

Predictive Value of Mean Platelet Volume and Red Blood Cell Distribution in Chronic Brucellosis

Kronik Bruselloz Hastalarında Ortalama Trombosit Hacmi ve Kırmızı Kan Hücre Dağılımının Prediktif Değeri

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SUMMARY

Introduction: Brucellosis is an inflammatory disease capable of infecting any organ and system in the body. Mean platelet volume (MPV) serves one of the most commonly used surrogate markers of platelet function. It has been shown that MPV reveals the existence of disease activity in a great number of inflammatory diseases. Red blood cell distribution (RDW) serves as a measure of the heterogeneity of the sizes of the circulating red blood cells. Its predictive value for inflammatory and infectious diseases has been proved. The aim of this study was to investigate whether MPV and RDW could have any role in the diagnosis of cases with osteoarticular involvement or relapsed brucellosis.

Materials and Methods: The present study was carried out by prospectively examining the inflammatory markers detected in adult patients with brucellosis between 2008 and 2014. Their follow-ups in the year after treatment were also examined.

Results: The study included two hundred and fifty patients in the acute brucellosis group and 101 patients in the control group, adding up to a total of 351 subjects. In the relapsed brucellosis group the mean MPV and RDW values were 7.52 ± 1.18 fL and $16.24 \pm 1.91\%$, respectively, while they were 7.77 ± 1.52 fL and $15.95 \pm 1.55\%$, respectively in the control group ($p < 0.001$). No significant difference was found in the osteoarticular involvement group when compared to the controls.

Conclusion: The study revealed that MPV, RDW and blood leukocyte count values in patients with relapsed brucellosis and with osteoarticular involvement were within normal limits and comparable with the control group. In cases of brucellosis with osteoarticular involvement, the most valuable inflammatory marker is still the CRP value.

Key Works: Brucellosis; C-reactive protein; Mean platelet volume; Erythrocytes

ÖZET

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Giriş: *Brucella* vücutta herhangi bir organ ya da sistemi infekte edebilen inflamatuvar bir hastalıktır. Ortalama trombosit hacmi (MPV), trombosit işlevini gösteren en sık kullanılan belirteçtir. Çok sayıda inflamatuvar hastalıkta, MPV'nin hastalık etkinliğini gösterdiği saptanmıştır. Kırmızı kan hücresi dağılımı (RDW) dolaşımdaki kırmızı kan hücrelerinin çeşitliliğinin bir ölçütü olarak kullanılır, inflamatuvar ve infeksiyon hastalıklarında öngördürücülüğü gösterilmiştir. Çalışmamızın amacı; osteoartiküler tutulumu olan ve relaps görülen bruselloz olgularında MPV ve RDW'nin tanısasal rolünün araştırılmasıdır.

Materyal ve Metod: Bu çalışmamızda 2008-2014 yılları arasında bruselloz tanısı koyulan yetişkin hastalarda saptanan inflamatuvar belirteçler prospektif olarak değerlendirilmiştir. Ayrıca tedaviden bir yıl sonraki takipleri de incelenmiştir.

Bulgular: Bu çalışmada, akut bruselloz geçiren 250 hasta ve 101 sağlıklı erişkin kontrol grubu incelenmiş olup toplam 351 kişi çalışmaya alınmıştır. Relaps görülen bruselloz hastalarının MPV ve RDW değerleri sırasıyla 7.52 ± 1.18 fL ve $16.24 \pm 1.91\%$ iken kontrol grubunda 7.77 ± 1.52 fL ve $15.95 \pm 1.55\%$ bulunmuştur ($p > 0.001$). Osteoartiküler tutulum olan grupta kontrol grubuna göre anlamlı fark saptanmamıştır.

Sonuç: Çalışmamızda relaps bruselloz geçiren hastalar ve osteoartiküler tutulumu olan hastalarda MPV, RDW ve kan lökosit sayısı normal sınırlarda ve kontrol grubuyla uyumlu idi. Relaps bruselloz ve osteoartiküler tutulumlu bruselloz olgularında bir inflamatuvar belirteç olarak CRP daha değerlidir.

Anahtar Kelimeler: Bruselloz; C-reaktif protein; Ortalama trombosit hacmi; Eritrositler

INTRODUCTION

Brucellosis, a zoonotic disease encountered often in developing countries, poses an important public health problem. Brucellosis is an inflammatory disease capable of infecting any organ or system in the body. It is diagnosed by examining the clinic of the patient as well as the serological and cultural test results^[1].

The acute phase reactants increase as a consequence of the inflammatory process in brucellosis^[1,2]. However, laboratory conditions available in endemic regions may not always prove suitable or sufficient for diagnosis. Since the second antibody titer may turn out to be high in the follow-up, it becomes difficult to decide whether to stop or continue the medical treatment^[1]. Therefore, employing additional methods of diagnosis during the follow-up process may be useful. Among the most commonly employed markers of infection in cases of brucellosis are leukocyte count and high sensitive C-reactive protein (hs-CRP). In addition to these markers, the present study investigated if the values of mean platelet volume (MPV) and red blood cell distribution (RDW) could be used as surrogate markers during the disease.

MPV constitutes a measure of platelet size generated by full blood count analyzers. Although it is a part of the routine complete blood count test cycle, it mostly remains overlooked by clinicians^[3]. MPV is one of the most commonly employed surrogate markers of platelet function revealing inflammatory burden and disease activity in various diseases such as preeclampsia, acute pancreatitis, unstable angina, myocardial infar-

ction, and cases of systemic inflammation like ulcerative colitis and Crohn's disease^[4].

RDW constitutes a measure of heterogeneity in the size of circulating red blood cells and is one of the components of the standard complete blood count. It is calculated in the form of a percentage by dividing the standard deviation of the red cell volume by the mean corpuscular volume. Additionally, its predictive value for inflammatory and infectious pathological diseases such as acute pancreatitis, inflammatory bowel disease, coronary artery disease, bacteremia, sepsis, and septic shock has already been demonstrated^[5]. Lippi et al. have reported the existence of a graded association of RDW with hs-CRP and erythrocyte sedimentation rate, an association which is independent of various confounding factors^[6].

Alongside inflammation, oxidative stress is also capable of contributing significantly to anisocytosis. While erythrocytes have considerable antioxidant capacity and function as the chief "oxidative sink", they are susceptible to oxidative damage which reduces cell survival^[7]. A population-based study reported that high RDW was independently associated with poorer pulmonary function, which was associated with oxidative stress^[8]. In the studies published thus far, a correlation of MPV and RDW with CRP in patients with osteoarticular involvement or relapsed brucellosis was not encountered. The purpose of the present study was to explore the value of MPV and RDW (alongside routine inflammatory markers) among brucellosis patients in distinguishing inactive ones from relapsed and osteoarticular involvement.

MATERIALS and METHODS

This study was conducted prospectively in Baskent University Konya Training and Research Center. Amongst the two hundred and fifty patients diagnosed with acute brucellosis in our hospital, 58 patients with relapse and 92 patients with osteoarticular involvement were assessed prospectively, while the control group consisted of 101 individuals selected from healthy check-up patients. The study was accepted by the Local Ethics Committee of Baskent University and the written consent of each patient was obtained in accordance with the Helsinki Declaration (KA08/198).

The study included patients over 18 diagnosed with brucellosis and followed up between 2008 and 2014. The clinic of patients with brucellosis revealed the presence of high fever, chills, shivering, fatigue, sweating, and muscle and joint aches. In cases with joint aches, the diagnosis of osteoarticular involvement was made radiologically. Their laboratory and serological checks were carried out. The patients included in the assessment were those with an agglutination titer $\geq 1/160$ positive and those with a growth of *Brucella* spp. in their blood culture. The patients in the study were administered a treatment of doxycycline (6 weeks), rifampicin (6 weeks), or streptomycin (21 days). The *Brucella* tube agglutination test results of the patients in the control group were negative. Their ESR and CRP levels were normal, and they had no complaints. The hemogram and high-sensitive C-reactive protein (hs-CRP) levels of the patients were compared with those of the control group. Those patients having abnormal renal and liver function test results or other inflammatory conditions and infectious diseases were excluded from the study.

Laboratory Measurements

Following a night of fasting, the blood samples were obtained. The analysis of the blood samples was carried out in the hematological laboratory of our hospital in standard tubes containing 2 mL of blood and 0.04 mL of the 7.5% K3 salt of ethylenediaminetetraacetic acid (EDTA). As it was possible for the MPV values to increase under the influence of EDTA, the necessary measurements were made within two hours^[9]. Afterwards, the serum samples were separated from cells by centrifuging them at 3000 rpm for ten minutes. The diagnoses of Brucellosis were made with the

standard tube agglutination test ($\geq 1/160$). An electronic cell counter (Cell-Dyne 3700, Abbott, Abbott Park, IL, USA) was used to determine the white blood cell (WBC) counts.

To analyze the hematological parameters, i.e. hemoglobin (Hb, range 14-18 g/dL for men, 12-16 g/L for women), white blood cell (WBC, range $4.5-11 \times 10^9/L$), platelet count (PLT, range $150-400 \times 10^9/L$), MPV (range 7-12 fL) and RDW (range 11.6-15.5%), standard methods with a time-to-result of approximately 5 min. were used. The threshold levels of CRP ranged between 0-10 mg/dL. In order to measure the acid (EDTA) and serum CRP levels, spectrophotometric methods (Abbott Aeroset, Tokyo, Japan) were used.

Statistical Analysis

Statistical analyses were made using the SPSS software. In the comparison of the groups, *t* test was used for continuous variables and chi-square test for categorical variables. Mann-Whitney *U* test was used in comparing nonhomogeneous groups in pairs. In order to detect the correlation between MPV and the other variables, a simple correlation test (Pearson's test) was used. The form mean \pm SD was used to express the numeric values. All values of $p < 0.05$ were accepted to be statistically significant.

RESULTS

The study included two hundred and fifty patients in the acute brucellosis group and 101 patients in the control group, adding up to a total of 351 subjects. Among the 250 patients with acute brucellosis who were followed up, the number of patients with a relapse was 58 (23%); 20 of them were male and 38 were female patients. In the control group, there were 50 male and 51 female patients. It was observed that the ratio of relapse was higher among female patients with brucellosis. Nevertheless, no statistically significant difference was detected in this regard. The total number of the patients with osteoarticular involvement was 92 (48 females and 42 males). No statistically significant difference was observed between the genders in cases of osteoarticular involvement. Generally, no significant difference was found between the acute brucellosis (AB) patients and controls regarding age and gender ($p > 0.05$) (Table 1).

In Patients with Acute Brucellosis and Relapse

The leukocyte count turned out to be significantly lower in the relapse (R) group ($p < 0.05$). Thus, the leukocyte count in the relapsed patients was found to be lower than that of the control group. The difference in between was found to be statistically significant.

The CRP level in the R group turned out to be significantly higher when compared to the control group ($p < 0.05$).

In comparison with the control group, the MPV level was not observed to be significantly higher in the R group ($p > 0.05$) (Table 2). In comparison with the control group, the RDW level was not significantly higher in the R group ($p > 0.05$) (Table 1). When the MPV and RDW values in the post-treatment period was compared with the control group, no statistically significant difference was detected (Tables 1,3).

In Patients with Osteoarticular (OA) Involvement

In comparison with the control group, the leukocyte count was not significantly higher in the osteoarticular (OA) involvement group ($p > 0.05$) and in comparison with the control group, the CRP level in the OA involvement group was significantly higher ($p < 0.05$). Additionally, in comparison with the control group, the MPV level was not significantly higher in the OA involvement group ($p > 0.05$) (Table 1) and in comparison with the control group, the RDW level was not significantly higher in the OA involvement group ($p > 0.05$) (Table 2,3).

Considering these results, it was observed that there was no difference between relapsed brucellosis patients and controls regarding CRP; however, this value was higher in patients with osteoarticular involvement. Compared to the controls, no statistically significant difference was observed in patients

Table 1. Comparison of the demographic features and the leukocyte count, CRP, MPW and RDW values of relapsed brucellosis patients and healthy controls

	Relapse brucellosis (R) (n= 58)	Control group (n= 101)	p	
Age (y)*	51.72 ± 14.20	50.61 ± 16.80	$p > 0.05$	0.159
Male/female	20/38	50/51	$p > 0.05$	0.064
Leukocyte (mm ³)*	6.73 ± 1.65	7.40 ± 1.97	$p < 0.05$	0.024
CRP (mg/L)*	9.95 ± 16.64	4.77 ± 4.90	$p < 0.05$	0.027
MPV (fL)*	7.52 ± 1.18	7.77 ± 1.52	$p > 0.05$	0.269
RDW (%)*	16.24 ± 1.91	15.95 ± 1.55	$p > 0.05$	0.328

* Values are in the form mean ± standard deviation.

CRP: C-reactive protein; MPV: Mean platelet volume; RDW: Red blood cell distribution.

Table 2. Comparison of the demographic features and the leukocyte count, CRP, MPW and RDW values of acute brucellosis patients with osteoarticular involvement and healthy controls

	Brucellosis with osteoarticular (OA) involvement (n= 92)	Control group (n= 101)	p	
Age (y)*	49.78 ± 17.18	51.51 ± 15.64	$p > 0.05$	0.644
Male/female	44/48	50/51	$p > 0.05$	0.817
Leukocyte (mm ³)*	7.21 ± 2.37	7.40 ± 1.97	$p > 0.05$	0.558
CRP (mg/L)*	27.54 ± 42.97	4.81 ± 4.89	$p < 0.05$	0.001
MPV (fL)*	7.68 ± 1.42	7.67 ± 1.29	$p > 0.05$	0.955
RDW (%)*	16.03 ± 1.84	15.90 ± 1.45	$p > 0.05$	0.586

* Values are in the form mean ± standard deviation.

CRP: C-reactive protein; MPV: Mean platelet volume; RDW: Red blood cell distribution.

Table 3. Comparison of the demographic features and the leukocyte count, CRP, MPV and RDW values of the patients with relapsed brucellosis and osteoarticular involvement in the first-year follow-up

	Relapsed brucellosis in the first-year follow-up (n= 90)	Osteoarticular involvement in the first-year follow-up	p
Leukocyte (mm ³)*	7.20 ± 2.03	6.83 ± 2.10	p> 0.05
CRP (mg/L)*	4.86 ± 6.95	6.63 ± 11.41	p> 0.05
MPV (fL)*	7.44 ± 2.00	7.87 ± 1.91	p> 0.05
RDW (%)*	16.17 ± 1.66	15.99 ± 1.88	p> 0.05

* Values are in the form mean ± standard deviation.

CRP: C-reactive protein; MPV: Mean platelet volume; RDW: Red blood cell distribution.

with osteoarticular involvement regarding leukocyte, MPV and RDW values (Tables 1,2). When MPV, RDW, CRP and leukocyte values of the patients with relapse and osteoarticular involvement were compared with the same values a year after the treatment, it was observed that the values were within the normal range and displayed no statistically significant difference (Table 3). It was found that the leukocyte count and gender were correlated in the relapsed brucellosis patients ($r = -0.309$ $p = 0.015$; $r = -0.125$, $p = 0.049$ respectively). Similarly, it was observed that CRP was correlated with gender and RDW with MPV ($r = -0.260$ $p = 0.045$; $r = -0.259$, $p = 0.044$ respectively). In brucellosis patients with osteoarticular involvement, no statistically significant correlation was found among the parameters age, gender, and leukocyte count, CRP, RDW and MPV.

DISCUSSION

Brucellosis is a zoonotic systemic inflammatory disease seen especially in the Mediterranean region^[10]. While laboratory tools like culture and serology can be used for diagnosing Brucellosis, certain difficulties are still encountered in diagnosis and monitoring the degree of the therapy's success. In endemic areas; however, difficulties may arise in classifying acute, chronic and recurrent cases of brucellosis^[1].

Mild anemia and leukopenia are commonly encountered conditions in brucellosis, while isolated thrombocytopenia and pancytopenia are less frequent. These complications are usually linked to acute infection^[5]. It has been suggested in some previous studies that an elevated WBC count is usually the first laboratory measure to indicate the presence of inflammation and leukocytosis^[11,12]. In

this present study, it was observed that the leukocyte count in patients with relapse and osteoarticular involvement were within the normal range.

CRP is a sensitive acute-phase protein which tends to increase in all acute inflammatory processes and therefore lacks specificity. Its concentration increases in direct proportion to the duration and extent of the inflammation. In acute Brucellosis cases, there is an increase in CRP returning to normal values after treatment. Thus, CRP can be considered a good marker of diagnosis and monitoring the success of therapy^[13-15]. High levels of CRP found in patients with relapse and osteoarticular involvement in our study reveal that it continues to be a highly valuable inflammatory marker.

The role played by platelets in the pathophysiology of Brucellosis has not been clarified yet. In this respect, the main purpose of our study was to compare the MPV and RDW values of Brucellosis patients with relapse and osteoarticular involvement, both in the acute and post-treatment phases of the disease, with the control group data. MPV is considered an important marker of platelet activation. Furthermore, MPV is correlated with the degree of platelet activation and inflammatory response. Various studies in the literature have reported that changes in MPV are linked to chronic inflammation and infectious diseases. Platelet distribution width (PDW) is a direct measure of the variability in platelet sizes. MPV is multiplied by PLT to calculate platelet mass (PM), a measure of the total platelet mass in blood^[5]. MPV, which constitutes the most commonly used measure of platelet size, is a simple marker of platelet function and activation^[16].

The size of the platelets is decided at the level of the progenitor cell (megakaryocyte). Previous studies have shown that cytokines, including IL-3 and IL-6, influence megakaryocyte ploidy and might induce the production of larger and more reactive platelets^[5]. As a result, platelet volume has been considered to constitute an indirect indicator of increased platelet reactivity. Activated platelets release antibacterial peptides as well; however, the existing evidence indicates that certain pathogens may have grown capable of taking advantage of activated platelets, binding to their surfaces to start or spread an infection^[14,15]. Furthermore, some previous studies indicate that changes in MPV are linked with various non-infectious inflammatory processes, an association suggesting that MPV changes could reveal disease activity in inflammation^[17-19]. Compared to other markers of inflammation, the overall accuracy of MPV in predicting diseases is reported to be superior in the literature. Another point of significance is the correlation of MPV with CRP. The main cause of the decreased MPV levels in Brucellosis remains unclear, but IL-1, IL-6, thrombopoietin and cytokines are known to have an important role in the regulation of megakaryocyte ploidy and platelet number^[20-22].

To our knowledge, this is the first study to report decreased MPV levels in brucellosis in comparison with healthy controls. As pointed out before, compared with other inflammation markers, MPV is generally of superior accuracy in predicting diseases. Although MPV was thus a guiding parameter for diagnosis and treatment in several previous studies, we found in the present study that it could not serve as a surrogate inflammatory marker in cases of relapsed brucellosis and brucellosis with osteoarticular involvement^[4,5,15,17-19,23-25]. While examining the values of the 58 relapsed brucellosis patients and the 92 patients with osteoarticular involvement who were followed up in the last decade, we did not find any statistically significant differences in the MPV values when compared with the controls. In one of the two comparable studies in the literature, Ozturk et al. investigated the MPV values of 39 patients. They found it to be 7.84 ± 1.15 fL in the acute phase and 7.83 ± 0.9 fL in the post-treatment phase^[1]. Although these figures remained within the normal range, the researchers

noticed a significant difference between them and the MPV values of the controls. In the other study conducted by Küçükbayrak et al. with 40 brucellosis patients, the mean MPV value was $7.58 + 1.96$ fL at the beginning of the therapy and $7.90 + 1.96$ fL in the end. While all the values remained within the normal range, they demonstrated that the pre- and post-treatment values were significantly different from each other^[5]. Apart from the issue of the existence of statistically significant differences between the MPV values in the patient and the control groups, the MPV values in our own prospective study disagreed with the results found in these two studies.

According to the results of the study by Lippi et al., there was a graded association of RDW with high-sensitivity C-reactive protein and erythrocyte sedimentation rate, which was independent of various confounding factors^[6]. Along with inflammation, oxidative stress may also contribute significantly to anisocytosis. Although erythrocytes possess a significant antioxidant capacity and function as the main "oxidative sink," they are liable to oxidative damage leading to a reduction in cell survival^[26]. In the study by Küçükbayrak et al., high RDW levels were reported in brucellosis patients prior to and after treatment; however, in this study we observed that the RDW values were within the normal range prior to and after therapy, and compared with the control group they did not display any differences of statistical significance^[5]. Thus, this study showed that RDW did not act as a marker in the treatment and follow-up of brucellosis patients. Although MPV and RDW are easily analyzed at low cost, the results in this study have shown that these two parameters have no place in the diagnosis of relapsed brucellosis or in the follow-up of brucellosis cases with osteoarticular involvement.

Compared to other studies about the inflammatory markers of MPV, RDW, leukocyte count and CRP in cases of brucellosis, the present study is the first one to include a considerably large group of patients. The present study has demonstrated that MPV and RDW do not serve as surrogate markers in the diagnosis, treatment, and follow-up of brucellosis. Thus, high levels of CRP still constitute the most valuable marker in the treatment and follow-up of patients with brucellosis. On the other hand, WBC was observed to be a significant inflammatory marker in cases of relapsed brucellosis.

The results of the literature on this subject remain controversial since most have been obtained from patient groups of limited size. On the other hand, the present study has been conducted on the most numerous patient group so far and it is still the only prospective study. Nevertheless, there is still some possibility that MPV and RDW may serve as guiding parameters for the diagnosis of brucellosis. To clarify this issue, we believe that further prospective and multicenter studies with a larger sample size are needed.

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