RESEARCH ARTICLE

Hospital Use and Mortality in Transition-Aged Patients With Sickle Cell Disease

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ABSTRACT

OBJECTIVES: Childhood mortality in sickle cell disease (SCD) has decreased, but the transition period is associated with poor outcomes and higher mortality rates. We analyzed recent US hospitalizations and mortality trends in the transition-aged population and evaluated for differences between patients with and without SCD.

METHODS: Nationwide Inpatient Sample database was used to analyze hospitalizations among individuals aged 16 to 24 years from 2003 to 2017. Diagnoses were coded by using *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, 10th Revision, Clinical Modification*. We performed bivariate analyses to assess associations between sociodemographic characteristics and SCD hospitalizations, joinpoint regression analysis to describe mortality rate trends in SCD hospitalizations, and adjusted survey logistic regression to assess associations between patient characteristics and in-hospital mortality among transition-aged SCD and non-SCD-related hospitalizations.

RESULTS: There were 37 344 532 hospital encounters of patients aged 16 to 24 years during 2003–2017; both SCD and non-SCD hospitalizations increased with age. Female patients accounted for 78% of non-SCD and 54.9% of SCD hospitalizations. Although there was a +3.2% average annual percent change in SCD hospitalizations, total SCD in-hospital mortality rates did not have a statistically significant increase in average annual percent change over the study period. Patients with SCD aged 19 to 21 and 22 to 24 were more likely to suffer in-hospital mortality than those aged 16 to 18 (odds ratio = 2.09 and 2.71, respectively); the increased odds in mortality by age were not seen in our non-SCD population.

CONCLUSIONS: Transition-aged hospitalizations increase with age, but SCD hospitalizations have disparate age-related mortality rates. Hospital-based comprehensive care models are vital to address the persistent burden of early adulthood mortality in SCD.

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In the United States, patients with sickle cell disease (SCD) are living longer, largely attributed to childhood mortality decreasing.[1–7] Notably, review of the Dallas Newborn Cohort estimated that 94% of children with SCD lived to adulthood.[5] Consequently, mortality trends within the sickle cell population have now shifted. Population studies suggest there are disproportionate mortality rates among patients in their young adult years versus adolescence. From 1999 to 2009, the SCD-related mortality rate in the United States in patients aged 15 to 19 was significantly lower than in those aged 20 to 24, with rates of 0.6 per 100 000 persons versus 1.4 per 100 000 persons, respectively.[4] Although younger age groups have shown anywhere from a 22% to 67% decline in mortality rate over the past few decades, the mortality rate in young adults aged 20 to 24 only decreased by 7% during the same time frame.[4] This disparate mortality trend is accredited to the presence of the "transition period," or the phase during which a patient transitions from pediatric to adult medical care. This period is often plagued by frequent pain episodes, amplified health care use, social and economic stressors, navigation of a new adult health care system, a possible change or loss of insurance, spiritual distress, negative stigma, and feelings of isolation.[8,9]

Previous SCD mortality studies were published during or before the last decade. In addition, researchers in few studies provided analysis of the characteristics of hospitalizations within the high-risk transition age. In this study, we evaluated a 15-year span of the most recent US hospitalization trends for the transition-aged population, deemed for our purposes as ages 16 to 24 years. The aims of the study are to describe demographic variations in both SCD and non-SCD populations and to assess factors associated with mortality rates.

METHODS

We analyzed hospitalization records from January 1, 2003, through December 31, 2017, that were contained in the Nationwide Inpatient Sample (NIS). The NIS data sets constitute the largest all-payer, publicly available inpatient database in the US and are made available by the Healthcare Cost and Utilization Project (HCUP). Although the systematic sampling process used to select the hospitalizations to be included in the NIS has changed over time, the result is an ∼20% sample of hospital discharges from participating states. The sampling strategy ensures that hospitalizations in the NIS are representative of the population on important factors including month of admission, primary reason for hospitalization, and hospital size, location, ownership, and teaching status. The NIS contained ∼7 million inpatient hospitalizations each year (35 million when weighted) from ∼47 participating states.

Our study sample included hospitalizations among transition-aged patients within the age range of 16 to 24 years. HCUP NIS database were available through 2017 at the time of study, and we wanted to include 15 years of data for performing temporal trends analyses and to have considerable sample size for multivariable modeling. Therefore, we collected data for the years 2003 through 2017. Diagnoses and procedures are coded using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes until the third quarter of 2015, after which HCUP transitioned to *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) format. To assess the study's primary exposure, we first scanned the diagnosis codes (the principal diagnosis and up to 29 secondary diagnoses) in each patient's discharge record for an indication of SCD (ICD-9-CM: 282.41, 282.42, 282.61, 282.62, 282.63, 282.64, 282.60, 282.68, 282.69; ICD-10-CM: D57.4X, D57.0X, D57.2X, D57.1X, D57.8X).

The covariates in this study included individual-level sociodemographic and hospital characteristics. We categorized patients' ages in groups of 16 to 18 years, 19 to 21 years, and 22 to 24 years. The rationale for this categorization was to include the years immediately before and after the transition period of 18 to 21 years (ie, <18 years and >21 years), and to divide the age groups on the basis of equal number of years. Ethnicity was first stratified on the basis of reported ethnicity (Hispanic, non-Hispanic), and the non-Hispanic group was subdivided (White, Black, or other). The primary payer for the hospitalization was classified into Medicare, Medicaid, private, self-pay, and other (including under- or uninsured). As a proxy for socioeconomic status, the Healthcare Cost and Utilization Project provides zip-code-level estimates of median household income, grouped into quartiles based on the patient's residence.

We conducted bivariate analyses to assess the association between sociodemographic characteristics of the patients and SCD status using Pearson's χ^2 test. Furthermore, to describe the trends in rates of in-hospital mortality among patients with SCD over the study period, we conducted joinpoint regression analysis, which is a statistical modeling approach specifically designed to evaluate and describe the extent to which the rate of a condition changes over time. The model first fits the annual rates of outcome of interest (ie, in-hospital mortality) to a model with the minimum number of joinpoints (0), suggesting that a straight line and single trend best fits the annual prevalence data.[10] Then, more joinpoints are added iteratively to test the statistical significance of the various models by using the Monte Carlo permutation method. Once the final (best-fitting) model with the optimal number of joinpoints has been selected, each joinpoint represents a statistically significant change in the trend, and each distinct trend is characterized by using an annual percent change measure and its 95% confidence interval (CI).

Next, we stratified the SCD-associated in-hospital mortality by age groups across the entire study period and by 5-year time span. Lastly, we conducted adjusted survey logistic regression model to assess the association between various patient characteristics and in-hospital mortality among patients with and without a diagnosis of SCD. Analyses were performed by using R (version 3·6·1) and RStudio (Version 1·2·5001) and the

Joinpoint Regression Program, version 4.7.0.0 (National Cancer Institute); we assumed a 5% type I error rate for all hypothesis tests (two-sided). This study was deemed exempt by the institution's institutional review board because the study was performed on secondary deidentified data.

RESULTS

Sociodemographic Characteristics

In Table 1, we review the sociodemographic characteristics of hospitalizations with SCD diagnosis code in comparison with those without SCD. Our data captured 37 344 532 hospitalizations between 2003 and 2017 of patients between the ages of 16 and 24 years old. Hospitalizations with a SCD diagnosis code accounted for 1.2% (446 503) of total hospitalizations over the 15-year period. The percentage of hospitalizations was higher in older age groups in comparison with younger age groups; those aged 16 to 18 years accounted for 22.9% of SCD hospitalizations and 20.9% of non-SCD hospitalizations, whereas those aged 22 to 24 years accounted for 40.9% and 44.9%, respectively.

When classified by sex, the distribution of non-SCD hospitalizations was composed of majority female patients (78%). In contrast, female patients accounted for only 54.9% of SCD hospitalizations. As expected, SCD hospitalizations had an increased prevalence to identify as non-Hispanic Black, with 81.5% identifying as such. Among discharge outcomes, 92% of SCD hospitalizations resulted in routine discharge, 2.1% were transferred, and

TABLE 1 Sociodemographic Characteristics of Hospitalized Transition-Aged Patients with SCD

	Total, *N* = 37 344 532	Non-SCD, *n* = 36 898 028, %	Any SCD, *n* = 446 504, %	Prevalence, %
Age group, y				
16–18	7 815 928	20.90	22.90	1.30
19–21	12 766 171	34.20	34.20	1.20
22–24	16 762 433	44.90	42.90	1.10
Sex				
Male	8 258 846	21.80	45.00	2.40
Female	29 027 842	78.00	54.90	0.80
Missing	57 844	0.20	0.10	0.50
Race				
Non-Hispanic White	15 867 911	43.00	1.20	0.00
Non-Hispanic Black	6 208 824	15.80	81.50	5.90
Hispanic	6 976 381	18.90	3.90	0.20
Other	2 240 252	6.00	2.00	0.40
Missing	6 051 164	16.30	11.50	0.90
Discharge status				
Routine	34 550 754	92.50	92.00	1.20
Transfer	1 203 126	3.20	2.10	0.80
Died	94 959	0.30	0.20	1.10
DAMA	476 499	1.20	3.70	3.40
Other	1 001 060	2.70	1.90	0.90
Missing	18 134	0.00	0.00	0.90
Zip income quartile				
Lowest quartile	12 828 779	34.20	48.50	1.70
Second quartile	9 989 343	26.80	22.70	1.00
Third quartile	8 103 363	21.80	16.40	0.90
Highest quartile	5 585 278	15.00	9.90	0.80
Missing	837 768	2.20	2.40	1.30
Primary payer				
Medicare	569 285	1.40	10.00	7.80
Medicaid	18 762 423	50.10	60.40	1.40
Private insurance	13 175 363	35.50	20.70	0.70
Self-pay	4 748 852	12.80	8.60	0.80
Other, missing	88 609	0.20	0.20	1.00

Prevalence denotes the proportion in each category who were diagnosed with SCD.

0.2% resulted in death; trends were similar in the non-SCD hospitalizations. Of note, SCD hospitalizations resulted in discharge from the hospital against medical advice (DAMA) 3.7% of time, whereas DAMA only accounted for 1.2% of non-SCD discharge status. Regarding zip code income, nearly half (48.5%) of all SCD hospitalizations fell into the lowest quartile. The payer mechanism for SCD hospitalizations had the higher prevalence to use public insurance rather than private insurance in comparison with non-SCD, with 70.4% of SCD hospitalizations using either Medicaid or Medicare.

SCD-Specific Hospitalizations and Overall Mortality

A temporal view revealed an upward trend in the annual percentage of total SCD hospitalizations (Fig 1); further analysis revealed a statistically significant average annual percentage change of +3.2%. The temporal trend of total in-hospital mortality rates for transition-aged patients with SCD is depicted in Fig 2. Crude rates exhibited considerable variation year by year, although examination using joinpoint regression analysis revealed an average annual percentage change of −0.7%, which did not achieve statistical significance.

Age-Specific SCD Mortality

The in-hospital mortality rates by age classification across 5-year intervals are shown in Fig 3. With passage of time, we noticed an increase in mortality rates in the 16 to 18 years group, whereas the mortality rates decreased over the 5-year intervals among the 19 to 21 years group. For the 22 to 24 years group, the mortality rate noted in 2013–2017 period was lower than in earlier time intervals. Overall, the lowest SCD-associated mortality rate of 129.1 per 100 000 hospitalization was observed among 16- to 18-year-olds, followed by 19- to 21-year-olds (272.9 per 100 0000) and 22- to 24-year-olds (343.2 per 100 000 hospitalization).

Mortality and Sociodemographic Factors

Table 2 further expounds on potential associations between sociodemographic characteristics and in-hospital mortality rates of transition-aged patients both with and without SCD. The most prominent finding was an association between increasing age and increased in-hospital mortality in patients with SCD. When using the 16 to 18 years subgroup as a reference, analysis revealed an odds ratio (OR) of 2.09 for the 19 to 21 years subgroup ($P < .0001$) and 2.71 for the 22 to 24 years subgroup ($P < .0001$). In contrast, this trend was not exhibited in the non-SCD group, with odd ratios of ∼1 for each of the subgroups.

In patients with SCD, no statistically significant difference in mortality was noted in respect to race (reference group = non-Hispanic Black). Female patients had a lower likelihood of mortality in both non-SCD and SCD groups, with an OR of 0.20 and 0.57, respectively (each $P < .0001$). Within the SCD group, there were no observed significant differences in mortality between income quartiles. Among primary payer types (Medicaid as reference group), patients with SCD with private insurance were 1.39 times as likely to suffer in-hospital mortality ($P = .05$), those with self-pay were 1.53 times as likely ($P = .04$), whereas those with Medicare were not found to have a significant increase in mortality.

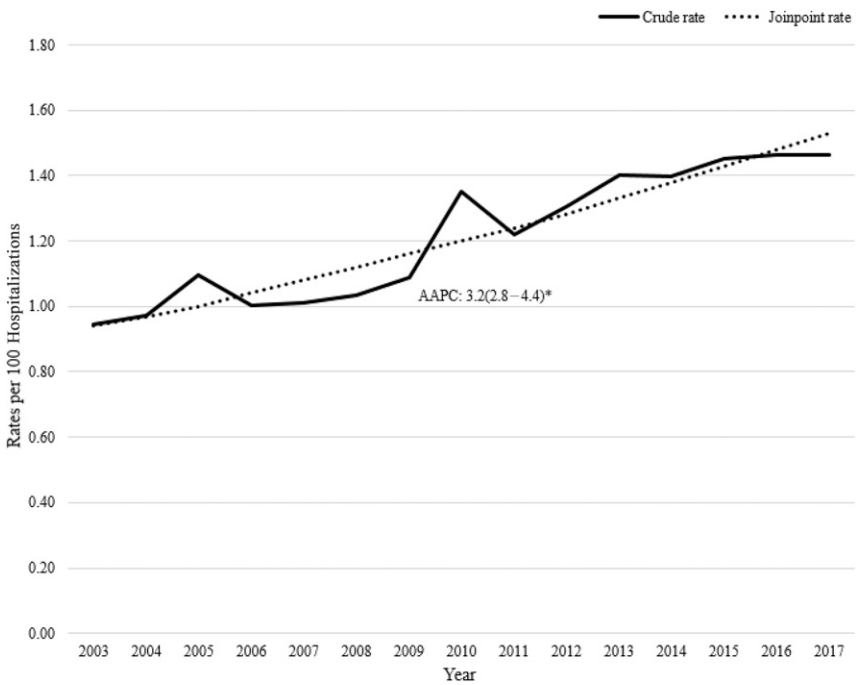

FIGURE 1 Temporal trends in hospitalization rates among transition aged patients with SCD: 2003–2017. *$P < .05$. AAPC, average annual percentage change.

DISCUSSION

Despite the evidence for increased hardships and hospitalizations for transition-aged patients with SCD, we lack recent, nationwide studies pertaining to the trends in this population's mortality. Previous studies are now dated[4] or had a narrow emphasis, focusing on specific demographics such as geographic regions.[11] We thus embarked on a comprehensive approach to examine recent, national data regarding transition-aged hospitalizations in the SCD population.

The central finding of our report is the preponderance of higher mortality in young adults in comparison with teenagers with SCD. We found a twofold higher risk of mortality for those aged 19

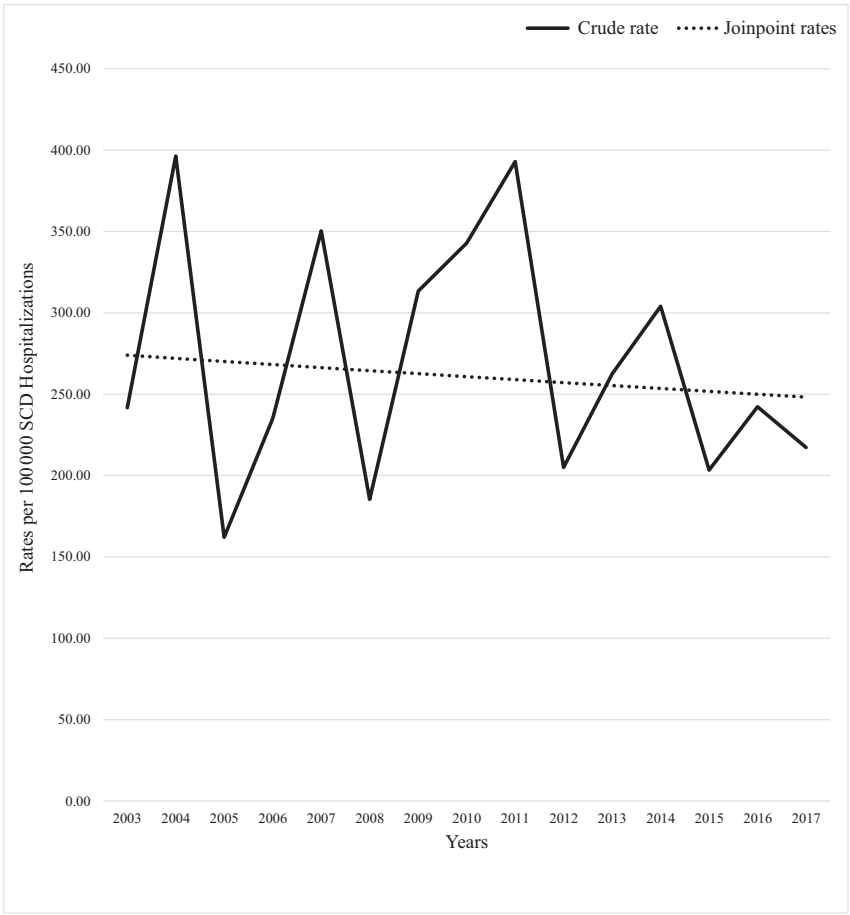

FIGURE 2 Temporal trends of in-hospital mortality among transition-aged patients with SCD: 2003–2017. AAPC, average annual percentage change.

to 21 compared with teenagers aged 16 to 18, and a nearly threefold higher risk of mortality for young adults aged 22 to 24. Of note, our analysis revealed increased prevalence of hospitalizations in the older age groups regardless of SCD status. However, patients with SCD also had an increase in mortality with age, which was not seen in their age-matched peers. These findings correspond with 1999–2009 data from Hamideh et al,[4] which revealed a sharp increase in the mortality rate in patients with SCD between 15 to 19 years to 20 to 24 years. Another congruency is that they reported a downward trend in SCD mortality rates in the 20 to 24 years group in 2004–2009 when compared with 1999–2003.[4] We noted a progressive decline in mortality rates in the 19 to 21 years group across 3 5-year intervals and in the 22 to 24 years group across 2 5-year intervals. Although the 16 to 18 years group exhibited less mortality than the other age groups, we observed gradual rises in mortality rates over 3 5-year periods. This may reflect more accurate coding with time, although other multifactorial causes cannot be ruled out. Of note, mortality rates in the Hamideh et al[4] study were calculated on the basis of the Black population, whereas our study only focused on mortality in SCD-associated hospitalizations regardless of race. Taken together, these differential mortality trends demand heightened attention and stress the urgency for evidence-based targeted interventions to improve outcomes and life span.

We also noted several trends within the SCD cohort. Female patients constituted a slight majority of patients hospitalized with SCD; however, they were less likely to suffer in-hospital mortality when compared with their male counterparts. These results align with a previous study in which researchers determined that pediatric male patients with SCD have a worse, more-aggressive clinical course than female patients and an increased morbidity.[12] In addition, we found that transition-aged patients with SCD were more likely to have public insurance, be in the lower zip income quartile, and have a discharge status of DAMA than their non-SCD peers. This aligns with previously documented socioeconomic differences between SCD and non-SCD admissions detailed in the recent HCUP Statistical Brief.[13] Notably, counter to previous established reports on the relationship between insurance and mortality,[14] we found that both SCD and non-SCD populations with private insurance had increased mortality rates in comparison with those with Medicaid. It is unclear if this is related to database differences, age, or other factors. For instance, in the Sorlie et al[14] report, the data were extracted from the National Census Bureau and not the NIS, and the authors focused on ages 25 to 65 years. Further studies are necessary to delineate the role of sociodemographic factors on SCD mortality in the transition age group versus other age groups.

Several groups have described the struggles of patients with chronic diseases during the transition period; the consensus is that it is plagued by social, psychological, and physiologic hardships.[8,9,15] Hence, during the transition period, gaps in comprehensive care can exacerbate disease-related morbidity and mortality.[3,16–19] Proposed solutions include the implementation of SCD transition programs and centers; however, the efficacy and sustainability of these programs is still being monitored.[16] Lack of knowledgeable providers is also a perceived barrier.[17,19] In a 2011 study, Sobata et al[17] surveyed pediatric providers at several SCD centers and found that only 60% of centers sent their patients to hematologists specializing in adult SCD and noted that some centers sent their patients to an internist instead. This corresponds with evidence that transition-aged patients are less likely to receive disease-modifying therapies after

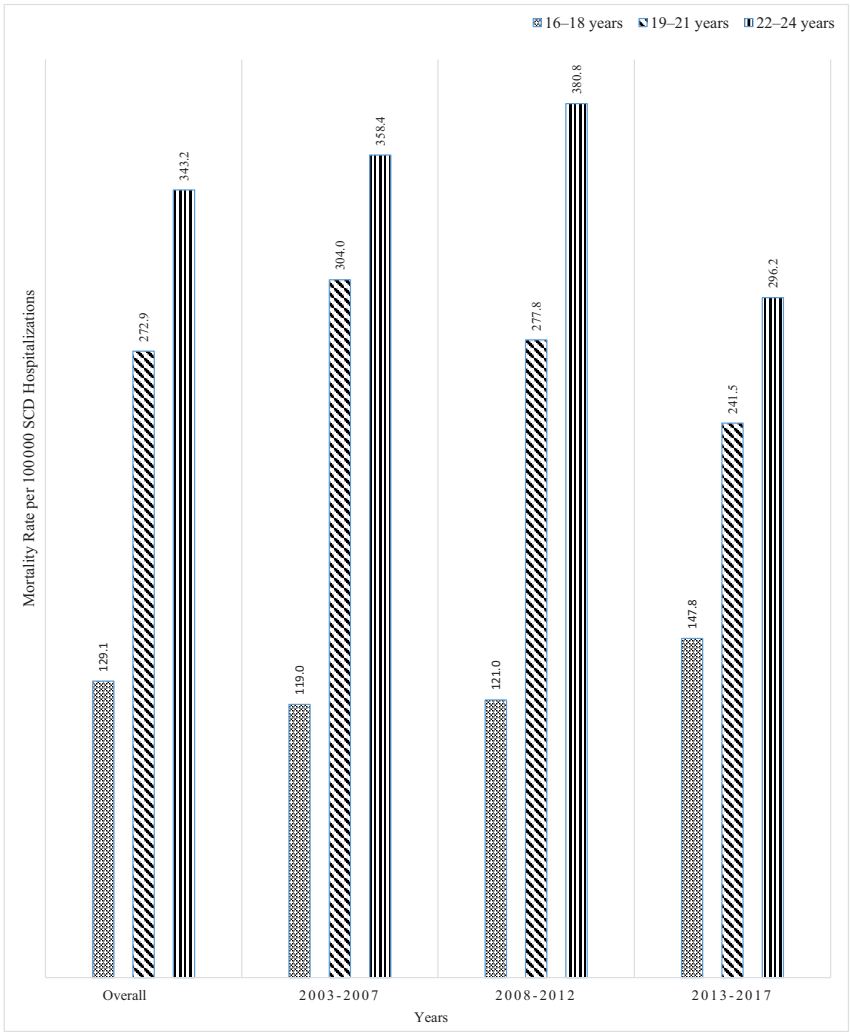

FIGURE 3 Rates of in-hospital mortality among patients with SCD by age group: 2003–2017.

childhood.[18] Altogether, these and other barriers are representations of the paucity of high-quality care for individuals with SCD.[19,20] Lee et al[20] delineated 3 strategies to address these disparities and promote sustainable change: (1) investing in SCD national surveillance program, (2) improving access-to-care models, and (3) increasing the number of knowledgeable providers. These and other strategies have been comprehensively reviewed in the recent National Academies of Sciences, Engineering, and Medicine SCD report[21] along with a blueprint of actionable goals. This momentous and promising step seeks to improve outcomes in individuals with SCD of all ages.

The ultimate goal would be for individuals with SCD to be cared for by high-quality comprehensive programs that at a minimum provide access to a dedicated SCD specialist, social worker, patient coordinator, and nursing staff.[19] Other optimal elements include, but are not limited to, a day hospital or infusion center targeted at decreasing emergency department use, behavioral health support, and transition plans to assist with the transfer to adult care.[19] There are ongoing efforts led by the American Society of Hematology to improve access to care by increasing the number of comprehensive SCD programs.[19] However, currently, adults with SCD are more likely to be cared for by a hospitalist than a hematologist.[22] Therefore, hospital-based care models that optimize the role of hospitalists should be also considered. We interviewed 2 pediatric hospitalists and 1 medicine-pediatric hospitalist who work in community hospital settings and, on the basis of those conversations, propose 5 areas for optimization: (1) Perform a hospital needs assessment and routine evaluations via patient-centered SCD focus groups or advisory boards that include transition-aged patients. (2) Increase access to quality, empathetic care by providing hospitalists expert-led education on SCD management and barriers faced by individuals with SCD. (3) Increase in-hospital access to support programs and staff, including social workers, community health workers, mental health support, mobile/tablet-based self-management tools, SCD empowerment media and Web sites, and peer groups. (4) Offer supplemental case management services for patients with high use. (5) Introduce patients to adult care systems by employing medicine-pediatric hospitalists and using telehealth for an introductory meeting with adult providers.

Limitations of our study are related to the nature of database use; specifically, the absence of granular data and the inability to track a patient over time. Because of this, although the reasons for hospitalization is captured in the data set, the exact cause of in-hospital death and other information regarding clinical course is unobtainable. Furthermore, the structure of the NIS data were confined to inpatient admissions only and did not contain ED visits, outpatient visits, or urgent care visits. We also did not report data for the different SCD genotypes because of less precise ICD-9-CM coding before the fourth quarter of 2015. Lastly, we understand that inclusion of SCD in any diagnostic position (principal or secondary) can impact the sensitivity and specificity of the results. But, because we wanted to capture all hospitalizations among those with SCD, irrespective of the primary reason of the hospitalization, we decided to include all the available details from up to 30 diagnosis codes in each hospitalization record. Despite some

TABLE 2 Association between Sociodemographic Characteristics and in-Hospital Mortality in Transition-Aged Patients with and without SCD

	No SCD		Any SCD	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, y				
16–18	reference	reference	reference	reference
19–21	1.02 (0.97–1.07)	.41	2.09 (1.36–3.22)	<.0001
22–24	1.01 (0.96–1.07)	.57	2.71 (1.77–4.16)	<.0001
Race				
Non-Hispanic Black	reference	reference	reference	reference
Non-Hispanic White	0.98 (0.93–1.04)	.50	0.62 (0.22–1.78)	.38
Hispanic	0.77 (0.72–0.83)	<.0001	0.41 (0.11–1.51)	.18
Other[a]	0.99 (0.92–1.07)	.83	1.16 (0.35–3.90)	.81
Sex				
Male	reference	reference	reference	reference
Female	0.20 (0.18–0.22)	<.0001	0.57 (0.44–0.73)	<.0001
Zip income quartile				
Highest quartile	reference	reference	reference	reference
Lowest quartile	1.08 (1.01–1.15)	.03	1.24 (0.78–1.98)	.36
Second quartile	1.13 (1.04–1.24)	<.0001	1.26 (0.77–2.04)	.36
Third quartile	1.09 (1.02–1.16)	.01	1.18 (0.71–1.97)	.52
Primary payer				
Medicaid	reference	reference	reference	reference
Medicare	1.89 (1.73–2.06)	<.0001	1.15 (0.75–1.75)	.52
Private insurance	1.14 (1.08–1.20)	<.0001	1.39 (0.99–1.95)	.05
Self-pay	1.54 (1.44–1.64)	<.0001	1.53 (1.02–2.30)	.04
Other	—	—	—	—

Adjusted estimates were generated by using logistic regression models that considered the contributing influences of all the covariates. —, not applicable.
[a] The 'other' category for race in this study includes Asians or Pacific Islanders, Native Americans, mixed races, and those belonging to races other than the ones listed above.

limitations, our study was highly powered in detecting differences in hospitalizations and mortality associated with SCD because of the large sample size. The NIS data were composed of weighted national samples, representative of the entire population rendering the findings in this study to be generalizable.

CONCLUSION

Advancements in the medical management of SCD have resulted in a growing population of young adults living with SCD. Our updated analysis of the most recent national trends underscores the persistent vulnerability faced by individuals with SCD during the transition period. Hence, maximizing access to care is key. Furthermore, in this study, we highlight a role for hospitalists and in-hospital care models as a real-time stopgap for individuals who lack access to high-quality, comprehensive SCD programs.

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