A Study of the Prognostic Significance of Platelet Distribution Width, Mean Platelet Volume, and Plateletcrit in Cerebral Venous Sinus Thrombosis

Usha Chowdary Madineni K.1 Naveen Prasad Siddam Venkata1 Vengamma Bhuma1

1 Department of Neurology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

Address for correspondence Usha Chowdary Madineni K., MD, DM, Department of Neurology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh 517 507, India (e-mail: usha.madineni123@gmail.com).

Abstract

Background Platelets play a vital role in thrombus formation and propagation and are thus implicated in the pathogenesis and morbidity of cerebral venous sinus thrombosis (CVST). A whole blood count can be used to objectively measure platelet function through platelet indices, namely platelet distribution width (PDW), mean platelet volume (MPV), and plateletcrit.

Objective This study examined how platelet indices (PDW, MPV, and plateletcrit) affect the CVST severity and functional outcome.

Methodology In this prospective, longitudinal, observational study, 66 patients with CVST from a tertiary care referral center were enrolled. A complete blood count including platelet indices was obtained using an automated hematology analyzer. Patients with and without parenchymal abnormalities on brain imaging were classified as having severe and nonsevere CVST, respectively. The modified Rankin Scale (mRS) was used to examine functional outcomes at admission and after 90 days. The patients were categorized into low mRS (0–1) and high mRS (2–6) functional groups.

Results The patients with severe CVST were older (p<0.05) and exhibited abnormally large PDW (p<0.05) which were statistically significant. Severe CSVT also had poor functional outcome score both at admission (p<0.05) and 90 days later (p<0.05) which were statistically significant. Multiple logistic regression analysis concluded age and PDW as the independent predictors of severe CVST (p<0.05). In receiver operating characteristic curve analysis, a cut-off value of 16.5 for PDW could predict CVST severity (p<0.05). Patients with high mRS scores at admission had significantly larger PDW. At 90 days, no association was noted between PDW and mRS scores. MPV and plateletcrit levels were similar in both the severe and nonsevere CVST groups and exerted no effect on functional outcomes. PDW was significantly and inversely related to plateletcrit (p<0.05).

Conclusion Severe CVST and PDW had a positive correlation. During the early phases of admission, PDW levels above a particular threshold were associated with poor functional outcomes; however, no such association was observed after 90 days. MPV and plateletcrit exerted no effect on CVST severity and prognosis.

Keywords
► cerebral venous sinus thrombosis
► functional outcome
► magnetic resonance venography
► mean platelet volume
► platelet distribution width
► plateletcrit

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Introduction

Cerebral venous sinus thrombosis (CVST) can cause considerable cerebrovascular damage including hemorrhagic stroke. 1 CVST affects approximately three to four individuals per million population in India annually. Furthermore, CVST is responsible for 10 to 20% of causes of cerebrovascular accidents among young people. 2 CVST is three times more common in women than in men, and the risk is particularly higher during pregnancy and while using oral contraceptives. 3 CVST has numerous risk factors, with each having a different odds ratio. Headache is the most common presentation of CVST. 4-6 Magnetic resonance imaging (MRI) of the brain can accurately diagnose CVST. 7

Platelets, which are vital in the formation and propagation of thrombus, are involved in the etiopathogenesis of and morbidity in CVST. 8 Platelet function can be examined using a total blood count analyzer, which provides the values of platelet indices, namely platelet distribution width (PDW), mean platelet volume (MPV), and plateletcrit. MPV is a simple and accurate marker of platelet activation and function. 9 PDW indicates the size variation range of platelets. It is, thus, a precise indicator of their activation. 9 Plateletcrit refers to the total platelet mass and is beneficial for identifying platelet-related quantitative disorders. 10

Platelet indices may be predictive and prognostic in a wide range of conditions. 11 PDW levels are higher in disease conditions such as myeloproliferative disorders, ischemic heart disease, and CVST. 12-14 Myocardial infarction, venous thromboembolism, poor coronary collaterals, and pulmonary embolism have been linked to increased MPV. 15-18 Plateletcrit has been examined in central retinal vein occlusion 19 and venous thromboembolism. 20 A higher plateletcrit value indicates a higher risk. Thus far, a Turkish study investigated the effects of platelet indices on CVST severity. 13 There is not enough research on this subject. This study investigated the effects of platelet indices (PDW, MPV, and plateletcrit) on CVST severity and functional outcomes.

Materials and Methods

Participants

In this single-center, prospective, longitudinal, observational study, 66 consecutive patients with CVST aged > 18 years who were willing to participate were recruited. Patients receiving antiplatelet drugs were excluded. Patients were enrolled from May 2018 to September 2019 from the outpatient and inpatient departments of a tertiary care referral center in Andhra Pradesh. The ethics committee at the university (Sri Venkateswara Institute of Medical Sciences) approved the study. Participants in the study provided informed consent. A complete medical history, as well as a comprehensive physical and neurological examination, were taken.

Definitions

Anemia is defined as the presence of a hemoglobin concentration of < 13 g/dL in men, < 12 g/dL in nonpregnant women, and < 11 g/dL in pregnant women. Hyperhomocysteinemia refers to a serum homocysteine level of > 15 µmol/L. Polycythemia refers to a hemoglobin level of > 18.5 g/dL in men and > 16.5 g/dL in women. The fifth edition of Diagnostic and Statistical Manual of mental disorders (DSM-5), “criteria for alcohol use disorder” were adopted to establish its diagnosis. Binge drinking was diagnosed when individuals consumed approximately five and four standard drinks, respectively, within 2 hours. A standard drink is considered to contain 14 g of alcohol. 21

Radiological and Laboratory Analysis

Plain computed tomography (CT), MRI brain plain, and magnetic resonance venography (MRV) brain were performed in all the patients. Imaging findings were used to confirm the clinical diagnosis. Prior to obtaining samples, adequate hydration of the patients was ensured. PDW, MPV, and plateletcrit were measured using the Auto Hematology Analyzer, Mindray BC-5300 series, Shenzhen Mindray Bio-Medical Electronics, China. 22 In addition, serum homocysteine levels were measured. After 48 hours, a second blood sample was collected to confirm laboratory results. If the first and second test results differed significantly, then a third sample was examined to minimize laboratory errors.

Severity Classification and Outcome Analysis

CVST severity was determined on the basis of alterations in MRI brain parenchymal signals. Patients with brain parenchymal signal abnormalities, which were determined as an altered intensity of signal change, were diagnosed as having severe CVST. Patients without brain parenchymal signal changes with or without cerebral edema were diagnosed as having nonsevere CVST. The modified Rankin Scale 23 (mRS) was used to examine functional outcomes, and the patients were categorized into “low mRS” (0–1) and “high mRS” (2–6) groups at admission and 90 days.

Statistical Analysis

Data were obtained from printed case record forms and entered into Microsoft Excel spreadsheets. Because data were normally distributed, parametric tests were conducted. Means and standard deviations were used to represent quantitative variables. Frequencies as percentages were used to represent qualitative variables. To examine qualitative and quantitative variables, the chi-square test and independent Student’s t-test were used. Multiple logistic regression analysis was used to find the independent predictors of severe CVST. In a multiple logistic regression analysis model, predictors having statistical significance (p < 0.05) in univariate analysis were evaluated, and their odds ratios with 95% confidence interval (CI) were determined. The ability of PDW to predict CVST severity was examined by analyzing the receiver operating characteristic (ROC) curve. A p-value of < 0.05 indicated statistical significance. All statistical analyses were performed using SPSS version 25.0 and MedCalc Software.
Results

In total, 66 patients (45 male and 21 female) were included to this study. The mean age of the study participants was 35.2 ± 24.6 years. Alcohol use disorder (n = 32), hyperhomocysteinemia (n = 27), anemia (n = 15), polycythemia (n = 10), oral contraceptive pill use (n = 5), and puerperium (n = 4) were the main risk factors. All the patients with alcohol consumption disorder binge drank within 1 to 3 days of symptom onset. The most frequent risk factors among the men were hyperhomocysteinemia and after that alcohol use disorder. Hyperhomocysteinemia was significantly associated with alcohol use disorder in the men. Hence, hyperhomocysteinemia was not identified as a distinct risk factor. Polycythemia was the next frequent risk factor among the men. The most frequent risk factors among the women were iron deficiency anemia and after that oral contraceptive usage. All the participants had increased intracranial pressure. Seizures and focal neurological deficits were noted in 59 and 29% of the participants, respectively. Furthermore, 16 and 11 patients had high mRS scores (2–6) during admission and after 90 days, respectively. Two-thirds of the patients exhibited abnormal brain CT findings, and all of them had abnormal MRV brain findings. Superior sagittal sinus, sigmoid sinus, left transverse sinus, and right transverse were thrombosed in 76, 38, 26, and 9% of study participants, respectively. In 47% of the participants, more than one sinus had been thrombosed (►Figs. 1 and 2).

We compared the patients’ platelet indices with their standard laboratory values (►Table 1). Their MPV values

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**Fig. 1** MRI brain T2 sequence showing (A) hyperintensities in the superior sagittal sinus, (B) right transverse sinus, and (C) right sigmoid sinus. (D) In the MR venogram brain, superior sagittal sinus is not visible, transverse and the sigmoid sinuses are narrowed bilaterally with several collaterals. MRI, magnetic resonance imaging.
were within normal ranges. However, PDW and plateletcrit values were at the upper end of the normal limit.

Severe CVST and nonsevere CVST were diagnosed in 33 and 33 patients, respectively. The patients’ age and sex were similar in both the groups (Table 2). The PDW was higher in severe CVST patients than in nonsevere CVST patients, and this difference was statistically significant ($p = 0.038$; Table 2 and Fig. 3). Other variables, namely old age ($p < 0.05$), high mRS scores at admission ($p < 0.05$), and high mRS scores at 90 days ($p < 0.05$), were significant.

**Table 1** Comparison of mean platelet indices values with normal laboratory values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± standard deviation</th>
<th>Standard laboratory normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPV (femtoliters)</td>
<td>8.4 ± 1.0</td>
<td>6.5–12</td>
</tr>
<tr>
<td>PDW</td>
<td>16.2 ± 0.9</td>
<td>9–17</td>
</tr>
<tr>
<td>Plateletcrit (%)</td>
<td>0.24 ± 0.11</td>
<td>0.10–0.28</td>
</tr>
</tbody>
</table>

Abbreviations: MPV, mean platelet volume; PDW, platelet distribution width.
No correlation was noted between CVST severity and risk factors (Table 2).

Multiple logistic regression analyzed older age and larger PDW ($p < 0.05$) as the independent predictors of severe CVST (Table 3). There was no significant difference in MPV or plateletcrit between the severe and nonsevere CVST groups. A comparison of PDW with clinical and laboratory parameters indicated that increased PDW ($>17$) was associated with high mRS scores at admission ($p < 0.05$). High PDW values were significantly and inversely related to plateletcrit levels ($p < 0.05$; Table 4). Among the platelet indices, PDW exhibited a significant association with higher mRS scores at admission ($p < 0.05$). However, at 90 days, no effect of platelet indices on mRS scores was observed (Table 5). In ROC analysis, a cutoff value of 16.5 for PDW could predict CVST severity with 45% sensitivity and 79% specificity (area under ROC curve = 0.649, 95% CI = 0.516–0.782, $p$-value = 0.037) (Fig. 4).

**Discussion**

The average age of the study participants is in accordance with that reported in a comprehensive series published by Nizam institute’s cerebral venous stroke register located in Hyderabad, India. A previous study conducted in India reported that CVST was more frequently observed in women. This study’s male predominance is consistent with the findings of a recent Indian study. Improvements in women’s health care during the puerperium may be caused by this shift in sex predominance. Increasing alcohol abuse may be responsible for the increased frequency of CVST in men.

This study’s findings agree with those of a previous Turkish study on the effects of platelet indices (PDW and MPV) on CVST severity. PDW significantly differed between CVST cases and controls ($p = 0.003$). In addition, MPV did not...
differ significantly between the CVST case and control groups \((p = 0.3)\). Alcohol use disorder did not affect mean MPV values in 40% of the patients. Moreover, age, sex, alcohol usage, smoking, and obesity did not affect MPV values. The results of this study demonstrated no link between CVST severity and its risk factors; this finding is in accordance with that of another Indian study. No effect of risk factors on clinical parameters, imaging results, and outcomes was noted. Old age, mechanical ventilation requirement, and Glasgow Coma Scale (GCS) scores were identified as the independent predictors of poor clinical outcomes.

Anemia \((p\text{-value} < 0.05)\) and hyperhomocysteinemia \((p\text{-value} < 0.05)\) risk factors demonstrated a statistically significant association with plateletcrit levels \((\text{►Supplementary Table S1, available in the online version only})\). Furthermore, no association was observed between MPV and PDW levels and risk factors for CVST. This study recruited patients from only one academic institution. Hence, multicenter studies should be performed to validate our findings. In conclusion, larger PDW is related to severe CVST and poor prognosis in the early stage. Studies determining the relationship between platelet indices and CVST outcomes are warranted. The findings can

### Table 4 Baseline characteristics categorized according platelet distribution width values

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal PDW (9–17), ((n = 62))</th>
<th>Elevated PDW (&gt;17) ((n = 4))</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean (\pm SD))</td>
<td>35.22 (\pm 14.56)</td>
<td>36.5 (\pm 23.69)</td>
<td>0.916</td>
</tr>
<tr>
<td>Hemoglobin-gm/dl (mean (\pm SD))</td>
<td>12.95 (\pm 3.60)</td>
<td>13.52 (\pm 3.96)</td>
<td>0.783</td>
</tr>
<tr>
<td>MPV-fL (mean (\pm SD))</td>
<td>8.38 (\pm 1.03)</td>
<td>9.42 (\pm 0.89)</td>
<td>0.037</td>
</tr>
<tr>
<td>Plateletcrit% (mean (\pm SD))</td>
<td>0.24 (\pm 0.10)</td>
<td>0.13 (\pm 0.08)</td>
<td>0.023</td>
</tr>
<tr>
<td>Male gender ((n))</td>
<td>42</td>
<td>3</td>
<td>0.762</td>
</tr>
<tr>
<td>Severe CVST ((n))</td>
<td>30</td>
<td>3</td>
<td>0.302</td>
</tr>
<tr>
<td>Alcohol intake ((n))</td>
<td>29</td>
<td>3</td>
<td>0.273</td>
</tr>
<tr>
<td>Anemia ((n))</td>
<td>14</td>
<td>1</td>
<td>0.910</td>
</tr>
<tr>
<td>Hyperhomocysteinemia ((n))</td>
<td>25</td>
<td>2</td>
<td>0.702</td>
</tr>
<tr>
<td>Polycythemia ((n))</td>
<td>9</td>
<td>1</td>
<td>0.490</td>
</tr>
<tr>
<td>Oral contraceptive usage ((n))</td>
<td>4</td>
<td>1</td>
<td>0.213</td>
</tr>
<tr>
<td>Puerperium ((n))</td>
<td>3</td>
<td>1</td>
<td>0.226</td>
</tr>
<tr>
<td>High mRS @ admission (2–6), ((n))</td>
<td>13</td>
<td>3</td>
<td>0.014</td>
</tr>
<tr>
<td>High mRS @ 90 d (2–6), ((n))</td>
<td>9</td>
<td>2</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Abbreviations: CVST, cerebral venous sinus thrombosis; MPV, mean platelet volume; mRS, modified Rankin Scale; \(n\), number of patients; PDW, platelet distribution width; SD, standard deviation.

### Table 5 Comparison between platelet indices and “high mRS” (2–6) at admission and after 90 days

<table>
<thead>
<tr>
<th>Variables</th>
<th>High mRS @ admission (2–6) ((n = 16))</th>
<th>(p)-Value</th>
<th>High mRS @ 90 d (2–6) ((n = 11))</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean (\pm SD))</td>
<td>8.20 (\pm 0.14)</td>
<td>0.477</td>
<td>8.1 (\pm 1.16)</td>
<td>0.381</td>
</tr>
<tr>
<td>PDW (mean (\pm SD))</td>
<td>16.66 (\pm 0.93)</td>
<td>0.012</td>
<td>16.64 (\pm 0.57)</td>
<td>0.056</td>
</tr>
<tr>
<td>mRS @ 90 days (mean (\pm SD))</td>
<td>0.23 (\pm 0.10)</td>
<td>0.540</td>
<td>0.2 (\pm 0.07)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Abbreviations: mRS, modified Rankin Scale; \(n\), number of patients; PDW, platelet distribution width; SD, standard deviation.

**Fig. 4** A receiver operating characteristic (ROC) curve showing platelet distribution width as a predictor of severity of cerebral venous sinus thrombosis.
facilitate the identification of patients who might benefit from early endovascular therapy.

**Note**
Data are available from the corresponding author on reasonable request.

**Funding**
None.

**Conflict of Interest**
None declared.

**References**