Etiologies, predictors, and economic impact of readmission within 1 month among patients with takotsubo cardiomyopathy.

Mahek Shah MD
Lehigh Valley Health Network, Mahek.Shah@lvhn.org

Pradhum Ram

Kevin Bryan U Lo

Natee Sirinvaravong

Brijesh Patel MD
Lehigh Valley Health Network, brijesh.patel@lvhn.org

See next page for additional authors

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Michael M. Myers, Ph.D.
William P. Fifer, Ph.D.
Columbia University College of Physicians and Surgeons
New York, New York

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Association between Pulmonary Hypertension and Clinical Outcomes in Hospitalized Patients with Sickle Cell Disease

To the Editor:

Pulmonary hypertension (PH) is a common complication of sickle cell disease (SCD) and is associated with increased morbidity and mortality in patients affected by SCD (1–3). Furthermore, SCD predominantly affects African Americans—a subgroup of patients that is associated with disparities in timely PH diagnosis and prognosis compared with other populations (4). However, the association between PH and clinical outcome and healthcare resource use in hospitalized African American patients with SCD is not known. We obtained data from a national cohort of patients with SCD who were hospitalized between 2003 and 2014 to determine the length of stay, postdischarge disposition, complication rate, and cost of hospitalization for inpatients with PH (SCD-PH) and without PH (SCD-noPH). Our data show that SCD-PH is an underrecognized cause of significant mortality and healthcare expenditures. This emphasizes the need for clinical care tracks and other strategies to prevent adverse clinical events and to improve healthcare efficiency for at-risk patients.

Methods

The U.S. National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project, contains deidentified data on patient demographics, insurance status, hospitalization characteristics, clinical comorbidities, and discharge disposition, as described in detail previously (5, 6). We searched the NIS database for hospitalizations between 2003 and 2014, and used *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9 CM) codes 282.41, 282.42, 282.60–282.64, 282.68, and 282.69 to identify all hospitalized patients ⩾18 years of age with a principal diagnosis of SCD and either African American or black race (6, 7). Patients for whom race information was not available (13.6% of the database) were excluded from further analyses. All patients who met the above criteria were then divided into two groups: those with a secondary diagnosis of PH (ICD-9 CM codes 416.0, 416.8, and 416.9; SCD-PH) (8) and those without PH (SCD-noPH). Using ICD-9 CM and clinical classification software codes, additional clinical comorbidities (dyslipidemia [53], tobacco use [V15.82, 305.1], and opioid dependence [304.00, 304.01–03, 304.70–73]), prior venous thromboembolism (VTE) (V12.51), acute stroke (430, 431, 434, 436), newly diagnosed VTE (415, 451, 453), acute chest syndrome (517.3), and invasive mechanical ventilation (96.70) were extracted. The outcomes were hospitalization duration, hospitalization cost, postdischarge disposition (e.g., nursing home or other circumspect postcare assistance), and in-hospital SCD clinical events (e.g., acute stroke, newly diagnosed VTE, acute chest syndrome, invasive mechanical ventilation, or in-hospital mortality).

Statistical analyses. The Pearson chi-square test for categorical variables and Student's *t* test or the Mann-Whitney *U* test (depending on the uniformity of distribution) for continuous variables were used to determine differences in hospitalizations between patients with SCD and those with SCD-PH. Multivariate logistic and linear regression models were constructed to analyze categorical (postdischarge disposition, acute stroke, newly diagnosed VTE, acute chest syndrome, invasive mechanical ventilation, and in-hospital mortality) and continuous outcomes (length of stay and hospitalization cost), respectively. The regression models were adjusted for the following covariates: age, sex, insurance status, median household income for residential zip code (in quartiles), calendar year, hospital characteristics (metropolitan location, bed size, and U.S. region), diabetes, dyslipidemia, hypertension, smoking, obesity, opioid dependence, alcoholism, heart failure,

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coagulopathies, collagen vascular disease, PH, depression, AIDS, prior VTE, chronic renal failure, fluid and electrolyte disorders, and liver disease. The adjusted odds ratio (AOR) and 95% confidence interval (95% CI) were used to express differences in clinical risk that emerged from the logistic regression. The annual rate of hospitalization among this cohort of African American patients with SCD was calculated as 100 × (number of adult SCD hospitalizations/total African American adult population by U.S. Census) (6).

Results

Among ~9.2 million all-cause hospitalizations involving African American patients between 2003 and 2014, we identified 623,943 hospitalizations (6.8%) with a primary diagnosis of SCD. The prevalence of SCD was 1:365 (~0.27%), and the SCD hospitalization rate during the study period was 0.2–0.3%/year, which is consistent with previous reports (6). Among SCD hospitalizations, we identified 31,727 patients (5.1%) with SCD-PH, which is also consistent with prior reports

Table 1. Demographics, Characteristics, and Clinical Comorbidities of Hospitalized Patients with Sickle Cell Disease

	Overall	Without Pulmonary Hypertension	With Pulmonary Hypertension	*P* Value
Number of hospitalizations	623,943	592,216	31,727	
Age, yr, median (IQR)	29 (23–38)	29 (23–37)	35 (27–45)	<0.001
Women, %	54.3	54.1	57.4	<0.001
Payer status, %				<0.001
Medicare	31.0	30.3	44.1	
Medicaid	45.6	46.0	38.2	
Private	16.1	16.2	13.8	
Self-pay	4.4	4.6	1.6	
Other/no charge	2.9	2.9	2.3	
Median household income national quartiles, %				0.067
First	49.8	49.9	49.4	
Second	23.2	23.3	22.1	
Third	16.6	16.5	18.1	
Fourth	10.3	10.3	10.4	
Hospital type, %				
Metropolitan location	94.3	94.1	98.1	<0.001
Large bed size	64.6	64.2	72.0	<0.001
Hospital U.S. region, %				<0.001
Northeast	23.5	23.7	19.6	
Midwest	14.7	14.3	21.1	
South	53.0	53.2	48.1	
West	8.9	8.8	11.2	
Clinical comorbidities, %				
Diabetes mellitus	3.1	3.1	3.8	<0.001
Dyslipidemia	1.2	1.1	2.1	<0.001
Hypertension	15.6	14.9	27.2	<0.001
Smoking	15.9	15.6	20.7	<0.001
Obesity	2.7	2.6	4.5	<0.001
Opioid dependence	2.3	2.2	3.5	<0.001
Alcoholism	0.7	0.7	0.8	0.049
Heart failure	3.8	2.9	19.8	<0.001
Coagulopathies	2.9	2.8	4.3	<0.001
Collagen vascular disease	1.1	1.1	1.7	<0.001
Depression	7.4	7.2	10.6	<0.001
AIDS	0.2	0.2	0.3	0.110
History of venous thromboembolic event	8.6	8.2	17.7	<0.001
Renal failure (chronic)	4.5	4.0	13.0	<0.001
Fluid-electrolyte disorders	19.4	19.0	27.2	<0.001
Liver disease	2.0	1.8	5.5	<0.001
Clinical outcomes, %				
Discharge to nursing home or similar facility	4.7	4.4	10.2	<0.001
Acute stroke	0.1	0.1	0.3	<0.001
Newly diagnosed venous thromboembolic event	2.3	2.1	5.0	<0.001
Mechanical invasive ventilation	0.6	0.5	2.1	<0.001
Acute chest syndrome	5.7	5.5	10.3	<0.001
In-hospital mortality	0.3	0.3	1.2	<0.001
Length of stay, d, median (IQR)	4 (3–7)	4 (2–7)	5 (3–9)	<0.001
Hospitalization charges, U.S.$, median (IQR)	16,889 (9,664–30,023)	16,553 (9,497–29,293)	25,012 (14,227–45,888)	<0.001

Definition of abbreviation: IQR = interquartile range.

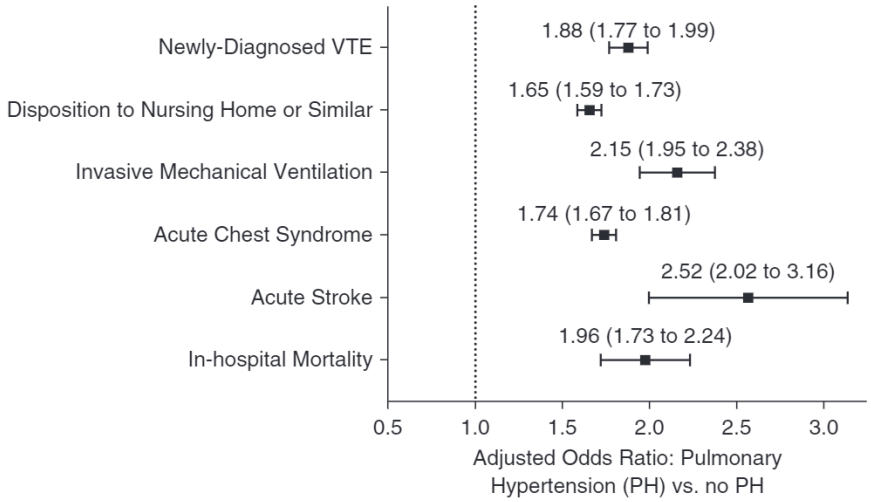

Figure 1. Forest plot demonstrating the association between pulmonary hypertension and outcomes in patients with sickle cell disease. VTE = venous thromboembolism.

of an SCD-PH prevalence of 6–11% (2). Compared with SCD-noPH patients, SCD-PH patients had a higher prevalence of heart failure (2.9% vs.19.8%), previous history of VTE (8.2% vs. 17.7%), and chronic renal failure (4.0% vs. 13.0%) ($P < 0.001$ for all comparisons). Furthermore, 36.6% of SCD-PH patients had a history of VTE, chronic renal failure, or acute chest syndrome. Patients with SCD-PH had a longer length of stay (5 d [3–9] vs. 4 d [2–7]; $P < 0.001$) and higher hospitalization costs ($25,012 [$14,227–45,888] vs. $16,553 [$9,497–29,293] USD; $P < 0.001$), than SCD-noPH patients. In the linear regression analysis, a diagnosis of PH was associated with a longer length of stay (+1.4 d) and significantly higher hospitalization cost (+$8,711). SCD-PH patients had a greater need for a nursing home or similar care facility postdischarge than SCD-noPH patients (10.0% vs. 4.7%; AOR, 1.65; 95% CI, 1.59–1.73).

Additionally, a higher rate of acute stroke (0.4% vs. 0.1%; AOR, 2.52; 95% CI, 2.02–3.16), acute chest syndrome (10.3% vs. 5.5%; AOR, 1.74; 95% CI, 1.67–1.81), newly diagnosed VTE (5.0% vs. 2.1%; AOR, 1.88; 95% CI, 1.77–1.99), invasive mechanical ventilation (2.1% vs. 0.5%; AOR, 2.15; 95% CI, 1.95–2.38), and in-hospital mortality (1.2% vs. 0.3%; AOR, 1.96; 95% CI, 1.73–2.24) was observed for SCD-PH patients versus SCD-noPH patients (Table 1 and Figure 1).

Discussion

These data show for the first time that SCD-PH in hospitalized patients is associated with significantly higher disease-associated clinical complications, including in-hospital mortality, which corresponds to increased healthcare resource use. Our findings are consistent with published longitudinal data identifying PH as a risk factor for adverse outcomes in SCD (2, 3). We now show that the presence of PH increases the short-term risk of major adverse events and healthcare resource use in hospitalized patients with SCD. These data also reinforce an expanding effort to recognize the effects of PH on outcomes in underserved minorities (9).

Further clinical studies are required to validate our findings and determine the causes of increased hospitalization costs, although clinicians' underrecognition of risk in patients with SCD-PH is likely a contributor. We observed regional variability for SCD-PH prevalence that seemed to overlap with the population distribution of African Americans in the United States (10). Interestingly, SCD-PH regionality also overlapped with geographic trends in PH-associated mortality (11). It is not possible to determine the basis for this finding using the current database; however, this observation may imply that SCD-PH contributes to PH outcome differences across geographic regions. Conversely, some factors related to geography and PH in the general population, such as high-altitude exposure, may also relate to PH prevalence in SCD. Additionally, we identified a number of significant adverse events whose rates were increased in SCD-PH, suggesting that a greater emphasis on standardized pathways incorporating multiple subspecialty care professionals may be useful to improve outcomes and reduce healthcare costs, similar to what has been reported for other complex cardiopulmonary diseases (12). For example, heart failure was a particularly common comorbidity in SCD-PH, although the extent to which this includes right and/or left ventricular dysfunction is not known, nor are data available regarding heart failure prevalence or treatment efficacy in this patient population. Our results identifying an association between stroke and PH in this population also lend epidemiological support to prior mechanistic and clinical reports implicating various pathophysiological mechanisms, particularly impaired nitric oxide bioavailability, in mediating cerebral and pulmonary circulatory dysfunction in SCD (13).

Our findings are limited by the inherent biases of retrospective, observational analyses involving large administrative databases, including confounding effects and coding errors. Also, we were not able to study detailed clinical, hemodynamic, or genetic information relevant to SCD-PH or distinguish comorbidities from actual hospital-related complications. In particular, the pharmacotherapeutic profile of patients was not available in the NIS database, and thus we were unable to analyze the relationship between drug prescriptions and clinical outcome in the study population. Additionally, this database does not contain information on cause of death or hemodynamic severity. Collectively, these data might have allowed us to characterize PH severity and clarified the prognostic relevance of specific PH risk factors in this study population, such as renal failure, VTE, and acute chest

syndrome. Nevertheless, our findings support accumulating data regarding the contribution of PH to healthcare resource use (14), and indicate that PH in SCD is associated with higher clinical event rates, which has been reported in previous studies even when the pulmonary artery pressure was only mildly increased (1, 3, 15).

In conclusion, PH is an important complication of SCD that is associated with higher in-hospital clinical events and a substantially higher healthcare resource burden compared with SCD without PH. Our data suggest that African American patients with SCD-PH represent a particularly vulnerable patient population. Further studies are needed to validate our findings and to determine the causes of the increased hospitalization costs and adverse events that we observed in our cohort of patients with SCD. Efforts can then be directed toward decreasing these events and reducing costs to optimize healthcare resource use. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Manyoo A. Agarwal, M.D.
University of Tennessee Health Science Center
Memphis, Tennessee

Mahek Shah, M.D.
Brijesh Patel, D.O.
Lehigh Valley Healthcare Network
Allentown, Pennsylvania

Vikki G. Nolan, D.Sc., M.P.H.
University of Memphis
Memphis, Tennessee

Guy L. Reed, M.D.
University of Arizona College of Medicine
Phoenix, Arizona

Ronald J. Oudiz, M.D.
LA Biomedical Research Institute at Harbor-UCLA Medical Center
Torrance, California

Gaurav Choudhary, M.D.
Brown University
Providence, Rhode Island
and
Providence VA Medical Center
Providence, Rhode Island

Bradley A. Maron, M.D.
Brigham and Women's Hospital
Boston, Massachusetts
and
Boston VA Medical Center
Boston, Massachusetts

ORCID ID: 0000-0002-0549-9440 (M.A.A.).

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Natural History over 8 Years of Pulmonary Vascular Disease in a Patient Carrying Biallelic *EIF2AK4* Mutations

To the Editor:

In a recent Pulmonary Perspective published in the *Journal*, Elinoff and colleagues summarized the key conclusions of a Joint National Institutes of Health Clinical Center and Pulmonary Hypertension Association symposium focusing on whether or not pulmonary arterial hypertension

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