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Sickle Cell Disease Related Vasculopathies and Early Evaluation in a Pediatric Population

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Abstract. *Background/Aim: Cardiovascular pathologies are ubiquitous in sickle cell disease (SCD). A targeted literature review was conducted to compare the overall epidemiology of selected vasculopathies seen in SCD (SCDVs) compared to the general population. Since many SCDV may originate in childhood, the study also focused on the retrospective investigation of SCDVs in a pediatric cohort at the Harbor-UCLA Medical Center. Patients and Methods: SCDVs were studied along patient age, β-globin genotypes, and fetal hemoglobin (HbF). Urine microalbumin/creatinine ratios (UM/Cr), trans-cranial doppler (TCD) and tricuspid regurgitant jet velocities (TRJV) were analyzed as well. Retinographies and overt vasculopathies were presented descriptively. Results: Among 20 females and 20 males [average 8.3 years (2.3-19 years)], 70% had HbSS/Sβ0, 22.5% HbSC and 7.5%-HbSβ+. The mean(±SD) HbF% was 17.4±12.7% (30% higher in <10 vs. ≥10 y/o, and 3 times higher in SS/Sβ0). Twenty-six patients received hydroxyurea and 13/26, L-glutamine. Thirty-six patients had TCDs within 1.4±0.9 years and all laboratory values were obtained within the last 12 months. TCDs showed low-normal velocities, but 2 were higher for HbSS/Sβ0 vs. HbSC/Sβ+ (MCA-96 vs. 86 cm/s, p=0.03; and PCA-50 vs. 41, p<0.001). Nineteen of 28 patients with echocardiograms had measurable TRJV (2.46±0.19 m/s); 9 had TRJV ≥2.5-2.8 m/s, but BNP ≤80 pg/ml. SS/Sβ0 was associated with higher UM/Cr. There were 2 cases with silent infarcts, 1-Moyamoya, 2-persistent macroalbuminuria, and 1-hematuria/renal papillary necrosis. Most ≥9 y/o patients had retinographies without SCD-related changes. There was no correlation among TCD (MCA), TRJV, and UM/Cr (n=17); thus, in this subpopulation, pathologies of cerebral, cardiopulmonary, and renal vasculatures evolved independently. Patients with higher TRJV and/or overt vasculopathy (n=14) were older than ones without (12.5±4.7 vs. 6.1±3.1 y/o, p<0.001), and had lower HbF (11.4±7.6 vs. 20.6±13.8%, p=0.026). Conclusion: While overt SCDVs are less frequent in children, age-dependent trends/surrogate markers suggest their early origination in youth, justifying intense screening to prevent their progression with disease-modifying measures.*

An estimated 100,000 individuals in the United States have sickle cell disease (SCD) (1), which is a genetic blood condition characterized by defective hemoglobin molecules in red blood cells known as hemoglobin S (HbS) (2). Affected red blood cells may stiffen and take on a crescent-shape because of polymerized aberrant hemoglobin molecules, which impedes their survivability and ability to deliver oxygen effectively. These changes eventually result in excessive hemolysis with poor tissue oxygenation and anemia. Additionally, sickled red cells are rigid and fail to pass through small blood vessels, leading to vaso-occlusion with poor tissue perfusion, which can clinically manifest as painful episodes (3). This pathognomonic triad and vicious cycle of chronic hemolysis, anemia, and vaso-occlusion can lead to multiple complications, including myriad cardiovascular pathologies (Figure 1) (4), multiple organ damage, increased susceptibility to infections (2), and painful vaso-occlusive episodes (3).

Numerous studies have shed light on the multifaceted nature of SCD, demonstrating that the impact of this disease

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Key Words: Sickle cell disease, vasculopathies, early evaluation, pediatric population.

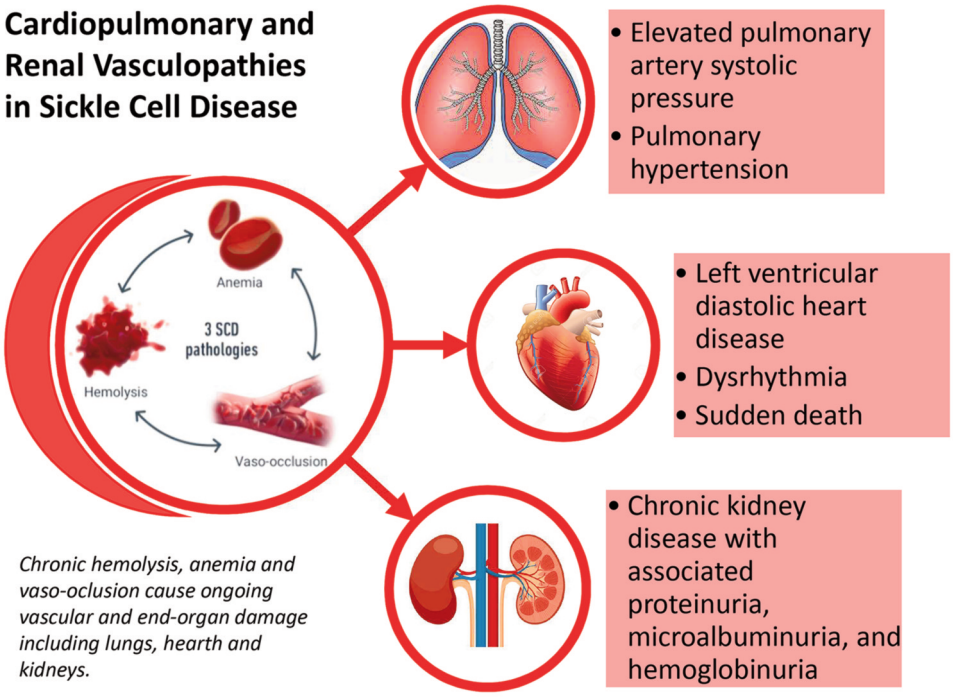


Figure 1. *Cardiopulmonary and renal vasculopathies in SCD. Chronic hemolysis, anemia and vaso-occlusion cause ongoing vascular and end-organ damage including lungs, heart, and kidneys. SCD: Sickle cell disease.*

extends beyond its well-known effects on the hematological system. For example, SCD can result in lung disease due to pulmonary vascular damage complicated by a hindered ability of the lungs to replenish hemoglobin with oxygen due to sickled red cells. Anemia demands increased cardiac output as compensation with increased workload of the heart, which is also strained by an increased difficulty of pumping blood through the stiffened systemic and pulmonary vasculature (5). Hemolysis and vascular damage in the kidneys cause nephropathy leading to albuminuria, hemoglobinuria, and kidney dysfunction (6). In summary, patients with SCD are at high risk for multiple complications including cardiovascular disease, as extensively described in the medical literature (4-7). Therefore, part of our background review compared the overall epidemiology of cardiovascular health issues commonly seen in patients with SCD to the general population (4). Next, we aimed to retrospectively study SCDVs in the pediatric cohort at Harbor-UCLA Medical Center. Figure 2 depicts the design of our two-part study. First the analysis of the extracted epidemiological data for the selected pathological conditions was conducted to estimate the frequencies of cardiovascular complications in SCD. Eventually, the main part of this work is the retrospective cross-sectional study, which contains analyzed data from the pediatric SCD population at Harbor-UCLA Medical Center.

Based on the analysis of referenced papers published within the last 20 years, the rate of SCD-related common cardiovascular complications was estimated to be ~5.5-fold higher (with a range of 2-fold to 10-fold higher) in patients with SCD than in the general population. An in-depth understanding of the multifactorial relationship between SCD and vascular disease is highly important, as it may have significant implications for patient management and overall healthcare outcomes. It may also aid in the development of targeted interventions, preventive strategies, and personalized treatment approaches. This may lead to improved clinical outcomes and quality of life for this vulnerable patient population.

Multiple factors are important to consider in the characterization of the complex epidemiological correlations of cardiovascular disease in patients with SCD (8). One such important factor, that could affect disease outcomes for many chronic conditions, including SCD, is age (3). Generally, the cumulative effect of ongoing vascular damage over time makes it more likely that vasculopathy clinically manifests with older age (9); thus, pediatric patients with SCD may have lower rates of the CV complications than shown in Figure 3 (10). In pediatric vasculopathy studies, relatively small sample sizes make it harder to adjust and match epidemiological comparisons for younger patients with SCD and "control" groups without SCD.

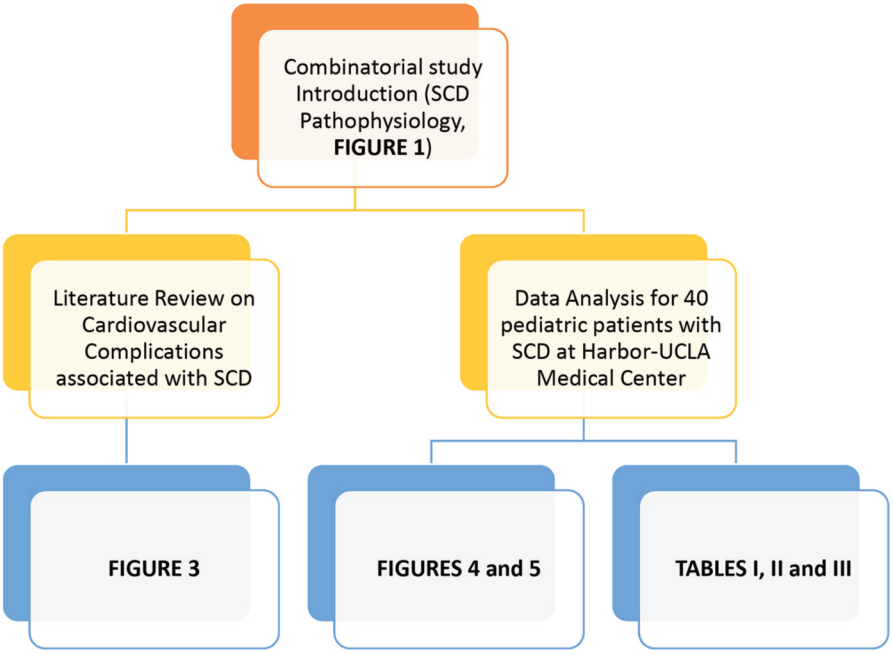


Figure 2. *Study design*.

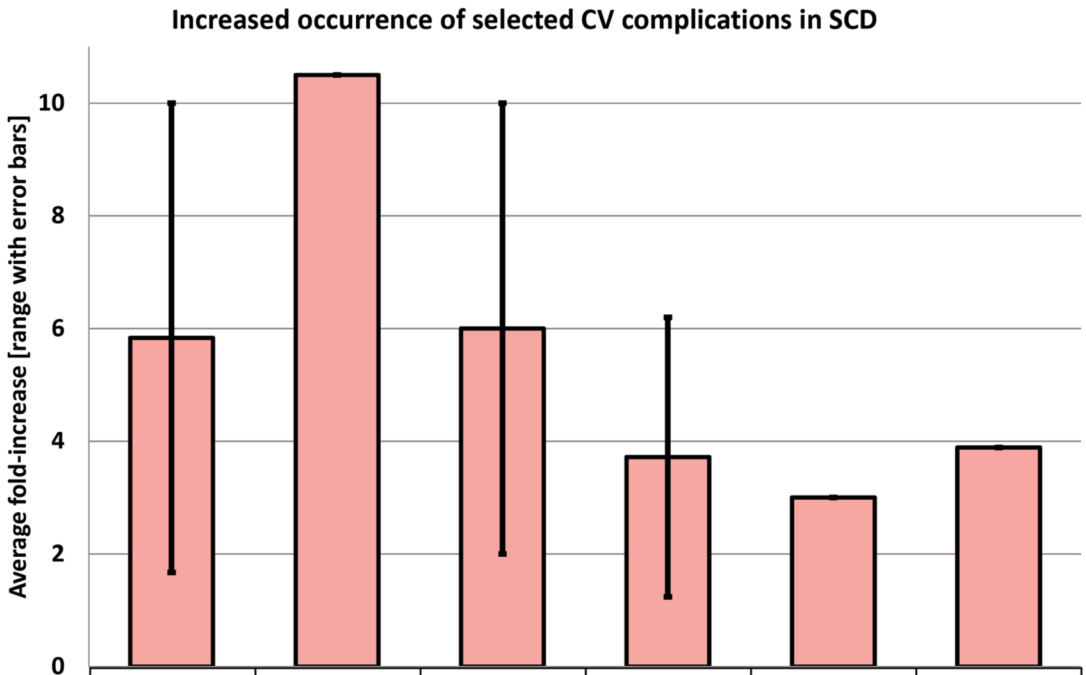
In addition to the targeted epidemiological review, our study ultimately aimed to describe the occurrence and severity of various vasculopathies in a small cohort of pediatric patients with different SCD subtypes (*i.e*. SS *vs*. SC, etc.), as well as possible associations between vasculopathies and selected laboratory and surrogate measurements.

Patients and Methods

Comparative review and patient cohort. We employed a focused approach to analyze the existing literature regarding the correlation between epidemiology of selected cardiovascular pathologies and sickle cell disease (SCD). We chose to limit these analyses to six pertinent disease categories extracted from an article by Dr. Gladwin (4), as shown in the columns of Figure 3. Relevant studies were identified from PubMed with keywords including "sickle cell disease", "cardiovascular complications", "pulmonary hypertension", "cardiovascular disease in sickle cell patients", "kidney disease in sickle cell patients", *etc*. Studies included were those investigating the association between SCD and cardiovascular diseases including cardiac, pulmonary, and renal disease. In addition, studies reporting relevant epidemiology of the aforementioned diseases in the general population were used for "control groups". Papers published within the last two decades were used for comparison. Papers with insufficient data or unclear methodology were excluded from this review. Numerical values for disease prevalence and sudden death were extracted as single number frequencies in percentages or as a range, depending on the study. All complications were considered as prevalence except for sudden death, which was considered as an incidence percentage of overall mortality in SCD or "natural deaths" in the general population.

Calculations. The estimated fold difference between the frequencies of complications in patients with SCD and the general population was calculated by dividing the percentage values in patients with SCD by that of the general population. Where a range of values was present, the lowest value in SCD patients was divided by the highest in the general population in order to obtain the lower end of the estimated fold difference. The highest value in SCD patients was divided by the lowest value in the general population to get the higher end of the estimated fold difference.

Patients, data collection, and analysis. This retrospective electronic medical record (EMR) review was approved by the Institutional Review Board (IRB) and conducted to study vasculopathies of pediatric patients with SCD at the Harbor-UCLA Medical Center (HUMC). All patients with SCD aged 1-21 years old who were actively and continuously treated at HUMC within the three years prior to study were included in this retrospective cross-sectional study. Patient demographics, clinical parameters, and laboratory data were obtained from the EMR, including outpatient visits and inpatient hospitalizations.



	ePASP	PH	HFpEF	Dysrhythmia	Sudden Death	CKD
Prevalence in SCD	10-30	10.5	11	6.2	30	38.9
General Population	3-6	1	1.1-5.5	1-5	10	10
References	*12-16*	*4, 17*	*7, 18*	*19, 20*	*21-23*	*6, 24*

Figure 3. *Increased occurrence of selected CV complications in SCD. Prevalence in SCD and in the General population are shown in the table as percentages for all complications except for sudden death, which was depicted as an incidence-percentage of overall mortality in SCD or "natural deaths" in the general population. CV: Cardiovascular; SCD: sickle cell disease; ePASP: elevated pulmonary artery systolic pressure; PH: pulmonary hypertension; HFpEF: heart failure with preserved ejection fraction; CKD: chronic kidney disease.*

Data extraction was through July 2023, then statistical analyses were performed.

Laboratory values and diagnostic studies. For fetal hemoglobin (HbF), urine microalbumin/creatinine ratio (UM/Cr), and brain natriuretic peptide (BNP), the latest available values were used, typically within the last 12-months. Age-specific trans-cranial doppler (TCD) velocity reference values were used to plot TCD data. Due to the retrospective nature of this study, the laboratory values utilized were from samples collected during routine clinical visits. Hydroxyurea and glutamine data were extracted from electronic prescriptions. Data on the presence or absence of vasculopathies were extracted from the EMR and were studied in relation to patients' age, subtype of SCD, HbF, and surrogate parameters. These included collection and analysis of the tricuspid valve jet velocity (TRJV) data from echocardiograms [for pulmonary hypertension (PH) risk assessment], TCD velocities, urine microalbumin/Cr (UM/Cr) values, retinal examinations, and fetal hemoglobin percentages. Overt vasculopathies, such as Moyamoya or renal papillary necrosis (RPN), are presented descriptively.

Statistical analysis. Descriptive statistics were used to evaluate associations between vasculopathies and increased TRJV *vs*. age and HbF percentage. Descriptive statistics include percentages for categorical variables or mean and standard deviations for continuous variables. The dichotomous variables of interest (presence *vs*. absence of vasculopathy, and presence *vs*. absence of an elevated TRJV) were combined into one binary variable (absence of both *vs*. presence of either one). For the two-group comparison, a two-sided two sample *t*-test was used (Table I, Table II, Table III). Unequal variance was assumed based on the result from F-test. A simple linear regression was used to evaluate the association between TRJV, MCA velocities and UM/Cr ratios. *p*-Values were computed using Excel and <0.05 considered statistically significant.

Table I. *Sickle cell genotypes, patient age, TRJV and selected laboratory values.*

Type	Age, years (N=40)	HbF % (N=39)	BNP, pg/ml (N=37)	UM/Cr, mg/g Cr (N=30)	TRJV, m/sec (N=19)
SS and Sβ^0 (N=26 and N=2)	<10 y/o (N=19) 5.4±2.5	23.9±12.4	45.6±74	33.8±82.3	2.4±0.2
	>10 y/o (N=9) 12.9±2.3	18.4±10.5	21±10.6	41.1±99	2.49±0.2
t-test, <10 *vs*. >10 y/o	*p*<0.001	*p*=0.26	*p*=0.22	*p*=0.87	*p*=0.64
SC and Sβ$^+$ (N=9 and N=3)	9.6±5.7 (N=12)	6.8±5.5	21±20.3	3.9±3.6	2.45±0.2
t-test, SS/Sβ^0 *vs*. SC/Sβ$^+$	*p*=0.35	*p*<0.001	*p*=0.28	*p*=0.07	*p*=0.44

Numbers are averages±standard deviations (SD). *p*-Values are based on a two-sided two sample *t*-test. TRJV: Tricuspid regurgitant jet velocity; HbF: fetal hemoglobin; BNP: brain natriuretic peptide; UM/Cr: urine microalbumin/creatinine.

Table II. *TCD velocities in pediatric patients with sickle cell disease.*

Type	Age, yr. (n)	ICA	MCA	ACA	PCA
SS and Sβ^0	<10 (n=16)	55.1±29.2	101.2±16.5	51.1±17.7	52.5±17.2
	>10 (n=8)	48.8±22.3	86.2±22.4	47.5±23.8	49.7±15.3
p-Value (<10 *vs*. >10 y/o)		0.45	0.1	0.19	0.67
SC and Sβ$^+$ (n=12)		48±11.6	85.7±21.4	44.9±11.2	40.6±9.8
p-Value (SS/Sβ^0 *vs*. SC/Sβ$^+$)		0.35	0.03	0.06	<0.001

TCD Velocities are cm/s. Values shown are Mean±SD. *p*-Values are based on a two-sided two sample *t*-test. ICA: Internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery; TCD: trans-cranial doppler.

Results

There were 20 females and 20 males (average age: 8.3 y/o, range=2.3-19.1 y/o). Beta-globin genotypes were: HbSS (n=26) and HbSβ0 (n=2) (70%); HbSC (n=9, 22.5%); and HbSβ+ (n=3, 7.5%). Twenty-six patients (65%) were on hydroxyurea, and half of those (n=13) were also on L-glutamine. The average of the latest HbF values was 17.4%±12.7% (mean±SD). Fetal hemoglobin was 30% higher for HbSS patients who were younger than 10 y/o *vs*. those that were older than 10 y/o, although this difference did not reach statistical significance (*p*=0.26, Table I). However, HbF was significantly higher (3.3-fold) in the SS/Sβ0 group *vs*. the SC/Sβ+ group (22.1±12.1% *vs*. 6.8±5.5%, *p*<0.001).

Thirty-six patients (90%) had trans-cranial Doppler (TCD) studies obtained within the last 1.4±0.9 years. TCD velocities generally were low normal to low abnormal (Figure 4). For bilateral MCAs and PCAs, they were significantly higher for HbSS and HbSβ^0 *vs*. HbSC and HbSβ$^+$ groups (respectively, 96 *vs*. 86 cm/s, *p*=0.03; and 50 *vs*. 41 cm/s, *p*<0.001; Table II). Concerning values of low TCD velocities triggered brain vasculature MRI studies. Overall, 13 patients had MRA/MRV done based on indications including abnormal TCD results and/or neuropsychiatric symptoms, such as headaches or poor memory. Out of 13 MRIs, 3 showed abnormal results: two revealed silent infarcts and one showed Moyamoya disease. The patient with Moyamoya disease had a surgical intervention for Moyamoya and is receiving chronic PRBC transfusions pending evaluation for potential hematopoietic stem cell transplantation (HSCT). The other two patients with

Table III. *Age and HbF by elevated TRJV and vasculopathies.*

TRJV and vasculopathy status	N	Age, years (Mean±SD)	HbF, % (Mean±SD)
TRJV <2.5 m/s, and no vasculopathy	26	6.1±3.1	20.6±13.8
TRJV ≥2.5-2.8 m/s, or any vasculopathy	14	12.5±4.7	11.4±7.6
p-Value		*p*<0.001	*p*=0.026

p-Values are based on a two-sided two sample *t*-test. TRJV: Tricuspid regurgitant jet velocity; HbF: fetal hemoglobin; SD: standard deviation.

silent infarcts continued pharmacotherapy with hydroxyurea and aspirin.

Echocardiograms were performed for 28 of 40 patients (70%). Of the 28 echocardiograms, TRJV was measurable for only 19 patients (mean±SD: 2.46±0.19 m/s). Six of the 28 echocardiograms demonstrated trivial tricuspid regurgitation insufficient for accurate TRJV measurements, and the remaining 3 had no tricuspid regurgitation. For HbSS patients younger than 10 y/o, the average TRJV was 2.43 m/sec, and for those older than 10 y/o, 2.49 m/s (p=0.6, Table I). Nine patients had an isolated peak TRJV ≥2.5 m/s and, based on the 2019 guidelines from the American Society of Hematology (11), had BNP measurements. All BNP concentrations were ≤80 pg/ml, therefore no cardiac catheterizations were conducted. Cardiac catheterization was performed for one patient due to chronic hypoxemia and chest pain, which did not reveal pulmonary hypertension.

Urine microalbumin/creatinine ratios (UM/Cr) were obtained in 30 patients and were largely within normal limits (<30 mg/g Cr), except for three patients. Of these three, one patient had microalbuminuria based on a single UM/Cr measurement of 52 mg/g Cr, with repeat measurement pending. Two other patients had significant and persistent macroalbuminuria (>300 mg/g Cr), which improved with ACE inhibitor treatment. UM/Cr ratios tended to be higher in patients with HbSS and HbSβ0 *vs*. HbSC and HbSβ+ (36.9 *vs*. 3.9 mg/g Cr, p=0.07; Table I). One patient had severe gross hematuria and was diagnosed with renal papillary necrosis (RPN). Hematuria in this patient resolved only after 6 months of exchange transfusions and initiation of voxelotor, in addition to hydroxyurea and L-glutamine. The majority of patients (87.5%) had a routine urinalysis done, and only one patient had trace proteinuria, pending re-evaluation. Estimated glomerular filtration rates remained within the normal range for this pediatric population.

Eighteen patients had retinographies which did not show retinopathy (16 of these patients were 9 years or older, and 2 of them were 8 years old). One patient with clinical evidence of vasculopathy (Moyamoya) also had a TRJV of 2.5 m/sec. In an attempt to examine the overall potential correlations among the vasculopathies, we analyzed numerical value-sets in 17 patients who all had measurements of TCD (MCA velocities), TRJV, and UM/Cr. As shown in Figure 5, there was no correlation among TCD (MCA), TRJV, and UM/Cr values in these 17 patients. The absence of such correlations and normal retinal photos supports the fact that in this population, pathologies of the cerebral, cardiopulmonary, renal, and retinal vascular beds may evolve relatively independently. However, when patients with overt vasculopathies and abnormal TRJVs are grouped, we observed that these patients are older and have lower HbF compared to those with no evidence of vasculopathy or abnormal TRJV (Table III).

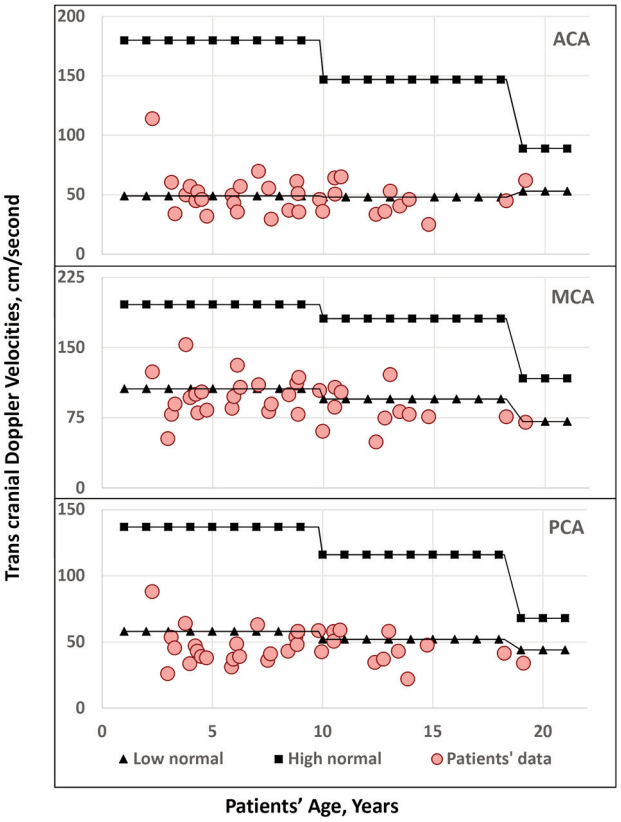


Figure 4. *Transcranial doppler velocities for 3 vessels: ACA, MCA and PCA. ACE: Anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery.*

Discussion

First, we summarized the selected CV complications in SCD shown in Figure 3 for comparisons.

Elevated pulmonary artery systolic pressure (ePASP). ePASP, which may present with or without pulmonary hypertension (PH), was associated with increased mortality in SCD (4). A study by Jankowich *et al*. (12), describing ePASP of 40 mm Hg as a cut-off showed 3-6% prevalence in general population. The ECHO-based ePASP was reported in ~30% of HbSS and 10-25% of HbSC cases (13). Thus, we estimated a 1.67 to 10-fold increase for ePASP prevalence in SCD.

Pulmonary hypertension (PH). It is defined as a mean pulmonary arterial pressure of 20 mm Hg or greater measured by right heart catheterization (13-16); however, a non-invasive screening by ECHO can identify SCD patients at risk. SCD patients with PH have a higher risk of death (5, 13). According to the largest study for PH in SCD conducted by NIH 56 out of 531 patients with SCD (10.5%) had PH (4). Current estimates suggest that the prevalence of PH in

the global population is approximately 1% (17). Therefore, in SCD, PH prevalence is increased 10.5-fold.

Left ventricular diastolic heart disease or heart failure with preserved (systolic) ejection fraction (HFpEF). Due to diagnostic challenges the precise prevalence of HFpEF is unknown, however it is estimated to be 1.1-5.5% in the general population (18). According to one SCD study utilizing cardiac MRIs 9 out of 82 (11%) fulfilled the criteria for HFpEF (7). Hence, the estimated range of increased risk for HFpEF in SCD is from 2 to 10.

Dysrhythmia. Also termed arrhythmia, it refers to a diverse group of abnormal heartbeats caused by aberrant electrical cardiac signaling. High frequency of arrhythmias in SCD patients is probably multifactorial and is linked to poorer outcomes such as higher mortality in hospitalized patients (19). A large study reported by Patel *et al*. in 2020, showed that 55,616 out of 891,450 hospitalized patients (6.2%) with SCD had a variety of arrhythmias (19). In general population, overall estimates of arrhythmias are about 1-5% (20). The calculated range of fold-increase for this group of disorders is 1.24-6.2 (Figure 3).

Sudden death. It is typically an unexpected natural event resulting in the death of an otherwise healthy individual who did not have any symptoms suggesting an abrupt death was likely (21). In the context of SCD, sudden death is defined as the unanticipated death of a relatively healthy patient, occurring at home or within 24 hours of being hospitalized, including, or excluding a vaso-occlusive crisis. Sudden death accounts for disproportionally higher numbers of premature death in SCD patients, who may have underlying cardiopulmonary disease (22). Prevalence is an irrelevant parameter for Sudden Death; therefore, the incidence of the Sudden Deaths as a percentage of overall mortality was used in this case. This percent-incidence is over 30% in one of the recent SCD studies reported by Dr. Nze *et al*. in 2018 (22). The corresponding overall parameter was approximately 10% of all deaths classified as 'natural' in a socioeconomically and racially diverse population (23). Thus, sudden death is estimated to be 3 times higher in SCD.

Chronic kidney disease (CKD). In SCD, it is often associated with albuminuria, hemoglobinuria, and kidney dysfunction. In a Nigerian study of 284 patients with HbSS disease, the prevalence of CKD (defined by GFR <60 ml/min/1.73m^2 and/or albuminuria) was 38.9% (6). This is almost 4 times higher than the pooled prevalence of 10% for possible CKD in a contemporary population of 2.4 million patients from 11 countries (24). A pediatric study from Ghana (25) showed a similarly high frequency of SCD-related CKD in children. In our pediatric population, we identified only three patients with evidence of significant nephropathy, two with persistent macroalbuminuria and one with gross hematuria/RPN. All three

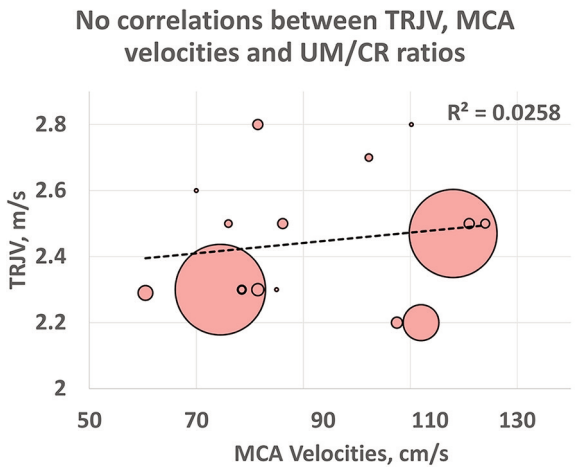


Figure 5. *No correlation was found between TRJV, MCA velocities and UM/Cr ratios in 17 patients. Slightly upward trending dotted tread line between MCA velocities (X-axis) vs. TRJV (Y-axis) shows an R^2 value that does not support a strong correlation between the two. The size of each dot/bubble corresponds to the amount of albuminuria for each patient, and the absence of clustering of the similar size bubbles demonstrates no association between the UM/Cr ratios and TRJV or MCA velocities. TRJV: Tricuspid regurgitant jet velocity; MCA: middle cerebral artery; UM/Cr: urine microalbumin/creatinine ratio.*

of these patients have HbSS disease, which represents 11.5% of our 26 patients with HbSS, compared to 16-27% rate of CKD reported for pediatric SCD (26). All three patients responded to disease-modifying interventions, which may be important in halting age-dependent progression of kidney disease (26, 27).

The aforementioned review and epidemiological comparison of the frequencies for the SCD-related cardiovascular complications represent only overall estimates with limited precision. However, these findings provide a broad overview with a markedly increased occurrence of selected CV complications in SCD, compared to the general population. The influence of various factors, such as genotype, disease severity, comorbidities (8), and socioeconomic determinants on these associations can be further elucidated. For example, some of the studies for SCD have mostly HbSS patients, such as the CKD study from Nigeria (6), whereas others studied populations consist of HbSS and HbSC patients (13). Sickle cell genotype is a well-known known factor affecting the clinical severity of the disease (2), and one could consider separating studies based on genotype for a more ideal review. Another important factor that could affect the disease outcomes for many chronic conditions including SCD is age (3). Generally, the accumulative effect of ongoing vascular damage makes it more likely to clinically manifest in older age (9), thus, pediatric patients with SCD have lower rates for the complications discussed here (10). Therefore, although the coupled studies here were not exactly matched for the same age groups, studies utilized for comparison were largely for adults.

Tricuspid regurgitant jet velocity (TRJV). Pediatric literature and the ASH-2019 guidelines suggest that TRJV ≥2.5 m/s can be utilized as an indirect measurement of ePASP (corresponding to ePASP of 30 mm Hg) and as screening tool for PH risk assessment (11, 28-30). In addition, no PH was found in our one case of cardiac catheterization, and no patients were identified with HFpEF amongst the population of 40. Therefore, we choose "isolated" peak TRJV values for assessing/screening the patients at risk for cardio-pulmonary vasculopathies. This has revealed sub-population of 9 patients (22.5%) with an increased TRJV, and although all had a BNP levels ≤80 pg/ml, we have decided to group them with vasculopathies because it is associated with increased SCD morbidity and mortality (5, 31). Augmented hemolysis with significantly higher LDH, reticulocyte count and AST and lower hemoglobin was associated with increased TRJV ≥2.5 m/s (32), which can be mitigated by disease modifying therapy (27).

Pediatric sudden death and dysrhythmia. Although the SCD-related sudden deaths are high, in the United States, from 1979 to 2017 SCD-related death rates amongst patients under 20 y/o decreased from 0.5-2% range to 0.25-0.7% (33). No deaths were observed in our pediatric population during this study period, therefore sudden death was irrelevant to our retrospective review. Similarly, we left out studying dysrhythmias in our pediatric retrospective section, because no clinically persistent cases were observed in our population. However, transient tachycardia during the hemolytic and painful crises was not uncommon, consistent with extrapolated 3.7% rate for hospitalized SCD patients under 18 years of age (19).

Cerebral vasculopathies. Papadakis *et al*. reported in 2022, that in pediatric SCD, clinically evident acute strokes were largely identified in patients with Moyamoya, and that revascularization improves long-term stroke outcomes compared to medical management (34). Based on abnormal TCDs, followed by MRIs, we identified 2 of our patients with silent infarcts who are on escalated pharmacotherapy, and another one with Moyamoya, who underwent a revascularization, is on chronic PRBC transfusion and is being evaluated for HSCT. Implementation of stroke-prevention measures (35-37) in pediatric-SCD may change future epidemiology for adults with SCD, about a quarter of whom historically had strokes by the age of 45 y/o (38).

Retinopathy. In a recent study of 1,904 SCD participants (39), assessment for SCD-related retinopathy showed that risk factors included older age, smoking, and lower HbF. An 11-year old follow-up study (40), also demonstrated that an older age and low HbF in addition to SC genotype are associated with SCD-related retinopathy. In contrary, younger age, absence of smoking, relatively higher HbF levels and the small number of SC patients (who were in average 9.6 y/o, n=9) in our cohort of 40, explains the absence of retinopathy findings.

Therefore, the pediatric section of our study included retrospective review of local SCD population with examination of surrogate parameters and targeted examinations used to screen for SCD-related vasculopathies: TCD velocities for cerebral vessels, TRJV as a potential marker for PH risk assessment, UM/Cr ratios for nephropathy, and retinal photos for retinopathy. Furthermore, overt clinical scenarios, such as Moyamoya or RPN, were included in our analysis. Main findings came to verify the importance of age and related HbF decrease in pathogenesis is of SCD-related vasculopathies. Also, our study shows that HbSS/Sβ0 genotypes may predispose to more vasculopathies in pediatric age group. Lastly, there was evidence suggesting that the effect of one vascular bed for a pediatric patient with SCD may not be linked with parallel vasculopathy in another organ-system (Figure 5). Similarly, in an adult study (40), microalbuminuria was not significantly associated with the progression of SCD-related retinopathy. Nevertheless, 2 of our adolescent patients with CNS vasculopathies (Moyamoya and silent infarcts) also had evidence of potentially evolving cardiopulmonary disease (increased TRJV and hypoxemia/intermittent chest pain with activities, respectively). It unfortunately points to the fact that with an increased age affection of more than one vascular bed is not very unlikely, as seen in adult SCD population with multiple co-morbidities (9).

In summary, the review of studies on cardiovascular complications in adult SCD patients and the retrospective EMR review of pediatric SCD population in our hospital confirms origination and early pathogenesis of SCD-related vasculopathies since childhood and their progressive evolution as detected in adults. Wider usage of various disease-modifying treatments for SCD, including new ones (41-43), may improve long-term outcomes, which can change the epidemiological picture of SCD complications and current landscape of CV epidemiology in SCD. From that perspective, data such as those presented herein can serve as a good baseline to show longitudinal effect of SCD modifying agents.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

All Authors contributed to writing and editing the manuscript. Daniel Panosyan and William Panosyan conducted the literature review, data extraction, analyses and writing of the manuscript supervised by Drs. Gotesman, Corral, and Hanudel. Dr Pak verified the data analysis and statistics sections.

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