Original Article

Investigation of hematologic findings related to brucellosis in Anatolian region

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ABSTRACT

الأهداف: دراسة مدى انتشار نتائج أمراض الدم والعلاقة بين متغيرات الرسم الدموي

الأهداف: دراسة مدى انتشار نتائج أمراض الدم والعلاقة بين متغيرات الرسم الدموي ومراحل داء البروسيلات لدى المرضى.

المنهجية: شملت هذه الدراسة متعددة المراكز المرضى الذين تزيد أعمارهم عن 16 عامًا والذين تمت متابعتهم بتشخيص داء البروسيلات. تم تحليل نتائج المرضى، بما في ذلك خلايا الدم البيضاء، والهيموجلوبين، والعدلات، والخلايا الليمفاوية، وحيدات الخلية، ومتوسط حجم الصفائح الدموية، وعدد الصفائح الدموية والحمضات في التشخيص الأولي.

النتائج: في هذه الدراسة كان 51.3% من المرضى الذين تم تشخيص إصابتهم بداء البروسيلات من الذكور. كان متوسط العمر 45 سنة للإناث و41 سنة للذكور. كان ما مجموعه 55.1% من المرضى يعانون من داء البروسيلات الحاد، و 28.2% كانوا تحت الحاد، و 7.4% كانوا مزمنين و 9% كانوا يعانون من الانتكاس. كانت النتائج الدموية الأكثر شيوعا في مرضى داء البروسيلات هي فقر الدم (25.9%)، كثرة الوحيدات (15.9%)، قلة اليوزينيات (10.3%) وزيادة عدد الكريات البيضاء (7.1%). حدثت قلة الكريات الشاملة في 0.8% من المرضى وكانت أكثر وضوحًا في المرحلة الحادة. كان لدى مجموعة داء البروسيلات الحادة انخفاض في عدد خلايا الدم البيضاء والهيموجلوبين والعدلات والحمضات والصفائح الدموية ومتوسط حجم الصفائح الدموية وعدد الكريات الوحيدة أعلى مقارنة بالمجموعات الفرعية تحت الحادة والمزمنة.

الخلاصة: إضافة إلى فقر الدم وكثرة الكريات البيضاء، فقد احتلت قلة اليوزينيات المركز الثالث في أبرز النتائج المخبرية في الدراسة. كانت معدلات قلة الكريات الشاملة ونقص الصفيحات منخفضة.

Objectives: To investigate the prevalence of hematologic findings and the relationship between hemogram parameters and brucellosis stages in patients.

Methods: This multi-center study included patients older than 16 years of age who were followed up with a diagnosis of brucellosis. Patients' results, including white blood cell, hemoglobin, neutrophil, lymphocyte, monocyte, mean platelet volume, platelet and eosinophil counts were analyzed at the initial diagnosis.

Results: In this study 51.3% of the patients diagnosed with brucellosis were male. The age median was 45 years for female and 41 years for male. A total of 55.1% of the patients had acute brucellosis, 28.2% had subacute, 7.4% had chronic and 9% had relapse. The most common hematologic findings in brucellosis patients were anemia (25.9%), monocytosis (15.9%), eosinopenia (10.3%), and leukocytosis (7.1%). Pancytopenia occurred in 0.8% of patients and was more prominent in the acute phase. The acute brucellosis group had lower white blood cell, hemoglobin, neutrophil, eosinophil, and platelet counts and mean platelet volume, and higher monocyte counts compared to subacute and chronic subgroups.

Conclusion: It was noteworthy that in addition to anemia and monocytosis, eosinopenia was third most prominent laboratory findings in the study. Pancytopenia and thrombocytopenia rates were low.

Keywords: anemia, brucellosis, eosinopenia, hematologic, monocytosis

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Brucellosis is the most common zoonotic infection worldwide and the annual number of cases is estimated to be 2.1 million. The disease is prevalent in Central and South America, Asia, Africa, the Middle East, the Arabian Peninsula, and the Mediterranean region. Although brucellosis is mostly under control in developed countries, it is a common public health issue in developing countries, including Turkey.[1,2] Turkey neighborliness to countries in the east and southeast, such as Iran, Iraq and Syria, has always played a role in the spread of brucellosis, because brucellosis is endemic in all of these countries.[3] According to the data of the Ministry of Health of the Republic of Turkey, the number of brucellosis cases between 2008-2019 was reported to be between 4100-10200, and it was especially seen more in the Eastern Anatolia Region.[4] Brucellosis is caused by bacteria of the *Brucella* genus, which are facultative intracellular Gram-negative *Coccobacilli*.[5] Transmission to humans occurs through direct contact with infected animals or consumption of infected unpasteurized milk/dairy products and meat products.[6] After infecting the host, *Brucella* enter the lymphatic system and then the bloodstream by overcoming mucosal barriers, eventually spreading throughout the body.[7,8] These microorganisms are retained within monocytes and macrophages of organs of the reticuloendothelial system (RES) such as the lymph nodes, liver, spleen, and bone marrow. They can also survive and proliferate in phagocytic cells by evading various host immune response mechanisms.[9]

Brucellosis is characterized by various clinical symptoms.[10] The clinical course of the disease can range from asymptomatic to severe symptoms with multi-organ involvement. Symptoms such as fever, malaise, weight loss, chills, sweating, arthralgia/arthritis, hepatosplenomegaly, lymphadenopathy, and hearing loss occur in the acute period. The disease may progress to subacute and chronic stages if the disease is not diagnosed and treated adequately.1[1,12] Isolation of *Brucella* species in blood or other body fluid cultures is the gold standard method for diagnosing brucellosis. However, the fact that bacterial isolation in culture requires time and the sensitivity of culture decreases in the advanced stages of the disease are important diagnostic problems. For this reason, immunological diagnostic methods such as Rose Bengal, standard tube agglutination (SAT), enzyme-linked immunosorbent assays (ELISA), Coombs and immunochromatographic tests are more widely used. Although molecular methods such as qualitative and quantitative polymerase chain reaction (PCR) targeting various genes have recently been used to diagnose the disease, these tests may not indicate an active infection.[13] Laboratory test results of most brucellosis patients show hematologic changes. Leukopenia, lymphomonocytosis, and mild anemia are the most common hematologic findings associated with brucellosis. Brucellosis may also rarely cause pancytopenia and severe thrombocytopenia due to hemophagocytosis, hypersplenism, and granulomatous changes in the bone marrow.[14] The aim of this study was to investigate the prevalence of hematologic findings and the relationship between hemogram parameters and brucellosis stages in patients with the disease.

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Methods. The study included 25 hospitals from 19 cities in 7 different geographical regions, where brucellosis is endemic, of Turkey. The study population consisted of 3472 patients older than 16 years of age who were diagnosed with brucellosis in the Infectious Diseases and Clinical Microbiology clinics of these hospitals between January 2017 and December 2022.

Institutional permission from the clinical centers, which participated in the study, the ethical approval of Harran University, Turkey University Clinical Research Ethics Committee numbered 2022/24/25 dated December 12, 2022, was obtained. This study was carried out in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association.

Demographic data of patients such as age and gender, as well as initial hemogram results was evaluated. The analyzed hemogram results include white blood cell, hemoglobin, neutrophil, lymphocyte, monocyte, mean platelet volume (MPV), platelet and eosinophil values.

Brucellosis diagnosis was determined with growth of *Brucella spp.* in blood or other body fluid cultures, or clinical symptoms such as fever, sweating, chills, muscle-joint pain, headache, and malaise with a serum *Brucella* tube agglutination titer of ≥1/160, or at least a 4-fold titer increase in serum samples obtained at least 2 weeks apart.

Brucellosis cases were classified as acute (<8 weeks), subacute (8-52 weeks) or chronic (>52 weeks) according to the duration of symptoms, and the reappearance of clinical signs and symptoms within 12 months after treatment was classified as a relapse.[15,16]

Definitions of hematological findings were as follow: i) anemia: hemoglobin <12 g/dl in women and <13 g/

dl in men; ii) leukocytosis: leukocyte count >11 uL; iii) leukopenia: leukocyte count <4 uL; iv) neutropenia: absolute neutrophil count <1.5 uL; v) neutrophilia: neutrophil count >7.7 uL; vi) lymphopenia: lymphocyte count <1 uL; vii) lymphocytosis: lymphocyte count >4 uL; viii) monocytopenia: monocyte count <0. 24 uL; ix) monocytosis: monocyte count >0.79 uL; X) thrombocytopenia: platelet count <150 uL; xi) thrombocytosis: platelet count >450 uL; xii) eosinophilia: eosinophil count ≥0. 5 uL; xiii) eosinopenia: eosinophil count ≥0.02 uL; xiv) pancytopenia: low levels of all 3 blood values (white blood cell, hemoglobin and platelet); xv) bicytopenia: low levels of at least 2 blood values.

Statistical analysis. The Statistical Package for the Social Sciences, version 22.0 (IBMCorp, Armonk, NY, USA) program was used for statistical analysis. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test whether the continuous variables had normal distribution. All continuous variables are presented as mean ± standard deviation (SD) and median. Mann-Whitney U test was used to compare the means of continuous variables with non-normal distribution. Kruskal-Wallis was employed to compare the means of more than 2 independent groups with non-normal distribution. In addition, Chi-square test was applied to determine the relationship between categorical variables. A *p*-value of <0.05 was considered significant.

Results. This study included 3472 patients, 51.3% were male. The age median was 45 years for female and 41 years for male. In terms of brucellosis subgroups, 55.1% of patients were categorized as acute, 28.2% as subacute, 7.4% as chronic, and 9% as relapse group. The median and mean age of patients in the chronic and relapse groups were higher (p<0.001). Hematologic abnormalities, which found at least one of white blood cell, hemoglobin, and platelet counts, were detected in 32% of all patients (Tables 1 & 2).

The acute brucellosis group had lower count of white blood cell, hemoglobin, neutrophil, eosinophil, platelet counts, and MPV, while monocyte counts were higher than the other subgroups. However, there were statistically significant differences in mentioned parameters except hemoglobin. Although lymphocyte counts in the acute brucellosis group were higher, this difference was not statistically significant.

According to the results of pairwise comparison of subgroups, there were differences: i) in eosinophil levels between the acute-subacute, acute-chronic, acute-relapse, subacute-relapse, and subacute-chronic groups; ii) in white blood cell levels between the acute-subacute groups; iii) in neutrophil levels between the acute-subacute and acute-chronic groups; iv) in monocyte levels between the acute-subacute, acute-chronic, acute-relapse groups; and v) in MPV levels between relapse-acute, relapse-subacute and relapse-chronic groups (Table 1).

When the relationship between laboratory parameters and gender was evaluated, it was observed that white blood cell, hemoglobin, neutrophil, lymphocyte, and monocyte were higher in males, whereas MPV and platelet count of pf were higher in females (p<0.001 to p=0.007; Table 2).

The most common hematologic findings in brucellosis patients were anemia (25.9%), monocytosis (15.9%), eosinopenia (10.3%), and leukocytosis (7.1%). Pancytopenia occurred in 0.8% of patients and was more prominent in the acute brucellosis group.

The most frequent findings in the subgroups were: i)anemia (26.9%), monocytosis (18.1%), and

Table 1 - Distribution of age and laboratory parameters according to stage.

Variables	Acute		Subacute		Chronic		Relapse		*P*-values*
	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	
Age	41.00	42.28±15.77	44.00	44.91±15.75	51.50	50.57±15.49	45.00	45.97±16.25	<0.001
Wbc	7.00	7.28±2.38	7.18	7.54±2.46	7.06	7.45±2.31	6.91	7.16±2.12	0.015
Hgb	13.50	13.40±1.81	13.50	13.57±1.84	13.50	13.50±2.03	13.30	13.34±1.74	0.278
Neut	3.62	4.06±1.97	3.94	4.32±2.14	3.86	4.34±1.98	3.84	4.10±1.74	<0.001
Lymp	2.32	2.45±0.97	2.28	2.43±1.06	2.22	2.34±0.85	2.19	2.30±0.76	0.272
Mono	0.55	0.59±0.25	0.53	0.59±0.25	0.50	0.54±0.19	0.49	0.54±0.21	0.001
MPV	9.40	9.37±1.33	9.50	9.47±1.36	9.50	9.50±1.38	9.80	9.75±1.25	<0.001
Eos	0.08	0.11±0.12	0.10	0.14±0.15	0.13	0.17±0.15	0.13	0.16±0.13	<0.001
Plt	252.00	259.77±84.22	249.00	263.13±86.07	264.00	269.13±68.82	253.00	264.01±77.64	0.008

Values are presented as median and mean ± standard deviation (SD). *Kruskall Wallis. Wbc: white blood cell, Hgb: hemoglobin, Neut: neutrophil, Lymp: lymphocyte, MPV: mean platelet volume, Plt: platelet, Eos: eosinophil

eosinopenia (13.6%) in the acute group; ii) anemia (25.6%), monocytosis (14.9%), and eosinopenia (7.8%) in the subacute group; iii) anemia (26.5%), monocytosis (9%), and leukocytosis (7.3%) in the chronic group; iv) and anemia (20%), monocytosis (11.3%), and leukocytosis (5.4%) in the relapse group (Table 3).

Discussion. This multicenter study examined the hematologic involvement of brucellosis. The most common hematologic findings observed were anemia, monocytosis, and leukocytosis. Pancytopenia was more common in the acute phase. Eosinopenia was among the most noteworthy laboratory findings in the study, in addition to those regarding anemia and monocytosis.

Although hematologic involvement is common in brucellosis, patients usually have a mild clinical picture and the disease rarely follows a severe course.[17] In a systematic review carried out in Turkey, hematologic involvement was observed in 33.3% of brucellosis patients.[18] Another study found it to be 44% involvement among that population.[17] The hematologic abnormalities rates (32%) observed in the current study were similar to prior studies.

Table 2 - Analysis of age and laboratory parameters of patients.

Variables	Median		Mean±SD		*P*-values*
	Female	Male	Female	Male	
Age	45.0	41.0	45.57±15.77)	42.58±16.00)	<0.001
Wbc	6.9	7.2	7.11±2.13)	7.60±2.57)	<0.001
Hgb	12.7	14.4	12.63±1.54)	14.23±1.74)	<0.001
Neut	3.8	3.8	3.99±1.73)	4.31±2.23)	0.004
Lymp	2.3	2.3	2.38±0.94)	2.46±1.01)	0.007
Mono	0.5	0.6	0.53±0.20)	0.62±0.28)	<0.001
MPV	9.6	9.4	9.62±1.33)	9.28±1.33)	<0.001
Eos	0.1	0.1	0.13±0.13)	0.13±0.14)	0.482
Plt	259.5	245.0	270.04±83.45)	254.16±82.01)	<0.001

Values are presented as median and mean ± standard deviatin (SD). *Pairwise comparisons were carried out between genders using Mann Whitney-U test. Wbc: white blood cell, Hgb: hemoglobin, Neut: neutrophil, Lymp: lymphocyte, MPV: mean platelet volume, Plt: platelet, Eos: eosinophil

Table 3 - Hematological findings of patients.

Findings	Acute (n=1916)			Subacute (n=981)			Chronic (n=260)			Relapse (n=315)			Total (N=3472)			*P*-values (group)‡
	n	% of total*	% of group†	n	% of total*	% of group†	n	% of total*	% of group†	n	% of total*	% of group†	n	% of total*	% of group†	
Anemia	516	14.9	26.9	251	7.2	25.6	69	2.0	26.5	63	1.8	20.0	899	25.9	25.9	0.076
Leukocytosis	143	4.1	7.5	68	2.0	6.9	19	0.5	7.3	17	0.5	5.4	247	7.1	7.1	0.610
Leukopenia	94	2.7	4.9	36	1.0	3.7	8	0.2	3.1	12	0.3	3.8	150	4.3	4.3	0.288
Neutropenia	46	1.3	2.4	19	0.5	1.9	1	0.0	0.4	8	0.2	2.5	74	2.1	2.1	0.179
Neutrophilia	100	2.9	5.2	55	1.6	5.6	10	0.3	3.8	13	0.4	4.1	178	5.1	5.1	0.568
Lymphopenia	74	2.1	3.9	36	1.0	3.7	7	0.2	2.7	8	0.2	2.5	125	3.6	3.6	0.566
Lymphocytosis	118	3.4	6.2	63	1.8	6.4	10	0.3	3.8	10	0.3	3.2	201	5.8	5.8	0.074
Monocytopenia	86	2.5	4.5	35	1.0	3.6	3	0.1	1.2	8	0.2	2.6	132	3.8	3.8	0.030
Monocytosis	342	10.0	18.1	146	4.3	14.9	23	0.7	9.0	35	1.0	11.3	546	15.9	15.9	<0.001
Thrombocytopenia	169	4.9	8.8	54	1.6	5.5	7	0.2	2.7	12	0.3	3.8	242	7.0	7.0	<0.001
Thrombocytosis	45	1.3	2.3	23	0.7	2.3	1	0.0	0.4	11	0.3	3.5	80	2.3	2.3	0.100
Eosinophilia	22	0.7	1.3	35	1.1	3.8	8	0.3	3.2	10	0.3	3.4	75	2.4	2.4	<0.001
Eosinopenia	233	7.3	13.6	72	2.3	7.8	8	0.3	3.3	15	0.5	5.2	328	10.3	10.3	<0.001
Pancytopenia	17	0.5	0.9	9	0.3	0.9	0	0.0	0.0	3	0.1	1.0	29	0.8	0.8	0.496
Bicytopenia	96	2.8	5.0	39	1.1	4.0	7	0.2	2.7	8	0.2	2.5	150	4.3	4.3	0.086

Values are presented as numbers and percentages (%). *Percentage of occurrence in all patients. †Percentage of occurrence in disease stage. ‡The relationship between the presence of pathologic findings and disease stages.

Anemia may occur in brucellosis patients due to changes in iron metabolism secondary to infection, hypersplenism, bleeding, bone marrow suppression or autoimmune hemolysis.[19,20] While the *Brucella* genome contains flagella-specific genes and various hemolysins, flagella formation and hemolysis are not observed. According to one hypothesis, it is suggested that various mutations may trigger hemolytic phenotypes, that *Brucella* may transform from a non-hemolytic phenotype to a hemolytic one, which may explain the correlation between acute brucellosis and hemolytic anemia.[21] In prior studies, the incidence of anemia in brucellosis patients was found to be between 17-56%.[2,18,20,22-24] In a study by Buzgan et al[17] they determined that anemia occurred in 40.3% of their patients, and that this rate was higher in the acute brucellosis stage (43.9%). In a study carried out in China, the incidence of anemia in brucellosis patients was found to be 65.1% and mean hemoglobin values were lower in the acute phase.[25] Studies have shown that hemoglobin and hematocrit values are higher in males in the healthy population. This is thought to be related to the effect of hormones on erythropoiesis and menstrual blood loss.[26] In the current study, anemia was the most common hematologic finding in all brucellosis subgroups. The mean hemoglobin was lower especially in the acute brucellosis stage. Comparison of hemoglobin values between different genders showed that mean hemoglobin value of females was lower. However, these results do not clearly indicate lower hemoglobin levels in females are due to gender differences or because brucellosis has a higher potential to cause low hemoglobin in females. In order to answer this question, case-control studies that evaluate the relationship between gender and hematologic parameters in brucellosis patients are required.

Brucella species proliferate in placental trophoblasts and mononuclear phagocytic cells such as monocytes, macrophages and dendritic cells. They infect B-lymphocytes, osteoblasts, granulocyte progenitor cells, fibroblasts, hepatocytes, and erythrocytes to a minimal extent. Mononuclear phagocytic leukocytes are the main effectors that aggregate at the site of infection and are associated with adaptive immunity. During the initial stage of infection and long incubation period, neutrophil aggregation at the infection site and target organs is lower than mononuclear phagocyte and lymphocyte aggregation, which are the primary inflammatory cells associated with *Brucella* infection.[27] Guler et al[28] found that 22.9% of brucellosis patients had thrombocytopenia, 21.3% had leukopenia, and 6.5% had pancytopenia. In a large case series including 850 patients diagnosed with brucellosis carried out in China, lymphocytosis was observed in 34.7% of patients, while eosinopenia was observed in 26.9%, leukopenia in 17.9%, thrombocytopenia in 9.2%, leukocytosis in 5.6%, and pancytopenia in 2.7%.[29] In Buzgan et al's[17] study, lymphomonocytosis was found in 28.2%, leukopenia in 10.9%, leukocytosis in 9%, thrombocytopenia in 9.5%, and pancytopenia in 4.9% of patients. They also found that the incidence of leukopenia (15.3%), leukocytosis (9.5%), and pancytopenia (7%) was higher in the acute brucellosis stage, while lymphomonocytosis (33.3%) was more common in the subacute stage. In the present study, monocytosis and leukocytosis were the foremost findings regarding leukocytes in all patients. Monocytosis was the most common finding regarding WBCs in all subgroups. Analysis of laboratory parameters showed that white blood cell, neutrophil, and eosinophil counts were lower and monocyte counts were higher in the acute brucellosis group compared to other subgroups. Although lymphocyte counts in the acute brucellosis group were higher, this difference was not statistically significant. These results reflect the general hematological manifestations of brucellosis. It was also noteworthy that eosinopenia was one of the most common findings, especially in the acute and subacute phases. While eosinophil counts differed statistically significantly between all brucellosis subgroups separately, they were especially lower in the acute brucellosis group. This suggests that eosinopenia may be an important indicator of acute brucellosis. The relationship between eosinopenia and brucellosis has been demonstrated in other research as well. Jiao et al[30] observed that eosinophil counts were lower in brucellosis patients compared to healthy volunteers and patients with other bacterial infections. In another case-control study, a similar relationship was found between brucellosis and eosinopenia.[31] Pancytopenia may develop in brucellosis patients due to possible mechanisms such as hypersplenism, granuloma formation in the bone marrow, hemophagocytosis, bone marrow hypoplasia, or bone marrow depression secondary to septicemia.[23,32] In various studies, the incidence of pancytopenia in brucellosis patients was discovered to be between 1.8-13.2%.[2,17,18,20,23,24] The incidence of pancytopenia was lower in the current study compared to the literature.

Although usually mild, thrombocytopenia is common in brucellosis. Thrombocytopenia may occur due to bone marrow suppression, hypersplenism, or immune mechanisms. In prior studies, the rate of thrombocytopenia in brucellosis patients ranged

between 9.5-18.8%.[17,20,22-24] In the present study, thrombocytopenia was found in 7% of patients, most commonly in the acute phase (8.8%). Similarly, Buzgan et al[17] and Shi et al[25] showed that platelet count was lower in the acute phase. Another noteworthy result of the study was that the mean platelet count of female patients was found to be higher than males. Gender hormones are known to have an effect on platelets. However, conflicting results have been reported regarding the effect of gender on various platelet functions.[33] Although this result of our study provides a different perspective, it is not yet known whether gender differences have effects on platelet functions in brucellosis patients. Further studies are needed for a conclusive answer to this issue.

Study limitations. The retrospective nature of the study, the fact that it did not include information on the clinical reflections of hematologic findings, and the fact that it did not provide insight into the concrete causes of pancytopenia are important limitations of this study.

In conclusion, brucellosis is an important zoonotic disease that can be confused with many diseases, shows multisystemic involvement, and has non-specific symptoms and signs. Although hematopoietic system involvement is common in brucellosis, the clinical course of the disease is usually mild. In this study, the most common laboratory findings in brucellosis patients were anemia and monocytosis, a discovery consistent with the well-known laboratory findings associated with the disease. Eosinopenia was surprisingly another of the most common findings, especially in the acute and subacute stages. Although less frequently, pancytopenia and thrombocytopenia were also found to occur. The diversity of hematologic findings associated with brucellosis and the absence of a specific laboratory indicator cause difficulties in diagnosis. The possibility of brucellosis should be considered when diagnosing patients presenting with non-specific complaints such as fever, muscle-joint pain, sweating and fatigue if they have various hematologic findings, especially anemia, monocytosis, eosinopenia, and leukocytosis.

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