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Original Research Article

Evaluating the role of C-reactive protein velocity in identifying viral infections in children with elevated C-reactive protein levels

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ABSTRACT

Background: C-reactive protein (CRP) is routinely used to differentiate between bacterial and viral infections in children. However, despite clinical features suggestive of viral illness, several viral infections may present with markedly elevated CRP levels, leading to diagnostic uncertainty and unnecessary antibiotic use. C-reactive protein velocity (CRPv) may improve identification of viral infections in children presenting with elevated CRP levels.
Methods: A prospective observational study was conducted among children aged 6 months to 12 years admitted with fever, and CRP >20 mg/l. Viral infection was confirmed using nasopharyngeal viral PCR. Serum CRP was measured at admission and after 24 hours to calculate CRPv. CRPv was compared between viral positive and viral negative groups using appropriate statistical tests.
Results: 61 children were enrolled, including 42 (68.9%) with PCR-confirmed viral infections and 19 (31.1%) in viral-negative group. CRP velocity was significantly lower in the viral-positive group (median (Q1–Q3): −0.458 (−1.39 to −0.177) vs. 0.375 (0.0625–0.458) mg/l/hour; p<0.001). ROC analysis demonstrated good performance of CRP velocity, with an AUC of 0.881 (95% CI: 0.786–0.976, p<0.001). A cutoff of ≤−0.125 mg/l/hour yielded a sensitivity of 78.6% and specificity of 94.7%.
Conclusion: CRP velocity demonstrated good discriminatory performance in identifying PCR-confirmed viral infections in children with elevated admission CRP level. A greater decline in CRP over the first 24 hours was strongly associated with viral infections, suggesting that serial CRP measurements may serve as a useful marker in early clinical decision-making and help optimize antimicrobial stewardship.

Keywords: C-reactive protein velocity, Viral infections, Children, Viral PCR, Antimicrobial stewardship, CRP velocity

INTRODUCTION

C-reactive protein (CRP) is one of the most widely used inflammatory biomarkers in the evaluation of febrile children and is routinely used to help differentiate between viral and bacterial infections. Because CRP rises rapidly in response to inflammation, its measurement frequently influences decisions regarding hospitalization and initiation of antibiotics. However, a single CRP measurement provides only a snapshot of the inflammatory response and has important limitations, as CRP concentrations vary with the stage of illness and the underlying pathogen, reducing its ability to reliably distinguish between viral and bacterial infections.[1,2] CRP is an acute-phase protein synthesized predominantly by hepatocytes in response to interleukin-6, with additional contributions from interleukin-1β and tumor necrosis factor-α.[3] Serum CRP begins to rise within approximately 6–8 hours after the onset of inflammation, reaches peak concentrations within 36–50 hours, and subsequently declines, with a relatively constant plasma half-life of approximately 19 hours, once the inflammatory stimulus subsides.[4] Thus, serial CRP measurements can provide information not only about the magnitude of inflammation but also about its temporal evolution. A declining CRP concentration may indicate resolution of the inflammatory

stimulus, whereas persistent or rising concentrations may reflect ongoing inflammation. Assessment of this temporal pattern, therefore, may provide additional discriminatory information when a single elevated CRP concentration is difficult to interpret.[5,6]

Children presenting with fever, viral prodromal symptoms, and elevated C-reactive protein concentrations represent a common diagnostic challenge. Although these clinical features often suggest a viral etiology, markedly elevated CRP levels frequently raise concern for bacterial infection, leading to additional investigations and empirical antibiotic therapy. Although bacterial infections are generally associated with higher CRP levels, several viral infections, particularly adenovirus and influenza, can also produce markedly elevated CRP concentrations.[7-9] Consequently, despite clinical features suggestive of a viral illness and the absence of an identifiable bacterial focus, children may present with high CRP values that prompt empirical antibiotic therapy. This diagnostic uncertainty contributes to unnecessary antibiotic exposure, increased healthcare costs, adverse drug effects, and the growing challenge of antimicrobial resistance.

These limitations have shifted attention from static biomarker measurements to the assessment of inflammatory kinetics. CRPv, defined as the rate of change in CRP concentration over time, provides a dynamic measure of the inflammatory response rather than a single-point estimate. While bacterial infections typically induce a rapid and sustained rise in CRP because of a robust inflammatory response, viral infections are expected to exhibit slower CRP kinetics or an early decline in CRP concentrations as the inflammatory response resolves.[10]

Recent studies have shown that assessment of CRP kinetics may provide greater diagnostic discrimination than isolated CRP measurements. Paran et al. introduced the concept of CRP kinetics by incorporating the duration of fever before presentation and demonstrated improved diagnostic discrimination compared with admission CRP alone.[10] Bernstein et al and Coster et al demonstrated that CRPv had superior diagnostic performance over a single CRP value.[4,11] However, evidence regarding its usefulness in children remains limited, particularly in studies where viral infections are confirmed by molecular diagnostic techniques.

The present study was therefore undertaken to evaluate the role of C-reactive protein velocity in identifying viral infections in febrile children with viral prodromal symptoms and elevated c-reactive protein levels among hospitalized children.

METHODS

Study design and setting

This prospective observational study was conducted in the pediatric ward of Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Kerala, over a period of six months, from February 2026 to July 2026. The study was approved by the Institutional Ethics Committee (approval no: SGMC IEC/69/989/02/2026F), and written informed consent was obtained from the parents or legal guardians of all participants before enrolment.

Study population and eligibility criteria

Children aged 6 months to 12 years admitted with acute febrile illness, an admission serum C-reactive protein (CRP) level >20 mg/l and suspected of having viral infection were eligible for inclusion. Children on antibiotic therapy, definite evidence of bacterial infection (including acute otitis media, lung consolidation, localized abscess, meningitis, septic arthritis, or urinary tract infection), immunosuppressive disorders, or those receiving anti-inflammatory therapy were excluded.

Sample size calculation

Sample size was calculated using the mean CRP velocity (CRPv) reported by Bernstein et al who observed mean CRPv values of 0.9 ± 1.2 mg/l/h in viral infections and 4.4 ± 2.7 mg/l/h in non-viral infections.[11] Using the standard formula for comparison of two independent means, the minimum required sample size was estimated to be 14. However, to obtain more reliable estimates and allow for potential variability between groups, the planned sample size was increased to 60 children.

Sampling technique, data collection and laboratory methods

Consecutive sampling was employed, and all eligible children admitted during the study period were enrolled. Serum CRP done on admission is marked as CRP 1. After obtaining informed consent, demographic and clinical details were recorded using a structured proforma. Serum CRP is repeated at 24 hours of admission and is marked as CRP 2. "CRPv was calculated as (CRP2 − CRP1)/24, and expressed as mg/l/hour. A nasopharyngeal swab was collected at admission for multiplex viral polymerase chain reaction (PCR) testing. Based on the results, participants were classified into viral-positive and viral-negative group. Respiratory pathogens were detected using the RevoDx respiratory pathogen detection kit (IDIL Biotech, Turkey) by real-time PCR on a QuantStudio™ 5 Real-Time PCR System (Thermo Fisher Scientific, USA). Serum CRP levels were measured using the Mispa i3 analyzer (Agappe Diagnostics Ltd., India) by nephelometry.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 29 statistical software. Continuous variables were assessed for normality. Normally distributed variables are presented as mean±SD and compared using

the independent-samples t-test. Non-normally distributed variables are expressed as median (IQR) and compared using the Mann–Whitney U test. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis.

Ethical considerations

Institutional Ethics Committee approval was obtained prior to commencement of the study. Written informed consent was obtained from the parents or primary caregivers of all participants. Confidentiality was maintained throughout the study, and the findings were used solely for scientific and academic purposes.

RESULTS

A total of 61 children fulfilling the eligibility criteria were enrolled in the study. Viral infection was confirmed by multiplex PCR in 42 (68.9%) children (viral-positive group), while 19 (31.1%) children constituted the viral-negative group. Among the viral-positive cases, majority were positive for influenza virus (n=18, 43%), followed by adenovirus (n=16, 38%) and RSV (n=8, 19%). There were no missing data, and all enrolled participants were included in the final analysis.

Participant Characteristics

The viral-positive group comprised younger children compared with the viral-negative group, with median ages of 3 and 5 years, respectively. Overall, males constituted approximately two-thirds of the study population (40 boys (65.6%) and 21 girls (34.4%)). The demographic characteristics of the study participants are presented in Table 1. Viral-positive children had higher admission total leukocyte counts compared with viral-negative children (11,501±3,432 vs. 9,688 ± 2,960 cells/mm^3; p=0.051). At 24 hours, total leukocyte counts were significantly lower in the viral-positive group compared with the viral-negative group (9,465±1,878 vs. 11,003±3,346 cells/mm^3; p=0.025). There were no statistically significant differences between the groups in hemoglobin concentration or platelet count at admission or after 24 hours (Table 2).

Comparison of CRP concentrations and CRP Velocity

Mean CRP concentrations at admission (CRP1) were 42.37±15.84 mg/l in viral-negative group, 56.26±30.74 mg/L in viral-positive group (p=0.068) After 24 hours (CRP2), the corresponding values were 48.00±18.39 mg/l and 38.60±18.18 mg/l, respectively (p=0.067). Admission CRP concentrations were higher in the viral-positive group than in the viral-negative group, although the difference was not statistically significant. Similarly, CRP concentrations at 24 hours did not differ significantly between the groups. In contrast, a marked difference was observed in the direction of change in CRP over the first 24 hours. CRP increased in the viral-negative group, whereas it declined in the majority of viral-positive children. Consequently, CRP velocity was significantly lower in the viral-positive group, with median values of −0.46 and 0.38 mg/l/hour, respectively (p<0.001) (Table 3 and Figure 1).

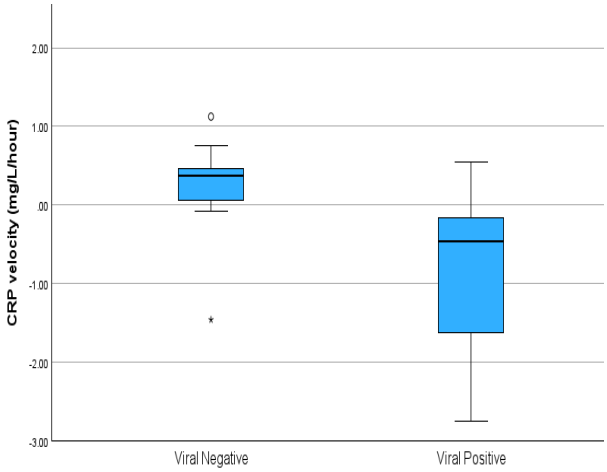

Figure 1: Box plot distribution of CRP velocity

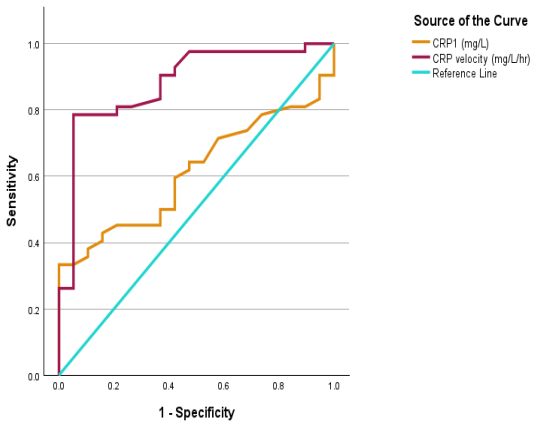

Figure 2: Receiver operating characteristic (ROC) curve of CRP velocity and admission CRP (CRP1).

Diagnostic performance of CRP velocity

CRP velocity demonstrated very good discriminatory performance, with an area under the ROC curve (AUC) of 0.881 (95% CI: 0.786–0.976, p < 0.001), indicating good discrimination between viral-positive and viral-negative children (Figure 2). The optimal cutoff value determined using the Youden Index was CRP velocity ≤−0.125 mg/l/hour, which yielded a sensitivity of 78.6%, specificity of 94.7% (Table 4). Direct comparison of the paired ROC curves using DeLong's test demonstrated significantly greater discriminatory performance of CRP velocity compared with admission CRP (AUC 0.881 vs. 0.613; AUC difference −0.268, 95% CI: −0.419 to −0.118; z=−3.50; p<0.001) Figure 2.

Table 1: Demographic characteristics of study participants.

Demographic characteristics	Viral-negative (n=19)	Viral-positive (n=42)	Total (n=61)
Age, years, median (IQR)	5 (3–7)	3 (2–5)	—
Male, n (%)	12	28	40 (65.6%)
Female, n (%)	7	14	21 (34.4%)

Table 2. Comparison of laboratory characteristics between viral-negative and viral-positive children.

Variables	Viral negative (n=19)	Viral positive (n=42)	P value
Total leukocyte count at admission (/mm³)	9,688±2,960	11,501±3,432	0.051
Total leukocyte count after 24 hours (/mm³)	11,003±3,346	9,465±1,878	0.025
Hemoglobin at admission (g/dl)	11.4±1.13	11.3±1.11	0.828
Hemoglobin after 24 hours (g/dl)	11.4±1.18	11.3±1.29	0.733
Platelet count at admission (/mm³)	273,382±56,067	244,026±58,815	0.072
Platelet count after 24 hours (/mm³)	284,522±68,361	256,596±58,421	0.107

Table 3. Comparison of CRP velocity between study groups.

Variables	Viral negative (n=19)	Viral positive (n=42)	P value
CRP1 (mg/l), Mean±SD	42.37±15.84	56.26±30.74	0.068*
CRP2 (mg/l), Mean±SD	48.00±18.39	38.60±18.18	0.067*
CRP velocity (mg/l/hour), Median (IQR)	0.38 (0.063–0.46)	−0.46 (−1.39 to −0.18)	<0.001**

*Independent t-test, **Mann–Whitney U

Table 4. Diagnostic performance of CRP velocity.

Parameters	Value
Area under the ROC curve (AUC)	0.881
Standard error	0.0486
95% Confidence interval	0.786–0.976
p value	<0.001
Optimal cutoff	CRP velocity ≤ −0.125 mg/l/hour
Sensitivity	78.6%
Specificity	94.7%

DISCUSSION

The present study demonstrated that CRP velocity differed significantly between children with PCR-confirmed viral infections and those without viral detection. While admission CRP (CRP1) values were comparable between the two groups, serial measurements over the first 24 hours revealed a marked decline in CRP among viral-positive children, resulting in negative CRP velocity, suggesting that CRP velocity may serve as a useful adjunct in identifying viral infections in children presenting with fever and elevated CRP. The absence of a significant difference in admission CRP between the groups highlights the limited utility of single CRP measurements. Several respiratory viruses, particularly influenza virus and adenovirus, are known to induce marked CRP elevations that may overlap with bacterial infections.[7] Previous pediatric studies have similarly demonstrated considerable overlap in CRP concentrations between viral and bacterial infections, reducing the specificity of single measurements.[9] In the cohort, influenza and adenovirus together accounted for nearly 80% of PCR-positive cases, which may explain the relatively high baseline CRP values observed in the viral-positive group. This observation is consistent with the known inflammatory response in influenza and adenoviral infections that can induce vigorous cytokine responses, particularly IL-6, resulting in substantial CRP production despite the absence of bacterial infection. Receiver operating characteristic analysis further supported the diagnostic utility of CRP velocity. The area under the ROC curve was 0.881 (95% CI: 0.786–0.976), indicating good discriminatory ability. A CRP velocity cutoff of ≤−0.125 mg/l/hour yielded a sensitivity of 78.6% and a specificity of 94.7% for identifying confirmed viral infections. These findings suggest that a falling CRP concentration is associated with viral etiology. Although the confidence intervals are relatively wide because of the modest sample size, the observed diagnostic performance is encouraging and supports further evaluation in larger prospective cohorts.

Importantly, direct comparison of the ROC curves demonstrated significantly greater discriminatory performance of CRP velocity compared with admission CRP. The AUC was 0.881 for CRP velocity compared with 0.613 for admission CRP, with a statistically significant difference by DeLong's test (AUC difference −0.268; 95% CI −0.419 to −0.118; p<0.001). These findings suggest that incorporating the temporal change in CRP provides greater diagnostic discrimination than reliance on a single admission CRP measurement

The concept of incorporating CRP kinetics into infection assessment was initially described by Paran et al. Their study demonstrated that CRP velocity improved discrimination between bacterial and viral febrile illness compared with absolute CRP, with AUC increasing from 0.783 for CRP to 0.871 for CRPv. CRPv was substantially higher in bacterial than viral infections (3.61 vs. 0.41 mg/l/hour). The present study is consistent with this fundamental observation that the temporal behavior of CRP provides additional information beyond its absolute concentration. However, Paran et al estimated CRPv using admission CRP and duration of fever, whereas the present study calculated CRPv directly from two measured CRP concentrations 24 hours apart.[10] The latter approach provides an objective measure of the change occurring after hospital admission. Evidence in children is relatively limited. Nahum et al evaluated CRP kinetics in children following cardiac surgery and found significantly higher CRPv among those with proven bacterial infection compared with children with fever without bacterial infection (4.0±4.2 vs 0.6±1.6 mg/dl/day)12. A similar study by Coster et al. evaluated serial CRP measurements in more than 1,600 adults and reported that the rate of change in CRP significantly improved diagnostic accuracy in patients (AUC 0.83 compared with 0.57 for admission CRP alone).[4]

Bernstein et al further demonstrated that although admission CRP values were similar in viral and bacterial infections, CRP velocity calculated from serial measurements within the first 24 hours was significantly greater in bacterial infections (4.4±2.7 vs 0.9±1.2 mg/l/h), confirming that CRP kinetics provide substantially greater diagnostic information than baseline CRP11. Our findings are consistent with these observations but extend them to a pediatric population with multiplex PCR-confirmed viral respiratory infections. Largman-Chalamish et al studied CRP kinetics using estimated CRP velocity (eCRPv). In their study of adults with confirmed bacterial or viral infection, eCRPv, calculated from admission CRP and the time from symptom onset, was significantly higher in bacterial infection than viral infection (1.1 vs. 0.25 mg/l/hour).[13] The difference was particularly evident in patients with intermediate CRP concentrations, where the absolute CRP value alone was less useful. Their approach differs from the present study because eCRPv incorporates the duration of illness before presentation, whereas our CRPv measures the subsequent change between two laboratory values. Nevertheless, both approaches support the broader principle that the rate of inflammatory change provides additional information beyond absolute CRP concentration. An additional finding in our study was that admission total leukocyte counts were higher in the viral-positive group than in the viral-negative group. This may initially appear unexpected because leukocytosis is traditionally associated with bacterial infections. However, influenza and adenovirus are well-recognized causes of transient leukocytosis during the acute phase of illness, and previous studies have reported considerable overlap in leukocyte counts between viral and bacterial infections. Moreover, at 24 hours, the total leukocyte count was significantly lower in the viral-positive group than in the viral-negative group. This temporal change suggests that leukocyte counts may also vary during the early course of illness and should be interpreted in conjunction with the clinical context and other biomarkers. No significant differences were observed in hemoglobin or platelet counts between the groups, suggesting that these conventional hematological parameters have limited discriminatory value when used in isolation. The hematological profile in the present study differed from that reported in previous CRP-kinetics studies. Paran et al. reported significantly higher total leukocyte and neutrophil counts in bacterial compared with viral infections, including among patients with lower admission CRP concentrations. Similarly, Largman-Chalamish et al reported higher leukocyte counts, neutrophil proportions and platelet counts in bacterial than viral infections. In contrast, the present study showed a tendency toward higher admission leukocyte counts in viral-positive children, followed by significantly lower leukocyte counts at 24 hours. Platelet counts did not differ significantly between groups. This discrepancy may reflect differences in age, pathogen distribution, timing of presentation and the clinical spectrum of the study populations. In our cohort, influenza and adenovirus constituted the majority of viral infections and may have contributed to the prominent early leukocyte response. These findings also suggest that conventional hematological parameters may have limited discriminatory value when compared with the temporal behavior of CRP in this particular pediatric population.

The clinical implications of these findings are potentially important. Incorporating serial CRP measurements into clinical assessment may provide additional information when evaluating children with elevated CRP concentrations despite features suggestive of viral illness. In clinically stable children, a declining CRP velocity may contribute to diagnostic confidence and support more judicious antimicrobial decision-making. However, whether use of CRP velocity can safely reduce antibiotic exposure or improve clinical outcomes requires prospective interventional evaluation.

The present study has several limitations. The sample size was relatively small, which limits the precision of the estimated diagnostic performance and precludes subgroup analysis according to specific viral pathogens. The study

was conducted at a single tertiary care centre, which may affect generalizability. Furthermore, the viral-negative group was defined by absence of viral detection on nasopharyngeal multiplex PCR and may have included bacterial as well as other non-respiratory viral illnesses.

Despite these limitations, this study provides preliminary evidence that CRP velocity is a promising biomarker in identifying viral infections in children. To the knowledge, this is among the first pediatric studies evaluating CRP velocity using molecular confirmation of viral respiratory infections. However, larger multicentre studies are needed to validate the proposed cutoff value, compare CRP velocity with established biomarkers such as procalcitonin, and determine whether incorporation of CRP kinetics in managing febrile children improves antibiotic stewardship and patient outcomes.

CONCLUSION

The present study demonstrates that CRP velocity provides greater diagnostic discrimination than a single admission CRP measurement and may represent a practical and inexpensive adjunct for identifying viral infections in febrile children with elevated CRP concentrations. While neither admission CRP nor CRP at 24 hours differed significantly between the groups, CRP velocity differed significantly, with viral PCR-positive children demonstrating a predominantly declining CRP pattern and negative CRP velocity. Direct comparison of ROC curves confirmed significantly greater discriminatory performance of CRP velocity than admission CRP. These findings suggest that assessment of CRP kinetics may provide additional diagnostic value beyond a single CRP measurement and could support clinical decisions and antimicrobial stewardship. Larger multicentre studies are warranted to validate these findings and establish standardized CRP velocity thresholds for routine pediatric practice.

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