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| Table 1 – Noninvasive tests for diagnosing advanced liver fibrosis in NAFLD. |
| Tests/Markers | Description | Feasibility | Diagnostic accuracy | Limitations | Validation set |
| Serum biomarker panels |
| Fibrometer VCTE | Serum + imaging panel: combining the results of TE with biomarkers (i.e., platelet count, α2-macroglobulin, urea, prothrombin time, AST, ALT, and γ-glutamyl transferase) | Moderate, since this study was carried out only in a specialist clinic without a cost-benefit analysis, it's unknown if less specialized clinics could screen a large volume of patients using this method | AUROC 0.968 (F3–F4 stage) | Small sample size (only Turkish participants), TE was not compared with other imaging tests | No |
| FibroTest-FibroSURE  | α2-macroglobulin, apolipoprotein-A, haptoglobin, total bilirubin, and γ-glutamyl transferase | Moderate feasibility; high prediction value in different types of chronic liver disease; accurate even in the presence of obesity | AUROC 0.88 (F3–F4 stage; overall population) AUROC 0.92 (F3–F4 stage; non-alcoholic + liver damage patient groups)Group I 0.92Group II 0.81 | Lower diagnostic accuracy for less advanced stages of fibrosis | Yes |
| BARDI score | BMI, AST/ALT ratio, and diabetes (QUICKI score or HOMA score), INR | High, due to routine parameters | AUROC 0.88 (F3–F4 stage) | Referral bias, incomplete data for some patients, including alcohol consumption | Yes |
| NAFLD fibrosis score | Age, hyperglycemia, BMI, platelet count, albumin, and AST/ALT ratio | High, due to routine parameters | AUROC (F3–F4 stage) estimation group 0.88 validation group 0.82 | Referral bias, sampling error, 90% of the population was Caucasian, results may vary according to pathologist expertise | Yes |
| ELF test | Age, hyaluronic acid, PIIINP, and TIMP-1 | Moderate | AUROCs (in pediatric patients) for predicting fibrosis(F1) 0.92 (F2) 0.98 (F3) 0.99  | Need further validation, expensive, not widely available in countries outside the UK, direct fibrosis markers are not liver-specific meaning that results become unreliable should the patient have fibrosis on other organs | Yes |
| ADAPT algorithm | Age, presence of diabetes, PRO-C3, and platelet count | Moderate, PRO-C3 not easily available in China or Asia | AUROC (F3–F4 stage) Derivation group 0.86 Validation group 0.87 | Referral bias, need investigation of the patient clinical outcome on longitudinal validation | Yes |
| Hepamet score | Sex, age, HOMA score, presence of diabetes, AST, albumin, and platelet count | High, due to routine parameters | AUROC (F0–F2 vs. F3–F4)Estimation set 0.850Validation set 0.844 | Its diagnostic capability among patients in non-specialized setting needs to be verified | Yes |
| Hepascore | Age, sex, bilirubin, γ-glutamytransferase, hyaluronic acid, and α2-macroglobulin | Moderate, since α2-macroglobulin is not performed regularly | AUROC 0.814 (F3-F4 stages) 0.907 (F4 stage) | Sampling error, referral bias, more accurate diagnosing fibrosis in Hepatitis and ALD than NAFLD | No |
| BARD score | BMI, AST/ALT ratio, and diabetes (QUICKI score or HOMA score) | High, due to routine parameters | AUROC 0.81 (F3-F4 stages) | Referral bias, incomplete data for some patients, including plasma insulin or glucose levels | Yes |
| Novel nomogram combining MACK-3 | Metabolic syndrome, platelet count, and MACK-3 | Moderate, since it requires to obtain data through MACK-3 first | AUROC (F≥2 stages)Estimation set 0.79Validation set 0.81 | Sub-optimal PPV, the two hepatology centers enrolled patients with different baseline characteristics, all patients are of Asian ethnicity | Yes |
| Fib-4 index | Age, platelet count, and the AST/ALT ratio | High, due to using standard parameters | AUROCs (F3–F4 stages) ≤35 years 0.60 36–45 years 0.79 46–55 years 0.77 56–64 years 0.84 ≥65 years 0.81 | Poor diagnostic performance for patients under 35 years, low specificity for patients over 65 years | No |
| APRI index | AST and platelet count | High, due to using standard parameters | AUROC 0.67 (F3-F4 stages) | Low accuracy regarding its diagnostic ability in NAFLD  | No |
| Imaging techniques |
| MRE | Magnetic resonance (MR) elastography | Can be installed on a normal MRI machine, examines the liver in its entirety; MRE-PDFF can assess fibrosis and steatosis simultaneously | AUROC 0.9 (F3-F4 stages) | Cost, MRI machine required, time-consuming | No |
| 2D-SWE | 2D shear wave elastography | Can be installed in normal ultrasound machine, allows simultaneous sonographic liver imaging | AUROCs 0.89 for F2 0.91 for F3 0.97 for F4 | Confounding factors such as severe obesity and ascites were not considered, selective reporting bias, inability to identify optimal thresholds, time and cost were disregarded, 2-hour fasting necessary | No |
| FibroScan (TE)  | Ultrasound transient elastography | Good reproducibility, user-friendly, easy to learn, quick | AUROC (F2-F4 stages) M-Probe 0.88 XL-Probe 0.85 | Requires specific device, probing area is fixed, lacks distinction in early stages of fibrosis, high likelihood of false positives if non-NAFLD liver damage present, 2-hour fasting necessary | No |
| pSWE (ARFI) | Point shear wave elastography (pSWE), acoustic, and radiation force impulse imaging (ARFI) | Can be installed in normal ultrasound machine, allows simultaneous sonographic liver imaging | AUROCs 0.77 for F2 0.84 for F3 0.84 for F4 | 2-hour fasting necessary, unrefined quality control criteria | No |
| Genomic markers |
| Methylated PPARγ | Detection of DNA methylation at the PPARγ promoter within the pool of cell-free DNA of human plasma | Moderate, due to high cost and high technological complexity | AUROC 0.91 (F3–F4 stages) | Small sample size, differences between ALD and NAFLD, and NAFL and NASH not emphasized | No |
| miR-122 | Categorization of circulating serum microRNAs in NAFLD patients | Inexpensive, moderate reproducibility due to complex technology | AUROC 0.61 (F2–F3 stages) | Low diagnostic accuracy compared to current biomarkers | No |
| ALD: Alcoholic liver disease; ALT: Alanine transaminase; AST: Aspartate transaminase; AUROC: area under the receiver operating curve; BMI: Body mass index; HOMA: Homeostatic model assessment; INR: International normalized ratio; MRE-PDFF: Magnetic resonance based elastography-computing proton-density fat traction; MRI: Magnetic resonance imaging; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PPV: Positive predictive value; PIIINP: N-terminal propeptide of type III pro-collagen; Pro-C3: Pro-collagen type III; PPARγ: peroxisome proliferator-activated receptor gamma; QUICKI: Quantitative insulin sensitivity check index; TE: Transient elastography; TIMP-1: Tissue inhibitor of matrix metalloproteinase 1; US: Ultrasound; miR: MicroRNA. |