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Clinical and laboratory risk factors for sickle cell retinopathy and maculopathy: a scoping review of the current evidence

RUNNING HEAD: RISK FACTORS FOR SICKLE CELL RETINOPATHY AND MACULOPATHY

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Data sharing is not applicable to this article as no new data were created or analyzed in this study. The review protocol is available from the corresponding author upon request, the search strategies are provided in Appendix A.

Author contributions
RPB, RMHD and BJB conceptualized this manuscript. AM created the search strategy. RPB and GK screened the eligible articles and performed the data extraction (and consulted RMHD in case of disagreement). RPB, RMDH and BJB wrote the initial draft. All authors contributed to interpretation of data, revisions of drafts of the manuscript and approved the final version.

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Abstract

Sickle cell retinopathy (SCR) is a complication of sickle cell disease (SCD) and can drastically impair visual acuity. Screening for SCR is therefore recommended, but evidence for optimal screening frequency on an individual level is lacking. This scoping review mapped the current evidence on risk factors for SCR and sickle cell maculopathy (SCM). A literature search (in Medline(Ovid), Embase(Ovid) and Scopus) resulted in 67 included articles, which covered demographic risk factors, genetic risk factors, systemic therapy, correlations with other forms of SCD-related organ damage and hematological risk factors. SCR risk factors include older age, male sex, HbSC genotype, hemolysis and HbF% <15% (in HbSS) and increased blood viscosity (in HbSC). For SCM, risk factors are older age, HbSS genotype and higher degree of hemolysis. The pathophysiology of SCR and SCM appears multifactorial, but distinct patterns emerge suggesting that vaso-occlusion and hemolysis cause SCM and NPSCR in HbSS, while hyperviscosity in HbSC leads to peripheral retinopathy. We recommend yearly screening for high-risk (older HbSC males) and triennial screening for low-risk (young females HbSS with HbF>15%) patients to ensure comprehensive yet proportionate ophthalmic care. However, to elucidate the sense and nonsense of screening, future studies are needed on the role of interventions for SCR and the long-term consequences of SCM.

Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy leading to chronic hemolysis, inflammation and vaso-occlusion, resulting in ischemic organ damage. The retina is sensitive to ischemia, which can cause sickle cell retinopathy (SCR) or sickle cell maculopathy (SCM). SCR is observed in many SCD patients and can be subclassified into non-proliferative SCR (NPSCR) and proliferative SCR (PSCR). NPSCR is characterized by retinal abnormalities like black sunbursts, salmon patches, and peripheral vascular tortuosity or occlusions. In contrast, PSCR is marked by peripheral neovascularization that can result in vitreous hemorrhage and retinal detachment, potentially leading to visual impairment. Many pathophysiological aspects have been suggested to contribute to the development of SCR including endothelial activation, increased viscosity leading to local vascular obstruction, ischemia and angiogenesis.[1, 2]

SCM results from SCD-related damage to the central part of the retina (the macula) and includes abnormalities such as local macular thinning, foveal avascular zone enlargement and lower vessel densities. These conditions are all classified under SCM, a broader term for these specific changes. Many studies on SCM often focus on a limited set of its features. SCM abnormalities are detectable through spectral-domain optical coherence tomography (SD-OCT) and optical coherence tomography angiography (OCTA).[3, 4] The functional consequences of SCM are unclear, but scotomas on visual fields, reduced contrast sensitivity and loss of color vision have been reported in SCD patients with severely diminished vessel density on OCTA, even when visual acuity was unaffected.[5]

With rising life-expectancy of SCD patients due to improved treatments and preventive measures like neonatal screening, vaccinations and stroke screening, the risk of SCR has probably increased.[6, 7] While NPSCR and SCM generally do not impair vision, PSCR can drastically impair visual acuity if complications occur. Currently, ophthalmologic screening is recommended for all SCD patients by dilated fundoscopy every one/two years, starting at age ten, although the optimal frequency for individual patients is not well defined, lacking sufficient evidence.[1, 8] A personalized risk-based approach could enhance monitoring of patients at risk of sight-threatening complications while avoiding redundant hospital visits in low-risk patients. To distinguish between high-risk and low-risk patients, knowledge about risk factors for SCR and SCM is important.

Several studies on SCR, SCM and their risk factors have been published.[9-12] However, a comprehensive review of the current literature has not been conducted recently. This scoping review aims to systematically map the literature in this area. The focus will be on the following research questions: (1) What is known about risk factors for SCR and SCM in SCD patients? (2) What is the current evidence supporting screening and the optimal frequency for SCR and SCM? (3) What are the current knowledge gaps?

Methods

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[13] The review protocol is available upon request.

A literature search (in Medline (Ovid), Embase (Ovid) and Scopus) was performed from inception up to May 23th 2023, in collaboration with a medical information specialist (AM). The search included

controlled terms and free text terms for synonyms of ‘sickle cell disease' combined with synonyms of ‘retina disease' and/or ‘incidence’. The search was performed without restrictions for methodology, date or language. Reference lists of relevant articles were manually reviewed for additional publications. The full search strategies can be found in appendix A. Duplicate articles were excluded by an in-house made deduplication tool.

To be included, studies had to focus risk factors for SCR or SCM in children and/or adults with SCD. Only randomized controlled trials, cross-sectional studies and cohort studies were considered. Case reports, letters, commentaries and editorials were excluded. Studies published in English, Dutch and French language were included.

After collection and deduplication in Endnote (version 20, Clarivate Analytics), two authors (RPB and GK) independently screened titles, abstracts and subsequently full texts of the articles resulting from the literature search. Disagreements regarding eligibility were resolved through discussion and consulting a third author if needed (RMHD). Data extraction was performed by the same two authors. The following data were collected: first author and publication year, country, study design, participant characteristics (including age, sex, genotype, stage of retinopathy) and reported risk factors for SCR.

Results

Literature search and study characteristics

The database search identified 821 records and an additional 28 records were identified through reference searching. After deduplication, 587 records were screened on their title and abstract. Full-text articles were sought for 117 records after title and abstract screening. For 18 records, the full-text articles could not be retrieved. Full-text screening was performed for 99 articles. After exclusion of 32 articles (all based on not reporting risk factors for SCR or information on screening), 67 articles were included in this review. A flow diagram of the selection process is shown in Figure 1.

Demographic risk factors and comorbidity

Table 1 provides an overview of identified risk factors. Older age was a risk factor for SCR in adult and pediatric populations.[2, 9, 10, 14-32] This was consistent across all genotypes, with HbSC patients diagnosed at a lower age than HbSS patients.[16, 32] Older patients had more peripheral retinal abnormalities and patients with PSCR were older than patients with NPSCR in both HbSS and HbSC genotypes.[15, 16, 21, 27, 28, 31] One study reported that the risk of developing PSCR was 1.8 times greater in those aged 25 compared to 20 (95% CI 1.5-2.3), 2.1 times greater in those aged 20 versus 15 (95% CI 1.7-2.9) and 2.9 times greater in those aged 15 versus 10 (95% CI 2.1-2.9).[16] Regarding SCM, older age was associated with (para)macular atrophy/thinning and decreased vessel densities in the superficial capillary plexus (SCP) and deep capillary plexus (DCP).[12, 33-35] One study reported an association between younger age and frequency of perimacular capillary abnormalities (e.g. microaneurysms and hairpin loops) on fluorescein angiography.[36]

Ten studies examined associations between sex and SCR. In nine, male sex correlated with NPSCR and PSCR.[10, 17-19, 21, 23, 28, 37, 38] This association was demonstrated in both adult (adjusted OR (aOR) 2.58, 95% CI 1.39-4.81, p=0.003) and pediatric (OR 4.20, 95% CI 1.58-11.14, p=0.004) populations.[19, 37] After adjustment for age, genotype and HbF%, female sex was associated with absence of SCR at follow-up in a retrospective 11-year follow-up analysis among 129 SCD patients (aOR 2.56, 95% CI

1.101-5.931, p=0.029).[10] One study demonstrated more retinal vascular tortuosity in female pediatric patients (43% versus 18%, p=0.030).[39]

Two publications from a Jamaican cohort study reported an association between SCR and weight/height. In the first publication, lower weight and height were associated with peripheral retinal vaso-occlusion in patients with HbSC disease,[40] but in a later publication this association was only described with a lower weight in HbSS patients.[21]

One study in mainly HbSS patients reported a (borderline) independent association between high systolic blood pressure and SCR (OR 6.85, 95% CI 1.05-44.45, p=0.059).[41] Hypertension was also independently associated with macular thinning in a USA-based SD-OCT study.[42]

Smoking was studied as a risk factor for SCR in the Cooperative Study of Sickle Cell Disease (CSSCD), showing associations with SCR in general (OR 1.67, 95% CI 1.22-2.28, p=0.001) and with PSCR specifically (OR 1.66, 95% CI 1.16-2.37, p=0.005).[9]

In a Nigerian study among pediatric SCD patients, data on parental profession and education were collected, as a measure of social class.[43] A higher social class was shown to be a protective factor against ocular abnormalities (OR 0.45, 95% CI 0.21-0.95, p=0.037).

Genetic risk factors

Table 2 outlines the identified genetic risk factors.

Genotype/alpha-thalassemia

HbSC genotype was a risk factor for SCR in most studies.[10, 11, 14-18, 20, 26, 29, 30, 32, 38, 41, 44-49] Specifically, the presence of black sunbursts, iridescent spots, non-perfusion areas, arteriovenous shunts, and neovascularization correlated with this genotype.[14, 25, 42, 50] One study reported increased ischemia in HbSC versus HbSS genotype.[51] SCR severity and bilateral involvement were also associated with HbSC.[17, 52] Furthermore, sight-threatening complications (vitreous hemorrhage and retinal detachment) were correlated with HbSC.[38, 42, 53] Fewer studies reported on other genotypes. One study that only included HbSS/HbSβ^+ patients reported that HbSS was associated with increased odds of SCR compared to HbSβ^+ (OR 20.0, 95% CI 3.464-115.446, p<0.001).[2] Another small study, which was hampered by inclusion of only three HbSC patients, reported an association between HbSS and SCR.[54] Furthermore, two studies reported increased retinal vascular tortuosity in HbSS genotype compared to HbSC/HbSβ-thalassemia.[14, 42] In a study reporting on the effect of Hb-genotype on untreated PSCR, spontaneous regression of neovascularization was associated with HbSS.[27] HbSS patients without alpha-thalassemia (n = 180) had more ocular abnormalities than HbSS patients with alpha-thalassemia (n = 9).[21] Associations between SCM and Hb-genotype have also been described. Several studies reported more macular thinning in HbSS/HbSβ-thalassemia than in HbSC.[35, 42, 54-57] Lower vessel densities in the SCP and DCP were associated with HbSS in one study,[48] but another study reported this association for HbSC.[58]

Polymorphisms/haplotypes

One study on polymorphisms of endothelial nitric oxide synthase (eNOS) demonstrated a higher prevalence of SCR in HbSS/HbSβ^0 patients with the 786CC polymorphism (which is associated with more vasoconstriction), although no difference was found in eNOS expression between these variants.[59] Another study demonstrated that the IL-6–597G>A polymorphism is correlated with SCR (p=0.010).[60]

The impact of the haplotypes of β-globin on SCD-related organ damage among HbSC patients was examined in one study.[61] Patients with the [+--++] haplotype of the β^C-allele (as previously defined by Boehm et al.[62]) were grouped as β^{Cl} patients and patients with other (less common) haplotypes were grouped as non-β^{Cl} patients. SCR was more common in non-β^{Cl} patients than in β^{Cl} patients (67% versus 33%, p=0.049). SCR onset was earlier in non-β^{Cl} patients (p=0.026). In patients that concurrently inherited the β^S Ben haplotype, the development of SCR was more common in non- β^{Cl} patients than in β^{Cl}-patients (p=0.028).

Systemic therapy

Table 3 summarizes the identified associations with systemic therapy.

Chronic transfusion

Transfusion therapy decreased the likelihood of developing PSCR (aOR 0.64, 95% CI 0.41-0.99, p=0.050) in one study.[9] This finding was corrected for age, sex, Hb genotype and other SCD-related organ complications. One prospective study described the impact of transfusion therapy on SCM: decreased foveal width and increased foveal depth were associated with chronic transfusion therapy (not corrected for genotype, age, sex or other SCD-related complications), indicating a better foveal contour.[63] Interestingly, the total and outer retinal thickness of the temporal macula were decreased in patients receiving chronic transfusion therapy, a finding the study hypothesized may have been present prior to the start of therapy.

Hydroxyurea

Hydroxyurea treatment has been linked to decreased risks of SCR and SCM. This was demonstrated in a study of 60 pediatric HbSS/HbSβ-thalassemia patients that related hydroxyurea non-adherence to SCR (p<0.001).[22] Another cross-sectional study among 15 pediatric patients (8 HbSS, 3 HbSC and 4 HbSβ-thalassemia) demonstrated that the absence of/non-adherence with hydroxyurea treatment was associated with SCR (p=0.010), macular thinning and vessel abnormalities in the DCP (p=0.046).[54]

Chelation

One study among 30 SCD patients demonstrated that chronic chelation therapy was a protective factor for SCM with a 94.2% decrease of the odds (p=0.0187).[64] Data on SCR was not included.

Sickle cell related organ damage and complications

Table 4 summarizes the associations with SCD-related organ damage and complications.

Cerebral complications

A history of stroke was associated with SCR in HbSS/HbSβ^0 populations and was specifically associated with PSCR in one study (aOR 1.91, 95% CI 1.03-3.53, p<0.050).[22, 65] A correlation with higher flow velocity in the middle cerebral arteries on transcranial Doppler was also demonstrated in patients with SCR.[22] Furthermore, stroke (including silent infarcts), cerebral vasculopathy, seizures and impaired cerebral oxygenation were associated with SCM in all genotypes.[34, 42, 55, 63]

Pulmonary complications

Pulmonary hypertension (arterial pulmonary pressure ≥40 mmHg) was associated with advanced PSCR stages in HbSC patients in a retrospective study including HbSS/HbSC patients.[19] In HbSS patients, PSCR was also correlated with a history of acute chest syndrome (ACS). Conversely, another study with only HbSS patients reported chronic pulmonary damage as a protective factor for PSCR (aOR 0.46, 95% CI 0.22-0.96, p<0.050).[65] Regarding SCM, one study among HbSS/HbSβ-thalassemia patients reported that a history of >1 ACS episodes was associated with increased foveal depth and

total retinal thickness.[63] Another study that also included HbSC patients found a correlation between >1 ACS episodes and SCM.[55]

Renal complications

No correlation between microalbuminuria and SCR has been reported. PSCR was associated with acute pyelonephritis and hematuria.[9, 19] Hematuria was associated with NPSCR and PSCR (aOR 1.53, 95% CI 1.01-2.23, p=0.050).[9] Another study, which did not include patients with PSCR, reported a correlation between a higher glomerular filtration rate and NPSCR.[12] One study reported that a history of renal failure in HbSS patients was a protective factor for PSCR (aOR 0.27, 95% CI 0.12-0.61, p<0.010).[65]

Vaso-occlusive events

Three studies demonstrated that the occurrence and frequency of vaso-occlusive painful events were positively correlated with SCR.[22, 37, 54] In one of these studies, macular thinning and flow voids in the DCP were also associated with the prevalence of painful events.[54]

Biliary complications

Biliary complications (including gallstones/cholecystectomy and cholecystitis) were associated with SCR in HbSS and HbSC patients.[19, 26, 65] One of these studies demonstrated that a history of biliary tract complications was independently associated with PSCR specifically (aOR 1.93, 95% CI 1.20-3.09, p<0.010).[65]

Splenic complications

A history of hypersplenism (including splenic sequestration) was associated with lower PSCR prevalence (aOR 0.48, 95% CI 0.23-0.97, p<0.050) in a study among 1056 HbSS patients.[65] However, another study among HbSS/HbSC/HbSβ-thalassemia patients reported that splenic sequestration was correlated with SCR (OR 4.00, 95% CI 1.34-11.97, p=0.013).[37] Another study (among HbSS/HbSβ-thalassemia patients) demonstrated an increased splenectomy rate in patients with SCR (p=0.004).[24]

Avascular necrosis

One study among 60 HbSS/HbSβ-thalassemia pediatric patients reported an association between SCR and avascular necrosis (AVN) (p<0.001).[22] Another study reported that AVN was more prevalent among patients with PSCR than patients with NPSCR (p<0.001), but this association was not significant in a multivariate analysis.[9] A third study found no association between AVN and SCR.[17]

Leg ulcers

In the Cameroon CADRE cohort study with 84 HbSS patients, patients with leg ulcers were less likely to have SCR (OR 0.27, 95% CI 0.09-0.78, p=0.018).[28] However, this association was not corrected for genotype, Hb level or hematocrit.

Hearing problems

In a retrospective study among 942 HbSS and HbSC patients, severe PSCR was independently correlated with deafness and tinnitus in HbSC patients, but not in HbSS patients.[19]

Thrombosis

Decreased macular thickness on SD-OCT was independently associated with a history of deep vein thrombosis in a study among 260 patients (HbSS/HbSC/HbSβ-thalassemia genotypes).[42] No studies on the relation with SCR were found.

Laboratory risk factors

An overview of laboratory risk factors is outlined in Table 5.

Hemoglobin level

Multiple studies reported associations with higher Hb-levels. SCR correlated with higher Hb-levels in both HbSS and HbSC,[9, 15, 18, 22, 28, 47, 66, 67] predominantly based on a correlation with PSCR in male patients.[18, 66, 67] One study identified a threshold of Hb >8g/dL (HbSS) and >10 g/dL (HbSC) as best fitting regarding SCR risk, adjusted for age and sex.[15] In contrast, two studies reported associations between lower Hb-levels and non-proliferative abnormalities.[12, 21] In one of these studies, which reported this association for HbSS, this correlation was only adjusted for HbF,[21] while the other study, performed among both HbSS and HbS-variant patients, was also adjusted for Ht, MCV, reticulocyte percentage and total bilirubin.[12]

Hematocrit

Lower hematocrit was associated with NPSCR in three studies.[12, 34, 57] However, this association remained significant in a multivariate analysis (correcting for hemoglobin level) in only one of them (aOR 0.037, 95% CI 0.003-0.505, p=0.013).[12] Another study found a higher hematocrit correlated with SCR in both univariate and multivariate analyses.[15] Regarding SCM, the opposite phenomenon was reported. Macular ischemia/thinning was associated with lower Hb/Ht levels.[12, 34, 56, 57] One of these studies reported that in HbSS, a 0.12 mm^3 decrease in macular volume, a 7-10 µm decrease in retinal thickness of the temporal macula and a 3 µm decrease of the average macular thickness were correlated with a one point decrease in Hb-level.[56]

Red cell indices

Higher MCV was correlated with SCR in HbSS and HbSC genotype and in both sexes.[12, 18, 21, 23] The use of hydroxyurea, which increases MCV, is only described in one of these studies (where only 2 of 18 patients used hydroxyurea) and the described correlation between MCV and SCR was not corrected for the use of hydroxyurea.[12] However, one study among HbSS/HbSβ-thalassemia patients found a correlation between retinal patches (NPSCR) and lower MCV.[68] PSCR was associated with elevated Mean Corpuscular Hemoglobin Concentration (MCHC) in HbSS and HbSC genotype.[23, 66] Furthermore, patients without PSCR had a lower Mean Cell Hemoglobin (MCH) than patients with PSCR in a study among HbSC patients.[69] Increased Red Cell Distribution Width (RDW) was associated with SCR in another HbSC population.[15]

HbF%

All studies reporting on HbF% demonstrated negative associations between HbF% and SCR.[9, 10, 12, 15, 18, 19, 21, 23, 26, 40, 52, 54, 66-71] This association was found for both sexes, for all genotypes and remained significant after adjusting for hydroxyurea use, age, genotype, hemoglobin level and a history of gallstones.[18, 26, 70, 71] HbF<15% was an independent predictor for SCR in two retrospective studies among children and adolescents.[70, 71] The first study was performed among 123 pediatric HbSS patients with a median age of 13 years.[70] The second study was performed among 42 pediatric patients (mean age 14±1.98 years) with HbSS/HbSC/HbS-thalassemia/HbSO-arab genotypes.[71] Another retrospective study among 300 adult patients (HbSS/HbSC/HbS-thalassemia or HbS/HPHF genotypes) reported that HbF>15% reduced the risk of SCR by half.[26]

HbS%

SCR was associated with higher hemoglobin-S percentage (HbS%) in three studies. The first study, a prospective study among pediatric HbSS/HbSβ-thalassemia patients, did not correct this finding for genotype.[22] However, another study among pediatric HbSS/HbSβ-thalassemia patients did correct for genotype and the association remained significant (aOR 1.135, 95% CI 1.049 – 1.228, p=0.002).[2] The last study demonstrating an association between higher HbS% and SCR included solely HbSS patients.[72] Furthermore, irreversibly sickled cells (ISC) count was correlated with the extent of retinal vaso-occlusion in a study among pediatric patients from the Jamaican cohort study.[40]

Leukocyte and platelet count

Lower leukocyte count was correlated with SCR among HbSS/HbSβ^0 patients (p=0.011) in a large retrospective study among 1604 HbSS/HbSC/HbSβ-thalassemia patients.[15] This correlation was not found for HbSC genotype.

A study among HbSS and HbSC patients from Guadeloupe demonstrated that patients with NPSCR had a lower platelet count than patients with PSCR.[73] This analysis was also performed for HbSC genotype separately (which remained significant). A lower INR was correlated with SCM in a cross-sectional study among HbSS/HbSC/HbSβ$^+$/HbS-lepore patients (p=0.010).[57] This study did not report on associations between SCR and INR.

Markers of hemolysis

SCR and SCM were associated with higher reticulocyte counts in multiple studies in HbSC, HbSS and HbSβ-thalassemia.[12, 40, 54, 55] One study reported an association between NPSCR and PSCR and higher reticulocyte counts in their univariate analysis, but in the multivariate analysis a negative correlation between reticulocyte counts and PSCR was found (aOR 0.95, p=0.011).[9] Associations with SCR and LDH were not reported. An association between SCM and elevated LDH levels was found in a study among 78 patients including HbSS/HbSC/HbSβ$^+$/HbS-Lepore genotypes (p=0.007).[57] Their multivariate analysis demonstrated that increased LDH levels were associated with an increase of the foveal avascular zone (p=0.020). The correlation between bilirubin and SCR was evaluated by one study. Total bilirubin levels were increased in patients with NPSCR (aOR 12.0, 95% CI 1.3 – 111.3, p=0.029) and SCM (aOR 16.3, 95% CI 1.3 – 197.8, p=0.028) in this study among 18 pediatric HbSS/HbSC/HbSβ$^+$ patients.[12] None of their patients had PSCR.

Ferritin

One study reported a negative correlation between serum ferritin levels and advanced stages of PSCR in HbSC patients in a large retrospective study performed among 942 SCD patients (HbSS and HbSC).[19]

Biomarkers of rheology, endothelial activation, angiogenesis or NO metabolism

Table 6 summarizes the identified biomarkers.

Viscosity

A cross-sectional study demonstrated that whole blood viscosity was lower in HbSC patients without SCR compared to those with PSCR.[73] This difference was not found among their HbSS patients. Another study among adult Jamaican HbSS patients demonstrated that increased whole blood viscosity was associated with PSCR in male patients only.[66]

Red cell deformability

The relation between red blood cell (RBC) deformability and SCR was not investigated. A French study among pediatric HbSS patients demonstrated decreased RBC deformability at a shear stress of 1.69 Pa and up in patients with SCM using ektacytometry: the thickness of the paramacular inner retina was inversely correlated with the deformability of RBCs.[34]

Endothelial activation

Higher plasma levels of pigment epithelium-derived factor (PEDF) were associated with SCR in HbSC (p=0.031).[74] SCR correlated with lower levels of plasma soluble intercellular adhesion molecule-1 (sICAM-1) (p=0.045).[74] However, when stratified by genotype, this association remained only significant for HbSC patients (p=0.012). Elevated plasma levels of E-selectin were an independent risk factor for SCR in a study among 50 adult HbSS/HbSC/HbSβ-thalassemia patients (p<0.001).[75]

Angiogenesis/NO-metabolism

Two studies reported a positive association between angiopoietin-2 (Ang-2) plasma levels and SCR.[2, 76] This association was found for HbSS patients in one of these studies that included both HbSS and HbSC patients.[76] The other study, which included HbSS and HbSβ$^+$ patients, reported that above a cut-off point of 9000 pg/mL, 100% of the patients appeared to have SCR, while none with an Ang-2 level <9000 pg/ml had SCR (100% sensitivity and specificity; p<0.001).[2] Increased plasma levels of asymmetric dimethyl arginine (ADMA) were associated with SCR in a study among 40 Egyptian pediatric patients (p<0.002).[77] SCR severity was also related to ADMA levels (p<0.011). Genotype specifications were not described in this study.

Discussion

In this scoping review, we systematically explored the literature on risk factors for SCR and SCM. An increasing number of articles has been published in recent decades, revealing a wide variety of possible risk factors. The most frequently reported risk factors for SCR were HbSC genotype, male sex, older age, lower HbF% and higher Hb level. Risk factors for SCM differed, with SCM more frequent in patients with HbSS genotype and/or lower Hb levels.

SCR is more prevalent in older male HbSC patients. Reported associations with other risk factors were harder to interpret due to contradictory findings. Higher Hb level is frequently noted as a risk factor for SCR, linked to higher viscosity, especially in HbSC patients, which may contribute to the high frequency of retinopathy in these patients.[78] One study demonstrated a direct relation between viscosity and SCR severity in HbSC patients.[73] However, some studies did not find a correlation between Hb level and SCR (even when stratified by genotype), including a retrospective cohort study from our own institution.[10, 17, 19] A possible explanation might be that SCR in HbSS relates more to anemia and vaso-occlusion mechanisms than to chronic hypoxia from hyperviscosity as may occur in HbSC. This might explain the higher NPSCR prevalence in HbSS compared to neovascularizations, which are mostly found in HbSC patients.[10] Several studies also found associations between SCR and complications/organ damage commonly observed in HbSS patients with lower hemoglobin levels related to hemolysis (such as cerebral infarctions, pulmonary hypertension and biliary complications). Reticulocyte counts show conflicting associations with SCR. One study with predominantly HbSS patients found a negative correlation with PSCR incidence,[9] while other studies report a positive correlation after adjusting for other hematologic indices and genotype.[12, 40, 54, 55]

A lower HbF% is widely studied as a risk factor for SCR. High HbF% prevents HbS polymerisation, is a protective factor for vaso-occlusive crises and ACS, and is associated with higher hemoglobin levels.[79] The fact that a lower HbF is associated with PSCR independent of genotype is interesting, since most patients with PSCR have HbSC genotype (with lower HbF levels compared to HbSS patients).[10, 80] In addition to higher viscosity, vaso-occlusion seems to play a role in the pathophysiology of PSCR. This is confirmed in a study analyzing the relationship between whole blood viscosity and SCR, where higher viscosity was associated with SCR in HbSC but not in HbSS patients.[73] This may explain the contradictory findings regarding the association between hemoglobin levels, hemolytic rate, and SCR. Several studies reported a cut-off value of 15% HbF for protection against (P)SCR.[26, 70, 71] High HbF% has also been associated with increased Hb levels in HbSS patients,[79] which contrasts with higher Hb levels being a risk factor for SCR. This might suggest that the reduction in vaso-occlusion with higher HbF outweighs the increased viscosity from higher HbF levels. The fact that hydroxyurea reduces the risk of SCR supports this hypothesis.

Other SCR risk factors are found in limited or conflicting studies. A clear positive association was found between higher platelet counts and SCR, while leukocyte counts and markers of endothelial damage such as sICAM-1 and E-selectin, were negatively associated with SCR. Remarkably, PEDF (an anti-angiogenic factor) is positively related to SCR, potentially counteracting hypoxia-induced angiogenesis. Determining if this could serve as a biomarker of PSCR requires further prospective studies.

The changes in the macula differ from those in the peripheral retina. SCM is characterized by macular thinning and loss of local microvascular structures, but does not lead to neovascularization. SCM has been associated with HbSS genotype, along with features or consequences of this genotype, such as laboratory hemolysis indicators and chronic transfusion indication. In contrast, SCR is associated with HbSC genotype and its features (e.g. higher Hb level, low HbF% and higher blood viscosity). This suggests that the underlying pathophysiology of SCM might differ from that of SCR and/or between HbSS and HbSC patients. The macula may be more susceptible to diffuse microvascular loss than the peripheral retina, where ongoing ischemia resulting in neovascularization is presumed to be the major problem.[81] However, the consequences of SCM remain unclear. One study revealed scotomas, reduced contrast sensitivity and loss of color in SCD patients with severely diminished vessel density on OCTA, but visual acuity was not impaired.[5] Longitudinal data on SCM and its consequences is still scarce. Currently, there are no screening guidelines for SCM and it is unclear whether screening would effectively prevent visual impairment, necessitating further research.

Screening aims to prevent vision-threatening complications by detecting SCR in early stages, but monitoring neovascular lesions instead of intervening is becoming more common. Laser photocoagulation was frequently used to prevent complications of neovascular lesions (bleeding, traction, retinal detachment), but evidence for its medical benefit in SCR is scarce and ambivalent.[82] Neovascular lesions usually regress spontaneously or remain stable for years and current literature shows no clear difference between treated and untreated patients.[82] More recently, the use of anti-angiogenic intravitreal injections has been reported, but evidence is limited with only two case reports showing regression of neovascular lesions and vitreous hemorrhage dissolution.[83, 84] Larger studies are needed to demonstrate whether anti-angiogenic therapy in SCR is valuable.

Systemic treatment impacts SCR risk. Hydroxyurea lowers SCR risk by increasing HbF% and inhibiting polymerization, while chronic transfusions affect SCR by reducing HbS levels. Recently, phlebotomy has been suggested as a new treatment for HbSC patients to prevent vaso-occlusive crises by reducing viscosity.[85] This might also be relevant for preventing PSCR, as hyperviscosity is postulated to be a cause of PSCR. However, studies on the effect of phlebotomy on SCR are lacking. More research is needed to evaluate the impact of interventions on SCR.

As long as the role of interventions in preventing visual complications is not completely elucidated, routine screening for SCR might remain the only way to detect SCR in earlier stages and allows physicians to educate patients on vitreous hemorrhage and retinal detachment. SCR progresses over time, as shown in our retrospective cohort study,[10] but the varying risk of SCR progression may justify a more risk-adapted screening approach. Important to note is that the variety of risk factors is wide and most patients will not meet the complete set. Furthermore, not all risk factor measurements will be available in clinical practice (e.g. viscosity/angiogenesis parameters). While it is challenging to define which factors should be taken into account, we propose to divide patients into two categories to determine screening frequency: high risk and low risk. Based on the most described risk factors and the availability in clinical practice, older male HbSC patients could be considered high-risk. Additional risk factors may include lower HbF% (<15%) and signs of hemolysis (e.g. increased reticulocytes and total bilirubin and/or the presence of hemolysis-related organ damage) in patients

with HbSS, and indicators of increased whole blood viscosity in HbSC patients (e.g. increased whole blood viscosity or high hemoglobin levels). We propose yearly screening for high-risk patients. Conversely, younger female HbSS patients with high HbF% (>15%) could be considered low-risk. We propose to decrease their screening frequency to once every three years, particularly for those on hydroxyurea or transfusion therapy with mild organ damage. Table 7 demonstrates our recommended screening intervals based on genotype and retinopathy status. However, evidence on whether the benefits of screening outweigh the burden for the patients and costs remains lacking. This is especially a relevant topic with the increasing tendency of monitoring PSCR and with the paucity of evidence on the consequences of SCM, for which the need for screening is unclear, though monitoring during SCR visits is advisable.

This review has a number of limitations. The full-text of 18 publications could not be retrieved, potentially excluding important studies. Additionally, a quality assessment of included studies was not performed. This was considered when interpreting results, leading us to view the scoping method as suitable for addressing our research questions.

In conclusion, the pathophysiology of SCR and SCM appears multifactorial, with vaso-occlusion and hyperviscosity potentially exerting distinct influences in different SCD genotypes. Despite increasing tendency to monitor instead of treating SCR, routine screening might remain the only way to detect SCR in earlier stages and educate patients on symptoms of vitreous hemorrhage and retinal detachment. To personalize screening, we recommend adapting the screening frequency according to the most relevant clinical risk factors, screening high-risk patients yearly and low-risk patients once every three years. However, to elucidate the rationale for screening, more research is needed on the role of interventions for SCR and the long-term impact of risk factors on SCR and SCM.

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Tables

Table 1. Demographic risk factors and comorbidity

Risk factor	Association with SCR	Association with SCM	References
Age	• Older age (in both adult and pediatric populations) • Lower age at diagnosis in HbSC compared with HbSS • SCR severity (and therefore the risk of developing PSCR) increases with age	• Older age associated with (para)macular atrophy/thinning + decreased vessel densities in superficial and deep capillary plexuses	2, 9, 10, 12, 14-35
Sex	•Male sex associated with NPSCR and PSCR •Female sex associated with absence of SCR	-	10, 17-19, 21, 23, 28, 37-39
Weight/height	• Lower weight + height associated with peripheral retinal vaso-occlusion in HbSC • In later publication, lower weight associated with peripheral retinal vaso-occlusion in HbSS	-	21, 40
Systolic blood pressure	• High systolic blood pressure borderline association with SCR	• Hypertension associated with macular thinning	41, 42
Smoking	• Associated with SCR (in general and PSCR specifically)	-	9
Social class (parental education)	• Higher social class is protective against ocular abnormalities	-	43

SCR = sickle cell retinopathy, SCM = sickle cell maculopathy, PSCR = proliferative sickle cell retinopathy

Table 2. Genetic risk factors

Risk factor	Association with SCR	Association with SCM	References
HbSC	• Associated with SCR (both NPSCR and PSCR) • Associated with bilateral involvement and sight-threatening complication • Higher ischemic index than HbSS	• Lower vessel densities in superficial and deep capillary plexus	10, 11, 14-18, 20, 25, 26, 29, 30, 32, 38, 41, 42, 44-53, 58
HbSS and HbSβ-thalassemia	• Increased odds of SCR compared to HbSβ^{+} • Increased vascular tortuosity in HbSS compared to HbSC/HbSβ-thalassemia • Associated with spontaneous regression of neovascularization • More ocular abnormalities in non-alpha-thalassemia HbSS patients	• More macular thinning in HbSS and HbSβ-thalassemia than in HbSC • Lower vessel densities in superficial and deep capillary plexus	2, 14, 21, 27, 35, 42, 48, 54-57
eNOS 786CC polymorphism	• Associated with SCR	-	59
IL-6−597G>A polymorphism	• Associated with SCR	-	60
Haplotypes of β-globin	• non-β^{Cl} associated with SCR • earlier onset of SCR in non-β^{Cl} • Concurrent inheritance of β^{S} Ben haplotype leads to more risk of SCR in non-β^{Cl}	-	61

SCR = sickle cell retinopathy, SCM = sickle cell maculopathy, NPSCR = non-proliferative sickle cell retinopathy, PSCR = proliferative sickle cell retinopathy

Table 3. Systemic therapy

Risk factor	Association with SCR	Association with SCM	References
Transfusion therapy	• Decreased likelihood of PSCR	• Decreased foveal width and depth • Decreased retinal thickness of temporal macula	9, 63
Hydroxyurea	• Protective against SCR	• Protective against macular thinning and vessel abnormalities in deep capillary plexus	22, 54
Chronic chelation therapy	-	• Protective against SCM	64

SCR = sickle cell retinopathy, SCM = sickle cell maculopathy, PSCR = proliferative sickle cell retinopathy

Table 4. Sickle cell related organ damage and complications

Risk factor	Association with SCR	Association with SCM	References
Cerebral complications	• History of hemorrhagic/ischemic stroke (including silent infarcts) associated with SCR • Higher flow velocity middle cerebral arteries associated with SCR • Cerebral vasculopathy, seizures and impaired cerebral oxygen delivery associated with SCR	-	22, 34, 42, 55, 63, 65
Pulmonary complications	• Pulmonary hypertension associated with advanced stages of PSCR in HbSC • Acute chest syndrome correlated with PSCR in HbSS • Chronic pulmonary damage protective against PSCR in one study	• History of >1 episode of acute chest syndrome associated with increased foveal depth + higher retinal thickness (HbSS/HbSβ-thalassemia)	19, 63, 55, 65
Renal complications	• Acute pyelonephritis associated with PSCR • Hematuria associated with SCR • Higher glomerular filtration rate associated with NPSCR • History of renal failure associated with lower risk of PSCR (HbSS)	-	9, 12, 19, 65
vaso-occlusive events	• Associated with SCR	• More macular thinning and flow voids in deep capillary plexus	22, 37, 54
Biliary complications	• Associated with SCR	-	19, 26, 65
Splenic complications	• Hypersplenism protective against PSCR • Splenic sequestration and splenectomy associated with SCR	-	65, 37, 24
Avascular necrosis	• Associated with SCR	-	22, 9
Leg ulcers	• Protective against SCR	-	28
Hearing problems	• Associated with severe PSCR in HbSC patients	-	19
Thrombosis	-	• Associated with macular thinning	42

SCR = sickle cell retinopathy, SCM = sickle cell maculopathy, NPSCR = non-proliferative sickle cell retinopathy, PSCR = proliferative sickle cell retinopathy

Table 5. Laboratory risk factors

Risk factor	Association with SCR	Association with SCM	References
Hb-level	• Positive correlation with SCR • Best threshold: Hb >8 g/dL (HbSS), Hb >10 g/dL (HbSC) • Two studies found association between lower Hb levels and NPSCR	• Lower Hb levels linked to macular ischemia and thinning	9, 12, 15, 18, 21, 22, 28, 47, 66, 67
Hematocrit	• Lower hematocrit associated with NPSCR in three studies • Higher hematocrit associated with SCR in one study	• Lower hematocrit associated with macular ischemia and thinning	12, 15, 34, 56, 57
MCV	• Higher MCV correlated with SCR in multiple studies • One study found correlation between lower MCV and retinal patches (NPSCR) in HbSS/HbSβ-thalassemia	-	12, 18, 21, 23, 68
MCHC	• Positive correlation with PSCR	-	23, 66
MCH	• Positive correlation with PSCR	-	69
RDW	• Positive correlation with SCR	-	15
HbF%	• Protective against SCR • HbF < 15% independent predictor for SCR • HbF > 15% reduces risk of SCR by half	-	9, 10, 12, 15, 18, 19, 21, 23, 26, 40, 52, 54, 66-71
HbS% and ISC	• Positive correlation with SCR • Higher ISC correlated with extent of retinal vaso-occlusion	-	2, 22, 40, 72
Leukocyte count	• Negative correlation with SCR in HbSS/HbSβ^0	-	15
Platelet count and INR	• Positive correlation with SCR (higher in PSCR than in NPSCR)	• Lower INR associated with SCM	57, 73
Reticulocyte count	• Higher counts associated with SCR (but negatively correlated in multivariate analysis of one study)	• Higher counts associated with SCM	9, 12, 40, 54, 55
LDH	-	• Elevated LDH associated with SCM (increase of FAZ)	57
Bilirubin	• Increased bilirubin associated with NPSCR	• Increased bilirubin associated with SCM	12
Serum ferritin levels	• Negative correlation with advanced PSCR in HbSC patients	-	19

SCR = sickle cell retinopathy, SCM = sickle cell maculopathy, NPSCR = non-proliferative sickle cell retinopathy, PSCR = proliferative sickle cell retinopathy, MCV = mean corpuscular volume, MCHC = mean corpuscular hemoglobin concentration, MCH = Mean Cell Hemoglobin, RDW = Red Cell Distribution Width, ISC = irreversibly sickled cells count

Table 6. Biomarkers of rheology, endothelial activation, angiogenesis or NO metabolism

Risk factor	Association with SCR	Association with SCM	References
Whole blood viscosity	• higher in PSCR	-	66, 73
RBC deformability	-	• decreased RBC deformability associated with SCM	34
PEDF	• higher plasma levels associated with SCR (HbSC)	-	74
sICAM-1	• Lower levels associated with SCR (HbSC)	-	74
E-selectin	• Higher plasma levels associated with SCR	-	75
Ang-2	• Higher plasma levels associated with SCR (HbSS/HbSβ^+)	-	2, 76
ADMA	• Higher plasma levels associated with SCR	-	77

SCR = sickle cell retinopathy, SCM = sickle cell maculopathy, PSCR = proliferative sickle cell retinopathy, RBC = red blood cell, PEDF = pigment epithelium-derived factor, sICAM-1 = plasma soluble intercellular adhesion molecule-1, Ang-2 = angiopoietin-2, ADMA = asymmetric dimethyl arginine

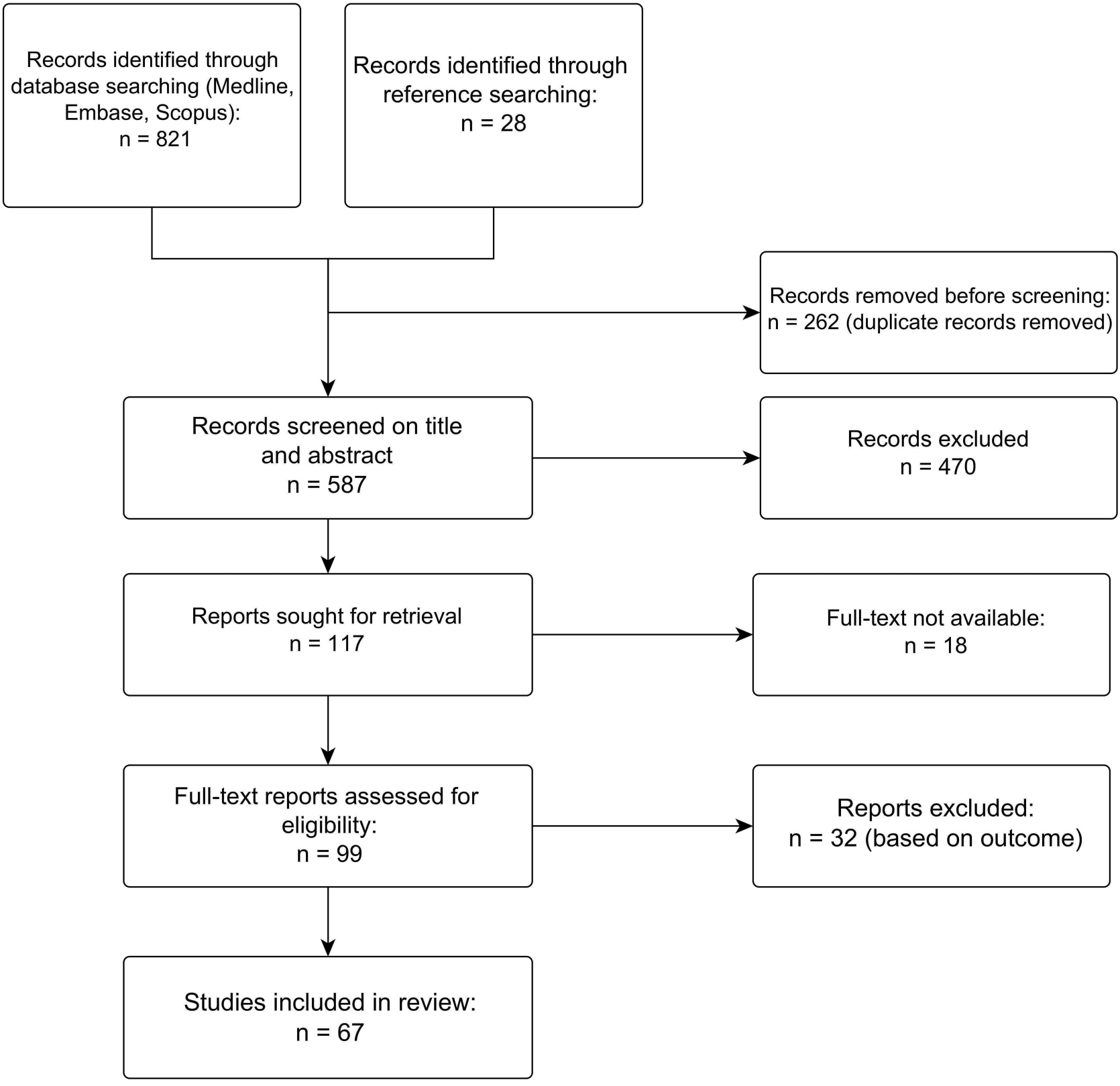
Table 7. Recommendations for screening interval for SCR

HbSC genotype	
Retinopathy status	**Recommended screening interval**
No SCR present	• High-risk: yearly screening • Otherwise: screening every two years
NPSCR present	• High-risk: yearly screening • Otherwise: screening every two years
PSCR present (without complications)	• Screening interval between 3 months and 1 year, depending on severity of PSCR
HbSS genotype	
Retinopathy status	**Recommended screening interval**
No SCR present	• Low-risk: screening every three years • Otherwise: screening every two years
NPSCR present	• Screening every two years
PSCR present (without complications)	• Screening interval between 3 months and 1 year, depending on severity of PSCR

SCR = sickle cell retinopathy, NPSCR = non-proliferative sickle cell retinopathy, PSCR = proliferative sickle cell retinopathy

Figure legends

Figure 1. Flow diagram for literature search


Records identified through database searching (Medline, Embase, Scopus): n = 821
Records identified through reference searching: n = 28
Records removed before screening: n = 262 (duplicate records removed)
Records screened on title and abstract n = 587
Records excluded n = 470
Reports sought for retrieval n = 117
Full-text not available: n = 18
Full-text reports assessed for eligibility: n = 99
Reports excluded: n = 32 (based on outcome)
Studies included in review: n = 67

Appendix A – Search strategies

Database(s): Ovid MEDLINE(R) ALL 1946 to May 22, 2023	
#	Searches
1	exp Anemia, Sickle Cell/ or exp Sickle Cell Trait/
2	(sickle adj3 cell adj3 (an?emia* or disease* or trait* or patholog* or disorder* or syndrom*)).ti,ab,kf.
3	((Hb or Hemoglobin) adj3 ("S disease*" or "SS disease")).ti,ab,kf.
4	or/1-3
5	exp Retinal Degeneration/ or exp Retinal Diseases/
6	((retinopath* or retin* or macul* or ocular or eye) adj4 (dystroph* or degenerat* or disease* or path* or abnormal*)).ti,ab,kf.
7	(retinopath* or maculopath*).ti,ab,kf.
8	or/5-7
9	4 and 8
10	exp Risk Factors/ or exp Incidence/ or exp Mass Screening/ or exp "Severity of Illness Index"/
11	(("fetal h?emoglobin" or h?emoglobin or incidence or (ophthalmic or systemic or biomarker* or laboratory or chemical* or risk or health* or vulnerab* or susceptib* or disease* or disoder* or clinical* or environmental* or genet* or genom* or epidemiolog* or prognostic or predict*)) adj3 (factor* or correlate* or indicator* or profile*)).ti,ab,kf.
12	((disease or retinopath* or retin* or macul* or ocular or eye or ophthalmological or strategy) adj3 (assess* or screen* or examination)).ti,ab,kf.
13	or/10-12
14	9 and 13

Database(s): Embase Classic+Embase 1947 to 2023 May 22	
#	Searches
1	exp sickle cell anemia/ or exp sickle cell trait/
2	("sickle cell" adj3 (an?emia* or disease* or trait* or patholog* or disorder* or syndrom*)).ti,ab,kw.

3	((Hb or Hemoglobin) adj3 ("S disease*" or "SS disease")).ti,ab,kw.
4	or/1-3
5	exp retina degeneration/ or exp retina disease/
6	((retinopath* or retin* or macul* or ocular or eye) adj4 (dystroph* or degenerat* or disease* or path* or abnormal*)).ti,ab,kw.
7	(retinopath* or maculopath*).ti,ab,kw.
8	or/5-7
9	4 and 8
10	exp risk factor/ or exp incidence/ or exp screening/ or exp "severity of illness index"/
11	(("fetal h?emoglobin" or h?emoglobin or incidence or (ophthalmic or systemic or biomarker* or laboratory or chemical* or risk or health* or vulnerability or susceptib* or disease* or disoder* or clinical* or environmental* or genet* or genom* or epidemiolog* or prognostic or predict*)) adj3 (factor* or correlate* or indicator* or profile*)).ti,ab,kw.
12	((disease or retinopath* or retin* or macul* or ocular or eye or ophthalmological or strategy) adj3 (assess* or screen* or examination)).ti,ab,kf.
13	or/10-12
14	9 and 13

Scopus

TITLE-ABS-KEY-AUTH (("sickle cell") W/3 (an?emia* OR disease* OR trait* OR patholog* OR disorder* OR syndrom*) OR ((hb OR hemoglobin) W/3 ("S disease*" OR "SS disease"))) AND TITLE-ABS-KEY-AUTH (retinopath* OR maculopath* OR ((retin* OR macul* OR ocular OR eye) W/4 (dystroph* OR degenerat* OR disease* OR patholog* OR abnormal*))) AND TITLE-ABS-KEY-AUTH ((("fetal h?emoglobin" OR h?emoglobin OR incidence OR (ophthalmic OR systemic OR biomarker* OR laboratory OR chemical* OR risk OR health* OR vulnerability OR susceptib* OR disease* OR disoder* OR clinical* OR environmental* OR genet* OR genom* OR epidemiolog* OR prognostic OR predict*)) W/3 (factor* OR correlate* OR indicator* OR profile*)) OR ((disease OR retinopath* OR retin* OR macul* OR ocular OR eye OR ophthalmological OR strategy) W/3 (assess* OR screen* OR examination)))