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NON-INVASIVE STAGING OF LIVER FIBROSIS IN CHRONIC HEPATITIS B AND C: CURRENT EVIDENCE AND CHALLENGES POST-HCV CURE

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Abstract: Accurate staging of liver fibrosis remains a major challenge in chronic viral hepatitis and other liver diseases. Although liver biopsy has long been considered the reference standard, its limitations—including sampling error, inter- and intraobserver variability, invasiveness, cost, and safety concerns—have prompted the development of non-invasive alternatives. Currently, both serological biomarkers and physical methods demonstrate acceptable diagnostic performance and are widely incorporated into routine clinical practice for fibrosis assessment in viral hepatitis. A meta-analysis of serum biomarker scores like FibroTest in 6,378 subjects (including 3,501 with HCV) reported an AUROC of 0.84 (95% CI 0.83–0.86) for significant fibrosis. Similarly, for transient elastography (TE), a meta-analysis of 50 studies showed AUROCs of 0.84 for significant fibrosis and 0.94 for cirrhosis in HCV patients. This review summarizes current evidence on liver fibrosis staging in chronic hepatitis B (CHB) and chronic hepatitis C (CHC), with particular emphasis on non-invasive serological and imaging-based methods. Additionally, a key unresolved issue is discussed: the assessment of liver fibrosis following hepatitis C virus (HCV) cure, where non-invasive tests may overestimate regression due to reduced inflammation, as evidenced by studies showing persistent stiffness despite histological improvements.

Keywords: liver fibrosis, chronic hepatitis, hepatitis B, hepatitis C, non-invasive tests, meta-analysis, sustained virological response

1. Introduction

Despite major therapeutic advances, chronic hepatitis B and C remain significant global public health concerns. Proper evaluation of hepatic inflammation and fibrosis is essential in patients with chronic viral hepatitis, as fibrosis stage is a critical determinant of prognosis and long-term outcomes. Historically, liver biopsy was the primary method used to assess histological liver damage. However, due to its invasive nature, associated risks, costs, and variability in interpretation, alternative non-invasive approaches have been developed and increasingly adopted in clinical practice.

Non-invasive methods include biological markers—both direct and indirect serum-based tests—and physical techniques, particularly imaging-based elastography. While these tools show good diagnostic accuracy, their interpretation requires caution in certain clinical settings, such as acute inflammation or cholestasis. For instance, a systematic review and meta-analysis highlighted that two-dimensional shear wave elastography (2D-SWE) outperforms transient elastography for significant fibrosis in chronic viral hepatitis, with AUROCs of 0.90 versus 0.85. This review focuses on non-invasive approaches for fibrosis staging in CHC and CHB, highlighting their strengths, limitations, and clinical applications, enriched with evidence from recent meta-analyses.

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2. Chronic Hepatitis C

HCV infection promotes liver fibrogenesis through both direct viral effects on cellular signaling and indirect immune-mediated inflammatory mechanisms. Progressive fibrosis is the main precursor to cirrhosis and is strongly associated with portal hypertension, hepatocellular carcinoma (HCC), and liver-related mortality.

With the advent of effective antiviral therapies, liver biopsy is now rarely used in CHC. Non-invasive tests (NITs) have demonstrated favorable cost-effectiveness and diagnostic performance, particularly for identifying advanced fibrosis and cirrhosis. Histological scoring systems such as METAVIR remain the benchmark for validation, defining significant fibrosis as F2 and advanced fibrosis or cirrhosis as F3–F4.

NITs are broadly classified into biological (serum-based) and physical (elastography-based) methods. Although no ideal test exists, many NITs perform well in identifying advanced disease and can often replace liver biopsy. In patients with clinically evident cirrhosis, conventional imaging may suffice for diagnosis, with additional tests reserved for risk stratification.

2.1. Biological Non-Invasive Tests

2.1.1. Indirect Biomarkers

Indirect serum markers rely on routine laboratory parameters and are widely used due to their simplicity and low cost. The most commonly applied scores are the AST-to-platelet ratio index (APRI) and the Fibrosis-4 (FIB-4) index. While these tests perform well for detecting cirrhosis, they have limited accuracy in intermediate fibrosis stages, often creating a diagnostic “gray zone.”

A meta-analysis of 4,266 HCV patients reported an AUROC of 0.76 (95% CI 0.74–0.79) for APRI in detecting significant fibrosis and 0.82 (95% CI 0.79–0.86) for cirrhosis, with sensitivities ranging from 41–91% and specificities 47–95% for significant fibrosis at cutoffs ≤0.5 and >1.5. APRI values above 2.0 show high specificity for cirrhosis, while FIB-4 values greater than 3.25 reliably identify advanced fibrosis, with AUROCs around 0.85 for cirrhosis and specificities up to 98% at cutoffs >3.25. Conversely, low FIB-4 values effectively exclude advanced disease. These characteristics make indirect markers particularly useful for identifying patients who require closer monitoring.

2.1.2. Direct Biomarkers

Direct markers reflect extracellular matrix turnover and fibrogenesis, including hyaluronic acid, laminin, collagen-related peptides, and matrix metalloproteinase regulators. Many of these markers were developed during the interferon-treatment era, when precise fibrosis staging influenced treatment decisions.

Composite panels combining direct and indirect markers—such as the Enhanced Liver Fibrosis (ELF) score, FibroTest®, FibroMeter®, and Hepascore®—demonstrate improved diagnostic

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accuracy. Among these, FibroMeter® and ELF score have shown strong performance for detecting advanced fibrosis. For ELF, a meta-analysis indicated AUROCs of 0.78 for significant fibrosis (sensitivity 90%, specificity 30%) and 0.89 for cirrhosis (sensitivity 91%, specificity 69%). FibroTest showed an AUROC of 0.84 for significant fibrosis in a large meta-analysis, with sensitivity 75% and specificity 85% at cutoff >0.48.

2.2. Physical Tests

Elastography-based techniques have become central to non-invasive fibrosis assessment over the past two decades. Vibration-controlled transient elastography (VCTE), commonly known as FibroScan®, is the most widely validated and used method in CHC.

VCTE is rapid, reproducible, and well tolerated, but its accuracy may be affected by acute inflammation, marked ALT elevations, cholestasis, hepatic congestion, or ascites. A meta-analysis of 50 studies reported AUROCs of 0.84 for significant fibrosis (optimal cutoff 7.6 kPa) and 0.94 for cirrhosis (optimal cutoff 13.0 kPa). Established cutoff values allow reliable identification of significant fibrosis, advanced fibrosis, and cirrhosis, though overlap between stages must be considered.

Other ultrasound-based techniques, such as point shear-wave elastography (p-SWE) and two-dimensional shear-wave elastography (2D-SWE), provide additional advantages by allowing real-time tissue visualization. A meta-analysis comparing TE and 2D-SWE in chronic viral hepatitis found 2D-SWE superior for significant fibrosis (AUROC 0.90 vs. 0.85, sensitivity 84% vs. 78%, specificity 84% vs. 79%), with comparable performance for advanced fibrosis and cirrhosis (AUROCs 0.93–0.97). However, variability between devices and operator dependence limit standardization. Magnetic resonance elastography offers excellent accuracy but remains limited by cost and accessibility.

2.3. Fibrosis Assessment after Sustained Virological Response

Following HCV eradication with direct-acting antivirals, fibrosis assessment remains challenging. Reductions in liver stiffness measurements after sustained virological response (SVR) are frequently observed but likely reflect decreased inflammation rather than true fibrosis regression. Studies show fibrosis regression in 1/3 to 2/3 of patients post-SVR, with greater likelihood in milder baseline fibrosis, and significant declines in TE values (e.g., from 20.4 kPa to 14.0 kPa at 48 weeks). Consequently, pre-treatment elastography cutoffs are not valid after SVR.

Currently, no non-invasive method is validated for accurately staging fibrosis regression post-SVR. Nevertheless, elastography retains prognostic value, particularly for assessing portal hypertension and HCC risk. Elevated baseline liver stiffness or limited post-treatment improvement has been associated with increased HCC incidence. Regression is linked to reduced mortality (HR=0.36) and fewer decompensating events, but non-invasive tests like TE may overestimate due to inflammation resolution. Annual non-invasive monitoring may therefore be reasonable in selected patients.

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3. Chronic Hepatitis B

Chronic HBV infection affects hundreds of millions worldwide and carries a substantial risk of cirrhosis and HCC. Accurate fibrosis staging is essential for treatment decisions and long-term surveillance. Non-invasive methods are now routinely recommended in international guidelines.

3.1. Biological Tests in CHB

Compared with CHC, serum biomarkers are less reliable in CHB. APRI and FIB-4 show limited sensitivity and frequently misclassify advanced fibrosis, particularly in older patients. An individual participant data meta-analysis of 3,548 CHB patients found APRI with AUROC 0.81 for cirrhosis (LSM >12.2 kPa) but low sensitivity (16.5%) at WHO threshold >2.0, improving to 56.2% at optimized threshold >0.65. FIB-4 had lower AUROC (0.77 for cirrhosis). Modified cutoffs have been proposed to improve diagnostic performance, but age-related variability remains a significant limitation.

Despite these shortcomings, serum markers may still be useful in resource-limited settings. However, elastography has largely replaced biomarkers as the preferred method for fibrosis assessment in CHB.

3.2. Physical Tests in CHB

3.2.1. Transient Elastography

VCTE is the most extensively validated non-invasive tool in CHB. Its accuracy is influenced by ALT flares and inflammatory activity, which are more common in HBV than HCV. Therefore, elastography should be avoided during acute hepatitis or marked ALT elevation.

When applied appropriately, VCTE outperforms serum markers in diagnosing advanced fibrosis and cirrhosis. Guideline-based cutoff values help stratify patients and guide treatment decisions, with liver biopsy reserved for cases with indeterminate results. In sub-Saharan African CHB cohorts, TE served as a reference with thresholds of 7.9 kPa for significant fibrosis and 12.2 kPa for cirrhosis.

Antiviral therapy often leads to reduced liver stiffness over time, although this may reflect inflammation resolution rather than fibrosis reversal. Baseline fibrosis stage remains the strongest predictor of histological improvement.

3.2.2. Shear-Wave Elastography

Point shear-wave and two-dimensional shear-wave elastography have demonstrated good diagnostic accuracy for advanced fibrosis and cirrhosis in CHB. A meta-analysis of 11 studies with 2,623 CHB patients reported 2D-SWE with sensitivity 88%, specificity 83%, and AUROC 0.92 for significant fibrosis (mean cutoff 7.91 kPa), with lower cutoffs in treatment-naïve patients (7.15 kPa). Meta-analyses suggest performance comparable to VCTE, with proposed

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cutoff values for different fibrosis stages. These methods may further reduce the need for liver biopsy when combined with serum markers.

Conclusion

Assessment of liver fibrosis in chronic viral hepatitis is essential for prognostication, treatment decisions, and surveillance strategies. Non-invasive tests have become the cornerstone of fibrosis evaluation, offering reliable and accessible alternatives to liver biopsy. In both CHC and CHB, elastography—particularly VCTE—is the most validated and clinically useful method, supported by meta-analyses showing high AUROCs for advanced stages. However, important limitations remain, especially regarding fibrosis assessment after HCV cure, where tests like TE may not accurately reflect true regression. Continued research is required to refine cutoff values and validate prognostic applications in post-treatment populations.

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