

Predictors of Intensive Care Admission Among Adult Patients with Sickle Cell Disease in Eastern Province of Saudi Arabia

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Purpose: Sickle cell disease (SCD) comprises a complex group of hematologic disorders that are collectively the most common monogenic disorder and are associated with increased risk of intensive care unit admission (ICU). The purpose of this study is to investigate factors that predict admission of adult patients with SCD to the ICU.

Patients and Methods: This was a cross-sectional study that enrolled adult patients with SCD from Saudi Arabia.

Results: A total of 107 patients with SCD, with a median age 31.9±12.1 years, were evaluated retrospectively. Regarding predictors of ICU admission, patients who indicated a history of blood transfusions were at 8.047-fold higher risk of ICU admission (OR=8.047; 95% CI=2.392–27.07; $p=0.001$). Patients who started hydroxyurea were at least 3.071 times more likely to be admitted than those who did not (OR=3.071; 95% CI=1.164–8.104; $p=0.023$). We also observed three or more hospitalizations per year to be associated with increased risk of ICU admission (OR=3.393; 95% CI=1.285–8.960; $p=0.014$), with those making 3 to 5 visits annually having at least 10.4 times higher risk (OR=10.38; 95% CI=10.098–98.19; $p=0.041$) and those with 6 to 10 ER admissions having 18 times higher risk (OR=18.00; 95% CI=2.149–150.8; $p=0.008$). Finally, patients with high WBC were predicted to have at least 3.34 times higher risk of ICU admission (OR=3.337; 95% CI=1.131–9.846; $p=0.029$).

Conclusion: SCD is a multi-systemic disease associated with increased morbidity and mortality. Recognition of high-risk features in patients helps to eliminate subjectivity in ICU referral decision. Frequent hospitalization and emergency visits, multiple blood transfusions, and elevated white blood cell count were significantly associated with a higher rate of ICU admission despite hydroxyurea usage.

Keywords: sickle cell disease, intensive care unit, hydroxyurea

Introduction

Sickle cell disease (SCD) is a group of inherited red blood cell disorders caused by a mutation in the β -globin gene that results in the polymerization of hemoglobin S (HbS).¹ There are different forms of SCD, however the most prevalent and severe form is homozygous HbSS (sickle cell anaemia).¹ In Saudi Arabia, SCD affects 0.26% of the population, with another 4.2% having the sickle cell trait. The Eastern province has the highest prevalence, with 1.2% diseased and about 17% having the trait.²

Patients with SCD experience a wide range of clinical symptoms and consequences, such as vaso-occlusive crises, acute chest syndrome, chronic hemolytic anemia, and multiple organ failure. The majority of complications are manageable without need for critical care, but some have life-threatening effects and may require admission to the intensive care unit (ICU).^{2,3} Currently, a variety of therapeutic options are available including disease-modifying therapies like

hydroxyurea and simple or exchange blood transfusions, which can improve quality of life, reduce the complication rate, and possibly prolong survival. However, the only curative option is stem cell transplantation, and its use is limited due to a lack of suitable donors.^{1,4} Despite these advances in management, the life expectancy of adult SCD patients is approximately twenty years shorter than the general population, with half of the mortality occurring in the ICU.^{5,6}

Several studies have been conducted to determine predictors of ICU outcomes, with the need for renal replacement therapy, advanced age, fewer hospitalizations, and shorter stays in the ICU having all been linked to increased mortality rates in SCD patients.⁷ In addition, it has been reported that low hemoglobin levels, respiratory distress, and renal failure at the time of ICU admission are significant predictors of a complicated outcome.⁶ Ultimately, it is believed that reducing the need for ICU admission among SCD patients will lower mortality and unfavorable outcomes. Therefore, the purpose of the current study was to investigate factors that predict admission of adult patients with SCD to the ICU.

Materials and Methods

This was an observational retrospective cohort study conducted in Saudi Arabia's eastern province, where SCD is more common than in other regions. All homozygous sickle cell patients between the age of 18 and 65, who attended hematology clinics or were admitted to King Fahad Hospital or Prince Saud Bin Jalawi Hospital between June and December 2022 were included in the study.

Participants initially underwent a survey through an interview conducted by a trained team member to collect demographic and clinical characteristics including age, education level, frequency of hospitalization, emergency visits, blood transfusion, previous ICU admission, frequency of ICU admission, cause of ICU admission, using and awareness about hydroxyurea. Hospital's electronic database was used to collect baseline patient's laboratory data from the most recent outpatient visit before ICU admission including complete blood count, hemoglobin electrophoresis, lactate dehydrogenase (LDH), and kidney function tests. Of note, using hydroxyurea was considered if patients have been on it for at least 2 months.

The study was approved by King Fahad Hospital's Ethical Committee (KFHH RCA 33-42-2021). Also, the purpose of the study, the use of data, benefits of doing this research, the right to participate, and the confidentiality and anonymity of the data were explained to the participants and informed consent was taken.

Analyses were performed using the Statistical Package for Software Sciences (SPSS) version 26 (IBM Corporation, Armonk, New York). Descriptive statistics were computed and are reported as frequencies and proportions (%) for categorical variables or means and standard deviations for continuous variables. Univariate regression analysis was performed to determine predictors of ICU admission with corresponding odds ratio (OR) and 95% confidence interval (CI). Statistical significance was identified at $p < 0.05$.

Results

A total of 107 patients with sickle cell disease were reviewed. As described in [Table 1](#), more than half (52.3%) were aged 30 years or less, and the majority were female (60.7%). Patients with bachelor's degrees constituted 40.2% of participants. The proportion with previous blood transfusions was 86.9%, with 30 (28%) who reported having more than 10 blood transfusions throughout their life. Around two-thirds (71%) were aware of hydroxyurea, but less than half (46.7%) had started using it. As regards hospitalizations, 11.2% had more than 10 hospitalizations per year, and 26.2% had that many emergency visits per year. A history of ICU admission was reported by 75.7%, and nearly one-third (31.8%) of participants had 2 to 5 times ICU admission per year. Among those with a previous ICU admission, 21% had received hydroxyurea. Moreover, the most common reason being acute chest syndrome (ACS) (49.4%) ([Figure 1](#)). The mean values of leukocyte count, hemoglobin level, and platelet were 10.4, 8.74, and 326, respectively. Other participants' baseline laboratory parameters are shown in [Table 2](#).

Regarding predictors of ICU admission, univariate analyses revealed previous blood transfusions, hydroxyurea initiation, frequency of hospitalizations per year, frequency of emergency visits per year, frequency of blood transfusions throughout life, and high WBC to be independent significant predictors of ICU admission. Specifically, compared to patients without a history of blood transfusion, those who indicated a history of blood transfusions were at 8.047-fold higher risk of ICU admission (OR=8.047; 95% CI=2.392–27.07; $p=0.001$). Patients who started hydroxyurea were predicted to have at least 3.071 times

Table 1 Demographic and Clinical Characteristics of the Patients (n=107)

Variable	N (%)
Age in years (mean ± SD)	31.9 ± 12.1
• ≤30 years	56 (52.3%)
• >30 years	51 (47.7%)
Gender	
• Male	42 (39.3)
• Female	65 (60.7)
Educational level	
• Illiterate	06 (05.6)
• Primary	11 (10.3)
• Intermediate	22 (20.6)
• Secondary education	43 (40.2)
• Bachelor's degree	22 (20.6)
• Master's degree	03 (02.8)
Complication and Comorbidity	
• Stroke	03 (02.8)
• Cholecystectomy	42 (39.3)
• Splenectomy	18 (16.8)
Previous blood transfusion	93 (86.9)
• Frequency of blood transfusions throughout life?	
• <3 times	25 (23.4)
• 3–5 times	29 (27.1)
• 6–10 times	23 (21.5)
• >10 times	30 (28.0)
Awareness about hydroxyurea	76 (71)
Hydroxyurea use	50 (46.7)
Frequency of hospitalization per year	
• <3 times	55 (51.4)
• 3–5 times	27 (25.2)
• 6–10 times	13 (12.1)
• >10 times	12 (11.2)

(Continued)

Table 1 (Continued).

Variable	N (%)
Frequency of emergency visit per year	
• <3 times	18 (16.8)
• 3–5 times	30 (28.0)
• 6–10 times	31 (29.0)
• >10 times	28 (26.2)
Previous ICU admission	81 (75.7)
• Frequency of ICU admission	
• One time	33 (30.8)
• 2–5 times	34 (31.8)
• More than 5 times	14 (13.1)
• No ICU Admission	26 (24.3)
Use of hydroxyurea during ICU admission ⁽ⁿ⁼⁸¹⁾	17 (21.0)

greater risk than those who did not (OR=3.071; 95% CI=1.164–8.104; $p=0.023$). Meanwhile, three or more hospitalizations per year was associated with 3.393-fold higher risk (OR=3.393; 95% CI=1.285–8.960; $p=0.014$), 3–5 blood transfusions with 8.862-fold higher risk (OR=8.862; 95% CI=2.643–29.71; $p<0.001$), and >5 transfusions with 4.320-fold higher risk (OR=4.320; 95% CI=1.287–14.51; $p=0.018$). Likewise, compared to patients with less than 3 ER visits per year, those who had 3 to 5 visits had at least 10.4 times higher risk of ICU admission (OR=10.38; 95% CI=10.098–98.19; $p=0.041$), those with 6 to 10 ER admissions had 18 times higher risk (OR=18.00; 95% CI=2.149–150.8; $p=0.008$), and those with more than 10 ER admissions had 9.39 times higher risk (OR=9.391; 95% CI=1.092–80.78; $p=0.041$). Finally, patients with high WBC were predicted to have at least 3.34 times higher risk of ICU admission than those with low WBC (OR=3.337; 95% CI=1.131–9.846; $p=0.029$). (Table 3).

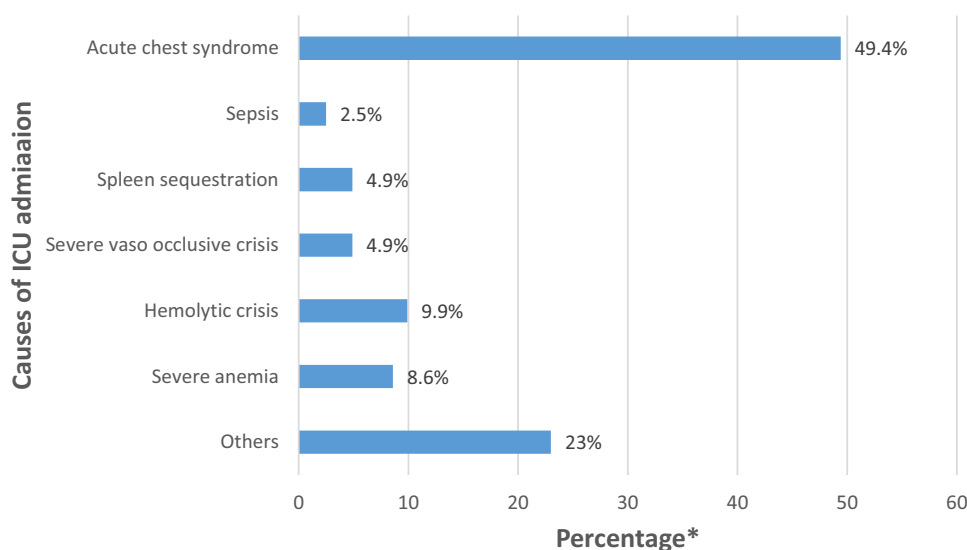


Figure 1 Causes of intensive care unit admission for sickle cell patients.
Note: *Percentage ≠ 100.

Table 2 Baseline Laboratory Data ⁽ⁿ⁼¹⁰⁷⁾

Variable	Mean ± SD
Leukocyte count, 10 ⁹ /L	10.4 ± 5.04
Hemoglobin level, g/dL	8.74 ± 1.54
Platelet, 10 ⁹ /L	326.0 ± 180.8
MCV, fL	78.3 ± 11.3
HbA, %	8.99 ± 16.5
HbA2, %	3.22 ± 1.08
HbS, %	74.4 ± 14.1
HbF, %	14.5 ± 6.89
LDH, U/L	415.1 ± 201.9
BUN, mmol/L	3.35 ± 2.35
Creatinine, µmol/L	52.1 ± 34.1
Total Bilirubin, µmol/L	45.2 ± 42.0
Direct Bilirubin, µmol/L	11.4 ± 14.5
Albumin, g/L	37.4 ± 4.97
AST, IU/L	37.7 ± 19.6
ALT, IU/L	32.4 ± 26.0

Abbreviations: MCV, Mean corpuscular volume; LDH, lactate dehydrogenase enzyme; BUN, Blood Urea Nitrogen; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase.

Table 3 Univariate Logistic Regression Analysis

Variables	ICU Admission		Univariate	
	Yes N (%) ⁽ⁿ⁼⁸¹⁾	No N (%) ⁽ⁿ⁼²⁶⁾	OR (95% CI)	P-value
Age group				
• ≤30 years	40 (49.4%)	16 (61.5%)	Ref 1	0.283
• >30 years	41 (50.6%)	10 (38.5%)	640 (0.665–4.043)	
Gender				
• Male	33 (40.7%)	09 (34.6%)	Ref	0.578
• Female	48 (59.3%)	17 (65.4%)	0.770 (0.306–1.935)	
Previous blood transfusion				
• Yes	76 (93.8%)	17 (65.4%)	8.047 (2.392–27.07)	0.001 **
• No	05 (06.2%)	09 (34.6%)	Ref	
Splenectomy				
• Yes	17 (21.0%)	01 (03.8%)	6.641 (0.839–52.58)	0.073
• No	64 (79.0%)	25 (96.2%)	Ref	

(Continued)

Table 3 (Continued).

Variables	ICU Admission		Univariate	
	Yes N (%) (n=81)	No N (%) (n=26)	OR (95% CI)	P-value
Cholecystectomy				
• Yes	35 (43.2%)	07 (26.9%)	2.065 (0.782–5.457)	0.144
• No	46 (56.8%)	19 (73.1%)	Ref	
Hydroxyurea Use				
• Yes	43 (53.1%)	07 (26.9%)	3.071 (1.164–8.104)	0.023 **
• No	38 (46.9%)	19 (73.1%)	Ref	
• <3 times	36 (44.4%)	19 (73.1%)	Ref	
• ≥3 times	45 (55.6%)	07 (26.9%)	3.393 (1.285–8.960)	0.014 **
Number of emergency visit per year				
• <3 times	13 (16.0%)	05 (19.2%)	Ref	0.041 **
• 3–5 times	18 (22.2%)	12 (46.2%)	10.38 (1.098–98.19)	0.008 **
• 6–10 times	23 (28.4%)	08 (30.8%)	18.00 (2.149–150.8)	0.0401 **
• >10 times	27 (33.3%)	01 (03.8%)	9.391 (1.092–80.78)	
Frequency of blood transfusion				
• <3 times	13 (16.0%)	12 (46.2%)	Ref	
• 3–5 times	20 (24.7%)	09 (34.6%)	8.862 (2.643–29.71)	<0.001 **
• >5 times	48 (59.3%)	05 (19.2%)	4.320 (1.287–14.51)	0.018 **
WBC				
• Low	04 (04.9%)	02 (07.7%)	Ref	
• Normal	41 (50.6%)	19 (73.1%)	3.600 (0.518–25.00)	0.195
• High	36 (44.4%)	05 (19.2%)	3.337 (1.131–9.846)	0.029 **
Hemoglobin				
• Low	80 (98.8%)	26 (100%)	–	1.000
• Normal	01 (01.2%)	0	Ref	
Platelet				
• Low	13 (16.0%)	04 (15.4%)	Ref	
• Normal	39 (48.1%)	13 (50.0%)	0.991 (0.258–3.814)	0.990
• High	29 (35.8%)	09 (34.6%)	1.074 (0.405–2.851)	0.886
MCV				
• Low	40 (49.4%)	16 (61.5%)	Ref	
• Normal	37 (45.7%)	10 (38.5%)	1.480 (0.597–3.669)	0.397
• High	04 (04.9%)	0	–	–
LDH				
• Low	01 (01.3%)	0	Ref	
• Normal	24 (31.2%)	09 (37.5%)	–	–
• High	52 (67.5%)	15 (62.5%)	1.300 (0.499–3.387)	0.591

(Continued)

Table 3 (Continued).

Variables	ICU Admission		Univariate	
	Yes N (%) (n=81)	No N (%) (n=26)	OR (95% CI)	P-value
BUN				
• Low	09 (11.1%)	04 (15.4%)	Ref	
• Normal	65 (80.2%)	22 (84.6%)	1.313 (0.368–4.691)	0.675
• High	07 (08.6%)	0	–	–
Creatinine				
• Low	43 (53.1%)	13 (50.0%)	Ref	
• Normal	35 (43.2%)	12 (46.2%)	0.907 (0.087–9.478)	0.935
• High	03 (03.7%)	01 (03.8%)	1.029 (0.097–10.85)	0.981
Na				
• Low	04 (04.9%)	0	Ref	
• Normal	77 (95.1%)	26 (100%)	–	0.570
T. Bilirubin				
• Normal	14 (17.5%)	07 (26.7%)	Ref	
• High	66 (82.5%)	19 (73.1%)	1.737 (0.613–4.919)	0.299
D. Bilirubin				
• Normal	21 (26.3%)	11 (42.3%)	Ref	
• High	59 (73.8%)	15 (57.7%)	2.060 (0.818–5.189)	0.125
Albumin				
• Low	24 (31.2%)	04 (17.4%)	Ref	
• Normal	53 (68.8%)	19 (82.6%)	0.465 (0.143–1.515)	0.204
AST				
• Normal	27 (33.8%)	12 (46.2%)	Ref	
• High	53 (66.3%)	14 (53.8%)	1.683 (0.684–4.137)	0.257
ALT				
• Normal	50 (62.5%)	17 (65.4%)	Ref	
• High	30 (37.5%)	09 (34.6%)	1.133 (0.449–2.861)	0.791
	Mean ± SD	Mean ± SD		
HbA	9.22 ± 16.7	8.23 ± 16.4	0.996 (0.967–1.027)	0.806
HbA2	3.31 ± 1.12	2.94 ± 0.95	0.709 (0.442–1.136)	0.153
HbS	74.6 ± 14.1	73.9 ± 14.2	0.997 (0.966–1.030)	0.862
HbF	14.2 ± 7.13	15.5 ± 6.12	1.028 (0.962–1.099)	0.409

Notes: **Significant at p<0.05 level.

Discussion

Although considered the most common monogenic disorder, sickle cell disease comprises a complex group of hemato-logic disorders with multiple mechanisms involved in their pathophysiologies.^{8,9} The clinical heterogeneity and complex-ity of the disease are further modulated by fetal hemoglobin concentration and coincident alpha thalassemia. Thus, the

SCD disease course spans a spectrum from very benign to very severe, with corresponding increases in morbidity and mortality.^{10,11} A previous study revealed that half of the mortality of individuals with SCD occurs in the ICU, with acute chest syndrome being the most common reason for admission.⁶ In our study, we found that around two-thirds of participants had required ICU admission at least once in their lifetime, with acute chest syndrome the most common reason for admission. Interestingly, participants taking hydroxyurea were more likely to be admitted compared to those who did not. This raises a concern that while hydroxyurea is an effective treatment, SCD is a complex disease and a multimodal approach likely remains needed.^{8,12} However, it is important to note that our study did not address whether patients were on the maximum tolerated dose of hydroxyurea or not and at which age hydroxyurea was offered.^{13,14}

Several previous studies have reported concurring findings of increased risk of mortality among patients with SCD admitted to the ICU. In addition, five-year mortality is linked with a history of long ICU stay.^{15,16} Several predictors of increased mortality at ICU admission or during an ICU stay have been reported among patients with SCD; these include older age, renal replacement therapy, and frequent hospitalization use of inotropic support or mechanical ventilation.^{7,17} To our knowledge, the present work is the first study to address predictors of ICU admission among patients with SCD. Our result found that patients with three or more annual hospitalizations and emergency visits were at higher risk of ICU admission. Additionally, although red blood cell transfusion is an established treatment option for prevention of chronic organ damage, preoperative care, and acute complications of SCD, particularly acute chest syndrome, we found that history of previous blood transfusions of more than three was a significant predictor for ICU admission.^{16,18} These findings support a previous report of SCD patients having received exchange transfusions a few days prior to ICU admission; these patients may have an increased rate of alloimmunization and risk of delayed hemolytic transfusion reaction.^{19,20}

Sickle cell disease is characterized by heightened inflammation involving leukocytes, platelets, and endothelial cells, and also by inflammation resolution failure. We observed that patients with high white blood cell count were at higher risk to be admitted compared to those with low counts. Meanwhile, baseline thrombocytosis or thrombocytopenia were poorly correlated with ICU admission in our study, which is contrary to prior findings that thrombocytopenia is a poor prognostic indicator among ICU-admitted SCD patients.^{21,22}

This study illuminated characteristics that are predictors of ICU admission among patients with SCD. These include frequent hospitalization and emergency visits, multiple blood transfusions and elevated white blood cell count; moreover, admission increased despite hydroxyurea usage. The constellation of these factors could be translated into a scoring system that could be utilized to identify a high-risk group for early initiation of disease-modifying agents and to make early referrals to the ICU in order to achieve better outcomes. However, our study is limited by its retrospective nature and by physician-to-physician variability in making the decision for ICU admission. On this basis, prospective future studies are required, with the consideration of hydroxyurea usage duration and being on the maximum tolerated dose are crucial.

Conclusion

In conclusion, SCD is a multi-systemic disease associated with increased morbidity and mortality, and has a complex pathophysiology that mandates a multimodal treatment approach. Frequent hospitalization and emergency visits, multiple blood transfusions, and elevated white blood cell count were significantly associated with higher rate of ICU admission despite hydroxyurea usage. Recognition of these high-risk features in patients and establishment of severity scoring system can prompt initiation of a disease-modifying agent at a younger age and help to eliminate subjectivity in the timing of an ICU referral.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical

The study was conducted in accordance with the Declaration of Helsinki and approved by King Fahad Hospital's Ethical Committee (KFHH RCA 33-42-2021). All participants provided informed consent before participation.

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Disclosure

The authors report no conflicts of interest in this work.

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