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# Mortality in Adults With Sickle Cell Disease and Pulmonary Hypertension:

## Sickle Cell Disease and Hypertension

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## To the Editor

Noninvasive echocardiographic markers of pulmonary artery pressure have been associated with early mortality in some studies in adults with sickle cell disease (SCD),[1,2] but considerable controversy remains regarding the prevalence of pulmonary hypertension and its contribution to mortality.[3] We assessed survival in a cohort of patients with SCD with pulmonary hypertension documented by right heart catheterization (RHC).

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**Author Contributions:** Dr Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Mehari and Gladwin contributed equally. Drs Machado and Kato (senior authors) contributed equally.
*Study concept and design:* Gladwin, Machado, Kato.
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## Methods

Patients provided written informed consent to protocols approved by the institutional review board at the National Institutes of Health. All adults with stable SCD seen consecutively in the outpatient clinic at the National Institutes of Health were screened with no exclusion criterion applied. Those who underwent RHC between March 13, 2002, and June 8, 2010, with elevated tricuspid regurgitant velocity (TRV) on echocardiography (≥2.8 m/s) and clinical suspicion of pulmonary hypertension (6-minute walk distance <500 m, unexplained dyspnea or desaturation, or both) were included. Pulmonary hypertension was defined as mean pulmonary artery pressure of 25 mm Hg or greater. Life status was ascertained from clinical records, the Social Security Death Index, state death certificates, and contact with the patient or family as of June 8, 2010. All causes of death were considered for survival analysis. Survival rates (estimated by the Kaplan-Meier method) were compared between (1) those with pulmonary hypertension documented by RHC, (2) those without pulmonary hypertension documented by RHC, and (3) those who did not undergo RHC. Hazard ratios (HRs) were calculated based on Cox proportional hazards regression. Statistical tests were 2-sided and performed using the statistical language R version 2.13.1. $P < .05$ was considered statistically significant.

## Results

Of 531 patients screened by echocardiography, 84 (15.8%) underwent RHC. Right heart catheterization was performed in 81 of 243 patients with a TRV of 2.5 m/s or greater, 67 of 128 with a TRV of 2.8 m/s or greater, 58 of 88 with a TRV of 3 m/s or greater, and 56 of 63 with both a TRV of 2.8 m/s or greater and a 6-minute walk distance of less than 500 m. Fifty-five patients had pulmonary hypertension (65.5% of those who underwent RHC and 10.4% of the total population) and 29 did not. Patients with pulmonary hypertension were older than those who did not undergo RHC and had lower levels of hematocrit and higher serum levels of lactate dehydrogenase, aspartate aminotransferase, direct bilirubin, and ferritin (Table). Patients with pulmonary hypertension demonstrated significantly abnormal cardiopulmonary markers and exercise capacity.

The median follow-up time since enrollment was 4.4 years, with a maximum of 9.6 years. A total of 73 deaths were observed. The overall mortality was worse in the pulmonary hypertension group (20 deaths, 6-year mortality of 37% [95% CI, 20%–50%]) than in either the group without pulmonary hypertension (3 deaths, 6-year mortality of 13% [95% CI, 0%–26%]; age-adjusted HR, 3.43 [95% CI, 1.02–11.55]; $P = .047$) or the group without RHC (50 deaths, 6-year mortality of 17% [95% CI, 12%–21%]; age-adjusted HR, 2.14 [95% CI, 1.25–3.67]; $P = .006$) (Figure, part A). Estimated median survival time was 6.8 years after ascertainment of pulmonary hypertension. Patients with SCD and pulmonary hypertension also died at a younger age than the group without RHC (Figure, part B).

## Comment

This is, to our knowledge, the largest cohort of adults with SCD and pulmonary hypertension detected using RHC consensus diagnostic criteria, and for the first time, an association has been shown between mortality and mean pulmonary artery pressure documented by RHC. This finding suggests a role for pulmonary hypertension in SCD mortality, previously suspected from noninvasive echocardiographic screening studies.[1,2] Our pulmonary hypertension prevalence is similar to 1 recent study[4] but higher than another,[5] which may relate to differences in study exclusion criteria and population characteristics. This was a retrospective, observational study with inherent limitations. Approximately 1.3% of patients screened had indications for catheterization but did not

undergo RHC, projecting to an estimate of 5 missed cases of pulmonary hypertension in the group without RHC. Our results therefore represent a conservative estimate of the prevalence and mortality of pulmonary hypertension in SCD.

Pulmonary hypertension mortality in SCD is high, and effective treatment approaches targeting this population are needed.

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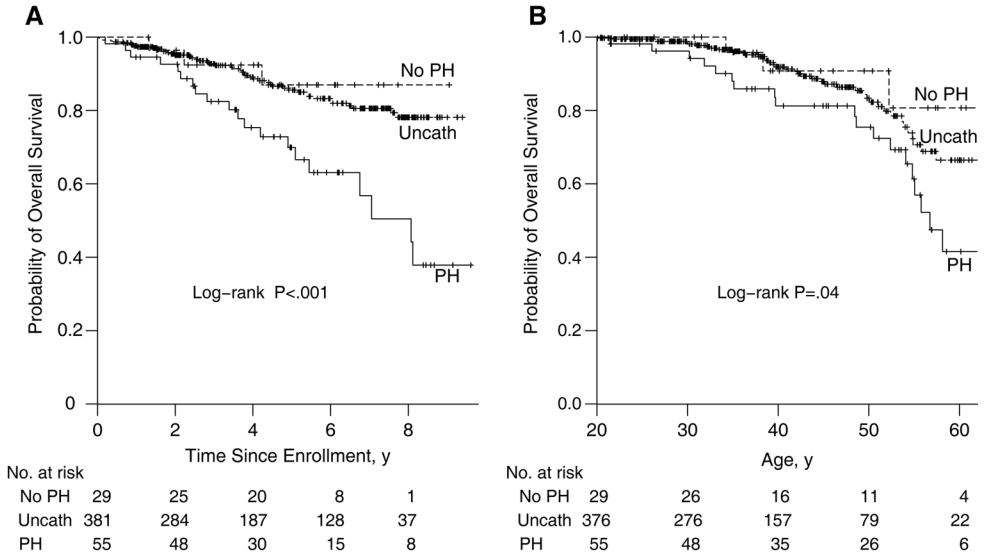


**Figure. Kaplan-Meier Estimates of Survival for Patients With Sickle Cell Disease by Pulmonary Hypertension Status**

A, The age-adjusted hazard ratio (AHR) was 3.43 (95% CI, 1.02–11.55; $P = .047$) for the comparison between patients with pulmonary hypertension documented by right heart catheterization (RHC) and those who did not have pulmonary hypertension documented by RHC; 2.14 (95% CI, 1.25–3.67; $P = .006$) for patients with pulmonary hypertension vs those who did not undergo RHC (uncatheterized); and 0.62 (95% CI, 0.19–2.03; $P = .43$) for patients without pulmonary hypertension vs those who did not undergo RHC (uncatheterized). B, The HR was 3.35 (95% CI, 1.01–11.31; $P = .04$) for the comparison between patients with pulmonary hypertension documented by RHC and those who did not have pulmonary hypertension documented by RHC; 1.73 (95% CI, 1.02–2.93; $P = .04$) for patients with pulmonary hypertension vs those who did not undergo RHC (uncatheterized); and 0.49 (95% CI, 0.15–1.59; $P = .23$) for patients without pulmonary hypertension vs those who did not undergo RHC (uncatheterized).

## Table

Clinical Characteristics of Patients With Sickle Cell Disease by Pulmonary Hypertension Status

| | Underwent Right Heart Catheterization (RHC) | | *P* Value[a] | Did Not Undergo RHC, Pulmonary Hypertension Status Unknown (n=447) | *P* Value for Group With Pulmonary Hypertension Documented by RHC vs No RHC Group[a] |
|---|---|---|---|---|---|
| | Pulmonary Hypertension (n=55) | Without Pulmonary Hypertension (n=29) | | | |
| | No. (%) | | | No. (%) | |
| Hemoglobin genotype | | | .84 | | .20 |
| HbSS | 44 (80.0) | 25 (86.2) | | 318 (71.1) | |
| HbSC | 10 (18.2) | 4 (13.8) | | 78 (17.5) | |
| HbS-β-thalassemia | 1 (1.8) | 0 | | 33 (7.4) | |
| Not identified | 0 | 0 | | 18 (4.0) | |
| | Mean (SD) | | | Mean (SD) | |
| Age, y | 41 (13) | 41 (14) | .61 | 35 (12) | <.001 |
| Alkaline phosphatase, U/L | 127 (85) | 105 (70) | .19 | 105 (65) | .11 |
| Serum level, U/L | | | | | |
| Alanine aminotransferase | 31 (18) | 30 (20) | .39 | 29 (19) | .22 |
| Aspartate aminotransferase | 49 (25) | 45 (19) | .76 | 41 (22) | .01 |
| Bilirubin, mg/dL | | | | | |
| Total | 3.0 (2.2) | 3.0 (2.1) | .86 | 2.7 (1.9) | .42 |
| Direct | 0.7 (0.8) | 0.5 (0.3) | .29 | 0.5 (0.6) | .02 |
| Serum lactate dehydrogenase, U/L | 475 (234) | 409 (174) | .25 | 339 (151) | <.001 |
| Uric acid, mg/dL | 6.7 (1.9) | 6.5 (2.3) | .66 | 6.0 (2.1) | .01 |
| Hemoglobin, % | | | | | |
| Sickle | 59 (26) | 65 (22) | .42 | 67 (20) | .14 |
| Fetal | 7.7 (6.8) | 8.5 (6.6) | .58 | 7.2 (6.4) | .57 |
| Hemoglobin, g/dL | 9.0 (1.7) | 8.4 (1.5) | .14 | 9.6 (1.9) | .02 |
| Hematocrit, % | 26 (5) | 24 (5) | .06 | 28 (6) | .02 |
| Reticulocyte, $\times 10^3/\mu L$ | 228 (151) | 195 (121) | .47 | 240 (126) | .21 |
| Leukocyte count, $\times 10^3/\mu L$ | 11.1 (4.3) | 10.0 (4.7) | .13 | 10.1 (3.4) | .11 |
| Transferrin, mg/dL | 192 (48) | 181 (38) | .52 | 204 (53) | .07 |

| | Underwent Right Heart Catheterization (RHC) | | *P* Value[a] | Did Not Undergo RHC, Pulmonary Hypertension Status Unknown (n=447) | *P* Value for Group With Pulmonary Hypertension Documented by RHC vs No RHC Group[a] |
|---|---|---|---|---|---|
| | Pulmonary Hypertension (n=55) | Without Pulmonary Hypertension (n=29) | | | |
| Tricuspid regurgitant velocity, m/s | 3.3 (0.5) | 2.9 (0.4) | <.001 | 2.3 (0.5) | <.001 |
| 6-Minute walk distance, m | 358 (115) | 437 (108) | .004 | 486 (88) | <.001 |
| | Median (IQR) | | | Median (IQR) | |
| Creatinine, mg/dL | 0.8 (0.6–1.1) | 0.7 (0.5–1.1) | .47 | 0.7 (0.5–0.9) | .02 |
| C-reactive protein, mg/L | 0.41 (0.40–0.76) | 0.51 (0.40–0.77) | .37 | 0.42 (0.20–0.79) | .009 |
| Ferritin, ng/mL | 804 (232–1667) | 721 (293–1511) | >.99 | 378 (107–1235) | .007 |
| NT-proBNP, pg/mL | 177 (83–530) | 101 (66–217) | .06 | 58 (29–123) | <.001 |

Abbreviations: IQR, interquartile range; NT-proBNP, *N*-terminal fragment of the prohormone brain-type natriuretic peptide.

SI conversion factors: To convert alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and lactate dehydrogenase to μkat/L, multiply by 0.0167; bilirubin (total and direct) to μmol/L, multiply by 17.104; C-reactive protein to nmol/L, multiply by 9.524; creatinine toμmol/L, multiply by 88.4; ferritin to pmol/L, multiply by 2.247; hemoglobin to g/L, multiply by 10; transferrin to μmol/L, multiply by 0.0123; uric acid to μmol/L, multiply by 59.485.

[a]The Wilcoxon rank sum test or Fisher's exact test was used for the comparison.