Arch Iran Med. November 2019;22(11):640-645

www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Original Article

Open Access

Predictive Value of Inflammation Markers in Brucellosis

Pinar Sen, MD[1*]; Tuna Demirdal, MD[1]; Salih Atakan Nemli, MD[1]

[1]Izmir Katip Celebi University Ataturk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey

Abstract

Background: It is important to identify new biomarkers for early detection of complications and treatment success in patients with brucellosis.

Methods: A total of 187 brucellosis patients in the Department of Infectious Diseases of Izmir Katip Celebi University Ataturk Training and Research Hospital were evaluated retrospectively from January 2010 to January 2016.Complications of brucellosis were hematologic, osteoarticular, genitourinary, neurologic, cardiovascular, gastrointestinal and ocular involvement. Specific organ involvement was defined as the presence of infection signs in any specific anatomic site except hematologic involvement. Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte-ratio (PLR) were evaluated statistically to predict complications and specific organ involvement of brucellosis.

Results: Complications occurred in 125 patients. We found that PLR and erythrocyte sedimentation rate (ESR) were higher in complicated patients ($P = 0.007$, $P < 0.001$). The area under curve (AUC) for PLR was 0.622 (95% confidence interval [CI], 0.538-0.707) with a cutoff value of >119.6 in predicting complications in brucellosis. LMR and NLR were not significant in terms of predicting complications in brucellosis. We also evaluated only specific organ involvement as a complication due to frequent occurrence of hematologic abnormalities in brucellosis. ESR, mean platelet volume (MPV), NLR, PLR and LMR were significantly different in patients with specific organ involvement ($P = 0.001$, $P = 0.011$, $P = 0.001$, $P = 0.013$ and $P = 0.040$). The AUC values for NLR and LMR were 0.649 (95% CI 0.570–0.728) and 0.589 (95% CI 0.507–0.671), respectively.

Conclusion: These biomarkers are cost-effective, simple and broadly available parameters for predicting complications and specific organ involvement of brucellosis.

Keywords: Brucellosis, Diagnosis, Inflammatory markers

Cite this article as: Sen P, Demirdal T, Nemli SA. Predictive value of inflammation markers in brucellosis. Arch Iran Med. 2019;22(11):640–645.

Received: March 11, 2019, Accepted: July 30, 2019, ePublished: November 1, 2019

Introduction

Brucellosis is a zoonotic disease caused by bacteria of the genus *Brucella* and constitutes a major public health problem in many developing countries.[1] More than 500 000 new human cases of brucellosis per year are reported but it is estimated that the true prevalence is much higher due to lack of valid reports, asymptomatic cases and inappropriate diagnostic tools.[2,3]

Human brucellosis has a broad spectrum of non-specific clinical presentation.[4] Therefore, the disease tends to be overlooked; underdiagnosis of brucellosis leads to increased rates of chronic and complicated cases.[4,5] Early recognition and treatment of complicated cases are important in preventing treatment failure or even mortality due to relapses and resistance development.[2] Therefore, it is necessary to identify new markers in patients with brucellosis.

The gold standard for diagnosis of brucellosis is growth of *Brucella* in blood or tissue culture. However, culture methods may be unsuccessful.[5] Hence, routine hematological parameters and serological tests are more widely used in the diagnosis of brucellosis. Nevertheless, these tests, which are useful in diagnosis, treatment response and relapse, have limited value in chronic and complicated cases.[5,6]

Chronic inflammation plays a major role in the etiopathogenesis of brucellosis and the occurrence of complications.[6-8] It has been recently highlighted that changes in circulating leukocyte levels are novel, simple, rapid, and promising inflammatory parameters in many diseases.[8] To the best of our knowledge, this is the first report to evaluate the distribution of neutrophil, monocyte, platelet and lymphocyte levels in brucellosis with regard to complications. In the present study, we aimed to investigate the value of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) in predicting complications and specific organ involvement of brucellosis.

Patients and Methods

Patients

A total of 187 patients diagnosed with brucellosis were evaluated retrospectively from January 2010 to January 2016 in a tertiary referral care center. Institutional

*Corresponding Author: Pinar Sen, MD; Izmir KatipCelebi University Ataturk Research and Training Hospital 35360, Karabaglar/Izmir, Turkey. Tel: +905058946042; Fax: +902322431530; Email: pinarozdemirsen@gmail.com

review board approval was obtained from our local ethics committee. The exclusion criteria were pregnancy, age under 16 years, malignancy, other foci of infection, autoimmune diseases, underlying hematological diseases and antibiotic use at the time of admission. The data of the brucellosis patients were recorded, including demographic findings, clinical findings, length of hospital stay, complications and laboratory parameters. Complications of brucellosis were defined by physical examination findings, laboratory parameters and imaging examinations. Complications of patients with brucellosis were hematologic, osteoarticular, genitourinary, neurologic, cardiovascular, gastrointestinal and ocular involvement. Specific organ involvement was defined as the presence of infection signs in any specific anatomic site except hematologic involvement in active brucellosis.

Laboratory Analysis

Infection markers such as white blood cell (WBC) counts (4000–10 000 K/μL), mean platelet volume (MPV) (6.5–12 fL), erythrocyte sedimentation rate (ESR) (0–15 mm/h), C-reactive protein (CRP) (0–0.5 mg/dL), procalcitonin (PCT) (0–0.1 ng/mL) and serological tests were examined as laboratory tests. Hemoglobin values <12 g/dL for females and <13 g/dL for males were defined as anemia. Leukocytosis was defined as leukocyte count over 11 000 K/μL. Leukopenia and thrombocytopenia were defined as leukocyte and thrombocyte count lower than 4000 K/μL and 150 000 K/μL, respectively. Elevated ESR, CRP and PCT were defined as ESR >30 mm/h, CRP >0.8 mg/dL and PCT >0.1 ng/mL, respectively. Brucellosis was diagnosed based on clinical and laboratory findings. Rose Bengal plate agglutination test was used as the screening test and positive results were supported by titrimetric tests.[9] The diagnosis was established according to the positive standard agglutination tube test (SAT) and/or isolation of *Brucella* species from blood culture specimens for patients presenting with compatible signs and symptoms of brucellosis. SAT (Wright or Coombs Wright agglutination test) titers at 1/160 and above were considered as positive for brucellosis. Coombs Wright test was used if the Wright titer was negative or slightly positive (≤1/80). The NLR, LMR and PLR levels were obtained using neutrophil, platelet, monocyte and lymphocyte counts in the complete blood count parameters. NLR was the ratio of absolute neutrophil count to the absolute lymphocyte count. PLR was the ratio of absolute platelet count to the absolute lymphocyte count. LMR was the ratio of absolute lymphocyte count to the absolute monocyte count. Blood cultures were taken from all patients. Microbiological cultures were performed on the obtained clinical specimens if the patients had undergone biopsy, drainage or surgery. Laboratory analyses were assessed according to the standard procedures of our clinical microbiology and clinical biochemistry laboratory departments. First, the patients were divided into two groups based on the presence or absence of complications including hematologic involvement, osteoarticular involvement, genitourinary involvement, neurologic involvement, cardiovascular involvement, gastrointestinal involvement and ocular involvement. Second, specific organ involvement was analyzed as a complication in terms of evaluating whether hematological changes might affect these parameters. NLR, LMR and PLR levels were analyzed statistically to predict complications and specific organ involvement of brucellosis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, ABD) and MedCalc version 14 (MedCalc Software). Descriptive statistics were presented as number of units (n) and percentage (%) in categorical variables. Descriptive statistics were presented as mean and 95% confidence interval (95% Cl), median and inter quartile range (IQR) for continuous variables. Normality of numerical variables was evaluated with the Shapiro-Wilk normality test and Q-Q graphs. Since none of the variables showed normal distribution, all comparisons between groups were performed with the Mann-Whitney U test. In the evaluation of NLR, PLR and LMR as a diagnostic test, receiver operating characteristic curves (ROC) analysis was used. The sensitivity, specificity and ROC analysis were calculated using MedCalc version 14 software. Cutoff values were determined using the Youden index. *P* value <0.05 was considered as statistically significant.

Results

Clinical Findings

A total of 187 brucellosis patients were evaluated including 89 (47.6%) women and 98 (52.4%) men. The mean age was 45.4 (17.4) years (range 16–86 years) at the time of diagnosis. The most common symptoms were fever (48.7%), backache (41.2%), night sweats (25.1%), malaise/weakness (24.6%), arthralgia (24.1%), lack of appetite (13.9%) and weight loss (12.8%).

Complications occurred in 125 (66.8%) patients. Hematologic involvement (43.8%) was the most common complication, followed by osteoarticular (32.1%), genitourinary (3.7%), neurologic (2.7%), cardiovascular (2.1%), gastrointestinal (0.5%) and ocular (0.5%) involvement. All complications in patients with brucellosis are listed in Table 1.

There were 40 (21.4%) patients with a prior history of brucellosis. The average duration of hospitalization was 10.2 (6.3) days. The mean duration of hospitalization was higher in complicated patients than in patients without complications (11.4 [6.4] and 7.8 [5.1] days, respectively; $P = 0.001$).

Table 1. Complications in 187 Patients with Brucellosis

Complications	No. (%)
Hematologic involvement	82 (43.8)
Anemia	69 (36.9)
Leukopenia	18 (9.6)
Thrombocytopenia	17 (9.1)
Pancytopenia	4 (2.1)
Osteoarticular involvement	60 (32.1)
Spondylodiscitis	45 (24.1)
Lumbar abscess	13 (6.9)
Peripheral arthritis	6 (3.2)
Sacroiliitis	5 (2.7)
Bursitis	2 (1.1)
Enthesitis	1 (1.1)
Genitourinary involvement	7 (3.7)
Epididymo-orchitis	6 (3.2)
Scrotal abscess	1 (0.5)
Neurologic involvement	
Meningoencephalitis	5 (2.7)
Cardiovascular involvement	4 (2.1)
Endocarditis	3 (1.6)
Aortic thrombus	1 (0.5)
Gastrointestinal involvement	
Free ascites in abdomen	1 (0.5)
Ocular involvement	
Optic neuritis	1 (0.5)

Laboratory Findings

Among all patients, 36.9% had anemia, 8.6% had leukocytosis, 9.6% had leukopenia, 9.1% had thrombocytopenia, 43.8% had elevated ESR, 72.5% had elevated CRP and 44.7% had elevated PCT.

The Rose Bengal test was found positive in 183 (97.9%) patients and the Wright test was positive in 166 (88.8%) patients. Twenty-one patients (11.2%) who had negative Wright test were diagnosed by Coombs Wright test and/or culture positivity. Positive blood culture results were obtained in 75 (40.1%) patients and only *Brucella melitensis* was isolated. The initial laboratory findings are shown in Table 2.

Diagnostic Value of Biomarkers in Predicting Complication

We investigated hematological parameters, NLR, PLR and LMR in patients with brucellosis according to complication status. We found that only ESR and PLR were significantly higher in complicated patients (median ESR: 37.5 mm/h, 95% CI: 35.2–44.9; $P<0.001$ and median PLR: 123.3, 95% Cl: 124–148.1; $P=0.007$, respectively). In addition, hemoglobin and lymphocyte levels were found to be significantly lower in complicated patients (median hemoglobin: 11.8 g/dL, 95% Cl: 11.7–12.3; $P<0.001$ and median lymphocyte: 1990 K/µL, 95% Cl: 1954–2275.5; $P=0.006$, respectively) (Table 2). NLR, MPV and LMR levels were insignificant in predicting complications in patients with brucellosis (median NLR: 1.9, 95% Cl: 1.9–2.3; $P=0.054$, median MPV: 8.7 fL, 95% Cl: 8.6–9.1; $P=0.136$ and median LMR: 4.3, 95% Cl: 4.4–5.6; $P=0.608$, respectively) (Table 2).

The AUC value for PLR was 0.622 (95% CI, 0.538–0.707) with a cutoff value of >119.6 in predicting complications in brucellosis. Performing ROC analyses at the cutoff value of >119.6, PLR yielded 57.6% sensitivity (95% CI: 48.4–66.4) and 70.9% (95% CI: 58.1–81.8) specificity. ROC analyses and AUC values for NLR, PLR and LMR according to the complication status are presented in Figure 1 and Table 3.

Diagnostic Value of Biomarkers in Predicting Specific Organ Involvement

Considering the frequent occurrence of hematologic

Table 2. Comparison of the Laboratory Values According to Presence or Absence of Complication and Specific Organ Involvement in Brucellosis

Laboratory Parameters	All patients (187, 100%) (Median±IQR)	Complication (+) (125, 66.8%) (Median±IQR)	Complication (-) (62, 33.2%) (Median±IQR)	*P*	Specific Organ Involvement (+) (75, %40.1) (Median±IQR)	Specific Organ Involvement (-) (112, %59.9) (Median±IQR)	*P*
Leukocyte (K/µL)	6795 (3295)	6640(3265)	6815 (2262.5)	0.257	6940 (3730)	6620 (3010)	0.007
Neutrophil (K/µL)	3870 (2397.5)	3730 (2450)	3795 (1932.5)	0.994	4170 (2830)	3860 (2420)	0.001
Lymphocyte (K/µL)	2060(1177.5)	1990 (955)	2310 (1135)	0.006	1990 (950)	2080 (1265)	0.844
Monocyte (K/µL)	514.5(293.2)	477 (297)	505.5 (255.5)	0.110	527 (284)	471 (335)	0.118
Platelet (K/µL)	241000 (140500)	239000 (131000)	241500 (93750)	0.884	296000 (187000)	200000 (115000)	0.001
Hemoglobin (g/dL)	12.6 (2.2)	11.8 (2.2)	13.1 (1.2)	<0.001	12.7 (2.3)	12.6 (2.2)	0.365
MPV (fL)	8.8 (2.1)	8.7 (1.8)	9.1 (2.5)	0.136	8.7 (1.4)	9.3 (3.2)	0.011
ESR (mm/h)	28.5 (34.2)	37.5 (39.5)	21 (19.2)	<0.001	44 (31)	22 (28)	0.001
CRP (mg/dL)	2.9 (3.75.8)	2.4 (4.9)	1.5 (3.9)	0.153	2.8 (7.1)	3.1 (5)	0.538
PCT (ng/mL)	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.372	0.1 (0.1)	0.1 (0.2)	0.408
NLR	1.9 (1.2)	1.9 (1.1)	1.5 (1.2)	0.054	2.3 (2.1)	1.8 (1.1)	0.001
PLR	121.9 (85.8)	123.3(78.9)	104 (55.2)	0.007	156.2 (74.5)	104.7 (87.4)	0.013
LMR	4.1 (2.6)	4.3(2.3)	4.5 (2.5)	0.608	3.9 (2)	4.4 (3)	0.040

IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate.

Table 3. NLR, PLR and LMR Values in Predicting Complication and Specific Organ Involvement in Brucellosis

Variables	AUC (95% CI)	*P*	Cutoff	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	+LR (95% CI)	-LR (95% CI)	+PV (%) (95% CI)	-PV (%) (95% CI)
Complication									
NLR	0.587 (0.499-0.675)	0.0538	>1.8	55.2 (46-64.1)	66.1 (53-77.7)	1.6 (1.1-2.4)	0.7 (0.5-0.9)	76.7 (66.6-84.9)	42.3 (32.3-52.7)
PLR	0.622 (0.538-0.707)	0.0046	>119.6	57.6 (48.4-66.4)	70.9 (58.1-81.8)	1.9 (1.3-3)	0.6 (0.5-0.8)	80 (70.2-87.7)	45.4 (35.2-55.8)
LMR	0.523 (0.436-0.610)	0.6024	≤4.1	45.6 (36.7-54.7)	67.7 (54.7-79.1)	1.4 (0.9-2.1)	0.8 (0.6-1)	74 (62.8-83.4)	38.2 (29.1-47.9)
Specific organ involvement									
NLR	0.649 (0.570-0.728)	0.0002	>1.4	84 (73.7-91.4)	46.4 (37-56.1)	1.6 (1.3-1.9)	0.3 (0.2-0.6)	51.2 (42-60.3)	81.2 (69.5-89.9)
PLR	0.607 (0.526-0.687)	0.0094	>116.6	66.7 (54.8-77.1)	59.8 (50.1-69)	1.7 (1.3-2.2)	0.6 (0.4-0.8)	52.6 (42.1-63)	72.8 (62.6-81.6)
LMR	0.589 (0.507-0.671)	0.0337	≤4.1	54.7 (42.7-66.2)	64.3 (54.7-73.1)	1.5 (1.1-2.1)	0.7 (0.5-0.9)	50.6 (39.3-61.9)	67.9 (58.2-76.7)

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; AUC, Area under the receiver operating characteristic curve; LR, likelihood ratio; PV, predictive value; 95% CI, 95% confidence intervals.

abnormalities in brucellosis, we also evaluated only specific organ involvement as a complication to assess whether hematologic findings affect the value of NLR, PLR and LMR. Therefore, we excluded hematological changes from the complications and reanalyzed NLR, PLR and LMR to predict specific organ involvement in brucellosis. Leukocyte, neutrophil, platelet, ESR, NLR and PLR values were significantly higher in patients with specific organ involvement (median leukocyte: 6940 K/µL, 95% Cl: 6275.6–8620.1; $P=0.007$, median neutrophil: 4170 K/µL, 95% Cl: 3634.8–5659.8; $P=0.001$, median platelet: 296 000 K/µL, 95% Cl: 263183–378395.9; $P=0.001$, median ESR: 44 mm/h, 95% Cl: 34.5–58.6; $P=0.001$, median NLR: 2.3, 95% Cl: 1.8–3.1; $P=0.001$ and median PLR: 156.2, 95% Cl: 130–201.6; $P=0.013$, respectively). On the other hand, MPV and LMR were significantly lower in specific organ involvement (median MPV: 8.7 fL, 95% Cl: 7.9–8.9; $P=0.011$ and median LMR: 3.9, 95% Cl: 3.2–5.1; $P=0.040$). The ROC analyses indicated a cutoff value of >1.4 for NLR, >116.6 for PLR and ≤4.1 for LMR (Figure 2 and Table 3). AUC levels for NLR, PLR and LMR were 0.649 (95% CI 0.570–0.728), 0.607 (95% Cl 0.526–0.687) and 0.589 (95% Cl 0.507–0.671), respectively (Table 3). The cutoff values, sensitivities, specificities, likelihood ratios and predictive values of biomarkers are shown in Table 3.

Discussion

This is the first study which evaluates the values of PLR, NLR and LMR in predicting complications and specific organ involvements of brucellosis. The findings of our study demonstrate that these new inflammatory markers, which are easily accessible and do not require additional cost, provide relevant information about the complications of brucellosis. Firstly, we observed that PLR was elevated in complicated brucellosis, including hematological manifestations. Secondly, we only examined specific organ involvement as a complication in order to evaluate whether hematological changes might affect these parameters; we found that increased NLR, increased PLR and decreased LMR were significantly associated with specific organ involvement.

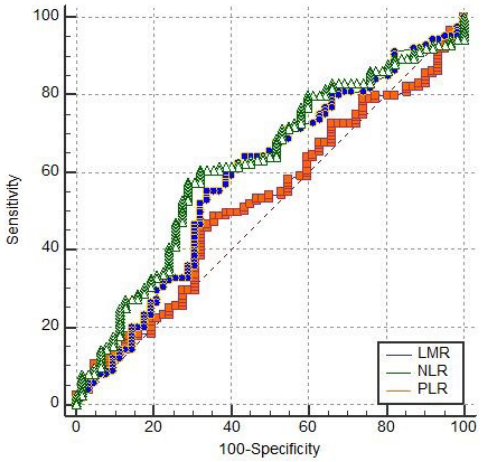

Figure 1. Receiver Operating Characteristic Curve (ROC) Analyses for Various Cutoff Levels of NLR, PLR and LMR in Predicting Complication in Brucellosis.

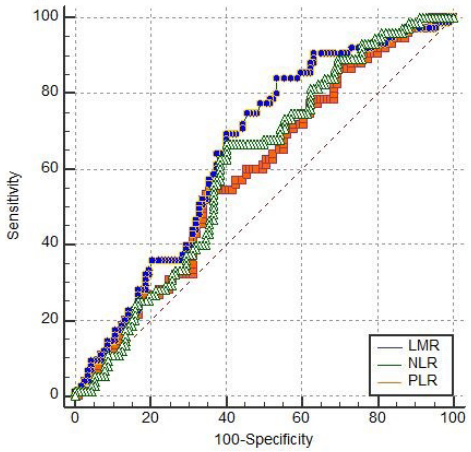

Figure 2. Receiver Operating Characteristic Curve (ROC) Analyses for Various Cutoff Levels of NLR, PLR and LMR in Predicting Specific Organ Involvement in Brucellosis.

Human brucellosis is a multisystem disease which causes a broad spectrum of clinical presentations. The reported incidence rates of complications in brucellosis vary from less than 1% to more than 50%.[5] Clinical signs are usually nonspecific and may vary according to the affected area in complicated patients which often leads to misdiagnosis and treatment delay.[10] Early recognition of complications is crucial in terms of treatment success due to the difference in the type and duration of treatment in complicated brucellosis. However, there is no specific test to identify complications of brucellosis.

Inflammation is a nonspecific response of the organism to endogenous or exogenous stimuli.[11]Tissue injury and infectious diseases such as brucellosis are usually classical initiators of inflammation; however, various physiological and pathological processes can trigger inflammation and the response to all these stimuli is similar.[12] Inflammatory mediators are released by mast cells and macrophages.[11,12] Plasma proteins and leukocytes are released by the action of these mediators.[13] Moreover, these mediators can stimulate thrombocytosis by inducing megakaryocytes.[14] Occasionally, thrombocytopenia may develop in patients with brucellosis.[5,6] Inflammatory states can also affect lymphocyte levels. Lymphocytes have a modulating effect in controlling inflammation. In systemic inflammation, lymphocytopenia develops due to increased apoptosis of lymphocytes.[11] Neutrophils are replaced by lymphocytes and macrophages if the acute inflammatory response is insufficient, and chronic inflammation begins.[11-14] As a result, systemic inflammation leads to changes in lymphocyte, neutrophil, monocyte, and platelet levels.[11] The low LMR, high NLR and PLR levels obtained in our study can be attributed to a contrasting effect of inflammation on lymphocyte levels.

Recent studies indicate that LMR, NLR and PLR may reflect systemic inflammation and these biomarkers can be useful in several diseases.[1,7,8] In spite of the close association between infection and inflammation, these biomarkers have not yet been well studied in brucellosis. To our knowledge, there are only four studies evaluating these biomarkers in brucellosis.[1,15-17] In a previous study conducted by Olt et al, NLR was significantly decreased in patients with brucellosis compared to healthy subjects.[15] The cutoff value for predicting brucellosis was reported at <1.5 in their study. Bozdemir et al noted that NLR was significantly higher in childhood brucellosis than healthy groups (median 0.99 and 0.89, $P=0.032$).[16] In addition, they showed that NLR was significantly higher (median 1.38) in arthritis-positive groups. In another study, significantly higher PLR and NLR were found in children with brucella arthritis.[17] Aydin et al showed that the monocyte-to-lymphocyte ratio was higher in patients with brucella epididymo-orchitis compared to non-brucella epididymo-orchitis.[1] However, the patients were not assessed in terms of all complications or other specific organ involvement in these studies. To the best of our knowledge, our study is the first report to assess the levels of PLR, NLR and LMR in predicting complications of brucellosis. We found that only PLR was significantly higher in complicated patients involving hematological manifestations. Unlike PLR, however, NLR and LMR were not significant in predicting complications of brucellosis. When we excluded hematological changes from the list of complications, increased NLR, increased PLR and decreased LMR were found to be significantly associated with specific organ involvement. We conclude that clinical use of these biomarkers may be beneficial in predicting specific organ involvement, as they are affected by hematological changes. More comprehensive studies are still needed to investigate the predictive value of these markers in complicated brucellosis with hematological involvement.

As another inflammatory marker, MPV has been also shown to be an indicator of inflammation in many diseases.[1,16-20] MPV, a parameter that can be obtained from complete blood count, is useful in evaluating platelet production and function.[1] As platelets are structurally and numerically affected by cytokines, it is hypothesized that MPV may be a useful biomarker for severity of inflammatory disorders.[1] However, few studies have examined the association between MPV and brucellosis. MPV was found significantly decreased in patients with brucellosis compared to healthy adults and children.[16,18,19] On the other hand, Togan et al demonstrated that MPV was not a surrogate marker in acute brucellosis.[20] In only three studies, MPV was investigated with regard to brucellosis complicated with arthritis and epididymo-orchitis.[1,16,17] Aydın et al demonstrated that MPV was significantly lower in brucella epididymo-orchitis compared to non-brucella epididymo-orchitis.[1] The other two studies conducted in children demonstrated that MPV was significantly higher in arthritis-positive brucellosis compared to healthy control subjects and arthritis-negative brucellosis.[16,17] However, the patients were not assessed in terms of all complications or other focal involvement in these studies. In our study, we demonstrated that MPV was significantly lower in brucellosis with specific organ involvement compared to non-complicated brucellosis (8.6±1.2 and 9.2±1.7, $P=0.005$). Therefore, we suggest that MPV may also be a valuable inflammatory marker in predicting specific organ involvement of brucellosis alongside NLR, PLR and LMR.

This study has some limitations. The main was its retrospective design. These biomarkers demonstrated moderate sensitivity; therefore, they need to be investigated in studies conducted with a large number of patients. In addition, the stabilities of these biomarkers were not assessed over time. Future larger studies are needed in order to investigate the diagnostic values of these biomarkers in predicting complications of brucellosis.

Based on the results of the present study, PLR can predict complications of brucellosis. PLR, NLR and LMR are predictive of specific organ involvement in brucellosis. We conclude that these biomarkers are broadly available, cost-effective and simple parameters in brucellosis.

Authors' Contribution

PS, TD and SAN researched data. PS wrote the manuscript. PS, TD and SAN reviewed the manuscript. TD and SAN analyzed the data statistically. All authors critically revised and approved the final manuscript.

Conflict of Interest Disclosures

The authors declare that there is no conflict of interest.

Ethical Statement

Ethical approval for this study was obtained from the Ethics Committee of Izmir Katip Celebi University (number of the document: 263/2015).

References

1. Aydin E, Karadag MA, Cecen K, Cigsar G, Aydin S, Demir A, et al. Association of mean platelet volume and the monocyte/lymphocyte ratio with brucella-caused epididymo-orchitis. Southeast Asian J Trop Med Public Health. 2016;47(3):450-456.
2. Tumwine G, Matovu E, Kabasa JD, Owiny DO, Majalija S. Human brucellosis: sero-prevalence and associated risk factors in agro-pastoral communities of Kiboga District, Central Uganda. BMC Public Health. 2015;15:900. doi: 10.1186/s12889-015-2242-z.
3. Marvi A, Asadi-Aliabadi M, Darabi M, Abedi G, Siamian H, Rostami-Maskopaee F. Trend analysis and affecting components of human brucellosis incidence during 2006 to 2016. Med Arch. 2018;72(1):17-21. doi: 10.5455/medarh.2018.72.17-21.
4. Galińska EM, Zagórski J. Brucellosis in humans-etiology, diagnostics, clinical forms. Ann Agric Environ Med. 2013;20(2):233-8.
5. Ulu Kilic A, Metan G, Alp E. Clinical presentations and diagnosis of brucellosis. Recent Pat Antiinfect Drug Discov. 2013;8(1):34-41. doi: 10.2174/1574891X11308010007.
6. Araj GF. Update on laboratory diagnosis of human brucellosis. Int J Antimicrob Agents. 2010;36(1):12-7. doi: 10.1016/j.ijantimicag.2010.06.014.
7. Sen V, Bozkurt IH, Aydogdu O, Yonguc T, Yarimoglu S, Sen P, et al. Significance of preoperative neutrophil-lymphocyte count ratio on predicting postoperative sepsis after percutaneous nephrolithotomy. Kaohsiung J Med Sci. 2016;32(10):507-13. doi: 10.1016/j.kjms.2016.08.008.
8. Peng J, Li H, Ou Q, Lin J, Wu X, Lu Z, et al. Preoperative lymphocyte-to-monocyte ratio represents a superior predictor compared with neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios for colorectal liver-only metastases survival. Onco Targets Ther. 2017;10:3789-99. doi: 10.2147/OTT.S140872.
9. Koçman EE, Erensoy MS, Taşbakan M, Çiçeklioğlu M. Comparison of Standard agglutination tests, enzyme immunoassay, and Coombs gel test used in laboratory diagnosis of human brucellosis. Turk J Med Sci. 2018;48(1):62-7. doi: 10.3906/sag-1707-122.
10. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis. 2010;14(6):e469-478. doi: 10.1016/j.ijid.2009.06.031.
11. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428-35. doi: 10.1038/nature07201.
12. Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. Nat Rev Immunol. 2007;7(10):803-15. doi: 10.1038/nri2171.
13. Barton GM. A calculated response: control of inflammation by the innate immune system. J Clin Invest. 2008;118(2): 413-20. doi: 10.1172/JCI34431.
14. Liu WY, Lin SG, Wang LR, Fang CC, Lin YQ, Braddock M, et al. Platelet-to-lymphocyte ratio: A novel prognostic factor for prediction of 90-day outcomes in critically ill patients with diabetic ketoacidosis. Medicine (Baltimore) 2016;95(4):e2596. doi: 10.1097/MD.0000000000002596.
15. Olt S, Ergenç H, Açıkgöz SB. Predictive contribution of neutrophil/lymphocyte ratio in diagnosis of brucellosis. Biomed Res Int. 2015;2015: 210502. doi: 10.1155/2015/210502.
16. Bozdemir ŞE, Altıntop YA, Uytun S, Aslaner H, Torun YA. Diagnostic role of mean platelet volume and neutrophil to lymphocyte ratio in childhood brucellosis. Korean J Intern Med. 2017;32(6): 1075-1081. doi: 10.3904/kjim.2016.092.
17. Aktar F, Tekin R, Bektaş MS, Güneş A, Köşker M, Ertuğrul S, et al. Diagnostic role of inflammatory markers in pediatric Brucella arthritis. Ital J Pediatr. 2016;42:3. doi: 10.1186/s13052-016-0211-5.
18. Okan DH, Gökmen Z, Seyit B, Yuksel K, Cevdet Z, Deniz A. Mean platelet volume in brucellosis: correlation between brucella standard serum agglutination test results, platelet count, and C-reactive protein. Afr Health Sci. 2014;14(4):797-801. doi: 10.4314/ahs.v14i4.4.
19. Küçükbayrak A, Taş T, Tosun M, Aktaş G, Alçelik A, NecatiHakyemez I, et al. Could thrombocyte parameters be an inflammatory marker in the brucellosis? Med Glas (Zenica). 2013;10(1):35-9.
20. Togan T, Narci H, Turan H, Ciftci O, Kursun E, Arslan H. The impact of acute brucellosis on mean platelet volume and red blood cell distribution. Jundishapur J Microbiol. 2015;8(2):e20039. doi: 10.5812/jjm.20039.