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Risks of organ involvement in brucellosis cases: A 3-year single center retrospective study

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ABSTRACT

Objective: To identify predictive factors for brucellosis by analyzing cases with and without focal involvement.

Methods: This single-center retrospective study included adults (≥18 years) diagnosed with brucellosis at Ağrı Training and Research Hospital between January 1, 2022 and December 31, 2024. Patients were evaluated for organ involvement based on localized symptoms and classified accordingly. Logistic regression analysis was performed to identify demographic, clinical, and laboratory predictors of organ involvement.

Results: A total of 210 cases were analyzed including 115 females (54.8%) and 95 males (45.2%). Among patients with focal involvement, the proportion of males was higher (54.4%), and comorbidities were also more common (34.4%). Days of complaints before hospital admission was significantly longer in patients with focal involvement (median 31 days) compared to those without focal involvement (median 20 days) (P=0.004). Lower back pain and testicular pain were more common in focal cases, with elevated levels of leukocytes, neutrophils, monocytes, C-reactive protein, and erythrocyte sedimentation rate (ESR). Osteoarticular involvement was found in 61/90 cases (67.7%). Logistic regression identified male sex (*OR* 2.56; 95% *CI* 1.29-5.04), subacute (*OR* 3.74; 95% *CI* 1.36-10.32) or chronic presentation (*OR* 29.01; 95% *CI* 2.96-284.20), and elevated ESR (*OR* 1.03; 95% *CI* 1.01-1.05) as independent risk factors for focal involvement. The model explained 33.9% of the variance, with 74.3% accuracy.

Conclusions: Male sex, subacute or chronic brucellosis, and elevated ESR are key risk factors for focal brucellosis.

KEYWORDS: Brucellosis; Complication; Risk factors; Warning signs; Zoonoses

1. Introduction

Brucellosis is a prevalent zoonotic infection globally, caused by *Brucella* spp., a Gram-negative, non-motile, non-spore-forming, aerobic coccobacillus that proliferates intracellularly. Human transmission occurs primarily through the consumption of unpasteurized milk and dairy products from infected animals, as well as through direct contact with the excretions of infected animals *via* compromised skin or mucous membranes[1,2].

Summary

Question: How can organ involvement be predicted in patients diagnosed with brucellosis?

Findings: In this retrospective, a single-center study of 210 patients, logistic regression identified male sex (*OR* 2.56; 95% *CI* 1.29-5.04), subacute (*OR* 3.74; 95% *CI* 1.36-10.32) or chronic presentation (*OR* 29.01; 95% *CI* 2.96-284.20), and elevated erythrocyte sedimentation rate (*OR* 1.03; 95% *CI* 1.01-1.05) as independent risk factors for focal involvement.

Meaning: Male patients, those with subacute or chronic presentation of brucellosis, and elevated erythrocyte sedimentation rate, greater awareness is required regarding organ involvement.

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The average incubation period for the microorganism is 2 to 4 weeks. Clinical symptoms commonly include fever, joint pain, muscle pain, headache, nausea, weakness, and fatigue[3,4]. Over 500 000 new cases of brucellosis are reported globally each year. However, the actual number of cases is believed to be higher, as patients often present with non-specific symptoms[3].

Following infection, the microorganism localizes in the lymph nodes, liver, spleen, and bone marrow, all of which are part of the reticuloendothelial system. While the majority of the microorganisms are cleared by macrophages, some manage to survive by evading antibodies within the host cells[5]. Focal infection or complications occur when the microorganism in the bloodstream disseminates and affects any organ[1,2]. Although various organs can be affected, osteoarticular system and genitourinary system involvement are the most common forms of focal infection observed in clinical practice[3].

The diagnosis of brucellosis is established through a thorough patient history and physical examination, alongside a combination of laboratory and radiological investigations[1]. Microbiologically, diagnosis relies on culture, serological testing, and nucleic acid amplification tests. Laboratory evaluations also include complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and liver function tests, although these are not specific to brucellosis[1,6].

Due to its clinical similarity to various other diseases, diagnosing brucellosis can be challenging. Delayed diagnosis often leads to organ involvement and complications, which can result in organ damage and increased healthcare costs[7]. Involvement of anatomical sites other than the hematologic system was classified as focal brucellosis. The aim of our study was to identify predictive factors that could facilitate early diagnosis by analyzing brucellosis cases with and without focal involvement.

2. Methods

2.1. Patient selection and parameters

This retrospective, single-center study was conducted at the Infectious Diseases and Clinical Microbiology Clinic of Agri Training and Research Hospital, where patients admitted between January 1, 2022, and December 31, 2024, were assessed.

Our study included cases that met the diagnostic criteria for brucellosis, presented with generalized symptoms, underwent appropriate diagnostic tests in the presence of localized symptoms, and were aged 18 years or older. Exclusion criteria encompassed pregnant or breastfeeding women, patients with chronic renal failure, malignancy, cirrhosis, autoimmune diseases, and those receiving immunosuppressive therapy.

Demographic data, including age, sex, place of residence, exposure history (such as consumption of raw milk and dairy products, animal husbandry, and laboratory exposure), comorbidities, date of presentation, history of previous brucellosis, duration of symptoms (in days), presenting symptoms, and clinical classifications (acute, subacute, and chronic), were retrospectively collected from the hospital's electronic record system. Additionally, information on blood cultures, serologic tests (standard tube agglutination or Coombs gel test), blood parameters (including hemogram, ESR, CRP, transaminases, glucose, urea, and creatinine), and organ involvement was gathered. The patients were categorized into two primary groups: those with organ involvement and those without.

2.2. Clinical definitions

Direct exposure to tissues and secretions from animals suspected of being infected with *Brucella* species, as well as contact with conjunctival membranes or damaged skin, consumption of raw or unpasteurized milk and dairy products, or inhalation of contaminated aerosols, are considered potential routes of exposure for brucellosis. Individuals presenting with clinical symptoms such as fever, malaise, anorexia, weight loss, headache, night sweats, and musculoskeletal pain are regarded as clinically suspicious for brucellosis.

Patients exhibiting symptoms for up to 8 weeks who met the diagnostic criteria for brucellosis were classified as having acute brucellosis. Those with symptoms persisting between 8 and 52 weeks were categorized as having subacute brucellosis, while patients with symptoms lasting longer than 52 weeks were diagnosed with chronic brucellosis[1].

Complications associated with brucellosis may involve the osteoarticular, hematologic, cardiovascular, genitourinary, neurological, ocular, and gastrointestinal systems[8]. Involvement of anatomical sites other than the hematologic system was classified as focal brucellosis. Focal manifestations include osteoarticular conditions (such as sacroiliitis, spondylodiscitis, and peripheral arthritis), genitourinary involvement (such as epididymoorchitis), organomegaly (hepatomegaly and splenomegaly), and dermatological manifestations (such as erythema nodosum). Diagnostic criteria for sacroiliitis include hip pain and radiographic or magnetic resonance imaging evidence of hip involvement; for

spondylodiscitis, low back pain and spinal magnetic resonance imaging findings; for peripheral arthritis, inflammatory changes in the joint and radiographic evidence; for epididymoorchitis, scrotal Doppler imaging; for hepatosplenomegaly, ultrasound findings; and for skin manifestations, the exclusion of other potential pathologies[9].

2.3. Microbiological definitions

Patients with a history of exposure and clinical suspicion of brucellosis were screened using the Rose Bengal test (THSK antigen, Turkey). Blood cultures were collected from those who tested positive in the Rose Bengal assay, followed by either standard tube agglutination (THSK antigen, Turkey) or the *Brucella* Coombs gel test (BCGT, ODAK, Turkey). Brucellosis was diagnosed in patients with a serologic titer of 1/160 or higher, or those showing a fourfold increase in serologic titer over a 2-week period[4].

Blood cultures were obtained in two sets (four bottles), including both aerobic and anaerobic bottles. The cultures were incubated using the Render automated blood culture system (BC256 Blood Culture Systems, China). Identification of *Brucella* spp. or *Brucella melitensis* at the species level was performed using the VITEK-2® Compact system (Biomerieux, France).

2.4. Statistical analysis

For continuous variables, the normality of numerical variables was assessed using the Shapiro-Wilk test. For variables that followed a normal distribution, data were presented as mean±standard deviation (SD) and intergroup comparisons were performed using the independent *t*-test, while the Mann-Whitney *U* test was applied to variables that did not follow a normal distribution. Categorical variables were expressed as number (*n*) and percentage (%) and the *Chi*-square test was used to compare categorical variables between groups. Receiver Operating Characteristic (ROC) analysis was conducted to assess focal involvement in relation to various quantitative laboratory parameters, and predictive values, including sensitivity and specificity, were calculated. To identify predictors of organ involvement, parameters that were significant in univariate analyses ($P<0.05$) or considered clinically relevant were selected and entered into a binary logistic regression model. All analyses were performed using SPSS 26 (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp, USA). A *P*-value of <0.05 was considered statistically significant.

2.5. Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval for the study was granted by the Clinical Research Ethics Committee of Ağrı İbrahim Çeçen University. The ethics committee approval was issued on October 31, 2024, under decision number 362.

3. Results

A total of 210 cases were included in the study. A flow chart illustrating patient selection is presented in Figure 1. The mean age of the participants was (42.6±14.8) years, with 115 (54.8%) females and 95 (45.2%) males. Male sex was more prevalent among patients with focal involvement (49/90, 54.4%), whereas female sex was more common in those without focal involvement (74/120, 61.7%) ($P=0.020$). In individuals with focal involvement, comorbidities were present in 31/90 patients (34.4%), compared to 25/120 patients (20.8%) among those without focal involvement ($P=0.040$). The demographic characteristics of the patients are summarized in Table 1.

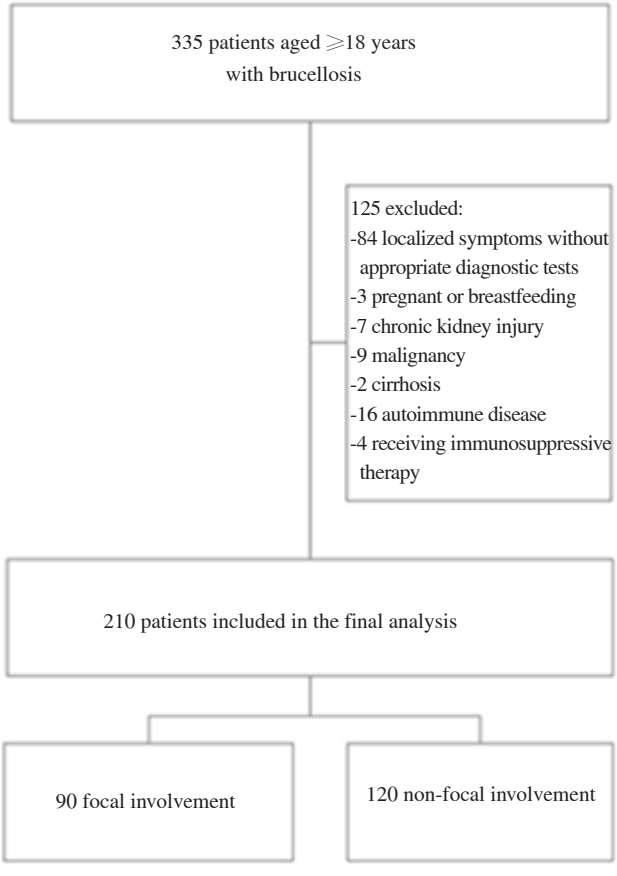

Figure 1. Patient inclusion flowchart.

Table 1. Demographic findings of the cases.

Characteristics	All cases (n=210)	Focal (n=90)	Non-focal (n=120)	P value
Age, mean±SD, years	42.6±14.8	43.9±14.7	41.7±14.8	0.276^
Sex, n (%)				0.020
Female	115 (54.8)	41 (45.6)	74 (61.7)	
Male	95 (45.2)	49 (54.4)	46 (38.3)	
Season of hospital admission, n (%)				0.174
Winter	58 (27.6)	22 (24.4)	36 (30.0)	
Spring	44 (21.0)	23 (25.6)	21 (17.5)	
Summer	51 (24.3)	17 (18.9)	34 (28.3)	
Autumn	57 (27.1)	28 (31.1)	29 (24.2)	
Comorbidities, n (%)				0.040
No	154 (73.3)	59 (65.6)	95 (79.2)	
Yes	56 (26.7)	31 (34.4)	25 (20.8)	
Residence, n (%)				0.368
Centrum	69 (32.9)	29 (32.2)	40 (33.3)	
Diyadin	58 (27.6)	24 (26.7)	34 (28.3)	
Taşlıçay	19 (9.0)	5 (5.6)	14 (11.7)	
Doğubayazıt	14 (6.7)	6 (6.7)	8 (6.7)	
Eleşkirt	13 (6.2)	6 (6.7)	7 (5.8)	
Patnos	12 (5.7)	9 (10.0)	3 (2.5)	
Hamur	10 (4.8)	3 (3.3)	7 (5.8)	
Tutak	9 (4.3)	5 (5.6)	4 (3.3)	
Other city	6 (2.9)	3 (3.3)	3 (2.5)	
Husbandry, n (%)				0.152
No	41 (19.5)	13 (14.4)	28 (23.3)	
Yes	169 (80.5)	77 (85.6)	92 (76.7)	
Raw milk consumption, n (%)				0.771
No	57 (27.1)	23 (25.6)	34 (28.3)	
Yes	153 (72.9)	67 (74.4)	86 (71.7)	
Laboratory transmission, n (%)				0.137
No	206 (98.1)	90 (100.0)	116 (96.7)	
Yes	4 (1.9)	0 (0.0)	4 (3.3)	
History of brucellosis, n (%)				0.222
No	183 (87.1)	75 (83.3)	108 (90.0)	
Yes	27 (12.9)	15 (16.7)	12 (10.0)	

n : number; SD: standard deviation. ^Independent simple t test, otherwise Chi-square test.

Days of complaints before hospital admission was significantly longer in patients with focal involvement (median 31 days) compared to those without focal involvement (median 20 days) (P=0.004). A significant difference was observed between focal involvement and the clinical classification of brucellosis (P=0.002). Chronic brucellosis was more prevalent among patients with focal involvement (8.9%), while acute brucellosis was more common in patients without focal involvement (90%) (P=0.010). Low back pain (P=0.035) and testicular pain (P=0.006) were more frequently reported in patients with focal brucellosis, whereas headache (P=0.004) and nausea (P=0.029) were more common in those without focal involvement. Leukocyte, neutrophil, monocyte, CRP, and sedimentation values were significantly higher in patients with focal involvement (P=0.011, 0.023, 0.023, <0.001, <0.001). The clinical and laboratory findings of the cases are presented in Table 2.

Among the cases included in the study, the standard tube agglutination test was more frequently used in the non-focal group (P=0.036), although no significant difference was found between titers and focal involvement. The number of cases tested with the Coombs gel test was similar between both groups (P=0.052). However, when analyzed at the titer level, a significant difference was observed between the groups (P=0.031).

Osteoarticular involvement was observed in 61/90 cases (67.7%), making it the most commonly affected system. The distribution of

Table 2. Clinical and laboratory findings of the cases.

Variables	All cases (*n*=210)	Focal (*n*=90)	Non-focal (*n*=120)	*P* value
Complaint day, median (IQR)	24 (13-44)	31 (15-71)	20 (13-32)	0.004[&]
Clinical classification, *n* (%)				0.002[^]
Acute	174 (82.9)	66 (73.3)	108 (90.0)	0.010[^^]
Subacute	27 (12.9)	16 (17.8)	11 (9.2)	0.200[^^]
Chronic	9 (4.3)	8 (8.9)	1 (0.8)	0.010[^^]
Symptoms, *n* (%)				
Muscle, joint pain	198 (94.3)	85 (94.4)	113 (94.2)	0.932[^]
Fatigue	164 (78.1)	67 (74.4)	97 (80.8)	0.348[^]
Sweating	162 (77.1)	67 (74.4)	95 (79.2)	0.420[^]
Fever	135 (64.3)	54 (60.0)	81 (67.5)	0.262[^]
Back pain	125 (59.5)	61 (67.8)	64 (53.3)	0.035[^]
Weight loss	124 (59.0)	52 (57.8)	72 (60.0)	0.746[^]
Anorexia	121 (57.6)	48 (53.3)	73 (60.8)	0.276[^]
Headache	117 (55.7)	40 (44.4)	77 (64.2)	0.004[^]
Abdominal pain	72 (34.3)	29 (32.2)	43 (35.8)	0.585[^]
Nausea	66 (31.4)	21 (23.3)	45 (37.5)	0.029[^]
Testicular pain	6 (2.9)	6 (6.7)	0 (0)	0.006[^]
Laboratory findings				
Leukocyte, per µL	6 811±1 896	7 200±2 217	6 525±1 567	0.011[#]
Neutrophil, per µL	4 189±1 829	4 608±2 241	3 874±1 374	0.023[#]
Lymphocyte, per µL	2 185±766	2 201±757	2 173±775	0.794[#]
Monocyte, per µL	450±151	487±173	423±126	0.023[#]
MPV, fL	9.84±1.19	9.88±1.29	9.82±1.12	0.718[#]
Hb, g/dL	13.9±1.5	13.7±1.5	14.0±1.5	0.175[#]
Plt, $\times 10^3$/µL	272±71	269±76	270±59	0.903[#]
ESR, mm/hour	25 (13-40)	36 (20-50)	20 (11-34)	<0.001[&]
CRP, g/L	8.7 (2.8-33.0)	19.6 (4.7-54.8)	5.4 (2.0-16.5)	<0.001[&]
ALT, U/L	27 (17-38)	27 (17-37)	26 (17-39)	0.518[&]
AST, U/L	24 (19-33)	24 (19-33)	23 (18-33)	0.560[&]
Urea, mg/dL	29.2±8.6	30.4±8.6	28.2±8.5	0.068[#]
Creatinine, mg/dL	0.72±0.16	0.74±0.16	0.72±0.17	0.378[#]
Blood culture, *n* (%)[a]	117 (55.7)	44 (48.9)	73 (60.8)	0.085[^]
Negative	75 (64.1)	29/44 (65.9)	46/73 (63.0)	0.907[^]
Positive	42 (35.9)[a]	15/44 (34.1)	27/73 (37.0)	
STA titers, *n* (%)[b]	167 (79.5)	65 (72.2)	102 (85.0)	0.036[^]
1/160	44 (26.3)	16 (24.6)	28 (27.5)	
1/320	39 (23.4)	14 (21.5)	25 (24.5)	0.815[^]
1/640	37 (22.2)	14 (21.5)	23 (22.5)	
1/1 280	47 (28.1)	21 (32.3)	26 (26.5)	
Coombs gel titers, *n* (%)[c]	60 (28.5)	32 (35.5)	28 (23.3)	0.052[^]
<1/320	23 (38.3)	8 (25.0)	15 (53.6)	
1/640	11 (18.3)	9 (28.1)	2 (7.1)	0.031[^]
1/1 280	26 (46.3)	15 (46.9)	11 (39.3)	

Data are presented as mean±SD for normally distributed variables and median (IQR) for non-normally distributed variables. ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, dL: deciliter, ESR: erythrocyte sedimentation rate, fL: femtoliter, g: gram, Hb: hemoglobin, IQR: Interquartile range, mg: miligram, mm: milimeter, MPV: mean platelet volume, L: liter, *n*: number, Plt: platelet, STA: standard tube agglutination, U: unit, µL: microliter. [&]Mann-Whitney *U* test, [^]*Chi*-square test, [^^]*Chi*-square test *post–hoc* analysis (Bonferroni correction *P*-value <0.016), [#]Independent simple *t* test, *P*<0.05. [a]Blood cultures were obtained in 117 cases (55.7%). *P*-values were calculated using the *Chi*-square test; the first *P*-value compares the proportion of cases in which cultures were obtained, while the second *P*-value compares the distribution of culture results. [b]STA titers were examined in 167 cases (79.5%). *P*-values were calculated using the *Chi*-square test; the first *P*-value compares the proportion of cases with STA titers examined, and the second compares titer level distributions between the groups. [c]Coombs gel tests were performed in 60 cases (28.5%). *P*-values were calculated using the *Chi*-square test; the first *P*-value compares the proportion of cases with Coombs gel test titers examined, and the second compares titer level distributions between the groups.

focal involvement by organ is detailed in Table 3. When comparing osteoarticular involvement to other organ involvement, the female, low back pain, and elevated platelet count were significantly more prevalent in the osteoarticular group (P=0.033, 0.001, 0.001). In contrast, abdominal pain, testicular pain, mean platelet volume (MPV), alanine aminotransferase, and aspartate aminotransferase (AST) were significantly more common in the other organ involvement group (P<0.001, 0.001, <0.001, 0.012, 0.006). The parameters showing significant differences between the two groups are presented in Table 4.

Table 3. Distribution of focal involvement [n (%)].

Focal involvements	All cases (n=90)
Osteoarticular	61 (67.8)
Sacroileitis	22 (24.4)
Spondylodiscitis	21 (23.3)
Peripheral arthritis	19 (21.1)
Organomegaly	20 (22.2)
Hepatomegaly	9 (10.0)
Splenomegaly	13 (14.4)
Genitourinary	9 (10)
Hepatitis	1 (1.1)
Skin	3 (3.3)

ROC curves were utilized to assess the relationships between the quantitatively significant parameters and focal involvement, with sensitivity and specificity determined based on the predicted values (Supplementary Figure 1). As no single parameter demonstrated both high sensitivity and specificity in the ROC analysis, a binary logistic regression model was constructed. This model explained 33.9% of the variance, with an overall accuracy of 74.3% (Table 5). According to the regression analysis, male sex was associated with a 2.5-fold increased risk of focal involvement. The risk of focal involvement was 3.7 times higher in the subacute clinic compared to the acute clinic, and 29 times higher in the chronic clinic. Elevated sedimentation increased the risk of focal involvement by 51%, while headache at presentation was associated with a 76.9% decrease in the risk of focal involvement.

4. Discussion

In our study, significant differences were observed in cases with focal involvement, including delayed hospital admission, low back

Table 4. Significant comparisons between osteoarticular involvement and other organ involvement.

Variables	Osteoarticular (n=61)	Other (n=29)	P value
Sex, n (%)			0.033
Female	33 (54.1)	8 (27.6)	
Male	28 (45.9)	21 (72.4)	
Symptoms, n (%)			
Back pain	49 (80.3)	12 (41.4)	0.001
Abdominal pain	10 (16.4)	19 (65.5)	<0.001
Testicular pain	0 (0.0)	6 (20.7)	0.001
Laboratory findings			
MPV, fL	9.55±1.16	10.50±1.29	<0.001
Plt, $\times 10^3$/μL	294±84	229±70	0.001
ALT, U/L	25 (16-35)	36 (21-56)	0.012
AST, U/L	23 (19-31)	31 (24-52)	0.006

Data are presented as mean±SD for normally distributed variables and median (IQR) for non-normally distributed variables. MPV: mean platelet volume, Plt: platelet, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

Table 5. Logistic regression analysis for predictors of organ involvement.

Variables	B	Se	Wald	Sd	P	Exp (B)	95% CI	
							Lower	Upper
Sex (male vs. female)	0.940	0.346	7.375	1	0.007	2.560	1.299	5.043
Comorbidities (yes vs. no)	0.634	0.384	2.720	1	0.099	1.885	0.887	4.002
Back pain (yes vs. no)	0.219	0.352	0.387	1	0.534	1.245	0.624	2.483
Headache (yes vs. no)	-1.196	0.377	10.070	1	0.002	0.302	0.144	0.633
Neutrophil[#], per μL	0.000	0.000	0.548	1	0.459	1.000	1.000	1.000
ESR, mm/hour	0.037	0.009	15.463	1	<0.001	1.037	1.019	1.056
Nausea (yes vs. no)	-0.325	0.398	0.666	1	0.415	0.723	0.331	1.577
Classification								
Subacute (vs. acute)	1.321	0.517	6.538	1	0.011	3.748	1.361	10.321
Chronic (vs. acute)	3.368	1.164	8.366	1	0.004	29.013	2.961	284.224

Se: standard error. Sd: standard deviation. [#]B=0.000 07, Se=0.000 10, Exp(B)=1.000 07, 95% CI 0.999 87-1.000 27.

pain, and testicular pain at presentation. Additionally, elevated levels of leukocytes, neutrophils, monocytes, CRP, ESR and high titers in the Coombs gel test were identified as significant factors.

Focal involvement in the osteoarticular system is commonly observed in patients with brucellosis[3,10]. Osteoarticular involvement in brucellosis can present as sacroiliitis, spondylitis, osteomyelitis, peripheral arthritis, bursitis, and tenosynovitis[11]. Buzgan *et al*. reported osteoarticular involvement in 21.8% of patients with acute brucellosis, 34.7% of those with subacute brucellosis, and 25.7% of chronic cases. Additionally, another study identified osteoarticular involvement as an early marker of chronic brucellosis[12]. In our study, osteoarticular involvement was the most prevalent focal involvement, consistent with the literature; however, no significant difference was found between the clinical classifications of brucellosis (acute, subacute, chronic).

Several studies on focal involvement have found no significant difference between the sexes[9,13]. Zhang *et al.* reported that male gender was associated with a 2.76-fold increased risk of focal involvement[14]. In our study, focal involvement was more prevalent in males. While it is suggested that delayed hospital admission due to health issues may contribute to an increased risk of focal involvement in men, there is insufficient literature on this topic.

In the study by Shi *et al*., it was found that the risk of focal involvement was 1.67 times higher in patients with underlying diseases[15]. In our study, we similarly found that focal involvement was more prevalent in patients with comorbidities. These comorbid conditions, such as chronic obstructive pulmonary disease, asthma, and diabetes mellitus, are associated with chronic inflammation and impaired immune function. We believe these factors contribute to an increased risk of focal involvement by delaying the clearance of microorganisms from the body.

Focal brucellosis may develop either as a consequence of chronic infection or as a complication of the acute form[2]. A study conducted in China found that focal involvement was more prevalent in patients during the subacute phase[15]. Another study identified long-term disease as an independent risk factor for focal involvement[7]. Zhang *et al*. reported no significant difference in focal involvement between patients with acute brucellosis and those with chronic brucellosis[14]. In our study, we observed that the risk of focal involvement was positively correlated with the duration of hospitalization. Specifically, the risk was 3.7 times higher in cases of subacute brucellosis and 29 times higher in cases of chronic brucellosis. These findings suggest that delayed diagnosis may have occurred due to the administration of non-specific treatments, as patients often presented with vague symptoms to primary healthcare facilities and outpatient clinics outside of infectious disease specialties.

Several studies in the literature have indicated that fever is more prevalent in brucellosis cases without focal involvement[9,16]. There are also studies that report contrary findings[17]. In our study, the incidence of fever was higher in brucellosis cases without focal involvement; however, no significant difference was observed between the groups. Additionally, low back pain was more prevalent in cases of focal brucellosis, a finding that aligns with existing literature[9,18]. The increased prevalence of low back pain is associated with osteoarticular involvement, which is the most common form of focal involvement. Additionally, testicular pain was significantly more common in patients with focal involvement. This finding is not unexpected, as those diagnosed with epididymoorchitis were included in the focal involvement group.

In terms of laboratory markers, Demirdal *et al*. observed elevated ESR, leukocytosis, neutrophilia, and thrombocytosis in cases of focal brucellosis, with no significant difference in CRP levels[9]. Similarly, Çopur *et al*. identified leukocytosis, neutrophilia, and elevated ESR levels in cases of focal brucellosis[18]. MPV, an additional complete blood count parameter used as an inflammatory marker, was significantly lower in patients with brucellosis and focal involvement. However, its measurement was influenced by the complete blood count devices and laboratory techniques employed, indicating that MPV may not serve as a definitive or reliable marker[9,19]. In our study, leukocytosis, neutrophilia, monocytosis, CRP, and ESR levels were significantly elevated in patients with focal involvement, whereas MPV, platelet, and hemoglobin levels showed no significant differences between the groups. The discrepancies between studies hindered the ability to evaluate these markers as specific indicators of brucellosis, apart from their role as general inflammation markers.

As isolating the causative agent in brucellosis diagnosis is not always feasible, various serological tests are employed. Among these, the Rose Bengal, standard tube agglutination, and Coombs tests are the most commonly utilized in clinical practice. In our study, no differences were observed between the groups in terms of standard tube agglutination titers; however, Coombs gel test titers were significantly higher in cases of focal brucellosis. The Coombs gel test proves particularly useful for detecting chronic and recurrent cases, as it can identify blocking antibodies, which the standard tube agglutination test cannot detect[6]. The differences between the two serological tests can be attributed to the longer duration of presentation and the higher prevalence of subacute and chronic cases in focal brucellosis.

In our study, female sex, low back pain, and thrombocytosis were more prevalent in patients with osteoarticular involvement compared

to those with involvement of other organs. Similarly, Kayaaslan *et al*. observed elevated ESR levels in patients with osteoarticular involvement[17]. In the study by Li *et al*., arthralgia was the most common symptom in the group with osteoarticular involvement, with thrombocytosis and anemia being significantly more prevalent. Conversely, in the group without osteoarticular involvement, headache, fatigue, anorexia, and elevated aspartate aminotransferase levels were significantly more common[20]. In another study, elevations in neutrophils, monocytes, and CRP levels were significantly higher in the group with osteoarticular brucellosis, while no significant differences were found in other laboratory parameters[21]. Although our study's findings are consistent with those of Li *et al.*, there are varying results in the literature. While this variability complicates making definitive conclusions about the determinants of osteoarticular involvement, brucellosis should be considered in cases presenting with arthralgia, low back pain, and diffuse myalgia, particularly in endemic regions.

Regression analysis conducted by Shi *et al*. identified several risk factors for focal involvement, including delayed diagnosis, presence of comorbidities, joint pain, myalgia, CRP levels >10 mg/L, elevated sedimentation rate, culture positivity, and a standard tube agglutination titer >400[15]. Kuruoğlu *et al*. reported that the risk of focal brucellosis was 4.16 times higher in the presence of low back pain and 13.54 times higher in the presence of splenomegaly. Additionally, the study found platelet count to be a significant predictor of complications[22]. In our study, regression analysis identified male sex, presentation with subacute or chronic brucellosis, and elevated sedimentation rate as risk factors for focal brucellosis.

One of the limitations of our study is its retrospective and single-center design. In our retrospective analysis, we found that patients were assessed for complications based on their reported symptoms, but were not comprehensively evaluated for other potential complications. Additionally, due to the use of varying methods for serologic testing at our hospital, the relationship between serologic tests and outcomes could not be clearly defined. Similarly, as blood cultures were not always obtained from patients, the association with culture positivity could not be thoroughly assessed. We believe that future well-designed multicenter and prospective studies could provide valuable insights into the predictors of focal brucellosis.

Brucellosis shares clinical characteristics with many other diseases, complicating its diagnosis. Delayed diagnosis can lead to progressive complications with focal involvement, which in turn increases morbidity and healthcare costs. In conclusion, male gender, presentation with subacute or chronic brucellosis, and elevated sedimentation rate were identified as risk factors for focal involvement. Additionally, the presence of headache was found to be a risk factor for non-focal brucellosis.

Conflict of interest statement

The authors declare no conflict of interests.

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Authors' contributions

EE: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing-original draft, writing-review & editing, visualization, supervision. KK: Investigation, writing-original draft, writing-review & editing, visualization, supervision.

References

[1] Gül HC, Erdem H. Brucellosis. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases.* 9th ed. Philadelphia: Churchill Livingstone; 2020, p. 2753-2758.

[2] Alp Meşe E, Doğanay M. Brucellosis. In: *Infectious diseases and microbiology*. İstanbul: Doc Design and Informatics Co. Ltd; 2019, p. 863-871.

[3] Negron M, Tiller R, Kharod G. Brucellosis. In: *CDC yellow book 2024, travel–associated infections & diseases.* [Online]. Available from: https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/brucellosis#epi. [Accessed on 17 March 2025].

[4] Şimşek-Yavuz S, Özger S, Benli A, Ateş C, Aydın M, Aygün G, et al. The Turkish clinical microbiology and infectious diseases society (KLİMİK) evidence-based guideline for the diagnosis and treatment of brucellosis, 2023. *Klimik Derg* 2023; **36**(2): 86-123.

[5] Hong PC, Joyce EA, Karandikar M, Matloubian M, Rubio L, Schwartz B, et al. Gram negative bacilli associated with animal sources (zoonotic microorganisms). In: *Medical microbiology and immunology*. New York: McGraw Hill Education; 2016, p. 643-654.

[6]Yagupsky P, Morata P, Colmenero JD. Laboratory diagnosis of human brucellosis. *Clin Microbiol Rev* 2019; **33**(1): e00073-19.

[7]Dabaja-Younis H, Atarieh M, Paul M, Nasrallah E, Geffen Y, Kassis

I, et al. Predictive factors for focal disease in human brucellosis, an observational cohort study. *Eur J Clin Microbiol Infect Dis* 2023; **42**(2): 221-226.

[8] Jin M, Fan Z, Gao R, Li X, Gao Z, Wang Z. Research progress on complications of brucellosis. *Front Cell Infect Microbiol* 2023; **13**: 1136674.

[9] Demirdal T, Sen P. Risk factors for focal involvement in brucellosis. *Diagn Microbiol Infect Dis* 2020; **97**(1): 115003.

[10]Kilic AU, Metan G, Alp E. *Clinical presentations and diagnosis of brucellosis*. [Online]. Available from: http://www.eurekaselect.com https://www.eurekaselect.com/article/49298. [Accessed on 19 March 2025].

[11]Esmaeilnejad-Ganji SM, Esmaeilnejad-Ganji SMR. Osteoarticular manifestations of human brucellosis: A review. *World J Orthoped* 2019; **10**(2): 54.

[12]Wang H, Liu H, Zhang Q, Lu X, Li D, Zhang H, et al. Natural history of and dynamic changes in clinical manifestation, serology, and treatment of brucellosis, China. *Emerg Infect Dis J* 2022; **28**(7): 1460.

[13]Alghamdi MS, Almalki AK, Attar AA, Alotaibi AL, Alamri MA. Prevalence and determinants of focal brucellosis in a tertiary healthcare center in Taif, Saudi Arabia (2020-2023). *J Comm Med Public Health* 2024; **8**: 475.

[14]Zhang Z, Zhang X, Chen X, Cui X, Cai M, Yang L, et al. Clinical features of human brucellosis and risk factors for focal complications: A retrospective analysis in a tertiary-care hospital in Beijing, China. *Int J Gen Med* 2022; **15**: 7373-7382.

[15]Shi Q, Qin H, Lu Q, Li S, Tao Z, Fan M, et al. Incidence and warning signs for complications of human brucellosis: A multi-center observational study from China. *Infect Dis Pov* 2024; **13**(1): 53-62.

[16]Xu N, Dong X, Yao Y, Guan Y, Chen F, Zheng F, et al. Improved early detection of focal brucellosis complications with anti-*Brucella* IgG. *J Clin Microbiol* 2020; **58**(10): e00903-20. doi: 10.1128/JCM.00903-20.

[17]Kayaaslan B, Bastug A, Aydin E, Akinci E, But A, Aslaner H, et al. A long-term survey of brucellosis: Is there any marker to predict the complicated cases? *Infect Dis* 2016; **48**(3): 215-221.

[18]Copur B, Sayili U. Laboratory and clinical predictors of focal involvement and bacteremia in brucellosis. *Eur J Clin Microbiol Infect Dis* 2022; **41**(5): 793-801.

[19]Beyan C, Beyan E. Mean platelet volume may not be a risk factor for focal involvement in patients with brucellosis. *Diagn Microbiol Infect Dis* 2020; **97**(2): 115036.

[20]Li D, Yuan G, Wang YO, Wang H, Zhang Q, Wang YA, et al. Clinical characteristics, treatment, and prognosis of osteoarticular brucellosis: A retrospective real-world study in Shenyang, China, 2014-2019. *Foodborne Pathog Dis* 2025; **22**(2): 86-96.

[21]Balın ŞÖ, Tartar AS, Akbulut A. The predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. *Afr Health Sci* 2018; **18**(4): 988-994.

[22]Kuruoglu T, Sensoy L, Atilla A, Temocin F, Gur D, Tanyel E. Evaluation of risk factors for the development of bacteremia and complications in patients with brucellosis: Is it possible to predict the clinical course? *J Infect Dev Ctries* 2023; **17**(9): 1277-1284.

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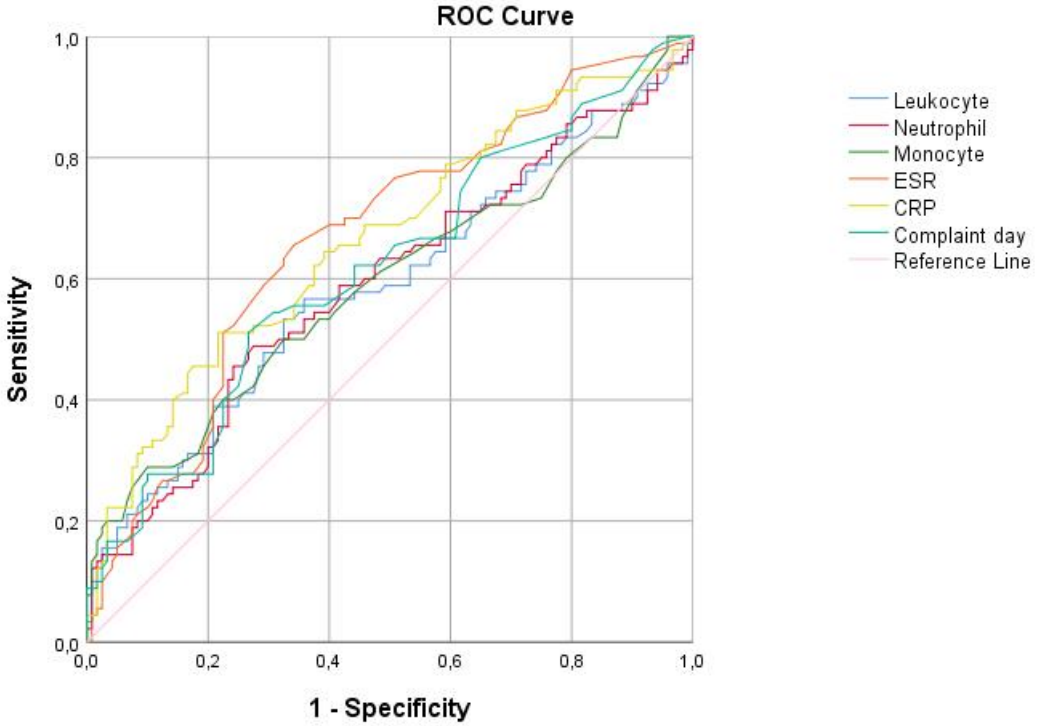

	AUC	S.e	P	%95 CI Lower	%95 CI Upper
Leukocyte (/µL)	0.588	0.041	**0.029**	0.508	0.668
Neutrophil (/µL)	0.592	0.040	**0.023**	0.512	0.671
Monocyte (/µL)	0.591	0.041	**0.023**	0.511	0.672
ESR (mm/hour)	0.668	0.038	**0.000**	0.594	0.742
CRP (g/L)	0.665	0.038	**0.000**	0.590	0.740
Complaint day	0.617	0.039	**0.004**	0.540	0.695

	Threshold	Sensitivity (%)	Specificity (%)
Leukocyte (/µL)	6875	56.7	64.2
Neutrophil (/µL)	3825	58.9	58.3
Monocyte (/µL)	425	54.4	59.2
ESR (mm/hour)	27	63.3	67.5
CRP (g/L)	9.8	62.2	62.5
Complaint day	21.5	62.2	55.8

Supplementary Figure 1. ROC analysis for leukocyte, neutrophil, monocyte, erythrocyte sedimentation rate, CRP and complaint day variables and sensitivity and specificity results according to the threshold values determined.

AUC: area under the curve, CI: confidence interval, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, g: gram, L: liter, mm: milimeter, S.e: standard error, μL: microliter