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Evaluation of Blood Culture Positivity, Acute Phase Reactants and Brucella Capture Titer in Pediatric Brucellosis: Single Center Seven Year Experience

Pediyatrik Brusellozda Kan Kültürü Pozitifliğinin, Akut Faz Reaktanlarının ve Brucella Capture Titresinin Değerlendirilmesi: Tek Merkez Yedi Yıllık Deneyim

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Abstract

Objective: Brucellosis is one of the most common zoonotic diseases in the world. This study evaluated the characteristics of brucellosis in childhood.

Material and Methods: The study included 103 patients diagnosed with brucellosis. Patient data were obtained retrospectively from the hospital's digital system and files.

Results: Mean age of the patients was 11.26 ± 4.705 years. The most common presenting complaints were arthralgia (88.3%), fever (65%) and fatigue (65%). There was a positive family history of brucellosis in 36.9% of the patients and a history of animal husbandry in 48.5%. Growth was observed in 37.7% of the 53 patients with blood culture samples. The highest number of admissions occurred during spring (37.8%), while the fewest admissions took place in winter (11.6%). Anemia was detected in 38 (36.9%) patients, neutropenia in 11 (10.7%), thrombocytopenia in 9 (8.7%), and pancytopenia was detected in 4 (3.9%) patients. Mean value of the Brucella capture test was significantly higher in patients with elevated C-reactive protein (CRP) levels and with organomegaly on abdominal ultrasonography ($p< 0.05$). It was observed that the presence of growth in blood culture was statistically significant in cases of low platelet count ($p< 0.05$). Correlation analysis was performed between all parameters. When evaluated with advanced regression analysis, it was found that there was a negative correlation between patients with growth in blood culture and CRP levels and platelet count and a

Öz

Giriş: Bruselloz dünyada en sık görülen zoonotik hastalıklardan biridir. Bu çalışmada çocukluk çağında brusellozun özellikleri değerlendirilmiştir.

Gereç ve Yöntemler: Çalışmaya bruselloz tanısı konulan 103 hasta dahil edildi. Hasta verileri hastanenin dijital sisteminden ve dosyalarından retrospektif olarak elde edildi.

Bulgular: Hastaların yaş ortalaması 11.26 ± 4.705 yıldı. En sık başvuru şikayetleri artralji (%88.3), ateş (%65) ve halsizlik (%65) idi. Hastaların %36.9'unda ailede pozitif bruselloz öyküsü ve %48.5'inde hayvancılık öyküsü vardı. Kan kültürü örneği alınan 53 hastanın %37.7'sinde üreme gözlenmiştir. En fazla başvuru ilkbaharda (%3.8), en az başvuru ise kış aylarında (%11.6) gerçekleşmiştir. Otuz sekiz (%36.9) hastada anemi, 11 (%10.7) hastada nötropeni, 9 (%8.7) hastada trombositopeni ve 4 (%3.9) hastada pansitopeni tespit edilmiştir. C-reaktif protein (CRP) düzeyi yüksek olan ve abdominal ultrasonografide organomegali saptanan hastalarda Brucella capture testinin ortalama değeri anlamlı derecede yüksek bulundu ($p< 0.05$). Kan kültüründe üreme saptanan hastalarda trombosit sayısı üreme olmayan hastalara göre istatistiksel olarak anlamlı derecede düşüktü ($p< 0.05$). Tüm parametreler arasında korelasyon analizi yapılmıştır. İleri regresyon analizi ile değerlendirildiğinde, kan kültüründe üreme olan hastalar ile CRP düzeyleri ve trombosit sayısı arasında negatif korelasyon, CRP düzeyleri ile kreatinin düzeyleri ve eritrosit sedimantasyon hızı arasında pozitif korelasyon olduğu bulunmuştur ($p< 0.05$).

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positive correlation between CRP levels and creatinine levels and erythrocyte sedimentation rate ($p< 0.05$).

Conclusion: Our study suggests that while Brucella titer and erythrocyte sedimentation rate may not directly correlate with systemic involvement and the development of disease complications, CRP levels could serve as a potential predictor for systemic involvement and the development of complications in pediatric brucellosis. These findings could have significant implications for the diagnosis and management of brucellosis in children, potentially leading to earlier intervention and improved outcomes.

Keywords: Brucella, brucella capture titer, CRP, blood culture

Sonuç: Çalışmamız, Brucella titresi ve eritrosit sedimantasyon hızının sistemik tutulum ve hastalık komplikasyonlarının gelişimi ile doğrudan ilişkili olmayabileceğini ancak CRP düzeylerinin pediyatrik brusellozda sistemik tutulum ve komplikasyon gelişimi için potansiyel bir öngörücü olabileceğini öne sürmektedir. Bu bulgular, çocuklarda brusellozun tanısı ve yönetimi için önemli çıkarımlara sahip olabilir ve potansiyel olarak daha erken müdahaleye ve iyileştirilmiş sonuçlara yol açabilir.

Anahtar Kelimeler: Brusella, brusella capture titresi, CRP, kan kültürü

Introduction

Brucellosis is one of the most common zoonotic diseases worldwide (1). It is particularly prevalent in Mediterranean countries, India, the Middle East, and Central/South America. Approximately 500.000 cases are reported worldwide each year, and it is estimated that 2.4 billion people are at risk (1,2). The prevalence of brucellosis is increasing due to heightened international tourism, trade, and migration. The main routes of transmission include the consumption of unpasteurized contaminated milk and dairy products, contact of the skin or mucous membranes with infected animal tissue (such as placenta or abortion products) or fluids (such as blood, urine, or milk) from infected animals, inhalation of infected aerosols, or inoculation into the conjunctiva (3). Brucellosis is a disease that can affect multiple organs and systems, including the heart, gastrointestinal system, central nervous system, genitourinary system, hematopoietic system, and particularly, the osteoarticular system (4). It typically presents with an insidious onset of fever, night sweats, fatigue, and arthralgia. Other symptoms may include weight loss, back pain, headache, dizziness, anorexia, dyspepsia, abdominal pain, cough, and depression. Physical examination is variable and nonspecific; hepatomegaly, splenomegaly, and/or lymphadenopathy may be observed. Since the complaints, symptoms, and physical examination findings are not specific to the disease, obtaining a thorough history is crucial for diagnosis (4). Delays in diagnosis and treatment can lead to increased morbidity and mortality (5). The definitive diagnosis of brucellosis can be established by culturing the organism (from blood, body fluids, or tissues) or by a ≥4-fold increase in Brucella antibody titer between acute and convalescent serum samples taken ≥2 weeks apart (6,7). A presumptive diagnosis can be made by an antibody titer of ≥1:160 measured using the standard tube agglutination test or by detecting Brucella DNA in a clinical sample via polymerase chain reaction. Brucellosis treatment aims to control the disease and prevent complications, relapses, sequelae, and mortality (6,7). This retrospective study aimed to examine the demographic and epidemiological characteristics of the patients, acute phase reactants, serological tests, biochemical and hematological parameters, culture results, and radiological findings, as well as to determine whether there was an association between Brucella capture titer, acute phase reactants, and the presence of growth in blood cultures and other parameters.

Materials and Methods

This study included 103 patients aged 1 month to 18 years who were diagnosed with acute brucellosis and who applied to Dicle University Faculty of Medicine Children's Health and Diseases Hospital as outpatients between January 1, 2016 and March 31, 2023. Brucellosis diagnosis was based on a comprehensive set of criteria including clinical findings, isolation of Brucella microorganisms from blood and/or Brucella capture agglutination titer >1/160.

Demographic characteristics of the patients, presenting complaints, complete blood counts, biochemical tests, blood culture results, serological laboratory data, radiological imaging findings, and administered treatments were obtained retrospectively from the hospital's digital system and the medical files of the patients. Patients with brucellosis from whom sufficient data could not be obtained were excluded from the study.

Biochemical parameters were evaluated using the Olympus AU5800 Beckman Coulter device.

Approximately 2 mL of blood was collected into an EDTA hemogram tube and evaluated using the Sysmex XN 1000 Hematology Analyzer for complete blood counts.

C-reactive protein (CRP) was evaluated using the nephelometric method on the olympus AU5800 Beckman Coulter device. The reference range for CRP levels was 0-5 mg/L, with values >5 considered elevated.

Erythrocyte sedimentation rate (ESR) was evaluated using the Grenier Sed Rate SCR Vision device. The reference range for ESR was 0-20 mm/h, and values >20 were considered elevated.

Blood cultures were collected upon admission to the hospital before initiating brucellosis treatment. Blood samples collected into BACTEC blood culture bottles were examined using the BD BACTEC FX automated blood culture device for at least seven days and monitored for Brucella spp. growth. Blood cultures were taken from patients who showed prolonged fever,

systemic symptoms, or suspected bacteremia. In our hospital, blood culture samples can only be taken from patients who are being followed up as inpatients. Therefore, blood cultures could not be taken from patients who applied to the outpatient clinic and continued their diagnosis and treatment as outpatients.

Complete blood count parameters of the patients, including hemoglobin (Hb), leukocyte count (WBC), and platelet count, were evaluated while considering the age of the patients. An Hb value of two SD or below was considered indicative of anemia. WBC values below the lower limit according to age were considered leukopenia, while those above the upper limit were considered leukocytosis (8). Platelet values below 150.000/mm^3 were classified as thrombocytopenia. Cases with WBC, Hb level, and platelet count values below the normal range for age were classified as pancytopenia; cases with two out of three of these values below the lower limit for age were classified as bi-cytopenia; neutrophil values below the lower limit for age were classified as neutropenia, and lymphocyte/monocyte values above the upper limit for age were classified as lymphomonocytosis.

In cases where the liver and/or spleen were above the upper age limit on abdominal ultrasound (USG), cases of enlarged liver only were classified as hepatomegaly, enlarged spleen only were classified as splenomegaly, and both enlarged liver and spleen were classified as hepatosplenomegaly (9).

Systemic involvement was determined according to hepatosplenomegaly, sacroiliitis, endocardial involvement (on echocardiography), changes in complete blood parameters and liver enzymes.

Ethical Considerations

Approval for the study was obtained from the Dicle University Faculty of Medicine Ethics Committee (Date: 17.05.2023, Number: 22).

Statistical Analysis

Study data were analyzed using SPSS 22. Fisher's exact test, Pearson's chi-squared test, Pearson correlation, multiple linear regression, T-test (for independent samples), and One-Way analysis of variance (ANOVA) were used for data comparison. Categorical data were expressed as frequency and percentage, while continuous data were expressed as mean ± standard deviation and min-max values. In the analyses, a p-value of <0.05 was considered statistically significant, and a p-value of >0.05 was considered statistically insignificant.

Results

Mean age of the patients was 11.26 ± 4.705 years (min: 2, max: 18 years). Of these, 43 (41.7%) were female and 60 (58.3%) were male. Geographical distribution revealed that 73 (70.8%) were from the Southeastern Anatolia Region, and 30 (29.2%) were from the Eastern Anatolia Region. Forty-six (44.7%) patients resided in the city center, while 57 (55.3%) lived in rural areas. A family history of brucellosis was reported in 38 (36.9%) patients, and 50 (48.5%) patients had a family history of animal husbandry (Table 1).

Regarding the timing of hospital admissions, it was found that admissions occurred most frequently in march (13.5%), april (13.5%), may (10.6%), and august (10.6%). The highest number of admissions occurred during spring (37.8%), while the fewest admissions took place in winter (11.6%) (Table 1). The most common complaints among the patients were as follows: Arthralgia in 91 (88.3%) patients, fever in 67 (65%), and fatigue in 67 (65%). Rare symptoms included scrotal pain in one patient and nosebleeds in two patients (Table 1). On admission, Brucella capture titers were found to be 1/5120 in

Table 1. Demographic and clinical characteristics of the patients

Features	**n (%) (min.-max.)**
Median age	11.26 ± 4.705 (2-18 year)
Sex (male/female)	60/43 (58.3%/41.7%)
Residence (rural/city)	57/ 46 (55.3%/44.7%)
Animal husbandary	50 (48.5%)
Family history of brucellosis	38 (36.9%)
Symptoms and physical examination findings	
Arthralgia	91 (88.3%)
Fever	67 (65%)
Fatigue	67 (65%)
Lack of appetite	54 (52.4%)
Sweating	43 (41.7%)
Myalgia	35 (34%)
Weight loss	34 (33%)
Nause/Vomiting	32 (31.1%)
Lower back pain	30 (29.1%)
Upper back pain	27 (26.2%)
Chills	26 (25.2%)
Headache	20 (19.4%)
Abdominal pain	14 (13.6%)
Cough	3 (2.9%)
Epistaxis	2 (1.9%)
Scrotal pain	1 (1.7%)
Brucella capture tube agglutination test	
1/160	3 (2.9%)
1/320	7 (6.8%)
1/640	16 (15.5%)
1/1280	13 (12%)
1/2560	17 (16.5%)
1/5120	47 (45.7%)
Growth of *Brucella* spp. in blood culture	20/53 (37.7%)

47 (45.7%) patients, 1/2560 in 17 (16.5%) patients, 1/1280 in 13 (12%) patients, 1/640 in 16 (15.5%) patients, and 1/320 in 7 (6.8%) patients. Only three (2.9%) patients had a titer of 1/160 on admission.

Laboratory parameters of the patients included in the study are shown in Table 2. In evaluating laboratory parameters according to age range and reference values, anemia was detected in 38 (36.9%) patients, neutropenia in

Table 2. Laboratory parameters and their association with Brucella capture titer and radiological findings

Laboratory Parameters	**Mean ± SD (min.-max.)**
CRP (ref. 0-5 mg/L)	18.30 ± 28.79 (0.10-223)
ESR (ref. 0-20 mm/h)	22.77 ± 16.06 (1.00-86)
Urea (ref. 10.8-38.4 mg/dL)	21.04 ± 7.78 (1.50-49)
Creatinine (ref. 0.45-0.77 mg/dL)	0.5353 ± 0.17039 (0.18-1.22)
Albumin (ref. 3.5-5.2 gr/dL)	3.77 ± 0.51 (2.3-4.93)
Total bilirubin (ref. 0.3-1.2 mg/dL)	0.53 ± 0.29 (0.16-1.91)
Direct bilirubin (ref. 0-0.2 mg/dL)	0.16 ± 0.10 (0.01-0.57)
ALT (ref. 0-35 U/L)	46.52 ± 78.76 (3.5-617)
AST (ref. 0-30 U/L)	50.88 ± 56.97 (11-395)
ALP (ref. 74-390 U/L)	153.63 ± 65.01 (45-406)
GGT (ref. 2-42 U/L)	30.00 ± 28.84 (8.20-131)
LDH (ref. 0-248 U/L)	347.37 ± 189.78 (150-1474)
Uric acid (ref. 3.5-7.2 mg/dL)	3.76 ± 1.31 (1.50-7.30)
WBC (ref. 3.7-10.1x10^3/Ul)	7.42 ± 2.64 (2.55-17.73)
HB (ref. 12.9-14.2 gr/dL)	12.28 ± 1.63 (5-15.8)
HCT (ref. 37.7-53.7) (%)	38.19 ± 4.15 (26.41-48.2)
MCV (ref. 81.1-96 fL)	77.79 ± 5.52 (65.02-87.61)
PLT (ref. 150-400x10^3/Ul)	266.4 ± 83.92 (22.02-491.00)
NEU (ref. 1.63-6.96x10^3/Ul)	3.46 ± 1.96 (0.49-10.15)
LYM (ref. 1.09-2.99x10^3/Ul)	**3.21 ± 1.52 (0.54-12.42)**

Relationship between laboratory/radiological results and Brucella capture titer (T-test)

		n	**Brucella capture Mean ± SD**	**p**
Thrombocytopenia	Present	9	3200.00 ± 2017.52	0.812
	Not present	94	3031.48 ± 2030.83	
Increased ESR	Present	42	3306.66 ± 1922.16	0.051
	Not present	30	2384.00 ± 1983.03	
Increased transaminase	Present	27	3638.51 ± 1905.89	0.056
	Not present	74	2774.05 ± 2021.65	
Increased CRP	Present	70	3508.57 ± 1965.89	**0.001**
	Not present	32	1970.00 ± 1735.39	
Blood culture	Not growth of *Brucella* spp.	33	2758.78 ± 1947.72	0.323
	Growth of *Brucella* spp.	20	3312.00 ± 1967.89	
Abdominal USG	Organomegalypresent	28	3611.43 ± 1735.00	**0.002**
	Normal	26	1956.92 ± 1894.39	
ECHO	Normal	66	3202.42 ± 1987.033	**0.009**
	Mitral or aortic regurgitation	8	1280.00 ± 888.787	
MRI	Normal	9	2413.33 ± 1830.847	0.555
	Sacroiliitis	8	2960.00 ± 1902.780	

SD: Standard deviation, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, LDH: Laktate dehidrogenase, WBC: White blood cell, HB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet count, NEU: Neutrophil count, LYM: Lymphocyte count, USG: Ultrasonography, ECHO: Echocardiyography, MRI: Magnetic resonance imaging.

11 (10.7%) patients, thrombocytopenia in 9 (8.7%) patients, and pancytopenia was detected in 4 (3.9%) patients. Additionally, elevated CRP levels were detected in 68.6% (n= 70) of the patients, and an increase in the ESR was found in 58.3% (n= 42/72) of the patients, with abnormalities in at least one liver function test (transaminase) detected in 27 (26.7%) patients. Blood culture samples were obtained from 53 patients, and growth was detected in 20 (37.7%) of these patients, with *Brucella melitensis* identified in all positive cultures.

In examining patients for radiological findings, hepatosplenomegaly was found on abdominal USG in 17 (16.5%) patients. Hepatomegaly alone was observed in 6 (5.8%) patients, while splenomegaly was noted in 5 (4.8%) patients. No endocarditis, myocarditis or serious cardiac complications were detected in any of the patients in echocardiographic (ECHO) evaluations. Mild mitral regurgitation was seen in seven patients and mild aortic regurgitation in one patient. Magnetic resonance imaging (MRI) was performed to detect sacroiliitis, and findings indicating sacroiliitis were observed in 8 (7.7%) patients.

In evaluating the relationship between growth status in blood culture and complete blood count, acute phase reactants, and biochemical parameters, the platelet count in patients with detected growth in blood culture was statistically significantly lower than that in patients without growth (198.25 ± 81.74 vs. 272.90 ± 101.33; p< 0.05). No significant differences were found in terms of other parameters. Comparing blood culture results with other nonparametric values, a statistically significant result was found between the presence of growth in blood culture and organomegaly (p< 0.05). No significant relationships were identified between anemia, thrombocytopenia, pancytopenia, elevated acute phase reactants (CRP, ESR), elevated transaminase levels, ECHO, and MRI findings.

In examining the relationship between nonparametric laboratory and imaging results and Brucella capture titer, it was found that the Brucella capture titer was significantly higher in patients with elevated CRP and organomegaly detected on abdominal USG (p< 0.05). Additionally, no statistically significant differences were observed between thrombocytopenia, elevated ESR, elevated transaminase levels, growth in blood culture, sacroiliitis, and Brucella capture titer (p> 0.05) (Table 2). In evaluating the correlation between Brucella capture titers and the results of complete blood counts and biochemical laboratory tests, a positive correlation was found between Brucella capture titers and levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and red cell distribution width. Conversely, a negative correlation was observed between Brucella capture titer and neutrophil count, albumin, and total bilirubin (p< 0.05). When a linear regression analysis was performed for the significant results obtained in the Pearson correlation analysis, no significant correlation among these parameters was established (p> 0.05) (Table 3). According to the ANOVA test results (F= 0.371; p> 0.05), there were no significant differences between the Brucella capture value and hematological findings (pancytopenia/bi-cytopenia/neutropenia).

In examining the correlation between patient (ESR) values and other laboratory parameters, a negative correlation was found between ESR and red blood cell count, Hb, hematocrit, and albumin. In contrast, a positive correlation was noted between ESR and CRP (p< 0.05). In advanced regression analysis performed for the five parameters correlated with ESR, only the positive correlation CRP was found to be significant (p< 0.05) (Table 4).

When examining the correlation between the patient's CRP values and other laboratory parameters, a negative correlation was observed between CRP values and albumin and platelet count. In contrast, a positive correlation was found between CRP values and creatinine, ESR, Brucella capture titer, AST, and urea (p< 0.05) (Table 5). A linear regression analysis for these results indicated a positive correlation between CRP values and creatinine and ESR (p< 0.05) and a negative correlation between CRP values and platelet count (p< 0.05) (Table 5).

Discussion

Brucellosis is the most common zoonotic disease in the world. It is a significant public health problem in developing countries, including ours. Brucellosis can affect any individual, regardless of sex and can occur at any age, depending on exposure. Given that it is a zoonotic disease, the occupation of animal husbandry is a critical risk factor for this condition.

Among the studies conducted on brucellosis in children, mean age of the patients was 7.75 ± 3.28 years in the study by Salman et al., where 69.6% of the participants were male and 30.4% were female. In the study by Özdem et al., where 61.4% of the patients were male, and 38.6% were female, the mean age was found to be 10.4 years, with 6% of the patients' families engaged in animal husbandry and 37% having a family history of brucellosis. The study by Ahmetagić et al. determined that 67% of the patients' families were involved in animal husbandry, and 58% had a family history of brucellosis. In the research conducted by Buzgan et al., it was reported that 42.3% of patients came from families engaged in animal husbandry, while 17.8% had a family history of brucellosis. Tanır et al. reported that 57.8% of patients lived in rural areas and 42.2% in urban areas. In our study, the patient's mean age was 11.26 ± 4.705 years; 58.3% were male, and 41.7% were female (10-14).

Table 3. Correlation between Brucella capture titer and laboratory parameters: Pearson and Linear regression analyses

Pearson correlation analysis					
Laboratory parameters	**r**	**p**			
RDW	0.269	**0.006**			
NEU	-0.201	**0.042**			
Albumin	-0.214	**0.042**			
Total bilirubin	-0.290	**0.008**			
Direct bilirubin	-0.308	**0.007**			
ALT	0.225	**0.024**			
AST	0.248	**0.013**			
Linear regresion analysis					
Variables	**B**	**SH**	**β**	**t**	**p**
Constant	7252.931	3208.875		2.260	.028
RDW	35.298	139.042	.034	.254	.801
NEU	-42.339	118.263	-.047	-.358	.722
Albumin	-1179.748	617.777	-.309	-1.910	.062
Total bilirubin	-515.126	1944.783	-.055	-.265	.792
Direct bilirubin	-5077.630	4820.226	-.229	-1.053	.297
ALT	3.101	4.386	.154	.707	.483
AST	.315	6.761	.011	.047	.963
LDH	1.277	1.493	.124	.855	.397

$r = .57$, $r^2 = .33$, $\Delta r^2 = .22$, $F = 2.93$, $p = .009$.
Note: Although some variables (e.g. ALT, albumin, NEU) demonstrated statistically significant Pearson correlations with Brucella capture titers. They did not remain significant in the multivariate linear regression model. This discrepancy may be attributed to potential confounding and shared variance among predictors. The β (beta) coefficients reflect the direction and adjusted strength of association after controlling for other variables.
RDW: Red cell distribution width, NEU: Neutrophil count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehidrogenase.

Table 4. Correlation between erythrocyte sedimentation rate and laboratory parameters: Pearson and Linear regression analyses

Pearson correlation analysis					
Laboratory parameters	**r**	**p**			
RBC	-0.280	**0.017**			
HB	-0.271	**0.021**			
HCT	-0.322	**0.006**			
Albumin	-0.287	**0.021**			
CRP	0.281	**0.018**			
Linear regression analysis					
Variables	**B**	**SH**	**β**	**t**	**p**
Constant	84.756	24.329		3.484	.001
RBC	-3.662	7.390	-.100	-.496	.622
HB	-1.591	3.179	-.126	-.500	.619
HCT	-.706	1.343	-.164	-.526	.601
Albumin	-.014	5.806	.000	-.002	.998
CRP	.134	.064	.274	2.087	**.041**

$r = .45$, $r^2 = .20$, $\Delta r^2 = .13$, $F = 2.95$, $p = .019$.
RBC: Red blood cell, HB: Hemoglobin, HCT: Hematocrit, CRP: C-reactive protein.

Table 5. Correlation analysis between CRP and laboratory parameters (Pearson-Linear regression analysis)

Pearson correlation analysis					
Laboratory parameters	**r**	**p**			
Creatinine	0.400	**0.001**			
ESR	0.281	**0.018**			
Brucella capture	0.206	**0.037**			
PLT	-0.284	**0.004**			
Albumin	-0.323	**0.002**			
AST	0.350	**0.001**			
Urea	0.301	**0.003**			
Linear regression analysis					
Variables	**B**	**SH**	**β**	**t**	**p**
Constant	33.056	41.036		.806	.424
Creatinine	62.185	20.463	.335	3.039	**.004**
ESR	.571	.207	.276	2.766	**.008**
Brucella capture	.001	.002	.055	.553	.583
PLT	-.137	.046	-.301	-2.964	**.005**
Albumin	-9.994	8.083	-.131	-1.236	.222
AST	.061	.057	.115	1.071	.289
Urea	.681	.438	.169	1.555	.126

r= .76, r^2= .57, Δr^2= .51, F= 9.42, p= .000.
ESR: Erythrocyte sedimentation rate, PLT: Platelet count, AST: Aspartate aminotransferase.

Additionally, 55.3% of the patients lived in rural areas, and 44.7% resided in the city center. A family occupation of animal husbandry was reported in 48.5% of the patients, and a family history of brucellosis in 36.9%. This data indicates that brucellosis is increasing among children in areas where the disease is common, especially in individuals residing in rural settings and whose families are engaged in animal husbandry.

Brucellosis is a multisystemic disease affecting various organ systems, leading to a diverse and often nonspecific clinical presentation. In the study conducted by Gündeşlioğlu et al., it was reported that 59% of patients presented with fever, 41% with arthralgia, 38% with leg pain, 25% with fatigue, and 17% with weight loss (15). Bosilkovski et al. noted that the most common presenting complaints were fever (78%), arthralgia (72%), sweating (64%), fatigue (60%), and headache (33%) (16). In our study, arthralgia was the most prevalent presenting complaint, noted in 88.3% of the patients. Fever and fatigue were also common, observed in 65% of the patients each.

Hematological complications are frequently encountered in brucellosis, as it can primarily affect the lymphoreticular system. In the study by El-Koumi et al., anemia was observed in 43% of the patients, leukopenia in 38%, leukocytosis in 20%, and pancytopenia in 18% (17). Kaman et al. found anemia in 31.7% of the patients, leukopenia in 10.6%, thrombocytopenia in 4.8%, and pancytopenia in 1.9% (18). Our study detected anemia in 36.9% of the patients upon evaluating complete blood count parameters. Additionally, neutropenia was found in 10.7%, thrombocytopenia in 8.7%, and pancytopenia in 3.9%. When examining the relationship between serum antibody levels and these complications, the Brucella capture titer did not significantly differ with the presence of pancytopenia, bicytopenia, or neutropenia. Regular monitoring of hematological parameters in brucellosis patients is essential, along with timely intervention if necessary.

Acute phase reactants typically increase in inflammatory infections such as brucellosis, although they may sometimes remain normal. CRP and ESR are commonly measured acute phase reactants. Demiroğlu et al. reported CRP elevation in 59.6% of their patients and sedimentation elevation in 61.6% (19). In the study by Jia et al., CRP elevation was found in 44.2% and sedimentation elevation in 64.7% (20). In our research, 58.3% of patients had elevated sedimentation rates, while 68.6% had elevated CRP levels. Although our findings align with the existing literature, it is crucial to note that CRP and sedimentation values are not specific indicators of brucellosis.

The definitive diagnosis of brucellosis is established by culturing the infectious agent from blood samples. It is important to note that the absence of growth in blood culture does not exclude the diagnosis. In the study by Özdem et al., the growth rate in blood culture was documented at 40.2%,

while Ahmetagić et al. reported it at 25.6% (12,13). In our study, growth was detected in 20 out of the 53 patients from whom blood culture samples were obtained, corresponding to a growth rate of 37.7%. In all 20 patients with positive blood cultures, the identified microorganism was *B. melitensis*. This finding emphasizes the importance of collecting sufficient and accurate samples for blood culture and extending culture incubation times in the laboratory to improve the chances of isolating the organism.

Cardiovascular complications related to brucellosis include endocarditis, myocarditis, pericarditis, mycotic aneurysms, aortic valve abscess, and thrombophlebitis. Although the incidence of endocarditis is not high, it remains one of the most significant causes of brucellosis-related mortality (21). In the study by Buzgan et al., the incidence of cardiovascular complications due to brucellosis was reported at 0.7%, while Ahmetagić et al. documented an endocarditis rate of 0.4% (14,13). In our study, ECHO evaluations revealed mild mitral regurgitation in seven patients and mild aortic regurgitation in one patient.

Brucellosis frequently leads to complications within the osteoarticular system. Çiftdoğan et al. reported a sacroiliitis rate of 9.4% and spondylitis at 5.7% (22). Our study detected MRI findings indicative of sacroiliitis in 7.7% of patients. We emphasize the need to evaluate brucellosis patients for sacroiliitis; imaging methods should be employed where suspicion exists to avoid missing this complication.

Understanding the association between Brucella capture titers and clinical parameters is essential for early recognition of systemic involvement in pediatric brucellosis. In our study, higher titers were significantly associated with organomegaly and elevated CRP levels ($p< 0.05$), reinforcing Brucella's known tropism for the reticuloendothelial system. Although no significant associations were observed with thrombocytopenia, ESR, liver enzyme elevation, blood culture positivity, or sacroiliitis, these parameters remain important in comprehensive evaluation. Interestingly, lower Brucella titers were found in patients with mild valvular regurgitation on echocardiography, suggesting that minor cardiac findings may not parallel serological activity. Nonetheless, ECHO screening can be valuable in prolonged or atypical cases.

In our study, while Brucella capture titer demonstrated a weak positive correlation with CRP in the univariate analysis, this association did not reach statistical significance in the multivariate linear regression model ($p= 0.583$). This discrepancy suggests that the observed correlation may be secondary to shared variance with other inflammatory markers, such as ESR, creatinine, or liver enzymes, rather than reflecting a direct relationship. It is also possible that Brucella antibody titers, being primarily indicators of immunological exposure, may not accurately reflect the dynamic inflammatory burden at the time of presentation, which is more directly captured by acute phase reactants like CRP. These findings underscore the importance of interpreting serological and inflammatory markers in context, as relying solely on antibody titers could lead to underestimation of ongoing systemic activity.

There is a scarcity of studies focusing on severe presentations of brucellosis and the increased frequency of complications associated with bacteremia. Özdem et al. observed that hepatomegaly and splenomegaly were more prevalent among patients with bacteremia (12). While no significant differences were noted in leukocyte counts, neutrophil counts, or lymphocyte counts, patients with detectable growth in blood cultures showed a higher frequency of thrombocytopenia and significantly elevated serum CRP, ALT, and AST levels (23). Apa et al. indicated that in patients with positive blood culture growth, occurrences of organomegaly, CRP, ALT, and AST values were significantly higher compared to those in patients without detected growth in blood cultures (24). Furthermore, a study by Chunhua et al. in China found that CRP levels were significantly elevated, while platelet and albumin values were lower in patients with growth in blood cultures (25).

In our study, platelet values were significantly lower in patients with positive blood cultures. Although differences in WBC, Hb, and albumin levels were not statistically significant, a trend showed that these values tended to be lower. In contrast, ESR, ALT, AST, and CRP levels were higher in patients with detected growth. Additionally, we observed increased hepatomegaly and splenomegaly among patients with positive blood cultures, further reinforcing prior findings.

Our study demonstrates that fever, fatigue, muscle pain, and arthralgia are common presenting complaints in patients with brucellosis. An increase in acute phase reactants, alongside elevations in complete blood count parameters and transaminases, may also be observed. When hepatomegaly and/or splenomegaly are present in endemic regions, brucellosis should be included in the differential diagnosis for children exhibiting the symptoms above, as well as in the physical examination findings and laboratory results.

While the definitive diagnosis of infections is typically established through the detection of growth in blood cultures, the data from our study reveal a relatively low growth rate (37.7%). This underscores the necessity for alternative diagnostic methods when diagnosing such patients, as reliance solely on blood culture results may lead to missed diagnoses.

In summary, while Brucella capture titer and ESR levels were not correlated concerning disease-related organ involvement and complication development, the negative correlation found between CRP levels and platelet count, as well as the positive correlation between CRP and creatinine

levels, suggests that CRP may serve as an essential predictor of systemic involvement and the potential for complications.

Patients exhibiting elevated CRP levels and positive blood culture results should be closely monitored during treatment through regular complete blood count and biochemical tests, as a decline in platelet count could lead to complications.

From a clinical perspective, the associations observed in this study offer valuable implications for the early recognition and management of pediatric brucellosis. The inverse relationship between CRP levels and platelet count may reflect a heightened inflammatory state that contributes to bone marrow suppression or peripheral platelet consumption. In everyday clinical practice, such findings may help clinicians identify patients at risk for hematologic complications or more severe disease progression. Similarly, the positive correlation between CRP and creatinine suggests that systemic inflammation could be linked with early renal stress or subclinical kidney involvement, which may otherwise go undetected in children. These correlations, although modest, highlight the potential utility of CRP not just as an inflammatory marker, but also as a predictor of disease severity and organ involvement. Given that CRP, platelet count, and creatinine are standard, cost-effective tests available in most healthcare settings, their combined interpretation may improve risk stratification in endemic areas where advanced diagnostic modalities are not readily accessible. Therefore, integrating such parameters into clinical algorithms could facilitate timely intervention, minimize complications, and ultimately improve patient outcomes.

Our findings indicate that brucellosis can affect multiple organ systems, demonstrating the need to understand its clinical and laboratory characteristics thoroughly. Continuous monitoring is essential to prevent additional complications if treatment is delayed or not administered correctly.

Limitation

The main limitation of the study is the lack of data on the patients' post-treatment status and the results of the response to treatment in a disease that can recur and whose complications can be seen over time. The main reason for this is that the standard treatment for the disease is a minimum of six weeks, and the patients did not attend regular follow-up visits or continue their follow-up at other centres.

Conclusion

Brucellosis remains a significant zoonotic disease that poses serious health risks, particularly in areas where animal husbandry is prevalent. The complexity of its clinical presentation and variabilities in laboratory findings underscores the necessity for heightened awareness among healthcare providers to facilitate timely diagnosis and treatment. Future studies are critical for enhancing our understanding of brucellosis and its complications, thus improving patient outcomes and guiding public health strategies effectively.

Finally, it is vital to emphasize that preventive measures and education are the most effective approach to combating this disease. Public authorities, including the Ministry of Food Agriculture and Livestock and the Ministry of Health, play a significant role. The incidence of brucellosis, a zoonotic disease, can be progressively reduced with appropriate management strategies.

Ethics Committe Approval: This study has been approved by the non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (Decision no: 22, Date: 17.05.2023).

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