ISSN: 2536-7153 SJMLS

Sokoto Journal of Medical Laboratory Science 2024; 9(2): 87 - 97

SJMLS - 9(2) - 012

Evaluation of Hepatitis B virus infection serological markers and viral load profile of potential blood donors attending Ahmadu Bello University Teaching Hospital, Zaria-Nigeria

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https://dx.doi.org/10.4314/sokjmls.v9i2.12

Abstract

With a global prevalence of 3.9% and a staggering 292 million individuals affected globally, hepatitis B virus (HBV) infection stands out as a prominent global public health problem. In locations with elevated prevalence rates, blood transfusions and related products emerge as significant vectors of HBV transmission stressing its importance as a potential complication in such environments. This is a hospital-based cross-sectional study that engaged 71 HBV positive potential blood donor samples attending the blood donor bay of ABUTH-Zaria. The aim of this study is to determine the HBV viral load using RT-PCR among HBV-infected individuals and the corresponding serological markers (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb) profile of potential blood donors using lateral flow chromatographic immunoassay technique. Data generated were analyzed using GraphPad prism version 6.01. Statistical significance was determined at $P \leq 0.05$. HBsAg was identified in all 71 cases (100%), HBeAg in 5 samples (7.04%), anti-HBs in 1 sample (1.41%), anti-HBe in 62 samples (87.32%), and anti-HBc in all 71 samples (100%). Participants within the 28-37 age group demonstrated the highest prevalence of both HBsAg and anti-HBc markers, comprising 27 (38%) each of the total. Participants aged 28-37 years also demonstrated the highest prevalence of anti-HBe. There was also an observed majority of male participants among HBV-infected individuals in our study. Predominantly, the participants in this study showed HBsAg-positive status in 71 cases (100%) ($X2=127.305$; $p<0.0001$); HBeAg-negative status in 66 cases (92.96%) ($X2=113.932$; $p<0.0001$); HBeAb-positive status in 62 cases (87.3%) ($X2=104.736$; $p<0.0001$); and HBV DNA levels <2000 IU/mL. These parameters collectively depict an inactive carrier phase (immune-control stage) of the disease among the study participants. This study reveals an inactive carrier phase of the disease in 7.04% of the participants, emphasizing chronic hepatitis B's prevalence that require antiviral treatment to prevent disease progression. Additionally, HBV serological indicators (excluding HBsAb) are more common in younger adults, highlighting the need for enhanced injection safety, vaccination protocols, and viral load testing in healthcare centers to prevent unnecessary antiretroviral therapies and ensure effective healthcare delivery to eliminate HBV infection.

Keywords: Blood donors, Serological markers, Hepatitis B virus, Viral load

Introduction

With a global prevalence of 3.9% and a staggering 292 million individuals affected globally, hepatitis B virus (HBV) infection stands out as a prominent global public health problem (Razavi, 2022). HBV, a member of the Hepadnaviridae family, harbors a double-stranded circular DNA genome (Seeger and Mason, 2015). It represents a DNA virus demonstrating a distinctive preference for hepatocytes, triggering either an acute or chronic infection. HBV distinguishes itself as one of the earliest identified blood-borne viral ailments, primarily disseminated through blood and its derivatives (White *et al.,* 2019; Ashor and Science, 2011). In locations with elevated prevalence rates, blood transfusions and related products emerge as significant vectors of HBV

transmission (Durro and Qyra, 2011), stressing its importance as a potential complication in such environments. Despite the widespread availability of vaccines, exemplified in Nigeria, the incidence rate of viral infection remains disquietingly high within the nation (8.4%) and globally (Razavi, 2022; Anka *et al.,* 2023). This enduring prevalence firmly establishes the virus as a principal instigator of chronic liver diseases (Guido *et al.,* 2022). In East Asia and sub-Saharan Africa, HBV's prevalence among the adult populace ranges from 5.5-20.5% (Organization, 2015), with 17 to 65% of the general populace exhibiting positivity for one or more HBV serological markers (Alhassan *et al.,* 2021).

Early epidemiological data uncovers a notable incidence of chronic HBV infection among neonates born to carrier mothers or young children (Stevens et al., 1975; Li *et al.,* 2015). Remarkably, there exists a noticeable gender asymmetry, with males demonstrating notably heightened vulnerability (Su *et al.,* 2007; Liaw and Chu, 2009; Wang et al., 2016, Migliore *et al.,* 2021). Crucial to deciphering and managing HBV are five distinct protein markers: Hepatitis B surface antigen (HBsAg), constituting the virus's external protein envelope; Hepatitis B envelope antigen (HBeAg), cast off during viral replication; Hepatitis B core antibodies (HBcAb), present within hepatocytes (Hu and Liu, 2017). Complementary markers encompass Anti-Hbe-Ab and Anti-HBs. A grasp of these proteins is vital for diagnostic and therapeutic methods.

In the life span of this virus within the human host, four key stages emerge, with the initial two labeled as the replicative phase and collectively identified as the integrative phase (Lee, 1997). Throughout the initial phase, HBsAg, HBeAg, and HBV DNA are evident in the bloodstream, signifying an active period characterized by immune tolerance. This period involves dynamic viral replication, initiated by the upsurge of HBV DNA, culminating in heightened infectivity within the host. The subsequent stage echoes the first, although with a notable decline in HBV DNA levels and increased hepatic enzyme profiles (Lee, 1997).

Transitioning to the third stage, HBV DNA is nonexistent, Anti-HBe is apparent in the bloodstream, and HBeAg is negative. This phase denotes the attainment of host immune regulation, resulting in the cessation of active viral replication. Ultimately, the fourth stage heralds the complete eradication of the virus, with HBsAg turning negative or untraceable. Consequently, host infectivity undergoes a dramatic reduction (Lee, 1997).

Investigations in Nigeria have brought to light different HBsAg prevalence levels among blood donors, although limited data exist regarding other HBV markers due to the impracticality of conducting cost-intensive DNA analyses on all procured units (Jeremiah *et al.,* 2011). This investigation, carried out in Nigeria, principally endeavors to ascertain the prevalence of extra hepatitis B virus markers. It scrutinizes the dependability of solely relying on the HBsAg marker for diagnosing HBV during screening of blood donors at transfusion centers.

Northwestern Nigeria wrestles with a substantial HBV endemicity rate of 8.4%, disproportionately impacting the youthful populace. Robust preventive and control measures are imperative, encompassing heightened dissemination of health information through educational initiatives, disease monitoring, stringent vaccination protocols, and active engagement of stakeholders (Anka *et al.,* 2023).

The data gathered from this investigation holds pragmatic significance for medical facilities, aiding in the deliberative process concerning transfusions utilizing rigorously screened donors and the implementation of preventative measures. Moreover, it fosters donor awareness regarding the importance of routine hepatitis B screenings and contributes to the adoption of sound donor screening practices to forestall HBV transmissions. In sum, this investigation concentrates on screening and evaluating the prevalence of Hepatitis B Virus infection among potential blood donors at a Northwestern Nigeria tertiary teaching hospital.

Materials and Methods

Study design.

This is a hospital-based cross-sectional study that engaged HBV-seropositive adult patients attending the blood donor bay within the

department of Haematology and Blood Transfusion Science at the tertiary hospital. Data collection proceeded through diagnostic investigation of these participants enrolled for the study spanning from November 2022 to September 2023. Two distinct analyses were conducted on blood samples obtained from the study participants: i) to determine the HBV viral load among hepatitis B infected individuals, RT-PCR [BIO-RAD® iQ5 Multicolor Real-Time PCR detection system/ BIOFlux® HBV PCR Fluorescence Quantitative Detection Kit] was employed for HBV DNA quantification at the mRNA level; ii) the serological markers of hepatitis B antigens (HBsAg, HBeAg) and antibodies (HBsAb, HBeAb, HBcAb) were identified using lateral flow chromatographic immunoassay technique (Onsite HBV-5 Rapid, CTK Biotech, Inc, USA).

Sample collection and processing.

This study was carried out on blood samples sourced from the phlebotomy units stationed at the hospital's blood donor bay. Prior to sampling, the HBV Research Team liaised with the Medical Laboratory staff in blood collection and sampling, using the purposive sampling technique. Each participant contributed a standard volume of three milliliters (3mL) of blood through conventional venipuncture methods. Subsequent to the sampling process and upon arrival at the research laboratory, individual blood samples underwent unique identification numbering. They were then left to clot at room temperature, following which sera were extracted via centrifugation at 3,000 revolutions per minute (rpm) for 10 minutes, and subsequently preserved at -20°C.

Study participants.

The participants were of both genders who were identified serologically as being positive for HBV and from whom informed consent was obtained. Individuals that had challenges giving their informed consent and/or with prior vaccination for HBV were not enrolled into the study. Written informed consent was obtained after careful explanation of the concept of the study to every participant before enrolling them into the study. This was accompanied by the issuance of an information sheet describing the study and a structured questionnaire.

Ethical Issues

The research team obtained ethical approval (reference number: ABUTHZ/HREC /H45/2022) from the Ethical and Human Research Committee of the tertiary teaching hospital. Participants provided informed consent, and confidentiality was safeguarded by analyzing samples anonymously, using numerical codes. A password-protected database linked to these codes stored certain participant information (such as date of birth, gender, vaccination history, and medications) electronically. Demographic, serological, and virological data were disassociated from participants' identities to ensure confidentiality.

Laboratory investigations

All samples were investigated for hepatitis B antigens (HBsAg, HBeAg) and antibodies (HBsAb, HBeAb, HBcAb) using enzyme immunoassay technique (Onsite HBV-5 Rapid, CTK Biotech, Inc, USA) and HBV DNA using RT-PCR [BIO-RAD® iQ5 Multicolor Real-Time PCR detection system/ BIOFlux® HBV PCR Fluorescence Quantitative Detection Kit]. Investigations were conducted based on the manufacturer's instruction.

Detection of HBV serological markers by enzyme immunoassay

The serological techniques for the detection of hepatitis B and antibodies were performed using sandwich and competitive enzyme immunoassays. While HBsAg and HBeAg strips are antibody-based sandwich immunoassays, the HBsAb strip is an antigen-based sandwich immunoassay. Both HBeAb and HBcAb strips are competitive immunoassays.

The conjugate pad within all strips comprises polyclonal antibodies specifically targeting HBV immunoglobulins (including anti-HBsAg, antiHBsAb, anti-HBcAb, anti-HBeAg, antiHBeAb), which are conjugated with colloidal gold. Additionally, the nitrocellulose membrane strip is pre-coated with corresponding monoclonal immunoglobulins (anti-HBsAg, antiHBsAb, anti-HBcAb, anti-HBeAg, antiHBeAb) at both the control and test lines, alongside the absorbent pad. These analyses revolved around antigen-antibody

interactions facilitated by chromogen, rendering the reaction visible within 15 minutes. Interpretation of results adhered to the instructions provided by the kit manufacturer.

HBV DNA isolation, amplification and quantification

The assessment of HBV viral load was carried out utilizing the RT-PCR [BIO-RAD® iQ5 Multicolor Real-Time PCR detection system/ BIOFlux® HBV PCR Fluorescence Quantitative Detection Kit], enabling automated amplification and quantification, with a detection limit between 20 to 170,000,000 IU/mL. Sample processing and polymerase chain reaction (PCR) amplification of the target DNA were conducted, followed by quantification of cleaved dual-labeled oligonucleotide detection probes specific to the target, in accordance with the manufacturer's guidelines.

Quantitative levels of HBV DNA viral load falling below the sensitivity threshold of 20 IU/mL were deemed undetectable, while those below 2,000 IU/L were categorized as indicative of low-level HBV replication. Conversely, levels exceeding 2,000 IU/mL signified rapid viral replication within the liver, aligning with previous studies (Adoga et al., 2010; Lau et al., 2002).

Statistical analysis of data

Data generated was analyzed using GraphPad prism version 6.01. Results of categorical variables were proportions and association between these variables were assessed using the Chi-square test for likelihood ratio. $P \leq 0.05$ was considered statistically significant.

Result

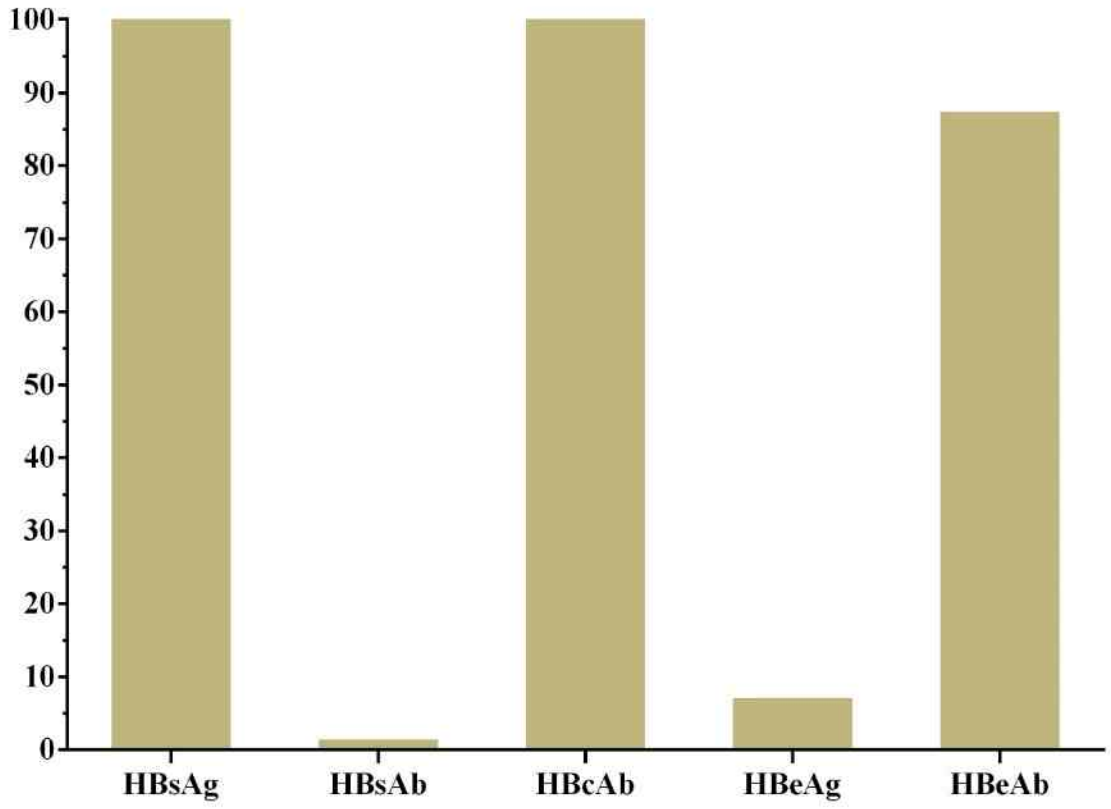

Figure 1: P*revalence of corresponding serological markers of hepatitis B virus infection among potential blood donors attending Blood donor bay at ABUTH-Zaria.*

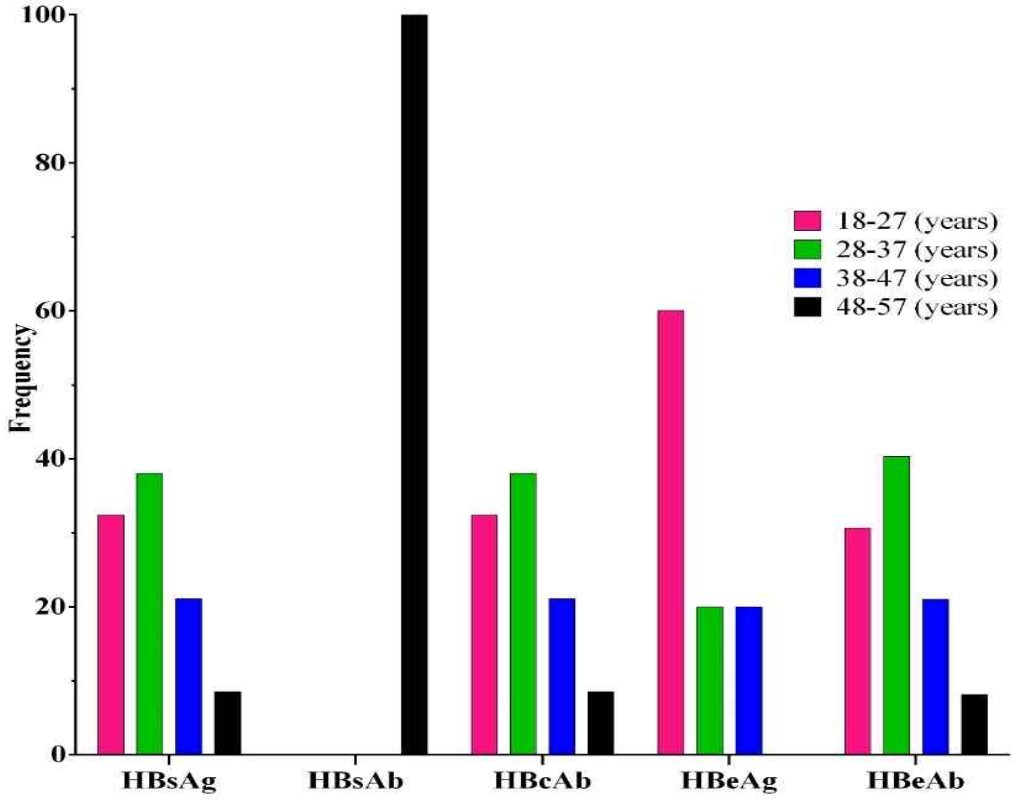

Figure 2: D*istribution of HBV serological markers into categories of age among potential blood donors attending Blood donor bay at ABUTH-Zaria.*

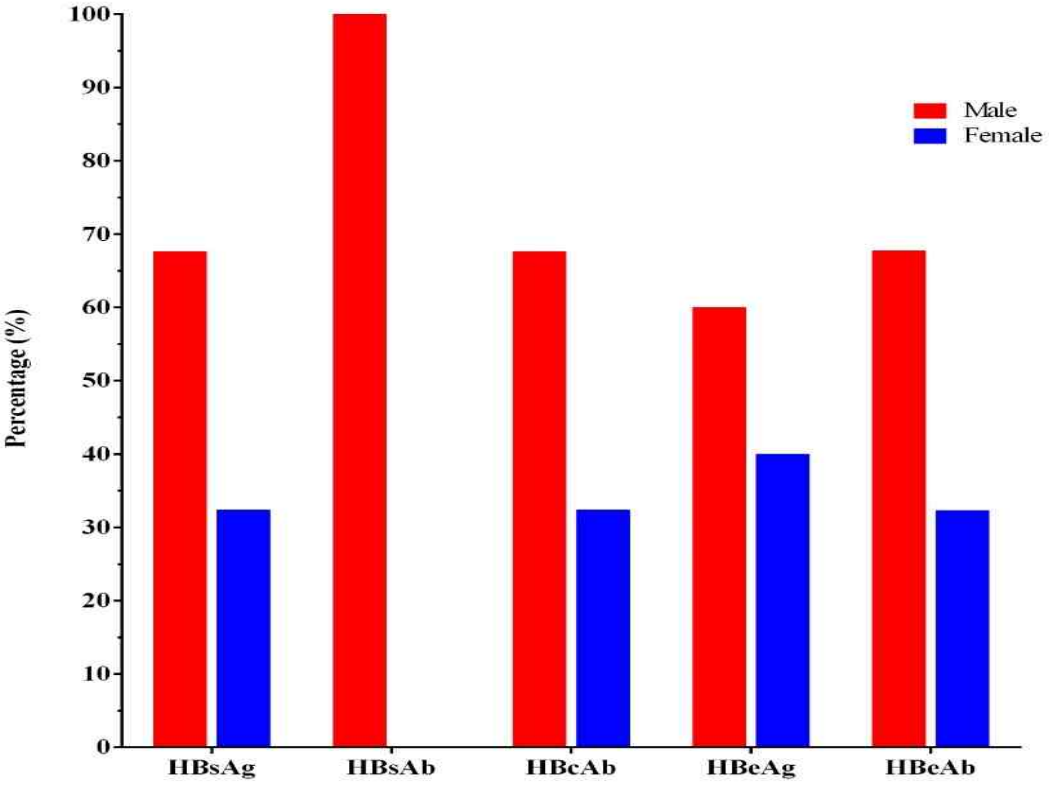

Figure 3: D*istribution of HBV serological markers according to sex among potential blood donors attending Blood donor bay at ABUTH-Zaria.*

Table 1 : Association between HBV DNA and HBV serological markers of potential blood donors attending Blood donor Bay at ABUTH-Zaria

Variable	*<20*	*20-1,000*	*1001-1,000,000*	*≥1,000,000*	X^2	*P-value*
HBsAg						
Positive	53 (100%)	1 (100%)	8 (100%)	9 (100%)	127.305	<0.0001
Negative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-	-
HBsAb						
Positive	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	3.011	0.3899323
Negative	52 (98.1%)	1 (100%)	8 (100%)	9 (100%)	123.231	<0.0001
HBcAb						
Positive	53 (100%)	1 (100%)	8 (100%)	9 (100%)	127.305	<0.0001
Negative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-	-
HBeAg						
Positive	4 (7.5%)	0 (0%)	1 (12.5%)	0 (0%)	8.754	0.03274686
Negative	49 (92.5)	1 (100%)	7 (87.5%)	9 (100%)	113.932	<0.0001
HBeAb						
Positive	46 (86.8%)	1 (100%)	7 (87.5%)	8 (88.9%)	104.736	<0.0001
Negative	7 (13.2%)	0 (0%)	1 (12.5%)	1 (11.1)	14.114	0.00275402

P≤0.05 was considered statistically significant.

Discussion

In the assessment of 71 HBV positive potential blood donor samples, HBsAg was identified in all 71 cases (100%), HBeAg in 5 samples (7.04%), anti-HBs in 1 sample (1.41%), anti-HBe in 62 samples (87.32%), and anti-HBc in all 71 samples (100%). The outcomes of this investigation demonstrated a significant prevalence of both HBsAg and anti-HBc (100% in 71 participants) HBV serological markers, aligning with previous reports (Emeribe et al., 2019; Alhassan *et al.,* 2021), and contrary to reports from Ibadan (Okonko *et al.,* 2012), the United Kingdom (Soldan *et al.,* 1999), the United States (Glynn *et al.,* 2013), Canadian blood donors (Gutiérrez-García et al., 2011), and Italy (Manzini *et al.,* 2007). Additionally, participants within the 28-37 age group demonstrated the highest prevalence of both HBsAg and anti-HBc markers, comprising 27 (38%) each of the total. The IgM classification of anti-HBc serves as an indicator of recent infection, while the IgG class of anti-HBc surfaces later during the infection, signifying a previous HBV infection. Despite an infected individual possessing protective levels of anti-HBs, anti-HBc IgG may persistently remain positive for life, yet the blood from such a donor might be devoid of transmitting HBV (Lukhwareni *et al.,* 2009).

Nevertheless, anti-HBs showed a remarkably low prevalence, representing only 1 (1.41%) of the participants. Our finding is consistent with the findings in Kaduna (Butt *et al.,* 2020) but in contrast to that in Sokoto (Alhassan *et al.,* 2021). HBeAg, as a serological marker, displayed a low prevalence, accounting for 5 participants (7%), aligning with reports by Emeribe et al. (2019) and Otegbayo *et al.* (2008).

On the contrary, the anti-HBe serological marker demonstrated a remarkably high prevalence, encompassing 62 (87.3%) participants. Our

finding is consistent with previous reports (Lesi *et al.,* 2019; Emeribe *et al.,* 2019). Participants aged 28-37 years also demonstrated the highest prevalence of anti-HBe. This data contradicts previous reports indicating a higher prevalence of HBV markers among older subjects aged 40 years and above compared to younger adults (Luka *et al.,* 2008; Lawal *et al.,* 2009), who reported elevated HBV prevalence among the older age groups. The findings of this study align with the observations made by Buseri *et al.* (2009) who highlighted that HBV infection is more prevalent in younger subjects. The possible rationale for this higher prevalence rate among younger individuals compared to older individuals may be attributed to their active sexual behaviors and potential drug abuse. However, it is noteworthy that HBV is not confined to any specific age group.

In various territories across sub-Saharan Africa, the documentation regarding the serological characteristics of hepatitis B infection has been reasonably consolidated. However, there remains a scarcity of studies concerning the determination of HBV DNA within the populace, likely attributed to the scarce availability and accessibility of molecular technology, as well as the exorbitant costs associated with molecular testing and maintenance.

Our investigation reaffirms the heightened prevalence of hepatitis B infection among both young and middle-aged adults. This aligns with the broader hepatitis B virus epidemic documented by numerous other studies conducted in Africa (Baig, 2009; Forbi *et al.,* 2012; Kolou *et al.,* 2017; Lesi *et al.,* 2019; Alhassan *et al.,* 2021; Anka *et al.,* 2023). The classification of HBV prevalence in our study adhered to the WHO categorization of HBV severity in endemic regions. According to the WHO, low, moderate, and high prevalence are recognized when HBsAg positivity rates are <2%, 2-8%, and >8%, respectively (Organization, 2010). In terms of gender, there was an observed majority or dominance of male participants among HBV-infected individuals in our study. In addition, the ratio of male to female generally increased during reproductive years when participants were divided based on age groups which was in accordance with previous studies (Amidu *et al.,* 2012; Iregbu *et al.,* 2016; Onwuliri *et al.,* 2014). Both Baig (2009) and Okwuraiwe *et al.* (2011) had similar findings. While Braig (2009) proposed that the female reproductive hormone (estrogen) may have the ability to mount protection or re-enforce the immunity in the female population against the destruction of hepatocytes by the hepatitis B virus, Okwuraiwe *et al.* (2011) suggested that the female population have relatively lower financial resources to test for the viral infection which may seem higher in the male population.

Regarding age, the younger individuals enrolled in the study showed a higher tendency for positive detection of all HBV serological markers compared to their older counterparts. These findings find corroboration in studies conducted in the northern region of Nigeria (Alhassan *et al.,* 2021; Forbi *et al.,* 2012), as well as in Togo (Kolou et al., 2017) and Japan (Tsukuma *et al.,* 1987), which indicated a decrease in the prevalence of these serological biomarkers with advancing age.

Recent investigations have unveiled hepatitis B infection as a dynamic disease, presenting with various clinical manifestations including acute infection, chronic progressive liver disease, chronic inactive carrier state, liver cirrhosis, and carcinoma (Baig, 2009; Liu and Liu, 2014). The patterns observed in the HBV panel serve as a guide for outlining the disease phase and determining the necessity for antiviral therapy. The array of HBV serological markers plays a definitive role in the detection of acute hepatitis B infections. Predominantly, the participants in this study showed HBsAg-positive status in 71 cases (100%) ($X2=127.305$; $p<0.0001$); HBeAg-negative status in 66 cases (92.96%) ($X2=113.932$; $p<0.0001$); HBeAb-positive status in 62 cases (87.3%) ($X2=104.736$; $p<0.0001$); and HBV DNA levels <2000 IU/mL. These parameters collectively depict an inactive carrier phase (immune-control stage) of the disease (Santantonio and Fasano, 2013). Individuals in this phase show a favorable prognosis, significantly reducing the risk of progression to cirrhosis or hepatocellular carcinoma (HCC) (Villa *et al.,* 2011).

Additionally, the investigation for HBeAg can aid in identifying patients with a high risk of developing liver cancer (Yang *et al.,* 2002; You *et al.,* 2004). HBeAg is recognized as a core antigen released by the HBV DNA and is considered a surrogate marker of active replication of wild-type HBV (Kao and Hepatology, 2008).

A significant portion of the study participants was classified in a low replicative phase of chronic HBV, characterized by HBeAg-negative status, HBeAb-positive status, and low-level hepatitis viral replication (i.e., HBV DNA levels <2000 IU/mL). Based on these findings, it is evident that this group of participants constitutes HBV inactive carriers who are less infectious and pose little or no risk of transmission.

Without corresponding liver trauma and normal liver enzyme levels, these pools of individuals are regarded as chronic inactive carriers. Due to low risk of disease progression in this category of individuals, antiviral treatment is not recommended (Isa *et al.,* 2015).

Contrarily, it was noted that just below one-fourth (17 out of 71) of participants who tested negative for HBeAg showed high-level hepatitis viral replication (HBV DNA >2000 IU/mL) alongside detectable HBeAb. This observation, identified in our study, is termed HBeAg-negative hepatitis and is recognized as the prevailing manifestation of chronic hepatitis B-associated hepatic disorder in Asia and sub-Saharan Africa (Iregbu *et al.,* 2016; Yang *et al.,* 2002).

To ensure effective healthcare delivery to individuals with hepatitis B infection, it is imperative to distinguish between these two patient groups (i.e., chronic inactive carriers and those with HBeAg-negative hepatitis). The active viral replication (HBV DNA >2000 IU/mL) characteristic of HBeAg-negative hepatitis sets it apart from chronic inactive carriers (HBV DNA <2000 IU/mL) and serves as a prognostic biomarker for monitoring disease progression and the replication of viral mutants in the absence of HBeAg (Nayagam *et al.,* 2016). Unlike chronic inactive carriers, individuals with HBeAg-negative hepatitis require antiviral therapy due to the heightened risk of disease progression (Lesi et al., 2019).

The prevalence of hepatitis B virus infection in our study as reported in our previous publication was 8.4% (Anka *et al.,* 2023), which was in consonance with reports from many Nigerian studies (Olayinka *et al.,* 2016; Lesi *et al.,* 2019) and a Gambian study (Lemoine *et al.,* 2016). Like the Nigerian study, our study involved hospital-based participants who were mostly asymptomatic with low viral load. The method for viral load detection using the nucleic acid testing (RT-PCR) technique with high level of sensitivity and specificity was a common technique used in our study as well as the work conducted by Lesi et al. (2019), but not for that conducted by Lemoine et al. (2016).

Conclusions

This research depicts an inactive carrier phase (immune-control stage) of the disease observed among the participants of the study, with 7.04% demonstrating HBeAg sero-negative, HBeAb-positive status, and low-level hepatitis viral replication (i.e., HBV DNA levels <2000 IU/mL). Such findings underscore a prevalent expression of chronic hepatitis B-linked hepatic disease across Asia and sub-Saharan Africa necessitating antiviral intervention due to the escalated risk of disease progression. Consequently, it demands attention within the framework of healthcare policy formulation and execution.

Moreover, the affirmative status for all HBV serological indicators (apart from HBsAb) manifested more frequently in youthful cohorts (18-37 years). This underscores the imperative to fortify injection safety measures and vaccination protocols. Additionally, it stresses the importance for healthcare facilities to integrate viral load assessments and/or evaluation for HBV biomarkers to avert unwarranted antiretroviral therapies, initiate timely interventions, and avoid financial wastage, all in the pursuit of delivering high-quality healthcare and eradicating HBV infection.

Conflict of interest

The authors declare no conflict of interest.

Funding

This research was funded by Tetfund through

Institutional Based Research (TETFUND-IBR) Grant (Grant No. TETF/DR&D/UNI/ZARIA/IBR/2020/VOL.1/48).

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Citation: Anka, A. U., Musa, B.O.P., Ella, E.E., Hassan, A., Manko, M., Umar, K., Abdullahi, I.N., Mohammed, M., Ahmad, A. E., Faruku, N., Chiroma, F.A., Suleiman, H.A., & Salisu, S. Evaluation of Hepatitis B virus infection serological markers and viral load profile of potential blood donors attending Ahmadu Bello University Teaching Hospital, Zaria-Nigeria. ***Sokoto Journal of Medical Laboratory Science*; 9(2): 87 – 97.** https://dx.doi.org/10.4314/sokjmls.v9i2.12