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Review Paper

A Review of Biomarkers for Liver Diseases

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ABSTRACT

Liver diseases present major global health challenges, making accurate, non-invasive biomarkers essential for early detection, diagnosis, and prognosis. This review summarizes classical biochemical markers, including aminotransferases, bilirubin, albumin, and coagulation parameters, alongside cholestatic indicators such as ALP and GGT. Advances in imaging-based biomarkers, particularly elastography and MRI-derived parameters, have enhanced fibrosis and steatosis assessment. Disease-specific biomarkers for viral, metabolic, alcoholic, autoimmune, and malignant liver disorders are examined, together with emerging genomic, metabolomic, and microbiome-derived signatures. Despite rapid progress, challenges in specificity, standardization, and validation persist. Integrated multi-omics and multi-marker approaches promise improved future clinical utility.

INTRODUCTION

Liver is the largest gland weighing between 1.44 to 1.66 kilograms, which is reddish brown in colour with a rubbery texture. The liver performs many functions including protein synthesis, bile production, xenobiotic metabolism and regulation of lipid and glucose homeostasis etc. Dysfunction of the liver may lead to serious outcomes including Jaundice, cirrhosis, portal hypertension, Ascites, liver failure and hepatocellular carcinoma etc. Biomarkers facilitate the distinction between acute and chronic liver injury, the etiology of disease, and the extent of functional impairment.

Biomarkers are very important for diagnostic, prognostic and early detection of liver dysfunction. The aim here is to survey biomarker applications across the spectrum of liver disease.

Classical Biomarkers of Liver Function

Aspartate transaminase (AST) and alanine transaminase (ALT) levels are indicators of hepatocellular injury; however, because these enzymes are also present in other tissues like muscle, their elevation is not exclusively specific to the liver and can occur in a variety of other conditions.

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Bilirubin levels (both total and direct) serve as indicators of the liver's ability to excrete waste products. Unconjugated hyperbilirubinemia suggests pre-hepatic etiologies (e.g., hemolysis, Gilbert syndrome), while conjugated hyperbilirubinemia indicates hepatocellular dysfunction or cholestasis.

Synthetic Function Markers:

Albumin and Prothrombin Time liver synthesizes albumin and most clotting factors, reductions in serum albumin and prolonged prothrombin time (PT) or international normalized ratio (INR) indicate impaired hepatic synthetic capacity. Unlike aminotransferases, these markers reflect chronic rather than acute liver damage and correlate with disease severity. PT/INR is also part of the MELD score and is a strong prognostic indicator in advanced cirrhosis.

Gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) ALP elevation requires confirmation with GGT to determine hepatic origin. Significant cholestasis, whether intrahepatic (e.g., primary biliary cholangitis) or extrahepatic (e.g., bile duct obstruction), causes increases in both ALP and GGT While easily available and inexpensive, these markers are limited by poor disease specificity and insensitivity in early diseases.

Imaging-Based Biomarkers

Ultrasound-Based Elastography: Non-invasive fibrosis assessment has been revolutionized by elastographic techniques. Vibration-controlled transient elastography (VCTE; FibroScan) measures liver stiffness, which correlates with fibrosis severity and portal hypertension. It also provides controlled attenuation parameter (CAP) for steatosis quantification.[1]

Magnetic Resonance Techniques

- **Magnetic resonance elastography (MRE)** is the most accurate non-invasive modality for fibrosis staging, outperforming both VCTE and SWE, especially in obese individuals.[2] MRI-proton density fat fraction (PDFF) quantifies hepatic steatosis with excellent reproducibility and is increasingly used in MASLD clinical trials.

- **MR spectroscopy** can measure hepatocellular triglyceride content, while contrast-enhanced MRI with extracellular or hepatocyte-specific agents aids in characterizing hepatic masses.

Biomarkers in Specific Liver Diseases

1. **Viral Hepatitis:**

In viral hepatitis (HBV, HCV), ALT and AST levels, and viral load (HBV DNA, HCV RNA) remain core. However, for fibrosis staging and prognosis, non-invasive indices such as AST-to-platelet ratio index (APRI) and FIB-4 (Fibrosis-4) have been studied.[3] A systematic review found moderate diagnostic utility for FIB-4 >3.25 for advanced fibrosis (F3–4) across chronic liver disease.[3]In hepatitis B virus (HBV), biomarkers include hepatitis B surface antigen (HBsAg), e antigen (HBeAg), HBV DNA level, and quantitative HBsAg, which help determine infection phase and treatment eligibility. HBV core-related antigen (HBcrAg) reflects covalently closed circular DNA (cccDNA) activity and is emerging as a predictor of disease activity and HCC risk.[4]

While in Hepatitis C virus (HCV) diagnosis requires testing for both anti-HCV antibodies and the presence of HCV RNA for confirmation. While viral load is used to monitor treatment effectiveness and achieving a sustained virologic

response (SVR) remains the key indicator of a successful cure.

2. Non-Alcoholic Fatty Liver Disease (NAFLD):

Traditional LFTs perform poorly as screening tools because many patients exhibit normal aminotransferase levels. Instead, composite scoring systems and fibrosis biomarkers provide better risk stratification. The NAFLD Fibrosis Score (NFS) and Fibrosis-4 (FIB-4) index combine age, platelet count, ALT, AST, and albumin values. These scores have strong negative predictive value for advanced fibrosis.Cytokeratin-18 (CK-18) fragments, released during hepatocyte apoptosis, are considered promising biomarkers for non-alcoholic steatohepatitis (NASH). However, their sensitivity and specificity remain insufficient for routine clinical use. A systematic review of prognostic non-invasive biomarkers in NAFLD reported that certain biomarkers correlated with all-cause mortality.[5]

3. Alcoholic Liver Disease (ALD):

Traditional biomarkers (AST/ALT ratio, GGT, MCV) have poor specificity. Carbohydrate-deficient transferrin (CDT) provides a more specific reflection of chronic alcohol consumption.[6] In Alcoholic Liver Disease (ALD), hazardous alcohol use may be indicated by standard biomarkers such as GGT and an AST to ALT ratio greater than one, as well as carbohydrate-deficient transferrin (CDT).

4. Autoimmune Liver Diseases:

Autoantibodies serve as critical biomarkers: antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), and anti–liver kidney microsomal type 1 (anti-LKM-1) support the diagnosis of autoimmune hepatitis. Primary biliary cholangitis (PBC) is strongly associated with anti-mitochondrial antibodies (AMA), present in >90% of cases.[7]

5. Liver Fibrosis:

Fibrogenesis involves deposition and remodeling of extracellular matrix (ECM) proteins. Hyaluronic acid, procollagen type III N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinases-1 (TIMP-1) reflect ECM turnover. Enhanced Liver Fibrosis (ELF) score—combining hyaluronic acid, P3NP, and TIMP-1—is validated for staging fibrosis in MASLD and hepatitis C.[8]

6. Hepatocellular Carcinoma (HCC):

Surveillance and early detection of HCC rely on imaging and serum biomarkers.

- Alpha-fetoprotein (AFP), though widely used, has suboptimal sensitivity.
- AFP-L3 (a glycoform of AFP) and des-gamma-carboxy prothrombin (DCP) improve specificity and are incorporated into risk prediction models.
- Multi-analyte panels such as GALAD (gender, age, AFP-L3, AFP, DCP) show superior performance for early HCC detection and are under increasing investigation.[9]

Emerging Molecular and Multi-Omics Biomarkers

Molecular biomarkers expand the horizon beyond conventional chemistry. Untargeted metabolomics in plasma and saliva recently identified novel candidate biomarkers in liver disease.[10]

CHALLENGES AND FUTURE PERSPECTIVES

Despite the proliferation of biomarkers, several challenges are always there. Standardisation across laboratories, inter-individual variability , and the fact that many biomarkers lack liver-specificity hinders the treatment. For example, ALT/AST may rise with muscle injury; HA may elevate with other fibrotic diseases.[11] Composite scores like MELD and Child–Pugh Scores can improve prognostication but cannot replace histology in certain contexts. Future research should prioritize multi-marker panels integrating biochemical, genomic, and imaging data to improve diagnostic accuracy.

CONCLUSIONS

Biomarkers of liver function and disease encompass a broad spectrum of biochemical tests, imaging modalities, virological markers, and emerging molecular signatures. While traditional liver biomarkers like ALT, AST, GLDH, GGT, ALP, albumin, total protein, lipids, platelets, bile acids, triglyceride, coagulation test, and CTP score remain essential for clinical decision-making, non-invasive fibrosis biomarkers and advanced imaging techniques have significantly improved diagnostic accuracy. While traditional LFTs remain important, their limitations underscore the need for more specific, sensitive and non-invasive biomarkers across liver diseases. Non-invasive panels for fibrosis, circulating microRNAs, metabolomic signatures and advanced imaging biomarkers complement traditional tests and hold promise for earlier detection, reliable staging and personalised management.

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