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Biomarkers of Liver Disease Progression and Severity among Individuals Infected with Hepatitis B Virus in Abakaliki, Nigeria

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Abstract | **Original Research Article**

Hepatitis B virus (HBV) infection remains a major global health challenge, particularly in Sub-Saharan Africa. Interleukin-6 (IL-6), a pro-inflammatory cytokine, is known to play a crucial role in the immune response and pathogenesis of HBV infection. However, its correlation with HBV serological profiles and disease progression is not well established. This study aimed at investigating the levels of IL-6 and ALT among HBV-infected individuals in Abakaliki, Nigeria. A cross-sectional study was conducted among 150 HBV-infected individuals attending health facilities in Abakaliki. Participants were screened using HBV panel tests and IL-6 levels were determined using fluorescence immunosorbent assay. Data were analyzed to determine the prevalence of various HBV status and the distribution of IL-6 levels among these groups. The most common HBV status was inactive infection (50%), followed by inactive chronic infection (26%). IL-6 levels varied significantly across infection status. Individuals with inactive infection mostly had IL-6 levels between 11–500 pg/ml, indicating moderate severity. Individuals with inactive sepsis and inactive chronic sepsis had IL-6 levels exceeding 1000 pg/ml, suggestive of systemic inflammation or cytokine storm. A clear association was observed between elevated IL-6 levels and disease severity. IL-6 levels were found to correlate strongly with HBV infection status, especially in cases involving sepsis and chronic active infection. These findings support the role of IL-6 as a potential biomarker for monitoring disease severity and immune activity in HBV-infected individuals. Routine IL-6 assessment alongside HBV serological profiling may enhance patient management and early detection of complications.

Keywords: Hepatitis B virus, Interleukin-6, Biomarker, Disease severity, Serological profile, Sub-Saharan Africa.

BACKGROUND OF THE STUDY

Hepatitis B Virus is a prototype member of the *Hepadnaviridae* family of viruses and genus orthohepatodnavirus. (Brook G.F, 2004). It is a small virus, 42 nm in diameter made up of a core of partially double-stranded DNA enveloped by a glycolipid shell. Historically, the earliest recorded evidence of Hepatitis B dates back to ancient Greece, around 400 BCE, where it was described as a disease that caused yellow skin and fever (Lauer & Walker, 2001).

During the Middle Ages, Hepatitis B was likely spread through contaminated water and food, leading to outbreaks in Europe. The disease was often confused with other liver ailments. In the 18th and 19th centuries, Hepatitis B was identified as a distinct clinical entity, often associated with epidemics and outbreaks (Prince *et al,* 1968). The virus was initially thought to be spread through contaminated food and water.

In the early 20th century, Hepatitis B was recognized as a major public health concern, particularly among healthcare workers and military personnel. The virus was transmitted through blood transfusions, tattoos, and medical procedures. In 1960s specifically in the year 1965, Baruch Blumberg discovered the Australia antigen, a protein on the surface of the Hepatitis B virus, which led to the development of diagnostic tests (Blumberg *et al*., 1965). This breakthrough earned Blumberg the Nobel Prize in Physiology/Medicine in 1976. Hepatitis B surface antigen (HBsAg) was formerly called Australia antigen because it was first described in the serum of an Australian aborigine in 1965. Two researchers named Okochi and Murakami in 1968, discovered that the Australian antigen was related to type B Hepatitis while David Dane found virus-like particles in the serum of individuals suffering from type B Hepatitis in 1973. These particles are called Dane particles and were

designated as the Hepatitis B virus (HBV) (Ajuwon *et al.*, 2021).

Hepatitis B Virus is a major public health problem worldwide, it's more prevalent in developing countries. More than 1.98 billion people are infected with HBV worldwide, while approximately 257 million are chronic carriers, harboring the virus in their liver (World Health Organization, 2022). About 786,000 of these carriers die each year as a result of cirrhosis or primary liver cell cancer induced by the virus (Lavanchy *et al*., 2020). This virus is responsible for 50-80% of all cases of primary liver cancer, which is one of the leading causes of death in Asia and Africa (Global Burden of Disease Study, 2023).

About 5-10% of infected adults become chronic carriers, while the rest eliminate the virus from their body without sequela (Lavanchy *et al*., 2020). Approximately 25% of chronic carriers will die from hepatic complications of chronic infection, some remain lifelong carriers, while others will clear the infection after varying intervals (Pollicino *et al*., 2020). Sub-Saharan Africa is considered a region of high endemicity, with an average carrier rate of 10-20% in the general population (World Health Organization, 2020). Notably, 70-95% of adults in Sub-Saharan Africa have at least one marker of HBV (Njouom *et al*., 2018). In West Africa, it has been estimated that 40% of children will be infected from age two years and above 90% by age ten years. The chronic carrier rate is 20% in these children (Adekanle *et al*., 2020). A chronic carrier rate above 7% in a population is classified as hyper-endemic. Studies done in Nigeria showed HBV carriage rates in the range of 9-39% (Ajuwon *et al.*, 2021).

Hepatitis B virus (HBV) infection can lead to a great number of clinical consequences, such as acute self-limited Hepatitis, chronic Hepatitis, liver failure, liver cirrhosis, and hepatocellular carcinoma. These complications do not result from a direct cytopathic effect of the virus itself, but from the immune response of the host that affects both outcome and disease progression (Lavanchy *et al*., 2020). The immune response to HBV is complex and involves various cytokines, among which interleukin 6 (IL-6) play crucial roles (Wang *et al*., 2020; Zhang *et al*., 2021).

The immune response plays a crucial role in HBV pathogenesis, with both innate and adaptive immune responses contributing to the control of viral replication and the development of liver disease (Zhang *et al*., 2020). The adaptive immune response, particularly CD8+ T cells, is essential for the elimination of HBV-infected hepatocytes (Li *et al*., 2020). However, the immune response can also cause liver damage and inflammation, leading to the development of chronic Hepatitis and hepatocellular carcinoma.

The immune response to HBV infection is important in determining the outcome of the infection. Cytokines, such as interleukin-6 (IL-6), are key players in the immune response to HBV infection. IL-6 is a pro-inflammatory cytokine that is produced in response to HBV infection and plays a role in the activation of immune cells, such as T cells and macrophages.

The HBV panel kit, also known as the hepatitis B serological panel, is a diagnostic tool used to determine an individual's HBV status. The panel typically includes tests for three main markers: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc).

An infected HBsAg result indicates current HBV infection, while a infected anti-HBs result indicates immunity to HBV, either through vaccination or past infection and the presence of anti-HBc, particularly IgM anti-HBc, can indicate acute HBV infection, while IgG anti-HBc suggests past or chronic infection. (Centre for disease control, 2020).

Interpreting HBV panel results requires careful consideration of the individual's clinical history, vaccination status, and laboratory results. Accurate diagnosis and monitoring of HBV infection are crucial for guiding treatment decisions and preventing disease progression (Terrault *et al.,* 2022).

The relationship between IL-6 and HBV status of HBV infected individuals is essential for elucidating the pathogenesis of the disease and developing potential therapeutic strategies.

MATERIAL AND METHODS

Study Area

Abakaliki is located in southeastern Nigeria, in Ebonyi state. It is situated about 150 kilometers (93 miles) from the state capital of Umuahia and about 200 kilometers (124 miles) from the federal capital of Abuja. The city is located in a tropical zone, with an average temperature of about 27°C. According to the last census data (WHO, 2022), the population of Abakaliki is approximately 723,000 people, with a median age of 18 years. The gender ratio is roughly equal, with about 49% male and 51% female.

Study Design

The study was a cross-sectional study conducted among different Hepatitis B infected individuals across different age groups in Abakaliki, Ebonyi state, Nigeria.

Study Population

The study was conducted among Hepatitis B infected individuals attending Alex Ekwueme Federal Teaching Hospital, Abakaliki (AEFUTHA) and other

Primary Health care centres in Abakaliki, Ebonyi State, Nigeria.

Sample Size

$n=z2p(1-p)/d2$

Where,
n = Minimum required sample size
z = Standard Normal deviation (1.96)
p = Prevalence of Hepatitis B in Abakaliki is 10.86%/100= 0.11
d = Precision tolerance margin of error (0.05)
n= 3.8416x0.11x0.89/0.0025
n=0.3761/0.0025
n=150+10% attrition making a total of 165 subjects who that were recruited for the study.

By reason of this calculation a total of 165 Hepatitis B infected persons were used for this study

Inclusion Criteria & Exclusion Criteria

Individuals who were infected for HBV surface antigen (HBsAg) were included in the study.

Sample Collection

Five millimeters (5ml) of whole blood was collected by venipuncture at the ante-cubital fossa using a sterile needle and syringe and dispensed into a plain container.

During the sampling 10% of the HBV infected individuals (15 individuals) didn't come back for the sampling, making a total of 150 individuals sampled.

Sample Analysis

Hepatitis B Virus Infection Panel Assay

The test works based on the principle of the antigen-antibody reaction. It is a serological assay that detects specific Hepatitis B viral antigens (like HBsAg) and antibodies (like anti-HBs, anti-HBc, IgM anti-HBc, HBeAg and anti-HBe) in the patient's serum.

The blood sample was centrifuged to obtain the serum, after centrifuging the HBV panel kit pouch was opened and the device was removed and placed on a clean flat surface. The device was labelled with the specimen's ID number. After labelling, the pipette dropper was filled with the serum, in a vertical position, 2-3 drops (about 60-90 ul) was dispensed into each of the sample well, making sure that there were no air bubbles. The timer was set for 15 minutes, and the result was read within 15 minutes, some infected results were visible in less than a minutes.

Interleukin 6 Assay using Fluorescence Immunosorbent Assay

The test is based on the principle of Fluorescence immunosorbent assay (FIA) technology. The anbio test kit uses a sandwich immune detection method. When sample is added to the sample well of the test, the fluorescence-labeled detector IL-6 antibody binds to the IL-6 antigen in the blood specimen.

Fluorescence immunosorbent assay works based the principle of antigen-antibody reaction. It quantifies antigens or antibodies based on the emission of light from a fluorescent dye attached to an antigen or antibody during a specific immune reaction. The blood sample was centrifuged to obtain the serum. Then the IC card information was checked or swiped on the Fluorescence Immunoassay Meter to load the machine. After loading the machine the IL-6 kit pouch was opened and the device was removed and was placed on a clean flat surface. The device was then labelled with the specimen's ID number and the pipette dropper was filled with the specimen (serum), in a vertical position, 50ul was dispensed into the sample well of the test cartridge, then it was incubated at room temperature for 15 minutes. After incubation it was inserted unto the test cartridge holder and quick test was selected, and after about 1-2 minutes the test result was displayed on the screen in pg/ml. Test test reference value: ≤7.0pg/ml.

ALT Assay

Serum samples from the subjects were analyzed using randox ALT kit according to the manufacturer instructions.

Ethical Consideration

Ethical approval was gotten from the ministry of health Abakaliki, and was also gotten from the Health Research and Ethics Committee (HREC) AEFUTHA.

Data Analysis

The data collected were entered into MS Word and analyzed using HP Windows 10 pro software Version 21H2 (HP Desktop 2010) and the results was interpreted using percentages.

RESULTS

Table 1: HBV Biomarkers Reaction and Progression Pattern

HBV Biomarkers reaction pattern	Infection Progression	No. of Subjects infected	Prevalence (%)
HBsAg (neg) Anti-HBs (neg) HBeAg(neg) Anti-HBe(neg) Anti-HBc(neg/Pos)	Never Infected Or Occult infections	12	8

HBV Biomarkers reaction pattern	Infection Progression	No. of Subjects infected	Prevalence (%)
HBsAg (pos) Anti-HBs (neg) HBeAg(neg) Anti-HBe(pos) Anti-HBc(pos)	Inactive Infection	75	50
HBsAg (pos) Anti-HBs (neg) HBeAg(neg) Anti-HBe(neg) Anti-HBc(pos)	Inactive Chronic Infection	39	26
HBsAg (pos) Anti-HBs (neg) HBeAg(neg) Anti-HBe(neg) Anti-HBc(pos)	Inactive chronic sepsis	3	2
HBsAg (pos) Anti-HBs (neg) HBeAg(neg) Anti-HBe(pos) Anti-HBc(pos)	Inactive sepsis	9	6
HBsAg (pos/neg) Anti-HBs (neg) HBeAg(neg) Anti-HBe(neg) Anti-HBc(neg/pos)	Early Infection or Occult HBV	12	8

Table 2: Gender Distribution of Individuals infected with Hepatitis B Virus

Gender	No. of Individuals Examined	No. of individuals infected	Prevalence of infected individuals (%)
Male	60	57	41.3
Female	90	81	58.7
Total	n=150	n=138	n=100

Table 3: Age Distribution of Individuals infected with Hepatitis B Virus.

Age Group	No. of Individuals Examined	No. of individuals infected	Prevalence of infected individuals (%)
20-25	12	12	8.7
26-30	33	30	21.7
31-35	45	39	28.3
36-40	39	36	26.1
41-45	12	12	8.7
46-50	9	9	6.5
Total	n=150	n=138	n=100

Table 4: Interleukin 6 Level and Distribution of Hepatitis B Virus Infectious Disease Progression

Hepatitis B virus Status	Interleukin 6 (IL-6) (Pg/ml) and ALT (U/L) Levels				
	<7.0	>7.0-10	>11-500	500-999	>1000
Never infected (n=12)	9 (75%)	3 (25%)	0 (0%)	0 (0%)	0 (0%)
Inactive infection (n=75)	33 (44%)	6 (8%)	30 (40%)	3 (4%)	3 (4%)
Inactive chronic infection (n=39)	9 (23%)	12 (30.8%)	12 (30.8%)	3 (7.7%)	3 (7.7%)
Inactive sepsis (n=9)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (100%)
Inactive chronic sepsis (n=3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
Early/occult Infection (n=12)	3 (25%)	3 (25%)	6 (50%)	0 (0%)	0 (0%)

Table 5: Interleukin 6 and ALT Levels of HBV Infected Individuals and Disease Severity (n=138)

IL-6 (pg/ml) Levels	ALT (U/L) Levels	Interpretation	Clinical Significance on severity	Prevalence (%)
≤7.0	≤12	Normal	Baseline value in healthy individuals, suggests absence of infection.	32.7
8-10	11-15	Intermediate or Low-grade elevation	It indicates early or mild infection or post-infection recovery phase.	10.8
11-500	16-20	Moderate elevation	It's indicative of an active viral infection.	39.1
501-1000	21-25	High elevation	It's indicative of systemic inflammation due to severe viral disease	8.7
≥1000	≥26	Very high or Cytokine storm	It's indicative of hyper inflammatory state, cytokine release syndrome due to viral sepsis	8.7

Table 1 shows the reaction pattern of HBV markers and groups it into different status among 150 infected persons confirmed by screening. The analysis reveals that half of the individuals (50%) have an inactive infection, which indicated the presence of the virus in an inactive state, while 26% have an inactive chronic infection. A small percentage (8%) were non-reactive or never infected which indicates that they are healthy individuals, and 8% were in the early stages of infection or had immune escape. Additionally, 6% had inactive sepsis which is indicative of systemic inflammation most likely sepsis and 2% had inactive chronic sepsis, which is indicative of a persistent systemic inflammation with a chronic cytokine storm.

Table 2 shows the gender distribution of individuals infected with Hepatitis B virus. Females had the highest number of individuals both examined (90) and infected (81), accounting for 58.7% of all infected individuals. Males made up 41.3% of the infected individuals with (60) examined and (57) infected.

Table 3 shows the age distribution of individuals infected with Hepatitis B virus. The age group 31-35 had the highest number of individuals examined (45) and the highest prevalence of (28.3%), while the age group 46-50 has the lowest number of individuals examined (9) with the lowest prevalence of (6.5%).

Table 4 shows the distribution of Interleukin-6 (IL-6) levels among different Hepatitis B virus (HBV) infection statuses. 75% non-reactive individuals had IL-6 levels of ≤7.0 pg/ml. Inactive infection cases were spread across all IL-6 levels, with 40% falling between 11–500 pg/ml.

Individuals with inactive chronic/immune-contained infection showed a peak IL-6 distribution at >7.0–10 and >11–500 pg/ml (30.8% each). All individuals with inactive sepsis or inactive chronic sepsis had IL-6 levels >1000 pg/ml (100%). In early infection/immune escape, 50% had IL-6 between 11–500 pg/ml, with none showing extremely high levels (>500 pg/ml).

Table 5 shows the levels of HBV infected individuals and their significance, IL-6 levels ≤7.0 pg/ml has a prevalence of 32.7%, IL-6 levels between >7–10 pg/ml has a prevalence of 0.8%, IL-6 levels between >10–500 pg/ml has a prevalence of 39.1%), IL-6 levels between 500–999 pg/ml and those >1000 pg/ml both has a prevalence of 8.7%.

DISCUSSION

This study examined the relationship between Interleukin-6 (IL-6) levels and various Hepatitis B virus (HBV) infection status among individuals in Abakaliki, Nigeria. The findings revealed that IL-6 levels varied significantly based on HBV infection classification, supporting the hypothesis that IL-6 plays a critical role in HBV disease progression and immune response.

In this study 50% of the HBsAg positive subjects, had inactive HBV infection, followed by a lower proportion of inactive chronic infection, a smaller percentage were non- reactive, while others had inactive sepsis, inactive chronic sepsis and an early infection/immune escape. These findings align with global and regional epidemiological data suggesting that a large proportion of HBV-infected individuals in endemic regions such as Sub-Saharan Africa remain in inactive carrier or immune-controlled states (WHO, 2022; Adekanle *et al*., 2020).

The detection of early infection and immune escape cases suggests active viral replication and possible viral mutation, which are known mechanisms of immune evasion and disease persistence (Sarin, *et al.,* 2020).

The distribution of IL-6 levels demonstrated a clear correlation with disease severity. Among the 138 HBV-infected individuals, some had IL-6 levels within the normal range (≤7 pg/ml), whereas some exhibited moderate elevation

(>10–500 pg/ml), suggestive of ongoing active viral infection. Elevated IL-6 levels were most notably seen in individuals with sepsis and chronic sepsis, 100% of these individuals had IL-6 concentrations exceeding 1000 pg/ml, indicative of systemic inflammation or cytokine storm. This agrees with findings from Jeng *et al.,* (2023), which identified IL-6 as a key player in liver fibrosis and systemic inflammatory responses in HBV.

Individuals with inactive or immune-controlled infection showed a distribution skewed towards normal or mildly elevated IL-6 levels, which supports the notion that controlled viral activity is associated with subdued inflammatory response. This is consistent with the literature, which notes that IL-6 contributes to immune activation in acute or progressive infections, but remains within normal limits in latent or controlled cases (Chisari *et al*., 2020; Rehermann *et al*., 2020).

The grouping of IL-6 values based on clinical thresholds revealed useful diagnostic patterns. Normal IL-6 levels indicated absence of active infection or a fully immune-contained state. Mild elevation (7–10 pg/ml) reflected early infection or post-infection recovery phases, while moderate to very high levels (>10 pg/ml) shows disease activity or immune dysregulation, as seen in immune escape and sepsis-related states.

These findings support earlier research (Wang *et al*., 2020; A. Mourtzikou *et al*., 2014) which showed a strong association between elevated IL-6 and chronic hepatitis progression. Additionally, IL-6's dual role as both a pro-inflammatory cytokine and an immune modulator explains its fluctuating levels depending on the infection stage being higher in uncontrolled infections and lower in resolved or managed infections.

Non-reactive individuals exhibited mostly normal IL-6 levels, supporting the conclusion that IL-6 is indeed reflective of true immune activation in confirmed HBV infection. This strengthens IL-6's potential utility in distinguishing between serological noise and active pathophysiological processes.

Moreover, early infection or immune escape cases demonstrated moderately elevated IL-6 levels, pointing to its role in the acute immune response and early inflammation. This reinforces IL-6's value not only in monitoring disease progression but also in identifying early immune challenges before chronicity develops.

The results of this study agrees with those of Jeng *et al.,*(2023), who noted that IL-6 levels did not strongly predict vaccine-induced immunity but did reflect immune system activity. The moderate to high IL-6 levels observed in chronically infected or sepsis-affected individuals in this study agrees with the findings from Jeng *et al.,* (2023) emphasizing IL-6's involvement in liver inflammation, fibrosis, and hepatocellular carcinoma.

Although IL-6 levels alone may not fully explain disease outcomes, their correlation with specific HBV serologic profiles provides a valuable supplementary diagnostic tool when interpreted alongside HBV panel results.

CONCLUSIONS

This study investigated the relationship between Interleukin-6 (IL-6) levels and Hepatitis B Virus (HBV) infection status among individuals in Abakaliki, Nigeria. The findings demonstrated a clear association between IL-6 levels and different stages or manifestations of HBV infection. IL-6 levels were significantly elevated in individuals with chronic infection, sepsis-related complications, and immune escape profiles, highlighting its role as a potential biomarker for disease progression, severity and immunity.

The results also reinforce the clinical utility of combining HBV serological profiling with cytokine assessment to provide a more comprehensive understanding of the patient's immune status and infection dynamics. These findings align with existing literature, emphasizing IL-6's central role in liver inflammation, fibrosis, and immunomodulation in HBV-infected individuals.

Recommendations

1. After screening with HBsAg test strip, further screening should be done with Hepatitis B panel test kit.
2. Antigenic or Molecular sequencing should be done to confirm the genetic sequence in cases such as early infection or Immune escape.
3. Routine assessment of IL-6 levels should be incorporated into HBV management protocols, especially for individuals with chronic or complicated HBV infection.

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