Clinical and Ophthalmic Factors Associated With the Severity of Sickle Cell Retinopathy

XIANGYUN J. DUAN, SOPHIE LANZKRON, MARGUERITE O. LINZ, CAROLINE EWING, JIANGXIA WANG, AND ADRIENNE W. SCOTT

• PURPOSE: To identify associations between severity of sickle cell retinopathy (SCR) and other clinical, laboratory, or treatment factors relevant to sickle cell disease (SCD).

• DESIGN: Retrospective cohort study.

• METHODS: We investigated clinical, laboratory, and demographic associations with the severity of SCR in 296 patients seen at both our SCD specialty clinic and our retina clinic. Multivariate multinomial logistic regression was used to estimate the association between each clinical variable and severity of SCR.

• RESULTS: Multivariate analysis showed that in patients with sickle cell anemia (SCA) genotypes, older age (95% confidence interval [CI], 1.04-1.15; $P < .001$) and male sex (95% CI, 0.13-0.87; $P = .02$) were associated with proliferative sickle cell retinopathy (PSR). In patients with genotypic variants, visual symptoms (95% CI, 1.36-21.62; $P = .02$) were associated with PSR. Laser photocoagulation and vitrectomy surgery, the standard interventions for PSR, were associated with older age (95% CI, 1.05-1.13; $P < .001$), visual symptoms (95% CI, 1.48-7.40; $P = .004$), higher hemoglobin level (95% CI, 1.14-1.65; $P = .001$), and no chronic transfusion (95% CI, 0.16-1.09; $P = .08$) across the whole cohort.

• CONCLUSIONS: These findings may inform clinicians of the symptoms, systemic findings, and disease-modifying therapies most frequently associated with SCR in SCD patients. Visual symptoms such as blurred vision or floaters were associated with progression of SCR and may be criteria for referral for retinal examination. Chronic transfusion therapy may be protective against the need for retinal laser photocoagulation or vitrectomy. Prospective studies are necessary to further explore risk factors for SCR and to identify which individuals with SCD are at risk for incident or progression of retinopathy. (Am J Ophthalmol 2019;197:105–113. © 2018 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Sep 25, 2018.

From the Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (X.J.D.); Department of Medicine (S.L., C.E.) and Wilmer Eye Institute (M.O.L., A.W.S.), Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and Department of Biostatistics, Johns Hopkins University School of Public Health, Baltimore, Maryland, USA (J.W.).

Inquiries to Adrienne W. Scott, Associate Professor, Wilmer Eye Institute, Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21287, USA; e-mail: ascott28@jhmi.edu

SICKLE CELL DISEASE (SCD) IS A GENETIC DISORDER involving mutations in the beta-globin gene, causing impaired hemoglobin function. This leads to erythrocyte sickling, hematologic dysfunction, and vasculopathy that result in a variety of clinical complications.[1] In sickle cell retinopathy (SCR), retinal ischemia and impaired perfusion may cause vision loss by vitreous hemorrhage, retinal artery occlusion, or tractional retinal detachment.[2]

Knowledge of associations with SCR is limited. Initial studies noted SC genotype, high hemoglobin level, and low fetal hemoglobin level as risk factors,[3] and subsequent population studies have investigated further associations between SCR and other sequelae of SCD. However, such studies have been limited in scope and geographic breadth. This study investigates potential associations between the severity of retinopathy and factors related to SCD, including visual symptoms, disease-modifying treatment, complications, and hematologic variables in adult patients at a U.S. urban, tertiary care academic center.

METHODS

WE CONDUCTED A RETROSPECTIVE CHART REVIEW OF adult patients with a known diagnosis of SCD who had baseline outpatient hematology encounters at the Sickle Cell Infusion Center (SCIC) between January 1, 2003, and December 31, 2015. A list of qualifying patients was generated from the SCIC Registry and was filtered for patients who also had a past visit with a retina specialist at the Wilmer Eye Institute within 1 year after a qualifying hematology encounter. This was considered the index retina visit. This study was approved by the Johns Hopkins Medicine Institutional Review Board and was conducted in accordance with the Declaration of Helsinki.

Variables were chosen based on review of related literature.[4–8] To investigate correlations between systemic disease and development or severity of retinopathy, we collected laboratory results including genotype, hemoglobin level, and fetal hemoglobin level, as previous literature has linked these variables to retinopathy.[5] The most recent hemoglobin level prior to the index retina visit was collected. Fetal hemoglobin level was collected from labortory visits at least 3 weeks posttransfusion unless the patient was on chronic transfusion, and within 1 year of the index retina visit. Patients were considered to be on chronic transfusion if their prescribed disease-modifying

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.09.025

therapy consisted of regularly scheduled simple or exchange transfusions.

We collected data regarding systemic complications of SCD, including avascular necrosis (AVN), chronic kidney disease (CKD), acute chest syndrome, cerebrovascular accident, severe pain crisis frequency, and echo-defined pulmonary hypertension (EDPHTN).[7,8] CKD was defined as clinical diagnosis or baseline creatinine level above 1.3. AVN, acute chest syndrome, and cerebrovascular accident were considered present if those diagnoses were ever made prior to the index retina visit. Frequency of severe pain crises was defined as "rare" if once a year or less, "occasional" if twice a year, and "frequent" if 3 times a year or more, averaged over the 2 years prior to the index retina visit. "Severe" pain crises were defined as requiring acute Emergency Department or SCIC visit, or inpatient admission. EDPHTN was defined as a history of tricuspid regurgitant jet elevated to 2.5 m/s or above, as measured by echocardiography.

To measure the effect of systemic treatment on retinopathy, we evaluated the use of anticoagulants, hydroxyurea, and chronic transfusion. Anticoagulant and hydroxyurea use were determined by examining medication lists at the time of the index retina visit. Diabetes as a comorbidity was identified to determine its relevance to development of retinopathy.

Data from index retina visits were used to describe ocular complications. Vitreoretinal findings were considered present if stated in the index visit examination notes from the written medical record. Distance visual acuity (VA) was measured using the patient's habitual correction with the Early Treatment Diabetic Retinopathy Study method. The best VA measurement made at that visit was used for analysis; pinhole acuity was preferred over corrected acuity, which in turn was preferred over uncorrected acuity. Other data collected included visual symptoms, descriptions of the conjunctiva, and key features of the dilated fundus examination, including the retinal vessels, macula, and retinal periphery. Visual symptoms were defined as ocular pain or vision loss of any kind.

Patients were classified as having proliferative sickle cell retinopathy (PSR) if they had a history of any of the following sequelae diagnosed by a retinal specialist: retinal neovascularization, vitreous hemorrhage, or tractional retinal detachment. Patients were classified as having nonproliferative sickle cell retinopathy (NPSR) if history was not indicative of sequelae related to PSR and the patient had a history of at least 1 of the following findings: black sunbursts/chorioretinal lesions, iridescent spots, salmon patches, vascular arteriovenous anastomoses, vessel tortuosity, retinal nonperfusion, sclerotic retinal vessels, or vascular loops. Patients without these signs of PSR or NPSR were deemed not to have retinopathy. Past ocular history, including past treatments for PSR such as laser photocoagulation or vitrectomy surgery, were extracted from the medical record.

• **STATISTICAL ANALYSIS:** In our statistical analysis, genotypes were grouped by similarity of clinical manifestations; the sickle cell genotypes exhibit different clinical manifestations and statistical comparison of uncommon genotypes was impractical. The SCA group included SS, Sβ0 thalassemia, SS with hereditary persistence of fetal hemoglobin, and SS with α thalassemia genotypes. The variant genotypes group included SC, Sβ+ thalassemia, and S Lepore. Analyses were performed using 3 categories of retinopathy: no disease (ND), NPSR, and PSR.

In univariate analyses, 1-way analysis of variance was used for age while the Kruskal-Wallis test was used for baseline hemoglobin and fetal hemoglobin levels. Fisher exact test was used for categorical or binary variables. Multivariate multinomial logistic regression was used to estimate associations between variables and retinopathy status. *P* values less than .05 were considered statistically significant, and *P* values between .05 and .1 were considered borderline associations. Factors that were at least borderline associated with retinopathy in the univariate analysis were included in multivariate models. Because complete data were not available for all patients, listwise deletion was used to form complete datasets for multivariate analyses. Multiple imputation was used where a significant proportion of data were missing. If missingness was associated with the outcome variable, multiple imputation was not used and the variable was excluded instead. Sensitivity analysis was performed by repeating multivariate models while replacing missing values with the 25th, 50th, or 75th percentile values. Data were analyzed using STATA 15.1 (StataCorp, College Station, Texas, USA).

RESULTS

TABLE 1 SHOWS DATA DESCRIBING THE COHORT. OF 810 qualifying sickle cell patients, 296 were examined by a retina specialist within 1 year of hematology examination. Patients with variant genotypes were more likely than patients with SCA to develop PSR (50% vs 22%, $P < .001$) and were more likely to have bilateral PSR (59% vs 20%, $P < .001$). Distance vision in eyes with PSR was lower by 0.15 in logMAR VA (range: hand motion at 2 feet to 20/12; median: 20/20-1) compared to visual acuity in eyes without PSR (range: 20/250-1 to 20/10-1; median: 20/20) (95% confidence interval [CI], 0.089-0.21; $P < .001$), corresponding to approximately 1.5 lines lower visual acuity. A total of 53.1% of eyes with PSR were treated with laser photocoagulation, 30.6% with observation, and 16.3% with laser photocoagulation and vitrectomy surgery. Table 2 shows prevalence of selected retina findings, chosen as factors of interest and in part to corroborate previous reports.[9] Sea-fan neovascularization was noted in 23 eyes. Of the 14 eyes where the retina examination

TABLE 1. Number and Percentage of Sickle Cell Disease Patents at the Sickle Cell Center for Adults by Genotype and Retinopathy Status

Genotype	Total N (%)	ND N (%)	NSCR N (%)	PSCR N (%)	*P*
Cohort	296 (100)	77 (26)	131 (44)	88 (30)	
Sickle cell anemia	212 (72)	61 (29)	104 (49)	47 (22)	<.001
SS	202				
Sβ0 thalassemia	5				
SS with HPFH	5				
SS with α thalassemia	1				
Variant	82 (28)	16 (20)	25 (30)	41 (50)	
SC	67				
Sβ+ thalassemia	14				
S Lepore	1				
Unknown	2 (1)	0	2 (100)	0	

HPFH = hereditary persistence of fetal hemoglobin; ND = no disease; NSCR = nonproliferative sickle cell retinopathy; PSCR = proliferative sickle cell retinopathy.

P value indicates significance level by Pearson χ^2 test on prevalence of retinopathy status between sickle cell anemia and variant groups.

TABLE 2. Selected Vitreoretinal Findings, Per Eye

Factor	n/N	%
Tortuous vessels	118/584	20.2
White without pressure	110/578	19.0
Retinal nonperfusion	64/582	11.0
Sclerotic vessels	59/588	10.0
Neovascularization	46/582	7.9
Tractional retinal detachment	19/592	3.2
Vitreous hemorrhage	10/582	1.7
Epiretinal membrane	6/578	1.0
Salmon patch	6/582	1.0
Angioid streaks	5/578	0.9
Asteroid hyalosis	4/578	0.7
Branch retinal artery occlusion	3/578	0.5
Retinal tear	2/578	0.3
Central retinal artery occlusion	1/578	0.2
Macular hole	0/578	0.0

Data for all findings were not available for some patients so denominators vary between different findings.

report included sea fan location, 11 eyes were found to have sea fans in the temporal quadrant.

Table 3 shows clinical findings and laboratory values with univariate analysis. In the univariate analysis, age and the presence of visual symptoms were significantly associated with retinopathy in the whole cohort and in both SCA and genotypic variant groups. Laser photocoagulation, vitrectomy surgery, and tractional retinal detachment are statistically associated with retinopathy, but these are expected outcomes; they are related to PSR by definition since they are the treatments for that condition. They are included in this table to indicate incidence in our population. Fetal hemoglobin level and anticoagulation were significantly associated with retinopathy in the SCA group. Of the 42 patients on anticoagulation, 17 were on aspirin, 13 were on warfarin, and 10 were on heparin. Two patients were on 1 other anticoagulant, and 4 patients were on 2 anticoagulants.

Table 4 shows the results of a multivariate logistic regression model on factors that were borderline or significantly associated with retinopathy in the univariate analysis. In SCA patients, older age and male sex were significantly associated with PSR and lower fetal hemoglobin level demonstrated a borderline association with PSR. In the genotypic variant group, visual symptoms were significantly associated with PSR and older age was borderline associated with PSR. Only older age was borderline associated with NSR in the SCA group. Multiple imputation was used to model the association between fetal hemoglobin level and retinopathy in the SCA group; a sensitivity analysis is shown in Table 5.

Clinical findings and laboratory values related to laser photocoagulation and vitrectomy surgery are shown in Table 6 with univariate analysis. Multivariate logistic regression models shown in Table 7 identified older age, visual symptoms, and higher hemoglobin level as significantly associated with interventions for PSR in the whole cohort. Chronic transfusion was a borderline association with absence of intervention in the whole cohort. Older age was significantly associated with intervention in the SCA and genotypic variant groups as well, while visual symptoms was significantly associated with intervention in the SCA group only.

Multivariate modeling on tractional retinal detachment, an uncommon but significant sequela of SCR, shows significant associations between retinal detachment and older age (odds ratio [OR] = 1.09; $P < .001$), male sex (OR = 0.24; $P = .02$), and visual symptoms (OR = 3.79; $P = .05$) in the whole cohort. Because few patients experienced tractional retinal detachment (n = 19), this analysis was not performed by syndrome.

DISCUSSION

THIS STUDY DEMONSTRATES A NUMBER OF NOTABLE ASSOciations between retinopathy, and its treatments, and the clinical course of SCD in a U.S. tertiary referral center. SCA and hemoglobin SS disease in particular are considered the more severe systemic disease overall; but

TABLE 3. Characteristics and Univariate Analysis of Sickle Cell Anemia and Variant Patients by Retinopathy Status

	Cohort (N = 296)				SCA (N = 212)				Variant (N = 82)			
	ND (N = 77)	NSCR (N = 131)	PSCR (N = 88)		ND (N = 61)	NSCR (N = 104)	PSCR (N = 47)		ND (N = 16)	NSCR (N = 25)	PSCR (N = 41)	
	N (%)	N (%)	N (%)	*P*	N (%)	N (%)	N (%)	*P*	N (%)	N (%)	N (%)	*P*
Age, mean (SD)	29.1 (9.0)	32.5 (11.3)	40.8 (13.3)	<.001	27.6 (7.9)	31.7 (10.9)	38.6 (12.1)	<.001	34.8 (10.7)	35.9 (12.8)	43.2 (14.3)	.03
Sex (F)	49 (63.6%)	71 (54.2%)	41 (46.6%)	.09	39 (63.9%)	54 (51.9%)	20 (42.6%)	.08	10 (63%)	17 (68%)	21 (51%)	.38
Visual symptoms	18 (23.4%)	38 (30.6%)	48 (57.1%)	<.001	14 (23%)	26 (27%)	20 (44%)	.04	4 (25%)	12 (50%)	28 (72%)	.005
Floaters	11 (14.5%)	28 (21.4%)	31 (35.6%)	.01	8 (13.3%)	19 (18.3%)	13 (28.3%)	.15	3 (19%)	9 (36%)	18 (44%)	.21
Photocoagulation	0 (0%)	1 (0.8%)	58 (65.9%)	<.001	0 (0%)	1 (1.0%)	22 (46.8%)	<.001	0 (0%)	0 (0%)	36 (88%)	<.001
Vitrectomy	0 (0%)	0 (0%)	21 (23.9%)	<.001	0 (0%)	0 (0.0%)	4 (8.5%)	<.001	0 (0%)	0 (0%)	17 (41%)	<.001
TRD	0 (0%)	0 (0%)	19 (21.6%)	<.001	0 (0%)	0 (0.0%)	3 (6.4%)	.01	0 (0%)	0 (0%)	16 (39%)	<.001
Crisis frequency[a]												
Rare	36 (48.6%)	59 (47.2%)	53 (61.6%)	.24	27 (46.6%)	47 (47.0%)	31 (67.4%)	.15	9 (56%)	12 (52%)	22 (55%)	.61
Occasional	11 (14.9%)	18 (14.4%)	12 (14.0%)		7 (12.1%)	13 (13.0%)	2 (4.3%)		4 (25%)	3 (13%)	10 (25%)	
Frequent	27 (36.5%)	48 (38.4%)	21 (24.4%)		24 (41.4%)	40 (40.0%)	13 (28.3%)		3 (19%)	8 (35%)	8 (20%)	
HGB, median (IQR)	9.1 (7.7, 10.5)	9.4 (7.9, 10.8)	10.2 (8.5, 11.1)	.05	8.6 (7.4, 9.7)	8.9 (7.7, 10.0)	8.8 (7.4, 10.4)	.67	11.1 (10.4, 12.6)	11.3 (10.5, 11.8)	10.8 (10.2, 12.1)	.95
HbF, median (IQR)	10.8 (4.2, 18.1)	7.6 (1.8, 11.1)	3.9 (1.8, 9.7)	.01	13.9 (6.5, 18.1)	8.5 (3.3, 13.8)	7.0 (2.3, 10.4)	.04	4.9 (1.4, 9.1)	1.6 (1.4, 5.4)	1.4 (1.4, 2.6)	.49
Hydroxyurea	25 (32.5%)	50 (38.2%)	24 (27.3%)	.24	22 (36.1%)	47 (45.2%)	21 (44.7%)	.49	3 (19%)	2 (8%)	3 (7%)	.40
Chronic transfusion	22 (28.6%)	29 (22.1%)	14 (15.9%)	.15	21 (34.4%)	28 (26.9%)	11 (23.4%)	.41	1 (6%)	1 (4%)	3 (7%)	.86
Anticoagulation	5 (6.5%)	19 (14.5%)	18 (20.5%)	.04	4 (6.6%)	14 (13.5%)	12 (25.5%)	.02	1 (6%)	5 (20%)	6 (15%)	.48
EDPHTN	16 (28%)	22 (23%)	18 (25%)	.79	12 (26%)	20 (25%)	12 (30%)	.84	4 (33%)	2 (12%)	6 (19%)	.35
Cerebrovascular accident	10 (13.2%)	23 (18.3%)	11 (12.6%)	.45	10 (16.7%)	21 (20.8%)	7 (15.2%)	.66	0 (0%)	2 (9%)	4 (10%)	.44
Chronic kidney disease	8 (10.4%)	18 (13.8%)	19 (21.6%)	.11	6 (9.8%)	16 (15.4%)	11 (23.4%)	.16	2 (13%)	2 (8%)	8 (20%)	.45
Diabetes mellitus	2 (2.6%)	4 (3.1%)	4 (4.5%)	.77	2 (3.3%)	1 (1.0%)	0 (0.0%)	.30	0 (0%)	3 (12%)	4 (10%)	.38
Acute chest syndrome	56 (74.7%)	82 (65.1%)	52 (60.5%)	.15	47 (79.7%)	70 (69.3%)	31 (67.4%)	.28	9 (56%)	11 (48%)	21 (53%)	.87
Avascular necrosis	24 (31.6%)	37 (28.5%)	38 (43.2%)	.07	18 (29.5%)	31 (30.1%)	17 (36.2%)	.71	6 (40%)	6 (24%)	21 (51%)	.09

EDPHTN = echo-defined pulmonary hypertension; HbF = fetal hemoglobin; HGB = hemoglobin; IQR = interquartile range; ND = no disease; NSCR = nonproliferative sickle cell retinopathy; PSCR = proliferative sickle cell retinopathy; SCA = sickle cell anemia; SD = standard deviation; TRD = tractional retinal detachment.

P values determined for univariate analysis using Pearson χ^2 test for categorical and binary variables, ANOVA for normally distributed continuous variables (Age), Kruskal-Wallis test for skewed continuous variables (HGB, HbF).

[a]Crisis frequency defined as "rare" if once a year or less, "occasional" if twice a year, or "frequent" if 3 times a year or more, averaged over 2 years prior to index retina visit.

TABLE 4. Factors Associated With Sickle Cell Anemia and Variant Genotypes By Multivariate Logistic Regression

	NSCR (N = 105) vs ND (N = 61)			PSCR (N = 47) vs ND (N = 61)		
SCA	RRR	95% CI	*P*	RRR	95% CI	*P*
Age	1.04	1.00, 1.09	.07	1.09	1.04, 1.15	<.001
Sex (F vs M)	0.60	0.29, 1.23	.16	0.34	0.13, 0.87	.02
Visual symptoms	1.17	0.51, 2.67	.71	2.00	0.71, 5.67	.19
HGB	1.14	0.92, 1.41	.24	1.11	0.85, 1.46	.45
HbF[a]	0.95	0.88, 1.02	.15	0.92	0.83, 1.01	.09
Anticoagulation	1.59	0.44, 5.81	.48	1.84	0.41, 8.21	.42
	NSCR (N = 25) vs ND (N = 16)			PSCR (N = 41) vs ND (N = 16)		
Variant	RRR	95% CI	*P*	RRR	95% CI	*P*
Age	1.02	0.95, 1.08	.64	1.06	0.99, 1.12	.08
Sex (F vs M)	1.73	0.43, 7.00	.45	0.73	0.19, 2.76	.64
Visual symptoms	2.82	0.67, 11.91	.16	5.43	1.36, 21.62	.02
Avascular necrosis	0.41	0.088, 1.95	.27	0.82	0.20, 3.46	.79

CI = confidence interval; HbF = fetal hemoglobin; HGB = hemoglobin; ND = no disease; NSCR = nonproliferative sickle cell retinopathy; PSCR = proliferative sickle cell retinopathy; RRR = relative risk ratio; SCA = sickle cell anemia.

[a]One hundred eighteen of 212 HbF values were missing in this analysis, and were imputed using 500 cycles of multiple imputation.

TABLE 5. Sensitivity Analysis for Multiple Imputation of Fetal Hemoglobin Level in Table 4

	NSCR (N = 105) vs ND (N = 61)			PSCR (N = 47) vs ND (N = 61)		
25th Percentile Substitution	RRR	95% CI	*P*	RRR	95% CI	*P*
Age	1.02	0.99, 1.05	.28	1.08	1.04, 1.12	<.001
Sex (F vs M)	0.66	0.36, 1.21	.18	0.40	0.19, 0.82	.01
Visual symptoms	1.39	0.70, 2.76	.34	3.14	1.47, 6.71	.003
HGB	1.02	0.87, 1.19	.84	1.13	0.95, 1.36	.16
HbF	0.95	0.91, 1.00	.03	0.94	0.88, 1.00	.05
Anticoagulation	1.92	0.66, 5.59	.23	1.53	0.47, 4.95	.48
	NSCR (N = 105) vs ND (N = 61)			PSCR (N = 47) vs ND (N = 61)		
50th Percentile Substitution	RRR	95% CI	*P*	RRR	95% CI	*P*
Age	1.02	0.99, 1.05	.24	1.08	1.04, 1.12	<.001
Sex (F vs M)	0.67	0.36, 1.24	.21	0.41	0.20, 0.86	.02
Visual symptoms	1.40	0.71, 2.78	.34	3.15	1.47, 6.76	.003
HGB	1.04	0.89, 1.21	.66	1.16	0.97, 1.39	.11
HbF	0.94	0.88, 0.99	.03	0.92	0.83, 0.98	.02
Anticoagulation	2.00	0.69, 5.84	.20	1.63	0.50, 5.31	.42
	NSCR (N = 105) vs ND (N = 61)			PSCR (N = 47) vs ND (N = 61)		
75th Percentile Substitution	RRR	95% CI	*P*	RRR	95% CI	*P*
Age	1.02	0.99, 1.05	.20	1.08	1.05, 1.12	<.001
Sex (F vs M)	0.67	0.37, 1.27	.23	0.43	0.21, 0.89	.02
Visual symptoms	1.43	0.72, 2.83	.31	3.20	1.50, 6.86	.003
HGB	1.06	0.91, 1.24	.47	1.20	1.00, 1.44	.05
HbF	0.95	0.90, 1.00	.07	0.92	0.86, 0.99	.02
Anticoagulation	2.14	0.74, 6.23	.16	1.76	0.54, 5.77	.35

CI = confidence interval; HbF = fetal hemoglobin; HGB = hemoglobin; ND = no disease; NSCR = nonproliferative sickle cell retinopathy; PSCR = proliferative sickle cell retinopathy; RRR = relative risk ratio.

TABLE 6. Descriptive Statistics of Factors Related to Laser Photocoagulation and Vitrectomy Treatments for Proliferative Sickle Cell Retinopathy

	Cohort (N = 296)			SCA (N = 212)			Variant (N = 82)		
	NT (N = 233)	T (N = 63)		NT (N = 188)	T (N = 24)		NT (N = 43)	T (N = 39)	
	N (%)	N (%)	*P*	N (%)	N (%)	*P*	N (%)	N (%)	*P*
Age, mean (SD)	31.5 (10.6)	43.6 (13.4)	<.001	30.5 (10.0)	44.4 (12.2)	<.001	35.9 (12.2)	43.1 (14.2)	.02
Sex (F)	131 (56.2%)	30 (47.6%)	.22	102 (54.3%)	11 (45.8%)	.44	29 (67%)	19 (49%)	.09
Visual symptoms	62 (27.7%)	42 (68.9%)	<.001	44 (24.4%)	16 (66.7%)	<.001	18 (43%)	26 (70%)	.01
Floaters	44 (19.0%)	26 (41.3%)	<.001	30 (16.1%)	10 (41.7%)	.003	14 (33%)	16 (41%)	.43
Crisis frequency[a]									
Rare	111 (49.8%)	37 (59.7%)	.11	89 (49.4%)	16 (66.7%)	.24	22 (54%)	21 (55%)	.42
Occasional	30 (13.5%)	11 (17.7%)		21 (11.7%)	1 (4.2%)		7 (17%)	10 (26%)	
Frequent	82 (36.8%)	14 (22.6%)		70 (38.9%)	7 (29.2%)		12 (29%)	7 (18%)	
HGB, median (IQR)	9.2 (7.8, 10.7)	10.5 (8.9, 11.6)	<.001	8.7 (7.5, 9.7)	8.9 (7.8, 10.6)	.54	11.3 (10.5, 12.1)	10.7 (10.2, 12.1)	.43
HbF, median (IQR)	7.7 (2.3, 14.2)	2.8 (1.4, 8.9)	.08	8.6 (3.4, 15.7)	9.6 (6.2, 12.7)	.96	1.7 (1.4, 7.0)	1.4 (1.4, 2.6)	.58
Hydroxyurea	83 (35.6%)	16 (25.4%)	.13	77 (41.0%)	13 (54.2%)	.22	5 (12%)	3 (8%)	.55
Chronic transfusion	57 (24.5%)	8 (12.7%)	.05	55 (29.3%)	5 (20.8%)	.39	2 (5%)	3 (8%)	.57
Anticoagulation	29 (12.4%)	13 (20.6%)	.10	23 (12.2%)	7 (29.2%)	.03	6 (14%)	6 (15%)	.85
EDPHTN	42 (23.9%)	14 (27.5%)	.60	36 (24.7%)	8 (40.0%)	.14	6 (20%)	6 (19%)	.95
Cerebrovascular accident	36 (15.9%)	8 (12.7%)	.53	34 (18.6%)	4 (16.7%)	.82	2 (5%)	4 (10%)	.36
Renal disease	30 (12.9%)	15 (23.8%)	.03	26 (13.8%)	7 (29.2%)	.05	4 (10%)	8 (21%)	.16
Diabetes mellitus	6 (2.6%)	4 (6.3%)	.15	3 (1.6%)	0 (0.0%)	.53	3 (7%)	4 (10%)	.60
Acute chest syndrome	151 (67.1%)	39 (62.9%)	.54	129 (70.9%)	19 (79.2%)	.40	21 (51%)	20 (53%)	.90
Avascular necrosis	70 (30.3%)	29 (46.0%)	.02	57 (30.5%)	9 (37.5%)	.49	13 (31%)	20 (51%)	.06

EDPHTN = echo-defined pulmonary hypertension; HbF = fetal hemoglobin; HGB = hemoglobin; IQR = interquartile range; NT = no treatment; SCA = sickle cell anemia; SD = standard deviation; T = treatment applied; laser photocoagulation or vitrectomy.

[a]Crisis frequency defined as "rare" if once a year or less, "occasional" if twice a year, or "frequent" if 3 times a year or more, averaged over the 2 years prior to the index retina visit.

consistent with prior reports, our results show worse ophthalmic outcomes in genotypic variants, in particular SC disease. Our findings build toward a more complete understanding of SCR and lay the foundation for future studies to establish a predictive model of SCR.

Although we defined NPSR as a distinct class of retinopathy, we found no associations between NPSR and measures of SCD. This may reflect the difficulty of distinguishing between NPSR and ND: early-stage NPSR findings are subtle and typically present in the peripheral retina, where appreciation on funduscopic examination may be challenging. However, because only retina specialists familiar with SCR in our university retina clinic contributed examination data, and diagnosis was based on a consistent set of findings characterizing NPSR and PSR, we have confidence in our findings.

Our study found that 22% of SCA patients had PSR compared with 50% of genotypic variant patients. This finding is consistent with previous studies, which report 3.5%-30.2% prevalence in SS patients and 25.3%-75.9% prevalence in SC patients.[3–8,10] Although the older age of genotypic variant patients in our cohort may contribute to higher prevalence of PSR, our results confirm the consensus that variant genotypes exhibit higher rates of PSR. What drives this difference between genotypes is unknown, although differing hemodynamic processes have been hypothesized to account for the discrepancies in prevalence of sequelae.[11]

Older age and male sex were associated with PSR in patients with SCA. Previous studies found the same association with age in both SS and SC genotypes.[4–7] These results reinforce the observation that prevalence of PSR increases throughout life.[3] It is not clear why male sex is associated with retinopathy; the literature offers no clear hypotheses. That we did not find a statistical association between male sex and PSR in patients with variant genotypes is discordant with previous literature.[3] This discrepancy may be attributed to our small population of patients with variant genotypes. However, the trend toward male sex is especially weak in our variant genotype cohort. Higher hemoglobin levels in the male sex may predispose to increased concentrations of sickled cells, lower oxygen level, and, therefore, retinal ischemia with stimulation of inflammatory and vascular mediators. This may partially explain the effect of sex, but our data show no associations between sex and other variables.

TABLE 7. Factors Associated With Laser Photocoagulation and Vitrectomy by Multivariate Logistic Regression

	NT (N = 233) vs T (N = 63)		
Cohort	OR	95% CI	*P*
Age	1.09	1.05, 1.13	<.001
Sex (F vs M)	0.63	0.31, 1.31	.22
Visual symptoms	3.31	1.48, 7.40	.004
Floaters	1.40	0.60, 3.23	.44
HGB	1.37	1.14, 1.65	.001
Chronic transfusion	0.42	0.16, 1.09	.08
Anticoagulation	0.91	0.33, 2.50	.86
Renal disease	1.02	0.35, 2.99	.97
Avascular necrosis	0.97	0.44, 2.14	.94
	NT (N = 188) vs T (N = 24)		
SCA	OR	95% CI	*P*
Age	1.10	1.05, 1.16	<.001
Sex (F vs M)	0.55	0.19, 1.61	.28
Visual Symptoms	3.60	1.06, 12.26	.04
Floaters	1.27	0.35, 4.63	.72
Anticoagulation	1.08	0.30, 3.87	.91
Renal disease	0.68	0.18, 2.53	.56
	NT (N = 43) vs T (N = 39)		
Variant	OR	95% CI	*P*
Age	1.04	1.00, 1.09	.05
Sex (F vs M)	0.42	0.15, 1.14	.09
Visual symptoms	2.28	0.84, 6.21	.11
Avascular necrosis	1.39	0.47, 4.14	.55

CI = confidence interval; HGB = hemoglobin; NT = no treatment; OR = odds ratio; T = treatment applied; laser photocoagulation or vitrectomy.

In the cohort analysis, fetal hemoglobin level was not included by multiple imputation because missingness of values was associated with treatment status ($P = .016$).

Hemoglobin level was higher in genotypic variant patients than in SCA patients, a finding consistent with previous studies.[3,5,7,12] However, we found no association between hemoglobin level and retinopathy. Preceding studies disagree on whether this relation is significant: Dembélé and associates[5] and Fox and associates[3] saw associations between hemoglobin level and retinopathy, although Leveziel and associates did not.[7] Chronic transfusion may be a confounding factor: whereas our study and that of Leveziel and associates attempted to account for chronic transfusion, it was not mentioned by Dembélé and associates and Fox and associates. This discrepancy may also be a phenotypic manifestation of different beta-globin S haplotypes.[12]

Although previous studies have found hydroxyurea use and elevated fetal hemoglobin level to be protective against retinopathy,[3,5,13,14] our study found no association between fetal hemoglobin level or hydroxyurea use and retinopathy. The relationship between fetal hemoglobin level and retinopathy may be obscured by chronic transfusion. More detailed data on hydroxyurea use, including dosage, reduction in absolute neutrophil count, duration of therapy, and medication adherence, may enable identification of an effect by hydroxyurea therapy on retinopathy.

No associations were found between retinopathy and systemic manifestations of SCD. Our cohort may be too small to achieve sufficient statistical power to detect such correlations. With a larger patient population, the borderline significant association between AVN and retinopathy may have reached statistical significance, and other possible associations may become statistically detectable. Furthermore, only symptomatic AVN was reported in our population; inclusion of radiographic evidence of asymptomatic AVN may increase the strength of this association.

Ocular findings were selected as factors of interest and in part to corroborate a previous study.[9] Compared with that report, this study population exhibited lower prevalence of directly comparable findings.

Visual symptoms were associated with PSR in the genotypic variant group. This is consistent with our severity classification: NPSR approximately corresponds to Goldberg stages I-III, which involve peripheral retina pathologies that typically do not cause visual symptoms.[2] Conversely, Goldberg stages IV-V involve vitreous hemorrhage and tractional retinal detachment, which may cause vision loss.[11] The relationship between visual symptoms and PSR in genotypic variant patients is consistent with the tendency for those genotypes to present with worse retinopathy.[3] This association further suggests that visual symptoms may be used clinically to identify patients who require referral for ophthalmic evaluation and possible treatment. The comparatively small number of patients in the genotypic variant group may preclude the identification of other factors associated with retinopathy.

Laser photocoagulation and vitrectomy surgery, the current standard interventions for PSR, were found to be associated with older age, visual symptoms, higher hemoglobin level, and no chronic transfusion in the cohort. Older age and visual symptoms were also identified as risk factors for PSR, so it is consistent that these are associated with intervention. Higher prevalence of intervention in the genotypic variant group is consistent with the higher prevalence of PSR in that group. The potential protective effect of chronic transfusion is worthy of further investigation: although chronic transfusion has been suggested as effective in prevention of stroke, acute chest syndrome, and painful episodes in a pediatric population,[15] no prior data have shown that it may have a role in prevention of retinopathy.

It is notable that the associations with PSR were not the same as the associations with the interventions for PSR. Specifically, higher hemoglobin level was associated with intervention for but not occurrence of PSR, and male sex

was associated with occurrence of PSR but not intervention. Male individuals have higher hemoglobin levels and, therefore, higher blood viscosity; thus, they may be more prone to neovascularization and advanced PSR, but it is not evident why they would not also need intervention at higher rates. Variability in disease process and between individual retinal physicians' treatment strategies may account for this discrepancy: it is known that up to 40% of sea fan neovascular lesions tend to auto-infarct without treatment, and the treatment paradigm for neovascularization in PSR is not standardized. We note that the retinal physicians involved in this study had different thresholds for treatment over observation. This variation may limit the correspondence between occurrence of PSR and intervention. Although higher hemoglobin was associated with intervention, the occurrence of this finding across the whole cohort is not directly comparable to analyses by clinical subgroup, in which hemoglobin level was not associated with retinopathy or intervention.

Our study had several limitations. Strict inclusion criteria, especially that patients were examined by a retina specialist within 1 year of a hematology visit, resulted in a high exclusion rate (63.5%). As a result, cohort size limited the strength of statistical findings; the genotypic variant group was particularly limited in number. Our hospital is a tertiary referral center receiving patients from a wide area, so many patients attend our hospital for hematologic care only and receive ophthalmologic care at more geographically accessible clinics. Because medical records are not available from outside clinics, data from our hematology clinic may understate the number of patients receiving regular ophthalmic care. Thus, we may underestimate the prevalence of SCR. For the same reason, we cannot measure compliance with referral for retinal examination. These limitations contribute to differences between our findings and those reported in other areas, such as in Jamaica,[3] Florida,[4] Mali,[5] France,[7] and Ghana.[8] Differences between healthcare systems and practices may also explain differences between this and other studies and limit the generalizability of our findings. Similarly, socioeconomic factors, including access to healthcare, may contribute to differences between our cohort and those of studies in other regions. Future prospective studies may clarify the associations identified here and establish findings that may be used to predict risk of retinopathy. Current treatments for SCD may also be evaluated for their efficacy in prevention of retinopathy.

In conclusion, SCR remains an incompletely understood ophthalmic disorder. Current guidelines recommend yearly screening for SCR, but this recommendation lacks strong supporting data and remains based on expert consensus.[16] In the absence of accurate predictive tests for the incidence and progression of SCR, yearly screening remains necessary to identify those patients at risk for vision loss. Notably, our findings suggest that changes in visual symptoms or new floaters should prompt referral for retinal evaluation. In addition, that chronic transfusion may protect against the need for interventions against SCR suggests a new potential therapy. This study sets the stage for future prospective studies to more accurately determine risk factors for SCR and to evaluate whether disease-modifying therapy for SCD might prevent SCR.

FUNDING/SUPPORT: THIS WORK WAS SUPPORTED IN PART BY PRIVATE PHILANTHROPY FROM GAIL C. AND HOWARD WOOLLEY and by the Wilmer Biostatistics Core Grant EY01765. Financial Disclosures: The following authors have no financial disclosures: Xiangyun J. Duan, Sophie Lanzkron, Marguerite O. Linz, Caroline Ewing, Jiangxia Wang, and Adrienne W. Scott. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in SCD: biology, pathophysiology, genetics, translational medicine, and new research directions. *Am J Hematol* 2009;84(9):618–625.
2. Goldberg MF. Natural history of untreated proliferative sickle retinopathy. *Arch Ophthalmol* 1971;85(4):428–437.
3. Fox PD, Dunn DT, Morris JS, Serjeant GR. Risk factors for proliferative sickle retinopathy. *Br J Ophthalmol* 1990;72(3):172–176.
4. Clarkson JG. The ocular manifestations of sickle-cell disease: a prevalence and natural history study. *Trans Am Ophthamol Soc* 1992;90:481–504.
5. Dembélé AK, Toure BA, Sarro YS, et al. Prévalence et facteurs de risqué de la rétinopathie drépanocytaire dans un centre de suivi drépanocytaire d'Afrique subsaharienne [Prevalence and risk factors for sickle retinopathy in a sub-Saharan comprehensive Sickle Cell Center]. *Rev Med Interne* 2017;38(9):572–577 [in French].
6. Downes SM, Hambleton IR, Chuang EL, Lois N, Serjeant GR, Bird AC. Incidence and natural history of proliferative SCR. *Ophthalmology* 2005;112(11):1869–1875.
7. Leveziel N, Bastuji-Garin S, Lalloum F, et al. Clinical and laboratory factors associated with the severity of proliferative SCR in patients with sickle cell hemoglobin C (SC) and homozygous sickle cell (SS) disease. *Medicine (Baltimore)* 2011;90(6):372–378.
8. Osafo-Kwaako A, Kimani K, Ilako D, et al. Ocular manifestations of SCD at the Korle-bu Hospital, Accra, Ghana. *Eur J Ophthalmol* 2011;21(4):484–489.
9. David RC, Moraes Júnior HV, Rodrigues MPM. Alterações oculares e eletrorretinográficas na doença falciforme [Ocular and electroretinographic changes in sickle cell disease]. *Arq Bras Oftalmol* 2011;74(3):190–194 [in Portuguese].

10. Diallo JW, Sanfo O, Blot I, et al. Étude épidémiologique et facteurs pronostiques de la rétinopathie drépanocytaire à Ouagadougou (Burkina Faso) [Epidemiology and prognostic factors for SCR in Ouagadougou (Burkina Faso)]. *J Fr Ophtalmol* 2009;32(7):496–500 [in French].
11. Scott AW. Ophthalmic manifestations of SCD. *South Med J* 2016;109(9):542–548.
12. Aleluia MM, Santiago RP, da Guarda CC, et al. Genetic modulation of fetal hemoglobin in hydroxyurea-treated sickle cell anemia. *Am J Hematol* 2017;92(5):E70–72.
13. Estepp JH, Smeltzer MP, Wang WC, Hoehn ME, Hankins JS, Aygun B. Protection from sickle cell retinopathy is associated with elevated HbF levels and hydroxycarbamide use in children. *Br J Haematol* 2013;161(3):402–405.
14. Kato GJ. New insights into sickle cell disease: mechanisms and investigational therapies. *Curr Opin Hematol* 2016;23(3):224–232.
15. Miller ST, Wright E, Abboud M, et al. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. *J Pediatr* 2001;139(6):785–789.
16. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease. Summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014;312(10):1033–1048.