Correlative Analysis of Red Blood Cell and Platelet Parameters Predicts the Risk of Thrombosis in Patients with Iron Deficiency Anemia

Lavanya Rajagopal¹, Veena Raja², Saleh Mohammed Abdullah³, Sundaram Arunachalam⁴, Shivashekar Ganapathy⁵

¹Assistant Professor, ²Assistant Professor, ³Professor and HOD, Department of Pathology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai.
⁴Dean (Medical), Professor, Department of Pathology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai.
⁵Faculty Of Applied Medical Sciences, Medical Laboratory Department, Jazan University, Jazan, Saudi Arabia.

ABSTRACT

INTRODUCTION: Iron deficiency Anemia (IDA) is one of the world's most common and potentially treatable health problems. In IDA, there is an increased risk of thrombotic events due to microthrombosis-related hypercoagulability.

AIMS AND OBJECTIVES: To compare and analyze blood cell (RBC) and platelet parameters in Iron Deficiency Anemia (IDA) patients with individuals without anemia and to establish the correlation between platelet size parameters especially mean Platelet Volume (MPV), Platelet Distribution Width (PDW) with RBC parameters.

MATERIAL AND METHODS: Totally 150 subjects (75 with IDA and 75 without anemia) were included. Blood samples analyzed for RBC parameters with iron profile and platelet parameters.

RESULTS: The difference in mean hemoglobin (Hb), RBC count, hematocrit (HCT), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red cell Distribution Width (RDW), Serum iron, serum ferritin levels and similarly the difference in mean Platelet count, Plateletcrit (PCT), MPV and PDW between patients with IDA and those without anemia were statistically significant (p<0.05). Significant direct linear relationship between PDW, MPV and RDW and a significant inverse linear relationship between Platelet count with Hb, RBC count, HCT, MCH, MCHC, serum iron and serum ferritin, MPV with HCT, MCH, MCHC, serum iron and PCT with MCH, MCHC. The following parameters were noticed and were statistically significant (p<0.05).

CONCLUSION: Our study demonstrates a significant association between RBC and platelet parameters in IDA. We speculate that platelets in IDA are increased, more aggregable and hence an increased risk of thrombosis owing to increased MPV and PDW. This insight should pave the way for pathophysiology-directed therapy, thus contributing to the avoidance of thrombosis associated with IDA and the importance of close monitoring in these patients.

KEYWORDS: Anemia, Iron deficiency, Red blood cell indices, Platelet indices, thrombosis
INTRODUCTION:

Iron deficiency is one of the world's most common and potentially treatable health problems, nevertheless little is known about its relationship with platelet parameters. The first observations were reported in 1904, when the effect of severe hemorrhage on the number of platelets was tested in rabbits. In Iron deficiency anemia (IDA), several changes in platelets have been reported. So, a relationship between iron metabolism and thrombopoiesis should be considered. Several research reports linked thrombosis, thrombocytosis and iron deficiency and the suggested relationship between the two assumes clinical importance.

A biphasic pattern of platelet response was noted in patients with IDA. Moderate IDA is usually associated with reactive thrombocytosis. Thrombocytopenia can be seen in patients with severe IDA. Both thrombocytosis and thrombocytopenia may disappear after iron therapy.

Erythropoietin (Epo) is the primary growth factor for the red cell lineage, regulating the survival, proliferation and differentiation of erythroid precursors but treatment with recombinant human Epo (rHuEpo) has been shown to increase platelet counts. A recent study conducted in dogs showed that EPO not only stimulates erythropoiesis but also affects platelet quality by increasing platelet reactivity.

Iron deficiency can cause hypercoagulability, reactive thrombocytosis, anemia, and increased viscosity due to red cell deformability related to microcytosis. In IDA, there is an increased risk of thrombotic events due to microthrombosis-related hypercoagulability.

Moreover, several recent studies and meta-analyses suggest that higher MPV and PDW values indicate platelets, which are metabolically and enzymatically more active with a great prothrombotic potential and can be used as an alternative marker for platelet activity. The relationship between platelet counts MPV, PDW and risk of thrombosis has been of special interest in IDA and healthy individuals in literature.

Although the exact mechanism of alterations in platelet parameters associated with iron deficiency is unknown, iron is postulated to play a key role in the synthesis of platelets and in the regulation of thrombopoiesis. This study demonstrates the effect of iron deficiency on platelet parameters and provides an insight into the pathogenesis of alterations in platelet parameters associated with iron deficiency.

There are only few reports in literature regarding the correlation of platelet parameters with red blood cell parameters. The objective of this study, therefore, was to compare and analyze red blood cell (RBC) and platelet parameters in IDA patients with individuals without anemia and furthermore to establish the correlation between platelet size parameters especially MPV, PDW with RBC parameters.

METHODS:

This descriptive analytical cross-sectional study was carried out in department of pathology over a period from August 2016 to August 2017, at SRM Medical College Hospital & Research Centre, Kattankulathur, Tamilnadu, India and approved by institutional ethical committee. Totally 150 subjects aged more than 20 years of both genders (75 with IDA and 75 without anemia) were
included in this study. Their blood samples (5 ml) were analyzed for red cell parameters [hemoglobin (Hb), RBC count, hematocrit (HCT), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Peripheral smear, Serum iron and Ferritin levels] and Platelet parameters [Platelet count, Plateletcrit (PCT), Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW)]. History of underlying hematologic disorder, chronic kidney disease, diabetes, pregnant woman and patients on antiplatelet drugs, hematinics were excluded from this study. Informed consent was obtained from all the subjects. Medical history recorded.

The anemic patients were selected based on their hemoglobin levels (Hb<13 gm% in males and <12 gm% in females) based on definition of World Health Organization (WHO) and those with predominantly microcytic red cell indices (MCV<76 fl), hypochromic red cell indices (MCH<27 pg/cell and MCHC<32 gm/dl) and on their peripheral smear (microcytic hypochromic) were considered to have IDA which was confirmed by low serum iron (<59 μg/dl in males and <37 μg/dl in females) & low serum ferritin (<15 ng/ml in males and <9 ng/ml in females).

Red cell and platelet parameters were estimated by SYSMEX XT-1800i automated Hematology analyzer. Serum ferritin (Bio-Rad Quanimmune Ferritin IRMA, Bio-Rad lab) & Serum iron (TPTZ) method.

STATISTICAL ANALYSIS

The data are presented as mean ± SD for continuous variables. A student’s t-test was applied for comparison of group means. Pearson’s co-efficient was calculated to determine correlation between two variables. P value <0.05 was considered statistically significant.

RESULTS

Table-1: Comparison of red cell parameters between anemic (IDA) and not anemic individuals.

<table>
<thead>
<tr>
<th>RBC parameters</th>
<th>Anemic (IDA) (n=75) mean ± SD</th>
<th>Not Anemic (n=75) mean ± SD</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB</td>
<td>9.22 ± 1.96</td>
<td>13.82 ± 1.16</td>
<td>18.1</td>
<td>0.0001*</td>
</tr>
<tr>
<td>RBC count</td>
<td>3.87 ± 0.80</td>
<td>4.82 ± 0.48</td>
<td>9.6</td>
<td>0.0001*</td>
</tr>
<tr>
<td>HCT</td>
<td>31.34 ± 6.15</td>
<td>41.61 ± 3.87</td>
<td>12.4</td>
<td>0.0001*</td>
</tr>
<tr>
<td>MCV</td>
<td>66.78 ± 13.23</td>
<td>87.40 ± 4.41</td>
<td>13</td>
<td>0.0001*</td>
</tr>
<tr>
<td>MCH</td>
<td>23.88 ± 4.34</td>
<td>29.04 ± 1.21</td>
<td>10</td>
<td>0.0001*</td>
</tr>
<tr>
<td>MCHC</td>
<td>29.29 ± 2.50</td>
<td>32.72 ± 0.70</td>
<td>11</td>
<td>0.0001*</td>
</tr>
<tr>
<td>RDW – CV</td>
<td>17.4 ± 2.93</td>
<td>13.81 ± 0.70</td>
<td>10.4</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Serum iron</td>
<td>29.58 ± 0.44</td>
<td>74.13 ± 9.54</td>
<td>57.1</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Serum Ferritin</td>
<td>8.70 ± 2.79</td>
<td>42.89 ± 12.91</td>
<td>7.2</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

In this study the difference in mean Hb, RBC count, Hct, MCV, MCH, MCHC, RDW, Serum iron and ferritin between patients with IDA and those without anemia was statistically significant (p<0.05).

Table-2: Comparison of platelet parameters between anemic (IDA) and not anemic individuals.

<table>
<thead>
<tr>
<th>Platelet parameters</th>
<th>Anemic (IDA) (n=75) mean ± SD</th>
<th>Not Anemic (n=75) mean ± SD</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT count</td>
<td>358.7 ± 69.16</td>
<td>260.61 ± 59.3</td>
<td>7.8</td>
<td>0.0001*</td>
</tr>
<tr>
<td>PDW</td>
<td>12.55 ± 2.27</td>
<td>11.41 ± 2.10</td>
<td>3.1</td>
<td>0.0021</td>
</tr>
<tr>
<td>MPV</td>
<td>10.4 ± 1.03</td>
<td>6.94 ± 1.01</td>
<td>21.4</td>
<td>0.0001*</td>
</tr>
<tr>
<td>PCT</td>
<td>0.31 ± 0.07</td>
<td>0.20 ± 0.01</td>
<td>78.04</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

Similarly, the difference in mean platelet count, PDW, MPV and PCT between patients with IDA and those without anemia was statistically significant (p<0.05).
Table 3: Correlation between red cell and platelet parameters among anemic (IDA) and not anemic individuals. Significant* (p < 0.05).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>IDA</th>
<th>RBC count</th>
<th>Hb</th>
<th>RBC count</th>
<th>Hb</th>
<th>PCV</th>
<th>HCT</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
<th>Serum iron</th>
<th>Serum ferritin</th>
<th>PCT</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
<th>Serum iron</th>
<th>Serum ferritin</th>
<th>Platelet</th>
<th>PCT</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
<th>Serum iron</th>
<th>Serum ferritin</th>
</tr>
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<tbody>
<tr>
<td>PCV</td>
<td>0.206</td>
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<tr>
<td>RBC count</td>
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<td>Hb</td>
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</table>

In patients with IDA, when Pearson's correlation test was performed, inverse correlation between platelet count, PCT and Hb, RBC count, HCT, MCV, MCH, MCHC, Serum iron, serum ferritin and linear correlation between platelet count, PCT and RDW was determined.

The observations derived from the present study also shows inverse correlation between PDW and Hb, RBC count, Hct, MCH, MCHC; linear correlation between PDW and MCV,RDW, serum iron and serum ferritin. Similarly, inverse correlation between MPV and HCT, MCH, MCHC, serum iron and serum ferritin; linear correlation between Hb, RBC count, RDW was determined.

In the stepwise logistic regression test, a statistically significant direct linear relationship between PDW, MPV and RDW (p<0.05) was seen. Similarly, a statistically significant inverse linear relationship between the following parameters was noticed.

I. Platelet count with Hb, RBC count, Hct, MCH, MCHC, serum iron and serum ferritin (p<0.05).

ii. MPV with Hct, MCH, MCHC, serum iron (p<0.05).

iii. PCT with MCH, MCHC (p<0.05).

No association of statistical significance was seen between other platelet and RBC parameters in patients with IDA. In individuals without anemia, we observed no significant correlation between RBC and platelet parameters except for Hb and MPV.

DISCUSSION:

The ontogeny of human hematopoietic cells has been an area of constant research and immense interest. Here we addressed the hypothesis that iron deficiency is also relevant for IDA-associated thrombocytosis and also a risk factor for thrombosis. This study is the first to underline the relevance of iron deficiency in this setting.

The uniquely anuclear red blood cell is one of the most highly specialized of cells. Platelets are small anuclear cell fragments that are derived from mature megakaryocytes. An increase in the circulating number of platelets may occur in circumstances such as neoplastic proliferative diseases (i.e. essential thrombocytosis) or reactive thrombocytosis secondary to IDA, malignancy etc.

Some of the features that are similar to both RBCs and platelets are: I) both develop from a common Megakaryocyte/Erythroid progenitor cell (MEP). A population of probable erythrocytic and megakaryocytic cell lineage precursors co-expressed glycoporphorin A and glycoprotein IIIa.

Such a bipotentery megakaryocytic progenitor has been characterized in human bone marrow, ii)Both red blood cells and platelets are anucleate form in the peripheral blood, iii) Both the cells have an immature peripheral blood stage called as reticulocyte for RBCs and reticulated platelets for platelets.
Erythropoietin and thrombopoietin share a high degree of amino acid sequence homology (first 155 amino acids are common). Based on this theory, thrombocytosis in children with iron deficiency anemia was explained by Bilic E et al. Munker M et al suggest that both thrombopoietin and erythropoietin belonging to the same hematopoietic growth factor subfamily, are majorly produced in the kidney and act similarly by activating the JAK/STAT pathway and Ras signal transduction on their respective precursors. GATA-1, a transcription factor is expressed in primitive and definite erythroid and megakaryocytic cells and expression of both lineages are dependent on the presence of an intact GATA site. Thus a large body of data supports the concept that megakaryocytic and erythrocytic cell lineages share a common progenitor. Megakaryocytes have been shown to express erythroid-specific transcription factors, such as GATA factors, a specific DNA-binding protein or a nuclear factor involved in the regulation of globin transcription.

Iron Deficiency (ID) is the world's most widespread nutritional disorder, irrespective of age, gender and socioeconomic status, affecting both industrialized and developing countries. Approximately one-third of patients with anemia exhibit iron deficiency. The annual incidence rate of iron deficiency anemia (IDA) is 7.2-13.96 per 1,000 people per year. Although few studies have linked IDA with altered platelet parameters, the relationship between them has long been a topic of debate in the literature.

Our study results show a statistical significant increase in platelet count and platelet crit in patients with IDA when compared with individuals without anemia(Table 2). This coincides with the results of Yuce S et al., Kodikoylu G et al., Park MJ et al but contradicts with results of Gupta et al., Perlman MK et al, Morris VK et al.

The mechanism leading to thrombocytosis in cases of iron deficiency anemia remains unclear. The duration and the degree of IDA may play a role in determining the mechanism of platelet production. In moderate IDA, the causes of thrombocytosis may be: 1) shortening of megakaryocyte maturation 2) increased rate of influx of precursor cells into the megakaryocyte compartment with an increased rate of efflux 3) stimulator effect of transferrin on megakaryopoiesis 4) inhibition of iron on megakaryocyte maturation. However, when iron deficiency becomes very severe, megakaryocyte numbers decreased, megakaryocyte size increased, and platelet counts tended to normalize. This may be due to the shortening of megakaryocyte maturation. This could, however, also be consistent with the previously described diphasic pattern of increased stimulation by endogenous Epoprecursors.

Bilic and Bilic reported that an amino acid sequence homology between erythropoietin and thrombopoietin may explain thrombocytosis in children with IDA.

Our study results show a statistically significant increase in MPV in patients with IDA when compared with individuals without anemia (Table 2). This coincides with the results of Park MJ et al but contradicts with results of Yuce S et al. Similarly a statistically significant increase in PDW in patients with IDA (Table 2). This coincides with the results of Timuragaogluet al. Our study results show a statistically significant direct linear...
relationship between MPV, PDW and RDW in patients with IDA (Table 3). This coincides with the results of Wiwanitkit V et al\(^{56}\) and Saouli Z et al.\(^{29}\)

Although thrombotic and bleeding events are much less likely to occur in association with reactive thrombocytosis than autonomous thrombocytosis,\(^{37}\) thrombotic complications were occasionally reported in iron deficiency anemia.\(^{28-59}\)

Previous studies have shown that elevation of collagen and ADP during IDA may lead to increased thrombocyte aggregation.\(^{60}\) However, other studies have not found increased collagen and ADP during IDA.\(^{61,62}\) Malhotra RK et al studied platelet aggregation with ADP, adrenaline and collagen before and after iron therapy in IDA patients. He found that in untreated patients platelet aggregation with all three reagents was reduced, and it became normal on iron repletion, with normalization of hemoglobin.\(^{63}\)

Larger platelets are younger, more reactive and aggregable, contain denser granules, secrete more serotonin and \(\beta\)-thromboglobulin, and produce more thromboxane A2 than smaller platelets. All these can produce a pro-coagulant effect and cause thrombotic vascular complications.\(^{64}\) Several recent studies and meta-analyses suggest that higher MPV and PDW values indicate platelets, which are metabolically and enzymatically more active with a great prothrombotic potential and can be used as an alternative marker for platelet activity.\(^{65}\) The activated platelets differ in size from non-activated ones mainly due to a change from a discoid to a spherical shape and pseudopodia formation, leading to a change in the Platelet Distribution Width (PDW).\(^{66}\) The differences in platelet volume vividly correlates with differences in density, platelet aggregation to adenosine diphosphate and serotonin uptake and release, supporting the relevance of the Mean Platelet Volume (MPV) as a measure of platelet function.\(^{67,68}\)

Thus Platelet size has become an important marker of platelet function and also a physiological variable of hemostatic importance.\(^{69}\)

**Table 4: Comparison of present study with different studies.**

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>STUDY</th>
<th>PARAMETERS COMPARED</th>
<th>INFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wiwanitkit V et al(^{56})</td>
<td>PCT, MPV, PDW with parallel red cell parameters (215 cases)</td>
<td>No significant correlation between PCT and HCT, MPV and MCV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1. A significant correlation between PDW and RDW.</td>
</tr>
<tr>
<td>2</td>
<td>Saouli Z et al(^{10})</td>
<td>PCT, MPV, PDW with parallel red cell parameters. (303 cases)</td>
<td>No significant correlation between PCT and HCT, MPV and MCV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. A significant correlation between PDW and RDW.</td>
</tr>
<tr>
<td>3</td>
<td>Kadikoylu G et al(^{49})</td>
<td>Iron metabolism and thrombocytosis. (67 cases)</td>
<td>Inverse relationship between PDW and MCV.</td>
</tr>
<tr>
<td>4</td>
<td>Present study</td>
<td>Platelet count, PCT, MPV, PDW with parallel red cell parameters in Iron deficiency anemia (150 cases)</td>
<td>1. Statistically significant direct linear relationship between PDW, MPV and RDW.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Significant inverse linear relationship between i) Platelet count with Hb, RBC count, Hct, MCH, MCHC, serum iron and serum ferritin ii) MPV with Hct, MCH, MCHC, serum iron iii) PCT with MCH, MCHC.</td>
</tr>
</tbody>
</table>

Another important clinical implication of this inverse relationship would be in voluntary plateletpheresis. The American Association of Blood Banks (AABB) demonstrated that higher donor platelet counts reflected a decrease in MCV, thus projecting a higher likelihood of donor iron deficiency in high plateletpheresis yields.\(^{70}\) Higher RDW has also been shown to concurrently occur with higher platelet counts in advanced cancer stages, particularly in lung cancer.\(^{71}\)

**LIMITATIONS OF THE STUDY:**

There are few limitations in our study such as small sample size and qualitative platelet disorders were not assessed.
CONCLUSION:

Our study clearly demonstrates a significant association between red cell and platelet parameters in IDA. This study has indicated that IDA could induce thrombocytosis. We speculate that platelets of IDA patients become more reactive and more aggregable due to red cell deformability related to microcytosis and hence an increased risk of thrombosis owing to increased MPV and PDW. This insight should pave the way for pathophysiology-directed therapy, thus contributing to the avoidance of several deleterious effects like thrombosis associated with IDA and the importance of close monitoring in these patients. Further studies with larger samples are needed to clarify these relations in terms of the pathogenesis.

REFERENCES:


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