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Analysis of Epidemiological, Clinical, and Laboratory Characteristics of Patients Diagnosed with Brucellosis: A Comprehensive Study

Bruselloz Tanılı Hastaların Epidemiyolojik, Klinik ve Laboratuvar Özelliklerinin Analizi: Kapsamlı Bir Çalışma

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ABSTRACT

Aim: Brucellosis, an endemic zoonotic disease within our nation, exhibits a notably high prevalence in the Southeastern, Eastern, and Central Anatolia regions. This study aims to assess the epidemiological, clinical, and laboratory characteristics, along with the complications, among both outpatient and inpatient cases diagnosed with brucellosis in Ağrı province.

Materials and Methods: This retrospective study analyzed 121 patients under the care of the Clinic of Infectious Diseases and Clinical Microbiology at Ağrı Training and Research Hospital between January 2022 and March 2024. Diagnosis of brucellosis was established based on clinical manifestations indicative of the disease, standard tube agglutination test titers of >=1/160, and/or isolation of *Brucella* spp./*Brucella melitensis* from blood cultures. Patients were categorized into acute, subacute, chronic (newly diagnosed), and relapsed groups based on their clinical presentations. Epidemiological, clinical, and laboratory parameters were evaluated across these patient groups.

Results: Among the 121 patients analyzed, 73 (60.3%) were female and 48 (39.7%) were male, with a mean age of 40.69 (±14.3) years. Of these patients, 87 (72%) were newly diagnosed, while 34 (28%) had experienced a relapse. Newly diagnosed patients exhibited notably higher rates of blood culture positivity and focal involvement compared to relapsed individuals (p=0.000, p=0.049, respectively). Elevated levels of C-reactive protein (CRP), sedimentation rate, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were observed among patients with organ involvement in comparison to those without organ involvement (p=0.001, p=0.022, p=0.013, p=0.035, respectively).

Conclusion: In regions where brucellosis is endemic, it should be considered among the primary differential diagnoses in patients presenting with fever. Biochemical markers such as CRP, sedimentation rate, ALT, and AST should be taken into consideration for assessing organ involvement in patients diagnosed with brucellosis. Combatting the disease requires a multidisciplinary approach, and healthcare professionals along with the local population should be educated about the disease and preventive measures.

Keywords: Brucellosis, epidemiologia, focal involvement, fever

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ÖZ

Amaç: Bruselloz ülkemizde endemik olarak görülen zoonotik bir hastalık olup, özellikle Güneydoğu, Doğu ve İç Anadolu bölgesinde yaygındır. Bu çalışmanın amacı Ağrı ilinde ayaktan ya da yatarak bruselloz tanısı alan hastaların epidemiyolojik, klinik ve laboratuvar bulgularını, komplikasyonlarını değerlendirmektir.

Gereç ve Yöntem: Bu çalışmada 2022 Ocak ve 2024 Mart tarihleri arasında Ağrı Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği'nde takip edilen 121 hasta geriye dönük incelendi. Bruselloz tanısı, bruselloz düşündüren klinik bulgularla birlikte standart tüp aglütinasyon testi titre >=1/160 olan ve/veya kan kültüründe *Brusella* spp./*Brusella melitensis* üreyen hastalara konuldu. Hastalar klinik durumuna göre, akut, subakut, kronik hasta grupları (yeni tanı alanlar) ve relaps olarak gruplara ayrıldı. Hasta grupları epidemiyolojik, klinik ve laboratuvar değerleri ile değerlendirildi.

Bulgular: Olguların 73'ü (%60,3) kadın, 48'i (%39,7) erkekti, yaş ortalamaları 40,69 (±14,3) idi. Hastaların 87'si (%72) yeni tanı, 34'i (%28) relaps olarak değerlendirildi. Yeni tanı alanlarda relaps hastalara göre kan kültür pozitifliği ve fokal tutulum açısından anlamlı yükseklik saptandı (p=0,000, p=0,049). Organ tutulumu olan hastalarda olmayan hastalara göre C-reaktif protein (CRP), sedimantasyon, alanin aminotransferaz (ALT), aspartat aminotransferaz (AST) anlamlı şekilde yüksek saptandı (p=0,001, p=0,022, p=0,013, p=0,035).

Sonuç: Brusellozun endemik olduğu bölgelerde ateş varlığında ilk akla gelecek hastalıklardan biri bruselloz olmalıdır. Bruselloz tanısı konulan hastalarda CRP, sedimantasyon, ALT, AST gibi biyokimyasal belirteçler organ tutulumu açısından dikkate alınmalıdır. Hastalıkla mücadele multidisipliner olmalı ve sağlık çalışanları ve yerel halk hastalık ve önleme yöntemi hakkında bilgilendirilmelidir.

Anahtar Kelimeler: Bruselloz, epidemiyoloji, fokal tutulum, ateş

INTRODUCTION

Brucellosis is a widespread zoonotic disease transmitted through the consumption of unpasteurized dairy products obtained from infected animals (such as cattle, sheep, goats, camels, and pigs), or through contact with the tissues or secretions of these animals[1]. Rare cases of transmission have been reported via blood transfusion, tissue transplantation, nosocomial infection, and sexual contact[2,3].

Brucellosis poses a significant threat to both human and animal health and imposes a substantial burden on national economies. The prevalence of brucellosis prevalence is closely associated with local livestock activities, with higher rates observed in rural areas known for intensive animal husbandry, particularly in regions such as Southeastern Anatolia, Eastern Anatolia, and Central Anatolia in Turkey. Individuals most commonly affected by the disease include those engaged in livestock farming, veterinarians, and laboratory workers[4].

The causative agent of brucellosis, *Brucella* spp., is a small, non-motile, facultative aerobic, intracellular bacterium that appears as Gram-negative coccobacilli in Gram staining. Among humans, *Brucella melitensis* is the most frequently encountered species[5].

The disease typically presents with symptoms such as fever, night sweats, and muscle and joint pain. Additionally, weight loss, headache, dizziness, loss of appetite, back pain, abdominal pain, and depression may also be present[6].

The incubation period of brucellosis is approximately 2-4 weeks. Based on the duration of symptoms, the disease is classified as acute if symptoms persist for the first 8 weeks, subacute if they last between 8 and 52 weeks, and chronic if symptoms persist for more than 52 weeks[7]. Recurrence of the disease within the first 6-12 months after treatment is classified as relapse[8].

Brucellosis can involve multiple tissues and organs. The most common manifestations include osteoarticular involvement, encompassing peripheral arthritis, sacroiliitis, and spondylodiscitis[9]. Additionally, it may affect the genitourinary system, central nervous system, cardiovascular system, ocular system, and skin[10,11].

Definitive diagnosis of brucellosis is established by isolating the causative agent from blood or other sterile body fluids through culture, or by observing a fourfold or greater increase in Brucella antibody titers between the acute and convalescent phases. A diagnosis may also be presumed if the standard tube agglutination (STA) test yields a titer of 1/160 or higher after the onset of symptoms[12].

Combination therapies form the cornerstone of brucellosis treatment. Nevertheless, despite treatment, relapse, chronicity, and organ involvement may occur, and there is no optimal recommendation for treatment regimen and duration in certain patient groups[13].

Brucellosis encompasses a wide range of clinical manifestations, from non-specific symptoms to severe organ involvement, mimicking many other diseases. This variability can lead

to delays in diagnosis and misdiagnosis[14]. Being the most common zoonotic disease worldwide, brucellosis continues to be of significance due to its impact on animal and human morbidity, reduction in animal productivity, and considerable economic burden, especially in endemic countries. Therefore, besides diagnosis and treatment, preventive measures to prevent disease transmission are equally important[15].

MATERIALS AND METHODS

This retrospective study analyzed 121 patients who were either seen as outpatients or admitted to the Clinic of Infectious Diseases and Clinical Microbiology at Ağrı Training and Research Hospital between January 2022 and March 2024. Patients aged 18 years and above were included in the study.

The diagnosis of brucellosis was established in patients presenting with clinical manifestations suggestive of the disease, along with a STA test titer of ≥1/160 and/or isolation of *Brucella* spp./*Brucella melitensis* from blood cultures. Patient demographics, including age, gender, presence of comorbidities, occupational exposure to livestock, initial symptoms, physical examination findings, previous diagnosis of brucellosis, routine laboratory results, rose bengal and STA test results, blood culture results, hemogram, and biochemical data, were recorded.

Medical records pertaining to clinical follow-ups were scrutinized for evidence of systemic involvement, relapse, and development of complications. Patients with symptoms lasting less than 8 weeks were categorized as acute, those lasting between 8 and 52 weeks as subacute, and those lasting more than 52 weeks as chronic brucellosis cases. Within one year after the completion of treatment, patients exhibiting recurrent symptoms supported by physical examination and laboratory findings were classified as relapsed cases.

Diagnosis of brucellosis relied on either serological or culture positivity in conjunction with clinical findings. Serological test positivity was defined as an STA test titer ≥1/160 using specific antiserum (Ankara Public Health Laboratory, Turkey) or a ≥4-fold increase in STA test titer repeated 2-3 weeks apart. Detection of *Brucella* spp. and *Brucella melitensis* was performed using VITEK2 Compact (BioMérieux, France) and VITEK MS (BioMérieux, France) devices.

Statistical Analysis

Descriptive statistics, including mean or median values for continuous variables and count (n) and percentage (%) values for categorical variables, were provided. The normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed variables, independent samples t-test was utilized for between-group comparisons, while the Mann-Whitney U test was employed for non-normally distributed variables. The chi-square test was applied for comparisons between categorical variables. Statistical analyses were conducted using SPSS version 26 for Windows. Results were considered significant at $p<0.05$ level.

The study was conducted after obtaining the necessary permissions from Ağrı İbrahim Çeçen University Scientific Research Ethics Committee (decision no: E-95531838-050.99-98272, date: 29.03.2024).

RESULTS

Of the cases, 73 (60.3%) were female and 48 (39.7%) were male, with a mean age of 40.69 (±14.3) years. Evaluation based on the place of residence revealed that 73 (60.3%) resided in rural areas, with 79 (65.3%) engaged in livestock farming, 104 (86%) consuming raw milk and dairy products, 3 (2.5%) exposed to laboratory hazards, and 4 (3.3%) with unidentified exposure. The most commonly observed comorbidities among patients were hypertension in 11 (9.1%) cases, coronary artery disease in 7 (5.8%) cases, and hyperlipidemia in 7 (5.8%) cases. Upon examining the demographic data of patients, no statistically significant differences were found between newly diagnosed and relapsed patients in terms of mean age, gender, comorbidities, place of residence, and exposure. The epidemiological data of patients are presented in Table 1.

The distribution of patients diagnosed with brucellosis by place of residence revealed the following proportions: city center 48 (39.7%), Diyadin 30 (24.8%), Taşlıçay 11 (9.1%), Hamur 9 (7.4%), Doğubayazıt 6 (5%), Patnos 6 (5%), Eleşkirt 6 (5%), and Tutak 5 (4.1%). The distribution of patients' places of residence throughout the province is depicted in Figure 1.

When patients were evaluated based on their clinical status at the time of diagnosis, 73 (60.3%) were diagnosed with acute brucellosis, 8 (6.6%) with subacute brucellosis, 34 (28%) with recurrent brucellosis, and 6 (5%) with chronic brucellosis. Assessment of presenting symptoms revealed that the predominant symptoms were joint pain in 113 (93.4%) cases, night sweats in 96 (79.3%), fatigue in 96 (79.3%), fever in 82 (67.8%), lower back pain in 80 (66.1%), and loss of appetite in 72 (59.5%). Fever was significantly more prevalent in patients with newly diagnosed brucellosis, while headache was more pronounced in relapsing cases. The presenting symptoms of patients are provided in Table 2.

Significant differences were observed in terms of blood culture positivity between newly diagnosed and relapse patients (p=0.000). All positive blood cultures were detected in newly diagnosed patients. Furthermore, a significant difference was found in terms of organ involvement between newly diagnosed and relapse patients (p=0.049-0.059), with a higher incidence of organ involvement observed in newly diagnosed cases. Focal

Table 1. Demographic characteristics of patients diagnosed with brucellosis

	All cases (n=121)	New diagnoses (n=87)	Relapses (n=34)	p value
Mean age	40.69 (±14.3)	39.3(±14.4)	44.2(±13.6)	0.074
Gender				
Female	73 (60.3%)	54 (62.1%)	19 (55.9%)	0.542
Male	48 (39.7%)	33 (37.9%)	15 (44.1%)	0.542
Comorbidity				
DM	6 (5%)	5 (5.8%)	1 (2.9%)	0.674
HT	11 (9.1%)	9 (10.3%)	2 (5.9%)	0.726
Autoimmune disease	2 (1.7%)	2 (2.3%)	0	1
CAD	7 (5.8%)	4 (4.6%)	3 (8.8%)	0.4
HL	7 (5.8%)	3 (3.4%)	4 (118%)	0.096
Osteoporosis	2 (1.7%)	0	2 (5.9%)	0.079
Asthma	4 (3.3%)	3 (3.4%)	1 (2.9%)	1
Place of residence		35 (40.2%)		
City center	48 (39.7%)	23 (26.4%)	13 (38.2%)	1
Diyadin	30 (24.8%)	7 (8%)	7 (20.6%)	0.641
Taşlıçay	11 (9.1%)	6 (6.9%)	4 (11.8%)	0.501
Hamur	9 (7.4%)	5 (5.7%)	3 (8.8%)	0.710
Doğubayazıt	6 (5%)	3 (3.4%)	1 (2.9%)	1
Patnos	6 (5%)	5 (5.7%)	3 (3.8%)	0.348
Eleşkirt	6 (5%)	3 (3.4%)	1 (2.9%)	1
Tutak	5 (4.1%)	35 (40.2%)	2 (5.9%)	0.619
Exposure				
Livestock	79 (65.3%)	56 (64.4%)	23 (67.6%)	0.833
Dairy products	104 (86%)	77 (88.5%)	27 (79.4%)	0.245
Lab exposure	3 (2.5%)	3 (3.4%)	0	0.558
Undetermined	4 (3.3%)	2 (2.3%)	2 (5.9%)	0.314

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, HL: Hyperlipidemia

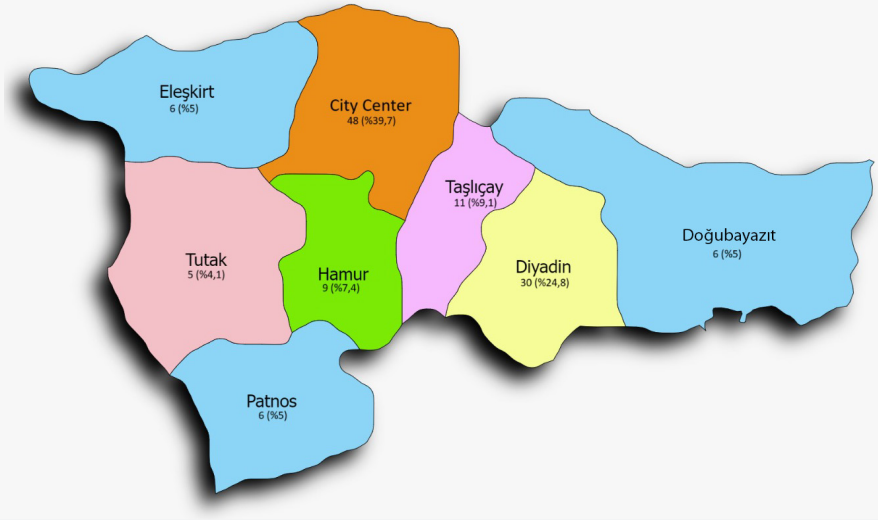

Figure 1. Distribution of patients throughout the province

involvement was present in 29 patients (24% of all cases), with the most common manifestations being sacroiliitis in 12 cases (41.3%), spondylodiscitis in 7 cases (24.1%), and peripheral arthritis in 9 cases (31%). Blood cultures were obtained from 84 patients (69.4%), with *Brucella melitensis* or *Brucella* spp. isolated in 24 cases. The results of blood cultures and organ involvement are presented in Table 3.

Out of the 84 patients from whom blood cultures were obtained, *Brucella* spp. or *Brucella melitensis* growth was observed in 24 cases. It was noted that blood culture positivity was mostly prevalent during the autumn season. The distribution of blood culture positivity according to months is presented in Figure 2.

Notably, when evaluating laboratory results, C-reactive protein (CRP), sedimentation rate, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were found to be significantly higher in complicated cases, with p values of 0.001, 0.002, 0.013, and 0.035, respectively. The laboratory values of patients with and without complications are presented in Table 4.

DISCUSSION

Brucellosis continues to be endemic in areas where economic resources are limited, sanitation measures are lacking, and veterinary services are insufficient. Globally, it persists as an endemic disease in regions such as the Middle East, the Mediterranean, and Central and South America[16]. In Turkey, it is most commonly observed in rural areas where livestock farming is prevalent, particularly in the Southeastern Anatolia, Eastern Anatolia, and Central Anatolia regions[4]. In our study, we evaluated patients diagnosed with brucellosis residing in Ağrı province, and it was observed that the majority of patients lived in districts. This observation is consistent with the tendency for livestock farming activities to occur in rural areas. The higher number of diagnosed patients in Diyadin district may indicate the intense livestock farming and insufficient veterinary services in the area. Despite being the largest districts in the city, the lower number of diagnosed patients residing in Doğubayazıt and Patnos suggests that brucellosis diagnosis and treatment may be conducted in district hospitals within these regions.

Table 2. Distribution of symptoms in patients diagnosed with brucellosis

Symptoms	All cases (n=121)	Newly diagnosed (n=87)	Relapse (n=34)	p value
Joint pain	113 (93.4%)	81 (93.1%)	32 (94.1%)	1
Night sweats	96 (79.3%)	69 (79.3%)	27 (79.4%)	1
Fatigue	96 (79.3%)	66 (75.9%)	30 (88.2%)	0.210
Fever	82 (67.8%)	64 (73.6%)	18 (52.9%)	**0.049**
Lower back pain	80 (66.1%)	55 (63.2%)	23 (73.5%)	0.393
Anorexia	72 (59.5%)	53 (60.9%)	19 (55.9%)	0.682
Headache	63 (52.1%)	39 (44.8%)	24 (70.6%)	**0.015**
Weight loss	55 (45.5%)	41 (47.1%)	14 (41.2%)	0.685
Abdominal pain	35 (28.9%)	24 (27.6%)	11 (32.4%)	0.658

Table 3. Distribution of blood culture results and organ involvement in brucellosis patients

Blood culture	All cases (n=121)	Newly diagnosed (n=87)	Relapse (n=34)	p value
Collection frequency	84 (69.4%)	63 (72.4%)	21 (61.7%)	0.114
Positivity	24 (32.6%)	24 (38%)	0	**0.000**
Brucellosis spp.	7 (29.2%)	7 (29.2%)	0	**0.000**
Brucellosis melitensis	17 (70.8%)	17 (70.8%)	0	**0.000**
Organ involvement				
Focal brucellosis	29 (24%)	25 (28.7%)	4 (11.8%)	**0.049**
Peripheral LAP	1 (3.4%)	1 (4%)	0	1
Splenic involvement	3 (10.3%)	2 (8%)	1 (25%)	1
Sacroiliitis	12 (41.3%)	10 (40%)	2 (50%)	0.506
Spondylodiscitis	7 (24.1%)	7 (28%)	0	0.189
Arthritis	9 (31%)	7 (28%)	2 (50%)	1
Epididymo-orchitis	2 (6.8%)	2 (8%)	0	1

LAP: Lymphadenopathy

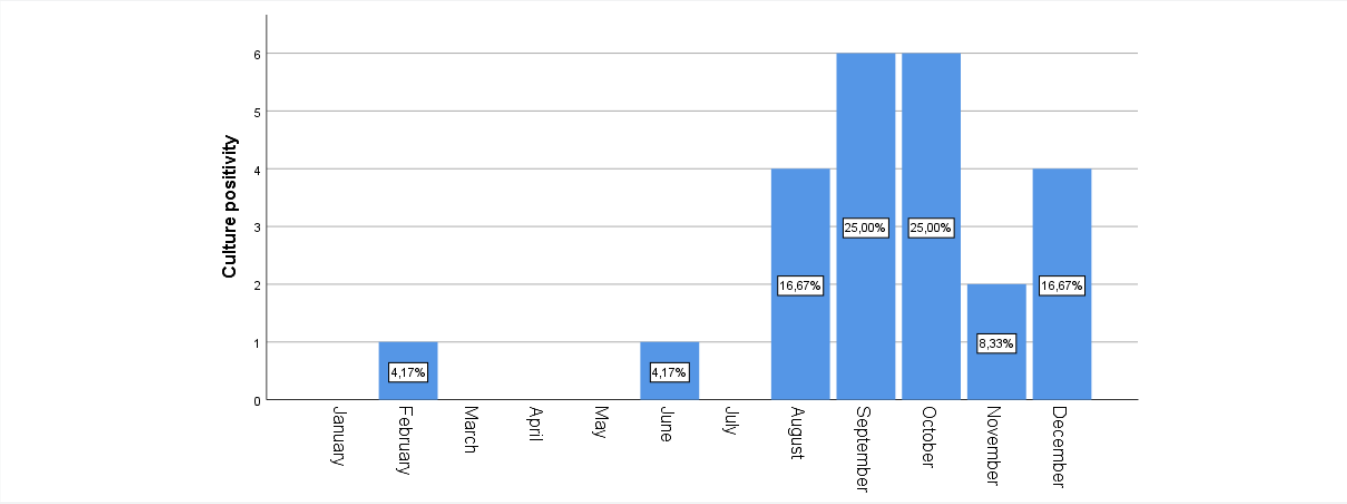

Figure 2. Distribution of blood culture positivity by month

Table 4. Median laboratory results of complicated and non-complicated patients

Parameter	Non-complicated (n=78)	Complicated (n=26)	p value
WBC	6595	7050	0.118
NEU	3885	3740	0.362
LYM	2125	2330	0.129
MONO	400	455	0.292
HB	13.8	13.7	0.550
PLT	261	258	0.993
CRP	4	13.5	**0.001**
SED	18.5	34.5	0.022
ALT	22	29	0.013
AST	22.5	24.5	0.035

WBC: White blood cell, NEU: Neutrophile, LYM: Lymphocyte, MONO: Monocyte, HB: Hemoglobin, PLT: Platelet, CRP: C-reactive protein, SED: Sedimentation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

In our study, 73 (60.3%) of the cases were female, and 48 (39.7%) were male, with a mean age of 40.69 (±14.3) years. In a study conducted by Turkoglu-Yilmaz and Arslan[17], a retrospective evaluation of brucellosis patients over a 5-year period was conducted, revealing that 170 (72%) of 236 patients were male. In a meta-analysis comprising 57 studies examining the clinical manifestations of human brucellosis, it was found that 55% of the patients were male across all participant groups[18]. The higher number of female patients in our study, contrary to the literature, can be attributed to the smaller sample size.

In a study conducted by Almuneef et al.[19], consumption of unpasteurized raw milk was reported as the source of brucellosis in 75% of cases, while 45% were attributed to livestock handling. In our study, when analyzed in terms of transmission routes, it was found that the disease was most commonly transmitted through the consumption of raw milk and dairy products, accounting for 86% of cases. Secondly, 65.9% of cases were associated with occupational livestock handling. This suggests that even if local residents do not engage in livestock farming themselves, they obtain raw milk and dairy products and use them without pasteurization.

In a study conducted by Kuruoglu et al.[20], significantly elevated fever was observed in patients diagnosed with brucellosis across acute, subacute, chronic, and relapse patient groups. Fever was found in 79.2% of patients diagnosed with acute brucellosis. In a retrospective study by Buzgan et al.[21], encompassing the last 10 years and evaluating 1028 brucellosis patients, acute, subacute, and chronic brucellosis patients comprising the newly diagnosed group accounted for 96.8% of all patients, while relapse patients constituted 3.2% of the total. The most common symptoms observed in these patients were arthralgia

(73.7%) and fever (72.2%). In our study, the number of newly diagnosed brucellosis patients was 87 (72%), while the number of relapse brucellosis cases was 34 (28%). The most common symptom observed was arthralgia in 113 patients (93.4%), followed by night sweats in 96 patients (79.3%), fatigue in 96 patients (79.3%), and fever in 82 patients (67.8%). Regarding laboratory findings, elevated levels of CRP sedimentation, and anemia were prominent. However, in our study, while elevated CRP and sedimentation levels were observed in the group with focal involvement, elevated ALT and AST levels were also detected. Anemia was rarely observed. The absence of anemia may be attributed to the high altitude of the city, which predisposes individuals to polycythemia.

In a study conducted by Özdem et al.[22] from Turkey, which included 189 patients, a comparison was made between bacteremic and non-bacteremic brucellosis cases. It was found that organ involvement was significantly higher in the group with positive blood cultures. However, in our study, no significant relationship was found between culture positivity and organ involvement (p=0.391). This may be attributed to the small number of patients in our study.

Large and small ruminants are most reproductively active during the spring season, coinciding with the production of fresh cheese during this period[23,24]. In our study, it was observed that the positivity of blood cultures in patients was lowest in the spring months and highest in the summer and autumn months. The most common exposure factor identified in our study was the consumption of fresh cheese. The higher number of blood culture isolates in the autumn and winter months may be explained by the incubation period of brucellosis.

In our study, CRP, sedimentation rate, ALT, and AST levels were found to be significantly higher in patients with complicated disease who had organ involvement compared to non-complicated patients. Elevated CRP and sedimentation levels in patients with organ involvement may be considered as indicators of inflammation. The elevation of ALT and AST levels can be explained by brucellosis being a disease that affects the reticuloendothelial system, with the liver being a part of this system.

In conclusion, brucellosis is a zoonotic disease with significant public health implications, mimicking various illnesses, and often leading to suboptimal diagnosis and treatment management, thereby increasing the economic burden on countries. It can cause morbidity in both animals and humans. Understanding the epidemiological data of countries and regions, maintaining veterinary services, increasing knowledge among healthcare workers and local populations about the disease are crucial in combating brucellosis. This necessitates interdisciplinary collaboration.

Study Limitations

The limited number of included patients and the inability to obtain blood cultures from every patient due to technical reasons are the primary limitations of this study.

CONCLUSION

Brucellosis continues to be of global significance, necessitating further research on the epidemiological data of countries and regions. In regions where brucellosis is endemic, it should be considered as one of the primary differential diagnoses in the presence of fever. Biochemical markers such as CRP, sedimentation rate, ALT, and AST should be considered for organ involvement in patients diagnosed with brucellosis. Combatting the disease requires a multidisciplinary approach, and healthcare professionals along with the local population should be educated about the disease and preventive measures.

Ethics

Ethics Committee Approval: The study was conducted after obtaining the necessary permissions from Ağrı İbrahim Çeçen University Scientific Research Ethics Committee (decision no: E-95531838-050.99-98272, date: 29.03.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.K.T., E.E., K.Ş., Concept: M.K.T., E.E., K.Ş., Design: M.K.T., Data Collection or Processing: M.K.T., E.E., K.Ş., Analysis or Interpretation: M.K.T., K.Ş., Literature Search: M.K.T., Writing: M.K.T., E.E.

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