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– ORIGINAL PAPER –

A Retrospective Study of Sickle Cell Disease Patients' Clinical and Laboratory Data as Predictors of Disease Morbidity and Mortality in a Single Center (KFHU), Saudi Arabia

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Abstract

Objectives*: Sickle cell disease (SCD) is an autosomal recessive multisystem disorder. It is associated with high morbidity and mortality and affects patients' quality of life. The global prevalence of SCD underscores the need for comprehensive strategies to improve disease outcomes. It is imperative to investigate the possible predictors of Vaso-occlusive crisis (VOC) to develop effective strategies to manage this serious complication.*
The aim of this study is to investigate the different laboratory and clinical findings which might be used as markers to predict the development of VOC.

Materials and Methods: *This retrospective cohort study included all homozygous sickle cell disease patients of all ages and both genders over 25 years, from 1993 to 2018. The hospital's electronic database was used to collect demographic, clinical, and different baseline laboratory data. In addition to retrieving the reported SCD complications. Eligible patients were divided into two groups based on the development of VOC at any time during the disease.*

Outcomes: *This study included 294 Saudi sickle cell disease patients aged from 6 to 31 years, with a mean age of 19.4 ± 6.3 years. 35 patients (11.9% of cases) suffered from bronchial asthma during their illness. The most frequent complication was VOC that was reported in 32.0% of cases. Multivariable regression analysis revealed that bronchial asthma was significantly associated with a more than threefold increased odds of VOC (AOR = 3.320; 95% CI: 1.531–7.201; p = 0.002), reflecting a higher risk of developing VOC in patients having asthma compared to those without asthma. Similarly, each 1% increase in reticulocyte count was associated with a 11.4% higher likelihood of VOC (AOR = 1.114; 95% CI: 1.056–1.175; p < 0.001). Elevated LDH also significantly predicted VOC, though with a smaller effect size (AOR = 1.002; 95% CI: 1.000–1.003; p = 0.009).*

Conclusion: *SCD patients who developed bronchial asthma are more likely to experience VOC. Besides, we found that elevated LDH levels and reticulocyte counts were significantly associated with higher incidence of VOC. We concluded that VOC could be predicted using a combination of routine baseline laboratory biomarkers, such as LDH levels and reticulocyte counts. The identified predictors are easy to assess and could be used as prognostic markers for tailored management of VOC complications in SCD patients.*

Conflict of interest: *We, the authors undersign, certificate that we do not have any financial or personal relationships that might bias the content of this work.*

Keywords: *Sickle cell disease, Vaso-occlusive crisis, Bronchial asthma, Reticulocyte count, LDH.*

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Introduction

Background:
Sickle cell disease (SCD) is an autosomal recessive disorder, in which a mutation in the β-globin gene results in the creation of sickle hemoglobin (HbS). Although SCD occurs in a variety of forms, the most common and severe form is the homozygous HbSS form (sickle cell anemia) [1].
Millions of people worldwide are affected by SCD [2]. Regarding Saudi Arabia, an earlier study in 2011 indicated a prevalence of SCD of up to 2.6% among the Saudi population. However, Bin Zuair et al. recently reported a prevalence rate of SCD exceeding 45,100 per 1,000,000 among Saudi adults and 2,400 per 1,000,000 among Saudi children and adolescents [3].
Sickle cell disease is a multisystem disorder associated with increased morbidity and mortality and impaired quality of life. The presence of disordered hemoglobin structure, abnormal endothelial interactions, systemic inflammation, oxidative stress, and activation of the coagulation system cause numerous consequences that may be acute or chronic [4].
The spectrum of complications encountered by patients with SCD includes Vaso-occlusive crises (VOC), chronic hemolytic anemia, acute chest syndrome, and multiple organ failure. In addition to that, leg ulcers, avascular necrosis of the femoral head, retinopathy, nephropathy, stroke, priapism, and chronic pain [5].
VOC is a debilitating and life-threatening acute complication characterized by severe pain, organ damage and potentially life-threatening complications. The development of VOC is thought to be the cause of 95% of hospitalizations in SCD patients and is a major predictor of death [6].
Previous research has attributed VOC to abnormal blood rheology, specifically increased blood viscosity due to the polymerization of hemoglobin S and the production of dense, dehydrated sickled erythrocytes. As sickle cell viscosity increases, it can adversely affect blood flow and contribute to the Vaso-occlusive process [7]. Another important factor is the role of inflammatory mediators released during bone infarction, which can activate afferent nerve fibers and cause severe pain [8]. SCD patients with higher levels of hemolysis may be at increased risk for VOC, as the release of free hemoglobin and other cellular components into the circulation may contribute to vascular dysfunction and inflammation [9].
The global prevalence and mortality burden of SCD highlight the urgent need for comprehensive strategies to improve outcomes. Understanding the predictors of VOC is critical to developing effective strategies to manage this serious complication. The study of clinical and laboratory biomarkers of VOC has great potential to improve the outcome of SCD by allowing timely intervention, avoiding hospitalization, and reducing the risk of complications [10, 11].

Objective

The aim of this study was to determine the possible utility of routine laboratory investigations as predictive markers for VOC development in sickle cell disease patients in our local community. This will help in tailoring management strategies for severe complications of SCD such as VOC. This might be reflected in the morbidity and mortality rates among the SCD patients in our local community.

Methods

Study design and settings

This retrospective cohort study was conducted at King Fahed Hospital of the University, Khobar, Saudi Arabia. Data of patients presenting over 25 years, from 1993 to 2018, were retrieved from the hospital patients' records at the IT department.

Eligibility criteria

All homozygous SCD patients of all ages and both sexes attending hematology clinics and admitted to King Fahed Hospital of the University were included in this study.
Patients were excluded from this study if they had incomplete data on the selected hematologic, clinical, and outcome covariates.

Patients' data collection

The hospital's electronic database was used to collect SCD patients' demographic data including age, gender, associated chronic comorbidities, vaccination status, and treatments including hydroxyurea and any surgical intervention and type of surgery. In addition, the patients' laboratory data includes initial complete blood count (CBC), hemoglobin electrophoresis, peripheral blood smear reports, lactate dehydrogenase enzyme levels (LDH), and liver function tests. Hematological parameters, total serum bilirubin, and LDH levels were categorized and presented as low or high according to age- and sex-specific reference ranges.
Furthermore, we analyzed the SCD associated complications including the VOC, hypersplenism, urinary tract infection (UTI), deep vein thrombosis (DVT),

pulmonary embolism (PE), acute chest syndrome (ACS), community-acquired pneumonia (CAP), bronchopneumonia, and hepatic stomatitis. In addition to that, chronic adeno-tonsilitis, erosive gastro-duodenitis, cholelithiasis, biliary pancreatitis, cellulitis, organomegaly, epilepsy, priapism, hemochromatosis, uveitis, meningitis, dactylitis, septic arthritis, osteomyelitis, avascular necrosis (AVN), and stroke.
Finally, the eligible patients were classified into two groups according to the development, or no development of VOC at any time during the disease.

Statistical analysis

Data were tabulated and analyzed using the Statistical Package for Software Sciences (SPSS) version 27 (IBM Corporation, Armonk, New York). Descriptive statistics were represented as frequencies and proportions (%) for categorical variables and means and standard deviations or median and interquartile ranges for continuous variables according to the normality distribution. Comparison between patients with and without VOC development was accomplished by Chi-Square, Independent samples T-test, or Mann-Whitney U tests for categorical, normally distributed, and skewed data, respectively. Furthermore, significant variables in the bivariate analyses were entered into a multivariable regression analysis to determine predictors of VOC crisis. Results were displayed as adjusted odds ratios and their 95% confidence intervals (CI). Statistical significance was considered at $p<0.05$.

Results

This study included 294 Saudi SCD patients aged 6 to 31 years, with a mean age of 19.4 ± 6.3 years. More than half (164, 55.8%) were male, and 35 (11.9%) reported having bronchial asthma. Of the 294 patients, 212 (72.1%) reported receiving vaccinations, with pneumococcal vaccination being the most common (194, 66.0%). The initial CBC revealed a low erythrocyte count (214, 72.8%), low hemoglobin (264, 89.8%), low hematocrit % (273, 92.9%), and low MCV, MCH, and MCHC (59.5%, 37.4%, 14.6%, respectively). High reticulocyte count was observed in 234 (79.6%) patients. The WBC count was high in more than half of the patients (156, 53.1%). About platelets, 66 (22.4%) had a high count, while 21 (7.1%) had a low count. In addition, high total bilirubin and LDH levels were observed in 181 (61.6%) and 221 (75.2%) patients, respectively. Seventy-eight patients (26.5%) were using hydroxyurea. Reported surgical procedures included cholecystectomy (43, 14.6%), splenectomy (12, 4.1%), tonsillectomy (11, 3.8%), and appendectomy (4, 1.4%) **(Table 1).**
The most common complications throughout the patients' lives included VOC (32.0%), acute chest syndrome (30, 10.2%), osteomyelitis (29, 9.9%), hemolytic crisis (25, 8.5%), and avascular necrosis (20, 6.8%), as demonstrated in **Table (2).**

Table 1. *Characteristics of sickle cell disease patients studied*

Variable	N=294	%
Age, year	6.0-31.0	
	19.4± 6.3	
Female	130	44.2%
Male	164	55.8%
Comorbidities		
Bronchial asthma	35	11.9%
Vaccinations		
Received vaccinations	212	72.1%
Influenza virus	36	12.2%
Hemophilus influenza B	37	12.6%
Pneumococcal	194	66.0%
Meningococcal	38	12.9%
BCG-HBV	66	22.4%
COVID-19	2	0.7%
Hematological and biochemistry parameters		
WBC count, 10^3/L (High)	156	53.1%

RBC count, 10^6/L (Low)	214	72.8%
Hemoglobin, g/dL (Low)	264	89.8%
Hematocrit, % (Low)	273	92.9%
MCV, fL (Low)	175	59.5%
MCH, g/dL (Low)	110	37.4%
MCHC, g/dL (Low)	43	14.6%
Platelet, 10^3/L (High)	66	22.4%
Platelets, 10^3/L (Low)	21	7.1%
Reticulocyte, % (High)	234	79.6%
Total bilirubin, mg/dL (High)	181	61.6%
LDH, U/L (High)	221	75.2%
Treatment (Throughout life)		
Hydroxyurea	78	26.5%
Exchange transfusion	27	9.2%
Need for ICU admission	31	10.5%
Need for ER visit	57	19.4%
Need for hospital admission	73	24.8%
Surgery		
Cholecystectomy	43	14.6%
Splenectomy	12	4.1%
Tonsillectomy	11	3.8%
Appendectomy	4	1.4%

N: number; ER: emergency room; HBV: hepatitis B virus; ICU: intensive care unit; LDH: lactate dehydrogenase; RBC: red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood cell

Table 2. *Frequencies of sickle cell disease complications among the studied patients*

Variable	N=294	%
Vaso-occlusive crisis	94	32.0%
Acute chest syndrome	30	10.2%
Osteomyelitis	29	9.9%
Sickle Cell/Beta Thalassemia	29	9.9%
Hemolytic crisis	25	8.5%
Avascular necrosis	20	6.8%
Arthritis	6	2.0%
Stroke	5	1.7%
Hemochromatosis	4	1.4%
Organomegaly	4	1.4%
Pulmonary embolism	4	1.4%
Splenic sequestration	4	1.4%
Aplastic crisis	2	0.7%
Painful crisis	2	0.7%
Meningitis	2	0.7%
Pancreatitis	2	0.7%
Pneumonia	2	0.7%
Gastroduodenitis	2	0.7%
Hypersplenism	2	0.7%
Major depressive disorder	2	0.7%
Seizures	2	0.7%
Cellulitis	1	0.3%
Dactylitis	1	0.3%
Hepatic crisis	1	0.3%

Uveitis	1	0.3%
Deep vein thrombosis	1	0.3%
Systemic lupus erythematosus	1	0.3%

Table (3) shows the comparison between patients with and without VOC development. The mean age of patients who developed VOC (21.0±6.3) was significantly higher than their counterparts (18.7±6.2). Gender was comparable in both groups, with no significant difference. There was a significant association between bronchial asthma and the development of VOC (p<0.001). Patients with VOC showed a higher frequency (22.3% vs 7.0%). The mean WBC count was significantly higher in patients having VOC (13.2±6.4) compared to those without VOC (11.7±4.3). There were also significant differences between the means of RBCs (3.35±.95 vs 3.74±.90) and hemoglobin levels (8.9±1.9 vs 9.5±2.4), with lower values in patients with VOC development. Alternatively, patients who developed VOC exhibited significantly higher reticulocyte values (Median: 6.5 vs 4.8, p<0.001). The distribution of LDL level values was higher among patients with VOC than among those without VOC (p=0.038).

Multivariable regression analysis revealed that bronchial asthma, reticulocyte count, and LDH level significantly contributed to the development of VOC. Bronchial asthma was significantly associated with a greater than 3-fold increased likelihood of VOC (AOR: 3.320, 95% CI: 1.531-7.201). Furthermore, an increase in reticulocyte count and LDH levels was directly linked to an elevated risk of VOC development **(Table 4).**

Table 3. Comparison between patients with and without VOC development

Clinical and hematological predictors		**SCD without VOC development N=200**	**SCD with VOC development N=94**	**P-Value**
Age, year	Mean ± SD	18.7±6.2	21.0±6.3	0.004*
Gender	Female, N (%)	93 (46.5%)	37 (39.4%)	0.250
	Male, N (%)	107 (53.5%)	57 (60.6%)	
Bronchial asthma	N (%)	14 (7.0%)	21 (22.3%)	<0.001*
WBC count, 10^3/L	Mean ± SD	11.7±4.3	13.2±6.4	0.036*
RBC count, 10^6/L	Mean ± SD	3.74±.90	3.35±.95	<0.001*
Hemoglobin, g/dL	Mean ± SD	9.5±2.4	8.9±1.9	0.023*
Hematocrit, %	Mean ± SD	28.5±6.8	27.3±6.1	0.124
MCV, fL	Mean ± SD	76.7±9.9	77.1±9.9	0.766
MCH, g/dL	Mean ± SD	25.5±3.7	25.9±4.1	0.383
MCHC, g/dL	Mean ± SD	33.1±1.1	33.4±1.2	0.063
Platelet, 10^3/L	Median	333.0	325.5	0.411
	IQR	242.5-436.5	205.0-450.0	
Reticulocyte, %	Median	4.8	6.5	<0.001*
	IQR	2.8-8.4	3.8-15.5	
Total bilirubin, mg/dL	Median	1.5	1.5	0.772
	IQR	0.9-2.2	1.0-2.0	
LDH, U/L	Median	420	425	0.038*
	IQR	318-532	345-666	

**Significant at p<0.05; SD: standard deviation; IQR: interquartile range; N: number; LDH: lactate dehydrogenase; RBC: red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; VOC: Vaso-occlusive crisis; SCD: sickle cell disease; WBC: white blood cell*

***Table 4.** Multivariable regression analysis for determining predictors of VOC*

Variable	**Beta coefficient**	**AOR**	**95% CI**	**P-value**	**Accuracy**	**P-value Model**
Reticulocyte, %	0.108	1.114	1.056-1.175	<0.001*	75.2%	<0.001*
LDH, U/L	0.002	1.002	1.000-1.003	0.009*		
Bronchial asthma	1.200	3.320	1.531-7.201	0.002*		
Constant	-2.471	0.085		<0.001*		

**Significant at p<0.05; AOR: adjusted odds ratio; CI: confidence interval; LDH: lactate dehydrogenase; VOC: Vaso-occlusive crisis*

Discussion

SCD is a serious hemoglobinopathy found throughout the world. Currently, the focus of research has shifted to improving the quality of life of SCD patients and reducing the major causes of morbidity, particularly VOC and acute chest syndrome [12].

The main aim of this study was to find potential predictor markers of VOC in patients with SCD who visited the hematology clinic or were hospitalized. A retrospective review of a cohort of 294 Saudi SCD patients was performed. We examined the differences between SCD patients who developed VOC versus SCD patients without VOC. Using a multivariable regression model, we identified bronchial asthma comorbidity as a significant predictor of VOC ($p=0.002$), with affected patients having more than a threefold higher risk compared with those without asthma. In addition, a higher reticulocyte percentage was significantly associated with increased odds of VOC ($p < 0.001$), and elevated LDH levels were also independently related to VOC ($p = 0.009$).

It was reported that Bronchial asthma is a common comorbid condition in SCD patients that affects 15% to 28% of children with SCD and predisposes those patients to complications such as pain crises, acute chest syndrome, and increased mortality [13]. Therefore, evaluation for bronchial asthma as a risk factor among children with SCD should be carried out routinely and repeatedly [13]. Early diagnosis, management and/or prevention of acute asthma exacerbation is crucial to decrease the pathological effects of asthma combined with SCD on the lungs. This is expected to improve the quality of life and SCD patients' survival [14].

In the present study, bronchial asthma was significantly associated with 3-fold increased risk of developing VOC. Previous research showed an increased incidence of painful crises among children with bronchial asthma compared with those without bronchial asthma after follow-up of a cohort of 291 children with SCD for a duration of 11 years [15]. In another multicenter cohort study which included 1016 children, bronchial asthma was associated with an increased rate of VOC and pain episodes that necessitated patients' hospitalization [16]. Likewise, Glassberg et al. concluded that bronchial asthma and chest wheezing are associated with an increased risk of painful episodes in individuals with SCD [17]. However, a single institution retrospective cohort study involving 297 children with sickle cell anemia did not find any association between bronchial asthma and pain episodes [18]. These contradictory results might be attributed to differences in the management protocols of pain crises employed at different institutes.

While bronchial asthma has been extensively studied in relation to sickle cell disease complications in pediatric patients, data focusing specifically on adult SCD patients are limited. Most available studies are either predominantly including children or combine pediatric and adult populations without stratified adult-specific analyses. There are currently no well-designed studies that exclusively assess the impact of bronchial asthma on the development or frequency of VOC in adult SCD patients.

It has been demonstrated that the lung is one of the primary organs adversely affected by SCD, and even in the steady state, abnormalities of pulmonary function tests are prevalent in most patients [19, 20]. Children with concomitant bronchial asthma may have worsened these abnormalities, making them more vulnerable to consequences like acute chest syndrome combined with severe VOC [19, 20].

Furthermore, it has been reported that SCD and bronchial asthma are associated with increased release of inflammatory cytokines [21]. High levels of leukotrienes, interleukins, soluble vascular adhesion molecules, tumor necrosis factor, and C-reactive protein contributed to the chronicity of both SCD associated with bronchial asthma [21]. Supporting evidence from an animal experimental study reported higher mortality in a transgenic mouse model of SCD with experimentally generated bronchial asthma compared to steady state SCD mice without induced bronchial asthma [22].

That same study reported a significant association between a high baseline reticulocyte count with the risk of developing VOC [22]. The high reticulocyte count indicates continuous destruction and increased synthesis of erythrocytes, which is usually observed in the early stages of VOC [23]. In agreement with our findings, Feugray et al., concluded that the development of VOC in SCD can be predicted using the reticulocyte count, immature reticulocyte count, and fluorescent reticulocyte fraction at steady state of SCD [24].

In addition, Bartolucci et al., developed a clinical score incorporating higher reticulocyte count, higher leukocyte count, and the presence of spine and/or pelvis pain as independent predictors of acute chest syndrome during VOC [25]. Furthermore, Carden et al., reported that reticulocytes in SCD have distinct structural and membrane characteristics that differentiate them from mature sickled erythrocytes, including lower density and increased adhesive properties. These features suggest a potential role for reticulocytes in the pathophysiology of SCD, particularly in VOC. Circulating reticulocyte counts may serve as a marker of disease severity, and early characterization of reticulocyte properties could help

predict prognosis and therapeutic response[26]. On the contrary, a research study from Saudi Arabia found no significant associations between the frequency of VOC and any hematological markers in SCD patients [27].
In SCD patients, VOC triggers hemolysis, leading to an increased concentration of unconjugated bilirubin and LDH in the blood. Additional causes of elevated LDH levels include ischemia of skeletal muscles and liver injury [11]. In this context, our study revealed a significant association between high serum LDH levels and the risk of developing VOC. In agreement with this finding, a previous study has shown that high serum LDH level is a significant predictor for the severity of VOC [28]. García-Morin and coworkers stated that LDH levels obtained in the emergency department were linked to more days of hospitalization and the requirement for significant opioids as pain killers after patient's admission, and it was a predictor of disease severity [29]. Moreover, severe VOC development was consistently associated with LDH levels greater than four-fold the upper limit of normal reference range [28]. Feugray et al., found a significant increase in LDH levels during VOC compared to disease steady state, and that serum LDH > 260 U/L was able to predict VOC risk with a sensitivity of 90%, and a specificity of 72.9% [30]. These results emphasize observing levels of LDH as potential biomarker for development and severity of VOC and directing early intervention strategies in SCD patients.

Conclusion

Based on the present findings, patients with SCD who had bronchial asthma are more likely to develop VOC. Furthermore, VOC could be predicted using a combination of routine baseline laboratory biomarkers, such as LDH levels and reticulocyte counts. The identified predictors are easy to assess, and could change the outcome of VOC. However, further multicenter and prospective studies on larger cohort of SCD patients should be done to confirm these findings.

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Ethical Statement: The study was conducted after getting approval from the Research Ethics Committee, Imam Abdulrahman Bin Faisal University (IRB approval number: IRB-PGS-2025-01-0460)
The confidentiality and anonymity of the data were maintained by making a code number for each patient. Written informed consent was waived because of the retrospective nature of the study, and the analysis was done on anonymous clinical data.

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