

Clinical and viral profile of children admitted in the paediatric intensive care unit due to severe acute respiratory infection during seasonal surge from a tertiary care centre in Eastern India

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Abstract

Background: Acute lower respiratory infections (ALRI), such as pneumonia and bronchiolitis are a leading cause of morbidity and mortality in young children worldwide. Aetiology in young children is mostly viral infection or viral and bacterial infection.

Objectives: To study various clinical characteristics among different age groups and viral profiling in children requiring intensive care due to ALRI.

Method: Children between 1 month to 12 years, who satisfied the case definition of severe acute respiratory infection (SARI) and who were shifted to the paediatric intensive care unit (PICU) for ventilatory support were included in the study. All children were subjected to history taking, detailed examination, required blood investigations, oropharyngeal and nasopharyngeal swab testing.

Results: Of the total 46 cases 32 (69.5%) were <1 year of age, 11 (24%) 1 to 5 years of age, and 3 (6.5%) above 5 years of age. There were 17 (36.9%) deaths. There was 2.3 times more risk of death in the absence of exclusive breastfeeding (OR- 2.3, 95% CI= 0.6-7.9) and 2.2 times higher risk of mortality in the absence of immunization (OR- 2.2, 95% CI= 0.6-7.9). Mortality was significantly associated with mechanical ventilation ($p<0.0001$). Mortality was 17 times higher in children with comorbidities (OR- 17, 95% CI= 2-146), 4.7 times higher in children with congenital heart disease (CHD) (OR-4.7 95%CI= 1-22) and 1.3 times higher in children with pre-existing central nervous system (CNS) abnormality (OR-1.33, 95% CI=0.3-6.8). From the

respiratory viral panel, 18 (41%) samples were positive for virus detection.

Conclusions: In this study 69.5% children with SARI were infants. Mortality was 36.9%. There was a statistically significant increased risk of death in the absence of exclusive breastfeeding, absence of immunization, use of mechanical ventilation, presence of comorbidities, presence of CHD and presence of pre-existing CNS abnormality.

(Key words: SARI, PICU, ILI, Pneumonia, Viral panel)

Introduction

Acute lower respiratory infections (ALRI), such as pneumonia and bronchiolitis, are a leading cause of morbidity and mortality in young children worldwide¹. As per 2019 report of the National Health Portal of India, 41,996,260 cases and 3,740 deaths from respiratory infections were recorded across India in 2018². Influenza-like illness (ILI) is defined as an acute respiratory infection with fever ($\geq 38^{\circ}\text{C}$) and cough with onset within the last 10 days³. Severe Acute Respiratory Infection (SARI) is defined as an acute respiratory infection with fever ($\geq 38^{\circ}\text{C}$) and cough with onset within the last 10 days requiring hospitalization due to respiratory failure³.

The aetiological factor in young children is mostly viral infection or a combination of viral and bacterial infection. A wide spectrum of viruses, such as respiratory syncytial virus (RSV), rhinovirus, para-influenza virus types 1, 2, and 3, influenza virus A and B, adenovirus, enterovirus, coronavirus and Epstein-Barr virus, have been identified in children⁴. Human respiratory syncytial virus (HRSV)/RSV is considered to be the most common viral cause of ALRI-related death, amounting to 22% of all episodes of ALRI and is the cause of the highest childhood mortality in low- and middle-income countries among all respiratory viral infections⁵. Younger age, male gender, family history of lower respiratory tract infection (LRTI), lack of breastfeeding, severe malnutrition and inadequate immunization emerged as independent significant risk factors for severe ALRI^{6,7}. Environmental tobacco smoke and use of bio-mass fuel contribute to indoor pollution leading to decreased respiratory defence mechanisms^{6,7}.

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Objectives

To study the clinical characteristics and viral spectrum of SARI patients admitted to the paediatric intensive care unit (PICU) and to assess the differences in the clinical profile of SARI between infants and older children.

Method

A prospective cross-sectional observational study was conducted in the PICU of a tertiary care hospital of Eastern India from September 2021 to February 2022. From previous experience in this hospital for the last 5 years, we considered this period to be the ideal time to carry out our study. This seasonality was also seen in a north Indian study⁸.

Our study population comprised children aged 1 month to 12 years who satisfied the case definition of SARI and who were shifted to the PICU for ventilatory support. A total of 55 children was included of which 9 were excluded in view of Covid-19 positivity. We excluded Covid-19 positive patients for 2 reasons. Firstly, our hospital was designated a non-Covid-19 hospital by the Government and we had to send Covid-19 positive patients to Covid-19 designated hospitals. Hence, follow-up was not possible. Secondly, we aimed to study the aetiological profile of respiratory viruses other than SARS-CoV-19 during the pandemic.

After admission to the PICU, relevant history was taken from parents and a detailed examination performed. 1ml of EDTA mixed blood was sent for complete blood count (CBC) along with 1ml of clotted blood for C-reactive protein (CRP). Oropharyngeal and nasopharyngeal swabs were obtained from all children on the day of admission to maintain uniformity. Each oropharyngeal and nasopharyngeal swab was collected using a nylon-tipped flexible plastic-shaft applicator from the posterior part of the throat and put into viral transport medium (VTM). All the VTMs were transported in ice within 1 hour to regional ICMR, NICED-Kolkata where nucleic acids were extracted

using Qiagen viral RNA/DNA mini kit and then subjected to reverse transcription polymerase chain reaction (RT-PCR) for detection of respiratory viruses. We tested for the following viruses: influenza A (H1N1), respiratory syncytial virus (RSV)-A, RSV-B, human metapneumovirus, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, adenovirus and rhinovirus.

All the patients were treated according to the national guidelines. Our study variables included demographic data, relevant history, positive examination findings, laboratory investigations (CBC, CRP), course during hospital stay, treatment received, outcome and viral pathogen isolated from the patient.

Ethical issues: Approval for the study was obtained from the Institutional Ethics Committee of the Institute of Post Graduate Medical Education and Research (No: IPGME&R/IEC/2022/025). Written informed consent was obtained from the parents of the participating children.

Statistical analysis: All the study variables were compiled using Microsoft Excel sheet and analysis was done by Graph pad Prism version 5 and SPSS version 22. Data have been summarized as mean with standard deviation for numerical variables and as percentages and proportions for categorical variables. Chi-square test was done to compare between 2 proportions and p-value <0.05 was considered statistically significant.

Results

The median age of presentation was 5.5 months (minimum 1 month to maximum 8 years). Median weight at presentation in <1 year age group was 4kg (IQR=2–9kg).

Table 1 is a comparison of attributes among different age groups in the study population.

Table 1: Comparison of attributes among different age groups in the study population (n=46)

Attribute	Below 1 year	1 to 5 years	Above 5 years	*p-value
Total number (%)	33 (69.5)	10 (24.0)	03 (06.5)	
Median weight	4kg	11kg	25kg	
Deaths – n (%)	12 (36.3)	02 (20.0)	03 (100.0)	0.1348
Mechanically ventilated – n (%)	16 (48.4)	04 (40.0)	03 (100.0)	0.427
Increased total leucocyte count – n (%)	19 (57.5)	07 (70.0)	03 (100.0)	0.643
Raised C-reactive protein – n (%)	30 (90.0)	10 (100.0)	03 (100.0)	0.9596
Complications – n (%)	18 (54.5)	06 (60.0)	02 (66.6)	0.9518
Comorbidities – n (%)	20 (60.6)	07 (70.0)	03 (100.0)	0.7050
Chest x-ray findings – n (%)	33 (100.0)	10 (100.0)	03 (100.0)	1
Secondary bacterial infection – n (%)	13 (39.3)	01 (10.0)	0	0.2064
Mean paediatric intensive care unit stay	6 days	7.5 days	3 days	
Virus isolated – n (%)	14 (42.4)	04 (40%)	0	0.5306

*p-value demonstrates any significant differences between infants and older age groups

There were 25 (54%) males and 21 (45%) females giving a male to female ratio of 1.1:1. There were 17 (36.9%) deaths whilst 29 (63.1%) cases were successfully discharged. There were 11 cases in

September 2021, 14 in October 2021, 4 in November 2021, 1 in December 2021, 12 in January 2022, and 4 in February 2022. (Figures 1 and 2).

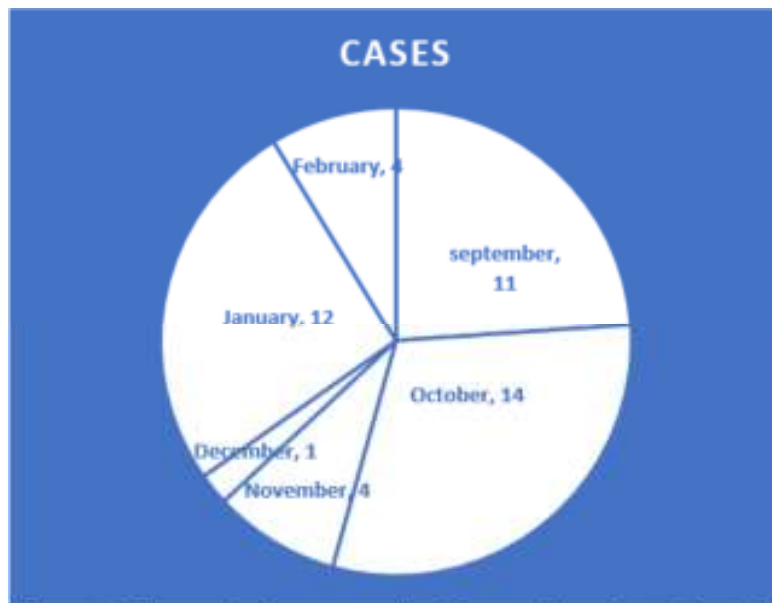


Figure 1: Figure showing seasonality of cases during the study period

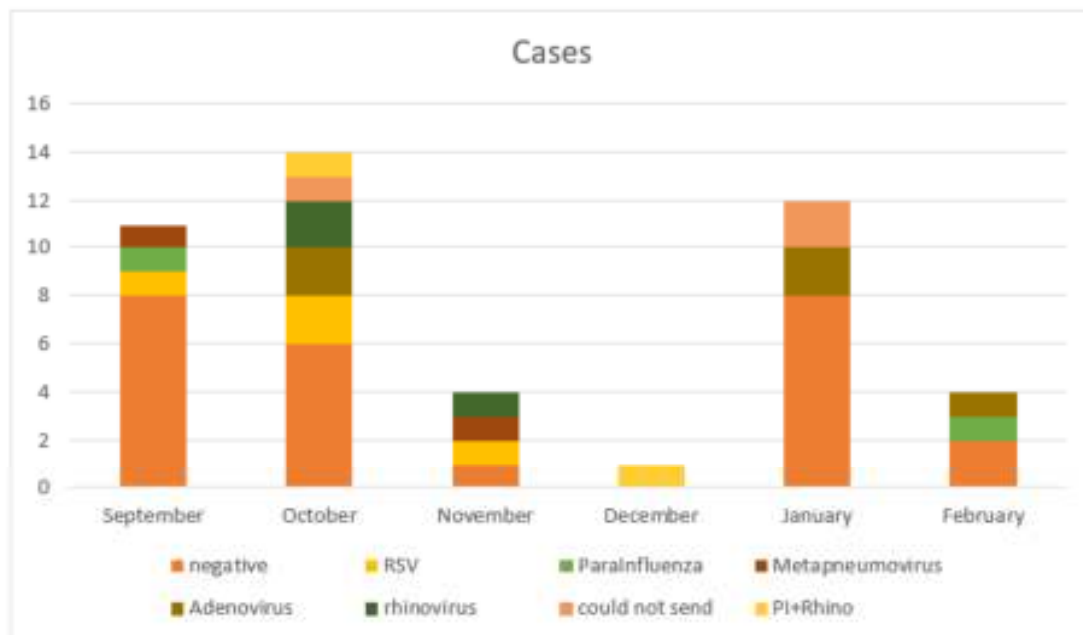


Figure 2: Figure showing different virus isolated during seasonal surge

Exclusive breastfeeding was done in 25 (54%) children, and the rest were either mixed-fed or top-fed. Only 32 (69%) children were immunized up to date according to the national immunization schedule and among them only 8 children had received the pneumococcal vaccine and only 4 had been given the influenza vaccine. In our study, there was 2.3 times more risk of death in the absence of

exclusive breastfeeding (OR- 2.3, 95% CI= 0.6-7.9) and 2.2 times more risk of death in the absence of immunization (OR- 2.2, 95% CI= 0.6-7.9). There were 4 cases who were born preterm.

Table 2 gives the demographic and clinical characteristics of the study population.

Table 2: Demographic and clinical characteristics of study population (n=46)

Variable	Value
Median age	5.5 months
Total deaths	17 (36.9%)
Median duration of fever	4 days (IQR 1-14 days)
Non rebreathing oxygen mask	10 (21.7%)
Non-invasive ventilation	13 (28.2%)
Invasive mechanical ventilation	23 (50.0%)
Median total white blood cell count	13,300/cu mm (IQR 5500-31,000/cu mm)
Median C-reactive protein	7.5 mg/dL (IQR 2.5-19.6 dL)
Raised C-reactive protein	43 (93.5%)
Total patients with comorbidities	30 (65.2%)
Total patients with complications	32 (69.5%)
Total patients with secondary bacterial infection	14 (30.4%)

IQR: inter-quartile range

All 46 children had respiratory distress at the time of admission into the PICU. Mortality was significantly associated with mechanical ventilation ($p < 0.0001$). Thirteen (28.2%) patients had either cardiogenic or septic shock which required inotropic support. The median duration of PICU stay was 6 days (IQR= 2 to 14 days). Neutrophilic leucocytosis was seen in 36 patients and lymphocytic predominance in 10; increased leucocytosis or high CRP was not significantly associated with mortality ($p=0.46$ and $p=0.255$ respectively). All the cases had chest x-ray findings, of which 22 had increased diffuse broncho-vascular markings and 24 had lobar consolidation-like changes.

In our study, 30 (65.2%) cases had comorbidities, of which 9 had congenital heart disease (CHD), 5 had central nervous system (CNS) involvement and 2 had type-1 diabetes. Other comorbidities included chronic kidney disease (3 cases), bleeding disorder (1 case) and syndromic with multiple congenital anomalies (2 cases), Kawasaki disease (1 case), nephrotic syndrome (3 cases), congenital hypothyroidism (1 case) and prematurity (4 cases). Mortality was 17 times higher in children with comorbidities (OR- 17, 95% CI= 2-146), 4.7 times

higher in children with CHD (OR- 4.7 95%CI= 1-22) and 1.3 times higher in children with pre-existing CNS abnormality (OR-1.33, 95% CI= 0.3-6.8).

Of the 46 cases 32 (69.5%) had complications involving single or multiple organs. Convulsions occurred in 11 cases, shock (hypovolaemic, septic and cardiogenic) in 13 cases, acute kidney injury in 9 cases, acute respiratory distress syndrome in 3 cases and disseminated intravascular coagulation in 13 cases. Coexistent diarrhoea was seen in 3 cases. There was a significant association of mortality with complications ($\chi^2 = 4.84$, df-1, $p = 0.0278$). The median PICU stay for children without complication was 6.5 days and with complications was 8 days. Secondary bacterial infection occurred in 14 (30.4%) cases. There was no significant association of secondary bacterial infection with mortality ($\chi^2 = 0.926$ dof-1 $p=0.33$) and the median PICU stay was also the same with or without secondary bacterial infection.

Figure 3 shows the count of various respiratory viruses isolated.

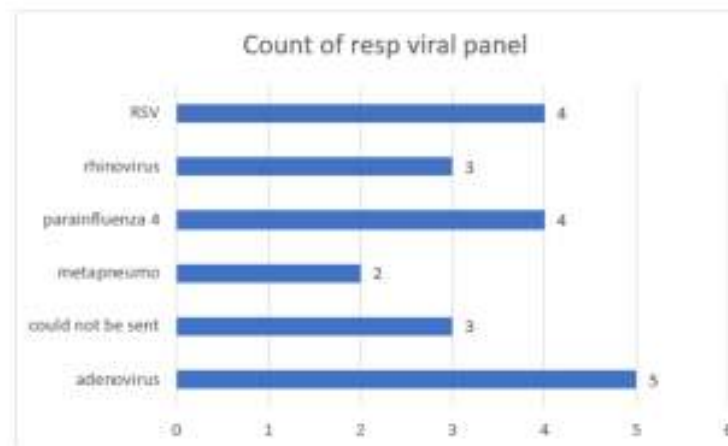


Figure 3: Figure showing count of various respiratory pathogens isolated

From the respiratory viral panel, 18 (41%) samples were positive for virus detection; 5 were positive for adenovirus, 2 for metapneumovirus, 4 for parainfluenza 4 virus, 3 for rhinovirus and 4 for respiratory syncytial virus (Figure 3). In 3 patients, viral swabs could not be sent and no virus was detected in 25 samples. Viral co-detection occurred in 2 (11%) cases.

Discussion

In our study 69.5% of children were less than 1 year old, 24% were 1-5 years old and 6.5% were 5-12 years old. This is similar to a study by Nair H, *et al*¹ where the disease incidence was highest in neonates (68.6 episodes/1000/year, CI 47-98) followed by infants aged 1-11 months (51.8 episodes/1000/year, 44-59). This study also shows boys more affected than girls which is similar to our study.

As in other studies, our study also depicted the seasonality of cases but the pattern was slightly different compared to north or south India. We had peak cases in pre-winter i.e., September, October and again in January, compared to northern studies which showed peak during the winter season (November, December)⁸.

Mortality rate in our study was higher than in other studies for the following reasons. Firstly, our study focused on PICU, where there are sicker children. Secondly, our hospital, being the highest referral centre of our state, received patients from remote rural areas; delayed hospitalization, delayed referral from lower hierarchical health facilities and prolonged transportation time caused most admissions to be in a more critical state. Age-wise mortality is depicted in table 1. In our study, there was 100% mortality in the >5-year age group, attributed to the underlying medical conditions that the patients had before admission. The estimated case fatality rate ranges from 1.6% to 3.9% in industrialized and non-industrialized countries respectively and more among the 0-5-year age group than the 5-12-year age group¹. A study by Jain N, *et al*⁹ reported a mortality of 13-16% in India due to acute respiratory infection (ARI).

The rates of exclusive breastfeeding and up-to-date vaccination, which are important risk factors determining the patient's recovery, were very low in our study. In our study, the odds of mortality in the absence of exclusive breastfeeding and immunisation were 2.3 and 2.2 respectively (95% CI=0.6-7.9) which is similar to other studies. In developing countries, children who were exclusive breast fed for 6 months had 30%-42% lower incidence of ARI compared to children who did not¹⁰. A recent longitudinal cohort study by Miharshahi S, *et al*¹¹ reported 2.3 times increased risk of ARI among children not breast fed adequately.

The presenting features like fever and respiratory distress in the form of retractions are similar to other studies^{1,9}.

As our study population was the PICU, oxygen requirement was universal, although the majority required invasive mode of ventilation initially which was later weaned off to non-invasive mode and other forms of oxygen delivery systems. Mechanical ventilation was significantly associated with mortality ($p<0.0001$), which is similar to other studies¹². The median duration of stay in the PICU was also similar to other studies^{1,9}. There was no significant association between neutrophilic leucocytosis and raised CRP with mortality in our study which is similar to other studies^{13,14}.

In our study, the mortality in children with comorbidities was 17 times higher than in children without comorbidities, more so in children with CHD. Similar observations were made in studies by Diller GP, *et al*¹⁵ and Khairy P, *et al*¹⁶. In our study, the majority of complications were in form of meningitis, shock and disseminated intravascular coagulation. Secondary bacterial infection, a predicted complication was similar to that seen in other studies. Mortality in children with secondary bacterial infection versus without secondary bacterial infection was not significant.

Virus detection rate in our study was 41% which is in agreement with many other studies. We could not get a higher yield as our facility does not provide RT-PCR tests for other respiratory viruses like enterovirus, echovirus, measles, etc. Adenovirus remained the most prevalent respiratory virus throughout the study period followed by influenza virus, respiratory syncytial virus (RSV) and metapneumovirus. This is in agreement with a study by Waghmode R, *et al*² in India (1970-2020), where it was shown that Eastern India had a higher prevalence of influenza (B>A) and parainfluenza rather than RSV. Viral co-detection was lower in our study compared to other studies¹⁷.

The strength of the study is that we have tried to isolate the causative viral pathogen. The limitations of the study are the small sample size and the short duration of the study.

Conclusions

In this study 69.5% of children with SARI were infants. Mortality was 36.9%. There was a statistically significant increased risk of death in the absence of exclusive breastfeeding, absence of immunization, use of mechanical ventilation, presence of comorbidities, presence of CHD and presence of pre-existing CNS abnormality.

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