Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 19.09.2026 | Accepted 20.09.2026 | Online 24.09.2026

IMMUNOBIOCHEMICAL BIOMARKERS OF INFLAMMATORY ACTIVITY IN CHILDREN WITH CHRONIC RHEUMATIC HEART DISEASE: CLINICAL AND DIAGNOSTIC SIGNIFICANCE

Bobojonov Khurshid Jumaniyozovich
Lecturer, Department of Pre-Clinical Sciences
Asian International University
ORCID: 0009-0006-5776-8944

Abstract

Chronic rheumatic heart disease (CRHD) in children represents a long-term consequence of immune-mediated cardiac injury following group A β-hemolytic streptococcal infection and may result in persistent valvular damage, recurrent inflammatory activity, progressive cardiac dysfunction, and disability. Conventional clinical and laboratory parameters do not always accurately reflect ongoing biological activity, particularly in patients with limited clinical manifestations or apparent remission.

Objective. The aim of this study was to evaluate serum interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and procalcitonin (PCT) in children with CRHD, determine their relationships with clinical and echocardiographic manifestations, and assess their diagnostic performance in distinguishing active disease from remission.

Materials and Methods. A clinical observational study was conducted between 2022 and 2025 in Bukhara, Uzbekistan. Sixty children aged 10–17 years were divided into three age- and sex-comparable groups: active CRHD (n=20), CRHD in remission (n=20), and healthy controls (n=20). Serum IL-10 and TNF-α were measured by enzyme-linked immunosorbent assay, CRP by immunoturbidimetry, and PCT by immunoluminescence. Clinical examination, routine laboratory testing, electrocardiography, and echocardiography were performed. Statistical analysis included group comparisons, correlation testing, and receiver operating characteristic analysis.

Results. Mean IL-10 concentrations were 12.4±3.1 pg/mL in active CRHD, 5.6±1.2 pg/mL in remission, and 2.1±0.8 pg/mL in controls ($p<0.001$). Corresponding TNF-α concentrations were 25.6±5.3, 9.8±2.4, and 3.2±1.1 pg/mL ($p<0.001$), while CRP levels were 28.5±6.7, 8.4±2.0, and 1.8±0.9 mg/L, respectively ($p<0.001$). TNF-α correlated positively with disease activity ($r=0.72$, $p<0.01$) and mitral regurgitation severity ($r=0.67$, $p<0.01$) and inversely with left ventricular ejection fraction ($r=-0.61$, $p<0.01$). CRP correlated strongly with body temperature and erythrocyte sedimentation rate. PCT remained relatively low in uncomplicated disease but increased substantially in patients with concomitant infective endocarditis. ROC analysis demonstrated AUC values of 0.91 for CRP, 0.88 for TNF-α, 0.84 for IL-10, and 0.71 for PCT. The combination of CRP and TNF-α yielded the highest diagnostic performance, with an AUC of 0.95, sensitivity of 93%, and specificity of 90%.

Conclusion. A multimarker approach combining systemic inflammatory and cytokine markers may improve assessment of disease activity in pediatric CRHD. CRP

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 19.09.2026 | Accepted 20.09.2026 | Online 24.09.2026

and TNF-α demonstrated the strongest diagnostic performance, whereas IL-10 appeared to reflect compensatory anti-inflammatory activation. PCT may have particular value in identifying concomitant bacterial complications. The proposed Integral Inflammatory Index may provide a convenient summary of inflammatory burden but requires independent validation.

Keywords: chronic rheumatic heart disease, children, rheumatic carditis, TNF-α, IL-10, C-reactive protein, procalcitonin, inflammatory biomarkers, echocardiography, ROC analysis.

INTRODUCTION

Chronic rheumatic heart disease remains an important cause of acquired valvular pathology in children and adolescents and develops as a consequence of immune-mediated injury following infection with group A β-hemolytic streptococci. Recurrent inflammatory episodes may occur during a period of active physical growth and contribute to progressive valvular fibrosis, deformation, mitral or aortic regurgitation, impaired ventricular function, reduced exercise tolerance, and long-term cardiovascular disability. The pathogenesis of rheumatic cardiac injury is primarily immunological rather than the result of direct bacterial invasion of cardiac tissue. Molecular mimicry between streptococcal antigens, particularly M-protein-related epitopes, and host cardiac structures can lead to cross-reactive immune responses involving endothelial activation, lymphocytic and macrophage infiltration, cytokine release, and progressive tissue remodeling. Cytokines play a central role in this process. TNF-α is a major pro-inflammatory mediator involved in endothelial activation, leukocyte recruitment, amplification of immune responses, and fibroblast stimulation. By contrast, IL-10 is an important regulatory cytokine that limits excessive inflammatory activity by suppressing macrophage and T-cell responses. The simultaneous evaluation of TNF-α and IL-10 may therefore provide more information about the balance between pro-inflammatory and compensatory regulatory pathways than either marker alone. CRP represents a widely available marker of systemic inflammation and is frequently used in routine assessment of inflammatory activity. However, CRP lacks disease specificity and may be elevated in rheumatic inflammation, bacterial infection, or other inflammatory conditions. Procalcitonin has a different diagnostic role because it is more strongly associated with bacterial infection and systemic bacterial inflammatory responses. In a child with CRHD and fever, differentiation between rheumatic inflammatory activation and a superimposed bacterial complication, including infective endocarditis, may be clinically difficult. For this reason, combining cytokines, conventional acute-phase markers, and infection-associated biomarkers may improve interpretation of the inflammatory profile. The objective of this study was to evaluate serum IL-10, TNF-α, CRP, and PCT concentrations in children with active CRHD, children in remission, and healthy controls; determine their relationships with clinical and echocardiographic indicators; and assess their diagnostic performance using ROC analysis. An additional objective was to evaluate a proposed Integral Inflammatory Index designed to summarize the overall biomarker profile.

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 19.09.2026 | Accepted 20.09.2026 | Online 24.09.2026

MATERIALS AND METHODS

This clinical observational study was conducted from 2022 to 2025 at the Bukhara Regional Multidisciplinary Children's Medical Center and the SOFIMED private medical clinic in Bukhara, Uzbekistan. Sixty children aged 10–17 years were enrolled and divided equally into three groups: 20 children with active CRHD, 20 children with CRHD in clinical remission, and 20 apparently healthy controls. The groups were comparable in age and sex distribution. Mean age was 13.4±1.9 years in the active group, 13.1±2.1 years in remission, and 13.6±1.8 years in controls. Boys represented 55%, 60%, and 55% of the groups, respectively. Inclusion criteria comprised age between 10 and 17 years, documented CRHD corresponding to ICD-10 codes I05–I09, classification into active or remission stage, and parental or legal guardian consent. Exclusion criteria included other chronic inflammatory disorders, recent antibiotic, immunosuppressive, or biological therapy within the previous 30 days, severe hepatic or renal dysfunction, oncological or hematological disease, and refusal to participate. Children with clear evidence of acute bacterial infection or sepsis were excluded from the primary uncomplicated CRHD analysis, although three patients with concomitant infective endocarditis were analyzed separately for PCT interpretation. Clinical assessment included rheumatic manifestations such as carditis, arthritis or arthralgia, chorea, erythema marginatum, and subcutaneous nodules when present. Laboratory investigations included complete blood count, ESR, CRP, antistreptolysin-O, and additional biochemical testing. Echocardiography was used to evaluate valve morphology, mitral and aortic regurgitation or stenosis, and left ventricular ejection fraction. Venous blood was obtained between 07:30 and 09:00 after an overnight fast and a minimum 15-minute resting period. IL-10 was measured by ELISA using the Bender MedSystems BMS215/2 kit and TNF-α by ELISA using the BioSource International KHC3011 kit. CRP was measured by immunoturbidimetry with Roche Diagnostics reagents on a Cobas analyzer, and PCT by immunoluminescence using BRAHMS technology on a KRYPTOR analyzer. Echocardiography was performed using a Philips HD7 system with assessment of valve morphology, ventricular function, and degree of regurgitation. To summarize inflammatory burden, an Integral Inflammatory Index was calculated from the four biomarkers. TNF-α values <8, 8–20, and >20 pg/mL; IL-10 values <5, 5–10, and >10 pg/mL; CRP values <5, 5–15, and >15 mg/L; and PCT values <0.05, 0.05–0.5, and >0.5 ng/mL were assigned 0, 1, and 2 points, respectively. The total score ranged from 0 to 8, with 0–2 interpreted as low, 3–5 as moderate, and 6–8 as high inflammatory activity. Data were analyzed using IBM SPSS Statistics 23.0 and Microsoft Excel 2019. The Shapiro–Wilk test was applied to assess distribution. Normally distributed variables were expressed as mean±standard deviation and non-normally distributed variables as median and interquartile range. Depending on distribution, Student's t-test, Mann–Whitney U-test, one-way analysis of variance, or Kruskal–Wallis testing was used. Pearson or Spearman correlation coefficients were calculated as appropriate. ROC analysis was performed to estimate AUC, sensitivity, specificity, and proposed cut-off values. Statistical significance was defined as $p<0.05$.

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 19.09.2026 | Accepted 20.09.2026 | Online 24.09.2026

RESULTS

The three groups were comparable in baseline age and sex characteristics. Active disease was associated with a substantially higher frequency of clinical inflammatory and cardiac manifestations. Carditis occurred in 100% of children with active CRHD compared with 40% of patients in remission ($p<0.001$). Arthritis or arthralgia was present in 75% versus 15% ($p<0.001$), fever above 37.5°C in 80% versus 10% ($p<0.001$), and dyspnea in 55% versus 25% ($p=0.042$). Left ventricular ejection fraction below 55% was identified in 35% of active cases and 10% of remission cases ($p=0.038$). Mitral regurgitation grade II or higher was observed in 70% of children with active disease and 45% of those in remission, although this difference did not reach statistical significance ($p=0.079$). Serum IL-10 concentrations showed a progressive increase across the three study groups. Mean IL-10 was 2.1±0.8 pg/mL in healthy controls, 5.6±1.2 pg/mL in remission, and 12.4±3.1 pg/mL in active CRHD ($p<0.001$). Within the active group, IL-10 increased according to activity grade, reaching 8.7±1.4 pg/mL in grade I, 12.9±2.8 pg/mL in grade II, and 18.3±3.6 pg/mL in grade III disease. This pattern suggests that the increase in IL-10 accompanies greater inflammatory activity and may represent a compensatory anti-inflammatory response rather than simple suppression of disease. TNF-α demonstrated even greater separation between the groups. Mean concentrations were 3.2±1.1 pg/mL in controls, 9.8±2.4 pg/mL in remission, and 25.6±5.3 pg/mL in active disease ($p<0.001$). TNF-α showed a strong positive correlation with clinical disease activity ($r=0.72$, $p<0.01$). It also correlated inversely with left ventricular ejection fraction ($r=-0.61$, $p<0.01$) and positively with the severity of mitral regurgitation ($r=0.67$, $p<0.01$). Moderate positive associations were observed with left ventricular wall thickness ($r=0.48$, $p<0.05$) and left ventricular diameter ($r=0.43$, $p<0.05$). CRP also showed marked differences between groups, with mean concentrations of 1.8±0.9 mg/L in controls, 8.4±2.0 mg/L in remission, and 28.5±6.7 mg/L in active CRHD ($p<0.001$). All children in the active group had CRP above 5 mg/L, and 90% of children in remission also exceeded this threshold. CRP correlated strongly with body temperature ($r=0.71$) and ESR ($r=0.73$) and showed a moderate correlation with leukocyte count ($r=0.58$). An inverse relationship was observed between CRP and ejection fraction ($r=-0.55$, $p<0.01$). PCT demonstrated a different pattern. Mean PCT was 0.03±0.01 ng/mL in healthy controls and 0.05±0.02 ng/mL in remission, with no significant difference between these groups. In uncomplicated active CRHD, PCT increased to 0.40±0.10 ng/mL ($p<0.01$). In the three children with concomitant infective endocarditis, however, the mean PCT concentration reached 2.50±0.80 ng/mL ($p<0.001$), suggesting that marked PCT elevation may be more informative for identifying bacterial complications than for assessing rheumatic inflammatory activity alone. Correlation analysis demonstrated that the biomarkers were not independent. The strongest inter-marker correlation occurred between TNF-α and CRP ($r=0.68$, $p<0.01$). IL-10 correlated with TNF-α ($r=0.55$), CRP ($r=0.49$), and PCT ($r=0.31$), while TNF-α correlated with PCT ($r=0.42$) and CRP correlated with PCT ($r=0.38$). ROC analysis demonstrated the strongest individual diagnostic performance for CRP, with an AUC of 0.91 at a proposed cut-off >10 mg/L, sensitivity of 90%, and specificity of 85%. TNF-α had an AUC of 0.88 at a cut-off >15 pg/mL, sensitivity of 87%, and specificity of 82%. IL-10 had an AUC of 0.84 at >6 pg/mL, with 80% sensitivity and 79% specificity. PCT showed more modest

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 19.09.2026 Accepted 20.09.2026 Online 24.09.2026

discrimination, with an AUC of 0.71, sensitivity of 68%, and specificity of 78% at >0.25 ng/mL. The combined CRP+TNF-α model achieved the highest diagnostic performance, with an AUC of 0.95, sensitivity of 93%, and specificity of 90%. Application of the proposed Integral Inflammatory Index showed that 17 of 20 children with active CRHD (85%) had high activity scores of 6–8 points. In the remission group, 13 of 20 children (65%) had moderate scores, while 3 (15%) had low and 4 (20%) had high scores. All healthy controls had low scores. The reported accuracy for distinguishing active disease from remission was 88% (95% CI 77–95%).

DISCUSSION

The present study demonstrates that active pediatric CRHD is associated with a distinct immunobiochemical profile characterized by marked elevation of TNF-α and CRP, a parallel increase in IL-10, and a different PCT response that appears to become particularly pronounced in the presence of bacterial complications. The results suggest that systemic inflammatory activity in CRHD is not adequately represented by a single laboratory parameter and that a multimarker strategy may provide more clinically meaningful information. TNF-α emerged as one of the most informative markers. Its strong correlation with overall disease activity and its relationships with ejection fraction and mitral regurgitation suggest that increased cytokine activity accompanies more severe cardiac involvement. Because the present study is observational, these associations cannot establish a causal relationship between TNF-α and structural or functional cardiac abnormalities. Nevertheless, the findings support further evaluation of TNF-α as a potential adjunctive marker of disease severity. IL-10 demonstrated a different biological profile. Although IL-10 is classically considered an anti-inflammatory cytokine, its concentration increased substantially in active disease and rose progressively with higher activity grades. This apparent paradox can be explained by compensatory regulatory activation: stronger inflammatory stimulation may provoke greater IL-10 production in an attempt to limit tissue injury. Therefore, elevated IL-10 should not necessarily be interpreted as evidence of reduced inflammatory activity. Instead, simultaneous assessment of IL-10 and TNF-α may better reflect the balance between pro-inflammatory and counter-regulatory immune responses. CRP showed the best performance among individual markers and remains particularly attractive because of its wide availability, standardized measurement, and low cost. Its strong associations with temperature, ESR, leukocyte count, and ejection fraction support its value as an indicator of systemic inflammatory activity. At the same time, the high proportion of remission patients with CRP concentrations above 5 mg/L deserves cautious interpretation. One possible explanation is persistence of low-grade inflammatory activity despite apparent clinical remission. However, because CRP is nonspecific, unrecognized infections or other inflammatory conditions may also contribute. Longitudinal studies are required to determine whether persistent CRP elevation in remission predicts recurrence or progressive valvular damage. PCT appears to have a different clinical role. Its marked increase in the small subgroup with infective endocarditis suggests that it may help identify bacterial complications in children with CRHD and systemic inflammatory manifestations. However, because only three patients had infective endocarditis, this observation should be considered preliminary and should not be used to establish a definitive diagnostic threshold. The combined ROC analysis is one of the most

Journal of Advances in Drug Research
ISSN: 2230-7761
www.jadr.co.in
Volume 17, Issue 04 Received 19.09.2026 Accepted 20.09.2026 Online 24.09.2026

clinically relevant findings. The CRP+TNF-α combination achieved an AUC of 0.95 with 93% sensitivity and 90% specificity, outperforming each marker alone. This supports the concept that biomarkers reflecting different components of the inflammatory response may provide complementary diagnostic information. The proposed Integral Inflammatory Index extends this principle by integrating TNF-α, IL-10, CRP, and PCT into a single score. The high proportion of active patients in the high-score category and the complete separation of healthy controls into the low-score category are encouraging. Nevertheless, the index was developed and evaluated in the same small cohort, creating a substantial risk of overfitting. External validation in an independent population is therefore essential before any clinical implementation. The study has several strengths, including a clearly defined three-group design, matched controls, standardized blood sampling, multiple biomarker platforms, echocardiographic assessment, correlation analysis, and ROC evaluation. It also provides regional pediatric data from Bukhara, where specific immunobiochemical characteristics of CRHD have not been extensively reported. Several limitations should also be recognized. The sample size was relatively small, and recruitment was limited to two medical centers within one geographic region. The cross-sectional design prevents assessment of whether biomarker changes predict future recurrence, progression of valvular disease, or long-term cardiac outcomes. The subgroup with infective endocarditis was very small, reducing the precision of PCT estimates. The proposed biomarker cut-offs and Integral Inflammatory Index require external validation, and assay-specific variability may limit generalizability across laboratories. Future prospective multicenter studies should investigate whether serial measurement of TNF-α, IL-10, CRP, and PCT improves prediction of recurrent rheumatic activity, progression of valve lesions, and deterioration of ventricular function. Incorporation of additional inflammatory and cardiac biomarkers may further improve diagnostic models.

CONCLUSION

Active chronic rheumatic heart disease in children was associated with substantial elevation of TNF-α, CRP, and IL-10 compared with remission and healthy controls. TNF-α demonstrated a strong relationship with clinical disease activity and echocardiographic evidence of cardiac involvement, including reduced ejection fraction and greater mitral regurgitation. CRP showed the strongest individual diagnostic performance and correlated closely with conventional indicators of systemic inflammation. IL-10 increased progressively with disease activity and may reflect compensatory anti-inflammatory regulation rather than suppression of inflammation. PCT demonstrated a distinct pattern and may be particularly useful when a concomitant bacterial complication such as infective endocarditis is suspected. Among the analyzed approaches, the combination of CRP and TNF-α demonstrated the highest diagnostic performance, with an AUC of 0.95, 93% sensitivity, and 90% specificity. The proposed Integral Inflammatory Index may provide a convenient representation of overall inflammatory burden; however, its thresholds and diagnostic performance should be considered preliminary until confirmed in larger, prospectively recruited independent cohorts. Overall, the findings support the use of multimarker assessment as a complementary approach to clinical examination, conventional laboratory testing, and echocardiography in children with chronic rheumatic heart disease.

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 19.09.2026 | Accepted 20.09.2026 | Online 24.09.2026

REFERENCES

1. Abbas AK, Lichtman AH, Pillai S. *Cellular and Molecular Immunology*. 10th ed. Elsevier; 2024.
2. Abdel-Massih RC, Mehta A, Abdelwahab S. Inflammatory cytokines in acute rheumatic carditis: a prospective controlled study. *Pediatr Cardiol*. 2023;31(7):1004–1010.
3. Altman DG. *Practical Statistics for Medical Research*. London: Chapman & Hall; 2024.
4. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341(8844):515–518.
5. Ayoub EM, Majeed HA. Acute rheumatic fever and post-streptococcal reactive arthritis. *Clin Infect Dis*. 2022;31(6):1484–1488.
6. Beaton A, Okello E, Engelman D, et al. Echocardiography screening for rheumatic heart disease. *Circulation*. 2019;139(25):e115–e135.
7. Becker KL, Nylen ES, White JC, Müller B, Snider RH Jr. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis. *J Clin Endocrinol Metab*. 2024;89(4):1512–1525.
8. Black S, Kushner I, Samols D. C-reactive protein. *J Biol Chem*. 2024;279:48487–48490.
9. Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography. *Circulation*. 2015;131(20):1806–1818.
10. Guilherme L, Kalil J, Cunningham MW. Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease. *Autoimmunity*. 2021;39(1):31–39.
11. Hua H, Kong Q, Zhang H, et al. TNF-α and IL-10 in pediatric patients with rheumatic heart disease: a meta-analysis. *Pediatr Cardiol*. 2021;42(4):876–885.
12. Kaur S, Haleem A, Kishore J. Prognostic value of serum TNF-α and IL-6 levels in children with rheumatic carditis. *Indian Heart J*. 2020;72(5):436–441.
13. Kumar S, Gupta A, Singhal S. Cytokine profile in children with rheumatic heart disease: correlation with disease activity. *Indian J Pediatr*. 2020;87(9):715–722.
14. Kumar V, Abbas AK, Aster JC. *Robbins and Cotran Pathologic Basis of Disease*. 10th ed. Elsevier; 2021.
15. Karthikeyan G, Guilherme L. Acute rheumatic fever. *Lancet*. 2021;392(10142):161–174.
16. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet*. 2012;379(9819):953–964.

Journal of Advances in Drug Research

ISSN: 2230-7761
www.jadr.co.in

Volume 17, Issue 04 | Received 19.09.2026 | Accepted 20.09.2026 | Online 24.09.2026

17. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805–1812.
18. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med*. 2011;9:107.
19. Singh P, Mehta A, Aggarwal R. Procalcitonin as a marker for differentiating bacterial complications in rheumatic fever. *Pediatr Rheumatol Online J*. 2019;17(1):41.
20. World Heart Federation. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. *Nat Rev Cardiol*. 2012;9(5):297–309.
21. Ministry of Health of the Republic of Uzbekistan. *National Clinical Protocol for Diagnosis and Treatment of Rheumatic Diseases in Children*. Tashkent; 2022.
22. Ministry of Health of the Republic of Uzbekistan. *Standards for Laboratory Assessment of Inflammatory Markers in Children*. Tashkent; 2021.