

## Role of Platelet Indices in Determining the Type of Thrombocytosis

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### ABSTRACT

#### BACKGROUND

We wanted to evaluate the role of platelet indices in differentiating reactive and clonal thrombocytosis.

#### METHODS

This is a cross sectional observational study conducted for two years among 150 patients with platelet counts of 5 lac and above. Thrombocytosis and utility of platelet indices like Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) for the differential diagnosis of thrombocytosis were done.

#### RESULTS

Out of total 150 cases, 144 (96 %) had reactive thrombocytosis, and 6 (4 %) had clonal thrombocytosis. Infectious aetiology is seen in 64 (42.6 %), tissue injury 35 (23 %), rebound thrombocytosis 22 (14.6 %), anaemia 13 (8.6 %), multiple causes 8 (5.3 %), clonal aetiology 6 (4 %), and inflammatory 2 (1.3 %). Patients with reactive thrombocytosis showed a lower mean platelet volume and platelet distribution width compared to primary thrombocytosis. In reactive thrombocytosis MPV range, 6.0 - 8.0 fl with mean MPV 6.5 fl and PDW ranges from 14.0 - 16.2 % with mean PDW 15.3 %. In clonal thrombocytosis MPV range, 6.9 - 8.5 fl with mean MPV 7.9 fl and PDW range was 15.9 - 17.2 % with mean PDW 16.4 %.

#### CONCLUSIONS

On analysing the platelet counts and indices, patients with high counts, low MPV and PDW suggested reactive aetiology and patients with high counts and high MPV and PDW suggested clonal aetiology.

#### KEYWORDS

Thrombocytosis, Mean Platelet Volume, Platelet Distribution Width

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## BACKGROUND

In the blood, the platelets are anucleate at concentrations of 150,000 to 400,000 cells /  $\mu\text{L}$ . Thrombocytosis is a condition with increased platelets in peripheral blood. The count  $> 4.5 \times 10^9 / \text{L}$  is a generally accepted definition.<sup>1</sup> Thrombocytosis becomes an important clinical problem for differential diagnosis of various clinical problems for differential diagnosis of pathological and physiological process<sup>2,3</sup> for definitive diagnosis needs a comprehensive evaluation of history, physical examination, and blood counts.

Thrombocytosis is classified based on their origin:

### **Clonal Thrombocytosis**

An elevation of platelet count was seen in clonal thrombocytosis due to the uncontrolled proliferation of haematopoietic cells, with an increased incidence of complications like thromboembolism.

### **Reactive Thrombocytosis (RT)**

It is due to a variety of etiological conditions ranging from infections, acute bleeding, major surgical procedures, iron deficiency anaemias, malignancy. Reactive thrombocytosis is due to increased megakaryopoiesis and thrombopoiesis. It is due to the overproduction of proinflammatory cytokines such as interleukin IL-1, 6 & 11. The IL 6 plays a significant role in platelet production by stimulating megakaryopoiesis or haematopoietic thrombopoietin (TPO) production. TPO levels usually correlate with IL-6 & C-reactive protein.<sup>4</sup>

The leading causes for childhood RT include respiratory infections, most common, second most common include gastrointestinal disease followed by urinary tract infection, meningitis, tuberculosis and human immune deficiency virus infection.<sup>4,5</sup>

The main interest of thrombocytosis differentiation as clonal and reactive resides in an increased incidence of thrombo-haemorrhagic complications in clonal aetiology. The underlying mechanism of cancer cell-induced thrombocytosis remains ill-defined. It has been suggested that it resulted from the overproduction of thrombocytopoietic hormones acting on megakaryocytes and their precursors, such as thrombopoietin. It is synthesized by the liver and released in plasma. In vitro, the major three growth factors, i.e., IL-6, 1, and leukaemia inhibitory factor, can promote megakaryocytopoiesis and subsequent thrombocytosis.

Activation of platelets occurs in cancers, during the process of haematogenous dissemination, cancer cells may activate platelets in the bloodstream,<sup>6,7</sup> and this phenomenon is known as tumour cell-induced platelet activation (TCIPA). Platelet activation, in turn, results in the release of the platelet-derived growth factors and the formation of fibrin-rich tumour cell platelet aggregates.

Mechanism of thrombus formation, platelets are recruited to sites of vascular injury and adhere to newly exposed extracellular matrix proteins such as collagen, which bind platelet receptor GP Ib-V-IX through von Willebrand factor (VWF).<sup>8</sup> Which results in cytoskeletal

rearrangement, and release of  $\alpha$ - and dense-granules contents, platelet agonists adenosine phosphate (ADP) and thromboxane (TXA<sub>2</sub>), and also procoagulant phosphatidylserine is exposed on the platelet surface, which serves as a site for generation of thrombin.

Thrombin, apart from its role in fibrin formation, it also activates protease-activated receptors (PARs) and triggers G-protein second messenger receptors. This drives the intracellular signalling cascade resulting rapid shift of platelet integrins to their active conformation to promote stable platelet adhesion and aggregation, and thrombus formation occurs.

Platelets with these two aetiologies also show the difference in morphology, membrane functions, granular contents, and platelet indices.<sup>9</sup>

Large platelets that are commonly encountered in clonal thrombocytosis have increased platelet volume and platelet distribution width. These large platelets that contain an increased number of dense granules and express higher levels of procoagulant activity and decreased effectiveness of prostacyclin on both platelet aggregation and the release reactions lead to having higher thrombotic potential.

Automated counting, which is used in the current study, is more reliable, precise, and accurate than manual counting of platelets, platelet indices like mean platelet volume (MPV), platelet distribution width (PDW) also easily measured, these parameters reflect the level of platelet function and activation.

### **Objectives**

To determine the aetiology, utility of platelet indices to distinguish between clonal and reactive thrombocytosis

## METHODS

It is a cross-sectional observational study conducted after obtaining permission from the Institutional Ethics Committee. Informed consent was obtained from the participants. Patients belong to various departments of Osmania General Hospital, who referred to the pathology laboratory for investigation as a convenient sampling method; patients attended during the study period 2011 - 2013 were included in the study. Bleeding disorder or recent blood transfusion patients were excluded from the study. The study sample consists of 150 patients with lab-confirmed thrombocytosis.

Two mL of fresh blood was drawn under aseptic conditions into EDTA vacutainers and processed immediately in one hour using a Mindray 3 part coulter counter. Patients with platelet count  $500 \times 10^9 / \text{L}$  and above were selected. For the confirmation of high platelet counts by repeating the tests and peripheral smear examination and platelet indices were analysed. These are classified into three groups based on their age. Group 1: 1 - 20 years, Group 2: 21 - 45 years, Group 3:  $> 45$  years.

Detailed relevant clinical history was collected along with the comprehensive physical examination and laboratory

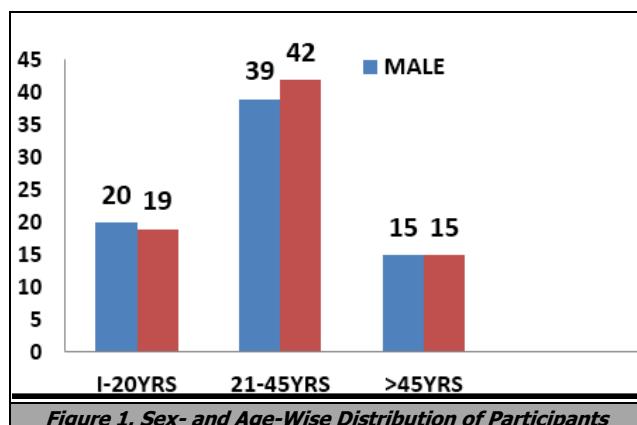
studies to make a diagnosis and exclude other possible causes.

### Statistical Analysis

All statistical analysis was done by Microsoft Excel, and the data were expressed as a percentage and difference between two groups (reactive & clonal thrombocytosis) evaluated by using chi-square test, it was done in both uncorrected and Yates correction. A p-value less than 0.05 was statistically significant.

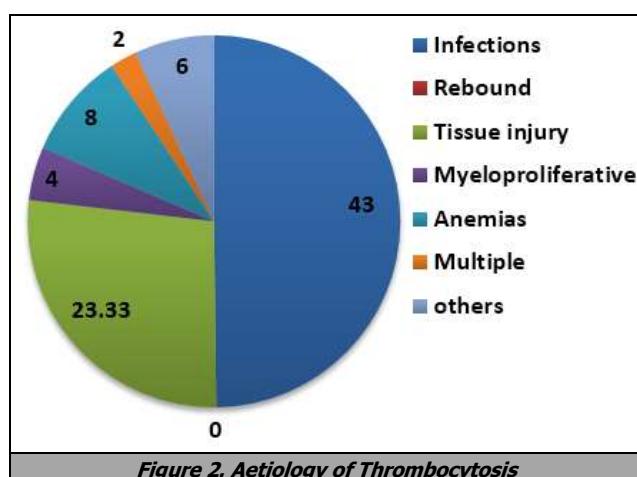
## RESULTS

A total of 150 patients with platelet counts  $500 \times 10^9 / L$  and above were studied. 76 cases (50.6 %) were females, 74 cases (49.3 %) were males. Thrombocytosis was most common in the age group 21 - 45 yrs. (54 %; 81 cases) followed by (25 %, 39 cases) in 1 - 20 yrs.



**Figure 1. Sex- and Age-Wise Distribution of Participants**

The various etiological causes underlying, with an elevated platelet count were listed in figure 2.



**Figure 2. Aetiology of Thrombocytosis**

Clonal thrombocytosis as the aetiological cause of elevated platelet count was found in 6 cases 4 %, reactive thrombocytosis as the etiological cause found in 144 cases (96 %).

Out of 144 patients of reactive thrombocytosis 68 (47.2 %) males, 76 (52.7 %) females, and age range from 1 yr. -

70 yrs., platelet count range  $518 \times 10^9 / L$  to  $1054 \times 10^9 / L$  with mean platelet count  $590 \times 10^9 / L$ .

Out of 6 patients of clonal thrombocytosis 5 (8.4 %) males, 1 (16.6 %) female and age range from 18 years to 60 years, chronic myeloid leukaemia 3 (2 %), polycythaemia vera 2 (1.33 %), essential thrombocythemia 1 (0.66 %) with platelet counts range  $558 \times 10^9 / L$  to  $793 \times 10^9 / L$  with a mean platelet count of  $630 \times 10^9 / L$ .

Extreme thrombocytosis with platelet count  $1000 \times 10^9 / L$  and above was seen in 3 cases 2 % cases.

### Analysis of Platelet Counts

It showed that 91 (60.6 %) patients with platelet count are in 5 Lac range, 39 (26 %) patients in 6 Lac, 9 (6 %) patients in 7 Lac, 5 (3.3 %) 8 Lac, respectively. The most common causes were Infections, tissue injury, and rebound thrombocytosis. 9 Lac count seen in 3 (2 %), extreme thrombocytosis with counts  $\geq 10$  Lac is noticed in 3 patients, all of them showed reactive aetiology, and the details include one 31 years male with pseudocyst of the pancreas, one 22 years female with sickle cell anaemia and one with post-splenectomy.

### Analysis of Platelet Indices

Platelet indices like MPV and PDW were analysed in 150 patients. In reactive thrombocytosis MPV 6 - 6.9 fl was seen in 116 (80.5 %), 7 - 7.9 fl was seen in 27 (17.3 %) cases and 8.0 fl in 1 (1.3 %) and MPV range 6 – 8 fl with mean MPV 6.5 fl.

In clonal thrombocytosis MPV 6.9 fl in 1 (16.6 %), 7.9 fl in 1 (16.6 %), and 8 - 8.9 fl in 4 cases (66.6 %). MPV range 6.9 - 8.5 fl with mean MPV 7.9 fl.

In reactive thrombocytosis PDW 14 - 14.9 % was seen in 2 (1.3 %), 15 - 15.9 % was seen in 140 (97 %), 16 - 16.9 % in 2 cases (1.3 %) and PDW ranges from 14 - 16.2 % with mean PDW 15.3 %.

In Clonal thrombocytosis PDW 15 - 15.9 was seen in 1 (16.6 %), 16 - 16.9 % was seen in four cases (66.6 %) 17 - 17.9 % in 1 (16.6 %). PDW range was 15.9 - 17.2 %, with mean PDW 16.4 depicts the mean values of MPV, PDW in both groups.

Cut off value 16 for PDW and 7 fl for MPV offered a better discrimination between the reactive and clonal thrombocytosis.

MPV less than 7 fl was seen in 122 reactive cases only one case of clonal thrombocytosis, more than 7fl was seen in 5 out of 6 cases of clonal thrombocytosis. P-value calculated and it was less than 0.05 it was found to be significant.

PDW less than 16 was seen in 140 reactive cases, only 2 cases of clonal thrombocytosis, more than 16 was seen in 4 out of 6 cases. P-value was calculated and it was less than 0.05 it was found to be significant.

Cut off value for MPV  $> 7$  fl and PDW  $> 16$  is useful to differentiate between clonal and reactive thrombocytosis, it was statistically proved.

The mean platelet volume in patients with clonal thrombocytosis is higher than the reactive group. There is

considerable overlap between these two groups. Platelet distribution width is also higher in clonal than reactive aetiology, and it shows a little overlap between these groups.

## DISCUSSION

The most common cause of thrombocytosis was found as infections (43 %), tissue injury (23 %), rebound thrombocytosis (14 %), anaemias (8 %), others (6 %), clonal causes (4 %), and multiple causes (2 %).

A study by Bashar Saeed 2009<sup>10</sup> et al. study infection was leading cause (27 %), non-haematological malignancies (25 %), iron deficiency anaemia (21.7 %), clonal causes (13 %), haemolytic anaemia (6.5 %), postoperative causes (5.4 %), collagen diseases (1.08 %).

Naveen Nazy et al 2007<sup>11</sup> infections (44.9 %), rebound thrombocytosis (10.2 %), tissue injury (11.4 %), myeloproliferative diseases (8.2 %), iron deficiency anaemias (7.9 %), malignancies (5.7 %), rheumatic arthritis (2 %), idiopathic (1.4 %), post splenectomy (1.4 %), miscellaneous causes (2.9 %), multiple causes (0.2 %).

In patients with primary thrombocytosis, exhibit increased heterogeneity while in secondary thrombocytosis, this heterogeneity is only rarely seen. This is confirmed by giant platelets on peripheral smears and platelet indices analysis by coulter counters.

J Vander Lie et al. study<sup>12</sup> analysed the reactive thrombocytosis and clonal thrombocytosis in CML cases, results showed mean MPV 6.8 fl, and in CML patients, it is 7.4 fl, in our study the MPV in CML patients showed 7.9 fl.

PDW in reactive cases mean 16.2, and in CML 17.8, in this study, reactive thrombocytosis means PDW 15.3 % and in CML mean PDW 16.4 correlating with my research.

Naveen Naz Syed study<sup>11</sup> platelet indices study showed that in reactive thrombocytosis, MPV range 4.5 -14.5 fl in my study MPV range 6.0 - 8.0 fl with mean MPV 6.5 fl and clonal thrombocytosis 6.4 - 13.1 fl. In the current study, the MPV range 6.9 - 8.5 fl with mean MPV 7.9 fl.

PDW indices range in reactive thrombocytosis 12 - 19.5 % in this study PDW ranges from 14.0 - 16.2 % with mean PDW 15.3 %. In Clonal thrombocytosis PDW 16.1 - 19.7 % in our study, the PDW range was 15.9 - 17.2 % with mean PDW 16.4.

Mehari Tafazzoli studies<sup>13</sup> median MPV in reactive group 8.04 fl, in a primary group, it is 9.2 fl. In my study, reactive group MPV range 6.0 fl - 8.0 fl with mean MPV 6.5 fl. In clonal thrombocytosis 6.4 - 13.1 fl, in ours, it was 6.9 - 8.5 fl with mean MPV 7.9 fl.

Toprak et al. study<sup>14</sup> medical records of 49 patients consisting of RT and essential thrombocytosis (ET) were retrospectively reviewed. The mean MPV level in the RT group was 7.49 fL, and in essential thrombocytosis, the group was 8.8 fL ( $p < 0.01$ ). He concluded that in the diagnosis of ET and had a sensitivity of 65 % and specificity of 89 % for ET. Investigation of MPV is cheap, quickly available parameter may serve as a predictor of primary thrombocytosis. In my study, MPV is 8.1 fL.

A study by Suleyman Yuceat al<sup>15</sup> was evaluated of mean platelet volume before and after iron deficiency anaemia

treatment. A total of 80 patients pre-treatment group of IDA MPV was  $7.9 \pm 1.5$  fL, haemoglobin (Hb) was  $9.8 \pm 1.5$  g / dl, and the post-treatment group MPV was  $8.6 \pm 2.0$  fL, Hb was  $12.5 \pm 6.6$  g / dL, and MPV ( $p < 0.001$ ), Hb ( $p < 0.001$ ) were significantly higher in the post-treatment group compared to the pre-treatment group. In our study, pre-treatment MPV mean is 6.6 fL.

Priyanka Meena et al.<sup>16</sup> study MPV shows a difference in cases and controls 11.88 (9.5 to 14.5) and 9.72 (7.6 to 13.2) the difference is statistically significant. MPV shows significance as compared with the various risk factors for stroke. In our study mean in stroke patients MPV 6.8 fL. When the platelet count is showing a slightly lower trend in the cases with an average of 96.52 (29 to 156) when compared to the controls in which the standard was 297.46 (157 to 523).

Vitthal Khode et al.<sup>17</sup> study MPV in acute myocardial infarction patients is increased 9.25 fl compared to stable coronary artery disease 9.15 fl; in our study MPV is 6.8 fl in acute myocardial infarction patients.

Morphological platelet differentiation also noted in these two groups, many studies in the past found that platelets in reactive thrombocytosis are young and platelets<sup>18,19</sup> and megakaryocytes in this small and of low nuclear ploidy<sup>5</sup> activation of these in marrow results from inflammation-induced stimulators.

In clonal thrombocytosis, patients show an increased percentage of micro-platelets and mega platelets,<sup>20,21,22</sup> which leads to improved heterogeneity results in an increase in PDW, probably maybe the reflection of megakaryocyte abnormality in the marrow of clonal thrombocytosis.

## CONCLUSIONS

Thrombocytosis is frequently associated with reactive aetiology as an acute phase reaction to infections, anaemias, and other rebound causes. The clonal proliferation causing thrombocytosis is generally confirmed with bone marrow studies, but the present study reflects the importance of platelet indices as a sensitive method in predicting the clonal thrombocytosis before any invasive procedure. Even though the clonal thrombocytosis cases are few, platelet indices in this case show that more than reactive thrombocytosis, platelet indices are more useful non-invasive parameter in differentiating thrombocytosis.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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