Introduction

The clinical picture of sickle cell disease (SCD) is dominated by complications arising from vaso-occlusive crisis (VOC). VOC is precipitated by complex interactions between sickled erythrocytes, endothelial cells, leukocytes, platelets, and plasma proteins. The role of platelets in these interactions is well documented.\(^{[1-6]}\)

In the baseline “steady-state,” platelets are generally normal to increase in number and functionally hyperactive.\(^{[3-6]}\) During sickle cell crisis, platelet counts decline in the initial phases and rise later during recovery.\(^{[3,7–10]}\) Thrombocytopenia is rarely reported but may occur with acute splenic sequestration, aplastic crisis with parvovirus B19 infection and fat embolism.\(^{[11–17]}\) However, there is little information about platelet counts and their relationship to disease severity and survival in acutely affected sickle cell patients admitted to an intensive care unit (ICU). This is the main reason for carrying out the present study. Our test hypothesis was that platelet counts in SCD crisis correlate significantly with disease severity and outcome.

Materials and Methods

Study design and input data

We did a retrospective cross-sectional chart review study of all adult SCD patients (homozygous sickle cell anemia and sickle-beta thalassemia) admitted to our adult ICU during a 1-year period. The inclusion criteria were as follow: (1) a diagnosis of sickle cell anemia (SS) or sickle-beta thalassemia and (2) admission to our ICU during the study period. The exclusion criteria were as follow: (1) patients with a diagnosis of sickle cell trait or sickle-beta thalassemia minor and (2) patients who died before ICU admission.

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on the basis of hemoglobin (Hb) analysis by high-performance liquid chromatography and (2) availability of a complete blood count (CBC) on day 1 of admission. The study was approved by the Research and Ethics Committees of the participating institutions.

All relevant clinical and laboratory data of patients during their period of ICU stay were documented from case-files and the hospital information system. This included data related to vitals, Glasgow coma score (GCS), blood gas results, electrolytes, hepatic and renal function tests, CBC, coagulation tests, microbiologic cultures and serology, history of chronic disease, and the final diagnosis at the time of ICU discharge or death. Platelet counts at admission (day 1) and the nadir platelet count during ICU stay were recorded.

**Definitions**

Diagnostic criteria were employed as follows: thrombocytopenia was defined as a platelet count of <100 × 10⁹/L; thrombocytosis as a count ≥450 × 10⁹/L. Acute chest syndrome (ACS) was defined as the appearance of a new pulmonary infiltrate along with chest pain, fever, tachypnea, wheezing, or coughs.[18] Aplastic crisis was diagnosed on the basis of anemia associated with reticulocytoaenia.[19] Hyperhemolysis was defined as a sudden fall in the Hb level with an elevated reticulocyte count above the baseline level.[19]

Relevant clinical and laboratory data were used in assessing crisis severity on admission (day 1). This was estimated by two methods: the acute physiology and chronic health evaluation (APACHE II) prognostic score and Multiple Organ Dysfunction estimated by the Marshall score (MODS).[20,21] The APACHE II is based on recording 12 physiologic variables, age and chronic health status; MODS is derived from parameters reflecting the function of six organ systems (respiratory, renal, cardiovascular, hepatic, hematological, and central nervous system). The patient outcomes were assessed by documenting mortality and number of days of ICU stay. Significant multiorgan failure was defined as MODS score >5.[20,21]

**Statistical analysis**

The Pearson correlation coefficient was used to evaluate correlations between platelet counts and other numeric variables and between MODS and APACHE scores. Nonparametric tests (Kruskal–Wallis and Mann–Whitney) were used to investigate differences between groups of patients stratified by their platelet counts; mortality versus recovered patient groups and differences between patient-groups stratified by diagnosis. Logistic and multiple regression analyses were employed to test for the influence of 14 selected clinical and laboratory variables on the admission outcomes (mortality and duration of ICU stay). Receiver operating characteristic (ROC) curves were constructed from the day 1 platelet counts, MODS and APACHE scores of patients and their survival/death outcome data.

**Results**

**Clinical and laboratory features**

The study population included 136 admissions (124 patients; 52 females and 72 males). Table 1 shows the diagnostic categories. The three most common sickle complications requiring ICU admission were severe pain crisis, ACS, and infection. Together, these comprised 82% of all cases.

Multiorgan failure was present in 35 patients who had sepsis (n = 8), ACS (n = 13), severe pain crises (n = 8), hyperhemolysis (n = 2), aplastic crisis (n = 2), heart failure (n = 1), and trauma (n = 1). The median platelet count in this group of patients was 76 × 10⁹/L as compared to 211 × 10⁹/L in the non-MODS group (P < 0.001).

Selected laboratory and clinical data are shown in Table 2. Common findings were mild/moderate anemia and leukocytosis, elevated serum bilirubin, and lactate dehydrogenase (LDH). The routine coagulation test profile was characterized by raised prothrombin time and international normalized ratio in the presence of low-normal activated partial thromboplastin.

**Table 1: Platelet counts and prognostic scores in different diagnostic categories of sickle cell disease patients admitted for intensive care**

| Diagnosis/outcome          | Number of cases | Median platelet count (×10⁹/L) | Thrombocytopenia (<100 ×10⁹/L), n (%) | Thrombocytosis (>450 ×10⁹/L), n (%) | MODS score (median) | APACHE II score (median) |
|-----------------------------|----------------|-------------------------------|-------------------------------------|------------------------------------|---------------------|--------------------------|
| Severe pain crisis          | 53             | 177                           | 9 (17)                              | 6 (11)                             | 2.0                 | 7.0                      |
| Acute chest syndrome        | 40             | 196                           | 8 (20)                              | 1 (3)                              | 4.0                 | 10.0                     |
| Infection/sepsis            | 18             | 171                           | 5 (28)                              | 3 (17)                             | 4.0                 | 7.5                      |
| Pulmonary embolism          | 4              | 195                           | 0                                   | 0                                  | 3.0                 | 5.5                      |
| Trauma                      | 4              | 285                           | 1 (25)                              | 0                                  | 5.0                 | 10.0                     |
| Hemolytic crisis            | 3              | 89                            | 2 (67)                              | 0                                  | 6.0                 | 8.0                      |
| Aplastic crisis             | 2              | 56                            | 2 (100)                             | 0                                  | 6.5                 | 10.0                     |
| Miscellaneous*              | 12             | 219                           | 3 (25)                              | 1 (8)                              | 3.0                 | 7.0                      |
| Total cases                 | 136            | 187                           | 30 (22)                             | 11 (8)                             | 3.0                 | 8.0                      |
| Survivors                   | 119            | 203                           | 22 (18)                             | 11 (9)                             | 3.0                 | 8.0                      |
| Nonsurvivors                | 17             | 125                           | 8 (47)                              | 0                                  | 8.0                 | 26.0                     |

*Represents percentage of the number of cases within the specific diagnosis/outcome group, *Miscellaneous conditions included: cor pulmonale (4), renal failure (3), cerebrovascular event (2), bronchial asthma (2), and cholecystitis (1). APACHE II: Acute Physiology and Chronic Health Evaluation II; MODS: Multiple Organ Dysfunction Syndrome.
time ratio, elevated fibrinogen, and marked elevation of D-dimer levels. APACHE scores were calculated in 104 study individuals. There was a significant correlation between the APACHE II and MODS scores ($r = 0.78; P < 0.001$).

**Platelet counts and correlations**

Platelet counts showed wide variation: Ranging from 19 to $838 \times 10^9$/$L$ (mean, $221 \pm 156 \times 10^9$/$L$). Thrombocytopenia was observed at admission in 30 patients (22% of admissions) and thrombocytosis in 11 (8%). Moreover, 51 patients (38%) developed thrombocytopenia at some point during their ICU stay. Day 1 and nadir platelet counts were strongly correlated ($r = 0.9, P < 0.001$). Platelet counts at admission also correlated moderately with MODS scores ($r = −0.43, P < 0.001$) and weakly with APACHE II ($r = −0.32, P = 0.001$). Figure 1 depicts the correlation trend between platelet counts and MODS scores.

Highly significant differences were observed between the thrombocytopenia group and the groups of patients with normal or increased platelet counts [Table 2]. Thrombocytopenic patients showed significantly lower Hb, leukocytes (white blood cell [WBC]), and reticulocytes; higher bilirubin, alanine aminotransferase (ALT), APACHE, and MODS scores. Significant differences between patients with normal platelet count and thrombocytosis were also noted in relation to several laboratory variables (WBC, ALT, and LDH), but the disease severity scores were not significantly different.

Thrombocytopenia was present within all diagnostic categories including VOC with severe pain ($n = 9$), ACS ($n = 8$), and sepsis ($n = 5$). Two patients with hyper-hemolysis and both patients in aplastic crisis also presented with thrombocytopenia. On the other hand, patients with thrombocytosis were admitted with severe pain ($n = 8$) or inflammation-associated etiology ($n = 3$). However, platelet count variations between the eight diagnostic categories did not reach statistical significance.

Specific mention of hydroxyurea (HU) treatment was available in 6/59 patients. None of the patients on HU were thrombocytopenic (median platelets $269 \times 10^9$/$L$). Spleen size was recorded in 25 patients; platelet counts in 8 patients with splenomegaly was significantly reduced versus 17 with noted “no splenomegaly” (Mann–Whitney, $P < 0.05$).

**Patient outcomes**

There were 17 nonsurvivors (12.5% of the study population). These patients were admitted with sepsis/infection ($n = 9$), ACS ($n = 4$), severe pain ($n = 2$), aplastic crisis ($n = 1$), and pulmonary hypertension with heart failure ($n = 1$). The platelet

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**Table 2: Laboratory and clinical data (mean±standard deviation) in study subjects and groups of sickle cell disease patients stratified by their platelet counts**

| Observations          | All study subjects | Platelet count ($\times 10^9$/L) | Kruskal-Wallis* (P) |
|-----------------------|--------------------|----------------------------------|---------------------|
|                       |                    | <100 ($n=30$) | 100-450 ($n=95$) | >450 ($n=11$)       |
| **Hb (g/dL)**         | 8.5±1.7            | 7.6±1.5            | 8.8±1.7            | 8.7±1.5             | $<0.01$ |
| **Leukocytes ($\times 10^9$/L)** | 14.5±8.7          | 10.5±7.0            | 15.0±8.7            | 20.9±9.0             | $<0.01$ |
| **Reticulocytes ($\times 10^9$/L)** | 0.23±0.56          | 0.13±0.10            | 0.26±0.66            | 0.20±0.12             | $<0.01$ |
| **APTT (ratio)**      | 1.2±0.4            | 1.3±0.4            | 1.2±0.4            | 1.1±0.1             | NS     |
| **PT (INR)**          | 1.4±0.4            | 1.5±0.4            | 1.4±0.4            | 1.3±0.2             | NS     |
| **Fibrinogen (mg/dL)** | 444±191           | 411±204            | 446±185            | 521±209             | NS     |
| **D-dimer (U/L)**     | 11.3±10.9          | 15.0±10.9           | 10.5±10.9           | 9.6±10.7             | NS     |
| **Bilirubin total (umol/L)** | 91±114            | 130±157            | 81±99              | 76±75              | NS     |
| **ALT (U/L)**         | 76±96              | 98±94              | 74±100             | 35±10              | $<0.001$ |
| **Creatinine (umol/L)** | 0.9±0.6           | 1.0±0.83           | 0.83±0.52           | 0.7±0.2             | NS     |
| **LDH (U/L)**         | 1250±1186         | 2043±1395          | 1089±1061          | 528±377            | $<0.001$ |
| **APACHE II score**   | 10.2±7.6           | 14.2±8.7           | 9.3±7.1            | 6.3±2.2             | $<0.01$ |
| **MODS score**        | 4.1±3.0            | 7.2±2.9            | 3.35±2.44           | 2.5±2.0             | $<0.001$ |
| **ICU stay (days)**   | 5.7±7.7            | 8.2±10.7           | 5.1±6.8            | 3.7±1.2             | NS     |

*Kruskal-Wallis test for comparison between groups of patients stratified by platelet count. APTT: Activated partial thromboplastin time; PT: Prothrombin time; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; APACHE II: Acute Physiology and Chronic Health Evaluation II; MODS: Multiple Organ Dysfunction Syndrome; ICU: Intensive Care Unit; Hb: Hemoglobin; NS: Not significant; INR: International normalized ratio.

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**Figure 1:** Correlation between platelet counts and multiple organ dysfunction scores in sickle cell patients admitted to the Intensive Care Unit. The trend line is shown
count at admission [Table 1] was significantly lower in the mortality group compared to patients who survived \((P=0.002\), Mann–Whitney test). The distribution of platelet counts in these two groups of patients is shown in Figure 2. Lower reticulocyte count \((P<0.01)\), higher D-dimer \((P=0.02)\), bilirubin, creatinine, LDH, APACHE, and MODS scores \((P<0.001\), respectively) also characterized the group of nonsurvivors.

Durations of patients’ stay in the ICU [Table 2] correlated moderately with MODS scores \((r=0.36, P<0.001)\) and weakly with day 1 as well as nadir platelet counts and APACHE scores. Multiple regression analysis revealed that GCS \((P<0.001)\) and arterial oxygen saturation \((P<0.01)\) were independent predictors of the duration of stay. Results of ROC curve analyses of the platelet count, MODS and APACHE scores as predictors of survival are shown in Table 3 and Figure 3. Importantly, the cutoff value of platelet count \(175 \times 10^9/L\) showed high specificity and positive predictive value (PPV) for survival outcome comparable to both MODS and APACHE scores but weak sensitivity and negative predictive value [negative predictive value; Table 3].

**DISCUSSION**

A CBC is probably the most commonly done laboratory investigation in sickle cell patients in the hospital. However, there is little information about frequencies of platelet-count abnormalities; clinical correlates in different types of sickle cell crisis and prognostic significance of platelet counts in these severely sick patients in the ICU setting. These were the primary reasons for doing this study.

**Platelet counts correlate with prognostic scores, clinical course, and outcome**

We found that in the ICU, abnormal platelet counts are relatively common in sickle cell patients suffering from different types of complications. Unlike platelet counts reported in the steady state, thrombocytopenia was more frequent than thrombocytosis. Platelet numbers correlated significantly with laboratory parameters indicative of organ dysfunction and with prognostic scores. In published studies limited to ACS cases, a platelet count \(<200 \times 10^9/L\) was found to be an independent predictor of respiratory failure and neurologic complications; thrombocytopenia preceded a rapidly progressive course and was its sole predictor.\[^{18,24}\] Similarly, in VOC, it was reported that thrombocytopenia may be associated with markedly elevated LDH and a severe course.\[^{25}\]

In contrast to platelet counts in crisis, thrombocytosis is a common observation in steady-state SCD.\[^{3-6}\] The prognostic implication of elevated baseline platelet counts is debatable with no conclusive evidence of its associations with disease severity or complications.\[^{4}\] The literature is silent on the question of thrombocytosis in sickle cell crises and its relevance to outcome. Findings in our study demonstrate that

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**Figure 3:** Receiver operating characteristic curve of the platelet count as predictor of survival in sickle cell disease patients admitted to the Intensive Care Unit (area under curve = 0.73)

**Table 3:** Receiver operated characteristic curve analyses of the platelet count, multiple organ dysfunction syndrome and Acute Physiology and Chronic Health Evaluation II scores as survival predictors

| Variables (number of cases) | AUC | Youden index | Associated cut-off value | Specificity (%) | Sensitivity (%) | PPV (%) | NPV (%) |
|-----------------------------|-----|--------------|--------------------------|-----------------|---------------|---------|---------|
| Platelet count (136)        | 0.73| 0.387        | >175 \times 10^9/L       | 82              | 56            | 96      | 21      |
| MODS score (136)            | 0.85| 0.647        | ≤5                       | 82              | 82            | 97      | 40      |
| Apache II score (104)       | 0.93| 0.768        | ≤17                      | 93              | 83            | 98      | 63      |

AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value; MODS: Multiple Organ Dysfunction Syndrome
higher platelet counts during crises are linked to lower disease severity scores and predict higher survival chance.

**Receiver operating characteristic curve analyses**

The APACHE II score performed best as a predictor of survival with a cutoff score of 17. The calculation of APACHE scores requires multiple data inputs whereas the platelet count is a readily available indicator with comparable specificity and PPV for predicting survival although its sensitivity is poor.

**Mechanisms contributing to platelet-count alterations**

The pathogenesis of thrombocytopenia in SCD crises is multifactorial. In our study, direct correlations of platelet counts with WBC and reticulocytes suggest that compromised marrow function is a contributory factor. A production-defect could result from vaso-occlusive marrow infarction or sepsis. Second, sickle cell-endothelial interaction results in coagulation factor activation and a state of compensated disseminated intravascular coagulation with platelet consumption. This situation is aggravated in crisis.[1,26‑29] Thrombocytopenia could be a consequence of HU therapy, although in this study all patients who were taking this medication had normal platelet counts.

Finally, genetic factors may be linked to the relatively high frequency of thrombocytopenia in our study population. Common genetic associations of SCD in our geographic regions such as the Arab-Indian haplotype, alpha thalassemia, and high HbF levels, are linked to more frequent splenomegaly and hypersplenism compared to African patients.[13,36‑32]

Autopsy examination of tissues and cytology of bronchial fluid have shown that marrow/fat embolism is a common etiologic factor in SCD crisis and could progress to multi-organ failure.[17,18,33‑36] In ACS, pulmonary vessels may be occluded by emboli or by platelet thrombi leading to thrombocytopenia.[10,37] Occasionally, the manifestations of marrow/fat emboli may resemble those seen in thrombotic thrombocytopenic purpura (TTP). Very high LDH, leukoerythroblastic blood picture, thrombocytopenia, schistocytosis, and multiorgan failure are typically seen.[34,36,38]

We have previously reported a subgroup of SCD patients who presented with these features and recovered after plasmapheresis.[39] Only one of the patients in the present study had TTP-like features. This condition may be under-diagnosed in the absence of a rigorous peripheral smear examination in all cases presenting with thrombocytopenia.

SCD is also a chronic inflammatory condition in which raised levels of cytokines such as IL-1 β and IL-6 may produce a reactive thrombocytosis.[10] Functional asplenia may also be a contributory factor.[10,39] Finally, since platelet counts may rise during recovery from crisis,[8] our patients who had thrombocytosis at admission were possibly in early recovery though symptomatic. This would also explain good outcomes in this group.

**Limitations of the study**

A major limitation of this study is that it is retrospective. Serial measurements of platelet counts noting the magnitude of change from their steady-state values in patients would provide further insight into the dynamics of platelet-count alterations and their implications. Our observations require validation in a larger group of patients.

**Conclusions**

This study presents a cross-section of sickle cell patients in severe crisis in an intensive care setting and demonstrates the value of the platelet count as a marker of disease severity and predictor of outcome in these critically sick patients. Platelet numbers correlate with clinical and laboratory indicators of disease severity. Thrombocytopenia is significantly more common in patients with multiorgan failure and nonsurvivors. A cutoff platelet count of 175 × 10^9/L predicts survival with high specificity and PPV. MODS and APACHE II scores perform better due to higher sensitivity; but the value of the platelet count, in addition to its diagnostic implications, lies in its simplicity as a prognosticator.

The pathogenesis and clinical expression of SCD crisis is complex and has the potential of rapid progression to a fatal outcome. A simple scrutiny of the CBC for the presence of thrombocytopenia readily identifies a subgroup of patients with poorer prognosis who would benefit from more stringent management protocols.

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**Conflicts of interest**

There are no conflicts of interest.

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