SCIENCE PHOTONS Publishers

Research Article

ISSN 3070-6238

Journal of Medical Research and Clinical Reviews

Correlation of C-Reactive Protein and Complete Blood Count Parameters in Pediatric Sepsis: A Retrospective Study from Hebron, Palestine

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Received Date: 10 May 2026;
Accepted Date: 15 Aug 2026;
Published Date: 08 Sep 2026.

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Citation: Adel Abdelhalim Salayma. Correlation of C-Reactive Protein and Complete Blood Count Parameters in Pediatric Sepsis: A Retrospective Study from Hebron, Palestine. J Med Res Clin Rev. 2026; 2(3): 1-6.

ABSTRACT

C-reactive protein (CRP) is one of the most characteristic acute-phase proteins. Elevated amounts of C-reactive protein are found in human serum during the acute-phase response.

The relationships between CRP results and gender, age, CBC parameters, and diagnosis were studied by taking the results of 201 patients from the database of Mohammad Ali Hospital Medical Laboratories and medical records during the period from April 27 to July 31, 2009. The tests were done by the medical technologist on duty using either Taytec reagents (Canada) or Atlas Medical (United Kingdom) for CRP tests. For CBC tests, Cell-Dyne 1800 was used.

Two hundred and thirteen CRP results out of three thousand and twenty-nine were found (7%). Twelve results were excluded from statistical analysis because there was no CBC result for the patient. The number of negative CRP results was 104 (51.7%), while the number of positive results was 97 (48.3%). 54.1% and 48.1% of the male and female patients had negative results, respectively. There was no statistical difference between age groups in terms of CRP results.

The concentration of CRP in the patient serum increased as the total WBC count increased, and its concentration in females was higher than that in males. The number of positive results and the median concentration of CRP in bacterial infections (neutrophils > 65% and lymphocytes < 35%) were higher than those in viral infections.

Keywords: *CRP; CBC; Correlation between CRP and CBC; Sepsis; Hebron-Palestine.*

Introduction

C-reactive protein (CRP) is a normal plasma protein; serum CRP values are widely measured in clinical practice as an objective index of disease activity. Its concentration rises dramatically in a cytokine-mediated response to most forms of tissue injury, infection, and inflammation. CRP has the capacity to activate complement and to stimulate tissue-factor production [1].

C-reactive protein (CRP) is one of the most characteristic acute-phase proteins. It was first discovered in 1930 by Tillett and Francis and has been found in most vertebrates [2]. CRP has the capacity to bind the phosphorylcholine group on C-polysaccharide, which leads to the precipitation of C-polysaccharide on the pneumococcal cell wall. This is calcium-dependent and is inhibited by free phosphocholine [3-6].

CRP levels can increase up to 1,000-fold in less than 48 h as a result of enhanced biosynthesis in liver hepatocytes, which is mediated by interleukin-1. The plasma half-life of CRP is approximately 19 hours and remains constant under all physiological and pathological conditions [3,7].

Daily measurement of CRP is useful in the detection of sepsis and infection. It is a more sensitive but less specific marker of infection than currently used markers, such as body temperature and WBC count [8-10]. CRP increases more rapidly than white cell count and erythrocyte sedimentation rate on resolution of the infectious process [4,6,11]. A CRP level that returns to the normal range in a neonate diagnosed with sepsis may indicate that the duration of antibiotic treatment has been sufficient [12].

Sepsis and septic shock remain major global healthcare challenges, detected daily by medical staff in emergency departments. It is estimated that there are 660,000 to 750,000 cases per year, with an increased rate of 8.7% per year and a mortality rate of 20% to 50% [7,13-16].

CRP is a preferred serological marker for acute inflammatory conditions because of its rapid kinetics and shorter half-life. Its clinical utility includes diagnostic purposes and monitoring treatment response [7].

Methodology

Three thousand and twenty-nine test results (performed during the period from April 27 to July 31, 2009) were reviewed for CRP and CBC results in the computer database of Mohammad Ali Hospital Medical Laboratory. (In 2009, there was no formal written IRB permission available, but verbal approval was obtained from the responsible hospital authorities, namely the hospital director, head of the pediatric department, nursing administration, and laboratory director. Patient confidentiality and anonymity were maintained throughout the study.) The search was performed on serology results to identify CRP results. If available, the result was recorded, and CBC results for the same patient were then sought. The CRP result was ignored if there was no CBC result. The tests were performed by the medical technologist on duty using either Taytec reagents (Canada) or Atlas Medical (United Kingdom) for CRP tests, and CRP titer was determined for positive tests. For CBC tests, Cell-Dyne 1800 was used.

CRP tests were performed by taking 50 µL of patient serum, mixing it with one drop of the reagent, and rotating it for two minutes. Negative results were recorded if there was no agglutination. The concentration of CRP in mg/L for positive results was obtained by multiplying the reciprocal of the highest dilution (from serial dilution of the patient serum) that gave agglutination by the sensitivity of the test (6 mg/L). A value above 6 mg/L was considered positive [17].

A face-to-face interview was conducted with the attending physicians, who were asked about the criteria on which they depended to request the test and the criteria used to interpret the results.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS version 13) was used for statistical analysis. Crosstabulation between age, gender, diagnosis, CBC parameters, and CRP was performed, from which different percentages were calculated, as well as the numbers and percentages of positive and negative CRP results. The chi-square test was used to determine whether there was a statistically significant difference between different groups in each category. Whisker box plots were used to compare the median concentrations of CRP between different groups in each category.

Results

Two hundred and thirteen CRP results out of three thousand and twenty-nine were found (7%). Twelve results were excluded from statistical analysis because there was no CBC result for the patient.

In Mohd Ali Hospital, CRP and CBC tests are frequently requested to confirm the diagnosis of patients with fever. The number of negative CRP results was 104 (51.7%), while the number of positive results was 97 (48.3%). Figure 1 shows the distribution of CRP results.

CRP and Gender

Of all the patients tested, 122 patients were male (60.7%) and 79 patients were female (39.3%). The percentages of negative results among male and female patients were 54.1% and 48.1%, respectively. The concentration of CRP in females was higher than that in males, since the median concentration in females was 12 mg/L and 6 mg/L in males, as illustrated in Figure 2.

There was no significant difference in the CRP results between males and females, since the P value of Pearson's chi-square test was 0.118.

CRP and Age

The age of the patients ranged from a few days (newborns) to 16 years old. Table 1 illustrates the distribution of the patients among age groups. Fifteen patients (14.2%) were below two months of age, and 12 of them (11.3%) had negative CRP results. There was no statistical difference between age groups in terms of CRP results, as the Pearson's chi-square P value was higher than 0.05 (0.863).

Table 1. Distribution of patients among age groups and numbers of positive and negative CRP results in each group at Mohammad Ali Hospital, Hebron, 2009.

Age Group	Count	Percentage	Positive CRP, n (%)	Negative CRP, n (%)
< 2 months	15	14.2%	3 (2.9%)	12 (11.3%)
2-6 months	13	12.3%	3 (2.8%)	10 (9.5%)
6-12 months	29	27.4%	17 (16.1%)	12 (11.3%)
1-5 years	35	33.0%	17 (17.9%)	16 (15.1%)
5-10 years	8	7.5%	6 (5.7%)	2 (1.8%)
>10 years	6	5.7%	3 (2.8%)	3 (2.8%)

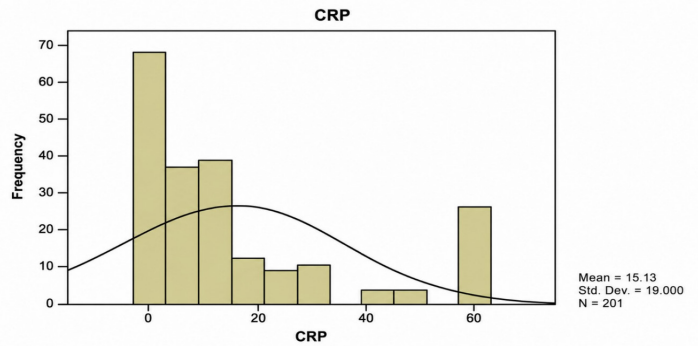

Figure 1. *Distribution of CRP results in Mohammad Ali Hospital, Hebron, 2009.*

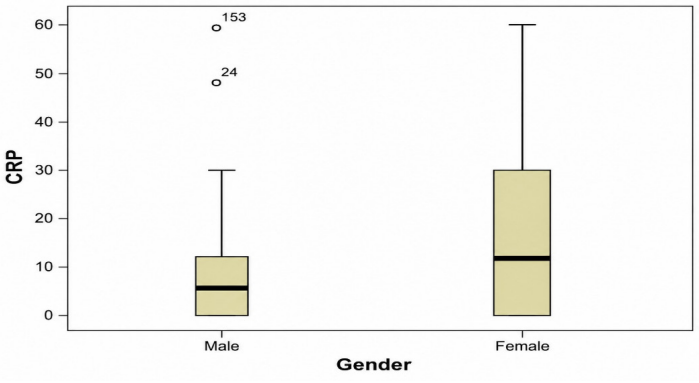

Figure 2. Whisker box plot of CRP concentrations in male and female patients in Mohammad Ali Hospital, Hebron, 2009.

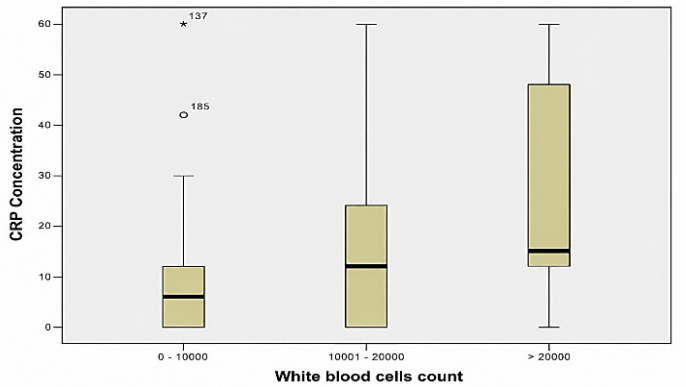

Figure 3. Whisker box plot of CRP concentrations and WBC counts in patients at Mohammad Ali Hospital, Hebron, 2009.

CRP and White Blood Cells

The WBC results ranged from 2,100 to 46,000. In this study, the WBC results were divided into three groups on the basis of normal (0-10,000) and abnormal results (10,001-20,000, >20,000). There was an increase in the number of positive CRP results as the WBC count increased (Table 2). This difference in the number of negative and positive results in each group was statistically significant, as the Pearson's chi-square P value (0.036) was lower than 0.05.

Table 2. Distribution of patients among WBC groups and numbers of positive and negative CRP results in each group at Mohammad Ali Hospital, Hebron, 2009.

WBC Group	Count	Percentage	Positive CRP, n (%)	Negative CRP, n (%)
WBC 0-10,000	94	46.8%	34 (15.9%)	60 (29.9%)
WBC 10,001-20,000	93	46.3%	52 (25.9%)	41 (20.4%)
WBC >20,000	14	7.0%	11 (5.5%)	3 (1.5%)
Neutro <65%	152	78.8%	62 (32.2%)	90 (46.6%)
Neutro >65%	41	21.2%	30 (15.5%)	11 (5.7%)
Lymph <35%	68	35.2%	42 (34.8%)	26 (13.4%)
Lymph >35%	125	64.8%	50 (25.9%)	75 (38.9%)

There was a weak positive correlation between CRP and neutrophils, where Pearson's correlation coefficients were 0.225 and 0.291, respectively, at the 0.01 level, while there was a weak negative correlation between CRP and lymphocytes, where Pearson's correlation coefficient was -0.302.

The CRP titer in the patient serum increased as the total WBC count increased. The median CRP titers were 6, 12, and 18 mg/L, respectively (Figure 3).

The median CRP titer in bacterial infections (neutrophil percentage >65% and lymphocyte percentage <35%) was higher than the median CRP titer when the neutrophil percentage was <65% and the lymphocyte percentage was >35% in viral infections (Figures 4 and 5).

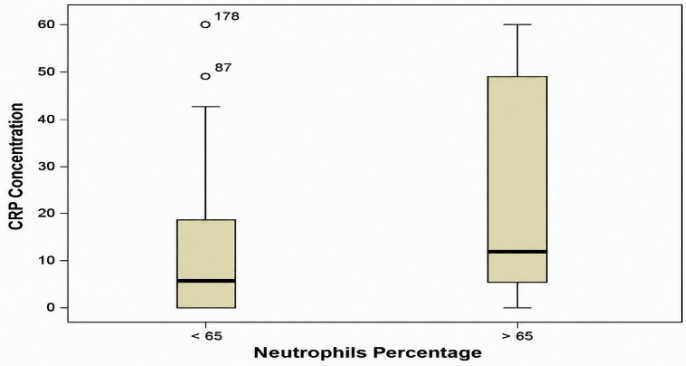

Figure 4. Whisker box plot of CRP concentrations and neutrophil percentages in patients at Mohammad Ali Hospital, Hebron, 2009.

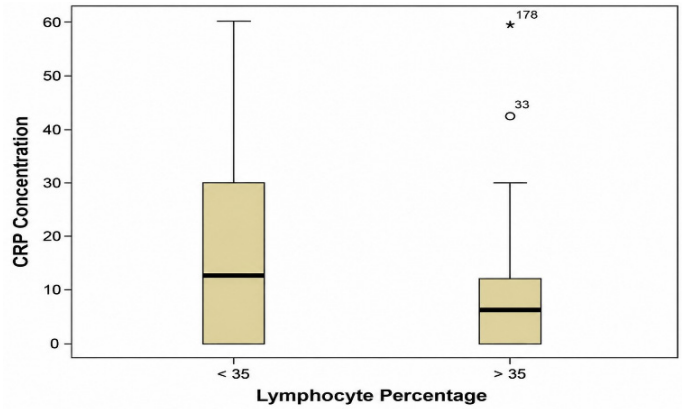

Figure 5. Whisker box plot of CRP concentrations and lymphocyte percentages in patients at Mohammad Ali Hospital, Hebron, 2009.

This difference in the number of negative and positive results in each group was statistically significant, as the Pearson's chi-square P value (0.003) was lower than 0.05 in the case of the neutrophil groups. However, the difference was not statistically significant, as the Pearson's chi-square P value (0.053) was higher than 0.05 in the case of the lymphocyte group.

CRP and Diagnosis

The provisional diagnosis for each patient was taken from the medical records of the emergency department, pediatric outpatient clinic, and pediatric ward. In 105 patients (52.2%), the diagnosis was not known because the patients may have come to do the laboratory tests from outside clinics or the diagnosis may have failed to be recorded for any reason.

No statistically significant difference was found between the different diagnostic groups, as the Pearson's chi-square P value (0.092) was higher than 0.05.

According to most of the attending physicians at Mohammad Ali Hospital, if the patient has a CRP result of 60 mg/L, the patient needs admission to the hospital for medical care. However, about 16 patients (8%) had no diagnosis, which means that they were missed and did not receive the necessary medical care. Twenty-seven patients out of 49 patients diagnosed with upper respiratory tract infections (URTI) had negative CRP results, which means that the CRP test is not specific for diagnosing URTI.

Two patients out of 9 who were diagnosed with meningitis had negative CRP results, and 6 patients out of 7 who were diagnosed with gastroenteritis had negative CRP results.

Based on clinical examination, serum CRP and peripheral WBC cannot differentiate between bacterial and viral causes of acute suppurative tonsillitis, whereas age was clearly the most important factor [18].

CRP and Platelets, Red Blood Cells

There was no correlation between platelets, RBCs, and CRP, since Pearson's correlation coefficients were very low, 0.055 and -0.012, respectively.

Discussion

Fever is a common presenting symptom in pediatric outpatient services and emergency rooms, particularly in children <3 years of age. Approximately 20% of these children will have no identifiable source of fever after history and physical examination [6,19]. Three to 11% of febrile children between the ages of 3 to 36 months may have bacteremia [6,20]. A percentage of children with bacteremia will go on to develop serious bacterial infection. Laboratory predictors identified to date include the white blood cell count (WBC), C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), and other acute inflammatory mediators [6,20].

Three clinical parameters have been used routinely for the diagnosis of infections in infants and to differentiate between bacterial and non-bacterial febrile illness: the number of circulating neutrophils (the absolute neutrophil count); the serum concentration of cytokines (IL-6); and the serum concentration of acute-phase proteins (CRP, procalcitonin). Among these, the measurement of CRP is particularly helpful in diagnosing early bacterial infections [11,17,21], while Pepys and Hirschfield (2003) stated that CRP values can never be diagnostic on their own and can only be interpreted at the bedside, in full knowledge of all other clinical and pathological results [28]. In the study by Devi and Pushpa (2008), the mothers of septic neonates were tested for WBC count, neutrophil count, ESR, and CRP. They found that WBC and neutrophil counts were very high during the onset of infection, with WBC counts between 22,501 and 25,000 in 50% of cases and neutrophils between 66% and 85% in 83.3% of cases, indicating that the newborn was already susceptible to infection [26].

Various studies report higher procalcitonin and CRP values in patients with bacterial infection as compared with those with viral infection, autoimmune disorders, or other nonbacterial infection-related inflammatory diseases, and in patients with sepsis, severe sepsis, or septic shock with documented infections. Procalcitonin and CRP were significantly higher in patients with infection as compared with those without infection. In septic patients, CRP values increased to a maximum level only at two to three days and remained elevated for many days [5]. The results of this study correlate well with these studies, since the CRP median titer in bacterial infections (neutrophil percentage >65% and lymphocyte percentage <35%) was higher than the CRP median titer in viral infections (Figures 4 and 5).

Paran et al. (2009) found that the mean concentration of CRP in bacterial febrile infection was higher than its mean concentration in nonbacterial febrile illness (63.77 mg/L and 23.2 mg/L, respectively). Kitahashi et al. (1998) and Paran et al. (2009) demonstrated that it is possible to improve the differentiation between acute bacterial and nonbacterial febrile illnesses in the emergency room by using the parameter of CRP velocity (CRPv) instead of procalcitonin and the absolute concentration of CRP alone. This diagnostic improvement proved to be significant and involved no additional cost due to the fact that it needed only the acquisition of additional information.

Deepa et al. (2024), in a study titled Association between Neonatal Sepsis and C-reactive Protein, concluded that CRP is a useful tool for initiating antibiotic therapy even before the blood culture report in neonatal sepsis [25].

Cytokines, e.g., interleukin-6 (IL-6), can also serve as markers of infection and are more useful for the diagnosis of infection in infants, especially at 24 h after birth, than the measurement of CRP. However, they are usually limited to experimental use due to high reagent costs. Measuring CRP is more practical, convenient, and economical [3,11].

The results of this study are consistent with the study conducted by Rasamoelisoa et al. (1999) and discussed by Naseri (2008) [27]. They retrospectively studied 361 febrile children and found a direct correlation between CRP values and leukocyte levels in presumed bacterial infections.

Recently, new inflammatory markers, named neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and C-reactive protein/platelet ratio (CRP/PLT), have been implemented in clinical practice for the diagnosis and assessment of prognosis in many conditions, such as malignancies (e.g., hepatocellular carcinoma and non-small cell lung cancer), cardiovascular diseases, acute appendicitis, and acute and end-stage renal disease [22,23].

Shen et al. (2019), in their study titled Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity, a retrospective study, concluded that in patients with sepsis, a high PLR was significantly associated with poor survival, while the association was nonsignificant for those with a low PLR. They recommended that further studies are needed to prove this hypothesis.

Motaz Sulaiman et al. (2023) concluded that NLR is not a good predictor for diagnosing acute appendicitis and is insignificant in predicting appendicitis severity in pediatric and adult patients. The CRP/PLT ratio is significant in diagnosing acute appendicitis in the pediatric age group but not in adults, and in assessing its severity in adults and pediatric patients.

The ratio of CRP to platelet count is a better tool for assessing neonatal sepsis, as it accounts for the inflammatory and coagulation status of patients with sepsis [24].

Conclusions

The titer of CRP in the patient serum increased as the total WBC count increased, and the median titer in females was higher than that in males. The median titer of CRP in bacterial infections (neutrophils >65% and lymphocytes <35%) was higher than the median titer in viral infections (neutrophils <65% and lymphocytes >35%).

Acknowledgements

The author would like to thank the medical laboratory and medical records staff at Mohammad Ali Hospital for their cooperation, namely Amer Shabaneh, Andaleeb Al-Horoub, Nader Hajaj, and Dr. Abdulsalam Al-Hadad.

The author would also like to express sincere thanks to Mr. Mohamad Al Qawasmi for his work in improving the quality of the figures.

Conflicts of Interest

The authors declare no conflict of interest and received no specific funding for this work.

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