Splenic infarction in sickle cell trait: A comprehensive systematic review of case studies

Jamal M. Jefferson | Wynton M. Sims | Nkeiruka Umeh | Yen Ji Julia Byeon | Khadijah E. Abdallah | Vence L. Bonham | Rakhi P. Naik | Kim Smith-Whitley

1 National Human Genome Research Institute, Division of Intramural Research, Social and Behavioral Research Branch, National Institutes of Health, Bethesda, Maryland
2 Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland
3 Division of Hematology and Director of the Comprehensive Sickle Cell Center, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania

Correspondence
Vence L. Bonham, National Human Genome Research Institute, Division of Intramural Research, Social and Behavioral Research Branch, National Institutes of Health, JD/31 Center Drive, Suite B1B37, Bethesda, MD 20892.
Email: Bonhamv@mail.nih.gov

Funding information
Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health, Grant/Award Number: 1ZIAHG200394-06; National Heart, Lung Blood Institute, Grant/Award Number: K08HL12510

Abstract
Sickle cell trait (SCT), a commonly asymptomatic condition, has many associated clinical complications that upon presentation, can be very difficult to attribute to SCT. The effects of SCT on the spleen, for example, are not completely understood, though there have been a number of case reports detailing related complications in diverse populations. Our objective was to perform the first comprehensive case report review of splenic infarction in SCT patients to highlight the relevance of this seemingly rare condition. We conducted an extensive literature search reviewing case reports and case series of acute splenic infarctions from 1970 to 2020. This comprehensive search resulted in 54 articles with a total of 85 individuals. The ages ranged from 7 to 65, 12% were female. Individuals were of African-American (26%), European (16%), South Asian (13%), Middle Eastern (7%), Latin American (7%), North or East African (4%), Mediterranean (4%), West African (1%), and unknown (22%) origins. Although splenic infarct in SCT patients has been associated with high altitudes, 39% of cases reporting altitude occurred below 3000 m. Among cases where HbS values were recorded, 88% occurred in individuals with HbS levels higher than 35%, suggesting that high HbS values may be a risk factor for splenic infarction. Our findings indicate that splenic infarct occurs across a wide range of demographic populations and environmental settings. While our understanding of SCT evolves, the findings here suggest that future advances in research and healthcare could benefit more from real-time surveillance and registry initiation for various SCT outcomes such as splenic infarct.

KEYWORDS
acute disease, asymptomatic condition, sickle cell trait, splenic infarction

1 | INTRODUCTION

Sickle cell trait is a heterozygous state that results from the inheritance of one variant gene for sickle hemoglobin and a normal gene for adult hemoglobin. SCT is estimated to affect one to three million individuals in the United States and over 300 million individuals worldwide.[1] The global distribution of SCT, which varies widely by geographic region, is hypothesized to have been driven by the protection that SCT confers against falciparum malaria in malaria-endemic regions such as sub-Saharan Africa, India, southern Europe, and the Middle East.[2–4] In
the United States, individuals who may have had ancestry in these regions, such as African Americans and Hispanic or Latinx/a/os, are more likely to be affected by SCT.[5]

Unlike as in sickle cell disease (SCD), the erythrocyte sickling does not generally occur in SCT carriers, and the carrier status has historically been described as benign. However, several high-profile cases involving SCT-associated clinical complications among athletes and military personnel continue to raise questions about the benignity of the heterozygous state. Research has suggested that some individuals living with SCT are at higher risk of certain conditions, including venous thromboembolism, chronic renal diseases, renal medullary cancer, hematuria, renal papillary necrosis, hyposthenuria, and splenic infarction.[6–8]

This review focuses specifically on SCT and splenic infarction, one of the most widely reported but possibly least understood complications associated with SCT [9]. The underlying pathophysiology is thought to result from subacute erythrocyte sickling in the spleen in settings of low oxygen tension [10]. The aim of this study is to conduct a case study literature review of splenic infarction in individuals with SCT and comprehensively examine the risk factors for the development of this complication in children and adults with SCT.

2 METHODS

A comprehensive literature review of peer-reviewed journal articles published between January 1, 1970 and February 1, 2020 was conducted (Figure 1). The literature search was conducted using bibliographic databases, including PubMed, Web of Science, Scopus, Google Scholar, Embase, and CINAHL. The following search terms were used: (“Splenic Infarction”[Mesh]) AND “Sickle Cell Trait”[Mesh]; “splenic infarction” AND “sickle cell trait”; “splenic infarction” AND “sickle cell trait,” respectively.

Five reviewers (JMJ, WS, and NU, KA, YJJB) screened articles based on predetermined criteria. Duplicate articles and publications not related to splenic infarction were excluded. Titles and abstracts were then assessed for eligibility to be included in the literature review. The following were excluded: (1) research articles that reported exclusively on patients with SCD or in vitro cells; (2) articles that were not case reports or case series, including meeting abstracts, prevalence studies and commentaries; and (3) case reports or case series not involving splenic infarction. The full texts of all remaining case reports and
RESULTS

The 1970-2020 literature searches and reference mining yielded 347 publications from PubMed \((n = 58)\), EMBASE \((n = 112)\), Scopus \((n = 79)\), Web of Science \((n = 61)\), CINAHL \((n = 12)\), and Google Scholar \((n = 25)\). After removing duplicates, we retrieved 161 articles. Each reviewer conducted two separate rounds of exclusions—the first round excluding publications based on titles and abstracts and the second excluding based on a full text review. From these exclusions, 54 articles \((11\text{ case series and }43\text{ case reports})\) were identified and abstracted \((\text{Figure 1})\).

From these 54 articles, we abstracted 85 cases of splenic infarction in individuals with SCT. Of the 85 individuals, 75 \((88\%)\) were male and 10 \((12\%)\) were female. A broad range of ages \((7-65\text{ years old})\) was represented. Thirteen \((15\%)\) individuals were 18 years or younger, 22 \((26\%)\) were between 19 and 25 years old, 24 \((28\%)\) were between 26 and 35 years old, 16 \((19\%)\) were between 36 and 45 years old, and 9 \((11\%)\) were 46 and older, and one individual’s age was unknown \((1\%)\).

Ethnicity data were examined for 85 subjects \([9,11-54]\). We divided individuals into population groups based on geographic areas of descent for purposes of analysis, acknowledging that population categorization can be an arbitrary process that may yield varying results depending on context. Twenty-two \((26\%)\) were of African descent, 14 \((16\%)\) were of European descent, 11 \((13\%)\) were of South Asian descent, 6 \((7\%)\) were of Middle Eastern descent, 6 \((7\%)\) were of Latin American descent, 3 \((4\%)\) were of North or East African descent, 3 \((4\%)\) were of Mediterranean descent, 1 \((1\%)\) was of West African descent, and 19 \((22\%)\) were of unknown descent. The demographics of all individuals included in the review are summarized in Table 1.

As outlined in Tables 2 and 3, the geographic location for the onset of the splenic infarction was examined for 85 cases \([9,11-23,25-41,43-52,54-61]\). Thirty-two \((38\%)\) cases occurred in the United States and 41 \((48\%)\) occurred internationally \((\text{Table 2})\). Twelve of the cases reported internationally occurred in Japan \((\text{on or near Mt. Fuji})\), while the remaining cases occurred in India, Iran, Italy, Ethiopia, Saudi Arabia, the Canary Islands, Spain, Peru, the Himalayas, Sri Lanka, Greece, Canada, and Ecuador. One splenic infarction case transpired in transit while the individual was on a pressurized airplane traveling from California to New Jersey \([34]\). Table 3.

Altitude levels were reported for 59 individuals \([9,11,13,17-23,26-28,30,34,37,39,41,43,44,46-48,50-52,55,57,59-61]\). Of the 59 cases reporting altitude, 2 \((3\%)\) cases occurred under 1000 m, 4 \((7\%)\) cases occurred between 1001 and 2000 m, 17 \((29\%)\) cases occurred between 2001 and 3000 m, 27 \((46\%)\) cases occurred between 3001 and 4000 m, 2 \((3\%)\) cases occurred above 4000 m, and 7 \((12\%)\) cases contained a range or ambiguous altitude levels. In evaluating exercise alone, 29 \((34\%)\) of the individuals were physically active during their infarction, 43 \((51\%)\) were not physically active, and 13 \((15\%)\) cases were unknown. Additionally, most of the cases involving physical activity occurred at high altitudes. Out of those 29 individuals who were physically active and experienced a splenic infarction, 16 \((55\%)\) occurred at an altitude > 3000 m, 9 \((31\%)\) occurred at an altitude < 3000 m, 1 \((3\%)\) occurred at 3000 m and 3 \((10\%)\) occurred at an unknown elevation.

Hemoglobin S \((\text{HbS})\) levels were reported for 48 cases \([9,11,12,15-17,19-27,29,30,32,33,35,36,38-41,43,46-51,53,54,56-58,62,63]\). The percentage of \(\text{HbS}\) ranged from 29.8% to 46.5%. The following \(\text{HbS}\) percentages occurred in 48 cases: \(\text{HbS}\) below 35% \((4\text{ cases or }5\%)\), \(\text{HbS}\) between 35% and 39.9% \((16\text{ cases or }19\%)\), \(\text{HbS}\) between 40% and 45% \((26\text{ cases or }31\%)\), \(\text{HbS}\) greater than 45% \((2\text{ cases or }2\%)\), and \(\text{HbS}\) unknown \((27\text{ cases or }43\%)\). All the descriptive characteristics of splenic infarction are summarized in Table 2, while table 3 presents the individual case reports.

Although symptoms varied in each case, most individuals presented with more than one symptom and/or sign of splenic infarction, including abdominal or left upper quadrant abdominal pain \((74\% \text{ or }95\%)\), vomiting \((30\% \text{ or }38\%)\), respiratory issues \((\text{e.g., shortness of breath, pain})\) \((19\% \text{ or }24\%)\), nausea \((16\% \text{ or }21\%)\), left flank pain \((5\% \text{ or }6\%)\), and jaundice \((2\% \text{ or }3\%)\). Individuals with past medical histories available had reports of alcoholism, gout, obesity, glucose-6-phosphate dehydrogenase \((\text{G6PD})\) deficiency, cocaine and heroin use, chronic pancreatitis, and sleep apnea.
TABLE 2  Descriptive characteristics of splenic infarction in 85 cases

| Variable | Category          | N  | %    |
|----------|-------------------|----|------|
| Onset location | US                | 32 | 38   |
|            | Internationally   | 41 | 48   |
|            | Not reported      | 12 | 14   |
| Altitude level (m) | ≤1000             | 2  | 2    |
|            | 1001-2000         | 4  | 5    |
|            | 2001-3000         | 17 | 20   |
|            | 3001-4000         | 27 | 32   |
|            | >4000             | 2  | 2    |
|            | Ambiguous         | 7  | 14   |
|            | Not reported      | 26 | 31   |
| HbS levels (%) | <35               | 4  | 5    |
|            | 35-39.9           | 16 | 19   |
|            | 40-45             | 26 | 31   |
|            | >45               | 2  | 2    |
|            | Not reported      | 37 | 44   |
| Physical activity | Yes               | 29 | 34   |
|            | No                | 43 | 51   |
|            | Not reported      | 13 | 15   |
| Aviation | Yes               | 19 | 22   |
|            | No                | 57 | 67   |
|            | Not reported      | 9  | 11   |
| Splenectomy | Yes              | 25 | 29   |
|            | No                | 57 | 67   |
|            | Not reported      | 3  | 4    |

4 | DISCUSSION

Although SCT is largely considered a benign carrier state, reports of clinical complications in rare circumstances exist [8]. More frequently, chronic complications of SCT such as chronic kidney disease and venous thromboembolism are reported in large epidemiologic studies [33, 64, 65]. However, acute complications of SCT, such as splenic infarction, are considerably rarer, and thus the literature is limited to case reports and series. We present the first comprehensive case study review of splenic infarction in SCT and find that the demographics and clinical presentations of this complication in individuals with SCT have considerable heterogeneity.

High altitude environments with low oxygen tension are recognized as a potential factor in the development of splenic infarction in people with SCT, such as during mountain climbing or travel in unpressurized airplanes [66]. In our study, 49% of cases reporting altitudes occurred at greater than 3000 m, and a number of these cases demonstrated resolution of symptoms upon descent to a lower altitude. However, 39% of cases reporting altitudes occurred below 3000 m, suggesting that altitude is not the sole environmental risk factor for this complication [9, 11, 13, 14, 22, 26, 30, 41, 44, 50, 51, 60, 61]. It is therefore difficult to deduce an approximate altitude at which splenic infarction is likely to occur and is important to acknowledge the possibility of infarction in the absence of a high altitude or hypoxic environment.

There is controversy over whether those of non-African ancestry with SCT are more susceptible to splenic infarcts. Several prior reports have suggested that splenic infarction is more likely to occur in SCT individuals of European descent compared to those of African descent [18, 38, 66]. Genetic differences, such as frequency of α-thalassemia mutations, have been postulated to underlie this difference [47]. In our current review, though we found that 22/83 cases were African-American, this area is limited by the small number of studies and ambiguous definitions of population categorizations across studies. In our current review, we found that there may be an under-reporting in AAs overall [9, 15, 16, 18, 22, 28, 31, 34-38, 44, 45, 53]. Underreporting may be due to misdiagnosis as presenting symptoms that are similar to “mountain sickness.” Nonetheless, our study demonstrates that SCT-related splenic infarction appears across multiple geographic-descent populations (Table 3).

As with ancestry, the association between sex, as a predisposing factor, and splenic infarction is unclear. Our review of the literature confirms that both men and women are at risk of splenic infarction. This contrasts with what was observed in Goodman et al. in which all the patients were male [66]. In our review, there were ten reported cases occurring in women, three of which occurred in high altitude environments (> 3000 m) [22, 34, 37]. Although there is more frequent reporting of males, the potential reasons underlying this phenomenon are manifold; for example, one cause among many may be related to more men than women historically engaging in mountain climbing and other strenuous activities at low oxygen levels [21].

The amount of circulating HbS may influence the prevalence of clinical complications in SCT. Co-inheritance of alpha-thalassemia, which lowers HbS levels, has been found to decrease urinary concentrating dysfunction among individuals with SCT [47]. In SCT carriers without alpha-thalassemia, the average HbS percent is between 35% and 45%. In our review, we found that most of the reports with recorded HbS values (44/48 or 88%) occurred in individuals with HbS levels above 35%; therefore, high HbS values may predispose individuals to splenic infarction in SCT. Additionally, several case reports noted other potential risk factors such as drug use, sleep apnea, and infection, which may contribute to the pathophysiology of splenic infarction in SCT individuals [14, 18, 38, 56].

The pathophysiology of splenic infarction in SCT is not clear. The risk of pulmonary embolism has been noted to be higher in individuals with SCT compared to those without [8], and a few of the case reports in our review did mention a history of pulmonary embolism or infarction in SCT carriers who also experienced splenic infarction [24, 39, 49]. While chronic hypercoagulability likely plays a role in venous thromboembolism, it is not known whether acute arterial complications such as splenic infarction also have a common underlying mechanism. Given the limitations of case series and reports, no definitive conclusions about clinical risk factors for SCT-related splenic infarction can be made. In general, splenic infarction in individuals with SCT is a rare event, no comprehensive research studies have been conducted...
| Reference          | Year published | Geographic location | Sample (age, sex, reported race/ancestral group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/additional comments | Hb levels       |
|--------------------|----------------|---------------------|--------------------------------------------------|--------------|-----------------------------|----------------|------------------------------------------|-----------------|
| O'Brien et al. [40] | 1972           | Mt. Washington, NH, USA | 26, M, Sicilian (white American)                  | 3 days after ascent | Physical activity: yes Aviation: no | 760 m          | Splenectomy: no Intervention unreported (patient was obese) | HbS: 42.4% HbF: 5% |
| King et al. [28]   | 1977           | Los Angeles, CA, USA | 58, M, Mexican                                   | Unknown      | Physical activity: no Aviation: no | No information | Splenectomy: yes Stayed in hospital 1 month (Patient was moderately obese, had a 15-year history of gout and had a transvenous demand pacemaker for bradycardia) | HbS: 31% HbA: 61% |
| Diep et al. [20]   | 1979           | Colorado, USA        | 23, M, German/English ancestry (white)           | 30 minutes into arrival of Leadville, CO | Physical activity: no Aviation: no | 3291 m         | Splenectomy: yes Rapid recovery and home 1 week later | HbS: 39.7% HbA: 55% HbF: 2% HbA2: 3.1% |
| Magnuson et al. [30]| 1980           | Minneapolis, MN, USA | 37, M, African American                          | Unknown      | Physical activity: no Aviation: no | Low (not specified) | Splenectomy: no Uneventful recovery; remained asymptomatic until one year later with onset of left-sided chest pain | Unknown |
| Buch et al. [15]   | 1982           | Queens, NY, USA      | 32, F, African American                          | Spontaneous  | Physical activity: no Aviation: no | Low (not specified) | Splenectomy: yes Uneventful recovery (patient had iron deficiency anemia) | HbS: 32% HbA: 64.6% HbF: 1.5% HbA2: 1.9% |
| Callis et al. [16] | 1982           | Canary Islands, Las Palmas | 13, M, Spanish                                   | Upon ascent on cable car (within 8 minutes of ascent) | Physical activity: no Aviation: no | 3555 m         | Splenectomy: no Conservative therapy (misdiagnosed with mountain sickness but actually splenic infarction) | HbF: 3.8% HbA2: 2% |
| Cox [19]           | 1982           | Pike’s Peak, CO, USA | 20, M, white American                            | During descent by train | Physical activity: no Aviation: no | 4297 m         | Splenectomy: no Treated with nasogastric suction, IV hydration, and meperidine for analgesia; discharged on the 8th day | HbS: 41.2% HbA: 55.2% HbA2: 3.6% |
| Nussbaum et al. [38]| 1984           | Quito, Ecuador       | 36, M, White (Ecuadorean-born)                   | After ascent  | Physical activity: no Aviation: no | 3000 m and 5000 m | Splenectomy: no Conservative therapy used on multiple occasions (patient had a life-long history of exertional intolerance, chronic hemolytic anemia and pulmonary infarctions. He also noted a long history of ascending to high altitudes and experiencing jaundice; eventually moved to sea level and had no recurrence of symptoms) | HbS: 41.3% HbA: 55.6% HbF: 0.6% HbA2: 2.6% |

(Continues)
| Reference          | Year published | Geographic location                  | Sample (age, sex, reported race/ancestral group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/additional comments | Hb levels            |
|--------------------|----------------|--------------------------------------|-------------------------------------------------|--------------|-----------------------------|----------------|------------------------------------------|---------------------|
| Lane et al. [29]   | 1985           | Colorado, USA                        | 18, M, Dutch-Sicilian descent (White)           | <24 hours after arrival to Colorado             | Physical activity: no  | 1646 m          | Splenectomy: no                           | HbS: 40.5%          |
|                    |                |                                      | 18, M, Belgian-Spanish-Italian descent (White) | 4 hours after arrival to Colorado              | Aviation: yes                         | 2134 m          | Splenectomy: no                           | HbA: 54.1%          |
|                    |                |                                      | 33, M, North European                           | < 12 hours after arrival to Colorado           | Physical activity: no                | 3353 m          | Splenectomy: no                           | HbF: 1.2%           |
|                    |                |                                      | 37, M, Arab                                     | 8 hours after arrival to Colorado              | Aviation: yes                         | 1829 m          | Splenectomy: no                           | HbA2: 4.2%          |
|                    |                |                                      | 19, M, Colombian                                | < 24 hours after arrival to Colorado           | Unknown                               | 3353 m          | Splenectomy: no                           | HbS: 39.1%          |
|                    |                |                                      | 30, M, African                                  | 48 hours after arrival to Colorado             | Unknown                               | Unknown         | Splenectomy: no                           | HbA: 55.3%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: yes                           | HbF: 2.3%           |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: yes                           | HbA2: 3.3%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbS: 41.3%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA: 57.3%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA2: 1.3%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbF: 41.1%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA: 56.0%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbF: 0.4%           |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA2: 2.5%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbS: 39.2%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA: 58.7%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA2: 2.1%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbS: 38.6%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA: 55.8%          |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbF: 0.8%           |
|                    |                |                                      |                                                 |                                             |                                           |                | Splenectomy: no                           | HbA2: 4.8%          |
| Goldberg et al. [25] | 1985           | New Mexico, USA                      | 18, M, White American                           | At Clines Corners, NM 3 hours after           | Physical activity: no                 | 2195 m          | Splenectomy: yes Postoperative course     | HbS: 45.8%          |
|                    |                |                                      |                                                 | arrival into Santa Fe                         | no                                      | 2134 m          | uncomplicated except for left pleural     | HbA: 51.4%          |
|                    |                |                                      |                                                 |                                              |                                          |                | effusion that resolved spontaneously;     | HbA2: 2.8%          |
|                    |                |                                      |                                                 |                                              |                                          |                | received nasal oxygen during postoperative| HbS: 41.0%          |
|                    |                |                                      |                                                 |                                              |                                          |                | period, which lasted 11 days              | HbA: 55.0%          |
|                    |                |                                      |                                                 |                                              |                                          |                | Splenectomy: yes                           | HbA2: 3.4%          |
|                    |                |                                      |                                                 |                                              |                                          |                | Postoperative course                      |                    |
|                    |                |                                      |                                                 |                                              |                                          |                | uncomplicated; discharged on 7th day      |                    |
| Shalev et al. [45] | 1988           | Sierra Mountains, CA, USA            | 22, M, white Israeli Jew of non-Ashkenazi origin| 3rd consecutive day of strenuous activity    | Physical activity: yes                 | 3536 m          | Splenectomy: yes                           | HbS: 46.5%          |
|                    |                |                                      |                                                 |                                              | Aviation: no                           |                |                                         | HbA: 50.2%          |
|                    |                |                                      |                                                 |                                              |                                          |                |                                         | HbF: 1.4%           |
|                    |                |                                      |                                                 |                                              |                                          |                |                                         | HbA2: 1.9%          |
| Reference          | Year published | Geographic location     | Sample (age, sex, reported race/ancestral group) | Time of onset        | Physical activity/aviation | Altitude level | Intervention/outcome/additional comments                                                                 | Hb levels |
|--------------------|----------------|-------------------------|-------------------------------------------------|----------------------|---------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------|-----------|
| Gitlin et al. [24] | 1989           | Michigan, USA           | 27, M, Middle Eastern descent                   | Middle of night      | Physical activity: no     | None           | Splenectomy: no Conservative therapy; patient recovered except for an episode of acute tophaceous gout that occurred 9 days after discharge | Unknown   |
| Narasimhan et al. [54] | 1990       | Unknown                 | 24, M, unknown                                 | Unknown              | Physical activity: no     | 1524 m         | Splenectomy: no Conservative therapy                                                                                              | Unknown   |
| Sugarman et al. [48] | 1990          | Durham, NC, USA         | 43, M, Black                                   | 8 days after being admitted for pulmonary thromboembolism | Unknown                  | None           | Splenectomy: No                                                                                                                   | HbS: 39% HbA: 61% |
| Novielli et al. [37] | 1991          | Pennsylvania, USA       | 38, F, Black                                   | Few hours after cocaine use | Physical activity: no     | None           | Splenectomy: no Conservative therapy (a high concentration of cocaine in spleen may have resulted in acute vasoconstriction leading to further lowering oxygen tension) | Unknown   |
| Genet et al. [23]  | 1996           | Unknown                 | 65, F, North African                           | Unknown              | Physical activity: no     | None           | Splenectomy: yes With a follow-up of 2 years, the patient was doing well (there was no arterial hypoxemia before splenic infarction; the patient suffered from multiple severe thrombotic processes without predisposing factors) | HbS: 40.3% HbA: 57.7% HbA2: 2.2% |
| Bodo et al. [14]   | 1997           | St. Louis, MO, USA      | 49, F, African American                        | During sleep         | Physical activity: no     | None           | Splenectomy: no Conservative therapy: yes                                                                                           | HbS: 37%  |

(Continues)
| Reference        | Year published | Geographic location          | Sample (age, sex, reported race/ancestral group)       | Time of onset                                                                 | Physical activity/aviation | Altitude level | Intervention/outcome/(additional comments)                                                                 |
|------------------|----------------|------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Franklin et al.  | 1999           | Bridgeport, CA, USA          | 21, M, African American                                | Within 12 hours of arriving in Bridgeport                                      | Physical activity: yes     | 2042 m         | Splenectomy: no                                                                                                                                             |
|                  |                | Vail, CO, USA                | 20, M, Mexican                                       | 2 days after descending from altitude                                          | Aviation: no               | 1524 m         | Stay in hospital was unremarkable (patient had history of G6PD)                                                                                             |
|                  |                | Utah, USA                    | 30, F, White                                        | 2nd day on vacation                                                          | Physical activity: yes     | 3048 m         | Splenectomy: no                                                                                                                                             |
|                  |                |                              | 34, M, African American                              |                                                                                 | Aviation: no               | 2438 m         | Graduation resolution of symptoms throughout his stay in hospital (has subsequently traveled to altitudes of similar altitudes without sequelae) |
|                  |                |                              |                                                      |                                                                                 | Physical activity: yes     |                | Splenectomy: no                                                                                                                                             |
|                  |                |                              |                                                      |                                                                                 | Aviation: no               |                | Conservative therapy and resolution of symptoms; avoided skiing for 2 years but on 4th ski trip at altitude of ~12000 ft, had recurrence of symptoms. She returned to sea level with gradual resolution of symptoms |
|                  |                |                              |                                                      |                                                                                 | Physical activity: yes     |                | Splenectomy: yes                                                                                                                                             |
|                  |                |                              |                                                      |                                                                                 | Aviation: no               |                | Postoperative course was complicated by left subdiaphragmatic abscess with colonic fistula formation                                                                 |
| Ozgen et al.     | 1999           | Unknown                      | 26, M, Cyprus                                       | 5 days after complaining of diarrhea                                           | Physical activity: no      | 2830 m         | Splenectomy: yes                                                                                                                                             |
|                  |                | Unknown                      | 19, M, Cyprus                                       | Unknown                                                                       | Aviation: no               | 2740 m         | Splenectomy: unreported                                                                                                                                       |
| Tiernan et al.   | 1999           | Sierra Nevada, USA           | 26, M, White American                                | Upon ascent to high altitude; chest pain in the middle of night After fishing for an hour | Physical activity: no      | 2830 m         | Splenectomy: no                                                                                                                                             |
|                  |                | Sierra Nevada, USA           | 17, M, White American                                |                                                                                 | Aviation: no               | 2740 m         | Conservative therapy; pain worsened over 3-4 days but resolved after 1 week                                                                             |
|                  |                |                               |                                                      |                                                                                 | Physical activity: no      |                | Splenectomy: no                                                                                                                                             |
|                  |                |                               |                                                      |                                                                                 | Aviation: no               |                | Pain resolved in a couple of hours after leaving elevation and was entirely asymptomatic                                                                           |

(Continues)
| Reference             | Year published | Geographic location | Sample (age, sex, reported race/ancestral group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/(additional comments)                                                                 | Hb levels |
|-----------------------|----------------|---------------------|--------------------------------------------------|---------------|----------------------------|----------------|--------------------------------------------------------------------------------------------------------------------------------|-----------|
| Symeonidis et al. [55] | 2001           | Greece              | 17, M, unknown                                  | 24 hours after fever | Physical activity: no     | None           | Splenectomy: no  
Patient’s course was benign; pain subsided after 7 days and fever resolved on the 10th day. He was discharged on the 16th day and follow-up after 3 years was uneventful (the congestion induced by EBV infection and high-grade fever may have contributed to splenic sequestration and subsequent infarcts) | HbS: 42.0% HbA: 56.0% HbA2: 2.0% |
| Sheikha [46]          | 2005           | Abha, Saudi Arabia  | 35, M, Yemeni Abha, Saudi Arabia 32, M, Saudi 23, M, Eritrean 26, M, Southern India | 2nd day after arrival to Abha 1st day after arrival to Abha After arrival into Abha After arrival into Abha after visit in lowlands | Physical activity: no Aviation: no Physical activity: no Aviation: no Physical activity: no Aviation: no | 3050 m 3050 m 3050 m 3050 m | Splenectomy: yes Splenectomy: yes Splenectomy: yes Splenectomy: yes | HbS: 42.0% HbA: 55.0% HbA2: 3.0% HbA: 57.0% HbA2: 3.0% HbA: 44.0% HbA: 53.0% HbA2: 3.0% HbA: 57.0% HbA2: 2.0% |
| Malik et al. [32]     | 2006           | Canada              | 41, M, East Indian Unknown                      | Unknown        | Physical activity: no     | None           | Splenectomy: no  
Conservative therapy: yes analgesia and fluid rehydration | HbS: 40% |
| Chamberland [17]      | 2007           | Utah, USA           | 51, M, African American Sudden                  | 4500 m         | Physical activity: no     | 4500 m         | Splenectomy: no  
Conservative therapy: was discharged after received supplemental oxygen (had a history of heroin use; he also did not travel to 4500 m because he lived there his entire life) | Unknown |

(Continues)
| Reference       | Year published | Geographic location                      | Sample (age, sex, reported race/ancestral group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/additional comments | Hb levels |
|-----------------|----------------|------------------------------------------|-------------------------------------------------|--------------|---------------------------|---------------|------------------------------------------|-----------|
| Arora et al.    | 2008           | India                                    | 36, M, Indian                                   | Unknown      | Physical activity unknown | 1676-3962 m   | Splenectomy: yes                         | Unknown   |
|                 |                | India                                    | 30, M, Indian                                   | Unknown      | Aviation: unknown         | 1676-3962 m   | Splenectomy: yes                         | Unknown   |
|                 |                |                                           |                                                 |              |                           | 1676-3962 m   |                                           | Unknown   |
| Cook            | 2008           | Cusco, Peru                               | 23, M, European                                 | On ascent    | Physical activity: yes    | 3300 m        | Splenectomy: yes                         | 37.9%     |
|                 |                |                                           |                                                 |              | Aviation: no              |               |                                          |           |
| Morishima et al.| 2008           | Mt. Fuji, Japan                           | 41, F, African American                         | On ascent    | Physical activity: yes    | ~3776 m        | Splenectomy: no                          | Unknown   |
|                 |                |                                           |                                                 |              | Aviation: no              |               | Conservative therapy; recovered without sequelae (patient had a history of alcoholism and cholelithiasis) |           |
| Pothula et al.  | 2008           | Mt. Fuji, Japan                           | 23, M, French and African American              | During ascent| Physical activity: yes   | 2286 m        | Splenectomy: no                          | Unknown   |
|                 |                |                                           | 26, M, Hispanic (white American)                | 1 week after climb | Aviation: no              | 3755 m        | Conservative therapy; symptoms resolved and patient went back to work | Unknown   |
|                 |                |                                           | 20, M, African American                         | During ascent| Physical activity: yes   | 3000 m        | Splenectomy: no                          | Unknown   |
|                 |                |                                           | 24, M, Mediterranean descent                    | 3 hours after began climb | Aviation: no              | 2194 m        | Conservative therapy: yes                | Unknown   |
|                 |                |                                           | 26, M, African American                         | During ascent| Physical activity: yes   | 3775 m        | Splenectomy: no                          | Unknown   |
|                 |                |                                           | 34, M, African American                         | 1 day after climb | Aviation: no              | 3657 m        | Conservative therapy: yes                | Unknown   |

(Continues)
| Reference          | Year published | Geographic location | Sample (age, sex, reported race/ancestral group) | Time of onset   | Physical activity/aviation | Altitude level | Intervention/outcome/additional comments | Hb levels        |
|--------------------|----------------|---------------------|-------------------------------------------------|-----------------|----------------------------|----------------|------------------------------------------|-----------------|
| Funakoshi et al.   | 2010           | Mt. Fuji, Japan     | 38, M, Mestizo                                  | During ascent   | Physical activity: yes      | 3400 m         | Splenectomy: no                          | HbS: 40.5%      |
|                    |                |                     |                                                 |                 | Aviation: no                |                | Conservative therapy: yes; 5-month follow-up was uncomplicated |                |
| Norii et al.       | 2011           | Mt. Fuji, Japan     | 21, M, African American 41, F, African American | During ascent   | Physical activity: yes      | Mt. Fuji: 3776 m | Splenectomy: no                          | Unknown         |
|                    |                | Mt. Fuji, Japan     |                                                 |                 | Aviation: yes (day after admission to hospital but no increased pain) | Cabin pressure altitude: 2438 m | Conservative therapy: yes; patient recovered without sequelae |                |
|                    |                |                     |                                                 |                 | Physical activity: yes      | Mt. Fuji: 3776 m | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Aviation: yes (day after admission to hospital but no increased pain) | Cabin pressure altitude: 2438 m | Conservative therapy: yes; patient recovered without sequelae (patient had a previous history of alcoholism) |                |
| Abeysekera et al.  | 2012           | Sri Lanka           | 31, M, Sri Lankan (Adam’s Peak)                 | Physical activity: yes | Aviation: no                | 2243 m         | Splenectomy: no                          | HbS: 42.6%      |
|                    |                |                     |                                                 |                 |                            |                | Conservative therapy: yes; completely recovered (this was his 4th trip to the same mountain during the last 10 years) | HbA: 49.3%      |
|                    |                |                     |                                                 |                 |                            |                |                                          | HbF: 0.9%       |
|                    |                |                     |                                                 |                 |                            |                |                                          | HbA2: 3.1%      |
| Gotlieb et al.     | 2012           | Unknown             | 45, M, unknown                                  | After 5 hour flight | Physical activity: no      | Unknown        | Splenectomy: no                          | HbS: 38.7%      |
|                    |                | Unknown             | 52, M, unknown                                  |                 | Physical activity: no      | Unknown        | Conservative therapy: yes; after aggressive hydration, pain resolved and patient discharged | Unknown         |
|                    |                | Unknown             | 38, M, unknown                                  |                 | Physical activity: no      | Unknown        | Splenectomy: no                          | Unknown         |
|                    |                | Unknown             | 45, M, unknown                                  |                 | Physical activity: no      | Unknown        | (History of renal cell carcinoma) Splenectomy: yes | Unknown         |
|                    |                |                     |                                                 |                 | Physical activity: no      | Unknown        | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Aviation: no                |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 |                            |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |
|                    |                |                     |                                                 |                 | Splenectomy: no                          |                | Splenectomy: no                          | Unknown         |

(Continues)
| Reference          | Year published | Geographic location | Sample (age, sex, reported race/ancestral group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/(additional comments) | Hb levels |
|--------------------|----------------|---------------------|--------------------------------------------------|--------------|----------------------------|----------------|------------------------------------------|-----------|
| Asfaw et al. [13]  | 2013           | Cleveland, OH, USA  | 50, F, unknown                                   | Unknown      | Physical activity: no      | Unknown        | Splenectomy: no Required endotracheal intubation and initiation of vasopressor support on 3rd day of hospital stay; developed multisystem organ failure after omentectomy, subtotal colectomy, and small bowel resection. Supportive care withdrawn and died (had history of cocaine use and pathology showed vascular congestion with sickled RBC) | Unknown   |
| Gupta et al. [26]  | 2013           | Nanda Devi, Garhwal, Himalayas | 21, M, Indian                                   | During ascent | Physical activity: yes Aviation: no | 3500 m          | Splenectomy: no Conservative therapy; patient recovered with sequelae | HbS: 38.7% HbA: 58.0% |
| Murano et al. [34] | 2013           | San Diego, CA, USA to Newark, NJ, USA | 49, M, African American | After alcoholic beverage in flight | Physically active: no Aviation: yes | Unknown | Splenectomy: yes Patient had an uneventful recovery and was discharged | HbS: 43.5% |
| Scordino et al. [44] | 2013          | Cusco, Peru         | 24, M, African American                         | During hike  | Physical activity: yes Aviation: no | Unknown        | Splenectomy: no Conservative therapy; after returning to US, pain improved but was not resolved. He had follow-up within 1 week and did not require surgical follow-up | Unknown   |
| Habibzadeh et al. [57] | 2015     | Ardabil, Iran       | 18, M, unknown                                   | After mountain climbing  | Physical activity: yes Aviation: no | Unknown        | Splenectomy: no Conservative therapy; yes; pain was controlled with opioid analgesics. | HbS: unknown HbA1: 54.1% HbA2: 2.7% Hbf: 43.2% |
| Hota et al. [58]   | 2015           | India, India, India | 27, M, unknown to 33, M, unknown to 31, M, unknown | Within 12 hours of exposure to altitude Within 24 hours Within 72 hours Within 12 hours Within 48 hours | Physical activity: no Aviation: yes Physical activity: no Aviation: yes Physical activity: no Aviation: yes Physical activity: no Aviation: yes | 3962 m to 3962 m to 3962 m to 3962 m to 3962 m | Splenectomy: yes Splenectomy: no Splenectomy: yes Splenectomy: no Splenectomy: no Conservative therapy: yes Conservative therapy: yes Conservative therapy: yes Conservative therapy: yes Conservative therapy: yes | Unknown |

(Continues)
| Reference          | Year published | Geographic location | Sample (age, sex, reported race/ancestral group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/(additional comments) | Hb levels |
|--------------------|----------------|---------------------|-------------------------------------------------|---------------|-----------------------------|----------------|--------------------------------------------|----------|
| Nofal et al. [35]  | 2015           | Unknown             | 7, M, African American                           | During acute phase of EBV infection | Physical activity: no Aviation: no | None           | Splenectomy: no Conservative therapy: yes; with RBC transfusion, hydration, and pain control. Patient was discharged home once stable | HbS: 33% HbA: 63.9% HbA2: 3.1% |
| Seegars [8]        | 2015           | Columbia, SC, USA   | 18, F, African American                          | Spontaneous   | Physical activity: no Aviation: no | Low (91 m)     | Splenectomy: no Conservative therapy: yes; 4 days after discharged, returned with fever and increasing pain in left upper abdomen. She was subsequently discharged with 48 hours | HbS: 39.2% HbA: 58.6% HbA2: 2.3% |
| Hayashi et al. [27]| 2016           | Japan               | 20s, M, African American                         | While climbing mountain | Physical activity: yes Aviation: no | >3000 m        | Splenectomy: no Conservative therapy: yes; led to improved symptoms | Unknown |
| Walcott-Sapp et al. [50] | 2016 | Oregon, USA         | 21, M, Spanish Italian-Irish-Seminole Tribe descent | 1 hour within arrival | Physical activity: no Aviation: no | 2712 m         | Splenectomy: no Conservative therapy: yes; diet was slowly advanced and pain was controlled | HbS: 40.1% HbA: 56.8% HbA2: 3.1% |
| Magro et al. [31]  | 2017           | Italy               | 11, M, Nigerian                                  | Two days after flying home | Physical activity: no Aviation: yes | Unknown        | Splenectomy: no Conservative therapy | HbS: 40.6% HbA: 55.2% HbA2: 3.5% HbF: 0.7% |
| O’Shea et al. [39] | 2017           | Ethiopia            | 24, M, Sudanese                                  | Upon landing in Ethiopia | Physical activity: no Aviation: yes | Unknown        | Splenectomy: no Conservative therapy: yes; symptoms improved over 6 days | HbS: 39% |
| Patro et al. [42]  | 2017           | Bangalore, India    | 44, M, Indian                                    | Upon ascent    | Physical activity: unknown Aviation: no | 3350 m         | Splenectomy: yes                          | HbS: 42.55% HbA: 53.87% HbA2: 3.57% |
| Sinha et al. [47]  | 2017           | India               | 55, M, Indian                                    | At the end of journey | Physical activity: yes Aviation: yes | 3888 m 3888 m | Splenectomy: no Conservative therapy: yes; symptoms subside in 10 days Splenectomy: no Conservative therapy: yes; symptoms subside in 5 days | HbS: 29.8% HbS: 32% |

(Continues)
| Reference                  | Year published | Geographic location | Sample (age, sex, racial group) | Time of onset | Physical activity/aviation | Altitude level | Intervention/outcome/(additional comments) | Hb levels       |
|----------------------------|----------------|---------------------|---------------------------------|---------------|----------------------------|----------------|-------------------------------------------|----------------|
| Alabbadi et al. [11]       | 2018           | Saudi Arabia        | 24, M, Saudi Arabian            | During flight | Physical activity: yes     | None           | Splenectomy: no                           | HbS: 40%        |
|                            |                |                     |                                 |               | Aviation: yes              |                | Conservative therapy: yes; pain control   | HbA1: 54.6%     |
|                            |                |                     |                                 |               |                            |                |                                           | HbA2: 1.8%      |
|                            |                |                     |                                 |               |                            |                |                                           | HbF: 3.6%       |
| Fernando et al. [56]       | 2018           | Hambantota, Sri Lanka| 26, M, unknown                  | During descent| Physical activity: yes    | 2243 m         | Splenectomy: no                           | HbS: 38.6%      |
|                            |                |                     |                                 |               | Aviation: yes              |                | Conservative therapy: yes; discharged on oral penicillin and immunization; platelets rose gradually | HbA: 50.6%     |
| Yanamandra et al. [51]     | 2018           | India               | 24, M, Indian                   | Upon ascent   | Physical activity: yes     | 3500 m         | Splenectomy: no                           | Unknown         |
|                            |                |                     |                                 |               | Aviation: no               |                | Conservative therapy: yes; recurrent symptoms over next year or so | Unknown         |
| Gross et al. [52]          | 2018           | Unknown             | 19, M, African American         | Unknown       | Physical activity: unknown | Unknown        | Splenectomy: no                           | HbS: 39.7%      |
|                            |                |                     |                                 |               | Aviation: Unknown          |                | Conservative therapy: unknown             |                 |
| Alsinan et al. [62]        | 2019           | Unknown             | 15, M, unknown                  | Unknown       | Physical activity: unknown | Unknown        | Splenectomy: yes                           | HbS: 45%        |
|                            |                |                     |                                 |               | Aviation: Unknown          |                | Conservative therapy: unknown             |                 |
| Kamada et al. [59]         | 2019           | Japan               | 38, M, unknown                  | While climbing Mt. Fuji | Physical activity: yes     | 2500 m         | Splenectomy: no                           | unknown         |
|                            |                |                     |                                 |               | Aviation: no               |                | Conservative therapy: unknown             |                 |
| Moideen et al. [53]        | 2019           | Tamil Nadu, India   | 27, M, Southern India           | Unknown       | Physical activity: unknown | unknown        | Splenectomy: no                           | HbS: 39.3%      |
|                            |                |                     |                                 |               | Aviation: Unknown          |                | Conservative therapy: yes; fluids          |                 |
| Rao E et al. [60]          | 2019           | Denver, CO, USA     | 17, M, unknown                  | 2 days after traveling into Frisco, CO | Physical activity: unknown | ~2800 m        | Splenectomy: no                           | Unknown         |
|                            |                |                     |                                 | 2 days after traveling into Frisco, CO | Aviation: yes     | ~2800 m         | Conservative therapy: pain control        | Unknown         |
|                            |                |                     |                                 |                |                            |                | Splenectomy: no                           | Unknown         |
|                            |                |                     |                                 |                |                            |                | Conservative therapy: unknown             | Unknown         |
of this clinical outcome, and our review was limited to case reports and case series.

There is a need for a more comprehensive reporting of splenic infarction and specifically, a better understanding of presenting symptoms and physical examination findings to reduce its misdiagnosis (e.g., mountain sickness) and improve clinical outcomes. We have not discussed clinical presentation of the cases. Future studies and more data collection, possibly through the initiation of patient registries, are needed to better characterize risk factors for this complication in people with SCT and to determine optimal clinical management.

ACKNOWLEDGMENTS

This research was supported in part by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health (1ZIAHG200394-06). The research is the sole responsibility of the authors and does not represent any position or policy of the National Human Genome Research Institute. This work was also funded in part by National Heart, Lung Blood Institute Grant K08HL12510 (RPN). We would like to thank the NIH Clinical Center librarians, Dera Tompkins and Brigit Sullivan, who assisted in the retrieval of study articles.

ORCID

Jamal M. Jefferson https://orcid.org/0000-0002-3691-8502

Yen Ji Julia Byeon https://orcid.org/0000-0002-3691-8502

Khadijah E. Abdullah https://orcid.org/0000-0003-2376-0443

Vence L. Bonham https://orcid.org/0000-0002-3649-5442

Rakhi P. Naik https://orcid.org/0000-0001-5562-1283

Kim Smith-Whitley https://orcid.org/0000-0002-2790-411X

REFERENCES

1. Naik RP, Derebail VK, Grams ME, Franceschini N, Auer PL, Pelosi GM, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. JAMA. 2014;312(20):2115-25.

2. Williams TN, Mwangi TW, Wambua S, Alexander ND, Kortok M, Snow RW, et al. Sickle cell trait and the risk of Plasmodium falciparum malaria and other childhood diseases. J Infect Dis. 2005;192(1):178-86.

3. Aidoor M, Terlouw DJ, Kolczak MS, Mcelroy PD, Ter Kuile FO, Kariuki S, et al. Protective effects of the sickle cell gene against malaria morbidity and mortality. Lancet. 2002;359(9131):1311-12.

4. Ferreira A, Marguti I, Bechmann I, Jeney V, Chora Â, Palha NR, et al. Sickle hemoglobin confers tolerance to Plasmodium falciparum malaria and other childhood diseases. J Infect Dis. 2005;192(1):178-86.

5. Hematology ASo. Sickle Cell Trait. 2019 [cited 2019 Apr 7]. Available from: https://www.hematology.org/Patients/Anemia/Sickle-Cell-Trait.aspx

6. Thoreson CK, O’connor MY, Ricks M, Chung ST, Sumner AE. Sickle cell trait from a metabolic, renal, and vascular perspective: linking history, knowledge, and health. J Racial Ethn Health Disparities. 2015;2(3):330-5.

7. Tantawy AAG. The scope of clinical morbidity in sickle cell trait. Egyptian J Med Human Genetics. 2014;15(4):319-26.

8. Naik RP, Smith-Whitley K, Hassell KL, Umemu NI, De Montalembert M, Sahota P, et al. Clinical outcomes associated with sickle cell trait: a systematic review. Ann Intern Med. 2018;169(9):619-27.

9. Seegars MB, Brett AS. Splenic infarction associated with sickle cell trait at low altitude. Hematology. 2015;20(10):607-9.

10. Goodman J, Hassell K, Irwin D, Witkowski EH. Nuss R. The splenic syndrome in individuals with sickle cell trait. High Alt Med Biol. 2014;15(4):468-71.

11. Abeyesekera WYM, De Silva WDD, Pinnaduwa SS, Banagala ASK. Acute massive splenic infarction with splenic vein thrombosis following altitude exposure of a Sri Lankan male with undetected sickle cell trait. High Alt Med Biol. 2012;13(4):288-90.

12. Alabaddi GS, Alsultan O, Alredwan AM. A traveler to Holland with a benign killer: a case report of a sickle cell trait male with splenic infarction. Egypt J Hosp Med. 2018;71(3):2646-64.

13. Arora MM, Bhatia JK, Khanna V, Jaiswal P, Charan VD. Sickle syndrome due to sickle cell trait amongst Indian soldiers serving in Kashmir. Med J Armed Forces India. 2008;64(2):123-26.

14. Asfaw SH, Fark GA, Morris-Stiff G, Tuthill RJ, Moorman ML, Samotwoka MA. A unique case of intestinal and splenic infarction in a sickle cell trait patient. Cases Reports in Surgery; 2013:1-3.

15. Bodo I, Dun Hey SP, Blinder M, Broze G. Low altitude splenic infarction in sickle cell trait. Is sleep apnea the solution to the mystery? A case report. Blood. 1997;90(10):2788.

16. Buch P, Prichep R, Rosner F. Sickle cell trait with splenic infarcts. N Y State J Med. 1982;82(7):1087-8.

17. Callis M, Petit JJ, Jordan C, Vives-Corrons JL, Ferrán C. Spleen infarction in a white boy with sickle cell trait. Acta Haematol. 1982;67(3):232.

18. Chamberland DL. Spleenic infarction in an African-American male with sickle cell trait. Am J Hematol. 2007;82(1):86-7.

19. Cook AL. Spleenic infarction in a high-altitude traveler with undiagnosed sickle cell trait. Wilderness Environ Med. 2008;19(4):318-20.

20. Cox RE. Spleenic infarct in a white man with sickle cell trait. Ann Emerg Med. 1982;11(12):668-9.

21. Diep BN, Scheirman K, Reeves WB, Mask DR, Eichner ER. Spleen infarction in a white man with sickle cell trait. South Med J. 1979;72(12):1611-2.

22. Franklin QJ, Compeeggie M. Sickle syndrome in sickle cell trait: four case presentations and a review of the literature. Mil Med. 1999;164(3):230-3.

23. Funakoshi H, Takada T, Miyahara M, Tsukamoto T, Noda K, Ohira Y, et al. Sickle cell trait as a cause of splenic infarction while climbing Mt. Fuji. Intern Med. 2010;49(16):1827-9.

24. Genet P, Pulik M, Lionnett F, Petitdidier C, Touahri T. Multiple spontaneous vascular infarcts in sickle-cell trait: a case report. Am J Hematol. 1996;51(2):173.

25. Gittin SD, Thompson CB. Non-altitude-related splenic infarction in a patient with sickle-cell trait. Am J Med. 1989;87(6):697-8.

26. Goldberg NM, Dorman JP, Riley CA, Armbruster EJ Jr. Altitude-related splenic infarction in a patient with sickle cell trait. South Med J. 1982;67(3):232.

27. Franklin QJ, Compeeggie M. Sickle syndrome in sickle cell trait: four case presentations and a review of the literature. Mil Med. 1999;164(3):230-3.

28. Fujino H, Iwakura T, Uchida H, Takada T, Miyahara M, Tsukamoto T, Noda K, Ohira Y, et al. Sickle cell trait as a cause of splenic infarction while climbing Mt. Fuji. Intern Med. 2010;49(16):1827-9.

29. Genet P, Pulik M, Lionnett F, Petitdidier C, Touahri T. Multiple spontaneous vascular infarcts in sickle-cell trait: a case report. Am J Hematol. 1996;51(2):173.

30. Gittin SD, Thompson CB. Non-altitude-related splenic infarction in a patient with sickle-cell trait. Am J Med. 1989;87(6):697-8.

31. Goldberg NM, Dorman JP, Riley CA, Armbruster EJ Jr. Altitude-related specific infarction in sickle cell trait—case reports of a father and son. West J Med. 1985;143(5):670-2.

32. Gupta M, Lehl SS, Singh K, Singh R. Acute splenic infarction in a hiker with previously unrecognised sickle cell trait. BMJ Case Rep. 2013;2013:bcr2013008931-bcr2013008931.

33. Hayashi TY, Matsuda I, Hagiwara K, Takayanagi T, Hagiwara A. Massive splenic infarction and splenic venous thrombosis observed in a patient with acute splenic syndrome of sickle cell traits on contrast-enhanced thin-slice computed tomography. Abdom Radiol (NY). 2016;41(9):1718-21.

34. King DT. Unusual cause of acute abdomen—sickle cell trait and non-hypoxic splenic infarction. JAMA. 1977;238(20):2173-4.

35. Lane PA. Spleenic syndrome at mountain altitudes in sickle cell trait. Its occurrence in nonblack persons. JAMA. 1985;253(15):2251-4.

36. Magnuson TR, Hunter SW, Bonnabeau RC Jr. Multiple vascular infarction. A manifestation of sickle cell trait in the absence of hypoxia. Minn Med. 1980;63(6):381-3.

37. Megro P, Izzo I, Saccani B, Casari S, Caligaris S, Tomasoni LR, et al. A Strange manifestation of malaria in a native Nigerian boy. Mediterr J Hematol Infect Dis. 2017;9.e2017023.
33. Malik S. Acute splenic infarction. CMAJ. 2006;175(3):244-4.
34. Morishima A, Schofer JM, Pelletier P, McKee JM. Images in emergency medicine: splenic infarction due to sickle cell trait after climbing Mt. Fuji. West J Emerg Med. 2008;9(3):179.
35. Murano T, Fox AD, Anjaria D. Acute splenic syndrome in an African-American male with sickle cell trait on a commercial airplane flight. J Emerg Med. 2013;45(5):e161-e165.
36. Noafal R, Sawaf H, Zeinali L. Splenic infarction induced by Epstein-Barr virus infection in a patient with sickle cell trait. Blood. 2015;126(23):4600.
37. Norii T, Freeman TH, Alseidi A, Butler WP, Gelford BL. Pressurized flight immediately after splenic infarction in two patients with the sickle cell trait. Aviat Space Environ Med. 2011;82(1):58-60.
38. Novelli KD. Splenic infarction after cocaine use. Ann Intern Med. 1991;114(3):251-2.
39. Nussbaum RL, Rice L. Morbidity of sickle cell trait at high altitude. South Med J. 1984;77(8):1049-50.
40. O'Shea J, Burke J, Murphy P, Quinn J. Splenic infarction in a young man with sickle cell trait following air travel at high altitude. Ir Med J. 2017;110(6):592.
41. O'Brien RT, Pearson HA, Godley JA, Spencer RL. Splenic infarct and sickle-(Cell) trait. N Engl J Med. 1972;287(14):720.
42. Ozgen A, Akata D, Arat A, Ozdogan M, Akhan O, Ozen MN. Splenic calcifications in heterozygote sickle cell patients. Abdom Imag. 1999;24(2):188-90.
43. Patro C, Patil HM, Shirodkar K, Prabhu M. A case of high altitude related splenic infarct in a previously undiagnosed sickle cell trait. Aust J Radiol. 2017;4(3):1073.
44. Pothula V, Saegusa E, Takekoshi D, Edson T, Ignacio R. Splenic syndrome: a rare indication for splenectomy. Mil Med. 2008;173(12):1233-7.
45. Scordino D, Kirsch T. Splenic infarction at high altitude secondary to sickle cell trait. Am J Emerg Med. 2013;31(2):446.e1-446.e3.
46. Shalev O, Boyle AL, Levene C, Oppenheim A, Rachmilewitz EA. Sickle cell trait in a white Jewish family presenting as splenic infarction at high altitude. Am J Hematol. 1988;27(1):46-8.
47. Sheikha A. Splenic syndrome in patients at high altitude with unrecognized sickle cell trait: splenectomy is often unnecessary. Can J Surg. 2005;48(5):377-81.
48. Sinha M, Raghuvanshi B, Bag N, Barman A. Splenic infarction in two members of the family with sickle cell trait: a case report of rare complication. Int J Appl Basic Med Res. 2017;7(4):272-4.
49. Sugarman J, Samuelson WM, Wilkinson RH, Rosse WF. Pulmonary-embolism and splenic infarction in a patient with sickle-cell trait. Am J Hematol. 1990;33(4):279-81.
50. Tiernan CJ. Splenic crisis at high altitude in 2 white men with sickle cell trait. Ann Emerg Med. 1999;33(2):230-3.
51. Walcott-Sapp S, Van Horn J, Phillips B, Gee A. Splenic hemorrhage at altitude in a patient with undiagnosed sickle-cell trait. Am Surg. 2016;82(3):E63-4.
52. Yanamandra U, Das R, Malhotra P, Varma S. A case of autopsplenectomy in sickle cell trait following an exposure to high altitude. Wilderness Environ Med. 2018;29(1):85-9.