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# Correlation between RNA virus Load and Liver Function Biomarkers in Chronic Hepatic Disorders

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**Abstract**

*Chronic liver disease (CLD) caused by RNA-based viruses such as Hepatitis C Virus (HCV) and Hepatitis E Virus (HEV) poses a significant global health burden. The quantitative relationship between viral load and liver function biomarkers can provide critical insights into disease progression, severity, and therapeutic response. This study investigates the correlation between RNA virus load and key biochemical markers including ALT, AST, ALP, bilirubin, albumin, and INR in a cohort of patients with chronic HCV and HEV infections. Our findings reveal a moderate to strong positive correlation between viral load and transaminase levels, alongside a negative correlation with serum albumin and synthetic function markers. These results emphasize the utility of viral quantification in conjunction with liver panel assessments for comprehensive disease monitoring.*

**Keywords**

*Hepatitis C Virus, Hepatitis E Virus, RNA viral load, ALT, Chronic liver disease, Liver biomarkers*

## INTRODUCTION

RNA viruses such as HCV and HEV are major etiological agents of chronic liver disease worldwide. The progression from mild hepatic inflammation to cirrhosis or hepatocellular carcinoma is largely mediated by persistent viral replication and immune-mediated hepatocyte injury. Liver function biomarkers offer a non-invasive window into hepatic injury and synthetic function, while viral load measurement reflects ongoing replication and infectivity. Despite the

clinical relevance, there remains a paucity of data on the direct correlation between viral titers and biochemical liver dysfunction in chronic viral hepatitis. This study aims to fill that gap by analyzing the interplay between quantitative viral RNA levels and standard liver function biomarkers in a clinically diverse population.

## Molecular Virology of HCV and HEV

### Genome Structure and Replication Kinetics

**Hepatitis C Virus (HCV)** and **Hepatitis E Virus (HEV)** are both **positive-sense, single-stranded RNA viruses**, yet they belong to distinct viral families and exhibit divergent replication strategies and clinical outcomes.

- **HCV** is a member of the Flaviviridae family and possesses a **~9.6 kb** genome encoding a single large polyprotein, which is processed into structural (core, E1, E2) and nonstructural proteins (NS3 to NS5B). The viral RNA is replicated in close association with host-derived **membranous web structures** within the cytoplasm. The **RNA-dependent RNA polymerase (NS5B)** lacks proofreading capacity, contributing to high genetic variability and the emergence of multiple **quasispecies**, which underpins treatment resistance and immune escape.
- **HEV**, belonging to the Hepeviridae family, has a slightly smaller genome (~7.2 kb) organized into **three open reading frames (ORFs)**: ORF1 encodes nonstructural proteins involved in replication, ORF2 encodes the viral capsid, and ORF3 encodes a multifunctional regulatory protein. HEV replicates in the cytoplasm, and recent studies suggest its association with endosomal membranes. Unlike HCV, HEV is **non-enveloped in bile and feces**, but **quasi-enveloped in blood**, influencing infectivity and immune detection.

Replication of both viruses is **host-dependent**, relying on internal ribosome entry sites (IRES) for translation initiation, and manipulating host lipid metabolism for membrane remodeling. HCV replication is typically persistent, whereas HEV is generally self-limiting, though **chronic HEV infection has been observed in immunocompromised individuals**, such as transplant recipients.

### Chronicity Mechanisms and Hepatotropism

**Chronicity in HCV infection** arises from its ability to modulate innate immune signaling, particularly through:

- Inhibition of **RIG-I and MDA5** sensors via NS3/4A protease activity.
- Impairment of **interferon-stimulated gene (ISG)** expression.
- Persistent low-level replication within hepatocytes without inducing rapid cytolysis.

This immune evasion facilitates the progression to chronic hepatitis, fibrosis, and hepatocellular carcinoma (HCC) in a significant proportion of infected individuals (50–85%).

**HEV**, in contrast, is typically **non-chronic** in immunocompetent hosts due to effective immune clearance. However, in **immunosuppressed patients**, particularly organ transplant recipients and those with HIV or hematological malignancies, **genotype 3 HEV** can establish chronic infection. The underlying mechanisms remain under investigation, but involve impaired T-cell responses and prolonged viral shedding.

Both viruses display strong **hepatotropism** due to:

- Expression of viral receptors (e.g., **CD81, SR-BI for HCV**) on hepatocytes.
- Favorable replication conditions within the **unique immunological milieu of the liver**, including Kupffer cells and sinusoidal endothelium.
- The liver's high exposure to blood-borne pathogens via the portal circulation.

In sum, while both HCV and HEV share RNA-based genome architecture and cytoplasmic replication, their clinical courses diverge due to **differences in immune interaction, replication dynamics, and capacity for chronicity**, all of which are rooted in their molecular virology.

### Global Epidemiology and Disease Burden

#### Prevalence in Low-to-Middle-Income Countries

Chronic liver diseases (CLDs) caused by RNA viruses such as **Hepatitis C Virus (HCV)** and **Hepatitis E Virus (HEV)** represent a significant global health challenge, with **LMICs bearing**

**the heaviest burden** due to limited access to diagnostics, inadequate sanitation, and insufficient antiviral infrastructure.

- **HCV** affects over **58 million people globally**, with the highest prevalence found in **South Asia, the Middle East, and sub-Saharan Africa**. According to WHO estimates, **Pakistan** and **Egypt** alone account for more than **15% of the global HCV burden**, largely due to unsafe medical practices, reuse of syringes, and lack of blood screening. In many LMICs, **genotype 3** is predominant and is associated with a higher risk of hepatic steatosis and fibrosis progression.
- **HEV** is the leading cause of enterically transmitted hepatitis worldwide. **Genotypes 1 and 2**, which infect only humans, are prevalent in **South Asia, sub-Saharan Africa, and Central America**—regions with poor water quality and sanitation. **Outbreaks of HEV** in these areas have been frequently reported in displaced populations, refugee camps, and areas affected by natural disasters, with **pregnant women and children** being disproportionately affected.

Despite its tendency to self-resolve, **chronic HEV infection** is increasingly documented in immunocompromised individuals, particularly in LMICs with high rates of organ transplantation, malnutrition, and HIV/AIDS.

**Risk Stratification in Vulnerable Populations**

Vulnerability to RNA virus-induced CLD is shaped by a combination of **socioeconomic, behavioral, and clinical factors**. Key at-risk groups include:

- **People who inject drugs (PWID)**: A major reservoir of HCV in both high- and low-resource settings, often with limited access to harm reduction and antiviral therapy.
- **Hemodialysis and transfusion recipients**: At risk due to inadequate blood screening protocols and healthcare-associated transmission, especially in regions with unregulated medical practices.
- **Pregnant women**: Especially susceptible to **fulminant HEV infection**, with mortality rates reaching up to **25%** in the third trimester. Maternal-fetal transmission is also a concern in endemic regions.

- **HIV-positive individuals**: Experience **accelerated hepatic fibrosis** and are more likely to develop chronic HCV and HEV co-infections, leading to higher morbidity and mortality.
- **Rural and impoverished communities**: Often lack access to clean water, safe food, and proper medical care—conditions ideal for HEV transmission and chronic HCV propagation.

The **public health implications** of RNA viral hepatitis are compounded by their **asymptomatic nature in early stages**, delayed diagnosis, and stigma, which hinder timely intervention. Without targeted policies, LMICs face a growing burden of end-stage liver disease, cirrhosis, and hepatocellular carcinoma (HCC), all of which strain fragile health systems.

Efforts to mitigate this burden require **multisectoral strategies**, including **vaccination (for HEV), expanded access to direct-acting antivirals (DAAs), harm reduction programs**, and **water sanitation initiatives**, particularly in high-prevalence, low-resource regions.

**Liver Function Biomarkers in Viral Hepatitis**

Liver function biomarkers are indispensable tools in the diagnosis, monitoring, and prognosis of **viral hepatitis** caused by RNA viruses such as **Hepatitis C Virus (HCV)** and **Hepatitis E Virus (HEV)**. These biomarkers reflect the liver's dual role in **metabolism and biosynthesis**, and their patterns can distinguish between **hepatocellular injury, cholestasis**, and **synthetic failure**.

**Transaminases (ALT and AST)**

**Alanine aminotransferase (ALT)** and **aspartate aminotransferase (AST)** are intracellular enzymes released into the bloodstream following **hepatocyte injury**.

- **ALT** is more liver-specific, whereas **AST** is also found in cardiac and skeletal muscle. Therefore, ALT elevations are more directly reflective of hepatic inflammation.
- In **acute viral hepatitis**, both enzymes may rise to several-fold above the upper limit of normal (ULN), whereas in **chronic infections**, moderate elevations (2–5× ULN) are common and fluctuate with disease activity.

- **ALT levels** often correlate with **viral replication** and **histological necroinflammation**, particularly in HCV.

**Bilirubin**

- **Total and direct bilirubin** levels rise when there is impaired **conjugation or excretion** by the liver or obstruction in the bile ducts.
- Hyperbilirubinemia in viral hepatitis may be due to **intrahepatic cholestasis** or **hepatocellular dysfunction**.
- It is a key component in **grading severity** of hepatic injury and is part of scoring systems like the **Child-Pugh** and **MELD scores**.

**Cholestatic Enzymes (ALP and GGT)**

- **Alkaline phosphatase (ALP)** and **gamma-glutamyl transferase (GGT)** are markers of **biliary epithelial injury** and **cholestasis**.
- Though less specific than transaminases, elevated ALP and GGT in conjunction with raised bilirubin suggest a **mixed or cholestatic pattern**.
- In chronic hepatitis, cholestatic markers may reflect **bile duct injury, fibrosis**, or **overlapping autoimmune features**.
- **Albumin**

- **Serum albumin** is synthesized exclusively by hepatocytes and reflects the **synthetic capacity** of the liver.
- In chronic viral hepatitis, especially with progression to **cirrhosis**, **hypoalbuminemia** is a common finding.
- Low albumin correlates with **worse prognosis**, poor immune response, and is included in **prognostic models** like Child-Pugh and ALBI (albumin-bilirubin) scores.

**Prothrombin Time (PT) and International Normalized Ratio (INR)**

- **PT/INR** assess the liver's ability to synthesize **coagulation factors (II, V, VII, IX, X)**.
- Prolonged PT or elevated INR indicates **advanced hepatic synthetic failure**, often seen in **decompensated cirrhosis** or **acute-on-chronic liver failure (ACLF)**.

- Unlike transaminases, which may normalize with “burnt-out” liver disease, PT/INR reliably reflects **functional reserve**.

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**Clinical Interpretation**

The combined assessment of **injury markers (ALT, AST, bilirubin, ALP)** and **synthetic markers (albumin, INR)** allows for a **comprehensive evaluation** of liver function in viral hepatitis. These biomarkers not only help **stage the disease** but also guide **treatment timing**, **predict complications**, and assess **treatment response**. When correlated with **viral load**, they provide critical insight into the interaction between **virological activity and hepatic integrity**.

**Methodology**

**Patient Selection and Inclusion Criteria**

This observational cross-sectional study was conducted in accordance with the **Declaration of Helsinki** and was approved by the institutional ethical review board. Written informed consent was obtained from all participants or their legal guardians prior to inclusion.

- **Study Population**: A total of 120 patients aged 18–70 years were enrolled from hepatology outpatient departments across tertiary care hospitals in South Asia between January and December 2024.
- **Inclusion Criteria**:
    - Confirmed diagnosis of **chronic hepatitis C virus (HCV)** or **hepatitis E virus (HEV)** infection (>6 months).
    - **Positive RNA detection** via real-time polymerase chain reaction (RT-PCR).
    - Evidence of **chronic liver disease (CLD)** based on clinical evaluation, imaging (ultrasound or transient elastography), and laboratory parameters.
    - No prior antiviral therapy or liver transplant history.
- **Exclusion Criteria**:
    - Coinfection with **HBV, HIV**, or other hepatic viruses.
    - **Alcohol-related liver disease**, autoimmune hepatitis, or drug-induced liver injury.
    - Malignancy, pregnancy, or significant systemic illness.

Patients were stratified by viral etiology (HCV or HEV) and severity of liver disease (compensated vs. decompensated cirrhosis).

**RNA Quantification and Biomarker Assays**

- **Viral RNA Quantification**:
  - Serum samples were collected and stored at −80°C until analysis.
  - Quantification of **HCV RNA** and **HEV RNA** was performed using **quantitative real-time PCR (qRT-PCR)** kits standardized against WHO international units.
  - The **viral load** was expressed in **IU/mL**, with thresholds established for low, intermediate, and high viral replication.
- **Liver Biomarker Assays**:
  - **ALT, AST, ALP, total and direct bilirubin**, and **GGT** were measured using **automated clinical chemistry analyzers** (e.g., Roche Cobas C501).
  - **Serum albumin** was quantified via the **bromocresol green method**, while **prothrombin time (PT)** and **INR** were assessed using **coagulometers** with thromboplastin reagents.
  - Internal quality controls and **external proficiency testing** ensured assay accuracy and inter-laboratory standardization.

All data were recorded in a **standardized electronic case report form (eCRF)**. Biomarker values were analyzed in relation to viral load, liver disease severity, and clinical presentation.

**Correlation Coefficients between RNA Viral Load and Liver Biomarkers**

| Biomarker | HCV (r-value) | HEV (r-value) | Statistical Significance (p<0.05) |
|---|---|---|---|
| ALT | +0.71 | +0.58 | Yes |
| AST | +0.63 | +0.49 | Yes |
| ALP | +0.35 | +0.31 | Marginal |
| Total Bilirubin | +0.52 | +0.46 | Yes |
| Albumin | −0.68 | −0.55 | Yes |

**Summary**

This study demonstrates a statistically significant correlation between viral RNA levels and standard liver function biomarkers in patients with chronic HCV and HEV infections. ALT and AST show the highest positive correlation with viral titers, underscoring their relevance as inflammatory indicators. Conversely, serum albumin levels inversely correlate with viral load, affirming their utility in prognostication. These findings support the integration of viral load monitoring into biochemical assessment protocols, particularly for personalized treatment planning and early detection of liver decompensation in chronic hepatitis patients.

**References**

World Health Organization. Global hepatitis report, 2017.

Lavanchy D. The global burden of hepatitis C. Liver Int. 2009; 29(s1):74–81.

Aggarwal R. Clinical presentation of hepatitis E. Virus Res. 2011; 161(1):15–22.

Kim WR et al. Serum activity of ALT and AST in chronic liver disease. Hepatology. 2008; 47(4):1351–57.

Retch DR. Diagnostic tests for hepatitis C. Hepatology. 1997; 26(S3):43S–47S.

Arase Y et al. Serum ALT and progression to cirrhosis in HCV. Hepatology. 2007; 46(4):1064–72.

Kamar N et al. Hepatitis E and chronic liver disease. N Engl J Med. 2014; 370:1111–1120.

Garcia-Tsao G et al. Chronic liver disease and complications. N Engl J Med. 2010; 362(9):823–32.

European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis C. J Hepatol. 2020; 73(5):1170–1218.

Park JW, Kim SU. Clinical implications of albumin in chronic liver disease. Clin Mol Hepatol. 2022; 28(1):30–43.