Epidemiological and clinical characteristics of COVID-19 in Indian children in the initial phase of the pandemic: A cross-sectional study

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Research Article

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Abstract

Background: India saw the largest and the most stringent lockdown in the world when the number of COVID-19 cases reached around 550. With some early benefits in containing the surge and restricting the R0 of the virus, the current relaxation of lockdown norms has witnessed an exponential rise in positive cases. With scarcity of Pediatric data from the Indian subcontinent, early observations in the pandemic are pivotal in improving the understanding of physiologic behaviors, identifying risks, and guiding clinicians in assessing time-tested interventions and augmenting the awareness in the masses about the manifold clinical profiles of an evolving disease.

Objective: To assess the epidemiological and clinical characteristics of children admitted with COVID-19 infection early in the pandemic.

Study Design: A cross-sectional study

Participants: Fifty children between one month and 18 years of age whose nasopharyngeal swab tested positive for SARS-CoV-2 by RT-PCR.

Results: 28 (56%) children were male. 41 (82%) came from government declared containment zones with only one child having history of travel to affected area. Home overcrowding was observed in 33 (66%). Of the 50 children, 29 (58%) were asymptomatic while 20 (40%) and one (2%) had mild and moderate symptoms respectively. Fever, cough, and sore throat were the most common symptoms. 49 (98%) children had BCG scar. Leucopenia was seen in three (6%) only. Mean (SD) Neutrophil-Lymphocyte-Ratio (NLR) was 0.78 (0.48) while mean (SD) CRP was 10.98 (23.90). All 50 (100%) were cured.

Conclusion: Our study reasserts the increasing pediatric burden of COVID-19 with all age groups affected and overcrowding as a risk factor for continued community transmission, thus beckoning that public health policies be directed to ensuring further preventive measures. It also re-iterates the milder disease pattern in children with COVID-19 in the initial phase of the pandemic with a high proportion of asymptomatic and mild illness. Though abnormal CRP values are synonymous with the illness in children; leucopenia may not be a consistent finding.

Introduction:

Coronaviruses have long been known as a group of viruses that cause diseases in mammals and birds. Enveloped with positive-sense single-stranded RNA, they cause respiratory and gastrointestinal symptoms ranging from common cold to more severe disease such as pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ dysfunction in humans. Coronaviruses are capable of re-combinations and rapid mutations leading to newer coronaviruses. The COVID-19 is one such infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is currently causing outbreaks globally.
The first infection caused by the SARS-CoV-2 was recorded in November 2019 from Wuhan, Hubei Province, China. This airborne infection spread mostly by droplets and contact with infected surfaces has invaded more than 200 countries and affected millions of people across the world. Pediatric cases in number were found to be negligible. But the highly contagious nature of the virus and the risk of spread from Pediatric cases are anything but negligible considering that the asymptomatic carriers are the most likely source of spread through community. Furthermore, the fact that children exhibit certain physiological intricacies and may not be able to describe their own symptoms or contact history makes it imperative to address the challenge of safeguarding, diagnosing early and treating this group.

The incubation period of COVID-19 is about 1 to 14 days but could extend up to 24 days. Most of the cases are asymptomatic or mild, but the elderly or those with underlying co-morbidities such as diabetes mellitus, hypertension, and chronic obstructive pulmonary disease are more likely to develop severe disease. A disproportionate burden of the disease has also been suggested with higher rates of poverty and within certain racial/ethnic groups, the scenario having been linked to living conditions, work circumstances, underlying health conditions, and lower access to care. There was an initial lack of data on children with COVID-19 across the globe in the previously reported studies. This was attributed to the children staying at home in the period of the beginning of the outbreak with lesser outdoor activities and lesser international travel. Since then, a steadily growing number of studies have focused on COVID-19, but limited data is available on epidemiological features, the diverse clinical manifestations, and transmission patterns of children with COVID-19, more so in India.

In this study, we prospectively recorded and evaluated the epidemiological and clinical characteristics of fifty children admitted to our tertiary care center with COVID-19 infection diagnosed by real-time polymerase chain reaction (RT-PCR). Early observations of a disease in a pandemic in different populations are crucial in improving the understanding of its physiologic behaviors, identifying associated risks, assessing the efficacy of the time-tested interventions and augmenting the awareness of clinicians as well as the masses in general about the myriad clinical profiles of an evolving pathogen. Such data thus also plays a pivotal role in guiding public health policymaking; hence this study to understand and help pick up these children early in routine Pediatric practice.

Materials And Methods:

This was a cross-sectional study conducted in a dedicated Pediatric COVID-19 center, Pune, Maharashtra state, India between 1st April 2020 and 20th May 2020. Prior approval was taken from the institutional ethics committee. Children between one month and 18 years of age who tested positive by the RT-PCR technique for nasopharyngeal swab were included in the study. Written and informed consent was obtained from the parents. Detailed information on demographic data, travel, contact, living conditions and overcrowding, symptoms, presence of co-morbid conditions were taken. All children were examined systematically and categorized to degree of severity based on pre-existing criteria. Baseline laboratory
parameters (Complete Hemogram and C-reactive protein) were evaluated and repeated as required. Chest radiograph was done where indicated in the presence of fever or respiratory system involvement including disproportionately increased respiratory rates, chest retractions, and presence of adventitious sounds on auscultation or oxygen saturation ($\text{SpO}_2$) less than 94% in room air. Children were managed based on severity of illness as per hospital protocol for COVID-19. The children were reviewed daily up to discharge and changes in disease pattern, if any, were recorded. Discharge was decided as per prescribed Indian Council of Medical Research (ICMR) guidelines which until 10th May 2020 stated that asymptomatic children who tested negative for two nasopharyngeal swabs taken 24 hours apart after day 14 of illness were fit for discharge. After 10th May, discharge criteria were changed as per revised ICMR and Ministry of Health and Family Welfare (MoHFW) guidelines stating that asymptomatic children could be discharged after day 10 of illness without repeating nasopharyngeal swabs.

Definitions used:

Severity of illness was defined as in Table. 1

Overcrowding: Persons per room criteria have been used for judging the presence of overcrowding.\(^4\)

Standard age-appropriate ranges for laboratory parameters as per Nelson Textbook of Pediatrics, 21\(^{st}\) Edition, were considered as normal.\(^5\)

Statistical Analysis: Continuous variables were described as means and standard deviations; categorical variables were expressed as counts or percentages. At the end of sample size collection, the data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 25.0.

Results:

A total of 50 children who tested positive for COVID-19 by RT-PCR were included in the study. Of these, 28 (56%) were male. The mean (SD) age of all children was 6.95 (5.22) years. 15 (30%) of the children were in the age group of 0 to 2 years. There was history of close contact with family members with COVID-19 in 45 (90%) children, while the remaining five (10%) had no positive contacts. Of those 45 children, 42 had positive family members with mild illness, while three had family members with severe illness. Travel history to affected area was documented in only one (2%) child (Table. 2). The region where children were hailing from was marked on the map of Pune to ascertain the areas with local transmission. It was noticed that 41(82%) of the cases hailed from containment zones in Pune (Figure. 1).

29 (58%) children were asymptomatic while 20 (40%) and one (2%) had mild and moderate symptoms respectively. In symptomatic children, fever was the chief complaint in 17(54%). Cough was present in eight (16%), sore throat in seven (14%), myalgia in four (8%), diarrhea in two (4%), headache in two (4%) while one (2%) child each had a rash and conjunctivitis. None of the children had hypoxemia measured by pulse oximeter. Only one (2%) child had history of simple febrile seizures and one (2%) child had underlying Type I diabetes mellitus who presented with diabetic ketoacidosis. The remaining 48 (96%)
were free of any co-morbidities. 49 (98%) children had BCG scar. Immunization was complete in 32 (64%) of the children as per universal immunization program.

The mean (SD) CRP of all the children was 10.98 (23.90). Mean (SD) Neutrophil-Lymphocyte-Ratio (NLR), Lymphocyte-Monocyte-Ratio (LMR), Platelet-Lymphocyte Ratio (PLR) were 0.78 (0.48), 8.81(4.88), 82.36 (34.31) respectively (Table. 3). Chest radiograph was done in 20 symptomatic children. It was found to be normal in 18, while two showed bilateral lower zone haziness.

**Discussion:**

In the early stages of the COVID-19 pandemic, the Pediatric data from across the globe stated a milder illness in children contracting the infection. As the pandemic runs its course, there are increasing concerns over the palpable threat of unidentified risks to children. In our study, we have witnessed a pattern similar to what has been previously described in other continents. However, the seemingly anonymous risk of an evolving disease pattern that could change course to a more life-threatening illness must be addressed based on such epidemiological and clinical data. The prime intention is to ensure an improved perception of the disease and better vigilance in handling it and containing its spread.

As of midnight, 25th May 2020, India had already recorded a total of 138,845 cases of COVID-19 with Maharashtra state leading the pack with number of cases accounting for 36.17% (50,231) of the total. Of these, children up to the age of 20 years account to only 10.54%. Pune had a total of 443 cases were less than 20 years of age, with one recorded death.

Majority of the children in this study were detected in the government declared containment zones of Pune thus highlighting the significance of improving vigilance while attending to children coming from these areas. Majority of the children reported exposure to a positive close contact, a family member in most cases, indicating the current community transmission considering that 98% of children had no history of travel.

About two-third children met the criteria for residing in an overcrowded home thus highlighting the increased risk of transmission of SARS-CoV-2 in lower socio-economic groups with them carrying a disproportionate burden of the disease. Though the disease was seen in all age groups (Table 3), children less than five years of age accounted for 48% of all the cases. This can be attributed to the inability of this age group to comprehend and follow social distancing norms and the need for parents to constantly handle the children to attend to their dispositions.

About 58% of the children were asymptomatic and were detected as a part of screening when one of the family members tested positive indicating the covert nature of the virus. 40% were mildly symptomatic. Pediatric observational studies published early in the pandemic across China in February 2020 reported similar findings with fever being the most common symptom followed by cough and sore throat.\(^6,7,8\)

However, as the pandemic progressed, newer ‘atypical’ manifestations were witnessed across different continents in the form of cutaneous exanthems,\(^9,10\) encephalitis,\(^11,12\) and myocarditis.\(^13,14\)
In this study, all 50 (100%) cases recovered completely with no morbidities. The adult COVID-19 mortality rate worldwide is 6.2% at present, with the mortality rate in children less than 18 years being much lesser at <1%. Various hypotheses have been suggested to explain the milder course of disease in children as compared to adults starting with constant exposure to multiple viral infections which helps the immune system response when infected with SARS-CoV-2. Children as opposed to adults have lesser co-morbidities and healthier respiratory tracts. SARS-CoV-2 uses nasal angiotensin-converting enzyme-2 (ACE2) as a portal of entry to host. Lower ACE2 expression in nasal cavity may also help explain why COVID-19 is less prevalent in children.

Almost all children in our study were vaccinated with BCG and 64% of them were completely vaccinated according to universal immunization program. Immunization of children with BCG is also thought to confer protection against the virus. Adults with COVID-19 have been found to have lymphopenia and reduced number of cytotoxic CD8+ T cells which as per some studies may be prevented by BCG vaccination induced stimulation of the CD4+ and CD8+ T-cell capabilities thus helping in destroying the virus-infected cells. However, countries like Iceland where BCG is not a part of routine vaccination policy have not seen significant morbidity or mortality in COVID-19, questioning the cross protectivity of BCG vaccine in SARS-CoV-2 infection. The available epidemiologic data has also formed a base for postulation of the Rubella component of MMR vaccine conferring protection against SARS-CoV-2 infection. Also, the previous consideration of live measles vaccine as a base for other Coronavirus vaccines including SARS due to possible cross-over reactivity has formed the basis to encourage further research on the role of MMR against SARS-CoV-2.

Malnutrition has been deemed a risk factor in adult COVID-19. In children, malnutrition is known to foster infections; however in this study, majority of the children were well nourished with respect to weight for age criteria. Also, only one (2%) child had underlying Type I Diabetes Mellitus and rest were free of co-morbidities thus maybe reducing the burden of severe disease.

The hematological profile of adult with COVID-19 has demonstrated leucopenia with associated neutrophilia, lymphopenia, eosinopenia and thrombocytopenia. Also, higher Neutrophil-to-Lymphocyte ratios (NLR), Lymphocyte-to-Monocyte Ratios (LMR) and Platelet-to-Lymphocyte ratios (PLR) have been associated with severe disease and used for prognostication. Leucopenia, however, was seen in only three (6%) of our children and there was no evidence of lymphopenia, thrombocytopenia or eosinopenia. Low NLR, LMR and PLR seen in our study correlated with asymptomatic or milder form of disease.

High CRP values have now become synonymous with severe COVID-19 infection among adults as seen in majority of the studies. Mean CRP in our study was found to be 10.98mg/dl. CRP as high as 153.77mg/dl were seen in asymptomatic children while CRP as low as 4.59mg/dl was seen in the severe case suggesting a milder immune response. Trends in CRP values may be used as a surrogate of inflammation in COVID-19 infection.
Early studies from China stated that despite COVID-19 pneumonia in children being mild, chest computed tomography (CT) scan can present with characteristic changes of subpleural ground-glass opacities and consolidations of lung with surrounding halo. Early detection of lung lesions on CT as an alternative for diagnosis to the COVID-19 nucleic acid test from pharyngeal swab samples due to lack of adequate sensitivity was also proposed. In our study, we did not perform CT chest for any children. However, of the 20 children for whom a chest radiograph was done in view of persistent fever and cough, only one showed minimal lower zone infiltrates (<50%) despite normal respiratory examination and oxygen saturation.

Repeat RT-PCR of nasopharyngeal swab was done on day 14 and 15 to check for infectivity status of the child. All the children except one were tested negative by RT-PCR for both the days. For the child who tested positive for one swab, a repeat swab was negative after three days, thus indicating that clearance of viral load may vary in different individuals. Similar findings were seen in other studies as well. The degree of infectivity of these individuals after 14 days remains questionable as RT-PCR detects genetic fragments of the virus and cannot distinguish between dead or live virus. In such scenarios, doing a viral culture may be the plausible method of detecting live virus and demonstrating continued infectivity. As performing a viral culture is difficult and requires advanced laboratory facilities, using GeneXpert platform with Ct values ≥ 24 may also be beneficial for predicting lack of infectivity.

Recently an alarming rise in the number of Pediatric and adolescent Kawasaki Disease and a multisystemic hyper-inflammatory syndrome associated with COVID-19 requiring admission to intensive care units have been reported in Europe as well as North America as the pandemic has progressed. An acute onset illness accompanied by a hyperinflammatory syndrome, leading to multi-organ failure and shock has been described. Initial hypotheses suggest association with COVID-19 either as a direct manifestation or an antibody positive post-infectious immune mediated response based on initial laboratory testing. The management in these cases included anti-inflammatory therapy, parenteral immunoglobulin and steroids. This makes it imperative to characterize this particular syndrome and its risk factors, to understand causality, and devise therapeutic strategies.

In conclusion, all age groups remain vulnerable to COVID-19. Our study re-iterates the milder disease pattern in children with COVID-19 in the early phase of the pandemic with majority being asymptomatic and mildly symptomatic. The epidemiological pattern indicates an ongoing community transmission of the disease. With a high proportion of asymptomatic and mild cases there is difficulty in identifying pediatric patients with COVID-19 infection. Even asymptomatic and mildly symptomatic patients may have high CRP despite showing no leucopenia, lymphopenia or thrombocytopenia early in the disease and normal leucocyte indices. Chest radiographs are normal in most mild cases but may occasionally show occasional infiltrates despite no clinical findings. All these factors put together create a potentially precarious situation of ongoing unchecked community spread of the virus, thus laying the foundation for increasing severity of illness and post-infectious immune-mediated syndromes. Public health policies must hence be directed to ensuring safe social distancing amongst children and adolescents taking into account the evolving epidemiology of COVID-19.
consideration the re-opening of day-care centers and schools which may emerge as a source of an uncontrollable spread of disease once the lockdown is lifted.

**Limitations of the study:** Being a study in the initial phase of the pandemic with lockdown in place, it may not cover the entire spectrum of clinical presentations, severity and magnitude of SARS-CoV-2 in children from different geographical areas.

**Key Message:** Majority of COVID-19 cases in children are asymptomatic and mildly symptomatic

**What is already known?** There is no Indian data available in the pediatric population with respect to the epidemiological and clinical characteristics of COVID-19.

**What this study adds?** Majority of Indian children with COVID-19 have a milder course of disease in the initial stages of the pandemic.

**Declarations:**

The authors of the preprint submission "Epidemiological and clinical characteristics of COVID-19 in Indian children in the initial phase of the pandemic: A cross-sectional study" declare no competing interest.

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**Tables**

**TABLES**

| Asymptomatic | Mild | Moderate | Severe |
|--------------|------|----------|--------|
| No clinical symptoms and signs | Any of the following: Fever, sore throat, cough, fatigue, myalgia, rash, nasal congestion. Gastrointestinal symptoms such as vomiting, loose stools and pain in abdomen | All symptoms of mild category PLUS any two of the following: SpO\(_2\) between 90% - 94% in room air Tachycardia, Tachypnea Presence of adventitious sounds on auscultation Abnormal chest radiograph with infiltrates <50% | All symptoms of moderate category PLUS any one of the following: SpO\(_2\) < 90% in room air Severe tachypnea or bradypnea with presence of adventitious sounds on auscultation Persistent disproportionate tachycardia or tachyarrhythmia Evidence of poor perfusion with or without hypotension GCS score <10 Presence of severe acidosis on arterial blood gas Abnormal chest radiograph with infiltrates >50% |
| SpO\(_2\) >94% in room air | | |

Table 1) Severity of illness
| Parameters                                                                 | n = Value (%) |
|---------------------------------------------------------------------------|---------------|
| Sex                                                                       |               |
| Male                                                                      | 28 (56)       |
| Female                                                                    | 22 (44)       |
| Distribution of children according to age (years)                         |               |
| 1 month to ≤5 years                                                       | 24 (48)       |
| >5 to ≤10 years                                                           | 12 (24)       |
| >10 to ≤15 years                                                          | 11 (22)       |
| >15 to 18 years                                                           | 3 (6)         |
| Appropriate Weight-for-age (3rd to 97th centile)                          | 45 (90)       |
| History of contact with patient of COVID-19                               | 45 (90)       |
| Travel History to affected area                                           | 1 (2)         |
| Overcrowding                                                              | 33 (66)       |
| Severity of Illness                                                       |               |
| Asymptomatic                                                              | 29 (58)       |
| Mild                                                                      | 20 (40)       |
| Moderate                                                                  | 1 (2)         |
| Severe                                                                    | 0 (0)         |
| Symptoms                                                                  |               |
| Fever                                                                     | 17 (34)       |
| Cough                                                                     | 8 (16)        |
| Sore Throat                                                               | 7 (14)        |
| Myalgia                                                                   | 4 (8)         |
| Condition               | Count (Percentage) |
|-------------------------|--------------------|
| Diarrhea                | 2 (4)              |
| Headache                | 2 (4)              |
| Rash                    | 1 (2)              |
| Conjunctivitis          | 1 (2)              |

**Immunization status**

| Vaccination              | Count (Percentage) |
|--------------------------|--------------------|
| BCG                      | 49 (98)            |
| Age appropriate vaccination as per universal immunization program | 32 (64) |

**Associated Co-morbidities**

| Condition                  | Count (Percentage) |
|----------------------------|--------------------|
| None                       | 48 (96)            |
| Simple Febrile Seizures    | 1 (2)              |
| Type I diabetes mellitus   | 1 (2)              |
| Cured                      | 50 (100)           |

*Table 2) Epidemiological and clinical characteristics of children*
| Parameter                           | Mean   | Standard Deviation | Minimum | Maximum |
|------------------------------------|--------|--------------------|---------|---------|
| Hemoglobin (g/dl)                  | 12.00  | 1.74               | 7.6     | 16.6    |
| Total Leucocyte Count (TLC) (/cumm) | 8863.83| 3727.21            | 3300    | 19300   |
| Absolute Neutrophil count (/cumm)  | 2982.26| 1500.56            | 696     | 7350    |
| Absolute Lymphocyte count (/cumm)  | 4973.38| 3092.61            | 1248    | 15826   |
| Absolute Monocyte count (/cumm)    | 584.17 | 202.24             | 156     | 1071    |
| Absolute Eosinophil count (/cumm)  | 307.64 | 402.28             | 43      | 2280    |
| CRP (mg/dl)                        | 10.98  | 23.90              | <2.8    | 153.77  |
| NLR                                | 0.78   | 0.48               | 0.10    | 2.25    |
| LMR                                | 8.81   | 4.88               | 2.13    | 27.00   |
| PLR                                | 82.36  | 34.31              | 26.79   | 170.54  |
| Leucopenia                         | 3 (6.00%) |                  |         |         |

**Table 3** Laboratory investigations of children (TLC- Total Leucocyte count, CRP- C-Reactive proteins, NLR- Neutrophil-Lymphocyte-Ratio, LMR- Lymphocyte-Monocyte-Ratio, PLR- Platelet-Lymphocyte Ratio, Leucopenia <4000cells/cumm, Lymphopenia <1000cells/cumm, Thrombocytopenia <1,50,000cells/cumm, Eosinopenia <10/cumm)

**Figures**
Figure 1

Fig. 1) Map of Pune with areas of endemicity [Color of the marker indicates the number of cases from that zone (Red- ≥ 8 cases, Orange- 5 to 7 cases, Dark green- 3 to 4 cases, Light green- ≤ 2 cases)] (Courtesy: Map data ©2020: Google)