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# Diagnostic role of inflammatory markers in patients with brucella

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**Abstract**

Systemic inflammation plays a significant role in the initiation and advancement of chronic diseases. This study aimed to evaluate the prognostic utility of these indices in patients with brucellosis. This retrospective comparative study included 483 patients and 495 controls who applied to Aksaray University Infectious Diseases and Clinical Microbiology Clinic between January 2022 and January 2023. Patients under the age of 18 were excluded from the study. Neutrophil, White Blood Cell (WBC), Alanine transaminase (ALT), Aspartate aminotransferase (AST) and lymphocyte scores showed statistically significant differences between the groups. Moreover, statistically significant differences were also observed in systemic immune inflammation index (SII), systemic inflammation response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and pan-immune-inflammation value (PIV) indices between the groups ($p<0.001$). Conversely, hemoglobin and platelet values did not differ significantly between the groups ($p>0.05$). In conclusion, NLR, PLR, SII, SIRI and PIV biomarkers are simple, cost-effective and broadly available for predicting disease's prognosis. These results suggest that NLR, PLR, SII, SIRI, and PIV could serve as reliable biomarkers for assessing disease severity, monitoring treatment response, and potentially predicting clinical outcomes in brucellosis.

**Keywords:** Brucellosis, inflammation, inflammatory markers

## Introduction

*Brucella* is a genus of Gram-negative bacteria that causes brucellosis, a zoonotic infection with a substantial impact on human and animal health globally [1]. The disease, transmitted mainly through contact with infected animals or consumption of unpasteurized dairy products, poses a significant public health concern, particularly in developing regions with extensive livestock rearing. Clinical manifestations of brucellosis vary widely, ranging from mild, flu-like symptoms to severe, chronic forms affecting various organ systems, thus complicating diagnosis and management [2].

Oxidative stress (OS) occurs as a result of the disruption of the balance between free radicals and antioxidants in our body [3-5]. OS plays a significant role in the pathophysiology of brucellosis, a zoonotic infection caused by *Brucella* species. This intracellular pathogen disrupts the host's redox balance by generating reactive oxygen species (ROS) while simultaneously impairing antioxidant defense mechanisms. Increased oxidative stress has been linked to tissue damage and immune dysregulation during *Brucella* infection [6].

Inflammatory markers play a critical role in the pathophysiology of brucellosis, as the host immune response to *Brucella* infection often leads to a complex inflammatory cascade [7]. During infection, the immune system activates several inflammatory mediators, including cytokines, acute-phase proteins, and other biomarkers, which serve both as indicators of disease activity and as potential tools for assessing the severity and prognosis of brucellosis [8]. *Brucella* infection, the causative agent of brucellosis, triggers a robust inflammatory response in the host as part of the immune system's effort to combat the infection [9]. Recent research has focused on identifying blood-based inflammatory markers that may provide insights into the disease's progression and severity. In particular, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-

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inflammation value (PIV) have emerged as valuable indicators of immune status and inflammation in various infectious and inflammatory diseases [7,10-14].

Each of these markers offers unique insights into the body's inflammatory and immune response during brucellosis. NLR and PLR are straightforward ratios derived from standard blood counts and are reflective of the balance between immune and inflammatory cells. SII and SIRI integrate additional components to provide a more comprehensive index of systemic inflammation, while PIV combines several hematological parameters to predict inflammatory status. These markers can serve as accessible and cost-effective indicators, potentially aiding in the assessment of brucellosis severity, treatment response, and prognosis. However, the exact relationship between *Brucella* infection and these indices is not fully elucidated, warranting further investigation to clarify their diagnostic and prognostic value in clinical practice.

This study aims to explore the association between *Brucella* infection and inflammatory markers, including NLR, PLR, SII, SIRI, and PIV, contributing to a deeper understanding of the immune response in brucellosis and providing potential tools for improved patient management.

## Material and Methods

This retrospective study included 483 patients aged ≥18 years and over diagnosed with brucellosis and 495 healthy controls who applied to the Infectious Diseases and Clinical Microbiology Clinic of Aksaray University Education and Research Hospital between 01.01.2022-01.01.2023. A total of 483 patients aged 18 years and older, presenting with symptoms such as fever, joint pain, fatigue, and night sweats, and having a Rose Bengal and *Brucella* tube agglutination test result of 1/160 or higher, were included in the study with a diagnosis of brucellosis. As the control group, 495 healthy individuals aged 18 years and older, with no symptoms and negative results in screening Rose Bengal and *Brucella* tube agglutination tests, were included in the study. Patients under the age of 18 were excluded from the study. Hemogram parameters included WBC, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, and monocyte levels and systemic inflammatory indices were evaluated. The following formulas were used to determine the NLR, PLR, SII, SIRI, and PIV, appropriately: the ratio of platelets to lymphocytes and neutrophils to lymphocytes. (Platelets x Neutrophils)/ Lymphocytes computed SII, (Neutrophils x Monocyte)/ Lymphocytes calculated SIRI, and (Neutrophils x Monocyte x Platelets )/Lymphocytes calculated PIV. This study acquired ethical consent from the Aksaray University local ethics board (Date: 23.05.2024 / Approval No: 2024/036). The present study adhered to the principles outlined in the Helsinki Declaration.

### Statistical Analysis

Data analysis for group comparisons was conducted using IBM SPSS version 22 software. To verify normal distribution of the quantitative variables, the Kolmogorov-Smirnov test was applied. Comparisons between the study groups were conducted using the Mann-Whitney U test and Student's t-test. Categorical variables, expressed as counts and percentages, were evaluated using the chi-square test. Statistical significance was determined by a p-value threshold of <0.05.

## Results

In the current study, a total of 978 individuals were involved, 483 healthy controls with an average age of 43.8.±14.8 and 495 *Brucella* patients with an average age of 47.5±14.9. Age and gender show no significant difference between groups (Table 1). Table 2 presents the median (range) values of the hemogram parameters and indices for both groups. We indicated that white blood cell count, neutrophils, and lymphocytes are significantly different, in the *Brucella* group. However, both ALT and AST levels are lower in the *Brucella* group. Neutrophil WBC, monocyte levels displayed notable differences in levels that reached statistical significance between study groups. Moreover, inflammatory indices calculated for the study groups showed significant differences in SII, SIRI, NLR, PLR, and PIV. (p<0.001, Table 2). Nonetheless, hemoglobin, monocyte and platelet levels were not significantly different (p>0.05).

**Table 1.** Demographic information of the study and control groups

| Parameters | | *Brucella* (n=495) Mean±SD | Control (n=483) Mean±SD | p* |
|---|---|---|---|---|
| Gender | Male | 265 (54.9%) | 209 (57.8%) | 0.485* |
| | Female | 218 (45.1%) | 286 (42.2%) | |
| Age (year) | | 43.8±14.8 | 47.5±14.9 | 0.876¥ |

*Chi-square test; ¥Student t –test

**Table 2.** Comparison of the hemogram parameters of the study and control groups

| Parameters | *Brucella* (n=495) median (min-max) | Control (n=483) median (min-max) | p* |
|---|---|---|---|
| WBC ($10^3$µL) | 6.9 (1.1-20.7) | 7.6 (1.1-18.6) | <0.001 |
| NEU ($10^3$µL) | 3.7 (0.6-17.8) | 4.5 (1.1-11.7) | <0.001 |
| LYM ($10^3$µL) | 2.4 (0.4- 8.8) | 2.2 (0.3-12.9) | <0.001 |
| Monocyte ($10^3$µL) | 0.5 (0.1-2.1) | 0.5 (0.1-1.2) | 0.502 |
| HGB (g/dL) | 14.1 (8.7-19) | 14.0 (8.5-18.7) | 0.943 |
| PLT ($10^3$µL) | 258 (33-559) | 258 (74-564) | 0.599 |
| ALT | 24 (5-155) | 17 (3-237) | <0.001 |
| AST | 23 (10- 311) | 20 (7-124) | <0.001 |
| NLR | 1.6 (0.5-19.1) | 1.9 (0.4-16.8) | <0.001 |
| PLR | 106.5 (10.1-396.9) | 115.1 (14-729.3) | <0.001 |
| SII | 398.1 (23.6-4528.1) | 513.2 (66.7-3034) | <0.001 |
| SIRI | 0.7 (0.13-12.8) | 1.9 (0.4-16.8) | <0.001 |
| PIV | 185.1 (7.4-3396.1) | 243.4 (3.8-1901.8) | <0.001 |

*Mann- Whitney U test NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic inflammatory index (neutrophil x platelet / lymphocyte count) , SIRI: systemic inflammatory response index (neutrophil × monocyte / lymphocyte count) and PIV: pan-immune inflammation value (neutrophil × platelet x monocyte /lymphocyte count)

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## Discussion

The main objective of this study was to asses the diagnostic role of inflammatory markers in patients with *Brucella*. Our findings revealed that neutrophil, WBC, and monocyte levels exhibited significant differences between the groups. Additionally, among the inflammatory indices, SII, SIRI, NLR, PLR, and PIV displayed statistically significant distinctions between the study groups. SII, SIRI, and PIV indices play diagnostic, prognostic, and predictive roles in a range of diseases [15-17].

In this study, AST and/or ALT levels detected in the control group were associated with hyperlipidemia, hepatosteatosis and collagen tissue disease in 2 newly diagnosed patients.

In brucellosis, involvement of the reticuloendothelial system organs, such as the liver and spleen, is frequently observed. This involvement often presents as granulomatous hepatitis, accompanied by hepatosplenomegaly and mild elevations in liver enzymes (AST, ALT). However, these enzyme elevations tend to regress rapidly with treatment, typically within an average of one week. In a study conducted by Lu YP et al. [18] aspartate aminotransferase (AST) levels >40 U/L were detected in 9.6% of cases, while alanine aminotransferase (ALT) levels >40 U/L were observed in 18.6%. In studies conducted in Türkiye, elevated liver function tests (LFTs) were reported in 15-43% of cases [19]. In another study, AST elevation was detected in 12 cases (14.8%), while ALT elevation was observed in 13 cases (16%) [20]. In our study, ALT elevation (≥40 U/L) was identified in 100 patients (20.7%), and AST elevation in 75 patients (15.5%), consistent with the average values reported in the literature. *Brucella* infection leads to a strong inflammatory response as the host's immune system attempts to control the bacteria. This response is critical because *Brucella* bacteria are intracellular pathogens, meaning they can live within host cells, especially macrophages, which are immune cells designed to ingest and destroy pathogens [21]. This intracellular lifestyle allows *Brucella* to evade certain immune defenses, causing a prolonged and often difficult-to-treat infection. These markers are useful for monitoring inflammation and can provide insights into the severity of the infection. Elevated levels of these markers suggest a more intense inflammatory response and, potentially, a higher bacterial load or more extensive tissue involvement.

In a study by Aktar et al. study in 64 pediatric *brucella* arthritis patients, showed that NLR and PLR were found significantly higher in *brucella* arthritis than the healthy controls. Moreover, a positive relationship was identified between NLR and MPV values. They hypothesized that NLR and PLR can present as elevated inflammatory markers in children with *brucella* arthritis [22]. Another study conducted with brucellosis patients by Sen et al. [23] they were evaluated NLR, PLR and LMR in order to predict complications and targeted organ involvement in brucellosis. They indicated that PLR and ESR were higher in complicated patients. However, they found LMR and NLR were not significant indicators for predicting brucellosis complications. They concluded that these biomarkers are affordable, easy to use, and widely accessible for forecasting complications and organ involvement in brucellosis.

In our study, we observed that NLR and PLR values were found to be high and statistically significant in patients with *brucella*. In the study conducted by Şah et al. with *brucella* spondylodiscitis and Modic type I changes (MC1) they showed that NLR, PLR, SII, SIRI and AISI were found similar between the groups [24]. They indicated that no significant differences were found between the groups regarding the scores for leukocytes, neutrophils, lymphocytes, and monocytes. They also showed that NLR, PLR, SII, SIRI aggregate index of systemic inflammation (AISI) were not statistically meaningful difference was observed between the groups. They concluded that hematological inflammatory indices could offer a unique distinction between *brucella* spondylodiscitis and MC1.

In this study, we observed statistically significant differences in NLR, PLR, SII, SIRI, and PIV between the study and healthy groups. We hypothesized that assessing systemic inflammatory markers offers important insights into the inflammatory response in individuals with brucellosis. These indices provide make an important contribution to improving the clinical decision-making process.

## Conclusion

The evaluation of systemic inflammatory indices provide valuable insight into the inflammatory response in patients with brucellosis. Our study underscores the role of these indices as accessible, cost-effective markers that reflect immune activation in response to *Brucella* infection. Elevated values of these indices in brucellosis patients are indicative of heightened systemic inflammation and may correlate with disease severity, aiding clinicians in assessing and monitoring infection status. Systemic inflammatory indices offer the potential for improved clinical decision-making by providing a quantitative measure of the immune response, which may support the diagnosis of brucellosis and enable more tailored therapeutic interventions.

Additional studies are needed to confirm these markers in larger populations and to explore their utility in predicting treatment outcomes, which may ultimately enhance the management of *Brucella* infections and reduce the disease's morbidity.

**Conflict of Interests**
*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**
*The authors declare that they have received no financial support for the study.*

**Ethical Approval**
*This study acquired ethical consent from the Aksaray University local ethics board (Date: 23.05.2024 / Approval No: 2024/036).*

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