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A Multi-institutional Comparison of Younger and Older Adults with Sickle Cell Disease

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To the Editor:

In the last 50 years, survival for patients with sickle cell disease (SCD) has substantially improved, with median survival as high as 60 years in a contemporary cohort[1]. Older adults with SCD (defined herein as age ≥ 50 years) make up 13% of the adult population cared for at four major academic medical health systems in North and South Carolina. As the older SCD population continues to grow, more data are needed to guide medical management appropriate to their needs.

To examine potential differences between older (age ≥ 50 years) and younger (age 18–49) adults with SCD, we analyzed multi-institutional data on 724 adults with SCD enrolled between 2002 and 2011 at Duke University Hospital, University of North Carolina Hospital, and Grady Health System. Data collection and methods on this population were previously described by Elmariah et al[1].

The younger adults comprised 88.5% of the study subjects and had a mean age of 30.5 years. The older adults comprised 11.5% of the study subjects, with a mean age of 56.9 and range of 50–84 years. In the younger adult group, 86.9% of patients had Hb SS or Hb $S\beta^0$ genotype, compared to 83.3% in the older adult group (p=0.37). We could not detect a significant difference in socioeconomic characteristics, such as household income, employment status, or disability status between age groups; however, younger adults had a higher high school graduation (Table 1).

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We detected several differences in hematologic parameters between younger and older adults (Supplemental Table 1). White blood cell count (WBC), hemoglobin, platelet count, and mean corpuscular volume (MCV) were all stratified by hydroxyurea (HU) use. Only 31.4% of older adults and 42.1% of younger adults were on hydroxyurea at study enrollment (p=0.13). Older adults had a lower hemoglobin when controlling for sex, hemoglobin genotype, and HU usage (9.8 g/dL for older adults vs. 10.3 g/dL for younger adults; p=0.008). When stratified by HU usage, older adults off HU had a lower hemoglobin compared to younger adults off of HU (9.5 g/dL for older adults off HU vs. 10.1 g/dL for younger adults off HU; p=0.006). We could not detect a significant difference in baseline hemoglobin between older and younger adults who were on HU (9.8 g/dL for older adults on HU vs. 10.1 g/dL for younger adults on HU; p=0.35). The older adults in this study also had a lower WBC regardless of HU usage (8.7 $\times 10^9$/L for older adults on HU vs. 10.6 $\times 10^9$/L for younger adults on HU; p=0.05 and 9.5$\times 10^9$/L for older adults off HU vs. 11.9 $\times 10^9$/L; p=0.0001 for younger adults off HU). Older adults also had a lower platelet count compared to younger adults if they were on HU; however, we could not detect a significant difference in platelet count if they were not on HU (327 $\times 10^9$/L older adults on HU vs. 426 $\times 10^9$/L for younger adults on HU; p=0.007 and 343 $\times 10^9$/L for older adults off HU vs. 383 $\times 10^9$/L for younger adults off HU; p=0.08). These hematologic findings were consistent with those observed in other studies on older adults with SCD[2–4]. The lower WBC seen in the older adults may be an effect of aging, since immunosenescence and stem cell exhaustion have been previously described as hallmarks of aging[5]. The more pronounced anemia seen in the older adults may also be worsened by age-related changes such as nutritional deficiencies, undiagnosed malignancy, renal disease, and anemia of chronic disease.

In agreement with prior studies, we also found that older adults with SCD had a lower eGFR at 82 mL/min/1.73 m^2 compared to 133 mL/min/1.73 m^2 in younger adults (p<0.0001) and higher baseline creatinines, with a mean of 1.30 mg/dL, compared to 0.86 mg/dL in younger adults (p<0.0001). A greater proportion of older adults also had proteinuria (defined as ≥ 1+ on urine dipstick, odds ratio (OR)=2.93, p<0.0001).

We found that 40.3% of older patients had been hospitalized for pain in the year preceding enrollment, compared to 60.0% of younger adults (OR=0.46, p=0.004) (supplemental Figure 1). There was a similar proportion of subjects with daily narcotic usage, a marker of chronic pain (60.8% of older adults vs. 55.5% of younger adults; p =0.50).

We could not detect a significant difference in the proportion of patients with a history of acute chest syndrome or a difference in mean tricuspid regurgitant jet velocity (TRJV) among subjects who had values available and measurable. Despite these similarities, older adults were more likely to have a presumptive diagnosis of pulmonary HTN (defined as TRJV ≥ 2.5 m/sec or having evidence of pulmonary HTN on echocardiogram interpretation, p=0.03) or a history of heart failure (p=0.004).

A higher proportion of older adults had a history of leg ulcers, avascular necrosis (AVN) involving the hip or shoulder joint, history of hip replacement, eye problems related to SCD, and TIAs, although they did not report an increased incidence of overt strokes (Table 1). We

could not detect a significant difference in the proportion of subjects being treated with chronic transfusions (9.0% of older adults vs. 5.6% of younger adults; p=0.39). These numbers were lower than the proportion of patients with a history of CVA for each group, which may suggest that some subjects were not receiving optimal secondary stroke prevention.

This is the largest study examining characteristics of aging in SCD to date. Strengths of this study include the large sample size, multi-institutional nature, and comprehensive standardized phenotypic information collected. Limitations of this study are that there were many fewer patients over the age of 50 compared to those aged 18–49. There was also a lack of inclusion of patients receiving care only outside of comprehensive sickle cell programs. In addition, the patients in this study were limited to the southeastern United States, so there may also be regional differences in outcomes.

As adults with SCD are living longer, there is a growing need for evidence-based health maintenance and treatment guidelines. There is also a need for better primary care for older adults with SCD, as noted by Sandhu et al[6]. Few older adults with SCD are included in studies addressing proper perioperative management. There is a need for guidelines addressingsuch CKD, CHF, and pulmonary HTN duringas physiologically stressful procedures such as joint replacements. Popular tools in the geriatrics field, such as geriatric assessment, may be useful as a pre-operative assessment and also may facilitate early identification of previously unrecognized problems in older adults with SCD. In Lopez-Otin et al.'s study on the hallmarks of aging, the authors also suggested that comparative genomic studies between short- and long-lived individuals may allow us to better understand genetic and epigenetic changes associated to longevity[5]. As we understand these differences, we can develop interventions targeted by age to further reduce mortality and improve health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

SCD	sickle cell disease
HU	hydroxyurea
eGFR	estimated glomerular filtration rate
Hb	hemoglobin
WBC	white blood cell count

TRJV	tricuspid regurgiant jet velocity
CSSCD	Cooperative Study of Sickle Cell Disease
AVN	avascular necrosis

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Table 1.

Characteristics of Younger vs Older Adults with Sickle Cell Disease

	age 18–49 (n/total available)	age ≥ 50 (n/total available)	P value
Mean age	30.5 (range 18–49)	56.9 (range 50–84)	
Female	52.9% (339/641)	65.1% (54/83)	**0.04**
Unemployed	64.0% (373/583)	74.3% (52/70)	0.09
Disability	58.6% (359/613)	64.1% (50/78)	0.38
Annual Household Income <$25k	64.4% (246/382)	57.1% (32/56)	0.29
High School Graduates	81.25% (520/640)	71.1% (59/83)	**0.02**
Current smoker	21.2% (128/603)	9.1% (7/77)	**0.02**
Acute Chest Syndrome	74.1% (398/537)	67.6% (50/73)	0.21
Pulmonary Hypertension	29.2% (63/216)	47.2% (17/36)	**0.03**
Daily Narcotic Use	55.5% (227/409)	60.8% (31/51)	0.50
Strokes	15.2% (80/528)	12.5% (9/72)	0.67
Transient Ischemic Attack	3.7% (19/512)	9.6% (7/73)	**0.04**
Seizures	12.5% (67/537)	4.1% (3/73)	**0.05**
Leg Ulcers	21.1% (111/525)	36.1% (26/72)	**0.004**
Any avascular necrosis (AVN)	27.1% (142/524)	47.2% (34/72)	**0.0006**
Hip replacement	7.7% (32/414)	33.3% (20/60)	**<0.0001**
Heart Failure	5.1% (27/533)	15.1% (11/73)	**0.004**
SCD-related Eye Complications	21.5% (107/498)	37.5% (27/72)	**0.004**