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Natural history and rate of progression of retinopathy in adult patients with sickle cell disease: an 11-year follow-up study

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Key Points

- Adult patients with SCD showed significant progression of SCR during follow-up.
- Differentiated strategies for screening and follow-up of retinopathy could be considered for patients at low or high risk.

Sickle cell retinopathy (SCR) is a complication of sickle cell disease (SCD). Proliferative SCR (PSCR) can lead to severe visual impairment due to vitreous hemorrhage or retinal detachment. Knowledge of risk factors for progression and complications of SCR is limited. The aim of this study is to describe the natural history of SCR and to identify risk factors for progressive SCR and development of PSCR. We retrospectively analyzed disease progression in 129 patients with SCD with a median follow-up period of 11 years (interquartile range, 8.5-12). Patients were divided in 2 groups. The genotypes hemoglobin SS (HbSS), HbSβ^0-thalassemia, and HbSβ^+-thalassemia were grouped together (n = 83; 64.3%), whereas patients with HbSC (n = 46; 35.7%) were grouped separately. Progression of SCR was observed in 28.7% (37 of 129) of patients. Older age (adjusted odds ratio [aOR], 1.073; 95% confidence interval [CI], 1.024-1.125; P = .003), HbSC genotype (aOR, 25.472; 95% CI, 3.788-171.285; $P \leq 0.001$), and lower HbF (aOR, 0.786; 95% CI, 0.623-0.993; P = .043) were associated with PSCR at end of follow-up. Lack of any SCR at end of follow-up was associated with female sex (aOR, 2.555; 95% CI, 1.101-5.931; P = .029), HbSS/HbSβ^0/HbSβ^+ genotype (aOR, 3.733; 95% CI, 1.131-12.321; P = .031), and higher HbF levels (aOR, 1.119; 95% CI, 1.007-1.243; P = .037). Differentiated strategies for screening and follow-up of SCR could be considered for patients at low or high risk.

Introduction

Sickle cell disease (SCD) is one of the most common hereditary diseases, characterized by chronic hemolysis and recurrent vaso-occlusion, resulting in tissue ischemia and organ damage. The retina is very sensitive to ischemic damage, which can result in sickle cell retinopathy (SCR). SCR can be divided into nonproliferative SCR (NPSCR) and proliferative SCR (PSCR). PSCR can be further complicated by vitreous hemorrhage and retinal detachment, resulting in severe visual impairment.

Previous studies have shown that retinopathy (and visual loss because of complications) is considerably more prevalent among patients with compound heterozygosity (in particular hemoglobin SC [HbSC]), and with increasing age.[1] However, most studies describing the incidence and risk factors of SCR were conducted in children or young adults. As a result of improvements in diagnosis, supportive care, and disease-modifying treatment options, the life expectancy of patients with SCD has risen to the sixth decade of life.[2] With respect to screening for retinopathy, the overall recommendation is to start from

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the age of 10 years and to repeat the screening every 1 or 2 years hereafter. However, this recommendation relies on expert consensus based on low quality evidence.[3] Knowledge of the natural history and risk factors for progression of SCR and subsequent complications is limited.[4-7] Therefore, it would be helpful to determine the cumulative incidence of SCR in a large population of adult patients with SCD and to identify risk factors predicting disease progression and vision-threatening complications.

In this study, we aim to describe the natural history of SCR in a systematically analyzed large cohort of patients with SCD. Secondly, we aim to determine potential associations between clinical and laboratory SCD characteristics and progression of SCR to identify risk factors for developing PSCR.

Methods

Patients with SCD (HbSS, HbSβ , HbSβ$^+$, and HbSC) consecutively visiting the Departments of Hematology and Ophthalmology of the Amsterdam University Medical Centers (Amsterdam, The Netherlands) between 2006 and 2011 were eligible for inclusion in the study. Patients lost to follow-up were excluded. Patients were referred to the Department of Ophthalmology if there was no prior or recent ophthalmic exam at our center and were typically examined every 2 years hereafter. This retrospective study was approved by the internal review board of the Amsterdam University Medical Centers and was carried out in accordance with the principles of the Declaration of Helsinki (seventh revision, 2013).

Data on demographics, ophthalmic and hematologic characteristics were collected from electronic medical records. Complete ophthalmic examination, including assessment of Snellen distance best-corrected visual acuity (VA), slit lamp examination of the anterior segment, and dilated fundus biomicroscopy, was performed for all eyes. Visual impairment was defined as a VA below 20/25. SCR stage was determined for each eye based on a modified version of Goldberg classification as (1) no SCR, (2) NPSCR (sunburst lesions, salmon patches, arteriolar occlusions, and peripheral anastomosis without neovascularization, ie, Goldberg stage I and II), or (3) PSCR (with neovascularization, ie, Goldberg stage ≥III).[8] Fluorescein angiography (FA) was not systematically performed for all patients but was used in case of doubtful diagnosis or for patients with stage III disease or worse. Optical coherence tomography (OCT) was not routinely performed for patients with SCD at our clinic until 2018. Therefore, there was no OCT data available from the baseline visits (and from many follow-up visits until 2018). Eyes with previously resolved vitreous hemorrhage and eyes treated for retinal detachment were also classified as stage IV or V, respectively. Progression of SCR was defined as an increase of the SCR stage or, in case of PSCR at baseline, the occurrence of complications. During hematology consultations, patients underwent routine laboratory screening. This consisted of complete blood count, renal and hepatic function, Hb electrophoresis, and urinalysis (including microalbuminuria). Microalbuminuria was defined as a ratio of urinary microalbumin (mg/L) to urinary creatinine (mmol/L) of >3.5.

Statistical analysis was performed using IBM SPSS Statistics (version 26.0; IBM Corp, Armonk, NY). Before the analysis, completeness of the data was checked. Patients with significant amounts of missing data were excluded from statistical analysis. For the remaining patients, the small amount of remaining missing data points was imputed using single imputation. Data from patients with HbSC disease were analyzed as a separate group because of the differences in pathophysiology and prevalence of organ damage compared with HbSS, HbSβ^0, and HbSβ$^+$ genotypes.[9] Analysis of progression to PSCR was performed among a subset of patients for whom progression to PSCR was possible (ie, patients without PSCR at their first examination). Medians and interquartile ranges (IQRs) were calculated for age and duration of follow-up. Categorical and binary variables are displayed as frequencies and percentages. Differences in counts between the groups were examined with the χ^2 test (or Mann-Whitney *U* test in case of nonnormal distribution). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression analyses. Results were considered statistically significant when $P < .05$. Because of the small numbers of patients per group and the exploratory character of this study, the given *P* values are uncorrected.

Results

A total of 163 patients with SCD were evaluated. Nine of these patients deceased before they had a follow-up consult; in 1 patient, the reason of death is unknown; and in 8 patients, death was due to fatal SCD-related complications: 2 patients died of liver failure, 3 died of acute chest syndrome, 2 died of morphine intoxication during treatment of a vaso-occlusive crisis, and 1 died of ischemic stroke (which was most likely related to the relatively high age of the patient, given the HbSS genotype [75 years old], although cerebral vasculopathy could not be excluded). Another 25 patients were lost to follow-up. In total, 129 patients were included in our study.

Patient characteristics at baseline are outlined in Table 1. The median follow-up was 11 years (IQR, 8.5-12 years). The median age at the end of follow-up was 34 years (range, 12-67 years; IQR, 28-45 years). The study cohort consisted of 59 male patients (45.7%) and 70 female patients (54.3%). HbSS genotype was

Table 1. Baseline characteristics

Characteristic	Patients (N = 129)
Median age at baseline (range, IQR), y	23 (9-55, 18-33)
Median age at follow-up (range, IQR), y	34 (12-67; 28-45)
Sex, n (%)	
Male	59 (45.7)
Female	70 (54.3)
Hb genotype, n (%)	
HbSS	62 (48.1)
HbSβ^0	8 (6.2)
HbSβ$^+$	13 (10.1)
HbSC	46 (35.7)
Median follow-up (IQR), y	11 (8.5-12)
Hydroxyurea use, n (%)	28 (21.7)
Chronic transfusion therapy, n (%)	9 (7.0)
Mean HbF (± standard deviation), %	
Patients with HbSS/HbSβ^0/HbSβ$^+$	7.5 (± 6.1)
Patients with HbSC	1.8 (± 1.3)

Table 2. Retinopathy at baseline and follow-up

	Retinopathy at baseline, n (%)	Retinopathy at follow-up, n (%)
No SCR	93 (72.1)	65 (50.4)
NPSCR	19 (14.7)	33 (25.6)
PSCR	17 (13.2)	31 (24)
1 eye	6 (4.7)	10 (7.8)
Both eyes	11 (8.5)	21 (16.3)
Progression of retinopathy	37 (28.7)	

present in 62 patients (48.1%), HbSβ^0 genotype in 8 patients (6.2%), and HbSβ^+ genotype in 13 patients (10.1%). For further analyses, these genotypes were considered as 1 group of 83 patients (64.3%). HbSC genotype was present in 46 patients (35.7%) and was considered as a separate group for further analyses. No significant differences in age, sex, and years of follow-up were present between these Hb genotype groups.

The presence of retinopathy at baseline and at follow-up is outlined in Table 2. Retinopathy was present in 36 patients (27.9%) at baseline, of whom 17 patients (13.2%) had PSCR. Progression of retinopathy during follow-up was observed in 37 patients (28.7%). At the end of follow-up, the percentage of patients with PSCR had almost doubled (24%).

Prevalence of SCR and rate of progression was also evaluated based on Hb genotype groups, as shown in Table 3. Both at baseline and at follow-up, significant differences in presence and severity of SCR between patients with HbSS/HbSβ^0/HbSβ^+ and HbSC were observed. The rate of progression appeared higher in the HbSC group, but this did not reach statistical significance.

VA and complications

Visual impairment was observed in 10 patients (13 eyes) at first consultation. In 3 patients (3 eyes), the impaired VA was directly related to PSCR (with retinal detachment in 2 of these eyes). In 7 patients (10 eyes), pathology other than SCR explained the visual impairment (high myopia, cataract, solar retinopathy, and vasculitis with exudates). Only visual impairment caused by retinal detachment was irreversible, all other causes reversed to a normal VA during follow-up. Six patients (7 eyes) without visual impairment at baseline developed visual impairment during follow-up, but none of these cases appeared to be directly related to SCR.

A history of ocular complications was present in 7 patients (7 eyes) at baseline. Five patients (5 eyes) had a vitreous hemorrhage, and 2 patients (2 eyes) had a history of retinal detachment. In 2 of the 7 patients, there were complications in the other eye during follow-up. At end of follow-up, 6 patients (7 eyes) without complications at baseline had developed a new eye complication. Four patients (4 eyes) had vitreous hemorrhage, and 2 (3 eyes) developed retinal detachment.

Table 3. Retinopathy by Hb genotype

	Patients with HbSS/HbSβ^0/HbSβ^+ (n = 83), n (%)	Patients with HbSC (n = 46), n (%)	*P* value
Baseline			.000*
No SCR	67 (80.7)	26 (56.5)	
NPSCR	12 (14.5)	7 (15.2)	
PSCR	4 (4.8)	13 (28.3)	
1 eye	3 (3.6)	3 (6.5)	
Both eyes	1 (1.2)	10 (21.7)	
Follow-up			.000*
No SCR	51 (61.4)	14 (30.4)	
NPSCR	23 (27.7)	10 (21.7)	
PSCR	9 (10.8)	22 (47.8)	
1 eye	3 (3.6)	7 (15.2)	
Both eyes	6 (7.2)	15 (32.6)	
Progression	20 (24.1)	17 (37.0)	.122†

*Linear-by-linear association.
†Pearson χ^2.

Factors associated with PSCR

The HbSC genotype (OR, 8.111; 95% CI, 3.264-20.157; $P \leq .001$), age (OR, 1.046; 95% CI, 1.009-1.084; $P = .014$), Hb level (OR, 2.052; 95% CI, 1.334-3.156; $P = .001$), and fetal Hb level (HbF; OR, 0.731; 95% CI, 0.604-0.886; $P = .001$) were significantly associated with PSCR at end of follow-up. After adjustment for Hb genotype, Hb level no longer reached statistical significance (adjusted OR [aOR], 1.259; 95% CI, 0.728-2.175; $P = .410$). Age remained a small but significant risk factor for PSCR at end of follow-up after adjustment for Hb genotype and sex (aOR, 1.073; 95% CI, 1.024-1.125; $P = .003$). Low HbF also remained significantly associated with PSCR at end of follow-up after correction for hydroxyurea use, Hb genotype, and sex (aOR, 0.786; 95% CI, 0.623-0.993; $P = .043$). HbSC genotype remained the strongest, statistically significant risk factor after adjustment for sex, age, HbF, lactate dehydrogenase, bilirubin, and reticulocytes (aOR, 25.472; 95% CI, 3.788-171.285; $P \leq .001$).

Factors associated with progression of retinopathy

Multivariate logistic regression analysis showed that the only predictor for progression of retinopathy, defined as an increase of the SCR stage or the occurrence of complications, is HbF; progression was significantly associated with a lower HbF level (aOR, 0.882; 95% CI, 0.792-0.983; $P = .023$).

The analysis of factors associated with progression to PSCR (defined as development of PSCR during follow-up in patients with no SCR or NPSCR at baseline) is shown in Table 4. HbSC genotype was significantly associated with progression to PSCR (OR, 5.973; 95% CI, 1.812-19.684; $P = .003$). This association remained significant after adjustment for sex and age (aOR, 6.541; 95% CI, 1.865-22.942; $P = .003$). There was also a significant association between a lower HbF level and progression to PSCR (OR, 0.812; 95% CI, 0.663-0.993; $P = .043$), but this did not remain significant after correction for hydroxyurea use, Hb genotype, and sex (aOR, 0.834; 95% CI, 0.635-1.094; $P = .189$). Furthermore, a remarkable difference in progression to PSCR was noted between male and female patients per Hb genotype group, as shown in Table 5. Almost half (46.7%) of the male patients with HbSC genotype progressed to PSCR during follow-up as compared with only 11.1% of the female patients with HbSC.

Table 4. Factors associated with progression to PSCR and no SCR at end of follow-up

	Progression to PSCR (analysis on n = 109)		No SCR at end of follow-up (analysis on n = 126)	
	Unadjusted OR (95% CI)	*P* value	Unadjusted OR (95% CI)	*P* value*
Gender				
Male	Reference		**Reference**	
Female	0.404 (0.126-1.297)	.128	**2.485 (1.210-5.101)**	**.013**
Hb genotype				
HbSS/HbSβ^0/HbSβ$^+$	**Reference**		**3.726 (1.699-8.169)**	
HbSC	**5.973 (1.812-19.684)**	**.003**	**Reference**	**.001**
Age				
y	0.988 (95% CI, 0.934-1.045)	.671	0.977 (95% CI, 0.946-1.009)	.161
HbF				
%	**0.812 (0.663-0.993)**	**.043**	**1.201 (1.093-1.319)**	**.001**
Hb level				
mmol/L	1.565 (0.883-2.774)	.125	**0.673 (0.479-0.946)**	**.022**
Lactate dehydrogenase				
U/L	0.997 (0.993-1.000)	.086	1.001 (0.999-1.003)	.232
Bilirubin				
μmol/L	1.001 (0.987-1.016)	.856	1.003 (0.993-1.013)	.601
Reticulocytes				
%	0.996 (0.882-1.124)	.944	1.019 (0.943-1.100)	.640

*Significant *P*-values ($P < 0.05$) are shown in bold.

Factors associated with absence of SCR

Factors associated with absence of SCR at end of follow-up are outlined in Table 4. Female sex (OR, 2.485; 95% CI, 1.210-5.101; $P = .013$), HbSS/HbSβ^0/HbSβ$^+$ genotype (OR, 3.726; 95% CI, 1.699-8.169; $P = .001$), a lower Hb level (OR, 0.673; 95% CI, 0.479-0.946; $P = .022$), and a higher HbF level (OR, 1.201; 95% CI, 1.093-1.319; $P = .001$) were significantly associated with the absence of SCR at the end of follow-up. After correction for Hb genotype, Hb level was not significantly associated (aOR, 0.914; 95% CI, 0.603-1.386; $P = .672$). Female sex remained significantly associated after correction for age, Hb genotype, and HbF (aOR, 2.555; 95% CI, 1.101-5.931; $P = .029$), and HbSS/HbSβ^0/HbSβ$^+$ genotype remained significantly associated after correction for sex, age, HbF, lactate dehydrogenase, bilirubin, and reticulocytes (aOR, 3.733; 95% CI, 1.131-12.321; $P = .031$). Similarly, HbF level remained significantly associated after correction for hydroxyurea use, Hb genotype, and sex (aOR, 1.119; 95% CI, 1.007-1.243; $P = .037$).

Table 5. Percentages of progression to PSCR by genotype and sex

	Progression to PSCR, N/total (%)	*P* value*
HbSS/HbSβ^0/HbSβ$^+$	5 of 79 (6.3)	.841
Male	2 of 35 (5.7)	
Female	3 of 44 (6.8)	
HbSC	9 of 33 (27.3)	.022
Male	7 of 15 (46.7)	
Female	2 of 18 (11.1)	

*Pearson χ^2.

When divided based on Hb genotype, a striking difference was observed between male and female patients, especially within the HbSS/HbSβ^0/HbSβ$^+$ genotype (Table 6). Among the female patients with HbSS/HbSβ^0/HbSβ$^+$ genotype, 3 of 4 (72.7%) did not develop any signs of SCR during 11 years of follow-up, compared with approximately 1 out of 2 (48.7%) male patients within the same genotype group. This was also, but to a lesser extent, observed in the HbSC genotype group (although this was not statistically significant); 38.5% of female patients did not develop any signs of SCR, compared with 20% of male patients.

Associations with microalbuminuria

Data on microalbuminuria at baseline and follow-up were available for 94 patients. At baseline, 12.8% (n = 12) of the patients had microalbuminuria. This increased to 22.3% (n = 21) during follow-up. Microalbuminuria was not significantly associated with the progression of SCR (OR, 0.718; 95% CI, 0.179-2.874; $P = .640$) or PSCR at end of follow-up (OR, 0.279; 95% CI, 0.059-1.308; $P = .105$) nor with the absence of SCR at follow-up (OR, 1.529; 95% CI, 0.575-4.071; $P = .395$).

Discussion

SCR is a form of SCD-related organ damage, which can drastically impair the VA if complications occur. However, the current knowledge of the natural history and rate of progression of SCR is limited. Our study not only describes the natural history, progression, and risk factors of progression in a

Table 6. Percentages of absence of SCR at follow-up

	No SCR at end of follow-up, n/total (%)	*P* value*
HbSS/HbSβ^0/HbSβ$^+$	51 of 83 (61.4)	.025
Male	19 of 39 (48.7)	
Female	32 of 44 (72.7)	
HbSC	14 of 46 (30.4)	.177
Male	4 of 20 (20)	
Female	10 of 26 (38.5)	

*Pearson χ^2.

systematically evaluated cohort of adult patients with SCD but also identifies a specific patient group with a low risk of progression, which may have clinical implications for the care of patients with SCD.

Progression of SCR, after a median follow-up of 11 years, was present in 28.7% of the patients. Previous studies on progression of retinopathy are very limited and mostly solely focused on PSCR. In 1975, Condon and Serjeant described progression of SCR in 63.8% of patients with HbSS (during a follow-up period of only 2 years and 8 months) and 74.5% in patients with HbSC (with a follow-up period of 2 years and 5 months).[10] An important difference with our study is that progression was scored as any vascular change on fundoscopy or FA, regardless of SCR classification, which may explain the difference with the rate of progression in our cohort. Another difference with our study is the age distribution. In the aforementioned study, progression was more prevalent in patients aged <30 years (71.1% compared with 49.1% in patients aged >30 years). Our study did not reproduce this observation: 29.2% of our patients aged <30 years showed progression compared with 28.4% of patients aged >30 years. In a small study reported by Clarkson, progression to PSCR was demonstrated in 7 of 59 (11.9%) patients with HbSS and 6 of 23 (26.1%) patients with HbSC. These rates seem similar to the rate of progression in this study (6.3% and 27.3% in the HbSS/HbSβ^0/HbSβ$^+$ and HbSC groups, respectively), although the mean follow-up was significantly shorter (6.7 years in the study by Clarkson vs 11 years in our study).[11] This might be explained by a difference in age between our cohorts and the fact that the percentage of male patients was higher in the HbSC group, which may have increased the risk of progression. In a large study in also relatively older patients with SCD, rates of progression to PSCR were similar to that per our observation; 41 of 737 (5.6%) patients without PSCR at baseline in the HbSS group showed progression to PSCR, and 71 of 361 (19.7%) in the HbSC group.[12] The age distribution and male-to-female ratio were also quite similar to those in our study. However, information on follow-up duration was limited and could therefore not be compared. A previous prospective cohort study of our group demonstrated an increase in the prevalence of retinopathy in general (both NPSCR and PSCR), from 14% in the HbSS/HbSβ^0 group and 15% in the HbSC/HbSβ$^+$ group over a follow-up period of 7 years.[13] Similarly to our study, no significant difference was found between either genotype group. However, the total increase in prevalence of retinopathy by their definition is moderately higher in our study (19.3% in the HbSS/HbSβ^0/HbSβ$^+$ group, and 26.1% in the HbSC group), which could possibly be related to our longer follow-up duration. However, the patients in that cohort were significantly older at baseline than patients in our study, with a median age of 33 years in their HbSS/HbSβ^0 group and 35 years in their HbSC/HbSβ$^+$ group, compared with a median age of 23 years in both our HbSS/HbSβ^0/HbSβ$^+$ and HbSC group. This might explain the fact that the difference in prevalence rates is not that extreme, because age is reported as a risk factor for retinopathy in previous literature.[4,6,7]

In our study, HbSC genotype and age were risk factors for PSCR, which is in line with previous studies on risk factors for PSCR.[4,6,7] The exact explanation for the relation between HbSC genotype and PSCR has not yet been elucidated, but a difference in blood viscosity has been hypothesized.[14] A hypothesis is that the higher viscosity in combination with the typical vascularization of the retina might be an explanation for the high prevalence and progression of retinopathy in this specific group of patients. The retinal arterioles consist of rather long sections with equal vessel diameters throughout its course, which may result in a relatively high vascular resistance. Combined with higher blood viscosity, this may impair blood flow and, therefore, oxygenation of the retina, resulting in a higher risk of progressive retinopathy. This might also explain the higher prevalence of maculopathy in the temporal segments of the retina in patients with SCD because those vessels are relatively long compared with those in other macular segments.[15-18] Although the Hb level was not found to be an independent risk factor for progression to PSCR after correcting for genotype, this might be because of the relative small number of patients that showed progression to PSCR.

Lower HbF was a predictor for progression of retinopathy (defined as an increase of the SCR stage or the occurrence of complications) and was independently associated with PSCR at end of follow-up. This is in line with previous studies.[12,19-21] Higher HbF levels restrict HbS polymerization and are a well-known protective factor for vaso-occlusion.[22] In patients with lower HbF levels, this protective effect is absent. The fact that a lower HbF is a risk factor for PSCR independent of genotype is interesting. Most of our patients with PSCR have the HbSC genotype and the mean HbF in these patients was 1.8%. Apparently, besides the higher viscosity in SCD, vaso-occlusion seems to also play a role in the pathophysiology of PSCR. Furthermore, the incidence of PSCR during follow-up was not significantly associated with lower HbF, whereas the prevalence of PSCR (at end of follow-up) was significantly associated. This might be because the relatively small number of patients that showed progression to PSCR during the follow-up period.

Female patients had a significant lower risk of developing SCR in our study, especially when they had the HbSS/HbSβ^0/HbSβ$^+$ genotype. Several studies have found significant associations between the male sex and (proliferative) retinopathy. However, the underlying reason for this association with a person's sex remains unclear. Duan et al speculated that males might be more prone to impaired retinal oxygenation because of higher Hb levels and therefore more sickling of red blood cells, but they were unable to confirm this hypothesis.[4] Similar observations were made in a study by Bilong et al that found that the association between males and PSCR remained significant after adjusting for Hb level.[23] Another hypothesis is the protective effect of estrogen on the endothelial function. Estrogen might decrease the risk of PSCR by altering

nitric oxide levels by increasing nitric oxide synthase expression. Increased nitric oxide levels lead to a lower risk of endothelial dysfunction and a lower risk of stimulation of coagulation pathways by regulation of tissue factor expression.[20,24-26]

The current recommendation for screening on SCR (based on the 2014 expert panel report) is to perform a dilated eye examination for all patients with SCD every 1 or 2 years, starting from the age of 10 years.[3] There are no distinctions made with regard to risk factors. Our study shows that genotype, HbF, and sex have an influence on the risk of developing SCR, which is in line with several other studies.[4,6,7,12,19] The disparity in risk of progression may justify a more risk-adapted approach with respect to frequency of screening (ie, annual screening for patients at high risk vs a more lenient interval for those at low risk).

Our study had several limitations. The retrospective design of the study resulted in missing data, leading to exclusion of some cases and the need for data imputation. The use of single data imputation may have caused a larger error rate compared with multiple imputation. Furthermore, the number of patients per subgroup was relatively small, which may influence analysis of data. Because of these small numbers and the exploratory character of this study, we chose to keep *P* values uncorrected. Although this can provide useful insight into results in small groups, this might increase the error rate with multiple analyses. Long-term prospective cohort studies in large SCD populations are therefore necessary for further in-depth understanding of SCR. Preferably, these studies should include detailed information at pediatric age as well because factors may also have an impact on the risk of developing SCR in adulthood. For our study, detailed information on age of onset of retinopathy and medical history at pediatric age was unfortunately not available. Another limitation is that FA was not routinely performed, which might have led to an underestimation of the prevalence of Goldberg stage I and II (which were classified as NPSCR in our study).[27] Furthermore, OCT scans were not routinely performed (especially in the earlier years of screening) and we therefore did not collect data on maculopathy.

In conclusion, we demonstrate that well-monitored adult patients with SCD showed significant progression of SCR during follow-up. Although the rate of progression was identical between patients with the HbSS/HbSβ^0/HbSβ^+ genotype and the HbSC genotype, HbSC genotype and age were independent risk factors for PSCR. Given the high rate of progression, screening of SCR remains important, but differentiated strategies for screening and follow-up of SCR could be considered for patients at low or high risk.

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Authorship

Contribution: R.P.B. and S.B. collected the data; R.P.B. performed the analysis, and the results were critically reviewed by R.M.H.D., E.N., R.O.S., and B.J.B.; R.P.B. drafted the manuscript; R.M.H.D. and B.J.B. designed the study and revised the manuscript; and all authors revised the final version of the manuscript.

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