

# The Impact of Acute Brucellosis on Mean Platelet Volume and Red Blood Cell Distribution

Turhan Togan<sup>1,\*</sup>; Huseyin Narci<sup>2</sup>; Hale Turan<sup>1</sup>; Ozgur Ciftci<sup>3</sup>; Ebru Kursun<sup>1</sup>; Hande Arslan<sup>1</sup>

<sup>1</sup>Department of Infectious Diseases and Clinical Microbiology, Baskent University, Ankara, Turkey

<sup>2</sup>Department of Emergency Medicine, Baskent University, Ankara, Turkey

<sup>3</sup>Department of Cardiology, Baskent University, Ankara, Turkey

\*Corresponding author: Turhan Togan, Department of Infectious Diseases and Clinical Microbiology, Selcuklu, Turkey. Tel: +90-3322570606, E-mail: drtogan@gmail.com

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**Background:** Brucellosis is an inflammatory disease which may infect any organs or systems in the body. Mean Platelet Volume (MPV) is one of the most frequently used surrogate markers of platelet function. It reveals the presence of disease activity in many inflammatory diseases. Red blood cell distribution width (RDW) is a parameter that measures variation in red blood cell size or red blood cell volume. Its predictive value approves inflammatory and infectious diseases.

**Objectives:** The current study aimed to determine the assessment levels of red blood cell distribution in cases with acute brucellosis.

**Patients and Methods:** The current study investigated whether MPV and RDW played any roles in acute brucellosis diagnosis. The study was conducted from 2008 to 2014 through prospective examination of the inflammatory markers found in adult patients with acute brucellosis.

**Results:** The follow-up within the year after treatment was examined. The values of age, gender, leukocyte count, C-reactive protein, RDW and MPV were recorded. The study included 351 subjects, 250 of them in the acute brucellosis group and 101 in the control group. The mean MPV levels were  $7.64 \pm 1.30$  fL, and  $7.67 \pm 1.29$  fL in the acute brucellosis and control groups, respectively ( $P > 0.05$ ). The mean CRP levels were  $32.57 \pm 53.20$  mg/dL, and  $4.81 \pm 4.89$  mg/dL in the acute brucellosis and control groups, respectively ( $P < 0.05$ ). There was no statistically significant difference between the two groups regarding the RDW level and the mean leukocyte count ( $P > 0.05$ ).

**Conclusions:** While the CRP value was in patients with acute brucellosis in the current study, the MPV, RDW and leukocyte counts were within the normal range. CRP value remains the most valuable inflammatory marker in cases of acute brucellosis.

**Keywords:** C-Reactive Protein; Mean Platelet Volume; Red Cell; Distribution; Brucellosis

## 1. Background

Brucellosis is a frequently encountered zoonotic disease in the developing countries, and considered as an important public health problem. People can be contracted especially through contaminated meat, milk, and dairy products as well as direct contact with the excrements or body secretions of the infected animals. *Brucella* spp. are small, Gram-negative, facultative, intracellular, and pathogenic bacteria; they invade mononuclear phagocytic system cells and proliferate there. Brucellosis is an inflammatory disease that can infect any organs or systems in the body. It is diagnosed through the clinical, serological, and microbiological test results of the patients (1). The acute phase reactants increase as a result of the inflammatory process in brucellosis (1, 2). In endemic regions; however, the laboratory conditions may not always be suitable or sufficient for diagnosis. Since the second antibody titer, assessed in the follow-up after treatment, may remain at a high level, it is difficult to decide whether to stop or continue the medical treatment (1). Therefore, authors believe that additional diagnosis methods may be useful in the follow-up process. Leuko-

cyte count and high sensitive C-reactive protein (hs-CRP) are frequently used as inflammatory markers in patients diagnosed with brucellosis.

Besides these markers, the current study investigated whether the values of mean platelet volume (MPV) and red blood cell distribution (RDW) could be considered as surrogate markers during the illness phase. Mean platelet volume (MPV) is a measure of platelet size. As part of the routine complete blood count test cycle, MPV is generated by full blood count analyzers but mostly overlooked by clinicians (3). MPV is one of the most commonly used surrogate markers of platelet function. Comparing with small platelets, large ones contain more granules, aggregate with collagen more quickly, have higher thromboxane A2 levels, and express more glycoprotein Ib and IIb/IIIa receptors (4-6).

It reveals the presence of inflammatory burden and disease activity in many diseases including preeclampsia, acute pancreatitis, unstable angina, myocardial infarction, and cases of systemic inflammation such as ulcerative colitis and Crohn's disease (7). As for RDW,

it is a measure of heterogeneity in the size of circulating red blood cells. It is one of the standard complete blood count components, and is calculated as a percentage by dividing the standard deviation of the red cell volume by the mean corpuscular volume. Various studies revealed the clinical implications of RDW about the presence of various pathologies such as inflammatory bowel disease, celiac disease, pulmonary embolism, and coronary artery disease. Moreover, inflammatory and infectious pathological diseases such as acute pancreatitis, bacteremia, sepsis, and septic shock are proven as predictive values (8). In a study by Lippi et al. (9), a graded association of RDW with hs-CRP and erythrocyte sedimentation rate were reported, independent of various confounding factors.

Besides inflammation, oxidative stress may also make a significant contribution to anisocytosis. Although erythrocytes possess a great antioxidant capacity and regularly serve as the chief oxidative sink, they are liable to oxidative damage which reduces cell survival (10). According to a population-based study (11), higher RDW were independently associated with poorer pulmonary function. Nevertheless, it still unknown whether RDW is a simple marker and not a mediator of carotid artery atherosclerosis. Indeed the discovery of a putative causative mechanism is prevented by the lack of epidemiological studies which would reveal the presence of an association between atherosclerosis and anisocytosis.

## 2. Objectives

Among the studies published to date, we encountered a single prospective study that examined the MPV, RDW and hs - CRP values of patients with acute brucellosis and those convalescing from brucellosis. The current study aimed to investigate the MPV, RDW, and CRP values as inflammatory markers of the disease (8).

## 3. Patients and Methods

This prospective study was carried out in Baskent University Konya Application and Research Center. The data of 250 patients diagnosed with in the university hospital, together with the data of 101 healthy controls were assessed. The study was approved by the Local Ethics Committee of Baskent University, and in conformity with the Helsinki Declaration, all patients signed the informed consents (KA08/198).

The study evaluated 88 patients with the history of acute brucellosis who were in their first first-year follow-up. The study included patients over the age of 18 diagnosed with brucellosis and followed-up from 2008 to 2014. In the clinic, the patients diagnosed with brucellosis had high fever, chills, shivering, fatigue, sweating, and muscle and joint aches. The microbiological and serological tests were performed on subjects' blood samples. Those with an agglutination titer  $\geq 1/160$  and/or *Brucella spp.* culture growth were considered as positive. The patients

participating in the study were treated with doxycycline (six weeks), rifampicin (six weeks), or streptomycin (21 days). The CRP level of the subjects was normal, and they did not have any complaints. The leukocyte counts and the MPV, RDW and high sensitive C-reactive protein (hs-CRP) values of the patients were compared with those of the controls. The study excluded patients with abnormal renal and liver function test results or with other infectious diseases and inflammatory conditions.

### 3.1. Clinical Measurements

Blood samples were analyzed in the hematological laboratory of the hospital, using standard tubes containing 2 mL blood and 0.04 mL of 7.5% K3 salt of ethylene di amine tetra acetic acid (EDTA). Since the MPV values could have increased under the influence of EDTA, the measurements were performed within two hours (12). Afterwards, the serum samples were separated from the cells by placing them in the centrifuge for ten minutes at 3000 rpm. The patients were diagnosed with brucellosis through the standard tube agglutination test (Standart Tube Agglutination, Spinreact, Spain), the coombs test ( $\geq 1/160$ ) and/or *Brucella spp.* culture growth. An electronic cell counter (Cell - Dyne 3700, Abbott, Abbott Park, IL, USA) was used to determine the WBC counts. Standard methods (within approximately five minutes.) were used to analyze the hematological parameters, which included hemoglobin (Hb, range 14 - 18 g/dL for male, 12 - 16 g/L for female), white blood cell count (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%). The threshold level for CRP ranged from 0 to 10 mg/dL. Spectrophotometric methods (Abbott Aeroset, Tokyo, Japan) were used to measure Serum CRP levels.

### 3.2. Statistical Analysis

The SPSS software was employed to carry out the statistical analyses. Comparing the groups, the t -test and chi-square tests were used for continuous categorical variables, respectively. Mann-Whitney U test was used to compare nonhomogeneous groups in pairs. In order to observe the correlation between MPV and the other variables, a simple correlation test (Pearson's test) was used. The numeric values were expressed as mean  $\pm$  SD, and the level of significance as  $P < 0.05$ .

## 4. Results

The study included 351 subjects, which 250 of them were categorized in the acute brucellosis group, and 101 in the control group. Among the 250 patients with brucellosis, 115 were male and 135 were female, while 50 of the 101 controls were male and 51 were female. The blood values of the 88 patients were recorded for further follow-ups a year after treatment. There was no significant difference between the acute brucellosis and control groups regarding age or gender ( $P > 0.05$ ) (Table 1).

#### 4.1. Patients With Acute Brucellosis

The mean leukocyte count was  $7.3 \pm 2.9$  and  $7.4 \pm 2.0$  ( $\times 10^3/\text{mm}^3$ ) in the AB and the control groups, respectively. The leukocyte count was insignificantly higher than that of in the control group ( $P > 0.05$ ). The mean leukocyte count found in the first year follow-up of the patients with brucellosis was  $7.1 \pm 2.0$  ( $\times 10^3/\text{mm}^3$ ). When the leukocyte counts in the acute phase and in the first-year follow-up were compared, no difference was observed and the counts were similar to those of the control group ( $P > 0.05$ ). The mean CRP levels were  $32.57 \pm 53.20$  mg/dL, and  $4.81 \pm 4.89$  mg/dL in the AB and control groups, respectively. The CRP level in the AB group was significantly higher compared with that of the control group ( $P < 0.05$ ). In the follow-up year, the CRP values remained in the normal range:  $5.44 \pm 8.91$  mg/dL ( $P > 0.05$ ).

The mean MPV levels were  $7.64 \pm 1.30$  fL, and  $7.67 \pm 1.29$  fL in the AB and control groups, respectively. Similar to the control group, the MPV level remained within the normal range in the AB group; this result was statistically significant ( $P > 0.05$ ). In the follow-up year the MPV value was  $7.65 \pm 1.54$  fL, same as those of the acute phase and the control group ( $P > 0.05$ ). The mean RDW levels were  $16.24 \pm 2.14\%$  and  $15.90 \pm 1.45\%$  in the AB and control groups, respectively. The RDW level was not significantly higher in the AB group compared to that of the controls. In the follow-up year, there was insignificant difference between

the RDW value in the AB and control groups ( $16.10 \pm 1.79\%$ ) ( $P > 0.05$ ) (Tables 1 and 2).

While the CRP values of the patients in the acute phase were higher compared to those of the controls, their MPV and RDW values had no differences. Similarly, the leukocyte counts of the brucellosis patients in the acute phase and during the follow-up did not differ, and were not different from those of the control group. When the blood parameters were compared after a year of follow-up, it was observed that the MPV, RDW and leukocyte values had not changed, while the CRP values had improved as expected in the period of convalescence. It was found that the leukocyte count in acute brucellosis patients correlated with MPV and RDW ( $r = -0.149$ ,  $P = 0.009$ ;  $r = +0.177$ ,  $P = 0.002$ ;  $r = +0.128$ ,  $P = 0.015$ , respectively). It was also observed that the age parameter correlated with CRP ( $r = +0.272$ ,  $P < 0.001$ , respectively), and the leukocyte count correlated with CRP and RDW ( $r = +0.438$ ,  $P < 0.001$ ;  $r = -0.124$ ,  $P = 0.029$ , respectively) (Table 3). Although the differences in some of these parameters appeared to be statistically significant in the former studies because of negative factors like insufficient size of the patient group, examining 250 patients with brucellosis in the recent decade during the acute phase and in the first-year follow-up showed that the MPV and RDW values of the patients failed to yield significant results in diagnosis and treatment.

**Table 1.** Comparison of the Demographic Features and Leukocyte Count, CRP, MPV and RDW Levels of the Subjects in the Acute Brucellosis and Control Groups <sup>a, b</sup>

	Acute Brucellosis (n = 250)	Control Group (n = 101)	P Value
Age, y	50.87 ± 16.21	48.89 ± 7.07	> 0.05 (0.113)
Male/Female	115/135 (1.54 ± 0.49)	50/51 (1.50 ± 0.50)	> 0.05 (0.530)
Leukocyte, $\times 10^3/\text{mm}^3$	7.3 ± 2.9	7.4 ± 2.0	> 0.05 (0.657)
CRP, mg/L	32.57 ± 53.20	4.81 ± 4.89	< 0.05 (< 0.001)
MPV, fL	7.64 ± 1.30	7.67 ± 1.29	> 0.05 (0.897)
RDW, %	16.23 ± 2.14	15.90 ± 1.45	> 0.05 (0.107)

<sup>a</sup> Abbreviations: CRP: C-Reactive Protein, MPV: Mean Platelet Volume, RDW: Red Blood Cell Distribution.

<sup>b</sup> Data are presented as Mean ± SD.

**Table 2.** Comparison of the Demographic Features and the Leukocyte, CRP, MPV and RDW Levels of the Subjects in the Control Group During Brucellosis Treatment and in the First-Year Follow-Up <sup>a, b</sup>

	Control Group (n = 101)	Control Group in the First Year Follow - Up (n = 88)	P Value
Age, y	48.89 ± 7.07	49.45 ± 12.68	> 0.05 (0.113)
Male/Female	50/51 (1.50 ± 0.50)	39/49 (1.51 ± 0.45)	> 0.05 (0.530)
Leukocyte, $\times 10^3/\text{mm}^3$	7.4 ± 2.0	7.1 ± 2.0	> 0.05 (0.150)
CRP, mg/L	4.81 ± 4.89	5.44 ± 8.91	> 0.05 (0.678)
MPV, fL	7.67 ± 1.29	7.65 ± 1.54	> 0.05 (0.940)
RDW, %	15.90 ± 1.45	16.10 ± 1.79	> 0.05 (0.326)

<sup>a</sup> Abbreviations: CRP: C-Reactive Protein, MPV: Mean Platelet Volume, RDW: Red Blood Cell Distribution.

<sup>b</sup> Data are presented as Mean ± SD.

**Table 3.** Acute Brucellosis Correlation Table <sup>a</sup>

	Gender	Age	Leukocyte	CRP	MPV	RDW	Acute Group
<b>Gender</b>							
r	1	0.080	- 0.149 <sup>b</sup>	- 0.014	0.177 <sup>b</sup>	0.128 <sup>b</sup>	- 0.034
P Value		0.133	0.009	0.813	0.002	0.015	0.529
<b>Age</b>							
R		1	0.107	0.272 <sup>b</sup>	0.059	0.009	- 0.063
P Value			0.059	< 0.001	0.305	0.880	0.238
<b>Leukocyte</b>							
r			1	0.438 <sup>b</sup>	0.066	-0.124 <sup>c</sup>	0.022
P Value				< 0.001	0.246	0.029	0.696
<b>CRP</b>							
r				1	-0.026	-0.099	-0.393 <sup>b</sup>
P Value					0.647	0.086	<0.001
<b>MPV</b>							
r					1	0.067	0.007
P Value						0.239	0.898
<b>RDW</b>							
r						1	- 0.081
P Value							0.156
<b>Acute group</b>							
r							1
P Value							

<sup>a</sup> Abbreviations: CRP: C-reactive protein, MPV: mean platelet volume, RDW: red blood cell distribution.

<sup>b</sup> Correlation is significant at the 0.01 level (2-tailed).

<sup>c</sup> Correlation is significant at the 0.05 level (2-tailed).

## 5. Discussion

Brucellosis is a zoonotic systemic inflammatory disease, which is particularly encountered around the Mediterranean (13). The role of platelets in the pathophysiology of brucellosis is not demonstrated yet. In this context, the current study mainly aimed to compare the MPV levels in the acute and post-treatment phases of brucellosis with those of the control group. The present study showed that the MPV and leukocyte values of patients with acute brucellosis were not different from those of the controls. Infections, and particularly respiratory, urinary, gastrointestinal, bone and meningeal infections, affect the thrombocyte count and functions in various ways. While mild anemia and leukopenia are frequently observed in brucellosis, isolated thrombocytopenia and pancytopenia are found less often. There is usually an association between these complications and acute infections (8, 14). Several reports indicate that elevated WBC count is generally the earliest laboratory result to reveal the presence of inflammation and leukocytosis (15, 16).

The current study indicated that the leukocyte count of patients with acute brucellosis remained within the normal range without early inflammatory marker. CRP

is a sensitive acute-phase protein; and increased in all acute inflammatory processes, however it lacks specificity. The CRP concentration increases with progression of the disease and extent of inflammation. It was observed that the leukocyte count in patients with acute brucellosis did not differ from those of the control group, while the CRP level was higher (Table 1). CRP increased during acute brucellosis and returned to normal level following the treatment. Thus, it proved to be a good marker to diagnose and monitor the efficiency of the treatment (17-19). The fact that the CRP values of the patients with acute brucellosis in the current study were high showed that it was still a very valuable inflammatory marker.

The role of platelets in brucellosis pathophysiology is not demonstrated yet. In this context, the current study mainly aimed to compare the MPV and RDW levels in the acute and post-treatment phases of brucellosis with their levels in the control group. Mean platelet volume (MPV) is an important platelet activation marker. Moreover, there was a correlation between MPV and the degree of platelet activation and inflammatory responses. Several studies reported the link between MPV and chronic in-

flammation and infectious diseases. Platelet distribution width (PDW) is a direct measurement of the platelet size variability. The most frequently used measure of platelet size, MPV, is a simple marker of platelet function and activation (20). It is a simple and accurate marker to determine the functional status of platelets. MPV is accepted as a suitable indicator of platelet activation (21, 22).

Platelet volume is offered as an indirect indicator of increased platelet reactivity. Although activated platelets normally release antibacterial peptides (23), there is evidence suggesting the presence of certain pathogens that can exploit activated platelets by binding to their surfaces to start or spread an infection (24). Moreover, previous studies reported that MPV changes were associated with various non-infectious inflammatory processes, a condition implying that such changes may indicate disease activity in the inflammation (25-27). However, the current study found no difference between the patients with acute brucellosis and the controls regarding the leukocyte, MPV, and RDW values; a result implying that these parameters are not significant markers to diagnose and treat this disease (Table 1). Compared with other inflammation markers, the overall accuracy of MPV to predict diseases was generally found superior in the literature. There was a correlation between MPV and CRP. (4, 28, 29). High MPV levels also occur in infectious diseases like pulmonary tuberculosis, CCHF, and hydatid cyst disease (30-32). On the other hand, lower MPV levels were detected by some researchers in active inflammatory bowel disease, rheumatic arthritis, ankylosing spondylitis, acute pancreatitis, and appendicitis (7, 8, 25, 33). What all these conflicting results indicate is that both higher and lower MPV levels may be of diagnostic and prognostic value for various inflammatory diseases.

To the authors' best knowledge, the current study was the first to report decreased MPV level in patients with acute brucellosis comparing the control group. As indicated above, MPV is generally superior in predicting diseases accuracy when compared with other inflammation markers. Ozturk et al. examined the MPV values of 39 patients and found the values of  $7.84 \pm 1.15$  fL in the acute phase and  $7.83 \pm 0.9$  fL in the post-treatment phase (1). While these values were within the normal range of MPV, the researchers detected a significant difference comparing them with the MPV values of the controls. However, when the current study examined the MPV values found in the prospective study on the 250 patients with brucellosis followed up in the last decade, no significant differences were observed among the controls, and the values were within the normal range.

In another study by Kucukbayrak et al., the main MPV value of 40 patients with brucellosis was  $7.58 \pm 1.96$  fL in the beginning of the treatment and  $7.90 \pm 1.96$  fL at the end. They showed that all the values remained within the normal range, but the difference between the pre- and post-treatment values was statistically significant (14).

The current study results on MPV were in disagreement with the results of these two studies. Although most studies in the literature reported MPV as an inflammatory marker in many infectious and rheumatological diseases as well as a guiding parameter in diagnosis and treatment (7, 8, 19, 25-27, 30, 32, 33), the present study determined that it is not a significant inflammatory marker for brucellosis patients.

A study by Lippi et al. (9) reported a graded association between RDW and high-sensitivity C-reactive protein and erythrocyte sedimentation rate, independent of various confounding factors. Besides inflammation, oxidative stress may also make a significant contribution to anisocytosis. Erythrocytes have immense antioxidant capacity and serve as the chief oxidative sink, but they are vulnerable against oxidative damage which decreases cell survival (34). Although Kucukbayrak et al. reported high RDW levels in patients with brucellosis before treatment and following it (8), the current study with 250 patients found that the RDW values remained within the normal range before and after treatment, without any statistically significant difference in comparison to those of the control group. Thus, the current study showed that RDW is not a reliable marker in the diagnosis and treatment of patients with brucellosis.

The MPV and RDW parameters can be easily analyzed at low cost. The current study results suggested that these values do not play an important role in the diagnosis and treatment of brucellosis. Among the studies in the literature on the inflammatory markers of MPV, RDW, leukocyte count and CRP for brucellosis, the present study has the greatest number of patients, and stands as the only prospective study made so far. It was found that MPV and RDW values are not surrogate markers in the diagnosis and treatment of brucellosis. Among other inflammatory markers, high CRP is still the most valuable marker for the treatment and follow-up of brucellosis. In contrast, leukocyte count was not found a significant inflammatory marker during the acute phase.

The data in the literature regarding this subject generally remain controversial, since they were obtained from patient groups of limited size. The current study was distinguished by the fact that it was performed on the largest patient group so far. It may still be possible for MPV and RDW to act as guiding parameters to diagnose brucellosis. There is still a need for further prospective, multicenter studies with a large sample size to fully clarify the issue.

### Authors' contributions

Study concept and design: Togan, Narci and Ciftci; analysis and interpretation of data: Togan, Turan and Arslan; drafting of the manuscript: Togan; critical revision of the manuscript for important intellectual content: Togan, Narci, Ciftci, Turan, Kursun and Arslan; statistical analysis: Ciftci.

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