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Prevalence and diagnostic impacts of viral hepatitis seromarkers among chronic liver disease patients and their influence on the serum levels of AFP, CA-125, and GGT.

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Abstract

Patients in the window phase of hepatitis B infection may be misdiagnosed as non-infected when hepatitis B surface antigen (HBsAg) is the only seromarker used for diagnosis. A delay in effective HBV treatment due to missed diagnosis may worsen liver injury with an early progression to hepatocellular carcinoma (HCC) in individuals with pre-existing chronic liver disease (CLD). Therefore, this study was conducted to ascertain the prevalence and diagnostic impacts of hepatitis B and C seromarkers among chronic liver disease patients and the influence of these seromarkers on the serum levels of Alpha-fetoprotein (AFP), Cancer Antigen 125 (CA-125), and Gamma-glutamyl transferase (GGT). Sixty-four CLD patients were recruited for this study and their sera tested for hepatitis B and C seromarkers, AFP, CA-125, and GGT. A total of 32 (50%), 12 (18.7%), 28 (43.7%), 40 (62.5%), and 26 (40.6%) of the CLD patients were seropositive for HBsAg, HBsAb, HBeAb, HBcAb, and Anti-HCV, respectively. Although the serum levels of AFP and CA-125 were significantly higher in patients seropositive for HBsAg than those who had seroconverted to hepatitis B surface antibody (HBsAb), the multivariate analysis showed that no one particular viral hepatitis seromarker is directly associated with elevated levels of AFP, CA-125, and GGT.

Keywords: Alpha-fetoprotein (AFP), CA-125, Chronic liver disease (CLD), Gamma-glutamyl transferase (GGT), HBV, HCV.

Introduction

Liver disease is a major cause of death globally with varying aetiologies (Sepanlou *et al*., 2020). Annually, chronic liver disease (CLD) accounts for over 2million morbidities and mortalities worldwide (Tapper and Parikh, 2018; Mokdad *et al*., 2014). Cirrhosis and hepatocellular carcinoma (HCC) are the major complication of CLD and account for 3.5% of all deaths globally (Asrani *et al*., 2019). Risk factors associated with CLD in developed nations include chronic hepatitis B (CHB), non-alcoholic steatohepatitis (NASH), chronic hepatitis C, and alcohol; however, in developing nations such as Nigeria, these factors include hepatitis C, hepatitis B, toxins, malnutrition, and sickle cell disease (Banait *et al*., 2021).

About 170 million people are living with hepatitis C virus (HCV) across the globe (Dennis *et al*., 2004) with approximately 71 million chronically infected (Falla *et al*., 2018; Polaris Observatory HCVC, 2017). HCV accounts for approximately 400,000 deaths linked to liver disease in 2015 (WHO, 2019a). Hepatitis B virus (HBV) is a DNA virus with a predilection for the liver. The virus causes hepatitis B which is of public health concern with a high rate of morbidity and mortality. Sub-Saharan Africa and the Western Pacific region have the highest rate of HBV infection, with about 5-10% of people with chronic hepatitis B (CHB) (Peligang *et al*., 2021; Ringehan *et al*., 2017; WHO, 2017). According to the World Health Organization, over 90% of HBV infections are missed during diagnosis and these cases continue to be sources of transmission of the virus (WHO, 2019b). The proportion of HBV diagnosed in low and middle-income countries such as Nigeria is low (0.8%) compare to 18% from high-income nations. HBV infection that goes undetected could progress to cirrhosis or liver cancer, both of which are responsible for over 1.4million deaths worldwide in 2015 (WHO, 2019b, WHO, 2018).

There are different seromarkers used in the diagnosis of hepatitis B each with different epidemiological and clinical significance. In individuals with immunity from HBV vaccination, hepatitis B surface antibody (HBsAb) is the only detectable seromarker (Kao, 2008). Hepatitis B surface antigen (HBsAg) is present in the serum of infected individuals within 4-6months, in the early phase of HBV infection. Hepatitis B e antigen (HBeAg) appears shortly after HBsAg seropositivity and is an indication of higher HBV replication, infectivity, and potential

chronicity. Seroconversions of HBeAg to HBeAb and HBsAg to HBsAb occur in individuals who had recovered from HBV infection (Shah and Singh, 2007). Although hepatitis B core antigen (HBcAg) is not detected in blood samples, antibody to this antigen (HBcAb) is found in people with previous or recent HBV exposure (Kao, 2008). HBcAb IgM is found in individuals with recent exposure and helps differentiate acute from chronic infection (Kryger, 1985). In developing countries such as Nigeria, HBsAg is a marker commonly used as a screening test. However, a negative HBsAg screening test does not rule out infection with HBV. Chronically infected or acute hepatitis B patients who are in the window phase could be falsely diagnosed as non-infected when HBsAg is used as the sole seromarker for diagnosis (Gish *et al*., 2015; Schmidt *et al*., 2006; Lok and McMahon, 2001). Therefore, during the window period of hepatitis B infection when HBsAg is often not detected, the antibody to the hepatitis B core antigen (HBcAb) could be a significant diagnostic marker (Japhet *et al*., 2011).

Liver-related seromarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), gamma-glutamyl transferase (GGT), total bilirubin, albumin, apolipoprotein A1 (apo A1), apolipoprotein B (apo B), total protein, gamma globulin, beta globulin, alpha -1 globulin, and alpha-2 globulin are commonly tested to evaluate the extent of inflammation, injury, fibrosis, and dysfunction of the liver (Baranova *et al*., 2011; Imbert-Bismut *et al*., 2001). In chronic hepatitis B patients, the serum level of AFP increases with increased inflammation and fibrosis (Liu, 2014). AFP has a sensitivity of about 60% for the detection of liver cancer (Assmar *et al*., 2016). Serum level above 400ng/ml is greatly associated with liver cancer (Masuzaki *et al*., 2012).

Individuals with pre-existing CLD and concurrent HBV and/or HCV infections could have their liver injury worsen with a concomitant early progression to HCC particularly when effective treatment is delayed due to missed diagnosis. A vast majority of HCCs are untreatable as this condition is usually detected at the later stages due to extreme liver reserve (Moustafa *et al*., 2005). Furthermore, there is a data gap on how the presence of HBV and HCV seromarkers influences the serum level of certain liver-related and tumour biomarkers. Therefore, this study was conducted to ascertain the prevalence and diagnostic impacts of hepatitis B and C seromarkers among chronic liver disease patients and the influence of these seromarkers on the serum levels of AFP, CA-125, and GGT.

Method

Recruitment Process

Sixty-four (23 female and 41 male) chronic liver disease patients attending Jos University Teaching Hospital, Plateau State, Nigeria, were recruited for this study. Chronic liver disease was confirmed using standard diagnostic guidelines assigned by the Gastroenterology unit of the study centre.

Inclusion criteria

1. Chronic liver disease patients ≤ 70 years.
2. Chronic liver disease patients without confirmed hepatic schistosomiasis.

Exclusion criteria

1. Apparently healthy individuals without confirmed chronic liver disease.
2. Chronic liver disease patients with confirmed hepatic schistosomiasis.

Ethical Consideration

Ethical approval was obtained from the Institutional Review Board Ethics Committee of Jos University Teaching Hospital, Plateau State, Nigeria. Each patient gave their informed consent.

Clinical Laboratory Investigation

Specimen collection and analysis

Ten millilitres of venous blood were taken aseptically from each participant and the serum was separated and stored at -20^{0}C in aliquots, until use. The serum levels of Alpha-fetoprotein and CA-125 were measured using Cobas E411 chemistry analyser by Roche Hitachi, while the Gamma-glutamyl transferase level was measured by Cobas C111 also by Roche Hitachi. All sera were tested for antibodies to the hepatitis C virus with HCV Kits (Micropoint Bioscience, Inc., CA, USA).

HBV serodiagnosis

Each participant's serum was tested for five hepatitis B seromarkers including HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb using HBV Kits by Micropoint Bioscience, Inc., CA, USA. Two drops of each participant's serum were added to the sample wells of the HBV Combo Cassette laid horizontally. The assays of HBsAg, HBsAb, and HBeAg were based on the Sandwich method, while that of HBcAb and HBeAb were Neutralization Competitive Inhibition. The manufacturer's instructions were followed when interpreting the results. Positive HBsAg, HBsAb, and HBeAg were indicated with the presence of 2 red bands (Control and Test bands). However, positive HBcAb and HBeAb were indicated when only one red band appeared (Control band). When no band appears on the cassette, the result was regarded as Invalid.

In the current study, the CLD patients were categorized into one of six (6) groups based on their HBVseromarkers (Aniche *et al*., 2022), viz.: Early stage of HBV infection [n=1] (positive HBsAg, negative HBsAb, negative HBcAb), Early convalescence stage [n=3] (positive HBsAg, positive HBsAb, positive HBcAb), Late acute or chronic HBV infection [n=28] (positive HBsAg, negative HBsAb, positive HBcAb, positive HBeAb), Immune from previous HBV infection [n=9] (negative HBsAg, positive HBsAb, positive HBcAb), Immune from vaccination [n=0] (negative HBsAg, positive HBsAb, negative HBcAb), and Susceptible or non-exposed [n=23](negative HBsAg, negative HBsAb, negative HBcAb).

Statistical Analysis

Continuous data were presented as mean ± standard deviation while categorical variables as percentages. One-way ANOVA with Tukey Post hoc test was used for comparison among continuous data, and P-value <0.05 was considered significant.

Results

In this study, 64 chronic liver disease patients attending Jos University Teaching Hospital, Plateau State, Nigeria, were recruited for this study; out of which 64.1% were male with a female-to-male ratio of 1:1.8. The participants were mainly between the age of 41 and 50 years (40.6%) with a mean age of 48.3±4.6 years (Table 1).

Half (50.0%)of the participants were seropositive for HBsAg, 18.7% for HBsAb, 43.7% for HBeAb, 62.5% for HBcAb, and 40.6% for Anti-HCV.Out of the 64 CLD patients in this study, 40 (62.5%) had more than one HBV seromarkers in their serum (Data not shown). A total of 41 (64.1%), 26 (40.6%), and 10 (15.6%) of the participants had had HBV, HCV, and HBV/HCV prior exposure (Table 1).

Table 1: Demographic characteristics and serodiagnosis of the participants.

Characteristics	Frequency N (%)
Sex	
Female	23 (35.9)
Male	41 (64.1)
Total	64 (100.0)
Age (years)	
21 – 30	0 (0.0)
31 – 40	20 (31.3)
41 – 50	26 (40.6)
51 – 60	18 (28.1)
61 – 70	0 (0.0)
Total	64 (100.0)
HBV Serology	
HBsAg	32/64 (50.0)
HBsAb	12/64 (18.7)
HBeAg	6/64 (9.4)
HBeAb	28/64 (43.7)
HBcAb	40/64 (62.5)
HCV Serology	
Anti-HCV	26/64 (40.6)
HBV	
Exposed	41 (64.1)
Non-Exposed	23 (35.9)
Total	64 (100.0)
HCV	
Exposed	26 (40.6)
Non-Exposed	38 (59.4)
Total	64 (100.0)
HBV/HCV Co-infection	
Yes	10 (15.6)
No	54 (84.4)
Total	64 (100.0)

HBV- Hepatitis B virus, HBsAg- Hepatitis B surface antigen,HBsAb- Hepatitis B surface antibody, HBeAg- Hepatitis B e antigen,HBeAb- Hepatitis B e antibody,HBcAb- Hepatitis B core antibody, HCV- Hepatitis C virus, Anti-HCV- Antibody to hepatitis C virus.

Most (43.7%) of the CLD patients with HBV exposure had late or chronic HBV infection while 1.6% were in the early stage of HBV infection. None of the patients in this study had immunity to HBV from vaccination; however, 14.1% were immune due to previous HBV infection. Twenty-three (35.9%) participants have no previous exposure to HBV (Figure 1).

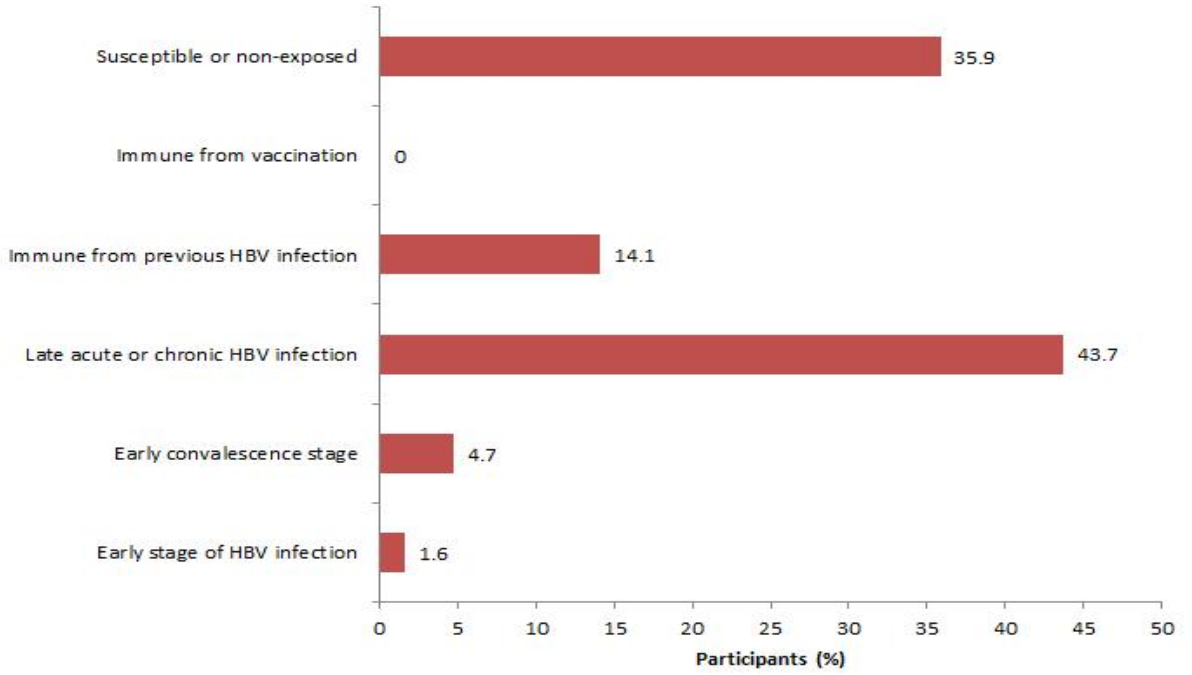

Figure 1: Hepatitis B exposure status among chronic liver disease patients.

The mean AFP, CA-125 and GGT serum levels of the study patients seropositive for HBsAg were 353.4±31.0 ng/mL, 198.0±9.3 U/mL, and 301.8±7.3 U/L, respectively. Similarly, these levels were 350.8±34.1 ng/mL, 151.3±9.5 U/mL, and 368.0±11.8 U/L, respectively, in participants seropositive for HBeAb. The serum levels of AFP and CA-125 in the participants seropositive for HBsAg were significantly higher than in those who had seroconverted to HBsAb. However, no statistical difference was observed when the GGT levels in these groups were compared. The AFP and GGT levels in the CLD patients seropositive for HBeAg were significantly lower compared to patients who had seroconverted to HBeAb. In contrast, the serum levels of CA-125 were higher in patients who were HBeAg seropositive than in HBeAb seropositive patients (Table 2). Furthermore, the multivariate regression analysis showed that there is no relationship between HBV or HCV seromarkers and elevated AFP, CA-125, and GGT levels among the study patients (Table 3).

Table 2: Influence of hepatitis B and hepatitis C seromarkers on serum levels of Alpha-fetoprotein, CA-125, and Gamma-glutamyl transferase among the participants.

Seromarkers	**AFP**(ng/mL) mean±SD	**CA-125**(U/mL) mean±SD	**GGT**(U/L) mean±SD
HBsAg (n=32)	353.4±31.0^{a}	198. 0±9.330	1.8±7.3^{a}
HBsAb(n=12)	78.5±36.5^{b}	75.5±21.7^{a}	290.4±23.4^{ab}
HBeAg (n=6)	146.2±40.6^{c}	284.4±27.3^{b}	233.1±12.9^{c}
HBeAb (n=28)	350.8±34.1^{a}	151.3±9.5^{c}	368.0±11.8^{d}
HBcAb (n=40)	419.0±25.8^{d}	173.8±8.5^{d}	362.4±7.5^{d}
Anti-HCV (n=26)	370.2±35.0^{a}	147.8±19.4^{c}	284.8±20.9^{b}
P-value	<0.001*	<0.001*	<0.001*

AFP- Alpha-fetoprotein, CA-125- Cancer antigen 125, GGT- Gamma-glutamyl transferase, HBsAg- Hepatitis B surface antigen, HBsAb- Hepatitis B surface antibody, HBeAg- Hepatitis B e antigen, HBeAb- Hepatitis B e antibody, HBcAb- Hepatitis B core antibody, Anti-HCV- Antibody to hepatitis C virus. Groups that share same letter are not significantly different at $p<0.05$. *significantly different at $p<0.05$.

Table 3: Predictors of elevated Alpha-fetoprotein, CA-125, and Gamma-glutamyl transferase among the participants.

Parameters	AFP		CA-125		GGT	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
HBsAg Seropositivity	1.00 (0.99-1.00)	0.29	1.00 (0.99-1.01)	0.20	1.00 (0.99-1.00)	0.94
HBcAb Seropositivity	1.00 (0.99-1.00)	0.15	1.00 (0.99-1.03)	0.67	1.00 (0.99-1.03)	0.32
Anti-HCV Seropositivity	1.00 (0.99-1.02)	0.34	1.00 (0.99-1.04)	0.33	1.00 (0.99-1.01)	0.96

AFP- Alpha-fetoprotein, CA-125- Cancer antigen 125, GGT- Gamma-glutamyl transferase, HBsAg- Hepatitis B surface antigen, HBcAb- Hepatitis B core antibody, Anti-HCV- Antibody to hepatitis C virus, OR- Odd Ratio, CI- Confidence Interval.

A statistically significant difference was observed in the serum level of AFP across the groups based on the status of HBV and HCV exposure. Cancer antigen 125 levels in the CLD patients infected with HBV were not significantly different from those infected with HCV. However, these levels were statistically higher than in patients who had neither been exposed to HBV nor HCV. The GGT serum levels of the HBV/ HCV non-exposed CLD patients were significantly higher than those infected with HBV, HCV, or concurrent HBV/HCV. Moreover, the GGT levels of patients with HBV/HCV co-infection were not statistically different from those who had a mono-infection (Table 4).

Table 4: Serum levels of Alpha-fetoprotein, CA-125, and Gamma-glutamyl transferase by status of HBV and HCV exposure.

HBV/HCV Status	AFP (ng/mL) mean±SD	CA-125 (U/mL) mean±SD	GGT (U/L) mean±SD
HBV/HCV Non-Exposed (n=7)	13.1±9.11	17.5±12.3[a]	758.0±20.1
HBV Mono-infection (n=22)	489.1±156.51	69.8±41.3[b]	373.0±109.1[a]
HCV Mono-infection (n=16)	377.6±46.91	53.0±37.3[ab]	287.0±53.1[b]
HBV/HCV Co-infection (n=10)	848.3±10.81	33.3±27.4[a]	353.2±15.4[ab]
P-value	<0.001*	<0.002*	<0.001*

HBV- Hepatitis B virus, HCV- Hepatitis C virus, AFP- Alpha-fetoprotein, CA-125- Cancer antigen 125, GGT- Gamma-glutamyl transferase. Groups that share same letter are not significantly different at $p<0.05$. *significantly different at $p<0.05$.

Discussion

Untreated hepatitis B and C infections could worsen liver injury in individuals with pre-existing CLD. Each year, both are associated with about 1.4 million viral hepatitis-related mortalities worldwide (Jefferies *et al*., 2018).Hepatitis B infection is poorly diagnosed and under-reported in most countries in Africa (Weimer *et al*., 2019; WHO, 2017). Although 50% of the patients in this present study were seropositive to HBsAg, more (62.5%) patients were seropositive to HBcAb. Hepatitis B core IgM antibody (HBcAb IgM) is a useful tool in the detection of HBV in patients in the window phase (Mühlbacher *et al*., 2001; Weber *et al*., 2001; Grob *et al*., 2000). This is of great importance, especially when screening blood donors in other to prevent the transmission of the virus during this period (Gish *et al*., 2015; Su*et al*., 2012; Allain, 2004).

When used alongside HBsAg, HBcAb could increase the sensitivity of detecting HBV exposure or infection. However, the most reliable test for HBV is the use of PCR for the detection of HBV DNA (Kurdi *et al*., 2014). The prevalence of HBsAg in our study is higher than 41.7% reported in a previous study from Kano (Emokpae *et al*., 2013), and 28% and 30.3% from Lagos (Lesi *et al*., 2002) and Pakistan (Tong *et al*., 1996), respectively. On the other hand, higher prevalence of 60.6% and 55% have been observed in India (Chakravarti and Verma, 2005) and Ethiopia (Zarski *et al*., 1998), respectively. This discrepancy in results is not understood and could be due to differences in the socio-economic status and cultural background of the study patients. Twenty-eight (43.7%) patients had seroconverted from HBeAg to HBeAb. Negative HBeAg/Positive HBeAb has been reported to be a common form of CHB in some parts of the world (Lok *et al*., 2001; Brunetto *et al*., 1999; Hadziyannis, 1995; Li *et al*., 1993). About 20% of patients seropositive for HBeAb can revert to HBeAg seropositivity (Christopher and Jeffrey, 2012). In CHB patients, HBeAg seropositivity usually implies infectivity due to an elevated level of viral replication (Henry and Vincent, 2012).The prevalence of HBeAb seropositivity in the present study is higher than those reported in other African countries, with 28% from Cameroon (Ducancelle *et al*., 2013), 8.8% from Kenya (Okoth *et al*., 2006), 3.9% from Eritrea (Fessehaye *et al*., 2018), and 14.9% from Uganda (Bayo *et al*., 2014). This low prevalence in these studies could be because the studies were conducted among pregnant women rather than CLD patients. Hepatitis B virus and HCV are the major viral aetiology of CLD (Paik *et al*., 2020).

The prevalence of HBV mono-infection (34.4%) in our study is comparable with the 30.3% reported by Khan and Rizvi (2003) but higher than the report of Lesi *et al* (2002). Prior to the study, none of the study patients had received the HBV vaccine. This lack of immunization against HBV among these patients may be responsible for the high prevalence of HBV infection observed in this study. In most African nations including Nigeria, the sensitization of HBV vaccination is mainly focused on infants and health workers with a proportion of high-risk individuals unaware of or unable to access the program. Other studies had reported HBV prevalence much higher than the result of the present study (Emokpae *et al*., 2013; Chakravarti and Verma, 2005; Zarski *et al*., 1998; Tong *et al*., 1996). Out of the 41 study participants with HBV exposure, only 9 (14.1%) had resolved infection with 28 (43.7%) having chronic hepatitis B (CHB) infection. The prevalence of CHB among these individuals is alarming and necessitates a more reliable diagnostic marker(s) for HBV screening in HBV-endemic countries such as Nigeria. Several studies have linked CHB infection to CLD (Khan and Rizvi, 2003; Carrao *et al*., 1998). It was not known in this present study whether the CHB observed among these patients was responsible for their CLD. One CLD patient (1.6%) had a recent HBV infection. This patient may eventually have his/her liver disease progresses early to cirrhosis or HCC compared to HBV-uninfected patients (Brunetto *et al*., 2002).

In this study, 23 (35.9%) of the participants have never been exposed to HBV. These unexposed individuals remained susceptible hosts to this pathogen and could aid in the transmission of the virus in the future (CDC, 2006). Immunization programs focused on these individuals would result in a decline in HBV transmission. A total of sixteen (25%) patients had HCV mono-infection while 15.6% had HBV/HCV co-infection. The prevalence of HCV mono-infection in our study is lower than 28% and 27.9% reported in Lagos (Lesi *et al*., 2002) and Kano (Emokpae *et al*., 2013), respectively but higher than 24.1% and 20.6%, respectively from Bangladesh (Khan and Ahmed, 1996) and Somalia (Aceti *et al*., 1993). Viral hepatitis as the cause of liver pathology changes over time and varies based on the geographical location (Emokpae *et al*., 2013).

AFP has a sensitivity of about 60% for the detection of liver cancer (Assmar *et al*., 2016). Alpha-fetoprotein and CA-125 levels in patients with HBV and/or HCV infections were significantly higher than in the patients unexposed to HBV/HCV. Chronic liver disease patients with

concurrent HBV/HCV infection had their AFP level greatly elevated which could be due to the severity of liver damage in HBV/HCV co-infection. Several studies had reported concurrent HBV/HCV infection causing more severe liver disease than mono-infection (Liaw, 1995; Sato *et al*., 1994). Serum level of AFP above 400ng/ml is greatly associated with liver cancer (Masuzaki *et al*., 2012). This significantly elevated AFP levels observed in this group may be a pointer to HCC which may require other standard examinations such as biopsy, ultrasound, computerized tomography (CT), or magnetic resonance imaging (MRI) for confirmation. The serum level of CA-125 in CLD patients infected with HBV was not significantly different from those infected with HCV. In contrast, elevated CA-125 levels among HCV-infected patients had been reported in a previous study (Assmar *et al*., 2016).This variation in results may be due to the fact that our study was carried out among confirmed CLD patients. Especially when physical examination is unclear, CA-125 is an indispensable tool in the detection of ascites in patients with liver cirrhosis (Zuckerman *et al*., 1999).The Gamma-glutamyl transferase levels in the CLD patient unexposed to HBV/HCV were higher compared to other groups. El-Emshaty and others in their work suggest that GGT cannot be used as a marker for assessing the severity of liver disease (El-Emshaty *et al*., 2019). Therefore, this implies that the elevated GGT levels in the HBV/HCV non-infected CLD patients observed in this present study do not indicate a more severe liver injury in these individuals. Multivariate analysis of our study showed that no one particular viral hepatitis seromarker was directly associated with elevated levels of AFP, CA-125, and GGT among patients with CLD.

Conclusion

There is a high burden of HBV infection among patients with pre-existing chronic liver disease. Appropriate detection is necessary for early diagnosis and prompt treatment to halt the transmission of the virus and the progression of liver disease. Hepatitis B core antibody (HBcAb) when used in combination with HBsAg is more reliable as a screening test for HBV infection than HBsAg used alone. Furthermore, no one particular viral hepatitis seromarker influences the serum levels of AFP, CA-125, and GGT. However, chronic liver disease patients with greatly elevated AFP serum levels should be tested for HBV/HCV co-infection.

Limitations of the Study

The cause of CLD in the study patients was not ascertained, further studies are required to establish the aetiology of CLD for a more persuasive result. Also, since some of the patients were on antiviral treatments this could have a potential influence on our results.

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Conflict of Interest Statement: None

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