



How reliable are the synovial cell count and blood parameters in the diagnosis of septic arthritis?

Toygun Kağan Eren, MD , Cem Nuri Aktekin, MD 

Department of Orthopedics and Traumatology, Ankara Training and Research Hospital, Ankara, Türkiye

Acute arthritis is a condition that may occur as a result of many pathologies. The annual incidence of acute monoarthritis is 10 out of 100,000 in the United States.^[1] The differential diagnosis includes joint-related pathologies such as septic arthritis (SA), crystal arthropathies, reactive arthritis, transient synovitis, hemarthrosis, malignancy or extra-articular pathologies such as cellulitis and osteomyelitis.^[2] Septic arthritis is one of the orthopedic emergencies. Its incidence varies between 4 and 12 per 100,000 in different studies.^[3-6] In recent years, the incidence of SA has increased with the increase in joint interventions and diagnostic possibilities.^[7,8] Although it is most common in the knee joint, SA can occur in all joints, and most commonly spreads hematogenously.^[1]

Delay in the treatment of SA can cause irreversible cartilage damage, permanent morbidity, sepsis and even mortality.^[9,10] Therefore, the clinical aim is to make the correct diagnosis as soon as possible. While making the diagnosis of SA, many different

ABSTRACT

Objectives: This study aims to investigate the reliability of the joint fluid cell count and blood parameters compared to the culture results in the diagnosis of septic arthritis (SA).

Patients and methods: A total of 192 patients (112 males, 80 females, mean age: 60.3±19.2 years; range, 18 to 98 years) who presented with SA between January 2018 and July 2022 were evaluated retrospectively. The recorded joint fluid cell count, complete blood count (CBC), white blood cell (WBC) count, serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) and culture results were analyzed comparatively according to SA diagnosis.

Results: The most commonly involved joint was the knee joint (82.3%), which was affected in 158 patients. Thirty-six (18.8%) of the patients who underwent joint aspiration had positive culture result. The cultures were positive in 10 (35.7%) of 28 patients with synovial WBC value greater than 50,000/mm³, while 26 (15.9%) of 164 patients with a synovial WBC value less than 50,000/mm³ had positive culture results (p=0.013).

Conclusion: Patients with SA may present variable blood and synovial parameters. Making decision based on the commonly used synovial WBC count cut-off value of 50,000/mm³ may lead to misdiagnosis. To avoid misdiagnosis or delay in treatment, it is of utmost importance not to exclude the diagnosis acutely, and suspicion of SA should remain even with unlikely values.

Keywords: Cell count, joint aspirate culture, septic arthritis, synovial fluid, white blood cells.

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Correspondence: Toygun Kağan Eren, MD. Ankara Eğitim ve Araştırma Hastanesi, Ortopedi ve Travmatoloji Kliniği, 06230 Altındağ, Ankara, Türkiye.

E-mail: toyguneren@gmail.com

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diagnostic tools such as blood parameters, cell count, biochemical markers in synovial fluid sample, microscopic examination of synovial fluid, joint aspirate culture and polymerase chain reaction (PCR) are used.^[11-13] Despite the availability of all these diagnostic options, the definitive diagnosis cannot be made immediately in acute presentation.^[14] At the time of admission of patients, a preliminary diagnosis is made by evaluating the patient's blood values and joint fluid values together with their clinical findings, and medical intervention is made according to this preliminary diagnosis.^[15] Although it is a

more reliable parameter for definitive diagnosis, the long time it takes for joint aspirate culture to give results may delay the treatment of joint infection.^[16] The typical synovial white blood cell (WBC) count threshold has been considered as 50,000/mm³, as the values higher than 50,000/mm³ is considered as indicative for SA.^[12,17] Also the American Rheumatism Association (ARA) has classified WBC into categories and considered the values as infectious which are higher than 50,000/mm³.^[18,19] However, it has also been reported that this cell count may not always yield reliable results.^[11,12]

In the present study, we aimed to compare the synovial cell count and the blood values of patients according to the diagnosis of SA and to evaluate how sufficient the information obtained in the cell count was to make the correct diagnosis.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ankara Training and Research Hospital, Department of Orthopedics and Traumatology between January 2018 and July 2022. The data of the patients who were admitted with the symptoms of acute arthritis and evaluated with the suspicion of SA were included. Patients with signs of acute joint arthritis such as painful and swollen joint, patients older than 18 years of age, patients whose joint fluid cell count was

performed, and who had complete blood count (CBC), serum erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP) tests were included in the study. Patients under the age of 18 years, patients who previously underwent arthroplasty in the same joint, patients with a previous history of SA in the same joint, patients who had a diagnosis of malignancy, lymphoma or immune deficiency and patients with missing data were excluded from the study. A total of 192 patients (112 males, 80 females, mean age: 60.3±19.2 years; range, 18 to 98 years) who presented with SA were included.

The CBC, ESR, and CRP levels of the patients, cell count in synovial fluid, and the results of the all available cultures including joint aspirate fluid, intraoperative joint fluid, and tissue samples were evaluated. These parameters were classified according to different cut-off values and comparisons were made between the groups. According to laboratory which the data of the present study were based, the normal range of values was 3.5-10.5×10⁹/L for WBC, 5-20 mm/h for ESR, and 0-5 mg/L for CRP. The cut-off values were 10.5×10⁹/L for blood WBC, 20 mm/h for ESR, 100 and 200 mg/L for serum CRP, and 50,000/mm³ and 100,000/mm³ for synovial WBC count. The culture results of the patients were considered as contaminated in consensus with the infectious disease specialists. In the contamination decision, the growth period of the culture, the type

	n	%	Mean±SD
Age (year)			60.3±19.2
Sex			
Male	112	58.3	
Female	80	41.7	
Blood WBC (×10 ⁹ /L)			10.03±3.39
Erythrocyte sedimentation rate (mm/h)			38.31±30.49
C-reactive protein (mg/L)			84.57±93.48
Synovial WBC (cells/mm ³)			28456±64717
Synovial RBC (cells/mm ³)			20621±88111
Involved joint			
Knee	158		82.3
Ankle	14		7.3
Wrist	10		5.2
Shoulder	7		3.6
Elbow	3		1.6
Total	192	100	

SD: Standard deviation; WBC: White blood cells; RBC: Red blood cells

TABLE II

Isolated pathogens from the cultures of patients

Pathogen	n
<i>Staphylococcus</i> species	18
<i>Staphylococcus aureus</i> (n=15)	
Coagulase negative <i>staphylococcus</i> (n=3)	
<i>Escherichia coli</i>	5
<i>Streptococcus</i> species	4
<i>Micrococcus</i> species	2
<i>Bacillus</i> species	3
<i>Klebsiella pneumoniae</i>	2
<i>Acinetobacter baumannii</i>	1
<i>Citrobacter braakii</i>	1

of growth medium, the type of bacteria, normal skin flora, the clinical condition of the patient and successful treatment outcome without the surgical intervention were taken into consideration. Antibiotic treatment was not started, until obtaining intraoperative culture samples (if surgery was planned according to primary diagnosis) or negative culture results (if primary diagnosis is not SA depending on the preliminary diagnosis. In case that the patient with primary SA diagnosis did not accept surgical treatment, antibiotic treatment was initiated immediately.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 21 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean \pm standard deviation (SD), median (min-max) or number and frequency, where applicable. The Shapiro-Wilk test was used to assess normality. The chi-square test was used to compare the categorical variables. Sensitivity, specificity, and likelihood ratio

(LR) for different cut-off values regarding blood parameters were investigated in 95% confidence intervals (95% CIs). The Student t-test and analysis of variance (ANOVA) tests were used for parametric distribution and the Mann-Whitney U test and Kruskal-Wallis test were used to for non-parametric distribution to compare the groups. A *p* value of <0.05 was considered statistically significant.

RESULTS

The most commonly involved joint was the knee joint (82.3%), which was affected in 158 patients. The demographic characteristics of the patients are summarized in Table I.

Culture results were considered positive in 36 (18.8%) of 192 patients who underwent joint aspiration. *Staphylococcus* spp. were the most common pathogen cultured in half of the patients (n=18). Among them, *Staphylococcus aureus* was found to be the most common growth pathogen (n=15) (Table II). Coagulase-negative *Staphylococci* were found in three culture-positive patients. Also, there were another three patients which were considered as contamination with growth of coagulase-negative *Staphylococci*.

The mean blood WBC value of the patients was $10.02 \pm 3.38 \times 10^9/L$, the ESR was 38.31 ± 30.49 mm/h, and the CRP value was 84.56 ± 93.48 mg/L. The mean synovial fluid WBC count value of the patients was $28,456 \pm 64,717/mm^3$, and the mean red blood cell (RBC) count value was $20,621 \pm 88,110/mm^3$.

The blood WBC count of culture positive patients was significantly higher than the patients with negative culture result ($10.86 \times 10^9/L$ vs. $9.58 \times 10^9/L$) (*p*=0.034). There was no other statistically significant variable between the groups regarding age, ESR, CRP, synovial WBC or synovial RBC compared to

TABLE III

Comparison of blood and synovial fluid parameters according to culture results

	Culture negative (n=156)		Culture positive (n=36)		<i>p</i>
	Median	Min-Max	Median	Min-Max	
Age (year)	61	23 -98	60	18-92	0.758
Blood WBC ($\times 10^9/L$)	9.58	4.12-23.23	10.86	4.82-20.6	0.034
Erythrocyte sedimentation rate (mm/h)	30	1-155.8	29	3-115	0.834
C-reactive protein (mg/L)	51.44	0.7-412	65.4	0.63-472.6	0.166
Synovial WBC (cells/mm ³)	9440	0-230400	12400	0-676000	0.149
Synovial RBC (cells/mm ³)	300	0-896000	1440	0-166000	0.084

WBC: White blood cells; RBC: Red blood cells.

TABLE IV
Comparison of groups according to cut-off values of different parameters

	Culture negative	Culture positive	<i>p</i>	Positive LR	Negative LR	Sensitivity	Specificity
	n	n				%	%
Blood WBC ($\times 10^9/L$)							
<10.500	95	15	0.036	1.49	0.68	58.3	60.9
≥ 10.500	61	21					
ESR (mm/h)							
<20	46	12	0.651	0.95	1.13	66.7	2.5
≥ 20	110	24					
CRP (mg/L)							
<10	29	7	1.000	0.99	1.05	80.6	18.6
≥ 10	127	29					
<100	113	19	0.022	1.71	0.73	47.2	72.4
≥ 100	43	17					
<200	143	27	0.005	3.01	0.82	25	91.7
≥ 200	13	9					
Synovial WBC (cells/mm³)							
<50000	138	26	0.013	2.42	0.82	27.8	88.5
≥ 50000	18	10					
<100000	151	30	0.002	5.22	0.86	16.7	96.8
≥ 100000	5	6					
Total	156	36					

WBC: White blood cells; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RBC: Red blood cells; LR: Likelihood ratio.

the culture results (Table III). When the patients were divided into groups according to the results of WBC count in the synovial fluid, 164 (85.4%) patients had a WBC value less than 50,000/mm³, 17 (8.9%) patients between 50,000-100,000/mm³, and 11 (5.7%) patients greater than 100,000/mm³. While positive culture was observed in 10 (35.7%) of 28 patients with synovial WBC value greater than 50,000/mm³, 26 of 164 patients with a synovial WBC value less than 50,000/mm³ had positive culture with a lower rate of 15.9% (*p*=0.013). Positive LR was 1.49 for blood WBC count equal or higher than 10.5 $\times 10^9/L$; 0.95 for ESR equal or higher than 20 mm/h; 1.71 for CRP value equal or higher than 100 mg/L; 3.01 mg/L for CRP value equal or higher than 200 mg/L; 2.42 for synovial WBC count equal or higher than 50,000/mm³; and 5.22 for synovial WBC count equal or higher than 100,000/mm³. There were statistically significant differences between the groups when the cut-off values were considered as 10.5 $\times 10^9/L$ for blood WBC count, 100 and 200 mg/L for CRP, 50,000/mm³ and 100,000/mm³ for synovial WBC (Table IV).

DISCUSSION

The main finding of the present study was that 26 (15.8%) of 164 patients who had a synovial WBC count less than 50,000/mm³ exhibited positive culture results. In line with the present study, Baran et al.^[20] reported that 29% of their patients which had a synovial WBC count less than 50,000/mm³ were diagnosed with SA. From a different perspective, McGillicuddy et al.^[21] showed that a synovial WBC count was less than 50,000/mm³ in 39% of the SA patients in their series. Similarly, Luo et al.^[12] found that 38.8% of the patients with SA had a synovial WBC count of <50,000/mm³. Li et al.^[22] also found that 36% of their patients with SA had a joint WBC count less than 50,000/mm³. Accordingly, the authors concluded that these values did not rule out SA accurately. In the present study, the ratio was even higher; 72% (26/36) of the culture-positive patients had a synovial WBC value less than 50,000/mm³. Obviously, the number of patients was different between culture-positive and culture-negative

patient groups (36 *vs.* 156 patients, respectively). However, this may be a warning for common belief that patients with SA have a synovial WBC count higher than 50,000/mm³. Despite the statistically significant difference between the groups and positive LR when the cut-off value of WBC count was established as 50,000/mm³, it is not safe to exclude SA in this group of patients, due to the high culture-positive patient ratio. Ruling out SA with synovial cell count alone would lead the physician to overlook or delay the treatment of an orthopedic emergency.^[23]

In the current study, we also compared the sensitivity and specificity of synovial WBC cut-off value with the previous studies.^[11,21,24-28] Sensitivity was 27.8% and specificity was 88.5% in the present study using a cut-off value of 50,000/mm³. Positive and negative LRs were 2.42 and 0.82, respectively. Previous studies reported different values for sensitivity between 31 and 70%, for specificity between 74 and 97%, for positive LR between 1.3 and 19.3, and for negative LR between 0.38 and 0.92.^[11,21,24-28] According to these results, particularly low sensitivity of the 50,000/mm³ cut-off draws attention. When the cut-off value was increased to 100,000/mm³, lower sensitivity (range, 6 to 31); higher specificity (range, 94 to 100), positive (range, 4.7 to infinite), and negative LR (range, 0.75 to 0.94) were reported in previous studies.^[22,24,27-29] These findings are comparable with the present study, as the sensitivity was 16.7, specificity was 96.8, and positive and negative LRs were 5.22 and 0.86, respectively. In line with previous studies, the findings of the present study indicate that ruling out of the diagnosis is not reliable based on these synovial WBC count cut-off values.^[11,21,24-28] However, high specificity values of the synovial WBC counts are confirmatory in case of serious suspicion and makes the test valuable, particularly for differential diagnosis.

Erythrocyte sedimentation rate has been frequently used in the diagnosis of SA. Sensitivity was 66.7% and specificity was 2.5% in the present study, when the cut-off value was considered as 20 mm/h. Although high sensitivity has been reported in previous studies, low specificity of this parameter was the main concern.^[1,14,22,26,30,31] Li et al.^[22] reported 11% specificity with a similar cut-off value. Jeng et al.^[31] found that specificity was 29% when the cut-off value was considered as 30 mm/h. It was also reported that specificity was only 42%, even the cut-off value was considered as 50 mm/h.^[26] Despite high sensitivity, low specificity suggests that ESR values alone do not provide reliable information in the diagnosis.

Furthermore, serum CRP levels are used widely in SA diagnosis and have similar drawbacks, particularly when the threshold is accepted as 10 mg/L. Previous studies have shown high sensitivity and low specificity.^[30,32] Positive LR was even lower than 1 and the cut-off value of 10 mg/L did not provide information in the present study. High specificity was only available with a cut-off value of 200 mg/L. Martinot et al.^[26] reported 83% specificity and 4.5 positive LR with a cut-off value of 150 mg/L. In line with the previous studies, the present findings indicate that particularly low CRP values are not reliable in the diagnosis of SA. High values should arouse serious suspicion of SA.

In the present study, culture results were chosen as diagnostic criteria after the exclusion of contaminated cultures, consistent with previous studies.^[12,20,33] In some studies, the diagnostic criteria were the presence of pus or Newman criteria.^[12,17] However, using these criteria, patients who do not actually have SA would be considered as SA and, therefore, the gold standard is the culture result. On the other hand, when the diagnosis is made based on culture results alone, both treatment can be delayed and culture-negative SA can be overlooked. Culture is imperfect at the time of diagnosis and its sensitivity varies between 75 and 95%.^[17,34] Visser and Tupper^[15] recommended that acute monoarthritis should be considered infectious until proven otherwise. It can be recommended for the physicians to make a preliminary diagnosis according to clinical suspicion and rapid diagnostic tools, and to approach SA like acute abdomen; it is crucial not to overlook the fact that untreated SA can have catastrophic consequences.^[23] In addition, we need more reliable diagnostic tests with higher sensitivity and specificity than culture to obtain more accurate results while examining both the definitive diagnosis and the natural history of the disease. The PCR can be useful in this regard. It has been reported that PCR may be more sensitive in the diagnosis of SA.^[35] Carter et al.^[13] also reported a higher bacterial detection rate in children using the PCR compared to joint fluid culture alone. Also, with the use of PCR, the physicians can reach the diagnosis reasonably fast, as it can give comparable results with culture in 3 h.^[16]

Nonetheless, the study has several limitations. First, the study design was single-center and retrospective and, therefore, it is more prone to recall bias. Second, the detection of crystals is unavailable in our center. This may have provided more information, particularly regarding the cases

with negative culture result. Cases with no growth in culture may have affected the results, however, the most reliable and objective criterion was considered as culture in the diagnosis of SA. In addition, although we excluded patients with malignancy or immunodeficiency, the wide age range of the patients and the fact that chronic diseases such as diabetes may affect the immune response may have affected the immune response.

In conclusion, patients with SA may present variable blood and synovial parameters. Making decision based on the commonly used synovial WBC count cut-off value of 50,000/mm³ may lead to misdiagnosis. To avoid misdiagnosis or delay in treatment, it is of utmost importance not to exclude the diagnosis acutely and suspicion of SA should remain even with unlikely values. Clinical follow-up of these patients should be continued and culture results should be followed.

Ethics Committee Approval: The study protocol was approved by the Ankara Training and Research Hospital Clinical Research Ethics Committee (date: 07.09.2022, no: 1035). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception, design, literature review, writer: T.K.E.; Supervision, data collection and/or processing, analysis and/or interpretation, critical review: C.N.A.

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