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Clinico-epidemiological characteristics of pediatric COVID-19 patients in Bangladesh

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ABSTRACT

Background: The objective of the study was to delineate the clinico-epidemiological characteristics of pediatric coronavirus disease-2019 (COVID-19) patients.

Methods: This observational study included 290 pediatric patients with a definite diagnosis of COVID-19 admitted to Dhaka Shishu hospital, Bangladesh, from April 2021 to October 2021. Clinical and epidemiological characteristics were analyzed based on demographic data, medical history, laboratory tests, and outcome information. Data analysis was performed with SPSS 26. Ethical measures were taken in compliance with the current declaration of Helsinki, and final analysis was performed using SPSS 26.

Results: Of all, 42 (14.5%) were neonates (<28 days), 88 (30.3%) were infants (28 days to <1 year) and 160 (55.2%) were children (1-17 years). The median age of the children was 18 (0.3-204) months, 58.3% were male, 62% had malnutrition, and presented with various clinical presentations. The main symptoms were fever (5.7%) and breathlessness (20%). Approximately 22% of children were asymptomatic, and 57% had at least one comorbidity. Fever and abdominal pain were predominant presenting symptoms in children compared with neonates and infants (p<0.01 for both), while cough and breathlessness were more frequent in infants (p<0.01 for both). The infants suffered significantly from neutropenia and lymphocytosis than neonates and children (p<0.001 for both). The discharge and death rates were 77.8% with 6.9%. Overall case fatality was higher among neonates than others.

Conclusions: Compared to other pediatric groups, neonatal case fatality was higher, and COVID-19 in neonates, infants, and children has similar epidemiological and clinical manifestations. The findings from this study might help to guide the development of measures to prevent and treat this ongoing global pandemic of these particular age groups.

Keywords: Children, COVID-19, Pandemic, Neonate, Infants, Clinical manifestations

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INTRODUCTION

Since December 2019, an outbreak of undiagnosed pneumonia cases with presumptive viral origin started in Wuhan, China, and began to spread rapidly throughout the world.¹ At the beginning of 2020, the international committee on taxonomy of viruses denominated this new virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).² The world health organization (WHO) designates this pandemic diseaseas coronavirus disease 2019 (COVID-19) and later declares a public health emergency of international concern.⁵ To date, over 140 million patients have been diagnosed with COVID-19 globally.6 The cumulative number of laboratoryconfirmed cases has been reported to be over 700,000, and more than 10,000 reported deaths.⁷ The clinical spectrum of COVID-19 is wide, varying from completely asymptomatic forms to those characterized by severe respiratory distress requiring intensive care resulting in death.⁸⁻¹⁰ All ages are susceptible to this infection. However, the number of confirmed cases in children with COVID-19 is relatively small; hence, very limited information is available compared to adults.^{11,12} One of the largest surveys revealed that 2.2% of children were affected in China, while in the USA, the number was 1.7%.14 The exact prevalence of COVID-19 among Bangladeshi children is still lacking.

Ample evidence suggests that compared to adults, children with COVID-19 have distinct epidemiological and clinical manifestations. 15 For example, when adult patients predominantly present with fever, cough, breathlessness, sore throat, and headache, children present with cough, pharyngitis, fever, diarrhea, vomiting, and a negligible amount of gustatory and olfactory symptoms. 16-18 In addition, there are fewer severe cases than adults. Most likely, therefore, very limited comprehensive guidelines are available focusing on the management of COVID-19 in children rather than adults.16 However, understanding the manifestation of the pediatric population and their variation in different age groups, including neonates (<28 days), infants (28 days to <1 year), and children (1 year to <18 years), is important for clinical and containment strategies. Considering the lack of detailed epidemiological information of pediatric patients, we conducted observational an study to record epidemiological and clinical features and outcome data up to discharge among the different pediatric populations (neonates, infants, and children <18 years) admitted to Dhaka Shishu hospital, Bangladesh.

METHODS

Study design and participants

This observational study was approved by the institutional review board (IRB) of Dhaka Shishu hospital (DSH), Dhaka, Bangladesh [ethical approval no. 651(1)/DSH/2020)]. Children admitted to the hospital

with clinical features consistent with COVID-19 were initially quarantined prior to SARS-CoV-2 nucleic acid detection.²¹ Bed-sided nasopharyngeal swab of suspected patients was collected using a swab stick by a skilled health care worker for RT-PCR. Suspected COVID-19 cases were defined as the presence of at least one clinical manifestation: fever, breathlessness, tachypnea, lethargy, poor feeding, cough, vomiting, diarrhea, sore throat, or runny nose during admission. A reverse transcriptasepolymerase chain reaction (RT-PCR) test was performed for all suspected cases with the samples collected from the respiratory tract. Laboratory-confirmed [positive RT-PCR (qualitative) for SARS-CoV-2] cases were finally included within the period spanning from May 2020 to December 2020. Parents who did not provide consent to participate in the study refrained from inclusion. Assessment of the children and management was ensured according to the recommendation of the national guidelines on clinical management of COVID-19 and interim guidance provided by the Bangladesh pediatric association (BPA). Details of the patient selection are in Figure 1.

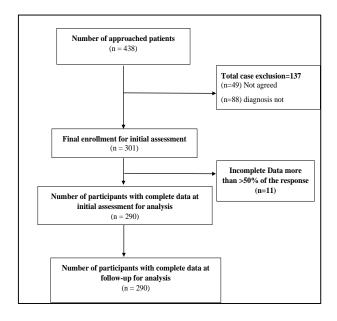


Figure 1: Patient selection flow chart.

Data collection procedure

A preformed questionnaire was prepared based on published literature and was piloted among 15 cases admitted to DSH. Experiences from the piloting were adjusted during the finalization of the questionnaire. The medical records of the included patients were accessed by the study research physicians. Prior to data collection, all of the research physicians (a total number of four) were trained for data collection and clinical record assessment. Clinical data were extracted, including demographic data, clinical symptoms, signs, comorbidities, and laboratory findings. Nutritional assessments were also performed by a growth monitoring promotion (GMP) card. Mid upper arm circumference (MUAC) tape was used during the

assessment of mid upper arm circumference (MUAC), and body weights of neonates and infants were measured with WS590-baby weighing scales. For children aged more than 1 year, a digital body weight measuring scale was used. All patients were managed by standard care for COVID-19. Comorbidities were also managed based on the diagnosis and treatment protocol of the disease. All patients were followed-up to the discharge. The outcome was defined as recovery, death, referred to the super specialized center, and left the hospital against advice. The discharge criteria followed in the study were as follows: normal body temperature or no fever for at least three consecutive days; alleviation of upper respiratory symptoms (in comparison to the admission day); and negative RT-PCR (qualitative) results obtained for SARS-CoV-2 nucleic acid detection at day 14 (from the index test). Written informed consent was provided by their parents or guardians before data collection.

Quality assurance of the data and reporting guidelines

The principal investigator and/or his team supervised the data collection procedures and randomly cross-checked the collected data to ensure quality control. In case of any breach of the standard procedure observed, the investigator team communicated with the research physicians and attending doctors to maintain the standard care and data collection process. After completion of the data collection, all data were sorted and stratified into three groups based on the age difference. Here, neonates were considered age less than 28 days, infants less than 1 year, and children between 1 year and <18 years of age.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 26, IBM statistics). Missing values were managed by subtracting the data from the final data set. No mean imputation was made. Continuous data are expressed as the mean ± standard deviation or median (range), while categorical data are presented as a number, frequency, or percentage. Both parametric and nonparametric tests were used whenever necessary. The results are expressed with 95% confidence intervals (CIs), and a p<0.05 was considered statistically significant.

RESULTS

A total of 290 pediatric patients with COVID-19 were included in the study. The median age of the patients was 18 months, with a range between 1 day and 17 years. Of all, 42 (14.5%) were neonates, 88 (30.3%) were infants and 160 (55.2%) were children. More than half of the pediatric patients were male (58.3%). Among all 73 (45.3%), 26 (16.1%) and 1 (0.6%) had severe malnutrition, moderate malnutrition and overnutrition, respectively. Nearly half of the pediatric patients (n=146, 50.3%) had at least one comorbidity, and 20 (6.9%) had more than one comorbidity. Single comorbidities were

significantly more common among children than neonates and infants, while more than one comorbidity was significantly more common among neonates (p<0.001) (Table 1).

The common clinical presentation was fever (n=150, 51.7%), followed by breathlessness (n=58, 20.0%), abdominal pain (n=48, 16.6%), cough (n=42, 14.5%), seizure (n=37, 12.8%), and vomiting (n=36, 12.4%), among others. Fever, abdominal pain, vomiting, rash, and weakness were significantly more common among children (p<0.05). Breathlessness, cough, seizure, and vomiting were significantly more common among infants (p<0.05) (Table 2).

Table 3 describes the investigation profile of the pediatric patients with COVID-19. The average hemoglobin level was 10.95±2.78 g/dl (SD), with a significantly higher level among neonates than infants and children (p<0.001). The average hematocrit was $34.54\pm9.72\%$ (SD), with a significantly higher value in neonates than in infants and children (p<0.001). The median WBC count 11.20×103/mm³, ranging from 127.80×103/mm³, with children having a significantly lower WBC count than neonates and infants (p<0.001). The percentage of neutrophils was significantly lower and lymphocytes was significantly higher among infants than among neonates and children (p<0.001). The median pediatric patients count among 2.80×106/mm³, with a significantly higher median value among infants than neonates and children (p<0.001). Serum creatinine was significantly higher among neonates than among infants and children (p=0.002).

Among 290 pediatric children, outcome data were available for 288. Out of 288 pediatric participants, 78% recovered, 11% were referred, 7% died and 4% left against advice (Figure 2).

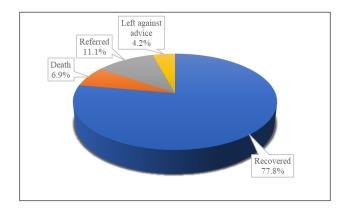


Figure 2: Outcome of pediatric patients with COVID-19, (n=288).

We compared the demographic, nutritional, comorbidity, and investigation profiles between pediatric patients with COVID-19 who died and those who recovered (Table 4).

Table 1: Demographic characteristics, nutritional status and comorbidities of pediatric patients with COVID-19, (n=290).

Variables	Total, n (%)	Neonate, n (%)	Infant, n (%)	Children, n (%)	P value	
Number	290	42 (14.5)	88 (30.3)	160 (55.2)		
Age (months)						
Median	18 (0.3-204)	0.25 (0.03-0.87)	6 (0.97-12.00)	64 (13-204)		
Sex						
Male	169 (58.3)	27 (64.3)	53 (60.2)	89 (55.6)	0.542	
Female	121 (41.7)	15 (35.7)	35 (39.8)	71 (44.4)	0.342	
Weight (kg)						
Mean ±SD	7.61±4.63	2.84 ± 0.49	5.73±2.07	12.28±3.67		
Nutritional status*						
Normal	61 (37.9)	12 (35.3)	23 (33.3)	26 (44.8)		
Severe malnutrition	73 (45.3)	17 (50.0)	36 (52.2)	20 (34.5)	0.448	
Moderate malnutrition	26 (16.1)	5 (14.7)	10 (14.5)	11 (19.0)	0.446	
Overnutrition	1 (0.6)	0	0	1 (1.7)		
Number of comorbidities						
One	146 (50.3)	5 (11.9)	37 (42.0)	104 (65.0)		
More than one	20 (6.9)	1 (24)	7 (8.0)	12 (7.5)	< 0.001	
None	124 (42.8)	36 (85.7)	44 (50.0)	44 (27.5)		

P value determined by Chi-square test.

Table 2: Clinical presentation of pediatric patients with COVID-19, (n=290).

	Total,	Neonate,	Infant,	Children,	
Variables	(n=290)	(n=42)	(n=88)	(n=160)	P value
	N (%)	N (%)	N (%)	N (%)	
Asymptomatic	65 (22.4)	35 (83.3)	13 (14.8)	17 (10.6)	< 0.001
Fever	150 (51.7)	5 (11.9)	47 (53.4)	98 (61.3)	< 0.001
Breathlessness	58 (20.0)	4 (9.5)	33 (37.5)	21 (13.1)	< 0.001
Abdominal pain	48 (16.6)	0	11 (12.5)	37 (23.1)	0.001
Cough	42 (14.5)	1 (2.4)	22 (25.0)	19 (11.9)	0.001
Seizure	37 (12.8)	3 (7.1)	15 (17.0)	19 (11.9)	0.268
Vomiting	36 (12.4)	0	9 (10.2)	27 (16.9)	0.009
Sepsis	17 (5.9)	5 (11.9)	7 (8.0)	5 (3.1)	0.059
Oedema	16 (5.5)	1 (2.4)	4 (4.5)	11 (6.9)	0.487
Loose motion	14 (4.8)	0	7 (8.0)	7 (4.4)	0.138
Rash	13 (4.5)	0	1 (1.1)	12 (7.5)	0.023
Seizure	12 (4.1)	0	5 (5.7)	7 (4.4)	0.321
Feeding problem	11 (3.8)	0	6 (6.8)	5 (3.1)	0.147
Weakness	9 (3.1)	0	0	9 (5.6)	0.021
Sore throat	3 (1.0)	0	0	3 (1.9)	0.722
Runny nose	2 (0.7)	0	1 (1.1)	1 (0.6)	1.000
Unconsciousness	2 (0.7)	0	1 (1.1)	1 (0.6)	1.000
Delayed cry	2 (0.7)	2 (4.8)	0	0	0.021
Local swelling	1 (0.3)	0	0	1 (0.6)	1.000

^{*}P value determined by Chi-square test.

Table 3: Investigation profile of pediatric patients with COVID-19, (n=290).

Investigations	Total, mean ±SD	Neonate, mean ±SD	Infant, mean ±SD	Children, mean ±SD	P value
Hemoglobin (g/dl)	10.95 ± 2.78	14.64 ± 3.02	10.46±1.75*	10.28±2.45*	< 0.001
Hematocrit (%)	34.54±9.72	46.71±10.10	33.43±6.77*	32.07±8.69*	< 0.001
RBC (×10 ⁶ /mm ³)	4.23±0.95	4.42±0.90	4.19±0.77	4.04±1.03	0.087
WBC $(\times 10^3 / \text{mm}^3)$	11.2 (0.01-127.8)	12.5 (3.80-37.10)	12.30 (0.01-126)	10.1 (1.10-127.8)*!	0.001
Neutrophil (%)	53.0 (3.0-91.0)	59.0 (17.0-89.0)	38 (9.0-85.0)*	54.50 (3.0-91.0)!	< 0.001

Continued.

Investigations	Total, mean ±SD	Neonate, mean ±SD	Infant, mean ±SD	Children, mean ±SD	P value
Lymphocyte (%)	41.00 (6.0-95.0)	31 (6-72.00)	51.50 (1084.00)*	38.50 (7.00-95.00)!	< 0.001
Monocyte (%)	5.00 (0-34.00)	6 (0-13.00)	6 (0-12.00)	4.00 (0-34.00)!	0.004
Eosinophil (%)	1.00 (0-17.00)	1.00 (0-7.00)	1.00 (0-17.00)	1.00 (0-16.00)	0.933
Platelet (×10 ⁶ /mm ³)	2.80 (0.12-8.06)	2.52 (0.24-6.76)	3.70 (0.22-8.06)*	2.57 (0.12-7.76)!	< 0.001
S. creatinine (mg/dl)	0.49 (0.01-10.71)	0.84 (0.33-5.11)	0.42 (0.01-5.72)*	0.50 (0.03-10.71)*	0.002
Sodium (mmol/l)	141.38±5.59	142.56±6.49	140.88±5.11	141.279±5.53	0.371
Potassium (mmol/l)	4.52±1.04	5.28±1.29	4.83±0.97	4.13±0.77*!	< 0.001
Chloride (mmol/l)	102.29±12.25	101.73±14.37	103.76±8.29	101.70±13.28	0.571

Data is expressed as mean $\pm SD$ or median (min-max). P value determined by ANOVA and Kruskal Wallis Test where appropriate. Post-hoc analysis was conducted using Bonferroni or Games-Howell test. p<0.05 in relation to Neonate* and Infant!.

Table 4: Outcome of pediatric patients with COVID-19 in relation different characteristics, (n=290).

Variables	Dead, n (%)	Recovered, n (%)	P value
N (%)	20 (8.2)	224 (91.8)	
Age (Months)			
Neonate	8 (19.5)	33 (80.5)	
Infant	5 (7.0)	66 (93.0)	0.023*
Children	7 (5.3)	125 (94.7)	
Sex			
Male	12 (8.3)	132 (91.7)	0.926*
Female	8 (8.0)	92 (92.0)	0.920*
Nutritional status			
Normal	1 (2.0)	49 (98.0)	
Severe malnutrition	6 (9.7)	56 (90.3)	0.247*
Moderate malnutrition	1 (4.3)	22 (95.7)	0.247
Overnutrition	0	1 (100.0)	
Number of comorbidities			
One	7 (5.7)	115 (94.3)	
More than one	3 (16.7)	15 (83.3)	0.176*
None	10 (9.6)	10 (9.6) 94 (90.4)	
Investigation			
Hemoglobin (g/dl)	13.04±4.02	10.93±2.53	0.049***
Hematocrit (%)	41.43±13.56	34.65±8.81	0.059***
RBC $(x10^6/mm^3)$	4.19±0.92	4.18±0.90	0.945***
WBC $(x10^3 / mm^3)$	14.50 (1.10-37.10)	10.80 (0.01-127.80)	0.014
Neutrophil (%)	61.00 (41.00-89.00)	52.50 (3.00-89.00)	0.008
Lymphocyte (%)	30.00 (6.00-54.00)	41.00 (6.00-94.00)	0.012
Monocyte (%)	4.00 (0-11.00)	5.00 (1.00-25.00)	0.028
Eosinophil (%)	0 (0-6.00)	1.00 (0-16.00)	0.256
Platelet (x10 ⁶ /mm ³)	2.55 (0.24-5.78)	2.84 (0.12-7.76)	0.374
Serum creatinine (mg/dl)	0.70 (0.45-2.27)	0.47 (0.03-5.72)	0.011
Sodium (mmol/l)	142.47±5.53	141.27±5.58	0.402***
Potassium (mmol/l)	5.40±0.90	4.41±1.02	<0.001***
Chloride (mmol/l)	104.44±6.07	101.84±13.52	0.436***

 $P\ value\ determined\ by\ *Chi\text{--}square\ test,\ Fisher's\ Exact\ test,\ ***Independent\ samples\ t\ test\ and\ Mann-Whitney\ U\ test\ where\ appropriate.$

The number of deaths was significantly higher among neonates than among infants and children (p<0.05). Death did not vary significantly with the sex, nutritional status, or comorbidity of the patients. On investigation, hemoglobin, WBC count, neutrophil percentage, serum creatinine, and serum potassium level were significantly higher among those who died than among those who recovered (p<0.05). However, lymphocyte and monocyte percentages were significantly lower among patients who died than among those who recovered (p<0.05).

DISCUSSION

COVID-19 affect any age. However, globally, frequency and case fatality of COVID-19 is comparatively low in the pediatric group.²³ Although several studies reported exclusively on children, a few studies compared the demographic and clinical features across different age ranges.^{24,25} Our study presents a comparative analysis of patient characteristics in neonates, infants, and children in

the pediatric age group. We also explored the factors affecting death among pediatric patients with COVID-19.

The median age of our participants was 18 months (1.5 years), and we obtained COVID-19-affected neonates aged as low as one day and children as high as 17 years. Nearly half of the participants were aged less than one year, which is higher than that found by Anwar et al he median age of pediatric patients with COVID-19 varies from study to study based on the target population and method of selection.²⁶ A systematic review on the pediatric group by Patel found that the reported median age ranges from 1 to 11 years. The author also presents a composite mean age of 7.9 years with an age range between 1 day and 17 years, similar to our study. These findings demonstrate the SARS-CoV-2 virus's ability to infect anyone and children most likely got the virus from their infected parents or family members. This assumption is supported by studies among neonates which showed that half of the patients had infections from their infected mother, and one-third were admitted to the hospital.²⁷

Males were more common than females in our study, which corresponds to the findings of other studies.²⁴ We found this true for all age range. The higher affinity of SARS CoV-2 towards males than females might be explained by the fact that angiotensin-converting enzyme 2 (ACE2), the receptor for the virus, is expressed more in the former sex than in the latter along with other sexbased immunological and hormonal differences.²⁸

We found that more than 60 percent of pediatric patients had malnutrition irrespective of age group. This finding is important, as nutrition shows a reciprocal relationship with infection, and good nutritional status is associated with good immune function.²⁹ Additionally, more than half of them had at least one comorbidity, with the frequency being significantly higher among children and infants than among neonates. However, the overall proportion of comorbidities found in our study was higher than that found in other studies and lower than that in those who needed neonatal intensive care unit admission.30 Most of the comorbidities were probably coincident or concomitant findings in COVID-19 rather than precipitating factors. As the virus spreads via airborne respiratory droplets and mostly causes mild or asymptomatic disease in the pediatric population, in most cases, it was a coincidental finding in children presenting with other diseases in the hospital. However, some of the diseases might be consequent of COVID-19 as well. We noted multisystem inflammatory syndrome in 3 children, which was previously established as a rare but severe complication of COVID-19 among children.³¹

Fever was the most common presentation, followed by breathlessness, abdominal pain, cough, seizure, and vomiting, among others. Two previous studies conducted among children with COVID-19 in Bangladesh also noted fever, cough, breathlessness, abdominal pain, and

vomiting among the most common presenting features. In a systematic review of individual participant data, Christopher et al reported similar patterns presentation.³³ However, the proportion of individual symptoms varied among studies. SARS CoV-2 binds with ACE2, which is ubiquitous in the human body with high expression in the lungs, heart, ileum, kidney, and bladder.34 Hence, despite its entry through the lung, it might produce symptoms involving multiple systems of the body. However, respiratory and gastrointestinal intestinal presentation is the most common mode of presentation of the disease. We found that neonates were relatively asymptomatic compared to infants and children. Gastrointestinal complaints such as abdominal pain and vomiting were more common among children. and respiratory complaints such as breathlessness and cough were more common among infants. Christopher et al noted that children less than 7 years old tended to present with gastrointestinal complaints compared to older children.33 Our findings also conform to their results, as most of the child participants in our study were young with a median age of 64 months (5.33 years).

On laboratory investigations, we noted that children had significantly lower WBC counts than neonates and infants, with infants having significantly lower neutrophils and higher lymphocyte counts than children. However, laboratory data varied across pediatric participants based on the presence of various comorbidities and were mostly within the normal range for the participants. Similarly, Patel noted that the test results presented in various studies of COVID-19 children were mostly within the reference range used for that particular study.²⁴ Interestingly, this is contrary to expected lymphopenia, and an elevated neutrophil-to-lymphocyte ratio has emerged as a characteristic feature of severe COVID-19, probably because of the predominantly milder form of the disease in children.

Out of 288 participants for whom the outcome was known, 20 (6.9%) pediatric patients with COVID-19 died. However, the case-fatality rate increased to 8.2% when referred patients were excluded. We found that age was associated with death in pediatric patients with COVID-19, while sex, nutritional status, and the presence of comorbidities did not show any association. The proportion of deaths was significantly higher among neonates than among infants and children. This rate is higher than that found by Ghosh et al (1.4%) and Anwar et al (4.1%). ^{26,32} The low number of neonates among their studies might explain the difference. However, Trevisanuto et al found zero case fatalities among 44 newborns with COVID-19.27 The provision of a wellequipped and adequate number of neonatal intensive care units (NICUs) is an important requirement for the appropriate management of these groups of patients. However, this is often not possible in developing countries because of a lack of adequate treatment facilities. This could explain the high mortality among neonates found in our study. Our analysis also revealed that certain investigation results were significantly different between dead and alive patients. However, this might have been influenced by the higher number of neonates dying instead of infants and children, as the physiology of neonates differs fundamentally from that of older children.

The current study was limited by the small sample size collected from a single center, lack of detection of quantitative RT-PCR, radiological investigations, and dynamic detection of inflammatory markers. However, our study provided important insights into similarities and differences in characteristics, presentation, and outcome of COVID-19 among neonates, infants, and children in the context of Bangladesh.

CONCLUSION

The study presents a detailed clinico-epidemiological pattern of COVID-19 among neonates, infants, and children. About one-third of the patients remain asymptomatic. Fever and abdominal pain were the most prominent manifestations among symptomatic patients. Slight variation in the symptoms and laboratory investigations exists. In comparison to others, neonates are more vulnerable than other pediatric groups.

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Institutional Ethics Committee

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