ASSESSMENT METHODS FOR HEPATOCELLULAR DAMAGE IN CHRONIC HEPATITIS: BIOCHEMICAL AND INSTRUMENTAL APPROACHES

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Abstract*. Chronic hepatitis remains a major global health concern due to its progressive nature and potential to cause liver fibrosis, cirrhosis, and hepatocellular carcinoma. Accurate and timely assessment of hepatocellular injury is essential for early diagnosis, effective disease staging, and monitoring of therapeutic response. This article provides a comprehensive overview of both biochemical and instrumental methods used to evaluate hepatocyte damage in patients with chronic hepatitis. Biochemical markers such as ALT, AST, ALP, GGT, and bilirubin levels serve as primary indicators of hepatocellular integrity and inflammation. Instrumental approaches, including ultrasonography, transient elastography (FibroScan), computed tomography (CT), magnetic resonance imaging (MRI), and MR elastography, offer valuable structural and functional insights into the liver. The paper also discusses the advantages and limitations of each modality, as well as the growing role of non-invasive technologies in routine clinical practice. Emphasis is placed on the need for an integrated diagnostic strategy that combines laboratory data with imaging findings to improve the accuracy of liver damage evaluation and guide patient management in chronic hepatitis.*

Keywords*: Chronic hepatitis, hepatocyte damage, biochemical markers, instrumental diagnostics, elastography, ultrasound, hepatic fibrosis, liver function tests.*

Introduction: Chronic hepatitis (CH) represents a group of liver disorders characterized by persistent inflammation of the hepatic parenchyma lasting for at least six months. It is a globally prevalent health concern, frequently caused by viral infections (hepatitis B and C), autoimmune processes, metabolic syndromes (e.g., non-alcoholic fatty liver disease), drug-induced liver injury, and toxic exposures. Regardless of etiology, ongoing hepatocellular inflammation and necrosis can lead to progressive fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC), making early assessment and monitoring of liver damage critical in clinical practice. The liver, being a central organ in metabolism, detoxification, and immune regulation, shows limited symptomatic response in the early stages of chronic disease.

Therefore, non-invasive diagnostic tools play a crucial role in evaluating liver pathology before irreversible damage occurs. Traditional biochemical markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and bilirubin provide essential information regarding hepatocellular injury and cholestasis. However, these parameters often lack specificity and do not always correlate well with the histological severity of liver damage. To overcome the limitations of biochemical assessments, instrumental diagnostic modalities have become increasingly important. Ultrasound imaging (US) remains the first-line, non-invasive imaging technique to detect liver texture changes, steatosis, and cirrhotic transformation.

Advanced techniques like transient elastography (FibroScan), shear-wave elastography, computed tomography (CT), and magnetic resonance imaging (MRI) offer improved accuracy in detecting fibrosis, assessing liver stiffness, and visualizing subtle morphological alterations. In recent years, significant progress has been made in the development of non-invasive algorithms and scoring systems that combine laboratory and imaging data to stratify disease severity and guide treatment decisions. Nevertheless, the integration of multiple diagnostic approaches remains essential to ensure accurate staging of liver injury and timely intervention. This article aims to provide a comprehensive overview of the current biochemical and instrumental methods used in the assessment of hepatocyte damage in chronic hepatitis. By comparing their diagnostic value, limitations, and potential for integration into clinical workflows, the paper emphasizes the necessity of a multidisciplinary approach for the effective management of chronic liver disease.

Biochemical Markers for Assessing Hepatocyte Damage

Biochemical markers play a fundamental role in the initial assessment and longitudinal monitoring of liver injury in chronic hepatitis. Hepatocytes, as the primary functional cells of the liver, are highly sensitive to pathological processes such as inflammation, necrosis, and fibrosis.

When damaged, they release intracellular enzymes into the bloodstream, which can be measured to evaluate the extent and type of hepatic injury. The two most widely used enzymes are alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT is localized predominantly in the cytosol of hepatocytes and is considered a more specific marker of liver cell injury, whereas AST is found in both the cytosol and mitochondria of hepatocytes as well as in extrahepatic tissues such as cardiac and skeletal muscle. In chronic viral hepatitis (e.g., HBV or HCV), persistent elevation of ALT levels is often correlated with ongoing necroinflammatory activity, and can serve as a surrogate marker for histological damage, although fluctuations in ALT levels can occur even in the absence of significant fibrosis. The AST/ALT ratio offers additional diagnostic utility. In chronic hepatitis, this ratio is usually less than 1, while in alcoholic liver disease the ratio often exceeds 2, owing to mitochondrial damage and pyridoxal phosphate deficiency. However, this ratio may become less reliable in advanced fibrosis or cirrhosis, where both enzymes may decrease due to decreased hepatic mass and synthetic function. Additional biochemical markers include gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP), which are associated with cholestasis or biliary tract involvement.

Elevations in these markers may suggest intrahepatic or extrahepatic obstruction, especially in autoimmune or drug-induced hepatitis. GGT is also sensitive to alcohol intake and certain medications (e.g., anticonvulsants), which may limit its specificity. Total bilirubin and direct (conjugated) bilirubin reflect the liver's ability to conjugate and excrete bilirubin.

Increased bilirubin levels may signal hepatocellular dysfunction or impaired bile flow. In early chronic hepatitis, bilirubin levels may remain within normal limits, but elevated levels usually indicate advanced disease or overlapping cholestatic injury.

In recent years, newer serum-based biomarkers have emerged. These include:

- Hyaluronic acid, procollagen III peptide (PIIINP), and tissue inhibitor of metalloproteinases (TIMP-1), which are components of fibrogenesis and extracellular matrix turnover;
- Cytokeratin-18 fragments, which reflect hepatocyte apoptosis;
- Alpha-fetoprotein (AFP), elevated in cases of hepatocellular carcinoma but also in chronic inflammation.

While these biomarkers offer valuable insight, they often lack the precision to replace liver biopsy in staging fibrosis. However, when used in combination — as in scoring systems like APRI (AST-to-Platelet Ratio Index) or FIB-4 (which includes age, AST, ALT, and platelet count) — they significantly improve the predictive accuracy for advanced fibrosis (≥F3).

Instrumental imaging techniques in hepatocyte assessment

Instrumental imaging methods are essential in the non-invasive assessment of hepatic pathology in patients with chronic hepatitis. While biochemical tests provide data on hepatocellular function and injury, they are limited in their ability to visualize the extent of structural damage or quantify fibrosis. Ultrasonography (US) is the first-line imaging modality due to its accessibility, cost-effectiveness, and safety profile. It is useful in identifying morphological changes such as liver surface nodularity, altered echogenicity, signs of portal hypertension, and biliary tract abnormalities. However, conventional US has limited sensitivity in early-stage fibrosis and is operator-dependent. Transient elastography (TE), commercially known as FibroScan, is a quantitative technique that measures liver stiffness by analyzing the velocity of shear wave propagation through liver tissue. It has shown excellent diagnostic accuracy in staging liver fibrosis, particularly for significant fibrosis (≥F2) and cirrhosis (F4), with AUROC values often exceeding 0.90. Despite its advantages, TE can produce unreliable results in patients with obesity, ascites, or acute inflammation. To address these limitations, modified probes (e.g., XL probe) and controlled attenuation parameter (CAP) technology have been developed to assess hepatic steatosis. Shear-wave elastography (SWE) and acoustic radiation force impulse (ARFI) imaging are advanced ultrasound-based methods that allow real-time quantitative assessment of liver stiffness with the added advantage of user-defined region-of-interest (ROI) selection. These techniques are less affected by external factors such as ascites and offer higher spatial resolution compared to TE. Computed tomography (CT) is primarily used to evaluate hepatic vascular anatomy, detect space-occupying lesions such as hepatocellular carcinoma (HCC), and assess complications like thrombosis or nodular transformation.

However, it involves ionizing radiation and nephrotoxic contrast agents, which limits its routine use in fibrosis staging. Magnetic resonance imaging (MRI) provides superior soft-tissue contrast and is highly effective in detecting hepatic steatosis, iron overload, and focal lesions.

Magnetic resonance elastography (MRE) combines standard MRI with mechanical wave imaging to measure liver stiffness. It is considered one of the most accurate and reproducible non-invasive methods for fibrosis staging, although its high cost and limited availability restrict its widespread use. Overall, imaging techniques complement biochemical assessments by providing structural and functional information that is critical for accurate diagnosis, staging, and monitoring of chronic liver disease.

Table: Comparative Overview of Diagnostic Methods for Hepatocyte Damage

Diagnostic method	Type	Advantage	Limitation
ALT, AST, GGT, ALP	Biochemical	Widely available, inexpensive	Non-specific, variable with time
Ultrasound	Instrumental	Accesible, real-time	Limeted in early-stage disease
Transient Elastography	Instrumental	Quantitative fibrosis measurement	Operator-dependent, obese patients

CT, MRI	Instrumental	High resolution, detects tumors	Expensive, radiation (CT)
MR Elastography	Instrumental	Accurate stiffness assessment	Limited availability, costy

Comparative evaluation and integration of diagnostic approaches

The comprehensive assessment of hepatocyte damage in chronic hepatitis necessitates the integration of both biochemical and instrumental diagnostic modalities, as neither approach alone provides a complete picture of disease severity and progression. Biochemical markers such as ALT, AST, GGT, ALP, and bilirubin are essential in identifying ongoing hepatocellular injury and cholestatic processes, yet they are limited by their lack of specificity, inter-individual variability, and poor correlation with histological fibrosis stages. On the other hand, imaging techniques such as ultrasonography, transient elastography, and MR elastography offer valuable information on liver morphology, stiffness, and tissue characteristics, but they do not provide insight into biochemical activity or cellular function.

Therefore, diagnostic accuracy and clinical decision-making can be significantly enhanced by a combined approach that leverages the strengths of both methods. Several non-invasive scoring systems have been developed to quantify liver fibrosis by integrating biochemical and hematological parameters. The AST-to-Platelet Ratio Index (APRI) is a widely used tool that combines AST levels and platelet count to estimate the degree of fibrosis, particularly effective in identifying significant fibrosis and cirrhosis. Similarly, the FIB-4 index incorporates age, AST, ALT, and platelet count to provide a more refined estimation of fibrosis severity, especially in hepatitis C and NAFLD patients. These scores are simple, cost-effective, and reproducible, making them suitable for use in both resource-limited and advanced clinical settings. When used in conjunction with imaging, such as elastography, their diagnostic accuracy improves markedly. For instance, a patient with elevated FIB-4 and high liver stiffness on transient elastography is more likely to have advanced fibrosis or cirrhosis, justifying the need for more intensive monitoring or treatment initiation.

Conversely, low scores and normal imaging findings may help avoid unnecessary liver biopsies. Liver biopsy remains the gold standard for definitive histological assessment of inflammation, fibrosis, and other architectural changes; however, due to its invasiveness, cost, sampling variability, and potential complications, it is increasingly reserved for cases with conflicting or inconclusive non-invasive results. In clinical practice, a stepwise diagnostic algorithm is often adopted, beginning with biochemical tests and fibrosis scores, followed by elastography or imaging-based confirmation, and ultimately, biopsy if diagnostic uncertainty persists. This integrated model not only improves diagnostic confidence but also enhances patient safety and resource utilization. Furthermore, ongoing advancements in biomarker discovery, machine learning algorithms, and artificial intelligence–assisted imaging interpretation are expected to further refine the accuracy and efficiency of non-invasive liver disease assessment in the near future. Ultimately, the combination of biochemical, imaging, and clinical parameters provides a holistic framework for diagnosing and managing chronic hepatitis, facilitating early intervention, monitoring therapeutic efficacy, and preventing complications such as cirrhosis and hepatocellular carcinoma.

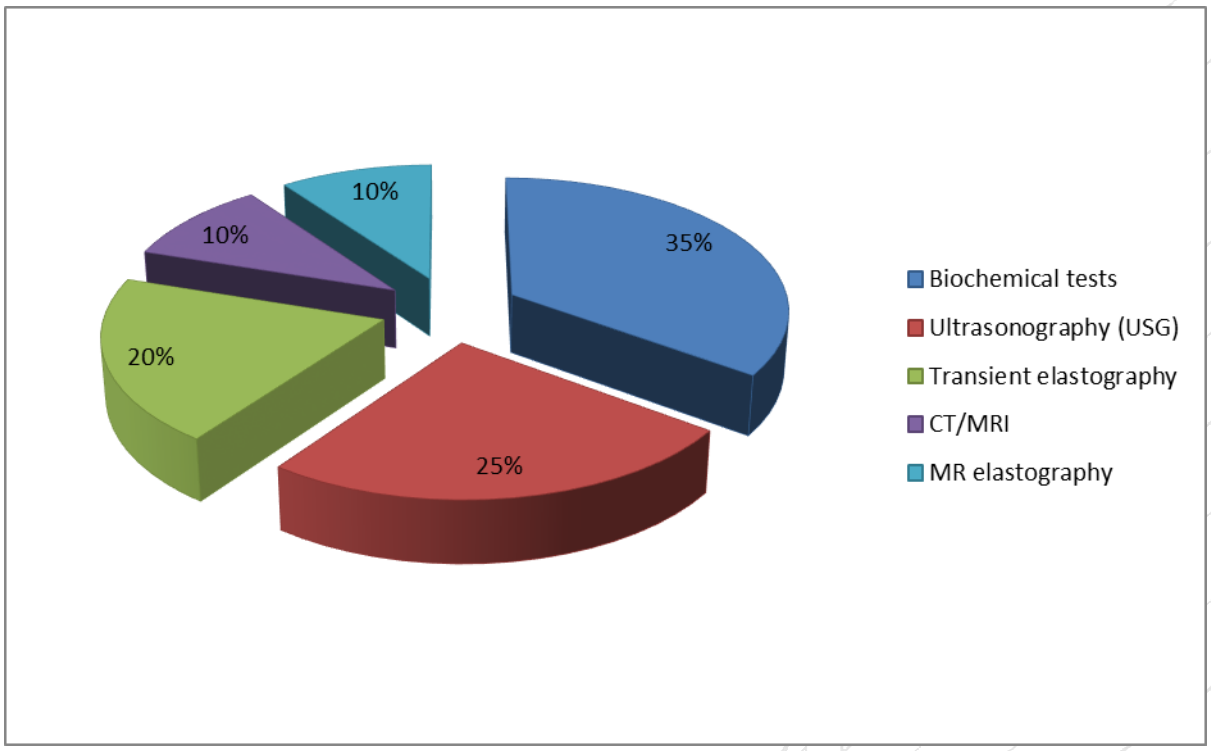

Figure: Proportional use of diagnostic methods in the evaluation of chronic hepatitis.

This pie chart illustrates the estimated distribution of commonly used diagnostic approaches in clinical hepatology. Biochemical tests (35%) are the most frequently used due to their accessibility and routine nature. Ultrasonography (25%) serves as a first-line imaging tool, while transient elastography (20%) is increasingly preferred for non-invasive fibrosis staging.

Computed tomography (CT) and magnetic resonance imaging (MRI) account for a smaller proportion (10%), typically reserved for complex cases. MR elastography (10%) is used in specialized centers for precise liver stiffness assessment.

Conclusion: In the evaluation of chronic hepatitis, accurate assessment of hepatocyte injury and fibrosis stage is critical for early diagnosis, appropriate treatment selection, and long-term disease monitoring. Biochemical markers such as ALT, AST, GGT, ALP, and bilirubin remain indispensable tools for detecting active liver damage and monitoring therapeutic response.

However, due to their limited specificity and poor correlation with histological changes, reliance on biochemical parameters alone is insufficient. Instrumental imaging modalities, including ultrasonography, transient elastography, shear-wave elastography, computed tomography, and magnetic resonance imaging, offer valuable structural and functional insights, particularly for staging fibrosis and identifying cirrhosis or hepatocellular carcinoma.

Transient and MR elastography, in particular, have demonstrated high diagnostic accuracy in non-invasively quantifying liver stiffness, which is a key surrogate for fibrosis.

Comparative evaluation highlights that the integration of biochemical and instrumental diagnostics provides a more comprehensive and reliable picture of hepatic pathology than either method alone. Non-invasive scoring systems such as APRI and FIB-4, when combined with elastographic techniques, enhance the prediction of advanced fibrosis and may reduce the need for invasive liver biopsy. A multidisciplinary diagnostic strategy that incorporates clinical evaluation, laboratory results, and imaging findings is essential to optimize patient outcomes, especially in the context of increasing chronic liver disease prevalence worldwide.

Furthermore, as diagnostic technologies continue to evolve—with the integration of artificial intelligence and novel serum biomarkers—the accuracy, accessibility, and cost-effectiveness of chronic hepatitis assessment are expected to improve. Therefore, adopting a combined and evidence-based approach to the evaluation of hepatocyte damage not only ensures early and accurate diagnosis but also enables personalized disease management, helping to prevent progression to end-stage liver disease and reduce the global burden of chronic hepatitis.

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