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Cardiopulmonary Complications Leading to Premature Deaths in Adult Patients with Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) is associated with early mortality. We sought to determine the incidence, cause, and risk factors for death in an adult population of patients with SCD. All patients aged ≥18 years seen at the Adult Sickle Cell Center at Duke University Medical Center between January 2000 and April 2005 were enrolled. Forty-three patients (21 males and 22 females) died during the study period. Median age of survival was 39 years for females (95% CI 34–56), 40 years for males (95% CI 34–48), and 40 years overall (95% CI 35–48). Cardiac causes of death accounted for 25.6% (11/43 patients); pulmonary, 14.0% (6 patients); other SCD related, 32.6% (14 patients); unknown, 14.0% (6 patients); and others, 14.0% (6 patients). Pulseless electrical activity arrest, pulmonary emboli, multi-organ failure, and stroke were the most frequent causes of death. Among the deceased patients, the most common pre-morbid conditions were cardiopulmonary: ACS/pneumonia (58.1%), pHTN (41.9%), systemic hypertension (HTN) (25.6%), congestive heart failure (CHF) (25.6%), myocardial infarction (20.9%), and arrhythmias (14.0%). Tricuspid regurgitant jet velocity (TRv) was significantly higher (3.1 m/s vs. 2.6 m/s, $p<0.001$) and hemoglobin significantly lower (8.3 g/dL vs. 9.2 g/dL, $p<0.05$) in deceased patients as compared to patients who lived, respectively. With improved preventive and therapeutic advances, including hydroxyurea therapy, acute complications such as infection are no longer the leading cause of death; instead causes of death and pre-morbid conditions are shifting to chronic cardiopulmonary complications. Further, arrhythmia leading to premature death is under-recognized in SCD and warrants further investigation.

Keywords

sickle cell disease; adult; mortality; risk factors; cardiopulmonary complications

Introduction

Since sickle cell disease (SCD) was first discovered in the early twentieth century and then attributed to a genetic mutation causing abnormal hemoglobin chemistry in 1949–1950,

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mortality has decreased substantially. In 1973, Diggs estimated a median survival of 14.3 years, with one third of the deaths occurring before age 5, half between ages 5 and 30 years, and one sixth occurring after age 30(1–3). By 1989, Leikin reported that the probability of patients with SCD who were at least 2 months of age surviving to age 20 years was approximately 85%(4). Powars and colleagues also reported that childhood survival to age 20 years improved from 79% for patients born before 1975 to 89% for children born in or after 1975(5). This improvement in mortality among pediatric patients was attributed to early parental education and counseling, early antibiotic administration for febrile episodes, penicillin prophylaxis, and widespread adoption of newborn screening programs for SCD(4, 6–8).

In 1994, prior to the widespread use of hydroxyurea, Platt et al studied patients with SCD who ranged from birth to 66 years of age(9). They reported a median age at death of 42 years for males and 48 years for females with sickle cell anemia, and 60 years for males and 68 years for females with hemoglobin (Hgb) SC disease. Further, they found that in patients with sickle cell anemia, renal failure, seizures, ACS, a low fetal Hgb level, and a baseline white blood cell count greater than 15,000 cells per cubic millimeter were associated with decreased survival. Hydroxyurea has been shown to decrease the frequency of painful crises, episodes of ACS, and the need for transfusions(10), and has also been shown to improve survival among adult patients with SCD(11). Pulmonary hypertension (pHTN), thought to be due in part to chronic hemolysis and is resistant to hydroxyurea therapy, may at least be partially responsible for a significant proportion of sudden and unexplained deaths(3, 12–17); asthma(18) and diastolic dysfunction(19) were additional risk factors that portend early death. Thus, new mortality data, particularly in the context of widespread hydroxyurea administration among patients with SCD throughout the United States, are needed. Further, as systemic HTN has recently been found to be associated with pulmonary HTN and renal failure(20), identification of potentially reversible comorbidities is also vital in order to decrease mortality in patients with SCD.

Deaths among patients with SCD are often unexpected and sudden(12, 21–25). In one series of 306 autopsies of patients with SCD, death was noted to be sudden and unexpected in 40.8%(24). And while the most common causes of death in adult patients with SCD have been reported to be ACS, infection, stroke, pHTN, and sickle cell-related lung injury(9, 11, 13–15, 23–29), the cause of death is commonly unknown(24, 27, 28, 30).

Despite evidence that the risk of serious arrhythmias is significantly increased during vasoocclusive crises(31), the frequency of sudden cardiac death in patients with SCD has been scantily studied. Since sudden cardiac death has been prevented in other high-risk patient populations with implantable cardioverter defibrillator therapy(32, 33), the frequency of sudden cardiac deaths in patients with SCD should be determined, in order to assess the possible need for a similar approach. Therefore, we sought to describe the causes of death in our adult sickle cell population at Duke University Medical Center (DUMC) over a 5 year period. We report the median age of survival and the associated comorbidities of the patients who died, and also attempt to identify risk factors associated with premature death.

Results

Clinical characteristics of deceased and living patients

Of the 240 adult patients with SCD who were followed at DUMC from January 2000 through April 2005, 43 patients died. There were an equal number of men and women when comparing the group of subjects who died to the subjects who lived (Table I). The majority of patients in each group had Hgb SS disease, followed by Hgb SC disease. The median age at death in the deceased patients was 39 years (range 21 to 83 years) compared to a median

age at last follow-up of 34 years in the group of patients who are still living (range 19 to 85 years); p<0.03 (Table I). When compared by gender, the median age differed between the 2 studied groups, but only reached statistical significance for the female subjects (43 vs. 36 years for deceased and living subjects, respectively; p=0.02). Three patients lived to be greater than 70 years of age (2 patients in the living group, one patient age 85 years with Hgb SC disease and one patient age 73 years with Hgb SS disease, and 1 patient in the deceased group with Hgb $S\beta^+$-thalassemia disease lived to be age 83 years). Eight of the patients were less than thirty years old when they died. The percentage of patients who were treated with hydroxyurea was not significantly different between the 2 groups studied (p= 0.06) (Table II).

Survival analysis

The median age of survival, calculated using Cox regression, was 40 years (95% CI 35–48). There was no significant difference between males (median 40 years, 95% CI 34–48) and females (median 39 years, 95% CI 34–56).

Cardiopulmonary and laboratory risk factors for death

Transthoracic echocardiograms were performed in 74% of the deceased and 64% of the living patients (Table II). The median TRv was 3.1 m/s in the patients who died, as compared to 2.6 m/s in the patients who lived, and pHTN was more prevalent in the deceased than in the living patients (56% vs. 26%, respectively, p < 0.001; (Table II, Figure 1). Further, deceased patients were significantly more anemic than the living patients (Hgb level 8.3 g/dL vs. 9.2 g/dL, respectively, p = <0.05). Ejection fractions were not statistically different between patients who died and patients who were still living, and the degree of fractional shortening did not differ between the two groups. The left ventricular size, percentage of patients with prolonged QTc intervals, white blood cell (WBC) count, and oxygen saturation were also not significantly different between the patients who died and the patients who lived (Table II). Ferritin levels measured while at steady state in 26 deceased patients, ranged from 69 to 7440 mcg/L. Fourteen patients had ferritin levels ≥ 1000 mcg/L, and eight had ferritin levels measuring ≥ 2000 mcg/L. Average ferritin levels were higher in patients with cardiac complications as compared to those patients without cardiac complications, though the difference was not statistically significant (2319 mcg/L vs. 1664 mcg/L, respectively, p= 0.454). Ferritin levels were not measured in five patients that have a history of cardiac complications.

Causes of death

As shown in Table III, cardiopulmonary causes accounted for 17 of 43 deaths (39.5%). The most common cause of death was cardiac in origin, pulseless electrical activity arrest. The other causes of death attributable to SCD were stroke, multi-organ failure, liver failure, renal failure, anoxic brain injury, and “sickle cell anemia”, totaling 14 (32.6%). Other causes of death included narcotic overdose, assault, complications after fall, foreign body aspiration, and intestinal disorder, totaling 6 (14.0%). The cause of death for six of the patients is unknown (14.0%).

Associated pre-morbid conditions

Medical complications often overlapped in both studied groups, and cardiopulmonary complications were frequent. The most common cardiopulmonary manifestations included ACS/pneumonia, pHTN, systemic hypertension (HTN), CHF, and stroke (Table IV). ACS and pneumonia did not necessarily predict pHTN and vice versa (data not shown). Deceased subjects were more likely to have a history of pHTN (p=0.001) and CHF (p=0.003), but not ACS/pneumonia and stroke. Some patients also had a history of cardiac arrhythmias, such as

atrial fibrillation, supraventricular tachycardia, and nonfatal ventricular fibrillation. Atrial fibrillation was significantly more prevalent in deceased subjects (p=0.004). The most frequent sickle cell-related complications included cholethiasis, proteinuria, avascular necrosis, and renal insufficiency. Proteinuria, renal insufficiency, and avascular necrosis occurred significantly more frequently in deceased subjects (Table IV).

Discussion

Platt et al reported in 1994 a median age of death of 42 years in adult patients with SCD(9). In contrast to Platt's study, where age of death was determined from birth, patients in our study had to have survived to the age of 18 years to be included. Therefore, the patients in Platt et al's work and our study represent two different populations and our median survival age cannot truly be compared. More recently based on an analysis from birth, Powars reported a median age of survival of 36.3 years for female patients and 38.7 years for male patients with SCD(5). The median survival ages from our study agree fairly well with the results by Platt et al and Powars, if 95% confidence intervals are considered. Further, Steiner el al have reported that in-hospital deaths and death rate in United States hospitals remained stable for adult patients with SCD from 1998–2004 as compared to 1994–1997(34). A likely explanation is that the causes of death are shifting from acute to chronic sickle-related complications.

Our results, representing an institution that specializes in the care of adult patients with SCD, show that a large proportion of the deaths were not from classic acute sickle-related complications. The most common known causes of death in our patient population while related to SCD were cardiopulmonary in nature, totaling 17 of 43 patients (39.5%) and the most prevalent was pulseless electrical activity arrest. This is likely in part secondary to hypoxia, myocardial infarction, CHF, and pulmonary disorders,. The other known causes of death included single or multi-organ failure (6 patients) and stroke (4 patients). Our findings are compatible with Steinberg et al(11), who showed that 21 of their 75 deaths were due to pulmonary diseases, with SCD crisis and stroke each accounting for an additional 9 and 6 patients. Steiner and Miller(34) also reported that of 113,098 hospital stays in the United States during which SCD was noted, cardiac and respiratory conditions accounted for 15% of deaths. Powars and colleagues reported that of 232 patients that died, the most common cause of death was chronic lung disease with pulmonary HTN and cor pulmonale in 47 patients (20%), and 12 of those patients had evidence of myocardial ischemia and fibrosis. An additional 7 patients (3%) died from cardiovascular disease(5). These studies collectively suggest that in the post-hydroxyurea era, acute non-sickle-related complications leading to death may become the most prevalent.

Three of the deceased patients in our study had a history of myocardial infarction, suggesting that a small proportion of SCD patients will develop this lethal disease; however, its clinical manifestations appear to be different than in patients without SCD. Exercise testing has a low positive predictive value of myocardial ischemia(35). Sickle vasculopathy has been shown to have many parallels with atherosclerosis, including endothelial activation and dysfunction, platelet activation, in situ thrombosis, and disordered apolipoproteins(36). Still, patients with SCD who are found to have evidence of myocardial infarction on autopsy generally have no signs of coronary atherosclerotic disease(35, 37–40). This lack of atheroma formation may be due to the significantly decreased total cholesterol and low-density lipoprotein levels that occur in patients with SCD(36).

The cause of death for six of the patients remains unknown. In addition, the cause of death listed on death certificates for three patients was "sickle cell anemia." In past clinical series, the cause of death was stated as "unknown" or as "sickle cell disease" in 7–75% of cases(5,

24, 27, 28, 30). This high proportion of ill-defined causes of death is thought to be secondary to the absence of uniformity in data collection and analyses among medical centers, lack of morphological evidence of some fatal physiological event, and insufficient interest, time, and/or resources for a more in-depth evaluation of the specific causes of death(24). From our experience, even when the exact circumstances surrounding death were detailed, the exact cause of death was frequently difficult to decipher.

The pattern of pre-morbid conditions of SCD seen in our deceased patients (Table IV) were similar to previous reports, with ACS/pneumonia, cholethiasis, pHTN, and avascular necrosis at the top of the list. However, chronic conditions such as proteinuria, renal insufficiency, systemic HTN, and CHF were also very common. Further, many cardiopulmonary complications such as pHTN, CHF, myocardial infarction, and atrial fibrillation, and chronic conditions such as sickle cell nephropathy occurred significantly more commonly in deceased as compared to living patients. These observations suggest that while hydroxyurea may reduce acute sickle-related complications, end-organ damage continues to be very prevalent in this patient population.

In our study, seven patients had a history of significant cardiac arrhythmias, including five patients with atrial fibrillation, one with supraventricular tachycardia, and one with a history of ventricular fibrillation arrest. Inadequate blood supply to areas with fibromuscular dysplasia, microthrombosis, hypoxemia, and rheological abnormalities(41) may lead to the development of fatal cardiac arrhythmias. The demonstration of both recent and old areas of fibrosis and degeneration near the cardiac conduction system suggests a chronic process. The risk of serious arrhythmia is increased during vasoocclusive crisis, as Maisel et al. demonstrated significant arrhythmias in 24 of 30 patients with continuous electrocardiographic monitoring during a vasoocclusive episode(31). Further, they detected atrial and ventricular arrhythmias in 60 and 67% of patients, respectively, via 12-lead and 24-hour ambulatory electrocardiograms during vasoocclusive crisis. Nine of the 30 patients had “complex arrhythmias,” including two patients with ventricular tachycardia. Early detection of serious electrical disturbance may decrease the incidence of sudden cardiac death in patients with SCD.

Sudden cardiac death has been treated successfully in high-risk populations with implanted cardioverter defibrillators (ICD). Initial studies using the ICD focused on patients with ischemic cardiomyopathy and history of acute myocardial infarction(32, 33). More recently, the sudden cardiac death in heart failure trial (SCD HeFT) has extended the use of ICD therapy to patients without previous myocardial infarction(42). These patients had heart failure due to left ventricular dysfunction and no other risk for sudden cardiac arrest. Nevertheless, ICD therapy was effective in preventing all cause mortality and sudden cardiac arrest. The key element in the success of ICD therapy has been the identification of a patient population at risk for sudden cardiac arrest and subsequent placement of an ICD. In our SCD patient population, usual risk factors for sudden cardiac death, including decreased ejection fraction and increased left ventricular size, were not significantly different between patients who were living and deceased. Further study is indicated to identify cardiac risk factors associated with increased mortality such that a select group of patients with SCD can be followed more closely and be exposed to more aggressive and invasive clinical interventions as deemed necessary if we hope to be successful in preventing premature death.

Increased anemia was found to be a risk factor for early death in our study. Sebastiani et al. have shown that an elevated lactate dehydrogenase level, due to hemolysis, contributed to an increased risk of death in patients with SCD(43). Baseline WBC and oxygen saturations were not significantly different between deceased and living patients. The presence or

absence of α-thalassemia was not available for our study groups. Platt and colleagues previously reported that α-thalassemia status was not associated with mortality in patients with SCD. Fourteen of the deceased patients had evidence of iron overload, with ferritin levels ≥ 1000 mcg/L, as a result of chronic transfusion therapy. Although our patients with history of cardiac complications had higher ferritin levels, this difference was not statistically significant. As ferritin levels do not correlate well with hepatic iron concentration and may not be a reliable marker of iron stores in patients with SCD(44, 45), our patients with cardiac complications may indeed have higher iron stores, contributing to the observed cardiac complications and premature mortality in our patients. In contrast to studies performed in patients with thalassemia(46, 47), severe iron overload has not been found to be associated with cardiac arrhythmias and CHF in patients with SCD. However, studies have shown that chronically transfused patients with SCD have increased mortality as compared to non-transfused patients with SCD(48, 49), though the contribution of iron overload to this increased mortality is difficult to decipher. Further, the ferritin level has been found to be a univariate predictor of death in patients with SCD(50).

In conclusion, despite advances in medical therapy, patients with SCD continue to die prematurely. Our patients died most commonly from cardiopulmonary disease and multi-organ failure, shifting from the previously reported infectious and sickle cell-related causes of death. As acute complications of SCD are ameliorated by hydroxyurea, end-organ damage continues to accumulate. Further studies are indicated to determine which patients should be aggressively treated to prevent early fatal cardiopulmonary complications.

Methods

Patient population

All patients aged 18 years and older who were followed at the Adult Sickle Cell Center at DUMC between January 2000 and April 2005 were enrolled in the study. The Institutional Review Board issued a consent waiver to allow the review of their DUMC medical records.

Laboratory and clinical data

Clinical, laboratory, and radiologic information, including type of SCD, age at death, cause of death, place of death, comorbidities, medications, complete blood count, ferritin, creatinine, urinalysis, oxygen saturation, electrocardiograms, and echocardiograms were reviewed. Variables, including patient age, baseline Hgb and WBC, left ventricular function, left ventricular size, QTc, and TRv, were compared between the patients who had died and those who were living. pHTN is defined as a TRv of at least 2.5 meters per second.

Cause of death was obtained from medical records at DUMC. If a patient died outside of DUMC, death certificate information was obtained from the medical examiner when available.

Statistical analysis

Statistical analyses, including evaluation of means, standard deviation, Fisher's exact t-test and the chi-squared test, were performed. P-value <0.05 was considered statistically significant. The Cox regression model was used to analyze age of survival. The age at entry (January 2000) was used for left censoring and the age at last follow up for right censoring. Median survival ages and their confidence intervals were calculated for each group from the survival functions.

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References

1. Diggs, LM. Sickle cell disease: diagnosis, management, education and research. Mosby: St. Louis; 1973. p. 189-229.
2. Schultz WH, Ware RE. Malignancy in patients with sickle cell disease. Am J Hematol. 2003; 74:249–253. [PubMed: 14635205]
3. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. Blood. 2003; 101:1257–1261. [PubMed: 12393669]
4. Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics. 1989; 84:500–508. [PubMed: 2671914]
5. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore). 2005; 84:363–376. [PubMed: 16267411]
6. Davis H, Schoendorf KC, Gergen PJ, Moore RM Jr. National trends in the mortality of children with sickle cell disease, 1968 through 1992. American journal of public health. 1997; 87:1317–1322. [PubMed: 9279267]
7. From the Centers for Disease Control and Prevention. Mortality among children with sickle cell disease identified by newborn screening during 1990–1994--California, Illinois, and New York. JAMA. 1998; 279:1059–1060. [PubMed: 9546552]
8. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. Blood. 2004; 103:4023–4027. [PubMed: 14764527]
9. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. The New England journal of medicine. 1994; 330:1639–1644. [see comments]. [PubMed: 7993409]
10. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. The Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. The New England journal of medicine. 1995; 332:1317–1322. [PubMed: 7715639]
11. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringer E, Bellevue R, Olivieri N, Eckman J, Varma M, Ramirez G, Adler B, Smith W, Carlos T, Ataga K, DeCastro L, Bigelow C, Saunthararajah Y, Telfer M, Vichinsky E, Claster S, Shurin S, Bridges K, Waclawiw M, Bonds D, Terrin M. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA. 2003; 289:1645–1651. [PubMed: 12672732]
12. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, Orringer EP. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol. 2006; 134:109–115. [PubMed: 16803576]
13. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder WC, Schechter AN, Rodgers GP, Castro O, Ognibene FP. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. The New England journal of medicine. 2004; 350:886–895. [PubMed: 14985486]
14. Hagar RW, Michlitsch JG, Gardner J, Vichinsky EP, Morris CR. Clinical differences between children and adults with pulmonary hypertension and sickle cell disease. Br J Haematol. 2008; 140:104–112. [PubMed: 17916102]

15. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: Clinical and laboratory endpoints and disease outcomes. Am J Hematol. 2008; 83:19–25. [PubMed: 17724699]
16. Taylor, JGt; Woods, GM.; Machado, R.; Kato, GJ.; Gladwin, MT. Severe pulmonary hypertension in an adolescent with sickle cell disease. Am J Hematol. 2008; 83:71–72. [PubMed: 17726682]
17. Klings ES. Pulmonary hypertension of sickle cell disease: more than just another lung disease. Am J Hematol. 2008; 83:4–5. [PubMed: 17924550]
18. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. Haematologica. 2007; 92:1115–1118. [PubMed: 17650441]
19. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, St Peter M, Coles WA, Rosing DR, Blackwelder WC, Castro O, Kato GJ, Gladwin MT. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol. 2007; 49:472–479. [PubMed: 17258093]
20. Gordeuk VR, Sachdev V, Taylor JG, Gladwin MT, Kato G, Castro OL. Relative systemic hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. Am J Hematol. 2008; 83:15–18. [PubMed: 17696198]
21. Gray A, Anionwu EN, Davies SC, Brozovic M. Patterns of mortality in sickle cell disease in the United Kingdom. J Clin Pathol. 1991; 44:459–463. [PubMed: 2066423]
22. TAttah E, Ekere MC. Death patterns in sickle cell anemia. JAMA. 1975; 233:889–890. [PubMed: 1173899]
23. Escoffery CT, Shirley SE. Causes of sudden natural death in Jamaica: a medicolegal (coroner's) autopsy study from the University Hospital of the West Indies. Forensic Sci Int. 2002; 129:116–121. [PubMed: 12243880]
24. Manci EA, Culberson DE, Yang YM, Gardner TM, Powell R, Haynes J Jr, Shah AK, Mankad VN. Causes of death in sickle cell disease: an autopsy study. Br J Haematol. 2003; 123:359–365. [PubMed: 14531921]
25. Graham JK, Mosunjac M, Hanzlick RL, Mosunjac M. Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. Am J Forensic Med Pathol. 2007; 28:168–172. [PubMed: 17525572]
26. Thomas AN, Pattison C, Serjeant GR. Causes of death in sickle-cell disease in Jamaica. Br Med J (Clin Res Ed). 1982; 285:633–635.
27. Prasad R, Hasan S, Castro O, Perlin E, Kim K. Long-term outcomes in patients with sickle cell disease and frequent vaso-occlusive crises. The American journal of the medical sciences. 2003; 325:107–109. [PubMed: 12640284]
28. Bakanay SM, Dainer E, Clair B, Adekile A, Daitch L, Wells L, Holley L, Smith D, Kutlar A. Mortality in sickle cell patients on hydroxyurea therapy. Blood. 2005; 105:545–547. [PubMed: 15454485]
29. Knight J, Murphy TM, Browning I. The lung in sickle cell disease. Pediatr Pulmonol. 1999; 28:205–216. [PubMed: 10495338]
30. Shankar SM, Arbogast PG, Mitchel E, Cooper WO, Wang WC, Griffin MR. Medical care utilization and mortality in sickle cell disease: a population-based study. Am J Hematol. 2005; 80:262–270. [PubMed: 16315251]
31. Maisel A, Friedman H, Flint L, Koshy M, Prabhu R. Continuous electrocardiographic monitoring in patients with sickle-cell anemia during pain crisis. Clin Cardiol. 1983; 6:339–344. [PubMed: 6883828]
32. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. The New England journal of medicine. 1996; 335:1933–1940. [PubMed: 8960472]
33. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. The New England journal of medicine. 2002; 346:877–883. [PubMed: 11907286]

34. Steiner CA, Miller JL. Sickle Cell Disease Patients in U.S. Hospitals, 2004. Statistical Brief #21: Healthcare cost and utilization project (HCUP). 2006
35. Maunoury C, Acar P, de Montalembert M, Sidi D. Myocardial perfusion in children with sickle cell disease. Am J Cardiol. 2003; 91:374–376. [PubMed: 12565106]
36. Kato GJ, Gladwin MT. Evolution of novel small-molecule therapeutics targeting sickle cell vasculopathy. JAMA. 2008; 300:2638–2646. [PubMed: 19066384]
37. Mansi IA, Rosner F. Myocardial infarction in sickle cell disease. J Natl Med Assoc. 2002; 94:448–452. [PubMed: 12078925]
38. Acar P, Sebahoun S, de Pontual L, Maunoury C. Myocardial perfusion in children with sickle cell anaemia. Pediatr Radiol. 2000; 30:352–354. [PubMed: 10836604]
39. Aessopos A, Tsironi M, Vassiliadis I, Farmakis D, Fountos A, Voskaridou E, Perakis A, Defteraios S, Loutradi A, Loukopoulos D. Exercise-induced myocardial perfusion abnormalities in sickle beta-thalassemia: Tc-99m tetrofosmin gated SPECT imaging study. Am J Med. 2001; 111:355–360. [PubMed: 11583637]
40. Raman SV, Simonetti OP, Cataland SR, Kraut EH. Myocardial ischemia and right ventricular dysfunction in adult patients with sickle cell disease. Haematologica. 2006; 91:1329–1335. [PubMed: 17018381]
41. Norris S, Johnson CS, Haywood LJ. Sickle cell anemia: does myocardial ischemia occur during crisis? J Natl Med Assoc. 1991; 83:209–213. [PubMed: 2038080]
42. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. The New England journal of medicine. 2005; 352:225–237. [PubMed: 15659722]
43. Sebastiani P, Nolan VG, Baldwin CT, Abad-Grau MM, Wang L, Adewoye AH, McMahon LC, Farrer LA, Taylor JGt, Kato GJ, Gladwin MT, Steinberg MH. A network model to predict the risk of death in sickle cell disease. Blood. 2007; 110:2727–2735. [PubMed: 17600133]
44. Harmatz P, Butensky E, Quirolo K, Williams R, Ferrell L, Moyer T, Golden D, Neumayr L, Vichinsky E. Severity of iron overload in patients with sickle cell disease receiving chronic red blood cell transfusion therapy. Blood. 2000; 96:76–79. [PubMed: 10891433]
45. Olivieri NF. Progression of iron overload in sickle cell disease. Seminars in hematology. 2001; 38:57–62. [PubMed: 11206962]
46. Buja LM, Roberts WC. Iron in the heart. Etiology and clinical significance. Am J Med. 1971; 51:209–221. [PubMed: 5095527]
47. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. The New England journal of medicine. 1994; 331:567–573. [PubMed: 8047080]
48. Fung EB, Harmatz P, Milet M, Ballas SK, De Castro L, Hagar W, Owen W, Olivieri N, Smith-Whitley K, Darbari D, Wang W, Vichinsky E. Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: A report from the multi-center study of iron overload. Am J Hematol. 2007; 82:255–265. [PubMed: 17094096]
49. Ballas SK. Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. Seminars in hematology. 2001; 38:30–36. [PubMed: 11206959]
50. Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, Taveira-DaSilva AM, Ballas SK, Blackwelder W, Xu X, Hunter L, Barton B, Waclawiw M, Castro O, Gladwin MT. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. JAMA. 2006; 296:310–318. [PubMed: 16849664]

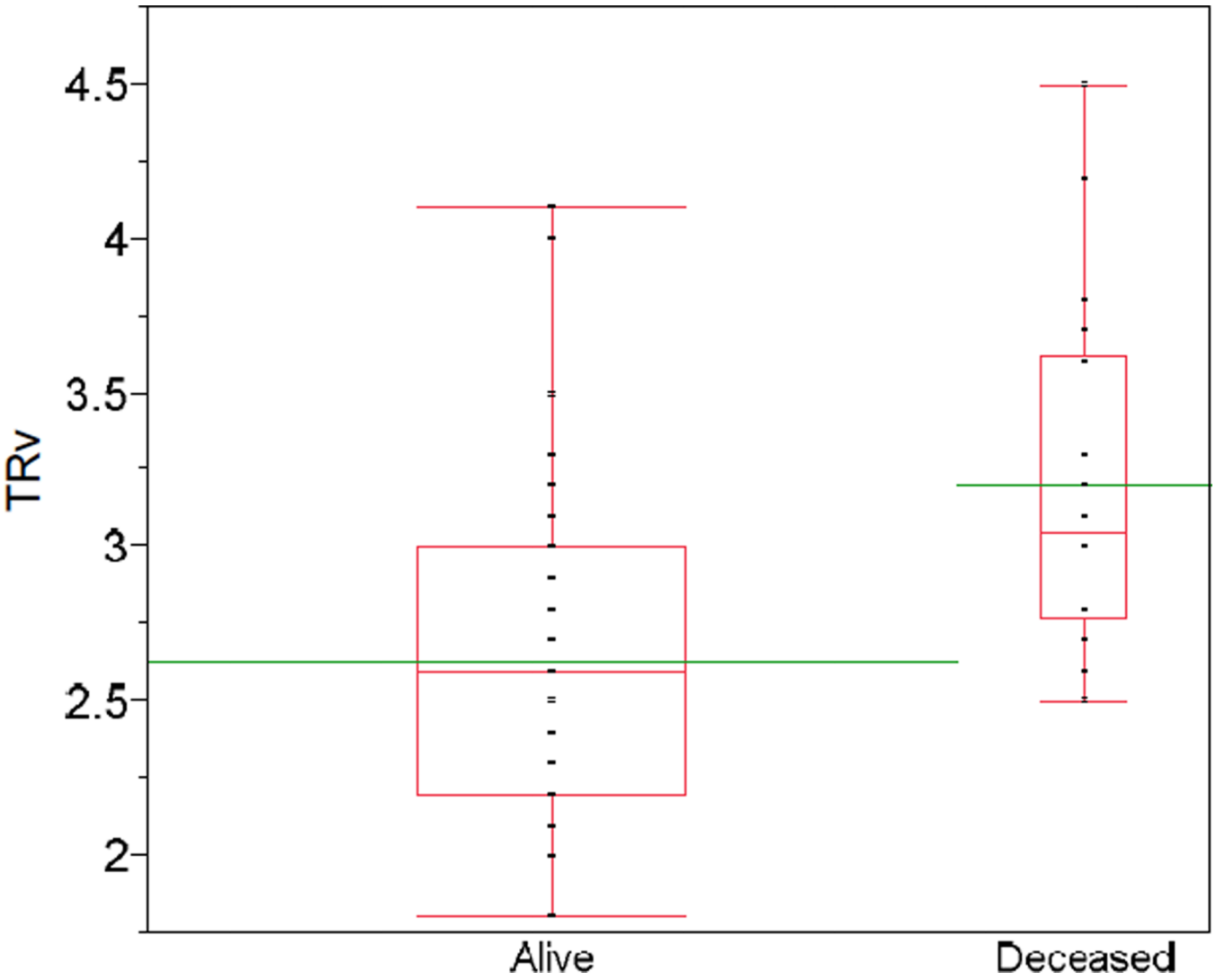

Figure 1. Comparison of distribution of tricuspid regurgitant velocity (TRv) in living and deceased patients

Median TRv is plotted for patients with a detectable TRv for the living (N=57, median 2.6 m/s) and deceased (N=18, median 3.1 m/s) patients. This difference is statistically significant ($p < 0.001$).

Table I

Basic clinical characteristics of patients with sickle cell disease under study.

Type of sickle cell disease	**# Deceased (%) [n=43]**	**# Living (%) [n=197]**
SS	37 (86)	149 (76)
SC	3 (7)	29 (15)
$S\beta^{O}$ thal	1 (2)	9 (5)
$S\beta^{+}$ thal	2 (5)	7 (4)
SO_{Arab}	0	2 (1)
Sδ-thal	0	1 (0.1)
Total	43	197
Sex		
Males	21 (49)	93 (47)
Females	22 (51)	104 (53)
Age (y) at death or last follow up*		
Total	39 (21 – 83)	34 (19 – 85)**
Males	36 (21–56)	32.5 (19–85)***
Females	43 (23–83)	36 (20–73)**

* Median (range)

** $p < 0.03$ when comparing deceased vs. living patients

*** $p > 0.05$ when comparing deceased vs. living patients

Table II

Comparison of clinical values between deceased and living patients as measured by medians, ranges and percentages

	Deceased (N=43) (%)[range][1]	**Living (N=197)**	**p value**
Transthoracic echocardiogram			0.60[2]
Yes	32 (74)	127 (64)	
No	11 (26)	70 (36)	
TRv[3] **(m/s)**	3.1 [2.5–4.5]	2.6 [1.8–4.1]	<0.001
Ejection fraction (%)	55.0 [15–55]	54.3 [30–55]	NS[4]
Left ventricle size (LVIDd –cm)	4.8 [3–7.2]	5.1 [3.6–7]	NS
ECHO (+) for pulmonary HTN[5]	18 (56)	34 (26)	<0.001
QTc prolonged[6]			0.08[2]
Yes	4 (9)	6 (3)	
No	26 (61)	135 (69)	
missing	13 (30)	56 (28)	
Hemoglobin (g/dL)	8.3 [4.1–13.3][7]	9.2 [4.2–12.6]	<0.05
White blood count (K/uL)	12.4 [5.5–25.9]	10.8 [2.49–21.6]	0.18
Oxygen saturation (%)	95.3 [85–99][8]	96.2 [84–99][9]	0.05
Used Hydroxyurea			0.06[2]
Yes	16 (37)	105 (53)	
No	22 (51)	90 (46)	
missing	5 (12)	2 (1)	

[1] ( )= (%), [ ]= range

[2] Fisher exact test, No/Missing treated as a group

[3] TRv= tricuspid regurgitant jet velocity in patients with detectable TRv (N=18 for deceased patients, N=57 for living patients)

[4] NS= not significant,

[5] Pulmonary hypertension (HTN) is defined by a tricuspid regurgitant jet velocity ≥2.5 m/s

[6] Prolonged QTc is defined as >450ms for male subjects; >470ms for female subjects

[7] n = 41

[8] n = 21

[9] n=188

Table III

Survival age and causes of death for deceased subjects

Median Survival Age	**Years (95% CI)**
Total	40 (35, 53)
Males	40 (34, 48)
Females	39 (33, 56)
Age at Death (y)	**Number of patients**
20–29	8
30–39	15
40–49	8
50–59	7
≥60	5
Cause of Death	**Number of diagnosis**
Cardiac	
Pulseless electrical activity arrest	5
Congestive heart failure	3
Myocardial infarction	3
Pulmonary	
Pulmonary embolus	4
Pulmonary hypertension	1
Respiratory disorder	1
Other Complications of SCD	
Stroke	4
Multiorgan failure	3
Liver failure	2
Chronic renal failure	1
Anoxic brain injury	1
“Sickle cell anemia”	3
Other	6*
Unknown	6

Median survival age and 95% CI are calculated from the Cox model

* Foreign body aspiration (2), intestinal disorder (1), complications after fall (1), narcotic overdose (1), assault (1)

Table IV

Clinical pre-morbid complications observed in the study subjects

	Deceased (N=43)	Living (N=196)	p value*
Cardiopulmonary Complications	**Number (%)**	**Number (%)**	
Acute chest syndrome/pneumonia	26 (60.5)	108 (55.1)	0.61
Pulmonary hypertension	18 (41.9)	36 (18.4)	0.001
Systemic hypertension	11 (25.6)	36 (18.4)	0.29
Congestive heart failure	11 (25.6)	16 (8.2)	0.003
Stroke	11 (25.6)	31 (15.8)	0.18
Myocardial infarction	9 (20.9)	3 (1.5)	<0.0001
Pericardial effusion	4 (9.3)	5 (2.6)	0.06
Pulmonary embolus	6 (14)	15 (7.7)	0.23
Atrial fibrillation	4 (9.3)	1 (0.5)	0.004
Supraventricular tachycardia	1 (2.3)	0 (0)	0.18
Ventricular fibrillation	1 (2.3)	0 (0)	0.18
Other SCD-Related Complications			
Cholethiasis	24 (55.8)	115 (58.7)	0.74
Proteinuria	22 (51.2)	32 (16.3)	<0.0001
Creatinine >1.0mg/dL	18 (41.9)	27 (13.8)	<0.0001
Avascular necrosis	16 (37.2)	13 (6.6)	<0.0001
Creatinine >1.4mg/dL	12 (27.9)	55 (28.1)	1.00
Lower extremity ulcers	9 (20.9)	28 (14.3)	0.35
Priapism	5 (11.6)	28 (14.3)	0.81
Worsening anemia	5 (11.6)	49 (25)	0.07
Retinopathy	4 (9.3)	18 (9.2)	1.00
Seizures	3 (7)	12 (6.1)	0.74
Human immunodeficiency virus	2 (4.7)	0 (0)	0.03
Hepatitis C virus	2 (4.7)	10 (5.1)	1.00

* Fisher Exact Test