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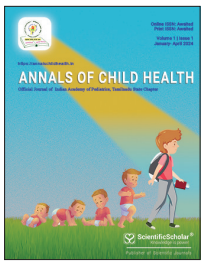

Original Article

Role of C-Reactive Protein in Predicting Adenoviral Infections in Children Aged 1 Month to 18 Years

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ABSTRACT

Objectives: High and varying cutoff values of C-reactive protein (CRP) levels are observed in human adenoviral infection. Our objectives were to determine the ideal cutoff of CRP level in adenoviral infection and compare the clinical features, investigations, and outcomes in adenoviral and other viral infections.

Material and Methods: This descriptive study includes 140 children satisfying inclusion criteria aged 1 month to 18 years admitted to our hospital. Seventy nasopharyngeal swabs positive for adenovirus and 70 positive for other viruses during the study period September 2022 to March 2023 were taken up for our analysis. Data for CRP levels, clinical features at admission, investigations, and outcomes were analyzed for both adenoviral and non-adenoviral groups (Groups 1 and 2). Our main outcome of the study was to analyze the data for both groups and determine the ideal cutoff for CRP in predicting adenoviral infection.

Results: Our results yielded that mean CRP levels were higher in the adenoviral group than in other viral infections (non-adenoviral). Based on the receiver operative characteristic curve, the cutoff value of CRP for predicting adenoviral infections is 5.5 mg/L with a sensitivity of 84.71 and specificity of 54.17. Conjunctivitis and tonsillitis/pharyngitis are significantly more in the adenoviral group, and when they are used as diagnostic tests the ideal cutoff of CRP in diagnosis becomes more specific.

Conclusion: We concluded that the ideal cutoff for CRP in predicting adenoviral infection is 5.5 mg/L. CRP, along with clinical features of tonsillitis/pharyngitis and conjunctivitis, make the diagnosis more specific.

Keywords: C--reactive protein, Adenoviral infection, Non-adenoviral infections, Clinical features

INTRODUCTION

Human adenovirus infections (HAdV infections) are associated with a wide range of respiratory and gastrointestinal (GI) tract symptoms and can cause fatal infections in healthy and immunocompromised patients.[1] HAdVs are double-stranded DNA viruses, divided into more than 55 distinct serotypes and other "new" genetic variants, classified into seven species (A–G). Some types are associated primarily with respiratory tract diseases, whereas others with gastroenteritis.[2] In clinical practice, mixed symptoms are often seen. Adenoviruses can be transmitted through respiratory tract secretions, fecal-oral spread, and exposure to infected tissue or blood. Children with respiratory or generalized infections excrete the virus for 3–6 weeks in throat mucosa or stool.[3] Consequently, HAdVs spread easily among children and people living in high-density areas and can be a serious threat to patients with immunodeficiencies.[4]

Clinical symptoms of HAdVs include – fever, cough, sore throat, and rhinorrhea. Involvement of the lower respiratory tract by HAdVs – bronchitis, bronchiolitis, and pneumonia can be severe and even fatal. HAdV infection can also be implicated in conjunctivitis, diarrhea, cystitis, myocarditis, cardiomyopathy, and meningoencephalitis (multisystemic involvement). Symptomatic HAdV infections are commonly characterized by high-grade and long-lasting fevers with elevated inflammatory cytokines.[5] Such recent trends of high C-reactive protein (CRP) with negative bacterial yield were observed in our hospital during a recent outbreak of flu-like illness during our study period. Due to limited data available in South India, this study is taken up to compare the available data in our hospital.

The study aimed to analyze the levels of CRP, complete blood count (CBC), clinical features, and outcome in children with adenovirus infection (GROUP-1) and to compare the same parameters in children with other viral infection (GROUP-2) presenting to a tertiary care hospital.

MATERIAL AND METHODS

This is a hospital-based descriptive study, which was done in an urban tertiary hospital. With the clearance from the Ethical Committee of the Institution, 140 children aged 1 month to 18 years presenting with generalized prodromal symptoms (upper respiratory infection (URI), fever, gastrointestinal (GI) symptoms, sore throat, cough, and conjunctivitis) with/without features suggestive of pneumonia were included in this study who are reported to have pure adenoviral infection (adenoviral group – group 1) and the other group of children with pure other viral infections (non-adenoviral group – group 2) detected in respiratory viral panel. Children with infection of skin or skin structures, bacterial pathogens in nasopharyngeal swab, non-sterile culture from blood or any other normally sterile site, urine culture yielding significant bacteriuria, respiratory viral panel showing bacterial infection coexisting with other viral infections, and children on immunosuppressants or chemotherapy were excluded from the study.

Cases with *adenovirus infection* were considered if adenovirus is detected in nasopharyngeal swabs by real-time polymerase chain reaction (RT-PCR) method.

Coinfection was defined as the detection of more than one pathogen, including viral, bacterial, or atypical pathogens. Such samples with coinfection are excluded from our study. All the nasopharyngeal swabs sent during our study period, that is, from September 2022 to March 2023, were obtained from our microbiology department, and the data were analyzed. The detection of viruses in the nasopharyngeal swab was done using the qualitative multiplexed TaqMan-based RT-PCR.

CRP levels were identified by the immunoturbidimetry method in the microbiology department of our hospital. CRP assessment was done by the same technician who was blinded to the results of the nasopharyngeal swabs.

Data were collected on the history, clinical features, and examination findings at admission. CRP levels, relevant laboratory investigations, and outcomes were taken in a predesigned case recording form.

Statistical analysis

Demographic variables in categorical/dichotomous were given in frequencies with their percentages. Clinical variables were given in mean and standard deviation. Quantitative variables difference between adenovirus and non-adenovirus was assessed using a student independent *t*-test. The qualitative variable's difference between adenovirus and non-adenovirus was assessed using the Chi-square test. Sensitivity, specificity, positive predictive value, negative predictive value, false-positive rate, and false-negative rate for assessing predictability of clinical features for adenoviral infection (presence of conjunctivitis, presence of conjunctivitis + URI signs [tonsillitis/pharyngitis], and presence of conjunctivitis + URI signs [tonsillitis/pharyngitis] + GI symptoms) were assessed. $P \leq 0.05$ was considered statistically significant, and two-tailed tests were used for testing significance. Statistical analysis was carried out using the Statistical Package for the Social Sciences version 22. Diagnostic characteristic sensitivity and specificity of CRP were arrived at. The optimum cutoff of CRP in predicting the adenoviral infections was arrived at by constructing the receiver operative characteristic (ROC) curve.

RESULTS

A total of 140 patients (70 in the adenoviral group and 70 in the non-adenoviral group) who satisfied our inclusion criteria were taken in our study.

Demographic features

In our study, 7 (10%) and 18 (25.71%) were <1 year of age in group 1 and group 2, respectively. Sixty (85.71%) and 52 (74.29%) of children were between 1 and 10 years old in group 1 and group 2, respectively. In our study, 3 (4.29%) and 0 (0%) were more than 10 years of age in group 1 and group 2, respectively. Among the subjects, 44 (62.86%) and 43 (61.43%) were male in adenoviral and non-adenoviral group, respectively. Twenty-six (37.12%) and 27 (38.57%) were female in the adenoviral and non-adenoviral groups, respectively [Table 1].

CRP as a predictor

CRP levels were significantly higher in the adenoviral group. The mean CRP levels were 42.5 mg/L (31.48) and 17.19 mg/L

Table 1: Demographic data, clinical features, investigations, and outcomes among the study groups.

	Group				Chi-square test
	Adeno viral group		Non-adeno viral group		
	n	%	*n*	%	
Age (in years)					
<1 year	7	10.00	18	25.71	χ^2=8.41
1–10 years	60	85.71	52	74.29	*P*=0.05 (S)
>10 years	3	4.29	0	0.00	
Gender					
Male	44	62.86	43	61.43	χ^2=0.03
Female	26	37.14	27	38.57	*P*=0.86 (NS)
Upper respiratory tract symptoms					
No	0	0.00	0	0.00	χ^2=0.00
Yes	70	100.00	70	100.00	*P*=1.00 (NS)
Lower respiratory tract symptoms					
No	15	21.43	14	20.00	χ^2=0.04
Yes	55	78.57	56	80.00	*P*=0.84 (NS)
Yes	24	34.29	9	12.86	
Conjunctivitis					
No	21	30.00	61	87.14	χ^2=47.10
Yes	49	70.00	9	12.86	*P*=0.001 (S)
URI signs (tonsillitis/pharyngitis)					
No	46	65.71	61	87.14	χ^2=8.92
Yes	24	34.29	9	12.86	*P*=0.01 (S)
Respiratory system involvement					
No	17	24.29	10	14.29	χ^2=2.24
Yes	53	75.71	60	85.71	*P*=0.13 (NS)
GI symptoms (vomiting/loose stools)					
No	33	47.14	48	68.57	χ^2=6.59
Yes	37	52.86	22	31.43	*P*=0.01 (S)
Urinary symptoms					
No	68	97.14	69	98.57	χ^2=0.34
Yes	2	2.86	1	1.43	*P*=0.54 (NS)
Chest X-ray s/o LRTI					
No	10	14.29	27	38.57	χ^2=10.62
Yes	60	85.71	43	61.43	*P*=0.001 (S)
Outcome					
WARD discharge	66	94.29	63	90.00	χ^2=0.89 *P*=0.35 (NS)
PICU discharge	4	5.71	7	10.00	
Requirement of O_2					
No	40	57.14	50	71.43	χ^2=3.11
Yes	30	42.86	20	28.57	*P*=0.08 (NS)
Requirement of HFNC					
No	67	95.71	66	94.29	χ^2=0.15
Yes	3	4.29	4	5.71	*P*=0.70 (NS)

GI: Gastrointestinal, O_2: Oxygen, HFNC: High-flow nasal cannula, PICU: Pediatric intensive care unit, LRTI: Lower respiratory tract infection, *n*: number of children, NS: not significant, S: significant, URI signs: Upper respiratory tract infection

(39.31) in group 1 and group 2, respectively, which was statistically significant ($P = 0.001$) [Table 2].

The maximum possible sensitivity of 89 % and specificity of 61% is observed for the CRP with the cutoff of 5.5 mg/L having an area under the curve in the ROC curve [Figure 1]. The level below 5.5 mg/L, the sensitivity is not affected whereas the specificity gets lowered. The total differential (neutrophil and leukocyte) counts were not contributory. When combining the clinical features like conjunctivitis, URI signs (tonsillitis/pharyngitis), and GI symptoms (reported significantly in more proportion among those children with adenoviral infections than those with non-adenoviral infections) [Table 1] along with the CRP cutoff of 5.5 mg/L have sensitivity and specificity 84.71% and 54.17%, respectively. The area under the curve is 78 [Figure 1].

Other investigations

The mean total count (per microliter) in the adenoviral group was 9773.86 (4190.87) and 10442.34 (4674.99) in the non-adenoviral group, which was not significant. The mean neutrophil count in the adenoviral group was 55.84 (20.23) and 51.20 (19.09) in the non-adenoviral group, which was not significant. The mean lymphocyte count in the adenoviral group was 35.12 (19.57) and 41.61 (18.91) in the non-adenoviral group, which was significant, indicating less lymphocyte count in the adenoviral group ($P = 0.05$) [Table 2].

Chest X-ray findings (bilateral peri-bronchial thickening, atelectasis, and consolidation) indicative of lower respiratory tract involvement were found in 60 children (85.71%) and 43 children (61.43%) in the adenoviral group and non-adenoviral group, respectively, which was significant.

Clinical features for adenoviral infection

The duration of illness was comparatively more in the adenoviral group (mean duration of illness in days is 7.36 (5.17) in the adenoviral and 5.81 (4.00) in the non-adenoviral group; $P < 0.05$), which was significant ($P = 0.05$). The mean duration of fever in the adenoviral group was 4.97 (4.15) in the adenoviral and 4.07 (4.28) in the non-adenoviral group which was not statistically significant. Bulbar conjunctivitis was present in 49 children (70%) and 9 children (12.86%) in group 1 and group 2, respectively, which was significant ($P = 0.001$). GI symptoms (vomiting/loose stools/pain in the abdomen) were present in 37 children (52.86%) and 22 children (31.43%) in group 1 and group 2, respectively, which was significant ($P = 0.01$). URI signs (tonsillitis/pharyngitis) were present in 24 children (34.29%) and 9 children (12.86%) in group 1 and group 2, respectively, which was significant ($P = 0.01$). Hence, conjunctivitis, GI symptoms, and URI signs (tonsillitis/pharyngitis) were more in the adenoviral group, which was statistically significant ($P < 0.05$). All of our study samples (140) had upper respiratory tract symptoms (cough/cold/rhinorrhea). About 78.57% of the

Table 2: Other investigations and duration of hospitalization.

	Group				Student independent *t*-test
	Adeno		Non-adeno		
	Mean	Standard deviation	Mean	Standard deviation	
CRP levels (mg/L)	42.50	31.48	17.19	39.31	*t*=4.21 *P*=0.001 (S)
Total count (per microliter)	9773.86	4190.87	10442.34	4674.99	*t*=0.89 *P*=0.38 (NS)
Differential count (neutrophil count)	55.84	20.23	51.20	19.09	*t*=1.40 *P*=0.16 (NS)
Differential count (Lymphocyte count)	35.12	19.57	41.61	18.91	*t*=1.20 *P*=0.05 (NS)
Duration of hospitalization (in days)	6.07	1.88	5.37	1.70	*t*=2.31 *P*=0.02 (S)

CRP: C-reactive protein, S: significant, NS: non-significant

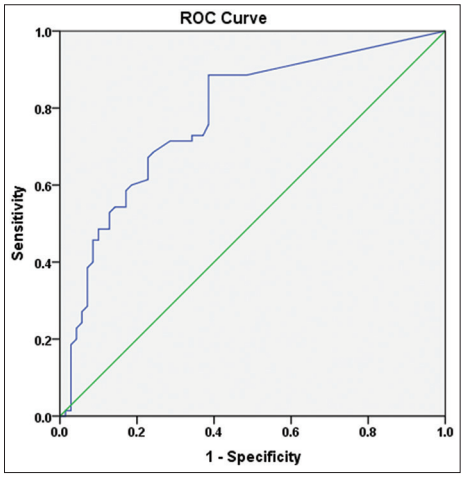

Figure 1: Receiver operative characteristic (ROC) curve for C-reactive protein levels (in mg/L).

adenoviral group and 80% of the non-adenoviral group had lower respiratory tract symptoms and signs. (Fast breathing, involvement of accessory muscles, evidence of adventitious lung sounds – crepitations, wheeze, rales, and requirement of oxygen). Significant involvement of genitourinary symptoms, central nervous system, myocardium, and liver was not found in either group [Table 1].

Outcome

Admissions to the ward were 66 children (94.29%) in group 1 and 63 children (90%) in group 2, which was not significant, while the number of children requiring pediatric intensive care unit admission was four (5.71%) and 7 (10%) in group 1 and group 2, respectively, which was not significant either.

The requirement of oxygen was present in 30 children (42.86%) and 20 children (28.57%) in group 1 and group 2, respectively, which was not significant. The requirement of high-flow nasal cannula was present in 3 children (4.29%) and 4 children (5.71%) in group 1 and group 2, respectively, which was not significant.

The duration of hospitalization is comparatively more in the adenoviral group (mean duration of hospitalization in days is 6.07 (1.88) in the adenoviral and 5.37 (1.70) in the non-adenoviral group), which was statistically significant ($P = 0.02$).

PREDICTABILITY OF ADENOVIRAL INFECTION WITH A CUTOFF OF CRP AT 5.5 MG/L

Our predictability of adenoviral infections at a cutoff of CRP (5.5 mg/L) with clinical features such as with conjunctivitis alone, the sensitivity is much higher but when combined with URI (Upper respiratory tract) signs the specificity is more. While with added GI (Gastrointestinal) symptoms along with conjunctivitis and URI signs, the predictability is more sensitive. [Table 3]

DISCUSSION

Human adenovirus (HAdV) is an important cause of respiratory infections in the pediatric population. Human adenovirus infections are one of the most common causes of fever requiring hospital admission when it occurs in younger age groups (<10 years old). The characteristics exhibited by adenovirus were slightly different from those of other viral infections. Our study conducted during the seasonal peak (between September 2022 and March 2023) mainly emphasizes the clinical features, laboratory parameters, and the outcome of proven adenoviral infection. The data are compared with other viral infections (non-adenoviral infections) taking the same parameters. The most frequently ordered outpatient and inpatient blood tests were CRP, CBC, Chest X-ray, and blood and urine culture and sensitivity. Hence, these parameters were taken up for our study to analyze our data. CRP levels

Table 3: Predictability of adenoviral infection with clinical features at a cutoff of CRP (5.5 mg/L).

Symptoms	Sensitivity (%)	Specificity (%)	Efficiency (%)	PPV (%)	NPV (%)	False positive rate (%)	False negative rate (%)
Conjunctivitis alone	88.57	61.43	75.00	69.66	84.31	84.31	84.31
Conjunctivitis+URI signs (tonsillitis/pharyngitis)	70.00	87.14	87.14	87.14	87.14	87.14	87.14
Conjuntivitis+URI signs (tonsillitis/pharyngitis)+GI symptoms	84.29	57.14	57.14	57.14	57.14	57.14	57.14

CRP: C-reactive protein, GI: Gastrointestinal, PPV: Positive predictive value, NPV: Negative predictive value, URI: Upper respiratory infection

in children with adenoviral infection without bacterial coinfection were found to be high. Children with bacterial infection was excluded by taking samples whose blood and urine cultures were sterile and uncomplicated recovery following infection without the need for antibiotics.

In our study, patients presenting with prodromal symptoms followed by a respiratory system infection had a higher CRP level mimicking a bacterial infection. The CRP level traditionally indicates a bacterial infection. Without another etiology explaining the presenting picture, it may result in the initiation of antibiotic therapy. In our study, as already explained, antibiotics were not started as nasopharyngeal swabs yielded viral infections, and negative blood culture was our inclusion criteria. Also, all these children had short, uncomplicated courses of illness and recovery, limiting the use of antibiotics.

In our study, 85.71% of our study group 1 and 74.29 % of study group 2 were in the age group of 1–10 years. In our study, the mean CRP levels of children with adenoviral infection and other viral infections were 42.5 and 17.4, respectively. This clearly states that children with adenoviral infection had higher CRP levels when compared with other bacterial infections. These high CRP levels are attributed to the cytokine storm, which occurs in adenoviral infection. This is in concordance with the study conducted by Appenzeller *et al*. in the Department of Pediatrics Institute for Infectious Diseases, University of Bern, Inselspital, Bern, Switzerland, where the median CRP in children with adenovirus infection and 130 children with influenza was 49 mg/L and 9 mg/L, respectively.[6] This is also consistent with observations in a study carried out by Kawasaki *et al*. and other studies,[7-9] where significantly higher CRP and INTERLEUKIN-6 concentrations were found in children with adenoviral infection when compared to other viral infections (Influenza and respiratory syncytial viruses). In 87 children with an adenoviral infection, CRP levels of <2 mg/L, <10 mg/L, and <100 mg/L were found in 4 (4%), 12 (13%), and 66 (76%) patients, respectively.[6] In a study conducted by De Oña CG *et al*.[10] in the microbiology department, Spain alterations in CRP and procalcitonin were established in patients with adenoviral infections.

Our study has more URI signs (tonsillitis/pharyngitis), conjunctivitis, and GI symptoms in an adenoviral group than in other viral infections (non-adenoviral group). This is similar to a study conducted to analyze the clinical parameters in adenoviral infections where chest retraction and extra-pulmonary manifestations were significantly more common in the adenovirus group, especially conjunctivitis, gastroenteritis, lymphadenopathy, bleeding diathesis, and exanthema.[11] In our study, the duration of hospitalization was more in the adenoviral group in contrast to studies where there was no difference in the length of hospitalization.[8,12] In our study, both adenovirus and other viral infections had higher leucocytes levels and higher neutrophil levels. This is in contrast with the findings of a study by Zheng *et al*.[9], where cases with adenovirus infection had lower leucocytes levels and higher neutrophil levels than cases without adenovirus infection.

Limitations

PCR test is used; hence, serotypes could not be diagnosed; hence, individual characteristics of human adenoviral infections could not be assessed.

CONCLUSION

CRP levels are significantly higher in the adenoviral group when compared to other viral infection group (Non- non-adenoviral group). While conjunctivitis, GI symptoms, and URI signs (tonsillitis and pharyngitis) significantly more in the adenoviral group, the presence of only conjunctivitis and URI signs has more predictability for adenoviral infection with CRP level cutoff 5.5 mg/L with maximum sensitivity and specificity.

What is already known?

CRP found to be a predictor for adenoviral infection with various cutoffs.

What is new in this study?

In the present study, CRP 5.5 mg/L was found to be the ideal cutoff to predict adenoviral infection. Apart from confirming earlier observations reports, combination of clinical features of pharyngitis/tonsillitis, conjunctivitis, and GI symptoms along with CRP make the test more specific one for adenoviral infections compared to the non-adenoviral infections.

Ethical approval

The research/study was approved by the Institutional Review Board at Dr.Mehtas Multispecialty Hospital Chennai, number EC.MMHIPL/21/2023, dated May 5, 2023.

Declaration of patient consent

Patient's consent is not required as the patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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