ASSOCIATION OF PLATELET INDICES WITH DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

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ABSTRACT

BACKGROUND

Rheumatoid arthritis is a chronic systemic inflammatory disease of uncertain aetiology that primarily affects synovium and also involves numerous extra-articular tissues. The amount of clinical disease activity indicates the level of inflammation and is the basis of treatment decisions. Treatment guidelines recommend starting with DMARD monotherapy. The goal of therapy is disease remission or very low disease activity. Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) are the commonly used markers of inflammation. Platelet have been shown to play an important role in inflammation by several mechanisms. Platelet indices have been studied in various inflammatory conditions including systemic lupus erythematosus, familial Mediterranean fever and inflammatory bowel disease.

MATERIALS AND METHODS

In the present study, normative survey cum longitudinal experimental observation technique were used. The equivalent two group design were selected for observation. Duration of the study was 10 months. The sample comprised of 30 patients aged 30-60 years each in a group. The sample was selected on the basis of inclusion and exclusion criteria. The tools such as clinical profile and 2010 ACR-EULAR classification criteria checklist were used. Initially, the general profile, checklist (ACR-EULAR) for joint involvement, serology, acute phase reactant and duration of symptoms were given. Assessment of current disease activity is important in treatment discussions in rheumatoid arthritis. Currently, ESR and CRP are the commonly used markers of inflammatory activity.

RESULTS

Platelet indices show variation with disease activity. In this study, there was an increase in platelet count and plateletcrit with disease activity, while MPV showed a decrease with active disease. There was also a significant correlation between the parameters and DAS 28 score.

CONCLUSION

Platelets have a significant role in the pathogenesis and progression of inflammatory disease including rheumatoid arthritis. Platelet indices maybe a cheaper and more easily available alternatives to ESR and CRP in assessing disease activity in patients with RA and this may help in guiding therapeutic strategies.

KEYWORDS

Rheumatoid Arthritis, Disease Activity, Platelet Indices, Plate Volume, Platelet Distribution Width, Plateletcrit.

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BACKGROUND

Rheumatoid arthritis is a chronic, progressive, autoimmune disease, affecting joints and cartilage as well as causing extra-articular manifestations including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis and haematologic abnormalities. It is the most common chronic inflammatory arthritis. The synovial tissue proliferates in an unregulated manner leading to excess fluid production, destruction of cartilage, erosion of marginal bone and stretching and damage of the tendons and ligaments. This ultimately leads to joint damage and deformities, which are the hallmark features of advanced disease.[1] The systemic inflammatory response also leads to dysfunction of other organ systems including endothelial damage and an increased risk of coronary artery disease and congestive cardiac failure in patients with RA.

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Clinical Features- The presenting symptoms are due to inflammation of joints, tendons and bursae. Early morning stiffness is a typical feature. Small joints of the hands and feet are usually the earliest joints to be affected by disease. Later on in the course of illness, the wrist, Metacarpophalangeal (MCP) and Proximal Interphalangeal (PIP) joints are the most frequently involved joints.

The progressive destruction of the joints and soft tissues ultimately leads to chronic irreversible deformities. Ulnar deviations results from subluxation of the MCP joints

with subluxation of the proximal phalanx to the volar side of the hand. Hyperextension of the PIP joint with flexion of the DIP joint, flexion of the PIP joint with hyperextension of the DIP joint and subluxation of the first MCP joint with hyperextension of the first Interphalangeal (IP) joint (Z-line deformity) occur due to damage to the tendons, joint capsule and other soft tissues in these small joints. "Piano-key movement" of the ulnar styloid occurs due to inflammation in the region of ulnar styloid and tenosynovitis of the extensor carpi ulnaris leading to subluxation of the distal ulna. Atlantoaxial involvement may lead to compressive myelopathy and neurologic sequelae. Chronic inflammation of the ankle and midtarsal joints may lead to pes planovalgus (flat feet) in established cases.

Classification- The first diagnostic criteria for RA was formulated by the American Rheumatism Association. Eleven criteria with 19 exclusions were proposed. "Definite RA" required a least 5 criteria and 6 weeks of joint symptoms. In 2010, a joint initiative by American College of Rheumatology and European league against rheumatism was found to develop new classification criteria.[2] They tried to identify those factors in patients with undifferentiated inflammatory synovitis, which best distinguished between those at high likelihood for developing present and/or erosive disease. This is crucial because treatment started early improves clinical outcomes and reduces joint damage and disability.

The diagnosis of RA has been based on clinical findings of a long-lasting inflammatory arthritis along with laboratory evidence of systemic inflammatory response and presence of auto antibodies in the serum. The current trend has been towards early diagnosis or cases so that treatment can be instituted at the very earliest in order to minimise the structural damage to tissues.[3]

The amount of clinical disease activity indicates the level of inflammation and is the basis of treatment decisions. The goal of therapy is disease remission or very low disease activity. Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) are the commonly used markers of inflammation.[4]

Platelets have been shown to play an important role in inflammation by several mechanisms. Platelet indices have been studied in various inflammatory conditions including systemic lupus erythematosus, familial Mediterranean fever and inflammatory bowel disease.

Need and Significance of the Study- The prevalence of RA has been estimated to be 0.5 to 1% in developed nations. However, the incidence and prevalence may vary with geographic locations, both globally and among certain ethnic groups within a country. RA is more common in females than in males with a ratio ranging from 2:1 to 3:1. This may be due to enhancement of immune response by oestrogens. The incidence of RA increases between the age of 2 and 55 years, after which it plateaus until the age of 75 years and then decreases. There is a 2-10 fold increased risk of disease in a first-degree relative of a patient when compared to the general population.

Investigations- Rheumatoid factor, anti-CCP antibodies, C-reactive protein, ESR, synovial fluid analysis and plain radiography. MRI has highest sensitivity in detecting RA.[5]

Disease activity- Platelet indices including Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and plateletcrit have been provided by automated analysers since the early 1970s.

Platelet inflammation- The role of platelets in haemostasis and thrombus formation has been known for long. The significance of these small anucleate cells in inflammation was first understood in studies on atherosclerosis.[6] A relationship between platelet volume and number was postulated first in 1974, which was later confirmed in subsequent studies.[7] Both large and small platelets are produced at similar rates and have similar age profiles; also young platelets do not decrease in size with age. In addition, young platelets released in stress situation may be small.[8] Megakaryocyte volume, ploidy and platelet release mechanisms have also been studied to have an effect on platelet volume.[9]

The COPCORD survey conducted by Bone and Joint Decade,(BJD) India, used a clinical approach and showed a standardised prevalence of 0.34%. This study demonstrated a few differences for RA in Indian patients- (i) An earlier age of onset in women; (ii) Lesser incidence of extra-articular features, including subcutaneous modules; and (iii) A lower frequency of rheumatoid factor positivity.[10]

Studies have evaluated the role of platelet indices in rheumatoid arthritis. In a study done by Isik et al, PCT was higher, whereas PDW and MPV was lower in active cases when compared to patients with remission.[11] Another study by Yazici et al showed a higher MPV value with active disease, which decreased with therapy.[12] Muddathir et al conducted a study in Sudanese population, which showed a higher MPV and PDW in RA cases as compared to controls.[13] In this context, this study conducted to find out the association between platelet indices and disease activity in patients with rheumatoid arthritis.

Objectives of the Study- To find out the association between platelet indices and disease activity in patients with rheumatoid arthritis based on-

a. Gender and age.
b. Haemoglobin value, MCV value, MCH value, MCHC value and total leucocyte count.
c. Platelet indices.

Hypothesis of the Study- There will be significant relationship between platelet indices and disease activity among patients with rheumatoid arthritis.

MATERIALS AND METHODS

In the present study, normative survey cum longitudinal experimental observation technique were used. The equivalent two group design were selected for observation. Duration of the study was continued 10 months in a year. The sample comprised of 30 rheumatoid arthritis patients aged 30-60 years in a group. The sample were selected on the basis of inclusion and exclusion criteria. RA was the

dependent variable and independent variables include age, gender, haemoglobin value, MCV, MCH, MCHC, total leucocyte value and platelet indices.

The tools such as clinical profile and 2010 ACR-EULAR Classification Criteria Checklist were used. Initially, the general profile, checklist (ACR-EULAR) for joint involvement, serology, acute phase reactant and duration of symptoms were given.

Detailed history and clinical examination was carried out after taking informed consent of the patients as per the prepared pro forma.

Blood samples were collected from the patients for the necessary investigations. Samples for Compete Blood Count (CBC) analysis including platelet indices and ESR were collected in EDTA-K bottles.

Clinical activity of the disease was assessed using disease activity score 28 (DAS 28).

Patients with DAS 28 >2.6 were classified as having active disease, whereas those having DAS 28 score ≤2.6 were classified as being in remission as per ACR disease activity measure criteria. The age and gender-matched patients were selected group 1 with DAS 28 score >2.6 (active disease) and group 2 with DAS 28 score ≤2.6 (inactive disease).

- Complete Blood Count (CBC) was analysed using Sysmex automated analyser.
- ESR was measured in mm/first hour using Westergren method.

Inclusion Criteria

- All patients diagnosed with rheumatoid arthritis according to 2010 ACR-EULAR classification criteria.
- Patients aged 30-60 years.
- Patients with no previous history of long-term treatment for other chronic illness.

Exclusion Criteria

- Patients with active infections.
- Patients who currently on any of the following drug statins, antihypertensive medications, antiplatelet drug, non-steroidal anti-inflammatory drugs and anticoagulants.

RESULTS AND DISCUSSION

I. Distribution of Rheumatoid Arthritis Patients Based on Disease Group- The total RA patients were subjected to percentage analysis based on disease group and tabulated as shown below.

Analytical Method

Category	Group 1 Active Disease		Group 2 Inactive Disease		Total	
Gender	**Number**	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Male	6	20	6	20	12	20
Female	24	80	24	80	48	80
Total	**30**	**100**	**30**	**100**	**60**	**100**

Table 1. Number and Percentage of RA Patients Belongs to Disease Group

The table shows that out of 30 patients with RA in active and inactive group 6 (20%) of them were males and 24 (80%) were females. It is inferred that female preponderance with male in both groups.

II. Distribution of Rheumatoid Arthritis Patients Based on Gender- The total RA patients in the disease group were subjected to mean and SD analysis of age and tabulated as shown below.

Category	Number	Mean	SD
Group 1 active disease	30	43.4	10.4
Group 2 inactive disease	30	43.9	10.5

Table 2. Mean and SD of Age of Patients Belong to Disease Group

The mean age of the active group were 43.4 and that of the inactive group were 43.9 with minimum and maximum age range were 26 and 62 and 24 and 62, respectively.

III. Clinical Profile Analysis of Patients with Rheumatoid Arthritis- The haemoglobin, MCV, MCH, MCHC and leucocyte values of two group patients with RA were subjected to test of significance and tabulated as shown below.

Category	Group				't' value	P
	G1 Active Disease		G2 Inactive Disease			
	Mean	SD	Mean	SD		
Haemoglobin	11.9	1.08	12.01	1.04	-0.267	0.79
MCV	87.5	7.4	90.0	8.2	1.254	0.21**
MCH	27.2	4.1	27.8	4.1	0.496	0.622**
MCHC	31.4	32.1	3.9	3.3	0.74	0.462**
Leucocyte	8.5	1.9	8.1	1.9	0.765	0.447*

Table 3. Result of Test of Significance of Haemoglobin, MCV, MCH, MCHC, Leucocyte Values of Patients with RA among Active and Inactive Disease Group

The mean value of haemoglobin (g/dL) was 11.9 ± 1.08 in group 1 and 12.0 ± 1.04 in group 2, which are significant. The mean value of MCV were 87.5 ± 7.4 fl in group 1 and 90 ± 8.2 fl in group 2, which are not significant. The mean value of MCH were 27.2 ± 4.1 pg in group 1 and 27.8 ± 4.1 pg in group 2, which are not significant. The mean value of MCHC were 31.4 ± 3.9 g/dI in group 1 and 32.1 ± 3.3 g/dI in group 2, which are not significant. The mean value of total leucocyte count (in thousands/mm3) were 8.5 ± 1.9 in group 1 and 8.1 ± 1.9 in group 2.

It is inferred that the active and inactive group were not significant in their MCV, MCH and MCHC values, but significant in their haemoglobin and total leucocyte values.

IV. Comparison of Platelet Indices and Disease Activity among Patients with Rheumatoid Arthritis- The mean value of platelet count, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and plateletcrit of two group patients with RA were subjected to test of significance and tabulated as shown below.

Category	Group				't' value	P
	G1 Active Disease		G2 Inactive Disease			
	Mean	SD	Mean	SD		
Platelet count	3.6	0.9	3.1	0.8	2.262	0.027*
Mean Platelet Volume (MPV)	8.8	0.5	9.3	0.7	-3.180	0.003*
Platelet Distribution Width (PDW)	12.8	1.6	12.1	1.4	1.695	0.096*
Plateletcrit	0.27	0.05	0.21	0.04	5.473	0.001*

Table 4. Result of Test of Significance of Platelet Indices of Patients with RA among Active and Inactive Disease Group

*- Significant.

The mean value of platelet count (in lakhs/mm^3) were 3.6 ± 0.9 in group 1 and 3.1 ± 0.8 in group 2. The mean value of MPV (in lakhs/mm^3) were 8.8 ± 0.5 fl in group 1 and 9.3 ± 0.7 fl in group 2. The mean value of PDW was 12.8 ± 1.6 in group 1 and 12.1 ± 1.4 in group 2. The mean value of plateletcrit were 0.27 ± 0.05 in group 1 and 0.21 ± 0.04 in group 2.

It is inferred that the active and inactive group were significant in their mean value of platelet count, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and plateletcrit.

DISCUSSION

In the study done by Muddathir et al[13] in a Sudanese population, patients with RA have higher values of MPV and PDW than controls. They also found that platelet count correlated significantly with WBC, ESR and CRP value ('p' value <0.05), while the MPV and PDW values were not correlated with the inflammatory markers.

V. Correlation between DAS 28 and Other Variables- The Pearson correlation coefficient between DAS 28 and age, Hb, TC, platelet count, MV, PDW and PCT were found out and tabulated as shown below.

Category	Variables	Age	Hb	TC	Platelet Count	MPV	PDW	PCT
DAS 28	R	0.91	0.11	0.04	0.34	-0.45	0.15	0.42
	P	0.001	0.39	0.8	0.008	0.001	0.26	0.001

Table 5. Pearson Coefficient of Correlation DAS 28 and Variables

The table shows that the coefficient of correlation between DAS 28 and Hb, total count and PDW were not significant and there was positive correlation between age and DAS 28 score.

A. Correlation between Platelet Count and DAS 28 Values-

There is positive correlation between platelet count 0.34 and DAS 28 values and is graphically shown below.

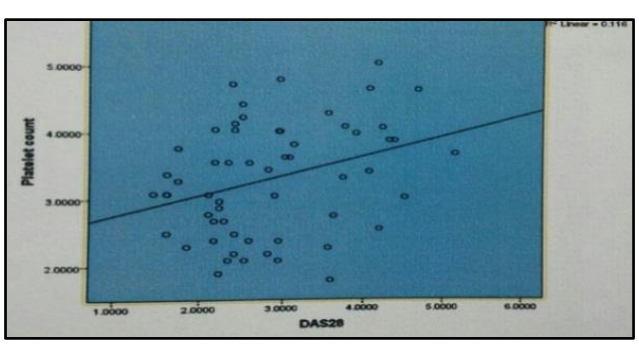

Figure 1. Correlation between Platelet Count and DAS 28 Score

B. Correlation between MPV and DAS 28 Scores-

The correlation coefficient was -0.45 with 'P' value of 0.001. The scatter plot diagram demonstrates the negative correlation between MPV and DAS 28.

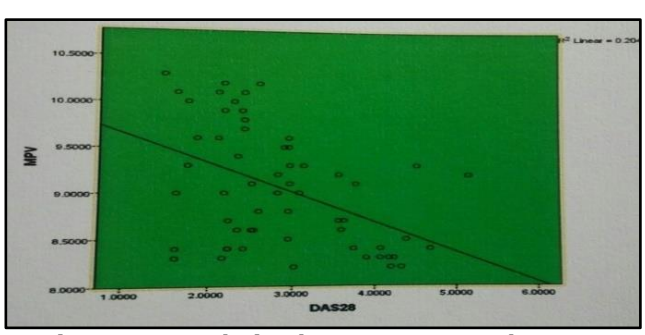

Figure 2. Correlation between MPV and DAS 28

C. Correlation between Plateletcrit and DAS 28 Score-

The Pearson correlation coefficient (r) was 0.42 with 'p' value of 0.001. The scatter plot diagram demonstrates positive correlation between plateletcrit and DAS 28 score.

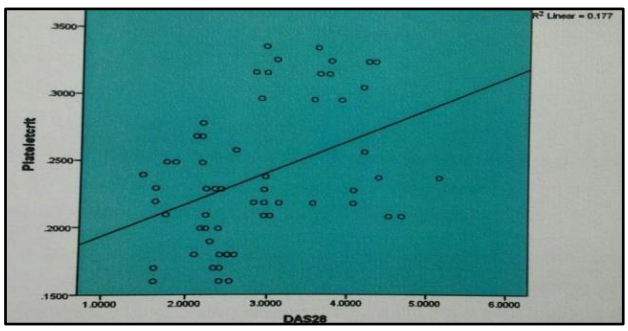

Figure 3. Correlation between Plateletcrit and DAS 28

Findings

1. It was found that the mean difference of haemoglobin values is significant. The mean value of haemoglobin/dL) was 11.9 ± 1.08 in group 1 and 12.0 ± 1.04 in group 2.
2. It was found that the active and inactive group were not significant in their MCV values. The mean value of MCV were 87.5± 7.4 fl in group 1 and 90 ± 8.2 fl in group 2.
3. It was inferred that the active and inactive group were not significant in their MCH values. The mean value of MCH were 27.2 ± 4.1 pg in group 1 and 27.8 ± 4.1 pg in group 2.
4. It was found that the active and inactive group were not significant in their MCHC values. The mean value of MCHC were 31.4 ± 3.9 g/dI in group 1 and 32.1 ± 3.3 g/dI in group 2.
5. It was found that the active and inactive group were significant in their total leucocyte values. The mean value of total leucocyte count (in thousands/mm3) were 8.5 ± 1.9 in group 1 and 8.1 ± 1.9 in group 2.
6. It was found that the active and inactive group were significant in their platelet count values. The mean value of platelet count (in lakhs/mm3) were 3.6 ± 0.9 in group 1 and 3.1 ± 0.8 in group 2.
7. It was found that the active and inactive group were significant in their mean platelet volume. The mean value of MPV (in lakhs/mm3) were 8.8 ± 0.5 fl in group 1 and 9.3 ± 0.7 fl in group 2.
8. It was found that the active and inactive group were significant in their platelet distribution width. The mean value of PDW was 12.8 ± 1.6 in group 1 and 12.1 ± 1.4 in group 2.
9. It was found that the active and inactive group were significant in their mean value of plateletcrit. The mean value of plateletcrit were 0.27 ± 0.05 in group 1 and 0.21 ± 0.04 in group 2.
10. There is positive correlation between platelet count 0.34 and DAS 28 values.
11. The correlation coefficient was -0.45 with 'p' value of 0.001 showed the negative correlation between MPV and DAS 28.
12. The Pearson correlation coefficient (r) was 0.42 with 'p' value of 0.001 showed a positive correlation between plateletcrit and DAS 28 score.

CONCLUSION

The study done by Harish et al[14] compared symptomatic active RA cases with age-matched controls. They found that there was increase in platelet count, MPV and PDW in the active cases. These value also showed a positive correlation with ESR. Another study by Verma et al[4] also showed that platelet count showed a significant increase with disease activity.

Assessment of current disease activity is important in treatment discussions in rheumatoid arthritis. Currently, ESR and CRP are the commonly used markers of inflammatory activity. Platelet indices show variation with disease activity. In this study, there was an increase in platelet count and plateletcrit with disease activity, while MPV showed a decrease with active disease. There was also a significant correlation between the parameters and DAS 28 score.

Platelets have a significant role in the pathogenesis and progression of inflammatory disease including rheumatoid arthritis. Platelet indices maybe a cheaper and more easily available alternatives to ESR and CRP in assessing disease activity in patients with RA and this may help in guiding therapeutic strategies.

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