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Association of viral etiology with disease severity in bronchiolitis

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Abstract

Acute bronchiolitis is a leading cause of lower respiratory tract infections in young children. While multiple viruses contribute to its pathogenesis, their impact on disease severity remains unclear.

In this cross-sectional observational study, children with bronchiolitis were enrolled. Baseline characteristics, bronchiolitis severity score, Respiratory Distress Assessment Instrument score, duration of hospitalization, and respiratory support requirements were recorded. Nasopharyngeal aspirates were analyzed *via* real-time polymerase chain reaction.

Among 52 enrolled children (median age: 3 months), viruses were detected in 33 (63.5%) children. Of these, 6 (11.5%) had co-infection with more than one virus. Human rhinovirus (HRV) was the most common (39.4%), followed by respiratory syncytial virus (RSV) (33.3%), parainfluenza virus (PIFV) (21.2%), enterovirus (EV) (12.1%), influenza virus (6.1%), and both human metapneumovirus (hMPV) and human coronavirus (3.0% each). Co-infections involved HRV-RSV (n=2), HRV-EV (n=2), RSV-PIFV (n=1), and EV-PIFV (n=1). HRV was significantly associated with mild bronchiolitis (p=0.03), while other viruses and co-infections did not impact severity. Children aged 13-24 months had a significantly longer median hospital stay than younger age groups (p=0.04). Notably, despite recent concerns about hMPV in younger children, we found only one case, presenting with mild bronchiolitis and no respiratory support requirement.

HRV is linked to milder bronchiolitis, while other viruses and co-infections do not significantly influence severity. These findings highlight regional viral variations and the need for larger studies to guide management.

Key words: bronchiolitis, parainfluenza virus, bronchiolitis severity score, respiratory syncytial virus.

Introduction

Acute viral bronchiolitis is a leading cause of lower respiratory tract infections in children under two years of age, with Respiratory Syncytial Virus (RSV) being the predominant pathogen [1]. Other viruses, including Human Rhinovirus (HRV), Parainfluenza Virus (PIFV), Human Metapneumovirus (HMPV), Adenovirus, Human Coronavirus (HCoV), Influenza Virus (IFNV), Bocavirus, and Enteroviruses (EV), are also implicated. The prevalence of viral co-infections ranges from 6% to 30%, with RSV and HRV being the most frequently detected combinations [2]. The severity of bronchiolitis is commonly assessed using parameters such as hospitalization rates, length of hospital stay (LOS), need for intensive care, apnea episodes, and respiratory support requirements, yet consensus on a universal scoring system remains elusive. Studies from Western countries have shown conflicting results when correlating viral etiology with disease severity. Despite the high burden of bronchiolitis in India, there is limited data on the relationship between viral etiology and clinical severity [3-5].

Therefore, this study was conducted to evaluate the viral etiology and its association with disease severity in children under two years diagnosed with bronchiolitis.

Materials and Methods

This cross-sectional study was conducted at Tertiary Care Hospital in Western India from 1st September 2019 to 28th February 2021 after obtaining approval from the Institutional Ethics Committee (IEC No: IEC/2019/821). The study included children under two years of age who presented to the Outpatient Department (OPD) or Emergency with clinical features of acute bronchiolitis as per standard guidelines [6]. Eligible children were enrolled at the time of presentation and were subsequently followed during the hospital stay, including transfers to inpatient wards, High Dependency Unit (HDU), or Intensive Care Unit (ICU), if required. Children with suspected bacterial etiology, prior antibiotic use, primary parenchymal lung disease (including bronchopulmonary dysplasia), prematurity, congenital heart or renal disease, neuromuscular disorders, severe malnutrition, recent hospitalization within the past month, immunodeficiency or immunosuppressive therapy were excluded.

Data collection

Baseline demographic and clinical characteristics were recorded at presentation. Disease severity was assessed using the Bronchiolitis Severity Score (BSS), categorizing cases as mild (0–3), moderate (4–8), or severe (9–11) [7]. The Respiratory Distress Assessment Instrument

(RDAI) scores were also recorded [8]. Details regarding the need for respiratory support, including oxygen therapy, continuous positive airway pressure (CPAP), high-flow nasal cannula (HFNC), or mechanical ventilation (MV), were documented. Other clinical management aspects, such as nebulization, antibiotic use, enteral or parenteral nutritional support, and LOS, were also recorded.

Sample collection and laboratory analysis

Nasopharyngeal aspirates (NPA) were collected from both nostrils of each patient under aseptic conditions using a catheter and preserved in viral transport medium (Hiviral™ transport kit, HiMedia, India). The samples were transported to the virology laboratory and stored at –80°C until further analysis**.** Viral nucleic acid (VNA) was extracted using the QIAmp 96 Virus QIAcube HT Kit (QIAGEN, Germany) and analyzed using real-time multiplex PCR assays (TRUPCR® Respiratory Pathogen Panel Kit, Kilpest India).

Sample size and statistical analysis

We conducted a time-driven study, enrolling patients with acute bronchiolitis from the emergency department, outpatient clinics, and inpatient wards, including the PICU, after obtaining written informed consent from parents or guardians. Descriptive statistics were used to summarize baseline characteristics. Categorical variables were analyzed using the Chi-square or Fisher's exact test, while continuous variables were compared using the Mann-Whitney U or Kruskal-Wallis test, as appropriate. Statistical analysis was performed using SPSS version 25, with a two-sided p-value <0.05 considered significant.

Results

During the study, 52 children with acute bronchiolitis were enrolled (Figure 1), with a median age of 3.0 months (IQR:1.0–6.8). The majority (75%) were between 1–6 months old, and 75% were male (Table 1). The median duration of symptoms before presentation was 5 days (IQR:3–7). Cough and wheezing were the most common symptoms, reported in 88.5% (n=46) of cases, while retractions were observed in 94.2% (n=49). Crepitations were heard along with wheeze in 73.1% (n=38) children. Twelve children had a history of prior nebulization; however, none had a significant personal history of atopy or asthma, and none required salbutamol during the current episode, supporting the diagnosis of bronchiolitis and effectively ruling out preschool wheeze or asthma.

At admission, the median BSS was 5 (IQR: 4–7), peaking at 5 (IQR: 4–9) and declining to 2 (IQR: 1–2) at discharge. The peak RDAI score had a median of 9 (IQR:6–11). A strong positive correlation was observed between BSS and RDAI scores (r_s=0.89; $p<0.001$). Disease severity based on BSS classification showed 17.3% (n=9) mild, 55.8% (n=29) moderate, and 26.9% (n=14) severe cases. The median LOS was 59.0 hours (IQR:14.9,143).

All patients received supportive care. Nebulization with epinephrine and hypertonic saline was administered in 79% of cases as per the available literature [9]. Current guidelines do not recommend routine administration of bronchodilators such as salbutamol before hypertonic saline, and accordingly, neither salbutamol nor corticosteroids were administered to any child in our cohort [5]. No child had received corticosteroids prior to admission. Although hypertonic saline can induce bronchospasm in some children, no such adverse events were observed in our cohort. During hospital admission, 4 (7.7%) children received antibiotics as per clinical discretion. Nasogastric feeding was required in 63.5% of infants. Eleven (21.2%) children received intravenous fluids due to poor oral intake or intolerance to nasogastric feeds. Hypoxemia was documented in 34 children (65.4%); 25 (48%) had hypoxemia at the time of admission, while 9 (17.3%) developed it during the hospital stay. Respiratory support was needed in children having hypoxemia, with 33 (65.5%) receiving low-flow oxygen, 11 (21.2%) requiring CPAP, 3 (5.8%) on HFNC, and 1 (1.9%) requiring MV. Bronchiolitis cases demonstrated seasonal variation, with 61.5% occurring in winter, 23.1% in autumn, and 15.4% in summer.

All 4 children (7.7%) who received antibiotics during hospitalization underwent chest X-rays prior to the onset of antibiotics. The main findings were hyperinflation in all children (100%), infiltrates in 2 (3.8%), and atelectasis in 2 (3.8%) children.

Viruses were detected in 63.5% (n=33) of cases. Among these, 27 cases had single-virus infections: HRV (n=9/27; 33.3%) was most prevalent, followed by RSV (n=8; 29.6%), PIFV (n=5; 18.5%), IFNV (n=2; 7.4%) and hCV, hMPV, and EV in 1 case each (3.7%). Co-infections were observed in 6 cases (11.5%): HRV-RSV (n=2), HRV-EV (n=2), RSV-PIV (n=1), and EV-PIV (n=1). Overall, HRV (n=13; 39.4%) was the most prevalent virus, followed by RSV (n=11; 33.3%).

For analysis, co-infection was treated as a distinct category, while individual viral cases included only those with a single detected virus. Severity assessment grouped moderate and severe cases. HRV infections were significantly associated with mild severity ($p = 0.03$) (Table 2). More severe cases were observed during winter (65.6% moderate, 28.1% severe) compared

to autumn and summer (p = 0.038). No specific viral agent showed a significant seasonal association. hMPV, IFV, HCoV, and EV infections were mild and resolved with supportive care alone.

We also assessed associations between viral etiology and clinical outcomes, but no significant findings were observed (Table 3).

Children aged 13–24 months had longer hospital stays (median:125 hours) than those aged 1–6 months (72 hours) or 7–12 months (19 hours) (p = 0.039). No significant associations were found between disease severity and gender, birth history, exclusive breastfeeding, anthropometry, environmental smoke exposure, or family history of asthma.

Discussion

This cross-sectional study aimed to assess the association between viral etiology and disease severity in children under two years with acute bronchiolitis. The majority of the cohort (75%) was under six months old, with a median age of three months, aligning with study by Bamberger et al., where 80% of RSV bronchiolitis cases were in this age group [10]. A significant male predominance (75%) was observed, consistent with previous studies [4,11], possibly attributed to gender-specific immune responses to RSV, as suggested by Nagayama et al. [12].

The viral detection rate in our study was 63.5%, notably higher than a previous Indian study (33.9%) [5]. The most frequently identified virus was HRV (39.4%), contrasting with prior Indian studies where RSV was the predominant pathogen [11,13,14]. This discrepancy may be due to regional differences in climate, including temperature, humidity influencing viral circulation. Seasonality analysis revealed a peak incidence in winter (62%), followed by autumn (23%), a trend consistent with findings from Saudi Arabia and previous Indian studies [13,15].

In our study, children aged 13–24 months had a significantly longer median hospital stay compared to younger infants. This observation warranted further discussion, as bronchiolitis typically presents in infants under 12 months of age. The distinction between bronchiolitis and pneumonia in this older age group can occasionally overlap. Of the four children who received antibiotics during hospitalization, 3 were in the older age group (13–24 months) and 1 was in the younger age group (<12 months). While the majority of children were managed with supportive care alone, this distribution suggests that most cases were of viral etiology, though

bacterial infection cannot be entirely excluded, particularly in older infants. Importantly, none of the children had bacterial etiology confirmed on respiratory culture.

Bronchiolitis severity was assessed using BSS with the majority of cases having moderate severity, consistent with Janahi et al., who used the Initial Clinical Severity Score [11]. In addition to the BSS, the RDAI score was also recorded, as it is commonly used in our geographical setting. Recording both scores allowed comparison and validation, and a strong positive correlation was subsequently observed between RDAI and BSS scores. A significant association was found between HRV infection and disease severity, particularly mild bronchiolitis. However, no such association was observed for RSV, PIFV, or viral co-infections, a finding that contradicts Janahi et al. [11], and large studies from North America and Europe [1,16], which reported no correlation between viral etiology and severity. This divergence may stem from differences in population characteristics, genetic susceptibility, or local viral epidemiology. Notably, hMPV, which has raised concerns regarding severe disease in younger children, was detected in only one case, which had a mild presentation and did not require respiratory support.

Moore et al. reported an increased hospitalization risk in LSCS-born infants, however, no significant association was observed in the current study [17]. Similarly, environmental smoke exposure was not associated with disease severity, LOS, or respiratory support requirements, aligning with Kini et al. [5], but contradicting Lanari et al. [18], who reported increased severity with smoke exposure. These discrepancies may be due to varying thresholds for defining exposure and severity.

While our study is the first of its kind in an Indian setting to explore viral associations with bronchiolitis severity, its limitations include a small sample size and single-center design, potentially limiting generalizability.

Conclusions

This study provides insights into the viral epidemiology and disease severity of bronchiolitis in an Indian cohort. HRV was the most frequently detected virus and was predominantly associated with mild disease, while no significant correlation was found between viral etiology and key clinical severity parameters. These findings highlight regional variations in viral prevalence and underscore the need for larger, multicentric studies to inform targeted management strategies for bronchiolitis.

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Table 1. Baseline characteristics of the study population (n=52).

Baseline Characteristics	n(%) / Median (IQR)
Age in Months,	3.0 (1.0, 6.8)
Male, n (%)	39 (75%)
Weight for age (Z-scores) median (IQR)	-1.1 (-2.0, -0.7)
Height for age (Z-scores) median (IQR)	-1.5 (-2.1, -0.5)
Weight for height (Z-scores) median (IQR)	-0.01 (-1.1, 0.6)
Birth weight (kg), median (IQR)	3.1 (2.7, 3.3)
Vaginal delivery, n (%)	40 (76.9)
Family history of atopy/asthma, n (%)	6 (11.5)
Socio-economic stats (as per Modified KPS) • Upper • Upper Middle • Lower Middle • Upper Lower • Lower	 6 (11.5) 14 (26.9) 22 (42.3) 6 (11.5) 4 (7.7)
Gestational Age • Appropriate for Gestational Age • Small for Gestational Age • Large for Gestational Age	 47(90.4) 4 (7.7) 1 (1.9)
History of smoke exposure, n (%)	12 (23.1)
Exclusive breastfeeding n (%)	32 (61.5)
History of nebulization in the past n (%)	15 (28.8)

KPS, Kuppuswamy scale.

Table 2. Association of viral etiology with disease severity in children with bronchiolitis.

Underlying etiology	Severity according to BSS		p-value
	Mild	Moderate-Severe	
HRV (n=9)	4 (44.4)	5 (55.5)	**0.03***
RSV (n=8)	2 (25)	6 (75)	0.62
PIF (n=5)	-	5 (100.0)	0.57
Co-infection (n=6)	1 (16.7)	5 (83.3)	1

*p-value is significant. BSS, Bronchiolitis Severity Score; HRV, human rhinovirus; PIF, para-influenza virus; RSV, respiratory-syncytial virus.

Table 3. Association of viral etiology with clinical outcomes in children with bronchiolitis.

Outcomes	HRV (n=9)	RSV (n=8)	PIFV (n=5)	Co-infection (n=6)
Need for respiratory support,n (%)	4 (44.4) *p*=0.25	5 (62.5) *p*=1	4 (80) *p*=0.65	3 (50) *p*=0.41
Length of hospital stay (hrs), median (IQR)	19 (4.3, 148) *p*=0.46	44.8 (15.8, 103.3) *p*=0.7	14 (6.8, 59.8) *p*=0.35	52 (7.3, 155.6) *p*=0.66
Maximum BSS score, median (IQR)	4 (3,9) *p*=0.54	5 (3,6) *p*=0.3	6 (4,6) *p*=0.93	6 (4,7) *p*=0.74
Maximum RDAI Score, median(IQR)	5 (5,12) *p*=0.82	9 (4,10) *p*=0.93	7 (6,12) *p*=0.71	10 (8,10) *p*=0.97

HRV, human rhinovirus; PIF, para-influenza virus; RDAI, Respiratory Distress Assessment Instrument; RSV, respiratory-syncytial virus.

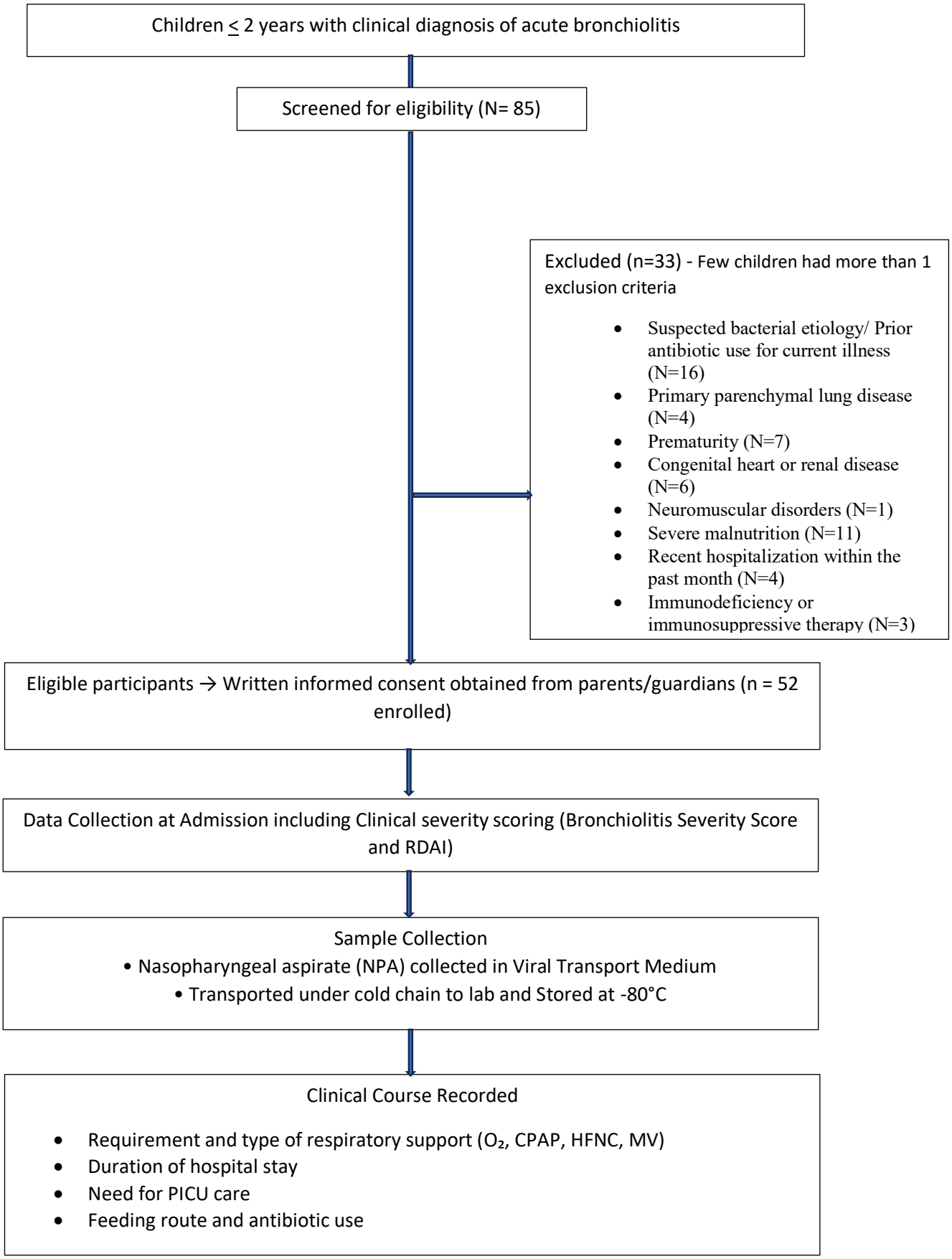

Figure 1. Study flow diagram.