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Research Article

Diagnostic Value of Antibodies with Inflammatory Markers, RDW and MPV in Rheumatoid Arthritis Patients

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Received: August 03, 2020; **Published:** September 28, 2020

Abstract

Background: The aim of the study was to assess relationship between the Red cell distribution width (RDW), mean platelet volume (MPV), rheumatoid arthritis (RA) autoantibodies against modified citrullinated vimentin antibodies (anti-MCV) and anticyclic citrullinated peptide antibodies (anti-CCP) in comparison to the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in RA.

Methods: 200 patients with RA were enrolled. We used the Disease Activity Score of 28 joints (DAS28) instrument to evaluate disease activity. Laboratory assessments included complete blood cell counts, ESR and assessment of CRP level, anti-CCP, anti-MCV and rheumatoid arthritis (RF).

Results: We found that RDW and MPV varied by disease activity status. RDW values correlated positively with the DAS28 scores of RA patients. Especially, higher RDW values (16.37 (S.D. 1.80), $P < 0.001$) were evident in the baseline, whereas the MPV values were lowest (6.06 (S.D. 1.66), $P < 0.001$) in this time.

Conclusion: Anti-MCV and anti-CCP were useful tools in the diagnosis of RA in early stages. RF, anti-CCP and anti-MCV antibodies can be considered along with ESR and CRP for monitoring RA patients to assess disease activity. We suggest that the MPV value can be used as negative phase reactant disease, whereas RDW is a positive marker.

Keywords: *Red Cell Distribution Width; Mean Platelet Volume; Rheumatoid Arthritis; Anti-Inflammatory Marker*

Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory disease which detected by swelling, tenderness and stiffness of the joints, with degeneration of cartilage and bone. It is characterized by involves symmetrical synovial joints in the periphery [1,2], also it can involve extra-articular organs such as skin, kidney, lung, and nerves [3]. This condition association with sever outcome and damage of functional capacity that results is low quality of life in patients with RA [4].

Early diagnosis can be restricted damage development and it is considered as the key role for improvement and decreasing functional disability [5]. The erythrocyte sedimentation rate (ESR) and reactive protein-C (CRP) used for the evaluation of activity and response to treatment for RA, but these are nonspecific [6]. Rheumatoid factor (RF) antibody is a diagnostic and prognostic biomarker for RA and can be measured in 60 - 80% of the patients [7]. In the past decade it has been manifested that citrullinated proteins/peptides (anti-CCP and anti-MCV antibodies), are likely to be connected with the development of this disease in at any rate 70% of the patients [8]. Citrullination of proteins Response to inflammation situation have local response (synovial) and humoral response which they haven't similar specificity. Humoral has highly specificity than synovial for RA [9]. They play clear role in the pathogenesis of RA, change of antigens in rheumatic

diseases (particularly RA) represents a cause for the generation of autoantibodies [10]. Nevertheless, published studies not investigated the possible correlations of RA autoantibodies, anti-MCV and anti-CCP in comparison to the ESR and CRP levels as biomarkers of disease activity.

Several new studies have shown the role of the mean platelet volume (MPV) and red blood cell range (RDW), in the measurement of the activity rate of rheumatoid arthritis [11,12]. Recent studies have shown that there is a direct relationship between high RDW and the risk of complication in patients with chronic heart failure [13], acute pancreatitis [14], hepatitis B infection [15], pneumonia [16] and have linked to inflammatory diseases such as IBD [17,18], Systemic Lupus Erythematosus (SLE) [19,20] or Behcet's disease [21]. According to studies, MPV is also associated with cardiovascular disease [22], hypertension, dyslipidemia [23], non-insulin dependent diabetes mellitus [24], brain stroke risk [25] and weight gain [23]. Although the relationship between RDW, MPV and its activity measurement indicators has not yet been proven and discussed by many rheumatologists [11,26,27].

Aim of the Study

The aim of the current study was to assess relationship between the changes of RDW, MPV, RA autoantibodies, anti-MCV and anti-CCP in comparison to the ESR and CRP levels as biomarkers of disease activity and indices of RA activity (DAS) in order to complete new studies on this issue.

Materials and Methods

Two hundred consecutive patients, who met the EULAR 2010 rheumatoid arthritis classification criteria [28] were visited from our rheumatology outpatient clinics from 25 March 2018 to 29 March 2019. This study was approved by the local research ethics committee of the Qom University of Medical Sciences (Ethical code: IR.MUQ.REC.1397.203) how they adhered to the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects. all participants provided written informed consent. Patients with age more than 18 less than 85 with active RA recruited in study. Patients with malignancy, liver disease (cirrhosis and hepatitis), end stage kidney disease, hematologic disease, infection and collagen vascular disease excluded.

Patients underwent thorough clinical evaluation and research laboratory, containing complete medical history and current disease activity score (DAS-28) [29] at baseline, 2 weeks and 3 months after the admission time and beginning of the treatment plan. Blood sample was drawn from all patients into vacutainers for Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurements and then in EDTA-containing tubes with and without anticoagulant for hematology analysis. Standard laboratory workup included: A complete blood count [including RDW (Normal Range: 11 - 16)], counts of white blood cells (WBC) and construction of a platelet diagram used to derive the MPV (marker of platelet activation) (Normal Rang: 6.5 - 12). All the above parameters were measured and computed using a Sysmex KX-21N automated hematology analyzer. RF and CRP levels were evaluated by Agglutination methods, using an ANISAN Company kits. ESR was evaluated by Westergren method. Anticyclic citrullinated peptide antibodies (anti-CCP) and antibodies against modified citrullinated vimentin antibodies (anti-MCV) were evaluated via enzyme-linked immunosorbent assay (ELISA) and a result was considered positive if the level was above a cut-off of five arbitrary units for anti-CCP and Value of 20.0 U/ml or greater considered to be positive for anti-MCV.

Results were presented as Mean, Standard Deviation (SD) and Median for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Correlations among variables were performed by Pearson's correlation testing using SPSS 22.0 software. One-way analysis of variance was used to compare WBC, MPV, CRP and RF values. P-value less than 0.05 considered statistically significant.

Result

Patients included in the cross-sectional study were Mean ± SD of age 51.77 ± 13.33 years (ranged 21 to 85 years) and 161/200 (80.5%) were women, had a BMI 28.30 ± 5.89 (ranged 14.67 - 50.44) and a median disease duration of 6.81 years (range 0.05 - 32) (Table 1).

Characteristics	RA patients
Gender	
Male	39 (19.5%)
Female	161 (80.5%)
Age	51.77 ± 13.33 (21 - 85)
BMI	28.30 ± 5.89 (14.67 - 50.44)
Duration of disease	6.81 (0.05 - 32)
RF	
Positive	92 (46%)
Negative	108 (54%)
Anti-CCP	103.16 ± 126.56
Anti-MCV	186.22 ± 274.65

Table 1: *Demographic data of rheumatoid arthritis patients.*

As showed in table 2 and about changes in reading parameters within 3 months of the assessment, considerable difference was noted in the rate of disease activity, ESR, CRP, RDW and WBC that significantly reduced at 3-month time point. The trend of the changes in DAS-28 score was significant, so that it was significantly decreased from its baseline level of 5.98 ± 1.41 to 1.93 ± 5.36 (P < 0.001) over 3 months of total assessment. The same differences were observed in ESR [35.56 (S.D. 22.09) vs 10.44 (S.D. 5.48), P < 0.001], CRP [24.41 (S.D. 19.20) vs 5.32 (S.D. 3.43), P < 0.001], RDW [16.37 (S.D. 1.80) vs 14.40 (S.D. 1.51), P < 0.001] and WBC [86.89 (S.D. 27.10) vs 64.61 (S.D. 14.79), P < 0.001]. However, the change along the 3 months of MPV was Increasing trend in patient [6.06 (S.D. 1.66) vs 9.02 (S.D. 1.60), P < 0.001] (Table 2).

Parameter	At baseline			At 2-weeks			At 3-months			P-value
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
DAS score	5.98	1.41	6.00	1.92	0.69	1.90	1.93	5.36	1.61	< 0.001
ESR	35.56	22.09	32.00	16.78	10.11	15.00	10.44	5.48	10.00	< 0.001
CRP	24.41	19.20	19.00	9.13	7.40	7.00	5.32	3.43	5.00	< 0.001
RDW	16.37	1.80	16.70	14.51	1.50	14.95	14.40	1.51	15.00	< 0.001
MPV	6.06	1.66	5.80	8.96	5.30	8.50	9.02	1.60	8.90	< 0.001
WBC	86.89	27.10	81.50	71.55	17.95	70.00	64.61	14.79	61.50	< 0.001
Disease activity	n	%		n	%		n	%		< 0.001
Remission	0	0		191	94.1		200	98.5		
Low	1	0.5		3	1.5		0	0		
Moderate	31	15.3		6	3.0		0	0		
High	168	82.8		0	0		0	0		

Table 2: *Differences in RA parameters within baseline, 2 weeks and 3 months.*

Next, to evaluate whether Rheumatoid Arthritis Activity could be associated with clinical and hematological features or inflammatory markers, we analyzed Rheumatoid Arthritis Activity score and disease parameters at the time of sampling in 200 RA patients with established disease. Moreover, Pearson's rank correlation test showed that DAS-28 was significantly associated with RF (r: 0.255, P < 0.001), Anti-CCP (r: 0.341, P < 0.001), Anti-MPV (r: 0.389, P < 0.001). Also, RDW exhibit significant correlation with RF (r: 0.326, P < 0.001), Anti-CCP (r: 0.449, P < 0.001), Anti-MPV (r: 0.391, P < 0.001). As well as MPV was associated with RF (r: -0.246, P < 0.001), Anti-CCP (r: -0.376, P < 0.001), Anti-MPV (r: -0.387, P < 0.001). Correlation analysis test showed that RDW and MPV was significantly associated with DAS-28 [(r: 0.437, p < 0.001) and (r: -0.539, p < 0.001)] and DAS-28 CRP [(r: 0.409, p < 0.001) and (r: -0.548, p < 0.001)]. All of this correlation was in baseline but was not significant in the fallow up (after 3 month), thus suggesting an association of RDW with disease activity and severity in baseline; after treatment MPV values significantly increased in patients (p < 0.001). There was a negative correlation between MPV values with disease activity and severity at the same time. Along with the RF and anti-CCP, the determination of anti-MCV can be a useful tool in the diagnosis of RA in early stages (Table 3 and 4).

Parameters	RF		Anti-CCP		Anti-MCV	
	Pearson correlation	P-value	Pearson correlation	P-value	Pearson correlation	P-value
DAS28 score						
Baseline	0.255	< 0.001	0.341	< 0.001	0.389	< 0.001
In 2 weeks	0.141	0.046	0.133	0.061	0.035	0.628
In 3 months	-0.46	0.514	-0.038	0.594	-0.037	0.600
RDW						
Baseline	0.326	< 0.001	0.449	< 0.001	0.391	< 0.001
In 2 weeks	0.119	0.093	0.100	0.158	0.059	0.407
In 3 months	0.118	0.095	0.063	0.376	-0.015	0.838
MPV						
Baseline	-0.246	< 0.001	-0.376	< 0.001	-0.387	< 0.001
In 2 weeks	0.110	0.122	-0.002	0.974	-0.006	0.930
In 3 months	-0.065	0.363	-0.046	0.519	-0.068	0.342
ESR						
Baseline	0.158	0.026	0.152	0.032	0.268	< 0.001
In 2 weeks	0.187	0.008	0.180	0.011	0.185	0.009
In 3 months	0.162	0.022	0.238	0.001	0.198	0.005
CRP						
Baseline	0.227	0.001	0.206	0.004	0.247	< 0.001
In 2 weeks	0.217	0.002	0.172	0.015	0.152	0.032
In 3 months	0.159	0.024	0.096	0.178	0.020	0.777

Table 3: *The correlation between different parameters of disease activity.*

Correlation analyses revealed that there was no significant correlation between ESR towards RF, anti-CCP and anti-MCV antibodies at baseline while highly significant correlation between CRP towards RF, anti-CCP and anti-MCV antibodies was observed. Serum CRP level change more quickly than those in the ESR, and therefore CRP concentration might be a better reflection of inflammation. So, this data investigated that the assessment of RF, anti-CCP and anti-MCV antibodies can be considered along with ESR and CRP level for monitoring RA patients to assess disease activity, especially when serum anti-CCP is negative. Also, serum RF and anti-MCV antibodies can be considered along with ESR and CRP for follow-up disease activity in RA patients (Table 5).

Parameters	RDW		MPV	
	Pearson correlation	P-value	Pearson correlation	P-value
DAS28 score				
Baseline	0.437	< 0.001	-0.539	< 0.001
In 2 weeks	0.236	0.001	0.004	0.958
In 3 months	-0.030	0.673	-0.016	0.826
Disease activity				
Baseline	0.409	< 0.001	-0.548	< 0.001
In 2 weeks	0.216	0.002	-0.037	0.604
In 3 months	-0.020	0.782	-0.082	0.250

Table 4: *The correlation between disease severity indices and MPV-RDW.*

Parameters	RF			Anti-CCP			Anti-MCV		
	Positive (n = 92)	Negative (n = 108)	P-value	Positive (n = 120)	Negative (n = 80)	P-value	Positive (n = 119)	Negative (n = 81)	P-value
DAS28 score									
Baseline	6.32	5.69	0.002	6.24	5.58	0.001	6.39	5.38	< 0.001
In 2 weeks	2.03	1.83	0.037	1.98	1.84	0.176	2.01	1.79	0.023
In 3 months	1.62	2.19	0.455	1.58	2.45	0.262	1.60	2.41	0.391
RDW									
Baseline	17.03	15.80	< 0.001	17.07	15.32	< 0.001	17.04	15.38	< 0.001
In 2 weeks	14.68	14.35	0.114	14.68	14.24	0.036	14.63	14.32	0.164
In 3 months	14.61	14.21	0.060	14.63	14.06	0.015	14.53	14.21	0.137
MPV									
Baseline	5.59	6.46	< 0.001	5.55	6.82	< 0.001	5.52	6.86	< 0.001
In 2 weeks	8.63	8.63	0.331	9.22	8.58	0.405	9.35	8.40	0.213
In 3 months	8.96	9.07	0.641	8.86	9.27	0.093	9.07	8.95	0.601
ESR									
Baseline	37.97	33.51	0.156	36.20	34.61	0.620	38.06	31.90	0.053
In 2 weeks	18.75	15.11	0.011	17.50	15.71	0.222	18.10	14.85	0.025
In 3 months	11.50	9.54	0.011	10.97	9.65	0.096	11.23	9.28	0.009
CRP									
Baseline	28.99	20.51	0.002	26.64	21.06	0.044	27.32	20.14	0.009
In 2 weeks	10.49	7.98	0.016	9.72	8.25	0.170	10.10	7.71	0.024
In 3 months	5.91	4.83	0.026	5.57	4.96	0.215	5.86	4.53	0.007

Table 5: *The difference between disease activity parameters.*

Regarding disease features, it is remarkable that patients in the lower RDW and lower MPV exhibited higher 28-joint DAS (DAS28) scores [(RDW) 7.41 vs 5.02 (S.D. 1.26), P < 0.001], [(MPV) 6.33 (S.D. 1.24) vs 4.32 (S.D. 0.79), P < 0.001] and DAS28 CRP [(RDW) 6.72 vs 4.92 (S.D. 1.61), P = 0.004], [(MPV) 6.21 (S.D. 2.90) vs 4.17 (S.D. 0.76), P < 0.001] and In second place patients with higher RDW and higher

MPV exhibited higher DAS28 scores [(RDW) 6.42 (S.D. 1.26) vs 5.02 (S.D. 1.26), P < 0.001], [(MPV) 5.06 (S.D. 3.32) vs 4.32 (S.D. 0.79), P < 0.001] and DAS28 Crp [(RDW) 6.29 (S.D. 3.08) vs 4.92 (S.D. 1.61), P = 0.004], [(MPV) 4.86 (S.D. 2.63) vs 4.17 (S.D. 0.76), P < 0.001] at base line, but in overall Pearson correlation analysis test showed a positive correlation with RDW and DAS, and a negative correlation with MPV and DAS. Thus, suggesting an association of RDW and MPV with progression of the disease (Table 6 and 7).

	First tertile RDW < 11	Second tertile 11 ≤ RDW ≤ 16	Third tertile RDW ≥ 16	P-value
DAS-28 score				
Baseline	7.41	5.02 ± 1.26	6.42 ± 1.26	< 0.001
In 2 weeks	2.28	1.87 ± 0.66	2.27 ± 0.69	0.024
In 6 months	1.70 ± 0.52	1.94 ± 5.51	1.73 ± 0.43	0.991
DAS-28 CRP score				
Baseline	6.72	4.92 ± 1.61	6.29 ± 3.08	0.004
In 2 weeks	1.96	1.72 ± 0.27	1.97 ± 0.59	0.002
In 6 months	1.55 ± 0.24	1.58 ± 0.22	1.45 ± 0.22	0.274

Table 6: *Disease activity of patients according to red cell distribution width tertiles.*

	First tertile MPV < 6.5	Second tertile 6.5 ≤ MPV ≤ 12	Third tertile MPV ≥ 12	P-value
DAS-28 score				
Baseline	6.33 ± 1.24	4.32 ± 0.79	5.06 ± 3.32	< 0.001
In 2 weeks	2.68 ± 0.78	1.89 ± 0.67	2.39 ± 0.90	0.004
In 6 months	1.46 ± 0.30	1.94 ± 5.47	1.73 ± 0.33	0.988
DAS-28 CRP score				
Baseline	6.21 ± 2.90	4.17 ± 0.76	4.86 ± 2.63	< 0.001
In 2 weeks	2.29 ± 0.71	1.73 ± 0.28	2.12 ± 0.70	< 0.001
In 6 months	1.61	1.57 ± 0.22	1.71 ± 0.11	0.317

Table 7: *Disease activity of patients according to mean platelet volume tertiles.*

Discussion and Conclusion

Currently, the ACR/ EULAR 2010 criteria for the RA diagnosis use the RF and antibodies anti-CCP [30]. A meta-analysis from 2010 that review 14 studies, in which the anti-CCP and anti-MCV for the RA diagnosis were tested; their Evidence show that there is no difference between the two tests. Thus, the anti-MCV may be used for the second line test, in patients suspected of RA, but with RF and anti-CCP negative [31]. YH Lee., *et al*. [32] demonstrates that anti-MCV is more sensitive but less specific and has lower diagnostic accuracy than anti-CCP in RA, although anti-MCV and anti-CCP showed comparable high platelet to lymphocyte ratio (PLRs) [32]. Our results are in line with those of similar studies, along with the RF and anti-CCP, the designation of anti-MCV can use to a useful tool in the diagnosis of RA in early stages.

Hematological biomarkers such as those related with red cell and platelet function are often neglected when considering the pathogenesis of inflammatory joint disease. The probable existence of (positive) relationships between RDW and (negative) MPV on the one hand, and RA clinical activity on the other, has been measured in only a few studies. Boilard., *et al*. [33] demonstrated, unexpectedly, that platelets action an important work in the development of inflammatory arthritis. Also, MPV, in combination with the ESR and the CRP level is an similar parameter in assessment of inflammatory activity [11]. Also, Yazici., *et al*. [34] showed that MPV correlated with inflammatory parameters (ESR and CRP) and disease activity (DAS-28 score) in RA patients [34].

A retrospective study revealed that computation of MPV values in RA and AS patients given additional information on inflammatory conditions. they demonstrated that MPV values in patients with active RA and AS were notably lower than those of controls, and a negative relationship was evident between the MPV value and the level of disease activity [35]. Also, Şahin., *et al.* [36] in RA patients detected that MPV negatively correlated with ESR and CRP level and inversely correlated with DAS-28 score [36]. Ahmet Omma., *et al*. [37] investigated primary Sjogren syndrome (PSS) patients and healthy controls and found that the MPV values were upper in patients compared to their control peers. The cited authors concluded that the MPV values served as useful inflammatory markers to evaluate disease activity [37]. In Overall, the lower MPV level substitute active and/or chronic inflammatory situation in the body [36] and can be used as a negative acute-phase parameter in rheumatic diseases [35].

In contrast, Moghimi., *et al*. [27] as they found that MPV value may not be able to estimate disease activity in RA patients (limitation of their examination group). In this study, regarding trend of the changes in RA severity, DAS-28CRP and DAS-28 score were slowly decreased within 3 months of study period. Implementation and changes in MPV and other biomarkers were remarkable but didn't have significant correlation at the end of study period. In addition, as awaited, we observed that the ESR and CRP levels were directly correlated with the trend of disease activity.

Another aim of our study was to investigate the correlation between disease activity, and the RDW value, in RA patients. Since it is measured frequently and previously validated and optimized, so it does not add any further costs to patient. A recent report showed that RDW at disease onset may be used as a primary marker of CV risk in RA, whereas in patients with recognized disease it was connected to the activity of the disease [38]. Javier Rodríguez-Carrio., *et al*. [39] showed that RDW level positively correlated with inflammation and association with vascular remodeling [39]. Duygu Tecer., *et al*. [11] Concluded that RDW was positively correlated with pain and DAS28 [11]. In the present study, the RDW level of RA patients were found to be significantly higher at disease onset.

In conclusion, anti-MCV and anti-CCP can be used to a useful tool in the diagnosis of RA in early stages. RF, anti-CCP and anti-MCV antibodies can be considered along with ESR and CRP for monitoring RA patients to assess disease activity, especially when serum anti-CCP is negative. Also, serum RF and anti-MCV antibodies can be considered along with ESR and CRP for follow-up disease activity in RA patients. Also, RDW and MPV values serve as useful markers of RA exacerbation in combination with the ESR and the CRP level. We suggest that the MPV value can be used to indicate as negative phase reactant disease, whereas the RDW is a positive marker for this situation.

Conflict of Interest Statement

Authors decline any conflict of interest.

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