PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Exploring Viral and Non-Viral causes of Alanine Aminotransferase Spikes above 1000 in a South Asian Cohort

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Abstract:

Background

Elevated ALT levels greater than 1000 U/L indicate severe hepatic injury. In Western studies, ischemic hepatitis and drug-induced liver injury (DILI) are common causes (1, 2). However, in South Asia, hepatitis E (HEV) predominates, contributing to a different clinical pattern. This study explores the causes and outcomes of ALT >1000 U/L in a South Asian cohort.

Methods

we prospectively analyzed 151 patients with ALT >1000 U/L from AIMS Hospital. Data on demographics, etiology, clinical presentation (acute hepatitis, acute liver failure [ALF], acute-on-chronic liver failure [ACLF]), hospital stay, and 30-day outcomes were collected. Statistical analysis was performed using IBM SPSS Version 22.

Results

Viral hepatitis was the leading cause (86.1%), with hepatitis E being the most frequent (55.6%). Non-viral causes, including ischemic hepatitis (4.6%) and DILI (3.3%), were rare. Acute hepatitis (63.6%) was the most common presentation, and hepatitis E was responsible for 63.5% of these cases. ALF occurred in 11.9%, primarily due to hepatitis E. The majority of patients (78.1%) had a short hospital stay (<48 hours), with 94% showing improvement. Severe cases (ischemic hepatitis, ACLF) resulted in a 4% mortality rate, and 2% were referred for liver transplantation.

Conclusion

Our study highlights the dominance of hepatitis E in ALT >1000 U/L in South Asia, contrasting with Western trends where ischemic hepatitis and DILI are more prevalent (1, 2). These findings suggest the need for regional-specific diagnostic strategies, particularly in endemic areas.

How to Cite this article:

Memon S, Nadeem F, kadir B, Sultana S, Zaki M, Dal N, Soomro U, Ghani U, Burney M, Keerio S. Exploring Viral and Non-Viral causes of Alanine Aminotransferase Spikes above 1000 in a South Asian Cohort**.** *PJG*. 2025;41(4)**:** 819-823

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Received: May 11, 2025

Accepted: July 20, 2025

Introduction:

Hepatitis E virus (HEV) is a significant cause of acute viral hepatitis globally, with Southeast Asia bearing a disproportionately high burden. HEV infections contribute to substantial morbidity and mortality, especially in regions with poor sanitation and limited access to safe drinking water. In Southeast Asia, HEV is responsible for 25–30% of acute hepatitis cases, with a prevalence reaching as high as 50% in endemic areas. Pregnant women and immune compromised individuals are particularly

vulnerable, often experiencing severe outcomes, including fulminant hepatitis. Despite advancements in public health initiatives, the burden of HEV remains a critical concern in the region, underscoring the need for region-specific data on the clinical course and outcomes associated with HEV infections.[1,2]

This study focuses on understanding the etiological distribution and clinical manifestations of patients presenting with severe hepatic injury, defined by ALT levels exceeding 1000 U/L, in a South Asian cohort. By analyzing the causes, clinical profiles, and outcomes of these cases, this study aims to shed light on the role of viral hepatitis particularly HEV and its contribution to severe liver disease. Furthermore, the study explores non-viral causes, such as ischemic hepatitis and drug-induced liver injury (DILI), to establish a comprehensive understanding of the spectrum of conditions leading to marked ALT elevation. Such findings are essential to guide regionally relevant diagnostic and therapeutic strategies.

Several studies in both global and regional contexts have investigated ALT elevations and their etiologies. Western studies frequently report ischemic hepatitis and DILI as leading causes of ALT spikes exceeding 1000 U/L.[3] Conversely, research from South Asia, including Pakistan and India, has highlighted viral hepatitis, predominantly HEV, as the principal etiology (4). For instance, Sharma et al. observed ischemic hepatitis as the leading cause in a Western cohort, while Khan et al. found HEV to account for over half of the cases in a South Asian setting.[4,5] Additionally, studies on HIV-positive cohorts in Asia suggest a multi factorial interplay between viral hepatitis co-infections and ALT elevations, emphasizing the complexity of hepatic injuries in the region.[6] These differences underline the necessity of region-specific investigations to address unique epidemiological patterns.

Despite extensive research on ALT elevation and its causes, significant gaps remain in understanding the clinical trajectory and outcomes of patients with HEV-related ALT spikes in South Asia. Most studies have focused on viral prevalence or clinical presentations without delving into comparative analyses of viral versus non-viral causes. Additionally, the role of non-viral etiologies like ischemic hepatitis in South Asia remains underexplored. Our study addresses this gap by providing a detailed analysis of 151 patients with ALT >1000 U/L, highlighting the dominance of HEV and its clinical outcomes. By comparing our findings with global data, we aim to contribute to the growing understanding of hepatic injuries in diverse populations and advocate for tailored diagnostic and management approaches.

Methodology:

Study Design and Setting

This prospective cross-sectional study was conducted at the Department of Gastroenterology, Asian Institute of Medical Sciences (AIMS) Hospital, Hyderabad, Pakistan, from January 2023 to December 2024. The study aimed to evaluate the etiological factors, clinical presentations, and outcomes of patients with alanine aminotransferase (ALT) levels exceeding 1000 U/L.

Study-Population:

A total of 151 patients presenting with ALT >1000 U/L during the study period were included in the analysis. Patients were selected consecutively based on the inclusion and exclusion criteria.

Inclusion Criteria:

1. Patients aged 18 years or older.
2. ALT levels exceeding 1000 U/L at presentation.
3. Availability of complete clinical, laboratory, and imaging data to determine the etiology and outcomes.

Exclusion Criteria:

1. Patients with pre-existing chronic liver disease or cirrhosis.
2. Those undergoing ongoing treatment for conditions associated with ALT

elevation (e.g., chemotherapy or antiretroviral therapy).
3. Patients with autoimmune liver disease or metabolic liver conditions such as Wilson's disease or alpha-1 antitrypsin deficiency.
4. Incomplete or missing critical data in medical records.

Data Collection:

Data were collected at the time of hospital admission using a standardized data collection form. Key variables included:

- **Demographics**: Age, gender, and relevant medical history.
- **Etiological Factors**: Viral hepatitis (A, B, C, D, E), and non-viral causes (ischemic hepatitis, drug-induced liver injury, sepsis).
- **Clinical Presentations**: Acute hepatitis, acute liver failure (ALF), and acute-on-chronic liver failure (ACLF).
- **Investigations**: Laboratory findings (ALT, AST, bilirubin, prothrombin time, albumin) and viral serologies (e.g., anti-HEVIgM, HBsAg, anti-HCV antibodies). Imaging studies, including ultrasound and CT scans, were performed as required.

Outcome-Measures:

The primary outcomes included clinical improvement, discharge, and adverse outcomes such as referral for liver transplantation or in-hospital mortality.

Statistical-Analysis

Data were analyzed using IBM SPSS Statistics Version 22. Categorical variables were reported as frequencies and percentages. Chi-square tests were used for categorical data comparisons, while t-tests or Mann-Whitney U tests were applied for continuous variables. Logistic regression analysis identified factors associated with adverse outcomes, p-value <0.05 was considered statistically significant.

Results:

In our cohort of 151 patients with ALT >1000 U/L, the majority were male (74.2%) and younger than 40 years old (69.5%). Most patients (68.2%) weighed ≥70 kg, and 67.5% had no co-morbidities. Among those with co-morbidities, diabetes (19.3%), ischemic heart disease (14.6%), and chronic liver disease (6.0%) were most common as shown in Table-1.

Viral hepatitis was the leading cause of elevated ALT levels, accounting for 86.1% of cases. Hepatitis E virus (HEV) was the most prevalent, responsible for 55.6% of cases, followed by hepatitis A (8.6%) and hepatitis B (7.3%). HEV was notably over-represented in pregnant women, emphasizing the heightened vulnerability in this group. Drug-induced liver injury (DILI) was the second most common non-viral cause, contributing to 3.3% of cases, primarily due to medication overdoses or idiosyncratic reactions.

Clinical outcomes revealed that the majority of patients improved without complications, with 142 (94.0%) showing recovery. Liver transplant was required in three cases, while six patients succumbed to their conditions. Mortality was highest among patients with hepatitis D (25.0%) and HEV (3.6%), underscoring the need for targeted prevention and management strategies in these high-risk groups clearly depicted in Table2.

Table-1: Demographic variables at Presentation

Variable		n=151 (%)
Age	<40 years	105 (69.5%)
	≥ 40 years	46 (30.5%)
Gender	Male	112(74.2%)
	Female	39 (25.8%)
Weight	<70 kg	48 (31.8%)
	≥ 70 kg	103 (68.2%)
Comorbidities	No co-morbidities	102 (67.5%)
	Diabetic	14 (19.3%)
	Hypertension	4 (2.6%)
	Ischemic Heart Disease	16 (14.6%)
	Chronic Liver Disease	9 (6.0%)
	Chronic Kidney Disease	6 (4.0%)

Table-2: Causes of ALT >1000 vs. Outcomes in 30 days

Cause	Improved	Referred for Liver transplant	Died	Total	% of Total
Hepatitis A	13	0	0	13	8.6%
Hepatitis B	11	0	0	11	7.3%
Hepatitis C	14	0	0	14	9.3%
Hepatitis D	5	1	2	8	5.3%
Hepatitis E	80	1	3	84	55.6%
Ischemic Hepatitis	6	1	0	7	4.6%
DILI / Non-Acetaminophen	5	0	0	5	3.3%
Sepsis	2	0	0	2	1.3%
Hepatitis B + E	2	0	0	2	1.3%
Hepatitis B + D	1	0	1	2	1.3%
Hepatitis C + A	1	0	0	1	0.7%
Hepatitis B + A	1	0	0	1	0.7%
Hepatitis C + E	1	0	0	1	0.7%
Total	142	3	6	151	100.0%

Discussion:

Our findings underscore regional differences in severe ALT elevation. Globally, a meta-analysis showed ischemic hepatitis in ~51% of ALT>1000 cases, with viral and DILI each ~13%.[7] By contrast, hepatitis E featured prominently in our cohort, consistent with its high prevalence in South Asia.[8,9] The pooled seroprevalence of HEV IgG in Southeast Asia is ~21% and rising over time,[10] reflecting ongoing transmission. HEV genotypes 1–2 cause outbreaks via contaminated water, disproportionately affecting young adults and pregnant women.[9,11] Indeed, HEV-related acute liver failure (HEV-ALF) carries significant mortality – estimated at ~32% in non-pregnant patients and >60% in pregnant patients in India.[8] This aligns with historical data (e.g. 30% fatality in third-trimester HEV) and emphasizes the need for vigilance.[8,11] By contrast, acetaminophen overdose is less common in our setting, although we counsel all ALF patients to avoid hepatotoxins. Per WHO guidance, diagnosis of HEV relies on anti-HEV IgM testing or RNA detection. Acute HEV treatment is mainly supportive; no specific antiviral is approved. Prevention (improving sanitation) and vaccination (a recombinant HEV239 vaccine is licensed in China) are key long-term strategies.[9] Meanwhile, prompt identification of ischemic or toxic causes is critical: ischemic hepatitis has markedly worse prognosis (our data mirror a 21-fold higher mortality vs. other causes.[7] Where available, N-acetylcysteine can be administered empirically in suspected DILI, and early transplant referral should be considered for fulminant cases.

Conclusion:

Our study emphasizes the multifactorial nature of severe liver injury and the need for a comprehensive approach to diagnosis and treatment. The findings suggest that both viral and non-viral causes contribute to severe transaminase elevations, and early intervention is critical to improving patient outcomes. Further research is needed to explore the long-term effects of these conditions and to develop more effective treatments, particularly for hepatitis E, which poses a growing public health challenge worldwide.

Ethical-Considerations:

The study was reviewed and approved by the AIMS Hospital Ethical Review Committee. All participants provided written informed consent, and the study adhered to the ethical guidelines of the Declaration of Helsinki.

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Author's Contribution:

SM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
FN, BK, SS, MZ, ND, US, UG, MB, SK: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.