Title

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Journal

Hepatology Research, 53(9)

ISSN

1386-6346

Authors

Imajo, Kento

Saigusa, Yusuke

Kobayashi, Takashi

et al.

Publication Date

2023-09-01

DOI

10.1111/hepr.13927

Peer reviewed

HHS Public Access

Author manuscript

Hepatol Res. Author manuscript; available in PMC 2024 January 17.

Published in final edited form as:

Hepatol Res. 2023 September ; 53(9): 844–856. doi:10.1111/hepr.13927.

M-PAST score is better than MAST score for the diagnosis of active fibrotic nonalcoholic steatohepatitis

Kento Imajo[1,2], **Yusuke Saigusa**[3], **Takashi Kobayashi**[1], **Koki Nagai**[1,2], **Shinya Nishida**[2], **Nobuyoshi Kawamura**[1,2], **Hiroyoshi Doi**[2], **Michihiro Iwaki**[1], **Asako Nogami**[1], **Yasushi Honda**[1], **Takaomi Kessoku**[1], **Yuji Ogawa**[4], **Hiroyuki Kirikoshi**[5], **Satoshi Yasuda**[6], **Hidenori Toyoda**[6], **Hideki Hayashi**[7], **Shigehiro Kokubu**[2], **Daisuke Utsunomiya**[8], **Hirokazu Takahashi**[9], **Shinichi Aishima**[10], **Beom Kyung Kim**[11], **Nobuharu Tamaki**[11,12], **Satoru Saito**[1], **Masato Yoneda**[1], **Rohit Loomba**[11], **Atsushi Nakajima**[1]

[1]Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[2]Department of Gastroenterology, Shin-yurigaoka General Hospital, Kawasaki, Japan

[3]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan

[4]Department of Gastroenterology, National Hospital Organization Yokohama Medical Center, Yokohama, Japan

[5]Department of Clinical Laboratory, Yokohama City University Hospital, Yokohama, Japan

[6]Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Gifu, Japan

[7]Department of Gastroenterology and Hepatology, Gifu Municipal Hospital, Gifu, Japan

[8]Department of Radiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

[9]Division of Metabolism and Endocrinology, Faculty of Medicine, Saga University, Saga, Japan

[10]Department of Pathology and Microbiology, Faculty of Medicine, Saga University, Saga, Japan

[11]NAFLD Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of California San Diego, La Jolla, California, USA

[12]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan

Correspondence: Atsushi Nakajima, Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. nakajima-tky@umin.ac.jp.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

ETHICS STATEMENTS

Approval of the research protocol by an institutional review board: The protocol for this study was approved by the Ethics Review Board in Yokohama City University Hospital.

Informed consent: Written informed consent was obtained from all patients.

Registry and the registration no. of the study/trial: UMIN Clinical Trials Registry (UMIN000012757).

Animal studies: N/A.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Abstract

Background: Clinical trials enroll patients with active fibrotic nonalcoholic steatohepatitis (NASH) (nonalcoholic fatty liver disease [NAFLD] activity score ≥ 4) and significant fibrosis ($F \geq 2$); however, screening failure rates are high following biopsy. We developed new scores to identify active fibrotic NASH using FibroScan and magnetic resonance imaging (MRI).

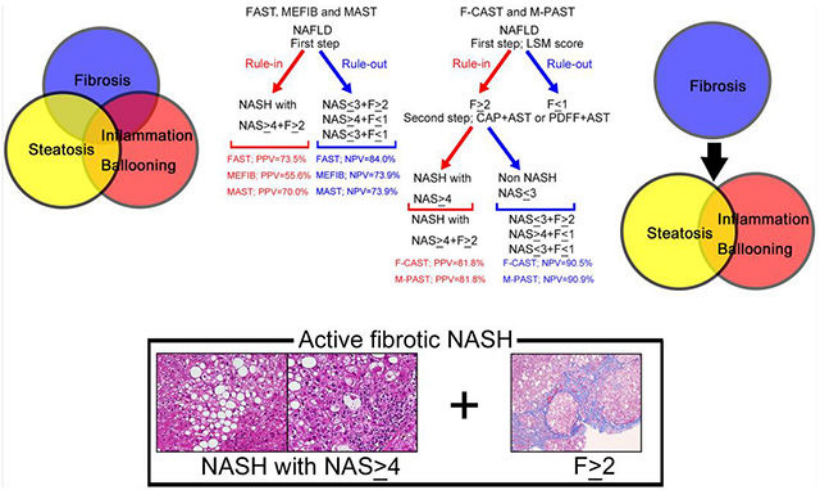
Methods: We undertook prospective primary ($n = 176$), retrospective validation ($n = 169$), and University of California San Diego (UCSD; $n = 234$) studies of liver biopsy-proven NAFLD. Liver stiffness measurement (LSM) using FibroScan or magnetic resonance elastography (MRE), controlled attenuation parameter (CAP), or proton density fat fraction (PDFF), and aspartate aminotransferase (AST) were combined to develop a two-step strategy–FibroScan-based LSM followed by CAP with AST (F-CAST) and MRE-based LSM followed by PDFF with AST (M-PAST)–and compared with FibroScan-AST (FAST) and MRI-AST (MAST) for diagnosing active fibrotic NASH. Each model was categorized using rule-in and rule-out criteria.

Results: Areas under receiver operating characteristic curves (AUROCs) of F-CAST (0.826) and M-PAST (0.832) were significantly higher than those of FAST (0.744, $p = 0.004$) and MAST (0.710, $p < 0.001$). Following the rule-in criteria, positive predictive values of F-CAST (81.8%) and M-PAST (81.8%) were higher than those of FAST (73.5%) and MAST (70.0%). Following the rule-out criteria, negative predictive values of F-CAST (90.5%) and M-PAST (90.9%) were higher than those of FAST (84.0%) and MAST (73.9%). In the validation and UCSD cohorts, AUROCs did not differ significantly between F-CAST and FAST, but M-PAST had a higher diagnostic performance than MAST.

Conclusions: The two-step strategy, especially M-PAST, showed reliability of rule-in/-out for active fibrotic NASH, with better predictive performance compared with MAST.

This study is registered with ClinicalTrials.gov (number, UMIN000012757).

Graphical Abstract



A two-step approach, especially M-PAST, has the potential to noninvasively and efficiently pick up active fibrotic nonalcoholic steatohepatitis (NASH) (NASH with nonalcoholic fatty liver

disease activity score ≥4 + fibrosis stage ≥2), which is prone to disease progression and is the inclusion criteria for clinical trials, and reduce the number of liver biopsies required.

Keywords

active fibrotic NASH; F-CAST; FAST; M-PAST; MAST

INTRODUCTION

Nonalcoholic fatty liver disease, one of the main causes of chronic liver disease, has been reported in more than 25% of the general population worldwide.[1] With the increase in the number of patients with diabetes and metabolic syndrome, the number of patients with NAFLD has increased and it has become an emerging major health issue.[2] Nonalcoholic steatohepatitis is a more progressive subtype of NAFLD, with 3%–12% prevalence.[3] Furthermore, NASH is predicted to become the leading etiology for liver transplantation.[4] Nonalcoholic steatohepatitis is characterized histologically by the presence of hepatic steatosis, hepatic inflammation, and ballooning degeneration of hepatocytes. This translates to increasing prevalence of end-stage liver disease, including cirrhosis and hepatocellular carcinoma, and cardiovascular disease, resulting in death.[5]

The NAS, developed by the NASH Clinical Research Network, is a histological scoring system that is frequently used in NASH clinical trials. The NAS is calculated by summing histological stages for steatosis (grades 0–3), hepatic inflammation (grades 0–3), and ballooning degeneration (grades 0–2). If the NAS is greater than or equal to grade 4 (NAS ≥ 4), it is generally considered as active NASH.[6] Although fibrosis stage is not a part of the NAS, the current criteria for enrollment in clinical trials for NASH require evidence of significant fibrosis at greater than or equal to stage 2 ($F \geq 2$), as well as NAS ≥ 4. The combination of these two criteria is important, because if fibrosis is advanced but the NAS is low (inactive status), the likelihood of further fibrosis development is low, and if the NAS is high but fibrosis is not progressing, the prognosis is not likely to worsen. On the other hand, active fibrotic NASH (NASH with NAS ≥ 4 + $F \geq 2$) is an advanced state of the disease and has a poorer prognosis than the aforementioned conditions. Consequently, active fibrotic NASH is often the entry criteria for aggressive treatment, especially in clinical studies.[7] Furthermore, the presence of hepatic inflammation and ballooning degeneration, as defined by NASH with NAS ≥ 4, could have important implications for identifying patients who may respond to anti-inflammatory therapies.[8] These interventions might not be worthwhile for patients with fibrosis who have no or minimal inflammatory injury. Histological responses to investigational medicines are reported to be more common in patients with elevated NAS.[8] Therefore, liver biopsy is often required for enrollment in NASH clinical trials. However, NASH clinical trials face high screening failure rates (>70%) due to the low prevalence of patients with NAFLD with significant fibrosis.[9] To mitigate these high screening failure rates in NASH clinical trials and reduce unnecessary liver biopsies, noninvasive indexes including the FAST score (combining LSM by VCTE, CAP, and AST),[10] MEFIB index (MRE and FIB-4),[11] and MAST score (combining MRE, MRI-PDFF, and AST)[12] have been proposed for detecting candidates for NASH clinical

trials by combining these noninvasive techniques. However, there is concern that these scoring systems might differ in diagnostic performance depending on race and cohort differences.[10,13]

This study aimed to establish a new algorithm to include or exclude patients with active fibrotic NASH (NASH with NAS ≥ 4 + $F \geq 2$) based on a two-step strategy, in which LSM measured by VCTE and MRE is followed by CAP and PDFF with AST measurements. Furthermore, we compared these with FAST and MAST in three well-characterized cohorts (two Japanese cohorts, and one from UCSD) of adults with liver biopsy-proven NAFLD.

METHODS

Study cohort

This prospective study included a well-characterized cohort with biopsy-proven NAFLD at Yokohama City University Hospital in Japan. The study protocol is presented in Table S1. This study included 176 consecutive patients with NAFLD who underwent liver biopsy with simultaneous assessment of VCTE with CAP and MRE with PDFF from August 2018 to March 2021. This study cohort included some of the patients analyzed in a previous report.[14] Furthermore, 169 consecutive patients with NAFLD who underwent liver biopsy with simultaneous assessment of MRE and PDFF (VCTE with CAP, $n = 122$) at Gifu Municipal Hospital, Ogaki Municipal Hospital, and Shin-yurigaoka General Hospital between March 2018 and April 2021 were also enrolled in the study as a validation cohort. As part of a non-Japanese cohort, 234 consecutive patients with NAFLD who underwent liver biopsy between August 2014 and March 2021 at UCSD were analyzed. This study cohort included some of the patients analyzed in a previous report.[15] The protocol for this study was approved by the Ethics Review Board in Yokohama City University Hospital, and written informed consent was obtained from all patients. This study was carried out in accordance with the ethical principles of the Declaration of Helsinki 2013 and registered in the UMIN Clinical Trials Registry (UMIN000012757).

Inclusion and exclusion criteria

The cohort included adults (age ≥18 years) with biopsy-proven NAFLD, including burned-out NASH. Vibration-controlled transient elastography with CAP and MRE with PDFF were carried out within 4 months from liver biopsy. The detailed exclusion criteria are presented in Supplementary information (section of Inclusion and exclusion criteria).

Histopathologic and immunohistochemical evaluations

All patients underwent liver biopsy. The central pathology was determined for the histological evaluation of the primary and validation cohorts; liver biopsy slides were sent to Saga University for central evaluation by a single experienced pathologist (SA) who specializes in liver histopathology and was blinded to the clinical data. In addition, experienced liver pathologists at UCSD assessed the biopsy specimens of the USCD cohort, while being blinded to the participants' clinical information. Patients were classified as having NASH or nonalcoholic fatty liver; specifically, patients with steatosis, hepatic inflammation, and ballooning were classified as having NASH, according to a previous

report.[16] Biopsy results were scored using the NASH CRN histologic scoring system.[6] Fibrosis was assessed in stages 0–4, with fibrosis stage 4 defined as cirrhosis. Hepatic inflammation plus ballooning grades were defined as indicators of disease activity in NAFLD, as previously reported.[17,18]

Vibration-controlled transient elastography and FibroScan-AST score

Liver stiffness measurement was assessed using VCTE (3.5-MHz M and/or 2.5-MHz XL probe, FibroScan; EchoSens) as previously described.[19] The VCTE methods are presented in detail in Supplementary information (section of Vibration controlled transient elastography (VCTE)). The median (IQR) intervals between liver biopsy and FibroScan assessment were 17 (−37 to 57), 38 (−42 to 85), and 13 (−41 to 19) days, in the primary, validation, and UCSD cohorts, respectively. The FAST score was calculated based on a previous study, and FAST values ≤0.35 and ≥0.67 were used as the rule-out and rule-in criteria, respectively.[10] The concept of FAST is to predict active fibrotic NASH by substituting VCTE-LSM for fibrosis, CAP for steatosis, and AST for HIB, as shown in Figure 1a.

Magnetic resonance imaging, MEFIB, and MAST

Magnetic resonance elastography and PDFF were undertaken using 3.0T imagers (GE Healthcare) as previously described.[20] Details are presented in Supplementary information (section of Magnetic resonance elastography (MRE) and proton density fat fraction (PDFF)). The MRE and PDFF images were interpreted as previously described.[21,22] The median (IQR) intervals between liver biopsy and MRI were 38 (−48 to 75), 32 (−21 to 72), and 27 (–11 to 70) days, in the primary, validation, and UCSD cohorts, respectively. Both MRE and FIB-4 were used to evaluate the MEFIB index, and the rule-out (MRE < 3.3 kPa and FIB-4 < 1.6) and rule-in (MRE ≥ 3.3 kPa and FIB-4 ≥ 1.6) criteria for MEFIB were used for stratification based on a previous study.[11] The MAST score was calculated based on a previous study, and MAST scores of <0.165 and ≥0.242 were used as the rule-out and rule-in criteria, respectively (Figure 1a).[12]

Statistical analysis

The parameters were selected based on the combination of LSM by VCTE or MRE (related to liver fibrosis), CAP or PDFF (related to liver steatosis), and AST (related to hepatic inflammation and hepatocyte ballooning). The lower cut-offs for the rule-out criteria based on sensitivity (≥0.90) and the higher cut-offs for the rule-in criteria based on specificity (≥0.90) were derived in the primary cohort. To directly compare the diagnostic accuracies, ROC curve analysis was undertaken for scores, and these parameters were categorized into three classes using rule-in and rule-out criteria, as previously reported.[15] Nested models were compared using the bootstrap test. The model was internally validated using 2000 bootstrap samples. Within each bootstrap iteration, we refitted the model and evaluated the performance in the bootstrap sample (apparent performance) and in the original data (test performance). Performance was assessed in terms of the AUROC. The categorical values were then used for ROC analysis. Statistical analyses were undertaken using JMP Pro 15 (SAS Institute Inc.). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Study cohort

A total of 176, 169, and 234 patients with biopsy-confirmed NAFLD were enrolled in the primary, validation, and UCSD cohorts, respectively. The baseline characteristics of the patients are presented in Table 1. In the primary cohort, MRI and VCTE assessments were attempted in all patients, but 6 (3.0%) MRI and 21 (10.7%) VCTE examinations failed because of iron overload/incorrect wave image and low success rate/unreliable measurements (Table S2).

Comparison of diagnostic accuracy for detecting steatosis and inflammation plus ballooning grade and fibrosis stage in patients with NAFLD between VCTE and MRI

The mean LSM values in the primary cohort for each fibrosis stage of VCTE and MRE, the mean values for each steatosis grade of CAP and PDFF, and the mean AST levels for each HIB grade are presented in Figures S1–S3 and Table S3. There was a significant negative correlation between PDFF and MRE-LSM but not between CAP and VCTE-LSM, in all cohorts (Figures S1d,S2d,S3d). Although there was no difference in diagnostic accuracy for detecting significant fibrosis (stage ≥2) between VCTE and MRE, PDFF had a higher diagnostic accuracy for detecting moderate steatosis (≥grade 2) than CAP (Table S4). The results of the validation and UCSD cohorts are presented in Tables S5 and S6.

In the two-step strategies, named F-CAST (FibroScan-CAP + AST) and M-PAST (MRE-PDFF + AST) scores, the optimal threshold was based on maximum likelihood estimation on two logistic regression models. The LSM was determined from the logistic model with stage ≥2 as the response variable and VCTE/MRE as the explanatory variable. The CAST and PAST scores were obtained from the logistic model with NAS ≥ 4 as the response variable, and CAP or PDFF for steatosis and AST for inflammation + ballooning grades as the explanatory variable, respectively. Then the optimal thresholds were selected from a combination of cut-offs of the predicted risks by the two models. The equation for the CAST score was as follows: CAST score = −7.01202 + CAP × 0.01809 + AST × 0.04854 (Figure 1b). The equation for the PAST score was as follows: PAST score = −4.38051 + PDFF × 0.29716 + AST × 0.03683 (Figure 1b).

Predictive performance of FAST, F-CAST, MEFIB, MAST, and M-PAST in noninvasively diagnosing significant fibrosis (*F* ≥ 2)

In terms of detecting significant fibrosis (*F* ≥ 2), the AUROC of MEFIB was the highest among the FAST, F-CAST, MEFIB, MAST, and M-PAST parameters in the primary cohort, with the categorized variables being 0.741 (0.656–0.811), 0.784 (0.708–0.844), 0.882 (0.820–0.927), 0.774 (0.713–0.826), and 0.792 (0.710–0.855), respectively (Table 2). In the validation cohort, the diagnostic accuracy of MEFIB (AUROC, 0.774 [95% CI, 0.701–0.833]) was not significantly different compared with those of the other scores (Table 2). In the UCSD cohort, MEFIB and M-PAST had the highest diagnostic performance compared with those of the other scores (Table 2).

Predictive performance of CAST and PAST in noninvasively diagnosing active NASH (NAS ≥ 4)

The AUROC for detecting NASH with NAS ≥ 4 was comparable in CAST (0.845) and PAST (0.885) in the primary cohort ($p = 0.132$) (Table S7). In the validation cohort, the AUROC of CAST and PAST was 0.771 and 0.806, respectively. In the UCSD cohort, PAST (0.777) had superior diagnostic performance to CAST (0.693) (Table S7).

Predictive performance of FAST, F-CAST, MEFIB, MAST, and M-PAST in noninvasively diagnosing active fibrotic NASH (NASH with NAS ≥ 4 + *F* ≥ 2)

Regarding detecting active fibrotic NASH, the AUROCs of F-CAST and M-PAST were higher than those of FAST, MEFIB, and MAST in the primary cohort, with the categorized AUROC variables being 0.744 (0.670–0.805), 0.826 (0.761–0.876), 0.669 (0.594–0.736), 0.710 (0.633–0.776), and 0.832 (0.768–0.882), for FAST, F-CAST, MEFIB, MAST, and M-PAST, respectively (Table 3). In the validation cohort, M-PAST had superior diagnostic performance to MEFIB and MAST, although there was no difference between FAST and F-CAST diagnoses (Table 3). In the UCSD cohort, M-PAST had the highest diagnostic performance compared with those of the other scores (Table 3). In addition, the AUROC of the various methods by BMI was calculated (Tables S8 and S9).

Positive predictive value and NPV of FAST, F-CAST, MEFIB, MAST, and M-PAST for detecting active fibrotic NASH as rule-in and rule-out criteria

The F-CAST, M-PAST, FAST, MEFIB, and MAST scores had PPVs of 81.8% (45/55), 81.8% (45/55), 73.5% (36/49), 55.6% (50/90), and 70.0% (42/60), respectively, using the rule-in criteria (Table 4). Using the rule-out criteria, F-CAST, M-PAST, FAST, MEFIB, and MAST had NPVs of 90.5% (57/63), 90.9% (60/66), 84.0% (47/56), 73.9% (51/69), and 73.9% (65/88), respectively.

Using the rule-out criteria in the validation cohort, F-CAST had a PPV of 82.5% (33/40), which was higher than that of FAST (71.1%, 27/38), MEFIB (63.8%, 37/58), MAST (73.3%, 33/45), and M-PAST (72.7%, 32/44). Using the rule-in criteria, M-PAST had the highest NPV (84.9%, 62/73) among FAST (81.8%, 36/44), F-CAST (81.4%, 35/43), MEFIB (71.9%, 41/57), and MAST (72.1%, 75/104).

Using the rule-out criteria in the UCSD cohort, M-PAST had the highest PPV (74.1%, 20/27) among FAST (48.6%, 17/35), F-CAST (50.0%, 29/58), MEFIB (61.8%, 21/34), and MAST (53.1%, 17/32). Using the rule-in criteria, MEFIB and M-PAST had the highest NPV (95.7%, 133/139%, and 95.8%, 158/165) among all scores (Table 4).

Characteristics of patients who were above the rule-in cut-off but not active fibrotic NASH (over-estimation) and those who were below the rule-out cut-off but active fibrotic NASH (under-estimation) in M-PAST are shown in the Table S10. Figure 2 shows the schematic view regarding the application of the rule-in and rule-out criteria by FAST, F-CAST, MEFIB, MAST, and M-PAST.

DISCUSSION

The present prospective study highlighted the usefulness of the novel two-step strategy, particularly M-PAST, which was defined as MRE-based LSM followed by PDFF with AST, compared with existing scores (FAST, MEFIB, and MAST), for identifying patients with active fibrotic NASH (NASH with NAS ≥ 4 + $F \geq 2$). It also validated this strategy in multicenter patient cohorts, including Japanese and UCSD cohorts.

The FAST score is a one-step strategy that combines LSM with VCTE, CAP, and AST, and has been reported to have high diagnostic accuracy for active fibrotic NASH.[10] The combination of these factors was found to improve the diagnostic accuracy compared with the use of each factor alone. Although the FAST score was validated in a Japanese cohort, its diagnostic performance was lower than that previously reported.[13] Cohort-associated differences might be relevant for this discrepancy.

Magnetic resonance elastography and MRI-PDFF are other noninvasive techniques for measuring LSM and hepatic fat accumulation.[23] Magnetic resonance elastography-LSM and MRI-PDFF have higher diagnostic accuracies for liver fibrosis and steatosis, respectively, than VCTE-LSM and CAP.[23,24] These results suggested that MRI might be more advantageous than VCTE as a method for the inclusion criteria in clinical trials.[25] In fact, the MEFIB score had a significantly higher diagnostic performance than those of other scores at detecting significant fibrosis ($F \geq 2$). However, it appeared to be unsuitable for the diagnosis of active fibrotic NASH. The most recently developed MRI-based complex equation, MAST, incorporates MRE, MRI-PDFF, and AST for diagnosing active fibrotic NASH.[12] However, the present study showed that using the existing MAST cut-offs for rule-in and rule-out, its diagnostic performance was poor in the primary and validation Japanese cohorts, as well as in the UCSD cohort–a cohort with a small number of patients with active fibrotic NASH. One of the reasons for this discrepancy might be the fact that MRE-LSM and MRI-PDFF, which are components of MAST, are inversely correlated (Figures 1,2,3d). Hence, a two-step strategy was devised to improve the diagnostic accuracy of the one-step strategy (Tables 2–4). It is possible that the effect of negative correlation between MRE and PDFF was reduced by dividing the data into two steps. The M-PAST model enabled classification of approximately 70% of the patients in the primary and validation cohorts, with PPVs ranging from 72.7% to 81.8% and NPVs ranging from 84.9% to 90.9%, and 94% of the patients in the UCSD cohort, with a PPV of 74.1% and an NPV of 91.7%. Thus, the M-PAST score can have a significant impact on clinical decision-making and can help in the identification of patients for clinical trials or initiation of drug therapy. Finally, F-CAST had a higher AUROC in active fibrotic NASH diagnosis than FAST in the primary cohort. In some cohorts, F-CAST could be more useful than FAST. Additionally, F-CAST was as accurate as M-PAST in the primary and validation cohorts. This is because, in the Japanese cohort, CAST and PAST had similar diagnostic performance in diagnosing NASH with NAS ≥ 4. This could be explained by the fact that the addition of AST to PDFF does not improve the diagnostic performance of NASH with NAS ≥ 4, but the addition of AST to CAP increases the diagnostic performance of NASH with NAS ≥ 4. In the clinical setting, if both are available, F-CAST should be preferred for cost-effectiveness and simplicity. However, according to a previous report, VCTE is difficult to carry out on NAFLD patients (5.4%)

with morbid obesity, Chilaiditi syndrome, and narrow intercostal spaces.[26] Additionally, noninvasive diagnostic methods have also been reported to reduce their diagnostic potential when BMI is high.[27] Indeed, in our study, the diagnostic performance of VCTE-based techniques (FAST and F-CAST) tended to be lower with higher BMI. However, MRI-based techniques (MEFIB, MAST, and M-PAST) did not seem to be affected by BMI. Hence, we believe that in cases where VCTE is not suitable, an alternative method is needed; we consider the MRI-based method to be suitable.

This study has some limitations. The mean time interval in the primary, validation, and UCSD cohorts between liver biopsy and VCTE/MRE was 17/38 days, 38/32 days, and 13/27 days, respectively, with some cases having intervals of approximately 4 months. We ensured that there were no drug interventions, changes in liver health, or weight changes of >5% during this period. Although fibrosis progression is reported to take 7 years,[28] NAS, including steatosis, inflammation, and ballooning grade, could change even within a short period of time, which might affect the interpretability of the data in these cohorts. Therefore, further validation studies should aim to minimize this interval. Finally, the superiority of the two-step strategy (M-PAST) over the one-step strategy (MAST) for the diagnosis of active fibrotic NASH was attributed in part to the negative correlation between MRE and PDFF. However, the negative correlation is weak and might not be sufficient to explain this alone. Further investigation is needed. In conclusion, M-PAST had higher diagnostic accuracy for patients with active fibrotic NASH who were at a high risk of poor prognosis and were candidates for clinical trials. Although the Japanese and UCSD cohorts had significantly different rates of active fibrotic NASH, the usefulness of the two-step strategy, especially the M-PAST score, was confirmed and validated at each site. Our results indicate that the M-PAST score could be applied to other patient cohorts, but further validation in other regions is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI (grant number JP 21K07987). Rohit Loomba received funding support from NCATS (5UL1TR001442), NIDDK (U01DK061734, U01DK130190, R01DK106419, R01DK121378, R01DK124318, and P30DK120515), NHLBI (P01HL147835), and NIAAA (U01AA029019).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations:

AST	aspartate aminotransferase
AUROC	area under the receiver operating characteristic curve
BMI	body mass index

CAP	controlled attenuation parameter
CI	confidence interval
FAST	FibroScan-AST
F-CAST	FibroScan with CAP + AST
FIB-4	Fibrosis-f
HIB	hepatic inflammation plus ballooning
IQR	interquartile range
LSM	liver stiffness measurement
MAST	MRE, MRI-PDFF, and AST
MEFIB	MRE and FIB-4
M-PAST	MRE with PDFF + AST
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	nonalcoholic steatohepatitis
NPV	negative predictive value
PDFF	proton density fat fraction
PPV	positive predictive value
UCSD	University of California San Diego
VCTE	vibration-controlled transient elastography

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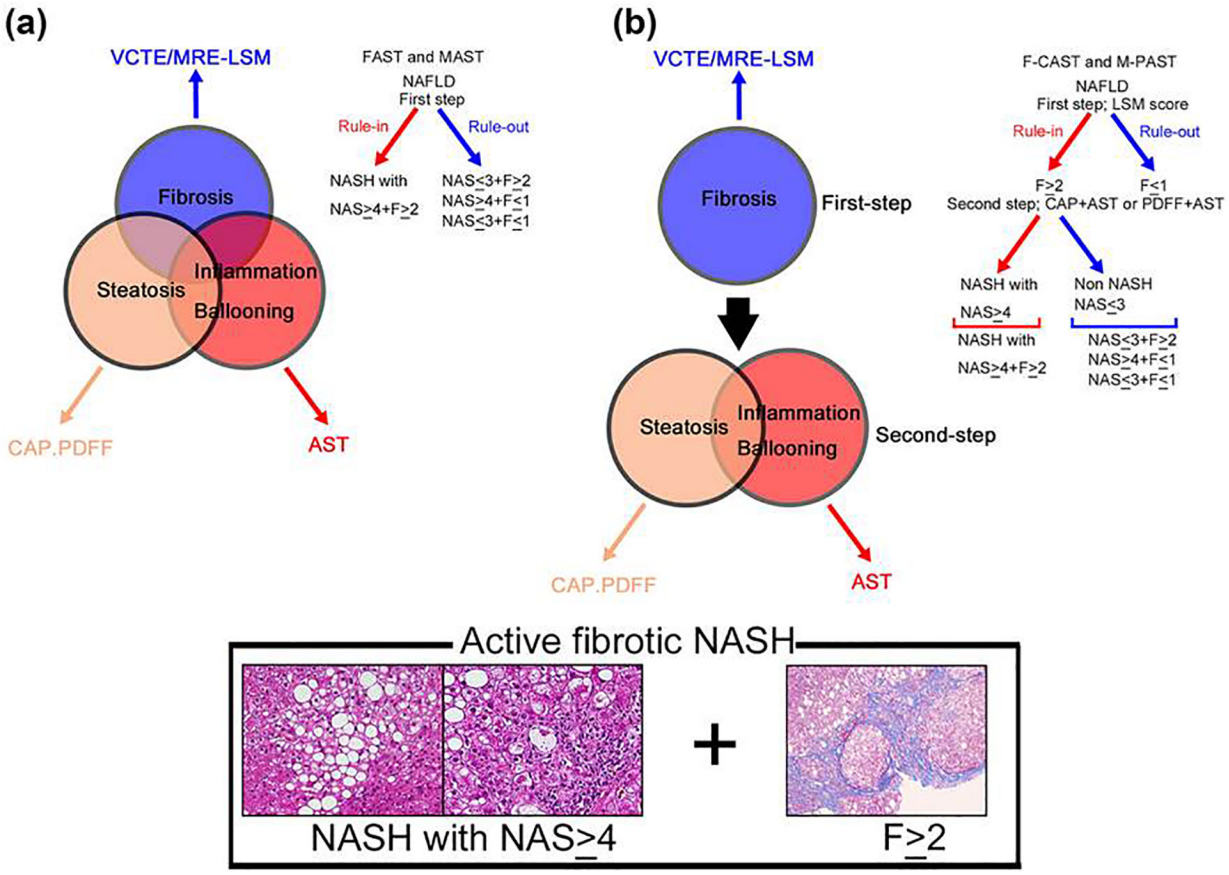

FIGURE 1.

Concept of one-step (a) (FibroScan + aspartate aminotransferase [AST] [FAST] and magnetic resonance imaging and AST [MAST]) and (b) two-step (FibroScan with controlled attenuation parameter [CAP] + AST [F-CAST] and magnetic resonance elastography [MRE] with proton density fat fraction [PDFF] + AST [M-PAST]) strategy for diagnosing active fibrotic nonalcoholic steatohepatitis (NASH). F-CAST and M-PAST were decomposed to vibration-controlled transient elastography (VCTE)/MRE-liver stiffness measurement (LSM) in the first step and CAP + AST or PDFF + AST in the second step. NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score.

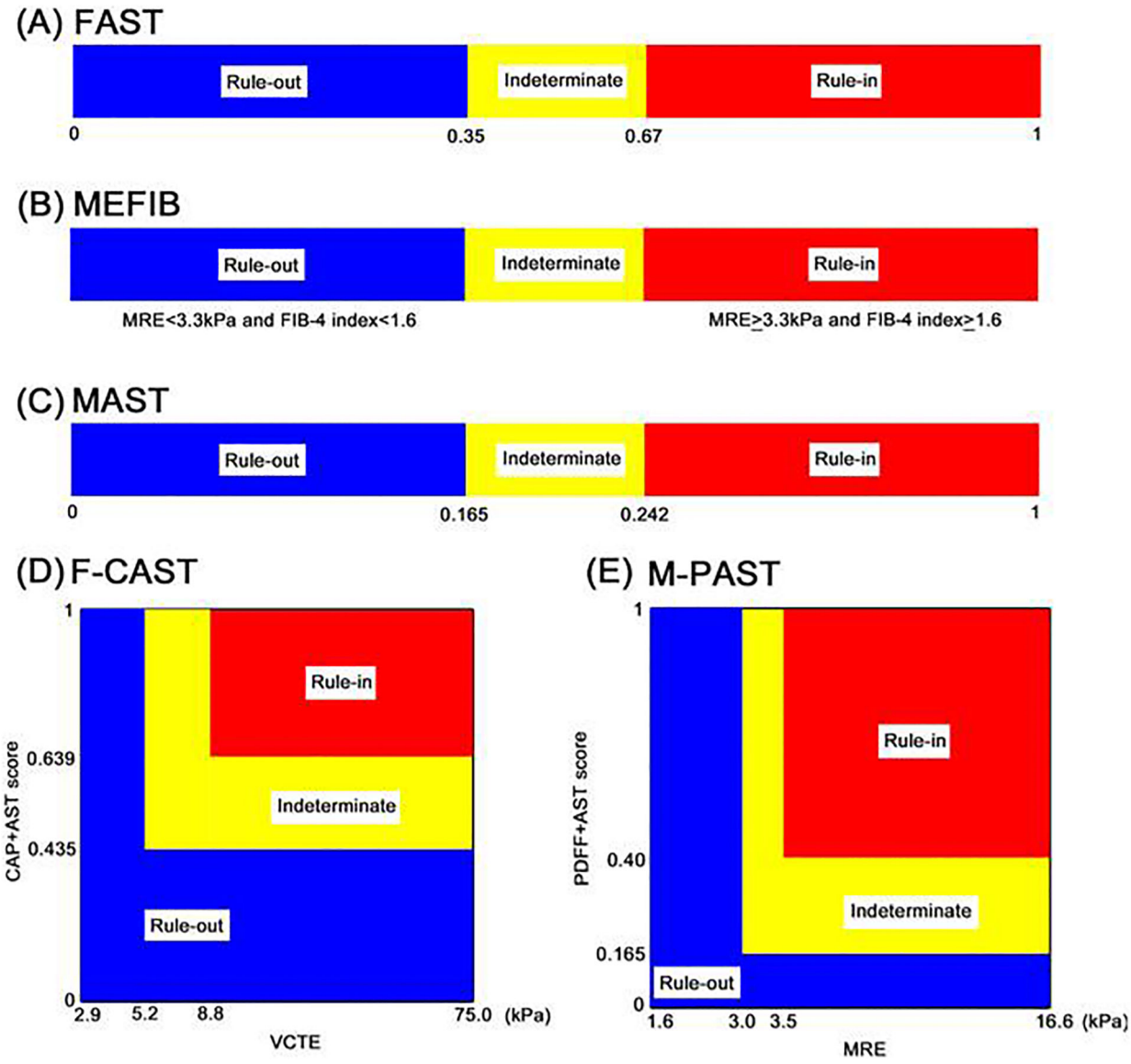

FIGURE 2.

Schematic of the application of the rule-in and rule-out criteria by (a) FibroScan + aspartate aminotransferase (AST) (FAST), (b) magnetic resonance elastography (MRE) and Fibrosis-4 (FIB-4) (MEFIB), (c) magnetic resonance imaging and AST (MAST), (d) FibroScan with controlled attenuation parameter [CAP] + AST (F-CAST), and (e) MRE with proton density fat fraction [PDFF] + AST (M-PAST). VCTE, vibration-controlled transient elastography.

TABLE 1.

Clinical, serological, and histological characteristics of all patients with nonalcoholic fatty liver disease (NAFLD) enrolled in this study.

	Japanese primary cohort	Japanese validation cohort	UCSD cohort
Number	176	169	234
Age (years)	60.9 ± 13.0	61.8 ± 15.5	52.4 ± 13.1
Gender, male : female	102:74	23:146	103:131
Race, Caucasian/Hispanic/Asian/others	0/0/176/0	0/0/176/0	103/66/48/17
Body mass index (kg/m^2)	28.4 ± 4.59	27.7 ± 4.86	31.7 ± 4.48
Plts (/10^4 μL)	19.1 ± 7.20	20.8 ± 6.35	23.8 ± 8.57
AST (IU/L)	47.4 ± 26.4	51.0 ± 28.1	43.3 ± 27.9
ALT (IU/L)	59.3 ± 46.6	64.3 ± 43.4	61.8 ± 43.7
γ-GTP (IU/L)	84.2 ± 88.2	75.1 ± 70.0	65.1 ± 66.9
Fasting blood glucose (mg/dL)	123.1 ± 33.7	113.5 ± 27.4	116.6 ± 44.5
Fasting insulin (μU/mL)	20.4 ± 13.9	16.7 ± 25.9	26.4 ± 23.0
HbA1c	6.53 ± 1.02	6.21 ± 0.87	6.16 ± 1.14
Diabetes mellitus, *n* (%)	115 (65.3)	61 (36.1)	95 (40.6)
Hypertension, *n* (%)	82 (46.6)	92 (54.4)	ND
Dyslipidemia, *n* (%)	132 (75.0)	85 (50.3)	ND
Steatosis grade, *n* (%)			
<5%	11 (6.3)	13 (7.7)	16 (6.8)
5%–33%	78 (44.3)	120 (71.0)	109 (46.6)
33%–66%	57 (32.4	33 (18.8)	79 (33.8)
>66%	30 (19.9)	3 (1.8)	30 (12.8)
Lobular inflammation, *n* (%)			
None	3 (1.7)	4 (2.4)	17 (7.3)
<2 foci per 200× field	93 (52.8	89 (52.7)	136 (58.1)
2–4 foci per 200× field	73 (41.5)	75 (44.4)	74 (31.6)
>4 foci per 200× field	7 (4.0)	1 (0.6)	7 (3.0)
Liver cell ballooning, *n* (%)			
None	55 (31.3)	35 (20.7)	106 (45.3)
Few balloon cells	92 (52.3)	75 (44.4)	107 (45.7)

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	Japanese primary cohort	Japanese validation cohort	UCSD cohort
Many balloon cells	29 (16.4)	59 (34.9)	21 (9.0)
NAFL/NASH *n* (%)	55/121	37/132	188/46
NAFLD activity score (NAS) *n* (%)			
0/1/2/3/4/5/6/7/8	2/9/31/33/30/38/21/10/2	1/7/19/44/49/38/10/1/0	6/15/38/58/63/33/4
NAS ≥ 4, *n* (%)	101 (57.4)	98 (58.0)	117 (50.0)
Fibrosis stage, *n* (%)			
None	8 (4.5)	9 (5.3)	87 (37.2)
Perisinusoidal or periportal	41 (23.3)	57 (33.7)	78 (33.3)
Perisinusoidal and portal/periportal	35 (19.9)	45 (26.6)	28 (12.0)
Bridging fibrosis	60 (34.1)	41 (24.3)	24 (10.3)
Cirrhosis	32 (18.2)	17 (10.0)	17 (7.3)
NASH with NAS ≥ 4 + *F* ≥ 2, *n* (%)	78 (44.3)	73 (43.2)	46 (19.7)
			Caucasian, 15 (14.6)
			Hispanic, 16 (24.2)
			Asian, 13 (27.1)
			Others, 2 (11.8)

Abbreviations: γ-GTP, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, hemoglobin A1c; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; ND, no data; Plts, platelets; UCSD, University of California San Diego.

TABLE 2.

Diagnostic accuracy of the FAST, F-CAST, MEFIB, MAST, and M-PAST scores in detecting significant fibrosis ($F \geq 2$) (three categories).

Models	AUROC (95% CI)	*p* value (FAST vs. F-CAST)	*p* value (FAST vs. MEFIB)	*p* value (FAST vs. MAST)	*p* value (FAST vs. M-PAST)	*p* value (F-CAST vs. MEFIB)	*p* value (F-CAST vs. MAST)	*p* value (F-CAST vs. M-PAST)	*p* value (MEFIB vs. MAST)	*p* value (MEFIB vs. M-PAST)	*p* value (MAST vs. M-PAST)
Primary cohort (n = 176)											
FAST	0.741 (0.656–0.811)	0.640	<0.001*	0.341	0.184	-	-	-	-	-	-
F-CAST	0.753 (0.677–0.811)	0.640	-	-	-	<0.001*	0.593	0.300	-	-	-
MEFIB	0.884 (0.822–0.929)	-	<0.001*	-	-	<0.001*	-	-	<0.001*	0.007*	-
MAST	0.774 (0.713–0.826)	-	-	0.341	-	-	0.593	-	<0.001*	-	0.585
M-PAST	0.792 (0.710–0.855)	-	-	-	0.184	-	-	0.300		0.007*	0.585
Validation cohort											
FAST (n = 122)	0.800 (0.704–0.871)	0.528	-	-	-	-	-	-	-	-	-
F-CAST (n = 122)	0.820 (0.734–0.883)	0.528	-	-	-	-	-	-	-	-	-
MEFIB (n = 169)	0.774 (0.701–0.833)	-	-	-	-	-	-	-	0.509	0.813	-
MAST (n = 169)	0.751 (0.689–0.804)	-	-	-	-	-	-	-	0.509	-	0.682
M-PAST (n = 169)	0.765 (0.697–0.821)	-	-	-	-	-	-	-	-	0.813	0.682
UCSD cohort (n = 234)											
FAST	0.757 (0.687–0.816)	0.930	0.005*	0.071	0.005*		-	-			-
F-CAST	0.754 (0.675–0.822)	0.930		-	-	0.005*	0.207	0.004*			-
MEFIB	0.860 (0.799–0.904)		0.005*			0.005*			<0.001*	0.900	
MAST	0.703 (0.638–0.761)	-		0.071	-		0.207	-	<0.001*		<0.001*
M-PAST	0.864 (0.801–0.909)	-		-	0.005*		-	0.004*		0.900	<0.001*

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Note: FibroScan + aspartate aminotransferase (AST) (FAST; ≥0.67/0.35–0.67/ ≤ 0.35), FibroScan with controlled attenuation parameter (CAP) + AST (F-CAST) (vibration-controlled transient elastography [VCTE] ≤ 5.2 kPa or CAST ≤ 0.435/Indeterminate/VCTE ≥ 8.8 kPa and CAST ≥ 0.639), magnetic resonance elastography (MRE) and Fibrosis-4 (FIB-4) (MEFIB) (MRE < 3.3 and FIB-4 < 1.6/Indeterminate/MRE ≥ 3.3 and FIB-4 ≥ 1.6), magnetic resonance imaging + AST (MAST score >0.242/0.165–0.242/<0.165), MRE with proton density fat fraction (PDFF) + AST (M-PAST) (MRE ≤ 3.0 kPa or PAST ≤ 0.165/Indeterminate/MRE ≥ 3.5 kPa and PAST ≥ 0.40).

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; UCSD, University of California San Diego.

*$p < 0.05$.

TABLE 3.

Diagnostic accuracy of the FAST, F-CAST, MEFIB, MAST, and M-PAST scores in detecting active fibrotic nonalcoholic steatohepatitis (NASH with nonalcoholic fatty liver disease activity score [NAS] ≥ 4 + $F \geq 2$) (three categories).

Models	AUROC (95% CI)	*p* value (FAST vs. F-CAST)	*p* value (FAST vs. MEFIB)	*p* value (FAST vs. MAST)	*p* value (FAST vs. M-PAST)	*p* value (F-CAST vs. MEFIB)	*p* value (F-CAST vs. MAST)	*p* value (F-CAST vs. M-PAST)	*p* value (MEFIB vs. MAST)	*p* value (MEFIB vs. M-PAST)	*p* value (MAST vs. M-PAST)
Primary cohort (n = 176)											
FAST	0.744 (0.670–0.805)	0.004*	0.054	0.268	0.008*	-	-	-	-	-	-
F-CAST	0.826 (0.761–0.876)	0.004*	-	-	-	<0.001*	0.003*	0.832	-	-	-
MEFIB	0.669 (0.594–0.736)	-	0.054	-	-	<0.001*	-	-	0.237	<0.001*	-
MAST	0.710 (0.633–0.776)	-	-	0.268	-	-	0.003*	-	0.237	-	<0.001*
M-PAST	0.832 (0.768–0.882)	-	-	-	0.008*	-	-	0.832	-	<0.001*	<0.001*
Validation cohort											
FAST (n = 122)	0.743 (0.649–0.818)	0.191	-	-	-	-	-	-	-	-	-
F-CAST (n = 122)	0.787 (0.700–0.854)	0.191	-	-	-	-	-	-	-	-	-
MEFIB (n = 169)	0.664 (0.581–0.737)	-	-	-	-	-	-	-	0.245	0.007*	-
MAST (n = 169)	0.704 (0.628–0.770)	-	-	-	-	-	-	-	0.245	-	0.049*
M-PAST (n = 169)	0.772 (0.698–0.833)	-	-	-	-	-	-	-	-	0.007*	0.049*
UCSD cohort (n = 234)											
FAST	0.743 (0.663–0.809)	0.774	0.053	0.231	0.002*	-	-	-	-	-	-
F-CAST	0.732 (0.638–0.810)	0.774	-	-	-	0.054	0.492	<0.001*	-	-	-
MEFIB	0.825 (0.752–0.880)	-	0.053	-	-	0.054	-	-	<0.001*	0.251	-
MAST	0.700 (0.619–0.770)	-	-	0.231	-	-	0.492	-	<0.001*	-	<0.001*
M-PAST	0.863 (0.791–0.913)	-	-	-	0.002*	-	-	<0.001*	-	0.251	<0.001*

Note: FibroScan + aspartate aminotransferase (AST) (FAST ≥ 0.67/0.35–0.67/ ≤ 0.35), FibroScan with controlled attenuation parameter (CAP) + AST (F-CAST) (vibration-controlled transient elastography [VCTE] ≤ 5.2 kPa or CAST ≤ 0.435/Indeterminate/VCTE ≥ 8.8 kPa and CAST ≥ 0.639), magnetic resonance elastography (MRE) and Fibrosis-4 (FIB-4) (MEFIB) (MRE < 3.3 and FIB-4 < 1.6/Indeterminate/MRE ≥ 3.3 and FIB-4 ≥ 1.6), magnetic resonance imaging + AST (MAST score > 0.242/0.165–0.242/ < 0.165), MRE with proton density fat fraction (PDFF) + AST (M-PAST) (MRE ≤ 3.0 kPa or PAST ≤ 0.165/Indeterminate/MRE ≥ 3.5 kPa and PAST ≥ 0.40).

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; UCSD, University of California San Diego.

*$p < 0.05$.

TABLE 4.

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of diagnostic models for detecting active fibrotic nonalcoholic steatohepatitis (NASH with nonalcoholic fatty liver disease activity score [NAS] > 4 + *F*> 2) (three categories).

	Rule-in diagnostic ability for NASH with NAS ≥ 4 + *F* ≥ 2					Indeterminate	Rule-out diagnostic ability for NASH with NAS ≥ 4 + *F* ≥ 2				
	Cut-off value	**Patient number**	**PPV (%)**	**Sensitivity (%)**	**Specificity (%)**	**Patient number (%)**	**Cut-off value**	**Patient number (%)**	**NPV**	**Sensitivity**	**Specificity**
Primary cohort (*n* = 176)											
FAST	0.67	49 (27.8%)	73.5 (36/49)	46.2 (36/78)	86.7 (85/98)	71 (40.3%)	0.35	56 (31.8%)	84.0 (47/56)	88.5 (69/78)	48.0 (47/98)
F-CAST	VCTE > 8.8 kPa and CAST > 0.48	55 (31.3%)	81.8 (45/55)	57.7 (45/78)	89.8 (89/98)	58 (33.0%)	VCTE < 5.2 kPa or CAST < 0.31	63 (35.8%)	90.5 (57/63)	92.3 (72/78)	58.2 (57/98)
MEFIB	MRE ≥ 3.3 and Fib4 ≥ 1.6	90 (38.5)	55.6 (50/90)	64.1 (50/78)	58/98 (59.2)	75 (32.1%)	MRE ≤ 3.3 and Fib4 ≤ 1.6	69 (29.5%)	73.9 (51/69)	76.9 (60/78)	52.0 (51/98)
MAST	0.242	60 (34.1%)	70.0 (42/60)	53.8 (42/78)	81.6 (80/98)	28 (15.9%)	0.165	88 (50.0%)	73.9 (65/88)	70.5 (55/78)	66.3 (65/98)
M-PAST	MRE > 3.5 kPa and PAST > 0.40	55 (31.3%)	81.8 (45/55)	57.7 (45/78)	89.8 (88/98)	55 (31.3%)	MRE < 3.0 kPa or PAST < 0.165	66 (37.5%)	90.9 (60/66)	92.3 (72/78)	61.2 (60/98)
Validation cohort											
FAST (*n* = 122)	0.67	38 (31.1%)	71.1 (27/38)	43.5 (27/62)	81.7 (49/60)	40 (32.8%)	0.35	44 (36.1%)	81.8 (36/44)	87.1 (54/62)	60.0 (36/60)
F-CAST (*n* = 122)	VCTE > 8.8 kPa and CAST > 0.48	40 (32.8%)	82.5 (33/40)	53.2 (33/62)	88.3 (53/60)	38 (31.1%)	VCTE < 5.2 kPa or CAST < 0.31	44 (36.1%)	81.4 (35/43)	87.1 (54/62)	58.3 (35/60)
MEFIB (*n* = 169)	MRE ≥ 3.3 and Fib4 ≥ 1.6	58 (24.8%)	63.8 (37/58)	50.7 (37/73)	78.1 (75/96)	54 (32.0%)	MRE ≤ 3.3 and Fib4 ≤ 1.6	57 (33.7%)	71.9 (41/57)	78.1 (57/73)	42.7 (41/96)
MAST (*n* = 169)	0.242	45 (26.6%)	73.3 (33/45)	45.2 (33/73)	87.5 (84/96)	20 (11.8%)	0.165	104 (61.5%)	72.1 (75/104)	60.3 (44/73)	78.1 (75/96)
M-PAST (*n* = 169)	MRE > 3.5 kPa and PAST > 0.40	44 (26.0%)	72.7 (32/44)	43.8 (32/73)	87.5 (84/96)	52 (30.8%)	MRE < 3.0 kPa or PAST < 0.165	73 (43.2%)	84.9 (62/73)	84.9 (62/73)	64.6 (62/96)
UCSD cohort (*n* = 234)											
FAST	0.67	35	48.6 (17/35)	37.0 (17/46)	90.4 (170/188)	88 (36.7%)	0.35	111	93.7 (104/111)	84.8 (39/46)	55.3 (104/188)
F-CAST	VCTE > 8.8 kPa and CAST > 0.48	58 (21.4%)	50.0 (29/58)	63.0 (29/46)	84.6 (159/188)	99 (42.3%)	VCTE < 5.2 kPa or CAST < 0.31	77 (32.9%)	89.6 (69/77)	82.6 (38/46)	36.7 (69/188)

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	Rule-in diagnostic ability for NASH with NAS ≥ 4 + *F* ≥ 2					Indeterminate	Rule-out diagnostic ability for NASH with NAS ≥ 4 + *F* ≥ 2				
	Cut-off value	**Patient number**	**PPV (%)**	**Sensitivity (%)**	**Specificity (%)**	**Patient number (%)**	**Cut-off value**	**Patient number (%)**	**NPV**	**Sensitivity**	**Specificity**
MEFIB	MRE ≥ 3.3 and Fib4 ≥ 1.6	34 (14.5%)	61.8 (21/34)	45.7 (21/46)	93.1 (175/188)	61 (26.1%)	MRE ≤ 3.3 and Fib4 ≤ 1.6	139 (59.4%)	95.7 (133/139)	87.0 (40/46)	70.7 (133/188)
MAST	0.242	32 (13.7%)	53.1 (17/32)	37.0 (17/46)	92.0 (173/188)	9 (3.8%)	0.165	193 (82.5%)	88.1 (170/193)	50.0 (23/46)	90.4 (170/188)
M-PAST	MRE > 3.5 kPa and PAST > 0.40	27 (11.5%)	74.1 (20/27)	43.5% (20/46)	96.3% (181/188)	42 (17.9%)	MRE < 3.0 kPa or PAST < 0.165	165 (70.5%)	95.8 (158/165)	84.5 (39/46)	84.0 (158/188)

Note: FibroScan + aspartate aminotransferase (AST) (FAST), FibroScan with controlled attenuation parameter (CAP) + AST (F-CAST) (F-CAST), magnetic resonance elastography (MRE) and Fibrosis-4 (FIB-4) (MEFIB), magnetic resonance imaging + AST (MAST), and MRE with proton density fat fraction (PDFF) + AST (M-PAST) were categorized into three classes using the rule-in, indeterminate, and rule-out criteria.