Leg Ulcers in Sickle Cell Disease: a protocol for systematic review and meta-analysis

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Protocol
Abstract

**Background:** Sickle cell disease affects about 112 per 100,000 live births globally. Leg ulcer is a major and clinically challenging complication of sickle cell disease. It affects about 1.0-75% of SCDs with exact prevalence unknown. This study aims to determine pooled prevalence of leg ulcer in sickle cell disease as well as evaluate moderating effects of single nucleotide polymorphisms, patient's age and sex, geographical locations, treatment modalities and expression of plasma cytokines.

**Methods:** A search strategy is developed using MeSH, text words and entry terms. Nine databases will be searched: PuMed, African Journal Online, Embase, Google Scholar, Scopus, Cochrane Library, CINAHL, Web of Science and ResearchGate. Only observational studies, retrievable in the English language will be included. The primary outcome is the proportion of leg ulcers in sickle cell disease. The effect size is prevalence. Identified studies will be screened and selected based on inclusion criteria using EndNote version 9. Quality scores and risk of bias for individual studies will be reported. Studies will be assessed for methodological, clinical, and statistical heterogeneity. Funnel Plots will be used to assess publication bias. Extracted data items will be arranged in Microsoft Excel before exporting them to CMA software for quantitative analysis. The random model computation for pooled effect size will be used. Results including pooled prevalence, standard error, 95% CI and subgroup analysis will be presented in forest plots.

**Discussion:** Ethical approval will not be required since this study is based on published data. This protocol will enable reproducible and accurate estimation of pooled prevalence of leg ulcers and effects of moderators in sickle cell disease. The data from such review will stimulate further research into leg ulcers in SCD. The final report of this study will be published in a peer-reviewed journal and the findings will be made available to various health experts that manage SCD patients especially haematologists.

**Trial Registration Number:** This protocol is registered in PROSPERO; with registration number CRD42020213310.

Background

Sickle cell disease (SCD) is one of the commonest genetic diseases worldwide. It results from mutation on the sickle β-globin gene at position 6. It is inherited in an autosomal recessive fashion either in the homozygous state as seen in haemoglobin (Hb) SS or in a heterozygous state such as the HbSC. Wastnedge et al, 2018 estimated the global burden of homozygous sickle cell disease at 112 per 100,000 live births [1]. SCD presents as a systemic and multiorgan disorder with a wide range of variability in its clinical presentation including vaso-occlusive pain crises, acute chest syndrome, pulmonary hypertension and leg ulcers among others [2].

Leg ulcer is one of the haemolysis-endothelial dysfunction manifestations of SCD. Its aetio-pathogenesis is complex and is thought to be multifactorial [3-4]. The prevalence varies from as low as 1.0% to as high as 75.0% depending on the Hb phenotype, geographical location, age and gender [5-7]. It commonly
occurs in areas of the body with thin skin, little or no subcutaneous fat with minimal blood flow such as the malleoli [6]. According to Antwi Boasiko and colleagues, the geographical distribution of sickle leg ulcers cuts across the entire globe affecting USA, UK, Italy with the highest prevalence observed in Sub-Saharan Africa especially Ghana 18.6% [7]. This high prevalence has been associated with HbSS genotype, older age and male gender [7,8].

Factors like marked haemolysis, low oxygen saturation, proteinuria, albuminuria, low haemoglobin, increased total bilirubin and lower body mass index could predict development of SCD leg ulcers [9]. Vasculopathy with attendant endothelial dysfunction which results from effects of recurrent vaso-occlusion, excessive elaboration of adhesion molecules and consequent tissue ischaemia is an independent predictor of leg ulcers in SCD [10,11,12].

Single nucleotide polymorphisms (SNPs) are known genetic modifiers of severity of sickle cell leg ulcer. In a recent genome wide association study (GWAS), robust associations of both individual SNPs and genes with leg ulcer were observed [13]. The SNP analysis identified several SNPs that were associated with leg-ulcer. These included SNPs in activated leukocyte cell adhesion molecule (ALCAM) which is supposed to regulate endothelial functions, as well as several SNPs located in gene desert regions [13,14].

High serum levels of pro-inflammatory and T-helper 17 cells related-cytokines (IL-6, IL-17A, IL-22 and IL-23) have all been strongly associated with increased risk of developing leg ulcers in sickle cell disease [15,16].

Leg ulcerations have been an age-long recognized complication of SCD, with the first sickle cell disease patient in North America reported to have leg ulcer [17]. Despite this, there is no clearly defined management protocol for the complication. Several practitioners and researchers have tried different treatment modalities with varying clinical outcomes. These modalities include chronic transfusion therapy, exchange blood transfusion, bacterial culture and sensitivity directed antibiotic use, hydroxyurea, topical sodium nitrite, hydrogen negative pressure therapy, high resting perfusion, and stem cell transplantation among others [18,19,20,21]. In all these, management remains a challenge. However, a multidisciplinary approach is strongly recommended. Sickle cell leg ulcer is a very disabling and dreaded complication of SCD characterized by severe pain, indolent clinical course, treatment challenges and high degree of recurrence [9,10]. The typical pain from leg ulcers in sickle cell disease patients, in addition to sleep disruption, depression, financial loss and overall reduction in quality of life, typifies the global manifestations of the disease complications [22]. Sickle Leg ulcers are associated with renal disease, severe anaemia, priapism, pulmonary hypertension and sometimes stroke [23,24]. Leg ulcers have been recognized as a marker of disease severity in SCD with associated morbidity and mortality [25]. Our protocol is aimed at enabling a transparent, accurate and reproducible review of pooled prevalence of leg ulcers in SCD and moderating effects of gender, patient’s age, types of SNPs and plasma levels of cytokines.

Method And Design
OBJECTIVE

The overall objective of this study is to determine the pooled global prevalence of leg ulcers in sickle cell disease and the associations of patients’ age and sex, SNPs, cytokines and geographical location with leg ulcers in SCD as well as therapeutic modalities available for the treatment.

Study objectives:

1. To determine the pooled global prevalence of leg ulcers in sickle cell
2. To determine the associations of patients’ age and sex, SNPs, cytokines and geographical location with leg ulcers in SCD.
3. To determine the therapeutic modalities available for the treatment.

Review Questions:

Specific questions to be addressed in a review using this protocol include:

a. What is the overall global prevalence of leg ulcers in sickle cell disease?
b. Do SNPs have significant associations with presence of leg ulcers in SCD?
c. Do mean plasma cytokine levels predict prevalence of leg ulcers in SCD?
d. Which treatment modalities are widely used for leg ulcers in SCD?
e. Are patients’ age and sex associated with frequency and severity of leg ulcers in SCD?
f. Does geographical distribution of leg ulcers in SCD vary globally?
g. What is the global mean age distribution of SCD patients with leg ulcers?

Study Design

This is a protocol for systematic review and meta-analysis. It is designed for observational studies only. There is no time frame or restriction on selection of studies. Screening and selection of studies will be done using the bibliography software, Endnote version 9. Other similar softwares can be used. Extracted data items will be arranged in Microsoft Excel and analyzed in the Comprehensive Meta-Analysis Software CMA version 3. This protocol follows PRISMA-P Checklist.

Inclusion criteria are

- observational studies like cross-sectional studies, case-control studies, cohort studies, and historical cohort
- study must report prevalence of leg ulcers in cell sickle disease as primary outcome.
- studies must be retrievable in the English
- studies that are available in electronic databases will be used. Grey literature will not be included.

Exclusion criteria are
a. letters to editors, reviews, commentaries, and editorials
b. duplicates of same studies,
c. studies with secondary outcomes but no primary outcome (prevalence of leg ulcer in SCD).
d. studies that are not retrievable in English language
e. Interventional studies including randomized clinical trials and quasi-clinical trials.

This review will be reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2015 Statement).

**PICO**

**Participants:** sickle cell patients with leg ulcer.

**Intervention:** there is no intervention.

**Comparator:** There is no comparator.

**Outcomes:** Primary outcome is prevalence of leg ulcers in sickle cell disease.

Secondary Outcomes: frequency and types of SNPs in leg ulcers in sickle cell disease, mean plasma or serum levels of cytokines, geographical distributions, and treatment modalities for leg ulcers.

**Information sources**

The search will employ sensitive topic-based strategies designed for each database. Nine databases will be searched: PubMed, AJOL, Google Scholar, Cochrane library, Embase, CINAHL, Web of Science, ResearchGate, and Scopus will be included. All the databases are electronic.

**Search strategy**

The search strategy will include MeSH terms, text words, and entry terms. The search strategies to be used in various databases are shown in Table 1.

**Data Extraction and Management**

a. **Screening of studies**

Studies will be searched using the search strategy shown in Table 1. There are four levels of data screening in this study:

a. level 1 is based on study design: only observational studies, published and/or retrievable in the English Language will be included; other study designs will be excluded.

b. level 2: selected studies will first be screened by titles and abstracts using entry terms, keywords, and MeSH terms.
c. level 3: selected studies will be further screened by full-text reading using the same strategy.
d. level 4: snowballing of literature from included studies.

Fourteen reviewers are involved in this study. A pair of reviewers will independently screen studies from each database. This is a blinded review. Conflicts will be resolved by a third independent reviewer. Screening will be done in Endnote version 9. After screening, data will be exported to Microsoft Excel. All eligible studies will be snowballed for further articles.

**b. Selection process:**

Studies are selected based on eligibility criteria, after blinded screening. Selection process is done in Endnote version 9. All selected studies are exported into Microsoft Excel. Authors of eligible studies with missing data will be contacted via email and telephone.

**c. Data collection process:**

De-duplication of the studies will then be done in the EndNote version 9. The following data items will be extracted from eligible full text articles:

a. first author's surname and year of publication.
b. proportion of leg ulcers in sickle cell disease.
c. proportion of SNPs in leg ulcers in sickle cell disease
d. mean plasma cytokine levels in leg ulcers in SCD
e. patient's age.
f. patient's sex.
g. geographical location of each study.
h. sample size.
i. treatment modalities for leg ulcers in SCD.

Extracted data items entered into Microsoft Excel before being exported to CMA Software for meta-analysis.

**Data items (Measurable outcomes)**

Data items to be extracted include the following:

a. Proportion of of leg ulcer in sickle cell disease (primary outcome) or any other primary index such as incidence etc that can be converted to prevalence, from studies that are of similar design and report outcome.
b. Geographical distribution of leg ulcers in SCD by country,
c. SNPs associated with leg ulcers in SCD,
d. Cytokines associated with sickle cell leg ulcers,
e. Treatment modalities for sickle cell leg ulcers, and
f. Age and gender distribution of sickle cell patients with leg ulcer

Risk of bias

The risk of bias in included studies will be assessed for the individual studies using the National Institute of Health (NIH) Quality assessment tool for observational, cohort and cross-sectional studies [29]. This will be cross-checked with the Cochrane tool of risk of bias assessment for the strength of the body of evidence; i.e. using specific relevant items from this tool to assess the strength of the body of evidence.

The following areas shall be assessed and any study with extreme bias will be excluded following a consensus decision.

1. Method of testing/reporting will be assessed at the outcome level.
2. Reporting of study: whether prevalence with 95% confidence interval or number of positive cases per sample size is reported at the outcome level.
3. Heterogeneity will be assessed at the study level.
4. Publication bias will be assessed at the study level.
5. Geographical location of participants will be checked in each study.

Data synthesis

a. Studies that passed the methodological quality assessment using the NIH quality assessment tool will be extracted. The eligible studies will be presented in tabular format. Narrative synthesis will be performed using all eligible

b. The following shall be included into meta-analysis.

i. Reported prevalence or number of sickle cell patients with leg ulcer and sample size by individual studies. Effect size is prevalence. This variable must be present for a study to be included for Quantitative analysis. It is the primary measurable outcome.
ii. Reported association of sickle cell leg ulcer with SNPs. Effect size is OR (odd ratio).
iii. Geographical location of each study as a categorical data.
iv. Mean value of cytokines in sickle cell leg ulcer. Effect size will be Cohen’s d.
vi. Reported mean age distribution of sickle cell patients with leg ulcers. Effect size is Cohen’s d.

Quantitative Analysis
Screened and eligible studies will be quantitatively analyzed using the CMA Software Version 3 (BioStat, USA). For each reported prevalence of leg ulcer, standard error and variance for each specific eligible study will be calculated by the CMA software. Subgroup analysis will also be done using variables such as geographical location, gender, treatment modalities and types of SNPs as moderators.

Meta-regression will be done with mean cytokine level and mean age as independent variables.

A cumulative meta-analysis will be performed to check for trend of prevalence over the years in the selected studies.

**Assessment of Meta-bias**

To test for heterogeneity, Cochrane's Q value and its p value, I², will be used. Sensitivity test using include/exclude function in the CMA Software will be performed to check the effect of heterogeneity on pooled prevalence of leg ulcers. Publication bias in the selection of studies will be tested using funnel plot (trim and fill method) and test for funnel plot asymmetry. As a rule of thumb, I² values of less than 40% will be considered low heterogeneity while values > 40 but < 75% will be considered moderate and values >75% are high.

Both random and fixed effect models will be assessed, and the appropriate model will be taken based on the forest plots.

**Discussion**

The study selection process will be summarized in a flow diagram according to the PRISMA 2015 Statement [30] and PRISMA-P Checklist [31]. A table of search strategy in various databases showing text words, MeSH and entry terms will be included. List of included studies will be summarized in a table. Quantitative data such as effect size (prevalence), 95% CI, P values, relative weights assigned to studies and heterogeneity tests will be included in the forest plots. A table of quality scores and risk of bias of each eligible study will be included. Forest plots to show sub-group analysis will be included. Regression plots on mean cytokine levels and mean age distributions will be included in separate plots. The burden of leg ulcers in SCD will be discussed in relation to the pooled prevalence. The association between SNPs, cytokines and prevalence of leg ulcers will be discussed. The modifying effects of SNPs and cytokines, if any, will be examined. A regression model that predicts prevalence of leg ulcers in SCD using explanatory variables such as mean cytokine level and patients’ age.

The final reports will be published in a peer-reviewed scientific journal and also made accessible to experts that handle sickle cell patients including Haematologists and Paediatricians.

**List Of Abbreviations**

AJOL: African Journal Online
Declarations

Ethics and Dissemination

Ethical approval will not be required since this study will rely solely on the secondary source of data, from published works.

Contributions: DA and EN conceived the project, EN, DA, HO, CU and IO designed the study, PI, NS and IC did PubMed searches, screening and review; JD and CT did AJOL and Embase searches and review; OC and OK did Google scholar searches and review; AD and IO did searches and review for CINAHL, Cochrane Database while HO did review of Researchgate

Support

Association for Good Clinical Practice in Nigeria (AGCPN) provided the platform and funding for this review.

Guarantor of the Review: Dr. Emmanuel Nna

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interest
The authors declare no competing interest

Acknowledgments

Not applicable

References

1 Wastnedge E, Waters D, Patel A, Morrison K, Goh MY, Adeloye D, et al. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. J Glob Health. 2018; 8: 021103

2 Sabastiani P, Nolan VG, Baldwin CT, Abad-Grau MM, Wang L, Adeboye H, et al. A model to predict the risk of death in sickle cell disease. Blood. 2007; 110: 2727-35

3 Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004; 17:410-6.

4 Da Silva RR, Pereira MC, Melo Rêgo MJ, et al. Evaluation of Th17 related cytokines associated with clinical and laboratorial parameters in sickle cell anemia patients with leg ulcers. Cytokine. 2014;65(2):143–147.

5 Delaney KH, Axelrod KC, Buscetta A, Hassell KL, Adams-Graves PE, Seamon C, et al. Leg ulcers in sickle cell disease: current patterns and practices. nHemoglobn. 2013; 37: 325-32

6 Adewoyin AS. Management of sickle cell disease: a review for physician education in Nigeria (Sub-Saharan Africa) Hindawi Publishing Corporation Anemia Volume 2015, Article ID 791498, 21 pages http://dx.doi.org/10.1155/2015/791498. Assessed on 06 October 2020.

7 Antwi-Boasiako C, Andemariam B, Colombatti R, et al. A study of the geographical distribution and associated risk factors of leg ulcers within an international cohort of sickle cell disease patients: the CASiRe group analysis. Ann Hematol. 2020; 99: 2073-79.

8 Bowers A.S, Reid H.L, Greenidge A, Landis C, Reid M. Blood Viscosity and the Expression of Inflammatory and Adhesion Markers in Homozygous Sickle Cell Disease Subjects with Chronic Leg Ulcers. PloS ONE (2013). 1-9.

9 Cumming V, King L, Fraser R, Serjeant G.M. et al. Venous incompetence, poverty and lactate dehydrogenase in Jamaica are important predictors of leg ulceration in sickle cell anaemia. British Journal of Haematology (2008): 142, 119–125.

10 Chung C, Cackovic M, Kerstein MD. Leg ulcers in patients with sickle cell disease. Adv Wound Care. 1996 (5):46-50.
11 Joseph L. Connor Jr, Joseph A. Sclafani, Gregory J. Kato, Matthew M. Hsieh et al, Brief topical sodium nitrite and its impact on the quality of life in patients with sickle leg ulcers. Medicine (2018): 97:46.

12 Koshy M, Entsuah R, Koranda A, Kraus AP, Johnson R, Bellvue R, Flournoy-Gill Z, Levy P. Leg ulcers in patients with sickle cell disease. Blood. 1989 74(4):1403-8.

13 Sebastiani P, Timofeev N, Dworkis DA, Perls TT, Steinberg MH. Genome-wide association studies and the genetic dissection of complex traits. American Journal of Hematology. 2009; 84:504–515

14 Adekunle Adekile. The Genetic and Clinical Significance of Fetal Hemoglobin Expression in Sickle Cell Disease. Medical Principles and Practice (2020). 1-31

15 Da Silva RR, Pereira MC, Melo Rêgo MJ et al. Evaluation of Th17 related cytokines associated with clinical and laboratorial parameters in sickle cell anemia patients with leg ulcers. Cytokine 65 (2014) 143–147

16 Domingos IF, Pereira-Martins DA, Sorreira MJVC, et al. High levels of proinflammatory cytokines IL-6 and IL-8 are associated with a poor clinical outcome in sickle cell anaemia. Ann Hematol. 2020; 99: 947-53

17 Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anaemia 1910. The Yale journal of biology and medicine. 2001; 74:179–184.

18 Monfort AB, Senet P. Leg ulcers in sickle cell disease: treatment update. Advances in Wound Care. 2020; 9: 348-56

19 Minniti CP, Gorbach AM, Xu D, et al. Topical sodium nitrite for chronic leg ulcers in patients with sickle cell anaemia: a phase I dose-finding safety and tolerability trial. Lancet Haematol 2014;1:e95–e103

20 Swe KM, Abas AB, Bhardwaj A, Barua A, Nair NS. Zinc supplements for treating thalassaemia and sickle cell disease. Cochrane Database Syst Rev 2013;6:CD009415

21 Altman IA, Kleinfelder RE, Quigley JG, Ennis WJ, Minniti CP. A treatment algorithm to identify therapeutic approaches for leg ulcers in patients with sickle cell disease. Int Wound J 2016; 13:1315–1324

22 El Khatib AM, Hayek SN. Leg ulcers in sickle cell patients; management challenges. Chronic Wound Care Management and Research. 2016; 3: 157-61

23 Serarslan G, Akgul F, Babayigit C. High prevalence of pulmonary hypertension in homozygous sickle cell patients with leg ulceration. Clin Exp Hypertens. 2009; 31: 41-48. 24Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore) 2005;84:363–376
25 Singh AP, Minniti CP. Leg ulceration in sickle cell disease: an early and visible sign of end-organ disease. Pain and common chronic complications. In: Sickle cell disease. 2016: DOI: 10.5772/64234:

26 Serarslan G, Akgul F, Babayigit C. High prevalence of pulmonary hypertension in homozygous sickle cell patients with leg ulceration. Clin Exp Hypertens. 2009; 31: 41-48

27 Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore) 2005;84:363–376

28 Singh AP, Minniti CP. Leg ulceration in sickle cell disease: an early and visible sign of end-organ disease. Pain and common chronic complications. In: Sickle cell disease. 2016: DOI: 10.5772/64234:

29 Lung NH, Institute B. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies-NHLBI, NIH. National Institutes of Health. 2014. 2015.

30 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement | SpringerLink [Internet]. [cited 2020 Oct 28]. Available from: https://link.springer.com/article/10.1186/2046-4053-4-1

31 Moher D, Stewart L, Shekelle P. Implementing PRISMA-P: recommendations for prospective authors. Syst Rev. 2016; 28;5(1):15.

Table

Table 1: Search terms used in Search Strategy
| S/No | Database         | Search strategy                                                                                                                                 |
|------|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| 1    | PubMed          | (((Leg Ulcers OR Foot Ulcer) OR "Leg Ulcer"[Mesh]) AND (Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease)) |
| 2    | AJOL            | Leg Ulcers OR Leg Ulcer AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease |
| 3    | Google Scholar  | Leg Ulcers OR Leg Ulcer AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease |
| 4    | Cochrane library| (Leg Ulcers OR Foot Ulcer OR "Leg Ulcer" AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease) |
| 5    | Embase          | Leg Ulcers OR Leg Ulcer AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease |
| 6    | CINAHL          | Leg Ulcers OR Leg Ulcer AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease |
| 7    | Web of Science  | Leg Ulcers OR Leg Ulcer AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease |
| 8    | Research Gate    | Leg Ulcers OR Leg Ulcer AND Anemias, Sickle Cell OR Sickle Cell Anemias OR Hemoglobin S Disease OR Hemoglobin S Diseases OR Sickle Cell Anemia OR Sickle Cell Disorder* OR Sickling Disorder Due to Hemoglobin S OR HbS Disease OR Sickle Cell Disease* OR Hemoglobin SC Disease |
| 9    | Scopus          |                                                                                                                                                 |