

Direk ve İndirek İnflamatuvar Belirteçler Brusella Epididimo-Orşiti Non-Brusella Epididimo-Orşitten Ayırabilir Mi?

Can Indirect Inflammatory Markers Differentiate Brucella Epididymo-Orchitis From Non-Brucella Epididymo-Orchitis?

Salih Polat¹, Abdullah Erdoğan²

1 Dogu Beyazit City Hospital, Department of Urology, Agri, Turkey

2 Erzincan University Faculty of Medicine, Department of Urology, Erzincan, Turkey



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Yazışma / Correspondence

Salih Polat

Amasya Üniversitesi Tıp Fakültesi

05220 Amasya / Türkiye

E mail: akyuzosman@hotmail.com

Tel: +90 850 444 02 05 -2157

Fax: +90 212 474 36 94

ORCID

S.P. 0000-0002-1402-7664

A.E. 0000-0002-1402-7664



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Özet

Amaç: Çalışmamızda inflamasyonu gösteren direk ve indirek belirteçlerin Brusella epididimo-orşit (BEO) tanısında ve Brusella dışı epididimo-orşit (NBEO) ayırıcı tanısındaki değerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2015 ve Ocak 2019 yılları arasında akut skrotum kliniği ile başvuran epididimo-orşit tanısı alan 152 hasta retrospektif olarak değerlendirildi. Hematolojik hastalığı, koroner arter hastalığı, malignite tanısı olan 15 hasta, 18 yaşından küçük 8 hasta, hemogram ve C-reaktif protein (CRP) sonuçlarına ulaşamayan 13 hasta çalışma dışı bırakıldı. Epididimo-orşit tanısı fizik muayene bulgularına ek olarak laboratuvar (lökositoz, CRP yüksekliği) ve radyolojik bulgular baz alınarak koyuldu. BEO tanısı orşit semptom ve bulgularına ek olarak pozitif kan kültürü ve standart tüp aglütinasyon (STA) testinde $\geq 1/160$ titre değeri olarak tanımlandı.

Bulgular: Ortalama WBC ($p=0.033$), nötrofil ($p=0.013$), monosit sayısı ($p=0.006$), nötrofil lenfosit oranı (NLR) ($p=0.014$) ve monosit lenfosit oranı (MLR) ($p=0.002$) BEO grubunda istatistiksel olarak anlamlı şekilde daha düşük izlendi. BEO tanısını öngörmeye MLR yüksek prediktif değere (AUC değeri: 0.725, 0.146-0.424; $p=0.002$), yüksek özgüllük (97.3%) ve tanı doğruluk oranına (83.5%) sahipti. BEO ve NBEO ayırıcı tanısında bağımsız bir öngörü değeri olan belirteç saptanmamıştır.

Sonuç: Kolay, hızlı ve düşük maliyetli hematolojik inflamatuvar belirteçler, BEO ve NBEO ayırıcı tanısında serolojik testlere ek olarak tanısız fayda sağlamaktadır. Özellikle MLR diğer parametrelere nazaran yüksek tanı doğruluk oranına sahiptir.

Anahtar Kelimeler: Brusella, epididimo-orşit, enfeksiyöz hastalıklar, monosit/lenfosit oran

Abstract

Objective: This study aimed to evaluate the value of direct and indirect markers showing inflammation in the diagnosis of Brucella epididymo-orchitis (BEO) and its differentiation from non-Brucella epididymo-orchitis.

Material and Methods: A total of 152 patients that presented to our clinic with acute scrotal complaints and were diagnosed with epididymo-orchitis between January 2015 and January 2019 were retrospectively evaluated. Excluded from the study were 15 patients with a hematologic disease, coronary artery disease or malignant diagnosis, eight patients aged below 18 years, and 13 patients whose hemogram and C-reactive protein (CRP) values were not available in their medical records. The diagnosis of epididymo-orchitis was based on laboratory (leukocytosis, CRP elevation) and radiological findings. The diagnosis of BEO was defined as $\geq 1/160$ titer value and/or positive blood culture in the standard tube agglutination (STA) test in addition to orchitis symptoms and signs.

Results: The median WBC ($p=0.033$), neutrophil ($p=0.013$) and monocyte ($p=0.006$) counts and NL ($p=0.014$) and ML ($p=0.002$) ratios were statistically significantly lower in the BEO group. The ML ratio had the highest predictive value with an AUC of 0.725 (95% CI = 0.146-0.424; $p=0.002$), as well as high specificity (97.3%) and diagnostic accuracy (83.5%) in predicting a BEO diagnosis. No parameter was an independent factor in the differentiation of BEO and NBEO.

Conclusions: Easy, fast and low-cost hemotological inflammatory markers provide diagnostic benefits complementing serological tests in distinguishing BEO from NBEO cases. In particular, MLR has a high diagnostic accuracy compared to other parameters.

Keywords: Brucella, epididymo-orchitis, infectious diseases, monocyte/lymphocyte ratio

INTRODUCTION

Brucellosis is a systemic disease with non-specific signs and symptoms, which can be transmitted from animals to humans, involves different systems (genitourinary system, central nervous system, respiratory system and cardiovascular system) through the hematogenous path, and progresses from mild to severe clinical conditions. According to the data from the World Health Organization (WHO), brucellosis is globally the most common bacterial zoonosis, seen in almost any region in the world, and endemic in the Mediterranean basin including Portugal, Spain, Southern France, Italy, Greece, Turkey and North African countries, as well as the Arabian Peninsula, India, Mexico, and Central and South America (1-3).

In addition to systemic involvement, focal involvement is seen in 20-40% of the cases. In the genitourinary system, testicular involvement is the most common, and 2-20% of the patients with brucellosis develop epididymo-orchitis (4,5). Although *Brucella* epididymo-orchitis (BEO) is the first condition to be considered in the presence of clinical history and accompanying findings, it is very difficult to distinguish isolated cases of epididymo-orchitis as the first symptom of brucellosis from non-*Brucella* epididymo-orchitis (NBEO). BEO has a good prognosis when treated in a timely manner, but delayed diagnosis and treatment can lead to serious complications, resulting in orchiectomy and infertility. Therefore, the differential diagnosis of epididymo-orchitis is very important (5,6).

Brucellosis causes an inflammatory response in which acute phase reactants increase. Many studies have defined direct and indirect markers showing the inflammatory response, including white blood cell (WBC) count, neutrophil/lymphocyte ratio (NLR), platelet (PLT) count, mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR). These markers have been shown to increase and provide information about the degree of inflammation and disease prognosis in some types of cancer and inflammatory events (e.g., acute appendicitis, sepsis) (7-12). Despite the availability of studies investigating the efficacy of inflammatory markers in various brucellosis cases, the

data is not clear due to the conflicting results. In the literature, only two studies evaluated direct and indirect markers in the differentiation of cases diagnosed with BEO and NBEO (13,14).

This study aimed to compare the hematologic inflammatory markers between BEO and NBEO cases, evaluate their efficacy in differential diagnosis, and contribute to the literature by reducing the uncertainty concerning this issue.

MATERIAL AND METHODS

A total of 152 patients that presented to the urology clinics of Agri Dogubeyazit State Hospital and Erzinçan University Mengucek Gazi Training and Research Hospital with acute scrotal complaints and were diagnosed with epididymo-orchitis between January 2015 and January 2019 were retrospectively evaluated. Of these 152 patients, 36 were excluded due to hematologic disease, coronary artery disease, malignancy or aged below 18 years, non-avaible hemogram and C-reactive protein (CRP) results. As a result, 22 patients with BEO and 76 patients with NBEO were included in the study. Due to the retrospective nature of the study informed consent was not required.

The diagnosis of epididymo-orchitis was based on clinical (pain, swelling, redness, tenderness), laboratory (elevated leukocytosis and CRP) and radiological (increased epididymis/testis size and blood supply, and parenchymal echo changes on color Doppler ultrasonography) findings. BEO was defined as $\geq 1/160$ titer value and/or positive blood culture in the standard tube agglutination (STA) test in addition to orchitis symptoms and findings.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether the distribution of continuous variables was normal. The continuous data were presented as mean \pm standard deviation (SD) or median (25th-75th) percentiles. The mean differences between the groups of normally distributed data were compared using the independent samples Student's t-test, while the MannWhitney U test was used to compare the data that were not normally distributed. The frequencies of categorical variables were compared using the Pearson χ^2 or Fisher's exact test, where appropriate.

The receiver operating characteristic (ROC) curves were constructed by calculating the sensitivity and specificity of each laboratory measurement. After the cut-off values were determined using the Youden index method, the diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each parameter. A logistic regression multivariate analysis was performed to determine the independent predictive factors for discriminating between BEO and NBEO. Any variable with $p < 0.25$ according to the univariate test was accepted as a candidate for the multivariate model. The odds ratio, 95% confidence interval, and the Wald statistics were also calculated for each independent variable. Data analysis was performed using IBM SPSS version 25.0 (SPSS®, IL, USA). A p value of <0.05 was considered

statistically significant.

RESULTS

In all patients with BEO, the Rose-Bengal test was positive and the titer value was above 1/160 in the STA test. The demographic data and laboratory results of the patients are shown in Table 1. The median age of the patients was 35.5 (26-46) years in the BEO group and 43 (26-55.5) years in the NBEO group. The median WBC ($p = 0.033$), neutrophil ($p = 0.013$) and monocyte ($p = 0.006$) counts were significantly lower in the BEO group, while the mean platelet count, median platelet count, RDW, PDW, PCT and MPV values did not significantly differ between the two groups. The median NLR and MLR were statistically significantly lower in the BEO group ($p = 0.014$ and 0.002 , respectively).

Table 1. Demographic datas and laboratory measurements of the two groups.

	Non-Brucella Epididymo-orchitis	Brucella Epididymo-orchitis	P-value ^a
No. of patients, n	76	22	
Age (years)	43 (26-55.5)	35.5 (26-46)	0.109
Laboratory parameters			
CRP	7.70 (2.94-21.0)	8.15 (1.40-47.4)	0.592
WBC	11.30 (9.74-16.38)	10.3 (5.85-12.0)	0.033
Neutrophil	8.83 (5.90-12.55)	7.20 (3.63-8.73)	0.013
Lymphocyte	2.34 ± 0.94	2.32 ± 1.03	0.371 ^b
Monocyte	0.75 (0.60-0.97)	0.56 (0.33-0.71)	0.006
Platelet count	259 (223.25-300.5)	207 (196-289)	0.138
Hemoglobin	15.3 (13.9-16.0)	15.1 (14.2-15.5)	0.720
RDW	13.0 (12.4-13.6)	12.95 (12.6-14.1)	0.946
PDW	15.7 (12.2-16.1)	16.0 (15.9-16.3)	0.105
PCT	0.25 (0.20-0.30)	0.25 (0.19-0.42)	0.695
MPV	9.13 ± 1.32	9.53 ± 0.55	0.177 ^b
PLR	117.5 (85.5-156.2)	96.2 (81.7-135.6)	0.077
NLR	3.84 (2.28-6.34)	3.00 (2.04-4.28)	0.014
MLR	0.35 (0.24-0.43)	0.19 (0.15-0.41)	0.002
Abnormal laboratory findings			
CRP > 5 mg/dL, n (%)	44 (59.5)	10 (50.0)	0.614 ^c
WBCs/mm ³ > 10.500 (n)	54 (71.1)	12 (54.5)	0.146 ^c

^a Mann-Whitney U test, data shown as median (25th and 75th) percentiles

^b Student's t test, data presented as mean ± SD

^c Continuity Correction

CRP=C-reactive protein, WBC=White blood cell, RDW=Red cell distribution width, PDW=Platelet Distribution Width, PCT=Platelet hematocrit, MPV=Mean platelet volume, PLR=Platelet to lymphocyte ratio, NLR=Neutrophil to lymphocyte ratio, MLR=Monocyte to lymphocyte ratio

Table 2 presents the results of ROC analysis evaluating the predictive power of the parameters in the differentiation of BEO and NBEO. The WBC, neutrophil and monocyte counts, and NLR and MLR were statistically significant in the prediction of a BEO diagnosis.

Among the five parameters investigated, MLR had the highest predictive value with an AUC of 0.725 (95% CI = 0.146-0.424 p = 0.002). Figure 1 and 2 shows the sensitivity and 1 – specificity of the NLR and MLR with respect to BEO for both NLR and MLR.

Table 2. Results of receiver operating characteristic curve analyses

	AUC	95% CI		P-value
		Lower	Upper	
CRP	0.539	0.371	0.708	0.592
WBC	0.650	0.524	0.775	0.033
Neutrophil	0.675	0.559	0.791	0.013
Lymphocyte	0.541	0.310	0.609	0.563
Monocyte	0.693	0.177	0.437	0.006
Platelet count	0.604	0.247	0.544	0.138
Hemoglobin	0.525	0.341	0.609	0.721
RDW	0.505	0.354	0.354	0.946
PDW	0.614	0.486	0.741	0.106
PCT	0.528	0.386	0.669	0.695
MPV	0.585	0.301	0.529	0.227
PLR	0.624	0.478	0.771	0.077
NLR	0.672	0.544	0.800	0.014
MLR	0.715	0.146	0.424	0.002

AUC=Area under the curve, CI=Confidence interval, CRP=C-reactive protein, WBC=White blood cell, RDW=Red cell distribution width, PDW=Platelet Distribution Width, PCT=Platelet hematocrit, MPV=Mean platelet volume, PLR=Platelet to lymphocyte ratio, NLR=Neutrophil to lymphocyte ratio, MLR=Monocyte to lymphocyte ratio

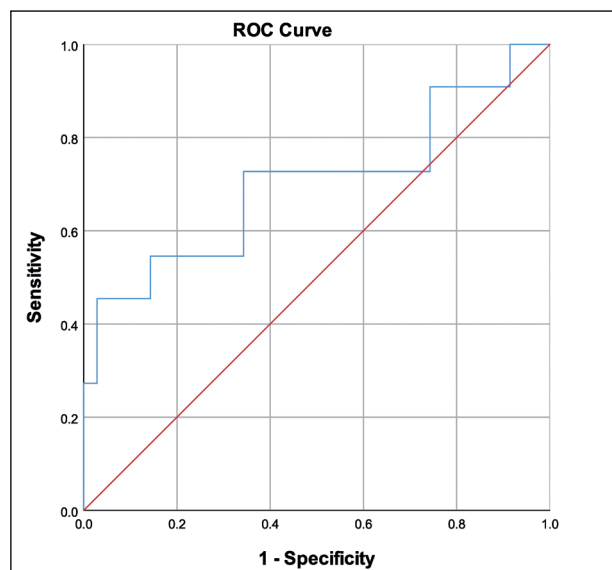


Figure 1: ROC curve of MLR for predicting Brucella Epididymo-orchitis (AUC: 0.715, p=0.002)

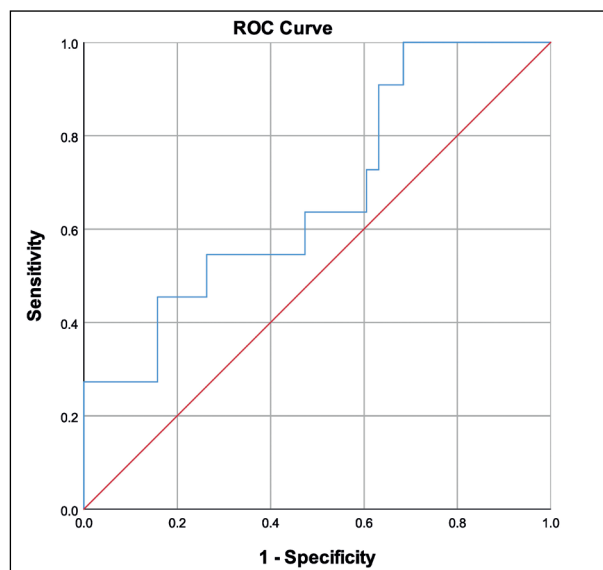


Figure 2: ROC curve of NLR for predicting Brucella Epididymo-orchitis (AUC: 0.672, p=0.014)

Table 3 shows the sensitivity, specificity, PPV, NPV and accuracy rate of the parameters in predicting BEO at the cut-off values obtained. According to the ROC analysis, the cut-off value of WBC count was found to be 14.4 in predicting a BEO diagnosis, indicating that the probability of such a diagnosis is increased below this value. At the cut-off value of 14.4, WBC count was found to have very high sensitivity (100%) but low specificity (34.2%). The accuracy of this parameter was

48.9% in the diagnosis of BEO. Similarly, neutrophil count, monocyte count and NLR had low specificity but high sensitivity. The cut-off value for MLR was calculated as 0.16 and the probability of a BEO diagnosis is increased at lower values. MLR had high specificity (97.3%) and diagnostic accuracy (83.5%) in predicting a BEO diagnosis. No parameter was an independent predictive factor for the differentiation of BEO and NBEO (Table 4).

Table 3. Cut-off, sensitivity, specificity, and accuracy rates of laboratory measurements in prediction of Brucella Epididymo-orchitis

	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
WBC	<14.4	100.0%	34.2%	30.6%	100.0%	48.9%
Neutrophil	<9.22	90.9%	44.7%	32.3%	94.4%	55.1%
Monocyte	<0.71	81.8%	57.9%	36.0%	91.7%	63.2%
NLR	<5.63	100.0%	31.6%	29.7%	100.0%	46.9%
MLR	<0.16	36.4%	97.3%	80.0%	83.9%	83.5%

PPV=Positive predictive value, NPV=Negative predictive value, WBC=White blood cell, NLR=Neutrophil to lymphocyte ratio, MLR=Monocyte to lymphocyte ratio

Table 4. Univariate and Multivariate logistic regression analysis of variables

	Odds ratio	P-value a	95% CI		Odds ratio	P-value	95% CI	
			Lower	Upper			Lower	Upper
WBC	0.843	0.010	0.740	0.960	1.340	0.255	0.810	2.216
Neutrophil	0.803	0.006	0.686	0.940	0.644	0.078	0.394	1.051
Monocyte	0.112	0.022	0.017	0.727	0.162	0.237	0.008	3.314
NLR	0.748	0.034	0.571	0.978				
MLR	0.013	0.034	0.000	0.718				

CI=Confidence interval, WBC=White blood cell, NLR=Neutrophil to lymphocyte ratio, MLR=Monocyte to lymphocyte ratio

^a p<0.25 as significant

DISCUSSION

Brucellosis is one of the most common zoonotic diseases caused by Brucella bacteria, and there is direct or indirect animal contact in all cases. In countries where the disease is endemic, the main transmission route is consumption of unpasteurized dairy products whereas in developed countries, it is predominantly transmitted through contact or inhalation (15). Brucellosis can involve any organ or system in the body and causes wide-ranging clinical symptoms. Therefore, patients are often misdiagnosed and treatment is delayed. In their review of 24 articles, Zheng et al. reported that 1,287

of 2,148 patients with brucellosis had been misdiagnosed with cold, rheumatism fever, rheumatoid arthritis, tuberculosis, malaria, septicemia, and lumbar disc herniation (16).

BEO, first described by Hardy in 1928, is the most common genitourinary system complication of brucellosis (17). In clinical practice, BEO can often be confused with NBEO, tuberculosis epididymo-orchitis, testicular abscess, and testicular tumor. In patients with BEO, delayed diagnosis/treatment or inappropriate treatment causes serious complications, such as testicular abscess, infarction, atrophy, necrosis, loss of sperma

togenic function, and infertility (6).

Scrotal pain and swelling are the most common symptoms in patients with BEO, seen in almost all cases. These are often accompanied by fever, sweating and fatigue. Arthralgia, anorexia, nausea-vomiting, and dysuria may also be present, albeit at a lower frequency. However, all these symptoms can also occur at a similar frequency in patients with an NBEO diagnosis (6,18,19). Despite many studies in the literature suggesting that the absence of lower urinary tract symptoms (LUTS) is an indication of BEO, Khan et al (18) reported that patients with BEO had similar rates of LUTS (62% vs. 64%, $p > 0.05$). The urinalysis results of patients with BEO were investigated in the differentiation of BEO and NBEO cases, and pyuria was detected at a rate of 58.8% -100% in patients with NBEO, indicating that this symptom might be a predictive factor for NBEO. However, in the literature, it is also reported that the urinalysis of 10–35% BEO cases reveals the presence of pyuria, hematuria, proteinuria or various combinations thereof (19-21). As a result, both clinical and urinalysis results seem to be insufficient in the differential diagnosis.

Many abnormal laboratory findings, mostly non-specific, have been reported in the diagnosis and differential diagnosis of BEO. These findings include erythrocyte sedimentation rate (ESR) and increased liver functions, anemia, thrombocytopenia, leukocytosis, leukopenia, and pancytopenia. Leukocyte counts are either normal or lower in patients with brucellosis; therefore, leukocytosis is not a determinant laboratory finding (21). Although the literature contains studies reporting 10% to 30% rates for leukocytosis in BEO cases, some publications found that this percentage reached 70% (18,20). In their study comparing BEO and NBEO cases, Cift et al. (13) noted that the mean WBC count was lower in the former whereas Aydın et al. (14) found no difference between the two groups in terms of the mean WBC count. In the current study, the rate of leukocytosis was determined as 54.5% and 71.1% in BEO and NBEO cases, respectively. In addition, similar to the study by Cift et al. (13) we found a significantly lower mean WBC count in patients with BEO. In our study, a WBC count of <14.4 had high sensitivity and

low specificity for BEO and accurately predicted the diagnosis in 48.9% of cases. Therefore, WBC is not considered to be an effective parameter. CRP, another inflammatory marker, was increased in 50-100% of BEO cases. In a study comparing CRP in patients with BEO and NBEO, no difference was observed between the two groups (21). Similarly, the mean CRP values and the number of patients with elevated CRP were similar in the BEO and NBEO groups of the current study.

As mentioned earlier in this paper, one of the abnormal laboratory findings caused by brucellosis is thrombocytopenia. Proinflammatory cytokines and acute phase reactants released during infection affect platelet size. MPV is an easy and low-cost marker that can be used to measure platelet size and function. High MPV values have been associated with pulmonary tuberculosis and hydatid cysts while low MPV values can be related to inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, acute pancreatitis, and appendicitis (9,22). In a study exploring the relationship between MPV and Brucella, the MPV values were found to be lower in brucellosis cases compared to the control group (23) Kücükbayrak et al. (24) reported that the MPV values increased after treatment in brucellosis cases. In contrast, Aktar et al. (7) determined higher MPV values in patients with Brucella arthritis compared to the control group. Togan et al. (25) reported similar results and concluded that MPV was not a good marker for both diagnosis and treatment of acute brucellosis. In their studies comparing the BEO and NBEO cases, Cift et al. (13) and Aydın et al. (14) reported that the MPV value was significantly lower in the former. Although inflammatory markers have been associated with many diseases in the literature, there is only limited research demonstrating their relationship with Brucella. In the current study, the median MPV value was similar in both groups and no significant difference was found.

RDW is a marker indicating heterogeneity in the size of erythrocytes and can be easily measured in a complete blood count. It has been reported to have predictive value in infectious pathologies, such as acute pancreatitis, bacteremia, sepsis, and septic shock (26). Lippi et al. (27) found a correlation between RDW and

CRP and ESR. However, conflicting results were obtained from studies investigating the relationship between RDW and Brucella. For example, in contrast to Kucukbayrak et al. (26) who reported high RDW values before and after brucellosis treatment, Togan et al. (25) noted no difference before and after brucellosis treatment or between the study and control groups. Similar contradictions are present in studies comparing the BEO and NBEO groups. Cift et al. (13) found that RDW was significantly higher in patients with BEO while Aydın et al. (14) found no significant difference between the two groups similar to our study. Our findings show that RDW cannot be used as a marker for the differentiation of BEO and NBEO cases.

It has been shown that NLR and PLR may be indicators of systemic inflammation and may be useful in differential diagnosis and providing information on the prognosis of many diseases. At the same time, these ratios were found to be correlated with ESR, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) values (28). Monocytes are one of the main components of the immune system due to their role of expressing antigens for lymphocytes. It has been suggested that MLR, together with NLR, can be used in the diagnosis of bacterial infections. Furthermore, in a study, abnormal MLR values (low or high) were determined in patients with active tuberculosis; thus, MLR was considered as a marker for active tuberculosis (29). However, there are only few studies showing the relationship between Brucella and NLR, PLR and MLR. Aktar et al. (7) comparatively evaluated pediatric Brucella arthritis cases with healthy children and determined higher NLR and PLR values for the former. In a similar study, Bozdemir et al. (30) found the NLR to be significantly higher in the group with Brucella arthritis, but there was no difference between the non-arthritic Brucella group and the healthy group. There are two studies in the literature comparing the NLR, PLR and MLR parameters between the BEO and NBEO cases, both conducted in Turkey with a similar number of patients. The first study was undertaken by Aydın et al. (14) who found that only MLR was significantly higher in the BEO group and concluded that an MLR value above ≥ 0.265 had a sensitivity of 71.4% and a speci-

ficity of 65.9% in the differential diagnosis of BEO. In the second study, Cift et al. (13) reported that NLR and MLR were significantly lower in patients with BEO and that an NLR value of < 2.3 was an independent marker in the diagnosis of BEO. In the current study, NLR and MLR were significantly lower in patients with BEO, but PLR was similar in the two groups.

To summarize, in our study, WBC, neutrophil and monocyte counts, NLR and MLR were found to be lower in BEO cases compared to NBEO cases. An MLR of lower than 0.16 had the highest diagnostic accuracy (83%) in the differentiation of BEO and NBEO. However, no parameter presented as an independent predictor of BEO diagnosis.

The main limitations of our study were that it had a retrospective nature and relatively small sample size. In addition, we did not know the time from the onset of patient complaints to hospital referral and performed evaluations based on the results of a single hemogram analysis.

CONCLUSION

The results of this study show that hemotological inflammatory markers that are easy, fast and inexpensive to obtain assist physicians in distinguishing BEO from NBEO in cases where such differentiation is not possible based on clinical and radiological findings, and these markers can complement serological tests in diagnosis. In particular, MLR appears to be superior considering the results of this study and previous research. However, the findings presented in this study should be supported by future prospective studies with a larger case series, and the relationship between BEO and inflammatory markers, as well as its underlying mechanism should be more clearly defined.

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