Supplementary file 1

The Fibrosis 4 (FIB-4) index, calculated by combining age, platelet count and serum aminotransferases (serum aspartate transaminase [AST] and alanine transaminase [ALT] levels), has moderate accuracy for assessing advanced fibrosis in NAFLD patients within the 35–65 year range, featuring an area under the receiver operating characteristic (AUROC) of 0.77–0.84, which is similar to the NAFLD fibrosis score (NFS) (AUROC 0.81–0.86).[1]

The NAFLD fibrosis score (NFS) includes age, impaired fasting glycemia/diabetes, body mass index (BMI), platelet count, serum albumin, and AST/ALT ratio in its formula. The NFS had an AUROC of 0.82 for identifying advanced liver fibrosis[1] and was able to significantly predict liver-related complications, liver transplantation and mortality.[2]

The AST-to-platelet ratio index (APRI) is a simple first-line screening test for assessing liver fibrosis, to identify patients who require further investigation, despite having a relatively low accuracy (area under the receiver operating characteristics [AUROC] of 0.67) for assessing advanced liver fibrosis.[3]

The BARD score is an integer points-based score (including BMI, AST-to-ALT ratio, and presence of diabetes) that has moderate accuracy for predicting advanced fibrosis (AUROC 0.81). The BARD score has relatively low accuracy when used in isolation but its diagnostic performance can be improved by including additional parameters in the panel.[4] The BARDI is an enhanced version of the BARD score that adds international normalized ratio (INR) to the panel. BARDI has better accuracy (AUROC 0.88) than the BARD score without adding substantial cost, maintaining the simplicity and accessibility that made BARD a good screening test.[5]

A nomogram with an improved staging of fibrotic NASH by combining the MACK-3[6] with other independent predictors of fibrotic NASH (MACK-3, platelet count and presence of metabolic syndrome) was recently developed.[7] When testing this novel nomogram against the original MACK-3, this study showed that the nomogram had higher accuracy diagnosis fibrotic NASH than MACK-3 alone (AUROC O.79–0.81 *vs.* 0.75 for MACK-3), while also having an improved positive predictive value (PPV).

The Hepamet score is capable of accurately discriminating advanced fibrosis with an AUROC of 0.85, while combining common clinical/biochemical parameters, such as sex, age, HOMA-insulin resistance score, presence of diabetes, serum AST, albumin and platelet count. In addition, a multicenter cohort of NAFLD patients (*n* =2452) showed that compared to NFS and FIB-4, the Hepamet score improved the diagnostic accuracy, especially amongst patients aged >65 years.[8]

The Enhanced Liver Fibrosis (ELF) test is a very accurate predictor of advanced liver fibrosis in both children and adolescents, that includes measurement of circulating HA, N-terminal Propeptide of type III Pro-collagen (PIIINP) and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) levels, with AUROCs of 0.92, 0.98, 0.99 for F1, F2, and F3, respectively, for predicting advanced fibrosis.[9] ELF test has a good positive predictive value for detecting significant/advancing fibrosis, which is useful since most of the studies on NAFLD/NASH have been conducted with cohorts where patient age ranges between 25 and 65 years old.[10]

The ADAPT algorithm is a recently proposed panel that combines age, presence of diabetes, serum PRO-C3 and platelet count.[11] ADAPT was developed in an Australian cohort of 150 biopsy-proven NAFLD patients and then validated in an international cohort of 281 biopsy-proven NAFLD patients. The accuracy of this algorithm is satisfactory (0.86 AUROC for derivation cohort and 0.87 AUROC for validation cohort), and it can stratify cirrhosis.[11]

The FibroTest is composed of serum α2-macroglobulin, apolipoprotein-A, haptoglobin, γ-glutamyl-transferase (GGT), and total bilirubin levels. With AUROC values of 0.92 and 0.81 (F3, F4) in patients with high serum ALT or GGT levels, it has better predictive ability than BARD and FIB-4 scores in patients with NAFLD.[12] The use of either imaging techniques, like vibration-controlled transient elastography (VCTE)[13] and 2-dimensional shear wave elastography (2D-SWE), or panels such as the Hepamet score, (that have good predictive values for less advanced stages of fibrosis), can be a useful addition to the FibroTest.[8] The FibroMeter-VCTE algorithm (combining FibroMeter and Fibroscan) is an example of combining serum biomarkers with imaging techniques to achieve better accuracy for predicting liver fibrosis (AUROC 0.968).[14]

Hepascore (combining age, sex, and circulating bilirubin, GGT, hyaluronic acid (HA) and α-2 macroglobulin levels) has similar diagnostic potential for advanced fibrosis as other panels (AUROC 0.814 [for F3–F4 stages] and 0.907 [for F4]).[15]

Our group has recently developed a new machine-learning algorithm through the least absolute shrinkage and selection operator regression (LASSO) analysis of 553 Chinese adult individuals with biopsy-proven NAFLD (data not published). In this ongoing study, we identified 5 significant predictors of liver fibrosis using the LASSO regression analysis (BMI and circulating levels of procollagen II, type-IV collagen, AST and albumin/globulin ratio) to construct a machine learning algorithm that had good accuracy for predicting advanced fibrosis (with AUROC of 0.902 in the derivation cohort, and 0.893 in the validation cohort).

The 2D-MRE uses a modified phase-contrast technology to represent the propagation of the shear wave in the liver. It can appraise the entirety of the liver, regardless of the patient's body weight, and has standardized mechanical parameters for shear stiffness. Analysis of the patient's data indicates that 2D-MRE has excellent diagnostic accuracy (AUROC 0.90) for identifying

advanced fibrosis and by adding hardware capable of generating mechanical waves and software to collect and process these waves, most of the available MR scanners should be able to perform this test.[16, 17]

The 2D-SWE relies both on the radiation force induced in tissues by focused ultrasonic beams and on a high-frequency frame rate ultrasonography imaging sequence displaying the propagation of shear waves in real-time and can also be adapted to use commercially available ultrasound machines while having higher diagnostic capabilities (AUROCs for F2, F3, and F4 stages are 0.89, 0.91, and 0.97, respectively).[13, 16]

The FibroScan® utilizes VCTE by the emission of a mechanical shear wave from the tip of the detection probe. The propagation speed is used to calculate liver stiffness measurement (LSM) while simultaneously, calculating by ultrasound, the Controlled Attenuation Parameter (CAP) measuring the extent of hepatic fat content. The AUCs using FibroScan M and XL probes for detecting advanced fibrosis ranged from (0.75–0.98) and (0.84–0.90), respectively.[13, 16]

The acoustic radiation force impulse imaging (ARFI) relies on the excitation of liver tissue using short-duration acoustic pulses that propagate shear waves, and it can be installed on most of the commercially available ultrasound machines, showing an AUROC of 0.77 for significant fibrosis, and AUROCs of 0.84 and 0.84 for advanced fibrosis and cirrhosis, respectively.[18, 19]

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