Platelets indices as prognostic markers in the critically ill

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Short title: Use of Platelet Indices as Prognostic Markers

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Key words: Platelet count; blood platelets; critical care; mean platelet volume.
**Author contributions**

Manuscript has been read and approved by all the authors that the requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work.

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Abstract

Platelet indices such as mean platelet volume (MPV), platelet (PLT) count, plateletcrit (PCT) and platelet distribution width (PDW) describe platelet morphology and proliferation kinetics. Our study aimed to evaluate the utility of platelet indices as prognostic markers in critically ill patients.

This was an observational, descriptive study conducted on 106 critically ill adults for a duration of 24 months in the medical intensive care units (MICUs) of a tertiary care hospital. Analysis of the data was done using statistical software R version 3.6.0 and MS Excel.

The mean age of patients was 42.3 ± 5.8 years. Non-survivors had lower PLT count and PCT when compared to survivors. PDW and MPV were higher for non-survivors when compared to survivors. PLT count of < 90,000 cells/cu mm displayed the highest sensitivity (94%) while PDW demonstrated the highest specificity (96%) in predicting mortality among critically ill patients.

Abnormally low PLT count, high PDW and high MPV values are associated with severe illness and put the patients at high risk of death as compared to patients with normal PLT indices.

Introduction

Platelets are an important constituent of blood, playing a significant role in physiological and pathological processes such as coagulation, thrombosis, inflammation and maintenance of vascular endothelial cell integrity. In addition to their important role in hemostasis and thrombosis, accumulating evidence demonstrate that platelets contribute to the inflammatory process, microbial host defense, wound healing, angiogenesis and remodeling. Platelet
indices such as platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) are simple indices which can be calculated by any 3-part differential cell counter. However, assessment of immature platelet fraction (IPF) can be done only at advanced centers using more complex cell counters. These are commonly used to measure the total number of platelets, its morphology and proliferation kinetics, and can be applied in the diagnosis of diseases affecting the hematological system.

A reduction in PLT count is an independent risk factor for critically ill patients in the intensive care unit (ICU). In addition, thrombocytopenia is included as an independent risk for mortality in the Acute Physiology and Chronic Health Evaluation II (APACHE II) system.

Numerous blood count parameters such as packed cell volume, PCT count and total leucocyte count are used in various scoring systems for intensive care patients, such as multiple organ dysfunction score, sequential organ failure assessment score and logistic organ dysfunction score. Lately, numerous studies have suggested an association between these indices and platelet activation, which is an independent risk factor in the critically ill. Increased platelet activity can be diagnosed by a raised platelet volume, which in turn suggests an increased prothrombotic state, associated with adverse outcomes in ICU patients. Factors such as Thromboxane A2 have prothrombotic properties and is produced during hemostasis by activated platelets. It increases platelet aggregation as well as stimulates activation of new platelets. Large platelets have increased platelet activity as they produce large amounts of thromboxane A2.

As platelet indices are inexpensive and relatively less time consuming, they can be ideal for use as prognostic factors for critically ill patients in a country like India, where healthcare
resources are scarce. The present research was intended to study the use of platelet indices as prognostic factors in critically ill patients at a tertiary care hospital.

Methodology

This was an observational, descriptive study conducted for a period of 24 months in the medical intensive care units (MICUs) of a tertiary care hospital on 106 patients. All critically ill adult patients admitted to MICUs were included in the study. Written informed consent was obtained from the patients. Pregnant women, patients with active hemorrhage, hematological diseases (including anemia, hypersplenism, lymphoma or leukemia and bone marrow disorders), infectious diseases that primarily affect the platelets (dengue fever, malaria, viral fever etc.), patients who have received radiotherapy or chemotherapy or bone marrow transplantation one month prior to admission, patients who have used anti platelet drugs (aspirin, clopidogrel) or other drugs which could reduce platelet count (e.g. non-steroidal anti-inflammatory drugs etc.) prior to admission were excluded from the study. Purpose of study was explained to the patients and their representatives and informed consent was obtained. Thereafter, the patients were assessed. Blood samples for complete blood count including platelet count, MPV, PDW and PCT were sent on admission. Other tests such as arterial blood gas, liver function tests and renal function tests were done. As a part of automated complete blood count, platelet indices were measured. Demographic data, history, examination findings and relevant laboratory tests were also performed.

Data was analyzed using statistical softwares R version 3.6.0 and Excel. Continuous variables were represented by mean ± standard deviation form. Categorical variables were represented by frequency tables and percentages. Independent t-test, Mann Whitney U-test and
Kolmogorov-Smirnov test were used whenever the data followed non-normative distribution. Categorical variables were compared using chi-square test and Odds Ratios.

**Results**

We conducted the present study on 106 patients for a duration of 24 months at a tertiary care hospital.

The mean age of our study subjects was found to be 46.85±14.08 (mean ± SD) years. From Figure 1, it is seen that most of the patients in our study were under the age group 40-69 years. Among the total study participants, 54 (50.94%) were females and 52 (49.05%) were males.

Among clinical symptoms studied (Table 1), fever was the most common presenting symptom and was present in 61 (57.33%) of the patients. Cough was the second most common presenting symptom and was present in 60 (56.60%) of the patients. Other presenting symptoms included dyspnea 33 (31.1%), vomiting 16 (15.09%) and pain abdomen 10 (9.43%).

When the patients were studied with respect to diagnosis (Table 1), patients with pneumonia 36 (33.9%), sepsis 26 (24.5%) and acute exacerbation of reactive airway disease 23 (21.6%) were the most common among those who were admitted to the ICU. Among the rest, 12 (11.3%) patients had urosepsis, 6 (5.6%) patients had acute pancreatitis and 3 (2.8%) patients had viral encephalitis. We observed that the survival rate was higher among the subjects diagnosed with pneumonia or acute exacerbation of reactive airway disease whereas the survival rate was poor for subjects diagnosed with acute pancreatitis or viral encephalitis.
Largely similar survival rates of 76.92% and 77.78% were noticed among males and females respectively.

From Table 2, we may conclude that the median of ICU stay was not significantly different between survivors and non-survivors (P=0.552). The distribution of TLC (P=0.0003) and serum creatinine (P<0.0001) was found to be statistically different between survivors and non-survivors. Also, various platelet indices studied such as PLT count (P<0.000), PDW (P<0.0002), MPV (P=0.0041) and plateletcrit (P<0.0001) were also found to be statistically significant between survivors and non-survivors.

The mean PLT count was lower among non survivors, when compared to survivors (77,500± 10,570 and 1,32,800± 17,500 cell/cumm respectively) (shown in Table 3). The difference was statistically significant with P<0.001. Mean PDW was higher in non survivors compared with survivors (13.6 ± 1.63 and 11.24 ± 2.61 respectively), with a statistically significant difference (P<0.038). Mean MPV was higher in non survivors when compared to survivors (15.2 ± 1.46 and 11.46 ± 2.71 respectively). The difference was again statistically significant with P<0.024. Mean PCT was lower in non survivors when compared to survivors (0.11±0.031 and 0.17± 0.048 respectively), with the difference being statistically significant (P<0.017).

Among 106 patients studied, 82 (77.36%) patients survived. Hence the mortality rate in our study was 22.64%.

In Figure 2, the area under the curve for PLT count was 83%, so PLT count was found to be a good and accurate measure in predicting the survival status. The area under the curve for PDW was 77%, PDW was also an accurate factor in predicting the survival status. The area under the curve for MPV was 71% and MPV was accurate in predicting the survival status as
well. The area under the curve for PCT was 84%, making PCT the most accurate indicator in predicting the survival status.

The survival status was significantly associated with PDW category and MPV category. For patients with PDW <13.5, the odds of non-survival were 6.39 times higher than in the patients with PDW ≤13.5. Also, the odds of mortality were 28.6 times more for the subjects with Plateletcrit <0.11 than for the subjects with Plateletcrit ≥0.11 (shown in Table 4).

**Discussion**

The frequently used platelet indices include PLT, MPV, PDW and PCT. Although there are a few studies evidencing the role of increased MPV in the etiopathogenesis of myriad disorders, lack of follow ups has hindered standardization of MPV measurements. Standardized platelet indices values can aid quicker assessment of illness severity, follow-up, and reliable outcome prediction in critically ill patients, especially in resource poor settings.

The aim of our study was to find the utility of platelet indices as prognostic markers in critically ill patients. Among the 106 patients studied, 82 patients survived, and 24 patients expired. The mortality in our study was 22.64%, in agreement with the study conducted by Zhongheng Zhang MM.

In the present study, diabetes mellitus (16.98%) and hypertension (16.98%) were the most common comorbid conditions. The findings are concordant with study done by Bhattacharjee et al. and Yang K et al. Main reasons for abnormal PLT functions in diabetes mellitus (DM) are the immature, larger platelets as well as activated platelets due to the metabolic milieu in DM or due to vascular damage. All these factors have been proven to be interlinked. Some studies suggest that the increased levels of platelets during high blood
pressure condition can be controlled by two possible mechanisms. Firstly, pulmonary vascular endothelial dysfunction was linked with the path mechanisms of hypertension, which might lead to the platelet activation and local thrombosis. Secondly, systemic inflammation and immune dysfunction in patients with high blood pressure might cause platelet activation.\textsuperscript{15}

Here, the mean platelet count was 1,32,800\textpm17,550 cells/cumm among survivors and 77,500 \textpm10,570 cells/cumm among non-survivors. Significantly lower PLT count was noticed in non survivors when compared to survivors. PLT count <90,000 cells/cumm had 94\% specificity and 93\% sensitivity in predicting mortality in critically ill patients. This was in concordance with the study done by Zhang et al.\textsuperscript{1}, Bunyamin Burunsuzoglu et al.\textsuperscript{16}, Seung Jun Choi et al.\textsuperscript{17}, Patki et al.\textsuperscript{18} Koyama et al.\textsuperscript{19} also reckoned that diminished PC and α2-PI activity, was followed by a decline in platelet count among septic intensive care unit patients.

The mean PDW in our study was found to be 11.24 \textpm 2.61\% among survivors and 13.6 \textpm 1.63\% among non survivors, and the difference was statistically significant. A PDW of >13.5\% had 90\% specificity and 96\% sensitivity in mortality prediction in critically ill patients. Similar results were observed in other studies by Guclu et al.\textsuperscript{20} and Sheng Zhang et al.\textsuperscript{1} Fogagnolo et al.\textsuperscript{21} found that the PDW values in the prediction of 90-day mortality were significant septic patients but not in non-septic patients (p<0.001).

The mean plateletcrit was 0.17\textpm0.048\% among survivors and 0.11\textpm0.031\% among non survivors, with a significant difference between the mean values of plateletcrit between the survivors and non-survivors (P=0.017). A plateletcrit of <0.11\% had 91\% sensitivity and a 95\% specificity in mortality prediction. The odds ratios for mortality prediction concluded that PCT and PDW were two significant factors affecting the survival status of the subjects. For patients with PDW <13.5, the odds of non-survival were 6.39 times higher than for the
patients with PDW ≤13.5. Also, the odds of mortality were 28.6 times higher for the subjects with plateletcrit <0.11 than for the subjects with plateletcrit ≥0.11. Our study results were consistent with various other studies such as by Zhang et al\textsuperscript{1} and Golwala et al.\textsuperscript{22}

Average MPV values noted among survivors and non-survivors showed statistically significant variation between the two groups. This is reinforced by the findings of Tajarernmuang et al.\textsuperscript{23} who extrapolated that following three days of patients’ admission, the MPV was significantly higher among non-survivors.

In our study, PLT count, PDW, MPV and PCT possessed large areas under ROC of 0.83, 0.77, 0.71 and 0.84 respectively. Among all four indices, PCT ranked supreme for predictive accuracy. Thus, PCT was inferred to be the optimal predictive indicator. This is in contrast with the study done by Zhang et al\textsuperscript{1} where MPV was the optimal predictive indicator studied. Liberski et al.\textsuperscript{24} however note that PLT/MPV are not reliable predictors of sepsis. In consonance to our findings, study by Samuel et al. demonstrated a significant influence of PLT indices including PLT, PDW, PCT and MPV adjusted to DM by a univariate regression analysis. Samuel et al. also observed that patients having low PCT, PLT values along with high levels of MPV and PDW were at a higher risk of severe illness, worsening prognosis, and mortality.\textsuperscript{25}

This study has certain limitations, such as only PLT indices were analyzed. Other disseminated intravascular coagulation (DIC) parameters (prothrombin time, activated partial thromboplastin time or D-dimer) were not recorded and analyzed in this study, which may be a major cofounding factor. Another limitation is that details regarding the cause of death among non-survivors were not noted. Hence, future studies can be designed by eliminating the above-mentioned limitations.
Although Platelet Count is a part of several clinically used scoring systems such as SOFA, APACHE II and APACHE III, platelet indices such as MPV (routinely included in hematology reports) are often overlooked parameters for clinical interpretation. In this study, we show that these platelet indices, when deranged, can also be useful in prognostication of the critically ill and must be taken into account in routine clinical practice. However, we suggest further studies in larger groups and multiple settings are essential to investigate the impact of incorporating these platelet indices into the currently used scoring systems to increase their accuracy of prognosticating septic and non-septic survivors and non-survivors.

**Conclusions**

The severity of illness as well as the clinical outcomes can be accurately predicted by platelet indices. Abnormally low PLT count, high PDW and high MPV are associated with severe illness. In addition, reduced PLT count and PCT or increased MPV and PDW put the patients at high risk of death as compared to patients with normal PLT indices. Platelet indices can be utilized as simple, inexpensive tools for prognostication in critically ill patients and must be validated by large multi-centric studies for incorporating them into standard clinical practice.

**Research ethics and patient consent**

The present study was initiated following the grant of approval by the ethical review board of the Institutional Ethics Committee on 18/10/2016. Written informed consent was obtained from the patients for their anonymized information to be published in this article. The study protocol adopted conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the prior approval of the institutional ethics committee.
References


Table 1. Distribution of patients based on clinical symptoms, comorbid conditions and diagnosis.

<table>
<thead>
<tr>
<th>Parameter studied</th>
<th>Survivors n=82 (%)</th>
<th>Non-survivors n=24 (%)</th>
<th>Total n=106 (%)</th>
<th>P-value</th>
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<td><strong>Clinical symptoms</strong></td>
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<tr>
<td>Fever</td>
<td>46 (56.10%)</td>
<td>15 (62.50%)</td>
<td>61 (57.55%)</td>
<td>0.04*</td>
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<td>Cough</td>
<td>48 (58.54%)</td>
<td>12 (14.63%)</td>
<td>60 (56.60%)</td>
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<tr>
<td>Dyspnea</td>
<td>22 (26.83%)</td>
<td>11 (13.41%)</td>
<td>33 (31.13%)</td>
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<tr>
<td>Vomiting</td>
<td>09 (10.98%)</td>
<td>07 (29.17%)</td>
<td>16 (15.09%)</td>
<td></td>
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<tr>
<td>Pain abdomen</td>
<td>06 (7.32%)</td>
<td>04 (4.88%)</td>
<td>10 (9.4%)</td>
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<tr>
<td><strong>Diagnosis</strong></td>
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<td></td>
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<tr>
<td>Pneumonia</td>
<td>20 (76.92%)</td>
<td>6 (23.08%)</td>
<td>26 (24.53%)</td>
<td>0.001*</td>
</tr>
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<td>Sepsis</td>
<td>29 (80.56%)</td>
<td>7 (19.44%)</td>
<td>36 (33.96%)</td>
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<tr>
<td>Acute exacerbation of reactive airway disease</td>
<td>18 (78.26%)</td>
<td>5 (21.74%)</td>
<td>23 (21.7%)</td>
<td></td>
</tr>
<tr>
<td>Urosepsis</td>
<td>9 (75%)</td>
<td>3 (25%)</td>
<td>12 (11.32%)</td>
<td></td>
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<tr>
<td>Acute pancreatitis</td>
<td>4 (66.67%)</td>
<td>2 (33.33%)</td>
<td>6 (5.66%)</td>
<td></td>
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<tr>
<td>Viral encephalitis</td>
<td>2 (66.67%)</td>
<td>1 (33.33%)</td>
<td>3 (2.83%)</td>
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*Significant

Table 2. Comparison of duration of stay and laboratory parameters among survivors and non-survivors.

<table>
<thead>
<tr>
<th>Parameters studied</th>
<th>Survivors (n=82)</th>
<th>Non-Survivors (n=24)</th>
<th>P-value</th>
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<tr>
<td><strong>Duration of ICU Stay (mean±SD)</strong></td>
<td>7.48±3.04</td>
<td>8±3.30</td>
<td>0.552</td>
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<td><strong>Laboratory parameters</strong></td>
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<td>Haemoglobin (gm/dL)</td>
<td>12.38±.93</td>
<td>12.58±2.00</td>
<td>0.6503</td>
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<td>TLC (cells/cumm)</td>
<td>13.30±5.04</td>
<td>16.76±7.67</td>
<td>0.0003*</td>
</tr>
<tr>
<td>ESR (mm/1st hour)</td>
<td>60.74±20.49</td>
<td>55.17±18.57</td>
<td>0.5208</td>
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<td>Serum Creatinine(mg/dL)</td>
<td>1.88±0.98</td>
<td>6±2.00</td>
<td>&lt;0.0001*</td>
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<td>Total bilirubin (mg/dL)</td>
<td>0.91±0.17</td>
<td>0.91±0.18</td>
<td>0.9038</td>
</tr>
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<td>Albumin (gm/dL)</td>
<td>3.55±0.54</td>
<td>3.57±0.50</td>
<td>0.9728</td>
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<td>AST (U/L)</td>
<td>33.62±6.88</td>
<td>31.46±6.46</td>
<td>0.2579</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>33.83±6.78</td>
<td>34.96±7.45</td>
<td>0.6942</td>
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<tr>
<td>Platelet count (cells/Cumm)</td>
<td>2.02±0.83</td>
<td>1.15±0.49</td>
<td>&lt;0.000*</td>
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<td>PDW (%)</td>
<td>13.44±2.32</td>
<td>15.71±2.42</td>
<td>&lt;0.0002*</td>
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<tr>
<td>MPV (%)</td>
<td>12.65±1.91</td>
<td>14.00±1.64</td>
<td>0.0041*</td>
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<tr>
<td>Plateletcrit (%)</td>
<td>0.19±0.05</td>
<td>0.13±0.06</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Significant; TLC-Total leucocyte count, ESR - Erythrocyte sedimentation rate, AST-Aspartate aminotransferase, ALT - Alanine aminotransferase; PDW-Platelet distribution width; MPV-Mean platelet volume.
Table 3: Mean values of platelet indices among survivors and non-survivors.

<table>
<thead>
<tr>
<th>Platelet Indices</th>
<th>Mean value – survivors (n=82)</th>
<th>Mean value – non survivors (n=24)</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Platelet count (cells/cumm)</td>
<td>132,800 ±17,550</td>
<td>77,500 ± 10,570</td>
<td>0.001*</td>
</tr>
<tr>
<td>PDW (%)</td>
<td>11.24 ± 2.61</td>
<td>13.6 ± 1.63</td>
<td>0.038*</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>11.46 ± 2.71</td>
<td>15.2 ± 1.46</td>
<td>0.024*</td>
</tr>
<tr>
<td>Plateletcrit (%)</td>
<td>0.17 ± 0.048</td>
<td>0.11 ± 0.031</td>
<td>0.017*</td>
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*Significant; PDW-Platelet distribution width; MPV-Mean platelet volume.

Table 4: Comparison of platelet indices with outcome

<table>
<thead>
<tr>
<th>Platelet indices</th>
<th>Non-survival</th>
<th>Survival</th>
<th>OR [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Platelet Count (in lakhs)</td>
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<td></td>
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<tr>
<td>&lt;70000</td>
<td>2</td>
<td>0</td>
<td>18.33 [0.85-395.70]</td>
<td>0.0699</td>
</tr>
<tr>
<td>≥70000</td>
<td>22</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;13.5</td>
<td>20</td>
<td>36</td>
<td>6.39 [2.01-20.35]</td>
<td>0.0015*</td>
</tr>
<tr>
<td>≤13.5</td>
<td>4</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td>6</td>
<td>9</td>
<td>2.70 [0.85-8.58]</td>
<td>0.0909</td>
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<tr>
<td>≤15</td>
<td>18</td>
<td>73</td>
<td></td>
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<tr>
<td>Plateletcrit</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.11</td>
<td>10</td>
<td>2</td>
<td>28.57 [5.65-144.50]</td>
<td>0.0005*</td>
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<tr>
<td>≥0.11</td>
<td>14</td>
<td>80</td>
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</table>

*Significant; OR-Odds ratio; CI-Confidence interval; MPV-Mean platelet volume; PDW-Platelet distribution width.
Figure 1. Distribution of study subjects based on age. *X-axis: Age group (in years); Y-axis: Percentage of study subjects.*

Figure 2. ROC curves for PLT count, PDW, MPV and PCT. *PLT count-Platelet count, PCT-Plateletcrit, MPV-Mean platelet volume, PDW-Platelet distribution width.*