Diagnostic significance of hematological parameters in brucellosis

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Abstract

Introduction: Changes in hematological parameters are frequently observed in brucellosis patients. In this study, it was aimed to evaluate the diagnostic significance of some hematological parameters in patients with brucellosis.

Material and methods: In this case-control study, the data of brucellosis patients and healthy volunteers followed up in the Outpatient Clinic of Infectious Diseases between 2018 and 2020 were retrospectively examined. In the hemogram examination of patients with brucellosis and health volunteers; hematological parameters such as the leukocyte, hemoglobin, neutrophil, lymphocyte, monocyte, platelet, ratio of neutrophil/lymphocyte, ratio of platelet/lymphocyte, ratio of monocyte/lymphocyte and mean platelet volume were compared.

Results: 255 people, 169 (66.3%) of whom were diagnosed with brucellosis and 86 (33.7%) from the control group, were included to the study. These participants of 112 (43.9%) were male and 143 (56.1%) were female. The patients diagnosed with brucellosis, of 62 (36.7%) were considered acute, of 62 (36.7%) subacute, and of 45 (26.6%) chronic brucellosis. leukocyte, hemoglobin, neutrophil, and neutrophil/lymphocyte levels were found to be lower in the brucellosis group compared to the control group, while mean platelet volume level was found to be higher. Hemoglobin was found to be lower and mean platelet volume higher in all brucellosis subgroups.

Conclusion: In this study, the following findings were determined to be important: the lowness of leucocyte and hemoglobin and highness of mean platelet volume in brucellosis patients, as well as the highness of lymphocyte levels and lowness of neutrophil/lymphocyte and platelet/lymphocyte levels in the subacute brucellosis subgroup. In addition, it was concluded that the mean platelet volume parameter can be used as a diagnostic test for brucellosis.

Key words: brucellosis, MPV, lymphocyte, NLR, PLR

Introduction

Brucellosis is a common zoonotic disease that is considered endemic worldwide and is caused by gram-negative coccobacilli from the *Brucella* genus [1]. Approximately 500,000 new cases of human brucellosis are reported each year [2]. The disease is a zoonotic infection seen most frequently in Turkiye especially in Eastern, Southeastern, and Central Anatolia [3]. The disease has a wide spectrum of clinical symptoms, such as fever, sweating, fatigue, and osteoarthritis, and sometimes it can lead to more serious damage in different organs [3-5].

Early and accurate diagnosis of brucellosis plays an important role both in controlling and eradicating the disease and in improving public health [6]. Microbiological diagnosis of human brucellosis is based on three different modalities: culture, serology, and nucleic acid amplification tests (NAATs). Bone

marrow and blood culture are the gold standard methods [7]. Hematological complications due to brucellosis are prevalent. *Brucella spp.* shows tropism to structures in the reticuloendothelial system (RES), such as bone marrow and some peripheral organs. Changes in hematological parameters are observed in most patients [8, 9].

Various hematological and inflammatory parameters have been widely used as biomarkers in the preliminary diagnosis of bacterial infections [6, 10, 11]. Hematological markers, including white blood cell count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), mean platelet volume (MPV), platelet count (PLT), platelet distribution width (PDW), red cell distribution width (RDW), and C-reactive protein (CRP) test, have been used in the preliminary diagnosis of brucellosis with serological tests [6, 12]. Recently, it has been reported that platelets are also associated with inflammation. MPV is associated with platelet activation and function, and it has been reported as an inflammatory marker in some diseases, such as community-acquired pneumonia and brucellosis [13-15]. In this study, it was aimed to evaluate whether some hematological parameters that can be examined in simple hemogram examination have a diagnostic importance in terms of brucellosis.

Material and methods
Study protocol

In this case-control study, the data of brucellosis patients and healthy volunteers followed up in the Outpatient Clinic of Infectious Diseases at Cizre State Hospital between 2018 and 2020 were retrospectively examined. Information about the patients, such as age, sex, and laboratory test results, obtained from the hospital information management system. Brucellosis was categorized into 3 subgroups according to the duration of clinical signs and symptoms: acute brucellosis (0–2 months), subacute brucellosis (2–12 months), and chronic brucellosis (> 12 months) [3]. The criteria used for the diagnosis of brucellosis are growth in the culture of *Brucella spp.* in blood or other body fluids together with clinical symptoms such as fever, sweating, chills, joint-muscle pain, headache, and weakness, being of serum Brucella tube agglutination titer equal to or greater than 1/160, or being of at least a four-fold titer increase in the serum sample taken at two-week intervals. The control group was selected from healthy volunteers without any symptoms or signs.

Blood sample analyses

2 ml of venous blood sample from each patient was taken into an anticoagulant tube containing ethylenediaminetetraacetic in a sterile environment. Immediately after blood collection, it was inverted for 8 seconds. The prepared sample was studied on the SYSMEX- XN-1000 (Japan) hemogram device with laser reading system.

From the hematological examinations at the time of the brucellosis patients and healthy volunteers inclusion in the study, the results of leukocytes, hemoglobin (HGB), neutrophils, lymphocytes, monocytes, platelets, NLR, PLR, MLR, and MPV were evaluated.

Ethical committee

This study was approved by the Clinical Research Ethics Committee of Harran University with the number 91074 on December 24, 2021. All procedures in the study were performed in accordance with the World Medical Association Declaration of Helsinki.

Statistical analysis

All statistical analyses were carried out using the SPSS 22 (SPSS Inc., Chicago, IL) packet program. A one-sample Kolmogorov–Smirnov test was used to check whether continuous variables such as leukocyte, HGB, and neutrophil follow the normal distribution. All continuous variables are presented as mean ± standard deviation. An independent samples t-test was used to compare the means of two continuous variables that followed the normal distribution, and a Mann–Whitney U test was used to compare the means of two continuous variables that did not follow the normal distribution. A one-way ANOVA test was used to compare the means of more than two normally distributed continuous variables, and a Kruskal–Wallis test was used to compare the means of more than two continuous variables that did not follow the normal distribution. To determine which groups the difference originated from, multiple comparison tests were used in cases where the assumption of normal distribution was provided, and the Mann–Whitney U test was used in cases where the assumption of normal distribution was not provided. Receiver Operating Characteristic (ROC) analysis was carried out to evaluate the overall diagnostic performance of the hematological variables. The Youden Index was used to determine the cut-off points of the parameters found to be statistically significant. We considered a *p-value < 0.05* statistically significant for all statistical analyses.

Results

A total of 255 participants, 169 (66.3%) of whom were patients with a diagnosis of brucellosis and 86 (33.7%) of whom constituted the control group, were included in the study. Of the participants, 112 (43.9%) were male, and 143 (56.1%) were female. Of the patients with brucellosis, 51 (30.2%) were male, and 118 (69.8%) were female. In the control group, 61 (70.9%) participants were male, and 25 (20.1%) were female. The mean age of the participants with brucellosis was 40.08, and the mean age of the participants in the control group was 39.71.

When the brucellosis patients and the control group participants were compared, the differences in, leukocyte HGB, neutrophil, MPV, and NLR were statistically significant. The brucellosis patients were found to have lower leukocyte, HGB, neutrophil, and NLR levels and higher MPV levels than the participants in the control group (Table 1).

| Table 1 | The results of the statistical analysis between brucellosis patients and the control group |

Parameters	Control	Brucellosis	p-value
Age	39.71±15.18	40.80±13.79	0.57
Leukocyte	7105.19±1344.90	6638.99±1696.00	**0.02**
HGB	14.59±1.58	13.13±1.49	**0.00**
Neutrophil	4009.98±1040.79	3585.27±1257.57	**0.00**
Lymphocyte	2282.77±489.44	2344.73±687.79	0.41
Monocyte	571.50±176.04	552.28±189.30	0.17
Platelet	253.57±48.26	246.75±61.70	0.24
MPV	9.58±1.24	9.99±0.90	**0.03**
NLR	1.82±0.55	1.65±0.72	**0.00**
PLR	0.12±0.03	0.11±0.04	0.27
MLR	0.26±0.08	0.25±0.09	0.06

HGB: hemoglobin, MPV: mean platelet volume, NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, MLR: monocyte–lymphocyte ratio

Table 2   Evaluation of hematological parameters according to the control group and brucellosis subgroups

Parameters	Control	Acute	Subacute	Chronic	p-value
Age	39.71±15.18	38.32±13.95	42.29±13.41	42.18±13.90	0.35
Leukocyte	7105.19±1344.90	6657.90±1802.18	6782.74±1526.10	6414.89±1780.53	**0.10**
HGB	14.59±1.58	13.11±1.58	13.15±1.35	13.15±1.57	**0.00**
Neutrophil	4009.98±1040.79	3595.81±1374.74	3583.39±1140.94	3573.33±1270.15	0.07
Lymphocyte	2282.77±489.44	2288.87±627.56	2545.00±619.48	2145.78±791.69	0.01
Monocyte	571.50±176.04	562.19±211.90	567.95±163.72	517.02±188.83	0.41
Platelet	253.57±48.26	245.40±67.75	251.15±60.55	242.56±55.13	0.70
MPV	9.58±1.24	10.00±0.91	9.89±0.88	10.12±0.91	**0.02**
NLR	1.82±0.55	1.66±0.73	1.46±0.50	1.88±0.90	**0.00**
PLR	0.12±0.03	0.11±0.04	0.10±0.03	0.13±0.05	**0.02**
MLR	0.26±0.08	0.25±0.10	0.23±0.06	0.26±0.11	0.20

Table 3   P-values of post-hoc and pairwise comparison tests for the significant hematological parameters

Parameters	Group/Subgroup	Control	Acute	Subacute	Chronic
HGB	Control	-	**0.00**	**0.00**	**0.00**
	Acute	-	-	0.88	0.88
	Subacute	-	-	-	0.99
Lymphocyte	Control	-	0.95	**0.01**	0.22
	Acute	-	-	**0.02**	0.24
	Subacute	-	-	-	**0.00**
MPV	Control	-	**0.02**	0.08	**0.01**
	Acute	-	-	0.54	0.57
	Subacute	-	-	-	0.26
NLR	Control	-	0.15	**0.00**	0.62
	Acute	-	-	0.1	0.09
	Subacute	-	-	-	**0.00**
PLR	Control	-	0.88	0.06	0.12
	Acute	-	-	0.11	0.11
	Subacute	-	-	-	**0.00**

Of the participants diagnosed with brucellosis, 62 (36.7%) had acute brucellosis, 62 (36.7%) had subacute brucellosis, and 45 (26.6%) had chronic brucellosis. The hematological parameters of the brucellosis subgroups were compared with those of the control group. According to the statistical results, it was observed that the HGB, lymphocyte, MPV, NLR, and PLR values included statistically significant differences (Table 2). Each brucellosis subgroup had lower HGB and higher MPV values than the control group. The subacute brucellosis subgroup had higher lymphocyte, lower NLR, and lower PLR values than the other brucellosis subgroups and control group. Multiple comparison and pairwise comparison tests revealed that the following groups had statistical differences between them: acute–control, subacute–control, chronic–control, in terms of HGB; control–subacute, acute–subacute, chronic–subacute, in terms of lymphocytes; acute–control and chronic–control, in terms of MPV; control-subacute and subacute–chronic, in terms of NLR; and subacute–chronic, in terms of PLR (Table 3).

With the aim of evaluating overall diagnosis performance of hematological parameters found as the significant, ROC analysis was performed between the following pairs: acute–control, subacute–control, chronic–control, acute-subacute, acute-chronic, subacute-chronic, and control-brucellosis (Table 4). The Youden Index was used to determine the cut-off points for the hematological parameters that were found to be statistically significant. The following distinctive parameters were found: HGB between the control group and the acute brucellosis subgroup, the control and the subacute brucellosis subgroup, and the control and the chronic brucellosis subgroup, lymphocyte counts between the control group and the subacute brucellosis subgroup, MPV between the control group and the chronic brucellosis subgroup, NLR between the control group and the subacute brucellosis group (Figure 1), lymphocyte counts between the acute and the subacute brucellosis subgroups and the subacute and the chronic brucellosis subgroups, NLR and PLR between the subacute and chronic brucellosis subgroups (Figure 2), and leucocyte, HGB, Neutrophil, MPV and NLR between the control group and the brucellosis group (Figure 3).

The Youden Index was used to determine the cut-off points of the parameters found to be statistically significant. The results of the cut-off values can be summarized as follows.

Results obtained for the brucellosis subgroups and the control:

• The cut-off value was calculated as 14.25 for the HGB parameter between the control and acute brucellosis group, and between the control and subacute brucellosis group. It was concluded that HGB could discriminate control group participants with 69% accuracy, acute patients with 79% accuracy, and subacute patients with 87% accuracy. The cut-off value was calculated as 14.15 for the HGB parameter between the control and chronic brucellosis group. It was concluded that HGB could discriminate control group participants with 70% accuracy and chronic patients with 78%.

• The cut-off value was calculated as 2305 for the lymphocyte parameter between the control group and the subacute brucellosis subgroup. It was concluded that lymphocyte

Results of ROC Analysis for Blood Parameters

Groups	Parameters	AUC	Cut off point	Sensitivity(%)	Specificity (%)	+PV	-PV	Accuracy
Control-Acute	HGB	0.75	14.25	79	69	0.64	0.82	0.73
	MPV	0.58	8.95	92	27	0.48	0.82	0.55
Control-Subacute	HGB	0.76	14.25	87	69	0.67	0.88	0.76
	LYMP	0.62	2305	68	58	0.54	0.71	0.62
	NLR	0.68	1.67	66	62	0.55	0.72	0.64
Control-Chronic	HGB	0.74	14.15	78	70	0.57	0.86	0.73
	MPV	0.63	9.65	73	49	0.43	0.78	0.57
Acute-Subacute	LYMP	0.62	2305	68	58	0.62	0.64	0.63
Subacute-Chronic	LYMP	0.66	2305	62	68	0.42	0.71	0.64
	NLR	0.63	1.96	38	87	0.68	0.66	0.66
	PLR	0.64	0.1093	60	66	0.56	0.69	0.64
Control-Brucellosis	Leucocyte	0.59	6065	42	79	0.80	0.41	0.55
	HGB	0.75	14.25	82	69	0.84	0.66	0.77
	NEUT	0.61	3805	60	58	0.74	0.43	0.60
	MPV	0.58	9.05	87	29	0.71	0.53	0.67
	NLR	0.61	1.1912	31	88	0.84	0.40	0.51

Figure 1 - The results of ROC analysis between the brucellosis subgroups and the control group for the significant hematological parameters
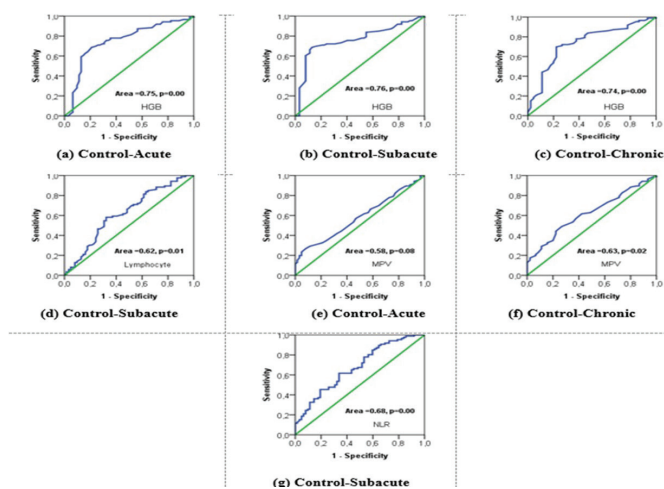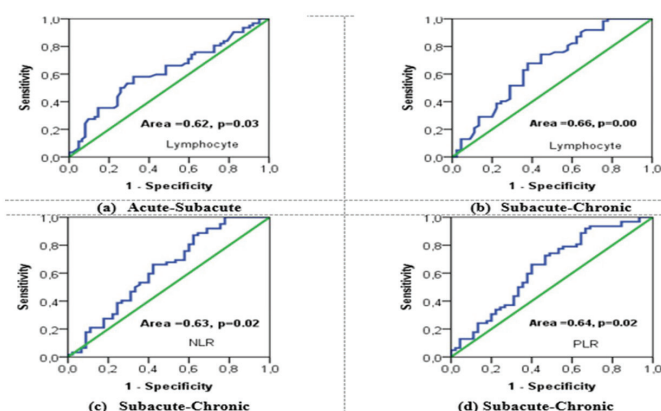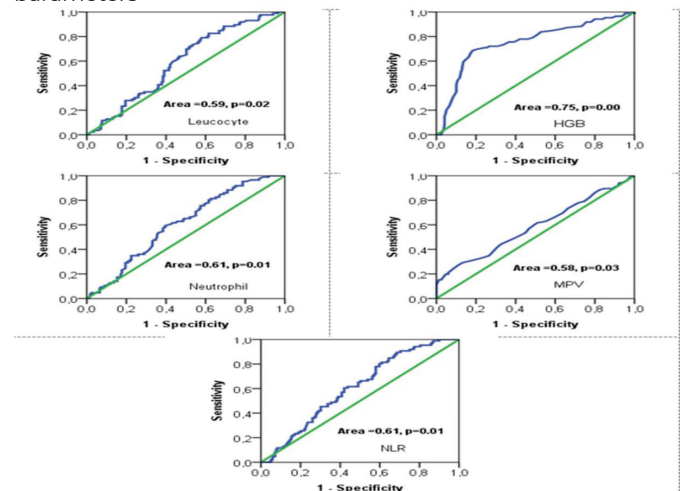

(a) Control-Acute
(b) Control-Subacute
(c) Control-Chronic
(d) Control-Subacute
(e) Control-Acute
(f) Control-Chronic
(g) Control-Subacute

Figure 3 - The results of ROC analysis between the brucellosis group and control group for significant hematological parameters

Figure 2 - The results of ROC analysis between the brucellosis subgroups for significant hematological parameters

(a) Acute-Subacute
(b) Subacute-Chronic
(c) Subacute-Chronic
(d) Subacute-Chronic

count could discriminate subacute patients with 68% accuracy and control group participants with 58% accuracy.

• The cut-off value between the control group and the chronic brucellosis subgroup was determined to be 9.65 for MPV. It was concluded that MPV could discriminate chronic brucellosis patients with 73% accuracy and control group participants with 49% accuracy.

• The cut-off value was calculated as 1.67 for the NLR parameter between the control group and the subacute brucellosis subgroup. It was concluded that NLR could discriminate subacute brucellosis patients with 66% accuracy and control group participants with 62% accuracy.

Results obtained for the brucellosis subgroups:

• The cut-off value was calculated as 2305 for the lymphocyte count parameter between the acute and the subacute brucellosis subgroups, and between subacute and chronic brucellosis subgroups. It was concluded that lymphocyte count could discriminate acute brucellosis patients with 58% accuracy, subacute brucellosis patients with 68% accuracy, chronic brucellosis patients with 62% accuracy.

• The cut-off values between the subacute and chronic brucellosis subgroups were 1.9602 for NLR and 0.1093 for PLR. It was concluded that subacute brucellosis patients could be discriminated with 87% accuracy via NLR and 56% accuracy via PLR, while chronic brucellosis patients could be discriminated with 38% accuracy via NLR and 60% accuracy via PLR.

Results obtained for the brucellosis group and control group:

• The cut-off value was 6065 for leucocyte. The brucellosis patients could be discriminated with 42% accuracy and the control group participants with 79% accuracy via leucocyte.

• The cut-off value was 14.25 for HGB. HGB could discriminate control group participants with 69% accuracy and brucellosis patients with 82% accuracy.
• The cut-off value of neutrophil was equal to 3802. It was concluded that neutrophil could discriminate control group participants with 58% accuracy and brucellosis patients with 60% accuracy.
• The cut-off value of MPV was 9.05. It was concluded that MPV could discriminate control group participants with 29% accuracy and brucellosis patients with 87% accuracy.
• The cut-off value was 1.1912 for NLR. It was concluded that NLR could discriminate control group participants with 88.4% accuracy and brucellosis patients with 31.32% accuracy.

Discussion

Brucella is an intracellular bacterium that can live in phagocytic cells, such as neutrophils and macrophages. Following primary infection, the disease spreads to the lymph nodes and then passes into the bloodstream, causing systemic infection. In addition to an increase in the number of leukocytes and neutrophils, changes in inflammatory indexes occur during infection. The disease also contributes to the pathogenesis of platelets [6]. Brucellosis can cause leukopenia, lymphomonocytes, and mild anemia [8]. Studies conducted in recent years have shown that some hematological biomarkers reflect systemic inflammation and can be used in the diagnosis of some diseases [6, 13, 16, 17]. Olt et al. [18] found a significant relationship between HGB and NLR levels and brucellosis. In a case-control study conducted in Iran, it was shown that leukocyte, CRP, and neutrophil counts can be used as biomarkers in the preliminary diagnosis of brucellosis [6]. Şen et al. [19] showed that the PLR value increased in patients with complicated brucellosis and that the increase in NLR and PLR values and the decrease in MLR were significantly associated with specific organ involvement. Bozdemir et al. [20] found that in the pediatric age group, there were significant differences in HGB, platelet, MPV, and NLR values between the patient and control groups; moreover, they stated that MPV and NLR values were particularly useful as inflammation markers in childhood brucellosis.

The hemogram plays an important role in the diagnosis of infectious diseases. MPV is one of the parameters that can be studied in a hemogram. It gives the mean platelet size and shows platelet activation. It has been shown that MPV levels are affected not only by prothrombotic conditions but also by rheumatic and infectious diseases [12]. In Parlak et al.'s [21] case-control study, the MPV value was found to be significantly higher in brucellosis patients, and it was stated may have prognostic value in brucellosis. Bozkurt et al. [22] and Kader et al. [23] predicted that MPV values before treatment in brucellosis patients were lower than after treatment and that MPV values could be a beneficial parameter in evaluating disease activity and response to treatment. Togan et al. [24] found no significant difference between the MPV values of patients with acute brucellosis and the control group participants.

The idea behind this study is that some hematological sub-parameters in the hemogram maybe distinctive among brucellosis clinical groups. In our literature review, no study was found in which hematological sub-parameters were compared between the brucellosis subgroups and the control group. Therefore, our study is significant in that it is the first study to carry out such comparisons.

The results obtained from the study can be summarized as follows. The differences between the brucellosis group and the control group in terms of leucocyte, HGB, neutrophil, MPV, and NLR were found to be statistically significant. The brucellosis group had higher MPV and lower mean leucocyte, HGB, neutrophil, and NLR levels than the control group. The brucellosis subgroups were compared with the control group, and the differences in HGB, lymphocyte, MPV, NLR, and PLR values were found to be statistically significant. Each brucellosis subgroup had a lower mean HGB and a higher mean MPV than the control group. In addition, it was observed that the following parameters could be used as diagnostic tests according to the results of ROC analysis: lymphocyte value for the subacute brucellosis subgroup and the other brucellosis subgroups and the control group, HGB for the control group and the brucellosis group, and the control group and the brucellosis subgroups, MPV values for the brucellosis group and the control group and the control group and the chronic brucellosis subgroups, NLR for the control group and subacute brucellosis subgroup, subacute and chronic brucellosis groups, and the control group and the brucellosis group, and PLR values for the subacute and the chronic brucellosis subgroups.

Conclusion

Brucellosis continues to impact both individual and public health. Although various tests are used in the diagnosis and follow-up of the disease, some hematological and biochemical parameters may be useful in the early diagnosis of the disease. In this study, the following findings were determined to be important: the lowness of leucocyte and HGB and highness of MPV in brucellosis patients, as well as the highness of lymphocyte levels and lowness of NLR and PLR levels in the subacute brucellosis subgroup. In addition, it was concluded that the MPV parameter can be used as a diagnostic test for brucellosis.

References

1. Bagheri Nejad R, Krecek RC, Khalaf OH, Hailat N, Arenas-Gamboa AM. Brucellosis in the Middle East: Current situation and a pathway forward. *PLoS Negl Trop Dis*. 2020;14(5):e0008071. https://doi.org/10.1371/journal.pntd.0008071
2. Dadar M, Shahali Y, Whatmore AM. Human brucellosis caused by raw dairy products: A review on the occurrence, major risk factors and prevention. *Int J Food Microbiol*. 2019;292:39-47. https://doi.org/10.1016/j.ijfoodmicro.2018.12.009

3. Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, Akdeniz H. 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-e478. https://doi:10.1016/j.ijid.2009.06.031

4. Moosazadeh M, Nikaeen R, Abedi G, Kheradmand M, Safiri S. Epidemiological and Clinical Features of People with Malta Fever in Iran: A Systematic Review and Meta-Analysis. *Osong Public Health Res Perspect*. 2016;7(3):157-167. https://doi.org/10.1016/j.phrp.2016.04.009

5. Zheng R, Xie S, Lu X, Sun L, Zhou Y, Zhang Y, Wang K. A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. *Biomed Res Int*. 2018;2018:5712920. https://doi.org/10.1155/2018/5712920

6. Akya A, Bozorgomid A, Ghadiri K, Ahmadi M, Elahi A, Mozafari H, Almasi A, et al. Usefulness of Blood Parameters for Preliminary Diagnosis of Brucellosis. J Blood Med. 2020;11:107-113. https://doi:10.2147/JBM.S245513

7. Yagupsky P, Morata P, Colmenero JD. Laboratory Diagnosis of Human Brucellosis. *Clin Microbiol Rev*. 2019;33(1):e00073-19. https://doi.org/10.1128/CMR.00073-19

8. Özlü C. Brucellosis From Hematology Perspective. *Dental and Medical Journal - Review*. 2022;4(1):72-78.

9. El-Koumi MA, Afify M, Al-Zahrani SH. A prospective study of brucellosis in children: relative frequency of pancytopenia. *Iran J Pediatr*. 2014;24(2):155-160. PMID: 25535533; PMCID: PMC4268834.

10. Markanday A. Acute phase reactants in infections: evidence-based review and a guide for clinicians. *Open Forum Infect Dis*. 2015;2(3):ofv098. https://doi.org/10.1093/ofid/ofv098

11. Akya A, Rostami-Far Z, Lorestani RC, Khazaei S, Elahi A, Rostamian M, Ghadiri K. Platelet indices as useful indicators of urinary tract infection. *Iran J Ped Hematol Oncol*. 2019;9(3):159-165. https://doi.org/10.18502/ijpho.v9i3.1165

12. Afyon M, Artuk C. Could mean platelet volume be a useful marker for infectious diseases? a review of literature. *Medicine Science*. 2016;5(4):1059-1062. https://doi.org/10.5455/medscience.2016.05.8460

13. Balın ŞÖ, Tartar AS, Akbulut A. The predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. *Afr Health Sci*. 2018;18(4):988-994. https://doi.org/10.4314/ahs.v18i4.19

14. Mirsaeidi M, Peyrani P, Aliberti S, Filardo G, Bordon J, Blasi F, Ramirez JA. Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. *Chest*. 2010;137(2):416-420. https://doi.org/10.1378/chest.09-0998

15. Zareifar S, Farahmand Far MR, Golfeshan F, Cohan N. Changes in platelet count and mean platelet volume during infectious and inflammatory disease and their correlation with ESR and CRP. *J Clin Lab Anal*. 2014;28(3):245-248. https://doi.org/10.1002/jcla.21673

16. Enginar AU, Kacar C. Neutrophil-lymphocyte and platelet-lymphocyte rate and their seasonal differences in ankylosing spondylitis and rheumatoid arthritis patients using anti-TNF medication. *Bratisl Lek Listy*. 2019;120(8):586-592. https://doi.org/10.4149/BLL_2019_096

17. Jimeno S, Ventura PS, Castellano JM, García-Adasme SI, Miranda M, Touza P, López-Escobar A. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. Eur J Clin Invest. 2021;51(1):e13404. https://doi.org/10.1111/eci.13404

18. Olt S, Ergenç H, Açıkgöz SB. Predictive contribution of neutrophil/lymphocyte ratio in diagnosis of brucellosis. *Biomed Res Int*. 2015;2015:210502. https://doi.org/10.1155/2015/210502

19. Sen P, Demirdal T, Nemli SA. Predictive Value of Inflammation Markers in Brucellosis. *Arch Iran Med*. 2019;22(11):640-645. https://doi.org/10.4103/ijccm.IJCCM_308_18

20. Bozdemir ŞE, Altıntop YA, Uytun S, Aslaner H, Torun YA. Diagnostic role of mean platelet volume and neutrophil to lymphocyte ratio in childhood brucellosis. Korean J Intern Med. 2017;32(6):1075-1081. https://doi.org/10.3904/kjim.2016.092

21. Parlak E, Alay H, Kesmez Can F, Parlak M, Koşan Z. An evaluation of mean platelet volume, sedimentation, and crp in brucellosis patients. *Turk Clin Lab*. 2019;10(4):479-483. https://doi.org/10.18663/tjcl.476643

22. Bozkurt F, Aslan E, Deveci Ö, Tekin R. Evaluation of Mean Platelet Volume Levels In Patients With Brucellosis. *Anatol J Clin Investig*. 2014;8(3):126-129.

23. Kader C, Yolcu S, Erbay A. Evaluation of mean platelet volume (MPV) levels in brucellosis patients. *Cumhuriyet Med J*. 2013;35(4):488-494. http://dx.doi.org/10.7197/1305-0028.2295

24. Togan T, Narci H, Turan H, Ciftci O, Kursun E, Arslan H. The impact of acute brucellosis on mean platelet volume and red blood cell distribution. *Jundishapur J Microbiol*. 2015;8(2):e20039. https://doi.org/10.5812/jjm.20039