

TO THE EDITOR:

Annual decline in lung function in adults with sickle cell disease is similar to that observed in adults with cystic fibrosis

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Sickle cell disease (SCD) and cystic fibrosis (CF) are 2 common monogenic diseases seen globally. SCD affects approximately 100 000 individuals in the United States,¹ and about 300 000 babies with SCD are born every year worldwide.² Approximately 30 000 individuals in the United States are living with CF and an estimated 70 000 are living with CF worldwide.³ Despite comprehensive medical care and significant advancements in disease-modifying therapies for individuals with SCD, median survival remains only 48 years of age.⁴ Similar to SCD,⁵⁻⁷ cardiopulmonary complications are the primary cause of death for individuals with CF.⁸

Pulmonary function testing (PFT), and specifically forced expiratory volume in 1 second (FEV₁), has been a vital marker associated with morbidity and mortality among individuals with CF.⁹ FEV₁% predicted is calculated from the measured FEV₁ based on an individual's age, sex, and height. Both measured FEV₁ and FEV₁% predicted have been associated with morbidity and mortality in CF. Although survival has improved with therapeutic advancements, individuals with CF and a low FEV₁% predicted are noted to have an increased risk of death within 5 years.¹⁰ Lower FEV₁% predicted has been associated with poor nutritional status¹¹ and poor pregnancy outcomes.¹²

Similarly, in SCD, FEV₁% predicted is a marker of SCD related mortality and morbidity. In a prospective cohort study of young adults with Hb SS (n = 430), the final multivariable model revealed lower FEV₁% predicted was associated with an increased hazard ratio (HR) of death (HR per % predicted 1.02; 95% confidence interval [CI], 1.00-1.04; *P* = .037) and higher acute chest syndrome incidence rate (HR per event/y, 10.4; 95% CI, 3.11-34.8; *P* < .001).¹³ Also similar to CF, lower FEV₁% predicted has been associated with poor nutritional status¹⁴ and adverse pregnancy outcomes.¹⁵ FEV₁ appears to decline over time in both children and adults with SCD,¹⁶⁻¹⁹ although only marginally in children with increasing age.²⁰

Given the clinical utility of FEV₁ assessment in CF, both the European Cystic Fibrosis Society and Cystic Fibrosis Foundation recommend lung function testing be performed at every routine clinic visit on all patients to closely monitor decline.^{21,22} However, the recent American Society of Hematology guidelines for SCD recommend against performing routine screening PFT in asymptomatic individuals.²³ Given similarities in pulmonary complications between the 2 diseases, we tested the hypothesis that annual decline in FEV₁ among adults with CF will be similar to annual decline in FEV₁ among adults with SCD.

In a retrospective cohort study at Vanderbilt University Medical Center (VUMC), we tested the hypothesis that adults with SCD have an absolute change per year in measured FEV₁ similar to adults with CF. Spirometry was performed according to the American Thoracic Society guidelines.²⁴ More than 969 and 14 000 PFTs were collected for the SCD and CF cohorts, respectively. A multivariable mixed model linear regression analysis was used to predict change over time in at least 2 spirometry evaluations with a prespecified set of covariates previously associated with FEV₁ decline in SCD or CF. VUMC institutional review board approval was obtained. The study was conducted in accordance with the Declaration of Helsinki.

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Requests for data sharing may be submitted to Shaina M. Willen (smwillen@ucdavis.edu).

The full-text version of this article contains a data supplement.

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For the SCD cohort, we identified 1283 individuals with SCD from our data warehouse of electronic health records at VUMC using a previously published algorithm.²⁵ We validated this cohort through manual chart review, which included hemoglobin electrophoresis results and hematologist-confirmed diagnoses. Annual to bi-annual PFTs measurements have been obtained at VUMC in asymptomatic adults with SCD for approximately a decade. All PFTs were included in adults with SCD (age range, 18-65 years) and were obtained at baseline. At least 2 spirometry measurements were required. The cohort was limited to adults with a specified genotype (HbSS, HbS β^0 thalassemia, HbS β^+ thalassemia, HbSC, HbSE, and HbSO-Arab). Five participants had a genotype that did not fall into 1 of the listed categories and were excluded from the study. After adjusting for at least 2 lifetime PFTs, the cohort was reduced to 201 eligible adults. Finally, we excluded those who had a bone marrow transplant before having 2 PFTs, leaving 193 eligible adults with SCD in the analysis (supplemental Figure 1A).

For the CF cohort, using the data warehouse at VUMC, we used a previously published algorithm, which discovers all individuals with ICD codes for CF (ICD-9 277.0 and ICD-10 E84) or had a pathology report for a genetic test of the *CFTR* gene.²⁶ We validated this cohort through chart review, which only included those with physician-verified CF diagnosis or those tested for *CFTR*. This approach resulted in an initial cohort of 862 individuals, which was limited to adults at least 18 years of age, leaving 564 individuals. After including at least 2 PFTs and excluding those with a lung transplant before having 2 PFTs, the final cohort was 309 eligible adults with CF (supplemental Figure 1A). Only the first spirometry measurement in each year was used for adults with CF because multiple PFTs are done per year as standard of care. If the first PFT of the year was taken within 8 weeks of a hospital admission, the next PFT was used to obtain baseline values if this was not within 8 weeks of the last hospital admission.

Table 1. Multivariable mixed linear regression model of longitudinal change in FEV₁ in 201 adults with sickle cell disease and 333 adults with cystic fibrosis at Vanderbilt University Medical Center

Covariate	B	95% CI	P
Multivariable model of change in FEV ₁ for SCD cohort (n = 201)*			
Male sex	0.425	0.239-0.612	<.001
Age	-0.023	-0.028 to -0.018	<.001
Genotype SS/S β thal0	-0.090	-0.294 to 0.115	.390
Height	0.026	0.018-0.034	<.001
Hemoglobin	0.028	-0.017 to 0.074	.243
Hydroxyurea use	-0.023	-0.184 to 0.138	.777
Bone marrow transplant	0.106	-0.003 to 0.216	.058
Multivariable model of change in FEV ₁ for CF cohort (n = 333)*			
Male sex	0.345	0.107-0.583	.005
Age	-0.029	-0.037 to -0.021	<.001
Height	0.041	0.030-0.052	<.001
Diabetes	0.040	-0.078 to 0.158	.503
Pancreatic insufficiency	-0.199	-0.383 to -0.014	.035
Lung transplant	1.689	1.500-1.880	<.001

SCA, sickle cell anemia.

*Model includes a random intercept and correlated random effects.

We used multivariable mixed linear regression models to measure longitudinal change in lung function separately for SCD and CF cohorts. Both models controlled for sex, age, and height. The SCD model included genotype, baseline hemoglobin, and hydroxyurea use. The CF model included CF-related diabetes and pancreatic insufficiency. For individuals with SCD and CF, FEV₁ declines 23

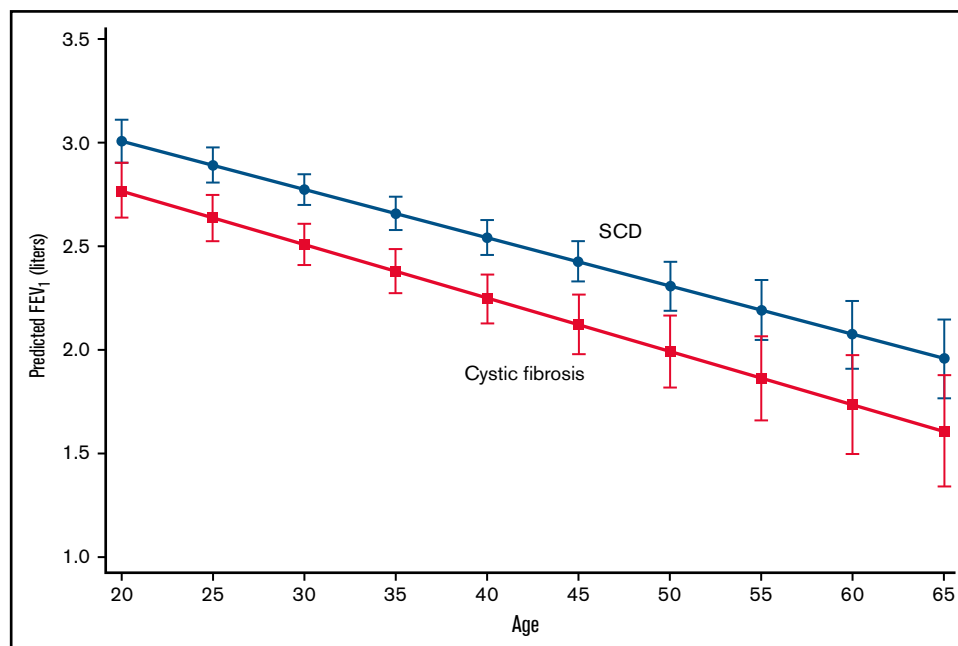


Figure 1. Annual rate of decline in FEV₁ (mL/y) is not statistically significant between adults with SCD and CF.

mL/y (95% CI, -28 to -18; $P < .001$) and 26 mL/y (95% CI, -33 to -18; $P < .001$), respectively (Table 1). No statistical difference was observed in the annual change in FEV₁ between the 2 cohorts (difference in slope = 2.5 mL; $P = .596$; Figure 1). Although initial FEV₁ is lower in individuals with CF than SCD (2.5 vs 2.7 L; $P = .01$), the annual decline over time is similar between the 2 diseases.

To our knowledge, there are no established therapies to increase or prevent a decline in FEV₁ in adults with SCD. However, bone marrow transplant in children with SCD may slow decline in lung function.²⁷ Additionally, established evidence-based practices can be implemented when an adult is noted to have a lower than expected or precipitous decline in FEV₁, such as smoking cessation,²⁸ inquiry and management of occupational exposures,²⁹ or other diagnostic considerations to investigate for comorbid conditions.³⁰ Close monitoring of lung function over time may provide additional information regarding the clinical status and possible response to different therapies, such as montelukast or inhaled corticosteroids.

Several limitations exist in this retrospective cohort study. Although strict testing criteria exist, trajectories of decline can be highly variable in healthy individuals and disease states.³¹ Additionally, excluding those participants with less than 2 spirometry results meant that individuals included in this analysis were more likely to have severe disease. Participants with SCD included in the analysis had SCD genotypes (HbSS or HbSβ⁰thalassemia) associated with a higher incidence rate of vaso-occlusive pain³² and acute chest syndrome events,³³ were on hydroxyurea, and had higher mortality (supplemental Table 2A). Similarly, participants with CF included in the analysis had more severe disease complications, such as pancreatic insufficiency. The study had participants with more severe SCD and CF than those excluded from the analysis. However, the results indicate that, for individuals with severe SCD and CF, the annual decline in pulmonary function is similar.

We provided evidence for progressive lung function decline in adults with SCD, and the rate of the decline is similar to individuals with CF. Despite the lack of a therapeutic intervention to prevent a decline in FEV₁, these data support routine spirometry evaluation in adults with SCD and asymptomatic lung disease. Evidence-based strategies for mitigating a decline in FEV₁ may be implemented for adults with declining lung function. Furthermore, knowledge of progressive lung disease may alter the perspective of risk-benefit ratio for considering curative therapy, tobacco smoke exposure, occupational exposures, or all of the above.

Contribution: B.H. analyzed the data and drafted the original manuscript; Z.I. revised and edited the manuscript; R.C. revised and edited the manuscript; M.R. performed all statistical analysis and revised and edited the manuscript; M.R.D. designed the research study, analyzed the data, and revised and edited the manuscript; and S.W. analyzed the data and revised and edited and manuscript.

Conflict-of-interest disclosure: M.R.D. and his institution are the sponsors of two externally funded research investigator-initiated projects. Global Blood Therapeutics will provide funding for the cost of these clinical studies but will not be a cosponsor of either study. M.R.D. is not receiving any compensation for the conduct of these two investigator-initiated observational studies. M.R.D. is a member of the Global Blood Therapeutics advisory board for a proposed

randomized controlled trial for which he receives compensation. M.R.D. is on the steering committee for a Novartis-sponsored phase 2 trial to prevent priapism in men. M.R.D. was a medical advisor for developing the CTX001 Early Economic Model. M.R.D. provided medical input on the economic model as part of an expert reference group for Vertex/CRISPR CTX001 Early Economic Model in 2020. M.D. provided a 2-hour consultation to the Forma Pharmaceutical company about sickle cell disease in 2021. All remaining author declare no competing financial interests.

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