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Original

Pattern of Liver Fibrosis among Individuals with Chronic Hepatitis B Infection in Sokoto, Northwestern Nigeria

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Abstract

Background: Chronic Hepatitis B (HBV) infection remains a global and significant public health challenge. It is estimated that about two billion people have been infected, 257 million of whom have current evidence of chronic infection. HBV is a major cause of morbidity and mortality due to its complications of liver cirrhosis and hepatocellular cancer. Depending on the stages of the disease, active liver inflammation and damage, advanced fibrosis can progress quickly, slowly, or intermittently.

Objective: To determine the pattern of fibrosis in patients with Chronic Hepatitis B Infection.

Method: This was a retrospective study carried out at the Usmanu Danfodiyo University Teaching Hospital (UDUTH) in Sokoto, Nigeria from June 2021 to May 2023. Thirty-one patients that had liver biopsy due to chronic Hepatitis B infection (CHBV) were retrieved. A proforma was used to collect information. Data was extracted and imputed into a computer and analyzed with IBM's Statistical Package for Social Sciences software version 25.

Results: The mean age of study subjects was 33.52±8.64. Twenty-eight (90.3%) had clinical indication of elevated viral load as against 2(9.7%) with elevated ALT as indication for liver biopsy. Non-significant fibrosis F0 and F1 were seen in 25.8% each while significant fibrosis F2 and F3 were seen in 22.6% and 19.4% respectively, however, 6.5% had cirrhosis. There was no significant relationship in the level of fibrosis to age and gender with p-value of 0.076 and 0.566 respectively.

Conclusion: Chronic HBV infection is a cause of liver injury and fibrosis. The study portraits the fact that liver biopsy can still be used as a tool to demonstrate evidence of fibrosis especially when transient elastography is not readily available. This can aid early initiation of treatment especially in resource poor setting where advance technology is limited.

Keywords: Pattern, Liver fibrosis, Chronic Hepatitis B Infection, Nigeria

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Introduction

Over two million people have contracted the Hepatitis B virus (HBV) at some point in their lives. Approximately 350 million of them are still chronically infected. Approximately 75% of the world's population resides in regions where infection rates are high. An estimated 1 million people die annually from primary liver cancer or cirrhosis linked to HBV (1). The primary cause of cirrhosis and liver cancer leading death worldwide, is still CHBV infection. It is still crucial to determine the natural course of CHBV patients to effectively prevent the emergence of serious complications. The depiction of CHB natural history in major international clinical practice recommendations mostly reflects knowledge of the relationships between host immune response and HBV replication (2). Hepatitis B has a wide range of pathologies that correspond to the various stages and gradings of the disease's clinical progression. Most people recover after an acute infection, but some progress to chronicity (3). The intricate natural history of HBV is centered in the liver, where a cycle of hepatocyte injury and tissue repair is caused by the interaction of viral proteins with the immune system. Repeated extracellular matrix deposition during this repair process causes liver fibrosis to worsen over time. Additionally, the HBV X protein may have specific carcinogenic and fibrogenic effects on the liver. Depending on the stage of the disease and the extent of active liver inflammation and damage, advanced fibrosis can progress quickly, slowly, or intermittently (1). There are three distinct phases in the natural history of CHBV infection: immune-tolerant, immune-reactive, and inactive HBV carrier. The conventional gold standard for assessing the extent of liver damage, including the stage of fibrosis and inflammatory activity, is liver biopsy. Liver biopsy helps to detect and assess complicating diseases such steatohepatitis, autoimmune hepatitis, and drug-induced liver disease, as well as precursor lesions of hepatocellular carcinoma (HCC) (3, 4). The national guidelines outline the grounds for liver biopsy in CHBV infections based on clinical, virological, and biochemical characteristics because the current guidelines for the therapy do not

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advocate for liver biopsy in all patients with CHBV (5). There are different levels of interfaces in hepatitis, patchy lobular inflammation, and mostly lymphocytic portal inflammation in CHBV. While inflammation is prevalent during the immune reactive phase, it is negligible throughout the immunological-tolerant and inactive carrier stages. An inflammation that "connects" portal tracts to central veins or to each other is known as bridging necrosis. As the name suggests, numerous contiguous hepatocytes are affected by confluent necrosis. Scarring, which ranges from a slight portal expansion to peri-portal fibrous strands, bridging fibrosis, and cirrhosis, is usually linked to inflammation (3, 6). The Batts-Ludwig scoring system is the most widely used scale in assessing the grade f necro-inflammatory activity and degree of fibrosis in chronic hepatitis. The scoring system provides a standardized framework for evaluating liver histology, ensures reproducibility and consistency among pathologists, correlates clinical outcomes and treatment decisions and assesses multiple features of liver damage (7,8). This study, therefore, was aimed at determining the pattern of fibrosis in patients with Chronic Hepatitis B Infection and their socio-demographic characteristics.

Methodology

A retrospective study was carried out at the Usmanu Danfodiyo University Teaching Hospital in Sokoto, Nigeria (UDUTH) from June 2021 to May 2023. Data of thirty-one adult patients that had clinical indications liver biopsy who had CHBV infection with a high serum level of viral deoxyribonucleic acid (DNA) but normal alanine transaminase (ALT), or normal viral load but with an elevated ALT were retrieved from the Medical Record and Histopathology Departments of the institution. All patients referred for liver biopsy who were below 18 years of age, did not have CHBV infection, those who had other co-existing liver conditions or those who did not consent were excluded from the study. A profoma was used to collect information including socio-demographic data, indication for the liver biopsy and level of fibrosis using the Batts-Ludwig Scoring System. The level of fibrosis was classified as F0, F1, F2, F3, and F4 (9).

Data Extracted was imputed into a computer and analyzed using IBM's Statistical Package for Social Sciences software (SPSS version Chicago, IL). Categorical variables were summarized as frequencies, proportions, and percentages while discrete variables were analyzed using the Chi-square test. Pattern of fibrosis among the subjects was reported. A p-value of less than 0.05 was accepted as statistically significant at a confidence interval of 95% signifying quantitative measure of evidence, enables comparison of results across studies and will guide decision making in clinical practices.

For this study F0 and F1 were regarded as non-significant fibrosis, F2 and F3 as significant fibrosis and F4 as cirrhosis (9).

Ethical Consideration

Approval for the study was obtained from the Research and Ethics Committee of Usmanu Danfodiyo University Teaching Hospital before the study was conducted.

Results

The mean age of the subjects was 33.52 8.64. More than 70% of the patients with CHBV that had liver biopsy within the period were at younger age between 20-29years. None of the CHBV subjects was above 60years. An almost equal number of male and female subjects found in the record during the period at the ratio of 1.06:1 (Table1).

Table 1: Socio-demographic characteristics of study subjects

Variables	Frequency (n -31)	Percent (%)
Age range (in years)		
20 – 29	10	32.3
30 – 39	14	45.2
40 – 49	4	12.9
50 -60	3	9.7
Gender		
Male	16	51.6
Female	15	48.4
Mean age of the subjects = 33.52 ±8.64		

Liver biopsy was indicated in 28(90.3%) of subjects and was due to elevated HBV viral load with no other parameters needed to commence HBV treatment according to national guidelines, while only 3(9.8%) that had a liver biopsy had clinical indication of elevated ALT (Table 2).

Table 2: Indication for Liver Biopsy among Chronic Hepatitis B patients

Indications	Frequency (n -31)	Percent (%)
High VL	28	90.3
Elevated ALT	3	9.7

VL=Viral load. ALT=Alanine aminotransferase

Pattern of fibrosis as seen in Table 3 showed F0 (No Fibrosis) and F1 (Portal fibrosis without septa) in 25.8% each of the subjects respectively. Similarly, 7(22.9%) had F2 fibrosis (Portal fibrosis with few septa) and F3 (Bridging Fibrosis) seen in 6 (19.4%) of the

subjects. Meanwhile F4 (cirrhosis) was seen in 2(6.5%) of the patients with chronic HBV infections.

Table 3: Pattern of Fibrosis among Chronic Hepatitis B

Level of fibrosis	Frequency(n- 31)	Percent (%)
F0	8	25.8
F1	8	25.8
F2	7	22.6
F3	6	19.4
F4	2	6.5

F0-No Fibrosis, F1-Portal fibrosis without septa, F2- Portal fibrosis with few septa, F3- Bridging Fibrosis, F4-Cirrhosis.

In Table 4 over 70% of the subjects with F1, F2 and F3 fibrosis were aged less than 40years and 100% of subjects with cirrhosis were in the older aged group between 50-59years. However, the results were not statistically significant (p-value 0.076).

Comparison in level of fibrosis between male, female subjects using descriptive statistics did not show any significant difference (p=0.566) as seen in Table 5. Although elevated viral load was the dominant indication, it showed no statistical difference with the pattern of fibrosis. See Table 7a and b.

Batts-Ludwig scoring system. The Batts-Ludwig scoring system is used for staging of fibrosis (a) and grading (b) of histological specimens obtained from the liver of patients with chronic hepatitis. Here, values of both stage (a) and (b) range from 0 to 4. (a) Staging is based on the presence of portal/periportal fibrosis and septa formation with/without cirrhosis, which corresponds to stage 4 (7,8).

Grading is based on either the portal/periportal activity or lobular activity. Here, whichever activity demonstrates greater severity is affirmed ie the overall grade is the one, which present at the greatest degree. Tables adapted from Rockey et al (7) and Batts-Ludwig, (8).

Discussion

Most of the patients with chronic HBV in the study were under forty years with mean age of 33.52±8.64. This tally with the guideline in which indications to liver biopsy in chronic HBV favors younger adults than elderly. In a study of HBV DNA level in predicting significant fibrosis in chronic hepatitis B by Praneerarat et al, the mean age of his study subjects was also in the younger age group (41.8±8.64) (10). In the study almost an equal number of male and female subjects were seen in the record that had liver biopsy during the period. This finding could be because the indication of liver biopsy in CHB does not rely on gender of the individuals (11).

The dominant indication warranting a liver biopsy in the index study was degree of hepatitis B viral elevation without other markers needed to commence treatment. A meta- analysis on Liver Fibrosis in the Natural Course of Chronic Hepatitis B Viral Infection conducted in Asia across different countries showed that most of the indications to liver biopsy in chronic HBV were related to elevated viral load (2). In a different study, the number one indication for liver biopsy was elevated liver enzymes as against the index study, although the study by the American Association for the Study of Liver Disease (AASLD) and Asian Pacific Association for the Study

Table 4: Comparison between Age and Stage of Fibrosis among Chronic Hepatitis B patients

Variables	F0 (n-31) n (%)	F1 (n-31) n (%)	F2 (n-31) n (%)	F3 (n-31) n (%)	F4 (n-31) n (%)	P value Test –statistics
20-29	3 (37.5)	2 (25.0)	4 (57.1)	1 (16.7)	0 (0.0)	P= 0.076
30-39	4 (50.0)	4 (50.0)	1 (14.3)	5(83.3)	0 (0.0)	
40-49	1 (12.5	2 (25.0)	1 (14.3)	0 (0.0)	0 (0.0)	
50-59	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	2 (100)	

Table 5: Comparison between Gender and Level of Fibrosis among Chronic Hepatitis B

Variables	F0 (n-31) n (%)	F1 (n-31) n (%)	F2 (n-31) n (%)	F3 (n-31) n (%)	F4 (n-31) n (%)	P value Test –statistics
Male	5 (31.2)	2 (12.5)	4 (25.0)	4 (25.0)	1 (6.2)	P= 0.566
Female	3 (20.0)	6 (40.0)	3 (20.0)	2(13.3)	1 (6.7)	

Table 6: Comparison between indications and level of Fibrosis among Chronic Hepatitis B

Variables	F0 (n-31) n (%)	F1 (n-31) n (%)	F2 (n-31) n (%)	F3 (n-31) n (%)	F4 (n-31) n (%)	P value Test –statistics
High VL	7 (25.0)	6 (21.4)	7 (25.0)	6 (21.4)	2 (7.1)	P= 0.665
Elevated ALT	1 (33.3)	2 (66.7)	0 (0.0)	0(0.0)	0 (0)	

VL= Viral load. ALT =Alanine Aminotransferase

Liver Disease (APASLD) guidelines differ from the National guidelines used in the study (10).

Table 7a: Batts-Ludwig scoring system (Stage of Fibrosis)

Batts-Ludwig scoring system STAGE (Fibrosis)		
Description	Numerical Stage	Severity of fibrosis
None	Stage 0	
Portal fibrosis	Stage 1	Mild fibrosis
Periportal fibrosis (or rare portal-to-portal septa	Stage 2	Moderate fibrosis
Septal fibrosis (septa with architectural distortion but no fibrosis	Stage 3	Severe fibrosis
Cirrhosis	Stage 4	

Table: 7b: Batts-Ludwig scoring system (Grade)

Batts-Ludwig scoring system GRADE (Necroinflammation /activity-whichever is greater		
Portal/Periportal Activity	Lobular Activity	Numerical Grade
None	None	Grade 0
Minimal (patchy)	Minimal (infrequent and spotty)	Grade 1
Mild (some or all portal tracts)	Mild (Little hepatocellular damage-scattered necrosis	Grade 2
Moderate (All portal tracts	Moderate (noticeable hepatocellular damage-necrotic clusters)	Grade 3
Severe (and may have bridging fibrosis	Severe (prominent diffuse hepatocellular damage)	Grade 4

A significant fibrosis was found in over 40% of the subjects while cirrhosis was seen in 6.9%. Over 50% of subjects with F2 fibrosis were between 20-29years of age and more than 80% with bridging fibrosis were also younger between 30-39years of age. However, all cirrhotic patients were in the older age group. A study by Musa et al (12) on hepatic fibrosis among HBV infected patients found that significant fibrosis was seen in 47% of his subjects also similar to our study. The patients in his study were also younger (less than 40years of age) (10). A study by Bonnard et al Burkina Faso (13) in which he compared elastography, serum marker score and histology for assessment of liver fibrosis in chronic HBV found that 46% of study subjects had either F2 or F3 fibrosis and 24% had cirrhosis. Overall, subjects were also younger under 40years (13). Another African study found a less percentage of patients with significant fibrosis (5.5%)(14) , This could be because the type of study was longitudinal , and only chronic carrier Chronic HBV patients were recruited in the study which could have lowered the overall percentage of subjects with fibrosis(14).Sebastiani et al found a higher percentage of significant fibrosis in 68.2% among 110 patients that he recruited in his study on sequential algorithms combining non-invasive markers and biopsy for the assessment of liver fibrosis in chronic hepatitis B. This significant number could be because the study population included subjects with other infections including Hepatitis C and Human Immunodeficiency Virus infection which is also an independent predictor of liver fibrosis even in the absence of chronic HBV infection(15).The intense fibrosis in chronic HBV infection could be explained from the fact that liver damage appears to be immune-mediated, with HBV-specific T cells playing a key role both in disease pathogenesis and viral clearance(3, 4).

Conclusion

Chronic HBV infection is one of the leading causes of liver injury and fibrosis especially in Asia and sub-Saharan Africa. The study portraits the fact that liver biopsy though an invasive procedure still remains a useful tool in demonstrating evidence of fibrosis in liver injury. This can aid in early initiation of treatment especially in resource poor setting where advance technology to demonstrate it is limited.

Limitation

The duration of the period of the study (three years) may have not clearly indicate the burden of liver fibrosis in chronic HBV when compared to a larger population size, small sample size and the inability to establish causality.

Recommendation

Liver biopsy though an invasive procedure but quite safe, a larger sample size will increase precision, reliability and enhance statistical power.

A larger sample size and longitudinal studies would help verify findings with better and reliable outcomes.

Conflict of Interest

There are no conflicts of interest

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