Hydroxyurea Use and Clinical Outcomes Among Adults with Severe Sickle Cell Disease: A retrospective Cohort Study using Electronic Health Record Data

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INTRODUCTION

- **The 2014 National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend hydroxyurea (HU) for adult patients with sickle cell anemia (SCA)[HbSS/HbSβ⁰ thalassemia] experiencing ≥3 moderate to severe vaso-occlusive crises (VOCs) within one year[1].**
- **Despite proven benefits, HU remains underutilized[2].**
- **Several limitations exist in the current literature evaluating HU use.**
  - Limited focus on guideline-based care.
  - Classification of non-SCA genotypes as "milder" forms of SCD is now challenged[3-4].
  - Growing evidence supports HU efficacy/effectiveness across multiple genotypes[5-6].
  - Previous studies relied heavily on ICD codes for genotypes.

OBJECTIVES

Primary Objective: To assess HU utilization rates at 30, 90, 180, and 365 days after HU is first recommended by clinical guidelines for adults with SCD across different genotypes.

Secondary Objective: To identify baseline demographic and clinical characteristics associated with HU utilization within 90 days after guidelines recommend HU use for adults with SCD.

METHODS

Data Source and Study Design: This retrospective cohort study analyzed Electronic Health Record (EHR) data from the University of Pittsburgh Medical Center (UPMC) from January 2014 to April 2024.

Population: Adult patients with SCD diagnosis and ≥3 VOCs per year.

VOC Definition: Pain crisis, Acute chest syndrome, Splenic sequestration, and Priapism.

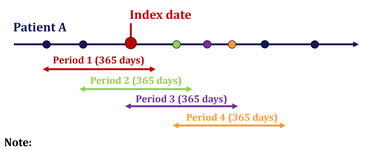
Exclusion Criteria: 1) HU treatment for hematologic malignancy and 2) history of hematopoietic stem cell transplantation (HSCT).

Index date: The date of the 3rd VOC-related Emergency Department or Inpatient visit of the earliest qualifying 1-year period for each patient.

Time Frame:

- **Primary Objective: 180** days before to **365** days after the index date.
- **Secondary Objective: 180** days before to **90** days after the index date.

Figure 1: Study Design Showing Index Date Definition



Note:
- Each dot represents a VOC-related visit.
- Colored dots indicate the 3rd visit within each period.

Study Outcomes and Analysis

Primary Objective:

- **Outcome:** HU utilization rates.
- **Analysis:** HU utilization was assessed descriptively.

Secondary Objective:

- **Outcome:** HU use within 90 days of the index date.
- **Independent variables:** Demographics (age, sex, race, SCD genotype), baseline clinical characteristics including blood transfusion history, opioid medication use, VOC frequency, and comorbidities (-180 ~ -1 Index Date).
- **Analysis:** Multivariable logistic regression to identify clinical and demographic factors associated with HU use.

RESULTS

Table 1: Baseline Characteristics of Adults with SCD and ≥3 VOCs within a year

	All	HU	No- HU	P-value
	N= (%)		N= (%)	
N	261	81	180	
Age Groups				
18~30	123(47.13)	52(64.20)	71(39.44)	**P<0.01[b]**
30~45	71(27.20)	23(28.40)	48(26.67)	
45+	67(25.67)	6(7.41)	61(33.89)	
Race				
Black/African American	206(78.93)	75(92.59)	131(72.78)	**P<0.05[b]**
Others	55(21.07)	6(7.41)	49(27.22)	
Sex				
Females	150(57.47)	40(49.38)	110(61.11)	P=0.08[c]
Males	111(42.53)	41(50.62)	70(38.89)	
HbSS/Sβ⁰				
Yes	159(60.92)	72(88.89)	87(48.33)	**P<0.01[b]**
Baseline Hydroxyurea Use				
Yes	75(28.74)	65(80.25)	10(5.56)	**P<0.01[b]**
Baseline Blood Transfusion				
Yes	22(8.43)	9(11.11)	13(7.22)	P=0.30[b]
Baseline Opioid Use				
Yes	89(34.40)	29(35.80)	60(33.33)	P=0.70[b]
Baseline VOC Count				
Mean ± SD	1.82±1.95	2.25±2.88	1.63±1.30	P=0.91[a]
Median (Q1, Q3)	1(1,2)	1(1,2)	2(1,2)	
Charlson Comorbidity Index				
0	132(50.57)	49(60.49)	83(46.11)	P=0.06[b]
1	91(34.87)	25(30.86)	66(36.67)	
2+	38(14.56)	7(8.64)	31(17.22)	
Stroke (Ischemic/Hemorrhagic)/[1]TIA				
Yes	16(6.13)	3(3.70)	13(7.22)	P=0.40[b]
Non-pain crisis [2]VOC complications: Acute chest syndrome / Splenic sequestration / Priapism				
Yes	55(21.07)	37(45.68)	18(10.00)	**P<0.01[b]**
Renal disease ([3]CKD, renal failure [acute or chronic], acute and chronic glomerulonephritis)				
Yes	22(8.43)	8(9.88)	14(7.78)	P=0.63[b]
Pulmonary complications: pneumonia / [4]URTI / pulmonary embolism / pulmonary [5]HTN				
Yes	65(24.90)	27(33.33)	38(21.11)	**P<0.05[c]**
Heart failure / [6]CAD				
Yes	20(7.66)	2(2.47)	18(10.00)	**P<0.05[b]**
Cardiometabolic complications: Diabetes / [5]HTN / Hyperlipidemia				
Yes	71(27.20)	11(13.58)	60(33.33)	**P<0.01[b]**
Anxiety / Depression				
Yes	77(29.50)	16(19.75)	61(33.89)	**P<0.05[b]**
Bipolar disorder/Schizophrenia				
Yes	25(9.58)	4(4.94)	21(11.67)	P=0.11[b]
Neoplasms				
Yes	21(8.05)	5(6.17)	16(8.89)	P=0.62[b]

Test performed: [a] Mann-Whitney U test, [b] Fisher's exact test, [c] Chi-square test

The following variables were not listed due to overall prevalence rates less than 5%: multiorgan failure, avascular necrosis, thrombosis, and leg ulcers.

Abbreviation:[1]TIA: Transient Ischemic Attack [2]VOC: Vaso-Occlusive Crisis [3]CKD: Chronic Kidney Disease [4]URTI: Upper Respiratory Tract Infection [5]HTN: Hypertension [6]CAD: Coronary artery disease

Figure 2: Hydroxyurea utilization rates, stratified by SCD genotype

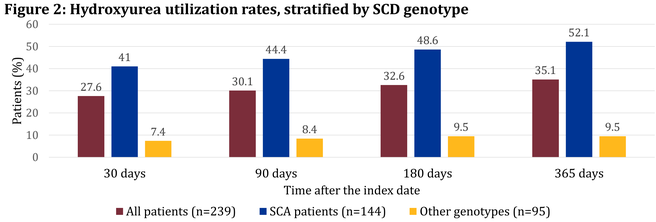


Figure 3: Adjusted Odds Ratios with 95% Confidence Interval for HU Utilization from Multivariate Logistic Regression (Adults with SCD and ≥3 VOCs within a year)

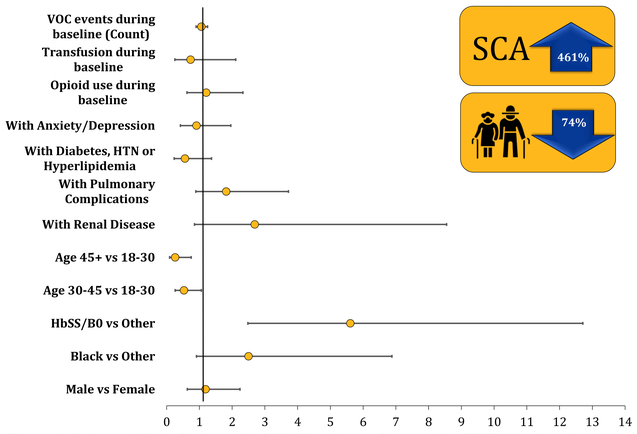
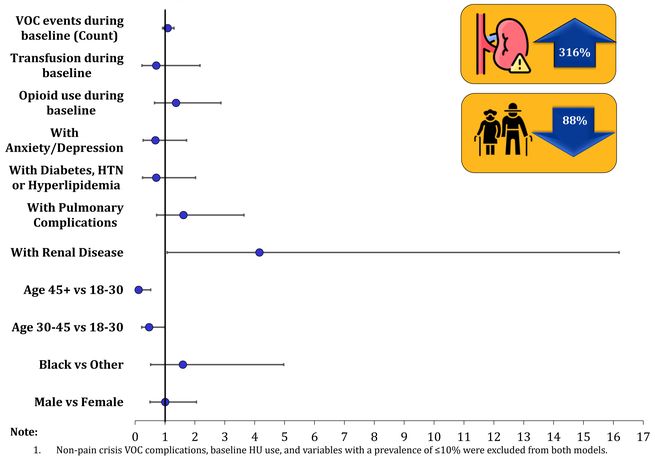


Figure 4: Adjusted Odds Ratios with 95% Confidence Interval for HU Utilization from Multivariate Logistic Regression (Adults with SCA and ≥3 VOCs within a year)



Note:
1. Non-pain crisis VOC complications, baseline HU use, and variables with a prevalence of ≤10% were excluded from both models.
2. Acute Chest Syndrome (ACS) was classified as a VOC event rather than a pulmonary complication to avoid double-counting, despite its clinical presentation often overlapping with pneumonia and other pulmonary manifestations.
3. Both models demonstrated good performance with no collinearity issues.

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CONCLUSIONS

Poor guideline adherence: HU utilization was highest among SCA patients, however, nearly 50% did not use HU within 1 year of eligibility.

Low Utilization in Non-SCA Genotypes: Among patients with non-SCA genotypes experiencing frequent severe VOCs, only 9.5% received HU within one year of eligibility.

Disparities in HU use: Older populations demonstrate lower HU utilization rates, potentially reflecting physicians' concerns about increased toxicity in older patients or decreased access to specialized care once patients leave the pediatric setting.

Early Initiation of HU Therapy: 80% of guideline-adherent patients had initiated HU before meeting current guideline criteria, which likely suggests:

1. Continuation of chronic therapy initiated during childhood through transition to adult care.
2. Treatment decisions were influenced by comorbidities (e.g., Renal Disease) rather than by guidelines based on VOC rate.

Genotype Impact on Treatment Decisions:

Genotype appears to play a strong role in HU utilization, warranting further investigation on the use of HU in non-SCA genotypes.

Limitations:

- Small sample size.
- The algorithm we applied for identifying SCA patients was only validated in pediatric populations.

Strengths:

- **Addresses Literature Gaps by:** Analyzing HU utilization across various genotypes based on guideline recommendations, applying a validated algorithm for genotype identification, and examining specific clinical factors influencing HU prescribing decisions.