ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Neutrophil-Lymphocyte Ratio in Septic Arthritis Diagnosis and Treatment Follow-Up

Septik Artritin Tanı ve Tedavi Takibinde Nötrofil-Lenfosit Oranı

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ABSTRACT

Aim: *This study aimed to determine the availability of neutrophil-to-lymphocyte ratio (NLR) in diagnosis and treatment follow-up by determining the changing values when septic arthritis (SA) is diagnosed and during treatment.*

Material and Method: *This retrospective study is based on examining the laboratory results of 44 adult patients with a diagnosis of SA. Laboratory values, white blood cell count (WBC), C-reactive protein (CRP), and NLR of the patients on days 0, 5, 10, and 14 and the results of the joint fluid analysis were evaluated.*

Results: *The mean number of cells in the joint fluid of the patients was 46 thousand, and the mean PMNL rate was 89.4%. Microorganisms were seen in gram staining of joint puncture fluid of only four patients (9.1%). The number of patients with growth in joint fluid culture was only 11 (25%). The mean values for days 0, 5, 10, and 14 were, respectively, 135.2, 88.1, 47.3, and 22.2 for CRP; 9.94, 7.86, 7.42, and 7.44 for WBC; 4.9, 3.8, 3.0 and 2.4 for NLR.*

Conclusion: *NLR may serve as a valuable biomarker for diagnosing and monitoring treatment in SA, particularly given the low prevalence of microorganisms in gram stains and joint fluid cultures and the variability in cell counts in joint fluid samples. In patients diagnosed with SA, the mean NLR value is 4.9 and consistently decreases during treatment. Within two weeks of initiating treatment, NLR typically decreases by approximately half. This biomarker can aid in diagnosing and ongoing managing SA, offering a cost-effective and readily available indicator that should be routinely considered.*

Key words: *arthritis; septic; neutrophils; lymphocytes; biomarkers*

ÖZET

Amaç: *Bu çalışmada nötrofil-lenfosit oranının (NLR), septik artrit (SA) tanısı konulduğundaki ve tedavi sürecindeki değişen değerleri belirlenerek tanı ve tedavi takibindeki kullanılabilirliğini saptamak amaçlanmıştır.*

Materyal ve Metot: *Bu retrospektif çalışma, SA tanısı ile tedavi edilen 44 erişkin hastanın laboratuvar sonuçlarının incelenmesine dayanmaktadır. Hastaların 0., 5., 10., 14. günlerdeki laboratuvar değerleri (WBC, CRP, NLR) ve eklem sıvısı analizinin sonuçları değerlendirildi.*

Bulgular: *Hastaların eklem sıvısındaki ortalama hücre sayısı 46 bin, ortalama PMNL oranı %89,4 idi. Sadece dört hastanın (%9,1) eklem ponksiyon sıvısının gram boyanmasında mikroorganizma görüldü. Eklem sıvısı kültüründe üreme görülen hasta sayısı sadece 11 idi (%25); 0., 5., 10. ve 14. günler için ortalama değerler CRP için sırasıyla 135,2, 88,1, 47,3 ve 22,2; WBC için 9,94, 7,86, 7,42 ve 7,44; NLR için 4,9, 3,8, 3,0 ve 2,4 idi.*

Sonuç: *Septik artritte gram boyama ve eklem sıvı kültüründe mikroorganizma görülme oranının oldukça düşük olması, eklem sıvısındaki hücre sayısının her zaman net fikir vermemesi nedeniyle tanı ve tedaviye yanıtı değerlendirmede biyobelirteç olarak NLR de yol gösterici olabilir. Septik artrit tanısı alan hastalarda ortalama NLR değeri 4,9 olup tedavi süresince düzenli olarak azalmaktadır. NLR, tedavinin 2. haftasında yaklaşık yarı değerine inmektedir. Bu biyobelirteç SA'nın tanı ve takibinde kullanılabilir. Ucuz ve kolay erişilebilir bir gösterge olduğu için NLR değeri her zaman dikkate alınmalıdır.*

Anahtar kelimeler: *artrit; septik; nötrofil; lenfosit; biyobelirteç*

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Introduction

Acute bacterial arthritis or septic arthritis (SA) is an orthopedic emergency. Bacterial replication and subsequent inflammatory processes develop in the joint. This may cause severe deterioration in the joint and cause mortality as a result of sepsis. Therefore, the diagnosis and appropriate treatment of the infected joint is critical to limit the morbidity and mortality associated with these infections.

The incidence of SA is estimated to be about 2 to 10 cases per 100,000 per year[1]. Patients with a history of prosthetic joint replacement, rheumatoid arthritis, systemic lupus erythematosus, gouty arthropathy, diabetes mellitus, and immunosuppressive drug use are at higher risk of developing septic arthritis[2].

Early use of antibiotics directed against the causative pathogen, surgical irrigation of the joint, and debridement, if necessary, are essential in treating SA. The treatment process of these patients lasts for weeks. Common inflammation markers such as white blood cell count (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) for diagnosis and evaluation of of these infections have poor discriminatory capacity between infectious and noninfectious pathologies[3,4]. Although new markers such as procalcitonin and adrenomedullin have been introduced, the use of these markers has been limited due to cost, accessibility, and appropriate validation problems[4]. For these reasons, the search for inexpensive and reliable markers to predict SA and evaluate the response to treatment persists.

In recent years, studies have been conducted on inflammatory markers obtained from complete blood count (CBC) for early diagnosis of infection and evaluation of response to treatment[5–7]. Markers such as neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV), and calculation of platelet-lymphocyte ratio (PLR) were evaluated in different disease groups[8]. Since a limited number of studies use these markers in the treatment follow-up of adult SA, this study aimed to determine the use of NLR in diagnosing and treating SA, which requires urgent and long-term treatment.

Materials and Methods

This retrospective study examines the laboratory results of 44 patients with a diagnosis of SA who were treated and followed up in our hospital's orthopedics and traumatology clinic between January 2018 and November 2021 and who met the inclusion criteria.

The diagnosis of SA was made according to the number and content of cells in the joint puncture after the causative microorganism was isolated from the joint fluid or after the physical examination revealed signs of infection such as increased temperature, redness, swelling, and limitation of movement in the joint. Elevated CRP values in the blood and more than 20 thousand cells in the joint fluid or polymorphonuclear leukocytes (PMNL) ratios above 80% were used to guide the diagnosis.

Inclusion criteria for the study: Patients over 18 years of age who underwent joint puncture by us and were diagnosed with SA and underwent intra-articular arthroscopic washing, whom we followed up for at least 14 days.

Exclusion criteria: Patients under 18 years of age, patients with multiple joint involvements, undergoing open surgery, a history of the rheumatological disease, immune compromisation, SA, prosthetic joint replacement, bleeding diathesis, history of previous granulomatous disease and malignancy, requiring intensive care, and those who were cachectic or morbidly obese.

The medical history of all patients included in the study, their eligibility for inclusion, and the evidence for the diagnosis of SA were reviewed. Age, gender, and laboratory values (WBC, CRP, NLR) of the patients on days 0, 5, 10, and 14 were recorded.

The patients included in the study underwent arthroscopic intervention. Joint irrigation and debridement, when necessary, were routinely performed during surgery. Empirical intravenous antibiotic treatment of all patients postoperatively was started after consultation with infectious diseases. Antibiotherapy was adjusted according to the culture result, if necessary. Intravenous antibiotherapy was continued until the inflammatory markers approached normal and the patients were clinically relieved (minimum two weeks). In contrast, outpatient follow-up and treatment with oral antibiotics were continued.

This retrospective study was conducted under the principles stated in the Declaration of Helsinki. The search for archival material and research permission was obtained from the hospital administration and approved by the local ethics committee (approval number: 2022/45).

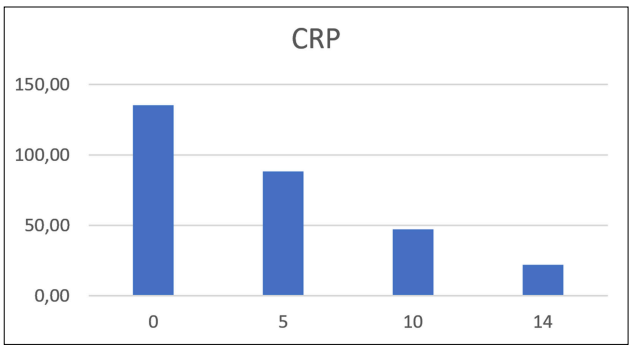

Figure 1. *Change of mean CRP value on days 0, 5, 10, and 14 (CRP: C-reactive protein).*

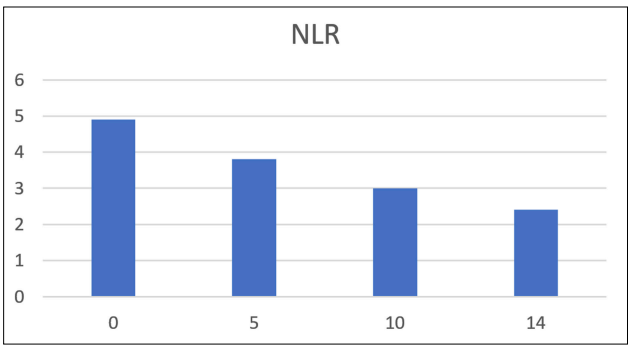

Figure 2. *Change of mean NLR value on days 0, 5, 10, and 14 (NLR: Neutrophil-to-lymphocyte ratio).*

Statistical method: The dataset was preprocessed (outlier, missing observation, normal distribution assumption). The descriptive statistics of the normally distributed continuous variables are given as X ± SD, the non-normally distributed continuous variables are given as median and min-max values, and the categorical variables (qualitative) are given as percentages and ratios. Comparisons were made between the normally distributed continuous variables and the groups using parametric methods. Statistical significance was accepted as $p < 0.05$.

Results

The mean age of 44 patients was 67.8 (range 40–91); 22 of them were male (50%) and 22 were female (50%). The involved joint in all cases was the knee, except for one in which the hip joint was affected.

The mean number of cells in the joint fluid of the patients was 46 thousand, and the mean PMNL rate was 89.4%. Microorganisms were seen in gram staining of joint puncture fluid of only four patients (9.1%), and these were gram (+) cocci. The number of patients with growth in joint fluid culture was only 11 (25%).

The mean values were calculated for 0, 5, 10, and 14 days when SA was diagnosed and during treatment (Table 1). Respectively, 135.2, 88.1, 47.3, and 22.2 for CRP (Fig. 1); 9.94, 7.86, 7.42 and 7.44 for WBC; 4.9, 3.8, 3.0 and 2.4 for NLR (Fig. 2).

The change in NLR value was compared according to the days, and p-values were calculated. Statistically, there was no significant decrease in the NLR value on the 5th day. Still, the p-value was <0.001 on the 10th and 14th days compared to the preoperative day. The comparison of the NLR value between itself according to the days is indicated below.

NLR (0) – NLR (5): p=0.098

NLR (0) – NLR (10): p<0.001

NLR (0) – NLR (14): p<0.001

NLR (5) – NLR (10): p=0.077

NLR (5) – NLR (14): p<0.001

NLR (10) – NLR (14): p=0.098

Discussion

In this study, in which septic arthritis diagnosis and response to treatment (we routinely prefer arthroscopic treatment as it is as effective as traditional open approaches, has a shorter hospital stay, additional benefits in postoperative wound healing, and offers better results than open surgery in postoperative joint range of motion[2,9]) were evaluated, the NLR value, which is an easily accessible and inexpensive biomarker, was calculated. The mean NLR value of patients diagnosed with septic arthritis was 4.9. The NLR value calculated as an alternative to the CRP value, primarily used in response to septic arthritis treatment, was found to be 3.8

Table 1. *Changes in CRP, WBC, and NLR values in the diagnosis of adult septic arthritis and during the treatment period*

PARAMETERS	Day 0	Day 5	Day 10	Day 14
CRP (0-5)	135.2	88.1	47.3	22.2
WBC (4-10)	9.94	7.86	7.42	7.44
NLR	4.9	3.8	3.0	2.4

CRP: C-reactive protein; **WBC:** White blood cell count; **NLR:** Neutrophil-to-lymphocyte ratio.

on the 5th day, 3.0 on the 10th day, and 2.4 on the 14th day of treatment. The NLR value decreased at similar rates to CRP in treating adult septic arthritis.

Bacterial isolation from synovial fluid obtained by joint puncture is the gold standard in diagnosing SA[10]. However, false-negative culture results may be seen due to antibiotic use before joint puncture[11] and false-positive results due to contamination[12,13]. In their prospective multicenter study, Gupta et al.[14] found growth in synovial fluid in only 57% of 82 patients diagnosed with SA. When they compared these patients with those lacking growth in the joint fluid, they reported that the groups' mortality and morbidity were similar. The fact that only 25% of the patients in our study had growth in the joint fluid culture supports the low sensitivity of joint fluid culture in diagnosing septic arthritis.

Although growth in blood culture is helpful in the diagnosis, Weston et al.[15] obtained a positive blood culture in only 24% of the 242 patients in their study. This result supports the idea that a negative blood culture cannot rule out infection. Therefore, additional objective marker inclusion in the diagnosis of septic arthritis will significantly benefit clinical practice. We do not routinely take blood cultures from patients who do not show signs of systemic infection.

A meta-analysis of 14 studies on SA evaluated 6242 patients[16]. They found joint pain (85%), joint redness (78%), an increase in joint temperature (57%), sweating (27%), and joint stiffness (19%). The same study showed that the probability of septic arthritis was low in patients with a leukocyte count below 25 thousand in the joint fluid, which increased significantly in those above 50 thousand, and it was specific for septic arthritis[2]. They also showed that the probability of SA was increased dramatically in those with a PMNL rate greater than 90%. The mean WBC count in the joint fluid of the patients with SA (43 thousand) and the rate of PMNL in the joint (89.4%) in this study are similar to those reported in this meta-analysis.

It is known that an increase in WBC in the blood may be associated with infection. Still, leukopenia can also be seen in infective conditions[17]. White blood cell count level is also frequently affected by non-infective conditions such as steroid use[18]. Many studies have shown that WBC has a low diagnostic value in the diagnosis of infection[18–20]. Our study determined that although some patients had high WBC values, the mean WBC value was within the normal reference range from the first day to the 14th day. However, the mean WBC value decreased with treatment. Although CRP has a high sensitivity in the diagnosis of infection, it is far from being reliable in the diagnosis and follow-up of infection since it increases in inflammatory conditions such as surgery and trauma[21–23], in patients with malignancy[24], and even in obesity[25].

In the differential diagnosis of septic arthritis, clinicians should also consider diseases such as transient synovitis, rheumatoid arthritis, reactive arthritis, abscess, avascular necrosis, cellulitis, crystal-induced arthropathies such as gout, Lyme disease, osteomyelitis, and malignancy[26]. A combination of biomarkers may help diagnose SA since physical examination findings may differ from patient to patient[16], blood results are affected by many clinical conditions [17,18,21–25,] and false negative culture may be present[11]. Manohar et al.[4] showed that high NLR has a similar diagnostic value to blood culture positivity in diagnosing systemic infection. We also evaluated NLR as a measure of systemic inflammation in the diagnosis and follow-up of SA, where early diagnosis and treatment are very important.

None of the readily available and inexpensive biomarkers, such as ESR, CRP, and WBC, have a cut-off value for septic arthritis. There is no acceptable sensitivity or diagnostic accuracy of the peripheral WBC count for diagnosing septic arthritis. Multiple studies demonstrated acceptable sensitivity for ESR of >30 mm/hour, but the specificities were poor. There is no cut-off for ESR or CRP yet for septic arthritis. Tumor necrosis factor and various cytokines, including interleukin-6 and interleukin-β, were generally specific with poor sensitivity. Procalcitonin levels are typically elevated because the etiology of septic arthritis is usually systemic[27]. Neutrophil-to-lymphocyte ratio is an inexpensive and readily available indicator of systemic inflammation based on complete blood count values. In general, the number of neutrophils in the blood increases with the progression of the inflammatory state. As the neutrophil count increases, the lymphocyte count decreases. As a result, NLR increases, which is considered an indicator of systemic inflammation[28]. But this is not always the case. In some cases, such as cachexia, false negativity may occur because the neutrophil count is not increased. The lymphocyte count reflects the patient's immune status and generally decreases as the inflammatory disease progresses[29]. Recent studies have shown that NLR is more reliable on patient survival than neutrophil or lymphocyte count alone[30].

In a study to determine the normal value of NLR, the mean NLR value in healthy adults was reported as 1.65 (0.78–3.53)[31]. Gurol et al.[32], in their study on the NLR value, showed that the cut-off value for sepsis was 5. In our research, while the mean NLR value of the patients on the first day was 4.9, it decreased to 3.8, 3.0, and 2.4 on the 5 th, 10 th, and 14th days after treatment, respectively. This 3-fold increase compared to the normal value on the first day may be significant in diagnosing SA. In addition, the decrease in NLR over time in patients who underwent surgical treatment and antibiotic therapy indicates that it may be a sign of response to treatment. While NLR decreased during treatment, there was also a regression in the clinic and symptoms. An improvement was observed in the patient's general condition and systemic findings, often starting from the second day. However, it was generally observed after the fifth day that patients mobilized without pain and felt that they were beginning to recover. This was parallel to the significant decrease in NLR.

Study Limitations

A limitation of this study was that it was retrospective and single-centered. Studies with a more extensive series, prospective, and comparing biomarkers will be more useful. It would be beneficial if other biomarkers, such as PLR MPV, were compared.

Conclusion

Due to the low incidence of microorganisms in gram staining in the diagnosis of SA, the need for time for reproduction in culture, and the number of cells in the joint fluid does not always give a clear idea; it may be useful to evaluate biomarkers for diagnosis and treatment in SA, which requires urgent diagnosis and treatment. NLR, calculated as a simple ratio between the neutrophil and lymphocyte counts measured in peripheral blood, is a biomarker that reflects the balance between two aspects of the immune system: acute and chronic inflammation (as indicated by the neutrophil count) and adaptive immunity (lymphocyte count). Neutrophil-to-lymphocyte ratio is not a new biomarker. It has been previously evaluated in many conditions, such as infection, malignancy, rheumatological disease, and appendicitis, and it has been shown that it can be used as a prognostic factor[4,8,33,34]. It is one of the few studies that show its importance in adult septic arthritis.

In patients diagnosed with septic arthritis in adults, the average NLR value is 4.9 and decreases regularly during the treatment process. After approximately two weeks of treatment, this rate decreases to half its value. Based on the results of this study, NLR is an inflammatory marker that can be used in the diagnosis and follow-up of SA treatment. Neutrophil-to-lymphocyte ratio value should always be considered because it is a cheap and easily accessible indicator.

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