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Evaluation of neutrophil-to-lymphocyte ratio as a marker of inflammatory response in septic arthritis

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Abstract

Is neutrophil-to-lymphocyte ratio high in patients with septic arthritis? Septic arthritis may lead to higher rates of morbidity or even mortality if not diagnosed on time. This study was planned to answer the question that "Could neutrophil-to-lymphocyte ratio be utilized to help to diagnose septic arthritis?" The cohort of the study consisted of 39 patients diagnosed with septic arthritis. After ruling out the patients who did not meet the research's inclusion criteria, the data of 26 patients were evaluated. The control group was collected from healthy volunteers who were admitted to the internal medicine outpatient clinic for a routine medical checkup at the same period (n = 26). Complete blood count (CBC) parameters, C-reactive protein, erythrocyte sedimentation rate, and neutrophil-to-lymphocyte ratios of the septic arthritis and control groups were compared statistically. In comparison, neutrophil-to-lymphocyte ratios of the septic arthritis group were significantly higher than the control group. In conclusion, neutrophil-to-lymphocyte ratio can be utilized in the emergency department or in outpatient clinics to support the diagnosis of septic arthritis.

Keywords

low cost diagnosis method, neutrophil-to-lymphocyte ratio, septic arthritis

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Introduction

Septic arthritis (SA), one of the leading orthopedic emergencies, is a condition characterized by suppurative inflammation of the joints, which may lead to higher rates of morbidity or even mortality if not diagnosed and treated on time.[1,2] SA may affect individuals from all ages, but its prevalence in children and older people is higher.[3] SA-related mortality rate is in the range of 8–24% with an average of 11%. Therefore, to reduce morbidity and mortality rates, proper treatment of SA by surgery must be initiated with early diagnosis.[4]

Although radiography, bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) have been used in the diagnosis of SA, in the differential diagnosis of SA from other

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arthritis forms, these investigation methods may not always provide definitive diagnosis.[5]

It is known that in diagnosis of SA, physical examination and clinical symptoms, like hyperemia, hyperthermia, pain, edema, and limitation of motion are very important. But these symptoms can also be encountered at transient arthritis, cellulitis, rheumatic fever, acute juvenile arthritis, rheumatoid arthritis, crystal arthropathy, reactive synovitis, viral arthritis, osteomyelitis, cellulitis, traumatic hemarthrosis, ruptured Baker's cyst, deep vein thrombosis, and pigments villonodular synovitis so SA should be differentiated from these diseases.[6]

Synovial fluid leukocyte count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are also examined routinely prior to diagnosis. Moreover, mucin clot test, joint aspirate Gram stain test, and (in patients with monoarthritis) monosodium urate and calcium pyrophosphate examination using polarized microscopy are also known to be useful.[7] Further, high-tech and costly culture antibiogram or polymerase chain reaction (PCR) tests are also helpful but costly tests.[8]

Recently neutrophil-to-lymphocyte ratio (NLR) – the level of neutrophil reflecting the severity of inflammation and lymphocyte count increasing after physiological stress – has been gaining popularity, which was, along with other inflammatory markers, commonly accepted as an accurate marker of the inflammatory status.[9] NLR, which is not routinely utilized like other markers of infection, such as leukocyte count, sedimentation, and CRP, has not been evaluated in SA in the literature.

This two-center study was conducted to evaluate the NLR's suitability to support the clinical diagnosis of the SA, in which case early diagnosis and treatment are essential. So instead of expensive and time-consuming laboratory investigations, cost-effectiveness, easiness, and rapidity of NLR might be useful in prompt diagnosis.

Materials and methods

The study involved 39 patients admitted to Istanbul Medipol University and GATA Haydarpasa Training Hospital and treated for SA between January 2012 and December 2014. The patients' demographic and clinical data were retrieved from the hospitals' electronic database. This retrospective, controlled, and multicentered study was approved by Istanbul Medipol University's ethical committee.

Study design

Cases, which are operated for diagnosis of SA and drained out purulent material, are included in this study (n = 39). Demographic and clinical features of the patients from both centers were incorporated into the analyses. Patients with any other condition that may potentially change ESR, CRP, or white blood cell (WBC) data and those with incomplete lab results were excluded (Figure 1).

The control group included patients admitted to either of the hospitals for a routine medical checkup, who did not have any serious disease or malignancy, and had no history of glucocorticoid use. The control group was compatible with the SA group in terms of age (45 years and below) and gender distribution (n = 26).

The number of joints affected in each patient was recorded. Joint aspirate culture and antibiotic sensitivity results, Gram-staining results, mucin clot test (if available), PCR, and blood culture results were also recorded. Further, the data regarding inspection for urate crystals on wet preparates using polarized light microscope was reported if present. Preoperative complete blood cell (CBC) count, CRP, ESR, and NLR levels were registered.

Statistical analyses

The data were analyzed using SPSS version 18.0. Descriptive statistics were presented as mean ± standard deviation or frequency (%). Since the data did not meet the parametric test assumptions, for the comparison of independent two groups, Mann-Whitney U test was used. For multivariate analyses, since the SA diagnosis was assumed as the dependent variable, independent variables that may affect the dependent variable and the odds ratio (OR) were analyzed using the logistic regression analysis.

Receiver operating characteristic (ROC) curves were used in order to eliminate the drawbacks of using just one sensitivity and specificity value in diagnosis.[10] For superiority of diagnostic tests, the area under the ROC curve was used as a comparison scale.[11–14]

Likelihood ratio (LR+), sensitivity, and specificity calculations were made. Positive LR value for each sensitivity and specificity value was calculated using the following formula: LR+ = Sensitivity / (1-Specificity). From the literature, taken as reference.[15] All analyses were carried out two-way

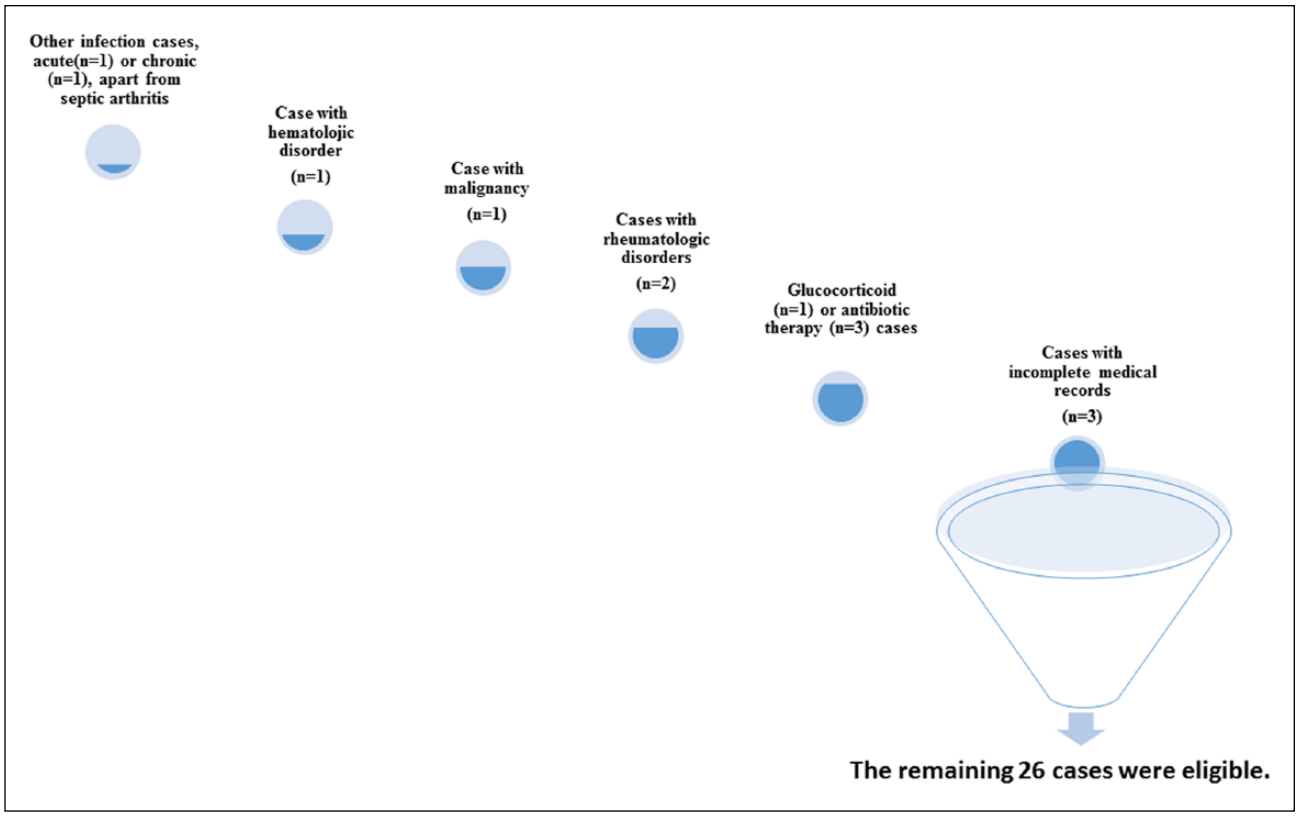

Figure 1. Patients.

Table 1. Comparison of peripheral vein parameters between groups.

Findings	Groups	n	Mean	Standard deviation	*P**
CRP (mg/dL)	Control	26	3.08	1.19	<0.001
	Patient	26	90.41	70.92	
ESR (mm/h)	Control	26	17.22	8.64	<0.001
	Patient	26	53.80	31.38	
WBC (e^3/UL)	Control	26	6.86	1.32	<0.001
	Patient	26	13.16	6.13	
Lymphocyte (e^3/UL)	Control	26	2,22	0.59	0.780†
	Patient	26	2,1	2.20	
Neutrophil (e^3/UL)	Control	26	3.5	0.79	<0.001
	Patient	26	9.81	3.54	

*t test for independent groups.
†Mann-Whitney U test.

with a confidence classification systems assuming any LR+ value larger than 10 as "perfect" was an interval of 95.

Results

The mean ages of the study and control groups were 45.72 ±23.05 and 45.15±22.77 years, respectively. No significant difference was observed between groups in terms of mean age ($P = 0.930$). The most common SA region was the knee (n = 23). Lab results of the patient group and the control group were compared (Table 1, Figure 2).

It was observed that there was no growth in 19 joint aspiration fluid samples (73.1%). The most common pathogen in samples was coagulase negative Staphylococcus aureus (n = 3) and 73.1% of the pathogens were Gram-positive (Table 2).

Logistic regression analysis, which was used to monitor the changes in hemogram parameters,

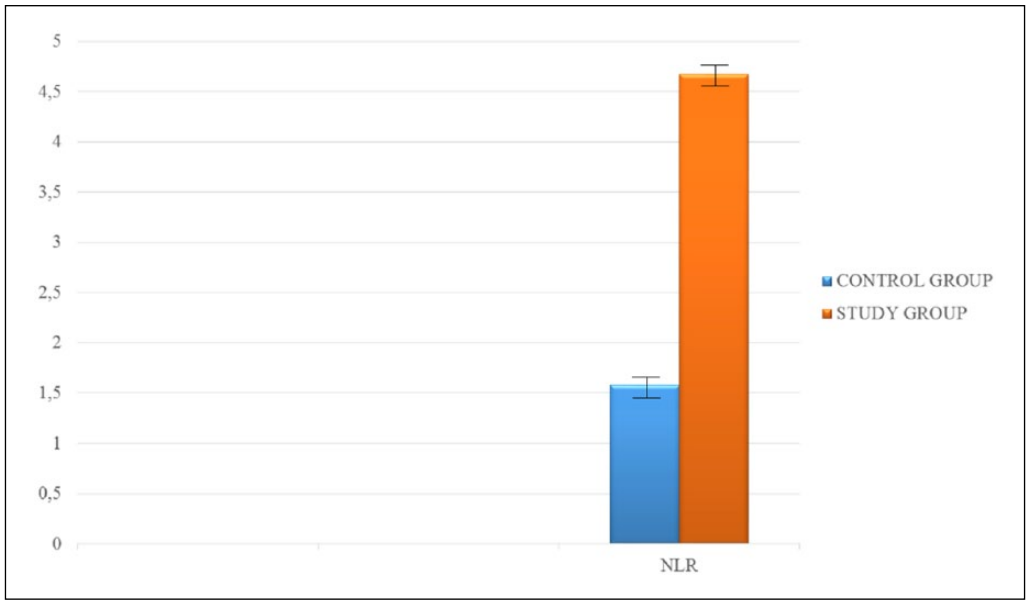

Figure 2. Comparison of peripheral vein parameters between groups.

Table 2. Joint fluid culture and Gram staining results of the study group.

Application	Patient group	
	Frequency	%
Synovial joint aspirate culture		
Culture negative	19	73.1
Coagulase negative Staphyloccus aureus	3	11.5
Gram-positive cocbacteria	2	7.7
Pseudomonas	2	7.7
Total	26	100.0
Synovial joint aspirate Gram staining		
Positive	19	73.1
Negative	7	26.9
Total	26	100.0

showed NLR OR as 4.22 (P = 0.005; 95% CI, 1.533–11.628). NLR in the septic group was found to be 4.22 times more than the control group. OR values of ESR and CRP were found to be 1.934 (P = 0.000; 95% CI, 1.079–3.467) and 1.126 (P = 0.027; 95% CI, 1.053–1.203), respectively. Based on these numbers, in the study group, NLR, ESR, and CRP values were 4.22, 1.93, and 1.13 times more than those of the control group, respectively (Table 3, Figure 3).

The NLR curve of the SA patients was observed to be over the reference line, and the area under the line was 0.896 (P <0.001; 95% CI, 0.796–0.996), which is very close to 1.

In the NLR validity calculation, the highest LR positive value was 11.89 and NLR was found to be 2.414. At this point, when the cutoff point for NLR was taken as 2.41, our method was observed to have a sensitivity and specificity of 88% and 93%, respectively.

Discussion

As it is known, SA is the inflammation of the synovial membrane and synovial fluid in joints caused by bacterial, viral, or fungal infections. Because of its highly vascular structure and absence of protective basement membrane, microorganisms can easily reach and colonize in synovial membranes by a hematogenous route.[16]

Septic arthritis is an important medical emergency with high morbidity. Epidemiological study is difficult to do for SA. For this reason incidence was given in variable ranges. While the incidence of SA in Europe is 4/100,000 per year, this rate is six times more common in eastern Europe and Australia. We could not find any report regarding incidence rate of SA in our country. Tarkowski et al. reported that the incidence in the general population is 6/100,000.[3] Furthermore there are too few reports in the USA after 2000.[17]

That is why we believe that our study results containing 26 cases could provide a valuable contribution to the literature even it appears to be a small cohort.

Table 3. Logistic regression models of the implicating factors in the study and control groups.

Logistic regression modeling		Wald	*P*	Exp (B)	95% CI for EXP (B)	
					Lower	Upper
Model 1	NLR	7.763	0.005	4.222	1.533	11.628
	Constant	11.655	0.001	0.013		
Model 2	CRP	4.909	0.027	1.934	1.079	3.467
	Constant	10.430	0.001	0.008		
Model 3	ESR	12.144	0.000	1.126	1.053	1.203
Constant	13.331	0.000	0.031			

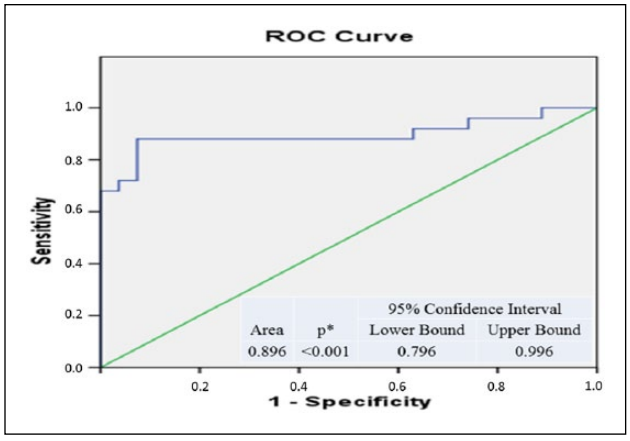

Figure 3. The ROC curve showing the performance of NLR in patients with septic arthritis (NLR area under the curve).

At the diagnosis stage of SA, time-consuming and high-cost tests are performed as a necessity. After the physical examination, increase of peripheral blood WBC, ESR, and CRP levels are beneficial in diagnosis. However, especially in the diagnosis of suspicious cases of SA, if the case has an inflammatory joint disease like rheumatoid arthritis, the raise of the ESR is not helpful in differential diagnosis.[18]

In order to save the cartilage, the diagnosis of SA, which is characterized by suppurative inflammation, must be made as early as possible – a few hours after the onset of the symptoms – and then the surgical procedure must be carried out based on this diagnosis. NLR, which is calculated from complete blood count with differential, is an inexpensive, easy to obtain, widely available marker of inflammation. So NLR can aid in the risk stratification of patients with various diseases in addition to the traditionally used markers. The NLR is reported to be increased in various inflammation-related diseases,[19] but their clinical significance in SA remains unclear.

For these reasons, in this study, we aimed to investigate the clinical significance of NLR value especially in patients who bear some features that cause some difficulties in differentiating and diagnosing SA to start treatment as soon as possible.

It was previously reported that surgical intervention 48 h after the onset of the symptoms would be too late and lead to damage in the cartilage. Therefore, the most important factor in SA was reported to be early diagnosis.[20,21]

In the present study, surgery was performed in the first 6 h on average.

In the literature, it is reported that SA was a serious disease and could be seen in all joints including the large, weight-bearing, lower limb joints. Especially in the cases with non-gonococcal pathogen, the disease is usually seen in a single joint.[22]

In our results, the most common joint that was involved was the knee (n = 23).

It was also reported in the literature that Gram staining and culture antibiograms in joint aspirations and crystal analyses must be performed as soon as possible.[7,23] Further, along with ESR, CRP increments, and a leucocyte count more than 50,000/mm^3, and predominance of neutrophils in synovial joint aspirate, supportive findings in the diagnosis were reported.[23,24] Literature reported that, based on the patients' clinical findings, they were treated with wide spectrum antibiotic therapy even though the culture antibiograms of synovial samples resulted negative in more than 50% of the participants.[25]

In the present study culture results were negative in 73.1% of the patients.

This is the first study in the literature supposing that NLR can support the diagnosis faster and more reliable compared to other inflammatory markers especially in uncertain SA cases.

In a previous study, no significant difference was found between healthy volunteers and ankylosing

spondylitis patients in terms of NLR values.[26] In another study, significantly higher NLR values were reported in ankylosing spondylitis group compared to the control.[27] SA diagnosis is easily made when patients' synovial leukocyte count is over 50,000/mm^3; however, it has been difficult to make SA diagnosis in patients with a count less than 50,000/mm^3.[28] On the other hand, synovial leucocyte count may not be increased over 50,000/mm^3 in some other conditions, such as corticosteroid or intravenous drug use, occurrence of malignant diseases, and in cases where immune system is deficient such as prematurity.

Further, polymorphonuclear leukocyte rate may generally be over 80% and there are studies in the literature reporting a PMNL increase in the synovial fluid following crystal accumulation with no rheumatoid arthritis infection.[28–30]

In addition, Gram staining and culturing of active pathogens in joint synovial fluid aspirations require selective media and techniques; the samples must therefore be transferred to the lab with detailed information, all of which is cumbersome and time-consuming. On the other hand, PCR technique, although it is not commonly used, may be utilized in some cases where Gram staining is not effective, such as Neisseria gonorrhea arthritis. Other lab findings, such as the number of leukocytes, ESR, and CRP, are supporting evidence for the diagnosis. Recently, the level of procalcitonin in blood has been used in SA diagnosis. Generally, CRP values in SA patients peak on day 1 and ESR values hit the maximum on days 3 and 5. These tests, like PCR technique, level of procalcitonin in blood, are expensive and time-consuming with respect to hemogram analysis. However, one of the most important thing in assessment of SA is immediate diagnosis and to start the proper treatment.[17,31,32]

All these findings are a result of NLR can be used as a differentiating marker for SA, transient arthritis, and other inflammatory arthritis. The results of research evaluating relationship between SA and NLR that was the first study we know in the literature showed that logistic regression analysis, which was used to monitor the changes in hemogram parameters, showed NLR OR as 4.22 (P = 0.005; 95% CI, 1.533–11.628). NLR in the septic group was found to be 4.22 times more than the control group. Based on these data, in the study group, NLR, values were 4.22 times more than those of the control group. The NLR curve of the SA patients was observed to be over the reference line, and the area under the line was 0.896 (P <0.001; 95% CI, 0.796–0.996), which is very close to 1. In the NLR validity calculation, the highest LR positive value was 11.89 and NLR was found to be 2.414. At this point, when the cutoff point for NLR was taken as 2.41, our method was observed to have 88% sensitivity and 93% specificity. So, there was a statistical difference between groups regarding NLR (P = 0.005).

Especially in patients in whom it is difficult to diagnose, in order to begin treatment as soon as possible, cost-effective, short-term received results of the NLR parameter may be used in order to be able to support the clinical diagnosis.

The present study has several limitations. Biochemistry and hemogram devices in each health center from which the data were obtained may have had different calibration settings. Besides, the present study is a retrospective design, so measurement errors, if any, could not be controlled. Since measurement, weighing, and titration were all carried out at different times, there may have been variations in temperature, pressure, and relative humidity. It is therefore not possible to identify measurement errors in the analytical phase. Due to retrospective study and ethical inappropriateness, synovial joint sample could not be aspirated from the control group. Therefore, NLR in the peripheral vein was compared between groups.

The specificity of NLR should always be looked at prospectively: in the first stage, the control group with joint interested other inflammatory events; and in the next step, patients diagnosed with distant infection. According to the obtained results, NLR may be used as a marker to monitor disease progression and indicate a subclinical inflammation in patients with SA.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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