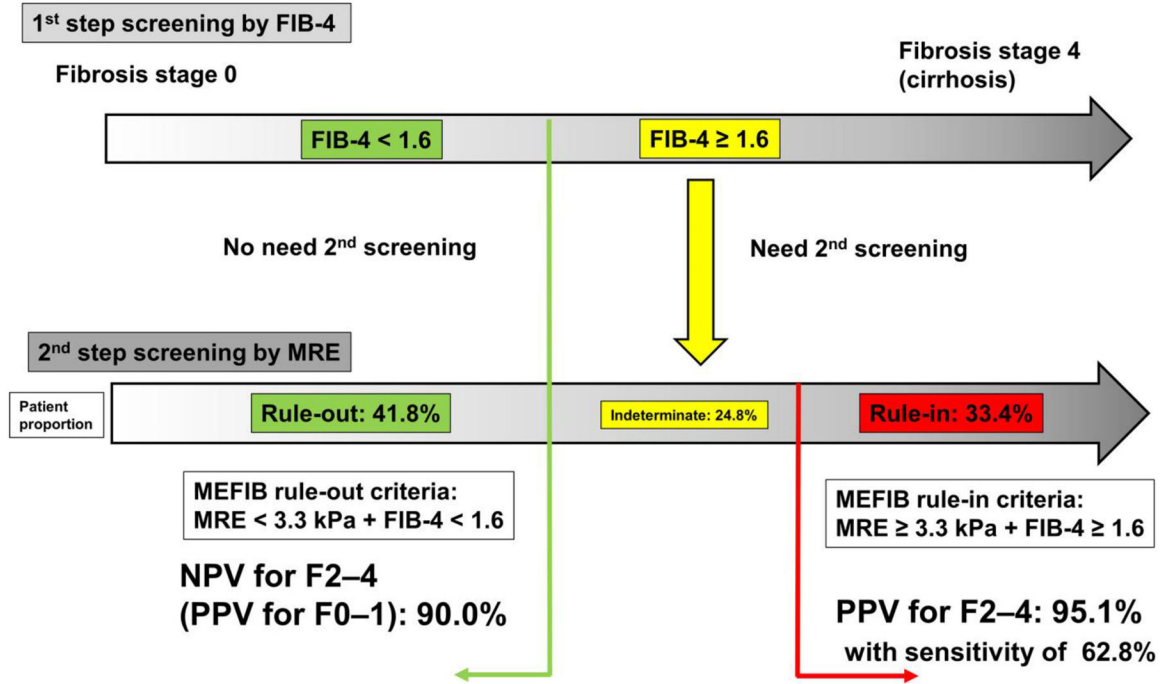
FIGURE 3.
A two-step screening strategy for significant fibrosis by MEFIB and the summary of the diagnostic ability of MEFIB. As a first screening step in a primary care center, FIB-4 could be applied for the first screening as a readily available blood-based test. Patients with FIB-4 < 1.6 need no further examination, and patients with FIB-4   1.6 need a further examination at a referral care center. As a second step, MRE could be applied. Patients with the MEFIB rule-in criteria (MRE   3.3 kPa and FIB-4   1.6) have a high PPV for significant fibrosis (95%) and are good candidates for clinical trials. Furthermore, patients with the MEFIB rule-out criteria (MRE < 3.3 kPa and FIB-4 < 1.6) have a high NPV (90%) for significant fibrosis (PPV for nonsignificant fibrosis), and these patients could be followed up by a repeat blood-based test (FIB-4)

TABLE 1

Patient characteristics

	UCSD (USA) cohort	Yokohama (Japan) cohort	p
	(n = 234)	(n = 314)	
Age (years)	54 (42–63)	61 (51–71)	<0.001
Gender, male (%)	103 (44.0%)	170 (31.4%)	0.02
BMI (kg/m^2)	31.5 (28–35)	27.4 (25–31)	<0.001
Diabetes mellitus, n (%)	95 (40.6%)	189 (60.2%)	<0.001
AST (IU/L)	35 (26–50)	40 (29–57)	0.01
ALT (IU/L)	48 (34–73)	46 (30–70)	0.1
Platelets (10^9/L)	230 (184–282)	202 (150–241)	<0.001
FIB-4	1.19 (0.8–1.8)	1.87 (1.1–3.2)	<0.001
FIB-4 < 1.6	167 (71.4%)	137 (43.6%)	<0.001
FIB-4 ≥ 1.6	67 (28.6%)	177 (56.4%)	
MRI findings			
Liver stiffness by MRE (kPa)	2.47 (2.1–3.3)	4.01 (2.6–5.4)	<0.001
MRE < 3.3 kPa	172 (73.5%)	118 (37.6%)	<0.001
MRE ≥ 3.3 kPa	62 (26.5%)	196 (62.4%)	
MEFIB index			
MEFIB rule-in (MRE ≥ 3.3 kPa + FIB-4 ≥ 1.6)	34 (14.5%)	149 (47.5%)	<0.001
MEFIB rule-out (MRE <3.3 kPa + FIB-4 < 1.6)	139 (59.4%)	90 (28.7%)	
MEFIB indeterminate	61 (26.1%)	75 (23.9%)	
FibroScan findings			
Liver stiffness by VCTE (kPa)	6.8 (5.0–10)	9.8 (6.3–15)	<0.001
CAP (dB/m)	320 (285–354)	291 (249–319)	<0.001
Probe type			<0.001
M probe	136 (58.1%)	276 (87.9%)	
XL probe	98 (41.9%)	38 (12.1%)	
FAST score	0.38 (0.23–0.57)	0.46 (0.26–0.64)	0.005
FAST ≥ 0.67	35 (15.0%)	65 (20.7%)	0.03
FAST ≤ 0.35	111 (47.4%)	116 (36.9%)	

	UCSD (USA) cohort	Yokohama (Japan) cohort	p
	(n = 234)	(n = 314)	
FAST 0.36–0.66 (indeterminate)	88 (37.6%)	133 (42.4%)	<0.001
Histological findings[a]			
Fibrosis stage			<0.001
0	87 (37.2%)	15 (4.8%)	
1	78 (33.3%)	91 (29.0%)	
2	28 (12.0%)	63 (20.1%)	
3	24 (10.2%)	100 (31.8%)	
4	17 (7.3%)	45 (14.3%)	
Steatosis grade			0.7
0	16 (6.8%)	15 (4.8%)	
1	109 (46.6%)	143 (45.5%)	
2	79 (33.8%)	111 (35.4%)	
3	30 (12.8%)	45 (14.3%)	
Lobular inflammation			0.004
0	17 (7.3%)	4 (1.3%)	
1	136 (58.1%)	185 (58.9%)	
2	74 (31.6%)	115 (36.6%)	
3	7 (3.0%)	10 (3.2%)	
Hepatocellular ballooning			<0.001
0	106 (45.3%)	83 (26.4%)	
1	107 (45.7%)	195 (62.1%)	
2	21 (9.0%)	36 (11.5%)	
NAS	4 (2–4)	4 (3–5)	0.007

Note: Data are shown as median (IQR). *p* value indicates difference between UCSD cohort and Yokohama cohort.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; NAS, NAFLD activity score.

[a]NASH Clinical Research Network Scoring System is used.

TABLE 2

Diagnostic ability of the MEFIB and FAST rule-in and rule-out criteria for significant fibrosis

	AUROC	p	Rule-in diagnostic ability for significant fibrosis				Indeterminate	Rule-out diagnostic ability for significant fibrosis			
			Patient number (%)	PPV	Sensitivity	Specificity	patient no. (%)	Patient no. (%)	NPV	Sensitivity	Specificity
UCSD cohort (n = 234)											
MEFIB	0.860 (0.81–0.91)	0.005	34 (14.5%)	91.2% (31/34)	44.9% (31/69)	98.2% (162/165)	61 (26.1%)	139 (59.4%)	92.8% (129/139)	85.5% (59/69)	78.2% (129/165)
FAST	0.757 (0.69–0.82)	Ref	35 (15.0%)	74.2% (26/35)	37.7% (26/69)	94.5% (156/165)	88 (37.6%)	111 (47.4%)	88.3% (98/111)	81.2% (56/69)	59.4% (98/165)
Yokohama cohort (n = 314)											
MEFIB	0.899 (0.86–0.94)	<0.001	149 (47.5%)	95.6% (143/149)	68.9% (143/208)	94.3% (100/106)	75 (23.9%)	90 (28.7%)	85.6% (77/90)	93.8% (195/208)	72.6% (77/106)
FAST	0.724 (0.67–0.78)	Ref	65 (20.7%)	89.2% (58/65)	27.9% (58/208)	93.4% (99/106)	133 (42.4%)	116 (36.9%)	57.8% (67/116)	76.4% (159/208)	63.2% (67/106)
Combined cohort (n = 548)											
MEFIB	0.899 (0.87–0.92)	<0.001	183 (33.4%)	95.1% (174/183)	62.8% (174/277)	96.7% (262/271)	136 (24.8%)	229 (41.8%)	90.0% (206/229)	91.7% (254/277)	76.0% (206/271)
FAST	0.729 (0.69–0.77)	Ref	100 (18.2%)	84.0% (84/100)	30.3% (84/277)	94.1% (255/271)	221 (40.3%)	227 (41.4%)	72.7% (165/227)	77.6% (215/277)	60.9% (165/271)

Note: The rule-in and rule-out criteria of MEFIB are defined as MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6 and MRE < 3.3 kPa and FIB-4 < 1.6, respectively. The rule-in and rule-out criteria of FAST are defined as FAST ≥ 0.67 and FAST ≤ 0.35, respectively. AUROCs of MEFIB and FAST are investigated using trichomotized data by the rule-in and out criteria.

TABLE 3

Diagnostic ability for fibrosis stages 2 and 3 (except fibrosis stage 4) in the combined cohort

| | AUROC (95% CI) | p | Rule-in diagnostic ability for fibrosis stages 2 and 3 | | |
			PPV	Sensitivity	Specificity
MEFIB	0.880 (0.85–0.91)	Ref	93.0% (119/128)	55.3% (119/215)	96.7% (262/271)
FAST	0.715 (0.67–0.76)	<0.001	78.7% (59/75)	27.4% (59/215)	94.1% (255/271)
MRE	0.863 (0.83–0.89)	0.06	89.6% (172/192)	80.0% (172/215)	92.6% (251/271)
VCTE	0.771 (0.73–0.81)	<0.001	71.9% (169/235)	75.6% (169/215)	75.6% (205/271)

Note: Patients with fibrosis stage 4 are excluded. The rule-in and rule-out criteria of MEFIB are defined. The rule-in and rule-out criteria of FAST are defined as FAST 0.67 and FAST 0.35, respectively. AUROCs of MEFIB and FAST are investigated using trichomotized data by the rule-in and out criteria. AUROCs of MRE and VCTE are investigated using dichotomized data by thresholds of 3.34 and 7.8 kPa determined by the Youden index, respectively.