Prevalence of Liver Fibrosis in Hepatitis B Virus Infection Using Aspartate Aminotransferase to Platelet Ratio Index (APRI) Score at Rukunyu Hospital, Kamwenge District, South Western Uganda.

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Abstract

Introduction: Liver fibrosis (LF) is a crucial factor in predicting adverse liver outcomes including cirrhosis and hepatic decompensation in chronic hepatitis. In addition, liver fibrosis is important in determining whether, when, and how to initiate antiviral therapy. The degree of LF or cirrhosis is an independent factor to predict mortality in chronic hepatitis B patients. Due to the limitations associated with the current diagnostic test for LF histology, the aspartate aminotransferase-to-platelet ratio index (APRI), has been suggested to identify patients with HBV-related liver fibrosis.

Objective: This study aimed at assessing the prevalence of liver fibrosis in hepatitis B using Aspartate Aminotransferase to Platelet Ratio index (APRI) score and its associated factors among patients attending Rukunyu Hospital, Kamwenge District, South Western Uganda.

Materials and methods: We recruited a total of 163 respondents, after informed consent. Blood was collected from them and was used for AST and complete blood count from which a platelet count was obtained. APRI score was calculated using the formula: APRI = AST (U/L)/(upper limit of the normal range) ×100/platelet count (10^9 /L). An APRI score of 0.5 and above was considered as an indicator of liver fibrosis.

Results: Out of 163 study respondents, 15(9.2%) had APRI score of > 0.5, which was indicative of liver fibrosis, with those in age bracket 40–59 years 8(53.3%), male 9(60.0%), not employed 10(66.7%), Christians 10(66.7%), having household monthly income of 50,000-200,000/= 10(66.7%), living with their spouse and children 14(93.3%), drinking alcohol 9(60.0%) and smoking 9(60.0%) being more affected. On bivariate analysis, age group 60–75 years (P = 0.008, OR: 0.109, 95%CI 0.06–0.742), drinking alcohol (P ≤ 0.001, OR: 6.155, 95%CI 2.029–18.67) and smoking (P ≤ 0.001, OR: 72.5, 95%CI 15.53-338.45) had statistically significant association with liver fibrosis. On multivariate logistic regression analysis, only smoking (P ≤ 0.001, OR: 55.563, 95CI 6.78-454.887) had statistically significant association with liver fibrosis.

Conclusion: The prevalence of liver fibrosis was high (9.2%) and there is a need for early screening of liver fibrosis in Hepatitis B patients to prevent further damage.

Introduction

Infection with hepatitis B virus (HBV) is a public health problem worldwide with 2 billion people exposed to the virus and 240 million people estimated to experience chronic HBV infection, of which 800,000 deaths occur per year [1]. Africa shares 25% of the total HBV burden, with 65 million chronic carriers [2]. Uganda Population-Based HIV Impact Assessment (UPHIA) has reported the prevalence of Hepatitis B virus infection in Uganda to be 4.1% [3]. Hepatitis B virus transmission occurs through blood and blood product exposures [4]. While sexual and needle stick exposures are common modes of transmission in low endemic areas, transmission in high endemic regions tends to occur in early childhood either perinatally or through child-to-child horizontal methods [2]. Hepatitis B related mortality and morbidity

occurs decades after acute infection, allowing chronic carriers to spread the infection [5] and Chronic liver diseases normally progress to liver cirrhosis and hepatocellular carcinoma through long-standing repetition of inflammation and healing process regardless of underlying causes[6].

It is important to detect liver fibrosis at an early stage to prevent cirrhotic complications or even to regress liver fibrosis using effective anti-fibrotic strategies [6].

The fibrosis stage is a crucial factor in predicting adverse liver outcomes, including cirrhosis, hepatic decompensation in CHB [7]. In addition, liver fibrosis (LF) is important in determining whether, when, and how to initiate antiviral therapy. The degree of LF or cirrhosis is an independent factor to predict mortality in chronic hepatitis B (CHB) patients [7].

Several clinical parameters, including male gender, older age, higher levels of alanine aminotransferase (ALT), and serum level of HBV DNA appear to be associated with the severity of liver disease (Shoaei et al., 2014s)

Currently, liver biopsy, the gold standard, is limited by invasiveness, prolonged hospital stay of 12–24 hours, sampling error, variability in pathological interpretation, and the reluctance of patients to undergo repeated biopsies to monitor disease progression and morbidity rate [9]. Moreover, procedure-related complications such as pain, bleeding, pneumothorax, bile acid peritonitis, or organ perforation might occur in up to 2% of patients [10]. Due to these limitations, the aspartate aminotransferase-to-platelet ratio index (APRI), a non-invasive method has been used to identify patients with HBV-related hepatic fibrosis [11]. This index has the advantage of including only 2 common and inexpensive markers, in aspartate aminotransferase, and platelet count laboratory tests [9] The APRI has shown great value in assessing the risk of liver fibrosis in Hepatitis B [12]. Thus, this study aimed at assessing the risk of liver fibrosis in hepatitis B using Aspartate Aminotransferase to Platelet Ratio index (APRI) score among patients attending Rukunyu Hospital.

Materials And Methods

Study design and participants

This was a cross-sectional study which involved 163 study participants attending Rukunyu Hospital, Kamwenge District, South Western Uganda.

Inclusion and exclusion criteria

Inclusion criteria

All Hepatitis B positive patients attending Rukunyu Hospital who consented/Assented were allowed to participate in the study.

Exclusion criteria: All participants vaccinated for hepatitis B in the last 1 month.

Data collection

A semistructured questionnaire consisting of open and closed-ended questions was administered. Research assistants were trained on how to collect data prior to data collection. Eligible participants were recruited in the study as they came to the laboratory after consenting or assenting to participate in the study.

Laboratory Procedures

Specimen collection and preparation

Venipuncture was performed to collect venous blood aseptically in EDTA purple top and plain red top vacutainer to obtain at least 4mls for platelet count, HBV and AST testing.

1ml of EDTA whole blood was used for platelet count using a sysmex-300 haematology analyser as per SOP for platelet count in appendix V and 4. 3mls of plain red top vacutainer blood sample was centrifuged for 10 minutes at 3500 rpm to obtain at least serum blood for HBV and AST tests using one step HBsAg dipstick immune chromatographic rapid test and Cobas C111 respectively.

Laboratory assay for HBV Testing

The specimen was allowed to react with a colored conjugate which was precoated on the testing strip. The mixture then moves upward on the membrane chromatographically by capillary action. For a reactive result, a purple-colored line with antibody-antigen-antibody gold particle complex will form in the test line region of the result window. Absence of this purple-colored line in the test line region suggests anon reactive result[13].

Platelet count using XP-300 Sysmex cell analyzer

Once XP-300 Sysmex cell analyzer was in the ready mode for blood cell analysis, a well-mixed blood sample was set to the sample probe. A start switch was pressed to begin analysis. The analysis results are displayed and printed after 60 seconds (XP-300 Sysmex manual, 2013) as per appendix V 4, SOP on Platelet count using XP-300 Sysmex cell analyzer

Aspartate Aminotransferase (AST) using Cabas c111 Analyzer

The serum sample was pressed on the sample area within 10 seconds of confirming the test for analysis as per Rukunyu Hospital SOP with Aspartate Aminotransferase (AST) using Cabas c111 Analyzer.

Calculation of APRI

APRI score was calculated using the formula: APRI= AST (U/L)/(upper limit of the normal range) ×100/platelet count (10^9 /L). The 40 U/L of AST was used as the upper limit of the normal rate.

An APRI score of 0.5 was considered as an indicator of liver fibrosis.

Data Analysis

The raw data was entered into a Microsoft Excel spread sheet and then imported into STATA (version 16) analysis software for further analysis. Descriptive statistics; frequencies and percentages were used to summarize the distributions of demographics. Regression analysis of the various variables was done to identify factors associated with liver fibrosis and raised APRI score. P value of less than or equal to 0.05 was considered statistically significant at the 95% confidence interval.

Ethical considerations.

Clearance to conduct the study was sought from Mbarara University of Science and Technology, Medical Laboratory Science department (Ref, MUST/MLS/030). Administrative clearance was sought from Rukunyu Hospital before commencement of the study (see attached letter).

Written informed consent/assent was sought from patients before participation in the study.

All study findings were treated with a high level of confidentiality under lock and key accessible to only the research team. All study documents and laboratory specimens were identified with study numbers and not names.

Quality control

Rukunyu Hospital clinical laboratory is accredited by South African National Accreditation System (SANAS) to conduct liver function tests and blood complete count. Cobas C111 and Sysmex regular calibration and running of daily quality control measurements was performed throughout the study period using a validated calibrator and external quality control material recommended by the manufacturer. All procedures were carried out following SOPs.

Results

Demographic characteristics

One hundred and sixty-three (163) participants were enrolled in the study and the response rate was 100%.

Majority, 97(59.5%) of the respondents were in the age bracket of 20–39 years while the minority, 6(3.7%) were in the age bracket 60–75 years. Most, 84(51.5%) of them were females whereas the least 79(48.5%) were males.

Majority of the respondents, 102(62.6%) were married, 85(52.1%) had primary level of education, 121(74.2%) were not employed, 111(68.1%) were Christians, 98(60.1%) had household monthly income of 50,000-200,000/= and 130(79.8%) lived with their spouse and children.

Most, 125(76.7%) of the respondents did not drink alcohol, whereas the least 38(23.3%) drunk alcohol. Majority, 151(92.6%) did not smoke while the minority, 12(7.4%) smoked, as shown in Table 1 below.

Table 1
Demographic characteristics of study participants

Variable	Category	Frequency (n)	Percentage (%)
Age in years	20–39	97	59.5
	40–59	60	36.8
	60–75	6	3.7
	Total	163	100.0
Gender	Male	79	48.5
	Female	84	51.5
	Total	163	100.0
Marital status	Single	10	6.1
	Married	102	62.6
	Divorced	7	4.3
	Cohabiting	40	24.5
	Widowed	4	2.5
	Total	163	100.0
Level of education	None	50	30.7
	Primary	85	52.1
	Secondary	21	12.9
	Tertiary	7	4.3
	Total	163	100.0
Employed	Yes	42	25.8
	No	121	74.2
	Total	163	100.0
Type of employment	Self employed	21	50.0
	Public servant	8	19.0
	Ngo/company	13	31.0
	Total	42	100.0

Variable	Category	Frequency (n)	Percentage (%)
Religion	Christian	111	68.1
	Moslems	50	30.7
	Cultural beliefs	2	1.2
	Total	163	100.0
Household monthly income	< 50,000/=	20	12.3
	50,000-200,000/=	98	60.1
	200,001-500,000/=	35	21.5
	> 500,000/=	10	6.1
	Total	163	100.0
Whom do you live with	Alone	7	4.3
	Spouse	12	7.4
	Spouse and children	130	79.8
	Own parents	9	5.5
	In laws	2	1.2
	Friends	3	1.8
	Total	163	100.0
Drink alcohol	Yes	38	23.3
	No	125	76.7
	Total	163	100.0
Smoke	Yes	12	7.4
	No	151	92.6
	Total	163	100.0

Prevalence of liver fibrosis among hepatitis B patients

Out of 163 study respondents, 15(9.2%) had APRI score of > 0.5, which was indicative of liver fibrosis while 148(90.8%) had no liver fibrosis, as shown in Fig. 1 below.

The prevalence of liver fibrosis was highest among the age group of 40–59 years 8(53.3%), followed by the age group 20–39 years 5(33.3%) and the lowest, 2(13.3%) in the age group 60–75 years. The

prevalence of liver fibrosis by gender was highest among males 9(60.0%) and lowest among females 6(40.0%). According to marital status, it was highest among married 6(40.0%) and lowest among singles 2(13.3%). No widowed respondent had liver fibrosis as shown in Table 2 below.

Majority of those who had liver fibrosis had primary level of education, 7(46.7%), were not employed, 10(66.7%), were Christians, 10(66.7%), had a household monthly income of 50,000-200,000/= 10(66.7%), lived with their spouse and children 14(93.3%), drunk alcohol 9(60.0%) and smoked 9(60.0%) as shown in Table 2 below.

Table 2
Distribution of liver fibrosis by population demographics

Variable	Category	Has Liver fibrosis	
		Frequency (n)	Percentage (%)
Age in years	20–39	5	33.3
	40–59	8	53.3
	60–75	2	13.3
	Total	15	100
Gender	Male	9	60.0
	Female	6	40.0
	Total	15	100
Marital status	Single	2	13.3
	Married	6	40.0
	Divorced	2	13.3
	Cohabiting	5	33.3
	Widowed	0	0
	Total	15	100
Level of education	None	5	33.3
	Primary	7	46.7
	Secondary	3	20.0
	Tertiary	0	0
	Total	15	100
Employed	Yes	5	33.3
	No	10	66.7
	Total	15	100
Type of employment	Self employed	2	40.0
	Public servant	2	40.0
	Ngo/company	1	20.0
	Total	5	100

Variable	Category	Has Liver fibrosis	
		Frequency (n)	Percentage (%)
Religion	Christian	10	66.7
	Moslems	5	33.3
	Cultural beliefs	0	0
	Total	15	100
Household monthly income	< 50,000/=	3	20.0
	50,000-200,000/=	10	66.7
	200,001-500,000/=	2	13.3
	> 500,000/=	0	0
	Total	15	100
Whom do you live with	Alone	0	0
	Spouse	1	6.7
	Spouse and children	14	93.3
	Own parents	0	0
	In laws	0	0
	Friends	0	0
	Total	15	100
Drink alcohol	Yes	9	60.0
	No	6	40.0
	Total	15	100
Smoke	Yes	9	60.0
	No	6	40.0
	Total	15	100

Factors associated with liver fibrosis among hepatitis B patients

On bivariate analysis, age group 60–75 years, drinking alcohol, and smoking had a statistically significant association with liver fibrosis with odds ratios of 0.109, 6.155, 72.5 and P values of 0.008, ≤

0.001, ≤ 0.001 respectively as shown in Table 3 below.

Of all those who had liver fibrosis, 15(100%) were HIV negative. Most of them had detectable hepatitis B viral load, 8(53.3%), never were transfused, 11(73.3%), had never been operated, 12(80.0%) and never cared for/stayed with hepatitis B infected person 8(53.3%). On bivariate analysis, HIV status, Hep B viral load, transfusion, operation history, and caring/staying with Hep B infected people had no statistically significant association with liver fibrosis (P > 0.05) as shown in Table 3 below.

Table 3
Bivariate analysis of the factors associated with liver fibrosis.

Variable	Category	Has liver fibrosis		OR (95% CI)	P value
		Frequency (n)	Percentage (%)		
Age in years	20–39	5	33.3	1	0.071
	40–59	8	53.3	0.353(0.110–1.136	0.008*
	60–75	2	13.3	0.109(0.016–0.742	
	Total	15	100		
Drink alcohol	No	6	40.0	1	≤ 0.001*
	Yes	9	60.0	6.155(2.029–18.67)	
	Total	15	100		
Smoke	No	6	40.0	1	≤ 0.001*
	Yes	9	60.0	72.5(15.53-338.45)	
	Total	15	100		
HIV status	Negative	15	100	1	0.389
	Positive	0	0	1.106(1.051–1.164)	
	Total	100	100		
Hep B viral load	Detectable	8	53.3	1	0.200
	Not detectable	7	46.7	1.989(0.684–5.789)	
	Total	15	100		
Ever been transfused	No	11	73.3	1	0.654
	Yes	4	26.7	1.318(0.393–4.418)	
	Total	15	100		
Ever been operated	No	12	80.0	1	0.203
	Yes	3	20.0	2.393(0.602–9.509)	
	Total	15	100		
Ever cared for/stayed	Yes	7	46.7	1	0.104
with hep B infected person	No	8	53.3	0.420(0.144–1.226)	
	Total	15	100		

Statistically significant, P < 0.05

On multivariate logistic regression analysis, only smoking (P ≤ 0.001, 95%CI 6.787-454.887, OR 55.563) had a statistically significant association with liver fibrosis as shown in Table 4 below.

Table 4
Multivariate logistic regression analysis of factors associated with liver fibrosis

Variable	P value	OR 95%CI
Age group 60–75 years	0.459	0.274(0.009–8.453)
Drinking alcohol	0.301	3.130(0.360-27.221)
Smoking	≤ 0.001*	55.563(6.787-454.887)

Statistically significant, P < 0.05

Discussion

Prevalence of liver fibrosis

This study found that the prevalence of liver fibrosis among hepatitis B patients attending Rukunyu Hospital as estimated by APRI score was 9.2%. This finding was in agreement with a study in Rakai district, Uganda, which reported a liver fibrosis prevalence of 11% among HIV negative individuals [15]. Our findings are also in agreement with the study by Wekesa et al., 2020 titled “prevalence and factors associated with liver fibrosis among adult HIV-infected patients attending urban and rural care clinics in Uganda” which reported a prevalence of 11% in rural clinics and 15% in urban clinics [16]. The agreement with our findings could be due to the fact that both studies were conducted in a similar setting (Uganda) targeting a similar populations while slight differences may be as a result of different geographical locations and different target populations.

Studies done elsewhere within Sub Saharan Africa(SSA) have reported a similar range in prevalence of liver fibrosis ranging between 2% and 24% depending on the study population and technique used [17]–[21]. Among western populations, the prevalence of liver fibrosis was in disagreement with the findings of our study and other studies in SSA, because it was higher in the study conducted in Germany, where significant liver fibrosis was present in 16% and 29% of patients in 1 and 2 years after study inclusion respectively [22]. Furthermore, our findings are in disagreement with the prevalence of 22.4%, 20.9%, 16.5%, 15.3%, and 12.9% among subjects with HBsAg positivity, diabetes mellitus, abnormal LFT, metabolic syndrome and obesity respectively conducted in Korean general population [23]. The disagreement can be explained by the fact that such study populations had other comorbidities like diabetes, metabolic syndrome, and obesity, which could have had an additional impact on the liver.

In addition, antiretroviral (ARV) therapy has been demonstrated to reduce the risk of liver fibrosis via adequate viral suppression and different adherence levels to ARVs may be behind slight differences in the prevalence of liver fibrosis [22], [24].

On bivariate analysis, age group 60-75 years (P=0.008, OR: 0.109, 95%CI 0.06-0.742), drinking alcohol (P≤0.001, OR: 6.155, 95%CI 2.029-18.67) and smoking (P≤0.001, OR: 72.5, 95%CI 15.53-338.45) had statistically significant association with liver fibrosis. However, on multivariate logistic regression analysis, only smoking (P≤0.001, OR: 55.563, 95%CI 6.787-454.887) had statistically significant association with liver fibrosis. Older age (60-75 years) being associated with liver fibrosis is consistent with the findings of previous studies [25], [26]. This may be due to increased liver stiffness in older individuals as a result of reduced number and volume of individual hepatocytes leading to a decline of the hepatic blood flow [26]. In addition, cellular and molecular mechanisms regulating hepatic regeneration are affected by ageing [27]. The association between smoking and liver fibrosis is in agreement with other studies which reported smoking as an independent risk factor for liver fibrosis [28], [29]. This may be due to tobacco carcinogen which has been documented to compromise the cancer surveillance system of the body and thus increasing the risk of liver fibrosis [29]. In addition, tobacco smoke contains cytotoxic properties that can lead to induction of fibrosis through activation of stellate cells, probably via nicotinic acetylcholine receptors[29]. Alcohol drinking affects the liver leading to alcoholic hepatitis, which eventually contributes to liver fibrosis.

Conclusion

The prevalence of liver fibrosis among HBV patients attending Rukunyu Hospital, Kamwenge District, was 9.2%. Alcohol drinking and smoking were associated with liver fibrosis.

Limitations Of The Study

Having used quantitative methods of data collection, patient experiences and opinions were not explored, which could have enabled us to expand on the factors associated with liver fibrosis.

List Of Acronyms And Abbreviations

APRI	Aspartate Aminotransferase to platelet ratio index
DNA	De-oxyribo Nucleic Acid
ELISA	Enzyme Linked Immunosorbent Assay
HepB	Hepatis B
HBeAg	Hepatitis B enveloped antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IDU	Injectable Drug Use
MSM	Men having sex with men
UPHIA	Uganda Population-based HIV Impact assessment
SOP	Standard Operating Procedure
WHO	World Health Organization

Declarations

Data availability: The data sets used in this study are available from the corresponding author upon a reasonable request

Conflicts of interest: The authors declare no competing interests

Authors Contributions: DN, IG, JK conceptualised the idea, BM and JLN collected data, PS analysed, BM, and DN wrote the first draft of the manuscript which was reviewed and approved by FS. All authors accepted the manuscript to be published.

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Figures

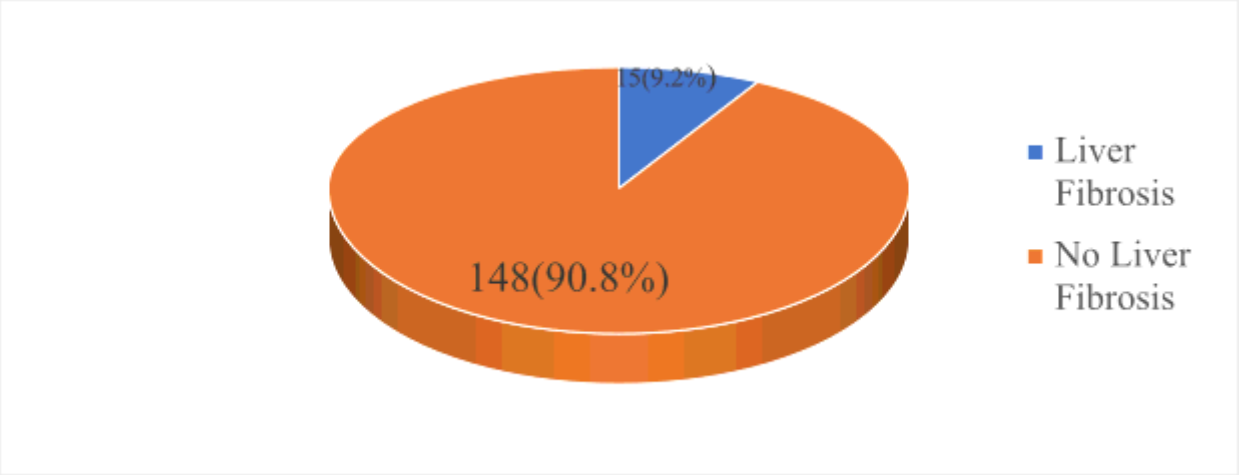

Figure 1

Prevalence of liver fibrosis among hepatitis B patients