

Factors associated with survival in a contemporary adult sickle cell disease cohort

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In this study, the relationship of clinical differences among patients with sickle cell disease (SCD) was examined to understand the major contributors to early mortality in a contemporary cohort. Survival data were obtained for 542 adult subjects who were enrolled since 2002 at three university hospitals in the southeast United States. Subjects were followed up for a median of 9.3 years. At enrollment, clinical parameters were collected, including hemoglobin (Hb) genotype, baseline laboratory values, comorbidities, and medication usage. Levels of soluble adhesion molecules were measured for a subset of 87 subjects. The relationship of clinical characteristics to survival was determined using regression analysis. Median age at enrollment was 32 years. Median survival was 61 years for all subjects. Median survival for Hb SS and $\text{S}\beta^0$ was 58 years and for Hb SC and $\text{S}\beta^+$ was 66 years. Elevated white blood count, lower estimated glomerular filtration rate, proteinuria, frequency of pain crises, pulmonary hypertension, cerebrovascular events, seizures, stroke, sVCAM-1, and short-acting narcotics use were significantly associated with decreased survival. Forty-two percent of subjects were on hydroxyurea therapy, which was not associated with survival. SCD continues to reduce life expectancy for affected individuals, particularly those with Hb $\text{S}\beta^0$ and SS. Not only were comorbidities individually associated with decreased survival but also an additive effect was observed, thus, those with a greater number of negative endpoints had worse survival ($P < 0.0001$). The association of higher sVCAM-1 levels with decreased survival suggests that targeted therapies to reduce endothelial damage and inflammation may also be beneficial.

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■ Background

Although it is clear that survival of patients with sickle cell disease (SCD) has improved over the last 40 years, the factors that portend positive and negative prognoses need be readdressed given the development of new treatment modalities, such as stem cell transplantation, that hold promise for cure but also carry considerable risk. Patients with SCD are now living long enough that many patients, families, and physicians might not wish to incur further risk to obtain a chance at cure. Thus, to give patients and physicians the opportunity to make informed decisions, more detailed data are needed to identify truly favorable and unfavorable phenotypic traits and thus help to better identify individualized treatment options for patients with this disease.

Sickle cell disease was long a disease of children and young adults because of its devastating natural progression. In the 1970s, studies estimated the median survival of homozygotes in the United States to be only 14.3 years [1]. Since that time, a number of interventions have been implemented to improve quality and duration of life [2–5]. With modern advances, the survival of patients with SCD was estimated in the 1990s to be 42 years for males and 48 years for females [6].

Clearly, SCD is manifested by diverse presentations, and its prognosis varies across the patient population. Most notably, hemoglobin (Hb) genotype influences severity of disease. Hb SS has a significantly lower survival than Hb SC disease and $\text{S}\beta^+$ thalassemia [2,6]. Within these groups, therefore, research has focused on identifying phenotypes that predict an unfavorable prognosis. Prior studies have shown renal failure, seizures, acute chest syndrome (ACS), low fetal Hb level, and baseline white blood cell (WBC) count greater than 15,000 cells per cubic millimeter to be associated with decreased survival [6]. Among patients with SCD on hydroxyurea therapy, it has been shown that higher total Hb, fetal Hb, reticulocyte counts, and fewer instances of ACS were all associated with improved survival [7].

Additional Supporting Information may be found in the online version of this article.

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TABLE I. Prevalence of Baseline Clinical Characteristics at the Time of Enrollment

Characteristic	N with characteristic	N total	% with characteristic
Comorbidities			
Pulmonary hypertension ^a	73	222	32.8
ACS	354	475	74.5
CHF	28	470	6.0
AVN	150	461	32.5
Leg ulcer	112	464	24.1
Stroke	73	465	15.7
Seizure	57	474	12.0
TIA	18	455	4.0
Retinopathy	103	443	23.3
Proteinuria	124	460	27.0
Gallstones	293	471	62.2
Chronic transfusion	30	469	6.4
Priapism	80	215	37.2
Surgical history			
Splenectomy	48	378	12.7
Cholecystectomy	257	383	67.1
Medications			
Iron chelator	24	463	5.2
Hydroxyurea	184	441	41.7
Daily long-acting narcotics	120	374	32.1
Antihypertensives	73	447	16.3
Antidepressants	43	447	9.6
Bronchodilators	27	448	6.0

^a Defined as tricuspid regurgitant velocity ≥ 2.5 m/sec by echocardiography.

Molecular phenotypes and biomarkers have become a new topic of investigation [8]. In particular, endothelial proteins that contribute to adhesion, such as VCAM-1, ICAM-1, $\alpha V\beta 3$ integrin, P-selectin, and E-selectin, have been described as contributors to the pathophysiology of vaso-occlusive crises [9–18]. Some of these proteins have been shown to circulate in free, soluble form at elevated levels in patients with SCD. In addition, in patients with SCD with crises, increased expression of these molecules on endothelial cells has been demonstrated [19,20]. Some studies have even suggested that the ability of hydroxyurea to decrease vaso-occlusive crises, long thought to be mediated by upregulation of fetal Hb, may actually also be related to downregulation of adhesion proteins and their ligands [21–23]. These correlations suggest that adhesion proteins are potentially useful targets for prognostication as well as novel treatments for SCD.

The goal of this study was to identify associations between the presence of certain clinical phenotypes at enrollment, such as comorbid conditions and laboratory data, and decreased survival among patients with SCD in a contemporary cohort.

Methods

Subjects

Institutional Review Board approval was obtained, and subjects were enrolled at their respective institutions. The present analysis included 542 adult subjects (≥ 18 years at the time of enrollment) diagnosed with SCD (Hb SS, SC, $S\beta^0$, or $S\beta^+$) by Hb electrophoresis, globin synthesis gene studies, or genetic analysis who were regularly followed in clinic at the Duke University Medical Center, the University of North Carolina Health Care System, and the Grady Health System. Subjects who had received blood transfusion within 90 days prior to enrollment were excluded.

Study design

At the time of enrollment, we evaluated subjects for characteristics suspected to influence mortality of patients with SCD using a standardized validated patient history questionnaire [24], laboratory data, and medical chart review. Included subjects were followed for a median of 9.3 years (minimum 2.7 years; maximum 10.5 years). The primary endpoint was death during the follow-up period. Using a

cross-sectional design, associations between baseline characteristics present at enrollment and decreased survival were determined. Baseline characteristics included comorbid conditions, baseline laboratory values, pain, and medication use, as shown in Tables I–III.

For comorbidities at enrollment, any history of the event, whether ongoing or resolved, was considered as positive. Pulmonary hypertension (pHTN) was defined as a tricuspid regurgitant jet (TR jet) ≥ 2.5 m/sec. When available, laboratory values included the average of three recent steady-state values to account for outliers. Laboratory data obtained during acute illness were excluded. Using these data, we calculated and included the hemolytic index (defined as the first principal component of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), bilirubin, and reticulocyte count) [25]. In a subset of 87 subjects from the Duke University and the University of North Carolina, we also obtained levels of plasma markers, including soluble adhesion molecules. Using the patient history questionnaire, pain was evaluated based on the number of hospitalizations in the past 12 months and the use of narcotic analgesics at home. Medication use was also evaluated with the questionnaire, and our final analysis examined use of hydroxyurea, migraine medications, bronchodilators, iron chelators, antihypertensives, and antidepressants.

Using a previously described model [26], an end organ severity score was generated using the following parameters: pulmonary (pHTN or O_2 saturation $< 92\%$), renal (proteinuria or creatinine > 1), cerebrovascular [stroke, transient ischemic attack (TIA), or seizures], avascular necrosis (AVN) of hip or shoulder, and leg ulcers. One point was recorded for organ damage in each category. Points were then summed to create the severity score ranging from 0 to 5.

Statistical methods

Contingency tables for categorical variables and means for continuous variables were generated using PROC FREQ and PROC MEANS in SAS v9.2 (SAS Systems, Cary, NC), respectively. Kaplan–Meier survival curves were created, and hazard ratios for mortality during the study period were calculated to determine baseline characteristics associated with decreased survival. Kaplan–Meier survival analyses were performed using PROC LIFETEST; survival curves were created using Prism (GraphPad). Regression analysis based on the Cox proportional hazards model was used to determine the effect of clinical phenotypes on survival time using PROC PHREG. All models were adjusted for gender and age at enrollment. Several diagnostic metrics were used to confirm that the assumption of proportional hazards for each model was met, including examination of log negative–log survival curves and plots of Schoenfeld residuals (<http://support.sas.com/resources/papers/proceedings13/428–2013.pdf>) as well as testing the interaction between each clinical predictor and survival time. Only LDH was found to violate the proportional hazards assumption.

Results

Baseline characteristics

Our study included 542 subjects. The median age at enrollment was 32 years (range, 18–84 years). Of these, 427 subjects (78.8%) had Hb SS, 70 (12.9%) had Hb SC, 23 (4.2%) had $S\beta^+$, and 22 (4.1%) had $S\beta^0$. Median follow-up time was 9.3 years (range, 2.7–10.5 years). At the conclusion of the study, 128 participants (23.6%) had died. The median age at death was 47 years for females, 44 years for males, and 45 years overall (range, 20–86 years), as shown in Supporting Information Table SI. Median survival was 61 years for all subjects, with no difference between males and females.

Table I and Supporting Information Table SII show baseline clinical characteristics of our cohort. Among our population, 79.4% had graduated high school. Tobacco use was reported by 34.2%. Approximately 42% of all subjects and 45% of subjects with Hb SS and $S\beta^0$ were on hydroxyurea at the onset of the study. Eighteen percent of HbSC and 31% of subjects with Hb $S\beta^+$ thalassemia were also taking hydroxyurea.

Survival data

Hemoglobin genotype. Among sickle cell genotypes, survival curves demonstrated that Hb SS and $S\beta^0$ portended the worst prognoses, followed by Hb SC and $S\beta^+$ (Fig. 1A). Overall median survival for Hb SS and $S\beta^0$ was 58 years and for Hb SC and $S\beta^+$ was 66 years, a difference that was statistically significant ($P = 0.0031$). In subjects with Hb SS, the median age at death was 44.5 years and 25.3% of the subjects had died by the conclusion of the study, whereas subjects with Hb $S\beta^0$ had a median age at death of 43 years

TABLE II. Hazard Ratios for Clinical Characteristics Reported as Dichotomous Variables

Characteristic	N with characteristic	N total	Hazard ratio	95% confidence interval	P-value
Medical history					
Pulmonary hypertension ^a	73	222	2.34	1.32–4.14	0.0036
Diastolic hypertension ^b	96	374	0.86	0.53–1.39	0.5308
Systolic hypertension ^b	97	374	1.11	0.66–1.85	0.6964
ACS	354	475	1.27	0.81–1.99	0.2945
CHF	28	470	1.51	0.81–2.84	0.1949
O ₂ saturation < 92%	21	333	0.88	0.38–2.06	0.7716
Leg ulcer	112	464	1.66	1.12–2.47	0.0118
AVN	150	461	0.84	0.57–1.25	0.3939
Proteinuria	124	460	1.86	1.27–2.73	0.0014
Cerebrovascular event	122	458	1.95	1.34–2.83	0.0005
Stroke	73	465	1.64	1.04–2.58	0.0335
Seizure	57	474	2.54	1.62–3.98	<0.0001
TIA	18	455	1.85	0.93–3.70	0.0803
Retinopathy	103	443	0.78	0.50–1.22	0.2815
Pain crisis in past year ^c	256	459	1.74	1.18–2.58	0.0054
Priapism	80	215	1.15	0.64–2.07	0.6348
Surgical history					
Splenectomy	48	378	1.51	0.87–2.64	0.1453
Cholecystectomy	257	383	1.03	0.67–1.59	0.8862
Medications					
Hydroxyurea ^d	172	386	0.82	0.55–1.22	0.3228
Bronchodilators	27	448	1.08	0.53–2.23	0.8309
Desferol	21	447	1.27	0.61–2.67	0.5271
Antihypertensives	73	447	1.74	1.10–2.73	0.0168
Antidepressants	43	447	1.55	0.81–2.97	0.1827
Narcotics (< daily)	379	477	1.30	0.81–2.09	0.2807
Long-acting narcotics (daily)	120	374	1.20	0.80–1.82	0.3811
Short-acting narcotics (daily)	144	345	1.55	1.02–2.36	0.0395
Long-acting narcotics only (daily)	42	342	1.07	0.58–1.98	0.8268
Short-acting narcotics only (daily)	66	342	1.60	1.01–2.56	0.0475
Long- and short-acting narcotics (daily)	75	342	1.15	0.72–1.86	0.5571
Long- or short-acting narcotics (daily)	189	348	1.68	1.08–2.61	0.0204
Acetaminophen	23	372	1.69	0.87–3.31	0.1244
Migraine therapy	4	446	1.17	0.16–8.52	0.8783

Hazard ratios > 1 reflect increased risk of death.

^a Defined as tricuspid regurgitant velocity ≥ 2.5 m/sec by echocardiography.

^b Trait is defined as the top quartile of patients in our sample.

^c Defined as pain crisis requiring inpatient admission within 1 year.

^d Calculated in Hb SS and Hb S β^0 patients only.

Bold signifies statistical significance.

and 40.9% mortality. However, these differences were not statistically significant ($P = 0.2188$).

Table II shows hazard ratios for dichotomous variables (reported as “present” or “not present”), and Table III shows hazard ratios for continuous variables.

Hematologic. As expected, low Hb was associated with poorer survival: for every gram per deciliter decrease in Hb, the HR increased by 1.2077 ($P = 0.0043$). However, this association disappeared when correcting for glomerular filtration rate (GFR). In addition, with every $10^3 \mu\text{L}^{-1}$ increase in WBC, the calculated hazard ratio increased by 1.059 ($P = 0.0419$). Hemolytic index was not a statistically significant factor in survival among subjects with HbSS and HbS β^0 (Table III).

Cardiopulmonary. Cardiopulmonary disease is known to be the primary etiology of death in adult subjects with SCD [27]. In our sample, pHTN was present in 32% of subjects with SCD. In our survival analysis, this proved to be a poor prognostic factor (HR = 2.3386, $P = 0.0036$). Similarly, elevated N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was a marker of early death (HR = 1.617, $P = 0.0004$). Although a diagnosis of hypertension did not correlate with early mortality, subjects with SCD who were on chronic antihypertensive therapy did suffer earlier death than their counterparts.

Neurologic. A history of neurologic disease was present in 32% of subjects and correlated with early mortality. A history of any cerebro-

vascular event, defined as at least one stroke, seizure, or TIA, was associated with decreased survival (HR = 1.9464, $P = 0.0005$). When analyzed individually, stroke (HR = 1.6373, $P = 0.0335$) and seizure (HR = 2.5369, $P < 0.0001$) were still associated with poor prognosis.

Renal. The presence of $\geq 1+$ proteinuria by dipstick, observed in 26% of our sample, was an indicator of decreased longevity (HR = 1.8618, $P = 0.0014$). An association between renal function and decreased survival was corroborated with estimated GFR [28], which demonstrated that the risk of death increased with worsening GFR (HR = 1.068 per ml/min decrease in GFR, $P < 0.0001$).

Hepatobiliary. As shown in Table I, gall bladder disease and cholecystectomy were among the most frequent comorbid conditions found in our subjects with SCD. However, none of the hepatobiliary disease measures evaluated in our study were associated with survival.

Musculoskeletal/cutaneous. Leg ulcers were a predictor of early mortality (HR = 1.6631, $P = 0.0118$). Avascular necrosis, although common with a prevalence of 32%, had no impact on prognosis.

Pain. As shown in Table II, having at least one crisis in the last year was associated with decreased survival (HR = 1.744, $P = 0.0054$, 95% CI = 1.18–2.58). In our cohort, 56% had suffered at least one pain crisis in the prior year, and 15% of those were hospitalized greater than four times. Survival was significantly lower in those who had experienced greater than four crises when compared with those

TABLE III. Hazard Ratios for Characteristics Measured as Continuous Variables Including All Genotypes

Trait	N	Hazard ratio	P-value
Hemoglobin (off HU)	362	1.21	0.0043
Hemoglobin (off HU) adjusted for GFR	319	0.93	0.3277
Hemoglobin (on HU)	168	1.36	0.0107
Hemoglobin (on HU) adjusted for GFR	157	0.83	0.1785
WBC (off HU)	351	1.06	0.0419
WBC (on HU) ^a	168	1.63	0.3181
Platelets (off HU)	350	1.00	0.9402
Platelets (on HU) ^a	167	0.65	0.3066
Fetal hemoglobin (off HU) ^a	180	1.00	0.9954
Fetal hemoglobin (on HU) ^a	124	0.79	0.3199
Ferritin ^a	153	1.27	0.0628
Mean corpuscular volume (off HU)	361	1.01	0.5220
Mean corpuscular volume (on HU)	168	1.02	0.2582
Lactate dehydrogenase ^a	382	0.82	0.1621
Reticulocytes (off HU) ^a	313	1.01	0.9663
Hemolytic index ^b	313	1.10	0.3206
Total bilirubin	410	1.01	0.8887
GFR	414	1.07	<0.0001
Body mass index	343	0.98	0.3138
Body mass index adjusted for HU	317	0.98	0.2711
NT-pro-BNP ^a	87	1.62	0.0004
sICAM-1	87		0.1376
sVCAM-1	87	2.03	0.0003
E-Selectin	87		0.1513
P-Selectin	87		0.8673
sCD40L	87		0.8235
IL-6	87		0.6459
IL-8	87		0.9505
IL-10	87		0.5447
TNF- α	87		0.5876

Abbreviation: HU, hydroxyurea.

^a Variables converted to logarithmic scale.

^b Calculated in subjects with Hb SS and Hb S β^0 only.

Bold signifies statistical significance.

with less than four crises (HR = 2.1849, $P = 0.0006$; Fig. 1B). These results were consistent when restricting the analysis to only subjects with Hb SS or S β^0 . Similarly, some patterns of narcotic use were related to decreased survival as shown in Table II.

Biomarkers. Of the evaluated adhesion molecules and inflammatory markers shown in Table III, only sVCAM-1 levels were associated with decreased survival (HR = 2.032, $P = 0.0003$). This association was also observed when including only subjects with SS or S β^0 (HR = 1.949, $P = 0.0009$).

Hydroxyurea. Hydroxyurea has previously been shown to decrease mortality in subjects with SCD [29]. Survival of subjects with Hb SS or S β^0 using hydroxyurea therapy was compared with those subjects not using hydroxyurea, and no difference in survival was observed ($P = 0.3228$). This analysis was extended to compare hydroxyurea among subjects with the previously mentioned comorbidities, and no significant improvement in survival was observed among subjects with specific comorbidities.

Organ system severity score. For 493 subjects with SCD, a severity score of 0–5 was calculated to assess damage to multiple end organs, as defined in the “Methods” section. One hundred forty-four subjects had a severity score of “0,” 175 scored “1,” 104 scored “2,” 56 scored “3,” and 14 subjects scored “4.” No subjects had a severity score of “5.” Subjects with a score of 0–1 had a favorable prognosis when compared with those with scores of >1 (HR = 1.502, $P = 0.0263$; Fig. 1C).

Discussion

Previous studies have reported an expected survival of 42–48 years in subjects with Hb SS and 60–68 years in subjects with Hb SC [6].

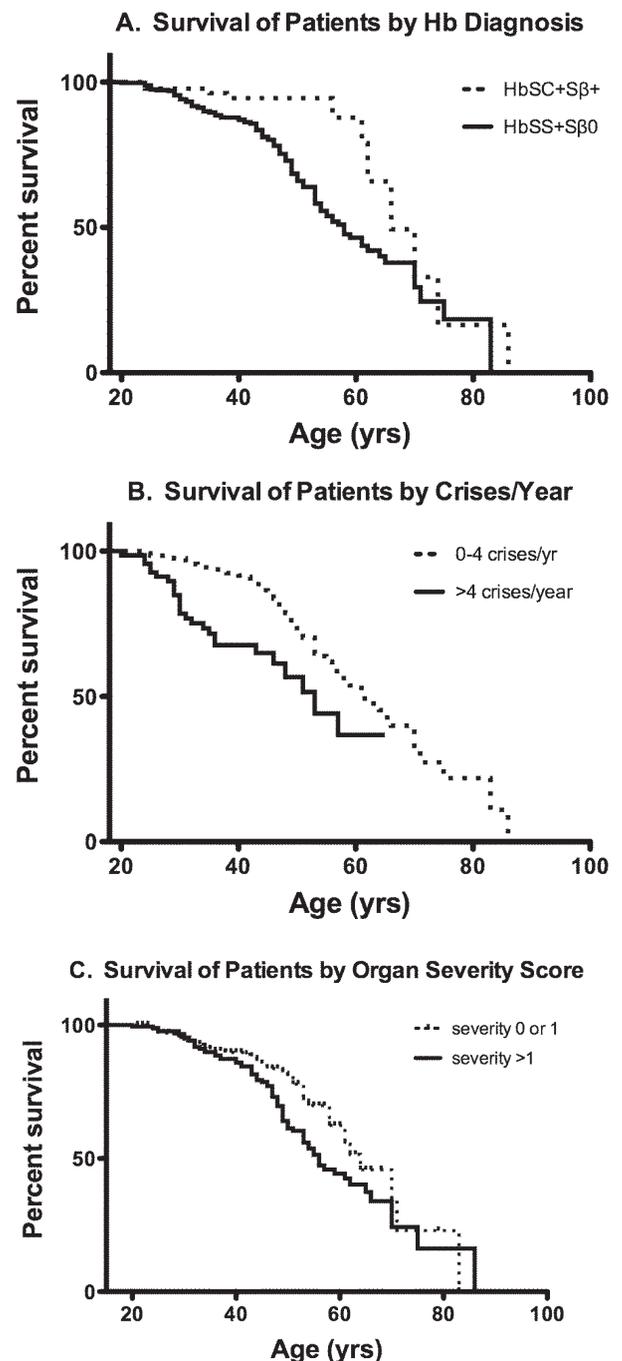


Figure 1. A: Survival curves by genotype. Hb SS and S β^0 thalassemia subjects (solid line) had a median survival of 58 years. Hb SC and S β^+ thalassemia subjects (dotted line) had a median survival of 66 years. The difference between curves is significant ($P = 0.0031$). B: Survival curves by frequency of vaso-occlusive pain crises defined as a crisis requiring inpatient admission. For subjects with 0–4 pain crises per year (dotted line), median survival was 61 years. For subjects with >4 crises per year, median survival was 53 years. Hazard ratio was 3.6982 ($P < 0.0001$). C: Survival curves by organ severity score. Degree to which subjects had organ-specific sequelae of SCD was rated on a scale of 0–5, as described; no subject had a score of >4. Median survival for subjects with a score of 0–1 (dotted line) was 64 years and for subjects with a score >1 was 56 years. Hazard ratio between the two curves was 1.502 ($P = 0.0263$).

Based on our hazard estimates, median survival in our population is now 58 years for Hb SS and S β^0 and 66 years for Hb SC and S β^+ . These data suggest that medical progress over the last 10–20 years

has led to improvement in the overall survival for patients with Hb SS and S β^0 .

However, these data must be considered with caution. Our study only enrolled adult patients with sickle cell. This exclusion of pediatric patients with sickle cell, a small number of whom die in childhood, may have caused some inflation in our survival estimates. However, recent data have shown that SCD-related survival to adulthood is nearly 94% [5], suggesting that exclusion of the pediatric population should not have drastically improved our survival estimates. Second, 6.18% of our original study population was lost to follow-up when we performed our “look back” for survival. However, it is the impression of the centers involved that most subjects lost to follow-up had simply moved away, although this cannot be rigorously confirmed. Additionally, the patient population studied was limited to a cohort of patients from the southeastern United States. Thus, regional variations in comorbid conditions, such as rates of obesity or tobacco use, might limit the generalizability of our findings to the entire country. Finally, our subject population, consisting of patients from three referral centers, may be skewed toward a higher severity of disease than that exists in the community.

In our evaluation of hematologic parameters, Hb level predicted survival, with the risk of early death inversely correlated to the baseline Hb level. The degree of WBC elevation was similarly related to survival, with a higher level predicting a shorter survival. However, when hazard ratios for Hb were corrected for GFR, the detected relationship was no longer statistically significant. This may suggest that Hb is a biological marker for the effect of kidney disease on survival and not independently associated with survival. In contrast to prior studies [2,6], Hb F level did not correlate with mortality in our study, even after controlling for hydroxyurea use.

With improvements in antibiotics and vaccination, the primary cause of death among patients with SCD has shifted from infection to cardiopulmonary disease [27]. Our study was not intended to identify the cause of death, but cardiopulmonary disease was clearly a risk factor for early death. Specifically, elevated TR jet velocity (≥ 2.5 m/sec) and pro-BNP levels were strongly associated with poor survival. Although our study used echocardiography rather than right heart catheterization to identify subjects with possible or presumed pHTN, thus likely identifying some patients without true pulmonary arterial hypertension [30,31], the use of TR jet velocity is a less invasive surrogate for evaluation with $\sim 25\%$ of positive predictive value in patients with SCD [31]. Moreover, our results are consistent with prior studies showing an association between presumptive pHTN, defined similarly by TR jet velocity ≥ 2.5 m/sec, and early mortality, and are furthermore corroborated by the significance of an elevated pro-BNP in our analysis [32].

Treatment with antihypertensive medications was a poor prognostic factor. This is not surprising, because patients who require antihypertensive medications likely had more severe hypertension and potentially other secondary comorbidities. However, to further evaluate this finding, we compared subjects in the highest quartile for both systolic and diastolic blood pressure to the rest of our sample and found no difference in survival. Finally, the relationship of antihypertensive medication use to survival was no longer significant when analyzed with GFR as a covariate. Hence, as some antihypertensives (specifically ACE inhibitors) are used for renal protection in the setting of proteinuria, the prognostic significance of these medications may reflect underlying kidney disease. Nevertheless, our findings do support the need for future studies addressing therapeutic goals for blood pressure levels and preferred approaches to antihypertensive therapy and proteinuria in patients with SCD.

Pulmonary comorbidities were not related to survival in our sample. The most notable of these was history of ACS, which has been a well-documented prognostic factor in prior studies [6,32]. In our methodol-

ogy, history of ACS was determined by patient report of ACS or pneumonia, thus leading to some inherent inaccuracy in the reported prevalence of ACS. Patients who died from ACS prior to enrollment could not be included in the analysis. Hence, our results cannot be used to show that ACS does not influence survival. Instead, our findings suggest that there is no change in the long-term survival of patients with SCD who survive an episode of ACS. In addition, asthma, as identified by the use of bronchodilators, also did not affect survival.

During episodes of inflammation and endothelial injury, such as vaso-occlusive crises, endothelial adhesion molecules are released into the plasma [20]. Hence, we anticipated that elevations in soluble adhesion molecules would also be related to severity of SCD and would prove useful in predicting early mortality. Indeed, in this respect, we have confirmed the findings of Kato et al. [33] that elevated sVCAM-1 is clearly related to poor prognosis. This raises the possibility that underlying vascular damage and inflammation is a primary facilitator of early death in patients with SCD and that future treatments targeting these inflammatory processes may prove to be life prolonging.

Our results also underscore the significance of pain in the natural history of SCD. We have shown associations between survival and pain frequency, hospitalizations due to pain, and narcotic use, consistent with prior studies [6]. However, the effects of pain on survival may not be reversible by improvements in pain management alone. Greater frequency and severity of pain may reflect more severe underlying disease. Furthermore, the relationship between narcotic use and decreased survival may reflect direct adverse effects of the medications such that more aggressive analgesia could worsen survival. Still, adequate management of SCD pain could yield improvements to patient's quality of life [34], and prevention of acute pain episodes might also be an effective strategy for decreasing healthcare costs [35].

Assessment using our previously developed organ severity score [26], based on the number of affected organ systems, also showed that, with each additional organ system affected, survival decreased. The largest incremental risk increase occurred as patients moved from two involved organ systems to three. Escalation of the severity score from three organ systems to four did not affect prognosis. However, because of the small number of patients with a severity score of four, we likely lacked adequate statistical power to detect significant differences in that analysis.

As we used a cross-sectional design, there are many limitations to our study. Our analysis could only assess associations between survival and characteristics present at baseline without proving causality. Additionally, we cannot determine whether subjects developed new comorbid conditions during the follow-up period or whether these influenced prognosis. Moreover, our design cannot be used to determine the risk of death from acute complications of SCD such as ACS, strokes, or seizures. Instead, we hope our results will help to predict the expected survival of patients with SCD who have survived such complications previously. Finally, the use of hydroxyurea was neither randomized nor monitored, thus, findings regarding the effects of this medication may not reflect ideal use or comparable populations.

In conclusion, our survival data highlight improvements in overall survival in patients with SCD over the last decade. Despite this progress, patients with SCD continue to experience decreased quality of life and, ultimately, a shortened life span when compared with the general population. Thus, there is a dire need for new therapeutic options. Although we have identified several predictors of decreased survival, the question remains whether treatments targeted at these factors would improve mortality. As emerging but riskier therapies such as bone marrow transplant and gene therapy begin to offer hope for a potential cure [36], our results may be useful to help identify high-risk patients most in need of these therapies. Furthermore, although we have identified phenotypes associated with prognosis, it

nevertheless remains unclear why the overall course of SCD is so varied across the patient population. Future studies identifying genetic variations associated with more severe phenotypes and overall survival could provide a dramatic improvement in our understanding of SCD, as well as unveil novel therapeutic targets.

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