Use of Fibroscan in assessment of Hepatic Fibrosis in patients with Chronic Hepatitis B infection

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ABSTRACT

Introduction: Assessment of the stage of liver fibrosis plays a prominent role in the decision process of treatment in chronic viral hepatitis.

Objective: To determine the stage of fibrosis in patients with chronic HBV infection using fibroscan.

Method: This is a cross sectional descriptive study involving patients with CHB with a valid transient elastography (TE) measurement. Liver function test and platelet count was determined. APRI and FIB-4 were calculated and Spermans rank coefficient was applied for correlation of transient elastography (TE) with either serum biomarkers.

Results: 190 patients were enrolled, mean age 36.3years, 64.2% males and 89.9% were asymptomatic. Most of the patients 131(68.9%) had no significant fibrosis(F0,F1) while those with significant fibrosis and cirrhosis were 59(31.1%) and 23(12.1%) respectively. TE correlated significantly with APRI and FIB-4 ($r = 0.58; P < 0.001$ and $r = 0.42; P < 0.001$, respectively).

Conclusion: The prevalence of significant fibrosis and cirrhosis is high in this population
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Key Words: Fibroscan, Hepatic fibrosis, APRI, FIB-4.

1.0   INTRODUCTION

The Hepatitis B virus is a DNA virus that causes infection of the liver that can either be acute or chronic infection. Chronic Hepatitis B (CHB) infection can progress to liver fibrosis, cirrhosis and hepatocellular cancer. Majority of people affected are unaware of their hepatitis B virus (HBV) infection and therefore often present with severe fibrosis and cirrhosis. The population of people with CHB worldwide is about 250 million. Early diagnosis of liver cirrhosis in CHB patients is important because cirrhosis is an independent predictor of mortality. HBV infection is endemic in Nigeria with a prevalence of about 12.2%, but the prevalence varies among the geo-political zones. The sero-prevalence of HBV varies between regions in Nigeria. A prevalence rate of 5.7% from Ilorin,11.6% from Maiduguri, and 8.3% from Zaria.

Chronic viral hepatitis leads to fibrogenesis through increased synthesis of extracellular matrix component such as collagen and glycoprotein. Assessment of the stage of fibrosis or the presence of cirrhosis will often dictate treatment options as well as provide an overall prognosis for patients with chronic liver disease.

Liver biopsy has been the primary means of identifying fibrosis and monitoring for disease progression. However due the risk of potential complication and invasiveness of the procedure, noninvasive and reliable means of evaluating for the presence of fibrosis has been developed. Noninvasive methods apart from assessing liver fibrosis, can be used in monitoring patients response to treatment and progression of disease and determining prognosis.

Transient elastography(TE) utilizing fibroscan now allows for a rapid measurement of liver stiffness. Using an ultrasound transducer probe, vibration of mild amplitude and low frequency (50Hz) are transmitted through the liver tissue and this result in an elastic shear wave that propagates through the underlying liver tissue. The probe then utilizes pulse – echo ultrasound to measure its velocity. The velocity of the wave is directly related to tissue stiffness which correlates with fibrosis. Fibroscan is a very simple and safe technique that takes about 5 minutes and can be done in an out‑patient setting.

OBJECTIVES: Aim of the work was to To determine the stage of fibrosis in patients with chronic hepatitis B virus infection using fibroscan.

METHODOLOGY

This is a cross sectional study conducted in Jos University Teaching Hospital. One hundred and eighty patients with CHB was recruited.

INCLUSION CRITERIA
1. Patients with chronic hepatitis B
2. Adults of both sexes aged 18years and above
3. Patient who give consent.

EXCLUSION CRITERIA
1. Patients with ascites.
2. Patients with $BMI > 28kg/m^2$.
3. Pregnant women.
4. Patients with significant alcohol ingestion i.e. 50g/day.
5. Patients with cholestasis.
6. Patients with ultrasound features of hepatic mass.

Consecutive patients seen at the medical out‑patient of department (MOPD) or admitted into the wards of the hospital who meet the inclusion criteria but none of the exclusion criteria were recruited into the study.

The data collection took place over a 6 month period from April to September 2015.

Medical history with special emphasis on: symptoms associated with CHB infection such as jaundice, easy tiredness (fatigue), unexplained loss of appetite, right upper abdominal pain, abdominal swelling, itching of the body and weight loss. Data on quantity and duration of alcohol ingestion and also use of HBV anti‑viral medication and other medication for liver disease were obtained. Written informed consent was obtained from each study participant. The institutional ethical committee approved the study.

The serum samples was used to determine alanine aminotransferase(ALT), aspartate aminotransferase(AST), total and direct bilirubin, alkaline phoshatase, total protein, albumin and platelet count. AST, ALT bilirubin, alkaline phosphatase, total serum protein and albumin were tested with the auto‑analyzer Hitachi 7600, Japan. The reference value was 0‑40/L for ALT and AST. Platelet count was obtained using Sysmex routine blood test pipeline, Japan.

Liver stiffness measurement was performed using the fibroscan equipped with an M probe. Ten valid measurements was performed to examine a patient (the mean of the measurement's was displayed on the screen), examination with a success rates higher that 60% and an inter‑quartile range >30% was considered. Patients were assigned to different fibrosis stages according to their TE results in conformity with previously published cut‑off values.

- F0/F1: 0 – 7.49 Kpa
- F2: 7.5 –9.49 Kpa
- F3: 9.5 – 11.99 Kp
- F4: 12 –75 Kpa

Liver stiffness measurement of 7.5 and 12.0kPa will be used as cutoff for significant fibrosis and cirrhosis respectively.

APRI(aspartate transaminase platelet ratio index), was calculated using the following formula

$$\frac{\dfrac{ALT}{ULN}}{Platelet\ Count} \times 100$$

Upper limit of normal for AST is 40U/L
FIB-4 was calculated using the following formula
FIB-4 Age $x AST \div Platelet Count x \sqrt{ALT}$

Statistical Analysis
Data obtained was analyzed using the Statistical Package for Social Sciences (SPSS) software version 20. Data will be represented using descriptive statistics such as tables and graphs. Spearman correlation coefficient (r) test was used to rank different variables against each other either positive or inverse. Student t-test was used for comparison of quantitative variable among more than two independent groups.

RESULTS
The age of the patients ranged from 18 years – 75years (median age 36.27year). The mean age was 36.3 years (SD = 11.4 years). The study population was made up of 122 (64.2%) males and 68 (35.8%) females. The male to female ratio was 1.8:1. Most of the patients in the study were asymptomatic accounting for 89.9% 0f the patients. Majority of the patients were HBeAg negative with 3.2% HBeAg positive.

TABLE 1: Clinical characteristics of the patients

Variable	Frequency	Percentage
SYMPTOMS		
FATIQUE	9	4.74
ABDOMINAL PAIN	7	3.68
ANOREXIA	3	1.58
WEIGHT LOSS	1	0.53
ASYMPTOMATIC	170	89.4

Most of the patients in the study were asymptomatic accounting for 89.9% 0f the patients.

Fig 1: Categorization of subjects into different levels of fibrosis stage
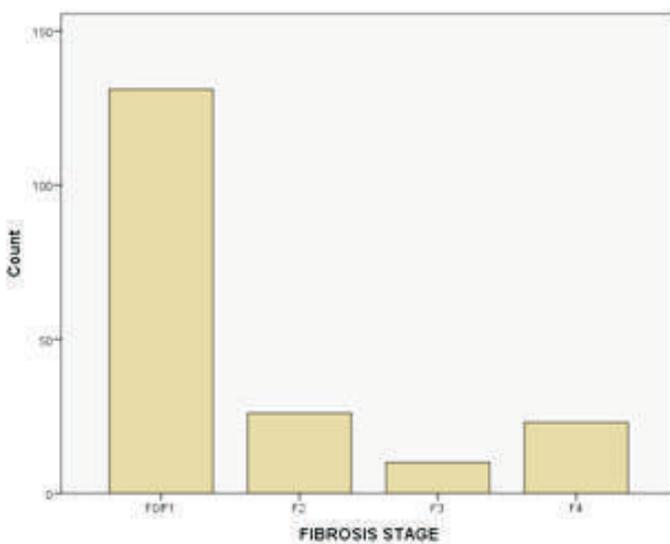
Categorization of subjects into levels of fibrosis stage.

Most of the patients 131(68.9%) had no significant fibrosis (F0/F1), while 26(13.7%), 10(5.3%) and 23(12.1%) had F2, F3 and F4 respectively. 59(31.1%) patients had significant fibrosis while 23(12.1%) had cirrhosis.

Table 2: Correlation of non-invasive serum marker with transient elastography

Variable	Correlation coefficient(Spearman)	P value
APRI	0.58	0.001
FIB-4	0.46	0.001

Both, APRI and FIB-4 were correlated with TE results in the overall cohort (r = 0.58; P < 0.001 and r = 0.42; P < 0.001, respectively). APRI is seen to have more correlation to TE compared to FIB-4 index.

APRI(aspartate transaminase platelet ratio index), FIB-4(fibrosis-4 index)

Table 3: Correlation of age and some blood parameters with results from transient elastography

Variable	Correlation coefficient(spearmans)	P value
AGE	0.03	0.94
SEX	0.12	0.09
TOTAL BILIRUBIN	0.151	0.038
ALT	0.347	0.0001
AST	0.511	0.0001
ALP	-0.09	0.906
INR	0.96	0.187
ALBUMIN	-0.181	0.013
PLATELET COUNT	-0.410	0.0001

In the overall cohort, liver stiffness results were correlated with AST ($r = 0.51$; $P < 0.001$) and ALT ($r = 0.34$; $P < 0.001$) levels. TE results were negatively correlated with albumin levels ($r = -0.18$; $P = 0.013$) and platelet count ($r = -0.41$; $P = 0.001$).). TE did not correlate with age, ALP and INR.

ALT(alanine transaminase), AST(aspartate

transaminase), INR(international normalize ratio),

PT(prothrombin time), ALP(alkaline phoshatase).

DISCUSSION

The use of non invasive methods for evaluating the stage of liver fibrosis in patients with CHB infection is now considered essential in the clinical evaluation and follow up of patients with CHB.

In this study we found that the prevalence of significant fibrosis and cirrhosis to be 31.1% and 12.1% respectively. The prevalence of significant fibrosis in this study is seen to be lower compared to other studies[.]. In contrast to a previous study done in Jos in which about half of the patients had HAI >7, this study has a lower prevalence of significant fibrosis. This difference might be as a result of some of the studies excluding patients without any histological grade of fibrosis (F0). It might also be as a result of the high number of asymptomatic patients (89.9%) in this study because patients with symptoms of chronic liver disease are more likely to have greater degree of fibrosis compared to asymptomatic patients. Our result is consistent with and complements those of previous studies that identified the prevalence of cirrhosis[.]. In a study by Ndububa et al 20.8% of the patients had cirrhosis, and all the cirrhotic patients were all symptomatic, but in this study not all the cirrhotic patients were symptomatic. A prevalence of 4.6% for cirrhosis was obtained in a study by Okeke et a which is much lower compared to the value in this study and this might be as a result of that study including only asymptomatic patients and also it may be due to the small sample size of that study.

In the present study, it has been shown that there is a significant correlation of fibroscan to APRI and FIB-4. The correlation in some studies showed a higher correlation but this study only showed a moderate correlation[.]. This finding may be partly due to the fact that this study included some CHB patients that were already on medication (livolin, silymarin, lamivudine, and tenofovir) that can affect the levels of serum AST and ALT thus affecting APRI FIB-4 values. Another reason could be due to the different population of patients in the studies, in those studies the patients had HCV or HIV/HCV co-infection while this study only included patients with CHB. But the correlation obtained in this study showed a result similar to that obtained by Aurora et al even though the study population was CHC patients. However, the Spearman's correlation coefficients suggest that APRI correlates more to fibroscan compared to FIB-4 (r = 0.57 and 0.47 for APRI and FIB-4 respectively which is the case most other studies[.]. But this is in contrast to a similar study by Ma et al, were FIB-4 was seen to be more significantly correlated with fibrosis stage compared to APRI. The exclusion of patients with no fibrosis(F0) in that study may account for this difference.

The study also demonstrates that fibroscan correlates significantly with some biochemical and haematological markers of chronic liver disease such as ALT,AST, total bilirubin, albumin and platelet count. Some study also showed a similar correlation with blood markers[.]. These correlations may be due to:

- Elevations in AST more than ALT have been associated with more advanced fibrosis and are in part related to delayed clearance of AST relative to ALT or to mitochondrial injury associated with more advanced fibrosis.
- Decrease in platelet count may be due to decrease *platelet mean lifetime, decrease thrombopoietin production and portal hypertention.*
- Serum albumin decreases with the increase of fibrosis and cirrhosis, the decrease in serum albumin correlates with the chronicity of liver disease.

Conclusion

The prevalence of significant fibrosis is high in this population (31%) measured with TE and the prevalence of cirrhosis is 12%. TE can be used as a non invasive alternative to liver biopsy to stage fibrosis in patients with chronic hepatitis B

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