ORIGINAL RESEARCH

Bagcilar Med Bull 2022;7(3):205-211
DOI: 10.4274/BMB.galenos.2022.2022-03-028

Evaluation of Complicated and Uncomplicated Brucellosis Cases in the Endemic Region

Endemik Bölgede Komplike ve Komplike Olmayan Bruselloz Olgularının Değerlendirilmesi

Merve Sefa Sayar[1], Dilek Bulut[2], Doğan Barış Öztürk[3]

[1]Bursa High Specialization Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Bursa, Turkey
[2]University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
[3]General Directorate for Public Health, The Ministry of Health, Ankara, Turkey

Abstract

Objective: It was aimed to investigate the clinical and laboratory changes in complicated and uncomplicated brucellosis cases.

Method: Within the scope of the study, 268 brucellosis patients (aged ≥18 years) hospitalized in the infectious diseases unit or seen in outpatient clinics were evaluated retrospectively. The complicated and uncomplicated brucellosis cases were assessed.

Results: In the study, 268 brucellosis patients were evaluated and it was observed that 80.7% of the patients consumed fresh cheese. Also, 93.2, 90.8, 88.8 and 84% of the cases had symptoms such as arthralgia, weakness, sweating and fever, respectively. Anemia, leukopenia, leukocytosis, thrombocytopenia and increased C-reactive protein (CRP) were also detected in 25.9, 4.9, 7.2, 9.2 and 60.2% of patients, respectively. It was found that 32.4% of the patients developed complications, and the complications were osteoarticular in 59 patients (67.8%), genitourinary in 17 (19.5%) and hematological in three (3.44%) cases. The complications were more common in male patients. CRP and neutrophil/lymphocyte ratios (NLR) were also found higher in complicated cases.

Conclusion: Since values such as gender, CRP and NLR were significantly different in complicated brucellosis cases from the non-complicated group, it is considered that a significant increase may have been detected in infection parameters due to the longer exposure time to the microorganism. For this reason, early detection of complications and timely diagnosis play a vital role to improve the prognosis.

Keywords: Brucellosis, complication, C-reactive protein, neutrophil/lymphocyte ratio

Öz

Amaç: Komplike ve komplike olmayan bruselloz olgularında klinik ve laboratuvar değişikliklerin araştırılması amaçlandı.

Yöntem: Çalışmada enfeksiyon hastalıkları biriminde yatan veya polikliniklerde izlenen 268 bruselloz hastası (≥18 yaş) retrospektif olarak değerlendirildi. Komplike ve komplike olmayan bruselloz olguları incelendi.

Bulgular: Çalışmada 268 bruselloz olgusu değerlendirilmiş olup; hastaların %80,7'sinde taze peynir tüketimi mevcuttu. Ayrıca olguların sırasıyla %93,2, %90,8, %88,8 ve %84'ünde artralji, halsizlik, terleme ve ateş gibi semptomlar vardı. Anemi, lökopeni, lökositoz, trombositopeni ve C-reaktif protein (CRP) artışı da sırasıyla hastaların %25,9, %4,9, %7,2, %9,2 ve %60,2'sinde saptandı. Hastaların %32,4'ünde komplikasyon geliştiği, 59 hastada (%67,8) osteoartiküler, 17 hastada (%19,5) genitoüriner ve üç olguda (%3,44) hematolojik komplikasyon geliştiği saptandı. Komplikasyonlar erkek hastalarda daha sıktı. Komplike olgularda CRP ve nötrofil/lenfosit oranları da (NLR) daha yüksek bulundu.

Sonuç: Komplike bruselloz olgularında cinsiyet, CRP ve NLR gibi değerlerin komplike olmayan gruptan anlamlı olarak farklı olması nedeniyle, mikroorganizmaya maruz kalma süresinin daha uzun olmasından dolayı enfeksiyon parametrelerinde anlamlı bir artış saptanmış olabileceği düşünülmektedir. Bu nedenle komplikasyonların erken tespiti ve zamanında teşhis, prognozu iyileştirmede hayati bir rol oynamaktadır.

Anahtar kelimeler: Bruselloz, C-reaktif protein, komplikasyon, nötrofil/lenfosit oranı

Address for Correspondence: Merve Sefa Sayar, Bursa High Specialization Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Bursa, Turkey
E-mail: drmervesefasayar@yahoo.com **ORCID:** orcid.org/0000-0002-0436-4122 **Received:** 15.03.2022 **Accepted:** 22.07.2022

Cite this article as: Sayar MS, Bulut D, Öztürk DB. Evaluation of Complicated and Uncomplicated Brucellosis Cases in the Endemic Region. Bagcilar Med Bull 2022;7(3):205-211

Introduction

Although brucellosis, known as a disease since ancient times, has been eradicated in various parts of the world, it still keeps being witnessed in many continents and 500,000 new cases are reported to be seen per annum by the World Health Organization (1-4). Basically, leading to infections in animals, *Brucella* spp. is transmitted to humans as a result of direct/indirect contact with contaminated milk/dairy products or infected animals, and can mimic many diseases by affecting various organs of the body (5-10). The condition with non-specific symptoms, such as fever, sweating, malaise and anorexia, appears to be an acute complication or chronic brucellosis (8,9). In this study, 268 cases of brucellosis were retrospectively investigated, primarily to guide clinicians working in areas where brucellosis is endemic, and to contribute to the literature by comparing the clinical and laboratory findings obtained as a result of the study with other brucellosis series.

Materials and Methods

The study was conducted between 1st January 2018 and 31st December 2018 in the departments of infectious diseases and clinical microbiology. A total of 268 brucellosis patients who were hospitalized in the infectious diseases department or seen in their outpatient clinics were evaluated retrospectively. However, since only adult patients were followed in our clinic, patients under the age of 18 years and patients over the age of 18 years who applied to the clinic more than once were excluded from the study. The demographic, epidemiological, clinical and laboratory findings, the methods used to diagnose the disease, antimicrobial regimens and duration of the treatment used in the treatment process were obtained from the patients' hospital records. Besides, as radiological imaging techniques, additional imaging methods such as X-ray, ultrasonography (USG), magnetic resonance imaging and echocardiography were peformed, as well as cranial computed tomography performed in all neurobrucellosis cases.

The cases of brucellosis were diagnosed in light of the following criteria in the presence of positive clinical signs and symptoms:

1. The determination through the standard tube agglutination (STA) (Cromatest, Linear Chemicals, Spain) as titer ≥1/160 and/or,

2. Observing a two-fold increase in two serological evaluations performed at 2 or 3-week intervals after the symptoms compatible with brucellosis started and/or,

3. The methods of isolating the microorganisms with automated culture identification system BACTEC 9240 (Becton-Dickinson, Sparks, MD, USA) in blood cultures, tissue samples or other body fluids and defining the microorganisms as *Brucella* spp. After positive signals passage was made from the blood culture bottles, gram stains and biochemical tests were performed from the colonies grown as a result of incubation for 48 hours. *Brucella* bacteria were identified as "catalase and oxidase positive Gram-negative *Coccobacilli*".

All of the cases were subdivided as acute brucellosis (0-2 months), subacute brucellosis (2-12 months) and chronic brucellosis (>12 months) according to the duration of symptoms (8).

Descriptions of Complicated and Non-complicated Patients

As a result of imaging and physical examination, the detection of infection findings in a certain anatomical region of a patient was defined as "complicated brucellosis". The definitions made according to the area of the organ involvement are as follows.

1. Osteoarticular involvement: The involvement was defined as the presence of inflammatory manifestations in any joint, such as increased temperature, skin erythema, pain, edema or loss of function. The diagnosis of osteoarticular involvement was supported by joint culture sampling and radiological examinations according to the osteoarticular region of involvement.

2. Neurobrucellosis: The condition was defined as the presence of STA positivity in any titer along with abnormal cerebrospinal fluid (CSF) findings, the isolation of *Brucella* spp. in the blood or bone marrow culture of a patient with abnormal CSF findings or the isolation of *Brucella* spp. in CSF of a patient with suspected brucellosis findings.

3. Gastrointestinal (GI) involvement: GI involvement was defined as a four-fold increase in aspartate aminotransferase and alanine aminotransferase values which cannot be explained by a different etiological condition, and/or the condition of total bilirubin value >2.5 g/dL.

4. Hematological involvement: The involvement was defined as the hematological abnormalities seen in the laboratory findings and the clinical findings -such as epistaxis, bleeding, petechia, purpura, disseminated intravascular coagulation and thrombophlebitis- witnessed upon excluding the asymptomatic cytopenias with weak symptoms or coagulation disorders.

5. Genitourinary involvement: In patients with brucellosis, the epididymal and testicular sensitivity accompanied by arthralgia and arthritis, skin erythema/inflammation in the scrotum and detection of epididymo-orchitis on USG were defined as genitourinary involvement.

6. Obstetric involvement: Challenges such as spontaneous abortus, early membrane rupture (EMR), intrauterine fetal death (IUF), the threat of abortus or development of preterm delivery during/after the treatment of brucellosis among brucellosis patients with pregnancy or the diagnosis of brucellosis in addition to spontaneous abortus, EMR, IUF, the threat of abortus or preterm delivery within such an obstetric condition, or the production of *Brucella* spp. in the blood culture of the newborn were defined as obstetric involvement.

7. Mucocutaneous involvement: Due to the immune response developing due to brucellosis, mucocutaneous involvement was defined as witnessing the features such as erythematous papular lesions, purpura, dermal cysts and Steven-Johnson syndrome in the early stage of the disease.

Modalities of Treatment

The standard combination treatment of doxycycline (100 mg every 12h) and rifampicin (600 mg every 24 h) was administered to the patient groups without complications for 6 weeks. Furthermore, an additional treatment modality was also developed as streptomycin (1g every 24 h) for 14-21 days at the initial treatment for the cases with osteoarticular involvement. In neurobrucellosis patients, however, intravenous ceftriaxone (2 g every 12 h) or trimethoprim sulfamethoxazole (TMP-SXT) (160/800 every 12 h) treatment was also added to the standard treatment. Other treatment regimens including ciprofloxacin or TMP-SXT (160/800 every 12 h) were preferred for the patients developing lactation, GI intolerance or other side effects, including allergic reactions such as rash or drug-induced hematological changes. The drug combinations and duration of treatment were determined according to some parameters such as the patient's anatomical region involved, response to treatment, side effects, and physician's approach. Patients diagnosed with complicated brucellosis were allowed to receive treatment for 3 months, 6 months or 1 year depending on the area of involvement. While the patients with the poor health conditions were treated and followed up by hospitalization, all of the out-patients were followed up through hospital visits every two weeks. In addition, all patients were followed up for one year after antibiotic treatment was completed. No relapse or recurrence was detected in any of these patients.

Ethics committee approval: The approval was obtained from the Non-Invasive Research Ethics Committee of the University of Health Sciences Turkey, Van Training and Research Hospital (date: 21st March 2019 and no: 2019/06).

Statistical Analysis

Statistical analyses of the study findings were performed with the Statistical Package for the Social Sciences Software Version 18.0 (SPSS Inc., Chicago, IL, USA). In addition, the appropriateness of laboratory parameter levels to the normal distribution was investigated using visual (histogram and probability graphics) and analytical (the Kolmogorov-Smirnov test) methods. For the comparisons between both groups, the chi-square, Fisher's Exact and Mann-Whitney U tests were used and if a p-value was lower than 0.05, it was considered to be significant.

Results

Of the patients included in the study, 60.4% (162) were male and 39.6% (106) were female. It was found that the development of complications was higher in males. While the mean age of all patients in the study was 38.7±14.5 years, the mean age was 37.2±13.6 years in complicated cases. When the relationship between the development of complications and age was examined, no significant relationship was found. The findings of the overall patients were arthralgia (93.2%), fatigue (90.8%), sweating (88.8%) and fever (84%), low-back pain (55.2%), and weight loss (51.6%). It was observed that symptoms such as arthralgia (96.4%), fever (90.2%), weight loss (69.9%) and low back pain (66.3%) were higher in patients with complications compared to uncomplicated cases. It was determined that 84.8% of the cases in the study had acute brucellosis and 1.3% had chronic brucellosis. Subacute brucellosis was more common in 20.0% of complicated cases. In all patients, 60.2% CRP (>8 mg/L), 34.3% ESR (>30 mm/h), 29.1% elevated transaminase, 25.9% anemia, 7.2% leukocytosis, 9.2% thrombocytopenia and 4.9% leukopenia were measured. Unlike similar studies, anemia, leukopenia, leukocytosis, thrombocytopenia, CRP and ESR were found to be higher in complicated patients. The findings are presented in Table 1.

STA was found to be 160 and above in all patients. *Brucella* spp. was isolated in 76.3% of 38 patients who underwent blood culture testing. The number of complicated and non-complicated patients was determined as 87 and 181,

Table 1. Socio-demographic, clinical and laboratory data of the patients

Characteristics		Complicated patients, n (%)	Non-complicated patients, n (%)
Age (yrs), mean ± SD		37.2±13.6	39.5±14.9
Symptoms, n, %	Fever (n=250)	74 (90.2)	136 (80.9)
	Sweating (n=249)	72 (87.8)	149 (89.2)
	Fatigue (n=249)	74 (90.2)	152 (91.0)
	Low-back pain (n=250)	55 (66.3)	83 (49.7)
	Arthralgia (n=251)	80 (96.4)	154 (91.7)
	Weight loss (n=250)	58 (69.9)	71 (42.5)
Disease stages	Acute	63 (78.7)	144 (87.8)
	Subacute	16 (20.0)	18 (10.9)
	Chronic	1 (1.3)	2 (1.3)
Laboratory findings, n, %	Anemia (Hgb g/dL) (women <12 and men <14)	27 (31.8)	40 (22.9)
	Leukopenia (<4.000/mm^3) (n=263)	5 (5.8)	8 (4.5)
	Leukocytosis (>12.000/mm^3) (n=263)	10 (11.6)	9 (5.1)
	Thrombocytopenia (<150.000/mm^3) (n=260)	10 (11.6)	14 (8.0)
	ESR (>30 mm/h) (n=216)	26 (42.6)	48 (30.9)
	CRP (>8 mg/L) (n=266)	70 (80.5)	90 (50.2)
	Transaminase height (AST >30 IU/mL, n=261) ALT 30>IU/mL, n=262)	24 (28.9)	52 (29.2)

ALT: Alanine transaminase, AST: Aspartate transaminase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, STA: Standard tube agglutination, Hgb: Hemoglobin

respectively. The rates of osteoarticular, genitourinary and hematological complications were also found to be 67.8% (n=59), 19.5% (n=17) and 3.44% (n=3), respectively (Table 2).

The combination of doxycycline (D) and rifampicin (R) was frequently preferred in complicated and non-complicated patients. In addition, it was determined that regimens containing streptomycin or gentamicin were frequently preferred combinations in both groups of patients (Table 3).

No deaths were observed in the brucellosis patients and all patients successfully completed the treatment process. The characteristic and laboratory parameters of the patients who developed complications are shown in Table 4. Accordingly, the complications were detected to develop more frequently in male patients in the study. In addition, CRP (>8 mg/dL) and NLR were also found to be higher in the cases with complications.

Table 2. Distribution of complications

Complications		n (%)
Osteoarticular (Spondylitis/spondylodiscitis/arthritis/tendinitis/bursitis etc.)		59 (67.8)
Genitourinary (Epididymo-orchitis/epididymitis/orchitis)		17 (19.5)
CNS*	Meningitis	2 (2.29)
	Brain abscess	1 (1.14)
Hematologic		3 (3.44)
Obstetric	Abortus	2 (2.29)
	Premature birth	1 (1.14)
Mucocutaneous		1 (1.14)
Hepatobiliary		1 (1.14)
Total		87

CNS*: Central nervous system

Discussion

Brucellosis, which presents with non-specific clinical findings and laboratory changes, complicates the treatment of patients by causing organ involvement. Many organs can also be affected by the complications arising from brucellosis. The involvements may develop in various organs due to brucellosis at different rates ranging from less than 1% to over 50% (8). In previous studies conducted to date, the osteoarticular, hematological, GI and genitourinary involvements have been seen at varying rates, such as 21.3-68%, 22-55%, 2.5-51% and 1-20%, respectively (11-13). In this study, 32.4% of the patients were complicated and 3.44% of the patients had hematological, 67.8% had osteoarticular, 19.5% had genitourinary involvement (Table 2). Moreover, it was revealed that different from osteoarticular involvement, which is frequently reported in other studies, various organ involvements ranging from obstetric and mucocutaneous involvement, which are

more rarely encountered, could develop. This fact shows that complicated brucellosis cases can be encountered not only by infection physicians, but also by clinicians working in different specialties and it is an important issue for providing appropriate treatment for patients.

Brucellosis is clinically staged according to the time of symptom onset (8). Complicated brucellosis is frequently seen in subacute and chronic brucellosis stages (8). The longer the contact time with the microorganism, the higher the probability of the disease being complicated. As it is known that the immune system is of a dynamic nature in which the regulatory molecules -such as cytokines composed of lymphocytes and granulocytes including neutrophils, eosinophils, basophils, mast cells, dendritic cells, monocyte-macrophages and phagocytes- are active (14). Neutrophils constitute the first line of defense mechanism against the infectious agents and among the target of neutrophils are bacteria, fungi, protozoa, viruses, and virus-infected cells (15). In recent years, there has been an increasing interest in the rates of leukocyte subgroups in reflecting the inflammation level in chronic and several acute diseases (16). Routine laboratory tests alone are not sufficient for the diagnosis of brucellosis cases, and in addition, complete blood count (CBC), ESR, CRP and liver function tests can be used to help support the diagnosis (9). The lipopolysaccharide structure on the cell surface of *Brucella* species prevents the formation of an immune response or the triggering of the alternative complement system (17). This situation enables the microorganism to easily invade tissues such as the liver, lymph node, and bone marrow and make laboratory changes (18). Laboratory findings such as leukocytosis (especially in those with focal complications), leukopenia, thrombocytopenia, anemia, ESR, CRP and increased liver enzymes can be seen in brucellosis (11,19). As seen in Table 1, hematological changes were observed more prominently in this study, especially in complicated brucellosis cases.

Neutrophil, lymphocyte, monocyte, and platelet counts are the components of CBC parameters and are routinely used in the follow-up of brucellosis patients. NLR is a simple and

Table 3. Distributions of treatment regimes

Patient groups	Treatment protocols	n (%)
Non-complicated cases	D+R	140 (77.3)
	S (14/21) + D + R	6 (3.3)
	G (7) + D + R	12 (6.6)
	Other combinations (TMP-SXT+D. TMP-SXT+R. D+CIPRO. D+R+TMP-SXT. TMP-SXT+RIF. D+R+CIPRO. D+G+TMP-SXT. CRO+SXT. D+SXT+S)	23 (12.8)
Complicated cases	D+R	30 (34.5)
	S (14/21) +D+R	28 (32.2)
	G (7) +D+R	17 (19.5)
	Other combinations (TMP-SXT+D. TMP-SXT+R. D+CIPRO. D+R+TMP-SXT. TMP-SXT+RIF. D+R+CIPRO. D+G+TMP-SXT. CRO+TMP-SXT. D+TMP-SXT+S. CRO+D+R)	12 (13.8)

CIPRO: Ciprofloxacin, CRO: Ceftriaxone, D: Doxycycline, G: Gentamycin, R: Rifampicin, S: Streptomycin, TMP-SXT: Trimethoprim sulfometaxazole

Table 4. The effects of patients' laboratory findings and general characteristics on the development of complications

All cases	Complicated mean, n	SD (%)	Non-complicated mean, n	SD (%)	p
Gender					
Male	60	37.0	102	63.0	0.048
Female	27	25.5	79	74.5	
Age (yrs)	37.2	13.6±1.5	39.5	14.9±1.1	0.289
CRP	51.6	58.6±6.3	22.9	35.4±2.6	**<0.001**
Sedimentation	27.9	20.6±2.6	21.9	17.4±1.4	0.060
AST	39.6	45.8±5.1	31.1	27.5±2.1	0.778
ALT	45.2	60.1±6.6	32.3	27.9±2.1	0.716
Platelets	262534	116860	254454	77952	0.711
Hgb	13.6	1.8±0.2	14.0	1.9±0.1	0.346
MPV	9.4	1.3±0.1	9.4	1.2±0.1	0.760
Neutrophil/lymphocyte	2.26	2.25±0.25	1.84	2.07±0.16	**0.007**
Monocyte/lymphocyte	0.23	0.13±0.01	0.25	0.41±0.03	0.152
Platelet/lymphocyte	114.4	67.8±7.4	111.5	49.5±3.9	0.802

ALT: Alanine transaminase, AST: Aspartate transaminase, CRP: C-reactive protein, Hgb: Hemoglobin, MPV: Mean platelet volume, SD: Standard deviation

inexpensive parameter that can be used in many areas to indicate the inflammatory or infectious pathologies and postoperative complications as a strong prognostic factor in the classification of major cardiac events and various types of cancer (20-22). In the study where the association of brucellosis and healthy volunteers with hematological parameters was investigated by Olt et al. (23), an important correlation was found between hemoglobin and NLR through the receiver operating characteristic curve analysis. In the study conducted by Kayaaslan et al. (10) on the patients with complicated brucellosis, the rates of anemia ($p<0.001$), increased CRP ($p=0.005$), ESR ($p=0.021$), and positivity of blood culture ($p=0.014$) were determined to be more frequent in complicated patients (10). In the study of Tekin et al. (24) -comparing the inflammatory markers of adult and pediatric brucellosis patients with the control group- the NLR and PLR values were significantly lower in adult patients than those in the control group subjects.

Based on the results of the above studies, it can be suggested that NLR and PLR ratios are inflammatory markers that can be used in brucellosis patients. This situation is also valid for MPV value investigated for many systemic inflammatory diseases including brucella (25). Changes in the release of proinflammatory cytokines by affecting macrophages can affect the number and structure of platelets (26). In some studies, it is stated that platelet count, MPV, neutrophil and monocyte are important markers in brucellosis (27,28). It was aimed to investigate the role of hematological parameters in complicated brucellosis cases. In addition, changes in MPV, NLR, MLR and PLR values and abnormalities in anemia, CRP, ESR and other laboratory parameters were also investigated. Anemia, thrombocytopenia, leukocytosis and leukopenia were more common in complicated cases, but this was not statistically significant. While it was found that complicated cases were more common in male patients ($p<0.05$), it was also observed that CRP and NLR values were higher in complicated cases ($p<0.05$). In the light of the data obtained, it would be appropriate to determine and support the cutoff values for NLR, MLR and PLR with different studies on brucellosis cases.

Study Limitations

The limitations of our study are;

1. Its retrospective nature,

2. The fact that a group having all complications had to be formed because there were not enough cases to separately evaluate each complication due to brucella in groups.

Conclusion

In this study, the rate of complicated brucellosis cases was observed to be higher among the male gender, as well as findings of higher CRP and NLR values. Moreover, it was found that NLR value was an important parameter in this patient group in addition to male gender and CRP values in complicated brucellosis cases. In previous studies, it has been emphasized that there is a relationship between the development of complications in brucellosis and the exposure time to the microorganism. As a result of these studies, this parameter is taken into consideration in the clinical staging of the disease. In addition to previous studies, it was revealed that the NLR value was a useful parameter as well as the exposure time to the microorganism in the clinical classifications of brucellosis in this study. However, since the study was performed at a single center and no cut-off value was detected in NLR values in cases with brucellosis, we consider that our study findings cannot be generalized to the other regions in Turkey and further studies are needed to support the data.

Ethics

Ethics Committee Approval: The approval was obtained from the Non-Invasive Research Ethics Committee of the University of Health Sciences Turkey, Van Training and Research Hospital (date: 21st March 2019 and no: 2019/06).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: M.S.S., D.B., D.B.Ö., Design: M.S.S., D.B., Data Collection or Processing: M.S.S., Analysis or Interpretation: D.B.Ö., Literature Search: M.S.S., Writing: M.S.S., D.B., D.B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Lai S, Zhou H, Xiong W, Gilbert M, Huang Z, Yu J, et al. Changing Epidemiology of Human Brucellosis, China, 1955-2014. Emerg Infect Dis 2017;23(2):184-194.

2. Dean AS, Crump L, Greter H, Schelling E, Zinsstag J. Global burden of human brucellosis: a systematic review of disease frequency. PLoS Negl Trop Dis 2012;6(10):e1865.

3. Akhvlediani T, Clark DV, Chubabria G, Zenaishvilli O, Hepburn MJ. The changing pattern of human brucellosis: clinical manifestations, epidemiology and treatment outcomes over three decades in Georgia. BMC Infect Dis 2010;10:346.

4. Buzgan T, Karahocagil MK, Irmak H, Baran Aİ, Karsen H, Evirgen O, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis 2010;14(6):e469-478.

5. T.C. Sağlık Bakanlığı, Türkiye Halk Sağlığı Kurumu Başkanlığı. Ulusal mikrobiyoloji stnadratları Bulaşıcı hastalıklar laboratuvar tanı rehberi, Cilt 1. 2014. Bruselloz. Erişim adresi: https://hsgm.saglik.gov.tr/depo/birimler/Mikrobiyoloji_Referans_Laboratuvarlari_ve_Biyolojik_Urunler_DB/rehberler/UMS_LabTaniRehberi_Cilt_1.pdf

6. World Health Organization. Corbel MJ. Brucellosis in humans and animals. 2006. Available from: https://www.who.int/csr/resources/publications/Brucellosis.pdf

7. CDC. Brucellosis reference guide: exposures, testing, and prevention. Atlanta, GA: US Department of Health and Human Services, CDC; 2017. Available from: https://www.cdc.gov/brucellosis/pdf/brucellosi-reference-guide.pdf

8. Ulu-Kilic A, Metan G, Alp E. Clinical presentations and diagnosis of brucellosis. Recent Pat Antiinfect Drug Discov 2013;8(1):34-41.

9. Gul HC, Erdem H. Brucellosis (Brucella species). In: Bennet JE, Dolin R, Blaser MJ, editors. Philadelphia: Elsevier; 2015. p. 2584-2589.

10. 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 (Lond) 2016;48(3):215-221.

11. Kurtaran B, Candevir A, İnal AS, Kömür S, Akyıldız Ö, Saltoğlu N, et al. Clinical appearance of brucellosis in adults: fourteen years of experience. Turk J Med Sci 2012;42(3):497-505.

12. Gür A, Geyik MF, Dikici B, Nas K, Cevik R, Sarac J, et al. Complications of brucellosis in different age groups: a study of 283 cases in southeastern Anatolia of Turkey. Yonsei Med J 2003;44(1):33-44.

13. Zheng R, Xie S, Lu X, Sun L, Zhou Y, Zhang Y, et al. A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. Biomed Res Int 2018;2018:5712920.

14. Parkin J, Cohen B. An overview of the immune system. Immunology. Lancet 2001;357(9270):1777-1789.

15. Cruse JM, Lewis RE, Wang H. Immunology guide book: Microbial Immunity. [Place unknown]: Academic press; 2004. Available at: https://doi.org/10.1016/B978-0-12-198382-6.X5022-5 Accessed July 7, 2020.

16. Özer Balın Ş, Sağmak Tartar A, Akbulut A. The predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. Afr Health Sci 2018;18(4):988-994.

17. Shi Y, Gao H, Pappas G, Chen Q, Li M, Xu J, et al. Clinical features of 2041 human brucellosis cases in China. PLoS One 2018;13(11):e0205500.

18. Kellerman R, Rakel D. Conn's Current therapy: Brucellosis. Elsevier; 2022. p. 547-551.

19. Salvana EMT, Salata RA. Goldman-Cecil Medicine: Brucellosis. Elsevier; 2020. p. 1948-1451.

20. Corbeau I, Jacot W, Guiu S. Neutrophil to Lymphocyte Ratio as Prognostic and Predictive Factor in Breast Cancer Patients: A Systematic Review. Cancers (Basel) 2020;12(4):958.

21. Wang L, Wang C, Jia X, Yang M, Yu J. Relationship between Neutrophil-to- Lymphocyte Ratio and Systemic Lupus Erythematosus: A Meta-analysis. Linics (Sao Paulo) 2020;75:e1450.

22. Balta S, Celik T, Mikhailidis DP, Ozturk C, Demirkol S, Aparci M, et al. The Relation Between Atherosclerosis and the Neutrophil–Lymphocyte Ratio. Clin Appl Thromb Hemost 2016;22(5):405-411.

23. Olt S, Ergenç H, Açıkgöz SB. Predictive Contribution of Neutrophil/Lymphocyte Ratio in Diagnosis of Brucellosis. BioMed Res Int 2015;2015:210502.

24. Tekin R, Aktar F, Yılmaz K, Tekin S, Ayaz C. Comparison of Inflammatory Markers between Adult and Pediatric Brucellosis Patients. Rev Soc Bras Med Trop 2020;53:e20190356.

25. Jioa H, Zhou Z, Li B, Xiao Y, Li M, Zeng H, et al. The Mechanism of Facultative Intracellular Parasitism of Brucella. Int J Mol Sci 2021;22:3673.

26. Kaushansky K. The molecular mechanisms that control thrombopoesis. J Clin Invest 2005;115(12):3339-3347.

27. Okan DH, Gökmen Z, Seyit B, Yuksel K, Cevdet Z, Deniz A. Mean platelet volume in brucellosis: correlation between brucella standard serum agglutination test results, platelet count, and C-reactive protein. Afr Health Sci 2014;14(4):797-801.

28. Küçükbayrak A, Taş T, Tosun M, Aktaş G, Alçelik A, Hakyemez İN, et al. Could thrombocyte parameters be an inflammatory marker in the brucellosis? Med Glas (Zenica) 2013;10(1):35-39.