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Original Article

Sickle Cell Trait, Clinical Manifestations and Outcomes: A Cross-Sectional Study in Colombia: Increasing Rate of Symptomatic Subjects Living in High Altitude

Diego A Vargas-Hernández[1], Adriana Catalina Uscategui-Ruiz[1], Andrés Jesus Prada-Rueda[1] and Consuelo Romero-Sánchez[2,3].

[1] Hospital Militar Central, Department of Internal Medicine, Universidad Militar Nueva Granada, Medical School, Bogotá, Colombia.
[2] Hospital Militar Central, Rheumatology and Immunology Department/Clinical Immunology Group, Bogotá, Colombia.
[3] Universidad El Bosque, Cellular and Molecular Immunology Group/INMUBO, Bogotá, Colombia.

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Abstract. ***Background:*** **Sickle cell trait (SCT) is an autosomal recessive blood disorder in which patients are heterozygous carriers for hemoglobin S (HbAS) and are usually asymptomatic. We performed a descriptive analysis of clinical manifestations and outcomes associated with SCT.** ***Methods:*** **This was a descriptive, cross-sectional study that included patients with SCT from 2014 to 2020 at Hospital Militar Central, the reference center of the Military forces in Bogota, Colombia.** ***Results:*** **Of 647 hemoglobin electrophoresis analyzed, we identified 51 patients with SCT, including 43 males (84.3%) and eight females (15.7%), with a median age of 22 years (IQR 15–36 years). Of these, 28 (54.8%) were Afro-Colombian, 23 (45.1%) were Colombian mestizos, and 31/51 (60.8%) of patients were active military members. Twenty-four patients (47.1%) were asymptomatic, and Twenty-seven patients (52.9%) were symptomatic (systemic complications); Most of the patients who presented symptoms were active military members of the Colombian military forces. Splenic complications were the most important (85.2%), p=0.0005, and there was a wide spectrum of splenic complications. In addition, we found significant elevations in leukocytes, bilirubin, LDH, and CRP. Eighteen patients (66.7%) received medical management, five (18.5%) required splenectomy, and only 5.9% of patients were sent for genetic counseling.**
Conclusions: **Military Personnel is a population with a high risk of developing symptoms, and splenic complications were the most relevant in symptomatic patients. Most patients received medical treatment, and 18.5% of patients required splenectomy. Our results reflect the absence of redirection of these patients to genetic counseling.**

Keywords: Sickle Cell Trait; Splenic Infarction; Splenic Diseases; Hemoglobinopathies; Military Personnel.

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Correspondence to: Diego A. Vargas-Hernández. Hospital Militar Central, Department of Internal Medicine, Tv 3 No 49-00 Bogotá, CO 110231 3598888, Universidad Militar Nueva Granada, Medical School Bogota, CO, 6500000. ORCID: https://orcid.org/0000-0002-2584-5195 E-mail: dvargashdez@gmail.com u0401551@unimilitar.edu.co

Introduction. Sickle cell trait (SCT) is an autosomal recessive inherited blood disorder caused by the substitution of glutamic acid for valine due to an abnormal allele mutation within the β globin gene, with

the other allele of the gene without alteration. These patients are heterozygous or carriers for hemoglobin S (HbAS); in contrast, if the other allele of the β globin gene also contains the mutation, patients are considered homozygous for the mutation (HbSS), or if patients have another mutation (e.g., HbC or β-thalassemia), the individual will develop sickle cell disease (SCD) among which hemoglobin variants SS, SC, Sβ-thalassemia are included.[1,2]

The HbS gene is distributed worldwide and affects millions of people with an especially high frequency in sub-Saharan Africa, the countries of the Middle East, and India.[2] The overall estimate of incidence in the United States for SCT was 15.5 cases per 1,000 births and is more prevalent in the black population (73.1 per 1,000) and less prevalent in Hispanic newborns (6.9 per 1,000 newborns);[3] it is estimated that the number of newborns with SCD globally will increase to more than 400,000 by 2050.[4]

Compared to SCD, which is associated with serious conditions and complications, most patients with SCT are asymptomatic, usually living their entire lives without a diagnosis. Consequently, in countries with no adequate screening programs, it is uncommon to diagnose this pathology, and descriptions of symptomatic patients with SCT are rare. Furthermore, most literature is limited to case reports or series and a systematic review of cases.[1,5–9] We did not find any reports or studies conducted in Colombia on patients with SCT.

Patients with SCT present symptoms only in extreme conditions of high altitude, severe dehydration, or high-intensity physical activity,[10–12] which is explained by red blood cell sickling and increased mechanical fragility due to the polymerization of hemoglobin HbS[13,14] with consequent microvascular occlusion resulting in complications or clinical conditions that can be life-threatening.[7,15,16] Symptoms are common with exposure to low oxygen tension or altitude, including nonpressurized aircraft cabins, or in people exercising in mountains or the military in high-altitude locations.[7,16]

When observing complications or manifestations, patients with SCT may present with splenic infarction,[6,9] venous thromboembolism (PE and DVT),[1,17] renal involvement (including proteinuria, hematuria, and chronic kidney disease),[1,18] rhabdomyolysis,19,20 sudden death,[21] and others; in paraclinical data, increased levels of bilirubin, lactate dehydrogenase (LDH), and increased reticulocyte count have been described, and on some occasions, anemia has been observed.[18,22,23]

Diagnostic confirmation of SCT is performed by hemoglobin electrophoresis in gel or capillary electrophoresis or high-performance liquid chromatography (HPLC).[24,25] The presence of SCT is established by finding both hemoglobin A (HbA) and hemoglobin S (HbS), with an amount of HbA greater than that of HbS (i.e., HbAS); typically, hemoglobin S levels are between 20% and 45%.[26,27]

Based on this, we conducted a descriptive observational, cross-sectional study in a quaternary care hospital in Bogota, Colombia. We included patients with an SCT diagnosis and described clinical manifestations, paraclinical and imaging findings, and the treatment to which they were subjected. In addition, we compared the clinical and paraclinical variables of patients with SCT who had clinical manifestations and patients who were asymptomatic.

Material and Methods.

Type of Study. This report is a descriptive, cross-sectional study with an analytical component that includes patients from the Hospital Militar Central, a reference center for military forces in Bogota, Colombia, with a diagnosis of SCT confirmed by hemoglobin electrophoresis in the institutional laboratory between January 2014 and December 2020.

Inclusion criteria. We included all patients who underwent hemoglobin electrophoresis at the Hospital Militar Central, including-active military members of the Colombian military forces and nonmilitary members (family, wife, children, and parents) who attend the Hospital Militar Central. In Colombia and its military forces, there are no screening programs for hemoglobinopathies, so the reasons for which hemoglobin electrophoresis was performed were variable; it was performed on symptomatic patients, patients with a family history, and patients with abnormalities in blood count, among other reasons.

Exclusion criteria. We exclude patients with a diagnosis of SCD defined as patients with HbSS, HbSC, HbSβ^+ thalassemia or HbSβ^0 thalassemia, repeat patients, or those without data in the clinical history.

Statistical analysis. We built a database of important variables, and statistical analyses were carried out using IBM SPSS Statistics; quantitative variables are expressed as the mean, median, and interquartile ranges, as appropriate; qualitative variables are expressed as absolute values and percentages. The qualitative variables were compared using the chi-square or Fisher's exact test. The quantitative variables between the clinical presentation groups were analyzed using the nonparametric Mann–Whitney U test. A p-value <0.05 was considered statistically significant. The project was endorsed by the Research Ethics Committee of the Hospital Militar Central, code-2021-030.

Results. A total of 647 hemoglobin electrophoresis results were analyzed, from which institutional medical history information was obtained; 123 (19.01%)

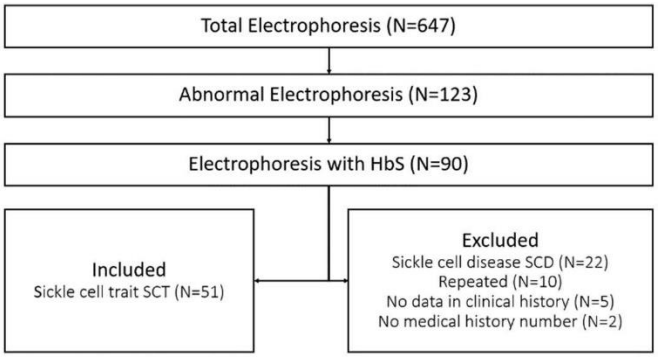

Figure 1. Flow Chart selection process of patients with Sickle cell trait.

abnormal results were found among patients with some hemoglobinopathy, and a total of 90 patients (13.91%) with HbS were found, of which 39 met exclusion criteria, resulting in a total of 51 patients (7.88%) diagnosed with SCT (**Figure 1**).

In the descriptive analysis, we found a total of 51 patients, of which 43 were male (84.3%) and 8 were female (15.7%), and the median age was 22 years old (IQR 15–36 years). Of the Colombian population analyzed, 28 (54.9%) were Afro-Colombian and 23 (45.1%) Colombian mestizos; additionally, 31/51 (60.8%) of patients were active military members of the Colombian military forces. These 51 patients in the analysis presented a percentage of HbS with a median of 38 (IQR 37-39), predominating between 35–40% (**Table 1**).

We found 24/51 patients (47.1%) with a diagnosis of SCT who had never presented with any symptoms or clinical manifestations associated with the diagnosis (classified as "asymptomatic" patients) and 27/51 patients (52.9%) who presented with systemic complications (splenic, hepatic, renal, urological, or other), which led to the diagnosis of the disease (classified as "symptomatic" patients). Most of the patients who presented symptoms were active military members of the Colombian military forces 24/27 (88,8%)

In patients classified as symptomatic (n=27), clinical manifestations were associated mainly with a change in altitude in 17 (63.0%) and, less frequently, with physical activity in two (7.4%), infection in two (7.4%), travel in three (11.1%), or no known factor in three (11.1%) (p= 0.0005) (**Supplementary Figure 1**). High altitude was the risk factor most commonly associated with clinical complications, with a likelihood ratio (LR) of 29.3. The three patients who presented clinical manifestations associated with travel were active military patients with symptoms associated with long trips by land, in which there were no significant changes at the altitude of the cities.

There was no association of any comorbidity (smoking, hypertension, diabetes mellitus, dyslipidemia, cancer or autoimmune disease.), or any known family history of hemoglobinopathy S with the development of symptoms (p = 0.054 and p = 0.139, respectively).

Table 1. Demographic characteristics of patients with Sickle cell trait.

Demographics characteristics	Frequency	Percent (%)
Sex		
Male	43	84,3
Female	8	15,7
Age		
Mean	25,84	SD 14,55
Median	22	IQR 15 - 36
Race		
Afro-Colombian	28	54,9
Mestizo Colombian	23	45,1
Occupation		
Non-military	20	39,2
Military	31	60,8
Clinical Manifestation		
Asymptomatic	24	47,1
Symptomatic	27	52,9
Percentage of HbS		
20 - 25 %	2	3,9
30 - 35 %	3	5,9
35 - 40 %	43	84,3
40 - 45 %	3	5,9

Symptomatic patients presented some characteristic symptoms and signs, the most important of which were abdominal pain and fever. The pain was increased by palpation and splenomegaly (p = 0.0001) (**Table 2**).

In symptomatic patients, splenic complications were the most frequent systemic manifestations in 23/27 patients (85.2%) vs. not having splenic complications in four (14.8%)] (p=0.0005); splenic infarction occurred in 10/23 of these patients (43.5%) and was the most common manifestation; however, other splenic complications were also found, including splenomegaly 5/23 (21.7%), subcapsular hematoma 4/23 (17.4%), splenic abscess 2/23 (8.7%), and splenic rupture 2/23

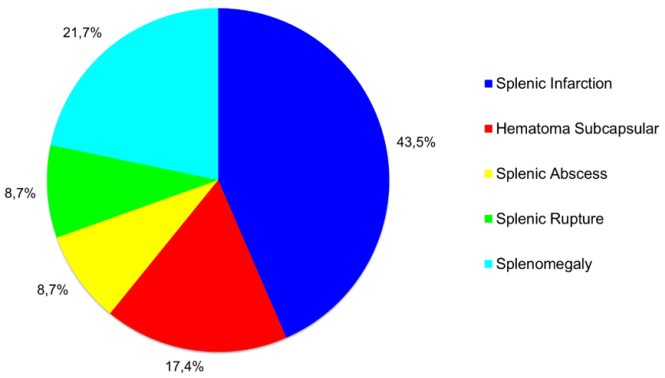

Figure 2. Splenic complications in symptomatic patients with Sickle cell trait.

Table 2. Symptoms and signs associated with sickle cell trait.

Symptoms and Signs in Symptomatic patients	Number of affected/Number studied	Percentage affected	Analysis
Abdominal Pain	**26/27**	**96,3%**	**p=0,001**
Fever	**12/27**	**44,4%**	**p=0,001**
Emesis	7/27	25,9%	p=0,011
Hematuria	1/27	3,7%	p=0,990
Palpation Pain	**22/27**	**81,5%**	**p=0,001**
Splenomegaly	**14/27**	**51,9%**	**p=0,001**
Jaundice	7/27	25,9%	p=0,011
Fever >38°C	7/27	25,9%	p=0,011

Statistical test: Fisher's exact test.

Table 3. Comparison of paraclinical variables in patients with sickle cell trait (Symptomatic and Asymptomatic).

Variable	Asymptomatic	Symptomatic	Analysis
Leukocytes	**4710 (3810 - 6600)**	**10870 (8900 -16190)**	**p=0,001**
Neutrophils	**2050 (1806 - 3610)**	**7672 (5521 - 13572)**	**p=0,001**
Lymphocytes	1830 (1340 - 2180)	1726 (1209 - 2235)	p=0,922
Monocytes	**375 (345 - 395)**	**790 (432 - 790)**	**p=0,002**
Eosinophils	88 (0-140)	105 (12 -228)	p=0,478
Hemoglobin	13,2 (12,3 - 14,7)	14,2 (12,4 - 15,0)	p=0,477
HCT	39,2 (26 - 42)	40,3 (34,7 - 42,6)	p=0,725
MCV	81,1 (73,8 - 87,2)	86,0 (83,2 - 88,2)	p=0,065
MCH	28,3 (26 - 29,7)	29,4 (28,3 - 30,7)	p=0,059
RDW	14,1 (12,5 - 16,2)	13,4 (12,9 - 15,6)	p=0,918
Platelets	273000 (185000 - 423000)	239000 (173000 - 480000)	p=0,711
TB	**0,7 (0,5 - 0,8)**	**1,8 (1,0 - 3,3)**	**p=0,004**
DB	**0,3 (0,2 - 0,4)**	**0,5 (0,4- 0,7)**	**p=0,001**
BI	**0,5 (0,3 - 0,7)**	**1,3 (0,5 - 2,1)**	**p=0,024**
AST	20 (16 - 23)	22 (19 - 29)	p=0,115
ALT	20 (12 - 26)	22,5 (17 - 34)	p=0,166
LDH	**225 (117 - 274)**	**326 (252 -416)**	**p=0,002**
ESR	4 (2-7,5)	6 (3,5 - 419)	p=0,510
CRP	**0,1 (0,05 - 0,4)**	**6,6 (2,0 - 15.9**	**p=0,020**
Creatinine	0,8 (0,6 - 1,0)	0,9 (0,8 - 1,0)	p=0,164
BUN	15 (12,8 - 17)	12,5 (9-17,3)	p=0,174
Albumin	4,2 (3,9 - 4,3)	4,4 (4,1 - 4,8)	p=0,698

Statistical test: Mann-Whitney U. HCT: Hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, RDW: Red blood cell distribution width, TB: Total bilirubin, DB: direct bilirubin, BI: indirect bilirubin, ALT: alanine transaminase, AST aspartate transaminase, LDH Lactate dehydrogenase, ESR erythrocyte sedimentation rate, CRP: C-reactive protein, BUN: blood urea nitrogen.

(8.7%) (**Figure 2**). The other systemic complications were present in 4/27 patients (14.8%); these were distributed among three patients with hepatic manifestation (11.1%) (i.e., cholelithiasis, jaundice, or liver abscess) and in one patient with a urological manifestation (3.7%) (i.e., priapism).

Among the relevant paraclinical data taken in the first medical contact (in the emergency room in symptomatic patients, and the medical consultation in asymptomatic), statistically significant differences were found in the leukocyte count and in the levels of bilirubin, LDH, and C-reactive protein (CRP) in patients who were symptomatic vs. asymptomatic (**Table 3**, **Figure 3**).

We found differences among the treatments performed in symptomatic patients: medical management was performed in 18 patients (66.7%), interventional radiology in three patients (11.1%), and surgery in six (22.2%) (p= 0.002). Among the surgical procedures, five (18.5%) required splenectomy for different causes, and one patient required

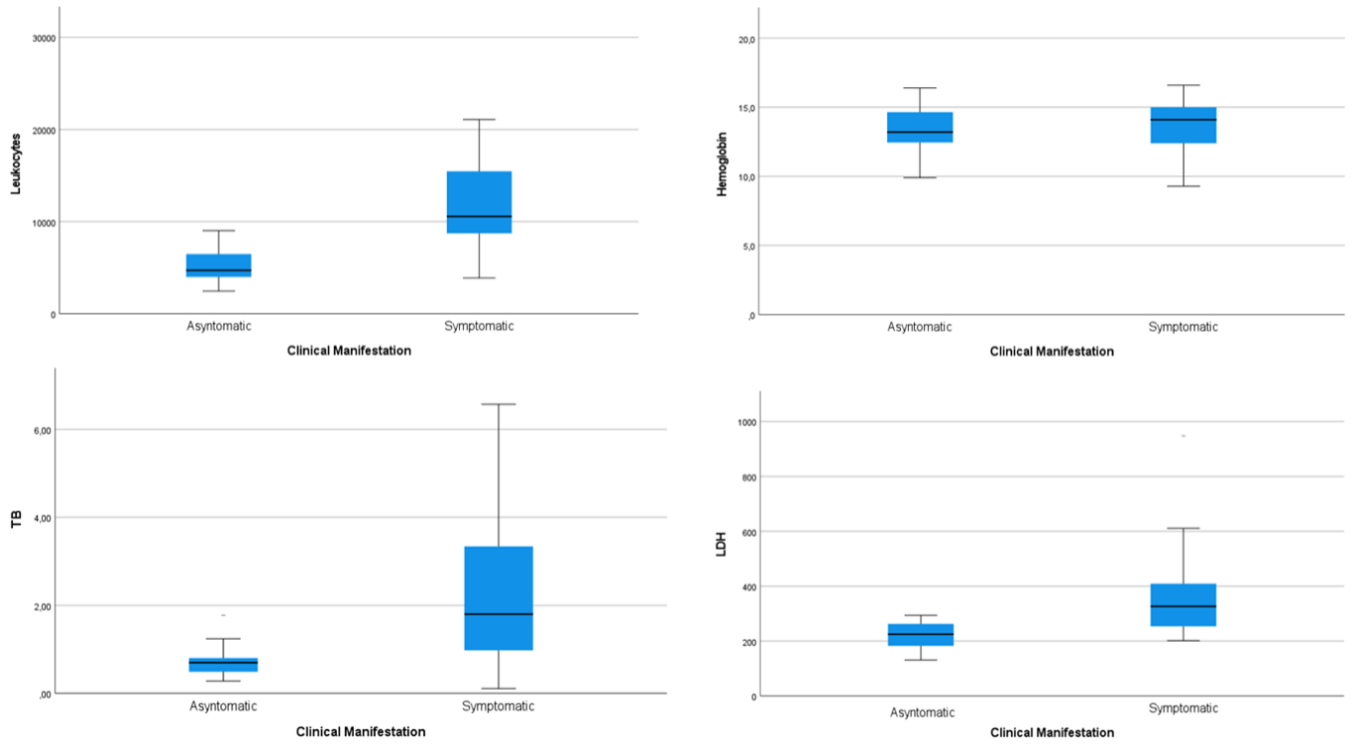

Figure 3. Comparison of leukocyte count, hemoglobin, total bilirubin, and LDH levels between symptomatic and asymptomatic individuals with SCT. Statistical test: Mann-Whitney U $p < 0.05$. TB: Total bilirubin, LDH: Lactate dehydrogenase.

cholecystectomy (3.7%) for cholelithiasis. However, there was no statistically significant association between the need for splenectomy and the percentage of HbS; no patients died in our study.

Finally, of the 51 patients with SCT, only three (5.9%) received genetic counseling, vs. 48 patients (94.1%) did not. These three patients were distributed between the two groups of patients in similar proportions: 1/27 in symptomatic patients and 2/24 in asymptomatic patients, without a statistically significant difference between the two groups (p=0.595) with Fisher's exact test (**Supplementary Figure 2**).

Discussion. The HbS gene is distributed worldwide, and its prevalence varies according to geographical region and country.[2] In our study, we found the presence of HbS in 13.91% of the studied population, with the presence of SCT in 7.88% of patients statistically more frequent in males than in females. Classically, it has been described that hemoglobinopathy S is associated with the black race or people of African descent; however, in our study, we found that 45.1% of the patients were Colombian Mestizos and 54.9% of patients with SCT were Afro-Colombians (African descent). Due to the wide distribution and ethnic mixtures of Colombia, SCT should be suspected in patients with compatible clinical manifestations, independent of race or ethnicity. The ancestry of the Colombian population has proceeded essentially from three racial groups: European, African, and Native American origin,[28] which is common for most South American countries.[29]

Although SCT is largely considered a benign carrier state, there are clear reports of clinical complications. Most of these associations have been described in epidemiological studies,[9,30] which found a clear association with chronic diseases, such as chronic kidney disease.[1] However, acute complications, such as splenic infarction, are considered rare, and the literature is limited to a few descriptions.[8,9] To the best of our knowledge, this is one of a few studies with the most SCT patients with acute symptoms.

In symptomatic patients, the most frequent systemic complication was splenic in 85.2% of cases. In addition, it has been described that the spleen is an organ highly prone to injury in SCD due to the unique characteristics of its microvasculature, along with the fact that sickle red globules decrease deformability and increase adhesion,[31,32] both of which mechanisms could also play an important role in splenic injury in SCT; however, there is no complete clarity on the mechanism in these patients.

High altitude was the main risk factor for presenting clinical manifestations in 63% of cases, along with a lower percentage of physical activity and infections. The places where clinical manifestations occurred most frequently in patients with symptomatic SCT were Bogotá and Pasto-Nariño, Colombia, where there are cities located at an altitude of 2,630 meters above sea level and 2,527 meters above sea level, respectively.

Compared with the largest reported study,[9] a systematic review of case studies between 1970 and 2020, consisting of 54 articles with 85 cases of splenic

infarction in individuals with SCT, found that 29% of cases occurred at an altitude between 2000 and 3000 m (similar to that of our patients), 46% occurred between 3000 and 4000 m, and 3% occurred at more than 4000 m. A low percentage of patients presented symptoms at less than 2000 meters. Physical activity was also an important risk factor for these patients;[9] physical activity or exercise was another trigger factor found in our patients. Military personnel are potentially at increased risk of triggering symptoms due to displacement to high-altitude regions and strenuous training;[16] therefore, it is important to evaluate for hemoglobinopathies in patients in these types of professions, who present with splenic manifestations when exposed to high altitude, despite not having a clear risk factor or family history known of SCT or SCD. In our study, most of the patients who presented symptoms were active military members of the Colombian military forces (88,8%); this explains the detection of a high number of SCT patients with acute symptoms.

The amount of circulating HbS can influence the prevalence of clinical complications in SCT. The co-inheritance of α-thalassemia (which reduces HbS levels) decreases the probability of clinical presentation.[30,33] In the same previously reported study,[9] the percentage of HbS varied from 29.8 to 46.5%, and only four cases (5%) had HbS less than 35%. In our study, no symptomatic patient had HbS less than 35%. Some reports find that co-inheritance of α-thalassemia and SCA, or SCD, has been associated with a lower MCV and a milder phenotype in SCA patients, e.g., lower stroke rates. Despite this, data are scarce on the co-inheritance of α-thalassemia and Sickle cell trait SCT,[33] and the effects remain unclear even in the African setting.[34] In our study, we perform hematological phenotypes, not hematological genotypes, or molecular diagnostic testing for the detection of 3.7 kb α-globin to evaluate the co-existing sickle cell trait/alpha thalassemia double heterozygosity.

We found a systematic review that described the spectrum of splenic complications in patients with SCD (defined by the genotypes HbSS, HbSC, HbSβ^+ thalassemia, or HbSβ^0 thalassemia) in Africa;34 they did not include patients with SCT. The spectrum of splenic complications reported includes splenomegaly in 12% to 73.2%, hypersplenism in 0.1% to 5%, splenic sequestration crisis in 2% to 3%, or as splenic rupture, splenic abscess, or splenic infarction, which were reported only in isolated studies.[34] Despite the important difference between the two pathologies (SCD and SCT), in our study, we also found a wide spectrum of splenic complications in SCT (splenic infarction, splenomegaly, splenic abscess, among others), being the most important systemic complications in these patients. In conclusion, although high-altitude splenic infarction is not uncommon and it is the main splenic complication that is reported in the literature, our findings emphasize that it is not the only splenic complication that SCT patients can have, but rather, there is a wide spectrum of splenic complications that must be included as classical manifestations of SCT.

In paraclinical data, increased bilirubin levels, LDH, reticulocyte count, and sometimes anemia have been described.[18,22,23] By contrast, we found no difference in hemoglobin levels or platelets among the symptomatic or asymptomatic groups; All complications are associated with different pathophysiological conditions in which the leukocyte count can increase,[14] which explains why a clear difference was found in WBC counts, with higher counts in symptomatic patients. However, although hemoglobin levels were similar, an interesting finding was statistically significant higher levels of bilirubin and LDH, possibly reflecting a low grade of hemolysis among "sickling" red blood cells, as described in these patients, which we can associate with the clinical presentation.[13–15] Therefore finding patients with splenic complications, increased LDH, and increased bilirubin should lead us to suspect a diagnosis of SCT, even in the absence of anemia.

Most cases of splenic complication can be successfully treated with hydration, analgesia, rest, oxygen, and other complementary measures. Splenectomy is indicated mainly in cases of splenic rupture with intraperitoneal hemorrhage, splenic abscess, or symptomatic massive splenomegaly and spleen sequestration crisis.[1,18] In our study; most patients were treated medically with symptomatic and supportive management, and 18.5% of patients required splenectomy for associated complications of those previously mentioned; patients who required splenectomy received prophylactic vaccination, which is essential in preventing secondary complications in the future.[35] One patient with SCT during hospitalization was taken for cholecystectomy for symptomatic cholelithiasis; although it has not yet been described that SCT increases the risk of cholelithiasis, chronic hemolysis could have contributed to its presentation in this patient.

Finally, of the 51 patients, only three (5.9%) were sent for genetic counseling; there was no difference between symptomatic and asymptomatic patients who were sent for genetic counseling (p=0.595); it is very important to appropriately refer to genetic counseling because of the type of inheritance of this pathology. There is misinformation among patients about the meaning of being a carrier and its implications for health and reproduction.[24] That is why strategies are necessary to increase the use of genetic counseling and improve the information of doctors and specialists in hematology and internal medicine, and pre-and postconception counseling is of great importance with high public health impact.[36-38]

There are no screening programs for hemoglobinopathies in Colombia and its military population. In our study, we found an ascertainment bias. The percentage of patients with SCT who either had or did not have a complication may not represent a true percentage, given that hemoglobin electrophoresis was performed on symptomatic patients, patients with a family history, patients with abnormalities in the blood count, or patients with an incidental diagnosis. Further studies are required to assess the prevalence of SCT in the population and the percentage of symptomatic patients. However, the fact that we found similar percentages of patients with or without symptoms allows us to compare them and describe the percentage of the different splenic complications.

Conclusions. SCT is a rare disease that is usually asymptomatic; the main risk factor for presenting with any symptoms is high altitude. Military Personnel is a population with a high risk of developing symptoms; in symptomatic patients, splenic complications were the most important, and splenic infarction was the most common; however, splenic infarction was not the only complication. As in SCD, there is also a wide spectrum of splenic complications in patients with SCT. Diagnostic search should be emphasized in patients with elevated bilirubin and LDH. Most patients received medical treatment, and only 18,5% required splenectomy. Our results reflect the absence of redirection of these patients to genetic counseling, which can impact public health.

Strengths. In our study, we obtained data from different geographical regions of Colombia, highlighting that the study population is enriched with active military members, a population already at risk of developing symptoms, which explains the detection of many SCT patients with acute symptoms.

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