Research Article

Liver fibrosis and its associations among people with hepatitis B in rural Uganda: A retrospective records review

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ABSTRACT

Introduction: Chronic hepatitis B affects about 240 million people worldwide, with significant complications including liver fibrosis and hepatocellular carcinoma. We aimed to study the prevalence of liver fibrosis and its associations among people with hepatitis B at Mbarara Regional Referral Hospital (MRRH).

Method: This study was a retrospective review of cross-sectionally collected data in an integrated hospital management system from July 2018 to August 2021 at MRRH. Socio-demographics, co-morbidities, and laboratory parameters were retrieved. Liver fibrosis was defined by an aspartate aminotransferase-to-platelet index score of >2. A bivariable and multivariable logistic regression analysis was used to identify factors associated with liver fibrosis. Associations in the multivariate model with a p-value ≤0.05 were considered statistically significant.

Results: Five hundred and thirty-seven records of hepatitis B patients were retrieved. The median age was 34 (Interquartile Range (IQR), 28-43) years, and 334 (62.2%) were males. One hundred and two (18.99 %) were alcohol consumers, and 189 (35.20 %) were cigarette smokers at the data collection time. The prevalence of liver fibrosis was 10.8% (CI: 8.4–13.7). Hepatitis B viral load ≥ 20,000 IU/ml (AOR: 3.58; 95% CI:1.2-1.1; p<0.016) and cigarette smokers (AOR: 5.33; 95% CI:1.4-19.9; p<0.013) were independently associated with liver fibrosis.

Conclusion: At our clinic, one in ten people with hepatitis B infection has liver fibrosis. We recommend regular screening of liver fibrosis in all people with hepatitis B, especially those with a viral load ≥20,000 IU/ml and cigarette smokers. Liver screening by a FibroScan in the hepatitis B prevalent areas of resource-limited settings may improve the detection rate.

Keywords: liver fibrosis, hepatitis B, Aspartate aminotransferase-to-platelet ratio index, Uganda

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Introduction

Globally, there are an estimated 240 million persons chronically infected with hepatitis B virus, particularly in developing countries.[1] Between 20% and 30% of those with chronic hepatitis B (CHB) develop cirrhosis and hepatocellular carcinoma. More than 640,000 people die annually from chronic hepatitis B.[1] The majority of people are unaware of their hepatitis B virus (HBV) status and, therefore, often present with advanced disease. [1] CHB is endemic in Uganda, and its prevalence is estimated at 4.6%.[2]

About 90% of people who acquire HBV at birth develop CHB. In comparison, only 5-10% of those who acquire the infection after five years progress to CHB.[3] Liver fibrosis is a known complication of a CHB that develops due to a chronic wound-healing response characterized by progressive accumulation of fibrillar extracellular matrix in the liver parenchyma.[4] If untreated, liver fibrosis develops into cirrhosis, leading to liver failure and death.[4]

Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a recommended non-invasive test to assess the presence of liver fibrosis in resource-limited settings and has been validated for diagnosing significant fibrosis and cirrhosis.[1] Despite this, there are limited data on the prevalence of liver fibrosis in rural Uganda. In our setting, chronic liver disease is among the most common causes of death, according to the mortality audit 2020 (unpublished). Therefore, we studied the prevalence of liver fibrosis and its associations among people with hepatitis B at Mbarara Regional Referral Hospital (MRRH).

Method

Study setting and data source

The data were collected and stored between July 2018 and August 2021 in the integrated hospital management system (HMIS), an electronic system that captures the medical data for patients attending MRRH's hepatitis clinic.

Study design, population, and eligibility criteria

The study was a retrospective record review of people with hepatitis B attending the MRRH hepatitis clinic. Data of people aged 18 years or more with a positive hepatitis B record were abstracted. Records missing AST or platelets were excluded from this study.

Study variables

The dependent variable was liver fibrosis, indirectly measured by the APRI score. The formula (AST/upper limit of normal of ASTx100)/ platelet count (109/L) determined the APRI score. An APRI score>2 signifies the presence of liver fibrosis. The sensitivity and specificity of the APRI score are 52% and 85%, respectively.[5] The independent variables include age described by median (IQR), sex as female or male, alcohol consumption (as

Table 1. Baseline characteristics

Characteristic	N=537
Male sex, n (%)	334 (62.20 %)
Age, median (IQR)	34 (28 - 43)
HIV positive, n (%)	63 (11.73 %)
HIV positive on ART, n (%)	38 (60.31%)
People on hepatitis B treatment, n (%)	103 (19.18 %)
Hepatitis C status, n (%)	
Negative	429 (79.89 %)
Positive	9 (1.68 %)
Missing	99 (18.44 %)
History of smoking, n (%)	
Never	234 (43.58 %)
Current	189 (35.20 %)
Former	43 (8.01 %)
Missing	71 (13.22 %)
History of alcohol intake, n (%)	
Never	333 (62.01 %)
Current	102 (18.99 %)
Former	31 (5.77 %)
Missing	71 (13.22 %)
History of diabetes mellitus, n (%)	
No	408 (75.98 %)
Yes	58 (10.80 %)
Missing	71 (13.22 %)
Viral load for hepatitis B, n (%)	
< 20,000 IU/ml	151 (22.53 %)
≥ 20,000 IU/ml	58 (10.80 %)
Missing	358 (66.67 %)

Table 2. Factors associated with liver fibrosis

Variable	Bi-variable Analysis		Multi-variable Analysis	
	OR (95% CI)	P-value	AOR (95% CI)	P-value
Male gender	1.75(0.96 – 3.21)	0.067	1.75(0.60-5.40)	0.284
HIV positive	1.19 (0.49-2.90)	0.693		
Hepatitis C positive	4.06(0.98-16.78)	0.053		
*Smoking history	5.09(2.49-10.41)	0.001	5.33(1.43-19.92)	0.013
**Alcohol history	1.60(0.88-2.92)	0.118	1.14(0.39-3.33)	0.800
History of diabetes mellitus	1.51(0.69-3.30)	0.291		
Hepatitis B viral load (≥20,000 i.u/L)	3.53 (1.45-8.54)	0.005	3.58 (1.26-10.12)	0.016

Note: **OR:** *Odds ratio,* **CI:** *Confidence Interval,* **AOR:** *Adjusted odds ratio. *Smoking history represents both current and former smokers combined. **Alcohol history represents both current and former alcohol consumers combined.*

current, former, never, or missing), cigarette smoking (as current, former, never, or missing, and smoking), and diabetes mellitus (as yes, no, or missing). HIV coinfection was categorized as yes, no, or missing, hepatitis C coinfection (yes, no, or missing), and the hepatitis viral load was categorized as ≥20,000 iu/L or <20,000 iu/L.

Statistical analysis

After ethical approval was sought from the relevant institutions, the abstracted data was exported to STATA version 14 for analysis. Means, medians, and frequencies were used to describe the baseline variables. The prevalence was determined as the proportion of liver fibrosis patients in the study sample. Bi- and multi-variable analyses were performed to determine associations. Variables with P<0.2 in the bi-variable analysis were put into the multivariate model. A p≤0.05 was considered statistically significant.

Results

Eight hundred and fifty-one records were screened for eligibility. Of those, 299 were missing AST or platelets, and 15 had ages <18 years. Hence, 537 records were included for final analysis. The median (IQR) age was 34(28-43), and 334(62.2%) participants were male. At the time of data collection, 102(18.9%) people were drinking alcohol 31(5.7%) and 189(35.2%) were cigarette smokers. HIV coinfection was found in 63(11.7%), hepatitis C in 9(1.6%), and viral load ≥20,000 i.u/L in 58(10.8%) (Table 1).

The prevalence of liver fibrosis was 10.8% (CI 8.44–13.73), with a standard error of 1.34 %. In the bi-variable analysis, male sex, viral load ≥20,000 i.u/L, and smoking cigarettes were associated with liver fibrosis. However, in the adjusted model, smoking cigarettes and a viral load ≥20,000 i.u/L remained significantly associated with liver fibrosis (Table 2).

Discussion

Our study aimed to provide insights into the prevalence and factors associated with liver fibrosis among patients with hepatitis B infection at MRRH.

We found that the prevalence of liver fibrosis was 10.8% among hepatitis B patients. Similar findings were found by Ramirez-Mena (2016) at Saint Francis Referral Hospital (Tanzania) and Laing (2019) at St. Mary's Hospital Lacor (Uganda), with a prevalence of 9.2% and 8%, respectively. Both studies used the APRI score with a threshold of >2 as the diagnostic method for liver fibrosis.[6, 7] However, a low prevalence of 4.3% was found when using an APRI score >2 in a study conducted at two health centres in Maputo City and Mozambique.[8] This variation may be attributed to genotype distribution, as most participants in the Chambal (2017) study were found to have genotype A. In contrast, a study conducted at St. Paul's Hospital Millennium Medical College (Ethiopia) reported a higher prevalence of 17.3% using transient elastography.[9] This difference might be attributed to our use of the APRI score, potentially explaining the reduced prevalence rates observed in our findings. Though fibroscan has the highest sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) compared to APRI and FIB-4 scores, Moosavy SH et al. (2023) concluded that APRI has >90% PPV and NPV and could reliably be used in settings with no fibroscans.[10]

Our study found that a high viral load (≥20,000 IU/ml) was associated with liver fibrosis. Similar results were found in two studies conducted in Gambia and Egypt.[11, 12] This association is likely due to the replicative HBV infection, which stimulates host immune responses, leading to the chronic destruction and regeneration of hepatocytes. This process contributes to the development of fibrosis and, eventually, cirrhosis.[13]

In our study, we found that smoking was associated with liver cirrhosis. Prior studies in France and Denmark reported similar findings.[14,15] Among other mechanisms, the cytotoxic chemicals in tobacco smoke induce fibrosis by activating the hepatic stellate cells.[15]

Despite many advantages of our study, our database lacked important variables such as alanine aminotransferase. This made it impossible to compare APRI and Fib-4, another low-cost score commonly used in resource-limited settings.

Conclusion

In the hepatitis clinic at MRRH, one in ten people with hepatitis B has liver fibrosis. Where available, we recommend using a FibroScan to screen for liver fibrosis in people with CHB. All people with hepatitis B infection are advised to refrain from smoking.

Conflicts of interest: None.

Sources of funding: None.

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