

Research Review on Early Diagnostic Markers and Intervention Strategies for Liver Fibrosis

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Abstract: Liver fibrosis represents a pivotal intermediate pathological stage in the progression from various chronic liver diseases to cirrhosis and hepatocellular carcinoma, characterized primarily by persistent hepatocyte injury leading to the activation of hepatic stellate cells, which subsequently results in excessive extracellular matrix deposition and hepatic tissue structural remodeling. Early-stage liver fibrosis is fully reversible; however, once it advances to late-stage fibrosis or cirrhosis, the difficulty of reversal significantly increases. Therefore, early and accurate diagnosis, coupled with timely intervention, is crucial for improving the prognosis of patients with chronic liver diseases and reducing mortality from end-stage liver diseases. This article systematically reviews current markers for the early diagnosis of liver fibrosis and summarizes mainstream intervention strategies, providing theoretical references and clinical practice evidence for the early diagnosis and treatment of liver fibrosis.

Keywords: Liver fibrosis; Early diagnosis; Biomarkers; Non-invasive diagnosis; Intervention strategies; Anti-fibrotic therapy

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1. Introduction

Chronic liver disease is a hepatic condition resulting from chronic injury caused by various factors, characterized by hepatocyte damage, often accompanied by abnormal liver function, and typically persisting for more than six months. The later stages of the disease are primarily marked by liver fibrosis and cirrhosis^[1]. According to global disease burden statistics, over 80% of deaths from cirrhosis and hepatocellular carcinoma annually are closely associated with the persistent progression of liver fibrosis^[2]. Liver fibrosis is not an independent disease but rather a pathological repair response of the liver to chronic injury. Under physiological conditions, the synthesis and degradation of the extracellular matrix in the liver are in dynamic equilibrium. However, under chronic injury conditions, this balance is disrupted, and activated hepatic stellate cells become the primary cells secreting collagen. Large amounts of extracellular matrix, including type I and type III collagen and fibronectin, abnormally deposit in the liver, gradually destroying the normal lobular structure of the liver and ultimately leading to cirrhosis^[3]. In recent years, with the rapid development of molecular biology, imaging, and omics

technologies, the early diagnostic system for liver fibrosis has been continuously improved, and targeted intervention methods have gradually transitioned from basic research to clinical application. This article provides a comprehensive review of research progress in this field.

2. Early diagnostic markers

2.1. Traditional serological markers

Traditional serological markers are the earliest indicators used in clinical non-invasive assessment of liver fibrosis, categorized into extracellular matrix metabolism and indirect liver function markers. They are convenient to detect, low-cost, and suitable for primary screening at the grassroots level. However, the sensitivity and specificity of a single marker are insufficient, necessitating combined use^[4].

Markers related to extracellular matrix metabolism are core indicators reflecting the fibrotic process. The clinically common “four markers of liver fibrosis” include hyaluronic acid (HA), type III procollagen N-terminal peptide (PIIINP), type IV collagen (CIV), and laminin (LN)^[5]. HA is metabolized by the liver, and its level is positively correlated with the degree of fibrosis, increasing early on. PIIINP directly reflects the rate of collagen synthesis, rising significantly early and declining in the late stage when synthesis slows. CIV is a core component of the hepatic basement membrane, with its level rapidly increasing early after basement membrane degradation, showing high specificity. LN can assist in evaluating the degree of hepatic sinusoidal capillarization, increasing in the progressive stage. Combined detection of these markers improves accuracy, but false positives may occur due to inflammation or connective tissue diseases, requiring clinical exclusion. Indirect liver function markers rely on routine test results to construct assessment models without additional detection.

Classic examples include the APRI and FIB-4 indices^[6]. The FIB-4 index integrates four indicators, age, AST, ALT, and platelets, and is easy to calculate. It has high sensitivity for early significant fibrosis and is recommended as a first-line primary screening tool by domestic and international guidelines, suitable for patients with fatty liver and chronic hepatitis B.

2.2. Emerging specific molecular markers

In recent years, with the continuous development of molecular biology techniques, a batch of highly sensitive and specific emerging markers for liver fibrosis have been gradually discovered. Most of these markers are directly related to the activation of hepatic stellate cells and inflammatory fibrotic pathways, accurately capturing the early fibrotic process and effectively compensating for the diagnostic shortcomings of traditional markers.

Chitinase 3-like protein 1 (CHI3L1/YKL-40) is currently the most well-researched indicator, primarily secreted by activated hepatic macrophages and hepatic stellate cells. It specifically increases early in fibrosis and is not affected by liver inflammation, biliary obstruction, or other factors, showing superior early diagnostic specificity compared to traditional markers^[7]. Clinical studies have confirmed a significant positive correlation between serum CHI3L1 levels and fibrosis staging in patients with chronic hepatitis B and non-alcoholic fatty liver disease. Combined detection with FIB-4 can significantly improve the detection rate of early mild fibrosis and has been listed as a supplementary diagnostic indicator in some liver disease treatment guidelines^[8].

Golgi protein 73 (GP73) is lowly expressed in hepatocytes under physiological conditions but is extensively released into the blood during hepatocyte damage and early fibrosis. Serum concentration is

highly correlated with fibrosis progression, showing prominent value in the early diagnosis of viral hepatitis-related fibrosis and the ability to distinguish liver fibrosis from simple liver inflammation ^[9].

2.3. Non-invasive imaging diagnostic techniques

Imaging examinations can visually observe liver structure and measure liver tissue stiffness, enabling non-invasive, quantitative, and dynamic assessment of liver fibrosis. They are important methods for clinical early diagnosis, primarily divided into elastography and functional imaging ^[10].

Transient elastography is simple, non-invasive, reproducible, and has a short detection time. It judges the degree of fibrosis based on liver stiffness and has good diagnostic performance for moderate to severe fibrosis and early cirrhosis, becoming the preferred non-invasive examination for chronic liver disease staging ^[11]. Shear wave elastography and acoustic radiation force impulse imaging, developed on this basis, are less affected by obesity, ascites, and bile stasis, have a broader application range, and exhibit stronger detection capabilities for mild fibrosis. Functional imaging includes magnetic resonance elastography (MRE) and CT perfusion imaging.

MRE is close to non-invasive liver biopsy, with sensitivity and specificity exceeding 90%, providing accurate grading and suitable for patients in whom elastography fails. However, it is expensive and has a long examination time, limiting its grassroots popularity ^[12]. CT perfusion imaging reflects hepatic sinusoidal microcirculation injury through blood flow changes and is often used in combination with morphological examinations to assist in judging early liver fibrosis ^[13].

2.4. Multi-omics combined diagnostic models

A single marker or technique is insufficient to meet the demands of early and accurate diagnosis. Multi-omics combined diagnostic models based on transcriptomics, metabolomics, and proteomics have become a new direction for the early diagnosis of liver fibrosis. These models integrate multiple serum markers, imaging parameters, and clinical indicators, constructing diagnostic formulas through machine learning algorithms, significantly improving the diagnostic accuracy of early fibrosis. For example, a model combining bile acids and lipid metabolite profiles selected based on metabolomics with elastography stiffness values improves the diagnostic sensitivity for early mild fibrosis by more than 30% compared to a single indicator ^[14]. Although multi-omics models have broad prospects, they are currently in the clinical validation stage, with complex detection processes and high costs. Future efforts should focus on simplifying processes, reducing costs, and achieving clinical translation and application.

3. Early intervention strategies

The core of liver fibrosis intervention lies in blocking chronic liver injury, inhibiting the activation of hepatic stellate cells, promoting extracellular matrix degradation, and achieving fibrosis reversal ^[15].

3.1. Etiological intervention

Etiological intervention is the primary step in liver fibrosis treatment. Only by completely removing or controlling the causative factors can the activation of hepatic stellate cells and fibrogenesis be blocked at the source, which is also crucial for the reversal of early fibrosis. Well-established clinical guidelines have been developed for intervention plans targeting different etiologies: for patients with viral hepatitis, timely

initiation of standardized antiviral therapy is necessary. Chronic hepatitis B patients require long-term oral administration of nucleoside (nucleotide) analogs, while chronic hepatitis C patients are treated with direct-acting antiviral drugs to continuously suppress viral replication, rapidly alleviate liver inflammation, and reverse early fibrosis ^[16]. For patients with alcoholic liver disease, strict abstinence from alcohol is essential, along with supplementation of B vitamins, proteins, and other nutrients to repair liver cell damage ^[17]. For patients with non-alcoholic fatty liver disease, the focus is on controlling metabolic disorders through weight loss, blood glucose and lipid control, and improvement of insulin resistance to alleviate liver fat deposition and inflammation; for patients with autoimmune liver disease and cholestatic liver disease, long-term administration of immunosuppressants and choleric drugs is required to control autoimmune reactions and cholestasis, preventing ongoing liver damage ^[18].

3.2. Targeted anti-fibrotic drug therapy

The mechanisms of action of anti-fibrotic drugs mainly include inhibiting the activation of hepatic stellate cells, promoting the apoptosis of activated stellate cells, inhibiting collagen synthesis, and promoting extracellular matrix degradation. Currently, drugs used clinically fall into two categories: Western medicines and traditional Chinese medicines (TCMs), most of which serve as adjuvant therapies and need to be combined with etiological treatment.

In terms of Western medicines, there are currently no specifically approved anti-fibrotic drugs. Clinically, drugs with anti-inflammatory and anti-fibrotic effects are often used for symptomatic treatment. For example, pirfenidone can inhibit the TGF- β 1 pathway, reduce collagen synthesis, and exert anti-inflammatory effects, showing certain intervention effects on mild to moderate liver fibrosis ^[19]. Obeticholic acid can regulate bile acid metabolism and improve insulin resistance, making it suitable for fibrosis associated with non-alcoholic fatty liver disease; ursodeoxycholic acid can promote bile excretion and protect the liver, alleviating cholestatic liver injury ^[20]. These drugs require long-term administration, and some patients may experience gastrointestinal reactions, abnormal liver function, and other side effects, necessitating close monitoring.

TCMs are widely used in liver fibrosis treatment, offering advantages such as multi-target effects and fewer side effects, which meet the treatment needs of chronic liver disease patients in China. Classic TCM formulas such as Compound Biejia Ruangan Tablets, Anluo Huaxian Pills, and Fuzheng Huayu Capsules have been clinically validated to effectively inhibit collagen synthesis, promote fiber degradation, and improve liver fibrosis staging, especially suitable for early fibrosis associated with viral hepatitis and non-alcoholic fatty liver disease. Combined with etiological treatment, they can significantly enhance the reversal rate ^[21]. TCM treatment emphasizes holistic regulation, combining liver protection, anti-inflammatory, and anti-fibrotic effects, making it suitable for long-term intervention. However, it requires syndrome differentiation and treatment to avoid blind medication.

3.3. Lifestyle and comprehensive intervention

Lifestyle intervention is an important component of early liver fibrosis intervention, particularly suitable for patients with fibrosis associated with non-alcoholic fatty liver disease and alcoholic liver disease, and can assist in improving treatment outcomes ^[22]. The core measures include: a reasonable diet following the principles of low fat, low sugar, high protein, and high dietary fiber, reducing the intake of refined

carbohydrates, fried foods, and sugary beverages, increasing the intake of vegetables, high-quality proteins, and whole grains, and controlling daily calorie intake; regular exercise, with a weekly commitment of 150 minutes of moderate-intensity aerobic exercise such as brisk walking, jogging, and swimming, combined with resistance training to control weight and reduce liver fat deposition ^[23]. Avoiding liver-damaging factors, strictly abstaining from alcohol, avoiding the misuse of drugs and health supplements, and reducing additional liver cell damage; regular follow-up, with liver function tests, liver fibrosis markers, and liver elastography performed every 3–6 months to dynamically monitor fibrosis progression and adjust intervention plans in a timely manner.

3.4. Novel intervention approaches: Translation from basic research to clinical practice

With in-depth research on the molecular mechanisms of liver fibrosis, a series of novel intervention approaches have entered clinical trial stages, providing new directions for refractory early fibrosis ^[24]. Targeted stem cell therapy, through the infusion of mesenchymal stem cells, can inhibit liver inflammation, promote liver cell regeneration, and degrade extracellular matrix. Preliminary clinical studies have confirmed its effectiveness in improving liver fibrosis staging ^[25]. Gene therapy and RNA interference technology target and silence pro-fibrotic genes such as TGF- β 1 and connective tissue growth factor to block fibrogenesis pathways, currently in animal experimental and early clinical stages ^[26]. Intestinal microecological regulation, through the use of probiotics and prebiotics to modulate the intestinal microbiota, reduces the absorption of intestinal-derived endotoxins, alleviating liver inflammation and fibrosis, and has become a hotspot for intervention in fibrosis associated with non-alcoholic fatty liver disease. Although these novel approaches hold great promise, they still require large-sample, long-term clinical studies to verify their safety and effectiveness and have not yet entered routine clinical practice.

4. Summary and outlook

Early diagnosis and intervention of liver fibrosis are core components of the prevention and treatment of chronic liver diseases. Currently, non-invasive diagnostic systems have been gradually improved, with traditional serological markers combined with elastography meeting the needs of preliminary clinical screening. Emerging molecular markers and multi-omics models have significantly enhanced early and accurate diagnostic capabilities, hopefully gradually replacing liver biopsy as the mainstream diagnostic method. Future research directions should focus on: developing highly specific and sensitive single-molecule early diagnostic markers, simplifying multi-omics diagnostic models for grassroots popularization; developing targeted and low-side-effect anti-fibrotic drugs, clarifying the molecular mechanisms of TCMs; promoting the clinical translation of novel stem cell and gene therapies, and constructing a standardized “screening-diagnosis-intervention-follow-up” full-process management system. Through multidisciplinary collaboration, early detection, diagnosis, and treatment of liver fibrosis can be achieved, ultimately reducing the incidence of liver cirrhosis and liver cancer and improving the long-term prognosis of chronic liver disease patients.

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