Aims: The link between inflammation and platelet activation was already proven. Only a few studies have been reported using platelet indices (platelet count (PC), mean platelet volume (MPV) and platelet distribution width (PDW)) as an indicator of acute phase response for assessment of disease activity. The aim of this study was to evaluate the PC, MPV and PDW trends in patients with rheumatoid arthritis (RA) comparing with control group. We also investigated whether these parameters were associated with disease activity score (DAS28-CRP) in RA patients.

Materials and methods: Ninety consecutive RA patients fulfilling American College of Rheumatology criteria (RA group) and 52 rheumatic disease free participants (control group) were included this study. PC, MPV and PDW values of RA group compared with controls. Correlation tests were used in order to evaluate the relationship between the DAS28-CRP scores and PC as well as MPV and PDW.

Results: We found significantly higher MPV and lower PDW values in the RA group when compared with controls. There were negative correlations between DAS28-CRP and MPV (r=-0.231, p=0.029) also PDW (r=-0.216, p=0.041) while correlation between DAS28-CRP and platelet count was not significant statistically.

Conclusion: This study demonstrated that platelet indices such as MPV and PDW may provide helpful information for assessment of disease activity in patients with RA.

Key words: rheumatoid arthritis, disease activity, mean platelet volume, platelet distribution width.

Introduction

Rheumatoid Arthritis (RA) is the most common chronic inflammatory disorder, associated with progressive destruction of synovial joints and physical disability\(^1\). It results in warm, swollen, and painful joints which are typically involved symmetrically. The majority of studies estimate a prevalence of 0.5-1\%, and the prevalence of RA is higher in females than males\(^2\). The incidence is reported to be higher 4-5 times below the age of 50, but above 60-70 years the female/male ratio is only about 2\(^9\). Similar to many rheumatic diseases, RA has a highly variable course with activation and remission periods over time\(^1\). An effective management in RA treatment depends on a closer monitoring of the disease activity. To determine the disease activity, clinicians use some clinical signs and symptoms (rheumatoid nodules, morning stiffness), radiological findings (bone erosion) and blood-derived parameters (RF values and some acute phase response markers). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most common measuring assays to detect the acute phase response due to their reliability and cost effectiveness\(^5\). ESR and CRP are widely requested by the clinicians in order to estimate the presence and severity of inflammatory diseases.
Rapid serum level changes of CRP reflecting the rate of inflammation is the major advantage of CRP. Unfortunately, ESR can be affected by age, gender, renal failure, anemia etc. which are unrelated with inflammation\(^{(7,8)}\). Although it is accepted that CRP and ESR correlate closely with clinical disease activity\(^{(9)}\), certain studies disclosed some discrepancies between ESR, CRP and the disease activity in patients with RA\(^{(8,10)}\). In addition to these parameters American College of Rheumatology (ACR) criteria\(^{(11)}\) and the Disease Activity Score (DAS) and its derived indexes (DAS28, DAS28-CRP\(^{(12)}\)) are widely used to evaluate patient’s response to treatment. The DAS28 index contains a count of 28 swollen and tender joints in addition to a measure of general health and ESR value with a score ranging from 0 to 9.4\(^{(13)}\). More recently, an alternative formulation of the DAS28 based on C-reactive protein (DAS28 (CRP)) has been proposed and developed. Especially DAS28-CRP is a validated tool to assess disease activity\(^{(14)}\).

The link between inflammation and platelet activation was already proven\(^{(15,16)}\). During the inflammation process, platelets can be increased in response to acute phase reaction. Only a few studies have been reported using platelet indices (platelet count (PC), mean platelet volume (MPV) and platelet distribution width (PDW)) as an indicator of acute phase response for assessment of disease activity and response to the treatment. Recently, it is reported that platelet indices (PC, MPV etc.) may indicate inflammation process over IL-6. Almost all of the studies about this issue concluded higher PC levels in patients with various inflammatory disorders\(^{(17-22)}\).

However, the same situation is not valid for the MPV. Some studies reported higher MPV\(^{(21,23,24)}\) while some others reported lower MPV values\(^{(25-28)}\) in inflammatory disorders. In a study comparing RA patients with controls, Gasparayan et al. found higher PC in addition to slightly but significantly greater MPV in RA patients compared with controls. Interestingly, PC was significantly greater in patients who have lower MPV (MPV<10.7fL) compared with those with higher ones (MPV>10.7fL).

was also found that MPV negatively correlated with platelet count in the whole RA cohort\(^{(24)}\). It seems that there is no consensus about MPV in literature unlike PC values. To the best of our knowledge only two studies\(^{(29,30)}\) reported the relationship between inflammation and PDW values including RA patients but its association with disease activity has not been studied yet.

The aim of this study was to evaluate the PC, MPV and PDW trend in patients with rheumatoid arthritis (RA) comparing with control group. We also investigated whether these parameters were associated with disease activity score (DAS28-CRP) in RA patients.

### Material and method

#### Setting and study population

The study was approved by the local ethics committee of the department and carried out in accordance with the Declaration of Helsinki as amended in 2008. Ninety consecutive patients fulfilling ACR-1987\(^{(31)}\) criteria for RA with at least 1 years’ time after diagnosis and 52 rheumatoid disease free participants were included this study. We excluded patients who have any rheumatic disease except RA and active and chronic infectious disease. We also excluded the associated conditions like hematologic disease, coronary artery disease, antiplatelet drugs use, pregnant, smoking, alcohol addiction, heart, renal or hepatic failure, chronic obstructive lung disease, hypertension, metabolic syndrome, malignancy and thyroid function disorder that may influence platelet indices. Blood samples were collected between 8 and 10 a.m. after a fasting period of 12h. Ethylenediaminetetraacetate (EDTA) containing test tubes were used and we limited the time between sampling and measurement at 30 minutes in order to prevent platelet swelling.

The complete medical history including disease duration and detailed examination including count of swollen and tender joints, presence of rheumatoid nodules, blood derived parameters (RF, ESR, CRP, PC, MPV, PDW values) of RA patients were recorded. All RA patients’ current DAS28-CRP scores (ranged from 0 to 9.4) were calculated.

#### Statistical analysis

By using SPSS program for statistical analyses (Statistical Package for Social Sciences, version 18, SPSS Inc., Chicago, Illinois, USA) homogeneity test was performed for the normal distribution of the patients’ and controls’ age and gender. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Independent samples t test was used to compare RA and control groups’ mean values of PC, MPV.
and PDW. Pearson correlation test was used in order to evaluate the relationship between the DAS28-CRP scores and PC as well as MPV and PDW. A p value smaller than 0.05 was considered to indicate a statistically significant difference.

**Results**

Demographic data of subjects were summarized in Table I. Age and gender distributions were similar in RA and control groups (p = 0.534 and p = 0.824, respectively).

**Table I:** Demographic data of study population.

<table>
<thead>
<tr>
<th></th>
<th>RA group (n=90)</th>
<th>Control group (n=52)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>90</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>47.08 ± 11.05</td>
<td>45.81 ± 12.74</td>
<td>0.534</td>
</tr>
<tr>
<td>Gender</td>
<td>21M / 69F</td>
<td>13M / 39F</td>
<td></td>
</tr>
</tbody>
</table>

**Table II:** The clinical features and laboratory values of patients with rheumatoid arthritis.

<table>
<thead>
<tr>
<th></th>
<th>Mean value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean disease duration</td>
<td>7.5 (12 – 396)</td>
</tr>
<tr>
<td>Number of tender joints</td>
<td>6.12 ± 7.88</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>0.16 ± 0.62</td>
</tr>
<tr>
<td>Global activity score</td>
<td>44.49 ± 28.12</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>29.51 ± 22.06</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12.87 ± 19.74</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>3.38 ± 1.17</td>
</tr>
</tbody>
</table>

**Table III:** Comparison of platelet indices between rheumatoid arthritis vs. control groups.

<table>
<thead>
<tr>
<th></th>
<th>RA Group (n=90)</th>
<th>Control Group (n=52)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (K/uL)</td>
<td>278.89 ± 68.7</td>
<td>275.83 ± 66.8</td>
<td>NS</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.76 ± 0.9</td>
<td>9.05 ± 2.0</td>
<td>0.004</td>
</tr>
<tr>
<td>PDW (fL)</td>
<td>11.43 ± 1.8</td>
<td>14.02 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Disease characteristics (mean disease duration, number of tender and swollen joints, global activity score, ESR, CRP and DAS28-CRP scores) of RA patients were summarized in Table II. We observed significantly higher MPV and lower PDW values in the RA group when compared with controls. PC values were also higher in RA group but not significant statistically. Comparison of platelet indices between RA vs. control groups was determined in Table III.

DAS28-CRP was correlated negatively with MPV (r = -0.231, p = 0.029) and PDW (r = -0.216, p = 0.041). The correlation between DAS28-CRP and PC was not significant statistically. Significant correlations between DAS28-CRP and platelet indices in RA group were shown in Figure 1.

**Discussion**

Suppression of local or systemic inflammation is the main goal of RA management to avoid joint destruction and progression of inflammation related comorbidities. Serum ESR and CRP levels are most common and well recognized laboratory tests assessing the activity of disease and response to treatment. Platelets are also one of the cellular parts of the immunity system. The relationship between inflammation and platelet activation was already proven and it is well known that platelet’s number is increased in patients with RA. The increase in platelets can reflect the bone marrow activity in response to the inflammation phase interleukins, such as IL-1 and IL-6. McEntegart et al. reported higher levels of prothrombotic factors (von Willebrand factor, fibrinogen, D-dimers and tissue plasminogen activator antigen) in patients with RA than in controls.

In 1983, Robbins and Barnard performed a RA cohort study and conclude increase in platelet count in response to infection. Milovanovic et al. also concluded that PC significantly increased during the disease activity in patients with RA.
Similar to studies mentioned above, we also found higher platelet counts in RA patients than in controls but it was not significant statistically.

MPV and PDW are usual platelets histogram indices reported by hospital laboratories in daily clinical practice. In particular, MPV is reported to be a simple and useful indicator for autoimmune or infective conditions\(^{(35-39)}\). Several reports showed the utility of MPV and PDW as markers of platelet activation\(^{(40)}\). During platelet activation process, the platelets’ shape change from discoid to spherical and their volume increase (higher MPV values) in order to obtain a larger surface\(^{(41)}\). There are some conflicting data in the literature concerning the values of MPV in patients with inflammatory disorders, in particular with RA. We have found significantly higher MPV values in RA subjects than in healthy controls. Similar to our results some studies reported higher MPV values in inflammatory disorders either in the active stage of the disease or when compare to controls\(^{(21, 25, 30, 42)}\). Yazici et al.\(^{(36)}\) analysed platelet indices, inflammatory markers and disease activity of 97 rheumatoid arthritis patients and reported higher values of MPV in patients with RA, which were correlated with the DAS28 disease activity score, decreasing after the treatment. Yavuz et al.\(^{(42)}\) concluded that MPV increased in patients with systemic lupus erythematosus (SLE) even in remission and might be used as an early indicator of reactivation in children with SLE. Coban et al.\(^{(25)}\) compared 35 patients with familial mediterranean fever (FMF) with 35 healthy control subjects and reported the levels of MPV were significantly higher in the FMF group. In contrast, some studies reported lower MPV values in inflammatory disorders\(^{(37-39)}\). Jurcud et al.\(^{(29)}\) reported deceased MPV values in response to infection with their RA cohort study. In a retrospective study Kisacik et al.\(^{(25)}\) reported lower values of MPV in patients with RA and anklylosing spondylitis than patients with osteoarthritis before treatment. The MPV values became higher significantly after treatment in RA group but not in anklyosing spondylitis patients. In a study Gasparyan et al.\(^{(45)}\) also reported significant increase in MPV in response to anti-TNF\(\alpha\) therapy over the duration of their study. Finally, Balbaloglu et al.\(^{(46)}\) found a significant lower MPV levels in patients with synovitis associated with knee osteoarthritis.

Limited numbers of studies investigated the indicator role of PDW in addition to PC and MPV during platelet activation\(^{(29, 30, 47, 48)}\). PDW measures the variability in platelet size directly\(^{(49)}\). Vagdatli et al.\(^{(48)}\) concluded that PDW seems to be a more specific indicator of platelet activation than MPV and combined use of MPV and PDW could predict activation of coagulation more efficiently. There are other authors who also suggest that PDW might be more specific as platelet activation index than MPV. Kucukbayrak et al.\(^{(47)}\) enrolled 40 brucellosis patients in the pre-treatment period and they found inverse correlation between MPV and ESR, PDW and ESR also PDW and CRP. To the best of our knowledge only two studies reported the relationship between inflammation and PDW values including RA patients\(^{(25, 30)}\). Mahmoud et al.\(^{(80)}\) compared 103 RA patients with 56 controls and reported significantly higher PDW values in RA patients. In our study, we also compared PDW values between RA and control group and found significant lower PDW values in RA group. When our study and above mentioned studies considered together, it seems that PDW can reflect inflammation and platelet activation process and may be a useful parameter in clinical practice. The combined use of MPV and PDW could predict inflammation more efficiently than MPW alone.

We also investigated the relationship between platelet indices and disease activity with correlation analysis. The results of our study showed significant negative correlation between DAS28-CRP and MPV also with PDW. Similar to our results some authors reported MPV values can be an independent marker for disease activity assessment in patients with various inflammatory diseases, in particular RA patients. Gasparyan et al.\(^{(45)}\) achieved that RA patients with high disease activity tend to have smaller size of platelets than those at recovery. After 3 months of therapy with anti-tumor necrosis factor alpha agents MPV values become higher significantly. They reported the comparison of baseline and after treatment results, but they did not correlate DAS28 scores with MPV or other platelet indices. Zareifar et al.\(^{(50)}\) studied with 100 children with diagnosis of infectious and inflammatory diseases and reported significant decrease in MPV at the time of disease activity. Milovanovic et al.\(^{(51)}\) reported the results of 16 active RA patients and found higher MPV values...
in active stage when compared in remission period after 2 years. Yavuz et al.\(^{14(2)}\) reported higher MPV values in patients with juvenile SLE when compared to healthy children and concluded an increase in MPV levels might be an indicator of worsening of childhood-onset SLE disease activity and MPV seemed to be more accurate than ESR and C3 for monitoring the disease activity in SLE. Douda et al.\(^{14(4)}\) also reported that MPV reduction was an independent marker for disease activity assessment, but its predictive value was not as high as PC and serum CRP. Also Kapsoritakis et al.\(^{26}\) reported a significant decrease in MPV during the disease activity phase on the cohort of patients with intestine inflammation and concluded that MPV could be used as an independent marker in disease activity assessments and may be a more sensitive marker than platelet count.

Our study is the only study investigating the association between PDW and disease activity by using DAS28-CRP scores in RA patients and our results showed that PDW can also predict disease activity in addition to MPV. During platelet activation and inflammation process over IL-6, PDW might be regarded as a marker of platelets activation reflecting a more important heterogeneity of the platelets dimensions. Unfortunately, the certain pathophysiology about the relationship between PDW and disease activity is still unclear. Further studies are required, in order to obtain more accurate conclusions concerning the pathophysiology of PDW and MPV changes by disease activity in patients with RA.

There are some limitations about this study. First, the patients included the study were represented from a single centre that may lead to a potential selection bias. Second, the study was conducted on cross-sectional design and we could not compare our available data with follow-up results after recovery time.

In conclusion, to the best of our knowledge, this is the second study investigating PDW in addition to MPV and PC in a RA cohort. At the same time, this is the first study correlating disease activity determined by DAS28-CRP scores with platelet indices including PDW in RA cohort. We have found significantly higher MPV and lower PDW values in RA subjects than in healthy controls. In addition, the results of our study showed significant negative correlation between DAS28-CRP and MPV as well as PDW. In order to obtain more accurate conclusions concerning the PDW and MPV values and also their changes by disease activity in patients with RA, further large studies are required.

**References**

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Abbreviations:
RA: rheumatoid arthritis
ESR: erythrocyte sedimentation rate
CRP: C-reactive protein
RF: rheumatoid factor
PC: platelet count
MPV: mean platelet volume
PDW: platelet distribution width
DAS: disease activity score
SLE: systemic lupus erythematosus

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