

C-reactive protein is associated with severity in hospitalized children with Respiratory Syncytial Virus bronchiolitis

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Abstract

Objective: Acute bronchiolitis, primarily caused by Respiratory syncytial virus (RSV), is the most common cause of hospitalization in young children. Despite international guidelines supporting clinical diagnosis, laboratory evaluations are often conducted with limited validity. We aim to evaluate the association between C-reactive protein (CRP) levels at admission and disease severity in children hospitalized due to RSV bronchiolitis. **Study design:** This single center retrospective cohort study included children (0-24 months old) who were hospitalized due to RSV bronchiolitis (January 2018 – March 2022) with CRP levels taken upon admission. Clinical data and severity parameters were extracted using MD-clone platform and the clinical research unit at SUMC. **Results:** 1,874 children (mean age of 6.7 months, 59% males) with a median CRP level of 1.92mg/dL were included. Children with elevated CRP ($>1.92\text{mg/dL}$) were significantly older (5.1 vs. 3.8 months, $p<0.001$), had higher rates of pneumonia (9.4% vs. 4.3%, $p<0.001$), urinary tract infection (UTI), (2.2% vs. 0.2%, $p<0.001$), acute otitis media (AOM), (1.7% vs 0.2%, $p<0.001$), admissions to pediatric intensive care unit (PICU) (7.4% vs 3.7%, $p<0.001$), antibiotic treatment (49.8% vs 37.2%, $p<0.001$) and longer hospitalizations (3.83 vs 3.31 days, $p=0.001$). Multivariable analysis predicted increased risk for UTI, PICU admission, pneumonia, and longer hospitalization (relative risk of 11.6, 2.25, 1.98, 1.44, respectively, $p<0.001$). CRP thresholds of 3.51, 1.9, and 2.81 mg/dL for PICU admission, UTI, and pneumonia, were calculated using Youden's index with AUC of 0.72, 0.62, and 0.61, respectively. **Conclusions:** Elevated CRP levels at admission are associated with increased disease severity and higher complication rates in children hospitalized with RSV bronchiolitis.

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Keywords: Bronchiolitis, Respiratory syncytial virus, C-reactive protein, urinary tract infection, disease severity, hospitalization.

List of Abbreviations:

AB Acute bronchiolitis

AOM Acute otitis media

BPD Bronchopulmonary dysplasia

CLD Chronic lung disease

CRP C-reactive protein

ED Emergency department

IQR Interquartile range

LOS Length of stay in the hospital

MOS Minimal Oxygen Saturation

PICU Pediatric intensive care unit

RDS Respiratory distress syndrome

RSV Respiratory syncytium virus

SD Standard Variation

SUMC Soroka University Medical Center

UTI Urinary tract infection

ABSTRACT

Objective : Acute bronchiolitis, primarily caused by Respiratory syncytial virus (RSV), is the most common cause of hospitalization in young children. Despite international guidelines supporting clinical diagnosis, laboratory evaluations are often conducted with limited validity. We aim to evaluate the association between C-reactive protein (CRP) levels at admission and disease severity in children hospitalized due to RSV bronchiolitis.

Study design: This single center retrospective cohort study included children (0-24 months old) who were hospitalized due to RSV bronchiolitis (January 2018 – March 2022) with CRP levels taken upon admission. Clinical data and severity parameters were extracted using MD-clone platform and the clinical research unit at SUMC.

Results: 1,874 children (mean age of 6.7 months, 59% males) with a median CRP level of 1.92mg/dL were included. Children with elevated CRP ($>1.92\text{mg/dL}$) were significantly older (5.1 vs. 3.8 months, $p<0.001$), had higher rates of pneumonia (9.4% vs. 4.3%, $p<0.001$), urinary tract infection (UTI), (2.2% vs. 0.2%, $p<0.001$), acute otitis media (AOM), (1.7% vs 0.2%, $p<0.001$), admissions to pediatric intensive care unit (PICU) (7.4% vs 3.7%, $p<0.001$), antibiotic treatment (49.8% vs 37.2%, $p<0.001$) and longer hospitalizations (3.83 vs 3.31 days, $p=0.001$). Multivariable analysis predicted increased risk for UTI, PICU admission, pneumonia, and longer hospitalization (relative risk of 11.6, 2.25, 1.98, 1.44, respectively, $p<0.001$). CRP thresholds of 3.51, 1.9, and 2.81 mg/dL for PICU admission, UTI, and pneumonia, were calculated using Youden's index with AUC of 0.72, 0.62, and 0.61, respectively.

Conclusions : Elevated CRP levels at admission are associated with increased disease severity and higher complication rates in children hospitalized with RSV bronchiolitis.

Statements and declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

IGT contributed to the study's conception and design. AA and NB were responsible for material preparation and data collection. Statistical analysis was performed by NB and BC. The initial draft of the manuscript was written by AA, and all authors provided feedback on earlier versions of the manuscript. All authors reviewed, edited, and approved the final manuscript.

Ethics approval

The study protocol was approved by the local ethical review board of SUMC (0296-21-SOR).

INTRODUCTION

Acute bronchiolitis (AB) is a lower respiratory tract infection that affects approximately 20% of all children, resulting in hospitalization for 2-3% of them under 12 months of age. Mortality from AB occurs predominantly in developing countries. In developed countries it is associated with various complex chronic conditions and sociodemographic risk factors.

AB classically presents with increased respiratory effort and wheezing, often accompanied by systemic manifestations such as fever or apnea, a common symptom in neonates. a common disease is of 14-21 days with peak symptoms at days 3-5. guidelines recommend avoiding laboratory or radiographic evaluations. Nonetheless, these are often performed in various clinical settings.

The most common viral pathogen associated with bronchiolitis is Respiratory Syncytial Virus (RSV), which accounts for 50-80% of cases, and is associated with more severe disease. Co-infections with other viruses are seen in up to 30% of cases. Secondary bacterial infections, such as AOM, Pneumonia, and UTI (37-74%, up to 32%, 1-7% respectively) (7,9) have been reported in hospitalized patients. (7,9-11). Respiratory failure requiring invasive or non-invasive ventilation occurs in 3-19% of hospitalized children, usually in PICU settings.

C-reactive protein (CRP), an acute phase reactant which is synthesized in the liver, acts as a mediator between the innate and acquired immune systems. Peaking 48-72 hours after the onset of an inflammatory response, it is a common clinical tool for diagnosis and monitoring of inflammatory responses. Only a few studies have examined the relevance of CRP in RSV bronchiolitis. These studies identified a correlation between higher CRP levels and an increased risk of severe disease particularly in cases of radiologically confirmed pneumonia, or the diagnosis of sepsis in PICU settings.

In this study, our objective is to investigate the correlation between CRP levels on admission and the severity of RSV bronchiolitis, as well as any related complications in hospitalized children. Additionally, we aim to propose specific cutoff values for CRP levels that are indicative of different severity outcomes, such as the incidence of secondary infections, prolonged length of stay in the hospital (LOS), and the need for PICU admission.

METHODS

Study design

This is a retrospective cohort study conducted at Soroka University Medical Center (SUMC), a tertiary hospital in southern Israel where approximately 450 children are hospitalized annually due to RSV bronchiolitis, many of whom undergo initial workup, including CRP levels. Clinical, demographic, and laboratory

data were extracted from Clalit Health Services (CHS) electronic medical records using Clalit's Data sharing platform powered by MD-clone (www.mdclone.com). The institution's computational unit extracted data on mechanical ventilation, oxygen supply, and oxygen saturation of the enrolled patients. The study protocol was approved by the local ethical review board of SUMC (0296-21-SOR).

Subjects

This study included children aged less than 2 years of age who were hospitalized between January 2018 and March 2022 due to acute bronchiolitis, with a positive RT-PCR for RSV on a nasal swab during the first week since admission and a CRP level measurement taken during the first 72 hours from admission. The exclusion criteria were major genetic or chromosomal abnormalities, immunodeficiencies, cyanotic heart conditions, neurologic diseases, hypotonia, and chronic lung diseases.

Clinical outcomes

Clinical outcomes included LOS, minimal oxygen saturation (MOS), rate of PICU admissions, and rates of secondary bacterial infections. LOS was calculated from the ED admission to discharge from the hospital. Prolonged LOS was defined as longer than the 75th percentile. MOS was the lowest recorded oxygen saturation in room air during hospitalization. PICU admission and assisted ventilation with continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation were also noted. The diagnoses of secondary infections, such as pneumonia, UTI, AOM, meningitis, and bacteremia, as well as the use of steroids or antibiotics during hospitalization, were extracted from the patient's electronic medical records.

Statistical analysis

The study evaluated children's clinical and demographical characteristics based on their CRP levels above or below the median. Results from the univariate analysis were presented as mean \pm SD for normally distributed variables or as a median with interquartile range (IQR) for variables not meeting the normal distribution assumption. Categorical variables were presented as counts and proportions of available data. Differences in quantitative variables between groups were analyzed using ANOVA or the nonparametric Wilcoxon rank sum test. Categorical parameters were compared using Chi-square χ^2 or Fisher's exact test. Quasi-Poisson regression modeling was used for multivariable analysis to investigate the association between the CRP value and clinical outcomes. The optimal cutoff values for CRP were determined using Youden's index with the R pROC package. The predictive ability of these cutoffs for severe clinical outcomes was evaluated using the receiver operating characteristic curve (ROC), and the area under the curve (AUC) was calculated to measure this ability. Statistical significance was indicated by a *P* value of 0.05 in all analyses. All statistical analyses were performed using R software (version 4.0.2), developed by the R Foundation for Statistical Computing, in Vienna, Austria (<http://www.R-project.org>).

RESULTS

A total of 2,301, children under the age of two were hospitalized due to RSV bronchiolitis, of which 1,874 were included in the study (Figure 1). Patients' mean age was 6.7 months (SD \pm 5.9), 55.9% were male and 62.6% were of Bedouin origin. The mean hospital LOS was 3.57 days. 104 children were admitted to the PICU (5.5%), with an average PICU LOS of 5 days (SD \pm 4.4 days). The mean MOS was 89%. Additionally, approximately one-quarter of the children had co-infection with a second virus, with adenovirus present in 8.9% of cases (Table 2b). additional demographic and clinical parameters are presented in Table 1.

The cohort was divided into a low-CRP group and a high-CRP group based on the median CRP value of 1.92 mg/dL (Table 2a). The two groups had similar gender, ethnicity, gestational age, and prior diagnosis of RDS. The high-CRP group had a significantly higher mean CRP level of 14 mg/dL compared to 1 mg/dL in the low-CRP group ($p < 0.001$). Children in the high-CRP group were older (7.3 vs. 6.0 months, $p < 0.001$) and had slightly lower birthweight (3,087 vs. 3,141 grams, $p = 0.047$). Additionally, they had longer hospital LOS (3.83 days VS. 3.31, $p = 0.001$) and a lower prevalence of BPD in their medical history (0.2% vs 1%, $p = 0.034$).

Children in the higher-CRP group had lower minimal saturation (88% vs. 89%, $p=0.002$), a higher rate of prolonged LOS (defined as \geq 75% of LOS percentile, 4.3 days) (28.9% vs. 21.0% $p<0.001$), and a higher incidence of pneumonia (9.4% vs. 4.3%, $p<0.001$), UTI (2.2% Vs., 0.2% $p<0.001$), and AOM (1.7% Vs. 0.2% $p<0.001$). Viral co-infection was more common in the low-CRP group (28.1% Vs. 25.2% $p<0.001$), while adenovirus infection was more common in the high-CRP group (10.5% Vs. 7.4% $p<0.001$). The PICU admission rate was twice as high in the high-CRP group (7.4% Vs. 3.7% $p<0.001$). We observed a higher rate of antibiotic treatment in the high-CRP group (49.8% Vs. 37.2% $p<0.001$). No significant differences in hyponatremia rates, bacteremia, glucocorticosteroid use, ventilation duration, or readmission rates were found between the two groups.

After adjusting for age and sex in a multivariable regression model, it was found that the high-CRP group had a higher risk for PICU admission (RR = 2.25 CI 1.40, 3.71 $p=0.001$), UTI (RR = 11.6, CI 3.67, 61.4 $p<0.001$), pneumonia (RR = 1.98 CI 1.39, 2.87 $p<0.001$), and prolonged LOS (RR = 1.44 CI 1.23, 1.70 $p<0.001$) (Table 3, Figure 2).

The optimal cutoff values of CRP for predicting severity outcomes, calculated using Youden's index, were 1.9 mg/dL with an AUC of 0.72 for predicting UTI, 2.81 mg/dL with an AUC of 0.62 for predicting pneumonia, and 3.51 mg/dL with an AUC of 0.61 for predicting PICU admission (Figure 3).

DISCUSSION

This study evaluated the association between CRP levels and measures of disease severity in infants who were hospitalized due to acute RSV bronchiolitis. The findings revealed that infants with elevated CRP levels were older, had lower MOS, longer LOS, and higher rates of secondary infections such as pneumonia, UTI, and AOM. Additionally, there were more likely to receive antibiotics and require hospitalization in the PICU. The study also proposes cutoff values for CRP that could predict the likelihood of UTI, pneumonia, and PICU admission.

The mean age of the children was 6.7 months, with a male predominance, and most were term infants, while 10.8% were born prematurely. These results align with previous medical literature regarding the demographic characteristics of pediatric patients with RSV bronchiolitis and those treated at the SUMC. Younger age is a known risk factor for severity in RSV, and indeed older age was a protective factor, according to the regression model. A relative immaturity of the immune system, supported by studies that demonstrate a severe RSV infection associated with lower levels of Interferon-gamma (IFN- γ) and lower fever due to inappropriate inflammatory response, could explain a more severe course of the disease in younger children. Our study revealed a significant correlation between elevated CRP and older children (rather than younger children), indicating the independent role of CRP in association with more severe disease. This finding is further supported by the lack of influence of prematurity and gestational age, which are prominent risk factors for severe disease, on CRP as a severity marker. This holds true even for premature infants under 35 weeks who routinely receive Palivizumab during RSV season. Additionally, we observed equal distribution of CRP levels, sex, and ethnicity in both the higher and lower CRP groups.

LOS

Although the length of hospitalization is an important aspect of RSV bronchiolitis, it has not been well studied. Mean LOS varies greatly, ranging from 2-3 days in the USA to 5-6 days in Europe and low-income countries. A recent study investigating the correlation between CRP levels and RSV bronchiolitis severity found no association with prolonged hospitalization. However, that study had a relatively small cohort with a relatively long mean hospitalization length of 5 days. Our study, on the other hand, found that children with elevated CRP had an average extended hospitalization length of half a day. In a multivariable model, children in the higher-CRP group had a 1.5 times higher risk of being hospitalized for an extended period (75th percentile, or 4.3 days).

PICU admissions

Multivariate analysis revealed a positive association between CRP and an increased risk of PICU admission

due to respiratory failure. Studies report an admission rate of 3-27% with variability in invasive ventilation usage, which correlates with younger age, especially those under 3 months. A recent study reported a PICU admission rate of 27%, with only 3.5% requiring invasive ventilation, and 96% utilizing high flow nasal cannula. This non-invasive ventilation method is routinely used in the PICU and was integrated into our pediatric wards in the middle of the study period. This may have contributed to the low rate of PICU admission in our study of 5.5%. Although few studies have examined the association between CRP and PICU admission, a preliminary study of 177 patients found an association between PICU admission and a mean CRP of 3.9 mg/dL when most patients had RSV bronchiolitis. However, another study failed to demonstrate such an association. Our study demonstrated an association between elevated CRP and PICU admission, reflected by a relative risk of 2.25 in a multivariable model. The suggested cutoff value's ability to differentiate between children admitted to PICU was limited (Figure 3). However, we found that a cutoff value of 3.295 was useful for children under three months old (AUC 0.68).

Secondary bacterial infections

Secondary bacterial infections are a known complication of RSV bronchiolitis, of which UTI is the most extensively studied. However, many of these studies have used various UTI definitions with differing levels of sensitivity and specificity. For instance, a recent meta-analysis reported that 3.1% of children with bronchiolitis were also diagnosed with a UTI. Many studies included only children under three months of age and not 24 months. Early detection of UTI can profoundly impact the clinical outcome of hospitalized infants.

In our cohort, 23 patients (1.2%) were diagnosed with UTI, with a relative risk of 11 for the high CRP group in a multivariable analysis. However, this association was highly sensitive but not specific. The highest AUC was in children 3-12 months old with a threshold of 3.42 mg/dL (AUC 0.79), although further investigation is needed since UTI incidence in our cohort was very low.

Lobar/alveolar pneumonia is another important complication of RSV bronchiolitis, but its definition varies in the literature and is based on clinical and radiographic features, often assisted by laboratory markers. A recent study from our center has demonstrated that RSV is associated with community-acquired pneumonia in a multivariable model in 50% of cases, most notably in children under 2 years of age (62%), indicating a significant role in its pathogenesis. This finding is supported by the decline in pneumonia and RSV prevalence during the COVID-19 pandemic despite persistent nasopharyngeal carriage of *S. pneumoniae*.

Several studies have assessed the association of elevated CRP with pneumonia in the context of RSV. One multinational study reported that increased CRP levels ($>4\text{mg/dL}$) were associated with bacterial rather than viral pneumonia in otherwise healthy children. However, another study showed only a slightly elevated CRP level in bacterial pneumonia (1.06 Vs. 0.62 mg/dL). In a prospective study of children with bronchiolitis in a PICU setting, elevated CRP and procalcitonin levels were significantly associated with pneumonia or sepsis. These results are similar to our study in the association of CRP with severe disease, but differ in the study population, which only isolated RSV in 65% of patients and only included severe cases, who often have other predisposing conditions that excluded them from our study. Our study found that elevated CRP was associated with secondary pneumonia (9% in the high-CRP group vs. 4.3% in the low group) with a relative risk of 1.98 in a multivariable analysis. However, we found that CRP had limited predictive ability, as the AUC for the suggested cutoff was low.

The main strength of our research is the large cohort size, which is larger than previous studies that have assessed CRP in acute bronchiolitis in children. Additionally, being a single tertiary medical center, SUMC was able to maintain a consistent clinical approach, with standardized protocols for hospitalization, discharge, antibiotic stewardship, and laboratory and radiologic evaluation, which further strengthens the reliability and validity of our findings.

Limitations of this study include its retrospective nature, as the inclusion and exclusion criteria may have resulted in the exclusion of mild cases who were likely discharged without CRP measurement, as well as critically ill patients with severe risk factors. Also, our definition of secondary infection was based on the

electronic medical records, which were determined by the treating physicians and not based on interpretation of radiological findings, with fixed criteria. As such, there may be potential for under or overdiagnosis. Furthermore, an elevated CRP level may have influenced the given pneumonia diagnosis, which was also based on inflammatory markers and not merely based on radiologic findings. Lastly, our medical documentation system prevented us from further analyzing data on the use of high-flow nasal cannula in the pediatric ward setting, which was implemented in 2020.

This study was conducted with the aim of providing clinicians an easy and accessible tool to aid decision making and management of hospitalized children with RSV bronchiolitis. Specifically, we sought to determine the usefulness of CRP levels measured at ED admission as an early detection method for severe disease. Our findings demonstrate that CRP can be a valuable tool for informing decisions related to hospitalization, diagnostic evaluation, and communication with parents about the anticipated duration of hospitalization.

CONCLUSIONS

Elevated CRP levels upon hospital admission are associated with severe disease in RSV bronchiolitis, leading to increased risks of prolonged hospitalization, PICU admission, and secondary bacterial infection. Since it is widely available and commonly used, CRP can aid decision-making in emergency departments.

REFERENCES

Legend

Table 1. Demographic and clinical characteristics of the study population (N = 1,874)

Table 2a. Demographics and background diseases of the study population, according to CRP

Table 2b. clinical characteristics of the study population, according to CRP

Table 3. Multivariable Model adjusted to age for different clinical outcomes.

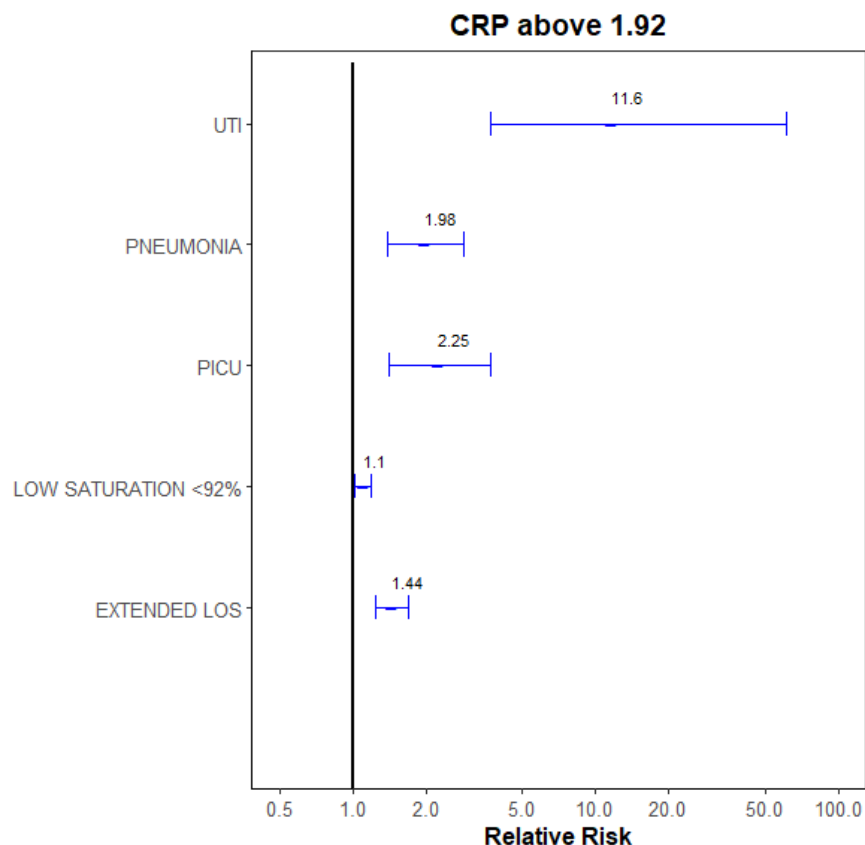
Figure 1. Flowchart of the Study population

Figure 2. Multivariable model for different clinical outcomes

Figure 3. ROC curves for predicting UTI (A), Pneumonia (B), PICU admission (C), and prolonged LOS (D), using the Youden's index.

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