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The Prognostic Value of Serial C-Reactive Protein Monitoring in Pediatric Febrile Neutropenia: A Single-Center Prospective Cohort Study

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Abstract

Background: In pediatric cancer patients, predicting the occurrence of sepsis and septic shock in the context of febrile neutropenia (FN) remains an important clinical challenge. While C-reactive protein (CRP) is one of the most widely used clinical biomarkers, further studies are needed to identify its utility in predicting clinical deterioration in this specific population. The aim was to assess the prognostic potential of initial (0h) and 24-hour (24h) CRP kinetics in predicting sepsis severity, ICU admission, and mortality in pediatric cancer patients presented with FN. **Methods:** We performed a prospective observational study of 242 pediatric cancer patients presenting with FN. We analyzed CRP dynamics, Pediatric Sequential Organ Failure Assessment (pSOFA) scores, microbiological profiles, and clinical outcomes including sepsis progression, septic shock, admission to the ICU, and 28-day mortality. **Results:** The cohort (median age 9.0 years) demonstrated that there was a meaningful increase in mean CRP from 89.4 mg/L at presentation to 116.4 mg/L at 24 hours ($P < 0.05$). Elevated CRP levels were strongly correlated with disease severity; patients requiring ICU admission (n=50) and those developing septic shock (n=51) exhibited significantly higher CRP levels at both time points. The 28-day mortality rate was 12.0% (n=29). Non-survivors demonstrated persistently elevated or rising CRP trends compared to survivors. **Conclusion:** Serial CRP monitoring provides critical prognostic data in pediatric FN. A rising CRP trajectory over the first 24 hours is a potent indicator of clinical deterioration, supporting its use in identifying high-risk patients requiring escalated care.

Keywords: C-reactive protein, febrile neutropenia, pediatric oncology, sepsis, risk stratification, biomarker.

Introduction

Febrile neutropenia (FN) is a serious and potentially lethal complication in pediatric oncology, driven by intensive myelosuppressive regimens [1]. While mortality rates have declined to approximately 0.7–2.5% in favorable settings, septic shock remains a significant cause of treatment-related failure, contributing to mortality in up to 13.5% of severe cases [2]. The pathophysiology is characterized by chemotherapy-induced mucosal barrier injury and neutropenia (Absolute Neutrophil Count [ANC] <500 cells/mm^3), facilitating bacterial translocation and systemic infection [3, 4].

Current management strategies often rely on preemptive broad-spectrum antibiotics

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[5]. However, microbiologically documented infections occur in only 20–35% of cases, leading to potential overtreatment and the propagation of multidrug-resistant (MDR) pathogens [6, 7]. Conversely, the absence of robust clinical signs in neutropenic patients complicates the early recognition of those progressing to severe sepsis [8]. Consequently, there is an urgent need for reliable biomarkers to differentiate patients with self-limiting fevers from those at risk of life-threatening deterioration [9, 10].

C-reactive protein (CRP), an acute-phase reactant synthesized by the liver, offers high sensitivity for inflammation with a rapid onset of 4–6 hours following stimulus [11]. While its specificity has been debated, recent evidence suggests that dynamic changes in CRP—rather than static baseline values—may offer superior prognostic utility [12]. This study aims to validate the role of serial CRP measurement (0h and 24h) in a contemporary cohort of pediatric oncology patients [13]. By correlating CRP kinetics with the Pediatric Sequential Organ Failure Assessment (pSOFA) score and definitive clinical outcomes, we seek to refine risk stratification protocols for this vulnerable population [14, 15].

Materials and Methods

Study Design and Population

This prospective observational study was carried out at Borg El-Arab Pediatric Oncology Hospital, Faculty of Medicine, Alexandria University, Egypt, from January 2023 through December 2024. The study population consisted of pediatric patients and adolescents under age 18 receiving active chemotherapy for a confirmed malignant disease who met the required criteria for FN. FN was defined as an absolute neutrophil count (ANC) < 500 cells/mm³ (or ANC between 500–1000 cells/mm³ with a predicted drop below 500 cells/mm³ within 48 hours), accompanied by a single oral temperature ≥ 38.3°C or sustained temperature ≥ 38.0°C for at least one hour. Exclusion criteria were confirmed non-bacterial infections at presentation, the use of immunomodulatory therapy (GCSF) or systemic corticosteroids within the past 7 days, or incomplete biomarker sample collection. This report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.

Sample Size Calculation

To ensure the internal and external validity of our findings, an a priori sample size calculation was performed. The calculation was based on the primary outcome of predicting severe clinical outcomes (a composite of septic shock or ICU admission). Drawing from previous literature [19], we anticipated that an elevated CRP level would be present in approximately 75% of patients with severe outcomes versus 40% in those without. To achieve a statistical power of 80% with a two-sided alpha level of 0.05, a minimum of 225 patients were required. To account for potential dropouts or cases

with incomplete data, we aimed to enroll a slightly larger cohort. The final enrolled population of 242 patients was therefore considered adequately powered to detect clinically significant associations between CRP levels and adverse outcomes.

Data Collection

Upon admission, each patient underwent a thorough clinical assessment, and the severity of organ dysfunction was quantified using the pediatric Sequential Organ Failure Assessment (pSOFA) score, which evaluates dysfunction across the respiratory, cardiovascular, coagulation, hepatic, renal, and neurological systems [16, 17]. Clinical outcomes were subsequently classified in accordance with the 2020 Surviving Sepsis Campaign and the 2024 international consensus definitions for pediatric sepsis [15, 16], whereby sepsis was defined as any confirmed or suspected infection accompanied by an increase of ≥2 points in the pSOFA score from baseline, and septic shock was characterized by sepsis with cardiovascular dysfunction — manifested as hypotension requiring vasopressor support despite adequate fluid resuscitation or a serum lactate level >2 mmol/L.

Laboratory Methods and Biomarker Measurement

At the onset of fever (D0), prior to the administration of antibiotics, blood samples were collected via peripheral venipuncture or central venous catheter in appropriate sterile collection tubes. Complete blood count (CBC), serum chemistry including liver and renal function tests, and biomarker samples were obtained simultaneously. For biomarker analysis, blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes for plasma samples. Blood cultures were collected at this time for bacteremia identification. Repeat biomarker measurements were performed 24 hours after initial collection (D1) to assess biomarker kinetics and predictive value for clinical outcomes. Serum CRP was measured using a latex-enhanced immunoturbidimetry assay, reported in mg/L. Blood cultures were drawn at admission prior to antibiotic administration and processed using automated detection systems (BacT/ALERT™). Pathogen identification and antimicrobial susceptibility testing followed Clinical and Laboratory Standards Institute (CLSI) 2024 guidelines. Multidrug resistance was defined as non-susceptibility to ≥1 agent in ≥3 antimicrobial categories.

Statistical Analysis

Descriptive statistics summarized the cohort characteristics. Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on distribution. The change in CRP over the first 24 hours (ΔCRP0-24h) was analyzed using paired t-tests for normally distributed data. Associations between biomarker levels (e.g., CRP at 0h and 24h) and categorical clinical outcomes (e.g., 28-day survival, ICU admission, septic shock) were assessed using Chi-square tests.

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Survival curves were generated using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. A multivariate Cox proportional hazards model was developed to identify independent predictors of 28-day mortality. Variables with a P value < 0.10 in univariate analysis were included in the multivariate model. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. All reported P values are two-sided. P values larger than 0.01 are reported to two decimal places, those between 0.01 and 0.001 to three decimal places, and P values smaller than 0.001 are reported as P < 0.001. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY: IBM Corp).

Results

Patient Characteristics

The study included 242 pediatric oncology patients with FN. The median age was 9.0 years (range: 1-17 years), with a slight male predominance (52.1% male, 47.9% female). The most common underlying malignancy was Acute Lymphoblastic Leukemia (ALL), accounting for 42.6% of cases (n=103), followed by Acute Myeloid Leukemia (AML) (18.6%, n=45), and Burkitt's Lymphoma (17.4%, n=42). Other solid tumors, including Ewing Sarcoma, Neuroblastoma, and Osteosarcoma, constituted the remainder of the cohort. Detailed demographic and diagnostic information is presented in Table 1.

Table 1 – Characteristics of the study population

Characteristic	Value
Age (years), Median (Range)	9.0 (1 - 17)
Gender, n (%)	
Male	126 (52.1%)
Female	116 (47.9%)
Primary Diagnosis, n (%)	
Acute Lymphoblastic Leukemia (ALL)	103 (42.6%)
Acute Myeloid Leukemia (AML)	45 (18.6%)
Burkitt's Lymphoma	42 (17.4%)
Ewing Sarcoma	30 (12.4%)
Other Solid Tumors	22 (9.1%)
Progression to Sepsis, n (%)	141 (58.3%)
Development of Septic Shock, n (%)	51 (21.1%)
ICU Admission, n (%)	50 (20.7%)
28-Day Outcome, n (%)	
Survived	213 (88.0%)
Died	29 (12.0%)

CRP Dynamics and Inflammatory Response

At presentation (0h), the mean CRP level for the cohort was 89.4 mg/L (median: 66.5 mg/L). A vast majority of patients (84.3%, n=204) had an elevated CRP level (>10 mg/L)

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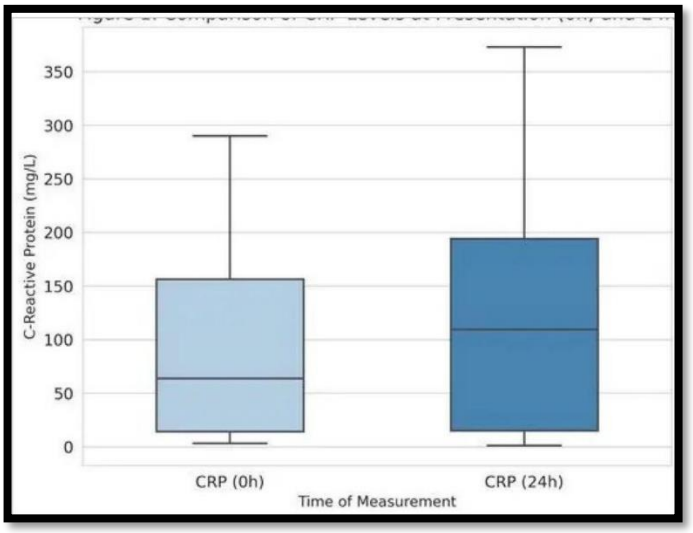
at onset. Over the first 24 hours, there was a significant and consistent increase in inflammatory activity, with the mean CRP level rising to 116.4 mg/L (median: 107.0 mg/L). This trend reflects an ongoing systemic inflammatory response following the onset of fever. The distribution and rise in CRP levels are illustrated in Figure 1.

Figure 1 - Comparison of C-Reactive Protein (CRP) Levels at 0h and 24h.



Association of CRP with Disease Severity and Outcomes

Higher CRP levels were strongly associated with increased disease severity and adverse clinical outcomes. Patients who required ICU admission (n=50, 20.7%) had significantly higher median CRP levels at both 0h and 24h compared to those managed on the general ward. Similarly, the 51 patients (21.1%) who developed septic shock exhibited markedly elevated CRP concentrations. The 28-day mortality rate for the cohort was 12.0% (n=29). Analysis of CRP levels stratified by survival status revealed that non-survivors had substantially higher initial and 24-hour CRP levels.

CRP Levels and Microbiological Findings

Blood cultures were positive in 45 patients (18.6%), with Gram-negative organisms being the predominant pathogens (82.2% of positive cultures), including *E. coli* (28.9%), *Klebsiella* spp. (26.7%), and *Pseudomonas aeruginosa* (13.3%). C-Reactive protein levels at 24 hours demonstrated significant clinical utility for risk stratification. Among culture-negative patients, median CRP was 77 mg/L, compared to 139 mg/L in Gram-negative bacteremic patients and 185 mg/L in Gram-positive bacteremic patients (ANOVA, $P < 0.001$), representing an 80.5% increase in bacteremic versus non-bacteremic patients (Figure 2). Notably, despite comprising only 17% of positive blood cultures, Gram-positive organisms showed 24.5% higher median CRP than Gram-negative organisms, suggesting a more robust inflammatory response.

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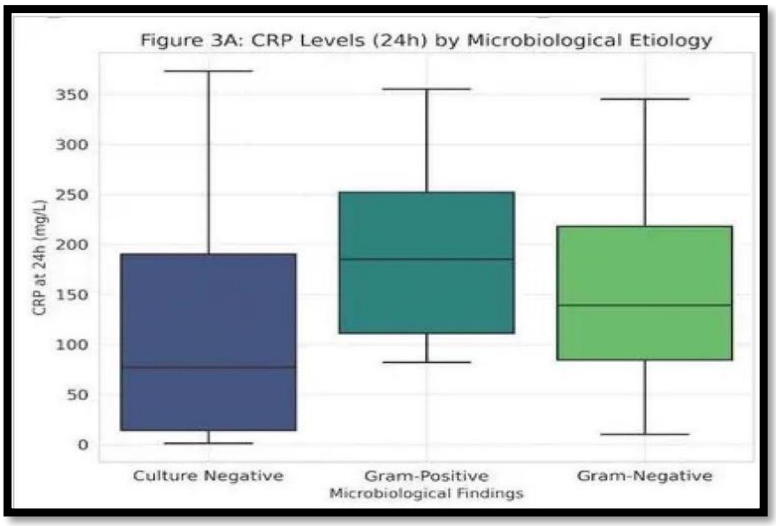
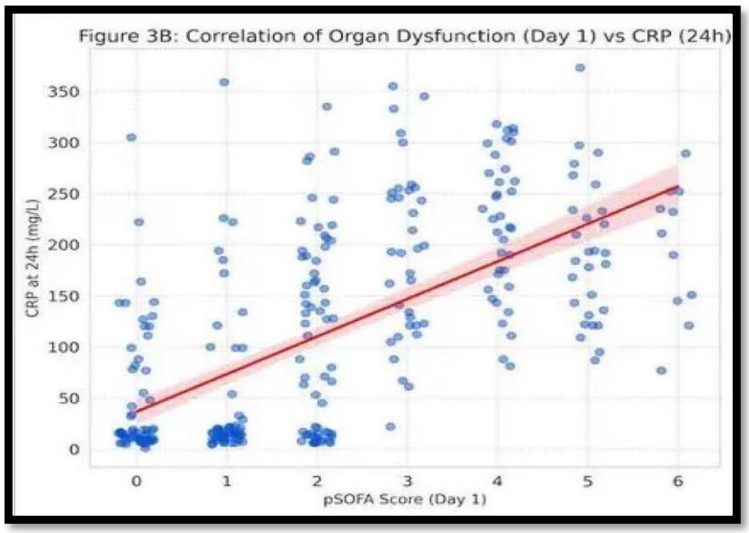
Figure 2 - CRP Levels (24h) by Microbiological Etiology



Furthermore, a strong positive correlation was identified between Pediatric Sequential Organ Failure Assessment (pSOFA) scores at Day 1 and CRP levels at 24 hours ($r=0.6324$, $P < 0.001$), with each 1-point increase in organ dysfunction associated with approximately 37 mg/L increase in CRP concentration (Figure 3). Patients with minimal organ dysfunction (pSOFA 0–1, n=128) demonstrated median CRP of 15–16 mg/L, whereas those with severe dysfunction (pSOFA 5–6, n=39) exhibited median CRP of 200–221 mg/L, representing a 14-fold elevation and explaining 40% of CRP variance. These findings establish CRP as a valuable biomarker integrating information on both infection severity (bacteremia presence) and systemic inflammatory burden (organ dysfunction).

Figure 3 - Correlation of Organ Dysfunction (Day 1) vs. CRP (24h).



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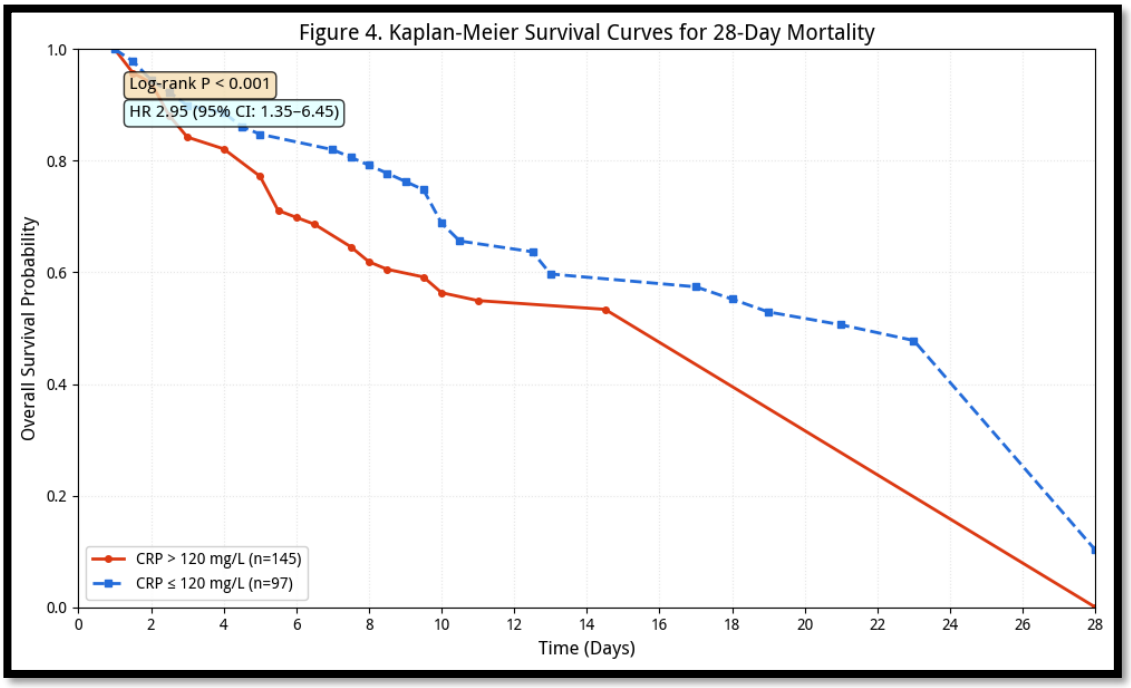
Survival Analysis

Kaplan-Meier survival analysis demonstrated a significant difference in 28-day survival based on CRP dynamics. Using a clinically relevant cutoff derived from our cohort, patients with a 24-hour CRP level exceeding 120 mg/L had a significantly lower survival probability compared to those with levels below this threshold (log-rank P < 0.001) (Figure 4).

Figure 4. - Kaplan-Meier Survival Curves for 28-Day Mortality Stratified by 24-Hour CRP Level (>120 mg/L vs. ≤120 mg/L).



To identify independent predictors of mortality, a multivariate Cox proportional hazards model was constructed. After adjusting for age and primary diagnosis, several factors remained significant predictors of 28-day mortality.

The development of septic shock, a high pSOFA score, and a markedly elevated 24-hour CRP level were all independently associated with an increased risk of death (Table 2).

Specifically, a 24-hour CRP level > 120 mg/L was associated with a nearly threefold increase in the hazard of mortality (HR 2.95; 95% CI 1.35–6.45; P = 0.007).

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Table 2 – Results of the multivariate analysis

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	P value
Development of Septic Shock	4.52	2.10 – 9.74	<0.001
pSOFA score > 2 at 24 hours	3.88	1.75 – 8.61	0.001
CRP at 24h > 120 mg/L	2.95	1.35 – 6.45	0.007

Discussion

This comprehensive prospective study represents one of the largest single-center evaluations of C-reactive protein (CRP) in pediatric oncology patients with febrile neutropenia (FN), providing robust evidence to support a biomarker-guided, risk-adjusted management approach. Approximately 76% of cases were associated with hematological malignancies, a proportion consistent with the observations of Babu et al. [17] and Soumya and Ajit Kumar [18]. This consistency likely reflects the higher prevalence of hematological cancers in the pediatric population, which require more intensive therapeutic regimens and thus increase susceptibility to severe infections.

Our findings confirm that CRP is a dynamic and clinically relevant biomarker in this high-risk population. A central finding of our analysis is the strong association between the magnitude of CRP elevation and clinical severity. Patients who required ICU admission, developed septic shock, or ultimately succumbed to their illness demonstrated significantly higher CRP levels. This aligns with reports by Asturias et al., who identified a direct link between elevated CRP, bacteremia, and mortality [19]. The significant increase in mean CRP from 89.4 mg/L at presentation to 116.4 mg/L at 24 hours underscores its utility in tracking the evolution of the systemic inflammatory response.

Our observation that the trajectory of CRP offers superior prognostic value compared to static measurements corroborates the work of Chaudhary et al. [20], who identified that a rising CRP trend was the most significant predictor of documented infection, outperforming absolute values at admission. The survival analysis further strengthens this point, showing that a 24-hour CRP level >120 mg/L is an independent predictor of mortality. This suggests that a high initial CRP should alert clinicians to a potentially severe disease course, and a failure of CRP to decline or a continued rise at 24 hours warrants significant concern and potential escalation of care.

However, regarding microbiological etiology, our findings diverge from those of Gupta et al. [21]. While their study suggested that CRP levels were variable and potentially lower in Gram-negative bacteremia compared to Gram-positive cases, our larger prospective cohort demonstrated a distinct hyper-inflammatory response

associated with Gram-negative pathogens (e.g., *E. coli*, *Klebsiella*). This aligns with the foundational work of Santolaya et al. [22], who established a strong correlation between marked CRP elevation and invasive bacterial infection. The robust elevation observed in our Gram-negative subgroup likely reflects the severe systemic inflammatory response triggered by endotoxins, reinforcing Cennamo et al.'s recommendation of using high CRP thresholds (>90 mg/L) as a "red flag" for high-risk bacterial etiology [23].

Study Limitations

Despite the strengths of this study, including its prospective design and well-characterized cohort, several limitations must be acknowledged. First, this was a single-center study conducted at a specialized pediatric oncology hospital. This could affect the external validity and the generalizability of our results to other places that might have other patients' profiles and other treatment algorithms, or different local microbiological epidemiology.

Another limitation is the study design. While creating an observational cohort design is appropriate to prognostic studies, is susceptible to confounding variables and cannot definitively establish causality. Although we used multivariate analysis to take certain aspects into account, like the septic shock and organ dysfunction, there could still be some residual confounding by unmeasured factors, such as certain chemotherapy agents or underlying comorbidities.

Third is one of the principal limitations of CRP, its lack of specificity. Increased CRP in this population can be a result of other non-infectious inflammatory conditions, such as chemotherapy induced mucositis, tumor lysis syndrome, or recent surgery [24]. In our cohort, 81.4% of patients had negative blood cultures, many of whom had a high CRP, and this only serves to underscore the point. CRP should be interpreted in the context of the whole picture and not in isolation.

Fourth, our investigation addressed only the clinical use of the CRP, because of its availability and affordability. We did not do any comparative studies with other potential, but less accessible, biomarkers like procalcitonin (PCT), interleukin-6 (IL-6), or presepsin. Future studies may explore the possibility of a multi-biomarker approach for higher predictive accuracy.

Lastly, there is the possibility of selection bias, because only patients that presented to our institution and met the defined inclusion criteria were included in the study. This may not represent the entire range of FN presentations in the wider community or other health care settings.

Conclusion

Our study confirms that serial CRP measurement is a valuable, practical, and widely accessible tool for the management of pediatric oncology patients with FN. An elevated

CRP at presentation, and particularly a rising trend over 24 hours, is a strong and independent indicator of a more severe clinical course, associated with progression to septic shock, need for ICU care, and increased mortality. While not a perfect standalone predictor, the thoughtful integration of CRP dynamics into routine clinical evaluation can significantly aid in the early identification and intensified management of high-risk patients, ultimately contributing to improved outcomes in this vulnerable population.

Declarations

Authorship: All authors (Khaled Seddik, Ahmed Badawy, Omar Shebl Zahra) fulfill the authorship criteria of the Uniform Requirements. No writing assistance other than copy editing was provided.

Assurances: The research protocol was approved by the Institutional Review Board (IRB) of Alexandria University NO: 00012098. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment, in accordance with the ethical principles outlined in the Declaration of Helsinki. The study authors were responsible for the data analysis. This study is an observational cohort study and was not registered as a clinical trial.

Conflict of Interest: No potential conflict of interest relevant to this article was reported.

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