

Ultrasonographic Assessment of the Splenic Size in Sickle Cell Anemia: *Single Splenic Span Measurement Vs Splenic Volume*

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Abstract:

Introduction: The spleen remains one of the most commonly affected organs in sickle cell anemia. The use of the palpation method to determine the splenic size can be unreliable and sometimes misleading. Ultrasonography is arguably one of the most reliable methods of splenic size evaluation. Most clinicians prefer the single splenic span (length) measurement because it is fast and is believed to be accurate. Splenic volume measurement is another method of evaluating the splenic size, though it may be more time consuming when compared to the single splenic span measurement.

Aims and Objectives: The aim of this study was to prospectively evaluate the splenic size in subjects with sickle cell anemia and normal subjects using the splenic volume measurement and the single splenic span (length) measurement to find out which method is more accurate

Materials and Methods: One hundred consenting patients with Hb SS and 100 consenting matching group with Hb AA were recruited in this case-control study. The age group was between 0 to 30 years. Study subjects were scanned using the trans-abdominal route with a 3.5MHz curvilinear transducer of a Sonoscape S40 Digital Colour Doppler Ultrasound System (Sonoscape Medical Corp. December 2018). The study duration was 7months. The splenic length, transverse, anteroposterior diameter and volume were measured.

Data Analysis: Data analysis was carried out using statistical package for social sciences version 22.0 (SPSS Inc Chicago, IL, USA).

Results: Thirty percent, 39% and 31% of patients with Hb SS have splenic lengths of <6cm, 7-12cm and >12cm respectively. The mean splenic volume (p-value = 0.001) and splenic AP diameter (p-value = 0.048) in subjects with Hb SS found were significantly higher in this study than those with Hb AA. There was no statistically significant difference between the splenic Length(p value = 0.659) and Transverse measurement (p value = 0.433) in both groups.

Conclusion: In Ebonyi State of Nigeria, the prevalence of autosplenectomy and splenomegaly among sickle cell anemia subjects are 30% and 31% respectively. Measurement of the splenic volume is more accurate than a single splenic length measurement in assessing the splenic size.

Keywords: Sickle Cell Anemia, Splenic size, Ultrasonography, Splenic volume, Splenic span.

I. INTRODUCTION

Peculiar, elongated and sickle-shaped” is how sickle cells were first described by an intern Ernest Edward Irons in 1904 when examining the blood of a 20-year-old first-year dental student Walter Clement Noel, who is from a wealthy Black family in Grenada. Walter had been admitted to the Chicago Presbyterian Hospital suffering from anemia and was re-admitted several times before completing his studies over the next three years and returning to Grenada to successfully practice dentistry[1]. Iron’s supervising physician, James B. Herrick, wrote a paper published in 1910 in the Archives of Internal Medicine documenting the first known case of sickle cell disease in the United States [1].

However Dr. Horton, a Sierra Leonian medical doctor, reportedly gave the first description of clinical symptoms and signs which is now referred to as sickle cell anemia in 1874[2].

The term sickle cell anemia refers to a condition in which an individual has inherited two abnormal hemoglobin genes, at least one of which is hemoglobin S and the resulting symptomatology or pathology is attributable to the sickling phenomenon[3]. It is among the most common of the inherited hemoglobinopathies.

In sickle cell anemia (SCA), Hb S is commonly as high as 90% of the total hemoglobin [4]. In other sickle cell disease haplotypes like Hb C, Hb β -thalassemia, Hb D, and Hb O Arab, etc; the Hb S is usually about 50% of the total hemoglobin. The level of HbS has a direct relationship with the severity of the symptoms.

Nwogoh et al[5] in a recent retrospective study done in Benin City, South-South Nigeria revealed an SCA prevalence rate of 2.39% and a carrier rate of about 23%. The findings of Nwogoh et al may be a classic case of the tip of the iceberg phenomenon since it is a hospital-based study. In Africa, the frequency of sickle cell trait has been estimated to be as high as 25-40%. In Nigeria, the figure is about 25%, while the homozygous SS state is found in about 3% of the population[6]. In the United States, sickle cell disease is the most common genetic disease occurring in 1/2,647 births. Sickle cell disease in the U.S. occurs among African-Americans at a rate of 1/396 births; among Hispanics at a rate

of 1/36,000 births; among those of Middle Eastern descent no cases were identified among 22,000 screened; and among Asian Indians at a rate of 1/16,000 screened[7].

A recent study suggests that about 77% of patients with sickle cell anemia present with splenic manifestations by the age of 2 years[8]. Some of these manifestations may be life-threatening. The medical effects and socioeconomic burden of splenic manifestations in SCA are enormous[9]. The effects include splenomegaly and autosplenectomy later in life[10]. These have been attributed to decreased fetal hemoglobin (Hb F), high levels of irreversible sickle cells (ISC), chronic malaria infection and an increased antibody production (IgG and IgM)[10]. The clinical effects of these splenic changes include acute splenic sequestration, hypersplenism and increased susceptibility to infection[11].

The microcirculation of the spleen is tortuous and slow. This makes the spleen susceptible to sludging, congestion, and polymerization[12]. Over 77% of patients with sickle cell anemia manifest with various degrees of splenic abnormalities before the age of 2years[8]. These abnormalities can be functional or structural. It can range from simple non-functional splenomegaly to splenic infarction and occasionally frank splenic abscess.

The need for a cheap, non-ionizing, non-invasive and readily available method of monitoring the spleen in sickle cell disease cannot be overemphasized. Clinicians use the palpation method which can be unreliable. Ultrasonography is one of the most accurate methods of evaluating the splenic size in patients with sickle cell anemia.

A good number of publications exist on the assessment of splenic size in sickle cell anemia but to the best of my knowledge, there is little or no data on different methods of splenic size estimation. This study aimed at determining the splenic size using the single splenic span measurement and using the splenic volume measurement, comparing the two methods to find out which method is more statistically accurate.

II. METHODS

This was a case-control study of 100 patients with homozygous hemoglobin SS matched with 100 subjects with normal hemoglobin aged 0 to 30 years conducted in the Ultrasound subunit of Radiology Department of Alex Ekwueme Federal Teaching Hospital Abakaliki (AE-FUTHA) in Ebonyi State, South East of Nigeria. The sample selection was by simple random sampling.

All the measurements were done by the researcher alone to eliminate inter-observer bias. The sonograms were obtained with a 3.5MHz curvilinear transducer of a Sonoscape S40 Digital Colour Doppler Ultrasound System (Sonoscape Medical Corp. December 2018). The subjects' privacy

ensured. On the examination couch, the subjects were positioned in the supine position or the right lateral decubitus position with the left arm raised,

The abdomen was subsequently exposed inferiorly from the pubic symphysis to the xiphisternum superiorly before the application of the coupling gel. The spleen was evaluated in longitudinal and transverse planes using the left intercostal coronal approach via the 9-10th intercostal space. A deep breath-holding technique was also used to get accurate results. The splenic length (L), transverse measurement (T) and anteroposterior measurement (AP) were measured three times and the final average was taken. The splenic volume was copied from the ultrasound machine and not manually calculated.

The data from these measurements were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, Version 22.0. P-values less than or equal to 0.05 were considered to be statistically significant.

III. RESULTS

Table I: Demographic data of the study population

AGE(years)	SEX	Genotype		Total
		AA	SS	
0-4	F	3	3	6
	M	4	4	8
0-4 Total		7	7	14
5-9	F	7	7	14
	M	7	7	14
5-9 Total		14	14	28
10-14	F	6	6	12
	M	8	8	16
10-14 Total		14	14	28
15-19	F	9	13	22
	M	11	9	20
15-19 Total		20	22	42
20-24	F	13	12	25
	M	11	12	23
20-24 Total		24	24	48
25-30	F	12	9	21
	M	9	10	19
25-30 Total		21	19	40
Grand Total		100	100	200

The peak age group from the above table is 20-24years in both the study group and the control group.

Table II: Showing age and splenic measurements

AA						SS					
Age (Yrs)	N	Length (cm) mean ±SD	AP (cm) mean ±SD	Transverse (cm) mean ±SD	Volume (cm ³) mean ±SD	N	Length (cm) mean ±SD	AP (cm) mean ±SD	Transverse (cm) mean ±SD	Volume (cm ³) mean ±SD	
0-4	8	7.47± 0.39	3.01±0.01	5.95±0.27	69.66±6.66	6	9.90±2.75	4.48±2.35	7.64±2.24	231.98±272.46	
5-9	14	8.51± 0.66	3.51±0.25	6.69±0.37	105.10±19.58	14	12.30±2.90	6.96±2.94	9.37±2.11	501.10±361.51	
10-14	16	9.86± 0.35	4.01±0.22	7.26±0.18	149.30±12.75	12	3.86±0.35	2.01±0.22	3.26±0.18	13.21±2.36	
15-19	19	10.62± 0.56	4.35±0.42	7.56±0.40	183.34±34.23	26	10.21±4.78	4.67±2.58	6.85±2.79	265.83±272.47	
20-24	27	12.08± 0.49	4.93±0.10	8.00±0.00	248.06±11.99	24	12.14±3.77	5.37±2.32	8.20±2.89	369.30±328.89	
25-29	16	11.75± 0.43	4.83±0.29	8.00±0	236.6±22.52	18	11.54±3.76	4.91±2.21	7.53±2.68	299.22±290.24	

Results from table 2 shows that 27% of those with AA Hb genotype had mean splenic L X AP X T of 12.08 X 4.93 X 8.00cm with a volume of 248.06cm³ while 26% of those with

Hb SS genotype had mean splenic L X AP X T of 10.21 X 4.67 X 6.85cm with a volume of 265.83cm³

Table III: Comparison of the splenic size in SCA patients and those with AA hemoglobin genotype

Splenic size	AA Mean±SD	SCA Mean±SD	Mean diff	t-test	df	P-value
			Spleen L(cm)	10.03±1.38	9.84±4.24	0.197
Spleen AP(cm)	4.12±0.58	4.63±2.52	-0.515	-1.991	198	0.048*
Spleen T(cm)	7.62±0.60	7.00±2.91	0.234	0.786	198	0.433
SpleenVol(cm ³)	161.27±53.98	267.26±298.54	-105.99	-3.494	198	0.001*

* P<0.05 there is a statistically significant difference

Statistically significant difference is noted in the Spleen AP (p-value =0.048) and volume (p-value =0.001). However, there is no statistically significant difference between the

Spleen length (P-value = 0.659) and Spleen Transverse diameter (P-value = 0.433) of the Hb AA and Hb SS patients respectively.

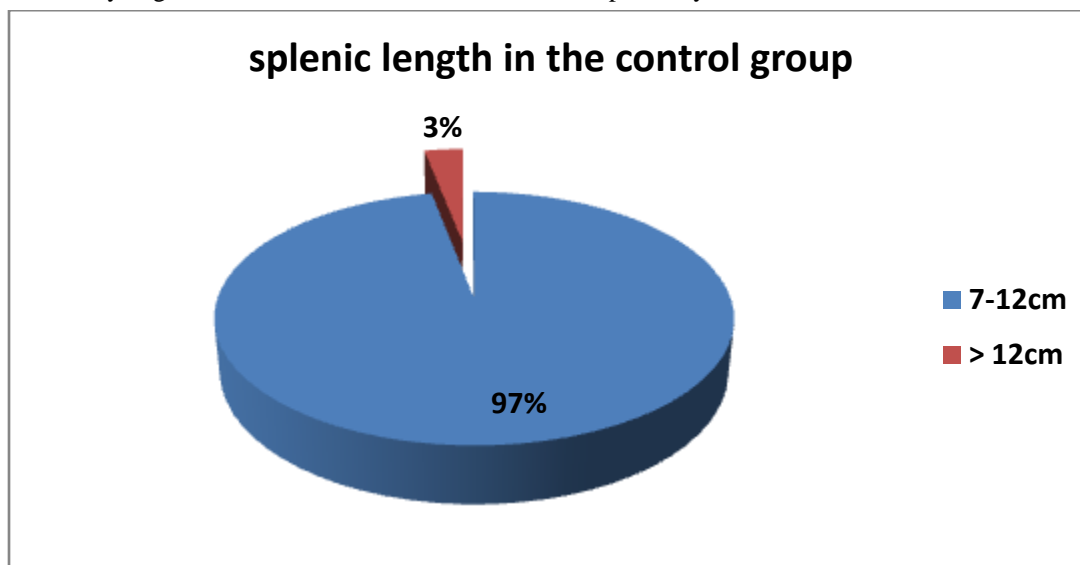


Fig 1: A pie chart showing the splenic length in subjects with Hb AA genotype

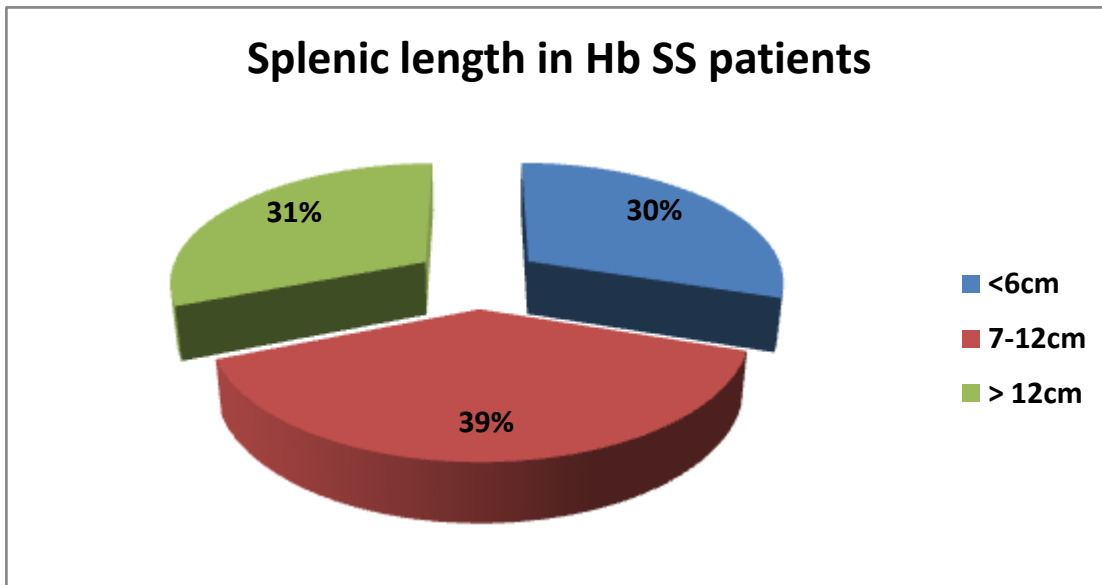


Fig 2: A pie chart showing splenic lengths in subjects with Hb AA genotype

In the control group, 97% and 3% of them have splenic lengths of 7-12cm and >12cm respectively. In those with Hb

SS genotype, 30%, 39% and 31% had splenic lengths of <6cm, 7-12cm and >12cm respectively.

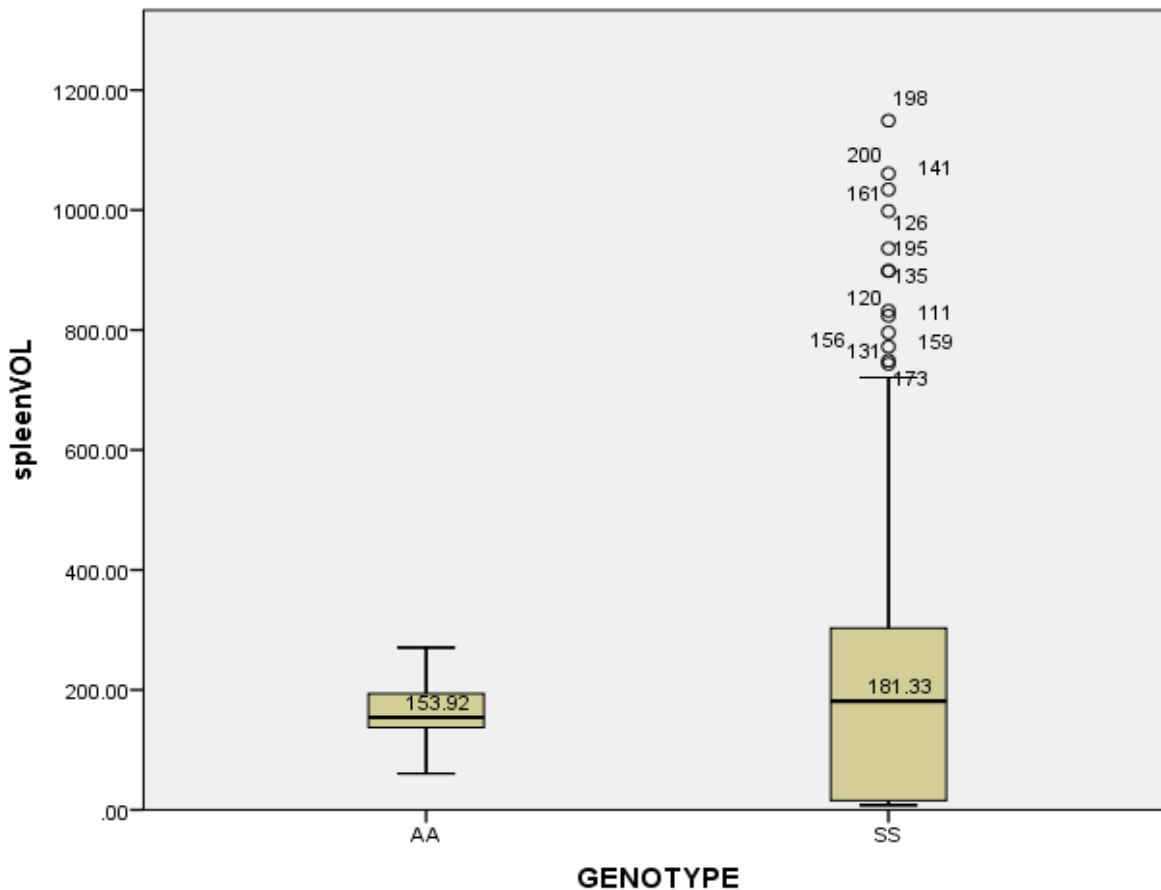


Fig 3: Box chart comparing the splenic volumes in AA and SS subjects

The box plot above shows that the median splenic volume in the subjects with Hb AA genotype is 153.92mls while that of the Hb SS patients is 181.33mls. This implies that the median splenic volume in those with SCA is higher than in those with Hb AA genotype.

IV. DISCUSSION

The mean splenic length (L), anteroposterior diameter (AP), transverse diameter (TS) and volume (Vol) from the study are 10.53 ± 1.60 cm, 4.30 ± 0.67 cm, 7.42 ± 0.67 cm, 182.72 ± 63.66 cm³ respectively for the males and 9.54 ± 0.89 cm, 3.94 ± 0.40 cm, 7.04 ± 0.47 cm, 139.82 ± 29.93 cm³ respectively for the females with normal Hb genotype. This slightly differs from the study by Ogbeide and Marchie in 2005 in Benin[13] Edo state of Nigeria. Their study recorded the following mean dimensions of splenic sizes, for the males: the mean splenic length, width, depth, and volume were 11.1 ± 0.9 cm, 4.4 cm ± 0.5 cm, 7.8 cm ± 0.6 cm, and 202.7 ± 49.4 cm³ respectively, and for the females the corresponding values of splenic length, width, depth, and volume were 10.1 ± 0.7 cm, 4.0 ± 0.4 cm, 7.1 ± 0.5 cm and 153.7 ± 33.2 cm³, respectively. The disparity between their result and this study may be due to the fact that the age range of their study population was 20-60years against 3-30years in this study. However, the findings of this work are similar to other studies done in Hong Kong and Brazil[14].

The mean splenic length (L), anteroposterior diameter (AP), transverse diameter (TS) and volume (Vol) from the study are 10.19 ± 4.42 cm, 4.76 ± 2.57 cm, 7.15 ± 2.97 cm, 287.15 ± 305.34 cm³ respectively for the males and 9.48 ± 4.07 cm, 4.50 ± 2.49 cm, 6.86 ± 2.87 cm, 247.37 ± 293.31 cm³ respectively for the females with Hb SS genotype.

Statistically, this work showed no significant difference in the mean splenic volume between the male and female Hb SS. This disagrees with the findings of Ogbeide and Marchie[13] who documented larger splenic volumes in males than in females with a p-value of < 0.01 . However, their study was done among normal subjects while the index study was done amongst patients with Hb SS who had autosplenectomy, normal splenic size, and splenomegaly.

The mean splenic volume and splenic AP diameter in subjects with Hb SS found in this study were larger than those with normal hemoglobin. The difference was statistically significant with p values of 0.048 and 0.001 for the AP diameter and volume respectively. Adeodu and Adekile[15] also found larger spleens in their study which they attributed to the malaria holo-endemicity. Rogers et al[8] **Error! Bookmark not defined.** found splenomegaly in up to 77% of patients with SCA by 24months of age in a community-based study.

Adekile et al[16] found splenomegaly in 33.8% of SCA patients aged between 10-16years in Nigeria, while Esan[17] reported 15% in adult Nigerians. Similar studies by Konotey-Ahulu[18] found 15% in Ghana while Serjeant[19]

reported 9% in Jamaica amongst SCA patients above 10years of age. The authors attributed these findings to low levels of irreversibly sickled cells (ISC), the persistence of a high level of fetal hemoglobin and an increased level of IgM and IgG due to chronic malaria infection. Adeodu and Adekile [15] found that persistent splenomegaly in sickle cell anemia is similar to tropical splenomegaly syndrome which is directly related to the malaria crude parasite rate.

On the other hand, the findings by Chauhan et al[20] suggested instead that spleen size was significantly decreased in people who had been affected by Plasmodium falciparum malaria. An ultrasound evaluation of spleens was done in 90 hale and hearty adult males, who had suffered from falciparum (n = 25) or vivax (n = 28) malaria in the past, as well as the controls (n = 22) and natives from an endemic falciparum area (n = 15) who never suffered from malaria. Chauhan et al found that the spleen size was significantly decreased (p < 0.01) in the group who had been affected by P. falciparum malaria; the smallest measured 7.8 cms. In P. vivax group the decrease was not significant (p < 0.1), but was highly significant in inhabitants of the endemic falciparum region (p < 0.001). Their findings might possibly have been affected by the small sample size per study group, subjects did not have Hb SS and the fact that only adult males were selected for the study. Females and children were excluded.

Lonergan[21] et al noted asplenia in 14% of patients with SCA at 6months of age; 58% at 2years while 94% of patients with SCA were asplenic by 5years of age. However, their study was not done in a malaria-endemic region.

Ogbeide and Marchie[13] found no effect of malaria parasite crude rate and other endemic infections and infestations on the spleen in their study. This may be due to the fact that their study was in normal subjects and there was no control group from a malaria-free population.

David-West[22] in a post mortem study of 5407 autopsies performed during an 8-year period (2444 were infants and children, while 2963 were adults) found that the mean adult spleen weight of specimens from the holoendemic belt of malaria was heavier than that of subjects in temperate climates.

There is no statistically significant difference between the LS and TS of the spleen in both those with Hb AA and Hb SS with p values of 0.659 and 0.433 for the LS and TS respectively in this study. This corroborates the study done by Ojo et al[23] which reported that there is no statistically significant difference (p-value = 0.332) in the median spleen size of HbS and HbA individuals. However, they studied only 40 sickle cell anemia patients in the steady-state attending Haematology clinic and 40 age and sex-matched healthy HbA control.

This is in contrast with many authors, who are of the opinion that a simple single measurement of spleen length is

an accurate estimate of spleen size as it correlates strongly with the actual spleen dimensions (spleen length, volume, and weight) at autopsy. Udoaka et al[24] in a study done in 2009 amongst the Ijaws in Niger Delta, southern Nigeria found that the spleen is best measured in its longitudinal axis and the Cranio-Caudal Length (CCL) measured from the superior to the inferior poles of the spleen. Nita et al[25] in a study done in Mumbai India in 2013 using 160 children with clinical splenomegaly found that a simple single measurement of the spleen showed splenomegaly for 100% of the children. A similar study done in 2008 by Ali et al[26] at the Center of Hemoglobinopathy of the Antakya State Hospital in Turkey found that the craniocaudal measurement of the spleen correlates with the clinical splenic size in patients with sickle cell disease. In a multicenter study done in 2004 amongst college athletes in Vancouver Canada, Durham England and Madison United States of America, Audrey et al[27] accurately measured the spleen size in the sagittal plane in the standard oblique coronal orientation to record the maximal length (in centimeters) of the spleen. Similarly, in a study that comprised 512 healthy children (274 girls) with ages ranging from 1 day (full-term neonate) to 17 years who were examined between 1996 and 2001, Stylianos et al[28] found that a simple single measurement of the splenic length was consistent with the normal range for age in the subjects studied.

Loftus et al.[14] in Hong Kong investigated the correlation between sonographic measurement of splenic length, volume, and weight. Sonographic measurements before autopsy were obtained in 30 cadavers and these values were compared with the actual length, volume and weight of the spleen at autopsy. They found a clear linear correlation between maximum sonographic length and actual length, volume, and weight. The study showed that a single simple sonographic measurement gives a clinically useful indication of true splenic size. The correlation coefficients are as follow: sonographic length and actual length ($r = 0.831$), volume ($r = 0.817$), and weight ($r = 0.810$). Also in a study in Brazil, Rodrigues et al[29] examined 32 morphologically normal spleens from adult corpses and found a roughly linear correlation between actual spleen volume and ultrasound spleen volume (i.e. $y=14.23 + 0.469x$).

The disparity between these studies and the current study is probably because the aforementioned studies did not include subjects with sickle cell anemia.

In this study, none of the subjects with normal Hb genotype have a splenic length of less than 6cm (autosplenectomy[23]) while 97% and 3% have splenic lengths of 7-12cm and > 12cm respectively. This is in keeping with normal splenic measurement on ultrasonography as documented in standard textbooks in gross and radiologic anatomy.[30,31,32,33]

Thirty percent, 39% and 31% of patients with Hb SS have splenic lengths of <6cm (autosplenectomy), 7-12cm and

>12cm respectively. The 30% prevalence rate of autosplenectomy and 31% rate of splenomegaly found in this study are higher than the reports by Ojo et al[23] who found 20% and 15% for autosplenectomy and splenomegaly respectively. Other studies found different prevalence rates of autosplenectomy in different parts of the world. Babadoko et al[34] in a study done in Zaria, northern Nigeria in 2010 found autosplenectomy in 55.4% of the Hb SS study subjects. In a study of 90 Sudanese children done between August 2004 and August 2005, Attalla[35] detected autosplenectomy 47.8% of patients. Balci[36] found a 33.3% prevalence rate of autosplenectomy in the study of 102 patients with sickle cell disease. Out of 363 subjects studied in Saudi Arabia by Alsalem et al[37], they found that only 24 (6.6%) of the subjects had autosplenectomy. The variability noted in the different studies including the index study mainly depends on the sickle cell haplotype in the different study locations. Other possible reasons may be due to the different study techniques and sample sizes. Thirty percent autosplenectomy prevalence rate found in the current study is similar to the 33.3% found by Balci ref probably because of a similar sample size.

Whereas the findings in this current study did not agree with earlier reports by Olatunji et al[38] at the University of Ilorin Teaching Hospital, who did not find anatomical autosplenectomy in their study of 98 patients with SCA, this study confirms the age-long belief of autosplenectomy among patients with SCA.

V. CONCLUSION

The study found that less than a third of patients with SCA each had autosplenectomy and splenomegaly while more than a third had normal splenic size. In subjects with sickle cell anemia, measurement of the splenic volume is a more accurate method of assessing the splenic size than a single splenic (length) span measurement.

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