

# ASSOCIATION OF MEAN PLATELET VOLUME AND THE MONOCYTE/LYMPHOCYTE RATIO WITH BRUCELLA-CAUSED EPIDIDYMO-ORCHITIS

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**Abstract.** We evaluated the association between the mean platelet volume (MPV) and monocyte/lymphocyte ratio (MLR) with brucella-caused epididymo-orchitis to determine if they could be used to differentiate between brucella and non-brucella epididymo-orchitis. The charts of 88 patients with non-brucella and 14 patients with brucella epididymo-orchitis were retrospectively reviewed. Brucellosis was diagnosed by isolating *Brucella* spp from a blood culture or from a serum agglutination titer  $\geq 1:160$  along with accompanying clinical findings. The patients with brucella epididymo-orchitis were significantly more likely to have a lower MPV and a higher MLR than those with non-brucella epididymo-orchitis. Using a MPV cut-off level of less than 9.25 fl to differentiate brucella from non-brucella epididymo-orchitis gives a sensitivity of 78.6%, a specificity of 78.4%, a positive predictive value of 36.7% and a negative predictive value of 95.8%. Using a MLR cut-off level of greater than 0.265 to differentiate brucella from non-brucella epididymo-orchitis gives a sensitivity of 71.4%, a specificity of 65.9%, a positive predictive value of 25% and a negative predictive value of 93.5%. MPV and MLR values may assist in differentiating between brucella and non-brucella epididymo-orchitis.

**Keywords:** Brucella, epididymo-orchitis, mean platelet volume, monocyte/lymphocyte ratio

## INTRODUCTION

Brucellosis is a potentially life threatening, multisystem zoonotic infection caused by *Brucella* species, which are small, intracellular gram-negative coccobacilli transmitted to humans from

domesticated animals (Erdem *et al*, 2014). The disease is endemic in India, the Mediterranean, South and Central America and the Middle East (Erdem *et al*, 2014). Brucellosis is a common, endemic infection in Turkey (Erdem *et al*, 2014). The Turkish Ministry of Health reported the incidence of brucellosis in 2004 was 256.7 cases per 1 million population (Yumuk and O'Callaghan, 2012). Human brucellosis can affect the central nervous system, respiratory system, cardiovascular system

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and genitourinary tract via a hematogenous route and causes night sweats, undulating fever, weight loss, arthralgia, anorexia and fatigue (Yuksekanik *et al*, 2014; Togan *et al*, 2015). Epididymo-orchitis is the most common genitourinary complication of brucellosis comprising 2-20.6% of total brucellosis cases (Gul *et al*, 2009). Brucella epididymo-orchitis should be in the differential diagnosis of causes of epididymo-orchitis (Gul *et al*, 2009; Moens *et al*, 2009). Although the prognosis of brucella orchitis is good if treated promptly, if there is a delay in diagnosis or if left untreated, it can cause serious complications, such as a testicular abscess which may result in orchiectomy (Erdem *et al*, 2014).

There has been increased interest worldwide recently in mean platelet volume (MPV) and leucocyte ratios in reflecting level of inflammation in some acute and chronic disorders (Ulasli *et al*, 2012; Kahramanca *et al*, 2014; Kounis *et al*, 2014). MPV is used to evaluate platelet function and production. It has been suggested excess production of proinflammatory cytokines and acute phase reactants may be associated with the size of platelets by changes in megakaryopoiesis (Ulasli *et al*, 2012). The MPV can show changes in the severity of several diseases, such as cancer, thrombosis, sepsis, respiratory distress syndrome and acute appendicitis (Canpolat *et al*, 2009; Albayrak *et al*, 2011). White blood cell (WBC) counts, leukocyte ratios and eosinophil counts have also been used to follow carcinomas and inflammatory processes (Açmaz *et al*, 2014; Kahramanca *et al*, 2014). This interest caused us to evaluate these factors in patients with brucella epididymo-orchitis to determine if there were any factors clinically useful in differentiating brucella from non-brucella epididymo-orchitis.

We conducted this study to determine if MPV and monocyte/lymphocyte ratio (MLR) can be used to differentiate brucella from non-brucella epididymo-orchitis. To the best of our knowledge, this is the first study of its kind in English.

## MATERIALS AND METHODS

We retrospectively reviewed the medical records of 146 patients with epididymo-orchitis, who attended the Kars State Hospital, Kafkas University, Faculty of Medicine during March 2006-May 2014. Exclusion criteria were patients with known malignancies, hematological problems, immunosuppressed conditions, coronary artery, cerebrovascular disease, or blood transfusion during the previous 1 month. Forty-four patients were excluded from the study based on exclusion criteria. Of the 102 remaining patients, 88 had non-brucella and 14 had brucella epididymo-orchitis. This study was approved by the ethics committee of Kafkas University, Faculty of Medicine and performed in accordance with the Helsinki Declaration from the World Medical Association.

The diagnosis of brucellosis was made by isolation of *Brucella* spp from blood culture, or having a serum agglutination test titer  $\geq 1:160$ , clinical findings consistent with brucellosis: fever, night sweats, arthralgia, hepatomegaly or splenomegaly (Araj, 2010). The diagnosis of acute epididymo-orchitis was based on ultrasonographic and physical examination findings, such as scrotal inflammation, swelling, enlargement, tenderness and pain of the epididymis and testicles.

The blood culture protocol followed was that of Celen *et al* (2014). Lymphocyte, monocyte, platelet and neutrophil counts and MPV were measured using an automated hematology analyzer (Coulter®

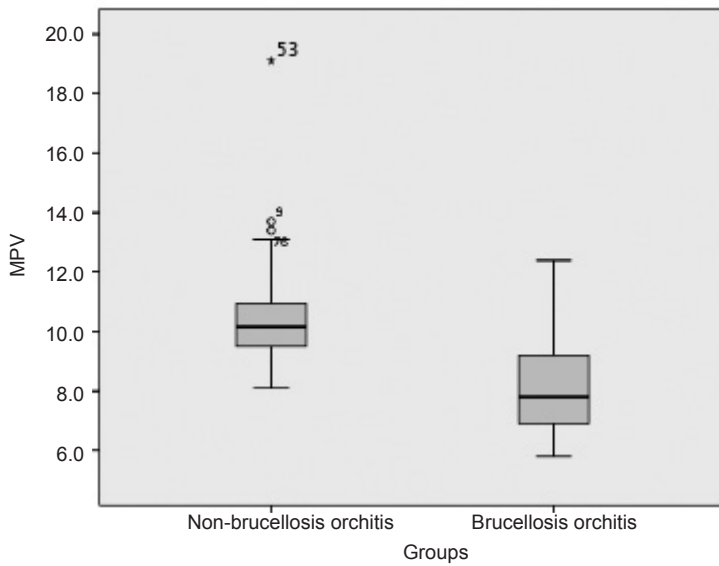


Fig 1–MPV among the 2 groups.

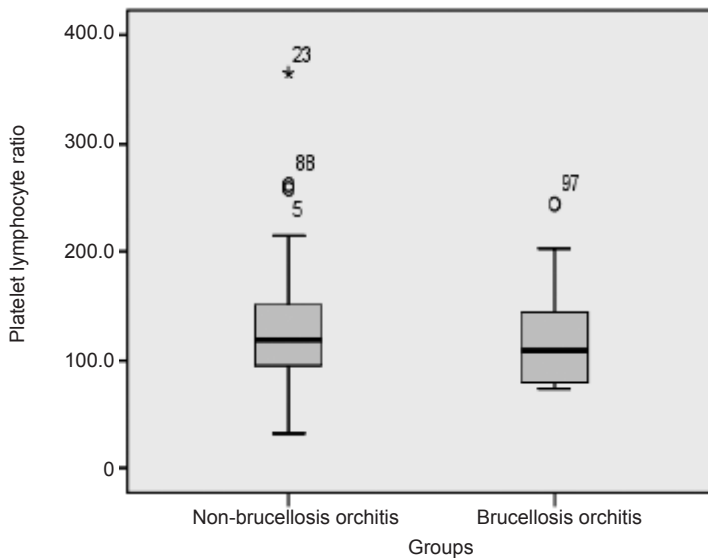


Fig 2–MLR among the 2 groups.

LH 780 Hematology Analyzer, Beckman Coulter, Brea, CA).

**Statistical analysis**

Data analysis was performed using SPSS for Windows, version 22 (SPSS, Armonk, NY). The Kolmogorov-Smirnov Z test was used to test for normality for

continuous variables. Means ± standard deviations, medians or ranges were calculated where applicable. Differences between groups were compared with the Student’s *t*-test or the Mann–Whitney *U* test where appropriate. Categorical data were analyzed using the Pearson chi-square test. The coefficient of regression and 95% confidence intervals for each independent variable were also calculated. A *p*-value <0.05 was considered statistically significant. The cutoff values for parameters used to discriminate between non-brucella and brucella epididymo-orchitis were determined using receiver operating characteristic (ROC) analysis. The sensitivity and specificity for each cut-off value were plotted, generating an ROC curve. The recommended cut-off values for the MPV and MLR were determined using ROC curve analyses.

**RESULTS**

A total of 102 patients were included in the study. The median age of the patients was 29 years old (range: 8-83). The patients were divided into two groups: Group 1,

88 non-brucella epididymo-orchitis patients; Group 2, 14 cases with brucella epididymo-orchitis. All the patients had scrotal symptoms for less than 2 weeks. In Group 2, 4 patients had a positive serum agglutination test and a negative blood culture and 10 patients had both a posi-

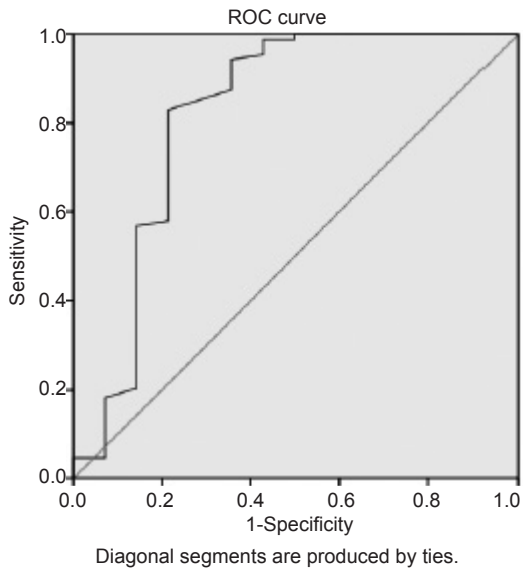


Fig 3–ROC curve for MPV.

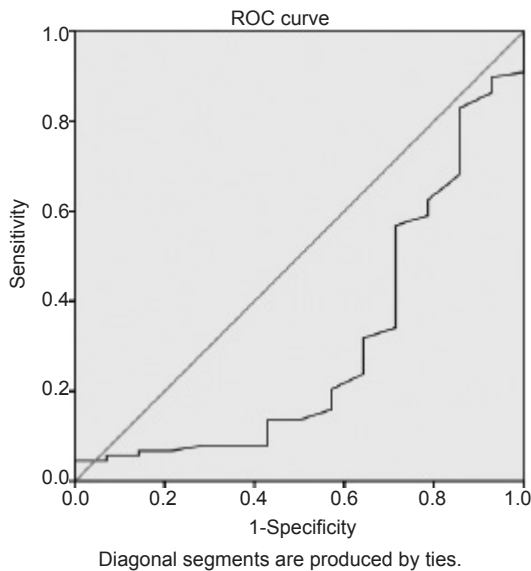


Fig 4–ROC curve for MLR.

tive blood culture and a positive serum agglutination test for brucellosis. Patients with non-brucella epididymo-orchitis had both a negative blood culture and a negative serum agglutination test for brucellosis. Table 1 shows a comparison of the laboratory tests in the two groups, The

MPV and MLR were significantly different between the 2 groups (Fig 1, 2). The best MPV cut-off value able to differentiate between the two groups was  $\leq 9.25$  fl, which gave a sensitivity of 78.6%, a specificity of 78.4% (95% CI: 0.655-0.981), a positive predictive value of 36.7% and a negative predictive value of 95.8%. The best MLR cut-off value able to differentiate between the two groups was  $\geq 0.265$ , which gave a sensitivity of 71.4%, a specificity of 65.9% (95% CI: 0.137-0.466), a positive predictive value of 25% and a negative predictive value of 93.5%. The ROC curves for these 2 factors are shown in Fig 3, 4.

Treatment of brucella epididymo-orchitis included: ciprofloxacin, doxycycline, rifampicin, trimethoprim/sulfamethoxazole, ceftriaxone and gentamicin. Non-brucella epididymo-orchitis cases were treated with ciprofloxacin and a single dose ceftriaxone.

## DISCUSSION

In our study, the mean MPV among patients with brucella epididymo-orchitis was significantly lower than in the non-brucella epididymo-orchitis group and the mean MLR in patients with brucella epididymo-orchitis was significantly higher than in the non-brucella epididymo-orchitis group. To our knowledge, this is the first published study of its kind in English. Most published studies on brucellosis have focused on case reports or literature reviews (Al-Tawfiq, 2006; Moens *et al*, 2009; Dean *et al*, 2012). We also found that the MPV gave a higher positive predictive value than the MLR. Further studies using the cut-off values found in our study are needed to determine the clinical benefit of MPV and MLR levels for differentiating brucella epididymo-orchitis from non-brucella epididymo-orchitis.

Table 1  
Comparison of various factors between the 2 study groups.

Variables	Non-brucella epididymo-orchitis (n=88)	Brucella epididymo-orchitis (n=14)	p-value
Age in years $\pm$ SD	35.3 $\pm$ 18.9	34.1 $\pm$ 8.1	0.309
Mean platelet volume	10.35 $\pm$ 1.43	8.26 $\pm$ 1.93	<0.001
Platelet/Lymphocyte ratio	125.35 $\pm$ 51.06	124.09 $\pm$ 52.94	0.690
Neutrophil/Lymphocyte ratio	2.71 $\pm$ 1.53	2.65 $\pm$ 1.40	0.969
Monocyte/Lymphocyte ratio	0.28 $\pm$ 0.39	0.35 $\pm$ 0.16	0.017
Random distribution of width of red blood cells	13.37 $\pm$ 1.12	13.62 $\pm$ 0.88	0.187
White blood cell count	8,302 $\pm$ 2,678	9,905 $\pm$ 3,639	0.173
Platelet count	0.39 $\pm$ 0.53	0.23 $\pm$ 0.06	0.155

The incidence of brucellosis among humans has increased in Turkey due to failure to eradicate it among domestic animals, especially goats and sheep (Gür *et al*, 2003). *Brucella melitensis* is the most common etiology of brucellosis in the eastern and southeastern parts of Turkey (Geyik *et al*, 2002). Many habitants in the study area are farmers and frequently consume unpasteurized dairy products obtained from domestic animals.

Blood tests for brucellosis have a low specificity. Some have proposed using hematological and biochemical tests to differentiate between brucella epididymo-orchitis and non-brucella epididymo-orchitis (Colmenero *et al*, 2007; Moens *et al*, 2009; Erdem *et al*, 2014), suggesting leukocytosis is unusual with brucella epididymo-orchitis. However, Celen *et al* (2014) reported leukocytosis in cases of brucellosis from southeastern Turkey. In our study, we found no statistical difference in the leukocyte counts between two groups. Mild pancytopenia has also been reported in brucella epididymo-orchitis cases (Crosby *et al*, 1984; Güler *et al*, 2007). We did not observe pancytopenia in our study.

The MPV has been reported to de-

crease among patients with some chronic inflammatory bowel diseases such as ulcerative colitis (Yüksel *et al*, 2009). This issue is thought to be related to release of bioactive molecules from pro-inflammatory active platelets in the presence of inflammation (Yüksel *et al*, 2009). Brucellosis is a chronic inflammatory, systematic disease. In our study, we saw a lower mean MPV among patients with brucella epididymo-orchitis than among patients with non-brucella epididymo-orchitis. Danese *et al* (2004) hypothesized the lower MPV in chronic inflammatory diseases might be attributable to collection or consumption of larger active platelets in the vascular segments of inflamed organs. The pathophysiology behind this phenomenon is not fully understood.

The MLR in peripheral blood was investigated among Kenyan children with malaria (Warimwe *et al*, 2013). The authors reported a higher MLR among children with plasmodium than children without plasmodium. In our study, we found a significantly higher mean MLR of patients with brucella epididymo-orchitis than those with non-brucella epididymo-orchitis.

There were also several limitations



in our study. The study was retrospective and had a small sample size. We were unable to evaluate and compare relapse rates, treatment duration and sperm studies between the two groups due to the sociocultural limitations of the study subjects.

Measuring the MPV and MLR is fast, inexpensive, easy to do and may help differentiate brucella epididymo-orchitis from non-brucella epididymo-orchitis. Further studies are needed to confirm this in clinical setting and clarify the reason for this finding.

## REFERENCES

- Açmaz G, Aksoy H, Unal D, *et al.* Are neutrophil/lymphocyte and platelet/lymphocyte ratios associated with endometrial precancerous and cancerous lesions in patients with abnormal uterine bleeding? *Asian Pac J Cancer Prev* 2014; 15: 1689-92.
- Albayrak Y, Albayrak A, Albayrak F, *et al.* Mean platelet volume: a new predictor in confirming acute appendicitis diagnosis. *Clin Appl Thromb Hemost* 2011; 17: 362-6.
- Araj GF. Update on laboratory diagnosis of human brucellosis. *Int J Antimicrob Agents* 2010; 36 (suppl 1): S12-7.
- Al-Tawfiq JA. Brucella epididymo-orchitis: a consideration in endemic area. *Int Braz J Urol* 2006; 32: 313-5.
- Canpolat FE, Yurdakök M, Armangil D, Yiğit S. Mean platelet volume in neonatal respiratory distress syndrome. *Pediatr Int* 2009; 51: 314-6.
- Celen MK, Ulug M, Ayaz C, Geyik MF, Hosoglu S. Brucellar epididymo-orchitis in southeastern part of Turkey: an 8 year experience. *Braz J Infect Dis* 2014; 14: 109-15.
- Colmenero JD, Muñoz-Roca NL, Bermudez P, *et al.* Clinical findings, diagnostic approach, and outcome of *Brucella melitensis* epididymo-orchitis. *Diagn Microbiol Infect Dis* 2007; 57: 367-72.
- Crosby E, Llosa L, Miro Quesada M, Carrillo C, Gotuzzo E. Hematologic changes in brucellosis. *J Infect Dis* 1984; 150: 419-24.
- Danese S, Motte Cd Cde L, Fiocchi C. Platelets in inflammatory bowel disease: clinical, pathogenic, and therapeutic implications. *Am J Gastroenterol* 2004; 99: 938-45.
- Dean AS, Crump L, Greter H, Hattendorf J, Schelling E, Zinsstag J. Clinical manifestations of human brucellosis: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2012; 6: e1929.
- Erdem H, Elaldi N, Ak O, *et al.* Genitourinary brucellosis: results of a multicentric study. *Clin Microbiol Infect* 2014; 20: 0847-53.
- Geyik MF, Gür A, Nas K, *et al.* Musculoskeletal involvement of brucellosis in different age groups: a study of 195 cases. *Swiss Med Wkly* 2002; 132: 98-105.
- Gul HC, Akyol I, Sen B, Adayener C, Haholu A. Epididymo-orchitis due to *Brucella melitensis*: review of 19 patients. *Urol Int* 2009; 82: 158-61.
- Guler E, Guler S, Ucmak H, Gul M. Epididymo-orchitis and pancytopenia caused by brucellosis. *Indian Pediatr* 2007; 44: 699-700.
- Gür A, Geyik MF, Dikici B, *et al.* Complications of brucellosis in different age groups: a study of 283 cases in southeastern Anatolia of Turkey. *Yonsei Med J* 2003; 44: 33-44.
- Kahramanca S, Ozgehan G, Seker D, *et al.* Neutrophil-to-lymphocyte ratio as a predictor of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2014; 20: 19-22.
- Kounis NG, Soufras GD, Tsigkas G, Hahalis G. White blood cell counts, leukocyte ratios, and eosinophils as inflammatory markers in patients with coronary artery disease. *Clin Appl Thromb Hemost* 2014; 21: 139-43.
- Moens A A, Vlaspolde F, Verlind J, Sepers JM, Stam F. Epididymo-orchitis due to brucellosis: not only to be considered in endemic areas. Two cases for the price of three patients. *Urol Int* 2009; 82: 481-3.
- Togan T, Ciftci O, Turan H, Narci H, Gullu H, Arslan H. Could there be an association be-

- tween chronic brucellosis and endothelial damage? *J Infect Dev Ctries* 2015; 9: 48-54.
- Ulasli SS, Ozyurek B A, Yilmaz EB, Ulubay G. Mean platelet volume as an inflammatory marker in acute exacerbation of chronic obstructive pulmonary disease. *Pol Arch Med Wewnętrznej* 2012; 122: 284-90.
- Yumuk Z, O'Callaghan D. Brucellosis in Turkey -- an overview. *Int J Infect Dis* 2012; 16: e228-35.
- Yuksekanik S, Gulhan B, Parlakay Ozkaya A, Tezer H. A case of childhood brucellosis with neurological involvement and epididymo-orchitis. *J Infect Dev Ctries* 2014; 8: 1636-8.
- Yüksel O, Helvacı K, Başar O, *et al.* An overlooked indicator of disease activity in ulcerative colitis: mean platelet volume. *Platelets* 2009; 20: 277-81.
- Warimwe GM, Murungi LM, Kamuyu G, *et al.* The ratio of monocytes to lymphocytes in peripheral blood correlates with increased susceptibility to clinical malaria in Kenyan children. *PLOS One* 2013; 8: e57320.