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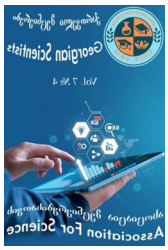

A Narrative Review of the Diagnostic Performance of Non-Invasive Scores for Predicting Fibrosis in MAFLD

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ABSTRACT

Background & aim: The burden of Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) is increasing, with an estimated prevalence of 32.4% globally. Although most patients present with simple steatosis, some progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Non-invasive scores offer a promising alternative to liver biopsy for fibrosis staging. This narrative review aims to compare the diagnostic performance of non-invasive scores for in detecting fibrosis in patients with MAFLD, with a focus on identifying the most accurate and reliable score.

Methods: This narrative review included studies with histologically confirmed fibrosis staging. The primary outcome was the overall diagnostic accuracy of each score in predicting significant fibrosis (F2-F4) and advanced fibrosis (F3-F4). Secondary outcomes included sensitivity, specificity, and positive and negative predictive values.

Results & Conclusion: Our analysis included a total of 11 studies with 5761 patients. The overall diagnostic performance for predicting advanced fibrosis was highest for Magnetic Resonance Elastography (MRE), followed by Transient Elastography (VCTE). In predicting significant fibrosis, Hepamet Fibrosis Score (HFS) demonstrated the highest performance. Significant variation was observed across studies, which was partially explained by differences in the prevalence of advanced fibrosis and the specific thresholds utilized for each score.

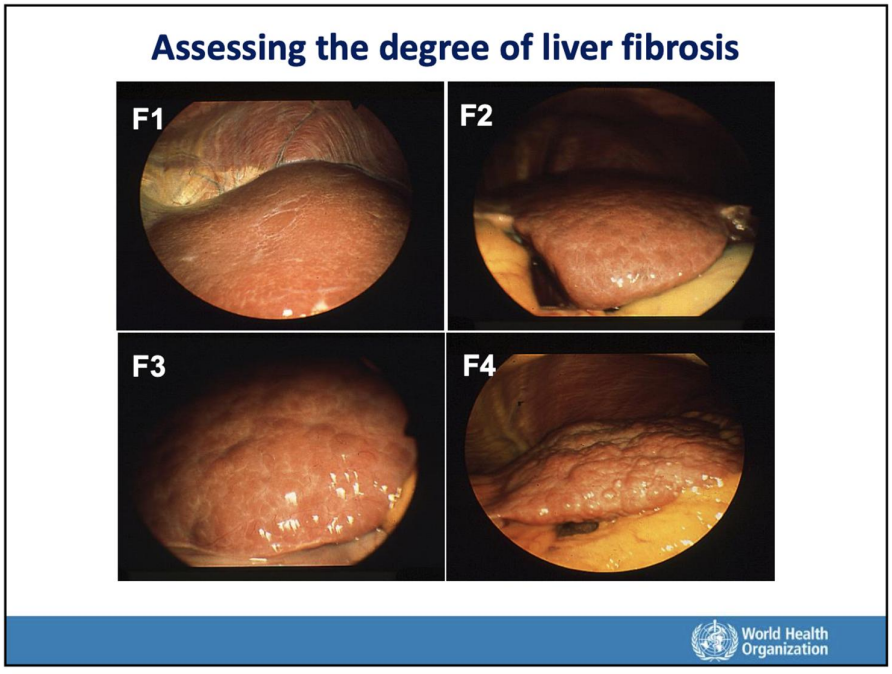
INTRODUCTION

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) has become the most common chronic liver disease worldwide, with an estimated 32.4% globally affected (1). MAFLD is linked to obesity, type 2 diabetes and other metabolic risk abnormalities (2). The spectrum of the disease varies from simple steatosis to liver fibrosis and cirrhosis and hepatocellular carcinoma (3). The severity of liver fibrosis stands out as the most influential

predictor of clinical outcomes. In fact, therapies targeting fibrosis have become one of the leading focus of research in MAFLD. (4). The current standard for diagnosing and staging liver fibrosis in MAFLD is a liver biopsy (5). This invasive procedure, where a small piece of liver tissue is removed with a needle for a pathologist to examine, carries a small but real risk of complications, including pain and bleeding. Additionally, a biopsy only samples a very small portion of the liver (about 1/50,000th of the organ), which may not accurately represent the overall state of fibrosis (6). It's an expensive procedure and requires specialized medical staff and facilities and the interpretation of the biopsy can vary between different pathologists (6).

These limitations are the primary reason why researchers are focused on developing non-invasive methods to assess liver fibrosis in MAFLD. the primary objective of this narrative review is to compare the diagnostic accuracy of the most commonly used non-invasive tests, for predicting different stages of fibrosis (significant fibrosis [≥F2], advanced fibrosis [≥F3], and cirrhosis [F4]) (Figure 1) in patients with metabolic dysfunction-associated fatty liver disease (MAFLD) (7). The diagnostic performance of noninvasive tests is commonly assessed using the Area Under the Receiver Operating Characteristic (AUROC) curve, which measures the overall accuracy of a test in distinguishing between diseased and non-diseased individuals. An AUROC value of 1.0 represents a perfect test, while a value of 0.5 indicates no diagnostic value beyond chance. In addition to AUROC, a test's ability to correctly identify patients with fibrosis (sensitivity) and those without it (specificity) are also critical measures of performance. This work provides a clear, evidence-based roadmap for clinicians to navigate the available tests and implement a rational, diagnostic strategy in clinical practice.

Figure 1. the cirrhotic liver in a laparoscopic view



NONINVASIVE SERUM BIOMARKERS FOR MAFLD

Noninvasive serum biomarkers for fibrosis were initially developed to use as a diagnostic assessment tool to detect patients who have advanced liver fibrosis and/or cirrhosis, offering an alternative and potential replacement to liver biopsy.

A number of noninvasive serum biomarkers have been developed over the last 20 years and we now have tests, such as fibrosis-4 (FIB-4) index (8), NAFLD fibrosis score (NFS) (9) and AST to Platelet Ratio Index (APRI) (10) and A modified APRI (m-APRI) (11), enhanced liver fibrosis (ELF) test (12), Hepamet fibrosis score (HFS) (13), FibroTest (14) and BARD score (15). (Table 1) These relatively common tests are widely available for use in both primary and secondary care and offer a variable degree of accuracy and reliability.

Table 1. Scores and formulas used in liver fibrosis staging

SCORE	FORMULA
FIB-4	AST (IU/L) × age (years)/(platelet count (109/L) × √(ALT (IU/L)))
NFS	–1.675 + (0.037 × age (year)) + (0.094 × BMI (kg/m2)) + (1.13 × IFG/diabetes (yes = 1, no = 2)) + (0.99 × AST/ALT ratio) – (0.013 × platelets (109/L)) – (0.66 × albumin (g/dL))
APRI	AST (IU/L)/upper limit of normal AST value (IU/L)/platelet count (109/L) × 100
m-APRI	Age (years) × (AST (IU/L)/upper limit of normal AST value (IU/L))/platelet count (109/L) × 100
ELF	2.494 + 0.846 ln (HA) + 0.735 ln (PIIINP) + 0.391 ln (TIMP-1)
HFS	$1/(1 + e^{[5.390 - 0.986 \times \text{age [45–64 years of age]} - 1.719 \times \text{age [≥65 years of age]} + 0.875 \times \text{male sex} - 0.896 \times \text{AST [35–69 IU/L]} - 2.126 \times \text{AST [≥70 IU/L]} - 0.027 \times \text{albumin [4–4.49 g/dL]} - 0.897 \times \text{albumin [<4 g/dL]} - 0.899 \times \text{HOMA–R [2 – 3.99 with no diabetes mellitus]} - 1.497 \times \text{HOMA–R [≥4 with no diabetes mellitus]} - 2.184 \times \text{diabetes mellitus} - 0.882 \times \text{platelets} \times 1.000/\mu L \text{ [155–219]} - 2.233 \times \text{platelets} \times 1.000/\mu L \text{ [<155]}]}$).
FibroTest	(4.467 × log (α2-MG)) – (1.357 × log (haptoglobin)) + (1.017 × log (GGT)) + (0.0281 × age (year)) + (1.737 × log (total bilirubin)) – (1.184 × apoA1) + (0.301 × sex (male = 1, female = 0)) – 5.540
BARD score	AST/ALT > 0.8 2 points, BMI > 28 1 point, Diabetes diagnosis 1 point

FIB-4

FIB-4 index which uses a patient's age, AST and ALT serum activities, and platelet concentration (Table 1). It is widely used serum index for staging fibrosis as a first step. It's recommended as a first-line assessment in major clinical guidelines, including the American Association for the Study of Liver Diseases (AASLD) Practice Guidance for managing metabolic dysfunction-associated steatotic liver disease (MAFLD) (16). The most accepted FIB-4 cut-off for advanced fibrosis is 2.67 (17) It is important to note that the specific cut-off values can vary slightly depending on the patient population and age.

According to a study by Itakura et al. (18) the FIB-4 index has an accuracy rate of approximately 71% for diagnosing cirrhosis in patients with chronic hepatitis B (HBV). Multiple meta-analyses (19) (20) have found that both the FIB-4 and APRI scores are effective for assessing fibrosis in patients with chronic hepatitis B, but one study (21) found that FIB-4 has a higher diagnostic accuracy than APRI for predicting moderate to advanced fibrosis and cirrhosis. The FIB-4 index is a practical and valuable tool for screening for liver fibrosis, primarily due to its high negative predictive value (NPV) (22). This means a cut-off of 1.3 can effectively rule out advanced fibrosis (23). However, the effectiveness of the FIB-4 index changes with age. In patients aged 65 or older, the score's specificity for advanced fibrosis is lower, which leads to a higher rate of false positives. a higher cut-off of 2.0 is recommended for this age group (24). Even with its usefulness, a single FIB-4 test may not be sufficient to rule out metabolic dysfunction-associated steatotic liver disease (MAFLD) in patients with a high prevalence of diabetics. If there is suspicion of advanced fibrosis, it is recommended to re-evaluate the patient or use more specific diagnostic methods (25).

1.1.1. *NAFLD fibrosis score (NFS)*

The NAFLD Fibrosis Score (NFS) uses a more comprehensive set of parameters than FIB-4, including BMI, the presence of diabetes, and albumin levels, in addition to the components shared with FIB-4. (table 1). The European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) Clinical Practice Guidelines recommend using the NFS for diagnosing advanced liver fibrosis in patients with MAFLD (26). However, despite their practicability, when used in the general population, they can have a significant number of false-positive and false-negative results. Because of this, their use is typically restricted to individuals at higher risk for liver disease (27).

1.1.2. *AST to platelets ratio index*

The AST to Platelet Ratio Index (APRI) was initially developed to determine the presence of liver fibrosis and to distinguish between different stages of fibrosis and cirrhosis in patients with hepatitis C virus (HCV) (28). A modified APRI (m-APRI) which incorporates

age and serum albumin levels in the APRI formula has been proposed (Table 1) (11). The addition of these parameters has been shown to improve the score's accuracy in predicting advanced fibrosis and cirrhosis in patients with viral hepatitis (29).

FibroTest

The FibroTest® has been validated for use in various liver diseases, including viral hepatitis, alcohol-associated liver disease, and MAFLD (30). To the age and gender of the patient, it combines several serum biomarkers, namely alpha-2-macroglobulin (A2M), haptoglobin, apolipoprotein A-1 (Apo-A1), bilirubin, and gamma-glutamyltranspeptidase (GGT) (31). A recent meta-analysis by Vali et al. (32) concluded that while FibroTest has an acceptable performance for detecting cirrhosis (AUC = 0.92) in MAFLD patients, its accuracy is limited when it comes to predicting moderate and advanced fibrosis. Despite this, FibroTest has good predictive values for diagnosing liver fibrosis in MAFLD patients and is included in the EASL-EASD-EASO Clinical Practice Guidelines (26).

1.1.3. *Hepamet fibrosis score (HFS)*

the Hepamet fibrosis score (HFS) uses variables also used by other NITs, like age, presence of diabetes, AST, albumin, and platelet count, but also gender and insulin resistance assessed by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (33). HFS is more accurate than both FIB-4 and NFS at identifying patients with advanced fibrosis. Several studies (34) (35) have validated its thresholds and confirmed that HFS has superior diagnostic accuracy and a higher negative predictive value (NPV) compared to NFS and FIB-4 in patients with metabolic hepatic steatosis. The HFS has also proven to be as reliable as NFS and FIB-4 for predicting cirrhosis, long-term liver-related events, hepatocarcinoma, and overall mortality. It performs particularly well in predicting moderate and severe fibrosis. As a newer NIT, it has not been as extensively validated as other scores, but it has demonstrated sensitivity and NPV values ranging from 74% to 90% and 90% to 98%, respectively (36).

BARD score

The BARD score, proposed by Harrison et al.(37), is a non-invasive tool that considers three factors to assess liver fibrosis:

- The presence of type 2 diabetes mellitus.
- The patient's body mass index (BMI).
- The AST/ALT ratio from liver serum enzyme activity.

This score has a high negative predictive value (NPV) of approximately 96% in patients with MAFLD (37).

Enhanced Liver Fibrosis (ELF) test

The Enhanced Liver Fibrosis (ELF) test is a blood test that measures three direct markers of fibrosis: hyaluronic acid (HA), procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP-1). It was developed in a mixed hepatitis C-dominated patient sample (38). the ELF test shows high diagnostic accuracy for advanced liver fibrosis with AUC values of 0.83 and 0.92 (39). The ELF test has been recommended by the National Institute for Health and Care Excellence (NICE) (40) and EASL (41) as a screening tool for liver fibrosis.

IMAGING MODALITIES FOR FIBROSIS ASSESSMENT

The most widely used imaging modality for this purpose is Transient Elastography (TE), commonly known by the name FibroScan. The ultrasound-based vibration-controlled transient elastography (VCTE) measures liver stiffness by using a low-frequency vibration to generate a shear wave that travels through the liver (42). The velocity of this wave is directly related to the stiffness of the liver tissue.

Transient Elastography is rapid, non-invasive, and can be performed at the point of care. It provides two key measurements: **Liver Stiffness Measurement (LSM)** which is a quantitative indicator of fibrosis in kilopascals (Table 2) and is computed from the velocity of these mechanical waves and **Controlled Attenuation Parameter (CAP)**, which quantifies liver steatosis (42). LSM by VCTE is only correlated with fibrosis and does not provide information, even if indirect, regarding other histological features (43). Its accuracy can be affected by factors like obesity, elevated liver enzymes.

Parallel to ultrasound-based transient elastography, magnetic resonance elastography (MRE) is an advanced technological approach used to determine liver stiffness through MRI imaging combined with low-frequency vibrations. In contrast with ultrasound-based VCTE, MRE offers a thorough assessment of the entire liver, presenting advantages such as minimal sampling error, a low failure rate, and high repeatability (44). However, it is also more expensive, less widely available, and requires a dedicated MRI machine, which limits its use.

Table 2. Fibrosis score

Liver Disease	F0 to F1 (Normal)	F2 (Moderate Scarring)	F3 (Severe Scarring)	F4 (Cirrhosis)
Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)	2 to 7 kPa	7.5 to 10 kPa	10 to 14 kPa	≥14 kPa

- **Normal Score** – No scarring or mild scarring.
- **Moderate to Severe Score** – Reversible changes in the liver that lifestyle modifications and a healthy diet can help manage. Patients may not be symptomatic.
- **Advanced Score** - The patient is cirrhotic with advanced liver diseases

A summary of the accuracy measures, including AUROC, sensitivity, and specificity for these non-invasive tests, is presented in Table 3

Table 3. Accuracy measures of NIT used the assessment of fibrosis in MAFLD

Noninvasive tests		Accuracy measures
Serum-based scores	APRI	AUROC 0.67-0.83, sensitivity 27-78.1%, specificity 66.7-90.5%
	BARD score	AUROC 0.70-0.87, sensitivity 72.7-89%, specificity 44-88.9%
	FIB-4	AUROC 0.70-0-90, sensitivity 42.9-100%, specificity 65-93%
	NFS	AUROC 0.65-0.88, sensitivity 44.2-82%, specificity 58-98%
	HFS	AUROC 0.69-0.88, sensitivity 51.9-90.5%, specificity 71.6-97%
Serum-based patented tests	ELF	AUROC 0.79-0.93, sensitivity 65-80%, specificity 72-90%
	FibroTest	AUROC 0.75-0.88, sensitivity 88-95%, specificity 69-71%
Imaging methods	VCTE	AUROC 0.80-0.95, sensitivity 71-92%, specificity 75-89.9%
	MRE	AUROC 0.89-0.96, sensitivity 78-98%, specificity 85-100%

RESULTS

This narrative review combined data from existing literature to compare the diagnostic accuracy of the most commonly used non-invasive tests for assessing liver fibrosis in patients with MAFLD. The key findings, summarized in Table 2, highlight a spectrum of diagnostic performance, ranging from simple serum-based scores to imaging modalities.

The serum-based scores showed variable accuracy for identifying significant to advanced fibrosis. The FIB-4 index, while widely recommended for its high negative predictive value, shows a broad AUROC range from 0.70 to 0.90, reflecting its variable performance across different patient populations and ages. Similarly, the NAFLD Fibrosis Score (NFS) and the AST to Platelet Ratio Index (APRI) also exhibited a wide range of accuracy, with AUROC values spanning from 0.65 to 0.88 and 0.67 to 0.83. The Hepamet Fibrosis Score (HFS) and the Enhanced Liver Fibrosis (ELF) test demonstrated superior accuracy, with AUROC values ranging from 0.69 to 0.88 for HFS and 0.79 to 0.93 for the ELF test, suggesting a more reliable performance, particularly for advanced fibrosis.

Imaging modalities consistently showed the highest diagnostic accuracy for fibrosis staging. Transient Elastography (VCTE), with an AUROC range of 0.80 to 0.95, exhibited high sensitivity and specificity in identifying advanced fibrosis. MRE consistently showed the highest diagnostic performance for fibrosis staging, with AUROC values ranging from 0.89 to 0.96. The high sensitivity and specificity of this method highlight its status as the most accurate non-invasive tool for assessing fibrosis and cirrhosis

DISCUSSION

The limitations of liver biopsy have driven the development of a non-invasive tests, each offering unique strengths and weaknesses. The findings of this narrative review provide a comprehensive comparison of these tools.

Comparison of Diagnostic Accuracy

As demonstrated in Table 2, a general pattern appears in which imaging modalities provide superior diagnostic accuracy compared to serum-based tests. MRE and VCTE consistently achieve the highest AUROC values, making them the most reliable non-invasive tools for staging liver fibrosis, particularly in advanced stages. Among the serum tests, the patented tests like FibroTest and the ELF test generally outperform the simple, calculator-based scores (e.g., FIB-4 and NFS). This highlights the value of using a combination of direct and indirect markers to improve diagnostic performance.

Clinical and Practical Utility

While diagnostic accuracy is important, clinical utility is determined by a test's accessibility, cost, and practicality. Simple serum-based scores like FIB-4 and NFS are widely available, inexpensive, and can be easily calculated in any clinical setting. Our analysis supports their use as first-line screening tools in primary care, particularly given their high negative predictive value, which effectively rules out advanced fibrosis in low-risk individuals and avoids unnecessary referrals. For patients flagged as high-risk, a more accurate second-line

test is warranted. VCTE represents an ideal second-line test. It is more accurate than simple serum scores, relatively affordable, and can be performed quickly at the point of care. MRE, despite being the most accurate non-invasive test, is the least practical due to its high cost and limited availability, positioning it as a third-line diagnostic tool for challenging cases.

Limitations

The non-invasive tests reviewed in this narrative review are not without limitations. Factors such as severe obesity and elevated liver enzymes can reduce the accuracy of VCTE. the simple serum-based scores like FIB-4 are not perfect. Their diagnostic performance can be influenced by age, as older patients tend to have higher scores even in the absence of advanced fibrosis, potentially leading to false-positive results. The patented serum tests are exclusive and have a higher cost, limiting their widespread use. This suggests that the ideal diagnostic strategy must balance accuracy, cost, and accessibility to be truly effective on a global scale.

CONCLUSION

Non-invasive approach to fibrosis assessment is not only useful but also offers a safe, effective and practical alternative to liver biopsy. This narrative review confirms that while simple serum-based scores like FIB-4 and NFS are valuable for initial population-wide screening, they are outmatched in diagnostic accuracy by imaging modalities like VCTE and MRE. A rational approach, starting with accessible scores for screening and escalating to more accurate imaging-based tests for at-risk patients, represents the most efficient strategy for managing liver fibrosis in MAFLD. This minimizes the need for liver biopsy and promises to improve clinical outcomes for the millions of people affected by this growing global health challenge.

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