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Research Article

The Role of Laboratory Parameters in Predicting Osteoarticular Involvement in Brucellosis

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Abstract

Objectives: Osteoarticular involvement in brucellosis, is a common complication, leads to prolonged treatment and morbidity. This study aimed to predict osteoarticular involvement using laboratory parameters.

Methods: A total of 210 patients diagnosed with brucellosis were retrospectively evaluated. Patients were divided into two groups based on the presence or absence of osteoarticular involvement. The variables between the two groups were analyzed for risk factors to predict osteoarticular involvement in brucellosis using laboratory parameters.

Results: The mean age of the patients was 47.5±15.1 years, and 60.5% were male. Osteoarticular involvement group was older. White blood cell (WBC) count, neutrophil count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels were significantly higher, lymphocyte-to-monocyte ratio (LMR) was lower in patients with osteoarticular involvement. The sensitivity and specificity for CRP at a cut-off value of 22.5 mg/L were determined as 90.7%. For ESR at a cut-off value of 59.5 mm/h, the specificity was 94.7%.

Conclusion: Laboratory parameters such as WBC, neutrophil count, NLR, LMR, CRP, and ESR may facilitate the clinical decision-making process in the early detection of osteoarticular involvement in patients with brucellosis. These findings may serve as a valuable guide in managing brucellosis complications, particularly in endemic regions.

Keywords: Brucellosis, ostoarticular involvement, zoonotic disease

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Brucellosis is a zoonotic disease that can be transmitted to humans from animals such as sheep, goats, cattle, and pigs. The disease is most commonly transmitted through the consumption of raw, unboiled, or unpasteurized milk and dairy products from infected animals. Less frequently, it can also be transmitted through direct contact of infected animal tissues or secretions (blood, urine, vaginal secretions, aborted fetuses, and especially the placenta) with the conjunctiva or damaged skin, inhalation of infected aerosols, or occupational exposure among farmers, slaughterhouse workers, and laboratory personnel. Although brucellosis has been eradicated in many regions of Europe, its global incidence ranges between 0.03 and 160 per 100,000 population.[1,2] It is most commonly observed in Mediterranean countries, the Balkans, the Persian Gulf, the Middle East, Central and South America.[1,2] Türkiye and its neighboring countries remain endemic for brucellosis. According to data from the Ministry of Health, the number of cases showed a declining trend between 2008 and 2015 but started to rise again thereafter. The incidence was reported as 12.2 per 100,000 in 2019.[3]

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Brucellosis is a disease that can affect various organs and systems, often mimicking the clinical presentation of many other conditions. Patients may present with nonspecific symptoms such as fever, nausea, vomiting, headache, sweating, arthralgia, back pain, lower back pain, weakness, weight loss, and fatigue, while some cases remain asymptomatic.[1,3] Predicting the occurrence of complications in brucellosis is challenging. The most common complication of brucellosis is osteoarticular involvement. Patients with bone and joint involvement experience a more prolonged and challenging treatment course. In the absence of specific symptoms, these cases may be overlooked or subjected to unnecessary imaging procedures to rule out the possibility. Clinical findings are diverse and nonspecific.[1,4] There are limited studies in the literature investigating parameters that may predict osteoarticular involvement in brucellosis. Therefore, in this study, we aimed to predict osteoarticular involvement in brucellosis patients using laboratory parameters independent of clinical symptoms, enabling appropriate radiological imaging and interventional planning for selected patients.

Methods

Study Design and Population

The study was conducted retrospectively between September 2022 and October 2023 at Giresun Training and Research Hospital and Kahramanmaraş Necip Fazıl City Hospital. A total of 210 adult patients (aged over 18) diagnosed with brucellosis were included. The diagnosis of brucellosis was established based on a *Brucella* standard tube agglutination (SAT) result of ≥1/160 and/or the growth of Brucella species in blood, bone marrow, bone tissue, or joint fluid cultures. Patients with relapsing brucellosis, a known history of concomitant infectious, neoplastic, or hematologic diseases were excluded from the study. Magnetic resonance imaging (MRI) reports were evaluated to determine osteoarticular involvement.

Demographic data and laboratory parameters, including white blood cell count (WBC), neutrophil count, hemoglobin (Hb), lymphocyte count, platelet count (PLT), platelet distribution width (PDW), red blood cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), mean platelet volume (MPV), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and *Brucella* SAT results, were recorded retrospectively. Patients were classified into two groups based on the presence or absence of osteoarticular involvement. The variables between the two groups were analyzed to assess risk factors for predicting osteoarticular involvement in brucellosis.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean, standard deviation, percentage, and median (minimum-maximum). The normal distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test and graphical evaluations. For comparisons of quantitative data, the independent sample t-test was used when normality was met, while the Mann-Whitney U test was applied otherwise. The chi-square test was used for comparing categorical variables between independent groups. The area under the receiver operating characteristic (ROC) curve was used to evaluate the effectiveness of CRP and ESR in identifying patients with osteoarticular involvement. Sensitivity and specificity values for these indicators were calculated based on ROC curves. A p-value of 0.05 was considered statistically significant.

Results

A total of 210 patients diagnosed with brucellosis were included in the study. The mean age was 47.5±15.1 years (range: 18–87), and 127 (60.5%) of the cases were male. Osteoarticular involvement was detected in 97 patients, while 113 patients had no involvement. Among those with osteoarticular involvement, 67 patients were diagnosed with spondylodiscitis, 26 with sacroiliitis, and 4 with peripheral arthritis.

The mean age of patients with osteoarticular involvement was 51.8±16.3 years (range: 18–87), while it was 43.8±12.9 years (range: 19–81) in the group without osteoarticular involvement ($p<0.001$). There was no statistically significant difference between the two groups in terms of gender. WBC count, neutrophil count, NLR, ESR, and CRP levels were significantly higher in the osteoarticular involvement group ($p<0.05$ for all). LMR was significantly lower in brucellosis patients with osteoarticular involvement ($p<0.007$). Hb, PLT, PDW, RDW, PLR, AST, ALT, MPV, and Brucella SAT titers were similar between the two groups ($p>0.05$). The data for both groups are presented in Table 1.

The ROC analysis results for ESR and CRP, which were found to be statistically significant in the osteoarticular involvement group, are shown in Table 2 to determine cut-off values for distinguishing osteoarticular involvement (Fig. 1). In the ROC analysis, a cut-off value of 22.5 mg/L for CRP had a sensitivity of 90.7% and a specificity of 61.1%. For ESR, a cut-off value of 59.5 mm/h showed a sensitivity of 28.9% and a specificity of 94.7%.

Table 1. Patients' laboratory results at admission

Variable	OA involvement (+) (n=97)	OA involvement (-) (n=113)	p
Age, mean±SD (min-max)	51.8±16.3	43.8±12.9	<0.001
Male, n (%)	59 (60.8)	68 (60.2)	0.924
WBC (×10^9 cells/l), mean±SD (min-max)	8.08±2.27 (4.12-14.95)	6.85±2.09 (2.47-15.06)	<0.001
Neutrophil (×10^9 cells/l), mean±SD (min-max)	4.87±1.85 (1.77-10.65)	3.81±1.58 (0.73-11.09)	<0.001
Hemoglobin (g/dl), mean±SD (min-max)	12.1±1 (8.8-14)	12.3±1.1 (9-15.1)	0.209
Lymphocyte (×10^9 cells/l), mean±SD (min-max)	2.43±0.96 (0.49-6.43)	2.3±1.09 (0.3-7.14)	0.489
Thrombocyte (×10^9 cells/l), mean±SD (min-max)	277.79±102.67 (77-721)	253.10±92.104(8-522)	0.137
PDW (fL)	13.36±2.08 (9.9-16.7)	14.06±2.07 (7.6-16.4)	0.117
RDW (fL)	42.95±5.85 (35.5-75.8)	41.93±6.82 (34.8-85.3)	0.09
NLR	2.35±1.4 (0.38-9.27)	2.06±1.75 (0.38-14.17)	0.018
PLR	135.67±93.09 (22.12-721)	133.14±110.28 (11.59-900)	0.469
LMR	4.29±2.12 (0.92-14.29)	5.44±4.08 (1.23-35.75)	0.007
MPV (fL)	9.51±1.17 (7-13.6)	9.32±1.23 (6.9-13.1)	0.250
AST (U/l), mean±SD (min-max)	28.55±17.57 (10-120)	33.17±21.98 (11-159)	0.081
ALT (U/l), mean±SD (min-max)	32.59±28.10 (9-206)	35.10±23.07 (2-111)	0.157
CRP (mg/l), mean±SD (min-max)	52.48±35.81 (6-228)	24.04±28.83 (1-159)	<0.001
ESR (mm/h), mean±SD (min-max)	49.44±21.64 (14-113)	26.98±18.47 (5-90)	<0.001
SAT	331.55±218.17 (160-1280)	331.33±175.94 (160-640)	0.817

ALT: alanine transaminase; AST: aspartate transaminase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; g/dl: gram/decilitre; l: litre; mg/dl: miligram/decilitre; fL: femtoliters; mm/h: mililitre/hour; mg/l: miligram/litre; SD: standard deviation; U/l: unite/litre; WBC: white blood cell; NLR: Neutrophil Lymphocyte Rate; LMR: Lymphocyte Monocyte Rate; PLR: Platelet Lymphocyte Rate; MPV: Mean platelet volume; PDW: Platelet Distribution Width; RDW: red cell distribution width; SAT: Serum Agglutination Test.

Table 2. Receiver operating characteristics (ROC) analysis to calculate the sensitivity and specificity of laboratory markers for osteoarticular involvement

Variable	Cut-off	AUC (95% CI)	p	Sensitivity (%)	Specificity (%)
CRP (mg/l), mean±SD (min-max)	22.5	0.804(0.744-0.865)	<0.001	90.7	61.1
ESR (mm/h), mean±SD (min-max)	59.5	0.799 (0.740-0.858)	<0.001	28.9	94.7

AUC: area underneath the ROC curve; CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Discussion

Brucellosis is an endemic zoonotic disease in our country, with osteoarticular involvement being the most common complication.[3,5] The clinical presentation of the disease varies widely, ranging from asymptomatic cases to symptoms that mimic many other conditions. The treatment duration for uncomplicated brucellosis is six weeks. However, when osteoarticular involvement occurs, the treatment period is prolonged, the number of drugs used increases, and treatment options specific to osteoarticular involvement may vary. If osteoarticular involvement is not recognized in time, it can lead to serious loss of work capacity and long-term sequelae.[1]

In our study, spinal involvement was observed in 93 of the 97 patients with osteoarticular involvement. Widespread joint and muscle pain are common symptoms in brucellosis,[1,3,6] and these complaints may often indicate osteoarticular involvement. Some studies have reported that lower back and back pain are significant findings for spinal involvement.[7-9] In another study examining 111 brucellosis patients, only 11 had osteoarticular involvement, while 79 reported lower back pain, highlighting the importance of this symptom.[10] A review also emphasized that back pain was the most frequently reported symptom in spinal brucellosis patients, with a reported rate of 50%.[5] In a study by Gheita et al.,[11] asymptomatic sacroilietis was found in 24% of brucellosis patients. This study, which analyzed 100 brucellosis patients, indicated that patients with sacroiliitis might not always present with back pain or related physical examination findings. Therefore, in our study, we aimed to predict osteoarticular involvement in brucellosis patients based on laboratory parameters independent of clinical symptoms.

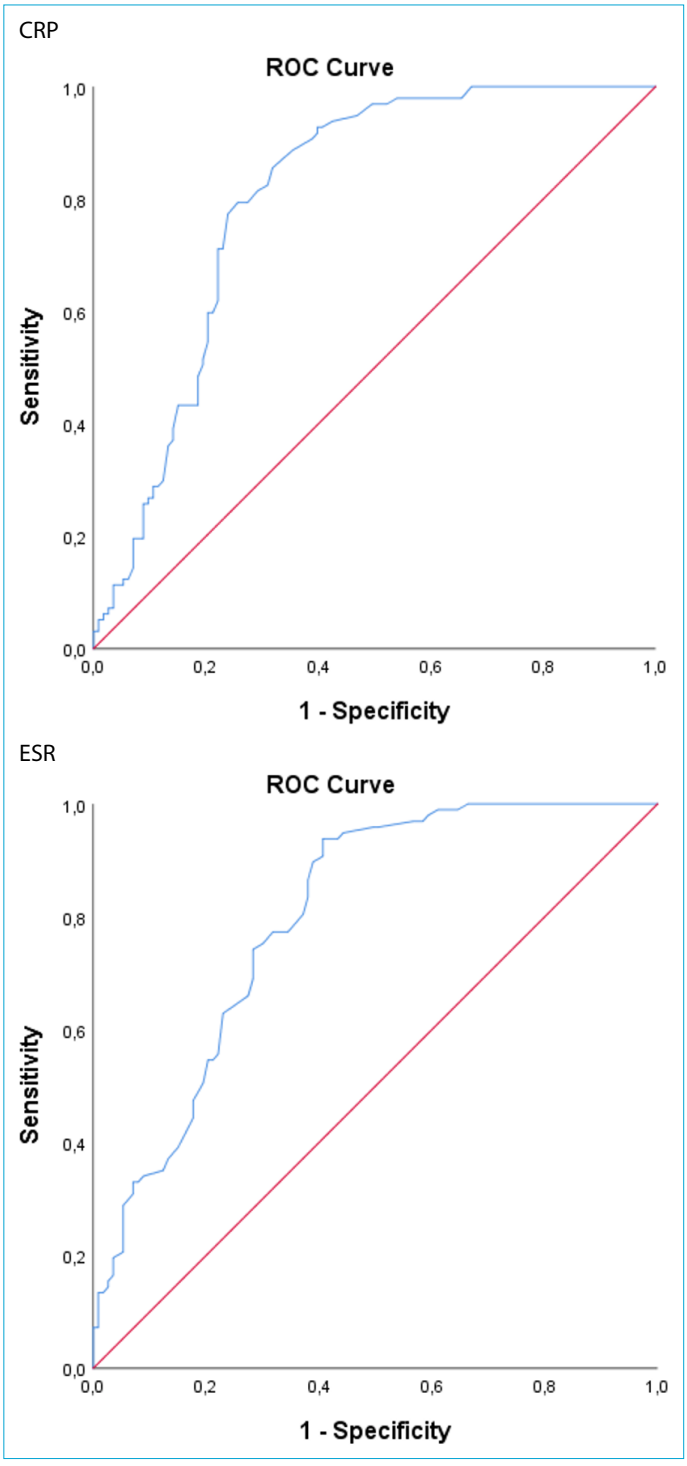

Figure 1. ROC curves for predicting osteoarticular involvement.

Although osteoarticular involvement is generally more common in males, both groups in our study were similar in terms of gender distribution.[5,12] The mean age of the group with osteoarticular involvement was 51.8±16.3 years (range: 18–87), while it was 43.8±12.9 years (range: 19–81) in the group without involvement ($p<0.001$). The finding that brucellosis patients with osteoarticular involvement were older aligns with the literature.[5,9] This may be explained by degenerative changes in the joints with aging, which facilitate bacterial colonization, and by the affinity of Brucella for synovial tissues.[13]

Leukocytosis or leukopenia are expected findings in brucellosis.[1] According to the Ministry of Health data, only 9% of patients develop leukocytosis, 11% develop leukopenia, while the majority have normal leukocyte counts.[3] In our study, the leukocyte count was higher in patients with osteoarticular involvement compared to those without, and this difference was statistically significant and consistent with the literature.[7,9] Although there was no significant overall increase in leukocyte count in both groups, the higher leukocyte count in osteoarticular involvement may be due to increased functional activity of leukocytes and the presence of chronic inflammation in osteoarticular involvement. Similarly, neutrophil count was also significantly higher in the osteoarticular involvement group for the same reason. However, no significant difference was found between the two groups in terms of platelet counts, which is consistent with the literature.[3,7]

NLR was proposed as an infection marker by Zahorec et al.[14] and has been evaluated in various studies since then. Some studies have reported that an elevated NLR is significant in predicting focal organ involvement in brucellosis.[15,16] Another study found that NLR was elevated at the beginning of brucellosis treatment and could be used as a follow-up parameter.[17] In our study, NLR elevation was also found to be a statistically significant indicator of osteoarticular involvement. Although there was no significant increase in neutrophil count, the elevated NLR in osteoarticular involvement may be explained by prolonged neutrophil activation due to chronic inflammation, suppression of lymphocytes, and the relative persistence of neutrophils at higher levels.

Studies on the LMR have yielded varying results regarding its predictive value for focal organ involvement.[7,16] In our study, LMR was significantly lower in the osteoarticular involvement group. Monocytes play a critical role in sustaining chronic inflammation by differentiating into macrophages in tissues and contributing to granuloma formation. Since osteoarticular involvement is a common chronic complication of brucellosis that involves granulomatous inflammation, we believe the increase in circulating monocytes affects this ratio.

CRP and ESR levels may vary in brucellosis patients.[18] According to Ministry of Health data and some publications, more than half of the cases present with elevated CRP levels.[3,10,19] Inflammatory markers are expected to be even higher in osteoarticular involvement.[7,20,21] ESR elevation

has been associated with focal organ involvement, particularly osteoarticular involvement, in various studies.[6,7] In our study, CRP and ESR levels were significantly higher in the osteoarticular involvement group compared to the group without involvement. The elevation of CRP, an acute-phase reactant, in osteoarticular involvement can be attributed to the persistent increase in proinflammatory cytokines due to chronic joint inflammation. A recent meta-analysis found that CRP and ESR elevations are good indicators for diagnosing osteomyelitis.[22] The role of ESR elevation in diagnosing osteomyelitis has been recognized for a long time.[23] Therefore, predicting osteoarticular involvement in brucellosis patients with elevated ESR may help prevent missed diagnoses and enable early treatment. In the ROC analysis performed for CRP and ESR, which we considered better markers for detecting osteoarticular involvement in clinical practice, a cut-off value of 22.5 mg/L for CRP was associated with a sensitivity of 90.7% and specificity of 61.1%. For ESR, a cut-off value of 59.5 mm/h showed a sensitivity of 28.9% and specificity of 94.7%. These results suggest that CRP, with its high sensitivity, is a valuable parameter for ruling out osteoarticular involvement, while ESR, due to its high specificity, serves as a strong indicator supporting the presence of osteoarticular involvement.

Given that brucellosis is a disease that can mimic many different conditions or even present asymptomatically, predicting its progression and complications based on clinical symptoms alone is often challenging. Osteoarticular involvement is the most common complication of brucellosis, and its prediction is important for avoiding unnecessary imaging tests and determining appropriate treatment duration. Evaluating laboratory markers such as WBC count, neutrophil count, NLR, LMR, ESR, and CRP in the early detection of osteoarticular involvement in brucellosis patients can facilitate clinical decision-making. In particular, CRP and ESR values, due to their high sensitivity and specificity, may serve as valuable guides for clinicians.

Disclosures

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