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Predicting Acute Chest Syndrome Risk in Sickle Cell Anemia Children During Vaso-occlusive Crisis Hospitalizations

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Abstract

Sickle cell anemia (SCA) is a globally prevalent inherited condition, with acute chest syndrome (ACS) being one of its most severe complications. ACS frequently leads to hospitalization, necessitates intensive care unit (ICU) admission, and can even result in death. This research aimed to discern early indicators of impending ACS in children with SCA who were initially hospitalized due to painful vaso-occlusive crises (VOC).

A retrospective, case-control investigation was carried out at the King Saud Medical City in Riyadh, Saudi Arabia, encompassing 120 patients aged 1 to 14 years from January 2021 to December 2022. Patients were classified into two groups: those who developed ACS during hospital stay (cases) and those who did not develop ACS (controls). The study compared demographic factors, laboratory results, vital and clinical signs, and treatment protocols between these groups.

Findings revealed that a previous diagnosis of asthma, a history of ACS, recent upper respiratory tract symptoms prior to admission, and the need for a blood transfusion within the first 24 hours of admission due to a drop in hemoglobin levels were all significant predictors of impending ACS. Further regression analysis indicated that elevated steady-state mean corpuscular volume (MCV), leukocyte count, total bilirubin, and an increased absolute neutrophil count (ANC) level 24 hours post-admission also foreshadowed impending ACS in patients admitted for VOC.

Additionally, the location of pain was found to be significant with ACS incidence being higher in patients experiencing back pain, while patients with pain confined to the limbs had a lower incidence of ACS during admission.

The average duration of hospital stay was notably longer for the ACS group, averaging 7.6 days compared to 5.8 days for VOC alone. 15.7% of patients initially admitted with VOC were diagnosed with ACS. Most ACS cases were managed with transfusions and antibiotics, and nearly one-third of patients required admission to an ICU or high dependency area.

Introduction and Background

Sickle cell anemia (SCA) is a prevalent genetic disorder in Saudi Arabia **[1, 2]**, characterized by hemolytic anemia and abnormal shaping of red blood cells. **[3]** Although its incidence is substantial, the full prevalence of SCA has been historically underestimated due to a lack of neonatal screening, **[4]** a situation that has begun to change with the recent implementation of neonatal screening in 2023. In Saudi Arabia, Sickle cell disorders carrier status ranges between 2% and 27%, with an estimated 1.4% of individuals diagnosed with the disease in eastern region of the country. **[4]** This high prevalence is linked to the substantial rate of consanguineous marriages, which reached 52%.**[5]**

One of the most severe complications of SCA is acute chest syndrome (ACS), an acute illness characterized by new segmental pulmonary infiltrate associated with fever and/or various respiratory

symptoms. **[1]** ACS accounts for a notable 43% of pediatric SCA-related admissions to the intensive care unit (ICU) and is the leading cause of death in patients with SCA, underscoring the crucial need for early diagnosis and intervention. **[1, 2, 6, 7]**

Previous research has demonstrated a temporal relationship between ACS and vaso-occlusive crises (VOC) in SCA patients. Studies have found that nearly half of ACS cases are diagnosed 2 to 3 days after admission for an acute painful crisis. **[1] [8]**

One retrospective study showed that 33% of patients who were diagnosed with ACS had sought medical advice for prodromal symptoms prior to the diagnosis of ACS itself. **[9]**

Additionally, elevated serum phospholipase A2 levels and a decline in platelet count greater than 10% have been shown to be significant predictors for the development of ACS in adult with SCA. **[10]**

A 2020 retrospective case-control study conducted in adult SCA patients demonstrated that asplenia, fever, reduced oxygen saturation, along with low hemoglobin and leukocytosis, are important risk factors for the onset of ACS. **[11]**

A variant of rapidly progressive ACS can quickly develop from mild hypoxemia to severe respiratory failure within just 24 hours, even in cases where chest X-ray results are normal. This rapid progression can potentially advance to multiorgan failure and death. This ACS variant mainly found in adult but can happen also in children. **[1] [12, 13]**

Despite extensive research into SCA and ACS, understanding of ACS risk determinants in pediatric SCA patients admitted for VOC is still incomplete. The current body of literature is limited, encompassing only a few adult studies [11, 14] and a single prospective pediatric study by Madhi et al. Their research pinpointed laboratory metrics (such as reticulocyte and neutrophil counts) and clinical indicators (including pain score and location) as potential harbingers of ACS. Additionally, variations in leukocyte count and CRP levels on the second day of admission were highlighted as notable predictors.[15]

Despite the strides being made, a significant gap still exists in our understanding of the risk factors for ACS in pediatric patients with SCA admitted due to VOC. This study aims to fill this gap by investigating these risk factors in a large cohort of patients through a retrospective chart review at one of Saudi Arabia's large pediatric hematology centers. Our goal is to enhance our understanding of these risk factors in order to improve patient care and outcomes for children with SCA admitted for VOC.

Materials and Methods

Study Design and Context

This study is a retrospective, case-control study carried out at the Pediatric Hematology and Oncology Department of King Saud Medical City, a tertiary care hospital situated in Riyadh, Saudi Arabia.

Study Participants

The study included pediatric patients aged between 1 and 14 years, diagnosed with sickle cell anemia (SCA), who were admitted due to vaso-occlusive pain crises (VOC) within a two-year period from January 2021 to December 2022.

Inclusion and Exclusion Criteria

Participants were considered eligible if they were diagnosed with SCA (either HbSS or HbS-β0 thalassemia) and were admitted during the study period for VOC. Exclusion criteria included having other SCA subtypes, being diagnosed with Acute chest syndrome (ACS) on the first day of admission, or being on a chronic transfusion program.

Data Collection

Data were obtained from electronic medical records. The collected demographic and clinical information encompassed age, gender, SCA type, details of pain, history of asthma/ACS, respiratory examination findings, and oxygen saturation at admission. Laboratory data incorporated complete blood counts, bilirubin, and hemoglobin levels at routine clinic visits, on emergency room arrival, and 24 hours post-admission. Instances, timing, management, and outcomes of ACS were also documented.

Definitions

SCA was defined as either Sickle Cell SS disease or S-beta zero thalassemia [16]. A VOC was designated as a hospitalization due to pain that necessitated parenteral narcotics. ACS was defined as any respiratory symptom, chest pain, or fever associated with a new lung infiltrate on chest x-ray [8]. A history of asthma was defined based on a pediatrician's report or a prescription history of asthma controller medication.

Ethical Considerations

The study received approval from the institutional ethics review board at research center in King Saud medical city Riyadh. Confidentiality was maintained for all patient data throughout the study. Given the retrospective chart review nature of the study, patient consent was not needed.

Statistical Analysis

Categorical variables were displayed as numbers and percentages. Continuous variables were depicted as mean and standard deviation. The relationship between ACS development and demographic/clinical characteristics was assessed using Chi-square tests and independent sample t-tests. Univariate and multivariate logistic regression analyses were conducted to identify predictors of ACS, and odds ratios and 95% confidence intervals were calculated. Paired t-tests were employed to compare laboratory values

at baseline, upon arrival at the emergency department, and 24 hours after admission. A p-value of less than 0.05 was deemed statistically significant. All analyses were performed using the SPSS version 26.

Result

In this retrospective study, our aim was to pinpoint risk factors for Acute chest syndrome (ACS) during hospital stays for vaso-occlusive crises (VOC) in children with sickle cell anemia. The study involved 197 VOC admissions from 120 pediatric patients over two years at a tertiary hospital.

In the patient demographic profile (Table 1), 50.8% of the patients were between 8 to 14 years old, with a mean age of 7.33 years (± 3.17). Females made up 55.8%, and a dominant 93.4% were of Saudi ethnicity and 74.1% of these patients had multiple hospital admissions in the studied period. Hemoglobin SS was the most frequently observed form (80%) of SCA, and 45.1% were taking Hydroxyurea before admission. Past medical histories revealed that 16.8% had asthma, 24.9% had previously experienced ACS, and 14.7% had a recent upper respiratory tract infection (URTI).

Table 1
Relaionship between ACS development among the episode demographic and clinical characteristics
(n=197)

Factor	All VOC admissions	ACS during VOC admission		P-value §
	N (%) (n=197)	Yes N (%) (n=31)	No N (%) (n=166)	
Age group				
• 1–7 years	97 (49.2%)	10 (32.3%)	87 (52.4%)	**0.039 ** **
• 8–14 years	100 (50.8%)	21 (67.7%)	79 (47.6%)	
Gender				
• Male	87 (44.2%)	12 (38.7%)	75 (45.2%)	0.505
• Female	110 (55.8%)	19 (61.3%)	91 (54.8%)	
Number of episodes for the patient during the study period				
• Single	51 (25.9%)	08 (25.8%)	43 (25.9%)	0.991
• Multiple	146 (74.1%)	23 (74.2%)	123 (74.1%)	
Type of SCA				
• Hemoglobin SS	152 (80.0%)	25 (83.3%)	127 (79.9%)	0.661
• HbS/β0 Thalassemia	37 (19.5%)	05 (16.7%)	32 (20.1%)	
Previous diagnosis of asthma No (%)	33 (16.8%)	13 (41.9%)	20 (12.0%)	**< 0.001 ** **

† Some patients have more than one finding.

§ P-value has been calculated using Chi-square test.

** Significant at p < 0.05 level.

SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome

Factor	All VOC admissions	ACS during VOC admission		P-value §
	N (%) (n=197)	Yes N (%) (n=31)	No N (%) (n=166)	
Previous acute chest syndrome	49 (24.9%)	13 (41.9%)	36 (21.7%)	**0.017 ** **
Previous PICU admission for ACS	24 (12.2%)	05 (16.1%)	19 (11.4%)	0.464
Previous history of splenectomy	25 (12.7%)	03 (09.7%)	22 (13.3%)	0.772
Recent history of URTI within one week of visit? (n=95)	29 (14.7%)	11 (64.7%)	18 (23.1%)	**0.001 ** **
On Hydroxyurea before admission	89 (45.1%)	18 (58.1%)	71 (42.8%)	0.116
Symptoms upon presentation to ER †				
• Cough	20 (10.2%)	05 (16.1%)	15 (09.0%)	0.326
• SOB	06 (3.1%)	01 (03.2%)	05 (03.0%)	1.000
• Fever	65 (32.9%)	07 (22.6%)	58 (34.9%)	0.179
Duration of pain before visit				
• One day	117 (59.4%)	16 (51.6%)	101 (60.8%)	0.287
• Two days	48 (24.4%)	11 (35.5%)	37 (22.3%)	
• Three days	32 (16.2%)	04 (12.9%)	28 (16.9%)	
Pain severity				

† Some patients have more than one finding.

§ P-value has been calculated using Chi-square test.

** Significant at p < 0.05 level.

SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome

Factor	All VOC admissions	ACS during VOC admission		P-value §
	N (%) (n=197)	Yes N (%) (n=31)	No N (%) (n=166)	
• Mild	76 (38.6%)	10 (32.3%)	66 (40.7%)	0.070
• Moderate	92 (46.7%)	20 (64.5%)	72 (44.4%)	
• Severe	25 (12.7%)	01 (03.2%)	24 (14.8%)	
Site of pain †				
• Back	104 (52.7%)	23 (74.2%)	81 (48.8%)	**0.009 ****
• Only upper and/or lower limb	51(25.8%)	03 (09.7%)	48 (28.9%)	**0.025 ****
• Chest/Sternum	32(16.2%)	07 (22.6%)	25 (15.1%)	0.297
• Upper limb	57(28.9%)	04 (12.9%)	53 (31.9%)	**0.032 ****
• Lower limb	104(52.7%)	14 (45.2%)	90 (54.2%)	0.354
• Abdomen	52(26.3%)	08 (25.8%)	44 (26.5%)	0.935
• Diffuse	19(09.6%)	02 (06.5%)	17 (10.2%)	0.512
† Some patients have more than one finding.				
§ P-value has been calculated using Chi-square test.				
** Significant at p < 0.05 level.				
SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome				

Upon admission, 98% of patients exhibited normal chest examinations. Moderate pain was reported in 46.7% of cases, while 44.2% underwent chest X-rays in the emergency room (ER). There were several factors significantly linked with an increased risk for ACS: older age (p = 0.039), a history of asthma (p < 0.001), prior ACS (p = 0.017), recent URTI (p = 0.001), and back pain (p = 0.009). Surprisingly, isolated limb

pain was linked with a decreased risk (p = 0.025, p = 0.032). The use of Hydroxyurea before admission didn't significantly alter the risk of developing ACS (p = 0.116). (Table 1)

In the ER (Table 2), decreased mean oxygen saturation was linked with a higher risk of ACS during hospitalization (p = 0.004). Fever ≥ 38°C in the ER was seen in 17.3% of cases, and a mere 3% had oxygen saturation < 94% initially in the ER.

Table 2
Initial vitals signs at the emergency department in relation to ACS development during VOC admission (n=197)

Vital signs	All VOC admissions	ACS during VOC admission		P-value §
	Mean ± SD	Yes	No	
		Mean ± SD	Mean ± SD	
Axillary body temperature, C‡	37.2 ± 0.75	37.2 ± 0.73	37.2 ± 0.75	0.094
Heart rate, beats/minutes‡	121.7 ± 20.5	127.8 ± 18.6	121.1 ± 20.9	0.351
Respiratory rate, breaths/minute‡	26.8 ± 3.78	26.7 ± 3.01	26.8 ± 3.91	0.876
Oxygen saturation (%)‡	97.4 ± 2.23	96.3 ± 2.30	97.6 ± 2.16	**0.004 ******
Documented Fever 38 C or more in ED N(%)§	34 (17.3%)	05 (16.1%)	29 (17.5%)	0.856
Oxygen saturation Less Than 94 in ED N(%)§	06 (03.0%)	03 (09.7%)	03 (01.8%)	0.051
§ P-value has been calculated using Chi-square test.				
‡ P-value has been calculated using independent sample t-test.				
** Significant at p < 0.05 level.				
SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome, ED emergency department				

Laboratory findings (Table 3) showed that a higher leukocyte count, platelet count, mean corpuscular volume, and total bilirubin at baseline were associated with more risk for post admission ACS (p < 0.05). Elevated neutrophil count, mean corpuscular volume, and platelet count in the emergency department (ED) were also associated with ACS occurrence (p < 0.05). Lower hemoglobin levels in the ED and a larger drop from baseline were significantly associated with ACS (p ≤ 0.019). Also, higher leukocyte count and total bilirubin 24 hours after admission were correlated with ACS risk (p < 0.05). Figure 2

Table 3
Laboratory values at baseline, upon arrival to emergency, and after 24 hours of admission in relation to ACS development during admission (n=197)

	All VOC admissions	ACS during VOC admission		P-value §
	(No.197)	Yes (No.31)	No (No.166)	
	Mean ± SD	Mean ± SD	Mean ± SD	
Steady-state lab				
Hemoglobin S (%)	80.7 ± 9.12	82.5 ± 9.65	80.4 ± 9.02	0.252
Hemoglobin F (%)	12.3 ± 6.72	10.6 ± 6.06	12.6 ± 6.80	0.149
Hemoglobin A2 (%)	3.87 ± 0.94	3.62 ± 0.65	3.91 ± 0.98	0.130
Leucocyte count 10^9/L	9.30 ± 2.43	10.2 ± 2.12	9.14 ± 2.45	**0.029 ****
Neutrophil count 10^9/L	4.02 ± 1.96	4.32 ± 1.72	3.97 ± 1.99	0.381
Hemoglobin, g/dL	9.03 ± 1.05	9.14 ± 1.08	9.01 ± 1.05	0.552
Platelet count 10^9/L	375.7 ± 153.2	446.9 ± 131.0	362.6 ± 153.7	**0.005 ****
Mean Corpuscular Volume, fl	80.8 ± 10.5	85.6 ± 10.2	79.9 ± 10.4	**0.005 ****
Reticulocyte percentage (%)	6.51 ± 2.92	7.31 ± 3.44	6.35 ± 2.79	0.094
Total bilirubin level, µmol/L	21.7 ± 11.4	26.5 ± 16.8	20.8 ± 9.84	**0.011 ****
Lab at presentation to ED				
Leucocyte count 10^9/L	15.2 ± 4.99	16.8 ± 5.53	14.9 ± 4.96	0.064
Neutrophil count 10^9/L	9.75 ± 4.34	11.7 ± 4.67	9.34 ± 4.25	**0.010 ****
Hemoglobin, g/dL	8.17 ± 1.24	7.66 ± 1.44	8.25 ± 1.18	**0.015 ****
Platelet count 10^9/L	397.8 ± 197.3	459.5 ± 268.6	381.1 ± 181.5	**0.044 ****
Mean Corpuscular Volume, fl	80.3 ± 9.89	83.5 ± 10.2	79.6 ± 9.77	**0.045 ****
Reticulocyte percentage (%)	9.74 ± 4.11	10.7 ± 4.42	9.53 ± 4.03	0.172

§ P-value has been calculated using independent sample t-test.

** Significant at $p < 0.05$ level.

SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome, ED emergency department

	All VOC admissions	ACS during VOC admission		P-value §
	(No.197)	Yes (No.31)	No (No.166)	
	Mean ± SD	Mean ± SD	Mean ± SD	
Steady-state lab				
Total bilirubin level, µmol/L	37.8 ± 35.0	41.3 ± 17.2	37.0 ± 37.2	0.541
Uric acid	221.9 ± 70.7	203.1 ± 70.6	225.6 ± 70.4	0.125
ESR		47.9 ± 38.4	43.8 ± 32.5	0.584
CRP	69.7 ± 83.9	80.4 ± 111.0	66.7 ± 75.3	0.522
Lab after 24 hours of admission				
Leucocyte count 10^9/L	13.7 ± 5.56	17.8 ± 5.57	12.9 ± 5.22	**< 0.001 ****
Neutrophil count 10^9/L	10.2 ± 30.6	12.2 ± 4.75	9.82 ± 3.4	0.718
Hemoglobin, g/dL	8.09 ± 1.16	7.91 ± 1.49	8.12 ± 1.09	0.361
Platelet count 10^9/L	343.9 ± 184.9	381.3 ± 206.2	336.7 ± 180.5	0.220
Reticulocyte percentage (%)	9.59 ± 4.62	9.44 ± 4.62	9.62 ± 4.64	0.854
Total bilirubin level, µmol/L	34.5 ± 28.7	47.7 ± 22.9	31.9 ± 29.1	**0.006 ****
§ P-value has been calculated using independent sample t-test.				
** Significant at p < 0.05 level.				
SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome, ED emergency department				

Initial management for VOC (Table 4) showed that 49.7% of patients received maintenance intravenous fluids, 83.2% received morphine (with 36% getting morphine infusions), and 12.2% used incentive spirometry within the first 24 hours. Interestingly, 25% of patients underwent blood transfusions within the first 24 hours, which was linked with a higher ACS risk ($p < 0.001$). However, using codeine was associated with a lower ACS risk ($p < 0.001$). Figure 4

Table 4

Relationship between management received initially for VOC and ACS development [(n=197)]

Factor	All VOC admissions	ACS during VOC admission		P-value §
	N (%) (n=197)	Yes N (%) (n=31)	No N (%) (n=166)	
IV fluid (IVF)				
• Maintenance	98 (49.7%)	14 (45.2%)	84 (51.2%)	0.729
• More than maintenance	80 (40.6%)	15 (48.4%)	65 (39.6%)	
• Less than maintenance or no IVF	19 (09.6%)	02 (06.5%)	17 (10.2%)	
Pain management †				
• Morphine infusion	72 (36.5%)	16 (51.6%)	56 (33.7%)	0.058
• Morphine intermittent doses (Regular)	64 (32.4%)	11 (35.5%)	53 (31.9%)	0.698
• Codeine	103 (52.2%)	07 (22.6%)	96 (57.8%)	**< 0.001 ** **
Incentive spirometry 1st 24 hours of admission	24 (12.2%)	07 (22.6%)	17 (10.2%)	0.054
Blood transfusion during first day of VOC admission before onset of ACS	49 (24.8%)	16 (51.6%)	33 (19.9%)	**< 0.001 ** **

† Some patients have more than one finding.

§ P-value has been calculated using Chi-square test.

** Significant at $p < 0.05$ level.

SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome,

The development of ACS during hospitalization was significantly associated with a considerable drop in hemoglobin levels in the ED compared to baseline steady-state levels and a significant increase in leukocyte count difference, as measured at the ED and again 24 hours later ($p < 0.001$).(Table 5)

Table 5
Difference in Laboratory values at baseline steady state, Emergency labs, and Labs after 24 hours of admission in relation to ACS diagnosis (n=197)

Variable	All VOC admissions	ACS during VOC admission		P-value §
	(No.197)	Yes (No.31)	No (No.166)	
Laboratory value at arrival to ED in comparison to steady stat value :				
WBC 10^9/L	+ 5.9	+ 6	+ 5	0.621
HB g/dl	-0.86	-1.47	− 0.75	**0.006 ****
PLT 10^9/L	+ 22.1	+ 23	+ 21	0.978
ANC 10^9/L	5.74	+ 7	+ 5	0.073
Laboratory value after 24 hours of admission in comparison to ED value :				
WBC 10^9/L	-1.5	+ 1	-2	**< 0.001 ****
HB g/dl	+ 0.07	+ 0.24	-0.13	0.080
PLT 10^9/L	-49.6	-78	-46	0.158
ANC 10^9/L	+ 0.45	+ 0.5	+ 0.48	0.856
§ P-value has been calculated using independent sample t-test.				
** Significant at p < 0.05 level.				
+ increased by				
- decreased by				
WBC Leukocyte count, HB hemoglobin g/dl, PLT platelet count ,ANC absolute Neutrophil count				
SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome, ED emergency department				

Using regression analysis (Table 6), the study found that certain factors were significantly associated with the development of ACS during VOC in children with SCA: older age, prior diagnosis of ACS or asthma, recent history of URTI, back pain, receiving a simple blood transfusion in the first 24 hours, lower initial O2 saturation and hemoglobin levels at ED, and a decrease in hemoglobin values compared to baseline. The use of codeine for pain management, however, reduced the ACS risk. **See** Fig. 3.

Table 6
Univariate and multivariate regression analysis to determine the influence predictors of the ACS development during admission:

Factor	OR (95% CI)	P-value	AOR (95% CI)	P-value
Age group				
• 1–7 years	Ref			
• 8–14 years	2.313 (1.026–5.211)	**0.043 **	2.245 (0.965–5.227)	0.061
Previous diagnosis of asthma	5.272 (2.247–12.37)	**< 0.001 **	5.683 (2.284–14.44)	**< 0.001 **
Previous acute chest syndrome	2.608 (1.168–5.823)	**0.019 **	2.651 (1.159–6.066)	**0.021 **
Recent history of URTI within 1 week of visit? (n=95)	6.111 (1.983–18.83)	**0.002 **	6.371 (1.672–20.58)	**0.002 **
Back pain	3.017 (1.277–7.131)	**0.012 **	2.537 (1.046–6.157)	**0.040 **
Site of pain: Upper limb	0.316 (0.105–0.949)	**0.040 **	0.290 (0.092–0.914)	**0.035 **
Only upper and/or lower limb pain	0.263 (0.076–0.907)	**0.035 **	0.279 (0.080–0.978)	**0.046 **
Pain management: Codeine	0.213 (0.087–0.521)	**0.001 **	0.180 (0.071–0.457)	**< 0.001 **
Simple blood transfusion In 1st 24hrs	4.299 (1.930–9.576)	**< 0.001 **	4.563 (1.969–10.45)	**< 0.001 **
Initial O2 saturation	1.249 (1.059–1.473)	**0.008 **	1.246 (1.053–1.474)	**0.010 **
Steady State laboratory Value				
Leucocyte count 10^9/L	0.847 (0.727–0.986)	**0.032 **	0.863 (0.737–1.009)	0.065

Adjusted with age, gender, nationality and BMI.

OR – Odds Ratio; AOR – Adjusted Odds Ratio; CI – Confidence Interval.

** Significant at p < 0.05 level.

SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome, ED emergency department

Factor	OR (95% CI)	P-value	AOR (95% CI)	P-value
Platelet count 10^9/L	0.997 (0.994–0.999)	**0.007 ****	0.996 (0.994–0.999)	**0.009 ****
Mean Corpuscular Volume, fl	0.947 (0.911–0.985)	**0.007 ****	0.953 (0.915–0.991)	**0.017 ****
Total bilirubin level, µmol/L	0.965 (0.937–0.993)	**0.016 ****	0.971 (0.941–1.002)	0.067
Emergency laboratory Value				
Neutrophil count 10^9/L	0.889 (0.810–0.975)	**0.013 ****	0.890 (0.808–0.981)	**0.018 ****
Hemoglobin, g/dL	1.423 (1.060–1.910)	**0.019 ****	1.496 (1.082–2.067)	**0.015 ****
Platelet count 10^9/L	0.998 (0.997–1.000)	0.055	0.998 (0.996–1.000)	0.061
Mean Corpuscular Volume, fl	0.960 (0.922–0.999)	**0.047 ****	0.961 (0.923–1.001)	0.055
24 hours post admission laboratory value				
Leucocyte count	0.862 (0.803–0.925)	**< 0.001 ****	0.859 (0.797–0.925	**< 0.001 ****
Total bilirubin level, µmol/L	0.984 (0.970–0.999)	**0.038 ****	0.987 (0.972–1.001)	0.078
Lab difference :				
Hemoglobin drop in ED versus steady state	0.687 (0.522–0.905)	**0.007 ****	0.661 (0.494–0.886)	**0.006 ****
Leucocyte increase after 24 hours of admission compared to ED	0.833 (0.753–0.922)	**< 0.001 ****	0.845 (0.762–0.937)	**0.001 ****
Adjusted with age, gender, nationality and BMI.				
OR – Odds Ratio; AOR – Adjusted Odds Ratio; CI – Confidence Interval.				
** Significant at $p < 0.05$ level.				
SCA sickle cell anemia ,VOC vaso-occlusive pain crises, ACS acute chest syndrome, ED emergency department				

In terms of ACS management, it was typically diagnosed after an average of 87.5 ± 174.0 hours from admission, presenting with fever (93.5%) and respiratory symptoms (93.5%), and chest X-rays showed

new infiltrates in all episodes most frequently in the right lower lobe (51.6%) followed by left upper lobe in 25.8%.

Antimicrobial management included Ceftriaxone (96.8% of cases), Azithromycin (90.3%), and Vancomycin (41.9%). Simple top-up red blood cell transfusions were used in 90.3% of cases, while exchange transfusion was only used in 6.5%. Ventolin nebulization was given to 80.6% of patients, and 29.0% of ACS patients required admission to pediatric intensive care or high dependency units.

Regarding hospital stay duration, it was longer when ACS developed, averaging 5.82 days for VOC alone and 7.65 days when ACS occurred during the VOC admission ($p = 0.002$). No In-hospital mortality was seen in our sample.

Discussion

Sickle cell disorder has a high prevalence in Saudi Arabia.[4] Acute chest syndrome (ACS) is a leading cause of mortality and intensive care unit admission among the sickle cell anemia (SCA) population.[2, 17, 18]

It is well established that vaso-occlusive crises (VOCs) are the commonest reason of hospitalization among SCA patients.[1, 2, 11, 17, 18] Previous research has shown that following admission for a VOC, approximately 13–20% of patients will go on to develop ACS in initial 3 days over an indolent clinical course.. [11, 12, 15, 19]

The aim of our study was to identify risk factors that could predict the development of ACS among pediatric patients with SCA. This will help clinicians focus monitoring and care efforts on higher-risk patient groups.

Among the SCA children admitted to our hospital specifically for a VOC, 15.7% developed ACS on average 87 hours (3.6 days) following admission.. Our finding afforded an important opportunity with such a substantial percentage of ACS emerging following admissions predominantly tied to crises like pain, we were well positioned to explore risk factors for post-admission ACS progression.

A previous study by Bellet et al. found that pediatric sickle cell patients hospitalized for VOC who performed incentive spirometry had an 87% lower relative risk of developing ACS compared to those who did not use it. [20] Our current study found incentive spirometry was underutilized, with only 12.2% of patients receiving it. Other research has shown the benefits of a multidisciplinary preventative approach, which reduced the risk of ACS from 25–12% during VOC admissions. [21] These findings indicate that evidence-based preventative measures do exist that could lower the incidence of ACS. The aim moving forward should be to identify which patients are at highest risk.

We found that patients aged 8–14 years exhibited a stronger association with ACS development during admission compared to younger children. This differed from the findings of Madhi et al.'s observational study, potentially due to dissimilar age groupings between the two.[15]

However, our observations aligned with a large multicenter study by Vichinsky et al. reporting median ages at first ACS episode of 5.4–14.6 years in age groups of 0–9 years and 10–19 years, respectively.[7] Notably, our study suggests gender does not influence post-admission ACS risk on its own within our population.

We observed that, a history of asthma and prior ACS episode predicted a higher risk of post VOC admission ACS. These findings align with multiple prospective and retrospective studies showing pediatric SCA patients with asthma face greater ACS incidence versus those without. [22, 23] proinflammatory effects of Asthma may contribute to this relationship. [23]

We found those with upper respiratory tract infection (URTI) symptoms in the week prior to VOC was linked to markedly higher post admission ACS risk ($p = 0.001$).Other research has also noted this relationship between recent URTI and ACS. [9] [19] [24, 25] Upper respiratory infection may induce pain episodes that promote ACS, or directly cause ACS through indolent viral infection exacerbated by pain.

In our analysis, there was no statistically significant difference observed between patients with Sickle Cell SS disease and those with Sickle S-beta-zero thalassemia in terms of risk for developing ACS during admission. It is important to note that our study only included these two specific types of sickle cell disease, while excluding other variants. Given this limited scope, our finding of no discernable risk difference between SS disease and S-beta-zero thalassemia for ACS occurrence is reasonable based on the sample sizes involved for each group.

We demonstrated that a majority (74.2%) of patients in the ACS group presented with back pain at admission, compared to 48% of the VOC-only group ($p = 0.009$). In contrast, only a minority (9.7%) of the ACS group reported exclusive limb pain versus 28.9% of those without ACS ($p = 0.025$). This suggests isolated extremity pain may signal lower risk of post-admission ACS, while back pain associate with increased risk. These findings align with Madhi et al.'s observational study [15] and pain induced hypoventilation theories linking pulmonary dysfunction to ACS development.[26]

In aligns with previous research, We found that decreased oxygen saturation on emergency department (ED) arrival was associated with greater risk of developing ACS. This emerging as an early ACS predictor corresponds well with past literature. [11, 15, 27]

In contrast to other research,[11, 15] we found no significant differences between ACS and VOC only groups for other initial exam findings in the ED, such as reported pain scores. While ACS patients tended to report more severe pain, this difference was not statistically significant, likely due to limitations of retrospective pain documentation review.

As reported previously in literature we found no statistically significant difference in ACS risk during VOC admission based on intravenous hydration volume. [28] [29]

We observed patients receiving codeine experienced significantly less ACS occurrence during admission. However, this may reflect an association rather than causation, as codeine was used for mild-moderate

pain at our study hospital. There was a trend toward increased ACS risk with morphine infusions ($p = 0.058$), consistent with other studies linking morphine to hypoventilation-driven ACS due to sedation effects and possibly reflecting more severe pain. [15]

Interestingly, our study found that patients receiving red blood cell transfusions within the first 24 hours of VOC admission were at significantly higher risk of developing ACS during hospitalization ($p < 0.001$).Transfusions correlated with hemoglobin drop ($p = 0.001$). Transfused patients also required additional transfusions post-ACS diagnosis. This suggests that while transfusions cannot be proven as the direct cause of ACS, they did not seem protective. In contrast, Madhi et al. found 17.9% of VOC-only children received early transfusions without later developing ACS during admission.[15] Additionally, a Cochrane analysis done on 2020 found no clear evidence for transfusions in ACS due to a lack of randomized data. [30, 31] Uncertainty remains around whether early transfusion during VOC or early in an ACS course improves outcomes. Prospective trials are needed to compare transfusions to supportive care approaches, to better guide clinical management, especially during VOC episodes.

On agreement with previous research, [2, 11, 13, 15, 32] higher leukocyte counts, platelet counts, mean corpuscular volume, and total bilirubin at baseline were associated with increased ACS risk during VOC admission. Elevations in these markers could reflect greater underlying hemolysis and disease severity.

Although not statistically significant, lower baseline hemoglobin F levels and higher reticulocyte percentages in the ACS group correlated with prior findings linking lower hemoglobin F and higher ACS risk. [2]

Upon ED arrival, patients who developed ACS later in admission had significantly lower hemoglobin levels. Additionally, their hemoglobin dropped more from steady-state levels (1.47 g/dL vs 0.75 g/dL, $p = 0.006$) compared to the VOC-only group. This may explain the higher transfusion rates seen in ACS patients before onset and questions transfusion benefits for preventing ACS during VOC episodes. Early hemoglobin changes could help anticipate which patients may develop ACS and guide preventive actions, though the exact pathophysiological cause requires further research.

Consistent with other pediatric and adult studies, [11, 15] higher white blood cell counts, especially neutrophils, and platelets at triage correlated with greater ACS risk during admission. These are known adhesion molecules that can promote endothelial adhesion and sickle cell disease pathogenesis. [33]

Leukocyte counts 24 hours post-admission remained significantly elevated in the ACS group compared to emergency levels, but dropped in the VOC-only group. This predictive pattern of leukocyte trajectory was also observed prospectively by Madhi et al. [15].

Further regression analysis showed that history of asthma, previous ACS ,recent history of upper respiratory tract infection within one week of presentation and presenting with back pain serve as independent risk factors for post admission ACS. This was observed in previous studies. [7, 15, 34–36]

Also Simple blood transfusion within the first 24 hours of admission again served as an independent risk factor for ACS in multivariate regression. On the other hand, pain localized only to the extremities significantly served as a reassuring factor, reducing risk of ACS during VOC admission. Similar findings were observed by Madhi et al. [15]

As noted in previous studies, [15, 32] higher platelet count and mean corpuscular volume at steady state were also independent risk factors for ACS during admission in our multivariate regression analysis. Lower hemoglobin and higher neutrophil count on emergency room presentation were confirmed as predictors of ACS in both univariate and multivariate analysis.

When we assessed laboratory values at three time points, we found, as reported previously by Madhi et al, [15] that a higher leukocyte count on emergency room presentation that did not improve by 24 hours after admission was a significant independent predictor of risk for ACS in this study. A drop in hemoglobin level from baseline to emergency room presentation was also an independent predictor based on multivariate regression analysis.

We found that 15.7% (31/197 episodes) of VOC admissions were complicated by the development of ACS, which occurred at a median of 3.6 days after admission. This is comparable to Madhi et al.'s finding that 19% (35/176) of children admitted for vaso-occlusive pain crises developed ACS at a median of 2–3 days after admission. Our observed rate of ACS and its timing of onset align with these prior studies. [15] [7, 37]

ACS was defined in our study based on the 2015 guidelines by Howard et al. [18] All ACS patients had infiltrates on chest X-ray, with the right lower lobe most commonly involved followed by the left upper lobe, aligning with previous reports. [38, 39] The majority of ACS patients exhibited fever and respiratory symptoms. Regarding management, simple top-up transfusions were administered in 90% of ACS patients, while 6% underwent exchange transfusions. Antibiotics were prescribed, most commonly ceftriaxone and azithromycin, for almost all patients, while vancomycin was used in 42% of patients. The NACSSG study found 13% of pediatric and adult ACS patients required non-invasive ventilation,[7] which was not assessed in our study. However, 29% of our ACS cohort did require pediatric intensive care or high dependency admission. Notably, no cerebrovascular events or mortality occurred among patients in our study population.

In agreement with other studies,[7, 15] we found that the duration of hospital admission was significantly longer in the ACS group at 7.65 days compared to 5.8 days in the VOC-only group (P value 0.004).

According to existing literature, it has been observed that episodes of pain can serve as potential indicators of various underlying conditions, including Osteomyelitis [40], stroke [41], splenic sequestration [42], and, notably, ACS (ACS), as seen in our study. To investigate this, we conducted a comparison of the admission and discharge diagnoses of patients (Fig. 1), which yielded an interesting finding. Initially, 59.9% of the patients were admitted with a simple VOC diagnosis. However, upon discharge, only 31% of patients retained the diagnosis of simple VOC. The majority of patients were discharged with different

diagnoses, providing evidence that VOC is indeed a diagnosis of exclusion. This underscores the critical importance of maintaining a high level of suspicion, even during seemingly uncomplicated pain crises.

The study provides valuable insights into the anticipation of ACS in with pediatric SCA patients admitted with VOC. However, it is important to acknowledge certain limitations that present opportunities for further research. Firstly, our study was conducted at a single center and relied on retrospective data, which may limit the generalizability of our findings to other settings with different patient populations.

An important goal for future research is to confirm these identified risk profiles through rigorous investigation, which could serve as the basis for developing a risk stratification tool.

Despite the limitations, we hope that our findings serve as a stimulus for further research aimed at early identification of at-risk pediatric patients with SCA. By targeting modifiable risks through prospective validation, we can ultimately improve outcomes for children affected by this disease.

Conclusion

This retrospective study identified several potential risk factors for developing acute chest syndrome (ACS) during admission for a vaso-occlusive crisis (VOC) in pediatric sickle cell anemia patients. Older age, history of asthma or prior ACS, back pain at presentation, blood transfusion in the first 24 hours, recent upper respiratory infection, higher baseline and presentation platelet count, leukocytosis, hemoglobin drop, and persistently elevated leukocyte count at 24 hours were associated with increased risk of ACS. In contrast, extremity-only pain was associated with reduced risk. These indicators may help identify high-risk patients who could benefit from closer monitoring or preventive measures during pain crises admissions. Further prospective research is needed to validate these early predictors of impending ACS in diverse pediatric sickle cell populations. Refining risk assessment could ultimately lead to improved outcomes for this vulnerable group of patients.

Declarations

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Conflict of Interest:

The authors declare that they have no conflicts of interest to acknowledge in relation to this study.

Data Availability

The raw data generated and analyzed during this study contains protected health information and is therefore not publicly available. De-identified data may be available from the corresponding author upon reasonable request, pending approval from the ethical review board at king Saud medical city research center. Any data shared will be fully anonymized to protect patient confidentiality and privacy in accordance with regulations.

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Contributions:

All authors made significant contributions to this research and have reviewed the final version. All were involved in the conception and design of the study, data acquisition, and data analysis and interpretation.

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Figures

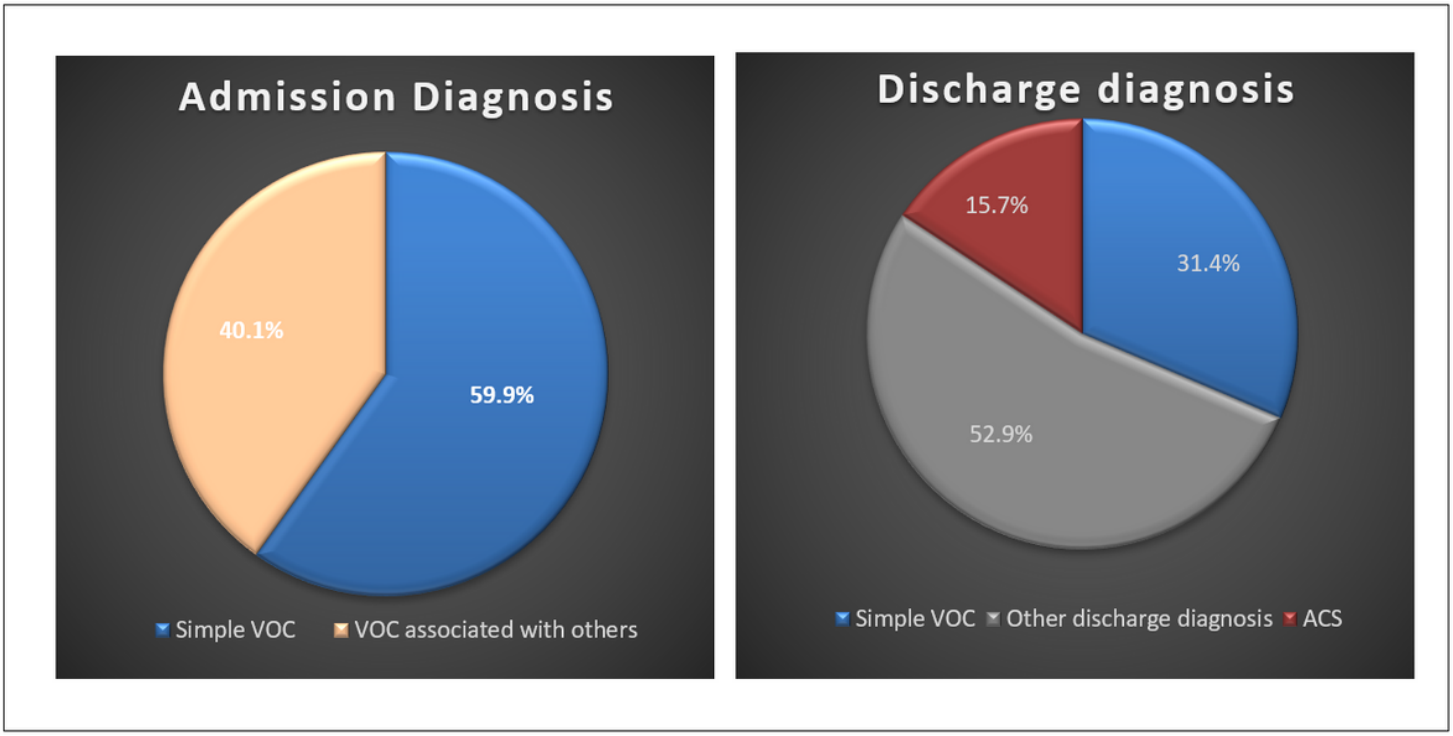

Figure 1

VOC is a diagnosis of exclusion:

Distribution of diagnoses at admission and discharge. At admission, 59.9% of patients were diagnosed with a simple vaso-occlusive crises (VOC), while 40.1% had VOC in conjunction with other diagnoses. Upon discharge, only 31.4% of patients maintained a diagnosis of simple VOC, while the remaining 69.6% had different discharge diagnoses.

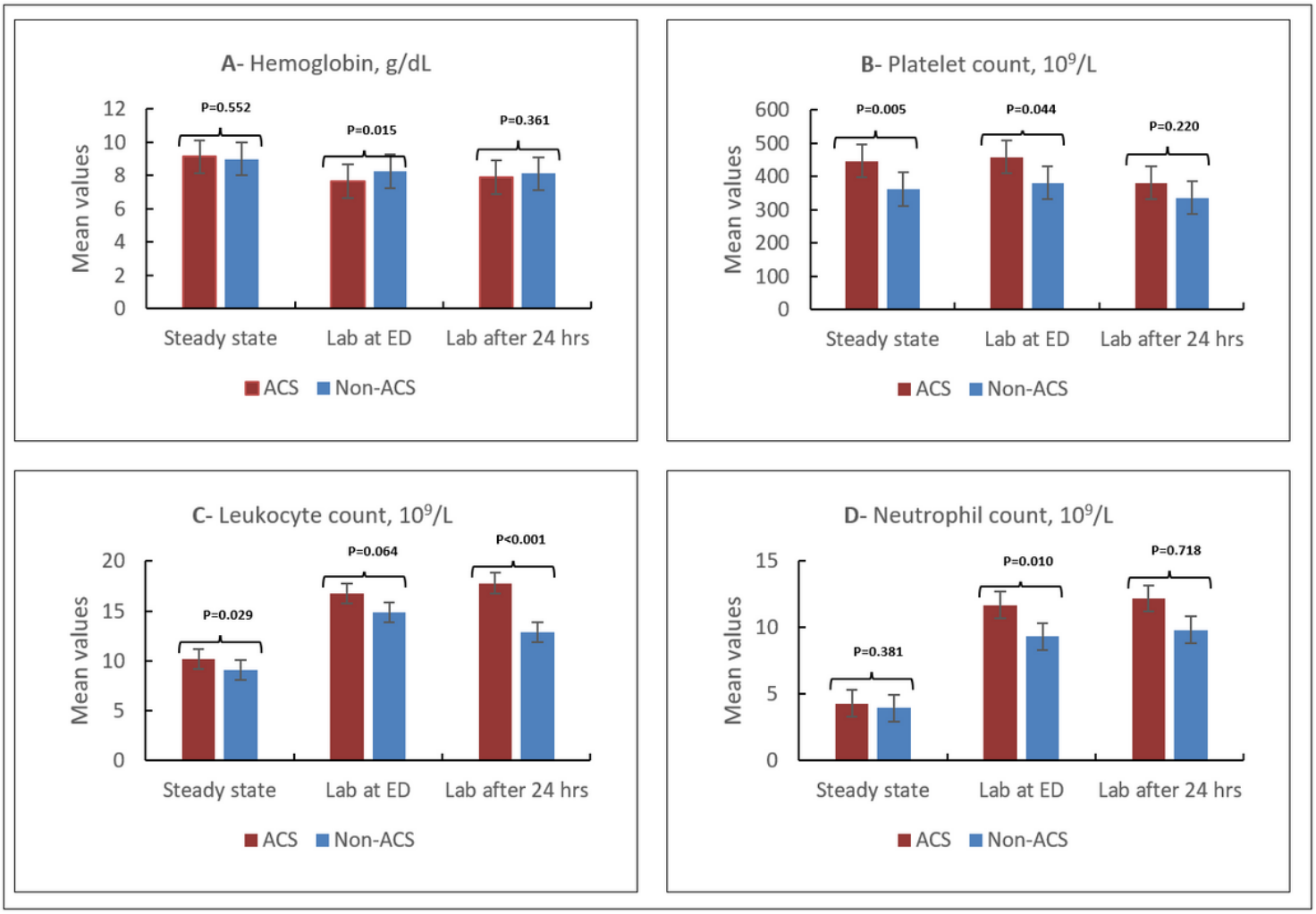

Figure 2

Comparison of Laboratory values at steady state, emergency and at 24 hours of VOC admission based on development of ACS: during admission:

Comparison of laboratory values for patients with acute chest syndrome (ACS) post vaso-occlusive crises (VOC) admission versus VOC only group. (a) Hemoglobin levels were significantly lower in the ACS group than the VOC-only group in the emergency department lab. (b) Platelet count was significantly higher in the ACS group at both steady state and in the emergency department. (c) Leukocyte count was significantly higher in the ACS group at steady state and after 24 hours in the lab. (d) Neutrophil count was significantly higher in the ACS group only at the emergency department lab.

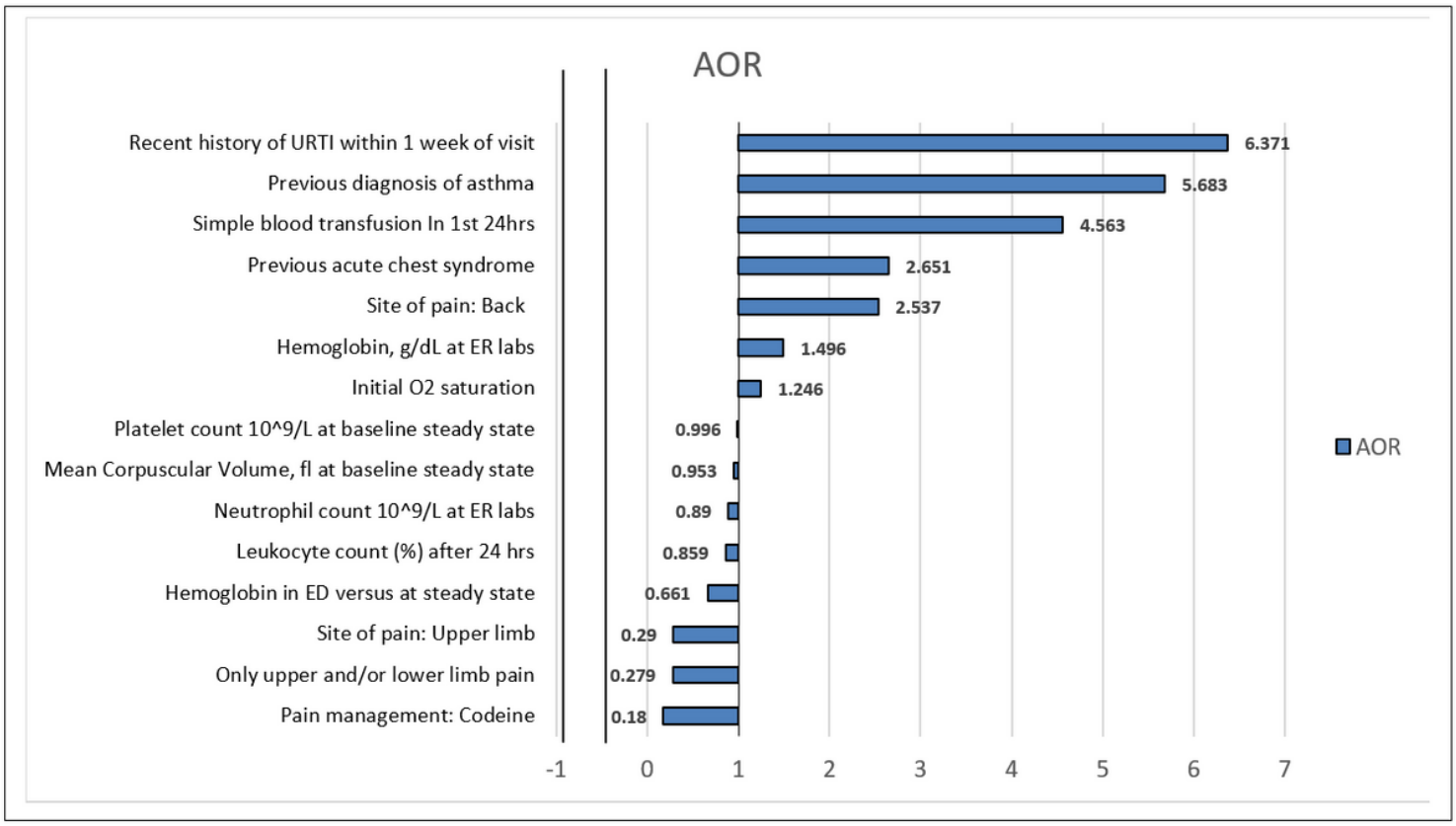

Figure 3

Forest plot for the multivariate regression results of the significant risk factors of ACS admission

URTI upper respiratory tract infection, ER/ED Emergency department

Forest plot for predictors of acute chest syndrome during vaso-occlusive crises admission based on multivariate adjusted odd ratio AOR

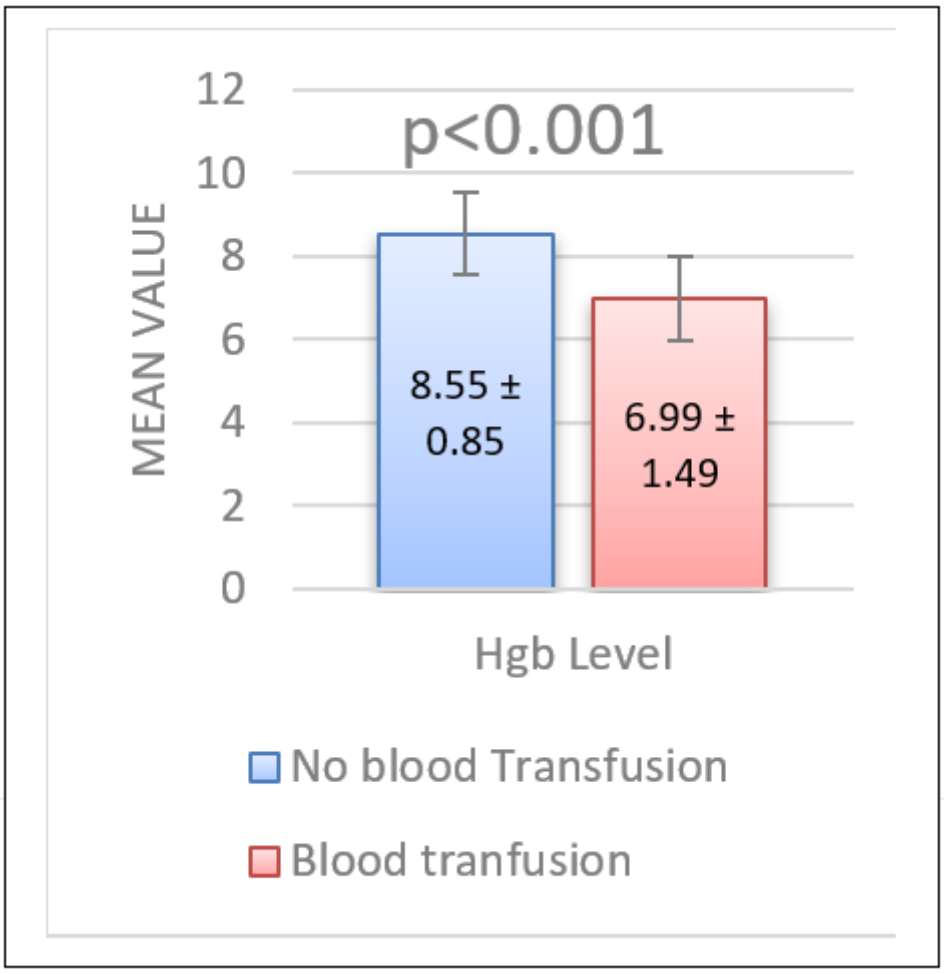

Figure 4

Association between blood transfusion in 1st 24 hours with Hemoglobin level in ED:

Patients who had blood transfusion were more associated with a lower mean value of hemoglobin level in ER ($p<0.001$).