

Platelet volume parameters as a tool in the evaluation of acute ischemic priapism in patients with sickle cell anemia

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Summary *Objective: This study aimed to evaluate the predictive value of platelet volume indices (PVI), such as mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), as prognostic parameters of detumescence in acute ischemic priapism (IP) patients with sickle cell anemia (SCA) in steady-state who received intracavernosal injections of phenylephrine with aspiration and saline irrigation.*

Methods: Fifty-six SCA patients with acute IP and 54 healthy male control subjects were included in the research. Priapism was diagnosed by penile Doppler ultrasound and corporal blood gas tests before intervention. Measurements of PVI (MPV, PDW, and PCT) and TLC were ordered for all participants. Additionally, the duration of priapism was recorded. The area under the curves was calculated by receiver operating characteristic (ROC) regression analysis.

Results: The detumescence rate was 71.4% after the intervention. Compared to the control group, priapic SCA patients showed significantly higher PLT ($p = 0.011$), MPV ($p = 0.002$), PDW ($p = 0.032$), PCT values ($p = 0.022$), and TLC ($p = 0.027$). Higher MPV, PDW, and PCT values were observed in unsuccessful detumescence patients compared to the resolution group ($p < 0.05$). Statistically significant cutoff values for persistent priapism were measured by ROC as PLT: $\geq 254 \times 10^3/\mu\text{L}$; MPV: $\geq 13.2 \text{ fL}$; PDW: $\geq 15.6 \text{ fL}$; PCT: $\geq 24\%$; and TLC $\geq 8.5 \times 10^3/L$. Priapism duration of ≤ 17.9 hours was significantly related to detumescence rate ($p = 0.000$). Multivariable logistic regression analysis showed that priapism duration and higher MPV are prognostic parameters for detumescence in SCA.

Conclusions: The higher MPV and duration of priapism can be used as parameters for evaluating detumescence outcomes in steady-state SCA with acute IP.

KEY WORDS: Sickle cell anemia; Acute ischemic priapism; Platelet volume indices.

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INTRODUCTION

Sickle cell anemia (SCA) is a polymorphic genetic disorder characterized by recurrent inflammatory damage and episodic vaso-occlusive complications such as acute chest syndrome, acute scrotal pain, and priapism (1, 2).

Priapism is a persistent and prolonged penile erection lasting > 4 hours that occurs in 35% of SCA patients (3, 4).

No conflict of interest declared.

Among the pathophysiologic mechanisms proposed for priapism development in the SCA population, the acute ischemic priapism (IP) (veno-occlusive, low flow) type is represented by painful and rigid penile erection (1, 4). Acute IP is a medical emergency that should be prevented and managed immediately to preserve the function of erectile tissue (5).

In this IP population, aspirated blood gas analysis of the corpus cavernosum usually reveals hypoxia, hypercapnia, and acidosis (4). In addition, penile Doppler ultrasound (PDUS) has improved the diagnosis of IP by demonstrating very low or absent arterial blood flow in the corpus cavernosum (6). Nevertheless, the risk of corpora cavernosal fibrosis and partial or complete impotence in SCA patients with IP suggests the need for careful evaluation and new diagnostic techniques (4).

Because of the vasculopathy, chronic hemolysis, and veno-occlusive pathogenesis of SCA, multiple hematologic markers are needed to predict the outcome of IP in SCA patients. The role of platelet count (PLT) and mean platelet volume (MPV) in these veno-occlusive mechanisms is well documented (7-11). Previous studies confirmed the association between IP, defined as a vasculogenic disease, and platelet activation leading to higher MPV (9, 10).

Therefore, platelet volume indices (PVI) can be measured as potential laboratory parameters for diagnosis and treatment of IP.

To our knowledge, the role of laboratory PVI, such as MPV, platelet distribution width (PDW), and plateletcrit (PCT), as prognostic markers for IP in SCA patients at steady-state has not yet been analyzed. The aim of this paper was to determine the diagnostic and cutoff values of PVI such as MPV, PDW, and PCT for the detumescence outcomes of acute IP in SCA patients.

PATIENTS AND METHODS

Study population

One hundred thirteen (113) SCA patients with steady-state were admitted to the emergency room with priapism. Of those case series, only 56 cases presenting acutely with IP were included in this research and required immediate intervention to avoid fibrosis of cavernosal tissues and subsequent erectile dysfunction. Fifty-

four (54) healthy control males from the subjects undergoing medical examination in our hospital were included in our study for comparison. Ages of the patients and controls were similar. The control participants had no history of priapism, malignancy, pelvic trauma, surgery, or hematologic disease. The research protocol for the study was approved by the *Institutional Reviewer Board* of the *Faculty of Medicine at Jazan University, Saudi Arabia* and was conducted in accordance with the principles of the Helsinki Declaration.

Selection criteria

Inclusion criteria: Patients (aged 19-54 years) with SCA who complained of an acute episode of priapism for the first time and were aware of having SCD were included. Suspected IP was diagnosed by PDUS by demonstration of absent or low cavernous blood flow (6). IP was confirmed by aspiration of hypoxic and dark blood from the corpora cavernosa and typical blood gas analysis values ($pO_2 < 30$ mmHg, $pCO_2 > 60$ mmHg, $pH < 7.25$) before any intervention (4). Included SCA participants were identified by qualitative and/or quantitative hemoglobin electrophoresis at pH 8.6 on cellulose acetate paper. Steady-state SCA was diagnosed according to criteria defined by *Ballas SK et al.* (12).

Exclusion criteria: SCA patients were included after excluding non-IP by blood gas analysis in the corporeal aspiration and normal blood flow levels in the cavernosal arteries in PDUS. Excluded patients were also those with myeloproliferative disorders and leukemic diseases. Patients with a history of strokes, recurring or previous priapism attacks, or hospitalization for an acute painful crisis within the previous year were excluded. Patients with a history of pelvic surgery and trauma, newly diagnosed coronary artery disease, active infectious disease, malignancy, immunological disease, or those taking antiplatelet or anticoagulant medication were all excluded.

Clinical examination

All SCA patients underwent a complete physical examination with a detailed history as soon as possible after initial presentation of priapism. Abdominal, perineal, and digital rectal examinations were also performed to exclude any evidence of trauma, pelvic infection or malignancy or the presence of any other systemic symptomatology associated with SCD, such as a sickle crisis.

A comprehensive history included information on the duration of priapism, any medication used, the presence of pain, and any previous history of priapism. Physical examination of the penis was essential to determine the extent and degree of rigidity, the involvement of the corpora cavernosa bodies, and the presence of penile tenderness. In this study, priapism was defined as a persistent painful erection lasting more than 1 hour without orgasm and ejaculation and requiring medical therapy (13).

During intervention, decisions regarding continuing the combination of aspiration, irrigation, and *intracavernous injection* (ICI) or proceeding with immediate surgical interventions were guided by the clinicians. All acute IP cases were treated by ICI therapy with phenylephrine in combination with aspiration and irrigation with 0.9% saline. ICI can be repeated every 3-5 minutes until

detumescence occurs, with a maximum of 1 mg administered within one hour. A physician should monitor the heart rate and blood pressure (14).

After repeated intervention, patients were evaluated for the resolution of priapism, which was indicated by the disappearance of corporal rigidity by exam, the absence of acidosis by cavernous blood gas testing, and the return of cavernosal artery flow by PDUS (14, 15).

Laboratory evaluation

Peripheral blood samples were collected in tubes containing EDTA-K2 (potassium ethylenediaminetetraacetic acid) anticoagulant before any form of priapism intervention from patients and control subjects. Samples were analyzed within one hour of the patient's referral (16-18). An automated blood cell counter (*Sysmex Corp., Japan*) was used to measure PLT, PVIs (MPV, PDW, and PCT), and *total leukocyte count* (TLC).

Statistical analysis

Analyses were conducted using IBM SPSS version 24.0 (*Armonk, NY*). Continuous variables were tested for normality of distribution with the Kolmogorov-Smirnov test. Depending on the distribution, data was presented as means, *standard deviation* (SD), or medians with the *interquartile range* (IQR). Differences in the means were compared using the unpaired Student's t-test for normally distributed data, whereas the non-parametric Mann-Whitney U test was carried out for comparing medians of non-normally distributed data. Chi-squared tests were carried out to analyze categorical variables. *Receiver operating characteristic* (ROC) curve analysis was performed to find out cut-off values and *areas under the curve* (AUC) for potential predictive values. Multivariable logistic regression analysis was conducted to identify the potential risk factors. A p-value of 0.05 was used as a threshold of significance.

RESULTS

The demographic and clinical characteristics of the studied patients are summarized in Table 1. In the IP and the control group, the median ages were 41.2 (IQR: 33.2-45.2) and 42.7 (IQR: 34.2-46.2) years, respectively. The median time of duration of priapism was 17.9 (IQR: 8.5-26.4) hours. Forty (71.4%) SCA patients were found to have detumescence during intracavernosal intervention. The remaining 16 (28.6%) patients received immediate spongiosocavernosal surgical shunting with tunneling for persistent priapism. In terms of duration of priapism, a priapism event ≤ 17.9 hours in duration ($n = 25$, 44.6%) was statistically significantly correlated to the detumescence rate in SCA patients ($p = 0.000$). On the contrary, PLT and PVIs (MPV, PDW, and PCT) had no significant relationship with the duration of priapism ($p = 0.130$, $p = 0.087$, $p = 0.145$, and $p = 0.245$, respectively).

In the acute IP group, the medians of PLT, MPV, PDW, and PCT were $254 \times 10^3/\mu L$ (IQR: 227-296), 13.2 fL (IQR: 10.5-14.1), 16.9 fL (IQR: 15.8-19.2), and 0.35% (IQR: 0.23-0.38), respectively. The medians of PLT, MPV, PDW, and PCT of the IP cases were detected to be significantly higher than those in the control group ($p =$

Table 1.
Demographic and clinical data amongst steady-state SCA patients with acute ischemic priapism (IP).

Numbers of patients	56
Age at presentation, yrs *	41.2 (33.2-45.2)
Follow-up, yrs *	3.4 (2.6-4.2)
Priapism duration, hrs *	17.9 (8.5-26.4)
Penile Doppler US (blood flow) n (%)	
Absent	53 (94.6)
Low	3 (5.4)
Penile aspiration outcome †, n (%)	
Non-resolution with full rigidity	16 (28.6)
Detumescence	40 (71.4)

Values are presented as median (interquartile range, IQR).
† Intracavernosal injections (ICI) of phenylephrine with aspiration and 0.9% saline irrigation.

Table 2.
Hematologic parameters amongst steady-state SCA men with acute ischemic priapism and controls in men without SCA.

Parameter	Ischemic priapism group	Control group	P-value *
Platelet count (PLT) ($\times 10^3/\mu\text{L}$)	254 (227-296)	249 (238-253)	0.011
Mean platelet volume (MPV) (fL)	13.2 (10.5-14.1)	7.6 (7.3-13.4)	0.002
Platelet Distribution width (PDW) (fL)	16.9 (15.8-19.2)	14.3 (5.7-15.7)	0.032
Plateletcrit (PCT) (%)	0.35 (0.23-0.38)	0.32 (0.27-0.38)	0.022
Total leucocyte count (TLC) ($\times 10^3/\text{L}$)	14.3 (7.4-21.1)	11.2 (8.4-13.2)	0.027

Values are presented as median (interquartile range, IQR). * Mann-Whitney U Test.

0.011, $p = 0.002$, $p = 0.032$, and $p = 0.022$, respectively) (Table 2). Persistent priapism in SCA cases had higher MPV, PCT, and PDW than those in the detumescence group, which was statistically significant ($p = 0.001$, $p = 0.042$, and $p = 0.035$, respectively).

Regarding the median TLC, there was a statistically significant difference among groups ($p = 0.027$) (Table 2). Additionally, SCA cases with priapism resolution had a significantly lower TLC than those in the persistent group ($p = 0.046$).

The evaluation made with ROC curve analysis detected that cut-off levels for PLT, MPV, PDW, PCT, TLC, and duration of priapism for the prediction of priapism resolution were $254 \times 10^3/\mu\text{L}$, 13.2 fL, 15.6 fL, 24%, $8.5 \times 10^3/\text{L}$ and 17.9 hours, respectively. The corresponding sensitivities were 62.5%, 81.3%, 75%, 69.8%, 68.8%, and 87.5%, and the corresponding specificities were 55.0%, 67.5%,

Table 3.
Prediction of the corporal detumescence outcomes according to the cut-off values of PLT, MPV, PDW, PCT, TLC, and duration of priapism.

	Cut-off value	AUC	P-value	95% CI	Sensitivity (%)	Specificity (%)
Platelet count (PLT)	$254 \times 10^3/\mu\text{L}$	0.652	0.079	0.499-0.804	62.5%	55%
Mean platelet volume (MPV)	13.2 fL	0.811	0.000	0.676-0.946	81.3%	67.5%
Platelet distribution width (PDW)	15.6 fL	0.630	0.130	0.442-0.819	75%	12.5%
Plateletcrit (PCT)	24%	0.548	0.574	0.370-0.727	69.8%	37.5%
Total leucocyte count (TLC)	$8.5 \times 10^3/\mu\text{L}$	0.521	0.807	0.360-0.682	68.8%	42.5%
Priapism duration	17.9 hrs	0.842	0.000	0.709-0.977	87.5%	62.5%

AUC, area under curve; CI, confidence interval.

Table 4.
Multivariate analysis of the risk factors for the corporal detumescence outcomes.

	OR	95% CI	P-value
Platelet count (PLT) ($\times 10^3/\mu\text{L}$)	0.623	0.177-2.195	0.462
Mean platelet volume (MPV) (fL)	8.895	1.000-79.089	0.050
Platelet distribution width (PDW) (fL)	2.005	0.219-18.362	0.538
Plateletcrit (PCT) (%)	0.602	0.129-2.800	0.517
Total leucocyte count (TLC) ($\times 10^3/\text{L}$)	0.267	0.051-1.389	0.117
Priapism duration (hrs)	26.079	2.401-283.259	0.007

OR: odds ratio; CI: confidence interval.

12.5%, 37.5%, 42.5%, and 62.5%. The area under the curves (AUC) for PLT, MPV, PDW, PCT, TLC, and duration of priapism were 0.652 ($p = 0.079$), 0.811 ($p = 0.000$), 0.630 ($p = 0.130$), 0.548 ($p = 0.574$), 0.521 ($p = 0.807$), and 0.842 ($p = 0.000$), respectively (Table 3).

Based on a multivariable logistic regression model after grouping predictor factors, both duration of priapism and MPV showed their independent prognostic impact on the outcome of priapism in steady-state SCA patients (Table 4).

DISCUSSION

The potential pathogenic and diagnostic roles of platelets in vascular pathologies have been described in many papers. The PLT and related *platelet volume indices* (PVIs) have been identified as markers of thrombocyte reactivity in various vascular and urological diseases (17-20). Priapism is a vascular disease with a veno-occlusive mechanism and endothelial damage as its main pathophysiological basis (20). Platelet hematological parameters play a significant role in IP pathophysiology. However, there is relatively little data on PVIs (MPV, PDW, and PCT) in priapic patients, as well as, their relationship with the outcome of primary emergency ICI of phenylephrine and the combination of aspiration and irrigation in SCA patients with acute IP (9, 10).

In the study by Sönmez *et al.* (9), the relationship between IP and high PLT and MPV was confirmed to be significant, similarly to the study by Ufuk *et al.* (10). However, PCT was not included in the platelet parameters analyzed in this series, and statistical studies were performed with predictive and cutoff values in IP patients without SCA.

The significance of our study was the addition of PCT, besides PLT, MPV, and PDW, and the statistical calculation of their cutoff values as suspected predictive factors in acute IP with SCA.

In this study, IP men with SCA had higher PVIs (MPV, PDW, and PCT) when compared to men who had never experienced priapism. Even so, MPV had a strong sensitivity (81.3%) effect on IP pathogenesis. PLT, MPV, PDW, and PCT levels of the detumescence cases also revealed a statistically significant cut-off of $254 \times 10^3/\mu\text{L}$,

13.2 fL, 15.6 fL, and 24% in priapic SCA patients as an indicator for cavernosal function. Moreover, the MPV value of unsuccessful detumescence patients revealed a higher significant cut-off of 13.2 fL than that of 9.11 fL for priapic cases without SCA as a parameter for erectile tissue function (10).

According to this study, the MPV has been suggested to have a role in the detumescence response in SCA patients who received ICI phenylephrine with aspiration and saline irrigation. Despite the encouraging resolution of corporal rigidity in this study, 28.6% of patients are still experiencing persistent priapic attacks. Those patients have a negatively significant correlation with higher MPV. Those patients with a higher MPV had a very low chance of improvement in their corporal rigidity in terms of the absence of cavernosal artery inflow and persistent acidosis. This finding was supported by increased thrombocyte activity, which is associated with increased thromboxane A2 synthesis, soluble P-selectin, and intravascular thrombosis in SCA (21). In our report, the high incidence of hemolysis in SCA results in a lowering of NO bioavailability and down regulation of phosphodiesterase type 5 protein expression, which impairs penile vascular reactivity (22). Also, the increased MPV triggers and increases corporal veno-occlusive dysfunction, leading to hypoxia and microvascular thrombosis of the corpora cavernosa (1, 7, 23). Consequently, high MPV can be used as a biomarker for the recovery of erectile tissue function in SCA patients with acute IP.

Interestingly, we found a significantly increased PDW in acute IP patients with SCA compared to healthy controls, with a positive relationship with detumescence. Even so, PDW levels of unresolved priapism showed a higher significant cut-off of 15.6 fL for cavernosal damage. However, *Ufuk et al.* found that the PDW levels were similar between IP patients without SCA and control healthy subjects, even though the platelet count was significantly lower in IP patients than in controls (10). Nonetheless, other investigators have observed that PDW is a specific sign of active platelet release for developing thromboembolic disorders (7, 24). The increased PDW in SCA with priapism is mainly related to the up-regulated production and average volume of megakaryocytes. Additionally, we detected a higher PCT with its effect on priapism resolution among those patients. This is in accordance with the *Adawi et al.* study that demonstrated higher PCT levels with significant implications on testicular torsion outcome among patients with steady-state SCA (18). *Mutlu et al.* found that values of PCT are low with little effect on thrombosis processes (19).

These findings demonstrated the significant role of priapism in the regulation of platelet count, and PVIs values in steady-state SCA patients.

In our study, TLC was significantly increased in acute IP with a predictive outcome on detumescence found in SCA as a result of acute inflammation and excessive hemolysis, which is associated with active hematopoiesis (10). This inflammation promotes vascular endothelial adherence to sickle erythrocytes, which is associated with the release of cytokines, causing veno-occlusion dysfunction (25). Moreover, the high TLC in SCA patients with and without priapism was demonstrated by *Ahmed et al.*

(26). Interestingly, *Madu et al.* found a positive relationship between low levels of TLC and the development of priapism, which is contrary to our observation (8).

These conflicting studies could be related to differences in various factors such as study design, sickle cell genotype, precipitating factors, genetic factors, effects of intervention, and laboratory methods, all of which can change the hematological values of priapic patients with SCA (8, 16, 27). In general, the prognostic value of a complete blood count includes other biomarkers (eosinophil, and reticulocyte count), has been associated with the development of acute IP in men with SCA (8, 11, 13).

Furthermore, in this report, patients with priapism > 17.9 hours had a positive correlation for predicting erectile tissue recovery. Similar results were found in other retrospective studies that observed cavernosal necrosis was more common with prolonged durations of > 12 hours. In IP, the histological damage in the erectile tissue appears to be time dependent. In patients with priapism < 12 hours, interstitial edema and minor endothelial defects predominate in the smooth muscle. On the contrary, extensive necrosis of the smooth muscle cells was detected after priapism lasting > 48 hours (28, 29). Moreover, the presence of intravascular clots inside the cavernous sinuses causes venous obstruction and recurrent priapism (30). Nonetheless, the duration of priapism had no significant effects on the PVIs in this retrospective case series. This may be due to the fact that not all cases who presented with a prolonged duration had a complete venous outflow occlusion, which may be related to stuttering priapism, which is associated with intermittent periods of detumescence, or because of focal necrosis/fibrosis in the infarcted corpora secondary to ischemic compartment syndrome in acute IP (4, 6, 14).

Our results confirmed an independent poor outcome of IP management for SCA patients with both increased MPV and longer priapism duration. Their measured cut-off levels were detected to have a significant relationship with the priapism outcome. However, such retrospective analysis has many limitations. The number of IP cases included in the analysis was relatively small. We did not evaluate other etiologies of acute priapic attacks, such as leukemia or thalassemia. In addition, the normal ranges of platelet indicators need adjustment. Also, the lack of association between priapism and genetic factors associated with SCA may indeed limit the statistical power of our study. Moreover, the diagnosis of IP was established mainly after clinical parameters and cavernosal aspiration, both of which are prone to error (6). Also, these populations should be investigated for asymptomatic erectile dysfunction because of the high risk of vascular dysfunction associated with SCA.

CONCLUSIONS

In summary, this study shows that increased PVIs in SCA may have a beneficial role in the veno-occlusive pathogenesis of IP, which was associated with cavernosal damage. Furthermore, prolonged duration of priapism with a high MPV may be a predictive parameter for the development of corpora fibrosis in men with acute priapic attacks. Additionally, the use of laboratory MPV factor

may guide the physician to identify high-risk sickle cell men presenting with acute IP, which is considered for primary nonsurgical resolution of the priapic event. Prospective clinical protocols involving large populations and different priapism types are also warranted to improve this issue.

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