Blood systemic inflammatory markers in adult brucella knee arthritis

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Research article

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Abstract

Background: Mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) have been documented as blood biomarkers of systemic inflammation. The aim of the current research was to examine these blood biomarkers in brucella knee arthritis. Methods: Fifty-three brucella knee arthritis subjects and 42 healthy subjects were included . The erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) levels were compared. White blood cells (WBC), MPV, platelet, neutrophil, and lymphocyte counts were determined from complete blood counts. The PLR and NLR were calculated. Results: We found that CRP, ESR, and MPV levels were considerably increased in brucella knee arthritis than control groups ($p<0.001$, $p=0.024$, $p=0.024$). Moreover, the brucella arthritis patients had lower NLR and neutrophil counts compared to the control participants ($p=0.027$, $p=0.007$). According to the Pearson's correlation analysis, the serum agglutination tests with titers were positively related to the lymphocyte counts ($p=0.009$, $r=0.355$) in the patients. Conclusions: We observed statistically significant differences between the brucella knee arthritis patients and the healthy subjects with respect to MPV and NLR. These parameters may be beneficial markers in the assessment of systemic inflammation in patients with brucella arthritis.

Background

Brucellosis, a bacterial zoonotic disorder, is transmitted with infected animals and contaminated dairy products throughout the world. The disease is an important public health problem in the world, particularly in the Mediterranean region (e.g., Turkey) (1). It can affect any organs or systems in the body. Brucellosis can lead to fever, sweating, joint pain, and arthritis (2,3). Moreover, it can cause large peripheral joint monoarthritis, mainly in the lower extremities such as knees or hips (4).

Brucellosis is diagnosed according to clinical, serological, and microbiological test results (5). The acute phase biomarkers of blood have been documented as having raised levels as a result of the inflammatory conditions of brucellosis (5). However, there are known important problems for physicians in endemic regions. In some cases, the laboratory findings may not be suitable or sufficient for diagnosis every time (6). Consequently, we believe that additional diagnosis biomarkers may be useful for follow-ups.

Higher erythrocyte sedimentation rates (ESR), leukocyte counts, and C-reactive proteins (CRP) along with leukopenia, relative lymphocytopenia, anemia, and thrombocytopenia are seen as inflammatory biomarkers in brucellosis patients (7). However, these markers do not help directly in diagnosing these patients. Moreover, external factors such as age, gender, and the presence of a co-morbid infection can influence ESR (8). CRP also has similar limitations as a clinical biomarker (8).

Besides these traditional markers, in recent years, some scholars have concluded that different changes in white blood cell (WBC) and subtype counts can be identified as biomarkers of inflammation in several diseases. Neutrophils are a subtype of leukocytes that have been studied as a surrogate marker during inflammatory response (9). The neutrophil to lymphocyte ratio (NLR), a simple, inexpensive, and effective

indicator of systemic inflammation in routine clinical practice, has been evaluated in combination with other inflammatory biomarkers to determine inflammation (10). Numerous studies have shown that NLR is a good indicator of inflammation (11,12). However, some studies regarding NLR in patients with brucellosis have found conflicting results (7,13,14).

By calculating the absolute platelet counts divided by the absolute lymphocyte counts, the platelet to lymphocyte ratio (PLR) has been described as a potential indicator for determining inflammation. PLR is also used as an index for the differential diagnosis or prognostic prediction of diverse diseases such as cancer and inflammatory diseases (15). A few studies have been conducted on PLR in brucellosis, but their data are in conflict (7,13,14).

Mean platelet volume (MPV), a determinant of platelet size, is a new biomarker of complete blood count (CBC) analysis (9). It is widely used to determine platelet function and activation (16,17). Previous studies have mentioned that MPV was linked with inflammation and reflects inflammatory burden in active inflammatory bowel disease (18), rheumatoid arthritis (RA), and ankylosing spondylitis (19,20). Various reports about the effects of MPV on brucellosis are controversial (5,13,14,21–24).

According to the literature, only a few papers about MPV, NLR, and PLR in pediatric brucella arthritis have been published (13,14). However, no studies have investigated the association between adult brucella arthritis and MPV, NLR, and PLR. Therefore, the current paper was designed to establish whether MPV, NLR, and PLR can be used as systemic inflammatory biomarkers to indicate adult brucella arthritis. This article is the first to report on the link between adult brucella arthritis and these blood biomarkers which are used as inflammation markers in many diseases.

Methods

Subjects

The medical data of participants who were diagnosed with brucellosis arthritis in the orthopedic clinic between January 2013 and January 2015 were documented. A total of 53 adult brucella arthritis subjects and 42 control participants were included in the retrospective research.

The diagnosis of brucella arthritis was examined if the brucella participants had joint pain, movement restriction and swelling. The diagnosis of brucellosis was confirmed by the presence of IgM antibodies against brucella with ELISA and a blood agglutination test with titers≥1:160 along with clinical presentation (25). The participants with brucella arthritis were not receiving any treatment.

Patients with any findings of infection or systemic diseases, hypertension, diabetes mellitus, chronic respiratory disease, rheumatoid arthritis, renal disease, liver disease, or coronary heart disease were excluded from the research.

The healthy groups consisted of healthy age-and gender-matched asymptomatic participants who had normal physical examinations and unremarkable medical histories. The healthy control groups were not receiving any drugs, were not smoking or consuming alcohol, and did not have any known systemic diseases.

The peripheral blood samples were analyzed for differential WBC counts by using an automatic blood counter (Beckman-Coulter, LH 780, USA). Hematological parameters including MPV and WBC, neutrophil, lymphocyte, and platelet counts were recorded for the study and the control groups. NLR and PLR were calculated as the ratio of neutrophils to lymphocytes and platelets to lymphocytes, respectively. The ESR and CRP of two groups were recorded.

Statistical analysis

All numerical data were written as the mean ± standard deviation. The numerical data of the two research groups were evaluated via the Student *t* test. All qualitative data were assessed using a Chi-square test. All correlation analyses were conducted by Pearson's correlation coefficients. P results if less than 0.05 were accepted as significant. The data were evaluated via SPSS® for Windows (Version 20.0).

Results

The demographic details of all the research participants are presented in *Table 1.* There were no important differences according to age and gender between the two research participants ($p>0.05$). The average age of the brucella arthritis patients was 35±18 years, and the average age of the healthy participants was 37±18 years. Of the 53 brucella arthritis patients, 26 were female and 27 were male. Of the 42 healthy participants, 19 were female and 23 were male (*Table 1).*.

Compared to the control participants, we detected that the CRP, ESR, and MPV in the brucella arthritis participants were considerablyraised ($p<0.001$, $p = 0.024$, $p = 0.024$). Moreover, the brucella arthritis patients had lower NLRs and neutrophil counts compared to the control participants ($p = 0.027$, $p = 0.007$). No considerable differences with respect to WBC, PLR, platelet, and lymphocyte counts between the two groups were detected ($p>0.05$) (*Table 2).*.

According to the Pearson's correlation analysis, the serum agglutination test with titers was positively related to lymphocyte count ($p = 0.009$, $r = 0.355$) in the brucella arthritis patients. Moreover, CRP was positively related to NLR ($p = 0.003$, $r = 0.396$) and MPV was negatively related with neutrophil count ($p = 0.047$, $r = -0.274$) and NLR ($p = 0.006$, $r = -0.376$) in the brucella arthritis patients.

Discussion

The main goal of our study was to compared MPV, PLR, and NLR as easy to obtain, noninvasive, inexpensive, and reliable independent indicators of systemic inflammation in brucella arthritis patients.

The study results show that brucella arthritis patients had higher MPV compared to the control group. Moreover, the brucella arthritis patients had lower NLR compared to the control participants. However, no considerable difference with respect to PLR between the two groups was detected. Finally, we observed statistically should important differences between the brucella arthritis participants and the healthy participants in respect to MPV and NLR. Therefore, these parameters may be beneficial markers for use in the assessment of patients with brucella arthritis.

Brucellosis is a systemic zoonotic infectious condition with different clinical manifestations (1). Bone and joint involvement is a frequent complication of brucellosis. Peripheral arthritis such as monoarthritis is the predominant musculoskeletal manifestation of brucellosis (4).

As we know, CRP and ESR are commonly used to indicate inflammation. The acute phase reactants rise as a result of the inflammatory conditions of brucellosis (6). However, there are some problems for physicians in endemic regions; first, in some cases, the laboratory findings may not always be suitable or sufficient for diagnosis (6). Besides, these markers do not help directly with diagnosis. Some factors, such as age, gender, and the presence of a co-morbid infection, can influence these biomarkers. ESR reacts slowly in an inflammatory condition; because of that, some scholars have thought that CRP should replace ESR (26). Several investigators have observed that brucellosis patients had significantly higher CRP and ESR compared to control groups (5,13,21,22). Kucukbayrak et al. (24) found a significant decrease in ESR and CRP after the treatment of subjects with brucellosis. In the present paper, our results have demonstrated that brucella arthritis patients had higher CRP and ESR when compared to the control participants.

The reports in the literature on WBC counts in brucellosis patients are controversial. Several authors have observed that brucella patients had significantly higher WBC compared to control participants (14,22), while other investigators could not detect a significant difference in the WBC counts between patients and healthy subjects (5,7,13,21). In the current paper, we show that there was no marked difference between the WBC counts of the two groups in our study.

Platelets, in the case of inflammation, undergo structural modification and secrete some cytokines, which results in a decrease in MPV (27). MPV is considered to be an indicator of platelet activation and function (16,17). It is a cheap and easily performed test that is often neglected by physicians. MPV may be performed as part of routine blood counts at no additional cost. Also, MPV is a marker in the assessment of systemic inflammation (28). Several investigators have observed that there is a link between MPV and inflammatory conditions (29,30). Yazıcı et al. (19) documented that MPV was linked with systemic inflammatory biomarkers in rheumatoid arthritis. Previous studies have obtained controversial findings about MPV in brucellosis patients (5,13,14,22–24). Aktar et al. (14) found a raised MPV in children with brucella arthritis compared to control groups. However, Bozdemir et al. (13) found that MPV was decreased in childhood brucella arthritis compared to control groups. Several other investigators have indicated that MPV was decreased in brucellosis participants compared to healthy groups (5,22,23). However, Togan et al. (21) could not detect a significant difference in the MPV between acute brucellosis

patients and healthy subjects, while Kucukbayrak et al. (24) showed a significant increase in MPV values after the treatment of patients with brucellosis. The results of our study showed that brucella arthritis participants had raised MPV compared to the control participants.

In medical practice, leukocyte and neutrophil counts are the most widely used laboratory parameters to detect systemic inflammation, but their specificity and sensitivity values are low. Thus, a stronger parameter of confidence in doubtful cases is needed. NLR, which is routinely performed, is evaluated by dividing neutrophil counts with lymphocyte counts. NLR, which is a biomarker of systemic inflammation, reflects the balance between neutrophil and lymphocyte levels (31). Lymphocyte counts decrease when neutrophil counts are elevated. NLR rises in systemic inflammatory conditions and the rise of this ratio is accepted as a marker of blood systemic inflammation (32). This ratio is an inflammatory biomarker that has been mentioned as a prognostic biomarker to determine the blood systemic inflammation response (10, 33). In numerous studies, this ratio has been documented as being raised in rheumatoid arthritis participants compared to control groups (34,35). The research of Tasoglu et al. (36) documented the link between severe knee osteoarthritis and this ratio. They observed that severe knee osteoarthritis subjects have increased blood NLR values compared to those with mild zoonotic knee osteoarthritis. Limited studies are available regarding NLR in patients with brucellosis and their results are conflicting (7,13,14). Aktar et al. (14) indicated that children with brucella arthritis had significantly elevated NLR compared to the control participants. Similarly, Bozdemir et al. (13) observed that their brucella arthritis group had significantly raised NLR compared to the control participants. In contrast to these studies, Olt et al. (7) found low NLR in brucellosis patients compared to control groups. In the current research, we wondered whether NLR is suitable as a diagnostic marker for brucellosis. Our results show that NLR was markedly lower in the adult brucellosis arthritis patients compared to the control group.

Platelets are especially involved in homeostasis, but previous authors have described them as having an important role in systemic inflammatory response as well (37). Inflammation is a strong thrombocyte activator (38). Cytokines such as IL–6 and IL–1 promote inflammation and contribute to elevated thrombocyte counts (38). Platelets play an important role in inflammation and have regulatory roles in the immune system, so PLR has been suggested in recent years as a potential inflammatory marker to determine inflammation in routine blood tests. This ratio change may be associated with inflammation and cytokines. A few studies are available regarding PLR in patients with brucellosis and the data are conflicting (7,13,14). Aktar et al. (14) indicated that children with brucella arthritis had significantly elevated PLR compared to the control participants. Conversely, several other authors could not detect a significant difference in the PLR between patients and healthy subjects (7,13). In the present study, no considerable difference with respect to PLR between the two groups was detected.

Limited studies are available regarding platelet counts in patients with brucellosis and their results are conflicting. Some studies have observed that brucella patients had significantly lower platelet counts compared to the control groups (5,13,14,23). In contrast, Kader et al. (22) observed that brucellosis subjects had markedly raised platelet counts when compared to the healthy participants. However, Olt et al. (7) could not detect a significant difference in the platelet counts of the brucellosis participants

compared to the healthy participants. In the current study, no considerable difference with respect to platelet counts between the two groups was detected.

In the current paper, we aimed to document these systemic inflammatory biomarkers could be used in diagnosing brucellosis arthritis. They are commonly used and inexpensive, easy, and more accessible. These biomarkers can be used to determine the existence of disease in clinical practice. The fact that these systemic biomarkers are raised in brucellosis arthritis may help to diagnose the disease.

The current study has several limitations. First, it would have been beneficial if the sample size had been larger. Second, these biomarkers could have been compared with other systemic inflammatory cytokines such as IL–6 and IL–1. Third, our study was retrospective research. The results of a prospective research with further larger research may be more helpful.

Conclusions

We observed statistically significant differences between brucella knee arthritis patients and healthy subjects with respect to MPV and NLR. These parameters may be beneficial markers for use in the assessment of patients with brucella arthritis. Further studies are required to confirm the current results.

Declarations

Ethics approval and consent to participate: The study protocol was conducted in accordance with the Helsinki Declaration as revised in 2000 and approved by the local ethics committee of Van Regional Training and Research Hospital, Van, Turkey. All subjects were informed about the study, and written consent was obtained from each subject.

Consent for publication: Not applicable

Availability of data and material: Not applicable

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Authors' contributions:
CA and MA: Conception and design;

CA and MA: Analysis and interpretation of the data;

CA and MA: Critical revision of the article for important intellectual content;

CA and MA: Final approval of the article;

CA and MA: Collection and assembly of data.

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Tables

Table 1. The demographic characteristics of the two groups

Parameters	Patients (n=53)	Controls (n=42)	p
Age (years)	35±18	37±18	0.603
Sex (female/male	27/26	23/19	0.711
Agglutination test titers	47.61±15.89	582.64±443.86	**0.001**

Values are mean ± SD

Table 2. The blood systemic inflammatory markers of the brucellosis patients and the healthy subjects

Parameters	Patients (n=53)	Controls (n=42)	p
Platelet number (x10^3/mm^3)	260.20±69.60		
MPV (fL)	261.42±64.83		0.930
Absolute neutrophil count (cell/mm^3)	9.55±1.62	8.74±1.82	**0.024**
Absolute lymphocyte count (cell/mm^3)	3699±1492	4549±1463	**0.007**
WBC (/µl)			
PLR			
NLR	2553±1085	2473±915	0.705
CRP (mg/L)			
ESR (mm/h)	6957±2201	7757±1883	0.064
	114.99±43.70	114.40±35.99	0.914
	1.63±0.88	2.05±0.96	**0.027**
	17.11±15.62	7.81±6.10	**0.001**
	10.21±8.58	6.01±3.97	**0.024**

Values are mean±SD;

MPV: Mean platelet volume; **WBC:** White blood cells; **PLR:** Platelet to lymphocyte

NLR: Neutrophil to lymphocyte ratio; **CRP:** C reactive protein

Bold values indicate statistical significance