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Value of Salivary C - Reactive Protein in the Diagnosis and Severity Assessment of Childhood Pneumonia

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Abstract

Patients with community-acquired pneumonia (CAP) reported higher C-reactive protein (CRP) levels at hospital admission among patients directly admitted to an intensive care unit (ICU), transferred subsequently to an ICU, or who died in the hospital. We aimed to determine the value of salivary C - reactive protein in the diagnosis and severity assessment of childhood pneumonia. This single-centre, case-control observational study was conducted on 80 children admitted at the Pediatric Department of Benha University Hospitals, Egypt. They were divided into patients group: including 40 children with CAP and subdivided into; severe pneumonia group (N=18), moderate pneumonia group (N=12) and mild pneumonia group (N=10), and control group included 40 apparently healthy children. All patients underwent detailed history taking general examination of vital signs and appearance, systemic examination and local examination of chest, laboratory investigations included detection of serum and salivary CRP and chest x-ray. Serum CRP, and salivary CRP were significantly higher in patients compared to controls (P<0.05). The multivariate logistic regression analysis revealed that one-unit increase in salivary CRP was associated with about three times increased risk of pneumonia (OR = 2.727, 95% CI = 1.565 - 4.75, P < 0.001). We concluded a strong correlation between salivary CRP levels and serum CRP levels, as well as various clinical features of CAP in pediatric patients. Salivary CRP measurement could be a useful, non-invasive tool for assessing and monitoring pediatric patients with CAP.

Keywords: Salivary; C-Reactive Protein; Childhood; Community-acquired pneumonia; Severity

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1. Introduction

Community-acquired pneumonia (CAP) is a highly prevalent infection and remains the first cause of early childhood mortality in developing countries [1]. Early life pneumonia can impair long-term lung health by decreasing lung function. Severe or recurrent pneumonia can have a worse effect on lung function; increasing evidence suggests that chronic obstructive pulmonary disease might be related to early childhood pneumonia. Associated symptoms include fever, cough, dyspnoea, and tachypnea with supporting evidence of parenchymal infection and inflammation, diagnosed according to findings at chest auscultation or the presence of focal opacity seen on chest radiographs [2]. In developed countries the diagnosis is usually based on clinical history, respiratory rate, fever, respiratory signs and symptoms and, possibly, radiography especially in severe or complicated cases [3]. Early diagnosis of CAP is essential to reduce the total burden of the disease. In many cases, clinical signs and symptoms strongly suggest the diagnosis. However, in a significant number of children, CAP remains a diagnostic challenge mainly because a number of viral respiratory diseases, which require a different therapeutic approach, mimic the clinical manifestations of CAP [4]. C-reactive protein (CRP) is an acute phase protein synthesized by the liver, primarily in response to interleukin-6. It plays multiple important roles in innate immunity and host-defence [5]. Its measurement is inexpensive and widely accessible. CRP levels have been shown to discriminate between pneumonia and healthy status, as well as between pneumonia and exacerbations of chronic obstructive pulmonary disease and asthma [6]. CRP levels have also been shown to distinguish between causative pathogens, including bacterial and non-bacterial causes. A recent investigation of patients with CAP reported higher CRP levels at hospital admission among patients directly admitted to an intensive care unit (ICU), transferred subsequently to an ICU, or who died in the hospital [7]. The interest of mucosal immunity in general and

the use of human salivary CRP as a diagnostic body fluid is increasing. Saliva contains a unique mixture of proteins, nucleic acids, electrolytes and hormones derived from systemic as well as local sources [8]. Advantages of using saliva as a diagnostic tool are that the collection is non-invasive, relatively easy and rapid, safe, stress- and pain-free and cheap because sampling is possible without professionals [9]. We aimed to determine the value of salivary CRP in the diagnosis and severity assessment of childhood pneumonia.

2. Materials and Methods

This single-centre, case-control observational study was conducted on 80 children admitted at the Pediatric Department of Benha University Hospitals, Egypt. Informed written consents were taken from the parents or caregivers of the enrolled children. The research was conducted within the approved guidelines of the Institutional Ethical Committee of Benha. The inclusion criteria of patients group were children aged more than 1 month and less than 17 years and who fulfilled the criteria of pneumonia of the WHO 2022 and supported by chest radiography. The exclusion criteria were children aged less than 1 month or more than 17 years, with conditions other than community acquired pneumonia included chronic inflammatory diseases and immunocompromising states.

2.1. Grouping

Patients group: including 40 children with CAP and subdivided into; severe pneumonia group (N=18) included patients with conditions deemed by the attending paediatrician and intensivist to merit paediatrics intensive care unit (PICU) admission, moderate pneumonia group (N=12) included patients admitted in the hospital words and mild pneumonia group (N=10) included patients admitted in the classic hospital words. Control group included 40 apparently healthy children matching the patients group for age & sex. They were selected from the outpatient clinic of Benha University Hospital. All patients were subjected to detailed history taking including personal, present, past, family and perinatal history, general examination of vital signs (temperature, respiratory rate, heart rate) and appearance (activity level and ability to talk, working ala nasi and colour), systemic examination of cardiovascular system, gastrointestinal tract and abdomen, central nervous system and musculoskeletal system (including mental status and neurological examination). Local examination of chest was performed including (inspection, palpation, percussion and auscultation). All patients were classified according to severity of pneumonia into [mild, moderate, severe] [10] and grades of respiratory distress into (Grade I: Tachypnea, Grade II: Tachypnea + chest indrawing, Grade III: Tachypnea + chest in drawing + grunting and Grade IV: Tachypnea + chest indrawing + grunting + cyanosis). All patients underwent laboratory investigations included (Complete blood count, blood culture and detection of serum and salivary CRP by ELISA technique using Human CRP enzyme-linked immunosorbent assay (ELISA) Kit (Cat No# 201-12-1799, SunRed Biotechnology, Shanghai-China). Radiological investigations by chest x-ray and the findings including opacity, infiltrates, atelectasis, peribronchial thickening, pleural effusion and air bronchograms were detected [11].

2.2. Statistical analysis

Statistical analysis was done by SPSS v28 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant. Multivariate logistic regression was used to estimate the relationship between a dependent variable and more independent variables. Pearson correlation was done to estimate the degree of correlation between two quantitative variables. The overall diagnostic performance of each test was assessed by ROC curve analysis. The area under the curve (AUC) evaluates the overall test performance.

3. Results and discussion

There were no significant differences between both groups regarding age, sex and residence. The clinical symptoms and physical findings of the patients group are demonstrated in Table 1. The mean respiratory rate, heart rate in patients were significantly higher compared to controls (P < 0.001, <0.001). Systolic and diastolic blood pressure and O_2 saturation were significantly lower in patients compared to controls (P < 0.05). Total leucocyte count, serum CRP, and salivary CRP were significantly higher in patients compared to controls (P<0.05). In contrast, other variables, such as hemoglobin, Platelets. Additionally, the findings of chest X-ray, blood culture results, and treatment modalities are demonstrated in Table 2. ROC analysis was done for salivary CRP to predict pneumonia. It revealed a significant AUC of 0.931, with a 95% confidence interval of 0.874 – 0.987. The best cutoff point was >5, at which sensitivity, specificity, PPV, and NPV were 80%, 100%, 100%, and 83.3%, respectively Figure 1. Several variables showed significant negative correlations with salivary C-reactive protein (CRP) levels. Age (r = -0.361, P = 0.022), systolic blood pressure (r = -0.552, P < 0.001), diastolic blood pressure (r = -0.698, P < 0.001), O_2 saturation (r = -0.760, P <0 .001), and platelets (r = -0.340, P = 0.032). On the other hand, severity of the condition was strongly positively correlated (r = 0.818, P <0 .001), as were distress grade (r = 0.498, P = 0.001), respiratory rate (r = 0.559, P < 0.001), heart rate (r = 0.628, P < 0.001), PCO2 (r = 0.328, P 0.039), serum CRP levels (r = 0.940, P < 0.001), and TLC (r = 0.731, P < 0.001). Several variables did not show a significant relationship with salivary CRP levels, including duration of the condition, haemoglobin. Table 3. Low fever was associated with salivary CRP levels of 6 mg/dl, moderate fever with 15 mg/dl, and high fever with 45 mg/dl, indicating a positive relation between fever severity and salivary CRP levels. Similarly, salivary CRP level was significantly relater to disease severity, with mild cases having CRP levels of 5 mg/dl, moderate cases 10 mg/dl, and severe cases 38 mg/dl, (P < 0.001). The presence of wheeze and crackles in the lungs also showed significant associations with the salivary CRP

level (P = 0.004). Expiratory wheeze was associated with CRP levels of 7 mg/dl, while the presence of both inspiratory and expiratory wheezes was associated with levels of 25mg/dl. Fine crackles were associated with a CRP level of 24 mg/dl compared to 11 mg/dl and 5 mg/dl in medium and coarse crackles. Respiratory distress (RD) grade was another significant factor (P 0.004), with Grade I associated with CRP levels of 5 mg/dl, Grade II with 16 mg/dl, and Grade III with 25 mg/dl. Bronchopneumonia on chest X-ray was associated with higher CRP levels of 22 mg/dl compared to 8 mg/dl in lobar pneumonia (P= 0.025). The patients who needed oxygen support had a CRP level of 18 mg/dl, those who needed IV fluids had a CRP level of 18 mg/dl, and those who needed inotropes had a CRP level of 66 mg/dl (P < 0.05). Specific antibiotics were associated with significant difference in salivary CRP. The patients who needed vancomycin+ meropenem had higher CRP levels (50 mg/dl, P < 0.001) compared to those who received ampicillin+ cephalosporin. Furthermore, patients with positive blood cultures were associated with notably higher CRP levels (50 mg/dl, P < 0.001). However, salivary CRP did not reveal significant differences according to sex or residence. Table 4. Table 5 shows that multivariate logistic regression analysis revealed that one-unit increase in salivary CRP was associated with about three times increased risk of pneumonia (OR = 2.727, 95% CI = 1.565 - 4.75, P < 0.001), controlling for age, sex, and residence. Pneumonia is an important cause of morbidity and occasional mortality among children in developed countries. CAP is defined as an acute lower respiratory tract infection acquired in a previously healthy individual. The severity of pneumonia is closely related to the extent of the inflammatory response. The diagnostic utility of inflammatory markers in CAP has been reported in the post-pneumococcal vaccination era. Several biomarkers are used for treatment evaluation in paediatric patients with pneumonia [12]. CRP levels have been shown to discriminate between pneumonia and healthy status, as well as between pneumonia and exacerbations of chronic obstructive pulmonary disease and asthma [13]. The current study found no significant differences in age, sex, and residence between the studied groups. However, it revealed that children from rural areas had higher odds of pneumonia.

In agreement with Dharel et al. [14] studied factors associated with childhood pneumonia and care-seeking practices. These studies collectively suggest that factors such as home type, fuel used for cooking, family size, socioeconomic status, and maternal education in rural areas may contribute to childhood pneumonia risk. In contrast to our findings, Zhuge et al. [15] observed that urban children had a higher prevalence of pneumonia compared to suburban and rural children. They also identified that urban dwellings harboured more residential risk factors for pneumonia. In our study, every patient (100%) experienced cough, 27.5% experienced low fever, another 27.5% had moderate fever, and 45% suffered from high fever. Chest pain was relatively uncommon, reported by only 5% of the patients. The average duration of these symptoms was 3 days, with a standard deviation of 1 day, 25% of patients experienced mild symptoms, 30% had moderate symptoms, and 45% faced severe symptoms. Inspiratory and expiratory wheezing were the predominant types of lung sounds observed, with expiratory wheezing being slightly more prevalent. Medium crackles were also commonly reported, while fine and coarse crackles were observed in smaller proportions of patients. Grade III respiratory distress was the most frequent. Comparing vital signs between patients and controls revealed notable differences. Patients exhibited higher respiratory and heart rates, indicative of increased physiological stress and respiratory effort. Lower blood pressure and decreased oxygen saturation further underscored the severity of respiratory compromise in the patient group. Kevat et al. [16] found that cough and fever were common in children aged 5-9 years with pneumonia. Tachypnea was documented in around half of patients. Dyspnoea/difficulty breathing and chest in drawing were present in approximately half of all-cause pneumonia cases, with no data on in drawing in the outpatient setting. Chest and abdominal pain were documented in around one third of cases of all-cause pneumonia. Our study revealed significantly higher total leukocyte counts in patients (P <0.001). In contrast, other variables, such as haemoglobin and Platelets did not show significant differences. Elevated white blood cell (WBC) counts are commonly associated with infection and have been utilized by clinicians for pneumonia diagnosis and prognosis [17]. However, it is noteworthy that several studies have suggested the limited ability of WBC count to predict severity in children with suspected CAP [18]. In the current study, chest X-ray findings showed that nearly half of the patients (47.5%) were diagnosed with bronchopneumonia, while a slightly higher percentage (52.5%) had lobar pneumonia. Fancourt et al. [19] documented chest radiograph findings in childhood pneumonia cases and similarly observed that at admission, individuals with severe pneumonia displaying tachypnea, hypoxemia, crackles, or fever were more likely to have an abnormal CXR, with pneumonic patches being the most common finding. Similarly, Omran et al. [13] reported that chest X-rays in pediatric pneumonia cases typically showed pneumonic patches and air bronchograms in the majority of patients. In the present study, Serum CRP levels exhibited significant differences, with patients presenting a median of 26 compared to a median of 3 in controls (P < 0.001). Similarly, salivary CRP demonstrated a comparable pattern, with patients displaying a median of 14 compared to 3 in controls, with a significant P-value of <0.001. Similarly, Tsai et al. [20] demonstrated significantly higher salivary CRP levels in pediatric patients with pneumonia compared to healthy controls. In contrast, Klein Kremer et al. [21] reported non-significantly elevated levels of salivary CRP. This discrepancy may be attributed to their small sample size and variability in patient etiology and severity. In the current study, various variables exhibited significant correlations with salivary CRP levels, age, systolic blood pressure, diastolic blood pressure, oxygen saturation, and platelets demonstrated significant negative correlations. In contrast, the severity of the condition showed a strong positive correlation, along with distress grade, respiratory rate, heart rate, serum CRP levels, and TLC. On the other hand, several variables did not demonstrate a significant relationship with salivary CRP levels, including the duration of the condition and haemoglobin levels. Consistent with our findings, Gofin et al. [22] also observed significant correlations between serum and salivary CRP levels.

Table 1. General characteristics, clinical symptoms and physical findings of the studied groups

		Patients (N = 40)	Controls (N = 40)	P-value
General characteristics				
Age (years)		3 (1 - 8)	3 (1 - 8)	0.203
Sex	**Males**	25 (62.5%)	22 (55%)	0.496
	Females	15 (37.5%)	18 (45%)	
Residence	**Rural**	31 (77.5%)	26 (65%)	0.217
	Urban	9 (22.5%)	14 (35%)	
Clinical symptoms				
Fever	**Low**	11 (27.5%)	-------	-------
	Moderate	11 (27.5%)	-------	-------
	High	18 (45%)	-------	-------
Cough		40 (100%)	-------	-------
Chest pain		2 (5%)	-------	-------
Severity of chest pain	**Mild**	10 (25%)	-------	-------
	Moderate	12 (30%)	-------	-------
	Severe	18 (45%)	-------	-------
Duration (days)		3 ±1	-------	-------
Physical findings				
Wheezes	**Expiratory**	17 (42.5%)	-------	-------
	Inspiratory & expiratory	20 (50%)	-------	-------
	No Wheezes	3 (7.5%)	-------	-------
Crackles	**Fine**	12 (30%)	-------	-------
	Medium	17 (42.5%)	-------	-------
	Coarse	11 (27.5%)	-------	-------
Respiratory distress	**Grade I**	9 (22.5%)	-------	-------
	Grade II	12 (30%)	-------	-------
	Grade III	19 (47.5%)	-------	-------

Data presented ad median (range), mean ± SD, or frequency (%).

Table 2. Vital signs, laboratory investigations and chest X-ray and blood culture in the studied groups

		Patients (N = 40)	Controls (N = 40)	P-value
Vital signs	**Respiratory rate**	41 ±8	21 ±4	**<0.001***
	Heart rate	128 ±20	84 ±5	**<0.001***
	Systolic blood pressure	82 ±10	97 ±14	**<0.001***
	Diastolic blood pressure	53 ±11	63 ±8	**<0.001***
	O_2 saturation	93 ±3	98 ±1	**<0.001***
Laboratory investigations	**TLC $X10^3$**	9.1 (5 – 20)	5.5 (4 – 8)	<0.001*
	Hemoglobin	11.1 ±1.1	11.7 ±1	0.12
	Platelets $X10^3$	332 ±85	342 ±72	0.595
	Serum CRP	26 (6 – 96)	3 (2 – 5)	<0.001*
	Salivary CRP	14 (2 – 76)	3 (1 – 5)	<0.001*
Chest X-ray	**Bronchopneumonia**	19 (47.5%)	-------	-------
	Lobar pneumonia	21 (52.5%)	-------	-------
Positive blood culture		17 (42.5%)	-------	-------
Organism	**E coli**	1 (5.9%)	-------	-------
	Klebsiella	5 (29.4%)	-------	-------
	MRSA	2 (11.8%)	-------	-------
	Staph	9 (52.9%)	-------	-------
Treatment modalities				
Oxygen support	**CPAP**	7 (17.5%)		
	High-flow nasal cannula	8 (20%)		
	Mechanical ventilation	11 (27.5%)		
	Nasal prongs	8 (20%)		
	No support	6 (15%)		
IV fluids		34 (85%)		
Inotrope		6 (15%)		
Antibiotics	**Ampicillin +Cephalosporin**	23 (57.5%)		
	Vancomycin + Meropenem	17 (42.5%)		

*Significant P-value; TLC: Total Leukocyte count; SD: Standard Deviation; CRP: C-Reactive Protein; E coli: Escherichia coli; MRSA: Methicillin-Resistant Staphylococcus Aureus, CPAP: Continuous Positive Airway Pressure; IV: Intravenous.

Table 3. Correlation between salivary CRP and other parameters in the patients' group

	Salivary CRP	
	R	**P**
Age (years)	-0.361	0.022*
Duration (days)	-0.277	0.083
Severity	0.818	<0.001*
RD grade	0.498	0.001*
Respiratory rate	0.559	<0.001*
Heart rate	0.628	<0.001*
Systolic blood pressure	-0.552	<0.001*
Diastolic blood pressure	-0.698	<0.001*
O_2 saturation	-0.760	<0.001*
TLC $X10^3$	0.731	<0.001*
Hemoglobin	-0.058	0.722
Platelets $X10^3$	-0.340	0.032*
Serum CRP	0.940	<0.001*

Significant P-value; RD: Respiratory Distress; O2: Oxygen; CRP: C-Reactive Protein; TLC: Total Leukocyte count.

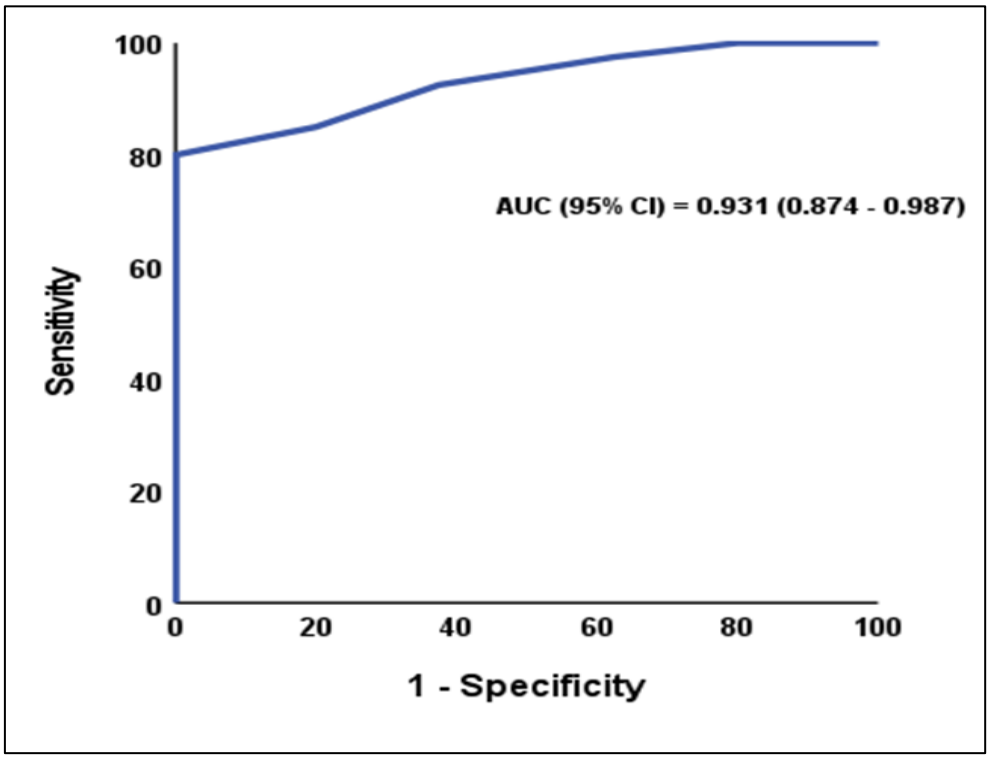

Figure 1. ROC analysis of salivary CRP to predict pneumonia

Table 4. Salivary CRP according to different study parameters in the patients' group

Variables		Salivary CRP (mg/dl) (mean/range)	P-value
Sex	**Males**	17 (2 - 76)	0.422
	Females	9 (3 - 72)	
Residence	**Rural**	17 (4 - 76)	0.276
	Urban	11 (2 - 59)	
Fever	**Low**	6 (4 - 12)	0.004*
	Moderate	15 (4 - 26)	
	High	45 (2 - 76)	
Severity of illness	**Mild**	5 (2 - 7)	<0.001*
	Moderate	10 (4 - 40)	
	Severe	38 (8 - 76)	
Wheeze	**Expiratory**	7 (2 - 50)	0.004*
	Ins & exp	25 (4 - 76)	
	No wheeze	4 (4 - 11)	
Crackles	**Fine**	24 (9 - 69)	0.003*
	Medium	11 (2 - 76)	
	Coarse	5 (3 - 40)	
RD grade	**G I**	5 (2 - 12)	0.004*
	G II	16 (6 - 50)	
	G III	25 (3 - 76)	
Chest Xray	**Bronchopneumonia**	22 (3 - 76)	0.025*
	Lobar pneumonia	8 (2 - 65)	
Oxygen support	**Yes**	18 (2 - 76)	<0.001*
	No	5 (3 - 7)	
IV fluids	**Yes**	18 (2 - 76)	<0.001*
	No	5 (3 - 7)	
Inotropes	**Yes**	66 (22 - 76)	<0.001*
	No	9 (2 - 70)	
Antibiotics	**Vancomycin + meropenem**	50 (9 - 76)	<0.001*
	Ampicillin + cephalosporin	6 (2 - 20)	
Blood culture	**Yes**	50 (17 - 76)	<0.001*
	No	6 (2 - 25)	

*Significant P-value; CRP: C - reactive protein; IV: Intravenous; Ins: Inspiratory; EXP: Expiratory; G: Grade; Xray: X-Ray.

Table 5. Multivariate logistic regression analysis to predict pneumonia

	OR (95% CI)	P-value
Age (years)	1.149 (0.784 - 1.683)	0.477
Sex	0.821 (0.184 - 3.668)	0.796
Residence	1.36 (0.225 - 8.235)	0.738
Salivary CRP	2.727 (1.565 - 4.75)	**<0.001***

* Significant P-value; OR: Odds Ratio; CI: Confidence Interval; CRP: C - reactive protein.

Ouellet-Morin's study provided initial evidence suggesting that non-invasive assessment of CRP in saliva allows valid prediction of serum CRP levels. Several studies support the notion that salivary CRP is a valid marker of systemic inflammation, with moderate-to-strong associations found between CRP measured in saliva and serum specimens. The study on salivary CRP levels in our patient cohort unveiled several significant associations. Fever severity displayed a noticeable trend, with increasing CRP levels corresponding to low, moderate, and high fevers, indicating a potential link between CRP levels and the severity of systemic inflammation. Similarly, disease severity followed this pattern, with higher CRP levels associated with more severe cases. Interestingly, salivary CRP levels did not significantly differ by sex or residence, suggesting consistency across demographic factors. In our study, salivary CRP was evaluated as a potential predictor of pneumonia. ROC analysis revealed a significant AUC, indicating strong predictive capability. The optimal cutoff point for salivary CRP was determined, highlighting its potential as a reliable predictor for identifying pneumonia, regardless of demographic factors. Moreover, a multivariate logistic regression analysis demonstrated that each unit increase in salivary CRP was associated with a nearly threefold increased risk of pneumonia, even after adjusting for age, sex, and residence, further underscoring its predictive value.

In a similar context, Omran et al. [13] analyzed ROC curves and found that salivary CRP at a specific cutoff value had high sensitivity and specificity in predicting late-onset neonatal pneumonia, further supporting the utility of salivary CRP as a predictive biomarker for pneumonia.

4. Conclusions

Our study has demonstrated a strong correlation between salivary CRP levels and serum CRP levels, as well as various clinical features of CAP in pediatric patients. Salivary CRP levels were found to be significantly higher in patients with CAP compared to healthy controls, and these levels exhibited associations with disease severity, respiratory distress, radiological findings, and treatment interventions. Furthermore, salivary CRP levels exhibited robust predictive capability for identifying pneumonia cases, with a high area under the curve in the ROC analysis. Our findings demonstrated that salivary CRP measurement could be a useful, non-invasive tool for assessing and monitoring pediatric patients with CAP.

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Conflict of Interest

Nil.

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