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REVIEW

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On the cutting edge of sickle cell disease: a snapshot narrative review

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Abstract

Background Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide, characterized by vaso-occlusive crises and ischemia that affects patients on a multi-system level. Despite being a genetically simple disease due to a single base mutation, SCD poses many therapeutic challenges. Additionally, its impact on patients' life remains significant. This narrative review aims to provide a snapshot of recent highlights of the significant progress in SCD therapy, and the impact of SCD on patients' life, including the complications, morbidity, and mortality factors of the disease.

Methodology Google Scholar and PubMed were searched for "sickle cell disease". Only full-text English language original research articles were included in this review. In total, 600 articles were screened, 300 from each database, which were published from 2020 to 2024-06-01. A total of 139 studies were included in this review, after screening for inclusion.

Conclusions The increasing global incidence of sickle cell disease underscores the urgency for healthcare interventions to address the health challenges of an aging population living with this chronic condition. While treatment options for sickle cell disease have broadened, their availability is still limited. Among these options, stem cell transplant stands out as the definitive treatment, with ongoing efforts to enhance the donor pool. The disease significantly affects patients' quality of life and overall health, with emerging neurological and psychiatric issues. Additionally, the impact of sickle cell disease on reproductive health in both men and women presents a pressing need for further research to meet reproductive challenges.

Keywords Sickle cell disease, SCD, Hemoglobinopathy, Review

Background

Sickle cell disease (SCD) is the most common hemoglobinopathy globally, which is typically prevalent in sub-Saharan African, Indian, and Middle Eastern regions [1]. Migration and population expansion have led to its presence in non-malarial endemic regions. Each year, around 300,000 babies are born with SCD [2]. SCD's pathophysiology involves the sickling and hemolysis of red blood cells, which obstructs blood flow in small blood vessels. This results in vaso-occlusion and ischemia episodes, which can significantly impact the physical and psychosocial health of patients with SCD [3]. Other complications of the disease include pain, infections, anemia, acute chest syndrome, kidney disease [4], pancreatitis [5], delayed growth and development, stroke, and organ damage [3]. Complications and manifestations of SCD are further compounded by the presence of other concurrent conditions like thalassemia [6, 7], G6PD deficiency [8, 9], and hemophilia [10, 11].

SCD was first described more than 110 years ago, and was only officially recognized as a disease of major public health issue by the World Health Organization in May 2006 [12]. Definitive treatment options for SCD remain limited and often require a multi-disciplinary approach

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[3, 13]. There are only four FDA-approved drugs available for the therapy of SCD—hydroxyurea, L-glutamine, crizanlizumab, and voxelotor [14]. However, some of these medications are largely unavailable in SCD endemic areas. Meanwhile, gene therapy such as CRISPR-Cas9 has emerged as a controversial therapy, but may be limited by off-target effects, safety concerns, issues related to the delivery of the system to the appropriate cells of the body, efficacy [15], and extremely high costs which is a major health equity concern [16]. Very recent advancements include the degradation of an HbF repressor, widely interspaced zinc finger—WIZ, which was tolerated in murine studies and induced fetal hemoglobin production; these findings could be the foundations for the development of another oral treatment for SCD [17, 18].

Hematopoietic stem cell transplant (HSCT) from a matched donor is the only treatment cure for SCD, but it is not always a viable option due to the lack of matched sibling donors resulting in a limited donor pool [19, 20], and it carries significant risks. Its use has been generally limited to those who have experienced severe complications, such as stroke [21]. Sustainable and equitable care for SCD is needed to improve the global care and health of patients with SCD [16].

Sickle cell disease continues to be a global concern. Updates in sickle cell disease (SCD) trends show a rising annual death rate among adult SCD patients in the USA, with the median age of death increasing from 28 to 43 years [22]. Deaths primarily stem from chronic conditions, emphasizing the need for improved management strategies as this population ages. Additionally, surveillance studies seem to identify more patients with SCD [23]. Globally, the incidence of SCD showed a 13.7% rise in newborns with SCD which is attributed to population expansion people ethnically from sub-Saharan Africa and the Caribbean. The clinical burdens of SCD are expected to progressively increase with patients requiring procedures such as dialysis or organ transplantation [24]. Similar trends are observed in high-income countries [24–26].

Given the critical impact of sickle cell disease (SCD) on patients and the escalating global need for comprehensive insights into advancements and trends in SCD therapy, and its continued acute and chronic impact on patients physical and psychosocial health, this snapshot narrative review aims to provide a highlight of recent research on SCD, focusing on therapeutic care progress, morbidity and associated complications, and the current impacts on patients with SCD.

Methodology

Google Scholar and PubMed was searched for ("sickle cell disease," "SCD") query on 2024-06-01 with a temporal limit since 2020. The first 300 articles were screened by title and abstract from each of the databases. We included only full-text English language original research articles (see Fig. 1).

We excluded non-original research articles such as reviews, short reports, letters to the editor, abstracts, conference meetings, policy documents, guidelines, commentaries, case reports, perspectives, dispatches, correspondence, drug profiles, research protocols, editorials, books, book chapters, and comments. Animal studies were also excluded. We excluded original research studies with primary outcomes related to financial, insurance, or economic aspects, as well as those examining health utilization. Studies not directly involving SCD patient outcomes and their data were excluded. Studies focusing on parents, caretakers, stakeholders, screening tools, online medical information, artificial intelligence/machine learning tools, policy or politics, public health efforts, COVID-19, current practice surveys, management of surveillance programs or clinics, and development of treatment programs were excluded. Preprint results, retracted articles, and articles with expressions of concern were part of the exclusion criteria.

For the purposes of a comprehensive narrative review of clinically relevant original research, we included full-text studies that addressed treatment and therapeutic research, disease impact on SCD patients, reported complications and factors influencing disease morbidity and mortality, as well as the impact on women's and men's health.

A total of 600 articles were screened. A final total of 139 original research articles were referenced in this narrative review. The original research studies included were conducted across 26 countries worldwide. The majority of studies were overwhelmingly published by authors from the USA.

Figure 2 presents a mind map highlighting some of the key findings in this study.

Medications and therapy

Although new adjunctive therapies have emerged for the therapy of SCD, none of them are considered cures for SCD[27]. Hematopoietic cell transplantation (HCST) is currently the only known cure, while advancements in gene editing technology offer promising prospects for the future. Recent original research on therapeutics reveals interesting clinical outcomes.

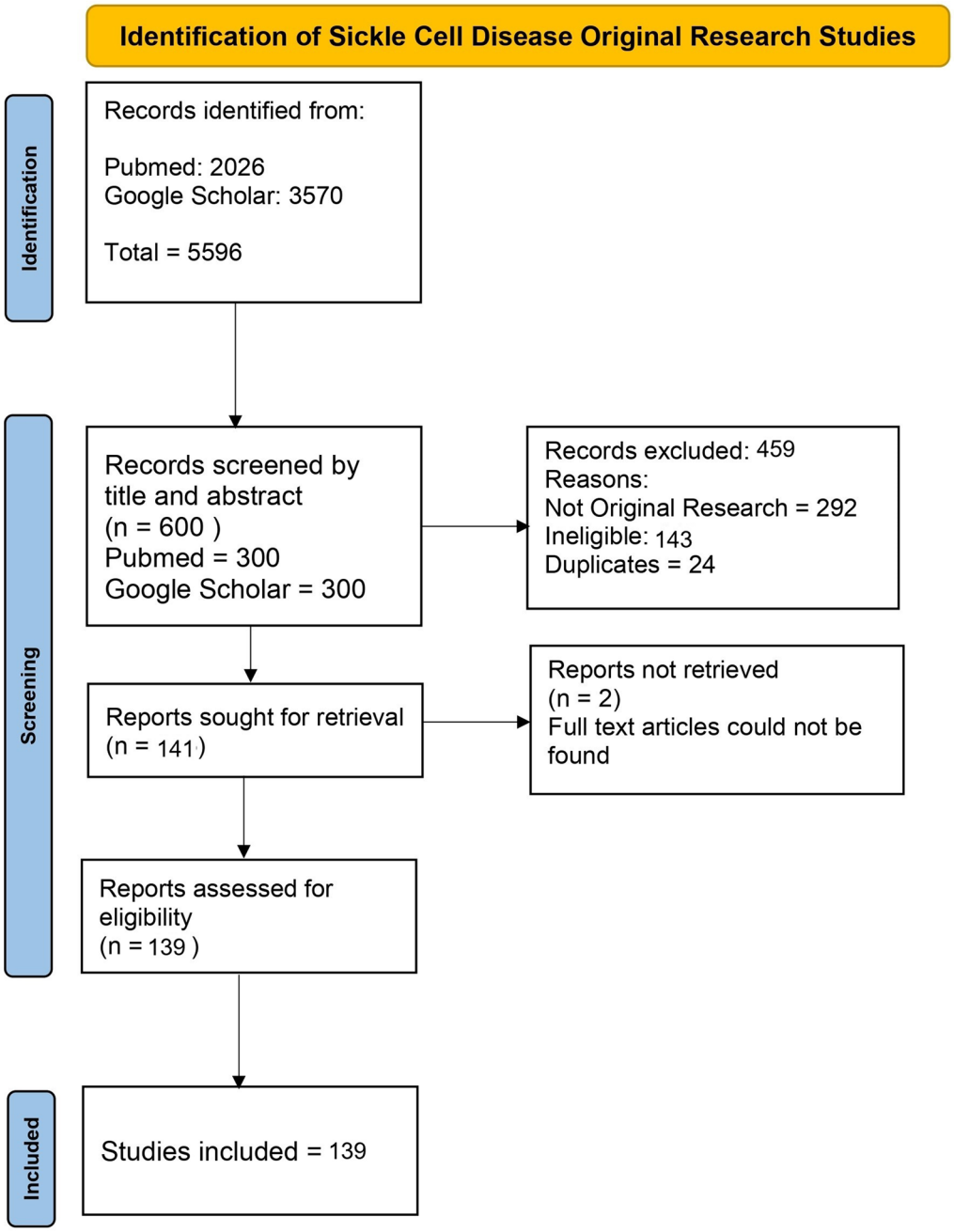

Fig. 1 Flowchart depicting the search strategy for this review. Only original full-text research published from 2020 to 2024 was included in this study

Gene and antibody therapy and CRISPR-Cas9

One study examined the efficacy of LentiGlobin, a type of gene therapy for SCD that involves autologous transplantation of hematopoietic stem cells transduced with a lentiviral vector which encodes for a modified B-globin gene. This results in the production of anti-sickling hemoglobin, designed to inhibit polymerization. In the examined patients, hemolysis markers were reduced and had resolution of severe vaso-occlusive crisis (VOC). No patients developed hematological malignancy at follow-up [28]. Meanwhile, in another study, autologous cells transduced with lentiviral vector were assessed for safety and clinical response. All patients were found to have stable HbF induction; the clinical manifestations of SCD were reduced or totally absent by the end of the follow-up period [29]. Exagamglogene autotemcel (exa-cel), a

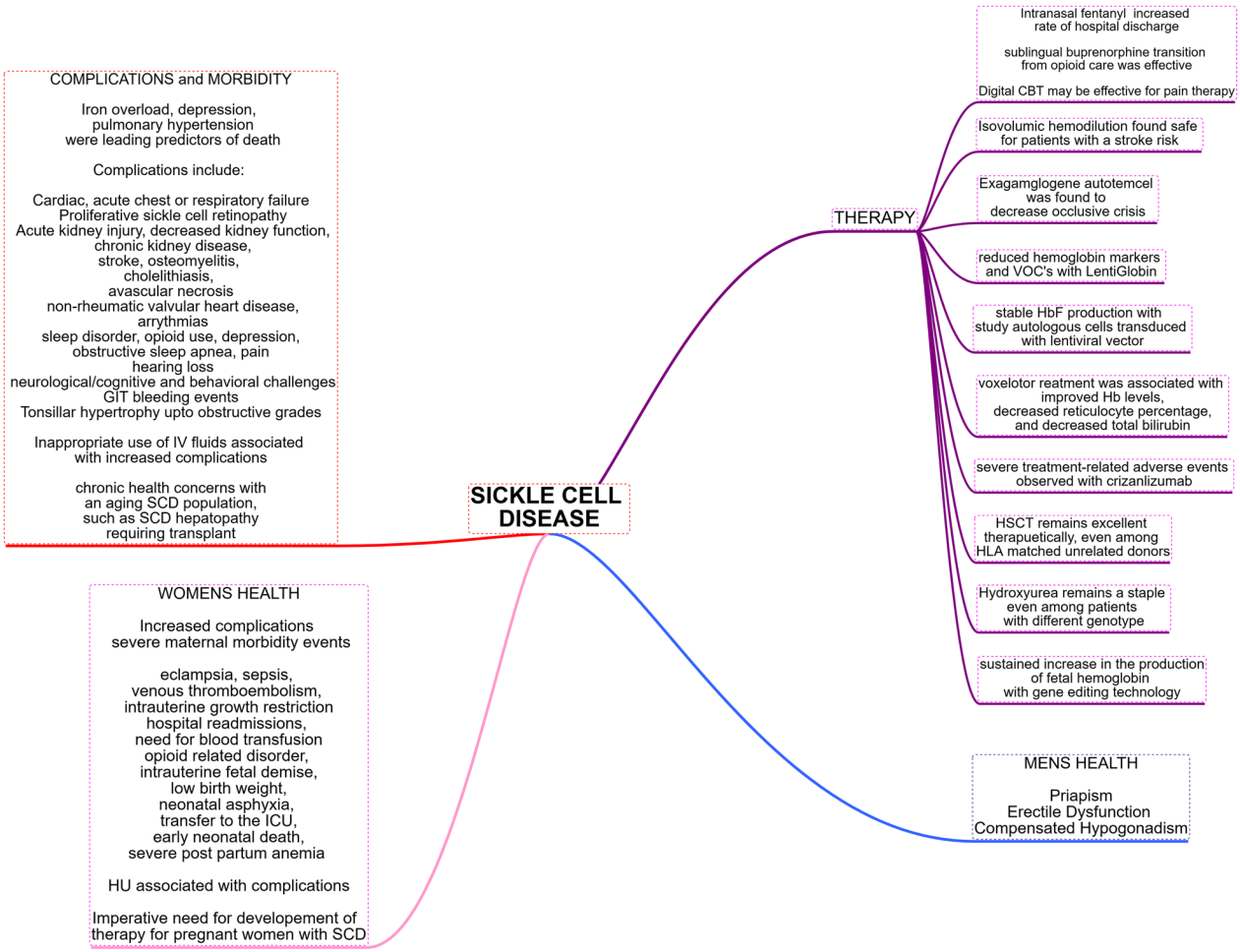

Fig. 2 Mind map depicting the key findings relevant to this review

non-viral cell therapy that works by reactivating fetal hemoglobin synthesis, was found to decrease occlusive crisis in 97% of patients [30]. However, long-term risks of genotoxicity are a concern. GHVD is a possible complication in autologous gene therapy, especially in scenarios with a degree of mismatching in African-American patients [31].

Gene editing for SCD has emerged as an interesting and controversial topic. The long-term response and safety of using gene editing technology remains to be determined. One study using CRISPR-Cas9 was used to disrupt *HBG1* and *HBG2* gene promoters, to induce the development of fetal hemoglobin. The infusion of OTQ923 in three individuals suffering from severe sickle cell disease led to a sustained increase in the production of fetal hemoglobin in their red blood cells [32].

Few studies have been published on crizanlizumab, a monoclonal antibody, for the treatment of sickle cell disease (SCD) [33]. One study using crizanlizumab at 5mg/kg body weight observed a decrease in acute care visits in SCD patients, but revealed a high discontinuation rate [33]. One German retrospective study found that crizanlizumab showed no difference than placebo, as well as significant severe events and admissions [34].

Hematopoietic stem cell transplant

Hematopoietic stem cell transplant (HSCT) from a matched donor remains as the ultimate cure for SCD [19, 20], but it is not a commonly utilized therapy (due to limited availability of matched donors), and is associated with complications like graft-versus-host disease (GVHD). HCST from a matched sibling donor consistently showed event-free survival and low incidence of GVHD [35]. One study reported the use of non-myeloablative HSCT. They found no clonal evolution or myeloid malignancies; graft failure was seen in some patients which appears to be dependent on ABO matching and non-ABO antibodies [36]. Plerixafor mobilization and apheresis in patients with sickle cell may allow the collection of sufficient hematopoietic stem cell collection,

the quantities of which vary among SCD patients. Factors affecting a higher yield included age < 30, a higher baseline and pre-apheresis CD34+ count, a high baseline white blood cell and platelet count, minimal hospitalizations, and no chronic pain [37]. HLA-matched unrelated donors were surprisingly found to have 100% overall survival and no severe GHVD. Unrelated donor transplantations may yield excellent outcomes, although patient risk factors such as advanced disease stage and comorbidities should be considered [38].

Hydroxyurea

Hydroxyurea (HU) remains a staple in the care of SCD. One study observed that HU treatment modulates inflammation and oxidative stress in both HbSS and HbSC genotypes [39]. Patients without the use of HU showed increased levels of plasma advanced oxidation protein product and interleukin-8 [39]. Some studies report on the efficacy of voxelotor, a once daily tablet that inhibits the polymerization of HbS [40]. Treatment was associated with improved hemoglobin levels, decreased reticulocyte percentage, and decreased total bilirubin. Concomitant use with hydroxyurea (HU) resulted in a more robust and complementary effect [41].

Pain

With regards to pain, a recent study showed a ninefold increase in the odds of discharge in children with SCD who were given intranasal fentanyl, and they were less likely to be admitted. Meanwhile, children who received oral opioids had a threefold greater odds of discharge than those who did not [42]. Additionally, the use of sublingual buprenorphine to transition from opioid care produced few medical adverse events, including recurrent or protracted withdrawal and worsened pain. Its use was associated with a marked reduction in acute care utilization by 72.5% on average [43]. Meanwhile, a randomized control trial found a significant response in pain management using digital cognitive behavioral therapy for pain intervention, among adolescents with SCD. Significant reductions in average pain intensity and the number of pain days were observed, while improvements were seen with coping attempts, mood, and fatigue [44].

Transfusions

Red blood cell exchange therapy was found to beneficial for pediatric patients requiring it for chronic transfusion, but its use in the prevention of stroke remains to be elucidated. Using a femoral double-lumen central venous catheter and 500 units in each lumen has been recommend due to limited venous access in this patient group [45]. Hemoglobin levels post-exchange therapy were significantly increased, and a total exchange volume of > 35 mL/kg was found to be the best way to reduce HbS to < 30% [45]. Blood transfusion may be pivotal in preoperative care in SCD patients, where one study reported increased risk of complications in the post-op period in those who did not receive transfusion. Prolonged hospitalization was observed in those who did not receive pre-op blood transfusion [46]. Meanwhile, preoperative blood transfusion did not show improved outcomes for semi-elective abdominal surgery (cholecystectomy, splenectomy, or appendectomy) in children with SCD. No statistically significant differences were found with regards to 30-day readmission or 30-day surgical complications, and this encourages investigations in order to minimize unnecessary transfusions [47].

With regard to hemodilution, one study confirmed the safety of isovolumic hemodilution in SCD patients with a history of stroke compared with the standard red cell exchange. Lower RBC usage and higher post-procedure hematocrit were observed, and this is clinically relevant, while no infarct progression was seen on MRI/MRA. Statistically significant drops in blood pressure were observed, but this was not clinically significant [48].

Impact of SCD on patients

Physical and psychosocial impact

Sickle Cell disease continues to have a significant impact on the quality of life of patients. Pain especially bears a significant impact [49]. One multi-country survey revealed that SCD significantly continued to affect aspects of patient life across areas including the performance of household daily activities, hygiene, family and social life, and relationships with spouse and partner [50]. Patients also reported significant impact on their emotional well-being, and a worry that their disease will worsen. SCD impaired patients total working hours, while some were dismissed from work as a result of their condition, and reported lower household income [51, 52]. Likewise, SCD affected students' attendance and adversely affected their school performance[50]. Meanwhile, academic performance in SCD patients may be linked to other social determinants such as household socioeconomic status [53]. SCD patients report a general experience of stigma, and this invites policy reform, programs, and health initiatives to overcome this [54].

Breakthrough solutions

There appears to be associations between adolescent health literacy and individual traits such as age, annual household income, and caregiver education level. The findings suggest that future research should explore additional factors, including media use, in order to better understand health literacy in adolescents with SCD, and inform future evaluation and intervention projects

[55]. Social support networks for patients with SCD are pivotal for their well-being, in order to provide emotional support and support during health crisis events [56]. Furthermore, improving disease knowledge using a web-based technological interface appears to have positive outcomes, especially in the transition of youth with SCD into adult care (which should be done ideally within the first 6 months of the transition of care) [57–59]. Promoting executive functioning [60], self-efficacy and self-management skills allowed SCD patients to take a more active role in managing their condition [61].

Complications and morbidity and mortality

Sickle cell disease (SCD) poses significant challenges in terms of mortality and morbidity, with a range of complications that can adversely impact patients' well-being and life expectancy, as well as the complications of therapy.

Systemic complications

Cardiac, acute chest or respiratory failure, and sudden unexplained death were the most common causes of death in one study [62]. Iron overload, depression, and pulmonary hypertension were leading predictors of death [62]. Meanwhile, elevated iron stores were found in patients with at least 3 transfusion per year [63]. An echocardiogram may be warranted in patients transitioning from adolescent to adult care as this population is at risk for cardiovascular disease [64].

Acute kidney injury, decreased kidney function, chronic kidney disease [65, 66], stroke [67, 68], osteomyelitis [69], cholelithiasis [70], avascular necrosis [71], non-rheumatic valvular heart disease [72], and arrhythmias are other complications that were reported on in the literature [73–75]. Meanwhile, adverse childhood experiences were linked to poor outcomes and increased morbidity [76]. Suicide risk was observed in one study [77]. Patients with SCD are at an increased risk of GIT bleeding events, especially upper GI bleeds. Any bleeding event was found to place a patient at a twofold increase in risk of death [78]. Infection [79, 80], acute chest syndrome, asthma [81, 82], pulmonary embolism, and death during a pain episode are causes of morbidity [83–86]. Meanwhile, pain and fever were among the commonest reasons for seeking acute care [87]. Tonisillar hypertrophy, up to obstructive grades, has been reported on in SCD patients [88]. Consultations with pulmonary care specialists are pivotal in the care of SCD patients [81].

Neuropsychological and special senses issues

Patients report significant impact on sleep [89], opioid use, depression [90], obstructive sleep apnea [91], pain [92–94] including gastrointestinal pain [95], hearing loss [96], and neurological/cognitive and behavioral challenges [97–111]. Proliferative sickle cell retinopathy has been reported among other ocular manifestations [112–114], which may be associated with elevated E-selectin levels [115].

A diagnosis of depression was found to significantly increased risk of readmission among the patients aged 18–29 years [116]. Meanwhile, hydroxyurea may play a role in mitigating neurocognitive decline in SCD patients [111, 117]. Interestingly, the neurocognitive dysfunction seen in SCD patients may not entirely be explained by iron overload effects on the brain [118]. Impaired cerebrovascular hemodynamics are evident in SCD patients [119, 120]. Meanwhile, early neuropsychological surveillance and assessment may protect from further neurocognitive decline [121].

Treatment-related issues

Complications associated with therapy are also prevalent. An association with inappropriate use of intravenous fluid use in the therapy of VOC's was found with complications such as acute kidney injury, volume overload, and acute chest syndrome, prompting the need for controlled trials to clarify the role of fluids in the treatment of VOCs [122]. Due to the need for blood transfusion, and increased hospital contact, SCD patients remain at an increased risk of infections like HCV [123].

No observed increase in mortality was found for SCD patients after cardiothoracic surgical procedures [124].

Chronic health concerns

In the context of an aging SCD population, more chronic conditions are a health concern. Liver complications, such as cirrhosis, are a significant cause of morbidity in SCD patients [125]. SCD hepatopathy is a condition that can arise from sickling into the hepatic sinusoids. Liver transplant may be warranted in patients with SCD in the case of acute liver failure or end stage chronic liver disease. One study observed the 1- and 5-year survival to be 75% and 65% respectively, while high morbidity is a concern in the early postoperative period [126]. A potential association may exist between SCD and autoimmune liver disease [127]

Risk factors for increased complications

Risk factors and exposures that can trigger SCD events or complications include short-term air pollution [128]. Also, vitamin deficiencies (A and D) in SCD patients can compound the risk of infection [129], while high-dose bolus of vitamin D plus 1000 IU daily was found effective to treat hypovitaminosis D in this patient group [130]. Meanwhile, lifetime risk of obesity and diabetes appears to be low among SCD patients [131]. The presence of Moyamoya syndrome (a disease defined as the chronic

and progressive narrowing of the arteries in the brain) conferred a 20× risk of stroke in patients with SCD [132]. Finally, it is important to differentiate between sickle cell genotypes as each may be associated with its own laboratory findings and clinical complications, with sickle cell anemia being the most severe form [133, 134]. SCD may be compounded by the coexistence of other hemoglobinopathies [135]. Interestingly, sickle cell anemia with co-inheritance with a-thalassemia appears to have a protective role against many disease-related complications [136]

Women's health and family planning

Pregnant individuals affected by sickle cell disease (SCD) encounter increased risk of pregnancy complications such as eclampsia, sepsis, venous thromboembolism, and intrauterine growth restriction compared to the general population [137]. The underlying causes of these unfavorable pregnancy outcomes can be attributed to the pathophysiology of the disease, compounded by socioeconomic disparities in care [138, 139]. Pregnant women with SCD were significantly associated with maternal anemia, maternal lower blood pressure, thromboembolism [140], inpatient mortality, preeclampsia/eclampsia [141] hospital readmissions, need for blood transfusion, opioid-related disorder [142], intrauterine fetal demise, low birth weight, neonatal asphyxia, transfer to the ICU, early neonatal death, and severe postpartum anemia [143–145]. Other studies confirm increased severe maternal morbidity among women with SCD [145–147]. There is a need for enhanced scientific and political effort to improve the outcomes for pregnant patients with SCD.

One study examined the impact of hydroxyurea use during conception, pregnancy, and infant outcomes. Hydroxyurea use during pregnancy was found to increase the risk of still birth or miscarriage, and it was also associated with decreased birth weight in infants born full term [148]. Caution for its use during pregnancy is still advised. Meanwhile, its use was associated with decreased ovarian reserve in women with SCD [149]. Therapy for pregnant women with SCD remains an underdeveloped area that needs more comprehensive research and therapy development to meet its challenge [150]. Overall, the risk of maternal and fetal adverse events may be determined by risk profiles including the presence of low first-trimester hemoglobin, admission in the year before pregnancy, multiple transfusions before pregnancy, a history of maternal cardiac complications, and the presence of HbSS/HbSβ^0-thalassemia genotype [151].

For parents wishing to conceive, only half knew about their hemoglobinopathy status [152] or their partners. Meanwhile, having SCD was a reason why some patients did not wish to conceive [133]. Knowledge about other reproductive options was limited, and choices such as IVF were limited due to personal, cultural, or financial factors [133]. Meanwhile, preimplantation genetic diagnosis may be a solution for the prevention of SCD [153]. Young adults shifting to adult care bring forth unique reproductive needs. Multi-disciplinary and intersectional care may meet these challenges [154], as well as fertility and genetic counseling [155]

Men's health

Priapism prevalence is higher in men with SCD than those without. Men report using exercise as a coping mechanism, as well as concerns for their self-image and feelings of sadness, embarrassment, and fear. Erectile dysfunction was found twofold more in men with SCD [156]. Compensated hypogonadism was also reported on in men with SCD [157]

Conclusions

SCD significantly impacts the lives of patients, affecting a broad range of physical and psychosocial aspects. Additionally, there is new hope as more therapeutic methods and findings will continue to shape the care for SCD patients. From this review, we can derive valuable insights into the significant impact of SCD on patients, which underscores the growing need for a unified global comprehensive approach to managing this disease, especially in the context of a chronically aging world population which will bring with it unique and complex healthcare challenges.

This review also highlights key findings in the literature that can point to new research directions, such as the rising concern of neurological and psychological complications among SCD patients that remains to be addressed. Another implication is the limited therapy options for pregnant women with SCD, which may inspire more research and targeted interventions and health policy, as this group is at significant risk of morbidity and mortality.

Our review findings can also delineate areas for policy and guideline development which highlight the necessity for targeted interventions that can focus on improving access to quality care, such as among adolescents transitioning into adult care, men's and women's health, and psychiatric and mental health support for SCD patients. Furthermore, exploring the intersectionality of genetics, personalized medicine, and social determinants of health in SCD care could pave the way for more effective and individualized treatment strategies for SCD patients. In summary, the practical implications and future research directions derived from this review underscore the importance of a comprehensive and proactive approach to SCD management, while

also serving as a concise summary of vital trends in therapy, care, and complications that may be valuable to physicians, students, educators, and patients alike.

This review has some limitations, as it only included the original research identified from two major databases. Therefore, there is a potential publication bias represented in the methods, which may not have included findings from research not identified by these databases, potentially leaving behind unique findings in studies from SCD endemic areas. To mitigate this, we screened the first 300 articles in each database in the order in which they appeared, and the majority of the studies included in this narrative were published in the USA and other Western countries, with limited findings from the African/SCD endemic area research narrative, yet this can be the focus of future studies. A publication date bias may also be present which may overlook older but relevant studies. Nonetheless, this review comprises a snapshot summary of the significant recent findings and outcomes from an exhaustive amount of literature, which should inspire more research and continued reading into the discourse on sickle cell disease.

Abbreviations

CRISPR-Cas9	Clustered regularly interspaced palindromic repeats
G6PD	Glucose-6-phosphate dehydrogenase
GIT	Gastrointestinal
GVHD	Graft-versus-host Disease
HBG1/2	Hemoglobin subunit gamma 1/2
HbS	Hemoglobin S
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
HU	Hydroxyurea
IU	International units
IVF	In vitro fertilization
SCD	Sickle cell disease
VOC	Vaso-occlusive crisis
WIZ	Widely interspaced zinc finger

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Author contributions
RM conceived the idea. RM and EM completed screened the relevant studies for inclusion and wrote the manuscript in its final form. All authors contributed in this work according to the ICJME criteria for authorship.

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