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A systematic review on contemporary serum biomarkers for predicting liver fibrosis

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Abstract

Excessive extracellular matrix (ECM) deposition in the liver is a hallmark of liver fibrosis, a basic pathological process in the majority of chronic liver disorders (CLD). It is basically a reversible wound-healing reaction that is accompanied by liver parenchymal cell necrosis and apoptosis. Tissue scarring brought on by the progressive build-up of extracellular matrix (ECM) eventually leads to cirrhosis, portal hypertension, and liver failure. After at least 15–20 years of chronic liver parenchymal injury, progressive fibrogenesis, chronic inflammation, and persistent liver injury interact to cause hepatic fibrosis and its consequences, including cirrhosis. Thus, there is an urgent need for reliable markers for liver fibrosis early diagnosis. The most widely used histological technique for evaluating liver fibrosis is the METAVIR scoring system, which includes no fibrosis (F0), mild fibrosis (F1), considerable fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4) [5]. Liver biopsy is the gold standard for diagnosing liver fibrosis. A single liver biopsy may misidentify between 10% and 30% of cases with hepatic fibrosis, notwithstanding possible consequences, according to recent research [6]. In normal dynamic clinical practice, non-invasive serum biomarkers are more chosen by patients and clinicians due to their simplicity, accessibility, and repeatability.

Keywords: Liver Fibrosis; BARD; NAFLD Fibrosis Score; γ-Glutamyl Transpeptidase; C IV

1. Introduction

Excessive extracellular matrix (ECM) deposition in the liver is a hallmark of liver fibrosis, a basic pathological process in the majority of chronic liver disorders (CLD). It is basically a reversible wound-healing reaction that is accompanied by liver parenchymal cell necrosis and apoptosis. Tissue scarring brought on by the progressive build-up of extracellular matrix (ECM) eventually leads to cirrhosis, portal hypertension, and liver failure [1].Early-stage CLD patients frequently have no symptoms. After at least 15–20 years of chronic liver parenchymal injury, progressive fibrogenesis, chronic inflammation, and persistent liver injury interact to cause hepatic fibrosis and its consequences, including cirrhosis [2]. Cirrhosis is a major global health issue because it ranks 11th in the world's main causes of death and causes around one million fatalities annually [3]. Although the development of hepatic decomposition is prevented and reduced in the reversal of severe fibrosis or cirrhosis, the elevated risk of liver cancer development remains [4].Thus, there is an urgent need for reliable markers for liver fibrosis early diagnosis. The most widely used histological technique for evaluating liver fibrosis is the METAVIR scoring system, which includes no fibrosis (F0), mild fibrosis (F1), considerable fibrosis (F2), advanced fibrosis (F3), and cirrhosis (F4) [5]. Liver biopsy is the gold standard for diagnosing liver fibrosis. A single liver biopsy may misidentify between 10% and 30% of cases with hepatic fibrosis, notwithstanding possible consequences, according to recent research [6]. In normal dynamic clinical practice, non-invasive serum biomarkers are more chosen by patients and clinicians due to their simplicity, accessibility, and repeatability. There are two classes of serum biomarkers: class I (direct) and class II (indirect). While indirect biomarkers indicate liver function, direct biomarkers are linked to the formation and breakdown of extracellular matrix [7]. Additionally, serum models can be

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divided into two groups: A) basic serum tests are "indirect" markers. As our understanding of the mechanisms underlying liver fibrosis has grown, a growing number of serum candidates have been identified and have demonstrated promising value in diagnosing liver fibrosis. When used to predict advanced fibrosis and cirrhosis, complex serum tests (B) contain some direct markers of fibrogenesis, which are more accurate than basic biomarkers [8].

2. Indirect Serum Markers

2.1. AST/ALT Ratio

The AST/ALT ratio was initially proposed in 1957 [9] as a diagnostic tool for viral hepatitis. Following this, several investigations discovered that in patients with alcoholic liver disease (ALD), primary biliary cirrhosis (PBC), non-alcoholic steatohepatitis (NASH), and chronic viral hepatitis, a ratio greater than 1.00 indicated cirrhosis [10–14]. Its predictive results, however, varied greatly between trials; the negative predictive value (NPV) ranged from 0.72 to 0.88, and the positive predictive value (PPV) from 0.64 to 1.00. As a result, severe fibrosis could not be predicted by the ratio alone [15].

2.2. BARD

Three factors were added together to determine the BARD score: BMI > 28 (1 point), AST/ALT ratio > 0.80 (2 points), andDiabetes (1 point). Advanced fibrosis is shown to have a high NPV for score values of 0 or 1 [16], and advanced fibrosis is connected with scores of 2 to 4 (AUROC = 0.70–0.81) [16]. Notably, in the assessment of advanced fibrosis, age and HDL-C are not predictive variables of BARD score [17]. Its ability to diagnose advanced fibrosis in NAFLD is limited, according to several meta-analyses, with summary AUROCs ranging from 0.67 to 0.76[18-20].

2.3. NAFLD Fibrosis Score

NFS -1.675 + 0.037 × age (year) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 2) The EASL-EASD-EASO Clinical Practice Guidelines propose 0.66 albumin (g/dL) 0.013 platelets (109 /L) 0.99 AST/ALT ratio to rule out extensive fibrosis in NAFLD [21]. There are two NFS cut-off scores: 0.68 can be used to diagnose advanced fibrosis (F3-F4) with a PPV of 0.82, and − 1.455 can be used to rule out advanced fibrosis with an NPV of 0.88 [22]. Following a meta-analysis of 64 studies involving 13,046 NAFLD patients, it was discovered that the summary AUROC of NFS for advanced fibrosis is 0.84, comparable to FIB-4 and greater than that of APRI (0.77) and BARD (0.76). The ability to forecast mortality and an elevated risk of liver-related diseases (ascites, gastro-esophageal varices, etc.) is one of NFS's benefits. Nonetheless, a lot of NFS values (20–58%) fall in between the two cut-off points, producing an unclear result [23].

2.4. γ-Glutamyl Transpeptidase (GGT)-to-platelet ratio (GPR)

A recently established serum model for predicting severe fibrosis and cirrhosis is the γ-glutamyl transpeptidase (GGT)-to-platelet ratio (GPR). GPR performed better than APRI and FIB-4 in predicting substantial liver fibrosis in Chinese and Gambian cohorts [24]. Subsequent studies, however, revealed that GPR performed passably and offered no appreciable benefit over APRI or FIB-4 [25]. Consequently, the disparity can be caused by the heterogeneity. In 96% of cases in the previous study, the Hepatitis B e antigen (HBeAg) was negative, and the quantity of HBV-DNA was comparatively low. On the other hand, a significant number of participants in the latter trial had elevated HBV-DNA levels and a greater frequency of HBeAg positivity (53 %). Another explanation might be the various laboratory techniques employed in the research: liver biopsies and Fibroscan.

2.5. Fibrotest

FibroTest (FT) = 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. FT was developed initially for patients with CHC [34], and it was later validated and suggested for use in patients with other common liver illnesses, such as CHB, ALD, and NAFLD [26–27]. In the HCV population (n = 152) and individuals with other chronic liver illnesses (n = 290), the AUROCs of five biochemical scores were compared in a study. The findings demonstrated that FT had comparable diagnostic efficiency in HCV patients and other CLD patients, and it outperformed Forns (platelet count, cholesterol levels, age, and GGT) in terms of superior diagnostic accuracy [28]. Moreover, patients with ALD and NAFLD showed proven FT prognostic values [29, 30]. On the other hand, FibroTest's performance in identifying cirrhosis was shown to be satisfactory in a meta-analysis of seven trials including NAFLD patients (AUROC = 0.92). By contrast, a review of five studies revealed poor accuracy in the diagnosis of advanced and substantial fibrosis (AUROC = 0.77 for both categories) [31]. In general, Fibrotest's predictive scores for fibrosis diagnosis are good.

2.6. HA, LN, C IV and PCIII

One of the most common glycosaminoglycan in the liver extracellular matrix (ECM) is hyaluronic acid (HA). Laminin (LN) and collagen type IV (CIV) are essential elements of basement membranes, whereas procollagen type III (PCIII) gauges the production of collagen [32]. When employed alone, these markers do not, however, demonstrate good sensitivity and specificity [33-34]. In comparison to the other three markers, HA linked most strongly with the fibrosis stage, according to a comprehensive evaluation that included 26 research of HCV patients [35]. Therefore, accuracy may be increased by combining these markers. Serum LN has been shown to be a sensitive screening test for liver fibrosis when combined with HA [36]. In patients with co-infections of HIV and HBV, COOP score, a novel model that incorporates CIV, exhibits a satisfactory diagnostic value in fibrosis staging [37,38]. In addition, the most reliable and accurate biomarkers for assessing the synthesis of type III collagen are propeptides of type III collagen (PRO-C3) and the N-terminal peptide of PCIII (PIIINP). Notably, PIIINP diagnosis of advanced fibrosis yielded NPV(0.95) and PPV(1.00) at 6.6 ng/ml and 11 ng/ml cut-offs [59]. PIIINP and HA are included in the Enhanced Liver Fibrosis (ELF) score, which indicates good potential for liver fibrosis prediction [39]. Additionally, it has been confirmed that ELF and PRO-C3 work better for advanced fibrosis detection then APRI and FIB-4.

2.7. Novel Serum Biomarkers

As our knowledge of the pathophysiology of fibrosis has grown, several promising biomarkers have been found in both clinical and experimental research. The biological involvement of extracellular vesicles (EVs) and non-coding RNAs (ncRNAs) in liver fibrosis have been confirmed by a growing body of research. However, before they can be employed as trustworthy blood biomarkers of liver fibrosis, several miRNAs are still in the in vitro research stage and require comprehensive clinical efficacy assessments. Below is a list of recently discovered or suggested ncRNA and EV-ncRNA biomarkers. Subtypes of circulating non-coding RNAs, such as miRNAs and lncRNAs, are a potent and less intrusive approach for tracking illnesses, offering good stability and simple testing. Apoptotic bodies, exosomes, and microvesicles are examples of cell-derived membrane structures known as EVs. These structures have gained notice for their ability to function as in vivo natural transporters of proteins, lipids, and nucleic acids. The most recent discovery of EVs-ncRNAs as indicators in many chronic liver disease situations [40,41].

2.8. miRNAs and EV-miRNAs

Short RNA molecules, known as miRNAs (19–24 nt), have been identified as prospective indicators for liver fibrosis because they alter gene expression at the posttranscriptional level [42]. Hepatic fibrosis and other chronic liver illnesses are associated with an up-regulation of miR-221, whose high expression level has been linked to active liver regeneration and recovery. Additionally, in vivo and in vitro fibrogenesis mitigation has been demonstrated by miR-221 inhibition [43]. Targeting TGF-β receptor 1, serum miR-98-5p is considerably down-regulated in patients with liver fibrosis compared to healthy controls and HBV carriers [44]. This finding may have diagnostic and therapeutic implications. In a cross-sectional analysis, miR-193a-5p, miR-122-5p, and miR-193b-3p were shown to correlate with liver fibrosis [45]. In addition, miR-193a-5p rose across all comparisons in a NAFLD cohort, and it increased significantly in cases with NAFLD activity scores. Exosomal miRNAs that are released are now thought to be possible indicators of liver fibrosis [46]. A study demonstrated that serum exosomal miR-92a-3p and miR-146a-5p increased with the aggravation of liver fibrosis by identifying fibrosis-related serum exosomal miRNAs in 9 CHB patients and verifying them in 282 CHB patients. Additionally, for diagnosing severe fibrosis, their AUROCs were 0.88 and 0.82, respectively, which were considerably higher than those of APRI, FIB-4, and liver stiffness test [47]. Remarkably, only exosomal miR-211 was able to differentiate between HCC and CHB when compared to circulating miR-211 [48], demonstrating the disparities in levels between circulating and exosomal miRNAs.

2.9. LncRNAs and EV-LncRNAs

LncRNAs are non-coding RNAs with over 200 nucleotides that control both transcriptional and posttranscriptional aspects of gene expression. The recently identified lncRNA TGFB2-Overlapping Transcript 1 (TGFB2-OT1) is up-regulated in NAFLD patients. When TGFB2-OT1 and FIB-4/Fibroscan are combined, the diagnostic performance for advanced fibrosis is improved, with AUROCs of 0.89 in both combinations [49]. Additionally, it was found that the blood level of lncRNA-MEG3 was lower in CHB patients and negatively connected with the stage of liver fibrosis, as well as negatively correlated with α-SMA and COL1A1, suggesting a relationship with the process of liver fibrosis in CHB [50]. Another marker that may be used to identify liver fibrosis in CHB patients is serum lncRNA-p21, which has a sensitivity of 0.85 and a negative correlation with the fibrotic stage of the disease. Additionally, there is promise to use serum lncRNA-p21 to identify liver fibrosis in CHB patients. It was found to have a negative correlation with the fibrotic stage in CHB and to have an AUROC of 0.85 in liver fibrosis prediction, with a sensitivity of 1.00 and specificity of 0.70 [51]. Further studies regarding its diagnostic efficacy are necessary, however, LncRNA SCARNA 10 was found to be raised in fibrosis/cirrhosis patients, similar to the fibrotic stage, and positively linked with Col1α1 [52]. Serum exosomal

lncRNAH19 levels in biliary atresia patients were positively linked with the severity of liver fibrosis, and were expressed almost six times more in severe liver fibrosis than in moderate liver fibrosis [53].

3. Conclusion

Early therapeutic intervention is helpful in preventing the development of liver cirrhosis and hepatocellular cancer by promptly identifying liver fibrosis. Serum biomarkers are easy to obtain and collect, offer high value for money, have small sampling mistakes, and are suitable for dynamic monitoring. Nevertheless, the majority of biomarkers provide high NPV but low PPV, suggesting that they are not sufficiently predictive when employed alone, but are best utilized in the exclusion of patients without severe fibrosis and cirrhosis to save unnecessary liver biopsies. Additionally, research is required to create biomarkers that can identify fibrosis at an earlier stage and be used in therapeutic settings. In the near future, new experimental serum indicators may help with the development of identifying liver fibrosis due to our growing understanding of the disease's pathogenesis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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