Section: Microbiology

Original Research Article

ASSESSMENT OF ACTIVE VIRAL REPLICATION IN CHRONIC HEPATITIS B BY EVALUATING HBEAG, ANTI-HBE, ALANINE AMINOTRANSFERASE, AND QUANTITATIVE HBV DNA LEVELS IN SOUTH INDIA: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Chronic hepatitis B virus (HBV) infection remains a major global public health concern and is a leading cause of liver cirrhosis and hepatocellular carcinoma (HCC). Assessment of viral replication is essential for determining disease activity, prognosis, and therapeutic response. Hepatitis B e antigen (HBeAg), antibody to hepatitis B e antigen (anti-HBe), alanine aminotransferase (ALT), and quantitative HBV DNA are important markers used in the evaluation of chronic hepatitis B (CHB). The aim is to assess active viral replication in chronic hepatitis B patients by evaluating the relationship between HBeAg, anti-HBe, ALT levels, and quantitative HBV DNA levels in a tertiary care center in South India.

Materials and Methods: This analytical cross-sectional study was conducted at Government Ariyalur Medical College Hospital, Tamil Nadu, India, from February 2025 to April 2025. Among 484 adults clinically suspected of chronic hepatitis B infection, 60 HBsAg-positive patients were enrolled. Serum samples were tested for HBeAg and anti-HBe using enzyme-linked immunosorbent assay (ELISA). ALT levels were measured using a fully automated biochemical analyzer, and quantitative HBV DNA estimation was performed by real-time polymerase chain reaction (RT-PCR). Statistical analysis was performed using SPSS software. Associations between categorical variables were analyzed using Chi-square and Fisher's exact tests. A p-value <0.05 was considered statistically significant.

Results: Of the 60 HBsAg-positive patients, 44 (73.3%) were males and 16 (26.7%) were females. HBeAg positivity was observed in 28 (46.7%) patients, while anti-HBe positivity was detected in 30 (50.0%) patients. HBV DNA was detectable in 96% of HBeAg-positive patients and 90% of anti-HBe-positive patients. High viral load (>20,000 IU/mL) was significantly associated with HBeAg positivity (p<0.001). Elevated ALT levels were more frequently observed among HBeAg-positive patients than among HBeAg-negative patients. Notably, a substantial proportion of anti-HBe-positive patients also demonstrated detectable HBV DNA and elevated viral loads, indicating ongoing viral replication despite seroconversion.

Conclusion: HBeAg positivity showed a strong association with elevated HBV DNA levels and active viral replication. However, detectable HBV DNA in a considerable number of anti-HBe-positive patients highlights the limitations of relying solely on serological markers. Quantitative HBV DNA remains the most reliable indicator of viral replication, while HBeAg and ALT may serve as useful surrogate markers in resource-limited settings.

Keywords: Chronic hepatitis B, HBeAg, Anti-HBe, HBV DNA, Alanine aminotransferase, Viral replication, South India

INTRODUCTION

Hepatitis B virus infection remains one of the most significant infectious diseases worldwide despite the availability of highly effective vaccines.[1,2] According to the World Health Organization (WHO), approximately 254 million people were living with chronic hepatitis B infection in 2022, with nearly 1.2 million new infections occurring annually.[3] Chronic hepatitis B contributes substantially to global morbidity and mortality, accounting for approximately 1.1 million deaths annually due to cirrhosis and hepatocellular carcinoma.[4] India carries one of the highest burdens of HBV infection globally, with an estimated 29.8 million individuals affected.[5] The prevalence of chronic hepatitis B in the general population ranges between 2% and 4%, while considerably higher rates are observed among high-risk groups such as healthcare workers, patients undergoing hemodialysis, and recipients of multiple blood transfusions.[6] Transmission occurs through both vertical and horizontal routes, and approximately 15–25% of chronic carriers eventually develop cirrhosis or its complications.[7] The clinical spectrum of HBV infection varies widely, ranging from asymptomatic carrier states to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Persistent detection of hepatitis B surface antigen (HBsAg) for more than six months is considered indicative of chronic infection.[8] HBeAg is a secreted viral protein traditionally regarded as a marker of active viral replication and infectivity. Seroconversion from HBeAg to anti-HBe generally indicates a decline in viral replication and improvement in disease activity.[9] However, HBeAg negativity does not necessarily indicate viral suppression. Mutations in the precore and basal core promoter regions of the HBV genome can inhibit HBeAg production while permitting continued viral replication.[10] Consequently, many patients with HBeAg-negative chronic hepatitis continue to demonstrate detectable HBV DNA levels and progressive liver disease.[11] Serum ALT is commonly used as a marker of hepatocellular injury and disease activity. Nevertheless, ALT levels alone may not accurately reflect viral replication because some patients with high HBV DNA levels may exhibit normal ALT concentrations.[12] Quantitative measurement of HBV DNA by molecular methods remains the gold standard for evaluating viral replication and guiding antiviral therapy.[13] Although HBV DNA quantification is widely recommended by international guidelines, its routine use remains limited in many developing countries because of financial and infrastructural constraints. Therefore, understanding the relationship between HBV DNA levels and more accessible markers such as HBeAg, anti-HBe, and ALT is important for optimizing patient management in resource-limited settings.[14,15] The present study was undertaken to evaluate the association between HBeAg, anti-HBe, ALT levels, and quantitative HBV DNA levels among chronic hepatitis B patients attending a tertiary care hospital in South India.

MATERIALS AND METHODS

Study Design and Setting: This analytical cross-sectional study was conducted in the Departments of Microbiology and Biochemistry at Government Ariyalur Medical College Hospital, Tamil Nadu, South India, over a period of three months from February 2025 to April 2025.

Ethical Considerations: The study was approved by the Institutional Ethics Committee before commencement. Written informed consent was obtained from all participants. Confidentiality was maintained throughout the study by assigning anonymized identification numbers to samples and patient records.

Study Population: A total of 484 adult patients clinically suspected of chronic hepatitis B infection were screened for HBsAg. Sixty patients who tested positive for HBsAg were included in the study.

Inclusion Criteria:

1. Adults aged ≥18 years
2. HBsAg positivity suggestive of chronic HBV infection
3. Provision of informed written consent

Exclusion Criteria:

1. HBsAg-negative patients
2. Co-infection with HIV or HCV
3. Chronic liver disease due to causes other than HBV
4. Pediatric patients
5. Autoimmune or metabolic liver diseases

Laboratory Investigations:

Detection of HBsAg:

Serum samples were tested using ErbaLisa SEN HBsAg ELISA kits according to the manufacturer's instructions.

Detection of HBeAg and Anti-HBe:

Qualitative detection of HBeAg and anti-HBe was performed using DIA.PRO Diagnostic Bioprobes ELISA kits. Samples with signal-to-cutoff (S/CO) ratios greater than 1.1 were considered positive.

ALT Estimation: Serum ALT levels were measured using ErbaLiquixx-R reagents on a fully automated biochemical analyzer. ALT values greater than 40 U/L were considered elevated.

HBV DNA Quantification: HBV DNA quantification was performed using the PathoDetect HBV Quantitative Real-Time PCR Kit on the QIAGEN Rotor-Gene Q platform. Viral DNA extraction was carried out using a dedicated viral nucleic acid extraction kit.Amplification utilized TaqMan probe chemistry targeting conserved HBV genomic regions. Viral loads were expressed as International Units per milliliter (IU/mL). The analytical sensitivity of the assay was 10 IU/mL.

Statistical Analysis: Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) software version 25.0. Categorical variables were summarized as frequencies and percentages. Associations were analyzed using Chi-square or Fisher's exact test as appropriate. Statistical significance was established at $p<0.05$.

RESULTS

Demographic Characteristics: Among the 60 HBsAg-positive patients, 44 (73.3%) were males and 16 (26.7%) were females, giving a male-to-female ratio of 2.75:1.The majority of patients belonged to the 31–40 years and 41–50 years age groups, each contributing 33.3% of the study population [Figure 1].

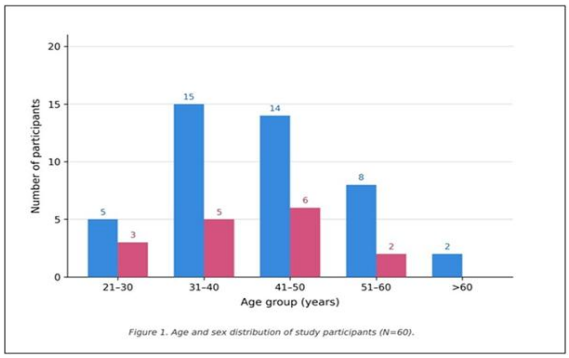

Figure 1: Gender wise distribution of study populations

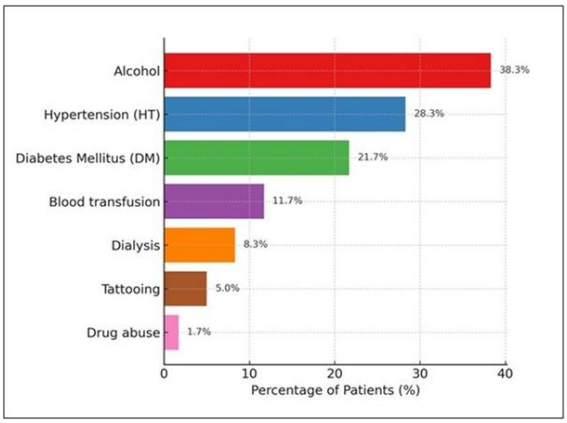

Figure 2: Distribution of risk factors among patients with Hepatitis B

Distribution of Risk Factors: Alcohol consumption was the most common associated risk factor, identified in 38.3% of patients. Other frequently observed comorbidities included hypertension (28.3%) and diabetes mellitus (21.7%) [Figure 2]. Less common risk factors included blood transfusion, hemodialysis, tattooing, and intravenous drug abuse.

HBeAg and Anti-HBe Serological Status: Among the 60 patients included in the study, 27 (45.0%) were HBeAg-positive and anti-HBe-negative, indicating active viral replication [Figure 3]. In contrast, 30 (50.0%) patients were HBeAg-negative and anti-HBe-positive, suggesting seroconversion and a relatively lower level of viral replication. One patient (1.7%) tested positive for both HBeAg and anti-HBe, representing a transitional serological phase, while two patients (3.3%) were negative for both markers. Overall, HBeAg positivity was observed in 28 patients (46.7%), whereas anti-HBe positivity was detected in 31 patients (51.7%), including the patient who was positive for both markers. These findings demonstrate a nearly equal distribution of HBeAg and anti-HBe serological profiles among the study population, with a slight predominance of anti-HBe positivity.

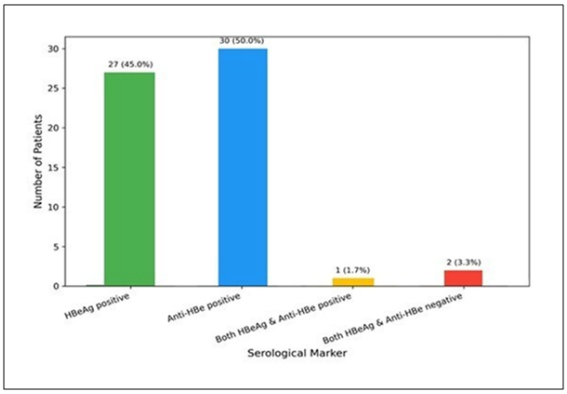

Figure 3: Distribution of HBeAg and Anti-HBe Status among Hepatitis B

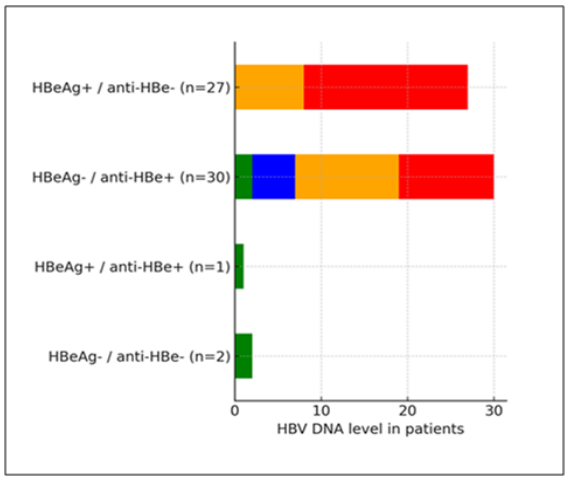

Figure 4: Distribution of HBV DNA levels according to HBeAg /anti-HBe status among patients with Hepatitis B.

Association Between HBeAg Status and HBV DNA Levels: HBV DNA was detectable in nearly all HBeAg-positive patients. The majority of HBeAg-positive individuals demonstrated viral loads exceeding 20,000 IU/mL. Among HBeAg-positive/anti-HBe-negative patients, 70.4% exhibited HBV DNA levels greater than 20,000 IU/mL. In contrast, among HBeAg-negative/anti-HBe-positive patients, only 36.7% demonstrated viral loads above 20,000 IU/mL. The association between HBeAg positivity and elevated HBV DNA levels was statistically significant ($p<0.001$) [Figure 4].

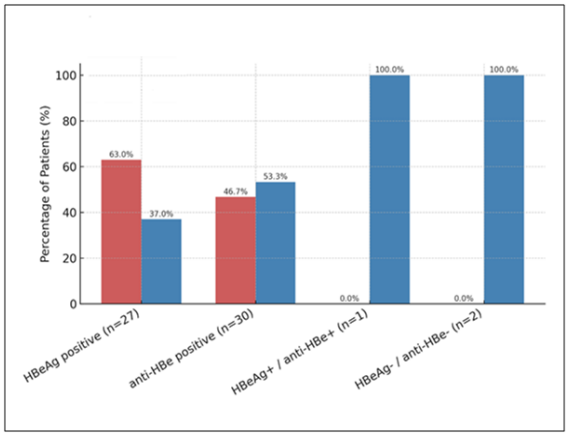

Figure 5: Distribution of ALT Levels by HBeAg/anti-HBe Status among patients with Hepatitis B

Association Between ALT Levels and Viral Replication: Elevated ALT levels were observed in 60.7% of HBeAg-positive patients compared with 46.7% of HBeAg-negative patients [Figure 5]. Among HBeAg-positive patients with elevated ALT, most had HBV DNA levels exceeding 20,000 IU/mL. However, a substantial number of HBeAg-negative patients also demonstrated elevated ALT levels and detectable HBV DNA. Interestingly, several HBeAg-negative patients with normal ALT levels continued to exhibit moderate-to-high HBV DNA levels, suggesting ongoing viral replication despite apparent biochemical quiescence.

Comparison of HBV DNA Levels and ALT According to HBeAg/Anti-HBe Status: Among the 60 hepatitis B patients, all 27 HBeAg-positive/anti-HBe-negative patients had detectable HBV DNA [Table 1]. Of these, 19 (70.4%) had HBV DNA levels >20,000 IU/mL, while 8 (29.6%) had HBV DNA levels between 2,000 and 20,000 IU/mL. Elevated ALT levels (>40 U/L) were observed in 17 (63.0%) patients, whereas 10 (37.0%) had normal ALT levels. High HBV DNA levels (>20,000 IU/mL) predominated irrespective of ALT status.Among the 30 HBeAg-negative/anti-HBe-positive patients, HBV DNA levels were more heterogeneous. Three (10.0%) patients had undetectable HBV DNA, 6 (20.0%) had HBV DNA <2,000 IU/mL, 10 (33.3%) had HBV DNA levels between 2,000 and 20,000 IU/mL, and 11 (36.7%) had HBV DNA >20,000 IU/mL. Elevated ALT levels were present in 14 (46.7%) patients, while 16 (53.3%) had normal ALT levels. The single patient who was positive for both HBeAg and anti-HBe had normal ALT with undetectable HBV DNA. Similarly, both patients who were negative for HBeAg and anti-HBe had normal ALT and undetectable HBV DNA. Overall, HBeAg-positive patients were more frequently associated with high HBV DNA levels (>20,000 IU/mL), whereas HBeAg-negative/anti-HBe-positive patients exhibited a wider distribution of HBV DNA levels, including undetectable and low-level viremia.

Table 1: Comparison of HBV DNA and ALT Levels in Hepatitis B Patients

Patients	ALT Level	HBV DNA not detected	HBV DNA <2000 IU/ml	HBV DNA 2000–20000 IU/ml	HBV DNA >20000 IU/ml	Total
HBeAg-positive / anti-HBe negative (n=27)	>40 U/L	–	–	5 (29.4%)	12 (70.6%)	17 (70.8%)
	<40 U/L	–	–	3 (30.0%)	7 (70.0%)	10 (29.2%)
HBeAg-negative / anti-HBe positive (n=30)	>40 U/L	–	3 (21.4%)	6 (42.9%)	5 (35.7%)	14 (46.7%)
	<40 U/L	3 (18.8%)	3 (18.8%)	4 (25.0%)	6 (37.5%)	16 (53.3%)
HBeAg-positive / anti-HBe positive	<40 U/L	1 (100%)	–	–	–	1 (100%)
HBeAg-negative / anti-HBe negative	<40 U/L	2 (100%)	–	–	–	2 (100%)

DISCUSSION

The present study evaluated the relationship between HBeAg status, anti-HBe status, serum ALT levels, and quantitative HBV DNA levels among patients with chronic hepatitis B infection in South India. The findings demonstrated a significant association between HBeAg positivity and elevated HBV DNA levels, highlighting the importance of HBeAg as a marker of active viral replication. Among the 60 HBsAg-positive patients included in the study, males constituted 73.3% of the study population. Similar male predominance has been reported in several Indian and international studies, which may be attributed to greater occupational exposure, behavioral risk factors, and possible hormonal influences on HBV persistence and immune response. Kumar et al. reported a male predominance of 76% among chronic hepatitis B patients, while Hossain et al., Li et al observed comparable findings in North Indian populations.[16-18] HBeAg is a well-established marker of active viral replication and infectivity. In the present study, 46.7% of patients were HBeAg positive, and HBV DNA was detectable in 96% of these patients. Furthermore, the majority of HBeAg-positive individuals had HBV DNA levels exceeding 20,000 IU/mL. These findings are consistent with previous reports by Kumar et al. and Preethi et al., who demonstrated significantly higher viral loads among HBeAg-positive patients compared with HBeAg-negative individuals.[16,17] International studies have also shown that HBeAg positivity correlates strongly with viral replication and increased risk of disease progression.[19] The mean HBV DNA level was higher among HBeAg-positive patients than among HBeAg-negative

patients, supporting the role of HBeAg as an indicator of active viral replication. However, the difference did not reach statistical significance, possibly because of the relatively small sample size. Similar observations have been reported by Kumar et al. and Karra et al.[16,20] A notable finding of the present study was the detection of HBV DNA in a substantial proportion of anti-HBe-positive patients. Among HBeAg-negative/anti-HBe-positive individuals, 90% had detectable HBV DNA, and more than one-third exhibited viral loads greater than 20,000 IU/mL. This observation is clinically important because anti-HBe positivity has traditionally been considered a marker of reduced infectivity and viral suppression. However, mutations in the precore and basal core promoter regions of HBV can abolish HBeAg production while permitting continued viral replication. Such patients represent HBeAg-negative chronic hepatitis B and remain at risk of progressive liver disease.[21,22] Several studies have reported similar findings. Kumar et al. demonstrated detectable HBV DNA in 82% of anti-HBe-positive patients, while Karra et al. reported persistent viral replication in HBeAg-negative individuals despite apparent seroconversion.[16,20] Chu and Liaw also described HBeAg-negative chronic hepatitis as an increasingly recognized form of active disease associated with fluctuating viremia and progressive hepatic injury.[23] Serum ALT is widely used as a biochemical marker of hepatocellular injury. In the present study, elevated ALT levels were observed more frequently among HBeAg-positive patients (60.7%) than among HBeAg-negative patients. These findings are in agreement with previous studies that demonstrated a positive association between active viral replication and hepatocellular damage.[20] However, several HBeAg-positive patients exhibited normal ALT levels despite high viral loads. This finding is consistent with the immune-tolerant phase of chronic HBV infection, during which active viral replication occurs in the absence of significant liver inflammation.[24] Interestingly, elevated ALT levels were also observed among anti-HBe-positive patients. Moreover, a proportion of patients with normal ALT values demonstrated significant HBV DNA levels, indicating that ALT alone may not accurately reflect viral replication status. Similar observations have been reported by Martinot-Peignoux et al. and Fattovich et al., who emphasized that normal ALT levels do not necessarily exclude active HBV replication or progressive liver disease.[25,26] The significant association observed between HBeAg positivity and elevated HBV DNA levels in the present study supports the continued utility of HBeAg as a practical marker of viral replication, particularly in resource-limited settings where molecular testing may not be routinely available. Nevertheless, the presence of substantial viremia among anti-HBe-positive patients underscores the limitations of relying solely on serological markers for clinical decision-making. Current international guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend quantitative HBV DNA measurement as the cornerstone for disease staging, treatment initiation, and monitoring therapeutic response.[27,28] The findings of the present study strongly support these recommendations. Although HBeAg and ALT remain useful surrogate markers, HBV DNA quantification remains the most reliable method for assessing viral replication and should be incorporated whenever feasible into the routine evaluation of patients with chronic hepatitis B infection.

Limitations: The study has several limitations. The sample size was relatively small and derived from a single tertiary care center. The cross-sectional design precluded longitudinal assessment of disease progression and treatment outcomes. HBV genotyping and precore mutation analysis were not performed, limiting characterization of HBeAg-negative chronic hepatitis. Liver fibrosis assessment was also not included. Future multicentric studies with larger sample sizes, longer follow-up periods, and molecular characterization of HBV strains are warranted.

CONCLUSION

The present study demonstrated a strong association between HBeAg positivity and elevated HBV DNA levels, confirming HBeAg as an important marker of active viral replication in chronic hepatitis B infection. However, a significant proportion of anti-HBe-positive patients also exhibited detectable HBV DNA levels, indicating ongoing viral replication despite seroconversion. Although HBeAg and ALT remain useful and affordable indicators of disease activity in resource-constrained settings, they cannot reliably identify all patients with active viral replication. Quantitative HBV DNA estimation remains the most sensitive and accurate method for assessing viral replication, determining disease activity, monitoring therapeutic response, and guiding antiviral treatment decisions. The combined use of HBeAg, anti-HBe, ALT, and HBV DNA testing provides a comprehensive approach to the management of chronic hepatitis B and may improve clinical outcomes through timely identification of patients requiring intervention.

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