High platelet distribution width can independently predict testicular survival in testicular torsion among patients with steady-state sickle cell anemia

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ABSTRACT

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 indicators of testicular viability in torsion patients with steady-state sickle cell anemia (SCA) who underwent surgical exploration.

Methods Forty-eight patients with SCA with testicular torsion and 46 male control subjects were enrolled in the study. All patients underwent scrotal color Doppler ultrasonography before surgery, and PVI (MPV, PDW, and PCT) values were measured in all participants. Symptom duration and testicular volume were also recorded.

Results The testicular salvage rate in patients with SCA was 73% after surgery. Analyses showed that MPV, PDW, and PCT values were significantly higher in torsed SCA compared with controls (p<0.05). Orchiectomy in patients with SCA showed significantly higher MPV, PDW, and PCT values than the orchiopexy group (p<0.05). The MPV values of orchiectomy patients showed a higher significant cut-off of ≥16.8 fL, which is higher than in torsed patients without SCA, as an indicator of testis survival. PDW also demonstrated a higher significant cut-off of ≥12.7 fL for detorsion outcomes in patients with SCA. Symptom duration of less than 7 hours was also significantly correlated with orchiopexy (p<0.001). Univariate analysis showed that higher MPV, increased PDW, and symptom duration were indicative of the outcome of testicular viability in SCA.

Conclusion Increased PDW and symptom duration can be used as parameters for predicting testicular detorsion outcomes in patients with steady-state SCA.

INTRODUCTION

Sickle cell anemia (SCA) is characterized by chronic hemolysis, inflammatory damage, and progressive vascular disease complications, such as acute chest syndrome, stroke, and priapism with acute scrotal pain.1 2 Scrotal pain in patients with SCA should always be treated as acute scrotal pathologies. Although majority of these pathologies are non-acute (eg, epididymo-orchitis), testicular torsion is a surgical emergency and should be diagnosed early and treated immediately to preserve a patient’s testes.3 4 Testicular torsion can occur at any age, but usually occurs in young boys, with a bimodal incidence in the...
pediatric population (during the first year of life and between the ages of 13 and 16 years). If treated within 6 hours of the presenting pain, there is a good chance of saving the affected testicle (90%–100% of the testicles will be saved). If treated within 6–12 hours, depending on the degree of the torsion, 20%–50% of the testicles will be saved. If treated within 12–24 hours, 0%–10% of the testicles will be saved. Nevertheless, the risk of testicular atrophy and unnecessary surgery in patients with SCA with acute scrotal pain suggests the need for novel diagnostic techniques.

Because the pathophysiology of sickle cell vascular complication is a microenvironmental inflammatory process, hematological inflammation parameters are needed for predicting the outcomes of testicular torsion in patients with SCA. The role of platelets in these interactions is well documented. Several studies confirmed that there is a relationship between testicular torsion, defined as an acute vascular disease, and platelet activation which results in higher mean platelet volume (MPV). Therefore, platelet volume indices (PVIs) can be introduced as potential markers of early diagnosis of testicular torsion.

Considering the chronic hemolysis and inflammatory nature of sickle cell disease, we expect that generalized alterations in hematological parameters will occur in SCA. To date, the utility of different PVIs, such as MPV, platelet distribution width (PDW), and plateletcrit (PCT), has not been analyzed as prognostic markers of testicular torsion in patients with SCA. The present study aimed to investigate the predictive value of PVIs, such as MPV, PDW, and PCT, in the outcome of testicular torsion in patients with SCA.

METHODS

Patients

One hundred and fifteen patients with steady-state SCA were referred to the emergency department with acute scrotal pain. From this group, only 48 patients diagnosed with testicular torsion were enrolled in the study and underwent surgical exploration.

Forty-six patients with clinically diagnosed healthy testicular torsion were also included as control subjects from patients admitted to the emergency department for testicular exploration, with a similar age between the two groups. The control subjects had no epididymo-orchitis, testicular tumor, history of scrotal trauma and surgery, or hematological diseases. All participants provided written informed consent before enrollment in the study.

Selection criteria

Inclusion criteria

Patients with a complaint of acute scrotal pain were initially included. Testicular torsion was diagnosed by scrotal color Doppler ultrasonography (CDUS) and was confirmed by surgical exploration. The included participants with SCA were confirmed by qualitative and/or quantitative hemoglobin electrophoresis.

Exclusion criteria

Patients with SCA were included after excluding perinatal testicular pathology (cryptorchidism, testicular tumor, and epididymo-orchitis), or cases associated with compromised vascular testicles. Excluded patients were also those with chronic hepatic, renal, or hematological (eg, myeloproliferative disorders and leukemia) diseases. Patients with previous overt stroke and acute pain crisis hospitalization within 1 year were also excluded. Any patient who underwent manual detorsion followed by elective testicular fixation at a later date was also excluded.

Clinical examination

All subjects underwent physical examination after their medical histories were taken. Clinical findings included scrotal characteristics (tenderness, erythema, and swelling), the affected side, high-riding testis, lower abdominal pain, fever (>38.5°C), nausea/vomiting, and pyuria. Symptom duration was defined as the time between onset of acute symptoms and detorsion.

CDUS was performed in all patients at the time of admission as the mainstay for evaluation of acute scrotal pain. Measurements obtained on CDUS included testicular volume of the normal and torsed testicles and the presence or absence of testicular blood flow.

All patients with presumed torsion underwent scrotal exploration. During exploration, decisions regarding orchiectomy or orchiopexy were made by the surgeon. All explored patients were managed by detorsion of the torsed testicle with bilateral orchiopexy or orchiectomy.

Outcome measures

The primary outcome measure was the rate of detorsion and testicular viability during surgical exploration. The secondary outcome was the correlation of PVI values in steady-state SCA with torsion surgical findings, considering patients’ data from medical and radiology reports, which included the following: testicular volume of both the torsed side and the contralateral side, duration of symptoms, and other torsion clinical findings.

Laboratory analysis

Blood samples were drawn in tubes containing EDTA-K2 (potassium EDTA) anticoagulant from the patients and the control subjects before the surgical intervention. Samples were analyzed within 1 hour. Platelet count (PLT), PVIs (MPV, PDW, and PCT), and total leucocyte count (TLC) were measured using an automated blood cell counter (Sysmex, Japan).

Statistical analysis

Data analysis was performed using IBM SPSS V.24.0. Continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Data were
reported as mean (with standard deviation (SD)) or as median (with interquartile range (IQR)) according to the distribution. Differences in means were compared using Student’s t-test for normally distributed data, whereas non-parametric Mann-Whitney U test was used to compare the medians of non-normally distributed data. \( \chi^2 \) test was used to analyze categorical variables. A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values and the area under the curve (AUC) of potential predictive factors. The criterion used in the ROC analysis to define the optimal cut-off value of a predictor was to find the observed value of the predictor that maximized the sum of the predictor’s sensitivity and specificity. This is mathematically equivalent to maximizing equally weighted sensitivities and specificities. Multivariable logistic regression analysis was used to identify potential risk predictors. A \( p \) value of 0.05 was considered to be the level for a statistically significant difference.

**RESULTS**

Patient demographic and clinical findings are summarized in table 1. The difference between groups was statistically not significant. Within the groups studied, the median time of symptom duration was 7.5 (IQR 6.2–10.0) and 7.9 (IQR 6.3–13.0) hours for both the patients and the controls, respectively. After a median follow-up of 33.8 (IQR 29.6–37.4) months, 35 (73%) patients with SCA were found to have a viable testis during exploration. The remaining 13 (27%) patients received orchiectomy for non-viable testes. In terms of symptom duration, it was found that a duration of <7 hours (n=34, 71.0%) was statistically significantly correlated with detorsion and testicular viability in patients with SCA (p<0.001).

The median PLT, MPV, PDW, and PCT were 236\( \times 10^3 \)/\( \mu \)L (IQR 197–298), 14.1 fL (IQR 8.4–18.1), 17.9 fL (IQR 15.9–18.4), and 0.34% (IQR 0.18%–0.38%) in torsed patients with SCA, respectively. The median MPV, PDW, and PCT of patients with SCA were significantly higher than those in the control group (p<0.05). PLT was higher in the patient group than in the control group but not significantly (p=0.001) (table 2). Also, MPV, PDW, and PCT had significant correlation with PLT count (p=0.247, p=0.329, and p=0.089, respectively). Patients with SCA with orchiectomy had higher MPV, higher PCT, and increased PDW count than those in the orchiopexy group, which was statistically significant (p=0.02, p=0.03, and p=0.001, respectively).

No statistically significant difference was found between the other clinical findings (scrotal tenderness, swelling, erythema, lower abdominal pain, fever, pyuria, nausea, and vomiting) and PVI values (p>0.05).

In the SCA torsed group, the median testicular volume of the torsed side (10.5 (IQR 8.4–12.2) cm\(^3\)) was lower than of the contralateral side (14.9 (IQR 12.1–17.4) cm\(^3\)), with a significant correlation (p=0.01) (table 1). Also, a significant correlation was observed between testicular volume and detorsion results (p=0.001). However, the testicular volume did not have any significant correlation with MPV, PDW, and PCT (p=0.838, p=0.568, and p=0.087, respectively).

The median TLC was significantly higher in the patient group compared with the control group (p=0.05) (table 2). At the same time, patients with SCA with orchiopexy had a significantly lower TLC than in the orchiectomy group (p=0.04).

The ROC curve analysis revealed that the optimal cut-off value for MPV, PDW, PCT, TLC, and symptom duration to predict testicular torsion was 11.5 fL, 12.7 fL, 26%, 10.5\( \times 10^3 \), and 7 hours, respectively. The corresponding sensitivities were 62.2%, 76.9%, 69.2%, 61.3%, and 84.6%, and the corresponding specificities were 60.0%, 77.1%, 48.6%, 57.1%, and 80.0%. The AUC for MPV, PDW, PCT, TLC, and symptom duration was 0.631 (p=0.167), 0.785 (p=0.003), 0.590 (p=0.342), 0.538 (p=0.685), and 0.812 (p=0.001), respectively (table 3 and figure 1).

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**Table 1** Patients’ demographic and clinical data

| Parameter | Patient group (n=48) | Control group (n=46) | P value* |
|-----------|---------------------|---------------------|----------|
| Median age at operation, years† | 16.7 (8.5–19.1) | 16.2 (10.1–18.8) | 0.226 |
| Side of torsion, n (%) | Right | 21 (44) | 22 (48) | |
| Left | 27 (56) | 24 (52) | |
| Clinical scrotal findings, n (%) | Tenderness | 44 (92) | 45 (98) | 0.829 |
| Swelling/erythema | 44 (92) | 42 (91) | 0.659 |
| High-riding testis | 39 (81) | 38 (87) | 0.271 |
| Lower abdominal pain | 3 (6) | 3 (6.5) | 0.121 |
| Nausea and vomiting | 3 (6) | 4 (9) | 0.109 |
| Fever >38.5°C | 1 (2) | 2 (4) | 0.831 |
| Pyuria | 1 (2) | 2 (4) | 0.831 |
| Scrotal Doppler ultrasonography (blood flow), n (%) | Absent | 45 (94) | 42 (91) | |
| Present | 3 (6) | 4 (9) | |
| Torsion outcome, n (%) | Detorsion (fixation) | 35 (73) | 36 (78) | 0.357 |
| Orchiectomy | 13 (27) | 10 (22) | |
| MTV of torsed testes, cm\(^3\)† | 10.5 (8.4–12.2) | 11.3 (9.3–12.3) | 0.301 |
| MTV of normal testes, cm\(^3\)† | 14.9 (12.1–17.4) | 16.1 (12.9–18.5) | 0.267 |

P value: comparison between the patient group and the control group. *Mann-Whitney U test. †Values are presented as median (interquantile range, IQR). MTV, median testicular volume.
A multivariable logistic regression model for the outcome was constructed and included all of the six predictors (MPV, PDW, PCT, TLC, symptom duration, and testicular volume). Based on this model, symptom duration (p=0.034, odd ratio (OR)=1.13, 95% confidence interval (CI) 1.054 to 1.868) and PDW (p=0.042, OR=6.586, 95% CI 1.033 to 41.985) were significant predictors of orchiectomy (table 4).

**DISCUSSION**

The results of the present study showed a significant increase in PDW in testicular torsion patients with SCA, with a significant correlation with detorsion outcome. The PDW values of orchectomy patients demonstrated a higher significant cut-off of ≥12.7 fL for testis survival. Several studies have also reported that PDW is a platelet activation risk marker of developing thromboembolic disorders. Some studies suggest that PDW seems to be a more specific marker of platelet activation than MPV. A key component of this increased PDW is increased platelet production and reactivity, and thus an increased average platelet volume, resulting in an increased PDW. Also, higher concentrations of platelet microparticles have been detected in steady-state SCA. Moreover, increased PDW has been detected in pediatric SCA. PDW also directly measures the changes in platelet size. Thus, PDW can also be used as a marker of testicular torsion outcomes in patients with SCA.

In the present study significantly higher levels of MPV were observed among the groups. The MPV values of orchectomy patients also demonstrated a higher significant cut-off of 11.5 fL, which is higher than its significant cut-off of 6.5 fL in torsed patients without SCA, as an indicator of testis viability. These findings are mainly related to the increased inflammatory and thrombotic activity, which is associated with increased platelet synthesis in SCA. Moreover, torsion in combination with SCA causes marked vascular pathology, alteration in vascular diameter, and induction of coagulation pathway. In addition, hypoxia increases the formation of microthrombi and the production of vasoconstricting endothelin-1. However, the diagnostic role of MPV in testicular torsion has not been demonstrated in other studies.

Interestingly, there was no significant correlation between PVI and PLT count. However, PVIs are known as indirect indicators of platelet activity and function. Even so, increased platelet activity with higher PVIs is more likely responsible for the endovascular complications in SCA. The lack of this significant correlation may be related to the accelerated production of megakaryocytes, resulting in an increase in platelet number. These larger platelets are metabolically more active owing to the presence of thromboxane A2 and soluble P-selectin. However, a higher PLT was found in these torsed patients with SCA, which may have resulted directly from increased platelet synthesis. We also reported increased PCT with its implications on exploration outcomes in such patients. This is not consistent with Mutlu et al’s observations, who found PCT values are low with ignorable effect on thrombosis development. It is noteworthy that some studies failed to confirm MPV,
PDW, and PCT as predictors of testicular torsion, probably due to differences in the laboratory methods and/or equipment used for analysis. Along with providing MPV, PDW, and PCT, complete blood count includes other biomarkers that are often investigated, such as TLC. In this study, the predictive value of TLC was demonstrated in accordance with Bitkin et al., where TLC was significantly increased in patients with torsion as a result of cremasteric muscle tissue torsion, which is associated with severe local hypoxia and reduced microcirculation. The prognostic value of leukocyte subtypes and the ratio of these biomarkers (neutrophils, lymphocytes, and monocytes) concerning inflammatory response have been confirmed in other studies.

The association between testicular torsion and testicular atrophy is well documented in this report. Moreover, testicular volume seems to be affected by higher PVI values, but without a significant correlation. This correlation indicates that the higher production of PVI by the activated platelet, induced by testicular torsion, is associated with high platelet endothelin-1 production, which in turn may result in testicular ischemia. This relationship was demonstrated experimentally by the reduction of ischemia-related testicular damage by administration of antiplatelet activating factor. There are also other factors induced by SCA pathogenic mechanisms that could invalidate such correlation (e.g., increased intratesticular vascular microthrombus and activation of the intrinsic coagulation pathway). Testicular atrophy in SCA with torsion is characterized by progressive necrotic testicular parenchyma and loss of testicular volume. In the present study, patients with symptom duration over 7 hours before detorsion had a significant correlation for predicting viability of the testicle preoperatively. This result is consistent with those of previous studies that reported testicular atrophy was significantly more common with durations longer than 6 hours. Nevertheless, symptom duration had no significant impact on the PVI in this torsion group. This may be because not all patients with a longer duration had complete testicular volume loss, which may be explained by intermittent torsion during the time between onset of symptoms and detorsion, or due to spotty scattered testicular parenchyma injury secondary to both interstitial edema and compression of the microcirculatory system.

There are other factors induced by SCA pathogenic mechanisms that could invalidate such correlation (e.g., increased intratesticular vascular microthrombus and activation of the intrinsic coagulation pathway). There are several limitations within this report. One is the study’s relatively small size sample. Another potential limitation is that we did not include an assessment of other causes of acute scrotum diseases, such as epididymitis or appendicular torsion, which are commonly misdiagnosed with testicular torsion. The diagnosis in

### Table 4 Multivariable analysis of the predictive factors for testicular torsion outcome

| Predictors                          | OR   | 95% CI       | P value |
|-------------------------------------|------|--------------|---------|
| Mean platelet volume (fL)           | 0.232| 0.027 - 1.980 | 0.182   |
| Platelet distribution width (fL)    | 6.586| 1.033 - 41.985| 0.042   |
| Plateletcrit (%)                    | 0.433| 0.073 - 2.578 | 0.358   |
| Total leukocyte count (x10^3/L)     | 1.343| 0.123 - 14.712| 0.809   |
| Symptom duration (h)                | 1.13 | 1.054 - 1.868 | 0.034   |
| Testicular volume (cm^3)            | 2.574| 0.245 - 27.015| 0.431   |

Cl, confidence interval; OR, odd ratio.
the present study was established mainly after surgical exploration.

In conclusion, this study shows that an increased PDW in SCA with testicular torsion is a poor platelet prognostic marker, which is associated with testicular salvage rate. Furthermore, longer symptom duration with increased PDW value may be diagnostic parameters for high-risk testicular atrophy in SCA with acute scrotum. Therefore, the use of PDW may help physicians in the diagnosis of a high-risk group of patients with SCA with acute scrotum, which is a candidate for emergency scrotal exploration. However, there is a great need for further multicenter investigations or prospective clinical research with a larger sample size to confirm this relationship.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES
1. Kato GJ, Steinberg MH, Gladwin MT. Intraocular hemolysis and the pathophysiology of sickle cell disease. J Clin Invest 2017;127:750–60.
2. Claudino MA, Fertrin KY. Sickling cells, cyclic nucleotides, and protein kinases: the pathophysiology of urointestinal disorders in sickle cell anemia. Anemia 2012;2012:1–13.
3. Gatti JM, Patrick Murphy J. Current management of the acute scrotum. Semin Pediatr Surg 2007;16:58–63.
4. Lian BSY, Ong CCW, Chiang LW, et al. Factors predicting testicular atrophy after testicular salvage following torsion. Eur J Pediatr Surg 2016;26:017–21.
5. Pogorelic Z, Milanović K, Verlić AB, et al. Is there an increased incidence of orchietomy in pediatric patients with acute testicular torsion during COVID-19 pandemic? A retrospective multicenter study. J Pediatr Urol 2021;17:479.e1–479.e6.
6. Pogorelic Z, Neumann C, Jukic M. An unusual presentation of testicular torsion in children: a single - centre retrospective study. Can J Urol 2019;26:10026–32.
7. Güner M, Umul M, Ahtok M, et al. Predictive role of hematologic parameters in testicular torsion. Korean J Urol 2015;56:324–32.
8. Bitkin A, Aydin M, Özgüz BC, et al. Can hematologic parameters be used for differential diagnosis of testicular torsion and epididymitis? Andrologia 2018;50:e12819.
9. Westwick J, Watson-Williams EJ, Krishnamurthi S, et al. Platelet activation during steady state sickle cell disease. J Med 1983;14:17–36.
10. Okpala I. Steady-State platelet count and complications of sickle cell disease. Hematol J 2002;3:214–5.
11. Ciclo T, Togan T, Akbabba K, et al. The value of serum mean platelet volume in testicular torsion. Afr J Med Sci 2015;43:452–9.
12. Peretti M, Zampieri N, Bertozzi M, et al. Mean platelet volume and testicular torsion: new findings. Urol J 2019;16:83–5.
13. He M, Zhang W, Sun N. Can haematologic parameters be used to predict testicular viability in testicular torsion? Andrologia 2019;51:e13527.
14. Vagdatti E, Gournari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010;14:28–32.
15. Hübner T, Klute T, Meineckeau J, et al. Color Doppler sonography reliably identifies testicular torsion in boys. Urology 2010;75:1170–4.
16. Lancé MD, van Oerle R, Henskens YM, et al. Do we need time adjusted mean platelet volume measurements? Lab Hematol 2010;16:28–31.
17. Ghanem MA, Adawi EA, Hakami NA, et al. The predictive value of the platelet volume parameters in evaluation of varicocelectomy outcome in infertile patients. Andrologia 2020;52:e13574.
18. Osselaer J-C, Jamart J, Scheiff J-M. Platelet distribution volume for differential diagnosis of thrombocytosis. Clin Chem 1997;43:1072–6.
19. Amin MA, Amin AP, Kulkarni HR. Platelet distribution width (PDW) is increased in vaso-occlusive crisis in sickle cell disease. Ann Hematol 2004;83:331–5.
20. De Franceschi L, Cappellini MD, Olivieri O. Thrombosis and sickle cell disease. Semin Thomb Hemost 2011;37:226–36.
21. Bajpai Z, Varga R, Janovszyk Agnes, et al. Microcirculatory effects of selective endothelin-A receptor antagonism in testicular torsion. J Urol 2014;192:1871–7.
22. Chakraborty J, Sinha Hickim AP, Jhunjhunwala JS. Stagnation of blood in the microvasculature of the affected and contralateral testes of man with short-term torsion of the spermatic cord. J Androl 1985;6:291–9.
23. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost 2010;8:148–56.
24. Yucel C, Ozlem ilbey Y. Predictive value of hematological parameters in testicular torsion: retrospective investigation of data from a high-volume tertiary care center. J Int Med Res 2019;47:730–7.
25. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets 2002;13:301–6.
26. Mohan JS, Lip GHY, Bareford D, et al. Platelet P-selectin and platelet mass, volume and component in sickle cell disease: relationship to genotype. Thromb Res 2006;117:623–9.
27. Dorn GW, Liel N, Trask JL, et al. Increased platelet thromboxane A2/prostaglandin H2 receptors in patients with acute myocardial infarction. Circulation 1990;81:212–8.
28. Mutlu H, Arils TA, Erden A, et al. Alteration in mean platelet volume and platelet volumes in patients with cancer that developed thrombosis. Clin Appl Thromb Hemost 2013;19:331–3.
29. Beurling-Harbury C, Schade SG. Platelet activation during pain crisis in sickle cell patients. Andrologia 2017;127:750–60.
30. Palmer JS, Cromie WJ, Pizak LF, et al. A platelet activating factor antagonist attenuates the effects of testicular ischemia. Am J Hematol 1989;31:237–41.
31. Józsa T, Klárik Z, Kiss F, et al. Can haematologic parameters be used to predict testicular viability in testicular torsion? Andrologia 2019;51:e13527.