bjh review

The spectrum of splenic complications in patients with sickle cell disease in Africa: a systematic review

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Summary

The majority of the global population of sickle cell disease (SCD) patients resides in Africa. Individuals with this condition are at great risk of serious infections and early mortality secondary to splenic dysfunction without preventative measures. This review investigated the spectrum of splenic complications encountered in SCD among populations in Africa. We systematically searched several databases for all articles published through March 3, 2020. We included 55 studies from 14 African countries. This review reveals the difference in frequency of splenic complications in SCD in Africa when compared with their counterparts in the United State and Europe. While several studies (n = 45) described splenomegaly with a prevalence of 12% to 73% among children, and 4% to 50% among adults with HbSS, the reported prevalence for acute splenic sequestration crisis (n = 6 studies) and hypersplenism (n = 4 studies) was <10% and <5% respectively. A total of 30 surgical splenectomy was reported across eight studies. Only two (3.7%) studies provided data on spleen function. A conflicting pattern was observed amongst studies that evaluated the relationship between splenomegaly and the presence of bacterial and malaria infections. This review reveals the paucity of studies describing the role of SCD-induced splenic dysfunction in morbidity and infection related mortality in Africa.

Keywords: sickle cell disease, spleen, complications, splenomegaly, infections, Africa.

About two-thirds of the global population of patients with sickle cell disease (SCD) reside in Africa,[1,2] and an estimated 50–90% of children born with SCD in Sub-Saharan Africa die before their fifth birthday.[3] This high mortality has partly been attributed to infections secondary to splenic dysfunction.[4,5] The repeated cycle of vaso-occlusion and ischaemia leads to progressive fibrosis, atrophy and autosplenectomy. Therefore, the spleen is rarely palpable beyond the age of 5 years in patients with SCD in the USA and Europe.[6,7] However, enlargement of the spleen (splenomegaly) tends to persist into late childhood or even adulthood in patients with SCD in Africa; earlier studies have linked this finding to the effect of malaria infection in a manner similar to what is observed in patients with the hyper-reactive malarial splenomegaly syndrome.[8,9] Also, persistently high level of fetal haemoglobin (HbF), co-inheritance of alpha thalassaemia trait and presence of other compound heterozygous forms of SCD have been attributed to the persistence of splenomegaly.[10–12] The enlarged spleen may be complicated by worsening anaemia due to trapping of blood within the spleen[13,14] and haemolytic crisis.[15] Other serious complications are acute splenic sequestration crisis (ASSC), massive splenic infarction, splenic abscess and hypersplenism, some of which may require splenectomy.[10,16–18]

The spleen serves as the major filter for blood of senescent red cells and micro-organisms, and is involved in both humoral and innate immunity.[19–21] The spleen parenchyma is divided into a white- and red-pulp compartment and separating these two is the marginal zone. The white pulp corresponds to the T and B lymphocyte cells zone and is responsible for adaptive immunity. Within the marginal zone, cells interaction and cell–cell sorting takes place; specialised marginal zone B lymphocyte cells respond to capsule polysaccharide antigens by differentiating into immunoglobulin M (IgM)-producing memory B cells. The red pulp is mainly responsible for the filtration function of the spleen; immature, damaged, or ageing red cells adhere to the reticular meshwork in this zone through specific signals or are captured by the macrophages and prevented from circulating again.[19]

At birth, the spleen appears morphologically and functionally normal in patients with SCD. The sequence of events that results in splenic injury begins following the haemoglobin switch that occurs at ~6 months of age.[7] The blood flow within the red pulp is particularly slow; the resulting high

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haematocrit promotes red cell stagnation, leading to hypoxia, acidosis, and further sickling of the red cells. Splenic dysfunction develops from blockage of the small inter-endothelial slits within the sinuses by the stiff and sickled red cells. An earlier study revealed that the phagocytic function becomes impaired first, while the filtration function may persist longer before it becomes compromised.[22]

Given the critical role the spleen plays in defence against micro-organisms, the loss of splenic function contributes significantly to the increased predisposition to bacterial infections seen in patients with SCD.[12,23] However, studies describing the role of SCD-induced splenic dysfunction as a cause of morbidity and mortality in patients with SCD in Africa are limited. The objective of the present systematic review was to describe and evaluate the existing data on the spectrum of splenic complications and associated morbidities amongst patients with SCD in Africa. The findings are a synthesis of the scarce information available from Africa about the relationship between size and function of the spleen, and the outcomes of SCD, and can provide the basis for more rational strategies to manage this common, chronic condition that places a high burden on resource-limited health services across the continent.

Methods

Inclusion Criteria

The review comprised studies conducted across African countries involving patients of all ages with SCD. For this review, we defined SCD as HbSS, HbSC, HbSβ^+ thalassaemia, or HbSβ^0 thalassaemia genotypes. We considered cross-sectional studies (prospective, retrospective), case-control studies, case series and case reports on splenic complications, in which the splenic complications were established through clinical assessment, abdominal ultrasound scan (USS) and other modalities. To be included in this review, articles needed to have original data on at least one splenic complication as a primary or secondary outcome of the study. Articles in all languages were included. We excluded review articles and studies conducted outside of Africa.

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] Four databases were searched from the dates shown in parentheses up to 3rd March 2020: the Medical Literature Analysis and Retrieval System Online (MEDLINE; 1963), Global Health Database (1973), Web of Science (1970) and Cumulative Index to Nursing and Allied Health Literature (CINAHL; 2002). We used Boolean logic with search terms including "sickle cell anaemia", "spleen", "splenic dysfunction", and "Africa south of Sahara". We used controlled vocabularies (e.g. Medical Subject Heading terms) to identify synonyms. We did additional searches in other electronic resources including Google Scholar and African Journals Online and several grey literature resources including Google Advanced, Electronic Theses Online Service (EThOS) library, Bielefeld Academic Search Engine (BASE) search, Networked digital library of thesis and dissertations, and open access theses and dissertations. We screened the reference lists of all retrieved articles for additional articles. Citations were uploaded into an EndNote X9 library where duplicates were removed. We applied no language restrictions to the search criteria and all non-English articles (i.e. 10 in French) were translated.

Data extraction

Titles and abstracts of studies retrieved from the databases and additional sources mentioned above were screened independently by two investigators (A.I.L. and A.O.A.) for their eligibility for full-text review. Differences of opinion were settled through discussion with a third author (I.B.) until consensus was achieved. Excluded studies were documented with reasons. Data were extracted using a predefined proforma that contained sections for authors, date of publication, location, study population, sample size, study design, age, gender, and method of assessing spleen size and assessment of spleen function. We also extracted laboratory data on Hb; counts for white blood cells (WBCs), platelets and reticulocytes; HbF; and the presence of malaria and bacterial infections.

Quality assessment of studies

The Joanna Briggs Institute Critical Appraisal tools for assessing the quality of observational studies were used.[25] Two authors (A.I.L., A.O.A.) independently appraised each article for quality using the following assessment criteria: description of study selection criteria and population; ascertainment of spleen size using a standard approach; reliable and valid method for measuring exposure variables; identification of confounding factors and strategies to deal with them; definition of outcome and use of appropriate statistical analysis. The quality of each of the criteria was assessed as either 'yes' or 'no' or 'unclear' or 'not applicable'. Points were assigned to each 'yes' question for a total of 7 points. Articles scoring 7 points were graded as 'A' quality, those scoring 5–6 points as 'B' quality, and those scoring <5 as 'C' quality.

Data synthesis and analysis

Variations in the study populations (children, adults, mixed population), study designs, methods of assessing spleen size (manual palpation using different cut-off values, USS), and reported outcomes in the studies retrieved made direct comparisons inappropriate, thus a descriptive method for data synthesis was employed and a narrative approach used for data analysis.

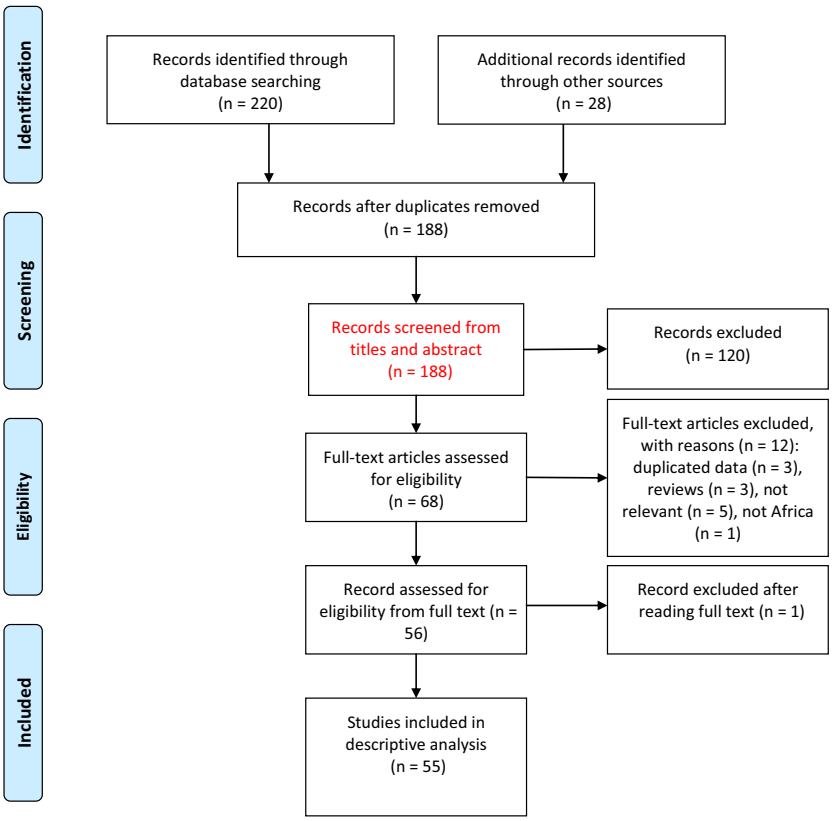

Fig. 1. Summary of data extraction. [Colour figure can be viewed at wileyonlinelibrary.com]

Results

Search results

A total of 202 articles were identified in the initial search and 28 in the additional search. After removal of duplicates, 188 articles remained. Their abstracts and titles were screened and 68 relevant articles, which met the inclusion criteria, were selected for full-text review; 55 studies were selected for inclusion into the final review and 13 studies were excluded on the following grounds: duplication of data (n = 3), reviews (n = 3), lack of original data (n = 5), study outside Africa (n = 1) (Fig 1). Another article was excluded because the authors inferred in the abstract that changes in haematological parameters (raised WBCs and platelets) were related to spleen effect; however, on full-text review, the study design did not include evaluation of the spleen. Of the 55 studies included in the systematic review 10 were in French and 45 in English.

General study description

The 55 studies were published between 1982 and 2019; 33 (60·0%) had a cross-sectional design, 10 (18·2%) were retrospective descriptive studies, 11 (20·0%) were case-control studies and one (1·8%) was a case study (Table I)[8–9,13–15,26–70,101–105]. Following quality assessment of all studies, seven (12·7%) were classified as Grade A, 36 (65·5%) as Grade B, and the remaining 12 (21·8%) as Grade C. The studies were conducted across 14 African countries. Seven of the countries were from the West African region, three from East Africa, and two each were from the Central and North African region. However, most studies [33 (60·0%)] were conducted in Nigeria, four (7·2%) were from the Democratic Republic of Congo (DRC) and two each (3·6%) from Congo, Senegal, and Ghana.

Of the studies from Nigeria, 17 (51·5%) were conducted in the south western part of the country across various institutions; four of these studies conducted between 1988 and 1993 were from a single author. The remaining 16 (48·5%) studies were conducted across various regions of the country.

Description of methodologies used in the studies

Apart from two large cross-sectional studies (n = 2305 and n = 4359), the sample size ranged between 40 and 591 for the prospective cross-sectional studies and 25–300 for the case-control studies. Whereas, 19 studies included children and adults with SCD, 23 studies consisted of children only and 13 adults only. In all, 32 studies included only individuals with HbSS, 12 had a combination of SCD genotypes (i.e. HbSS, HbSC, HbS-β-thalassaemia (HbS-β-thal), and the remaining 11 consisted of patients with HbSS and normal

Table I. General study characteristics.

Reference	Country	Study size, *n*	Hb phenotype	Mean age, years (SD, range)	Hb, g/l/PCV, %, mean (SD)	HbF level, %, mean (SD)	Spleen size assessment	Splenomegaly, %	Study design
Studies involving children only (N = 23)									
Belhani *et al.*, 1984[48]	Algeria	84	HbS-β-thal^0 HbS-β-thal$^+$ HbSS	NR (NR, <15)	Hb: HbS-β-thal^0: 82 (17) HbS-β-thal$^+$: 102 (17) HbSS: 77 (15)	HbS-β-thal^0: 14·3 (8·9) HbS-β-thal$^+$: 6·8(3·7) HbSS:8·5 (8·3)	Manual palpation	HbS-β-thal^0: 2292·0 HbSS: 34·0	Case-control study
Adekile *et al.*, 1988 [8]	Nigeria	139	HbSS, HbAA	7·1 (4·2, 0·5–15)	NA	NA	Manual palpation	33·8	Case-control study
Okoro *et al.*, 1989 [56]	Nigeria	4359	HbSS	NRC	NA	NA	Manual palpation	NRC	Cross sectional
Adeodu and Adekile, 1990 [15]	Nigeria	25	HbSS	11·3 (2·9, 8—15)	PCV: 20·5(2·4)	NA	Manual palpation	HbSS with PGS (15) and without PGS	Case-control study
Adekile *et al.*, 1991 [33]	Nigeria	54	HbSS, HbAS, HbAA	8·9 (NR, 3—7)	NA	NA	Manual palpation	25·0	Case-control study
Doumbo *et al.*, 1992 [39]	Mali	236	HbSS, HbAA	-	NA	NA	Manual palpation	12·0	Cross sectional
Thuilliez *et al.*, 1996 [49]	Gabon	302	HbSS	NR	Hb: 70 (NR)	NA	Manual palpation	33·0	Cross sectional
Mouélé *et al.*, 1999 [66]	Republic of the Congo	116	HbSS	9·4 (5·3, 1–32)	Hb: 66 (14)	8·8 (5·8)	Manual palpation	40	Cross sectional
Ambe *et al.*, 2001 [59]	Nigeria	104	HbSS	NR (NR, 0·5—15)	NA	NA	Manual palpation	NA	Cross sectional
Goussanou *et al.*, 2003 [58]	Republic of Benin	236	HbSS	Median 2·9 (0·6–12)	Hb: 78 (11) PCV: 25·3 (3·7)	10·1(5·8)	Manual palpation	NR	Cross sectional
Awotua-Efebo *et al.*, 2004 [69]	Nigeria	100	HbSS, HbAA	NR (NR, 0·5—15)	NA	NA	USS	27·0	Comparative, cross sectional
Darko *et al.*, 2005 [101]	Ghana	315	HbSS, HbSC, HbS-β-thal$^+$	NR (NR, 2–13)	NA	NA	USS	NR	Cross sectional
Gnassingbe *et al.*, 2007 [40]	Togo	8	HbSS, HbSC	NR (NR, 8–13)	NA	NA	Manual palpation	Yes, n = 5 (HbSS 3, HbSC 2)	Retrospective review over 17 years
Kizito *et al.*, 2007 [67]	Uganda	155	HbSS	4·4 (NR, 0·3—14·8)	NA	NA	Manual palpation	36·0	Cross sectional
Sadarangani *et al.*, 2009 [50]	Kenya	124	HbSS	6·3 (NR, 0·8—13·7)	NA	NA	Manual palpation	33·0	Cross sectional
Diagne *et al.*, 2010 [14]	Senegal	698	HbSS, HbSC HbS-β-thal$^+$	12·2(NR, 0·7–24)	Hb: 80 (11)	8·3 (7·9)	Manual palpation	HbSS: 20·1 HbSC: 41·9 Hb S-β-thal$^+$: 57·1	Retrospective review over 15 years
Brown *et al.*, 2012 [44]	Nigeria	415	HbSS, HbSC	7·3 (4·4, 0·5—17)	PCV HbSS: 24 (3·7) HbSC: 28 (4·5)	NA	Manual palpation	HbSS: 31·7 HbSC: 33·3	Retrospective review over 10 years

Table I. (*Continued*)

Reference	Country	Study size, *n*	Hb phenotype	Mean age, years (SD, range)	Hb, g/l/PCV, %, mean (SD)	HbF level, %, mean (SD)	Spleen size assessment	Splenomegaly, %	Study design
Aloni *et al.*, 2013 [102]	DRC	108	HbSS	Median 5·4 (0·5–13)	NA	NA	Manual palpation	37·8	Retrospective review over 10 years
Abdullahi *et al.*, 2014 [26]	Nigeria	300	HbSS, HbAA	NR (NR, 0·5−15)	Hb: 73 (13)	4·6 (1·7)	USS	35·3	Case-control study
Shongo *et al.*, 2014 [42]	DRC	205	HbSS	3·2 (1·4, NR)	NA	NA	Manual palpation	73·2	Cross sectional
Adegoke *et al.*, 2015 [35]	Nigeria	240	HbSS,HbSC	5·9 (3·7, 0·5−15)	PCV:18·7 (7·8)	NA	Manual palpation	HbSS: 12·5 HbSC: 4·3	Cross sectional
Yakubu *et al.*, 2017 [103]]	Nigeria	200	HbSS	7·9 (4, 1–15)	NA	NA	USS	53·5	Cross sectional
Akinlosotu *et al.*, 2018 [36]	Nigeria	105	HbSS	7·3 (3·6, NR)	Hb: 77 (11) PCV:23·4 (2·2)	9·9 (6)	Combined: Manual, USS	26·0	Cross sectional
Studies involving children and adults (N = 19)									
Kaine, 1982 [51]	Nigeria	210	HbSS	6·1 (NR, 0·8−19)	NA	NA	Manual palpation	<5 years: 55 5–10 years: 45 >10 years: 18	Cross sectional
Bayoumi *et al.*, 1988 [47]	Sudan	50	HbSS, HbS-β-thal^{+}	6·4 (NR, 0·5–38)	Hb: 73 (NR)	7·0 (NR)	Manual palpation	42·0[†]	Descriptive cross sectional
Adekile *et al.*, 1993 [34]	Nigeria	410	HbSS, HbAS, HbAA	9·7 (0·3,1–25)	Hb: 76 (NR)	9·3 (NR)	Manual palpation	23·3	Comparative cross sectional
Tshilolo *et al.*, 1996 [38]	DRC	591	HbSS	NR, (NR, 3–12)	NA	NA	Manual palpation	44·4	Cross sectional
Olatunji *et al.*, 2001 [46]	Nigeria	98	HbSS, HbAA	13·9 (7·4, 3–47)	NA	NA	USS	NR	Case-control study
Alufohai and Odusanya, 2006 [61]	Nigeria	17	HbSS	11·8 (NR, 10−15)	NA	NA	Manual palpation	NA	Retrospective review over 12 years
Makani *et al.*, 2010 [68]	Tanzania	2305	HbSS	Median 11 (0·3–47)	NA	NA	Manual palpation	10·0	Cross sectional
Jebbin and Adotey, 2011 [63]	Nigeria	6	HbSS	NR(NR, 11–20)	NA	NA	NA	NA	Case-studies
Ma'aji *et al.*, 2012 [104]]	Nigeria	71	HbSS	NA	NA	NA	USS	21·1	Cross sectional
Mpalampa *et al.*, 2012 [64]	Uganda	216	HbSS	9·3 (4·8, 1−18)	NA	NA	Manual palpation	24·0	Cross sectional
Akpan, 2015 [52]	Nigeria	220	HbSS	12·1 (8·3, 1–41)	NA	NA	USS	2·3	Cross sectional
Eze *et al.*, 2015 [54]	Nigeria	104	HbSS, HbSC, HbAA	NR (NR, 2–58)	NA	NA	USS	33·0[†]	Comparative cross sectional
Thiam *et al.*, 2017 [60]	Senegal	46	HbSS	8, (NR, 0·92–21)	Hb: 86 (5)	4·0 (NR)	Manual palpation	21·7	Retrospective review over 2 years
Inah and Ekanem, 2018 [31]	Nigeria	120	HbSS	Median 14·5 (6–25)	NA	NA	USS	0·83	Cross sectional
Luntsi *et al.*, 2018 [30]	Nigeria	126	HbSS	18 (6·3, 3–38)	NA	NA	USS	50·0	Cross sectional
Ugwu *et al.*, 2018 [53]	Nigeria	237	HbSS	Median 9·8, (1–49)	NA	NA	USS	NR	Cross sectional
Banza *et al.*, 2019 [57]	DRC	206	HbSS	11·8 (21·9, 1·1–38)	NA	NA	USS	13·1	Retrospective, 3 years review
Ezeike, 2019 [28]	Nigeria	100	HbSS, HbAA	NR (NR, 0–30)	NA	NA	USS	31·0	Case-control study
Kazadi *et al.*, 2019 [41]	DRC	256	HbSS	8·4 (4·9, 0·5–24)	Hb: 74 (15) PCV: 23·3 (4·5)	NA	Manual palpation	41·7	Cross sectional

Table I. (*Continued*)

Reference	Country	Study size, *n*	Hb phenotype	Mean age, years (SD, range)	Hb, g/l/PCV, %, mean (SD)	HbF level, %, mean (SD)	Spleen size assessment	Splenomegaly, %	Study design
Studies involving adults only (*N* = 13)									
Bedu-Addo and Bates, 2002 [9]	Ghana	221	HbAA,HbSS, HbSC, Other*	Median 31(8–75)	NA	NA	Manual palpation	Yes, all 6 with HbSS(*n* = 2) and HbSC(*n* = 4)	Descriptive cross sectional
Gassaye *et al*., 2000 [62]	Republic of Congo	13	HbSS	NR (NR, 4–62)	NA	NA	USS	NA	Retrospective review over 5 years
Yetunde and Anyaegbu, 2001 [55]	Nigeria	98	HbSS	NR, (NR, 30–52)	PCV: 24 (NR)	NA	Manual palpation	35·0	Cross sectional
Abjah and Aken'Ova, 2003 [37]	Nigeria	70	HbSS, HbSC, HbAA	NR (NR, 15–54)	NA	NA	Manual palpation	HbSS: 50 HbSC: 67	Case-control study
Durosinmi *et al*., 2005 [13]	Nigeria	71	HbSS	Median 21 (16–48)	PCV: 24 (0·1)	4·3 (NR)	Manual palpation	26·8	Case-control study
Olaniyi and Abjah, 2007 [105]]	Nigeria	220	HbSS, HbSC	24·7 (8·7, 12–60)	PCV:22·3 (5·2)	NA	Manual palpation	HbSS: 20·2 HbSC: 25·9	Cross sectional
Kotila et al., 2000 [65]	Nigeria	50	HbSS	20 (NR, NR)	NA	7·4 (3·6)	Manual palpation	16	Cross sectional
Akinola *et al*., 2009 [45]	Nigeria	154	HbSS, HbSC	22·5 (7·3, NR)	PCV: HbSS: 23 (3·7) HbSC: 29 (3·8)	NA	Manual palpation	HbSS: 17·2 HbSC: 19·2	Retrospective review
Tolo-Diebkilé *et al*., 2010 [43]	Ivory coast	48	HbSS	26·1 (NR, 21–56)	Hb: 95 (NR)	10·6 (NR)	Manual palpation	0	Retrospective review
Babadoko *et al*., 2012 [29]	Nigeria	74	HbSS, HbAA	23·3 (5·3, NR)	PCV: 25·9(3·9)	NA	USS	4·1	Case-control study
Ojo *et al*., 2014 [27]	Nigeria	40	HbSS, HbAA	25·2 (2·2, 16—40)	NA	NA	USS	15·0	Cross sectional
Okongwu *et al*., 2018 [70]	Nigeria	40	HbSS	29·3 (8,17–51)	NA	NA	USS	12·5	Cross sectional
Fasola and Adekanmi, 2019 [32]	Nigeria	42	HbSS, HbAA	29 (8·1, NR)	Hb: 77 (159) PCV:25·5 (5·3)	NA	USS	10·0	Case-control study

DRC, Democratic Republic of Congo; Hb, Haemoglobin; HbF, Haemoglobin FNA, not assessed; NR, not reported; NRC, no record; ; PCV, packed cell volume; PGS, persistent gross splenomegaly; USS, ultrasound scan. *Patients with abnormal electrophoretic pattern including HbAS, HbAC, HbCC; †Sickle cell disease phenotype not specified.

controls (HbAA). In all, 45 studies provided prevalence rates for splenomegaly amongst their study population; we found substantial variation in the criteria used in defining splenomegaly. Based on USS, splenomegaly was defined as the long axis of the spleen >12 cm in three studies,[26–28] and >13 cm in four studies.[29–32] In six studies involving children, using manual palpation, the authors defined massive splenomegaly as spleen size of at least 10 cm below the coastal margin during steady state condition, and persistent gross splenomegaly as spleen size of ≥10 cm during steady state.[8,15,33–36] In seven other studies, the Hackett classification was used in grading spleen size.[37–43] In all, 25 studies did not report on the parameters used to define splenomegaly. Only two studies (3·6%) reported an assessment of splenic function. The method employed in both studies was counting of pitted red cells using direct interference, phase-contrast microscopy.[33,34]

Spectrum of splenic complications

Splenomegaly. Of the 45 (81·8%) studies that provided data on the prevalence of splenomegaly in patients with HbSS, 19 (42·2%) consisted of children only, 11 (24·4%) adults only, and the remaining 15 (33·3%) consisted of children and adult participants. In studies involving only children, the estimate ranged from 12% in Nigeria and Mali to 73·2% in the DRC. Four of these studies determined spleen size using USS and the remaining 15 by manual palpation. Notably, all 11 studies that provided data on the prevalence of splenomegaly in the adult SCD population were conducted in Nigeria ($n = 10$) and Ghana ($n = 1$). The estimate ranged from 4% to 50%. Seven of these studies determined spleen size by manual palpation and the remaining four by USS. Seven studies, all from the West African countries of Nigeria ($n = 5$), Senegal ($n = 1$) and Ghana ($n = 1$), reported on splenomegaly in individuals with HbSC. The prevalence varied from 4% to 42% in children and adolescent,[14,35,44] and 15% to 67% in adults with HbSC respectively.[9,37,45,46] Three other studies, two from Northern Africa[47,48] and one from West Africa[14] reported data from individuals with HbS-β-thal^0 and HbS-β-thal$^+$ (Table I). In these studies the prevalence of splenomegaly ranged from 54% to 88%.[14,48]

The relationship between spleen size and age was described in 17 studies (Table II[14,26,28,34,36,38,44,46,49–55,102,103]). In studies involving children only, persistence of the spleen beyond the age of 5 years was noted in most of the patients with SCD.[14,26,49,50] In studies with a mixed population of adults and children, while some demonstrated decreasing spleen size with increasing age,[34,51–53] a few showed a steady increase in the spleen size up to the second[54] and third decade[46] before the size began to decline. In one study involving adults with SCD aged >30 years, a third of the patients still had a palpable spleen.[55] Three studies used USS to compare the spleen sizes in patients with SCD with those of normal controls.[28,46,54] In one of these studies involving children (age range, 2–17 years), the mean (SD) spleen length in patents SCD was 97·67 (39·61) cm, while that of the controls was 80·84 (16·89) cm ($P < 0·05$).[54] In another report, the mean (SD) longitudinal length of the spleen in patients with SCD (age range, 3–47 years) was 101·7 (18) cm, while in the controls was 95·6 (13) cm ($P < 0·02$).[46] In the third study, the mean splenic volume and anterior–posterior diameter in patients with SCD (age range, 0–30 years) was 267·3 cm^3 and 4·63 cm, and differed significantly from the values in the controls of 161·3 cm^3 ($P = 0·001$) and 4·12 cm ($P = 0·048$) respectively. However, there was no significant difference between the spleen length ($P = 0·659$) and transverse diameter ($P = 0·433$).[28]

Hypersplenism. Only four studies provided information on hypersplenism. This was defined in one of the studies as splenomegaly of at least 5 cm in association with haemoglobin level of <10 g/l from baseline value, low platelets (<200 × 10^9/l) and increased reticulocytes (>150 × 10^9/l) observed on at least two occasions in the absence of any other cause of hyperhaemolysis.[14] The prevalence of hypersplenism was generally low across all studies. Two studies involving children in Nigeria and Senegal reported rates of 0·1%[56] and 5%[14] respectively. Similar figures of 1%[57] and 4·2%[13] were also reported in the adult studies in Nigeria and the DRC respectively. Improvement in the haematological indices after splenectomy was observed in three studies.[13,14,56]

Acute splenic sequestration crisis (ASSC). Only six studies from four countries reported on the occurrence of ASSC. This was defined in two of the studies as sudden enlargement of the spleen accompanied by worsening anaemia, requiring immediate blood transfusion.[14,58] The highest prevalence of 27·3% was reported from Nigeria,[59] whereas, two studies, from Senegal[60] and Congo[41] reported a prevalence rate of 7%. The prevalence was low at 3% in a study from the Republic of Benin,[58] and 2% in two studies from Senegal[14] and the DRC.[57] Two studies provided information on ASSC-related mortality in their patient population; in both studies, all 11 deaths recorded were related to non-availability of blood for transfusion.[58,59]

Surgical splenectomy. A total of eight studies reported data on splenectomy across six countries including Nigeria ($n = 3$), Algeria ($n = 1$), Senegal ($n = 1$), Ivory Coast ($n = 1$), Togo ($n = 1$) and the DRC ($n = 1$). The indications for splenectomy included hypersplenism in three studies,[13,14,56] therapeutic for symptomatic splenomegaly in two studies[48,61] and drainage of splenic abscess in one study.[62] In one other study, splenectomy was performed following traumatic rupture of the spleen in five patients and as prophylaxis in three other patients.[40] The indication for splenectomy was not indicated in one study.[43] In the small series from Togo, the authors reported on eight children with SCD (five HbSS and three HbSC; age range 6–13 years), who underwent splenectomy between 1987 and 2004. All were on prophylaxis with penicillin

Table II. Summary of studies that reported on the variation in spleen size across different ages (n = 17).

Country	Study year	Study size	Prevalence of splenomegaly, %	Summary of findings	Reference
1. Studies involving children only					
Gabon	1996	302	33·0	A third of the patients with SCD still had splenomegaly beyond 5 years of age.	Thuilliez *et al.*[49]
Kenya	2009	124	33·0	The peak prevalence of splenomegaly occurred in the age group of 6–8 years. The largest mean spleen size of 4·8 cm was seen in the age group of 8–10 years. However, there were no significant relationship between spleen size and age	Sadarangani *et al.*[50]
Senegal	2010	698	HbSS: 20·1 HbSC: 41·9 HbS-β-thal: 57·0	The prevalence of splenomegaly showed a steady increase from infancy up to the age of 10 years before it started decreasing	Diagne*et al.*[14]
Nigeria	2012	415	HbSS: 31·7 HbSC: 33·3	A relatively stable prevalence of palpable spleen, occurring in about a third of patients until the age of 15 years was observed before it started dropping. The patients with HbSC had a higher frequency of splenomegaly between the ages of 5 and 14 years	Brown *et al.*[44]
DRC	2013	90	37·8	Splenomegaly was more common in those aged <5 years (61·7%) of age compared to those >5 years (11·6%)	Aloni *et al.*[102]
Nigeria	2014	150	35·3	Splenomegaly persisted into older age patients. The prevalence of splenomegaly among children with SCD who were aged >10 years was 11·3%	Abdullahi *et al.*[26]
Nigeria	2017	200	53·5	The splenic volume was higher in the age group of ≥12 years and lowest in the age group of 1–2 years.	Yakubu *et al.*,[103]
Nigeria	2018	105	26·0	All patients aged <8 years had their spleen detectable on USS, while 4 out of the remaining 44 patients aged >8 years had autosplenectomy	Akinlosotu *et al.*[36]
2. Studies involving children and adults					
Nigeria	1982	210	55·0	The spleen size decreased progressively with increasing age: 55% for <5 years, 45% for 5−10years and 18% for >10years	Kaine[51]
Nigeria	1993	310	23·0	Frequency of splenomegaly across the age groups was: 20·3% for <5 years; 25·7% for 6–10 years; 23·7% for 11–15 years; and 17·9% for >15 years. No significant differences in the mean ages of those with or without splenic enlargement was observed	Adekile *et al.*[34]
DRC	1996	591	44·0	Splenomegaly rarely occurred before 3 years of age in the patients with SCD compared with normal control, but persisted longer in the SCD group compared with normal control	Tshilolo *et al.*[38]
Nigeria	2001	91	NR	The longitudinal spleen length increased continuously up to the age of 30 years. A reduction in the coronal diameter after the age of 30 years was the only indicator of splenic size reduction.	Olatunji *et al.*[46]
Nigeria	2015	220	2·3	Splenomegaly was confined to children aged <10 years. A third of the study group had a normal spleen and most belonged to the <5-years age group, while one-third of the patients had autosplenectomy and most belonged to the adolescent group.	Akpan[52]
Nigeria	2015	104	33·1	The spleen of SCD subjects generally had undulating variations in size increasing rapidly from 2 years of age to the childhood/ adulthood transitional age of 18 years. At >18 years, there was a mixture of sharp reduction and increase in spleen size in an undulating form up to the age of 58 years.	Eze *et al.*[54]
Nigeria	2018	237	NR	The mean spleen length of SCD patients in this study was enlarged in the age group of 1–10 years; a progressive decrease was observed with each successive age group afterwards.	Ugwu *et al.*[53]
Nigeria	2019	100	31·0	The largest spleen length and volume was recorded in the age group of 5–9 years, being twice the dimension compared to the 0–4-years age group.	Ezeike[28]
3. Studies involving adults only					
Nigeria	2001	98	35·0	More than one-third of the study population had palpable spleen despite an average age of ≥30 years.	Yetunde *et al.*[55]

DRC, Democratic Republic of Congo; NR, Not reported; SCD, sickle cell disease; USS, ultrasound scan.

V, and received pre- and postoperative vaccination against *pneumococcus*, *meningococcus*, and *Haemophilus influenzae b*. There was a reduction in their transfusion requirement when followed-up for 3 years. In another small series from Eastern Nigeria, the authors reported on 17 patients who underwent splenectomy over a 12-year period for various conditions including patients with SCD with splenomegaly ($n = 5$; 29%).[61] The outcome of surgery was uneventful and none of the patients with SCD required further blood transfusion when compared to the preoperative period.

Splenic rupture. Traumatic rupture of enlarged spleen was reported in five out of eight patients with SCD who underwent splenectomy as described in a retrospective review conducted over a 17-year period from Togo.[40] The complication occurred in three patients with HbSS and two with HbSC. Clinical examination on presentation revealed evidence of peritoneal irritation and ascites; abdominal USS confirmed rupture of the enlarged spleen. All the patients had a total splenectomy performed.

Splenic abscess. Two studies from Nigeria and the DRC reported on splenic abscesses. In one of these studies, a case report from Nigeria, the abscess was treated by laparotomy and surgical drainage and the spleen preserved.[63] Whereas, splenectomy was performed in all three patients with SCD with splenic abscess from the DRC study.[62]

Splenic infarction and calcification. Only one study each, reported on splenic infarction[54] and splenic calcification.[30] In both studies, these complications were asymptomatic and detected during USS in steady state patients with HbSS.

Autosplenectomy. In all, 16 studies provided information on autosplenectomy. This was defined as the non-visualisation of the spleen on USS in the absence of surgical splenectomy by most of the studies. The reported prevalence varied from 4% to 20% among children, and 20–54% among adult patients with SCD.

Other associations with spleen size in patients with SCD

Splenic function. Although only two of the 55 studies reported on spleen function, both studies showed increased spleen size was associated with retained function.[33,34] One of the studies was a multicentre study, involving seven centres across Nigeria, and a comparative arm in the USA.[34] The mean pitted erythrocyte count was 4·3% in patients with HbSS with splenomegaly and 12·3% in those without splenomegaly ($P = 0{\cdot}001$),[33] indicating that spleen function was better in those with splenomegaly compared to those without. The mean pitted erythrocyte count was 11·1% in patients HbSS compared to 1·8% in the HbAA population ($P = 0{\cdot}001$).[33]

HbF level. While 12 studies provided results for HbF level in their patients with SCD, only five of these studies evaluated the relationship with spleen size. Three of these studies from Nigeria,[36] Uganda[64] and Senegal[14] found no significant relationship between spleen size and HbF level in children with HbSS. In contrast, two other studies conducted in Nigeria amongst adults with HbSS, reported a parallel increase in HbF level with increased spleen size.[13,65] In two studies, one involving children[35] and the other mixed population of children and adults,[57] the authors indicated that 5·4% and 29·2% of their study population were on hydroxyurea respectively. However, no relationship between spleen size and hydroxyurea therapy was mentioned in either study.

Alpha thalassaemia trait. Two out of the 55 studies evaluated the association between alpha thalassaemia trait and spleen size. One of the reports from the DRC indicated that patients with the alpha-thal-2 deletion were more likely to have splenomegaly.[66] However, the second study from Nigeria showed that 33·3% of patients with HbSS with splenomegaly were heterozygous for alpha-thal-2 deletion compared to 39·0% for those without splenomegaly; suggesting alpha-thal-2 deletion was not related to splenomegaly.[34]

Haematological parameters. There was no consistent association between spleen size and haematological parameters among the studies. For example, while some studies found a negative correlation between haematocrit and spleen size,[14,44] one found a positive correlation,[32] and others found no correlation between the two variables.[13,46] Similarly, splenomegaly was associated with cytopenia in some studies,[15,26,35] but not others.[53] Likewise, the reticulocyte count increased with increasing spleen size in one study,[26] while another report found no relationship between the spleen size and reticulocyte count.[13]

Association between spleen size and infections

Splenomegaly was noted in 16 studies from six countries that reported on the frequency of bacterial and malaria infections in patients with SCD (Table III)[8,13,34,35,37–39,41,47,50,59,67–70,102]. Most of these studies ($n = 11$) involved children. Malaria diagnosis was based on peripheral blood smear in most of the reports. The prevalence of symptomatic malaria was highest in Nigeria and the DRC at >50%, compared to prevalence rates from Mali (4%), Kenya (6%), Tanzania (3%) and Uganda (9·7%). Eight studies reported on bacterial infections; three of these studies reported using blood culture for diagnosis. The reported prevalence rates were 23.8%[35] and 25·6%[59] from Nigeria, and 28% from Uganda.[67] The remaining five studies provided no clear description of how infection was diagnosed.

Among the 15 studies reporting on both malaria and bacterial infections, 10 evaluated the relationship between spleen size and infections (Table III). Three of these studies indicated no relationship between the frequency of malaria

Table III. Summary of studies reporting on the relationship between spleen size and infections in patients with SCD (n = 16).

Country	Study year	Mean age, years (SD, range)	Study size	Bacterial infection	Malaria infection	Spleen size, %	Evaluation of spleen size and infection (s)	Reference
Nigeria	1988	7·1 (4·2, 0·5–15)	139	NA	Serum IgM level and response to anti-malaria treatment assessed in patient with PGS	Splenomegaly: 33·8 PGS: 10·8	Significant reduction in spleen size followed treatment with anti-malarial (proguanil) over a 6-month period (P = 0·01). Serum IgM levels were significantly higher in patients with PGS compared to HbSS without splenomegaly and HbAA controls (P = 0·01)	Adekile *et al.*[8]
Sudan	1988	6·4 (NR, 0·5–38)	50	Diagnosis: Not described Prevalence 8·0%	NA	Splenomegaly: 42·0	NA	Bayoumi *et al.*[47]
Mali	1992	NR (NR, 0–12)	236	NA	Diagnosis: Rectal temp. >38°C; thick and thin blood smears for parasites Prevalence: 4·0%	Splenomegaly: 12·0	NA	Doumbo *et al.*[39]
Nigeria	1993	9·7 (0·3, 1–25)	310	Diagnosis: Not explicitly defined. Clinical syndrome of pneumonia, osteomyelitis and septicaemia stated. Prevalence: 7·4%	Diagnosis: Thick blood smears for parasites Prevalence: 8·1%	Splenomegaly: 23·3	Immunoglobulin IgA, IgG, IgM levels increased with increasing spleen size. IgG anti-malaria antibody titre also increased with increasing spleen size.	Adekile *et al.*[34]
DRC	1996	NR (NR, 0·5–15)	591	Diagnosis: Not described Prevalence: 2·4%	NA	Splenomegaly: 44·4	NA	Tshilolo *et al.*[38]
Nigeria	2001	NR (NR, 0·5—15)	104	Diagnosis: Positive blood culture Prevalence: 25·6%	Diagnosis: Blood smears for parasites Prevalence: 66·0%	NR	NA	Ambe *et al.*[59]
Nigeria	2003	NR (NR, 15–54)	50	NA	Anti-malaria IgG levels assessed in asymptomatic patients	Splenomegaly: HbSS: 50·0 HbSC: 67·0	The mean plasmodium falciparum IgG correlated directly with the spleen size.	Abjah and Aken'Ova [37]

Table III. (*Continued*)

Country	Study year	Mean age, years (SD, range)	Study size	Bacterial infection	Malaria infection	Spleen size, %	Evaluation of spleen size and infection (s)	Reference
Nigeria	2004	NR (NR, 0·5–15)	100	NA	Diagnosis: Thick blood smears for parasites Prevalence: 30·0% (asymptomatic)	Splenomegaly: 27·0 Autosplenectomy: 20·0	Parasite density was higher in SCA patients with splenomegaly and normal sized spleen when compared with those with autosplenectomy.	Awotua-Efebo *et al.*[69]
Nigeria	2005	Median: 21 (16–48)	72	NA	Diagnosis: Thick blood smears for parasites Prevalence 46·3% (asymptomatic)	Splenomegaly: 26·8	There was no difference in malaria parasite density between patients with PGS and those without. There was no significant correlation between malaria parasitaemia and splenomegaly (r = 0·06).	Durosinmi *et al.*[13]
Uganda	2007	Median 4·4 (0·3–14·8)	165	Diagnosis: Positive blood and urine cultures; +/- CXR; fever >38°C Prevalence: Bacteraemia 28·0% UTI 11·0%	Diagnosis: Blood smears: parasite density graded from +1 to +3 Prevalence: 9·7% (symptomatic)	Splenomegaly: 36·0	There was no relationship between splenomegaly and positive blood cultures, or type of organism isolated.	Kizito *et al.*[67]
Kenya	2009	Median 6·3 (0·8–13·7)	124	NA	Diagnosis: Thick and thin blood smears for parasites; parasite density computed against WBCs Prevalence: 6·0%	Splenomegaly: 33·0	There was no relationship between spleen size and the number of episodes of malaria, malaria parasitaemia or use of proguanil.	Sadarangani *et al.*[50]
Tanzania	2010	Median 11 (0·3–47)	1808 - OPD 697 - Inpatients	NA	Diagnosis: RDT; thick blood smears; parasite density computed against WBCs Prevalence: 0·7%: OPD visits 3·0%: Inpatients	Splenomegaly: 10·0: OPD visits 22·0: Inpatients	The prevalence of splenomegaly and malaria parasitaemia in patients with SCA was higher during hospitalisation; however, splenomegaly was not a predictor of malaria parasitaemia.	Makani *et al.*[68]
DRC	2013	Median 5·4 (0·5–13)	90	NA	Diagnosis: Fever >38°C; clinical malaria, positive blood smears Prevalence: 63·3% (symptomatic)	Splenomegaly: 37·8	Acute malaria and splenomegaly were more common in those aged <5 years during acute crisis.	Aloni *et al.*[102]

Table III. (*Continued*)

Country	Study year	Mean age, years (SD, range)	Study size	Bacterial infection	Malaria infection	Spleen size, %	Evaluation of spleen size and infection (s)	Reference
Nigeria	2015	5·9 (3·7, 0·5–15)	240	Diagnosis: Positive blood cultures. Prevalence: 23·8%	Diagnosis: Thick blood smears for parasites Prevalence: 53·0%	Splenomegaly: HbSS:12·5 HbSC: 4·6	NA	Adegoke *et al.*[35]
Nigeria	2018	29·3 (8, 17–51)	46	Diagnosis: Not explicitly described. Annual frequency of hospitalisation and fever assessed.	NA	Splenomegaly: 12·5 Autosplenectomy:20·0	Infection rate of more than once a year was reported in 87·5% of those with autosplenectomy compared to 50% in those without. No correlation between interferon gamma level and spleen size	Okongwu *et al.*[70]
DRC	2019	8·4 (4·9, 0·5–24)	256	Diagnosis: Not described Prevalence: 3·9%	NA	Splenomegaly: 41·7	NA	Kazadi *et al.*[41]

DRC, Democratic republic of Congo; IgG, immunoglobulin G; NA, not assessed; OPD, Outpatient department; PGR, persistent gross splenomegaly; RDT, rapid diagnostic tests; UTI, urinary tract infection; WBCs, white blood cells.

parasitaemia or parasite density, clinical malaria and spleen size,[13,50,68] while one study reported a higher parasite density in patients with normal-sized or enlarged spleens compared to those with autosplenectomy.[69] Three other studies mentioned a direct association between increasing spleen size and levels of serum IgM and anti-malaria IgG.[8,34,37] The spleen size was also reported to have decreased following treatment with anti-malaria therapy.[8]

One study evaluated the relationship between splenomegaly and bacterial infections,[67] while two studies evaluated the association between autosplenectomy and risk of infections[69,70] (Table III). Notably, the relationship between risk of infections and spleen function was not evaluated in two of the studies that assessed function.

Discussion

In the present review, we identified 55 studies with data on various forms of splenic complications among patients with SCD in Africa. Several studies [$n = 45$ studies (81·8%)] described splenomegaly either by palpation or imaging in patients with SCD, with a prevalence of 12–73% among children and 4–50% among adults with HbSS. Amongst studies involving patients with HbSC, the prevalence of splenomegaly varied from 4·3% to 33% among children and 19–67% among adults. The reported rates in the HbSS population from the present review appear high compared to the figures of 5–19% reported from the USA in children and young adults with HbSS.[71,72] Splenomegaly in patients with SCD in Africa appears to be less common than in the Middle East, where the occurrence of splenomegaly in patients with SCD ranges from 69% to 82% across all age groups.[73–75] This may be attributed to the inclusion of individuals with HbS-β-thal$^+$ in studies from this region.

In patients with SCD, the spleen commonly enlarges during childhood, but then undergoes autosplenectomy by about 5 years of age due to repeated attacks of vaso-occlusion and infarction.[76] A palpable spleen is unusual beyond this age in patients with HbSS in the USA and Europe,[6,77,78] and only few reports from the West have documented persistence of the spleen beyond childhood.[72] However, this was not what we observed in African patients with SCD in the present review. We noted persistence of the spleen into late childhood and adulthood across several studies. In one of adult studies, comprising patients with SCD aged ≥30 years, more than a third still had an enlarged spleen.[55] Indeed, haemoglobinopathies accounted for 3% of the causes of massive splenomegaly in adults patients in Ghana.[9] This finding indicates that the late persistence of spleen in patients with SCD in Africa is comparable to what is observed in the Middle East, where a large number of adult patients still have a palpable spleen.[74,79] In their report, Al-Salem *et al.*[74] observed that the spleen size increased with age in their patients with SCD until ~40 years of age before slowly decreasing.

The persistence of splenomegaly in patients with SCD in Africa has been attributed to exposure to bacterial and parasitic infections, in particular malaria infection. It is suggested that the parasite causes hyperplasia of the reticuloendothelial tissues in the host spleen that counteract the natural progression to autosplenectomy, and hence the persistence of the spleen.[80] This view is supported by reports from the present review that documented increasing IgG anti-malaria antibody titre with increasing spleen size,[34,37] high malaria parasite density in children with splenomegaly compared to those without[69] and significant reduction in the spleen size after treatment with the anti-malaria drug proguanil.[8] Additionally, significantly high IgM values for children with HbSS with persistent splenomegaly when compared with those without splenomegaly was observed and the splenic reticuloendothelial function was intact in some patients with HbSS with splenomegaly.[33,34] Taken together, the late persistence of the spleen beyond childhood in patients with SCD in Africa may represent highly active immune response mechanisms against malaria and other infective organisms in the region. We also observed that, all the studies that provided data about the persistence of splenomegaly in adults with SCD were from the West African countries of Nigeria and Ghana. This raises the question as to whether the persistence of splenomegaly in SCD in Africa could also be due to geographical variation. Nevertheless, few studies in the present review found no association between splenomegaly and malaria parasitaemia or episodes of clinical malaria in both children and adults.[13,50,68] Given the number of studies that provided data on the prevalence of splenomegaly in SCD ($n = 35$), and the limited number of studies exploring the association between spleen size and infections ($n = 10$), along with the conflicting findings from these reports, further studies are needed to ascertain the relationship between splenomegaly and the risk of infections in SCD in Africa.

Reports from other parts of the world suggest that the persistence of splenomegaly is linked to modifiers of disease severity such as co-inheritance of alpha thalassaemia trait and high HbF.[81,82] The high HbF level, by its ameliorating influence on the sickling process, may play a role in the persistence of splenomegaly. However, the effects of these factors remains unclear in the African setting as evidenced by the present review, as only two of the nine studies that evaluated the level of HbF showed an association with presence of splenomegaly.[13,32] The two studies that provided information about the co-inheritance of alpha thalassaemia trait and splenomegaly had conflicting findings.[34,66]

Splenomegaly-related complications

The present review highlighted that the presence of an enlarged spleen may predispose patients with SCD to further morbidities as described below:

Acute splenic sequestration crisis (ASSC). Splenomegaly was complicated by ASSC in six studies and in most of these studies ($n = 5$), the reported prevalence was <10%. This is lower than reported in children from other parts of the world[83,84] and in adults with SCD.[73] In a cohort of 216 children with HbSS followed since birth, 52 (24%) had at least one episode of ASSC over the study period of 6 years.[85] Also, a total of 437 episodes (0·06/patient-year) of ASSC was reported over a 9-year period in the French cohort.[83] ASSC also seems to be less frequent in patients with SCD in Africa compared to the Middle East, a region with comparable rates of enlarged spleens persisting into adulthood.[73,75,81] The low report of ASSC in Africa may be related to the late age of patients recruited in most of the studies. It could also be linked to the expression of different haplotypes across the geographical regions.

Regular clinical examination and parental education to identify acute enlargement of the spleen in febrile patients can facilitate prompt diagnosis of suspected cases. Urgent treatment with top-up transfusion or red blood cells exchange is mandatory, as delays can lead to circulatory collapse and death from acute anaemia as evidenced in studies from Nigeria[59] and the Republic of Benin[58] that provided data on ASSC-related mortality. All the ASSC-related deaths ($n = 4$) occurred during the first year of the Benin study, which was designed to determine the effect of a comprehensive clinical care programme on disease course in patients with SCD. With sustained and intensive parental education on spleen palpation, no other death was recorded in the remaining 4 years of the study.[58]

Hypersplenism. Only a few studies provided information on hypersplenism, and within these studies, the reported prevalence rates were low (<5%). The chronic sequestration of blood within the enlarged spleen and the accompanying red cell haemolysis results in cytopenia. The increased transfusion need linked to hypersplenism was the main indication for splenectomy in most of the studies in the present review.[13,14,56] Also, the resulting expansion in erythropoietic drive to compensate for the excessive haemolysis imposes a high metabolic requirement in patients with SCD and may interfere with normal growth in children.[86] This is of particular concern in patients with SCD in most low-income countries of Africa where malnutrition is high, because any additional malnutrition from increased demand can exacerbate the susceptibility to infection.[87]

Surgical splenectomy. A total of 30 patients had splenectomy performed across 10 studies over a four-decade period in the present review. This is low compared to reports from the Middle East, where splenectomy was performed in 44 (20%) patients (age range, 4–52 years) with SCD over a 4-year period[79] and 134 children (mean age, 7·6 years) over a 14-year period for various splenic complications.[10,88] The splenectomy rate in a USA study [nine children (8%)] aged >12 years[72] was higher than that in any study in our present

review. Due to the better availability of specialist surgical expertise, as well as conjugate vaccine[89] and prophylactic antibiotics [90] in developed countries, splenectomy is more likely to be considered feasible across all age groups of patients with SCD.[91] However, in Africa, where these resources are limited, coupled with the high burden of infection, surgeons may be reluctant to perform splenectomy in patients with SCD. The operative risk of removing an enlarged spleen is also high when blood and components for transfusion may not be reliably available. General anaesthesia may induce vaso-occlusive crisis, therefore, maintenance of optimal oxygenation and hydration intraoperatively and minimising anaesthetic duration is critical.[40,61]

Despite the limited data on splenectomies performed in patients with SCD in Africa, most of the studies [$n = 5$ (83·3%)] reported improved clinical symptoms and haematological parameters following the procedure. Two studies reported absence of infection-related complications in the post-splenectomy period after 18 months[56] and 3 years[40] of follow-up in their patients; while the remaining eight studies did not provide information about the risk of infection post-splenectomy. Careful patient selection and adequate preventive measures before and after splenectomy to control for infections are crucial to improve the outcome.

Assessing spleen function in SCD in Africa and implication for future research

The two studies that provided information on spleen function, noted that most of the patients with palpable spleen had lower red cell pit counts, indicating that the splenic reticuloendothelial function was still preserved.[33,34] One of the studies compared splenic function between patients with HbSS from a malaria zone (Nigeria) and those living in a malaria-free zone (USA). Patients with palpable spleens in both groups had significantly lower pit counts when compared to those without splenic enlargement.[34] This would imply that, although functional asplenia has been described in patients with SCD with splenomegaly, reticuloendothelial function is not always compromised. This finding is corroborated by reports from the Middle East, which also showed preservation of spleen function into adulthood among patients with SCD with splenomegaly.[73,92] However, in contrast reports from the West suggest loss of splenic function in most patients by the age of 2 years.[6,93,94] In view of these conflicting data across regions, further studies are needed to fill this gap in knowledge regarding the age and prevalence of splenic dysfunction in patients with SCD in Africa. Additionally, several studies have evaluated the role of hydroxyurea in improving spleen function in patients with SCD.[95,96] The splenic filtration function was preserved after 3 years on treatment in a third of the patients following hydroxyurea; starting treatment at a younger age and baseline spleen function were both associated with a favourable outcome. Recently, the safety and efficacy of hydroxyurea in young children with SCD residing in malaria endemic regions of Africa has been demonstrated.[97,98] Therefore, the development of new tools to assess splenic function or the optimisation of existing ones in low-income countries can play a role in identifying those patients who can benefit from such therapy, especially in Africa, where there is a high prevalence of diseases such as SCD and malaria that can affect the spleen concurrently.

Splenic function can be measured using several methods including liver spleen scintigraphy, enumeration of Howell–Jolly bodies in red blood cells either manually or by flow cytometry, and counting of pitted red cells using direct interference, phase-contrast microscopy.[99] Unfortunately, these tests are not readily available in most low-income settings of Africa, as evidenced by the scarcity of data in the present review. A simple method has been described, which is based on counting red cells containing argyrophilic inclusions using a light microscope. This method has a good correlation with the pitted red cells count method and a good inter- and intra-observer reliability.[100] This method may be suitable to assess splenic function in patients with SCD in Africa, where resources for spleen scintigraphy and interference phase-contrast microscopy are absent.

Strengths and limitations of the present review

The major strength of our present review is the comprehensive inclusion of many studies reporting on various splenic complications across Africa. It included articles from non-indexed journals to avoid publication bias, and there were no age, language, or time inclusion restrictions. However, the findings of the review should be interpreted with caution. The studies measured spleen size in patients with SCD using different approaches, which made it difficult to compare reported spleen sizes among the studies. Criteria used to define some of the splenic complications and infections were not stated or were inconsistent. Only a few studies reported on spleen-related complications, so we were unable to combine the data to provide pooled estimates for these complications.

Conclusion

In Africa, SCD is a prevalent, chronic condition that places a high burden on the health services and on patients and their families. Evidence from the present review indicates that splenomegaly is prevalent among patients with SCD; however, splenomegaly-related complications are under reported and may contribute to significant but unrecognised complications. The spleen seems to persist longer in patients with SCD in Africa when compared to their counterparts in the West, although this maybe similar to what is observed in the Middle East; however, factors explaining this occurrence may be different. In patients with SCD in Africa there was less association between splenomegaly and factors such as HbF level and the presence of alpha thalassaemia traits compared

to similar patients in the Middle East; instead, a link between malaria and splenomegaly seems to be indicated by the data in the present review. There was evidence of an association between splenomegaly and retention of the spleen function in patients with splenomegaly, although the data are limited. Furthermore, there was no information in any of the studies in the present review regarding the link between spleen function and the risk of infection. In Africa, where the majority of children with SCD may die because of infections and with splenic dysfunction contributing a significant part, the importance of detecting those at high risk cannot be over emphasised. Thus, further studies are needed to fill this gap in knowledge regarding the age and prevalence of splenic dysfunction in patients with SCD in Africa. Such knowledge can be employed in the management of infection risk in patients with SCD and ensure a more effective use of the limited resources available.

Author contributions

Adama I. Ladu designed the study, collected data, analysed the results, and wrote the paper. Abiola O. Aiyenigba collected data, reviewed the results, and commented on draft manuscripts. Adekunle Adekile reviewed the results and commented on draft manuscripts. Imelda Bates assisted with the study design, reviewed the results, and commented on draft manuscripts. The authors have read and approved the final manuscript.

Conflict of interest disclosure

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