HSPI The Open Access Publisher

ASCR ARCHIVES OF SURGERY AND CLINICAL RESEARCH
ISSN 2576-9537

Mini Review

Non-invasive Serological Markers of Hepatic Fibrosis – Mini Review

Elena Popa[1]*, Raluca Ioana Avram[2], Andrei Emilian Popa[3] and Adorata Elena Coman[1]

[1]Preventive Medicine and Interdisciplinarity Department, Grigore T. Popa University of Medicine, and Pharmacy, 700115 Iasi, Romania

[2]Internal Medicine Department, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, 700115 Iasi, Romania

[3]Prof. Dr. Nicolae Oblu" Emergency Clinic Hospital, 700309, Iasi, Romania

Abstract

Aim: This study examines the pathological outcomes of chronic liver injuries, with a focus on liver fibrosis. It emphasizes understanding the structural changes within the liver that may lead to cirrhosis and functional impairments, crucial for developing targeted antifibrotic therapies.

Methods: Our approach reviews existing literature detailing the use of traditional diagnostic methods—biochemical and serological tests alongside liver biopsies. Additionally, we evaluate the reliability and efficacy of non-invasive techniques such as serological test panels and imaging examinations. These methods are compared to understand their viability as supplementary or alternative diagnostic tools to liver biopsy.

Significance: Liver fibrosis, if unmanaged, can progress to severe conditions such as cirrhosis and hepatocellular carcinoma, making it vital to understand its progression and treatment options. This study underscores the need for precise and non-invasive diagnostic tools in the clinical management of liver fibrosis, providing insight into the progression of chronic liver diseases and potential therapeutic targets.

Conclusion and future perspectives: The research confirms that while liver biopsy remains the definitive method for staging liver fibrosis, its risks and limitations necessitate the use of enhanced non-invasive diagnostic techniques. These methods have shown promising results in accuracy and are critical for broadening clinical applications and patient safety.

It is recommended that the scientific community continue to develop and validate non-invasive diagnostic tools. Enhancing the accuracy and reliability of these tools can provide a cost-effective, accessible, and safer alternative for large-scale screening and management of liver fibrosis in asymptomatic populations. Additionally, integrating advancements in radiologic and serological markers can further refine these diagnostic methods, improving overall patient outcomes.

More Information

***Address for correspondence:** Elena Popa, Preventive Medicine and Interdisciplinarity Department, Grigore T. Popa University of Medicine, and Pharmacy Iasi, 700115 Iasi, Romania, Email: elenapopadr@yahoo.com

Submitted: April 26, 2024
Approved: May 13, 2024
Published: May 14, 2024

How to cite this article: Popa E, Avram RI, Popa AE, Coman AE. Non-invasive Serological Markers of Hepatic Fibrosis – Mini Review. Arch Surg Clin Res. 2024; 8: 032-038.

DOI: 10.29328/journal.ascr.1001081

Keywords: Liver fibrosis; Non-invasive diagnostic methods; Serological markers; Hepatic cirrhosis; Fibrogenesis

Introduction

Hepatic fibrosis emerges as a direct consequence of chronic liver injury, manifesting regardless of the underlying cause. This condition typically involves a complex response where hepatic lobules collapse, fibrous septa form, and hepatocyte regeneration occurs, leading to nodule formation. The accumulation of extracellular matrix components in the liver due to imbalances in their production, deposition, and degradation marks the severity of this condition, which can culminate in cirrhosis. This latter stage brings about significant clinical complications such as portal hypertension and impaired liver functionality [1].

Historically, hepatic fibrosis was viewed as an irreversible end stage of liver pathology; however, current understanding recognizes it as a dynamic process that may potentially resolve [2]. This shift underscores the evolving insights into molecular pathways of fibrogenesis and fibrosis regression, which illuminate possible targets for therapeutic intervention. The dynamic nature of fibrosis, coupled with its reversible potential under certain conditions, provides a strong impetus for developing precise, non-invasive diagnostic methods.

The conventional approach to assessing liver fibrosis includes biochemical and serological tests, as well as critical histopathological examinations via liver biopsy. While liver biopsy remains the gold standard due to its direct assessment of tissue pathology, it is not without limitations. The procedure is invasive and carries risks such as pain, bleeding, and potential damage to adjacent organsm [1]. Furthermore, liver biopsy samples only a tiny portion of the liver, which could lead to sampling errors and variations in

interpretation among observers [2]. These challenges have increased interest in non-invasive methods. These methods can reliably estimate the level of hepatic fibrosis, enhancing patient safety and comfort.

This study aims to comprehensively evaluate and compare traditional and emerging non-invasive diagnostic methods for hepatic fibrosis. By investigating these methods' efficacy and reliability, this research seeks to contribute to the clinical management of liver fibrosis, facilitating early detection and ongoing monitoring of chronic liver diseases to improve patient outcomes and reduce the incidence of severe complications [2].

Stages of hepatic fibrosis

Non-invasive tests for hepatic fibrosis aim to predict the histologically observed stage of fibrosis. Several standardized histological assessment systems exist for chronic liver disease (Knodell, Ishak, Metavir) [1].

The Metavir score for hepatic fibrosis is as follows:

F0: No fibrosis

F1: Portal fibrosis without septa

F2: Few septa

F3: Numerous septa without cirrhosis

F4: Cirrhosis

Patients are typically considered to have significant fibrosis if their fibrosis score is ≥ F2.

Clinical significance

Non-invasive tests for hepatic fibrosis are primarily used for staging fibrosis in patients with chronic liver disease. Typically, these tests are performed on patients with chronic viral hepatitis during the initial evaluation to determine the likelihood of advanced hepatic fibrosis. For patients not successfully treated, subsequent tests are useful in assessing fibrosis progression. These tests are also used in patients with other chronic liver diseases, such as non-alcoholic fatty liver disease and primary sclerosing cholangitis [1,3].

These tests are often used to differentiate patients with significant fibrosis (F2 to F4) from those with minimal or absent fibrosis (F0 to F1). Many of these tests have been evaluated in specific populations (often patients with chronic hepatitis C virus - HCV), which should be considered when attempting to generalize results to other populations [1,3].

In patients with chronic hepatitis C [3], evaluating fibrosis progression can be valuable for several reasons:

- The presence of advanced fibrosis (bridging fibrosis or cirrhosis) guides certain treatment decisions, including the optimal regimen and duration, and is a key factor in determining treatment urgency.
- The approximate time until the development of cirrhosis can be estimated.
- Patients with cirrhosis require screening for complications such as hepatocellular carcinoma and portal hypertension.

Non-invasive testing for hepatic fibrosis can also play a role in monitoring patients taking medications associated with chronic liver injury, such as methotrexate [3,4]. In a study of 24 patients taking methotrexate who had undergone a liver biopsy, elastography correctly identified 88% of patients without significant fibrosis, and FibroTest identified 83% of patients with significant fibrosis [4].

There are two general categories of non-invasive tests for fibrosis: serological test panels and imaging examinations. Serological tests are widely available. However, despite considerable progress in improving the accuracy of serological markers of hepatic fibrosis, they still cannot replace direct histological analysis. When available, radiologic measurement of elasticity can be used alone or in combination with serological testing [1,3].

Usually, a combination of serological tests and transient elastography (TE) based on ultrasound is used. Combining tests results in fewer patients with an undetermined fibrosis score and increased specificity. TE is the most widely used imaging method as it is widely available and has been validated in large population studies. Other imaging methods for evaluating hepatic fibrosis include magnetic resonance elastography (MRE), acoustic radiation force imaging (ARFI), and cross-sectional imaging [1-3].

Four commercial serum marker systems have been extensively validated, viz., FibroTest/FibroSure, Hepascore, FibroSpect, and the ELF score. In addition, the aspartate aminotransferase-to-platelet ratio index (APRI) has also been extensively studied. APRI has the advantage of being easily calculable using available data from routine laboratory tests [1,3].

All serum tests have limitations:

- They usually reflect the rate of matrix remodeling, not deposition, and thus tend to be higher when there is high inflammatory activity. Conversely, extensive matrix deposition may go undetected if there is minimal inflammation.
- None of the markers are liver-specific, and concomitant sites of inflammation or fibrosis may contribute to altered serum concentrations.
- Serum levels are affected by clearance rates, which may be impaired either due to sinusoidal endothelial cell dysfunction or deficient biliary excretion.
- These are surrogates/substitutes and do not constitute biomarkers.

Serological tests

A variety of serologic markers have been evaluated to predict the degree of liver fibrosis, and to improve predictive ability, panels have been developed that combine tests for multiple markers. Overall, studies of different panels suggest that they have a good ability to differentiate patients with significant fibrosis (F2 to F4) from those without significant fibrosis (F0 to F1) [5]. A disadvantage of these panels is that they cannot reliably differentiate between different stages of fibrosis, and indeterminate results are common (up to 50% with FibroTest). No panel has yet become the standard for determination, and its choice is often dictated by local test availability [1].

Serological markers of liver fibrosis can be broadly classified in [1,5]:

- Indirect markers reflect changes in liver function but do not directly reflect extracellular matrix metabolism (eg platelet count, coagulation marker studies, and liver aminotransferases).
- Direct markers of fibrosis reflect extracellular matrix turnover. These are represented by procollagen types I and III, hyaluronic acid, and tissue inhibitors of metalloproteinase.

In addition to detecting significant fibrosis, test panels may also be able to monitor the progression of liver fibrosis. This monitoring over time may be more important than assessing the stage of the disease at a specific point in time, because liver fibrogenesis is a dynamic process.

I. Indirect fibrosis marker panels

Interpretation of serum aminotransferase levels, coagulation parameters, and platelet counts have been used in clinical practice to predict the presence or absence of cirrhosis. Several studies have also evaluated the accuracy of combinations (or ratios) of these measures [1,6]. The most studied combinations include APRI, FibroTest/FibroSure, and Hepascore [1].

- APRI Score (AST to platelet ratio index) was originally described by Wai, et al. [7], being calculated as APRI = (AST/ Upper limit of normal AST range)/Platelets (109/L)) × 100) [8].
- FibroTest, FibroSure and ActiTest

  FibroTest and FibroSure are identical tests marketed under different names in Europe and America respectively. ActiTest is a modification of FibroTest. These tests were mainly studied in patients with hepatitis B and C [1,9].

FibroTest involves the evaluation of alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), gamma globulin, apolipoprotein A1, GGT (gamma-glutamyl-transferase) and total bilirubin [9]. It also takes into account the age and gender of the patient. The results from the individual tests are combined and used to classify patients with mild fibrosis (F0 to F1), significant fibrosis (F2 to F4), or an indeterminate fibrosis stage. The sensitivity for detecting significant fibrosis is approximately 60% - 75%, and the specificity is approximately 80% - 90%, respectively [1,9,10]. In a study by Rossi, et al. [11], disease severity was correctly identified as mild or significant in approximately 46% of patients.

ActiTest is a modification of FibroTest that includes ALT (alanine aminotransferase) and reflects both liver fibrosis and necroinflammatory activity. ActiTest appears to improve the identification of more advanced fibrosis associated with histological inflammation [12]. Patients with chronic hepatitis C treated with pegylated interferon therapy show improvement in both ActiTest and FibroTest scores compared to an untreated control group, supporting the role of this test in monitoring treatment response [9]. The meta-analysis by Poynard [10] which included a total of 1570 patients concluded that these tests are reliable alternatives to liver biopsy in patients with chronic postviral hepatitis C.

Hepascore: Hepascore involves a combination of clinical parameters (age and sex) with laboratory determinations (bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin) [13].

AST/ALT Ratio: The AST/ALT ratio is approximately 0.8 in normal subjects. Some studies have suggested that a ratio > 1 suggests the presence of cirrhosis [1]. However, study results were inconsistent, and the clinical utility of this report for the diagnosis of cirrhosis remains uncertain. The AST/ALT ratio has also been incorporated into predictive models in NAFLD patients [1,14].

Other indirect markers: Tests continue to be developed to detect serological fibrosis, although they have not been studied as extensively as APRI or FibroTest/FibroSure.

Some of these have been derived for use in specific patient groups (eg, fibrosis testing in patients with NAFLD).

- **FIB-4 index:** The FIB-4 Index combines biochemical values (platelet count, ALT, and AST) and age. It had good predictive accuracy for advanced fibrosis in at least two studies involving patients with chronic HCV and performed better than other serological markers for predicting advanced fibrosis in patients with NAFLD It also appears to be useful for predicting patient outcomes with NAFLD. FIB-4 values have also been associated with the risk of developing hepatocellular carcinoma (HCC) among patients who consume alcohol [1,15]

FIB4 is a simple score that can play a "red flag" role in the early identification of patients at high risk of advanced liver fibrosis and their referral to specialized care [16].

- **NAFLD fibrosis score:** The NAFLD Fibrosis Score is another score used to assess the likelihood of fibrosis in patients with NAFLD. In determining the score, the patient's age, body mass index (BMI), blood sugar, aminotransferase values, platelet count, and albumin are included [17].
- **PGA index:** The PGA Index combines the measurement of prothrombin index, GGT level, and apolipoprotein A1 level. It has been validated in patients with a variety of chronic liver diseases, but especially in alcohol-induced liver damage [18].
- **FibroIndex:** The FibroIndex is derived from the measurement of platelet count, AST, and gamma globulin. It has been proposed as a marker of significant fibrosis in chronic HCV. Its accuracy is still being determined [19].
- **Forns idex:** The Forns Index takes into account age, GGT, cholesterol, and platelet count. It has been studied mainly in HCV patients. It appears to have similar performance characteristics to those observed with APRI [20].
- **Fibrometer:** The fibrometer test involves a combination of platelet count, prothrombin index, AST, alpha-2-macroglobulin, hyaluronic acid, urea (blood urea nitrogen), and age. It performed well in predicting severe fibrosis in patients with chronic viral hepatitis but was no better than FibroTest in predicting severe fibrosis in alcoholic liver disease [21].
- **BARD score:** The BARD score was developed to predict fibrosis in patients with NAFLD. The BARD score takes into account BMI, the AST/ALT ratio, and the presence of diabetes [22].
- **Proteonomics and glycomics:** Protein or glycoprotein patterns can be assessed by mass spectroscopy of serum samples. These methods represent "surrogate" markers of fibrosis and the identities of the peaks are generally not known [1,23]. However, important correlations have been reported: combining serum glycomics with FibroTest resulted in a sensitivity for predicting cirrhosis of 100% and a specificity of 75% [1].

New markers: Previous experimental data led to the identification of placental growth factor (PLGF), growth differentiation factor (GDF), and liver growth factor (HGF) as crucial in liver fibrogenesis [14].

II. Direct markers of fibrosis

Liver fibrosis results in both qualitative and quantitative changes in extracellular matrix markers. Potential markers of fibrosis include products of collagen synthesis or degradation, enzymes involved in matrix biosynthesis or degradation, extracellular matrix glycoproteins, and proteoglycans/glycosaminoglycans [1]. Direct markers of fibrosis can be divided into:

a. Markers associated with matrix deposition/deposition.

b. Markers associated with matrix degradation.

c. Cytokines and chemokines associated with fibrogenesis.

Panels of direct fibrosis markers: Direct fibrosis markers have been combined into panels to predict liver fibrosis. Panels may also include indirect markers of fibrosis. These panels include FibroSpect II, SHASTA (serum hyaluronic acid level, serum AST, and albumin level), and the European Liver Fibrosis (ELF) panel. As with indirect markers, none has yet evolved as a standard for clinical practice [1].

FibroSpect II: The FibroSpect II panel uses a combination of tests: serum hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP-1), and alpha-2-macroglobulin. The combination of these tests reliably differentiates chronic HCV patients with moderate to severe fibrosis from those with mild or no fibrosis [1,24].

European liver fibrosis panel: ELF is a proprietary algorithm that takes into account the level of hyaluronic acid, the amino-terminal propeptide of collagen type III and TIMP-1 [1,24,25].

Specific markers: Direct individual markers incorporated into serological panels may be associated with matrix deposition or degradation or maybe cytokines and chemokines associated with fibrogenesis [1,26].

a. Markers associated with matrix deposition: Several markers associated with matrix deposition have been studied. Most are based on the detection of various procollagen peptides, including type I procollagen carboxy-terminal peptide, type III procollagen amino-terminal peptide, type I and type IV collagen, laminin, hyaluronic acid, and YKL-40 (chondrex) [1,27].

- **Procollagen I carboxyterminal peptide (PICP):** PICP levels are increased in patients with cirrhosis. In patients with alcoholic liver disease, PICP levels are not as accurate as collagen type IV or procollagen amino-terminal peptide type III (PIIINP) levels for detecting the presence of cirrhosis, quantifying disease severity, and indicating the presence of associated alcoholic hepatitis [26,27].
- **Procollagen III N-terminal peptide (PIIINP):** PIIINP levels are increased in acute and chronic liver diseases

and correlate with serum aminotransferase levels in patients with active hepatitis and with serum bilirubin levels in those with cirrhosis [26,27].

- **Type I and Type IV collagen:** Type I collagen levels are increased in all types of liver fibrosis. Type I collagen messenger RNA (mRNA) levels are increased 60- to 70-fold in activated hepatic stellate cells. In patients with chronic liver disease, serum levels of type I collagen are increased and correlate with the fibrosis score, but not with the inflammatory activity score [28].

Serum levels of type IV collagen are increased in patients with chronic liver disease compared with normal controls. Type IV collagen is located in the basement membranes of blood and lymphatic vessels and bile ducts, around nerve axons, and in perisinusoidal spaces. One hypothesis suggests that increased levels may reflect the capillarization of the perisinusoidal wall observed in liver fibrogenesis [28,29].

- **Laminin:** Laminin is a non-collagenous glycoprotein synthesized by hepatic stellate cells and deposited at the level of the hepatic basement membrane. In chronic liver injury, basement membrane components, especially laminin, are increasingly deposited around the vessels, in the perisinusoidal spaces and portal system. Laminin appears to be superior to PIIINP, but not as faithful compared to type IV collagen, in predicting the fibrotic stage in chronic viral hepatitis. Serum levels of laminin and the pepsin-resistant fragment of laminin (laminin P1) are increased in patients with chronic alcoholic liver disease and viral hepatitis, which may reflect increased perisinusoidal fibrosis. Serum laminin levels correlate with the severity of fibrosis and hepatitis, Child-Pugh score, hepatic venous pressure gradient, and complications of liver cirrhosis. Alcohol withdrawal has been associated with a reduction in laminin levels. However, a response to HCV treatment is not always associated with normalization of serum laminin levels [1,30,31].

- **Hyaluronic acid:** Hyaluronic acid, a glycosaminoglycan synthesized by hepatic stellate cells and degraded by hepatic sinusoidal cells, is a component of the extracellular matrix. High levels of hyaluronic acid in patients with liver disease (especially those with cirrhosis) have been linked to impaired sinusoidal endothelial cell function and reflect increased fibrogenesis. Increased levels of hyaluronic acid correlate with liver inflammation and fibrosis in alcoholic liver disease and with fibrosis in patients with chronic hepatitis B or C virus, NAFLD. A reduction in hyaluronic acid levels was observed in HCV patients who had a biochemical response to interferon monotherapy. Additionally, reduced levels of hyaluronic acid correlated with an improvement in fibrosis, while increased levels were associated with worsening fibrosis. Serum hyaluronic acid levels have the highest predictive accuracy for advanced fibrosis [1,30,31].

- **YKL-40 (chondrex) /Chitinase-3-like protein 1-CHI3L1:** Is a glycoprotein of 38 kDA. Its function is unknown, but its expression pattern in certain tissues, such as the human liver or cartilage, suggests a function in extracellular matrix remodeling or degradation.

Immunohistochemical staining of fibrotic liver tissue demonstrated YKL-40 in areas of fibrosis and particularly in areas of active fibrogenesis. Serum levels of YKL-40 are increased in patients with alcoholic liver disease, especially those with alcoholic hepatitis. Serum levels are significantly correlated with the degree of liver fibrosis and the plasma level of hyaluronic acid. Elevated serum levels have also been described in patients with posthepatic causes of cirrhosis. YKL-40 increase correlates with the degree of liver fibrosis [32,33].

b. Matrix metalloproteinases (MMPs): Are enzymes that play an important role in the degradation and remodeling of the extracellular matrix (ECM), capable of degrading and reorganizing ECM components, including collagen, elastin, and other extracellular proteins, thus contributing to physiological and pathological processes. MMPs are in turn inhibited by tissue inhibitors of metalloproteinases (TIMP) [1].

The observation that MMPs are expressed in liver lesions suggests that degradation of the normal liver matrix may contribute to the pathogenesis of liver fibrosis. The three most important MMPs are MMP-2 (gelatinase-A), MMP-3 (stromelysin), and MMP-9 (gelatinase-B). However, studies looking to see if MMP-2, MMP-3, or MMP-9 levels correlate with liver fibrosis have been inconclusive [1].

Matrix metalloproteinase-1 (MMP-1): Also known as interstitial collagenase or fibroblastic collagenase has a role in the regression of liver fibrosis in rodents. However, in humans, MMP-1 is known to increase tissue fibrosis in non-alcoholic steatohepatitis (NASH), suggesting that MMP-1 might contribute to liver repair and regeneration. Matrix metalloproteinase-8 (MMP-8), also known as collagenase-2, is considered to be a hallmark of liver cirrhosis in alcoholics. The activity and concentrations of MMP-8, along with MMP-2 and MMP-9 have been reported to be elevated in patients with liver cirrhosis [34].

Matrix metalloproteinase-2 (MMP-2): Also known as gelatinase A, is involved in extracellular matrix remodeling. MMP-2 is secreted as a proenzyme and activated by membrane-type MMPs (MT-MMPs), such as MT1-MMP. In liver fibrosis, MMP-2 is highly expressed in myofibroblasts and is thought to have a profibrogenic role [34].

Matrix metalloproteinase-9 (MMP-9): Also known as Gelatinase-B [35], is expressed by leukocytes in liver ischemia and reperfusion injury. MMP-9 is a multifaceted metalloproteinase that has a role in impairing liver regeneration. MMP-2 activity is inversely proportional to MMP-9 activity. Lack of MMP-2 also leads to spontaneous leukocyte infiltration into the liver and enhanced MMP-9-dependent leukocyte transmigration in vitro and after liver reperfusion injury.

Matrix metalloproteinase-3 (MMP-3): Also called stromelysin-1, is known for its degrading activity against collagens, proteoglycans, fibronectin, laminin, and elastin, thereby regulating matrix remodeling. MMP-3 plays a vital role in the activation of MMP-1, MMP-7, and MMP-9, explaining the involvement in connective tissue remodeling [34].

TIMP-1 and -2 – TIMP-1 and -2: Inhibit matrix degradation, which may promote fibrosis progression. Studies of explanted livers from liver transplant patients have demonstrated increased hepatic expression of TIMP-1 and -2 in patients with sclerosing cholangitis, biliary atresia, PBC, and autoimmune hepatitis. In patients with chronic HCV, serum levels of TIMP-1 and -2 were significantly correlated with histological activity index and fibrosis, respectively [1,3,5,34,35].

C. Cytokines and chemokines associated with liver fibrosis: Several cytokines have been identified as having a role in liver fibrogenesis, some of which may be useful clinical markers of liver fibrogenesis. These include the growth factors TGF-alpha, TGF-beta, and platelet-derived growth factor (PDGF) [1].

TGF-alpha: TGF-alpha is a potent stimulator of normal and neoplastic hepatocyte mitosis. In addition, TGF-alpha also appears to have an essential role in hepatocarcinogenesis. TGF-alpha levels are elevated in cirrhotic patients and correlate with bilirubin and Child-Pugh classification, suggesting that they are closely related to the severity of liver dysfunction [1,36,37].

TGF-beta: TGF-beta is the dominant stimulus for extracellular matrix production by hepatic stellate cells. Hepatic TGF-beta mRNA levels are increased in chronic liver disease in association with increases in type I collagen mRNA levels. Serum levels of total and biologically active TGF-beta are increased in patients with HBV-associated chronic liver disease, compared to controls, and correlate with fibrosis scores [1,36,37].

PDGF: PDGF is upregulated following liver injury, and PDGF levels are correlated with the severity of liver disease. PDGF is a growth factor that promotes the division and proliferation of hepatic stellate cells [1, 36,37].

Combined tests

The use of multiple serologic panels or the combination of serologic panels with imaging studies may improve the ability to accurately assess a patient's degree of fibrosis. Furthermore, it is possible to improve the diagnostic performance of these panels if they are gradually used in combination [1].

Perspectives

Some of the experimental serum markers, especially those that are liver specific, combined with new imaging and physical techniques [38] could create an almost biopsy-free diagnostic scenario in the future.

Author contributions: The authors contributed equally to this work.

References

1. Curry MP, Afdhal NH. UpToDate [Internet]. Noninvasive Assessment of Hepatic Fibrosis: Overview of Serologic Tests and Imaging Examinations. (Jan 12, 2024). https://www.uptodate.com.
2. Trifan A, Muzica CM, Nastasa R, Zenovia S, Stratina E, Stafie R, Rotaru A, Singeap AM, Cojocariu C, Sfarti C, Girleanu I, Chiriac S, Cuciureanu T, Huiban L, Stanciu C. High prevalence of liver fibrosis among general population: a Romanian population-based study. Hepatol Commun. 2023 Jan 18;7(2):e0032. doi: 10.1097/HC9.0000000000000032. Erratum in: Hepatol Commun. 2023 Feb 1;7(2):e00c6. Abstract corrected. PMID: 36691959; PMCID: PMC9851682.
3. Gheorghe G, Bungău S, Ceobanu G, Ilie M, Bacalbaşa N, Bratu OG, Vesa CM, Găman MA, Diaconu CC. The non-invasive assessment of hepatic fibrosis. J Formos Med Assoc. 2021 Feb;120(2):794-803. doi: 10.1016/j.jfma.2020.08.019. Epub 2020 Aug 26. PMID: 32861550.
4. Cheng HS, Rademaker M. Monitoring methotrexate-induced liver fibrosis in patients with psoriasis: utility of transient elastography. Psoriasis (Auckl). 2018 May 9;8:21-29. doi: 10.2147/PTT.S141629. PMID: 29785393; PMCID: PMC5953305.
5. Joseph J. Serum Marker Panels for Predicting Liver Fibrosis - An Update. Clin Biochem Rev. 2020 May;41(2):67-73. doi: 10.33176/AACB-20-00002. PMID: 32518428; PMCID: PMC7255312.
6. Wang Z, Zhou Y, Yu P, Liu Y, Mei M, Bian Z, Shao W, Lv J, Li X, Lu W, Xu L. Retrospective Evaluation of Non-Invasive Assessment Based on Routine Laboratory Markers for Assessing Advanced Liver Fibrosis in Chronic Hepatitis B Patients. Int J Gen Med. 2022 May 25;15:5159-5171. doi: 10.2147/IJGM.S364216. PMID: 35642202; PMCID: PMC9148603.
7. Huang C, Seah JJ, Tan CK, Kam JW, Tan J, Teo EK, Kwek A, Wong YJ, Tan M, Ang TL, Kumar R. Modified AST to platelet ratio index improves APRI and better predicts advanced fibrosis and liver cirrhosis in patients with non-alcoholic fatty liver disease. Clin Res Hepatol Gastroenterol. 2021 Jul;45(4):101528. doi: 10.1016/j.clinre.2020.08.006. Epub 2020 Nov 29. PMID: 33268036.
8. Forsgren MF, Nasr P, Karlsson M, Dahlström N, Norén B, Ignatova S, Sinkus R, Cedersund G, Leinhard OD, Ekstedt M, Kechagias S, Lundberg P. Biomarkers of liver fibrosis: prospective comparison of multimodal magnetic resonance, serum algorithms and transient elastography. Scand J Gastroenterol. 2020 Jul;55(7):848-859. doi: 10.1080/00365521.2020.1786599. Epub 2020 Jul 20. PMID: 32684060.
9. Rasmussen DN, Thiele M, Johansen S, Kjærgaard M, Lindvig KP, Israelsen M, Antonsen S, Detlefsen S, Krag A; GALAXY; MicrobLiver consortia. Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. J Hepatol. 2021 Nov;75(5):1017-1025. doi: 10.1016/j.jhep.2021.05.037. Epub 2021 Jun 10. PMID: 34118335; PMCID: PMC8522804.
10. Kaur N, Goyal G, Garg R, Tapasvi C, Chawla S, Kaur R. Potential role of noninvasive biomarkers during liver fibrosis. World J Hepatol. 2021 Dec 27;13(12):1919-1935.doi:10.4254/wjh.v13.i12.1919.PMID:35069998; PMCID: PMC8727215.

11. Bernstein D, Kovalic AJ. Noninvasive assessment of fibrosis among patients with nonalcoholic fatty liver disease [NAFLD]. Metabol Open. 2022 Jan 5;13:100158. doi: 10.1016/j.metop.2021.100158. PMID: 35036892; PMCID: PMC8749444.

12. Canivet CM, Boursier J. Screening for Liver Fibrosis in the General Population: Where Do We Stand in 2022? Diagnostics (Basel). 2022 Dec 28;13(1):91. doi: 10.3390/diagnostics13010091. PMID: 36611384; PMCID: PMC9818643.

13. Lai M, Afdhal NH. Liver Fibrosis Determination. Gastroenterol Clin North Am. 2019 Jun;48(2):281-289. doi: 10.1016/j.gtc.2019.02.002. Epub 2019 Apr 1. PMID: 31046975.

14. Amernia B, Moosavy SH, Banookh F, Zoghi G. FIB-4, APRI, and AST/ALT ratio compared to FibroScan for the assessment of hepatic fibrosis in patients with non-alcoholic fatty liver disease in Bandar Abbas, Iran. BMC Gastroenterol. 2021 Dec 3;21(1):453. doi: 10.1186/s12876-021-02038-3. PMID: 34861841; PMCID: PMC8642865.

15. Sumida Y, Yoneda M, Tokushige K, Kawanaka M, Fujii H, Yoneda M, Imajo K, Takahashi H, Eguchi Y, Ono M, Nozaki Y, Hyogo H, Koseki M, Yoshida Y, Kawaguchi T, Kamada Y, Okanoue T, Nakajima A, Japan Study Group Of Nafld Jsg-Nafld. FIB-4 First in the Diagnostic Algorithm of Metabolic-Dysfunction-Associated Fatty Liver Disease in the Era of the Global Metabodemic. Life (Basel). 2021 Feb 14;11(2):143. doi: 10.3390/life11020143. PMID: 33672864; PMCID: PMC7917687.

16. Blanco-Grau A, Gabriel-Medina P, Rodriguez-Algarra F, Villena Y, Lopez-Martínez R, Augustín S, Pons M, Cruz LM, Rando-Segura A, Enfedaque B, Riveiro M, Casis E, Ferrer-Costa R, Buti M, Rodriguez-Frias F. Assessing Liver Fibrosis Using the FIB4 Index in the Community Setting. Diagnostics (Basel). 2021 Nov 29;11(12):2236. doi: 10.3390/diagnostics11122236. PMID: 34943471; PMCID: PMC8700445.

17. Drolz A, Wolter S, Wehmeyer MH, Piecha F, Horvatits T, Schulze Zur Wiesch J, Lohse AW, Mann O, Kluwe J. Performance of non-invasive fibrosis scores in non-alcoholic fatty liver disease with and without morbid obesity. Int J Obes (Lond). 2021 Oct;45(10):2197-2204. doi: 10.1038/s41366-021-00881-8. Epub 2021 Jun 24. PMID: 34168277; PMCID: PMC8455320.

18. Tincopa MA, Loomba R. Non-invasive diagnosis and monitoring of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Lancet Gastroenterol Hepatol. 2023 Jul;8(7):660-670. doi: 10.1016/S2468-1253(23)00066-3. Epub 2023 Apr 13. PMID: 37060912.

19. Okdemir S, Cakmak E. A novel non-invasive score for the prediction of advanced fibrosis in patients with chronic hepatitis B. Ann Hepatol. 2022 Jan-Feb;27(1):100544. doi: 10.1016/j.aohep.2021.100544. Epub 2021 Sep 24. PMID: 34571267.

20. Bukhari T, Jafri L, Majid H, Ahmed S, Khan AHH, Abid S, Raza A, Siddiqui I. Diagnostic Accuracy of the Forns Score for Liver Cirrhosis in Patients With Chronic Viral Hepatitis. Cureus. 2021 Apr 13;13(4):e14477. doi: 10.7759/cureus.14477. PMID: 33996335; PMCID: PMC8120009.

21. Van Dijk AM, Vali Y, Mak AL, Lee J, Tushuizen ME, Zafarmand MH, Anstee QM, Brosnan MJ, Nieuwdorp M, Bossuyt PM, Holleboom AG. Systematic Review with Meta-Analyses: Diagnostic Accuracy of FibroMeter Tests in Patients with Non-Alcoholic Fatty Liver Disease. J Clin Med. 2021 Jun 29;10(13):2910. doi: 10.3390/jcm10132910. PMID: 34209858; PMCID: PMC8269151.

22. Younes R, Caviglia GP, Govaere O, Rosso C, Armandi A, Sanavia T, Pennisi G, Liguori A, Francione P, Gallego-Durán R, Ampuero J, Garcia Blanco MJ, Aller R, Tiniakos D, Burt A, David E, Vecchio FM, Maggioni M, Cabibi D, Pareja MJ, Zaki MYW, Grieco A, Fracanzani AL, Valenti L, Miele L, Fariselli P, Petta S, Romero-Gomez M, Anstee QM, Bugianesi E. Long-term outcomes and predictive ability of non-invasive scoring systems in patients with non-alcoholic fatty liver disease. J Hepatol. 2021 Oct;75(4):786-794. doi: 10.1016/j.jhep.2021.05.008. Epub 2021 Jun 4. PMID: 34090928.

23. Heyens LJM, Busschots D, Koek GH, Robaeys G, Francque S. Liver Fibrosis in Non-alcoholic Fatty Liver Disease: From Liver Biopsy to Non-invasive Biomarkers in Diagnosis and Treatment. Front Med (Lausanne). 2021 Apr 14;8:615978. doi: 10.3389/fmed.2021.615978. PMID: 33937277; PMCID: PMC8079659.

24. Han MAT. Noninvasive Tests (NITs) for Hepatic Fibrosis in Fatty Liver Syndrome. Life (Basel). 2020 Sep 13;10(9):198. doi: 10.3390/life10090198. PMID: 32933184; PMCID: PMC7555355.

25. Schiavon Lde L, Narciso-Schiavon JL, de Carvalho-Filho RJ. Non-invasive diagnosis of liver fibrosis in chronic hepatitis C. World J Gastroenterol. 2014 Mar 21;20(11):2854-66. doi: 10.3748/wjg.v20.i11.2854. PMID: 24659877; PMCID: PMC3961992.

26. Soresi M, Giannitrapani L, Cervello M, Licata A, Montalto G. Non invasive tools for the diagnosis of liver cirrhosis. World J Gastroenterol. 2014 Dec 28;20(48):18131-50. doi: 10.3748/wjg.v20.i48.18131. PMID: 25561782; PMCID: PMC4277952.

27. Maroto-García J, Moreno Álvarez A, Sanz de Pedro MP, Buño-Soto A, González A. Serum biomarkers for liver fibrosis assessment. Advances in Laboratory Medicine. Advances in Laboratory Medicine. 2023. https://doi.org/10.1515/almed-2023-0081

28. Aleknavičiūtė-Valienė G, Banys V. Clinical importance of laboratory biomarkers in liver fibrosis. Biochem Med (Zagreb). 2022 Oct 1;32(3):030501. doi: 10.11613/BM.2022.030501. Epub 2022 Oct 1. PMID: 36277426; PMCID: PMC9562801.

29. Caligiuri A, Gentilini A, Pastore M, Gitto S, Marra F. Cellular and Molecular Mechanisms Underlying Liver Fibrosis Regression. Cells. 2021 Oct 15;10(10):2759. doi: 10.3390/cells10102759. PMID: 34685739; PMCID: PMC8534788.

30. Younesi S, Parsian H. Diagnostic accuracy of glycoproteins in the assessment of liver fibrosis: A comparison between laminin, fibronectin, and hyaluronic acid. Turk J Gastroenterol. 2019 Jun;30(6):524-531. doi: 10.5152/tjg.2019.17339. PMID: 31144658; PMCID: PMC6565348.

31. Mei L, Ma Y, Zhao L. Correlation between serum liver fibrosis markers and early gastroesophageal varices among patients with compensated liver cirrhosis: a cross-sectional analysis [published correction appears in BMC Gastroenterol. 2023 Mar 30;23(1):99]. BMC Gastroenterol. 2022; 22(1):515. Published 2022 Dec 12. doi:10.1186/s12876-022-02546-w.

32. Bao J, Ouyang Y, Qiao L, He J, Liu F, Wang Y, Miao L, Fu A, Lou Z, Zang Q, Huang W, Huang J, Li Z. Serum CHI3L1 as a Biomarker for Non-invasive Diagnosis of Liver Fibrosis. Discov Med. 2022 Jan-Feb;33(168):41-49. PMID: 36274212.

33. Nishimura N, De Battista D, McGivern DR, Engle RE, Tice A, Fares-Gusmao R, Kabat J, Pomerenke A, Nguyen H, Sato S, Bock KW, Moore IN, Kleiner DE, Zamboni F, Alter HJ, Govindarajan S, Farci P. Chitinase 3-like 1 is a profibrogenic factor overexpressed in the aging liver and in patients with liver cirrhosis. Proc Natl Acad Sci U S A. 2021 Apr 27;118(17):e2019633118. doi: 10.1073/pnas.2019633118. PMID: 33888584; PMCID: PMC8092404.

34. Naim A, Pan Q, Baig MS. Matrix Metalloproteinases (MMPs) in Liver Diseases. J Clin Exp Hepatol. 2017 Dec;7(4):367-372. doi: 10.1016/j.jceh.2017.09.004. Epub 2017 Oct 3. PMID: 29234202; PMCID: PMC5715451.

35. Masuzaki R, Kanda T, Sasaki R, Matsumoto N, Ogawa M, Matsuoka S, Karp SJ, Moriyama M. Noninvasive Assessment of Liver Fibrosis: Current and Future Clinical and Molecular Perspectives. Int J Mol Sci. 2020 Jul 11;21(14):4906. doi: 10.3390/ijms21144906. PMID: 32664553; PMCID: PMC7402287.

36. Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. Cells. 2020 Apr 3;9(4):875. doi: 10.3390/cells9040875. PMID: 32260126; PMCID: PMC7226751.

37. Kimura M, Moteki H, Ogihara M. Role of Hepatocyte Growth Regulators in Liver Regeneration. Cells. 2023 Jan 4;12(2):208. doi: 10.3390/cells12020208. PMID: 36672143; PMCID: PMC9856461.

38. Bai X, Su G, Zhai S. Recent Advances in Nanomedicine for the Diagnosis and Therapy of Liver Fibrosis. Nanomaterials (Basel). 2020 Sep 29;10(10):1945. doi: 10.3390/nano10101945. PMID: 33003520; PMCID: PMC7599596.