European Review for Medical and Pharmacological Sciences 2023; 27: 1278-1287

Acute monoarthritis in children: clinical and laboratory factors distinguishing septic arthritis from noninfectious inflammatory arthritis

Ö. BAYRAK DEMİREL[1], M. DEMİREL[2], R.N. ÖMEROĞLU[3], S. HANÇERLİ TÖRÜN[4], F. BİLGİLİ[2], A. KILIÇ[5]

[1]Istanbul University, Institute of Child Health, Istanbul, Turkey
[2]Department of Orthopedics and Traumatology, [3]Department of Pediatrics, Division of Pediatric Rheumatology, [4]Department of Pediatrics, Division of Pediatric Infectious Diseases, [5]Department of Pediatrics, Division of General Pediatrics, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey

Abstract. – OBJECTIVE: Distinguishing septic arthritis from specific inflammatory arthritis in children with acute monoarthritis can be a clinical challenge. This study aimed to assess the diagnostic performance of presenting clinical and laboratory findings for distinguishing septic arthritis from common forms of noninfectious inflammatory arthritis in children with acute monoarthritis.

PATIENTS AND METHODS: Children presented for the first episode of monoarthritis were retrospectively reviewed and then divided into two groups: (1) the septic group, 57 children with true septic arthritis, and (2) the non-septic group, 60 children with several types of noninfectious inflammatory arthritis. Several clinical findings and serum inflammatory markers on admission were documented.

RESULTS: Univariate analyses demonstrated that body temperature, weight-bearing status, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WCC), absolute neutrophil count (ANC), and neutrophil percentage (NP) levels were significantly higher in the septic group than in the non-septic group ($p<0.001$ for each variable). Based on the ROC analysis, optimum diagnostic cut-off values were 63 mg/L for CRP, 6,300/mm^3 for ANC, 53 mm/h for ESR, 65% for NP, 37.1°C for body temperature, and 12,100/mm^3 for WCC. While children with no presenting factor had a 4.3% risk of having septic arthritis, those with six predictors had a risk of 96.2%.

CONCLUSIONS: A CRP level of ≥63 mg/L is the best independent predictor of septic arthritis among the commonly used serum inflammatory markers (ESR, WCC, ANP, NP). It should be borne in mind that a child with zero predictors may still have a 4.3% risk of septic arthritis. Thus, clinical assessment is still imperative in managing children presenting with acute mono-arthritis.

Key Words:
Septic arthritis, Noninfectious arthritis, Inflammatory arthritis, Pediatric monoarthritis, C-reactive protein, Predictive criteria.

Introduction

Septic arthritis in children is often caused by bacteremia and typically presents as an acute monoarthritis of the large joints such as the knee, hip, and ankle[1]. Acute monoarthritis may also be a manifestation of noninfectious inflammatory arthritis, including juvenile idiopathic arthritis (JIA), reactive arthritis, transient synovitis, etc[2].

In children with acute monoarthritis, distinguishing septic arthritis from common forms of noninfectious inflammatory arthritis is imperative as treatment options and prognosis of these disorders are markedly different[2,3]. Septic arthritis represents an emergency that requires early diagnosis, adequate surgical drainage, and proper antibiotic therapy to prevent serious complications and permanent damage to the affected joint[4]. In contrast, children with noninfectious inflammatory arthritis are typically managed by a pediatric rheumatologist based on specific treatment protocols, consisting of nonsteroidal anti-inflammatory drugs, corticosteroids, and biologic agents[2]. Nonetheless, septic arthritis in the pediatric population poses a diagnostic challenge to clinicians, with no single test available to accurately identify patients with acute monoarthritis[3,4].

The diagnosis of septic arthritis is mainly established based on clinical findings and complementary laboratory tests. Positive sy-

Corresponding Author: Mehmet Demirel, MD; e-mail: dr88.mehmet.demirel@gmail.com

Table I. Eligibility criteria for the inclusion and exclusion of participants.

Inclusion criteria	Exclusion criteria
• A diagnosis of acute non-traumatic monoarthritis (septic arthritis or specific inflammatory arthritis) • The diagnosis of true septic arthritis • An age between 1 and 16 years • Admission to hospital for a first episode of arthritis • Onset of symptoms less than a week prior to admission (acute onset) • Availability of medical records and laboratory findings within the first day of admission	• Cases with documented sepsis and secondary arthritis • Concomitant osteomyelitis • Concomitant trauma or fracture • Prior anti-inflammatory treatment • Underlying immunosuppressive conditions such as: ◦ Hematological malignancy or disorder, ◦ Solid neoplasm, ◦ Chronic renal failure, ◦ HIV- or drug-induced immunosuppression.

novial fluid culture is the only definitive diagnostic laboratory test, but culture results can be false negative[5] and are not usually available for twenty-four hours and more[6,7]. Easily administered serum inflammatory markers such as white blood cell count (WCC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are still widely used in diagnosing this complex clinical scenario. However, to our knowledge, evidence from the literature is scarce regarding the diagnostic cut-off values and diagnostic performance characteristics of these inflammatory markers in predicting septic arthritis.

In this study, we compared clinical and laboratory findings between septic arthritis and common forms of noninfectious inflammatory arthritis in children with acute monoarthritis. We aimed to:

1) determine optimum diagnostic cut-off levels for presenting clinical, and laboratory findings,
2) evaluate their diagnostic performance for distinguishing septic arthritis from specific inflammatory arthritis,
3) develop a probability algorithm for the prediction of septic arthritis in children presenting with acute monoarthritis.

Patients and Methods

Study Population and Eligibility Criteria

Children aged 1 to 16 years who were presented to a Tertiary Care Medical Institution between 2005 and 2019 for the first episode of acute monoarthritis lasting for less than a week were retrospectively reviewed. The electronic medical archives of the Orthopedics and Pediatric Rheumatology Departments were used to identify the study population.

Based on the eligibility criteria (Table I), after 42 children were excluded, the remaining 117 children were included in the study and categorized into two groups based on the final diagnosis: (1) the septic group, children diagnosed with true septic arthritis, and (2) the non-septic group, children diagnosed with a form of noninfectious inflammatory arthritis (Figure 1). Septic arthritis was defined as true septic cases detected with a positive synovial fluid culture or a positive synovial fluid gram-staining based on the definition of Kocher et al[8]. Inflammatory arthritis was regarded as acute onset, non-traumatic, specific inflammatory arthritis. The institutional Ethical

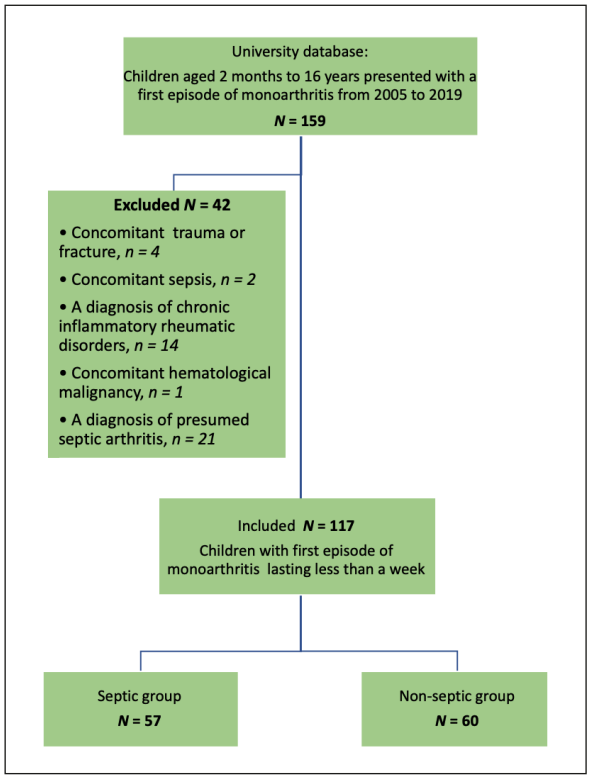

Figure 1. Flow chart of the study participants.

Committee approved this study protocol on human research (Ethical permit number 2018/1057), and data collection was in accordance with the guidelines of the Declaration of Helsinki.

Diagnosis and Management

In the septic group, all children were diagnosed and treated with surgical drainage and appropriate antibiotic therapy performed by orthopedic surgeons. In the non-septic group, after ruling out septic arthritis at the emergency room visit, children with acute monoarthritis were referred to the Department of Pediatric Rheumatology. Several types of specific inflammatory arthritis were then diagnosed and treated accordingly by pediatric rheumatologists.

Outcome Measures

We retrospectively collected the following data from medical and laboratory records of children at the time of their first admission.

Clinical variables

Body temperature (degrees Celsius) was measured using a tympanic thermometer at the emergency room visit. Weight-bearing status was determined based on the clinical history of children with lower limb septic arthritis. "Weight-bearing" was defined as walking with an abnormal gait or limping[7].

Laboratory variables

The following serum inflammatory markers were documented: C-reactive protein (CRP) (mg/L), erythrocyte sedimentation rate (ESR), white blood cell count (WCC) (/mm^3), absolute neutrophil count (ANC) (/mm^3), absolute platelet count (APC) (10^9/L), and neutrophil percentage (NP) (%).

Statistical Analysis

Statistical software package SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for analysis. Statistical significance was set at $p<0.05$. The test for normality of the variables was done by Shapiro-Wilk Test. Descriptive data are given as frequencies, percentages, means, and standard deviations or medians and ranges (minimum and maximum). The power analysis before the study showed that a minimum of 40 patients per group was needed to detect significant differences between the two groups, with a power of 80% at a 0.05 significant level.

In univariate analysis, comparisons of parametric data were undertaken using paired sample *t*-test for normally distributed variables and Mann-Whitney U test for non-normally distributed ones. Comparisons of non-parametric data were made using the Chi-square test and Fisher's exact test. Receiver operating characteristic (ROC) curves were generated to determine the variables' optimum diagnostic cut-off values. The areas under the ROC curves (AUCs) were calculated to compare their overall predictive performance for septic arthritis. The AUC values were interpreted as follows: 0.5-0.7=minimal; 0.7-0.9=moderate; >0.9=high discriminatory power[9,10]. The diagnostic performance of the respective cut-off values was measured by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A multivariate logistic regression analysis was conducted to identify independent predictors of septic arthritis.

Results

Baseline Data

The septic group included 57 children (28 girls, 29 boys), and the non-septic group had 60 children (30 girls, 30 boys). The mean age on admission was 83 months (range=12-186) in the septic group and 103 months (range=17-189) in the non-septic group. Demographic data of study participants are given in Table II.

Table II. Demographic characteristics of the study participants.

Characteristic		Septic group (57 children)	Non-septic group (60 children)	*p*-values
Age on admission (month)	Min-Max	12-186	17-189	0.09[a]
	(Median)	88	88	
	Mean ± SD	83 ± 54	103 ± 57	
Gender	Girl/Boy	25/32	30/30	0.067[b]
Side	Right/Left	27/30	33/27	0.409[b]

[a]Student *t*-test; [b]Pearson Chi-square test. Statistical significance was set at $p < 0.05$.

Table III. Location of affected joints, n (%)*.

	Septic group (57 joints)	Non-septic group (60 joints)
Knee	34 (59.6)	30 (50)
Hip	16 (28.1)	11 (18.3)
Ankle	2 (3.5)	16 (26.7)
Shoulder	2 (3.5)	0 (0)
Elbow	3 (5.3)	3 (5)

*Fisher's exact test was used for the comparison, and a significant difference was observed (p = 0.002).

In the septic group, of 57 children, 36 (63%) exhibited positive culture results. The most common pathogens identified were methicillin-sensitive *Staphylococcus aureus* in 22 children (61%), *Streptococcus pneumoniae* in 9 (25%), and methicillin-resistance *Staphylococcus aureus* in 5 (14%). The remaining 21 children were not identified by positive joint fluid culture, but all had positive gram stains of joint fluid demonstrating gram-positive cocci.

In the non-septic group, the underlying diagnosis was oligoarticular juvenile idiopathic arthritis (JIA) in 32 children (53%), enthesitis-related arthritis in 12 (20%), familial Mediterranean fever in 7 (12%), toxic synovitis of the hip in 5 (8%), psoriatic arthritis in 2 (3%), polyarticular JIA in 1 (2%), and systemic JIA in 1 (2%).

Although the most common joint involved was the knee in both groups, the second most commonly involved joint was the hip in the septic group, but the ankle in the non-septic group (Table III). In terms of the location of affected joints, a statistically significant difference was observed between the two groups (p=0.002).

Univariate Analysis: Comparison of Clinical and Laboratory Measures

The septic group significantly differed from the non-septic group concerning seven measures: body temperature, weight-bearing status, CRP, ESR, WBC count, ANC, and NP (Table IV).

The mean body temperature was significantly higher in the septic group (37.55 ± 0.88°C) than in the non-septic group (36.72 ± 0.9°C) (p=0.001; p<0.01). In the septic group, all the children with lower limb septic arthritis failed to bear weight on the affected limb. In the non-septic group, while 36 children (60%) developed non-weight bearing, the remaining 21 children were able to bear on their affected limbs. Non-weight bearing status was significantly higher in the septic group than in the non-septic group (p=0.001; p<0.01).

Except for APC, all other serum inflammatory markers, i.e., CRP, ESR, WBC count, ANC, NP, were significantly higher in the septic group compared to the non-septic group (p=0.001; p<0.01).

ROC Analysis: Diagnostic Cut-Off Points and Overall Predictive Performance

Measures differing significantly with a p-value lower than 0.01 in the univariate analysis were chosen as candidates for the ROC analysis. In-

Table IV. Comparative analyses of laboratory parameters between septic and non-septic groups.

		Septic group	Non-septic group	p-values*
Body temperature (°C)	Min-Max Mean ± SD	36-39 37.55 ± 0.9	36-38.1 36.72 ± 0.65	0.001**
CRP (mg/L)	Min-Max Mean ± SD	5-185 89.79 ± 47.97	7-181 41.44 ± 37.25	0.001**
ESR	Min-Max Mean ± SD	13-126 70.16 ± 29.72	2-92 34.78 ± 23.79	0.001**
WBC count (/mm^3)	Min-Max Mean ± SD	2,100-34,900 14,365.26 ± 6,035.31	4,440-20,800 9,877.83 ± 3,652.59	0.001**
ANC (/mm^3)	Min-Max Mean ± SD	1,600-24,300 9,787.37 ± 4,489.91	1,600-16,100 5,563.50 ± 2,991.99	0.001**
NP (%)	Min-Max Mean ± SD	41-81 66.81 ± 8.98	25-82 54.50 ± 13.32	0.001**
APC (10^9/L)	Min-Max Mean ± SD	161-589 345 ± 95	152-692 348 ± 111	0.859

CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; WBC = White blood cells; ANC = Absolute neutrophil count; NP = Neutrophil percentage; APC = Absolute platelet count. *Mann-Whitney U Test; **p < 0.01.

deed, the mean APC was higher in the septic group, but this difference reached no statistical significance (p=0.859), and thus APC was not included in the ROC analysis. Also, since weight-bearing status is a binary categorical variable (yes/no), it was considered inappropriate for ROC analysis[11].

The optimum diagnostic cut-off values were as follows (Figure 2):

- 63 mg/L for CRP (AUC: 0.817; SE: 0.039; 95% CI: 0.634-0.913),
- 6,300/mm^3 for ANC (AUC: 0.797; SE: 0.043; 95% CI: 0.636-0.912),
- 53 mm/h for ESR (AUC: 0.794; SE: 0.043; 95% CI: 0.632-0.902),
- 65% for NP (AUC: 0.782; SE: 0.044; 95% CI: 0.633-0.905),
- 37.1°C for body temperature [AUC: 0.757; standard error (SE): 0.047; 95% confidence interval (CI): 0.552-0.894],
- 12,100/mm^3 for WCC (AUC: 0.754; SE: 0.046; 95% CI: 0.554-0.898).

All the measures exhibited moderate discriminatory power for distinguishing septic arthritis from specific inflammatory arthritis based on the above ROC-AUC values. CRP was of the best overall predictive performance, followed by ANC, ESR, NP, body temperature, and WCC (Figure 2).

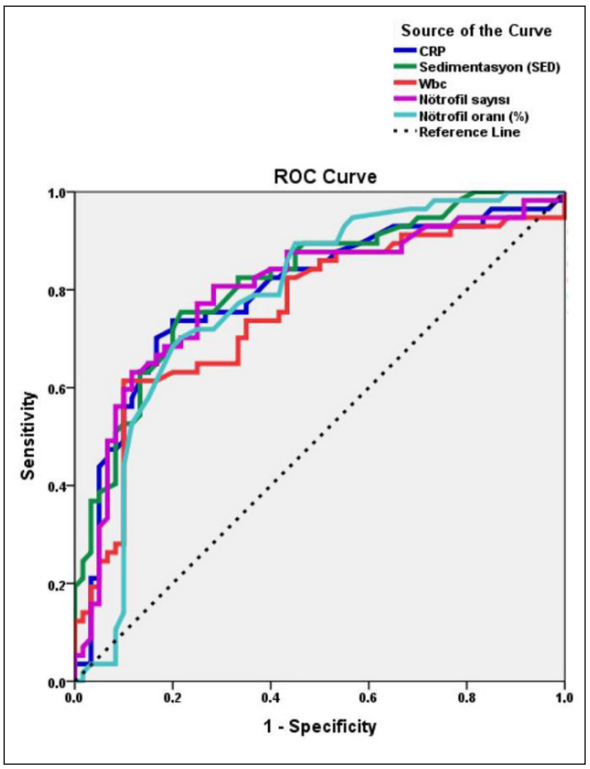

Figure 2. Receiver operating characteristic curves for CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), WBC (white blood cell count), ANC (absolute neutrophil count), and NP (neutrophil percentage). CRP, area under the curve (AUC): 0.817; standard error (SE): 0.039; 95% confidence interval (CI): 0.634-0.913. ANC, AUC: 0.797; SE: 0.043; 95% CI: 0.636-0.912. ESR, AUC: 0.794; SE: 0.043; 95% CI: 0.632-0.902. NP, AUC: 0.782; SE: 0.044; 95% CI: 0.633-0.905. Body temperature, AUC: 0.757; SE: 0.047; 95% CI: 0.552-0.894. WCC, AUC: 0.754; SE: 0.046; 95% CI: 0.554-0.898.

Diagnostic Performance of the Respective Cut-Off Values

The diagnostic performance characteristics of the respective cut-off values are presented in Table V. In predicting septic arthritis, while the CRP level of ≥63 mg/L demonstrated the highest specificity and positive predictive value (80%, and 78%, respectively), WCC showed the lowest specificity (63%). Whereas ANC had the highest sensitivity and negative predictive value (80% and 80%, respectively), WCC illustrated the lowest sensitivity and negative predictive value (63% and 70%, respectively).

Multivariate Analysis

Variables found to be statistically significant at a p-value lower than 0.1 in the univariate model,

Table V. Diagnostic performance characteristics of clinical and laboratory parameters for predicting septic arthritis.

Performance	Body temperature (≥ 37.1°C)	CRP (≥ 63 mg/L)	ESR (≥ 53 mm/h)	WCC (≥ 12,100 mm^3)	ANC (6,300 /mm^3)	NP (≥ 65%)
Sensitivity	75	74	75	63	80	70
Specificity	77	80	80	78	72	78
Positive predictive value	75	78	77	75	73	75
Negative predictive value	77	76	77	70	80	73

CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; WCC = White blood cells count; ANC = Absolute neutrophil count; NP = Neutrophil percentage. Data are expressed as percentages.

including CRP, ANC, ESR, NP, body temperature, and WCC, were entered into the multivariate logistic regression analysis at their optimum diagnostic cut-off points, in order to measure their adjusted effects on the diagnosis of septic arthritis. Then, four significant independent predictors that were strongly associated with the risk of developing septic arthritis were identified:
1) CRP ≥63 mg/L,
2) ESR ≥53 mm/h,
3) WCC ≥12,100/mm^3,
4) body temperature >37.1°C.

Otherwise, ANC and NP were not significantly associated with the outcome (p>0.05; Table VI).

Following univariate and multivariate analyses, a probability algorithm for predicting septic arthritis was developed using the six presenting factors differing significantly in the univariate analysis between children with septic arthritis and those with specific inflammatory arthritis. The predicted probability of a child having septic arthritis was calculated as a function of the number of these positive presenting factors (Table VII). To assess the fit of the model, the coefficient of determination (R2) was calculated, which was 0.863, indicating the good fit of the model to the study data and statistically significant regression.

Discussion

In children presenting acute monoarthritis, distinguishing septic arthritis from common forms of noninfectious inflammatory arthritis is essential as treatment options and prognosis of these disorders are markedly different[2,3]. However, no single serum laboratory test enables a rapid and reliable identification of early bacterial infection[2-4]. Positive synovial fluid culture is the only definitive diagnostic laboratory test, but culture results can be false negative[5] and are not usually available for twenty-four hours and more[6,7]. Easily administered serum inflammatory markers such as WCC, CRP, and ESR are still widely used today in assisting the diagnosis of this complex clinical scenario. However, according to our literature review, evidence for these inflammatory markers' diagnostic cut-off levels and diagnostic performance characteristics in predicting septic arthritis is limited and inconsistent in the medical literature. In the present study, we primarily sought to identify optimum diagnostic cut-off values for the commonly used laboratory findings and then determine the predicted probabilities for septic arthritis as per the predictor count to help clinicians manage children with acute monoarthritis.

Several multivariate algorithms (Table VIII) have been proposed to distinguish septic arthritis from transient synovitis of the hip in children with hip irritability[4,7,8,12,13]. Kocher et al[8] first identified four independent predictors of septic arthritis in their retrospective study:
1) a history of fever ≥38.5°C,
2) non-weight bearing status,
3) an ESR ≥40 mm/hr,
4) a serum WBC count of >12,000 cells/mm^3 (>12.0 × 10^9/L).

The authors determined the predicted probability of septic arthritis to be lower than 0.2% for zero predictors, 3% for one predictor, 40% for two predictors, 93.1% for three predictors, and 99.6% for four predictors. Kocher et al[12] later prospectively tested the diagnostic performance of their predictive criteria and found the performance reduced compared to the previous one but

Table VI. Multivariate analysis: septic arthritis *vs.* specific inflammatory arthritis.

			95% confidence interval	
	p-value	Odds ratio	Lower limit	Upper limit
CRP (≥ 63 mg/L)	0.001*	11.2	3.4	35.9
ESR (≥ 53 mm/h)	0.001**	7.4	2.3	23.7
Body temperature (≥ 37.1°C)	0.011**	4.5	1.3	14.6
WCC (≥ 12,100 mm^3)	0.011*	4.4	1.3	13.8
ANC (6,300/mm^3)	0.09	2.7	1.2	5.4
NP (≥ 65%)	0.12	1.7	0.3	4.9

CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; WBC = White blood cells; ANC = Absolute neutrophil count; NP = Neutrophil percentage; APC = Absolute platelet count. *$p < 0.05$; **$p < 0.01$.

Table VII. Predicted probabilities of septic arthritis as per the number of positive presenting factor.

Number of the positive presenting factors	Overall study population n (%)	Septic group (n = 57) n (%)	Non-septic group (n = 60) n (%)	Predicted probability for septic arthritis (%)
0	24 (20.5)	0 (0)	24 (40)	4.3
1	18 (15.4)	3 (5.3)	15 (25)	11.4
2	11 (9.4)	3 (5.3)	8 (13.3)	27
3	13 (11)	7 (12.3)	6 (10)	51.6
4	17 (14.5)	14 (24.6)	3 (5)	75.4
5	20 (17.1)	16 (28.1)	4 (6.7)	89.8
6	14 (12)	14 (24.6)	0 (0)	96.2

The predicted probability of a child with septic arthritis was calculated as a function of the number of positive presenting factors using binary logistic regression models.

Table VIII. Summary of predictors for septic arthritis.

Predictors	Studies	Predicted probability of septic arthritis as per the positive predictor count						
		0	1	2	3	4	5	6
• A history of a fever ≥ 38.5°C • Non-weight bearing status • ESR ≥ 40 mm/h • Serum WCC > 12,000 cells/mm^3	Kocher et al[9]	< 0.2	3	40	93	93.6	-	-
	Kocher et al[12]	2	9.5	35	72.8	93	-	-
• A history of a fever ≥ 38.5°C • Non-weight bearing status ESR ≥ 40 mm/h • Serum WCC > 12,000 cells/mm^3								
• A history of a fever ≥ 38.5°C • Non-weight bearing status, • ESR ≥ 40 mm/h • WCC > 12,000 cells/mm^3	Luhmann et al[4]					59.1		
• Body temperature > 37°C, • ESR > 20 mm/h, • CRP > 1 mg/dL, • Serum WCC > 11,000/mL, • Increased hip joint space of > 2 mm	Jung et al[13]	0.1	-	-	-	99.1	-	-
• Oral temperature > 38.5°C • CRP > 20 mg/L • ESR > 40 mm/h • Refusal to bear weight • Serum WCC > 12,000/mm^3	Caird et al[7]	16.9	36.7	62.4	82.6	93.1	97.5	-
• CRP ≥ 63 mg/L • ESR ≥ 53 mm/h • Body temperature (tympanic) ≥ 37.1°C • Serum WCC ≥ 12,100 mm^3 • Serum ANC 6,300/mm^3 • Serum NP ≥ 65%	The present study	4.3	11.4	27	51.6	75.4	89.8	96.2

CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; WBC = White blood cells; ANC = Absolute neutrophil count; NP = Neutrophil percentage; APC = Absolute platelet count.

still very good. In another study, Luhmann et al[4] applied Kocher's clinical algorithm retrospectively to their cohorts and suggested the predicted probability of septic arthritis to be 59% for four predictors. Accordingly, the authors were unable to confirm the utility of Kocher's prediction algorithm and recommended that this prediction algorithm should be used with attention at other institutions. In 2006, Caird et al[7] reproduced the above findings in 53 children who underwent hip aspiration because of a suspicion of septic arthritis. The authors found an oral temperature of >38.5°C as the best predictor of septic arthritis, followed by a CRP level of >20 mg/L, an ESR of >40 mm/h, non-weight bearing status, and a serum WBC count of >12,000/mm^3. In their study[7], children with five predictive factors had a 98% risk of having septic arthritis.

We attempted to analyze the predictive values of common presenting laboratory findings of septic arthritis in addition to Kocher's variables in diagnosing septic arthritis. Although weight-bearing status significantly differed between the two groups in the univariate analysis, it was not entered in the ROC analysis due to statistical problems with being a purely subjective binary categorical variable (yes/no). Based on the ROC-AUC values, our results revealed that all the serum inflammatory markers exhibited moderate discriminatory power for septic arthritis with AUCs ranging between 0.754 and 0.817, and CRP was of the best overall predictive function, followed by ANC, ESR, NP, body temperature, and WCC.

Unlike the previous studies[14] on the topic, we redefined the optimum diagnostic cut-off levels of presenting factors in our cohorts and investigated their diagnostic performance, since predictive values of diagnostic tests may be changed based on the prevalence of a disease in the population. We found the CRP level >63 mg/L to be the highest specificity and positive predictive value (80%, and 78%, respectively) and the ANC level ≥6,300/mm^3 to be the highest sensitivity and negative predictive value (80% and 80%, respectively). It can be interpreted that considering CRP and ANC together may be more beneficial than other commonly used serum inflammatory markers in assisting clinical diagnosis. Furthermore, the WCC level of ≥12,100 mm^3 had the lowest sensitivity and negative predictive value (63% and 70%, respectively). Accordingly, along with the lowest overall predictive performance, the WCC level of ≥12,100 mm^3 should be used with caution in determining the final diagnosis.

An interesting finding of the present study is the identification of the four independent predictors of septic arthritis according to the multivariate analysis:
1) CRP ≥63 mg/L,
2) ESR ≥53 mm/h,
3) WCC ≥12,100/mm^3,
4) body temperature >37.1°C.

The odds for CRP indicated that CRP had the most significant association with the risk of developing septic arthritis. Although ANC and NP showed acceptable predictive and diagnostic performance in univariate analysis, multivariate analysis revealed that these markers had no significant impact on the outcome. ANC and NP exhibit acceptable diagnostic performance individually, but these markers should be assessed together with other inflammatory markers. Furthermore, although non-weight-bearing status has been suggested as an independent predictor of septic arthritis by several authors[4,8,12], this finding is a purely subjective variable, and it is limited to cases with lower limb involvement. Therefore, we did not include non-weight bearing in the multivariate analyses.

According to our literature review, only a few studies[2,7,13,15] investigated CRP's clinical utility in differentiating septic arthritis from non-septic arthritis. In one study, Caird et al[7] found a CRP level of >20 mg/L to be an independent risk factor strongly related to septic hip arthritis. In another study, Levine et al[15] determined that a CRP level of 10 mg/L is a better independent predictor of septic arthritis in children than ESR. Similarly, Jung et al[13] found the CRP level of 10 mg/L to be the better predictor of septic arthritis compared with ESR, WBC, body temperature, and increased hip joint space of >2 mm. Most recently, in a study with a similar design to ours, Aupiais et al[2] retrospectively compared clinical and biological characteristics of septic arthritis *vs.* JIA in the pediatric population. The authors reported that CRP might not be a reliable predictor for distinguishing septic arthritis from JIA. The main strength of the present study lies in its statistical analysis. Unlike the previous studies, we did not arbitrarily select the predictors' cut-off values. Optimum diagnostic cut-off levels were first determined using ROC analysis, and then the test characteristics of the variables were investigated as per their optimum diagnostic serum levels. Our results demonstrated that a CRP level ≥63 mg/L is the best independent predictor with high

sensitivity and specificity to distinguish between septic arthritis and noninfectious inflammatory arthritis.

Using a similar model to that of Kocher et al[12] and Luchmann et al[4] (Table VIII), we conducted a multivariate algorithm with the six presenting factors and found the predicted probability of septic arthritis to be 75.4% for four factors, 89.8% for five factors, and 96.2% for six factors. Nonetheless, it should be noted that our and Kocher's criteria seem to be very helpful in diagnosing septic arthritis; in practice, they may not be so[14]. As mentioned in a critical analysis of the available studies by Alshryda and Wright[14], a child with no predictive criterion still carries a risk of sustaining septic arthritis (0.2-17%) (Table VIII). Otherwise, more than half of the children (78%) in our study presented with four to six presenting factors (Table VI), and this can be interpreted that our algorithm can show a relatively high prediction rate ranging between 76% and 96%. All in all, in addition to the above criteria, clinical assessment is imperative in managing children with acute mono-arthritis.

When interpreting the present study's findings, some limitations and strengths should be considered. First, this study was conducted retrospectively on a relatively small number of patients, which may limit the results' power. However, our cohort size was larger than most of the above-mentioned studies, and the power analysis before the study showed that 40 patients per group were needed to determine significant differences with a power of 80%. Furthermore, the balanced ratios of the number of patients between the two groups (-1/1) may increase the accuracy of statistical analyses. Second, the patient data were retrospectively collected and analyzed. In contrast, the septic group consisted entirely of true septic cases with a positive synovial fluid culture or a positive synovial fluid on gram staining. Accordingly, the data may provide increased accuracy in clinical relevance. Finally, our study population is heterogeneous in terms of affected joint location. Despite these limitations, our study is one of the few that investigated the clinical utility of the commonly used serum inflammatory markers in diagnosing septic arthritis.

Conclusions

Evidence from this study has revealed that CRP is a valuable laboratory test to distinguish septic arthritis from common forms of noninfectious inflammatory arthritis, and a CRP level of ≥63 mg/L is the best independent predictor of septic arthritis with high sensitivity and specificity among the commonly used serum inflammatory markers (ESR, WCC, ANP, NP). ANC and NP seem helpful in predicting septic arthritis with acceptable overall diagnostic performance. However, levels of ≥6,300/mm^3 ANC and ≥65% NP should be used in combination with other presenting factors as these factors appeared not to be independent predictors. In children with acute monoarthritis, the predicted risk of septic arthritis increased with the number of presenting factors and may be 96.2% in the presence of all six factors. Nevertheless, it should be borne in mind that a child with zero predictors may still have a 4.3% risk of septic arthritis. Thus, clinical assessment is still imperative in managing children with acute mono-arthritis.

Conflict of Interest

Each author certifies that he or she has no commercial associations that might pose a conflict of interests in connection with the submitted article.

Ethics Approval

The institutional Ethical Committee approved this study protocol on human research (Ethical permit number 2018/1057), and data collection was in accordance with the guidelines of the Declaration of Helsinki.

Informed Consent

Not applicable due to the retrospective nature of the study.

Authors' Contribution

ÖBD: conceptualization, data curation, methodology, investigation, supervision. MD: conceptualization, validation, writing - original draft. RNÖ: methodology, formal analysis, writing - original draft. SHT: supervision, validation. FB: supervision, validation, writing - review and editing.AK: supervision, validation, writing - review and editing.

ORCID ID

Özge Bayrak Demirel: 0000-0001-7780-0231; Mehmet Demirel: 0000-0003-1131-7719; Rukiye Nurten Ömeroğlu: 0000-0002-3740-6552; Selda Hançerli Törün: 0000-0002-9549-6330; Fuat Bilgili: 0000-0002-9417-2166; Ayşe Kılıç: 0000-0002-8189-3407.

References

1) Pääkkönen M, Peltola H. Treatment of acute septic arthritis. Pediatr Infect Dis J 2013; 32: 684-685.
2) Aupiais C, Basmaci R, Ilharreborde B, Blachier A, Desmarest M, Job-Deslandre C, Faye A, Bonacorsi S, Alberti C, Lorrot M. Arthritis in children: comparison of clinical and biological characteristics of septic arthritis and juvenile idiopathic arthritis. Arch Dis Child 2017; 102: 316-322.
3) Devauchelle-Pensec V, Thepaut M, Pecquery R, Houx L. Managing monoarthritis in children. Joint Bone Spine 2016; 83: 25-30.
4) Luhmann SJ, Jones A, Schootman M, Gordon JE, Schoenecker PL, Luhmann JD. Differentiation between septic arthritis and transient synovitis of the hip in children with clinical prediction algorithms. J Bone Joint Surg Am 2004; 86: 956-962.
5) Spyridakis E, Gerber JS, Schriver E, Grundmeier RW, Porsch EA, St Geme JW, Downes KJ. Clinical Features and Outcomes of Children with Culture-Negative Septic Arthritis. J Pediatric Infect Dis Soc 2019; 8: 228-234.
6) Mitha A, Boulyana M, Hue V, Pruvost I, Martinot A; European French-speaking expert group, Dubos F. Consensus in diagnostic definitions for bone or joint infections in children by a Delphi method with European French-speaking experts. Acta Paediatr 2012; 101: 350-356.
7) Caird MS, Flynn JM, Leung YL, Millman JE, Joann G, Dormans JP. Factors distinguishing septic arthritis from transient synovitis of the hip in children: a prospective study. J Bone Joint Surg Am 2006; 88: 1251-1257.
8) Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. J Bone Joint Surg Am 1999; 81: 1662-1670.
9) Greiner M, Sohr D, Göbel P. A modified ROC analysis for the selection of cut-off values and the definition of intermediate results of serodiagnostic tests. J Immunol Methods 1995; 185: 123-132.
10) Swets JA. Measuring the accuracy of diagnostic systems. Science 1988; 240: 1285-1293.
11) Muschelli J. Roc and auc with a binary predictor: a potentially misleading metric. J Classif 2020; 37: 696-708.
12) Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. J Bone Joint Surg Am 2004; 86: 1629-1635.
13) Jung ST, Rowe SM, Moon ES, Song EK, Yoon TR, Seo HY. Significance of laboratory and radiologic findings for differentiating between septic arthritis and transient synovitis of the hip. J Pediatr Orthop 2003; 23: 368-372.
14) Alshryda S, Wright J. Differentiating Between Septic Arthritis and Transient Synovitis of the Hip in Children: An Evidence-Based Clinical Prediction Algorithm. Classic Papers in Orthopaedics. Springer 2014; 585-587.
15) Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. J Pediatr Orthop 2003; 23: 373-377.