The Turkish Journal of Pediatrics 2024; 66(6): 681-689
https://doi.org/10.24953/turkjpediatr.2024.4889

Original Article

Role of serum procalcitonin in differentiating disease flare and systemic bacterial infection among febrile children with known chronic rheumatic diseases: a cross-sectional study

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ABSTRACT

Objectives. To evaluate the role of serum procalcitonin (PCT) as a diagnostic tool to differentiate bacterial sepsis from flare-ups during febrile episodes in children with known rheumatic disorders compared to other inflammatory markers like C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Methods. Previously diagnosed patients with known rheumatic disorders presenting in emergency or outpatient departments with febrile episodes were included in the study. Blood samples were collected upon admission to test for signs of infection, including serum PCT levels with routine laboratory and radiological tests. Patients with juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) were stratified using the Juvenile Arthritis Disease Activity Score (JADAS-27) and SLE Disease Activity Index (SLEDAI) respectively. Patients without bacterial focus with high disease activity were included in the flare-up group and the rest in the sepsis cohort. The diagnostic value of PCT was calculated using receiver operating characteristic (ROC) curve analysis.

Results. In the study (N=73), 41 (56.2%) patients were previously diagnosed with JIA and 28 (38.3%) had SLE. 38 patients had definite evidence of sepsis and 35 had disease flare-ups as per respective disease activity scores. There was a significant difference in PCT and CRP among the flare-up and sepsis groups. For detecting sepsis, the area under curve (0.959), sensitivity (94.7%), and specificity (74.3%) of PCT at a cut-off of 0.275 ng/mL were significantly better than those of CRP.

Conclusion. PCT is a better diagnostic test than CRP or ESR during febrile episodes in differentiating flare-ups from infection and PCT >0.275 ng/mL indicates bacterial infection with good specificity and sensitivity in children with low disease activity.

Key words: systemic lupus erythematosus, procalcitonin, rheumatic flare-ups, juvenile idiopathic arthritis, sepsis.

Children with rheumatic diseases are at an increased risk of infections[1] due to multiple reasons such as the intrinsic disturbances of immune responses[2], long-term use of immunosuppressive drugs, and associated organ complications.[3] Fever is one of the most

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Received 26th Jun 2024, revised 19th Aug 2024, accepted 30th Sep 2024.

The preliminary data of the study was presented in RCPCH Conference, 2023, and published as an abstract in the meeting proceedings (https://adc.bmj.com/content/108/Suppl_2).

common presentations of chronic rheumatic diseases, either as a flare-up in the disease course itself or an infection. Both disease flare and secondary bacterial infection follow a similar pattern of presentations, ranging from mere febrile episodes to more complex symptoms like joint pain, myalgia, shortness of breath, etc. Although huge advancements have been made in the management of sepsis and related complications, it is still a major cause of mortality across all age groups, especially in developing countries. Hence, it is of paramount importance to identify sepsis at an early stage and start the treatment before further deterioration.

Apart from sepsis, these patients typically suffer from frequent episodes of worsening of the primary disease, called disease flares. Both sepsis and flare can be life-threatening and need urgent identification. However, they fall into two opposite spectrums, having entirely different pathophysiologies and needing different lines of treatment. Early exclusion of bacterial sepsis can allow prompt administration of specific treatment of inflammatory disease with escalating immunomodulators and avoid the use of empirical antibiotics. On the other hand, timely detection and management of bacterial infections with appropriate antibiotics can prevent sepsis-related morbidity. The fact, that these two phenomena have strikingly similar presentations, makes it challenging to differentiate between them clinically.[4,5] The search for a laboratory marker has been ongoing for a long time which can distinctly point in favor of the underlying disease entity and aid in timely therapy. Conventional laboratory markers pose several limitations in assessing patients with clinical suspicion of infection. Hence in recent years, significant effort has been made to identify a novel biological marker, successfully discriminating infectious aetiologies of fever from the non-infectious ones in known rheumatic patients. The classical inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) are of limited use due to their lack of specificity.[6] Their diagnostic sensitivity is blunted due to the long-term use of immunosuppressive medications, especially corticosteroids, in such patients.[7] Procalcitonin (PCT) level has been studied as a reliable marker differentiating systemic bacterial and fungal infections in different trials. PCT is a 13-kDa precursor protein of calcitonin of 116 amino acids, produced by the parafollicular C cells.[8] The body produces it in the liver, lung, kidney, adipocyte, and muscle, and its serum levels increase in response to bacterial toxins and IL-1b stimulus. PCT is virtually undetectable in the plasma of healthy individuals (<0.005 ng/mL)[9] and even in case of viral infections or systemic inflammatory disorders, it is only slightly elevated. However, bacterial and fungal infections lead to a sharp increase in this value. It often ranges between 10-100 ng/mL, depending on the severity of sepsis and the inflammatory response of the body to it.[10] When the infection is controlled, its serum level is reduced promptly. This study aims to utilize this property of PCT in distinguishing bacterial infection from inflammatory flare and compare its role with other inflammatory markers in children with chronic rheumatic illnesses.

Materials and Methods

This analytical cross-sectional study was conducted in a tertiary care hospital in eastern India from January 31, 2020, to December 31, 2022.

Patients

This is a cross-sectional study where data collection was done prospectively. Purposive sampling technique was chosen to include all febrile children with diagnosed rheumatic diseases like systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), and antiphospholipid syndrome (APLA), visiting the out-patient or emergency department within the data collection phase of the study fulfilling the inclusion criteria.

Scheme of the study

All children between the ages of 1 month to 12 years with previously diagnosed rheumatic disorders for at least 6 months (this excludes acute conditions like Henoch Schönlein purpura and Kawasaki disease), presenting in an emergency (ER) / outpatient department (OPD) with febrile episodes for more than 3 days (temperature > 38 °C) and being admitted, were considered for inclusion in the study. Patients with visible signs of sepsis, such as abscess, having a recent history of major trauma, known thyroid disorder, malignancies, pancreatitis, and non-bacterial infections like dengue, malaria, scrub typhus, COVID-19, etc. were planned to be excluded.

Patients with JIA and SLE were stratified using the Juvenile Arthritis Disease Activity Score (JADAS-27)[11] and the SLE Disease Activity Index (SLEDAI), respectively. The JADAS-27 score is calculated by adding the scores of 4 core set criteria and it ranges between 0-57. Worsening in any 3 out of the 4 JADAS core criteria by >30% in any JIA patient is considered a flare.[12] A lower JADAS-27 score signifies lower disease activity and is favourable for the patient's prognosis. A high JADAS-27 score indicates increased disease activity and might need escalation of therapy.[13] Children without evidence of bacterial focus with high disease activity satisfying flare criteria were placed in the "Flare-up" group while the rest were in the "Sepsis" cohort. Similarly, for SLE patients, disease activity was assessed by the SLEDAI scores, and an increase of more than three points compared to the patient's previous score was considered an SLE flare.[14,15]

Upon admission, a pre-designed and pre-tested proforma was used to record each patient's background epidemiological, clinical, and treatment information. Blood samples on the day of admission were collected from the recruited children for hemoglobin, total leukocyte count, differential count, platelet count, ESR, CRP, PCT, serum complement, anti-double-stranded DNA (dsDNA), serum ferritin, serum triglyceride, and serum fibrinogen. Culture sensitivity of blood and other body fluids was sent as mandated clinically, before starting antibiotics.

PCT values were measured using the immune-fluorescence technique on an SIEMENS ADVIA Centaur® BRAHMS machine and recorded in tabular form. Chest X-ray, abdominal ultrasound, and urine analysis were done based on the clinical scenario. Of these, three patients were excluded because of diagnostic ambiguity and the possibility of macrophage activation syndrome (MAS). The children received parenteral ceftriaxone and amikacin after collection of blood for culture and sensitivity as first-line antibiotics as per hospital policy.

Clinical presentations and findings, positive blood cultures, imaging studies, and prompt clinical response to antibiotics were considered the "gold standard" in detecting sepsis. Blood cultures are not always positive in all bacterial infections and false positives (colonization) can occur. Hence the final diagnosis was made comprehensively using all clinical findings. The children included were divided into two groups retrospectively, either disease flare or sepsis based on the final diagnosis. There were no cases in this study where sepsis and flare were clinically suspected at the same time.

Statistical analysis

All the data regarding parameters under study were maintained in a Microsoft Excel 2007 spreadsheet. Further statistical analysis was done using the Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp. 2011. Armonk, NY, USA) for Windows.

Categorical variables were presented in terms of number and percentage (%). Normally distributed continuous variables were expressed using mean ± standard deviation (SD). Serum PCT, CRP, and ESR values between the two groups were compared using an independent t-test. The diagnostic value of PCT was calculated using the Youden method

in receiver operating characteristic curve (ROC) curve analysis. The area under the curve (AUC), sensitivity, specificity, and diagnostic accuracy at the specific cutoffs were calculated to compare the different indicators. A p-value <5% was considered to be statistically significant.

Ethics statement

The Institutional Ethics Review Committee granted ethical clearance. Informed consents from parents / legal guardians in written forms were taken before including the children as study participants. All tests were performed according to relevant guidelines and indications and in adherence to the tenets of the Declaration of Helsinki.

Results

A total of 137 children, diagnosed with chronic rheumatic diseases, attended the ER/OPD of the institute during the study period. Among them, 55 children didn't present with febrile episodes, hence they were excluded. Guardians of six children declined to take part in the study and three were excluded due to a possible diagnosis of MAS. A total of 73 children were included in the study, out of which 41 (56.2%) were JIA, 28 (38.3%) were SLE patients, 2 patients had anti-phospholipid syndrome (APLA), and the remaining two children had polyarteritis nodosa (PAN) and granulomatosis with polyangiitis, respectively (Fig. 1). The background characteristics of the patients are given in Table I.

The mean±SD age of the patients was 9.66+2.3 years, with a female:male ratio of 2.7:1. The mean age of the flare group was 9.51+2.6 years and that of the sepsis group was 9.80+2.1 years (Table I). The mean period of the primary illness was 2.53+1.6 years. All the children had fever at presentation with a mean duration of 8.04 +3.4 days. Apart from fever, the most common presenting feature of the study population was arthritis (64%) followed by rash (48%) and hepatosplenomegaly (32%). Net 38 patients were identified with detectable foci of infections without worsening of disease activity and, hence were included in the sepsis group. Among them, 11 children had positive blood cultures, cerebrospinal fluid (CSF) analysis of 9 children was suggestive of bacterial meningitis, 14 had culture-positive urinary tract infection (UTI), while others had radiological evidence of bacterial infection.

The sepsis group had higher values than the flare-up group in terms of CRP (43.79+30.4 versus 17.90+11.7 mg/dL) and serum PCT (1.86+0.8 versus 0.24+0.3 ng/mL), both of which were statistically significant ($p<0.05$). However, differences in absolute neutrophil count (ANC), platelet count, and ESR between the two groups were all nonsignificant (Table II).

The AUC (0.959), sensitivity (94.7%), and specificity (74.3%) of PCT at the cutoff value of >0.275 ng/mL, with a diagnostic accuracy of 84.9% were significantly better than those of CRP with AUC (0.827), sensitivity (73.7%), and specificity (73.6%) with a diagnostic accuracy

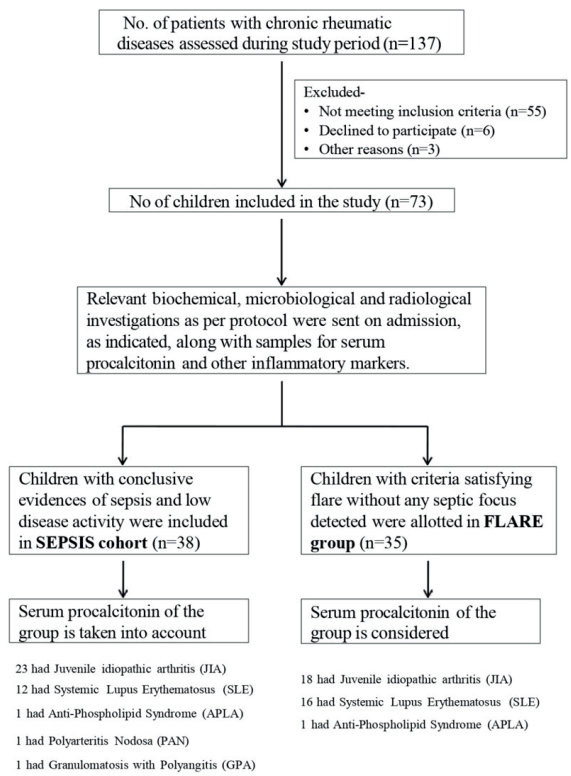

Fig. 1. Flow chart of the study population.

Table I. Demographic characteristics of the study population.

	Overall (n=73)	Flare-up (n=35)	Sepsis (n=38)
Age, yr, mean±SD	9.66 ± 2.3	9.51 ± 2.6	9.80 ± 2.1
Male gender, n (%)	20 (27.4)	9 (25.7)	11 (28.9)
Duration of fever, days, mean±SD	8.04 ± 3.4	8.54 ± 4.4	7.58 ± 2.9
Underlying condition, n (%)			
JIA	41 (56.2)	18 (51.4)	23 (60.5)
SLE	28 (38.3)	16 (45.7)	12 (31.6)
Others	4 (5.5)	1 (2.8)	3 (7.9)
Age at primary diagnosis, yr, mean±SD	7.30 ± 1.6	7.27 ± 1.8	7.31 ± 1.40
Interval since primary diagnosis, yr, mean±SD	2.53 ± 1.6	2.21 ± 1.4	2.78 ± 1.7

JIA, juvenile idiopathic arthritis; SD, standard deviation; SLE, systemic lupus erythematosus.

Table II. Comparison of inflammatory markers between subgroups of the study population (n=73).

	Flare-up (n=35)	Sepsis (n=38)	Significance*
CRP, mg/dL	17.90 ± 11.7	43.79 ± 30.4	0.001$
ESR, mm/hr	41.58 ± 15.2	49.74 ± 13.1	0.289$
Procalcitonin, ng/mL	0.24 ± 0.3	1.86 ± 0.8	<0.001$
Platelet count, $x10^9$/L	282.09 ± 199.1	205.83 ± 175.3	0.172$
Absolute neutrophil count, $x10^9$/L	5.48 ± 3.4	6.11 ± 3.0	0.180$

*p-value of independent t-test. Data presented as mean ± standard deviation.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

of 72.60% for differentiating between flare and infection (Fig. 2). Using PCT ≥0.275 ng/mL, the sensitivity (94.7%), specificity (74.3%), positive predictive value (PPV) (80.00%), and negative predictive value (NPV) (92.8%) were higher than those of other inflammatory markers (Table III).

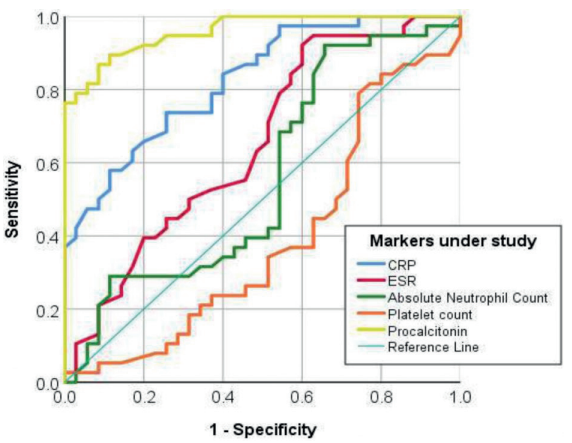

Fig. 2. Receiver operative characteristics (ROC) curve, showing different inflammatory markers under study to differentiate flare-up from bacterial sepsis. CRP, C-reactive protein, ESR, erythrocyte sedimentation rate.

Serum PCT levels on admission in all cases were compared with CRP, ESR, platelet count, and ANC using ROC curve analysis, and the optimum cut-off values for each of them were calculated by Youden's method. The cut-off values of PCT, CRP, and ESR were found to be 0.275 ng/mL, 24.1 ng/dL, and 44.5 mm/hr respectively, a value above which indicates more chance of sepsis. AUC of these parameters were 0.959, 0.827, and 0.653 respectively. Comparative ROC curve analysis reveals that serum PCT at a cut-off value of 0.275 ng/dL has the best diagnostic value among all studied parameters in differentiating flare-ups from sepsis in febrile patients with known rheumatic diseases. Serum PCT values of > 0.275 ng/dL correspond to a higher diagnostic accuracy of 84.90% with acceptable sensitivity, specificity, PPV, and NPV in predicting sepsis than the other markers, followed by CRP.

Table III. Areas under the curve of different markers as per ROC curve.

Markers	Area under curve	Cut-off value	95% confidence interval	p value	Sensitivity	Specificity
Procalcitonin, ng/mL	0.959	0.275	0.921-0.997	<0.001	94.7%	74.3%
ESR, mm/hr	0.653	44.5	0.526-0.780	0.025	63.2%	51.4%
CRP, mg/dL	0.827	24.1	0.736-0.918	0.002	73.7%	73.6%
ANC, /μL	0.561	4510	0.526-0.780	0.371	68.4%	42.9%
Platelets, /L	0.389	$170x10^9$	0.257-0.521	0.102	44.7%	37.1%

*The optimum cut-off values were calculated by Youden's method.
ANC, absolute neutrophil count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Discussion

Sepsis and disease flare-ups are the two most important but diametrically opposite complications of any chronic rheumatic illness. Ongoing efforts are being made to establish a biomarker for the early differentiation between these two conditions in pediatric patients with chronic rheumatic conditions. However, the attempt is challenging due to scarce data among the children, especially in the Indian scenario. The current study aims to investigate the effectiveness of PCT in this regard. In addition, this study endeavors to conduct a comparative analysis between PCT and other commonly used laboratory markers, including ESR, CRP, platelet count, and ANC. Furthermore, it seeks to establish a cutoff value for diagnosis.

Bacterial infections are major causes of sepsis in SLE with the most frequent sites of infection being the respiratory tract, urinary tract, and skin. Nonetheless, a majority of SLE patients also get admitted with serious disease flares. A study in Southeast Asia on SLE patients admitted for serious complications revealed higher serum PCT levels in the bacterial infection group, a median value of 1.66 (0.04-8.45) ng/mL compared to the non–infection group, median value of 0.12 (0.02-0.81) ng/mL.[16] This study demonstrated a notable difference in serum PCT levels between the bacterial infection group and non-infection/flare groups in SLE patients. This resonates with our study, wherein only PCT and CRP were statistically significantly higher among children with sepsis. Contrary to our results, one of the studies conducted in France[17], which focused on SLE patients however concluded PCT can't reliably differentiate between flare and sepsis. However, their results were based on only 5 patients suffering from chronic infections. Supporting the relevance of our work, a systematic review and meta-analysis in 2021 illustrated that serum PCT and CRP levels were markedly elevated in SLE with bacterial infections. Notably, the authors identified PCT as a superior diagnostic marker to CRP with a high value of positive likelihood ratio.[18] Similar findings were documented in a Korean study where both CRP and PCT levels were higher in the infection group compared to the disease flare group.[19]

Research involving PCT and autoimmune diseases had already been started decades ago, but authors were unsure about a positive correlation. A study in Poland assessed PCT, CRP, and ESR in 28 children with autoimmune disease, including 9 with juvenile arthritis. They found that while ESR and CRP are sometimes elevated in children with autoimmune disease, PCT remains low in this population, but the study had its limitations.[20] Subsequent research on children with JIA suggested that serum ESR, CRP, and PCT levels could serve as viable biomarkers for distinguishing serious bacterial infection (SBI) from active JIA at presentation. Among these markers, PCT demonstrated the highest accuracy, showing minimal overlap between patients with infection and non-infectious inflammatory arthritis with a high sensitivity and specificity.[21] The current study also has similar findings where PCT at a cut-off of ≥ 0.275 ng/mL, had higher sensitivity

(94.7%) and specificity (74.3%) than the other inflammatory biomarkers in distinguishing sepsis.

Though a considerable number of studies on this topic have found serum PCT as the best diagnostic tool to differentiate the flare-up from bacterial sepsis, only a few have tried to reach an objective cut-off of PCT level. A PCT cut-off value as high as 0.5 ng/mL was observed in a study on heterogeneous rheumatic diseases.[22] A study on adult patients reported that the best cut-off value for PCT was 0.09 ng/mL.[19]

In cases of arthritis in adults, research has also shown PCT to be a useful biomarker. High PCT levels strongly suggest bacterial infection and it is better than either CRP, ESR, or WBC count in patients with RA.[23] This Japanese study used a cut-off value of 0.5 ng/mL for serum PCT with 98.2% specificity and 14.33% positive likelihood ratio. Our study had higher sensitivity and specificity at lower cut-offs, which can be explained by differences in disease activity, age, and ethnicity of the study population. One of the pediatric studies on rheumatic arthritis patients found a PCT concentration of less than 0.15 μg/mL in flare-up children[21], which is almost in congruence with our results.

A project on chronic rheumatic diseases in adults showed an area under the ROC curves (AUC; 95% CI) for CRP [0.70; (0.58-0.82)] and PCT [0.84; (0.75-0.93)] which indicated a significant difference (p<0.05). On the contrary, the authors didn't find any significant difference in predicted AUC between the CRP/ PCT levels combined and PCT levels alone (P=0.80). They determined 7.18 mg/dL to be the best cut-off value for CRP, with a sensitivity of 71.9% and a specificity of 68.1%. For PCT, the cut-off was 0.09 ng/mL, with 81.3% sensitivity and 78.7% specificity.[19]

The current study is one of the very few conducted on the pediatric population in eastern India, concerning this rather important problem with significant clinical implications. However, this study has its fair share of limitations as well. Firstly, this was a single-center study carried out in a tertiary care hospital, so hospital bias couldn't be ruled out. The sample size was small, more so, due to the COVID-19 pandemic and the consequent lockdown. Mostly JIA and SLE patients were studied in the wide spectrum of childhood rheumatic diseases as there was a lesser influx of patients with other chronic rheumatic conditions.

Secondly, there is a lack of a universally accepted uniform defining criterion for flare in JIA unlike in SLE. The core response value (CRV) criteria[9] are difficult to apply to the majority of the Indian population. Also, the authors of JADAS have themselves indicated that, although the score was devised to cover all categories of JIA, it still possesses certain limitations. A scoring system incorporating the extra-articular manifestations of systemic JIA, particularly fever and rash, would make the evaluation more robust and valid. Thirdly, PCT is elevated only in cases of bacterial and fungal infection but not non-bacterial infections like viral infections, thus making it difficult to differentiate from flare-ups. And finally, follow-up regarding long-term survival was beyond the scope of our study.

Conclusion

This study indicates that serum PCT can help differentiate between disease flare and sepsis in febrile children with chronic rheumatic diseases. PCT levels above 0.275 ng/mL in febrile patients with chronic rheumatic diseases can indicate sepsis, while a lower value may suggest non-infectious inflammation and reduce unnecessary antibiotic use.

Ethical approval

The study was approved by NRS Medical College and Hospital Institutional Ethical Committee (date: 27.01.2020, number: No/ NMC/446).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SM, MN, SM; data collection: SM, SS; analysis and interpretation of results: SM, SM, SS; draft manuscript preparation: MN, SM, SS. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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