Anti-Mutated Citrullinated Vimentin (Anti-MCV) Antibodies as a Diagnostic Aid for Rheumatoid Arthritis

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Abstract

Background: This study aimed to evaluate the role of anti-MCV antibodies in the diagnosis of RA and correlate anti-MCV with other markers of disease activity.

Subjects and methods: The study was carried out on 70 individuals, categorized as follows; 40 patients diagnosed as rheumatoid arthritis (RA) (Group I), 15 patients diagnosed as osteoarthritis disease (OA) (Group II) and their results were compared to 15 apparently healthy persons as control group (Group III). All participants were subjected to careful history taking, general examination, routine laboratory investigations, in addition to, anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) assays.

Results: Anti-CCP and anti-MCV values were significantly higher in group I when compared to group II and III (P-value<0.001 and 0.001). The optimum diagnostic cut-off point in RA patients for anti-MCV was >27.5 U/ml at which Sensitivity was 99.1, Specificity was 93.3, PPV was 97.8 and NPV was 99.8. The AUC (area under the curve) value for anti-MCV was 0.997. There were highly significant positive correlations between anti-MCV, anti-CCP and ESR in group I (P-value<0.001 and 0.001). Anti-CCP and anti-MCV were significantly higher in RF positive patients compared to RF negative patients (P-values=0.005 and 0.011 respectively), while no significant differences in anti-CCP and anti-MCV were found between CRP positive and CRP negative patients in group I.

Conclusion: Anti-MCV is an excellent marker for early diagnosis of RA with high sensitivity and specificity especially when other markers are negative. The use of anti-MCV and anti-CCP collectively give the best result for the diagnosis of rheumatoid disease.

Keywords: Rheumatoid arthritis; Anti-CCP; Anti-MCV

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by chronic joint inflammation that often leads to destruction of bone and cartilage, affects women three times as men, and usually appears in middle age [1].

Although the etiology of RA remains unknown, it is widely accepted that multiple accumulative genetic and environmental factors are required between the initiation of self-peptide recognition, subsequent loss of tolerance, and the development of autoimmunity. Disease onset is insidious, initially affecting the small joints of the hands, feet and wrists [2].

Clinical course of the disease varies between individuals but may be mild, relapsing, remitting, or progressive. Early definitive diagnosis is essential in RA patients, as they have a true chance for achieving a "cure" of the disease if they are treated early and this needs sensitive clinical and laboratory diagnostic tools [3].

Rheumatoid factor and anti-cyclic citrullinated antibodies (anti-CCP) have been shown to be present prior to the appearance of clinical symptoms of arthritis suggesting that the initial immune deregulation in RA occurs years before symptomatic disease [4].

Rheumatoid factor is not specific to RA, as it is present in patients suffering from other autoimmune and infectious diseases, also found in apparently healthy elderly patients [5].

Anti- CCP has been shown to be a specific prognostic marker for RA and predict the erosive or non-erosive progression of the disease. Thus, it is a useful tool for the optimal therapeutic management of RA patients. The diagnosis of RA has been improved by the introduction of other standardized immunoassays for the detection of auto-antibodies against different citrullinated antigens as anti-mutated citrullinated vimentin antibodies (Anti-MCV). Anti-MCV antibodies have been recommended to be better diagnostic marker for early arthritis [6]. Vimentin is an intermediate filament that is widely expressed by mesenchymal cells and macrophages and easy to detect in the synovium. Modification of the protein occurs in macrophages undergoing apoptosis, and antibodies to citrullinated vimentin may emerge if the apoptotic material is inadequately cleared [7].

A significant correlation has been established between anti-MCV antibodies titers and both the severity of RA and the disease-activity score (DAS28), anti-MCV-positive patients exhibited significantly lower reduction in disease activity and a greater number of swollen

joints. Thus, it appears that, anti-MCV antibodies may have the advantage of correlating better with disease activity and patient outcome [1].

Aim of the work is to assess the feasibility of anti-MCV antibodies as a diagnostic tool for RA and correlate anti-MCV with other markers of disease activity.

Subjects and Methods

The study population included 75 subjects; 45 patients with classic RA (Group I) according to current American College of Rheumatology criteria (ACR) [8]. They were selected from outpatient clinic of Rheumatology Department in El-Minia University Hospital, 15 patients with osteoarthritis (Group II) and 15 apparently healthy subjects (Group III) as control group, during a period of six months from May to October 2013.

All patients and controls were subjected to: I) History taking; Considering age, history of any other diseases, detailed RA history concerning disease duration, morning stiffness, duration of treatment, Body Mass Index (BMI) and family history.

II) Clinical examination; including rheumatological examination, special stress was laid upon manifestations of disease activity e.g. number of swollen Joints, number of tender Joints and assessment of disease activity by 28 joint disease activity score (DAS 28) [9].

III) Laboratory investigations

Sampling: Under complete sterile conditions and after making disinfection to the site of sampling by a cotton soaked with alcohol, 5 ml of venous blood was drown, 0.5 ml was used for complete blood count in a tube containing (EDTA), 0.8 ml of venous blood used for ESR in citrate containing tube (0.2 ml trisodium citrate 3.8%), 3.0 ml in a plane tube, left until clotting then centrifuged and serum sample was used for CRP and RF measurement and the remaining serum was stored at –20°C for the assessment of Anti-MCV and Anti-CCP.

The following tests were performed for all participants; 1) Complete blood count (CBC): Determined by automated cell counter Sysmex KX-21-N (TAO Medical Incorporation, Japan), 2) Erythrocyte Sedimentation Rate (ESR): determined by Westergren method, 3) C-reactive protein: determined using semi quantitative assay, kits was supplied by CRP TECO diagnostics, U.S.A, 4) Rheumatoid factor (RF): was determined using semi quantitative assay supplied by Teco diagnostic latex agglutination test, U.S.A. 5) Anti-CCP assay by ELISA using ORGENTEC Diagnostika GmbH (Carl-Zeiss-Straße 49-51, 55129 Mainz–Germany): The principle of assay is the quantitative measurement of IgG class autoantibodies against cyclic citrullinated peptides (CCP) in human serum or plasma *in vitro* by enzyme-linked immunosorbent assay (ELISA) [10]. 6) Assesment of Anti-MCV by ELISA using ORGENTEC Diagnostika GmbH (Carl-Zeiss-Straße 49-51, 55129 Mainz–Germany): The principle of assay is the quantitative measurement of IgG class autoantibodies against mutated citrullinated vimentin (MCV) in human serum or plasma *in vitro* by enzyme-linked immunosorbent assay (ELISA) [11].

Statistical analysis

Data were analyzed by SPSS (Statistical Package for the Social Sciences). Discrete values were presented as counts and percentages.

Continuous values were expressed as mean ± SD; comparison of discrete data between two independent groups was done using Chi-square test. Comparison of continuous data between three groups was done using student *t*-test; linear correlation was measured using Pearson's correlation coefficient. A probability level of P-value<0.05 was considered significant, and the level<0.01 was considered highly significant.

Results

All obtained results of different groups were summarized in Tables 1-4 and Figures 1-6.
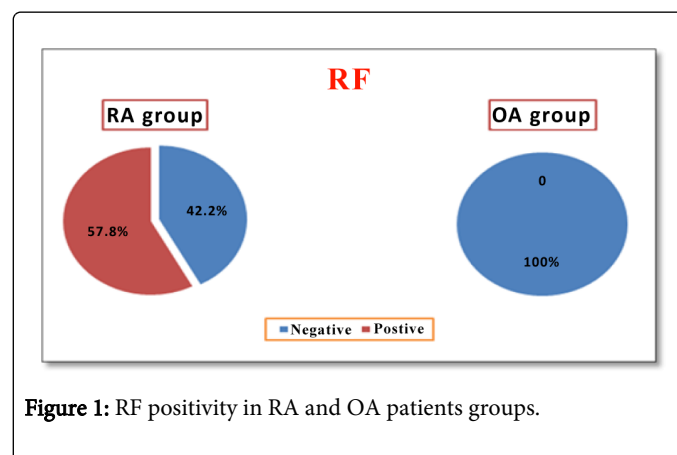
Figure 1: RF positivity in RA and OA patients groups.
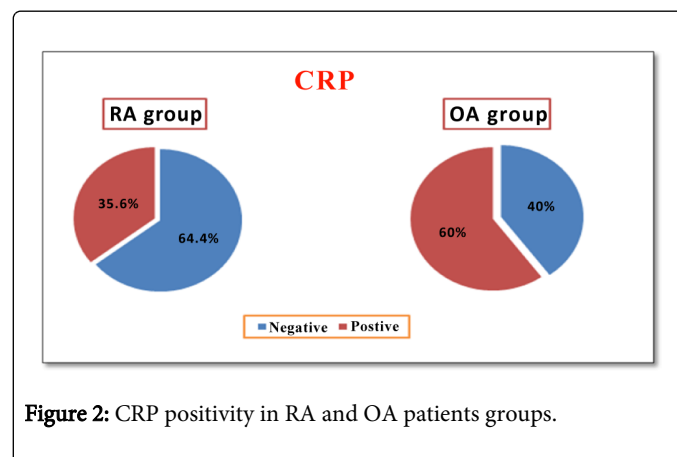
Figure 2: CRP positivity in RA and OA patients groups.

|	Group I (RA) N=45	Group II (OA) N=15	Group III (Control) N=15	P value
Age (years)	(20-60)	(40-60)	(20-35)	<0.001*
Range M ± SD	40.11 ± 10.7	51.66 ± 6.1	27.6 ± 4.11	
Sex				
Male	8 (17.8%)	1 (6.7%)	3 (20%)	0.679
Female	37 (82.2%)	14 (93.3%)	12 (80%)	

Table 1: Demographic data of the studied groups.

	Group I (RA) N=45	Group II (OA) N=15	Group III (Control) N=15	P value		
Anti CCP: (u/ml) **Range M ± SD**	(0.023-971.83) 165.01 ± 248.27	(0.01-15.7) 1.32 ± 4.01	(0.01-0.2) 0.03 ± 0.05	<0.001		
				I vs. II	I vs. III	II vs. III
				<0.001	<0.001	0.001
Anti MCV: (u/ml) **Range M ± SD**	(7.24-891) 158.31 ± 232.09	(0.02-27) 6.43 ± 9.15	(0.01-18.7) 1.65 ± 4.81	<0.001		
				I vs. II	I vs. III	II vs. III
				<0.001	<0.001	0.01

Table 2: Comparison between anti-CCP and anti-MCV in different studied groups.

Highly significant values of anti CCP and anti MCV were observed in RA patients group when compared to OA and control groups (P-values<0.001).
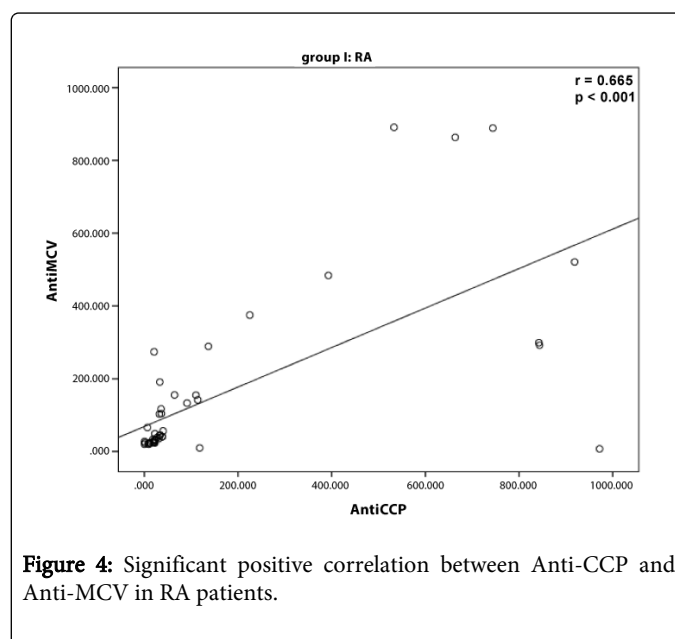
The mean age was significantly higher in OA group when compared to RA and control groups (P-value<0.001) while anti-CCP and anti-MCV levels were significantly increased in RA patients when compared to both OA and control groups (P-value<0.001).
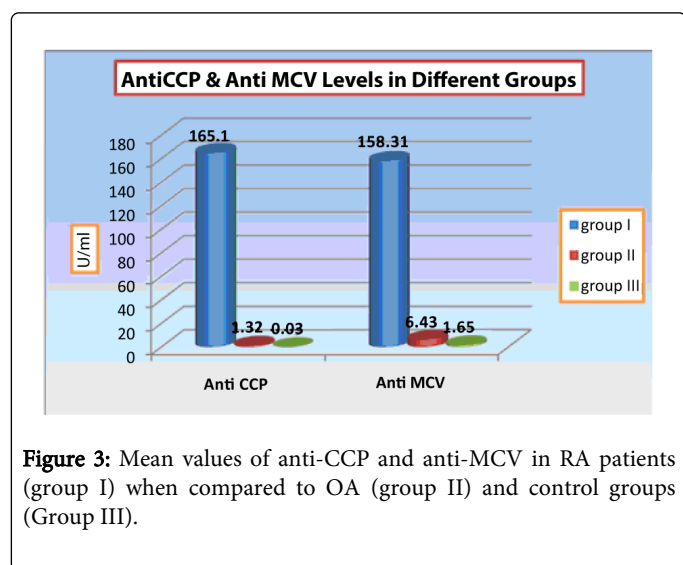
Figure 3: Mean values of anti-CCP and anti-MCV in RA patients (group I) when compared to OA (group II) and control groups (Group III).
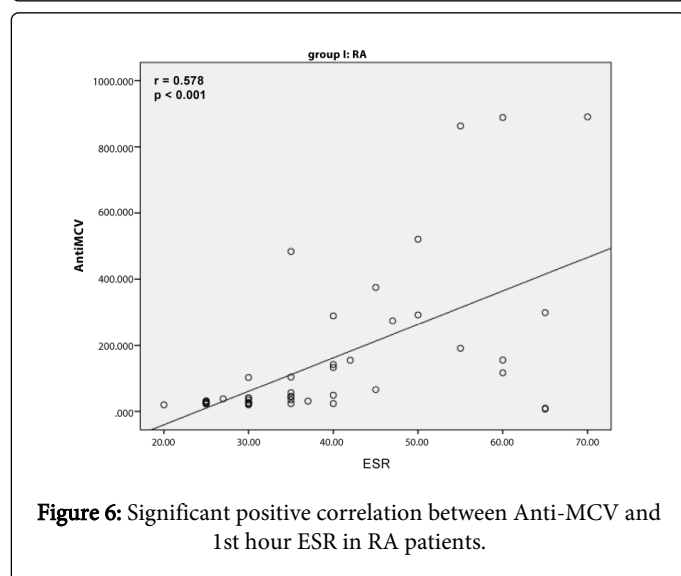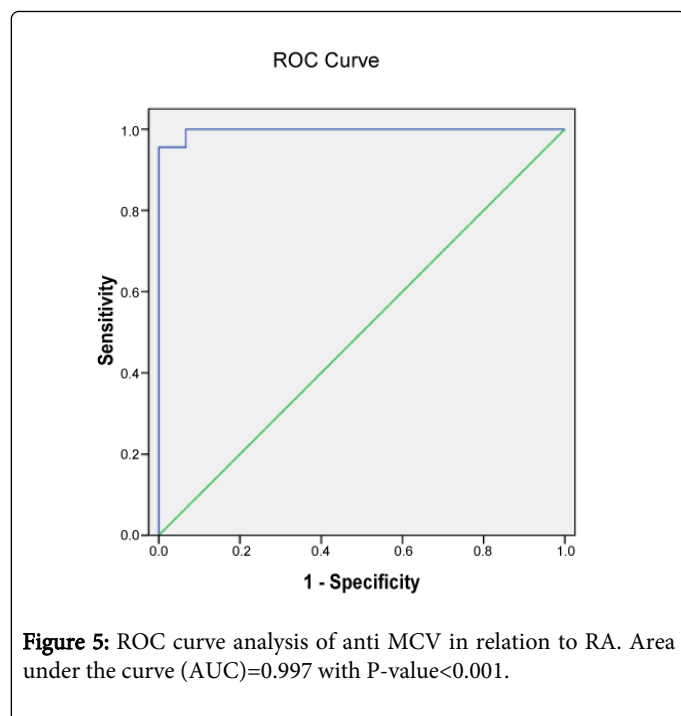

Figure 4: Significant positive correlation between Anti-CCP and Anti-MCV in RA patients.

There were statistically significant higher levels of Anti-CCP and anti-MCV in RF positive patients when compared to RF negative patients (P-values=0.005 and 0.011 respectively), while, there was no significant difference between positive and negative CRP patients in group I regarding serum levels of anti-CCP and anti-MCV (P-values=0.407 and 0.776 respectively).

The optimum diagnostic cut-off point when value of anti-MCV was >27.5 u/ml at which Sensitivity was 99.1, Specificity was 93.3, PPV was 97.8 and NPV was 99.8. The AUC (area under the curve) value for anti-MCV was 0.997 with accuracy of 97%.

The optimum diagnostic cut-off value of anti-CCP was >20 u/ml at which Sensitivity was 76, Specificity was 100, PPV was 100 and NPV was 58. The AUC (area under the curve) value for anti-CCP was 0.993 with accuracy of 82%.

Combined anti-CCP and anti-MCV testing gave us a higher Sensitivity value of 100, Specificity=100, PPV=100 and NPV=100 with accuracy of 100%.

Cutoff points	Sensitivity	Specificity	PPV	NPV
>20.2	97.3	48.2	80.5	95.2
>22.5	98.1	53.3	86.5	98.3
>24.2	98.7	80.4	93.7	98.5
>27.5	99.1	93.3	97.8	99.8
>30.7	95.5	98.5	98.3	88.2
>33.2	93.3	98.9	99.1	83.3

Table 3: Sensitivity, Specificity, PPV, and NPV of anti-MCV in RA patients at different points of cut-off, value of >27.5 represents the highest sensitivity of anti MCV test.

Figure 5: ROC curve analysis of anti MCV in relation to RA. Area under the curve (AUC)=0.997 with P-value<0.001.

Figure 6: Significant positive correlation between Anti-MCV and 1st hour ESR in RA patients.

Group I (n=45)	Anti CCP		Anti MCV	
	r	P	r	P
RF	0.423	0.004*	0.125	0.413
CRP	0.381	0.010*	0.043	0.780

Table 4: RF and CRP correlations to Anti-CCP and Anti-MCV in RA patients group.

Non parametric correlation (spearman correlation) showed significant positive correlations between anti CCP with RF and CRP, while no significant correlations were found between anti MCV with RF and CRP in RA patients group.

Discussion

Rheumatoid arthritis (RA) is the most common inflammatory joint disease, affecting 0.5% –1% of the world population. Increasing evidence shows that therapeutic intervention early in the course of RA results in more efficient disease control, less joint damage and better prognosis of disease outcome. Rheumatoid factor (RF), the first autoantibody correlated with RA, is directed at the Fc region of IgG and is usually IgM isotype. It is the commonly accepted and widely used serologic test for RA; however, it is not specific in diagnosing early RA because it may be present in healthy elderly persons or in patients with other autoimmune and infectious diseases [12].

Anti-CCP is considerable motivation to accurately diagnose RA in patients with inflammatory arthritis early in the course of disease. It was significantly associated with some parameters of both disease activity and severity [13]. Anti-CCP assays are effective and widely used for diagnosing RA, however, their sensitivity is limited in patients with early RA [14]. CCP is not expressed in the synovium, and citrullinated proteins expressed in the rheumatoid joint would probably be more relevant as targets of auto-antibodies used to diagnose RA. Citrullinated vimentin is present in synovial membranes and is released in increased amounts in response to growth factors and pro inflammatory cytokines, suggesting its involvement in the pathophysiology of RA [15].

The present study focuses on the level of anti-MCV in patients with early RA. In addition, sensitivity and specificity of the anti-MCV test were determined in patients with RA. This study included 75 subjects; 45 patients diagnosed as RA, 15 patients complain from osteoarthritis and 15 apparently healthy persons as control group. Our results showed significant difference in the age between the OA, RA patients and the control group (P value<0.001), also, our study showed that RA are more likely to occur between middle and old age. This result was in agreement with the results of Elbordeny et al., [16], El-barbary et al., [17] and Abdul Wahab et al., [18] who reported similar results regarding earlier onset of RA and that OA increases progressively with age at all joint sites.

There was no difference regarding patients sex in RA and OA groups as both prevail mainly in female patients (82.2% and 93.3%), this can be attributed to changes in sex hormone levels which may play a role in the development of RA and OA [19,20]. Studies conducted by several investigators reported similar results as current study in term of RA is mainly affecting middle age group and female is the predominant gender [21,22].

In the preset study, RF was mainly positive in patients with RA (57.8%), while in all OA patients RF was negative. This result was in agreement with the result of Shukaili et al., [1] who found that 59% of RA patients were positive for RF.

The levels of anti-MCV and anti-CCP were significantly higher in RA patients when compared with their levels in OA and control groups (P value<0.001). This was in agreement with the results of Abou el-Fetouh and Abo zaid, [23]. This can be explained by the hypothesis that vimentin might trigger the initial immune response in RA [24]. It activates T lymphocytes by binding to HLA-DR4 on the surface of antigen presenting cells and may contribute to certain pathways in the pathogenesis of RA. Several studies demonstrated significant elevation in serum anti-MCV in RA patients versus controls [25].

Nugraha et al., [26] showed that values of anti-MCV can be used for diagnosing rheumatoid arthritis in anti-CCP-negative patients. So anti-MCV is superior in comparison to anti-CCP.

In our study, specificity of anti-MCV at the cutoff value of 20.2 U/ml was 48.2%. Then we compared sensitivity at values of 24.2 U/ml and 27.5 U/ml respectively and we found these values has advantages on sensitivity and NPV, while the latter was slightly better on specificity (93.3%) and PPV (97.8%) (high specificity means that a positive result markedly increases the probability that the patient will have RA). That is why the best cutoff value was obtained at the level of 27.5 U/ml and the Area Under the Curve (AUC) was 0.997. These results were in agreement with the result of Rulin et al., [27] who found the specificity at the cutoff value of 20 U/ml was only 45.6%. The cutoff value of 30 U/ml has advantages on sensitivity (78.2%) and NPV (77.4%) while specificity was 93.4% and PPV 93.7%. Moreover, the best Youden's index was obtained at the cutoff value of 30 U/ml. Nugraha et al., [26] have revealed that anti-MCV has good specificity of more than 93.75% in rheumatoid arthritis. Anti-MCV is produced earlier than anti-CCP in the course of the synovial and joint damage.

In the current study, significant positive correlation was found between anti-MCV and anti-CCP in patients with RA (P value<0.001). This was in agreement with study of Khalifa et al., [7] who reported same significant correlations between anti-CCP and anti-MCV antibodies. This was explained by what is documented by Engelmann et al., [28]; the cross-reactivity experiments between anti-MCV and anti-CCP antibodies indicate that anti-MCV and anti-CCP target some shared epitopes which may explain the high positive correlation between these antibodies. Several studies by Mutlu et al., [29] and El Shazly et al., [30] reported same high significant positive correlations between anti-MCV levels and anti-CCP. Other studies reported a strong correlations between levels of anti-MCV and clinical parameters (number of swollen joint, disease activity and DAS-28) making anti-MCV a better prognostic marker for future radiographic changes [31-33].

In RA patients, there was significant positive correlation between RF and anti-CCP (P value=0.004) this result was in agreement with the result of Abdul Wahab et al., [18] who found that anti-CCP is positively correlated with RF (P<0.001) and in agreement with the result of Greiner et al., [34] who found weak but significant linear correlation between anti-CCP and RF (r=0.2, P=0.03).

In the present study, no significant correlation was found between RF and anti-MCV (P value=0.413). This was in contrary with, Al-Shukaili et al., [1] who reported significant positive correlation between Anti-MCV and RF (P value=0.040). This may be due to difference in the methods used in both studies. CRP results were positive in only 35.6% of RA group. This result was in accordance with Al-Shukaili et al., [1] who found only 16% of RA patients are positive for CRP.

Significant positive correlation was found between anti-MCV and 1st hour ESR (P value<0.001) in RA group. This was in agreement with Ursum et al., [5] who reported that anti-MCV antibodies are correlated with disease activity parameters such as erythrocyte sedimentation rate and serum C-reactive protein, also, there were significant positive correlations between levels of anti-CCP antibodies, CRP and ESR in RA patients (P value=0.010 and<0.001) respectively.

In conclusion, our results for anti-MCV antibodies were comparable with other reported results in RA patients. Generally, anti-MCV antibodies appear to be a very useful diagnostic test for RA.

Anti-MCV is a good marker for early diagnosis of RA with higher sensitivity and specificity when compared to other markers. The use of Anti-MCV and Anti-CCP collectively give the best result for the diagnosis of rheumatoid disease.

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