

Chronic Liver Disease among Adult Patients with Sickle Cell Anemia in Steady State in Ile-Ife, Nigeria

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ABSTRACT

AIM: Chronic liver disease encompasses a range of hepatic pathology arising from a wide variety of insults to the liver which can occur in patients with sickle cell anemia. This study is aimed to investigate the state of chronic liver disease among adult patients with sickle cell anemia in steady state attending the hematology clinic of a federal tertiary health institution in Ile-Ife, Nigeria.

METHODS: Basic demographic data, liver ultrasound scan as well as liver function test and Child-Turcotte-Pugh class of 50 consecutive sickle cell anemia (HbSS) patients were compared with

those of 50 age- and sex-matched subjects with HbAA as controls.

RESULTS: Each of the study groups (patients and controls) comprised of 21 (42%) males and 29 (58%) females. The age range of the patients was 18-45 years with a mean (\pm SD) of 27.6 ± 7.607 while that of the controls was 21-43 years with a mean (\pm SD) of 28.0 ± 5.079 ($p = 0.746$). Amongst the patients, 32 (64%) had hepatomegaly while 18 (36%) had normal liver ultrasound findings. In the control group, 1 (2%) had fatty liver but none had hepatomegaly. Forty-nine (98%) of the controls had normal liver ultrasound findings. There was a statistically significant difference in the prevalence of hepatomegaly between the patients and controls with p value < 0.001 . Twenty-four (48%) of the patients were in CTP class A; 7 (29.2%) males and 17 (70.8%) females, while the remaining 26 (52%) patients were in CTP class B; 14 (53.8%) males and 12 (46.2%) females. None of the patients was in CTP class C.

CONCLUSION: In this study, hepatomegaly was a common ultrasound finding in patients with sickle cell anemia. It is essential to assess for evidence of liver disease in patients with sickle cell anemia even when they are not yet symptomatic.

Key words: Chronic liver disease; Child-Turcotte-Pugh; Liver function test; Sickle cell anemia

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Abbreviations

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

CTP: Child-Turcotte-Pugh

HBsAg: Hepatitis B surface antigen

HBV: Hepatitis B virus
 HbSS: Hemoglobin SS
 HbAA: Hemoglobin AA
 HCV: Hepatitis C virus
 OAUTHC: Obafemi Awolowo University Teaching Hospitals Complex
 SCA: Sickle cell anemia
 SD: Standard deviation

INTRODUCTION

Sickle cell anemia is an autosomal recessive genetic disorder caused by a defect in the HBB gene which codes for hemoglobin β chain^[1,2]. This leads to the production of abnormal hemoglobin chains within the red blood cell, which cause rigidity and sickling of the cell, leading to vascular occlusion and ischemia in multiple organs^[3,4]. The normal human hemoglobin molecule is a hetero-tetramer composed of four hemoglobin chains (two α and two β) and the normal adult hemoglobin is Hemoglobin AA^[3]. The abnormal genes occur as a result of glutamic acid-to-valine substitution at the sixth base position in the β hemoglobin gene on chromosome 11^[3]. Sickle cell anemia results from the inheritance of two sickle β hemoglobin genes as HbSS^[4].

Sickle cell anemia (SCA) is particularly common among people whose ancestors come from sub-Saharan Africa, India, Saudi Arabia and Mediterranean countries. Each year about 300,000 infants are born with major hemoglobin disorders – including more than 200,000 cases of sickle-cell anemia in Africa^[5,6]. In Nigeria, by far the most populous country in the sub-region, 24% of the population are carriers of the mutant gene (HbAS) and the prevalence of sickle-cell anemia (HbSS) is about 2%^[5,7-9].

Repeated vascular occlusion, chronic hemolysis with increased excretion of bilirubin and deposition of pigments, long-standing anemia, repeated transfusions leading to iron overload and transfusional hemosiderosis, stagnation of sickled red cells in the hepatic sinusoids with sinusoidal obstruction, vascular occlusion by agglutinative thrombi, and infections, especially chronic viral hepatitis all contribute to the pathogenesis of the multiple hepatobiliary manifestations of sickle cell anemia^[10,11].

Chronic liver disease encompasses a range of hepatic pathology arising from a wide variety of insults to the liver which can occur in patients with sickle cell anemia and there are reports of these patients eventually developing liver cirrhosis in the literature^[12,13].

Evaluation of these patients with sickle cell anemia while they are in steady state affords us the opportunity to know the baseline features of these patients in their best state of health and departures from the normal can be taken as reflecting the onset of development of liver disease. Early identification of evidence of liver disease in these patients will aid prompt intervention, thereby preventing or reducing the complications that otherwise would have resulted. This would reduce the overall morbidity and mortality associated with sickle cell anemia.

Presently, there is paucity of data on this topic in the Nigerian adult population with sickle cell anemia, hence this study. This study provided the much needed information as well as scientific data for holistic evaluation of patients with sickle cell anemia as well as stimulates interest for further research on this topic.

MATERIALS AND METHODS

Study Definitions

Sickle cell anemia: Persons with Hemoglobin genotype SS (HbSS).

Normal individuals: Persons with Hemoglobin genotype AA (HbAA).

Steady state: A patient with sickle cell anemia is said to be in steady state when there is no recent drop in the hemoglobin level and there is absence of infection, pain, acute complicating factors or acute clinical symptoms or crisis for at least three months established by a careful history and complete physical examination^[14].

Sickle cell crisis: Crisis in patients with sickle cell anemia refers to episodes of acute illness attributable to the sickling phenomenon in which there is a sudden exacerbation of symptoms and signs of patients who had hitherto been in stable condition. This could be in the form of pain or vaso-occlusive crisis, aplastic crisis, acute sequestration crisis or hemolytic crisis^[14].

Chronic liver disease: Chronic liver disease is a clinico-pathological syndrome of varied etiology characterized by varying degrees of hepatocellular necro-inflammation, fibrosis and nodular regeneration lasting for more than 6 months with or without malignant transformation^[12,13].

Ethical Approval

Ethical approval was obtained from the Ethics and Research Committee of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

Informed Consent

A written informed consent was obtained from all the study subjects (patients and controls).

Selection of Study Subjects

This was a cross-sectional study that was carried out at the Hematology Clinic of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Osun state in the South Western geopolitical zone of Nigeria between June 2014 and April 2015. The inclusion criteria for this study consisted of patients ≥ 18 years of age with sickle cell anemia [Hemoglobin SS (HbSS) genotype], who must be in steady state and have given written informed consent to be recruited.

The following categories of patients were excluded from the study; patients less than 18 years of age, patients with other hemoglobinopathies such as HbSC, HbCC, HbS B thalassaemia etc., patients in sickle cell crisis and patients who were pregnant. A total of 100 study subjects (patients and controls) were recruited for the study. Selection of patients for the study was by consecutive selection of fifty (50) consenting sickle cell anemia patients. Fifty (50) age- and sex-matched subjects with HbAA who are members of staff, medical students, nursing students and blood donors at the blood bank of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria were recruited as controls.

Evaluation of Study Subjects

A structured questionnaire was designed for the study which was used to collect demographic and relevant clinical information. The patients were interviewed to elicit important relevant history and to ensure that they fulfill the set inclusion criteria for the study. The following information was obtained from the patients' case files (hospital records): frequency of crisis, last episode of crisis, nature of crisis, complications, previous hospitalizations, history of liver disease, hepatitis b vaccination status, total units of blood transfusion ever received, steady state hemoglobin level, co-morbidities, family history of hemoglobinopathies, drug history and history of alcohol consumption.

A physical examination was also conducted on the study subjects (patients and controls) including measurement of anthropometric parameters (height and weight to calculate body mass index) and examination of the abdomen. Blood samples were collected to ascertain the hemoglobin genotype of the study subjects as well as a full blood count, prothrombin time/international normalized ratio and liver function test. The Child-Turcotte-Pugh score and class were then determined.

Hepatic ultrasonographic evaluation was done in the ultrasound room of the Radiology Department of the institution (OAUTHC, Ile-Ife). The liver ultrasound scan was done by the same Consultant Radiologist for all patients and controls in order to avoid inter-observer variations and differences. A high resolution ultrasound machine in B-mode was used with a sensitive probe at a frequency of 3.5-6.5 MHz. A Mindray Real Time Ultrasound machine model DC-7 was used.

The liver area was scanned in multiple planes (sagittal, transverse and oblique) and a detailed examination of the liver was carried out. The liver span was taken as the liver length measured at the level of the mid-clavicular line along the long axis of the right lobe of the liver. In adults, hepatomegaly is defined as the long axis of the liver longer than 155 mm and a shrunken liver has a span less than 105 mm^[15]. The architecture and echogenicity of the liver were determined in comparison to the right kidney. A diffuse increase in liver echogenicity was defined as “bright liver or echogenic liver”. Abnormalities such as hepatomegaly, features of cirrhosis and ascites were looked for.

B-mode parameters such as frequency, focus, gain, and tissue harmonics application were optimized by the radiologist on a case-by-case basis. Image analysis was performed visually and quantitatively. The findings obtained from the patients were compared with those of the control group.

Data Analysis

The data obtained was analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0 computer software package (SPSS Chicago Inc. IL U.S.A). Descriptive statistics used included frequency tables, means, standard deviations and graphs. The statistical significant differences in the findings between the patients and

controls were determined using appropriate statistical tests. Parametric test such as “t” test for analyzing continuous variables and non-parametric test such as chi-square (χ^2) test were employed for the analysis of qualitative variables. Correlation analysis of some variables was also done where applicable using Pearson’s correlation. A *p*-value of less than 0.05 was considered as statistically significant.

RESULTS

The socio-demographic characteristics of the study subjects (patients and controls) were as shown in Table 1. The BMI of the patients ranged from 15.10-26.50 kg/m² with a mean (\pm SD) of 19.36 \pm 2.185 while that of the controls ranged from 18.30-32.88 kg/m² with a mean (\pm SD) of 23.56 \pm 2.936. The mean BMI for the patients and controls were within the normal range. However, the patients had a significantly lower BMI than the control group (*p* < 0.001).

The hepatic ultrasonographic findings of the study subjects (patients and controls) were as shown in Table 2. Eighteen (36%) of the patients and 49 (98%) of the controls had normal liver ultrasound findings. Thirty-two (64%) of the patients had hepatomegaly 11 (22%) males and 21 (42%) females but none of the controls had hepatomegaly. There was a statistically significant difference in the prevalence of hepatomegaly between the patients and controls both with *p* value < 0.001.

The liver span ranged from 12.3-25.57cm and 11.67-15.37cm in the patients and controls respectively (Table 3). The mean (\pm SD) liver span of the patients (16.56 \pm 2.357) was significantly higher than that of the controls (13.87 \pm 0.790) with *p* < 0.001. Figure 1 is a sonogram showing massive hepatomegaly in a sickle cell anemia patient. The lower lobe of the liver extends well below the lower pole of right kidney and the liver measures 22.3 cm in span exceeding the normal limit of 15.5 cm.

Twenty-two (68.75 %) patients with hepatomegaly were within the age range of 18-30 years while 7 (21.87 %) were within the age range of 31-35 years. Only 1 (3.13%) patient with hepatomegaly was above 40years of age. There was no statistically significant difference in the mean (\pm SD) age of the patients with hepatomegaly (28.8 \pm 6.21) when compared with patients without hepatomegaly (25.4 \pm 9.42); *p* = 0.131 (Table 3), and there was also no significant difference in the

Table 1 Socio-Demographic characteristics of the study subjects.

Characteristics	Patients (HbSS)			Controls (HbAA)			P -Value
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)	
Sex	21 (42)	29 (58)	50 (100)	21 (42)	29 (58)	50 (100)	
Age (Years)							
Range	18-43	18-45	18-45	23-43	21-35	21-43	
MEAN \pm SD	26.05 \pm 6.975	28.76 \pm 7.958	27.62 \pm 7.607	30.48 \pm 5.988	26.28 \pm 3.442	28.04 \pm 5.079	0.746
Age Group							
18-25	14 (66.7)	9 (31)	23 (46)	6 (28.6)	18 (62.1)	24 (48)	
26-30	3 (14.3)	10 (34.5)	13 (26)	6 (28.6)	9 (31.0)	15 (30)	
31-35	2 (9.5)	6 (20.7)	8 (16)	5 (23.8)	2 (6.9)	7 (14)	
36-40	1 (4.8)	1 (3.4)	2 (4)	2 (9.5)	0 (0)	2 (4)	
41-45	1 (4.8)	3 (10.3)	4 (8)	2 (9.5)	0 (0)	2 (4)	
Marital Status							
Single	18 (85.7)	22 (75.9)	40 (80)	20 (95.2)	28 (96.6)	48 (96)	
Married	3 (14.3)	7 (24.1)	10 (20)	1 (4.8)	1 (3.4)	2 (4)	
Education							
Secondary	2 (9.5)	3 (10.3)	5 (10)	1 (4.8)	1 (3.4)	2 (4)	
Post Secondary	19 (90.5)	26 (89.7)	45 (90)	20 (95.2)	28 (96.6)	48 (96)	
Social Status							
Civil Servant	1 (4.8)	6 (20.7)	7 (14)	11 (52.4)	14 (48.3)	25 (50)	
Trader	1 (4.8)	5 (17.2)	6 (12)	0 (0)	0 (0)	0 (0)	
Teacher	0 (0)	1 (3.4)	1 (2)	0 (0)	0 (0)	0 (0)	
Student	16 (76.2)	12 (41.4)	28 (56)	10 (47.6)	15 (51.7)	25 (50)	
Unemployed	1 (4.8)	2 (6.9)	3 (6)	0 (0)	0 (0)	0 (0)	
Artisan	2 (9.5)	3 (10.3)	5 (10)	0 (0)	0 (0)	0 (0)	

mean (\pm SD) BMI of the patients with hepatomegaly (19.06 ± 1.963) when compared with those without hepatomegaly (19.89 ± 2.503); $p = 0.200$.

One (2%) female control had ultrasound evidence of fatty liver. None of the patients had fatty liver. There was no statistically significant difference in the prevalence of fatty liver between the patients and controls with p value = 0.315.

None of the study patients or controls had ultrasound evidence of liver cirrhosis and no focal hepatic lesion was seen. Their hepatic echogenicity, echotexture, outline, intrahepatic biliary ducts and vascular channels were all within normal limits.

The hematological and biochemical investigation results of the study subjects (patients and controls) were as shown in Table 4. The range of the steady state hemoglobin concentration (g/dL) of the patients from their hospital records was 6.3-11.3g/dL with a mean (\pm SD) of 8.52 ± 1.114 . The range of the newly analyzed hemoglobin concentration of the patients was 5-12 g/dL with a mean (\pm SD) of

8.52 ± 1.329 while that of the controls was 9-17.9 g/dL with a mean (\pm SD) of 14.37 ± 4.792 . The controls had a statistically higher hemoglobin concentration than the patients with p value < 0.001 .

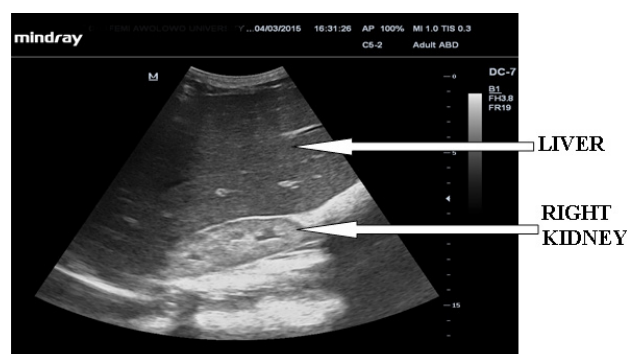


Figure 1 Sonogram showing massive hepatomegaly in a patient with sickle cell anemia.

Table 2 Liver ultrasound findings.

Diagnosis	Patients (HbSS)			Controls (HbAA)		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
Normal	9 (18)	5 (10)	14 (28)	20 (42.6)	27 (57.4)	47 (94)
Hepatomegaly	11 (22)	21 (42)	32 (64)	0 (0)	0 (0)	0 (0)
Cholelithiasis	4 (8)	11 (22)	15 (30)	0 (0)	1 (2)	1 (2)
Choledocholithiasis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Biliary Sludge	1 (2)	2 (4)	3 (6)	1 (2)	0 (0)	1 (2)
Fatty Liver	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)
Liver Cirrhosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 3 Age group and liver span characteristics of the patients with hepatomegaly.

Hepatomegaly	Patients (HbSS)			Controls (HbAA)			P -Value
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)	
Yes	11 (52.4)	21 (72.4)	32 (64)	0 (0)	0 (0)	0 (0)	
No	10 (47.6)	8 (27.6)	18 (36)	21 (100)	29 (100)	50(100)	
Liver Span							
Range	13.57-20.33	12.3-25.57	12.3-25.57	12.02-15.37	11.67-15.15	11.67-15.37	
Mean \pm SD	16.18 \pm 1.923	16.83 \pm 2.627	16.56 \pm 2.357	13.96 \pm 0.852	13.81 \pm 0.751	13.87 \pm 0.790	<0.001
Age group (years)							
	Patients (HbSS) with hepatomegaly			Controls (HbAA) with hepatomegaly			
	Total	Number (%)		Total	Number (%)		
18-25	23	10 (31.25)		24	0 (0)		
26-30	13	12 (37.5)		15	0 (0)		
31-35	8	7 (21.87)		7	0 (0)		
36-40	2	2 (6.25)		2	0 (0)		
41-45	4	1 (3.13)		2	0 (0)		
Total	50	32 (100)		50	0 (0)		

Table 4 Hematological and biochemical investigation results of the study subjects.

Parameters	Patients (HbSS)			Controls (HbAA)		P -value
	Reference values ⁴	Range	Mean \pm SD	Range	Mean \pm SD	
SS Hb. Conc. (g/dL)	5-9	6.3-11.3	8.52 \pm 1.114	NA	NA	
SS PCV (%)	15-27	19-34	25.54 \pm 3.406	NA	NA	
Hb. Conc. (g/dL)	11.5-17.5	5-12	8.52 \pm 1.329	9-17.9	14.37 \pm 1.792	<0.001
PCV (%)	36-52	17-36	25.85 \pm 3.924	28.3-53.5	43.15 \pm 5.159	<0.001
WBC (/mm ³)	3000-9000	3300-17500	10236.00 \pm 3448.277	2700-8200	5356.00 \pm 1153.55	<0.001
PLT ($\times 10^3$ /mm ³)	100-300	71-568	293.920 \pm 139.342	74-398	191.920.0 \pm 74.534	<0.001
B1 (μ mol/L)	<20	8.6-93.0	40.51 \pm 20.871	4-24	9.18 \pm 5.220	<0.001
B2 (μ mol/L)	<5	0.5-44.0	7.81 \pm 8.382	1-6	2.60 \pm 1.399	<0.001
PROTEIN (g/dL)	6-8	5-9	6.54 \pm 0.790	5.3-7.8	6.68 \pm 0.581	0.330
ALBUMIN (g/dL)	3.5-5.0	2.5-4.8	3.48 \pm 0.443	2.8-4.6	3.65 \pm 0.389	0.040
GLOBULIN (g/dL)	2.0-4.5	1.6-4.8	3.04 \pm 0.764	1.8-4.4	2.97 \pm 0.514	0.614
ALT (iu/L)	<12	2-25	5.34 \pm 4.284	1-7	2.30 \pm 1.216	<0.001
AST (iu/L)	<12	4.1-88	13.72 \pm 12.747	2-26	6.62 \pm 4.135	<0.001
ALP (iu/L)	60-170	53-317	125.06 \pm 46.367	6.8-216	105.86 \pm 34.309	0.021
PT (seconds)	12-15	13-22	17.76 \pm 2.446	14-16	15.00 \pm 1.010	<0.001
INR	0.9-1.2	0.88-1.71	1.27 \pm 0.247			

SS Hb. Conc.: Steady State Hemoglobin Concentration; SS PCV: Steady State Packed Cell Volume; WBC: White Cell Count; PLT: Platelet Count; B1: Total Bilirubin; B2: Conjugated Bilirubin; ALT: Alanine Transaminase; AST: Aspartate Transaminase; ALP: Alkaline Phosphatase; PT: Prothrombin Time; INR: International Normalized Ratio; NA: Not Applicable.

The means of the total white blood count (WBC), platelet count, total bilirubin and conjugated bilirubin of the patients were statistically significantly higher than those of the controls ($p < 0.001$). The mean ALT, AST and ALP levels of the patients were significantly higher than those of the controls with p values < 0.001 , < 0.001 and 0.021 respectively.

Serum albumin ranged from 2.5-4.8 in the patients with a mean (\pm SD) of 3.48 ± 0.443 and from 2.8-4.6 in the controls with a mean (\pm SD) of 3.65 ± 0.389 . The controls had statistically higher serum albumin levels than the patients with p value = 0.040. The prothrombin time of the patients ranged from 13-22 seconds with a mean (\pm SD) of 17.76 ± 2.446 while that of the controls was 14-16 seconds with a mean (\pm SD) of 15.00 ± 1.010 . The patients had a significantly longer prothrombin time than the patients with p value < 0.001 .

Table 5 shows the relationship between hepatomegaly and hematological/biochemical test results. There was no statistically significant difference in the mean hemoglobin concentration, serum albumin, ALT and AST of the patients with hepatomegaly when compared with those without hepatomegaly; $p = 0.174$, 0.502 , 0.191 and 0.508 respectively.

The mean (\pm SD) age at first diagnosis of SCA in the patients was 6.46 ± 4.827 with a range of 3 months – 19 years. All of them had had one form of sickle cell crisis or the other in the past. All the patients had had vaso-occlusive crisis (VOC) in the past. Only 25 (50 %) of the patients had had hemolytic crisis in the past. Only 1 patient (2%) had hepatic sequestration crises in the past and only 2 (4%) had ever had a splenic sequestration crisis in the past. None had aplastic crisis.

Table 6 shows the relationship between hepatomegaly and vaso-occlusive crisis and hemolytic crisis. Fourteen (43.8%) of the patients with hepatomegaly had 1 episode of VOC per year whereas 6 (33.3%) of the patients without hepatomegaly had 3 episodes of VOC per year. There was no statistically significant relationship between the frequency of VOC and hepatomegaly; $p = 0.501$. Only 25 (50%) patients had a past history of hemolytic crisis. Among the remaining 25 (50%) patients without history of hemolytic crisis, 13 (52%) had hepatomegaly while 12 (48%) did not have. There was no statistically significant relationship between a past history of hemolytic crisis and hepatomegaly; $p = 0.077$. Sixteen (50%) of the patients with hepatomegaly had 1 episode of hemolytic crises per year while 4 (22.2%) of the patients who did not have hepatomegaly also had 1 episode of hemolytic crisis per year. All the 3 patients who had 2 episodes of hemolytic crisis per year had hepatomegaly. A statistically significant relationship exists between the frequency of hemolytic crisis and hepatomegaly; $p = 0.029$.

The CTP score of the patients ranged from 5-8 with a mean (\pm SD) of 6.48 ± 0.953 . Twenty-four (48%) of the patients had a CTP score of between 5 and 6 while 26 (52%) of the patients had a score of between 7 and 8. Twenty-four (48 %) of the patients were in CTP class A; 7 (29.2%) males and 17 (70.8%) females, while the remaining 26

(52%) patients were in CTP class B; 14 (53.8%) males and 12 (46.2%) females. None of the patients was in CTP class C. In this study, 15 (46.9%) of the patients who had hepatomegaly were in CTP class A while the remaining 17 (53.1%) patients with hepatomegaly were in CTP class B. There was no statistically significant relationship between hepatomegaly and CTP class ($p = 0.832$). None of the controls had hepatomegaly.

Table 7 shows the results of the serological screening obtained during this study. Four (8%) of the patients (1 male and 3 females) were positive for HBsAg whereas 3 (6%) of the controls (all males) were positive for HBsAg. One (2%) 26 year old female patient was positive for anti-HCV whereas none of the controls was positive for anti-HCV. None of the study subjects (patients and controls) was positive for HIV 1 and 2.

There was no statistical significant difference in the mean (\pm SD) serum ALT between the patients with positive HBsAg (4.75 ± 2.062)

Table 5 Hematological and biochemical investigation results of the patients.

Parameters	Patients (HbSS) with hepatomegaly N = 32		Patients (HbSS) without hepatomegaly N = 18	P-Value
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
Hb Conc. (g/dL)	8.32 \pm 1.150	8.86 \pm 1.582	8.86 \pm 1.582	0.167
B1 (μ mol/L)	59.80 \pm 114.744	49.68 \pm 33.603	49.68 \pm 33.603	0.718
B2 (μ mol/L)	26.43 \pm 100.269	9.05 \pm 9.975	9.05 \pm 9.975	0.469
PROTEIN (g/dL)	6.48 \pm 0.849	6.61 \pm 0.701	6.61 \pm 0.701	0.593
ALBUMIN (g/dL)	3.43 \pm 0.479	3.54 \pm 0.393	3.54 \pm 0.393	0.435
GLOBULIN (g/dL)	3.05 \pm 0.837	3.02 \pm 0.637	3.02 \pm 0.637	0.903
ALT (iu/L)	5.91 \pm 4.934	4.28 \pm 2.081	4.28 \pm 2.081	0.190
AST (iu/L)	14.59 \pm 14.626	12.11 \pm 8.079	12.11 \pm 8.079	0.510
ALP (iu/L)	116.56 \pm 34.149	140.11 \pm 60.769	140.11 \pm 60.769	0.085

Hb. Conc.: Haemoglobin Concentration; B1: Total Bilirubin; B2: Conjugated Bilirubin; ALT: Alanine Transaminase; AST: Aspartate Transaminase; ALP: Alkaline Phosphatase.

Table 6 Relationship between hepatomegaly and frequency of crisis using CHI-SQUARE (χ^2) TEST.

Vaso-Occlusive Crisis: $P = 0.501$			
Frequency of crisis	No. of patients	Hepatomegaly Number (%)	No hepatomegaly Number (%)
1 in 5 years	1	0 (0)	1 (5.5)
1 per year	19	14 (43.8)	5 (27.8)
2 per year	15	10 (31.2)	5 (27.8)
3 per year	13	7 (21.9)	6 (33.3)
4 per year	2	1 (3.1)	1 (5.5)
TOTAL	50	32 (100)	18 (100)
Hemolytic Crisis: $P = 0.029$			
Frequency of crisis	No. of patients	Hepatomegaly Number (%)	No hepatomegaly Number (%)
None	25	13 (40.6)	12 (66.7)
Once Only	2	0 (0)	2 (11.1)
1 per year	20	16 (50)	4 (22.2)
2 per year	3	3 (9.4)	0 (0)
TOTAL	50	32 (100)	18 (100)

Table 7 HBV, HCV and HIV serology results.

Parameters	Patients (HbSS)			Controls (HbAA)		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
HBsAg						
Reactive	1 (4.8)	3 (10.3)	4 (8)	3 (14.3)	0 (0)	3 (6)
Non-reactive	20 (95.2)	26 (89.7)	46 (92)	18 (85.7)	29 (100)	47 (94)
Anti-HCV						
Reactive	0 (0)	1 (3.4)	1 (2)	0 (0)	0 (0)	0 (0)
Non-reactive	21 (100)	28 (96.6)	49 (98)	21 (100)	29 (100)	50 (100)
HIV						
Reactive	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non-reactive	21 (100)	29 (100)	50 (100)	21 (100)	29 (100)	50 (100)

and controls with positive HBsAg (4.33 ± 2.309); $p = 0.811$, and there was also no significant difference in the mean (\pm SD) serum albumin between the patients with positive HBsAg (3.80 ± 0.762) and controls with positive HBsAg (3.53 ± 0.473); $p = 0.620$. The only patient who had a positive anti-HCV had a normal serum ALT of 4 iu/L and albumin of 4.4g/dL.

There was no statistically significant difference in the mean (\pm SD) liver span of the patients with positive HBsAg (17.16 ± 1.766) when compared with controls with positive HBsAg (14.86 ± 0.669); $p = 0.089$. Three out of the four patients with positive HBsAg were in CTP class A while the fourth patient was in CTP class B. The only patient with a positive anti-HCV had a liver span of 16.5 cm and was in CTP class A.

DISCUSSION

Chronic liver disease in patients with sickle cell anemia can be due to repeated small, clinically silent microvascular occlusions due to the sickling of red blood cells occurring throughout the life of a patient with sickle cell anemia, eventually leading to liver fibrosis and then liver cirrhosis^[13]. There is a high rate of liver cirrhosis of 18% among young patients with sickle cell disease and causing death in 11% of cases. Autopsy series indicate a 16% to 29% prevalence of cirrhosis in patients with sickle cell anemia^[16,17].

Liver cirrhosis in sickle cell disease can also be due to chronic viral hepatitis, right heart failure, iron overload from transfusional hemosiderosis, gallstones, chronic alcohol intake or chronic use of hepatotoxic agents^[18].

Abnormal liver function tests are common in patients with sickle cell anemia, even in the absence of liver disease^[19,20]. Raised bilirubin levels, predominantly unconjugated, are universal in sickle cell patients due to chronic hemolysis. Hemolysis also raises plasma aspartate transaminase (AST) levels thus elevated plasma alanine transaminase (ALT) levels reflects hepatocyte injury more accurately in patients with sickle cell anemia^[19]. Elevations in the serum alkaline phosphatase are commonly seen in patients with sickle cell anemia, particularly during pain crises. However, studies suggest that bone alkaline phosphatase is the major enzyme fraction contributing to this increase^[13].

The SCA patients in this study, all of whom were in steady states, had significantly higher total WBC, platelet count, total bilirubin, prothrombin time, ALT, AST and ALP but lower hemoglobin concentration and albumin than the controls. These findings are consistent with the results from previous studies on SCA patients reflecting the chronic hemolytic state in these patients even though they were not in crisis^[19,20]. Also the increased prothrombin time and lower serum albumin levels seen in these patients reflects deterioration in their hepatic synthetic function. The increased ALT levels reflect on-going hepatocyte hypoxic injury due to sickling^[21].

The liver ultrasound findings from this study were similar to what had been previously reported in the literature in which hepatomegaly was also a common finding among patients with sickle cell anemia^[22,23]. Hepatomegaly is largely due to extramedullary hematopoiesis in response to the chronic anemia in this condition^[3,4]. Hepatomegaly can also be due to transfusional hemosiderosis and chronic viral hepatitis^[12,24]. However, in this environment which is a malaria endemic area, frequent episodes of malaria is also a major cause of the hepatomegaly seen in these patients^[24]. In this study, the most common indication for hospital admission in the SCA patients apart from sickle cell crisis was malaria; this could have contributed to the development of the hepatomegaly seen in these patients.

Olaniyi *et al*^[24] found a prevalence of hepatomegaly of 62.2% among SCA patients in Ibadan, Nigeria. Balci *et al*^[23] found a prevalence of 72.6% among SCA patients in Turkey and Papadaki *et al*^[22] found a prevalence of 70.5% among sickle cell disease patients in Greece.

Sixty-four percent of the patients in this study had hepatomegaly following ultrasonographic evaluation. Persistent hepatomegaly is one of the established markers of disease severity in SCA patients^[25,26]. Olatunji *et al*^[27] in Ilorin, Nigeria also established that persistent hepatomegaly is an index of disease severity in patients with sickle cell anemia. Persistent hepatomegaly in patients with SCA implies that such patients have the tendency to run a more severe clinical course than those without and there is a need to pay more attention to them.

The CTP scoring system is a well validated tool for assessing the severity of liver disease and this was employed in this study^[28]. A total score of 5-6 is considered Class A (well-compensated disease), 7-9 is Class B (significant functional compromise) and 10-15 is Class C (decompensated disease). It however has its limitations. In the setting of hemolytic states, such as in SCA patients, serum bilirubin will be raised and this will give a falsely higher CTP score. In this study, 24 (48%) of the patients were in CTP class A while 26 (52%) were in class B. None of the patients was in CTP class C. None of the patients showed symptomatology suggestive of liver disease.

The hepatic disease in patients with sickle cell anemia is primarily caused by the sickling process and the rate of progression of liver disease is enhanced by the presence of increasing numbers of sickle cell severity markers (indices) present in an individual patient^[25,26,29]. The rate of progression of liver disease can also be enhanced by the presence of other risk factors for liver disease such as chronic viral hepatitis, alcohol consumption and use of hepatotoxic drugs or other toxic substances such as herbs.

From this study, it can therefore be said that many of the sickle cell anemia patients had evidence of liver disease but they were well compensated. This could be due to the large functional reserve capacity of the liver and its regenerative capabilities^[30]. Also, majority of the patients in this study don't have the other risk factors for liver disease mentioned above that could enhance the progression of the liver disease in them.

In this study, the prevalence of hepatitis B surface antigenemia in the SCA patients was 8% while that of anti-HCV was 2%; these prevalence rates are low compared to results of similar studies in Nigeria and other parts of the world^[31,32].

Angyo *et al*^[31] found a prevalence of hepatitis B surface antigenemia of 22.7% among children with SCA in Jos, Nigeria while Fasola *et al*^[32] found a prevalence of hepatitis B surface antigenemia of 23.8% and anti-HCV of 19.8% among adult SCA patients in Ibadan, Nigeria. Ejiofor *et al*^[33] found a prevalence of 6% of anti-HCV among children with SCA in Benin City while Lesi *et al*^[34] found a prevalence of 5% of anti-HCV among adult SCA patients in Lagos.

Majority of the patients in this study had not been previously screened for Hepatitis B virus and Hepatitis C virus infection; 38 (76%) and 39 (78%) respectively. None of the patients has had the Hepatitis B vaccine. It was also observed while interviewing these patients that the level of awareness about the hepatitis viruses was quite low when compared with their knowledge about the human immunodeficiency virus infection. Thirty percent of the patients had been previously screened for HIV.

Furthermore, in this study there was no significant relationship between HBsAg positivity and a previous history of blood transfusion

($p = 0.118$) or the number of units of blood received ($p = 0.401$). This suggests that the patients with positive HBsAg might have contracted the HBV through other means of its transmission. The patients with positive HBsAg would however require HBV DNA viral load assays among other tests in order to categorize them properly and to determine their eligibility for treatment. The only patient in this study who tested positive for anti-HCV would also require HCV RNA viral load and HCV genotype tests for further evaluation.

Limitations of the study

The findings from this study should be considered in line with some limitations which include absence of long term patient follow-up in order to re-assess for disease progression. Also, these patients could have been evaluated with a more definitive investigative modality such as a liver biopsy, although invasive, as against the CTP scoring classification that was employed in this study which has its shortcomings.

CONCLUSION

Evaluation for chronic liver disease should be carried out routinely in all patients with sickle cell anemia, for which they may not yet be symptomatic. Early identification of liver disease in these patients will aid prompt intervention, thereby preventing or reducing the complications that otherwise would have resulted. This would reduce the overall morbidity and mortality associated with sickle cell anemia.

Majority of the patients in this study had not been previously screened for Hepatitis B virus and Hepatitis C virus infection. All patients with sickle cell anemia should be routinely screened for Hepatitis B and C viruses and those who test negative for HBsAg should get vaccinated against the Hepatitis B virus while those who test positive for HBsAg and/or anti-HCV should be referred to a Gastroenterologist/Hepatologist for further evaluation.

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CONFLICT OF INTEREST

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