P-ISSN: 2664-3685
E-ISSN: 2664-3693
www.paediatricjournal.com
IJPG 2024; 7(2): 78-82
Received: 01-05-2024
Accepted: 06-06-2024

Shahana Begum
Assistant Professor, Department of Paediatrics, Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh

Galiba Tasnim
Junior Consultant (Paediatrics), Pabna Medical College Hospital, Pabna, Bangladesh

Faisal Mohammad Pasha
Assistant Professor, Department of Community Medicine & Public Health, Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh

Saiful Islam
Junior Consultant, Department of Paediatrics, Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh

Amena Bintay Yousuf Muna
Assistant Professor, Department of Ophthalmology, Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh

Corresponding Author:
Shahana Begum
Assistant Professor, Department of Paediatrics, Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh

Clinical profile and outcome of CRP levels in children with acute bronchiolitis: A retrospective, cross-sectional and analytical study

Shahana Begum, Galiba Tasnim, Faisal Mohammad Pasha, Saiful Islam and Amena Bintay Yousuf Muna

DOI: https://doi.org/10.33545/26643685.2024.v7.i2b.245

Abstract
Introduction: C-reactive protein (CRP), which is an acute phase reactant and one of the indicators of acute inflammation, has been linked to bacterial coinfections like bacterial pneumonia. Accordingly, identification of CRP levels can be an important indirect marker for viral infections and an indicator for progression of infection and effectiveness of the treatment. Pneumonia elicits a powerful inflammatory response, both locally and systemically with chemotatic cytokine release into the peripheral circulation.
Objective: To assess the frequency of elevated CRP in children with acute bronchiolitis and at comparing the clinical characteristics, laboratory and radiological findings, antibiotics use, and outcome according to CRP levels.
Methods: This was a retrospective, cross-sectional, and analytical study where the medical records of all patients with a clinical impression of acute bronchiolitis who were admitted to the pediatric department Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh from January to December 2023 for the period of one year were retrieved. During the study period, a total of 125 patients were admitted with a clinical presentation of acute bronchiolitis. 25 (20%) patients were excluded due to of unavailability of data of CRP levels. The remaining 100 (80%) patients were included in the study.
Results: Total of 125 patients were admitted with a clinical presentation of acute bronchiolitis. 25 (20%) patients were excluded due to of unavailability of data of CRP levels. The remaining 100 (80%) patients were included in the study. 53(53.0%) patients were males. The most common clinical presentation was cough (80 (80.0%) patients) followed by fever (70 (70.0%) patients). Antibiotics were used in 80.0% patients. Patients with high CRP were older at presentation (p<0:0001) and had more fever (p<0:0001) and cough (P = 0:002), but lower hemoglobin level (p<0:0001) compared to those with normal CRP. Fever (P = 0:016) and hemoglobin level (p= 0:002) were independent factors.
Conclusion: Most children with acute bronchiolitis had high rate of elevated CRP values that did not correlate with the rate of bacterial coinfection. High CRP levels were found in older children, those presented with more fever and cough, and had a lower hemoglobin level despite that those factors were previously reported to be associated with disease severity and bacterial coinfection.

Keywords: CRP, bronchiolitis, antibiotics, children

Introduction
C-reactive protein (CRP), an acute phase reactant and one of the indicators of acute inflammation, is associated with bacterial co-infections, such as bacterial pneumonia [1, 2]. However, patients with RSV bronchiolitis, bronchopneumonia, and RSV pneumonia have been found to have elevated CRP levels as well as high white blood cell (WBC) counts and erythrocyte sedimentation rates (ESR), all of which are indicative of bacterial co-infection [1-3]. Thus, determining CRP levels may be an important indirect marker of viral infection and an indicator of the progression of infection and the effectiveness of treatment [1]. It is noteworthy that in patients with RSV bronchiolitis, elevated CRP levels are associated with a longer hospital stay [1, 4, 5]. Although many diseases, such as pulmonary infarction, inflammation, and neoplasms, stimulate CRP synthesis, the most potent stimulus is bacterial infection, which significantly increases serum CRP levels within a few hours. Pneumonia induces a strong local and systemic inflammatory response, accompanied by the release of chemotactic cytokines into the peripheral circulation.

There are few reports on the diagnostic utility of CRP in pneumonia. CRP has also been shown to be useful in distinguishing bacterial from viral pneumonia [6]. CRP has also been used as an indicator of response to treatment of rheumatic fever and certain other diseases. CRP is tested by capillary precipitation of patient serum with antiserum raised in rabbits against purified CRP or by passive agglutination with latex particles coated with anti-CRP antibodies [7]. Antimicrobial resistance represents a growing threat, leading to increased morbidity and mortality as well as unnecessary burdens from side effects and increased healthcare costs [8, 9]. Recent studies have shown that antimicrobial resistance was responsible for an estimated 1.27 million deaths in 2019 [10]. Acute bronchiolitis, a very common lower respiratory tract infection in children, is a viral infection with respiratory syncytial virus (RSV) being the most commonly involved pathogen [11, 12]. However, other pathogens such as parainfluenza viruses and some adenoviruses may also be found [12]. The disease is characterized by acute inflammation, edema, and necrosis of epithelial cells lining the small airways and the resulting obstruction. Clinically, it is manifested by coughing, tachypnea, use of accessory respiratory muscles, wheezing, and crackles on lung auscultation [11]. Moreover, elevated CRP levels are more commonly found in patients with respiratory tract infections due to adenoviruses than in those with RSV or influenza infections 6. Several studies have attempted to establish the usefulness of CRP levels in distinguishing between viral and bacterial lower respiratory tract infections. They have shown that high CRP levels are more likely to have a bacterial cause [13], but the remaining cases yield very similar results between groups, making it difficult to distinguish between viral and bacterial pneumonias based on CRP measurement (PCR) [14]. We compare the frequency of CRP elevation in children with acute bronchiolitis and the clinical characteristics, laboratory and radiological findings, antibiotic use and outcome according to CRP levels.

Materials and Methods

This was a retrospective, cross-sectional study was carried out at pediatric department Shaheed Monsur Ali Medical College & Hospital, Dhaka, Bangladesh from January to December 2023. During the study period, a total of 125 patients were admitted with a clinical presentation of acute bronchiolitis. 25 (20%) patients were excluded due to of unavailability of data of CRP levels. The remaining 100 (80%) patients were included in the study.

The study included children under the age of 5 years who were hospitalized with acute bronchiolitis and had nasopharyngeal swabs tested for RSV infection by direct antigen detection and/or polymerase chain reaction (PCR) and had CRP levels checked. Patients were suspected of acute bronchiolitis based on the American Academy of Pediatrics criteria, which state that the diagnosis is based on signs and symptoms suggestive of bronchiolitis, such as rhinorrhea, cough, tachypnea, wheezing, rales, grunting, nasal flaring, and increased work of breathing manifested by intercostal and/or subcostal contractions. X-rays and laboratory tests should not be used routinely to diagnose acute bronchiolitis [15]. CRP levels were measured using enzyme-linked immunosorbent assay (ELISA) and expressed as quantitative values. Normal CRP values were ≤ 3 mg/L. Laboratory test results including complete blood count, CRP level, blood cultures, urine cultures, cerebrospinal fluid (CSF) cultures, and nasopharyngeal swabs for direct RSV antigen detection and/or PCR were obtained. Radiologic findings from chest x-rays reported by a senior radiologist were documented. Pharmacotherapy including antibiotic use, patient outcomes, and complications were also evaluated.

Statistical Analysis

The data were statistically analyzed using SPSS version 23 software. Demographic data were presented as frequencies and percentages. Normally distributed continuous variables were presented as mean and standard deviation (SD). Median and interquartile range (IQR) were calculated for nonnormally distributed variables. Chi-Square Fisher's test was used to compare categorical variables. Student's T-test or Mann–Whitney U-test was used to compare continuous variables. Variables found to be significant in the univariate analysis and had no multicollinearity using a variation inflation factor >8 were included in a binary logistic regression to detect the independent factors of high CRP levels. P value <0.05 was considered statistically significant. Confidence interval was set at 95%.

Results

Total of 125 patients were admitted with a clinical presentation of acute bronchiolitis. 25 (20%) patients were excluded due to of unavailability of data of CRP levels. The remaining 100 (80%) patients were included in the study. 53 (53.0%) patients were males.

Table 1: Age and sex distribution of children with acute bronchiolitis (N=100)

Variables (Sex)	N	%
Male	53	53.0
Female	47	47.0
Age at presentation (month), median (IQR)	3.5 (1.27-12.33)	
Current age (y), median (IQR)	1.35 (1.14-2.1)	
Length of stay (d), median (IQR)	5.0 (3.0-8.0)	

Table 2: Clinical symptoms of children with acute bronchiolitis (N=100)

Clinical symptoms	N	%
Cough	80	80.0
Fever	70	70.0
Rhinorrhea	70	70.0
Shortness of breath	33	33.0
Reduced feeding	30	30.0
Vomiting	24	24.0
Hypoactivity	15	15.0
Sepsis	08	8.0
Cyanosis/Desaturation	08	8.0
Nasal blockage/Congestion	08	8.0

The most common clinical presentation was cough (80 (80.0%) patients) followed by fever (70 (70.0%) patients).

Table 3: Blood investigations for 100 children with acute bronchiolitis

Investigation	Mean	SD	Median	Minimum	Maximum	Normal range
White blood cells count (×106/µL)	11.4	8.6	9.6	0.8	111.4	3.6-9.6
Hemoglobin (g/dL)	11.3	2.2	10.9	5.7	20.0	12-14.5
Platelet's count (×106/µL)	418.5	176.4	393.0	14.5	971.0	150-400
C-reactive protein (mg/L)	27.5	39.0	10.4	0.1	297.0	0-3

Table 4: Comparison between C-reactive protein positive and negative patients (n=100)

Variable		C-reactive protein level		p-value
		High n=75	Low n=25	
Gender	Male	45 (60.0)	13 (52.0)	0.450
	Female	30 (40.0)	11 (44.0)	
Age at presentation (month), mean±SD		11:76±13:91	6:26±17:60	<0.0001
Age at the time of study (month), mean±SD		32:22±14:20	27:07±17:44	<0.0001
Length of hospital stay (d), mean±SD		10±39	12±69	0.250
History of fever		61 (81.3)	13 (52.0)	<0.0001
History of cough		60 (80.0)	15 (60.0)	0.002
White blood cells count (×106/µL), mean±SD		11:92±9:65	9:95±4:78	0.131
Hemoglobin (g/dL), mean±SD		10:9±1:8	12:5±2:7	<0.0001
Platelet's count (×106/µL), mean±SD		417:3±175:5	421:6±180:1	0.910
Positive blood culture		7 (9.3)	2 (8.0)	0.780
Positive urine culture		7 (9.3)	2 (8.0)	1.000
Positive cerebrospinal fluid culture		3 (4)	0	1.000
Positive chest X ray		52 (69.3)	16 (64.0)	0.630
Antibiotic use		60 (80)	17 (68.0)	0.064
Complications		7 (9.3)	3 (12.0)	1.000
Admission to intensive care unit		4 (5.3)	2 (8.0)	0.750
Mortality		1 (1.3)	1 (4.0)	1.000

Antibiotics were used in 80.0% patients. Patients with high CRP were older at presentation (p<0:0001) and had more fever (p<0:0001) and cough (p=0:002), but lower hemoglobin level (p<0:0001) compared to those with normal CRP. Fever (P = 0:016) and hemoglobin level (p= 0:002) were independent factors.

Discussion

Acute bronchiolitis is one of the most common respiratory diseases in children under 2 years of age [4]. It is most often caused by respiratory syncytial virus (RSV) [4]. By the age of 2 years, nearly all children will have had at least one RSV bronchiolitis infection [16]. Preterm infants and male patients are more commonly affected [17, 18]. C-reactive protein (CRP), an acute phase reactant and an indicator of acute inflammation, is associated with bacterial coinfections, such as bacterial pneumonia [19, 20]. However, patients with RSV bronchiolitis, bronchopneumonia, and RSV pneumonia have been found to have elevated CRP levels, as well as high white blood cell (WBC) counts and erythrocyte sedimentation rates (ESR), all of which indicate bacterial co-infection [19-21]. Thus, measurement of CRP levels can be an important indirect marker of viral infection and an indicator of the progression of infection and the effectiveness of treatment [19]. It is noteworthy that in patients with RSV bronchiolitis, elevated CRP levels are associated with a longer hospital stay [19, 22, 23]. It is known that RSV infection occurs mainly in men, but the mechanism has not yet been studied. This finding may be due to the suppression of eosinophil numbers in the blood or the immunosuppressive effect of male hormones. In our study, CRP levels in male patients were higher than in females. However, gender was not a significant risk factor for high CRP levels. In contrast, Nagayama *et al*. showed that high CRP levels were more common in women (37.0%) than in men (19%) p<0:05. This variation has been also explained by the presence of immunologic differences between boys and girls [24]. The most common clinical presentations of patients with acute bronchiolitis in this study were cough (80%) and fever (70%), which is ingoing with the findings of several other studies [25-27]. Nonetheless, cough was more frequent in Lamarão *et al*. and Sawatzky *et al*. studies (98.0% and 93.0%, respectively); but the fever was of less frequency (72.0% and 51.0%, respectively) [25, 27]. For the laboratory investigations, the current study had a median WBC count of 9.6 g/dL, which was similar to what was reported by Do *et al*. (9.7 g/dL) [26]. Mean WBC count in our study was higher in children with high CRP compared to those with normal levels, but this was not statistically significant. Similarly, Fares *et al*. found that WBC count was not predictive for bacterial coinfection in children with bronchiolitis [23]. Nonetheless, majority of children with viral infections have low WBC counts [21]. Moreover, WBC count did not differ between RSV-positive and RSV- negative infants in Resch *et al*.'s study [28]. Despite that there was no significant difference between RSV-positive and RSV-negative patients in terms of the percentage of patients with high CRP levels, the mean CRP level was found to be significantly lower in RSV positive (21:5±27:7mg/L) compared to RSV-negative patients (31:3±44:3 mg/L) in this study (P = 0:042). Peltola *et al* study showed that most children with viral infections has low CRP levels including those with RSV [21]. This result may be due to the presence of a higher proportion of bacterial coinfections in RSV-negative patients, which may not be detected in blood, urine, or CSF cultures. However, found no difference in CRP levels between RSV-positive and RSV-negative infants [28]. Patients with acute severe bronchiolitis who require admission to the PICU tend to be more ill, may require mechanical ventilation, or may have

bacterial coinfections. In contrast, patients treated in general pediatric wards tend to have milder illness. In a study by Papoff *et al*., critically ill infants with extensive consolidation or atelectasis had significantly higher CRP values (P = 0.04) [29]. Furthermore, in a study by Tavares M *et al*., CRP levels were statistically significantly associated with admission to the PICU (P = 0.008). In this study, it was hypothesized that CRP levels may serve as an indirect marker of disease severity [30]. Thus, patients admitted to the PICU tend to have higher CRP levels than those who were not admitted to the PICU. The mean CRP levels in this study were higher in patients who were not admitted to the PICU than in those who were admitted to the PICU, but this difference was not statistically significant. This study also showed that there was no significant difference between patients with high and normal CRP levels in terms of complications and mortality. Similar to our study, studies by Fares *et al*. [21] and Resch *et al*. [28] reported that the severity of acute bronchiolitis is not affected by CRP levels. In children with acute bronchiolitis, unnecessary antibiotic use is common due to the difficulty in differential diagnosis between invasive bacterial infection and isolated viral infection [31]. A study by Desmarest *et al*. [32] found an association between antibiotic prescriptions and high CRP levels. However, these high values cannot predict the presence of alveolar condensation on chest radiographs [32]. High CRP levels may mislead doctors and lead them to use antibiotics unnecessarily for viral illnesses.

Conclusion

The study showed that most patients with acute bronchiolitis had a high rate of elevated CRP levels, which did not correlate with the rate of bacterial co-infection. Children with higher CRP levels were older at presentation, had more fever and cough symptoms, and had lower hemoglobin levels, factors that have previously been associated with disease severity and bacterial co-infection. The study also showed an overall high rate of antibiotic prescriptions for primarily viral illnesses. Further studies are needed to determine a critical CRP cutoff at which bacterial infection may be highly suspicious and to develop clinical treatment algorithms that minimize unnecessary antibiotic use in children with acute bronchiolitis.

References

1. Jeon JS, Rheem I, Kim JK. C-reactive protein and respiratory viral infection. Korean J Clin Lab Sci. 2017;49(1):15–21. DOI: 10.15324/kjcls.2017.49.1.15.
2. Alejandre C, Guitart C, Balaguer M, *et al*. Use of procalcitonin and C-reactive protein in the diagnosis of bacterial infection in infants with severe bronchiolitis. Eur J Pediatr. 2021;180(3):833–842. DOI: 10.1007/s00431-020-03790-6.
3. Peltola V, Mertsola J, Ruuskanen O. Comparison of total white blood cell count and serum C-reactive protein levels in confirmed bacterial and viral infections. J Pediatr. 2006;149(5):721–724. DOI: 10.1016/j.jpeds.2006.08.051.
4. Fares M, Mourad S, Rajab M, Rifai N. The use of C-reactive protein in predicting bacterial co-infection in children with bronchiolitis. North Am J Med Sci. 2011;3(3):152–156. DOI: 10.4297/najms.2011.3152.
5. Higdon MM, Le T, O'Brien KL, *et al*. Association of C-reactive protein with bacterial and respiratory syncytial virus–associated pneumonia among children aged <5 years in the PERCH study. Clin Infect Dis. 2017;64(suppl 3)–S386. DOI: 10.1093/cid/cix150.
6. McCarthy PL, Frank AL, Ablow RC, Masters SJ, Dolan Jr TF. Value of the C-reactive protein test in the differentiation of bacterial and viral pneumonia. J Pediatr. 1978;92(3):454–456.
7. Ananthnaryan R, Paniker CKH. Textbook of Microbiology. 4th ed. Orient Longman Publications; c1990.
8. HTA of C-reactive protein point-of-care testing to guide antibiotic prescribing | HIQA [Internet].
9. Lemiengre MB, Verbakel JY, Colman R, *et al*. Reducing inappropriate antibiotic prescribing for children in primary care: A cluster randomised controlled trial of two interventions. Br J Gen Pract. 2018;68(668):210.
10. Murray CJ, Ikuta KS, Sharara F, *et al*. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet. 2022;399(10325):629–655.
11. Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis – clinical practice guideline. Pediatrics. 2006;118(4):1774–1793.
12. Goodman D. Bronchiolitis. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics. 16th ed. Philadelphia: WB Saunders; c2004. p. 1415–1417.
13. Prat C, Domínguez J, Rodrigo C, *et al*. Procalcitonin, C-reactive protein and leukocyte count in children with lower respiratory tract infection. Pediatr Infect Dis J. 2003;22(11):963–967.
14. Toikka P, Irjala K, Juven T, *et al*. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. Pediatr Infect Dis J. 2000;19(7):598–602.
15. Van den Bruel A, Haj-Hassan T, Thompson M, *et al*. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: A systematic review. Lancet. 2010;375(9717):834–845.
16. Piedimonte G, Perez MK. Respiratory syncytial virus infection and bronchiolitis. Pediatrics in Review. 2014;35(12):519–530. DOI: 10.1542/pir.35.12.519.
17. Park HW, Lee BS, Kim AR, *et al*. Epidemiology of respiratory syncytial virus infection in infants born at less than thirty-five weeks of gestational age. Pediatr Infect Dis J. 2012;31(8):104. DOI: 10.1097/INF.0b013e318257f619.
18. Kenneth M. Respiratory syncytial virus. In: Berman RE, Kliegman RM, editors. Nelson Textbook of Pediatrics. 16th ed. Philadelphia: WB Saunders; c2000.
19. Jeon JS, Rheem I, Kim JK. C-reactive protein and respiratory viral infection. Korean J Clin Lab Sci. 2017;49(1):15–21.
20. Alejandre C, Guitart C, Balaguer M, *et al*. Use of procalcitonin and C-reactive protein in the diagnosis of bacterial infection in infants with severe bronchiolitis. Eur J Pediatr. 2021;180:833-842.
21. Peltola V, Mertsola J, Ruuskanen O. Comparison of total white blood cell count and serum C-reactive protein levels in confirmed bacterial and viral infections. J Pediatr. 2006;149(5):721–724.
22. Higdon MM, Le T, O'Brien KL, *et al*. Association of

C-reactive protein with bacterial and respiratory syncytial virus–associated pneumonia among children aged <5 years in the PERCH study. Clin Infect Dis. 2017;64(suppl 3):S386.
23. Fares M, Mourad S, Rajab M, Rifai N. The use of C-reactive protein in predicting bacterial co-infection in children with bronchiolitis. North Am J Med Sci. 2011;3(3):152.
24. Nagayama Y, Tsubaki T, Nakayama S, *et al*. Gender analysis in acute bronchiolitis due to respiratory syncytial virus. Pediatr Allergy Immunol. 2006;17(1):29-36.
25. Lamarão LM, Ramos FL, Mello WA, *et al*. Prevalence and clinical features of respiratory syncytial virus in children hospitalized for community-acquired pneumonia in northern Brazil. BMC Infect Dis. 2012;12(1):1-7.
26. Do Q, Dao TM, Nguyen TN, *et al*. Procalcitonin identifies bacterial coinfections in Vietnamese children with severe respiratory syncytial virus pneumonia. Biomed Res Int. 2020; 2020:1–6.
27. Sawatzky J, Soo J, Conroy AL, *et al*. Biomarkers of systemic inflammation in Ugandan infants and children hospitalized with respiratory syncytial virus infection. Pediatr Infect Dis J. 2019;38(8):854–859.
28. Resch B, Gusenleitner W, Müller W. Procalcitonin, interleukin-6, C-reactive protein and leukocyte counts in infants with bronchiolitis. Pediatr Infect Dis J. 2003;22(5):475–476.
29. Papoff P, Moretti C, Cangiano G, *et al*. Incidence and predisposing factors for severe disease in previously healthy term infants experiencing their first episode of bronchiolitis. Acta Paediatr. 2011, 100(7). –23.
30. Tavares M, Bonito-Vítor A, Costa S, *et al*. Proteina C Reactiva e gravidade da Bronquiolite aguda. Rev Port Pneumol. 2009;15(1):55–65.
31. Alejandre C, Balaguer M, Guitart C, *et al*. Procalcitonin-guided protocol decreased the antibiotic use in paediatric patients with severe bronchiolitis. Acta Paediatr. 2020;109(6):1190–1195.
DOI: 10.1111/apa.15148.
32. Desmarest M, Aupiais C, Le Gal J, *et al*. Value of procalcitonin for infants with bronchiolitis in an emergency department. Arch Pediatr. 2017;24(11):1060–1066.