Characterizing the Population with Severe Manifestations of Sickle Cell Disease Using US Real World Evidence

Clark Paramore[1], Amanda M. Kong[2], Sachiyo Minegishi[1], Weiliang Shi[1]

[1]bluebird bio, Cambridge, MA; [2]IBM Watson Health, Cambridge, MA

BACKGROUND

- Sickle cell disease (SCD) is a progressively debilitating and life-threatening, genetic disease characterized by hemolytic anemia, painful vaso-occlusive events (VOEs) and persistent vasculopathy that result in significant morbidity, poor quality of life, and early mortality.[1,2]
- In the United States (US), approximately approximately 100,000 individuals are living with SCD and it is estimated that SCD affects 1 in every 1,941 newborns.[1,3,4]
- Polymerization of abnormal, sickle hemoglobin leads to all of the acute and chronic complications of SCD.
- Given vaso-occlusion and vasculopathy in patients with SCD can occur in any organ, patients may experience a diverse set of clinical manifestations.[1] However, limited real world data are available on SCD clinical complications and their management, and further research is needed.[5]

OBJECTIVES

- To examine treatment patterns and the rates of clinical complications among patients with SCD in the US, across different age groups.
- To identify the proportion of patients with SCD in the US with clinical outcomes indicative of severe disease.
- To estimate lifetime costs for SCD in the US based on current, age-specific annual reimbursed amounts.

METHODS

Data Source

- These retrospective cohort analyses utilized patient-level data, accrued between January 1, 2010 and September 30, 2016, from three IBM Watson Health MarketScan research databases.
  - MarketScan® Commercial Claims and Encounters database (Commercial) contains the healthcare experience of approximately 93 million employees and their dependents, covered under a variety of fee-for-service and managed care health plans, between 2010 and 2016.
  - MarketScan® Medicare Supplemental and Coordination of Benefits database (Medicare) contains the healthcare experience of approximately 4.5 million retirees with Medicare supplemental insurance paid for by employers between 2010 and 2016.
  - MarketScan® Medicaid Multi-State database (Medicaid) contains the healthcare experience of approximately 18 million Medicaid beneficiaries across the US in the period between 2010 and 2016.

Inclusion Criteria

- Patients with ≥2 medical claims with a diagnosis code for SCD on separate dates (based on International Classification of Diseases, Ninth/ Tenth Edition, Clinical Modification codes) between January 1, 2010 and September 30, 2016 (Commercial/Medicare) or between January 1, 2010 and June 30, 2016 (Medicaid)
  - First claim for SCD during the given time period was defined as the index date
- Patients with ≥2 years of continuous health plan enrollment following the index date

METHODS (CONT'D)

Study Variables and Outcomes

- Demographic characteristics: Age, gender, US census region (for Commercial/Medicare only), and race (for Medicaid only).
- The following comorbidities, which occurred within the two years after the index date and were identified based on relevant diagnosis codes on medical claims: cardiomegaly, depression, anxiety, osteonecrosis, retinal disorders, pulmonary hypertension, chronic kidney disease, epilepsy, history of stroke, hyposplenism, leg ulcers, hepatitis C, and hepatitis B.
- Treatment approaches and severe clinical outcomes within the two years after the index date; identified using a pre-specified list of diagnosis, procedures, and drug codes:
  - Treatment approach
    1) ≥1 outpatient pharmacy claim for hydroxyurea
  - Severe clinical outcomes:
    1) ≥4 hospitalizations/emergency room (ER) visits for VOEs based on diagnosis codes for SCD indicating crisis (including splenic sequestration, but excluding acute chest syndrome [ACS])
    2) ≥1 medical claim with a diagnosis of stroke or history of stroke
    3) Chronic red blood cell (RBC) transfusions, i.e. claims for 8-14 transfusions each year
    4) ≥1 medical claim with a diagnosis of ACS
- Total costs (accruing from birth through an assumed life expectancy of 50 years) and their net present value (NPV) in 2018, estimated based on the annualized, age-specific, all-cause healthcare costs (the total paid amounts on all medical and pharmacy claims) for patients with SCD with ≥4 VOEs over a 2-year post-index date period; followed for a total of 4 years, and not undergoing chronic RBC transfusions or stem cell transplant.

RESULTS

- A total of 18,740 SCD patients met the study criteria; 61% were from the Medicaid database.
- Approximately half of the total sample (55%) were <18 years of age; and only 12% were ≥45 years of age as compared to nearly 40% of the general U.S. population;[6] there were slightly more females (56.4%) than males.
- The majority of the Commercial/Medicare patients (55.6%) were from the Southern US region and three-fourths of Medicaid patients (75.1%) were Black.

Table 1. Demographic Characteristics of SCD Patients

	Commercial/Medicare N=7,312	Medicaid N=11,428	Combined N=18,740
Mean age, years (SD)	28.3 (19.9)	14.7 (14.0)	20.0 (17.8)
Age group, years, N (%)			
0-17	2,744 (37.5%)	7,559 (66.1%)	10,303 (55.0%)
18-34	1,813 (24.8%)	2,690 (23.5%)	4,503 (24.0%)
35-44	1,059 (14.5%)	630 (5.5%)	1,689 (9.0%)
45-54	866 (11.8%)	394 (3.4%)	1,260 (6.7%)
55-64	540 (7.4%)	149 (1.3%)	689 (3.7%)
≥65	290 (4.0%)	6 (0.1%)	296 (1.6%)
Female, N (%)	4,251 (58.1%)	6,309 (55.2%)	10,560 (56.4%)
Geographic region,* N (%)			
Northeast	1,389 (19.0%)		
North Central	1,077 (14.7%)		
South	4,062 (55.6%)		
West	634 (8.7%)		
Missing	150 (2.1%)		
Race,* N (%)			
White		270 (2.4%)	
Black		8,581 (75.1%)	
Hispanic		123 (1.1%)	
Other		77 (0.7%)	
Missing		2,377 (20.8%)	

SCD, sickle cell disease

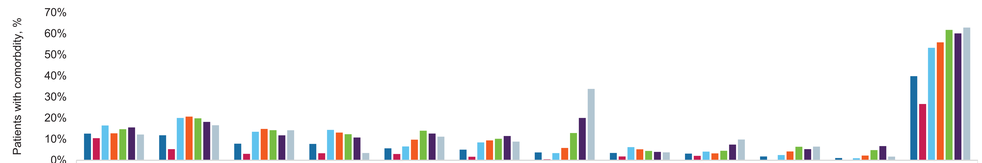
* Geographic region is only available for patients insured through commercial/Medicare plans and race is only available for patients insured through Medicaid.

RESULTS (CONT'D)

Comorbidities

- A total of 7,463 SCD patients (39.8%) had ≥1 of the 13 assessed comorbidities.
- The proportion of patients with ≥1 comorbidity increased with age: 26.6% of the patients <18 years old compared to between 53.3%-62.8% in each of the older age groups (≥18-34, 35-44, 45-54, 55-64, ≥65 years).
- The 5 most common comorbidities were cardiomegaly (12.6%), depression (11.8%), anxiety (7.8%), osteonecrosis (7.7%), and retinal disorders (5.6%).
- Prevalence of chronic kidney disease increased dramatically with age from 0.4% in patients <18 years to 33.8% in those 65+ years old.

Figure 1. Comorbidities among SCD patients over the two-year follow-up period



	Cardiomegaly (N=2,356)	Depression (N=2,213)	Anxiety (N=1,567)	Osteonecrosis (N=1,447)	Retinal Disorders (N=1,055)	PAH (N=936)	CKD (N=689)	Epilepsy (N=641)	Stroke/ Stroke History (N=584)	Leg Ulcers (N=333)	Hepatitis C (N=194)	Any Comorbidity (N=7,463)
Total	12.6%	11.8%	7.8%	7.7%	5.6%	5.0%	3.7%	3.4%	3.1%	1.8%	1.0%	39.8%
0-17 years	10.4%	5.2%	3.0%	3.3%	2.9%	1.6%	0.4%	1.8%	2.0%	0.2%	0.0%	26.6%
18-34 years	16.4%	20.0%	13.5%	14.4%	6.5%	8.4%	3.4%	6.2%	4.1%	2.4%	0.9%	53.3%
35-44 years	12.7%	20.7%	14.8%	13.1%	9.7%	9.4%	5.8%	5.2%	3.2%	4.1%	2.2%	55.8%
45-54 years	14.7%	19.8%	14.2%	12.3%	14.0%	10.2%	12.9%	4.4%	4.4%	6.3%	4.8%	61.7%
55-64 years	15.5%	18.1%	11.8%	10.7%	12.6%	11.5%	20.0%	3.9%	7.4%	5.2%	6.7%	60.1%
65+ years	12.2%	16.6%	14.2%	3.4%	11.1%	8.8%	33.8%	3.7%	9.8%	6.4%	1.7%	62.8%

CKD, chronic kidney disease; PAH, pulmonary hypertension; SCD, sickle cell disease. Notes: Hyposplenism, and hepatitis B were noted in <5% of total patients (data not shown) but contribute to the any comorbidity data.

Treatment with Hydroxyurea

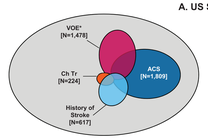
- 23.5% filled ≥1 prescription for hydroxyurea over a two-year period.
- The proportion of patients on hydroxyurea treatment decreased with age: 23.0% and 31.6% for 0-17 and 18-34 age groups, respectively, compared to 1.7% for 65+ age group.

Clinical Outcomes

- 31.8% of SCD patients <18 years old had ≥1 of the severe clinical outcomes of interest, as did 35.6% of SCD patients ≥18 years old.
- ACS was the most common severe clinical outcome (n=1,809 [17.6%]) among < 18 year old patients with SCD, while multiple VOE-related hospitalizations/ER visits (n=2,167 [25.7%]) was the most common among the adult group (≥18 years).
- Approximately one-third of SCD patients (36% among patients <18 years old and 29% among patients ≥18 years old) with multiple VOE-related hospitalizations/ER visits also had a medical encounter for ACS.
- Among patients <18 years old, there was little overlap between patients receiving chronic RBC transfusions and those with multiple VOE-related hospitalizations/ER visits (7%) or those with ACS (13%).
- Among patients ≥18 years old, between 26%-35% of patients with chronic transfusions, also had multiple VOE-related hospitalizations/ER visits, a medical encounter for ACS, or a medical encounter for stroke.

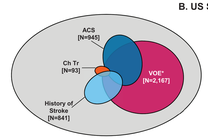
Figures 2A and 2B. Overlap of Clinical Outcomes* over the Two-Year Follow-Up Period

A. US SCD Ages <18 years (N=10,303)



	VOE*	ACS	History of Stroke	Ch Tr
Patient Totals	1,478	1,809	617	224
Patient also in:				
VOE*	100%	30%	16%	7%
ACS	36%	100%	24%	13%
History of Stroke	7%	8%	100%	48%
Ch Tr	1%	2%	17%	100%

B. US SCD Ages ≥18 years (N=8,437)



	VOE*	ACS	History of Stroke	Ch Tr
Patient Totals	2,167	945	841	93
Patient also in:				
VOE*	100%	67%	36%	35%
ACS	29%	100%	20%	26%
History of Stroke	14%	18%	100%	35%
Ch Tr	2%	3%	4%	100%

ACS, acute chest syndrome; Chr Transf, chronic transfusions; SCD, sickle cell disease; VOE, vaso-occlusive crisis event.

*Definitions of Clinical Outcomes

VOEs: ≥4 hospitalizations/ER visits for VOEs during the two years of follow-up.

History of stroke: ≥1 claim with a diagnosis of stroke or history of stroke during the two years of follow-up.

Chr Transf: 8-14 transfusions in each of two follow-up years.

ACS: ≥1 claim with a diagnosis of ACS during the two years of follow-up.

Lifetime Healthcare Costs for Patients with SCD

- Projected total lifetime healthcare costs (reported as mean [Q1, Q3]) for a subset of patients with SCD who had ≥4 VOEs over a 2-year period:
  - Medicaid: $2.5M ($1.2M, $3.3M), with 2018 NPV of $1.2M ($0.6M, $1.6M)
  - Commercial/Medicare: $4.0M ($1.9M, $5.3M), with 2018 NPV of $1.9M ($1.0M, $2.6M)
- By comparison, these SCD lifetime healthcare costs are 7-fold (Medicaid) and 11-fold (Commercial/Medicare) higher than the estimated per capita lifetime healthcare expenditures of the general US population ($165,000 NPV); and SCD patients accrue these costs over a shortened lifespan (i.e. approximately 50% reduced lifespan compared to overall US population).[7-12]
- For the 'very high cost' SCD patients in this analysis (i.e. 99th percentile), total costs averaged $770,000 for Medicaid and $1.7M for Commercial patients, in just a 4-year follow-up period post the index date.

LIMITATIONS

- Study limitations are those inherent to any retrospective claims-based studies including:
  - Data may be subject to coding error, and data entry error.
  - Findings may not be generalizable to patients without health insurance or patients with Medicaid in other states.
- The distribution of patients insured through commercial plans, Medicare supplemental plans, and Medicaid plans in the combined analyses may not be representative of the distribution of insurance type for the entire US population with SCD.
- Patients who did not have two years of continuous enrollment, including those who died within two years after their first SCD diagnosis recorded in the databases, were excluded.

CONCLUSIONS

- The age distribution of this observational SCD cohort is enriched for younger patients, which indicates there are still critical gaps in current standard of care in addressing the significant morbidity and early mortality of SCD.
- Based on this current real-world evidence in the US setting, there is a substantial proportion of the SCD population experiencing a range of comorbidities, with many affected by severe clinical manifestations of disease. This study focused on specific manifestations and further research is needed on the broader life impact for the entire SCD population.
- Chronic transfusion is recommended for patients with SCD who experienced stroke or are at risk of stroke; so the higher relative overlap in these groups is expected; but the results suggest that still many patients with SCD with stroke risk do not receive adequate care.
- Chronic transfusions are not necessarily indicated for treatment of recurrent VOEs or ACS in SCD patients, therefore lower utilization is expected.
- SCD patients' per capita, lifetime healthcare costs are 7-fold (Medicaid) to 11-fold (Commercial/Medicare) higher than general US population per capita, lifetime expenditures; and SCD patients accrue these substantial costs over a shortened lifespan (i.e. approximately 50% reduced lifespan compared to overall US population).

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DISCLOSURES

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