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Age of first pain crisis and associated complications in the CASiRe international sickle cell disease cohort

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ABSTRACT

Pain is a hallmark of Sickle Cell Disease (SCD) affecting patients throughout their life; the first pain crisis may occur at any age and is often the first presentation of the disease. Universal newborn screening identifies children with SCD at birth, significantly improving morbidity and mortality. Without early screening, diagnosis is generally made after disease manifestations appear. The Consortium for the Advancement of Sickle Cell Research (CASiRe) is an international collaborative group evaluating the clinical severity of subjects with SCD using a validated questionnaire and medical chart review, standardized across 4 countries (United States, United Kingdom, Italy and Ghana). We investigated the age of first pain crisis in 555 sickle cell subjects, 344 adults and 211 children. Median age of the first crisis in the whole group was 4 years old, 5 years old among adults and 2 years old among children. Patients from the United States generally reported the first crisis earlier than Ghanaians. Experiencing the first pain crisis early in life correlated with the genotype and disease severity. Early recognition of the first pain crisis could be useful to guide counseling and management of the disease.

Sickle Cell Disease (SCD) is a group of inherited blood disorders characterized by a single nucleotide mutation in the beta globin gene (Glu6Val) resulting in the predominance of Hemoglobin S; this causes hemoglobin polymerization in the case of deoxygenation, with subsequent sickling of red blood cells. The mutation may be inherited as heterozygous trait, homozygous (SS genotype), or compound heterozygote combined with another beta globin defect (Sickle Beta Thalassemia Zero or Plus: S/Beta0, S/Beta+; SC genotypes), contributing to the

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broad spectrum of disease severity.

Genotypes SS and S/Beta0 are generally more severe than S/Beta+ and SC [1], but the genotype alone is not predictive of the clinical course. Several studies attempted to find models or scores to predict disease severity; vaso-occlusive complications and pain are among the most studied factors. Platt et al. [2] showed that, in 3578 subjects within the Cooperative Study of Sickle Cell Disease (CSSCD), adults experiencing more pain crises per year had higher risk of dying earlier. Miller and colleagues, for the CSSCD, showed children who experienced episodes of dactylitis in the first year of life were more likely to have adverse outcomes later in childhood including stroke, frequent pain, recurrent acute chest syndrome (ACS) and death [3]. This finding has not been confirmed in other cohorts. For example, in the Dallas Newborn Cohort, dactylitis in young children was not associated with increased mortality or stroke, but to early hospitalization for pain within the first 3 years of life [4].

Early diagnosis of SCD is critical for early anticipatory guidance for disease management and to initiate preventive strategies against infectious disease; understanding the possible clinical course based on the early manifestations of the disease could help alleviate potential future complications. In high-resource countries, increasing efforts to implement universal newborn screening for SCD correlated with reduced morbidity and mortality during the first 20 years of life due to prophylactic interventions started soon after birth [5,6]. In developing countries, like sub-Saharan Africa and central India, where the prevalence of the disease is higher, only pilot newborn screening programs have been implemented, largely due to costs and logistics [7]. Therefore, up to 85% of children with SS disease in Subsaharan Africa are thought not to survive after 5 years of age and many of them die undiagnosed [8,28]. Thus, more needs to be done for developing countries to investigate the early presentation of SCD that will aid in the diagnosis and treatment.

This study describes the age of first pain crisis within an international cohort of patients and analyzed its value as a predictor of SCD complications and need for disease modifying therapy.

The Consortium for the Advancement of Sickle Cell Research (CASiRe) is an international multi-institutional collaborative group evaluating the clinical severity of adults and children with SCD across four countries (United States, United Kingdom, Italy and Ghana) using a validated questionnaire and medical charts review; data were abstracted from IRB approved registry in the UK and in Padova. The United Kingdom could not be included in this analysis as the age of first pain crisis had not been collected. Data were collected from 2011 to 2017 with IRB approval from each participating site as reported previously [9,10].

Painful episodes of extremities, bones, chest and abdomen not explained by any other known cause were registered as pain crises. Information regarding the age of first pain crisis, total number of painful events in the preceding 12 months, including home only, Day Hospital/Emergency Room (ER) visit, or Hospitalization were included. Patients were grouped according to the age of the first pain crisis: younger than 1 year, 1 to 2 years, 2 to 5 years, 5 to 10 years, and older than 10 years.

SCD complications (stroke, renal disease, ACS, priapism, gallbladder disease, leg ulcers, pulmonary hypertension, asthma and splenic sequestration) were registered if clinically diagnosed according to the local and international guidelines [11–14], and confirmed by the reporting investigator. Additional clinical data included patients on chronic blood transfusion and hydroxyurea, as well as main laboratory parameters available at the time of enrollment. For subgroup analyses, SS and S/Beta0 genotypes and SC and S/Beta+ genotypes were classified as two separate groups.

2.1. Statistics

Data was analyzed using SPSS 25.0 (IBM SPSS Statistics for Windows, Version 25.0). Continuous variables were expressed as means and standard deviations (SD) if normally distributed, and as medians and interquartile range (IQR) when not normally distributed; comparisons were made using *t*-test and Mann-Whitney *U* test. Categorical variables were expressed as frequencies and percentages, and groups were compared using Chi-square analysis and Fisher's Exact test. Significance was set at $p<0.05$.

3.1. Study subjects

Among the 700 patients that were enrolled in US, Ghana and Italy, data regarding age of first pain crisis were evaluable in 555 patients. Demographics and clinical characteristics are reported in Table 1. More information about geographic origin of patients and genotype distribution in the participating countries are detailed in Campbell et al. [9]

3.2. Age of first pain crisis

Median age of reported first pain crisis in the whole group was 4 years (IQR 7.00), earlier than 2 in 40.9% of patients (Table 2); in females

Baseline characteristics of study subjects.

Variables	Whole group (*n*=555)	Adult group (*n*=344)	Pediatric group (*n*=211)	p value[a]
Age, years, mean±SD	22.4±13.7	30.2±11.3	9.6 ± 4.4	
Range	0.5–69.2	18.0–69.2	0.5–17.8	
Gender				
Females, n (%)	309 (55.7)	197 (57.3)	112 (53.1)	ns
Males, n (%)	246 (44.3)	147 (42.7)	99 (46.9)	ns
Genotype				
SS, n (%)	391 (70.5)	248 (72.1)	143 (67.8)	ns
S/Beta0, n (%)	17 (3.1)	11 (3.2)	6 (2.8)	ns
S/Beta+, n (%)	21 (3.8)	12 (3.5)	9 (4.3)	ns
SC, n (%)	126 (22.7)	73 (21.2)	53 (25.1)	ns
Countries				
US, n (%)	209 (37.7)	97 (28.2)	112 (53.1)	<0.00001
Ghana, n (%)	328 (59.1)	239 (69.5)	89 (42.2)	<0.00001
Italy, n (%)	18 (3.2)	8 (2.3)	10 (4.7)	ns
Hematology				
Hb, g/dl, mean±SD	9.0 ± 2.9	8.9 ±2.9	9.1±2.8	ns
WBC, cells × 103/μl	11.0 ± 5.9	10.7± 5.3	11.4± 6.6	ns
PLT, cells × 103/μl	365.4±186.3	373.7 ±177.8	350.0 ± 191.0	ns
Medical history				
Stroke, n (%)	28/549 (5.1)	17/341 (5.0)	11/208 (5.3)	ns
Acute chest syndrome, n (%)	168/539 (30.3)	97/333 (29.1)	71/206 (34.5)	ns
Splenic sequestration, n (%)	45/529 (8.5)	20/318 (6.3)	25/211 (12.3)	0.025
Priapism, n (%)	42/246 (17.1)	34/147 (23.1)	8/99 (8.1)	0.002
Gallstones, n (%)	89/506(17.6)	67/302 (22.2)	22/204 (10.8)	0.0009
Cholecystectomy, n (%)	81/507 (16.0)	60/304 (19.7)	21/203 (10.3)	0.0046
Chronic transfusion, n (%)	44/555 (7.9)	26/344 (7.6)	18/211 (8.5)	ns
On HU, n (%)	120/555 (21.6)	53/344 (15.4)	67/211 (31.7)	<0.00001

[a] Adults vs peds.

Categorized age of 1st pain crisis.

	Whole group *n*=555		Adult group n=344		Pediatric group n=211		p value[a]
	n (%)	Cumulative %	n (%)	Cumulative %	n (%)	Cumulative %	
Age of 1st PC <1yo	152 (27.4)	27.4	75 (21.8)	21.8	77 (36.5)	36.5	0.000
Age of 1st PC 1–2 yo	75 (13.5)	40.9	36 (10.5)	32.3	39 (18.5)	55.0	0.000
Age of 1st PC 2–5 yo	116 (20.9)	61.8	67 (19.5)	51.7	49 (23.2)	78.2	0.017
Age of 1st PC 5–10 yo	117 (21.1)	82.9	81 (23.5)	75.3	36 (17.1)	95.3	0.024
Age of 1st PC >10yo	95 (17.1)	100.0	85 (24.7)	100.0	10 (4.7)	100.0	0.000

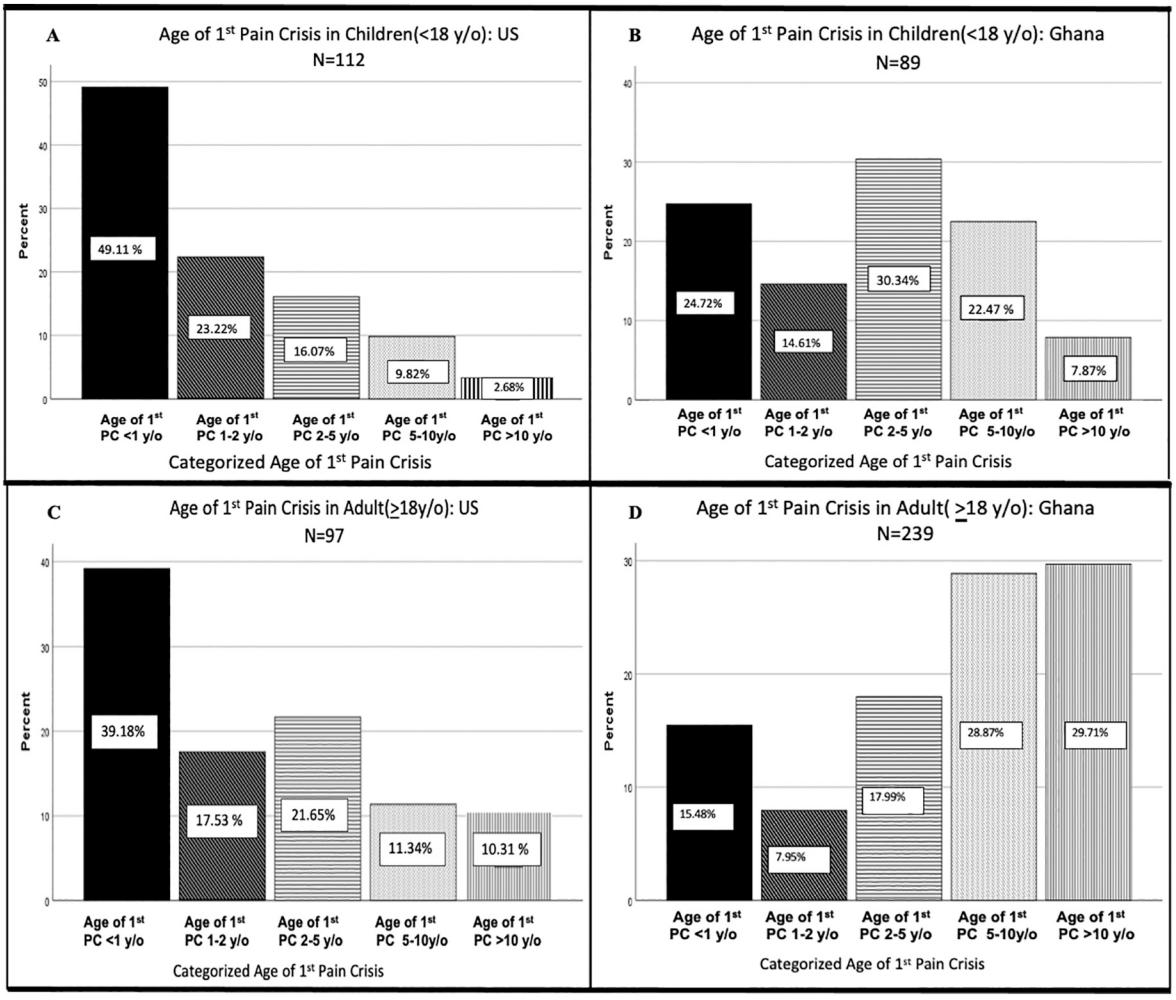
PC=Pain Crisis.
[a] (adult vs pediatric).

the median age was 4 (IQR 7.0) and in males 3.2 (IQR 7.0), $p = 0.98$.

Among the adults, the median age of reported first pain crisis was 5 years (IQR 8), with 32.3% before the age of 2; in the pediatric group, the median age was 2 years (IQR 4), earlier than 2 in 55%, and earlier than 1 in 36.5% of patients ($p<0.0001$ comparing adults and children's age of first pain crisis, both means and categories) (Table 2).

The difference in the age of first pain crisis between children and adults was maintained even after analyzing the three countries separately. In pediatric patients, the first pain crisis was reported in the first 2 years of life by 72.33% of children in the US but only 39.33% in Ghana (Fig. 1A–B). Among the adults, the first pain episode occurred by the first 2 years in 56.71% of patients in the US and 23.43% of adults in Ghana (Fig. 1C–D). In Italy, no patients in either the pediatric or adult group reported the first painful event before age 1 year (see Supplemental Figure).

Patients with SS or S/Beta0 genotype experienced their first PC generally earlier than those with SC or S/Beta+ genotypes, and within each genotype and age subgroup in US the median age reported was



Age of first pain crisis per country: A: categorized age in children in US; B: categorized age in adults in the US; C: categorized age in children in Ghana; D: categorized age in adults in Ghana.

earlier than in Ghana, apart from children with genotype SC or S/Beta+, for whom the age at presentation was similar between US and Ghana (Fig. 2).

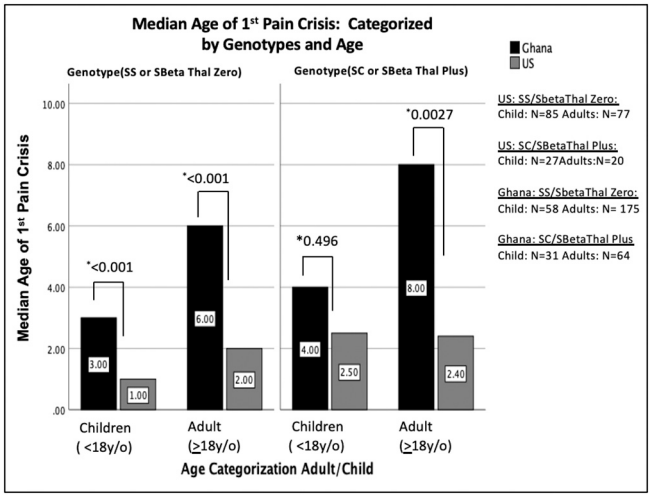
3.3. Age of first pain crisis, pain burden and health resources utilization

For the entire cohort, patients who presented with their first pain crisis before 1 year of age reported more pain crises requiring hospitalizations per year in children (median 1 vs 0, p=0.023) and adults (median 1 vs 0, p=0.004) in the 12 months preceding the enrollment. No significant difference in total number of pain crises and those requiring ED visit was noted in either children or adults. Among children with the SS or S/Beta genotypes, those who experienced the first pain crisis before 1 year reported more painful episodes per year (median 4 and 2 respectively, p: 0.010), and more hospitalizations/year (median 1 vs 0, p=0.019), compared to those who presented the first crisis later. No correlation with pain burden and early pain presentation was noted in the pediatric SC and S/Beta+ genotype group, nor in adults analyzed by either genotype or country.

In the US cohort, pediatric SCD patients (all genotypes) who reported pain crisis before 1 year old reported more pain crises per year (median 4 vs 2, p=0.046) compared to those with later presentation of pain. In patients with the SS and S/Beta0 genotype, those who reported pain before 1 year old experienced a higher number of pain crises per year (median 4 vs 2, p=0.016). US patients with SC and S/Beta+ did not show any correlation between age of first pain crisis <1 year old and pain burden. In the Ghanaian children, there was no association between age of first pain crisis and pain burden regardless of genotypes.

3.4. Age of first pain crisis and transfusion requirement

No Ghanaian patients were on chronic transfusions. In the US both children and adults who experienced earlier pain crisis were more likely to be placed on chronic transfusions (in children the median age of first pain crisis in those on transfusions at the time of enrollment was 0.54 years old, IQR 0.85, versus 2, IQR 3.1, in those not transfused (p=0.023); among adults, median ages were 2, IQR 3.7, in those on chronic transfusions, versus 5, IQR 8 (p=0.014), in those who were not). The same association was found among children with the SS and S/Beta0 genotype group in the US (median age 0.5, IQR 0.5, versus 1.37, IQR 1.63, p=0.025), but not in adults. The primary reasons for starting transfusions were primary and secondary stroke prevention (n=11) and chronic pain (n=7), recurrent priapism (n=1), recurrent ACS (n=1), pre-BMT (n=1), splenic sequestration (n=1), symptomatic anemia (n=1), thromboembolism (n=1).



Median Age of first pain crisis in Children and Adults in the US and Ghana according to genotypes; *p value <0.05 significant.

3.5. Age of first pain crisis and hydroxyurea therapy

Children reporting their first crisis before 1 year were more likely to be on hydroxyurea compared to others (median age 1, IQR 1.3, vs 3, IQR 4.4, p=0.001) at the time of enrollment. Limited to the U.S. children who had their first crisis before 1 year old, 32/54 (59.3%) were taking hydroxyurea compared to 20/57 (35.1%) of those who did not (p-value 0.010). Those taking hydroxyurea at the time of data collection had their first crisis at mean age 1.72 years old (median 1), those not on hydroxyurea at mean 2.57 years old, (median 2), p=0.024. In the US the main reason for starting HU in those who had a crisis before age 1 was refractory pain (19/32) and recurrent ACS (14/32), and both in 6 patients. Only two Ghanaian patients were on hydroxyurea. There was no correlation with age of first pain crisis and hydroxyurea therapy in adults.

3.6. Age of first pain crisis and sickle cell related complications

Eleven pediatric patients were reported to have had a stroke; all strokes were in the US group, occurring in 9/55 patients who reported their first pain crisis earlier than 1 year (median age 0.54 years) and in 2/57 of those having their first crisis after 1 year (p=0.022). Ten strokes were in the SS and S/Beta0 subgroup, with 8/62 (12.9%) of those who had the first crisis earlier than 1 year and 2/83 (2.4%) of those who had a first crisis after 1 year (p=*0.013*). Only 1 patient within the "SC and S/Beta+ genotype" group had a stroke, and, in that patient (SC genotype), the first pain crisis had occurred at 0.5 years old and stroke at 15 years old. No correlation was found with stroke in adults.

The statistically significant associations between the age of first pain crisis earlier than 1 year and SCD related complications in pediatric and adult patients are presented in Table 3.

3.7. Age of first pain crisis and laboratory parameters

Children (p=0.012) and adults (p=0.007) with SS and S/Beta0 genotypes who had their first pain crisis before 1 year old had lower MCV at the time of enrollment compared to those in the same genotype group who presented with the first pain crisis later. Adults who reported their first pain crisis before 1 year old had a higher LDH (p=0.022) in

Clinical correlation with age of first Pain Crisis (PC) <1 year/old; * p value <0.05 is significant. Correlations were analyzed for all the sickle cell related complications listed in Methods; only the statistically significant outcomes were reported.

Clinical outcome		Age of 1st PC >1 y/o: N (%)	Age of 1st PC <1y/o N (%)	p value
Pediatric group				
Genotype: SS and S-Beta0				
History of stroke	No:	81 (97.6)	54 (87.1)	*0.019
(N=145)	Yes:	2 (2.4)	8 (12.9)	
History of gallstones	No:	75 (90.4)	46 (76.7)	*0.034
(N=143)	Yes:	8 (9.6)	14 (23.3)	
Adult group				
Genotype: SS and S-Beta0				
History ACS (N=252)	No:	31 (55.4)	144 (73.5)	*0.013
	Yes:	25 (44.6)	52 (26.5)	
History of gallstones	No:	32 (62.7)	145 (79.7)	*0.016
(N=233)	Yes:	19 (37.3)	37 (20.3)	
History of cholecystectomy	No:	33 (66.0)	150 (81.5)	*0.032
(N=234)	Yes:	17 (34.0)	34 (18.5)	
Genotype SC and SBeta+				
History ACS (N=81)	No:	52 (82.6)	9 (50)	*0.004
	Yes	11 (17.4)	9 (50)	

comparison to subjects who experienced their first pain crisis later. Children with SC and S/Beta+ genotype who had the first crisis earlier than 1 year old had lower platelets at the time of enrollment (p=0.019).

This cross-sectional multicenter study provided a wide overview on the age distribution of the first pain crisis in SCD in adults and children with both severe and mild genotypes across different countries; it also investigated the association of this event with the disease course. Globally, whatever the patient's age, country or genotype, by the fifth year of life more than half of patients have already experienced the first pain crisis. However, the data change slightly according to the above-mentioned variables, as discussed below.

Our study reported the age of first pain crisis earlier in children than adults. This could be a result of the study design, as parents of patients are more likely to remember such events than adult patients. However, discrepancies emerge when comparing countries; in the US, both adults and children experienced their first pain crisis earlier than in Ghana. Lower disease awareness in spite of the higher prevalence of SCD and sickle trait in Africa may contribute to diagnostic delay and older age of first pain crisis [15,16]. Disease awareness, however, cannot fully explain the outcome, even in the US, which has a robust universal neonatal screening program [17,18]. Environmental factors, such as climate and air pollution, diet and nutritional status could influence frequency and severity of pain and explain the differential reporting between the countries [18,19] [20].

Our data show that age of first pain crisis categorization in Ghana appears randomly distributed, contrasting with the linearly decreasing trend observed in the US, suggesting the possible role of neonatal screening. Universal newborn screening programs identify children with SCD at risk of pneumococcal disease in order to start penicillin prophylaxis and immunizations; by recognizing patients at birth, more intensive follow up and potential introduction of hydroxyurea has been shown to lower disease burden and reduce complications [21,22]. Where newborn screening is not routinely performed, diagnosis occurs after one or more symptoms, with pain often the earliest to appear [23,24]. Various studies from other countries reported the age at diagnosis but did not provide details regarding age of first pain crisis [25,26]. Our data on age of first pain crisis in US patients is consistent with age of first pain crisis in a French newborn cohort study [24] (median: 12 months of age versus 12.8 months), considerably sooner than a Nigerian study reported by Chukwu (median 24 months) [26], suggesting a critical role for newborn screening, which is available in the US and France, but not Nigeria.

Genotype has previously been shown to predict age of first pain crisis, correlating with both disease severity and treatment with transfusion and hydroxyurea. Our data confirm the association between an early onset of the first pain crisis and increased pain burden and disease related complications. However, it is important to note the change in treatment paradigm that occurred over the last several years, as clinician choice to start hydroxurea therapy is influenced by the current recommendation in favor of offering hydroxyurea to all young SS/SBeta0 patients regardless of disease severity [11], including in Africa, where our Ghanaian colleagues report well over 600 patients on hydroxyurea, representing over 10% of their patients (personal communication, Dr. C. Segbefia).

The onset of pain has already been studied as a predictor of disease course. Although the Dallas Newborn Cohort, a study whose subjects were diagnosed at birth by newborn screening and received comprehensive care, did not identify a link between early VOC and mortality and stroke risk, the study did suggest an association between early hospitalizations for pain, including dactylitis, and higher disease burden later in life [4]. Our data confirms this finding, and also reveals an increased risk of stroke in children, but not in adults. While it may be possible that children and adult patients were not included due to early mortality, it is more likely related to how and where patients were enrolled for the study. For example, recruitment of our subjects in Ghana occurred during the general SCD clinic and not in the specialty clinic where most stroke patients were seen (personal communication, Dr. C Segbefia). An increased mortality in patients who experience their first crisis early in life could also be another possible explanation of the difference between adults and children, as well as between Ghana and the USA.

Our study also revealed an increased risk of gallstones and cholecystectomy within the SS and S/Beta0 genotype group suggesting a link between early first pain crisis and a more pronounced hemolytic phenotype. In addition, both children and adults with early first PC had a lower MCV compared to others, that, given the high prevalence of SS genotype in both groups, suggests a possible coexistence of alpha gene mutation. The role of the coinheritance of alpha thalassemia with sickle mutation has recently been shown to correlate with higher pain frequency and a higher iron burden, discounting the possibility of MCV being a result of iron deficiency. [27] Alpha thalassemia has been reported to reduce the hemolysis and the risk of strokes, but also to increase the rate of avascular necrosis and painful episodes [1].

4.1. Limits of the study

Cross-sectional retrospective questionnaire cohort studies have limitations particularly regarding collection of data that could result in inaccurate reporting, or missing information. While it is possible that recall bias played a role in the recollection of our adult patients' first pain episode, the data suggest that bias played a minimal role in the outcome of the study. Although the questionnaire did not ask specific information regarding age at diagnosis, dactylitis, or coinheritance of alpha thalassemia, 145 subjects of the available cohort could not be included as they did not respond to the question regarding the age of first pain crisis, making it impossible to discriminate whether they forgot to respond or if they never had a crisis. The correlation between age of first crisis and likelihood of being on regular preventive treatment in the whole cohort was biased by the low number of Ghanaian patients on regular transfusion or hydroxyurea. Moreover, the 18 additional patients from Italy were not included in the analysis on phenotype, because of the heterogeneity and fewer numbers compared to the other countries.

Though the prediction of the severity of phenotype has been very challenging after decades of related research, our findings support that the age of the first pain crisis could represent a useful indicator of disease severity, with a more severe phenotype in patients with earlier crises. The implication for the need to develop newborn screening programs should be apparent, as disparities in the first pain crisis identification emerge between countries. A universal early-initiated preventive management for SCD with hydroxyurea and possibly other new medications coming down the pipeline could avoid the severe complications, poor quality of life, and increased morbidity of the disease.

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IT: Conceptualization, Resources, Writing Original Draft, Data Curation, Formal Analysis, Visualization; CS: Resources, Visualization, Investigation, Review and Edits. AC: Conceptualization, Methodology, Validation, Formal Analysis, Data Curation, Funding Acquisition, Supervision, Project Administration, Visualization. All the authors: Resources (data collection from patients), Investigation, reviewed, edited and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

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Declaration of competing interest

The following authors declare conflict of interest:

A Campbell: research funding and consultancy from Global Blood Therapeutics (GBT), Novartis and Bluebird Bio; and consultancy for Imara; D Manwani: research funding from Grifols; consultancy for Novartis, Pfizer, Global Blood Therapeutics; B Andemariam: consultancy for Novartis, Pfizer, NovoNordisk, Emmaus, Cyclerion, Terumo, Sanofi, CRISPR/Vertex, Forma Therapeutics, Global Blood Therapeutics, Roche; research funding: Imara; B Inusa: education funding: Novartis AstraZeneca, Global Blood Therapeutics, Celgene, Vertex; C. Strunk: consultancy Global Blood Therapeutics, Medunik, and Novartis; R Colombatti: research funding: Global Blood Therapeutics, Novartis. W Zempsky: consultancy for Pfizer and Glycomimetics; No disclosures to declare from the other co-authors.

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