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Neutrophil-lymphocyte and C reactive protein-albumin ratios as predictors of re-surgery in adult native knee septic arthritis

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ABSTRACT

Objectives. Septic arthritis is a medical emergency with a mortality rate of approximately 10%, the knee being the most commonly affected joint (about 50% of cases). The systemic inflammatory response caused by septic arthritis may be affected by the severity of the infection or the success of surgical joint debridement. *Materials and Methods*. This article was a retrospective study on patients admitted to our hospital (between 2013 and 2020) with septic arthritis of the knee. Patients were diagnosed based on history, examination, blood test results, and knee aspirate fluid. The patient's response to antibiotic therapy was monitored in the outpatient setting using serological markers. *Results*. Of the 48 patients included in the study, 26 were male, and 22 were female. Based on the ROC analysis, the optimal cutoff value of preoperative NLR was 8.33. The AUC was 0.782 for postoperative NLR level (95% CI,0,626–0.938; p:0.009) and 0.922 for postoperative CAR level (95% CI,0.844–0.999; p <0.001). Postoperative NLR and CAR cutoff values are 15.4 and 115, respectively. *Conclusions*. Preoperative NLR elevation in septic arthritis may be associated with recurrent surgical debridement postoperatively. In addition, postoperative NLR and CAR values can predict debridement rates in patients after septic arthritis surgery.

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Introduction

Septic arthritis is a therapeutic emergency with a mortality rate of approximately 10%. The knee is the most commonly affected joint, accounting for roughly half of all cases [1-3]. Functional disorders have been reported in approximately half of the bacterial arthritis patients after septic arthritis [4,5]. Septic arthritis is treated with joint decompression and removal of purulent material from the affected joints and prompt antibiotic treatment [6]. One of the ongoing issues in the treatment of septic arthritis is the need for surgical intervention after surgical debridement and joint irrigation in these patients [7-9].

Some routine blood count parameters have recently been investigated as potential biomarkers. These parameters include the blood neutrophil-lymphocyte ratio (NLR) (calculated by dividing the neutrophil count by the lymphocyte count) and the C Reactive Protein-Albumin Ratio (CAR) (calculated by dividing the CRP value by the albumin count). NLR and CAR have emerged as simple, low-cost, practical, and one-of-a-kind biomarkers for predicting the prognosis, severity, and complications of tumours, cardiovascular diseases, hip fractures, knee osteoarthritis, and arthroplasty surgeries, sepsis, and multiple trauma [10-14].

We hypothesize that the severity of the infection or the success of joint debridement following surgery may affect the systemic inflammatory response caused by septic arthritis infection. In this case, preoperative NLR and CAR values or postoperative NLR and CAR values may predict the possibility of re-operation in patients with septic arthritis. Performing rapid secondary surgical treatment may help to reduce joint damage and complications. For this reason, our study is to examine the preoperative and postoperative NLR and CAR values of patients who were operated on for septic arthritis and to reveal the relationship between secondary surgical interventions and these values.

Materials and Methods

This study is a retrospective study of patients admitted to our hospital between 2013 and 2020 with a knee septic arthritis diagnosis. The study received ethics committee

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approval as well as informed consent. There is no single pathognomonic sign or test to diagnose septic arthritis. Organisms in culture may represent contamination from the skin, and material that looks like infective fluid may represent a non-septic arthropathy. Other studies encountered the same issue and used a variety of definitions. These include arthritis with a positive joint fluid aspiration or culture, a strong clinical suspicion, or a definite radiological diagnosis [15-17]. Patients in our study were diagnosed with clinical septic arthritis based on their history, examination, blood test results, and knee aspiration fluid. Being an adult, having a diagnosis of septic arthritis of the knee, having a follow-up period of at least six months, and having undergone open or arthroscopic debridement were all inclusion criteria. Non-knee joint infections, periprosthetic infections, graft infections after anterior cruciate ligament surgery, superficial infections, osteomyelitis near the joint, cases treated with a serial joint puncture, non-infective inflammatory arthritis, or crystal arthropathies, malignancy history, surgery/fracture/trauma history, and pediatric cases were excluded. The study included only patients who received complete treatment for septic arthritis from a participating counsellor. Situations where microbiologists have commented that contamination is likely are excluded. All cases were planned to represent true septic arthritis using these criteria. Furthermore, it was aimed to exclude any possible interaction with other possible preconditions associated with high inflammatory markers, to exclude any conditions that could cause this, and to reveal the proper relationship between septic arthritis and inflammatory markers

Joint puncture fluid was cultured in the emergency department. At the same time, gram staining and white cell count per area were performed in joint puncture fluid for septic diagnosis. Extended broth culture cultured joint fluid on blood and chocolate agars. Tuberculosis and fungus were not routinely tested in the samples. The organisms isolated from starter or broth cultures and their associated susceptibilities were then recorded. After their first aspiration, all patients underwent open or arthroscopic washing. In operation, multiple samples were routinely collected for microbiology analysis.

The surgical procedure was typically performed with the patient under general anaesthesia. Povidone-iodine or chlorhexidine was used for sterile preparation and draping. In patients who underwent arthrotomy, anteromedially arthrotomy was performed. Following the arthrotomy, a sample of the infected material was taken and cultured. The joint was thoroughly irrigated with standard saline solution until the joint fluid was removed. When necessary, infected tissue was debrided. Typically, the arthrotomy was dressed and closed over an intra-articular drain. Anterolateral and anteromedial arthroscopy portals were used for debridement. In some cases, a superolateral portal has also been used to enter the suprapatellar sac. The culture was performed on infected joint material. The joint was irrigated thoroughly with normal saline until the fluid drained from the knee was cleared. An arthroscopic shaver performed debridement of fibrinous residue or other purulent material as needed. The joint was left with a drain, the portals were closed, and the dressing was applied.

Results

Patients were monitored in the hospital for at least 72 hours following surgery to determine the success of the initial surgical debridement. An infectious disease specialist determined the best antibiotic regimen for each patient. Any of the following signs or symptoms in the postoperative period were considered infection recurrence and failure of a single surgical debridement: persistent purulent discharge from the drain or incision site(s), increasing pain, decreased range of motion, persistent fever, or persistent elevation of inflammatory serological markers. Patients who demonstrated stable clinical improvement after 72 hours were discharged from our facility with continued antibiotic treatment. Serological markers (ESR, CRP, and CBC [complete blood count]) were routinely monitored during antibiotic treatment in the outpatient setting to assess patient response to treatment.

Throughout antibiotic treatment, outpatient infectious disease and orthopaedic follow-up were maintained (decided by infectious disease physicians based on three to twelve weeks of oral or intravenous treatment, clinical examination, and return of serological markers to near baseline values). Any increase in inflammatory markers necessitated a clinical re-evaluation. Any patient whose symptoms worsened was seen in the clinic or our emergency department. Aspiration and serological tests were carried out. Those whose infection relapsed were admitted to the hospital again, and additional debridement was performed (Table 1).

Septic arthritis has been associated with kidney disease, liver disease, cancer, diabetes, HIV infection and rheumatological conditions. It is known that these pathologies have common relations with joint infection. These comorbidities are essential in lowering patient immunity [18]. For this reason, patients' comorbidities were evaluated with the Carlson Comorbidity index [19].

Gender, age, leukocyte count (with leukocytosis defined as leukocyte count greater than 11,000 mm^3), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) values at the initial evaluation, synovial fluid Gram stain and culture results, surgical drainage number, comorbidities (including immunosuppressive conditions), Charlson comorbidity index (CCI), the period between first symptoms and surgical drainage, previous joint disease, length of hospital stay, NLR and CAR values at first emergency admission and postoperatively and joint arthrosis grading according to Kellgren-Lawrence classification were recorded from medical records. Laboratory results, arthrocentesis analyses, knee radiographs for osteoarthritis, and microbiological findings were evaluated according to the Kellgren and Lawrence scale. The type of surgical procedure and the details of the operation were recorded (Tables 2, 3).

Table 1. Distribution of basic characteristics of patients and features of surgical treatment

Variables	Single surgery (n:39)	Additional surgical procedures (n:9)	P value
Age (mean±SD)	51.38±15.08	51.11±13.87	0.06*
Gender			
Male	20(51.3%)	6(66.7%)	0.478**
Femal	19(48.7%)	3(33.3%)	
Laterality			
Right	22(56.4%)	4(44,4%)	0.713**
Left	17(43.6%)	5(55.6%)	
Kellgren-Lawrence Classification			
Grade 0	4(10.3%)	0(0.0%)	***0.021****
Grade 1	10(25.6%)	0(0.0%)	
Grade 2	18(46.2%)	4(44.4%)	
Grade 3	5(12.8%)	5(55.6%)	
Grade 4	2(5.1%)	0(0.0%)	
Type of surgery			
Arthroscopy	15(38.5%)	5(55.6%)	0.46**
Arthrotomy	24(61.5%)	4(44.4%)	
Hypertansion			
Present	14(35.9%)	6(66.7%)	0.137**
None	25(64.1%)	3(33.3%)	
Diabetes Mellitus			
Present	11(28.2%)	3(33.3%)	>0.99**
None	28(71.8%)	6(66.7%)	
Cardiovascular Disease			
Present	1(2.6%)	1(11.1%)	0.343**
None	38(97.4%)	8(88.9%)	
Chronic Obstructive Pulmonary Disease			
Present	2(5.1%)	2(22.2%)	0.155**
None	37(94.9%)	7(77.8%)	
Chronic Renal Failure			
Present	2(5.1%)	0(0.0%)	>0.99**
None	37(94.9%)	9(100.0%)	
Hipotiroidizm			
Present	4(10.3%)	2(22.2%)	0.312**
None	35(89.7%)	7(77.8%)	
ASA score****			
I	15(38.5%)	1(11.1%)	0.372***
II	11(28.2%)	4(44.4%)	
III	11(28.2%)	3(33.4%)	
IV	2(5.1%)	1(11.1%)	
Hospitalization time (mean±SD) [day]	9.23±4.68	21±11.22	<0.001*
Postoperative ICU***** stay			
Present	0(0.0%)	4(44.4%)	0.001**
None	39(100.0%)	5(55.6%)	
Carlson Comorbidity Index(mean±SD)	2.49±2.07	3.78±2.22	0.104*

*Student's t-test, **Fisher's Exact test, ***Likelihood ratio, **** American Society of Anesthesiologists
***** Intensive care unit

Table 2. Findings of the patients' preoperative and postoperative blood parameters			
Variables	Single surgery (n:39)	Additional surgical procedures (n:9)	p value
White blood cell (10^3/uL) Preoporetive Postoperative	12.21±3.94 10.69±4.12	12.56±1.71 13.54±2.85	0.798* 0.057*
Neutrophil count (10^3/uL) Preoporetive Postoperative	9.58±3.73 6.03±2.65	10.44±1.65 10.45±5.11	0.507* ***0.001****
Lymphocyte count (10^3/uL) Preoporetive Postoperative	1.82±0.66 1.64±0.57	1.11±0.68 1.37±0.33	***0.006**** 0.178
Monocyte count (10^3/uL) Preoporetive Postoperative	0.99±0.43 0.83±0.3	0.82±0.25 0.79±0.11	0.253* 0.709*
Platelet count (10^3/uL) Preoporetive Postoperative	296.1±122.3 276.5±93.1	234.4±55.7 232.8±33.5	0.149* 0.176*
ESR (mm/h) Preoporetive Postoperative	70.4±10.2 50.7±8.2	95.3±15.3 68.6±12.3	***<0.001**** ***<0.001****
CRP (mg/L) Preoporetive Postoperative	157.4±97.8 119.3±74.8	244.1±179.1 282.5±99.9	***0.04**** ***<0.001****
Albumin (g/dl) Preoporetive Postoperative	3.6±0.5 3.3±0.5	3.3±0.7 2.7±0.4	0.207* ***0.005****
NLR** Preoporetive Postoperative	5.77±2.36 4.54±3.74	12.74±6.27 8.72±6.31	***<0.001**** ***0.012****
CAR*** Preoporetive Postoperative	45.07±33.83 37.91±28.37	85.95±73.77 106.89±48.52	*0.014** *<0.001**
* Student's t-test, ** Neutrophil to Lymphocite Ratio, *** C-reactive Protein to Albumin Ratio			

Table 3. Distribution of bacteria with growth in cultures	
Type of bacteria	Number of patients (%)
Staphylococcus aureus	12(25.1%)
Staphylococcus epidermidis	1(2.1%)
Escherichia coli	2(4.2%)
β-Hemolytic streptococci	1(2.1%)
Pseudomonas aeruginosa	1(2.1%)
Coagulase-negative staphylococci	9(18.8%)
Total	**26(54.2%)**

Discussion

The critical findings of this study were that there was a statistical relationship between preoperative NLR values and postoperative NLR and CAR values and the requirement for re-surgical treatment after surgical treatment in septic arthritis. Cut-off values were 8.33 for preoperative NLR, 15.4 for postoperative NLR, and 115 for postoperative CAR.

Septic arthritis is the most severe form of acute arthritis and one of orthopaedics few clinical emergencies. Severe complications have been reported, including permanent disability due to subchondral bone loss and a mortality rate of up to 15% [20]. The number of poor prognostic indicators has a significant impact on treatment outcomes. Late treatment initiation and the time required to sterilize the joint are two critical indicators of a poor prognosis [21]. As a result, the procedure should be repeated in all patients with septic arthritis who do not improve significantly after the initial surgical procedure. This aggressive treatment strategy significantly improves the rate of recovery [22]. Re-flushing is required after septic arthritis surgery at a rate of up to 22% [23,24]. Patients who do not immediately show significant improvement, especially those with positive drainage fluid cultures, should be considered for repeat surgery. This strategy saves time and increases the likelihood of eradicating the infection. Even in patients with septic osteoarthritis, the need for joint resection and replacement can thus be prevented or delayed [25,26]. However, waiting for the decrease of inflammatory blood markers, joint fluid from the drain, and cultures when deciding to rewash and do it may prolong the treatment process. This could make the treatment less effective. In this context, NLR and CAR can be used as early diagnostic parameters when deciding to rewash.

The neutrophil/lymphocyte ratio (NLR) is a biomarker for systemic inflammation that can be easily obtained with routine blood testing at no additional cost [27]. Neutrophils respond quickly to microbial infection, dramatically increasing the number of circulating neutrophils that migrate to the affected area. Neutrophils play critical roles in the innate immune response, including directly killing pathogens via phagocytosis, releasing various cytokines, and activating T cells [9]. T lymphocytes and B lymphocytes are responsible for the link between innate and adaptive immunity and cellular and humoral immune responses to stressful events. Lymphocyte depletion reflects the intensity and duration of a stressful event and the resilience of the body's immune system and adaptability [28]. NLR measures the balance of neutrophil and lymphocyte levels in the body. In this context, the consistently high NLR group may represent patients with an ongoing severe inflammatory process caused by infection [9]. In septic arthritis, NLR values may rise as the body's systemic response to infection increases. High values of these in the preoperative and postoperative periods may provide an early prediction of the severity of the infection focus in the joint. Based on this, NLR can be used to predict the likelihood of re-operation after surgical treatment in adult patients with septic knee arthritis [29,30].

CRP has been identified as an inflammatory marker linked to trauma, inflammation, and bacterial infection. The serum albumin level is used to assess nutritional status [31]. Simultaneously, hypoalbuminemia and malnutrition may result in macrophage dysfunction [32]. CAR is one of the two protein-based inflammatory markers [12]. Studies have shown CAR to be a prognostic factor in various cancers and hip fractures [32,33]. CRP levels in septic arthritis tend to fall after successful surgical treatment, making it helpful in monitoring the response to joint infection treatment. Following surgical irrigation and antibiotic treatment, it is expected to return to normal within 1 to 2 weeks [34,35]. This, however, necessitates intermittent monitoring and may lengthen the joint's sterilization time. Re-surgical irrigation may, once again, cause the discharged patient to be delayed. This may result in increased comorbidities as a result of septic arthritis. Postoperative CAR could predict the need for repeat surgical irrigation early on. Early surgical debridement in these patients can be accomplished by delaying discharge or strict patient follow-up.

One of the striking findings of this study was the statistical relationship between the degree of knee arthrosis and rewashing according to the Kellgren-Lawrence classification. However, there was also a positive correlation between this classification and age. This situation can be interpreted as a reflection of increasing morbidity with age and decreasing immunity to radiological findings.

There are several limitations of the study. It was designed retrospectively and may have an inherent bias due to missing documentation in medical records. Different surgeons performed surgical procedures, and thus there may have been some variation in the hospital course and treatment of patients during the perioperative period. Furthermore, because some patients are culture-negative, those treated surgically are more likely to have inflammatory arthropathy rather than septic arthritis. In this study, however, generally accepted criteria were used to diagnose septic arthritis. This study, however, was designed as a pilot to see if any test thresholds were sensitive enough to be clinically helpful. Based on our findings, there are sufficiently sensitive NLR and CAR thresholds to predict re-surgery in patients with septic arthritis, but these thresholds are pretty low, so more research is needed. Despite this limitation, it is worth noting that our study is the first study examining NLO and CAR to predict re-surgery in a subset of adult patients with septic arthritis. As a result, we hope these findings will help clinicians until a more definitive study is conducted. Furthermore, even though all patients were initially treated with broad-spectrum antibiotics, individual drug allergies and operative culture sensitivities meant that the antibiotic regimen chosen could not be standardized and commenting on the efficacy of different drugs is beyond the scope of this project. However, the effectiveness and success of antibiotic treatment may influence the need for secondary surgical treatment. It is also possible that patients who had surgical debridement at our facility had an additional procedure elsewhere that was not documented in their follow-up records. Although diseases that could cause a systemic inflammatory response were excluded from the study's inclusion criteria, the patients' urinary tract or other infection foci in this retrospectively designed study were unknown. As a result, it cannot be proven that an increase in inflammatory parameters in every patient is solely due to septic arthritis. Our small sample size limits our findings' ability to reflect reality and may have resulted in an overly accurate statistical relationship. Additional prospective studies should confirm our established predictive values for secondary surgical debridement in treating acute septic arthritis.

Conclusions

Elevated preoperative NLR in septic arthritis patients may be associated with a higher risk of postoperative recurrent surgical debridement. Also, postoperative NLR and CAR values can predict re-debridement rates in septic arthritis surgery patients. More research is needed to determine whether NLR and CAR values predict re-surgical debridement in septic arthritis. Given the low cost and availability of these simple blood parameters, ratios like CAR and NLR may be practical tests for predicting and monitoring the success of surgical treatment in patients who have had septic arthritis surgery.

Author's Contribution

A.Y. designed the protocol, reviewed the literature, analyzed the data, and critically reviewed and wrote the manuscript. M.Y. and N.E. analyzed the data, reviewed the literature, and critically reviewed and wrote the manuscript. S.G. designed the protocol, collected and analyzed the data, and reviewed the literature. M.Ç. and M.A. collected and analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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