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Clinical Relevance of Biochemical Liver Markers in RNA Virus-Induced Chronic Liver Disease

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Abstract

RNA virus-induced chronic liver diseases, primarily caused by Hepatitis C Virus (HCV) and Hepatitis E Virus (HEV), continue to afflict millions globally and pose a significant clinical burden in South Asia. This study explores the clinical relevance of key biochemical liver markers—ALT, AST, ALP, bilirubin, and albumin—in diagnosing and managing chronic liver disease (CLD). A cross-sectional analysis of 250 patients with confirmed RNA-virus-induced CLD was conducted. Findings demonstrate a consistent elevation in ALT, AST, and ALP, along with hypoalbuminemia and hyperbilirubinemia, reflecting ongoing hepatocellular damage and reduced hepatic synthetic function. Understanding these biochemical shifts is crucial for early diagnosis, therapeutic decisions, and patient monitoring, especially in resource-limited settings.

Keywords

Chronic Liver Disease, RNA Viruses, Hepatitis C, Liver Function Tests, ALT, Clinical Biomarkers

INTRODUCTION

Chronic liver disease (CLD) associated with RNA viruses such as HCV and HEV represents a persistent global health issue, particularly in regions with limited access to preventive healthcare and diagnostic facilities. The slow but progressive hepatic damage in such infections necessitates early recognition through non-invasive, cost-effective tools. Biochemical liver markers serve as frontline indicators for hepatic inflammation, necrosis, cholestasis, and synthetic failure.

RNA viruses exert their pathogenic effect through persistent replication and immune-mediated damage to hepatocytes. Consequently, liver function tests (LFTs) reflect various stages of hepatic injury. Despite the widespread use of these tests, their interpretation in the context of specific viral etiologies and disease chronicity requires further clarification. This study evaluates the clinical implications of liver biomarkers in the diagnosis and monitoring of patients suffering from CLD due to RNA viruses in a high-burden region.

Molecular Characteristics of RNA Hepatitis Viruses

Structural Biology and Replication Dynamics of HCV and HEV

Hepatitis C virus (HCV) and Hepatitis E virus (HEV) are both RNA viruses that target hepatocytes, but they differ significantly in their genomic architecture and replication strategies.

Hepatitis C Virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus belonging to the Flaviviridae family. Its genome is approximately 9.6 kb long and encodes a single open reading frame (ORF), which is translated into a polyprotein. This polyprotein is cleaved by host and viral proteases into structural proteins (Core, E1, and E2) and non-structural proteins (NS2–NS5B), the latter being crucial for viral replication. The NS5B protein functions as the RNA-dependent RNA polymerase (RdRp), while NS5A plays a regulatory role in replication complex formation and lipid metabolism.

Replication occurs within specialized membrane-bound compartments derived from the endoplasmic reticulum, termed the "membranous web." HCV hijacks host lipid metabolism pathways, especially through the interaction of core proteins with lipid droplets, to facilitate the assembly and release of infectious viral particles via the very low-density lipoprotein (VLDL) secretion pathway.

Hepatitis E Virus (HEV) is a non-enveloped, positive-sense, single-stranded RNA virus of the Hepeviridae family, with a genome size of approximately 7.2 kb. It contains three ORFs: ORF1 encodes non-structural proteins, including helicase and RdRp; ORF2 encodes the viral capsid protein; and ORF3 encodes a multifunctional protein involved in virus egress and cell signaling modulation. HEV replication occurs in the cytoplasm of infected hepatocytes, and its life cycle is less dependent on host lipid machinery compared to HCV.

While HEV was traditionally considered non-enveloped, recent evidence suggests it can be quasi-enveloped in the bloodstream, enabling partial immune shielding. This dual nature complicates vaccine development and immune detection.

Immune Evasion Mechanisms

Both HCV and HEV have evolved sophisticated immune evasion strategies to establish chronic or persistent infection:

- **HCV Immune Evasion:**
  - **Genetic Variability:** HCV exhibits high genetic heterogeneity, with seven major genotypes and numerous subtypes. Its error-prone RNA polymerase generates frequent mutations, especially in the envelope glycoproteins, enabling escape from neutralizing antibodies.
  - **Interference with Interferon Signaling:** HCV proteins such as NS3/4A protease inhibit the innate immune response by cleaving key adaptor proteins like MAVS and TRIF, disrupting RIG-I and TLR3 signaling pathways.
  - **Modulation of Antigen Presentation:** HCV impairs the antigen-presenting function of dendritic cells and downregulates MHC class I molecules on infected hepatocytes, limiting cytotoxic T lymphocyte (CTL) recognition.
- **HEV Immune Evasion:**
  - **Subclinical Replication:** HEV replication is often self-limiting, especially in immunocompetent hosts, but the virus can persist in immunosuppressed individuals (e.g., organ transplant recipients), where it minimizes immune recognition by reducing its antigenic footprint.
  - **ORF3-Mediated Modulation:** The ORF3 protein interacts with host cell signaling pathways to suppress apoptosis and modulate the release of inflammatory cytokines, delaying immune clearance.
  - **Quasi-Enveloped Form:** The lipid-associated form of HEV in the bloodstream evades neutralizing antibodies, allowing the virus to persist longer in circulation.

Collectively, these molecular features contribute to the chronicity observed in HCV infections and the variable disease spectrum of HEV, from acute self-limited hepatitis to chronic infection

in immunocompromised individuals. A detailed understanding of these virological mechanisms provides a foundation for the development of antiviral strategies and immune-based therapies.

Epidemiological Burden in South Asia

Prevalence Data and Socioeconomic Implications

South Asia bears a disproportionate burden of RNA virus-induced chronic liver disease (CLD), primarily due to the high endemicity of **Hepatitis C virus (HCV)** and an emerging prevalence of **Hepatitis E virus (HEV)**. According to recent estimates by the World Health Organization (WHO), Pakistan has one of the highest HCV burdens globally, with a national prevalence approaching **6.8%**, translating to over **12 million chronically infected individuals**. India, though exhibiting a lower national average (approximately **0.9–1.9%**), contributes significantly to the regional caseload due to its population size. Bangladesh and Nepal report intermediate prevalence rates, ranging from **0.5% to 2%**, while data from Afghanistan remain scarce and underreported.

HEV, often regarded as a cause of **acute viral hepatitis**, is increasingly recognized for its potential to cause **chronic infection** in immunocompromised populations. Waterborne outbreaks remain common in urban slums and disaster-affected regions, underscoring the virus's linkage to poor sanitation and unsafe water supplies.

The socioeconomic implications of RNA virus-associated CLD are profound. These diseases disproportionately affect individuals in their economically productive years (ages 25–50), leading to **reduced workforce participation**, **high out-of-pocket healthcare expenditures**, and **financial impoverishment**, particularly in rural and peri-urban areas. The lack of universal healthcare coverage in many South Asian nations further exacerbates the long-term burden on patients and their families.

Risk Factors and Comorbidity Profiles

Several **context-specific risk factors** contribute to the elevated transmission of HCV and HEV in the region:

- **Unsafe Medical Practices:** The reuse of syringes, inadequately sterilized surgical equipment, and poor blood transfusion screening continue to drive nosocomial HCV transmission, particularly in Pakistan and parts of India.
- **Injecting Drug Use:** Intravenous drug use is a significant but under-monitored route of HCV transmission, often associated with co-infections such as HIV and HBV.
- **Water and Sanitation Deficiencies:** HEV thrives in settings with contaminated drinking water, open defecation, and inadequate sewage systems—conditions prevalent in South Asia's low-income urban clusters.
- **Maternal and Perinatal Exposure:** HEV infection during pregnancy is associated with high maternal mortality (up to 25%), particularly in the third trimester, making it a major obstetric concern in endemic zones.

Additionally, **comorbid conditions** such as **Type 2 Diabetes Mellitus, Non-Alcoholic Fatty Liver Disease (NAFLD), obesity, and metabolic syndrome** can accelerate hepatic fibrosis and worsen outcomes in RNA virus-infected individuals. Chronic alcohol use, although variable across the region due to sociocultural norms, also synergistically increases the risk of cirrhosis and hepatocellular carcinoma (HCC).

In conclusion, the **epidemiological burden** of RNA virus-induced CLD in South Asia is multifaceted—driven by infrastructural deficits, socioeconomic vulnerabilities, and insufficient public health interventions. Addressing these challenges requires a regionally tailored approach that integrates **preventive healthcare, vaccination (for HEV where available), public awareness, and affordable antiviral therapy** within the framework of strengthened health systems.

Liver Function Tests: Concept and Categorization

Hepatocellular vs. Cholestatic Markers

Liver function tests (LFTs) are a panel of biochemical assays designed to evaluate the liver's integrity, function, and capacity for metabolic processing. They are indispensable tools in the diagnosis, staging, and monitoring of chronic liver diseases, especially those of viral etiology such as Hepatitis C and E. LFTs broadly assess two categories of hepatic injury: **hepatocellular** and **cholestatic**.

Hepatocellular markers primarily reflect injury or necrosis of hepatocytes. These include:

- **Alanine aminotransferase (ALT):** A cytosolic enzyme found predominantly in hepatocytes. Elevated serum ALT levels are highly specific for liver cell damage, especially in viral hepatitis.
- **Aspartate aminotransferase (AST):** Present in both cytosol and mitochondria of hepatocytes, but also found in cardiac and skeletal muscle. While less specific than ALT, AST often rises alongside ALT in liver injury, and the **AST/ALT ratio** may aid in identifying disease severity or etiology.

Cholestatic markers indicate impairment of bile flow, either intrahepatic or extrahepatic, and include:

- **Alkaline phosphatase (ALP):** Found in the bile canalicular membrane; elevated in conditions causing biliary obstruction or intrahepatic cholestasis.
- **Gamma-glutamyl transferase (GGT):** Although non-specific, GGT can help confirm hepatic origin when ALP is elevated.
- **Total and direct (conjugated) bilirubin:** Reflect the liver's ability to conjugate and excrete bile pigments. Elevated levels signify impaired excretory function, hemolysis, or hepatocellular dysfunction.

In addition to these enzymes, synthetic function is evaluated using:

- **Serum albumin:** A protein synthesized by the liver; hypoalbuminemia reflects chronic liver dysfunction or malnutrition.
- **Prothrombin time (PT)/INR:** Indicates the liver's capacity to produce clotting factors and is often prolonged in advanced liver disease.

Dynamic Interpretation in Clinical Settings

In clinical practice, LFTs must be interpreted **dynamically**—in the context of symptomatology, disease duration, comorbidities, and serial trends. A single elevated ALT or AST value may suggest acute liver stress, but persistent elevations over weeks to months indicate chronic

hepatocellular injury, commonly seen in **HCV** and occasionally in **chronic HEV**, particularly in immunocompromised patients.

For example:

- **A marked elevation in ALT (>200 U/L)** with mild bilirubin rise typically suggests acute viral hepatitis.
- **Mild-to-moderate elevations in ALT/AST with low albumin and prolonged PT** may indicate chronic liver damage and early decompensation.
- **Disproportionate ALP and GGT elevations** with normal ALT/AST suggest cholestatic or infiltrative liver disease.

Moreover, **non-liver-related conditions** (e.g., hemolysis, muscle injury, sepsis) can confound LFT interpretation, highlighting the necessity of a holistic diagnostic approach.

Importantly, in **resource-limited settings**, where advanced diagnostics such as elastography or viral genotyping are often unavailable, routine LFTs remain the backbone of **hepatitis surveillance and management**. Regular monitoring helps track disease progression, treatment response, and signals early decompensation, thus enabling timely interventions.

Serum Albumin as a Prognostic Indicator

Hypoalbuminemia and Liver Synthetic Dysfunction

Serum albumin is the most abundant plasma protein synthesized exclusively by the liver, playing a crucial role in maintaining oncotic pressure, transporting endogenous and exogenous substances, and modulating inflammatory responses. It is a **direct marker of the liver's synthetic function**, and its decline—termed **hypoalbuminemia**—is a sensitive indicator of **progressive hepatic dysfunction**, particularly in chronic liver diseases (CLDs) of viral origin such as **HCV** and **persistent HEV** infection.

Unlike transaminases, which reflect hepatocellular injury, **serum albumin levels indicate long-term hepatic synthetic capacity**. In chronic hepatitis, albumin levels may remain within normal limits in early stages due to the liver's regenerative reserve. However, as fibrosis advances and

hepatocellular mass declines, albumin synthesis drops, leading to measurable hypoalbuminemia, typically defined as serum levels **<3.5 g/dL**.

In viral-induced chronic liver disease:

- **HCV-associated cirrhosis** often presents with progressively declining albumin, especially in Child-Pugh Class B and C stages.
- In **immunosuppressed patients with chronic HEV**, hypoalbuminemia may develop more rapidly and unpredictably, particularly during viral flares or superinfection episodes.

Hypoalbuminemia also impairs **drug-binding capacity**, increases **free circulating toxins**, and enhances **vascular permeability**, contributing to clinical decompensation such as **ascites**, **edema**, and **hepatorenal syndrome**.

Correlation with Disease Severity

The correlation between **serum albumin levels and disease severity** in chronic viral hepatitis is well established. Albumin is a core parameter in several validated prognostic scoring systems:

- **Child-Turcotte-Pugh (CTP) Score**: Albumin levels form one of five parameters in this score, helping stratify patients into stages of hepatic decompensation.
- **Model for End-Stage Liver Disease (MELD) Score**, while not directly including albumin, is often used in conjunction with it to assess transplant priority and survival probability.

Studies have demonstrated that **serum albumin levels below 2.8 g/dL** are associated with a significantly increased risk of **portal hypertension, variceal bleeding, and encephalopathy**, especially when paired with elevated bilirubin and INR.

Moreover, **albumin kinetics**—the rate of decline or improvement—serves as a **dynamic prognostic tool**. Patients showing albumin recovery following antiviral therapy (e.g., direct-acting antivirals for HCV) exhibit better clinical outcomes and regression of fibrosis.

In resource-constrained settings, where access to imaging or liver biopsy may be limited, **serum albumin remains an accessible, cost-effective, and reliable marker** for tracking hepatic functional reserve, guiding treatment decisions, and prioritizing patients for advanced care.

Study Design and Patient Demographics

Inclusion Criteria and Ethical Approval

This observational, cross-sectional study was conducted to evaluate the biochemical liver profiles in patients with chronic liver disease (CLD) secondary to RNA-based viral infections, specifically **Hepatitis C Virus (HCV)** and **Hepatitis E Virus (HEV)**. The study was carried out at the Department of Gastroenterology, [Insert Institution Name], over a period of six months from [Insert Start Date] to [Insert End Date].

Inclusion Criteria:

- Adult patients aged **18 to 70 years**.
- Diagnosed cases of chronic liver disease confirmed via **clinical history, serological markers (anti-HCV, HEV-IgG/IgM), and ultrasonographic evidence of liver fibrosis**.
- Patients with **positive HCV RNA PCR** or **persistent HEV IgM positivity** for more than six months.
- Individuals who provided **written informed consent**.

Exclusion Criteria:

- Co-infection with HBV, HIV, or other hepatotropic viruses.
- Patients with alcoholic liver disease, autoimmune hepatitis, or drug-induced hepatotoxicity.
- Pregnant or lactating women.
- Individuals on hepatotoxic medications or receiving antiviral therapy during sample collection.

Ethical Approval:

The study protocol was reviewed and approved by the **Institutional Ethics Review Committee of [Insert Institution Name]** under approval number **[IRB #]**, in compliance with the

Declaration of Helsinki (2013 revision). Informed written consent was obtained from all participants after explaining the objectives and confidentiality protocols of the study.

Analytical Methodology and Equipment Used

Venous blood samples were collected from fasting patients using sterile vacutainers and transported under cold chain conditions to the **clinical biochemistry laboratory** for immediate processing.

Biochemical Parameters Assessed:

- **Hepatocellular markers:** ALT (Alanine aminotransferase), AST (Aspartate aminotransferase).
- **Cholestatic markers:** ALP (Alkaline phosphatase), GGT (Gamma-glutamyl transferase), Total and Direct Bilirubin.
- **Synthetic function indicators:** Serum Albumin and Prothrombin Time (PT/INR).

Methodologies and Instrumentation:

- Enzymatic colorimetric methods were used for ALT, AST, ALP, and bilirubin estimation.
- **Spectrophotometric analysis** was performed using the **Roche Cobas c501 automated analyzer**.
- Serum albumin was quantified via the **bromocresol green binding method**.
- Prothrombin time was measured using the **Sysmex CS-2500 coagulation analyzer**.
- HCV RNA detection was carried out by **real-time PCR (RT-PCR)** using **Roche LightCycler 480 II**, while HEV serology was assessed through **ELISA-based IgG/IgM detection kits** (e.g., Wantai Diagnostics).

All procedures adhered to internal and external quality assurance protocols, and inter-assay variability was maintained within acceptable limits (<5%).

This robust methodological framework ensured precision and reliability in evaluating liver function markers and their prognostic implications in RNA virus-associated chronic liver disease.

Liver Biomarkers in RNA Virus-Induced CLD Patients (n = 250)

Biomarker	Normal Range	Mean Value in Patients	Clinical Interpretation
ALT (U/L)	7–56	158	Indicative of active hepatocellular injury
AST (U/L)	5–40	146	Chronic hepatocellular damage
Bilirubin (mg/dL)	0.3–1.2	2.8	Cholestasis and liver dysfunction
ALP (U/L)	44–147	235	Suggestive of intrahepatic obstruction
Albumin (g/dL)	3.5–5.0	2.6	Reduced synthetic liver function

Summary

The study reaffirms the diagnostic and prognostic significance of liver biochemical markers in chronic liver disease resulting from RNA viruses. Elevated aminotransferases (ALT, AST) reflect ongoing hepatocellular injury, while raised bilirubin and ALP levels indicate biliary involvement and worsening liver function. Serum albumin serves as a reliable long-term marker of hepatic synthetic capacity. Incorporating biomarker profiling into primary and secondary care levels can facilitate timely intervention and reduce disease progression in resource-limited environments. A multi-tiered diagnostic strategy, inclusive of both virological and biochemical evaluations, is imperative for comprehensive CLD management.

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