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Original Article

Diagnostic value of serum markers and C-reactive protein of joint fluid in purulent arthritis

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Abstract

Introduction: Predicting purulent arthritis with a single marker may result in low sensitivity and specificity. We investigated the diagnostic value of serum markers and joint fluid C-reactive protein (CRP) in purulent arthritis.

Methodology: A total of 183 patients with acute joint infection, who were treated at our hospital between April 2019 and September 2022, were retrospectively analyzed via convenient sampling. Serum markers and joint fluid CRP levels were compared between the infection group and the control group to assess their early diagnostic value.

Results: Based on multivariate analysis, delta neutrophil index, DNI (odds ratio (OR) = 8.428, 95% confidence interval (CI): 4.753–9.134, $p < 0.001$); erythrocyte sedimentation rate, ESR (OR = 1.981, 95% CI: 1.435–4.123, $p < 0.001$); procalcitonin, PCT (OR = 2.418, 95% CI: 1.575–5.639, $p < 0.001$); serum CRP (OR = 2.784, 95% CI: 1.982–4.243, $p < 0.001$); and joint fluid CRP (OR = 3.279, 95% CI: 2.142–5.510, $p < 0.001$) were identified as risk factors for purulent arthritis. Predictive value assessment showed that the DNI, ESR, PCT, serum CRP, and joint fluid CRP all held a predictive value for purulent arthritis ($p < 0.05$), with the highest predictive value in the combination of all five markers, yielding an area under the curve (AUC) of 0.922 (95% CI: 0.854–0.962).

Conclusions: The DNI, ESR, PCT, serum CRP, and joint fluid CRP are crucial diagnostic indicators for identifying acute purulent arthritis. Notably, joint fluid CRP demonstrated the highest predictive value among the indicators.

Key words: markers; arthritis; CRP; ESR; DNI; PCT.

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Introduction

Purulent arthritis is an intra-articular infection caused by purulent bacteria and is characterized by rapid progression and a mortality rate of approximately 10% [1]. It often involves the knee joint, which accounts for approximately 50% of all purulent arthritis cases [2-3]. The most common pathogens behind these infections are *Staphylococcus aureus*, closely followed by *Streptococcus,* and other Gram-positive bacteria [4]. Infection can stem from bacterial dissemination through the bloodstream or result from a range of factors, such as local trauma or medical interventions [5–6]. Purulent arthritis may progress rapidly, highlighting the significance of timely diagnosis and treatment. There is substantial evidence to support an intimate connection between early, proactive treatment, and the success of purulent arthritis therapy [7–8]. The key to the treatment of this disease is the timely and thorough removal of intra-articular infection foci [9]. In contrast, incorrect therapeutic approaches or delays can result in permanent damages to joint structures. A delay of over three weeks in treatment can notably restrict the knee joint's range of motion and increase the risk of joint stiffness, thereby causing irreversible loss of joint function in 25–50% of the patients [4].

Presently, the diagnosing method of purulent arthritis primarily relies on clinical history and culture of bacteria from blood and joint fluid, which are time-consuming and may delay diagnosis and treatment of acute infections. Hence, identification of a rapid and accurate diagnostic method is necessary. Previous studies have indicated that purulent arthritis can be differentiated by several serum markers to some extent. Inflammatory cytokines of procalcitonin (PCT) [10] and C-reactive protein (CRP) [11] are sensitive to bacterial infections and their levels can rise within 6–8 hours during the early stages of inflammation, serving as indicators of inflammatory changes. The erythrocyte sedimentation rate (ESR) [12] and CRP are used for diagnosing purulent arthritis, but not all patients show positive results. The ESR reflects changes in fibrinogen within 24–48 hours after inflammation, while CRP is a

timely marker for changes in inflammation and necrosis. In addition, D-dimer [13] is significantly elevated in infectious diseases, such as pneumonia and cholangitis.

Recent studies have generally explored single markers or a few serum markers for diagnosing purulent arthritis to uncover their separate predictive values. However, the use of a single marker for predicting purulent arthritis may result in low sensitivity and specificity, potentially leading to missed diagnoses and treatment delays. Therefore, this study measured serological and joint fluid CRP data from patients with purulent arthritis to compare the predictive value of various markers for this disease, aiming to provide a basis for developing clinical diagnosis and treatment strategies.

Methodology

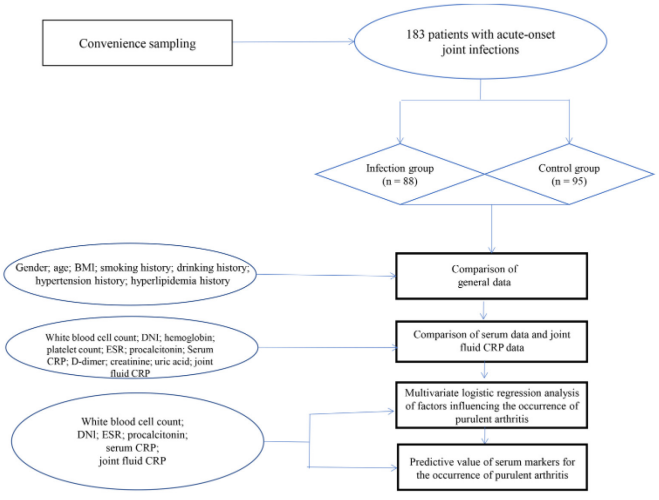
Study participants

A total of 183 patients with acute-onset joint infections treated at our hospital between April 2019 and September 2022 were included through convenience sampling for retrospective analysis. The enrolled patients were divided into two groups: infection group (purulent arthritis, n = 88) and control group (no purulent arthritis, n = 95).

Inclusion criteria were patients who (1) exhibited signs of acute joint arthritis, including joint redness, swelling, heat and pain, and had not received antibiotic treatment before hospitalization; (2) had pathogenic bacteria cultured from joint aspiration fluid (infection group); and (3) did not receive antibiotic treatment to control disease, ruling out the possibility of infection (control group).

Exclusion criteria were patients (1) with coexisting diseases that could affect the study outcomes, such as thrombosis, connective tissue diseases, tumors and hematologic disorders; (2) with infections in other body parts; (3) who were automatically discharged and lost to follow-up due to uncontrolled conditions; (4) who were taking antiplatelet and other anticoagulant medications; (5) who had a history of significant trauma or surgery within 3 months prior to this study; (6) who had severe hemorrhagic joint fluid or insufficient joint fluid; and (7) with other diseases and conditions leading to an increase in serum PCT levels, diseases reducing the content of oxygen in the tissues (e.g. bronchial asthma and pulmonary pneumonia), prolonged severe organ hypoperfusion, and known tumors with paraneoplastic hormonal production, overheating (pyrexia) and burns [14].

Figure 1. Flow chart of the study



BMI: body mass index; CRP: C-reactive protein; DNI: delta neutrophil index; ESR: erythrocyte sedimentation rate.

Study design

The time frame from symptom onset to blood sampling ranged from 0.5 to 24 hours. A total of 10–20 mL of peripheral blood specimens was collected, centrifuged at 3,000 rpm for 10 minutes to separate serum and plasma and stored at − 80°C for further analysis. The Rayto RT7200 (Shenzhen, China) fully automated blood analyzer and the Olympus AU2700 (Tokyo, Japan) fully automated biochemical analyzer were used to measure biochemical parameters, including the white blood cell (WBC) count, hemoglobin, platelet count, ESR, CRP, urea nitrogen, creatinine, and uric acid levels. Specifically, CRP levels were determined using immunoturbidimetry, while ESR was measured using the Westergren method. The delta neutrophil index (DNI) data were obtained using the Siemens ADVIA2120 (Chapel Lane, Swords, Co. Dublin, Ireland) flow cytometry analyzer, following established protocols [15]. Joint fluid was obtained through aseptic puncture and aspiration, and CRP levels were measured using the same method as mentioned above. D-dimer levels were determined using immunoturbidimetry, with a normal reference range of 0–0.55 mg/L. Procalcitonin was detected using double-antibody sandwich chemiluminescence immunoassay, with a normal reference range of 0–0.1 ng/mL.

Data collection

General data, serum data and joint fluid CRP levels of all participants were recorded. General data included gender; age; body mass index (BMI); and smoking, drinking, diabetes, hypertension, and hyperlipidemia

Table 1. Comparison of general data between the two groups.

Clinical data	Infection group (n = 88)	Control group (n = 95)	t/χ^2 value	*p* value
Gender (M/F)	45/43	51/44	0.119	0.730
Age (years, x ± sd)	53.39 ± 12.51	52.71 ± 11.77	1.371	0.172
BMI (kg/m^2, x ± sd)	19.52 ± 7.63	20.32 ± 8.75	0.798	0.440
Smoking history (n)	19	21	0.007	0.933
Drinking history (n)	15	19	0.583	0.445
Hypertension history (n)	21	23	0.003	0.956
Hyperlipidemia history (n)	18	13	1.488	0.222

BMI: body mass index.

history. Serum data consisted of the WBC count, DNI, hemoglobin, platelet count, ESR, CRP, PCT, D-dimer, creatinine and uric acid levels (Figure 1).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 26.00 software (IBM Corp, Armonk, NY, USA). The normality of data was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables were described as mean ± standard deviation (x ± s), and inter-group means were compared using the t-test. Non-normally distributed continuous variables were expressed as median (interquartile range), and inter-group comparisons were made using the Mann–Whitney U test. Categorical data were presented as frequency (n) or percentage (%), and comparisons were conducted using the $\chi 2$ test. Multivariate analysis was conducted through logistic regression analysis. Additionally, the predictive value of relevant factors for purulent arthritis was explored using receiver operating characteristic (ROC) curves, with a significance level of $\alpha = 0.05$.

Results

Comparison of general data between the two groups

The infection group (n = 88) comprised 45 men and 43 women, with an average age of 53.39 ± 12.51 years and an average body mass index (BMI) of 19.52 ± 7.63 kg/m^2. The control group (n = 95) comprised 51 men and 44 women, with an average age of 52.71 ± 11.77 years and an average BMI of 20.32 ± 8.75 kg/m^2. No statistically significant differences were observed between the two groups in terms of gender, age, BMI, smoking history, drinking history, diabetes history, hypertension history, or hyperlipidemia ($p > 0.05$; Table 1).

Comparison of serum data and joint fluid C-reactive protein data between the two groups

There were statistically significant differences between the two groups of patients in the following parameters: WBC count (11.33 ± 3.02 vs 9.15 ± 2.88 103/mm^3, t = 5.352, $p < 0.001$), DNI (4.02 ± 1.25 vs 0.77 ± 0.25%, t = 6.353, $p < 0.001$), ESR (75.61 ± 23.44 vs 60.25 ± 25.24 mm/h, t = 4.521, $p < 0.001$), PCT (5.56 ± 1.85 vs 2.19 ± 1.16 μg/L, t = 13.482, $p < 0.001$), serum CRP (99.05 [35.40, 135.00] vs. 19.20 [3.65, 49.95] mg/L, Z = 5.678, $p < 0.001$), and joint fluid CRP (75.25 [39.50, 110.80] vs. 12.60 [1.80, 33.35] mg/L, Z = 6.538, $p < 0.001$) (Table 2). No statistically significant differences were observed between the two groups of patients in hemoglobin, platelet count, D-dimer, creatinine, and uric acid ($p > 0.05$).

Multivariate analysis of factors influencing the occurrence of purulent arthritis

A logistic regression model was established with the occurrence of purulent arthritis as the dependent variable (occurrence = 1, no occurrence = 0) and factors with statistical significance in the univariate analysis as independent variables (using their original values). DNI (OR = 8.428, 95% CI: 4.753–9.134, $p < 0.001$), ESR (OR = 1.981, 95% CI: 1.435–4.123, $p < 0.001$), PCT

Table 2. Comparison of serum data and joint fluid CRP data between the two groups.

Clinical data	Infection group (n = 88)	Control group (n = 95)	*t*/*Z* value	*p* value
White blood cell count (10^3/mm^3)	11.33 ± 3.02	9.15 ± 2.88	5.352	< 0.001
DNI (%)	4.02 ± 1.25	0.77 ± 0.25	6.353	< 0.001
Hemoglobin (g/L)	120.15 ± 20.15	120.05 ± 20.03	0.788	0.440
Platelet count (10^3/mm^3)	264.02 ± 31.05	255.26 ± 30.84	0.007	0.933
ESR (mm/h)	75.61 ± 23.44	60.25 ± 25.24	4.521	< 0.001
Procalcitonin (ng/mL)	5.56 ± 1.85	2.19 ± 1.16	13.482	< 0.001
Serum CRP (mg/L)	99.05 (35.40, 135.00)	19.20 (3.65, 49.95)	5.678	< 0.001
D-dimer (mg/mL)	1.16 (0.60, 3.27)	0.95 (0.34, 2.08)	1.545	0.122
Creatinine (mg/L)	10.14 ± 2.12	11.15 ± 3.22	1.328	1.240
Uric acid (mg/L)	30.57 ± 6.33	31.67 ± 5.23	1.118	1.020
Joint fluid CRP (mg/L)	75.25 (39.50, 110.80)	12.60 (1.80, 33.35)	6.538	< 0.001

CRP: C-reactive protein; DNI: delta neutrophil index; ESR: erythrocyte sedimentation rate.

Table 3. Multivariate logistic regression analysis of factors influencing the occurrence of purulent arthritis.

Influencing factor	SE	Wald χ^2	*p* value	OR	OR（95% CI）
White blood cell count (10^3/mm^3)	0.749	0.234	0.687	1.596	0.975~2.123
DNI (%)	0.829	4.398	0.001	8.428	4.753~9.134
ESR (mm/h)	0.729	5.284	0.001	1.981	1.435~4.123
Procalcitonin (ng/mL)	1.427	6.350	0.001	2.418	1.575~5.639
Serum CRP (mg/L)	1.520	6.123	0.001	2.784	1.982~4.243
Joint fluid CRP (mg/L)	0.755	5.535	0.001	3.279	2.142~5.510

CRP: C-reactive protein; DNI: delta neutrophil index; ESR: erythrocyte sedimentation rate; OR: odds ratio; SE: standard error.

(OR = 2.418, 95% CI: 1.575–5.639, $p < 0.001$), serum CRP (OR = 2.784, 95% CI: 1.982–4.243, $p < 0.001$), and joint fluid CRP (OR = 3.279, 95% CI: 2.142–5.510, $p < 0.001$) were risk factors for the occurrence of purulent arthritis (Table 3).

Predictive value of serum markers for the occurrence of purulent arthritis

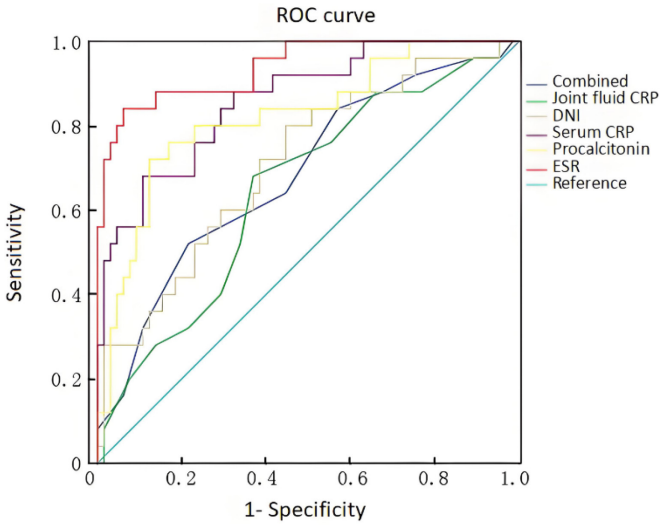
DNI, ESR, PCT, serum CRP and joint fluid CRP; all had predictive values for the occurrence of purulent arthritis in patients ($p < 0.05$; Table 4). Specifically, the area under the curve (AUC) for predicting the occurrence of purulent arthritis was 0.783 (95% CI: 0.681–0.856) for DNI, 0.711 (95% CI: 0.680–0.882) for ESR, 0.766 (95% CI: 0.679–0.854) for PCT, 0.781 (95% CI: 0.715–0.838) for serum CRP, and 0.801 (95% CI: 0.827–0.912) for joint fluid CRP. Notably, combined use of these five markers demonstrated the highest predictive value, with an AUC of 0.922 (95% CI: 0.854–0.962) (Figure 2). For specific details, see Table 4 and Figure 2.

Discussion

Timely diagnosis is crucial for the management of purulent arthritis to minimize its destructive impact on native joints. According to international reports, 8–27% of patients with acute monoarticular arthritis can progress to septic arthritis, with mortality rate reaching 11% [16–17]. Early diagnosis of joint infections is pivotal for the formulation of appropriate therapeutic regimes. Reportedly, 1–3% of patients experience periprosthetic joint infection after joint replacement [18]. There is no absolute gold standard for diagnosing purulent arthritis. Bacterial culture is generally considered the diagnostic gold standard in clinical practice. However, the results that are generated can be influenced by antibiotics or sample contamination, and the time-consuming nature may delay the diagnosis and treatment of acute infections. This highlights the pressing need for more convenient, rapid, and accurate diagnostic methods.

DNI is a calculated parameter that reflects the ratio of the count of immature granulocytes to different WBC subtypes in peripheral circulation. It is subject to individual variations and influenced by factors such as diet, bacterial infections and metabolic levels. While referring to Yankov *et al*. [19,20] on the role of DNI and PCT in odontogenic and non-odontogenic infections, this article focuses on the differences between DNI levels in purulent arthritis and non-suppurative arthritis. DNI is closely associated with mortality, severity of septic diseases, blood culture

Figure 2. ROC curve of prediction



CRP: C-reactive protein; DNI: delta neutrophil index; ROC: receiver operating characteristic.

Table 4. Predictive value of serum markers for the occurrence of purulent arthritis.

Item	AUC	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)
DNI (%)	0.783	0.681–0.856	2.00	87.31	74.54
ESR (mm/h)	0.711	0.680–0.882	19.00	87.31	74.54
Procalcitonin (ng/mL)	0.766	0.679–0.854	1.03	80.61	85.70
Serum CRP (mg/L)	0.781	0.715–0.838	32.71	92.01	63.82
Joint fluid CRP (mg/L)	0.801	0.827–0.912	37.20	80.00	80.40
Combined prediction	0.922	0.845–0.962	-	91.45	90.65

AUC: area under curve; CI: confidence interval; CRP: C-reactive protein; DNI: delta neutrophil index; ESR: erythrocyte sedimentation rate.

detection rates, and disseminated intravascular coagulation scores [21–22]. It has been reported to distinguish between patients with acute gouty arthritis within 24 hours of admission and those with purulent arthritis, with DNI ≥ 1.9% being an important parameter for predicting purulent arthritis [23]. In this study, a DNI value of 2.0% was found to be the optimal cut-off point for distinguishing purulent arthritis from other patients with acute arthritis. This discrepancy with the previous study results may be attributed to variations in the clinical data of the enrolled patients.

Detection of ESR may indicate changes in fibrinogen levels within 24–48 hours of inflammation, and ESR may be valuable for identifying purulent arthritis [24]. Meanwhile, CRP is an acute-phase protein commonly used as a leading indicator for diagnosing infections to detect the onset of inflammation. However, it may not yield positive results until 2 days after the onset of diseases, and its low sensitivity limits its value in early assessment [25]. Additionally, surgical procedures and acute rejection reactions can also cause an increase in CRP, reducing its specificity for infection. Even after the removal of the inflammatory stimulus, the liver continues to synthesize CRP at high levels for several days [26–27]. CRP has a short half-life of approximately 5–7 hours, and its level in serum correlates positively with the degree of inflammatory response. As inflammation subsides, CRP levels rapidly decrease, supporting its significance in assessing treatment efficacy and discontinuing antibiotic therapy [28].

According to prior continuous studies on the role of joint fluid CRP in diagnosing purulent arthritis, joint fluid CRP has better diagnostic accuracy than serum CRP [29]. In this study, joint fluid CRP had a higher AUC compared to other parameters, with a threshold significantly higher than that reported in other studies. This difference may be attributed to the inclusion of patients with both chronic and acute infections in this study. Serum D-dimer is a breakdown product of fibrinolysis. Considering that abnormal coagulation is a host's inflammatory response, D-dimer has proven to be a major determinant of the prognosis of systemic sepsis (similar to established inflammatory markers such as CRP and ESR) [30]. In this study, there was no statistically significant difference in D-dimer levels between the infection group and the control group. This may be attributed to the impact of hypercoagulation or inflammation resulting from patient immobilization in both groups. Considering a relatively low diagnostic accuracy of D-dimer due to a limited positive sample size in this study, further multicenter studies and additional data are needed to confirm the value of serum D-dimer.

Procalcitonin has been widely used in the diagnosis of systemic bacterial infections in recent years. It has also been applied for the diagnosis of purulent arthritis, with high sensitivity [31]. Furthermore, PCT and CRP are both acute-phase inflammatory markers, and both may show increased trends in response to bacterial infection. However, both markers differ in their mechanisms of elevation and the timing of their increase. The plasma half-life of PCT is longer than that of CRP, and PCT is believed to respond faster to bacterial reactions than CRP, reaching its peak within 8–24 hours. Moreover, PCT normalizes its blood values more quickly after the infection is eliminated. Therefore, it is more accurate in determining the course of local purulent inflammation and is a better prognostic indicator than CRP [32]. Bayrak Demirel *et al.* [33] and Aggarwal *et al.* [34] found that serum PCT had a high specificity for distinguishing purulent arthritis (with a cut-off set at PCT > 0.5 ng/mL). However, different cut-off points for PCT have been proposed for diagnosing purulent arthritis by other researchers. For instance, Santagada *et al*. [35] proposed PCT > 0.4 ng/mL, while Baron *et al.* [36] argued for PCT > 0.25 ng/mL. Yankov *et al.* [37] examined and analyzed patients with odontogenic and non-odontogenic head and neck focal purulent infections. In addition, a meta-analysis conducted by Zhang *et al*. [38] concluded that serum PCT levels could serve as an effective indicator for diagnosing bone and joint infections. In this study, higher serum PCT levels were detected in most cases of purulent arthritis when compared with those in the control group, with the optimal diagnostic threshold being 1.03 ng/mL, which was consistent with aforementioned studies.

Study limitations

This study also has some limitations. First, it is a single-center study with a relatively small sample size, which may have limited the accuracy of the conclusions. Second, other unknown influencing factors might not have been determined among the included patients, which could have also impacted the conclusions. In addition, due to different sampling time points of the blood samples from the enrolled patients, the DNI values might have been associated with the progression of the disease. Finally, as the paper was designed as a retrospective study, it failed to establish a causal relationship between various parameters and patients with purulent arthritis.

Conclusions

DNI, ESR, PCT, serum CRP, and joint fluid CRP can serve as crucial diagnostic indicators for distinguishing patients during the acute phase of purulent arthritis. Notably, joint fluid CRP demonstrated the highest predictive value among the indicators.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Affiliated SanMing Frist Hospital of Fujian Medical University [NO. MYL(2021)19].

Data availability

All data generated or analyzed during this study are included in this published article.

Authors' contributions

Conception and design: CX; data collection, CL, DY, PW, MS, YL; data analysis and interpretation: DQ, XH, ZF, XY; statistical analysis: CX, CL; manuscript draft: CX; critical revision of manuscript: CX, CL; supervision: CX, CL; approval of final manuscript: all authors.

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