Clinical and Laboratory Predictors of Painful Vaso-Occlusive Crisis Among Sickle Cell Disease Patients: A Single-Center Study in Saudi Arabia

Ossama Zakaria 1, Rayan A. Buhalim 2, Fahad Almulhim 2, Faisal A. Al Jibr 2, Aqeel Alrashid 2, Mohammed Almutairi 2

1. Department of Surgery, College of Medicine, Al-Ahsa, SAU 2. College of Medicine, King Faisal University, Al-Ahsa, SAU

Corresponding author: Rayan A. Buhalim, rayan.buhalim@gmail.com

Abstract
Introduction
Vaso-occlusive crisis (VOC) episodes are considered to be the cause of 95% of hospitalizations for sickle cell disease (SCD) patients. The frequency of VOC is significantly associated with higher or lower lactate dehydrogenase levels, higher hemoglobin concentration, higher white blood cell, and neutrophil count, and lower platelet counts. In this study, we highlighted the association and predictors of VOC episodes in Saudi Arabia.

Methods
This is a retrospective observational study that was conducted in a period from January 2018 to December 2019 which included patients who were admitted and treated as sickle cell disease patients were included in this study. Retrieved data included patients' age, sex, and other demographic data items as well as the clinical history of SCD. The patients were divided into two groups. Those patients who developed one or two VOC episodes in the period between 2018-2019 were considered mild in severity and patients who developed three or more VOC episodes in the period between 2018-2019 were categorized as moderate to severe.

Results
A total of ninety-four patients (58 males and 36 females) with a male to female ratio of 1.6 were included in this study. The prevalence of patients who had severe vaso-occlusive crisis was 39.4% while mild-moderate were detected among 60.6% of the patients. It was found that there was no significant difference between the frequency of vaso-occlusive crisis and all the hematological parameters (all p>0.05). It was found that the risk of having vaso-occlusive crisis for those patients who were admitted more than three times was 30 times higher than those patients who were admitted by three times or less [adjusted odds ratio (AOR) = 30.081; 95% confidence interval (CI) = 8.204 – 110.3; p<0.001].

Conclusion
It was found that those patients who had three times VOC episodes in our studied period are more liable to have frequent episodes in the future which might necessitate urgent intervention for these patients.

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sickled erythrocytes are more rigid and have lost their normal flow properties through the microcirculation, with the outcome of erythrocytes being aggregated as well as adhering to the vascular endothelium which causes vaso-occlusion [2,3,8]. This eventually results in ischemic tissue damage and inflammation causing severe pain [9,10]. As a result, VOC manifests as severe pain, especially in the back, joints, and extremities that lasts between three and seven days with the prodromal phase of one to two days [8,11].

In general, the different complications of SCD have their own predictive values. For example, a splenic sequestration crisis has a higher recurrence rate if the spleen size is more than 3 cm, reticulocyte count is greater than 300,000/mm2, and chronic pallor [12]. Moreover, in the case of AVN, the laboratory predictive value for the recurrence is a high steady-state platelet count [13]. However, the frequent VOC are clinical predictors for more symptomatic AVN [14].

In VOC, the frequency of painful crises is significantly associated with higher [15] or lower lactate dehydrogenase levels [16], higher hemoglobin concentration, higher white blood cell and neutrophils count [16,17], and lower platelet counts [18]. It is also significantly correlated with pain-related gene variants [19], hospitalization rates [20], presence of thalassemia [16], and some SCD complications like nephropathy, stroke, and AVN [17]. To our knowledge, there are no studies in regards to clinical and laboratory predictors for painful VOC in Saudi Arabia. Thus, this study is the first to evaluate these predictors thoroughly.

Materials And Methods

Study procedure

This is a retrospective observational study that was conducted in a period from January 2018 to December 2019 for admitted patients in the same period.

This study was conducted from all patients' records to retrieve their data including sociodemographic data as well as the clinical presentations, hospital course including the laboratory findings, performed surgeries, and comorbidities.

The patients were divided into two groups according to the severity of the VOC in SCD patients defined as mild or moderate to severe as it was used in previous work [17]. Those patients who developed one or two VOC episodes in the period between 2018-2019 year were categorized as mild in severity. Patients who developed three or more VOC episodes in the period between 2018-2019 were categorized as moderate to severe.

Those who are Saudis, have SCD, previously admitted in the ward, males, and females, aged 18 and above were included in this study. However, others were excluded from this study.

Statistical analysis

The descriptive statistics were presented using numbers, percentages mean, and standard deviation, whenever appropriate. Univariate analyses were performed using Fischer Exact test as well as an independent t-test. Multivariate regression analysis was also conducted to determine the effect of the severe Vaso-occlusive crisis where the adjusted odds ratio, as well as 95% confidence interval, were also being reported. A P-value 0.05 was considered statistically significant. The data analyses were performed using Statistical Packages for Social Sciences (SPSS) version 21 Armonk, NY: IBM Corporation.

Ethical considerations

Ethical approval was obtained from the ethical committee of the College of Medicine at King Faisal University. Also, consent and approval from the studied setting were obtained before the commencement of the study.

Results

We analyzed 94 patients who were diagnosed with sickle cell disease. As seen in Table 1, approximately 60% were in the younger age group (<30 years) with the majority were males (61.7%) and more than half (56.4%) were not married. We further observed 55.1% who were having associated comorbidities. However, 61.8% of the patients were admitted to the hospital three times or less during the last year. Furthermore, the prevalence of patients who had severe vaso-occlusive crisis was 59.4% while mild-moderate ones were detected among 66.6% of the patients. Likewise, the proportion of patients who underwent the operation was 53.2% while the proportion of patients who experienced complications was 68.1%. In addition, all patients took medication for the management of the disease.
### Study variables

| Study variables                     | N (%)     |
|-------------------------------------|-----------|
| **Age group**                       |           |
| ≤30 years                           | 55 (58.5%)|
| >30 years                           | 39 (41.5%)|
| **Gender**                          |           |
| Male                                | 58 (61.7%)|
| Female                              | 36 (38.3%)|
| **Marital status**                  |           |
| Unmarried                           | 53 (56.4%)|
| Married                             | 41 (43.6%)|
| **Comorbidities**                   |           |
| Yes                                 | 33 (35.1%)|
| No                                  | 61 (64.9%)|
| **Frequency of hospitalization**    |           |
| ≤3 times                            | 64 (68.1%)|
| >3 times                            | 30 (31.9%)|
| **Frequency of vaso-occlusive crisis** |         |
| Mild-Moderate (<3 times)            | 57 (60.8%)|
| Severe (≥3 times)                   | 37 (39.4%)|
| **Operation**                       |           |
| Yes                                 | 50 (53.2%)|
| No                                  | 44 (46.8%)|
| **Medications**                     |           |
| Yes                                 | 94 (100%) |
| No                                  | 0         |
| **Complications**                   |           |
| Yes                                 | 64 (68.1%)|
| No                                  | 30 (31.9%)|

### TABLE 1: Baseline characteristics of the patients (n=94)

SCD: Sickle Cell Disease; ACS: Acute Chest Syndrome.

Table 2 showed the mean values of different hematological parameters. It was found that the mean values of white blood cells, hemoglobin, platelet, Lactate dehydrogenase (LDH), total bilirubin, and direct bilirubin were 11.4, 9.32, 351.4, 409.2, 36.9, and 22.7, respectively while the mean values of hemoglobin electrophoresis, hemoglobin S, hemoglobin A2, hemoglobin A, and hemoglobin F were 1.85, 64.0, 2.87, 34.3 and 15.6, respectively. Additionally, the mean number of blood transfusions was 3.81.
| Variables                     | Mean ± SD              |
|-------------------------------|------------------------|
| White blood count            | 11.4 ± 5.77            |
| Hemoglobin                   | 9.32 ± 1.75            |
| Platelet                     | 351.4 ± 439.0          |
| Lactate dehydrogenase        | 409.2 ± 421.2          |
| Total Bilirubin              | 36.9 ± 43.8            |
| Direct Bilirubin             | 22.7 ± 60.8            |
| Hemoglobin Electrophoresis   | 1.85 ± 0.36            |
| Hemoglobin S                 | 64.0 ± 24.1            |
| Hemoglobin A2                | 2.87 ± 0.91            |
| Hemoglobin A                 | 34.3 ± 38.4            |
| Hemoglobin F                 | 15.6 ± 10.0            |
| Number of blood transfusion  | 3.81 ± 2.49            |

**TABLE 2: Hematological parameters (n=94)**

Figure 1 presented the type of procedure done to the patients. It was revealed that the most commonly performed procedure was cholecystectomy (36.2%), followed by splenectomy (12.8%) and hip replacement (3.2%).

![Figure 1: Type of procedure performed to patients](image)

**FIGURE 1: Type of procedure performed to patients**

Figure 2 depicted the prescribed medications to patients. It was found that the most commonly prescribed medication was analgesics (100%), followed by folic acid (95.7%) and narcotics (91.5%).
In Figure 3, the most frequently mentioned complication was a hemolytic crisis (30.9%) and acute chest syndrome (30.9%) followed by gallstone (26.6%) while the least of them was an aplastic crisis (1.1%).

In univariate analysis of the vaso-occlusive crisis, it was revealed that frequency of hospitalization ($p<0.001$), other procedures ($p=0.050$), narcotics ($p=0.020$), hydroxyurea ($p=0.045$), and avascular necrosis ($p<0.001$) were the factors associated with vaso-occlusive crisis (Table 3).
In the comparison between vaso-occlusive crisis and hematological parameters. It was found that there was no significant difference between the frequency of vaso-occlusive crisis and all the hematological parameters (all p>0.05) (Table 4).
| Parameters                | Frequency of Vaso-occlusive Crisis | P-value‡ |
|---------------------------|-----------------------------------|----------|
|                           | Severe (≥3) Mean ± SD | Mild-moderate (<3) Mean ± SD |
| White blood count         | 10.8 ± 4.41                   | 11.8 ± 6.57 | 0.397 |
| Hemoglobin                | 9.03 ± 1.57                    | 9.52 ± 1.86 | 0.187 |
| Platelet                  | 412.2 ± 629.0                  | 306.4 ± 206.8 | 0.269 |
| Lactate dehydrogenase     | 499.9 ± 447.3                  | 322.0 ± 382.9 | 0.133 |
| Total Bilirubin           | 37.2 ± 36.3                    | 36.8 ± 49.4 | 0.973 |
| Direct Bilirubin          | 25.6 ± 76.9                    | 20.3 ± 44.2 | 0.738 |
| Hemoglobin Electrophoresis| 1.84 ± 0.37                    | 1.86 ± 0.35 | 0.775 |
| Hemoglobin S              | 59.3 ± 23.4                    | 68.0 ± 25.8 | 0.538 |
| Hemoglobin A2             | 2.50 ± 0.72                    | 3.10 ± 0.98 | 0.260 |
| Hemoglobin A              | 54.4 ± 41.9                    | 24.2 ± 38.2 | 0.424 |
| Hemoglobin F              | 18.2 ± 13.8                    | 14.0 ± 7.45 | 0.489 |
| Number of blood transfusion| 4.08 ± 2.45                   | 3.59 ± 2.55 | 0.470 |

**TABLE 4: Comparison between vaso-occlusive crisis and hematological parameters (n=94)**

§ P-value has been calculated using Fischer Exact test. ‡ P-value has been calculated using Independent t-test.
** Significant at p≤0.05 level.

When conducting multivariate regression analysis to determine the effect of severe vaso-occlusive crisis in relation to the selected baseline characteristics of the patients, we have learned that the risk of having vaso-occlusive crisis for those patients who were admitted more than three times was 30 times higher than those patients who were admitted by three times or less (AOR=30.081; 95% CI=8.204 - 110.3; p<0.001). Other variables included in the model such as other procedures, narcotics, and hydroxyurea were observed to have no significant effect with vaso-occlusive after adjustment to regression model (Table 5).
| Factor                  | AOR    | 95% CI          | P-value |
|------------------------|--------|-----------------|---------|
| **Frequency of hospitalization** |        |                 |         |
| ≤3 times               | Ref    |                 |         |
| >3 times               | 30.081 | 8.204 – 110.3   | <0.001 ** |
| **Other procedures**   |        |                 |         |
| Yes                    | 0.283  | 0.039 – 2.053   | 0.212   |
| No                     | Ref    |                 |         |
| **Narcotics**          |        |                 |         |
| Yes                    | 2.990  | 0.627 – 14.270  | 0.170   |
| No                     | Ref    |                 |         |
| **Hydroxyurea**        |        |                 |         |
| Yes                    | 3.411  | 0.738 – 15.775  | 0.116   |
| No                     | Ref    |                 |         |

**TABLE 5: Multivariate regression analysis to determine the effect of severe Vaso-occlusive crisis (n=94)**

AOR: Adjusted Odds Ratio; CI: Confidence Interval. ** Significant at p≤0.05 level.

**Discussion**

Sickle cell disease (SCD) is one of the most prevalent hematological diseases in Saudi Arabia [21], in which it is associated with several complications such as vaso-occlusive crises, avascular necrosis (AVN), gallstones, acute chest syndrome, splenic atrophy, and others [2,3,6]. Several studies showed that various clinical and laboratory findings could be associated with the frequency of their complications. However, they were not conducted in Saudi Arabia. Thus, in this study, we highlighted this issue to make it a base for further studies.

As demonstrated in Table 1, the majority of our patients were less than 30 years of age, which is similar to a previous study from the literature [17]. As observed in Table 3, the most common surgical operation for SCD patients is cholecystectomy, which is consistent with a previous study [22]. This is because these patients tend to have chronic hemolysis which causes the formation of pigment gall stones and necessitates cholecystectomy. However, a previous study stated that most of the included patients were hospitalized less than three times which is similar to our findings in Table 1. We also support the findings in which hemolytic crisis is the most common complication among SCD patients [23].

As demonstrated in Table 3, it is revealed in our study that several factors are significantly associated with the vaso-occlusive crisis severity such as increased number of hospitalizations, number of the administered narcotic analgesia, taking hydroxyurea, and AVN. Similarly, a previously conducted study supports our findings which is, an increased number of vaso-occlusive events is significantly associated with an increased number of hospitalizations as well as AVN [17], and another study supports the finding of the AVN [14]. This similarity of the results between the studies suggests serious consideration of these factors as predictors of further vaso-occlusive attacks. Moreover, further studies are needed to confirm and explore the reason behind these findings and to put the required preventive measures.

Previous studies have shown that there are several significant predictors for the severity of the vaso-occlusive crisis such as higher white blood cell count, higher lactate dehydrogenase, higher hemoglobin level, higher steady platelet count, alpha-thalassemia trait, hemoglobin SS phenotype [8,15,17,18,20]. On the other hand, there was no significant difference between the frequency of vaso-occlusive crisis and all the hematological parameters included in our study as seen in Table 2. Furthermore, another study showed similar results to our study [14].

Our study has significantly shown that patients who have been admitted more than three times have a 30 times higher risk for severe vaso-occlusive crisis compared to patients who were admitted three times or less. Also, one study showed that patients with frequent hospital readmissions because of vaso-occlusive crisis have poor outcomes, prognosis, and demand more care and monitoring [7].
Limitations
Besides the limitation of being a low sample size study, the authors recommend that future prospective studies should be conducted to enhance the quality of data.

Conclusions
Despite the authors could not find a significant association between VOC episodes and the hematological parameters, the study concluded that those patients who had three times VOC episodes are more liable to have frequent episodes in the future. This study supports the earlier use of hydroxyurea to avoid such complications of frequent crises. However, a larger sample size with prospective studies is recommended to be done in the future.

Additional Information
Disclosures
Human subjects: Consent was obtained or waived by all participants in this study. College of Medicine, King Faisal University issued approval 2020 - 10 - 10. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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