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Original Research Article

Morbidity, mortality and clinico-laboratory profile of COVID-19 related illness in children: a retrospective observational study from a tertiary care centre in India

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ABSTRACT

Background: As India is poised for a third wave of SARS Co-V2 infection with a large unvaccinated pediatric population, it becomes imperative and pertinent for a study to find out its demographic, clinico-laboratory profile, and outcome in children with COVID-19 disease and its related illness.
Methods: This is a retrospective observational study undertaken for Children and Adolescent admitted in the department of pediatrics of a teaching and tertiary care referral hospital, Delhi.
Results: The median age of admitted children with COVID-19 disease was 11 years with an interquartile range 3 to 16 years. The median duration of hospital stay was 10 days (mean: 18±14 days). Mortality was 9/62 (14%). Recovery in non-severe (asymptomatic, mild, moderate) was 41/41 (100%), and in severe and critical illness including MISC was 42.8% (9/21). Mortality in severe and critical patients managed in SARI and COVID ward was 44% (8/18). Death among MISC patient in PICU was 33% (1/3). Difference in CRP rise was significant in severe and non-severe group of COVID-19 (p=0.017).
Conclusions: Even though the morbidity and mortality associated with COVID-19 infection and related illness seems to be miniscule, the infection causes significant illness in the subgroup of children who requires hospitalization and can be fatal in those with comorbidity.

Keywords: Morbidity, Mortality, Clinico-laboratory profile, COVID-19, MISC

INTRODUCTION

Since the outbreak of the clusters of pneumonia of unknown etiology in Wuhan city of China in December 2019, and subsequent identification of SARS-CoV-2 as its etiology and designation of the disease as COVID-19 by WHO, COVID has become a gigantic pandemic and has ravaged the whole globe. The world is grappling to have a grip over the disease, and the full spectrum of the infections and its consequences are still unravelling.[1-3]Amidst this bleak scenario, the pediatric population accounted for a significantly lesser number of cases and have witnessed milder forms of disease with better outcomes compared to adults. As per the available data from China and other western countries, the pediatric population accounts for 1-5% of all diagnosed COVID-19 cases.[4-6] The studies have also reported that children are not only at low risk of contracting the infection but have a lesser degree of disease severity possibly due to a healthy respiratory system, fewer outdoor activities, protective immunity due to other viral infections, and premature ACE2 receptors.[7,8] With the progression of pandemic over time, pediatric morbidity and mortality related to COVID-19 infection are being noted to rise

with varying multi-organ failure. In May 2020, CDC USA reported a different subset of manifestations presenting as severe inflammation, multiorgan failure in a small percentage of children positive for SARS-COV2 termed as a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. The children with this subset of condition had persistent fever, evidence of severe inflammation, organ failure and some also shared features of Kawasaki disease, toxic shock syndrome, or cytokine storm syndrome. The PCR test is more often negative though most of the children have antibodies to SARS-CoV-2 in the absence of other known infections[11]. the Royal college of pediatrics and child health (RCPCH) published a guide for raising awareness amongst clinicians for this newly recognized condition called pediatric inflammatory multisystem syndrome-temporally associated with the SARS-CoV-2 (PIMS-TS).[12]

As the pandemic continues to linger with recurrent waves in many countries with reports of variable viral mutations and current exclusion of pediatric population for COVID-19 vaccination, children are vulnerable for contracting the infection in coming days and hence the predictions that the future waves will be dominated by pediatric morbidity and mortality. There is limited data on COVID-19 in children with the full spectrum of its clinical manifestations and outcome. India anticipating the third spike of cases in near future that may have a major hit on the pediatric population because of the huge non-vaccinated population, there is an immense need for awareness of disease manifestations and timely interventions for an optimal outcome. Hence, this study is planned to find out the clinical characteristics and Outcomes of novel coronavirus disease 2019 (COVID-19) and its related conditions in children and the adolescents admitted to the tertiary care teaching hospital in the India.

METHODS

Study type

This is a retrospective observational study of sixty-two confirmed COVID-19 pediatric patients.

Place of study

The study has been conducted in a tertiary care referral hospital located in Delhi. This hospital is one of the first four institutions designated by govt. of India for management of COVID-19 patients, and has adopted, and implemented from the outset severe acute respiratory illness (SARI) and COVID-19 disease isolation and management guidelines of government of India and WHO for pediatric patients.

Study period

The children admitted to the hospital between the date from 01 March 2020 to 31 January 2021 were included in the current study.

Inclusion criteria

Children admitted in the department of Pediatrics with COVID-19 disease and confirmed by any of the COVID-19 tests (RT PCR, Rapid Antigen test or COVID ab tests) were included in the study.

Exclusion criteria

Children below 1 month and admitted in other departments of the hospital were excluded from the study.

Details of the method

All the suspected cases (admitted in SARI isolation ward and other pediatric wards) have undergone screening for COVID-19 by COVID (RT PCR/RAT/COVID Ab) tests. As a sentinel laboratory of the country, RT-PCR test for COVID was provided by the microbiology department of the hospital provided from the very outset of the pandemic. Later, RAT tests were available for screening of the patients in the wards. Children with strong suspicion of MISC had undergone COVID Antibody tests. All COVID-19 confirmed cases have been managed in the designated and dedicated pediatric COVID ward by a uniform department management protocol aligned with national ICMR and WHO guidelines.

Patient data included age and sex, nutritional and immunization status, source of contact, clustering of the case in family and residing area, area of residence, pre-existing comorbidities, mode of presentation (asymptomatic, respiratory, gastrointestinal, circulatory, neurological, multiorgan). We described the clinical course in terms of symptoms (asymptomatic and symptomatic), and severity-mild, moderate, severe, and critically ill, and nature of organ failure in terms of organ support therapy (oxygen therapy, non-invasive, invasive respiratory supports, use of vasoactive medical support, renal replacement therapy, anticonvulsant drugs therapy). Information was also acquired related to pharmacotherapy targeting COVID-19 infection and modulating its course and outcome (i.e., hydroxychloroquine, azithromycin, remdesivir, and tocilizumab). Clinical outcomes included survival, duration of hospital stay, as well as persisting organ damage.

Laboratory data included blood count (Total leucocyte count, differential leukocyte count, neutrophil/ lymphocyte ratio), raised inflammatory markers (Serum CRP, serum ferritin, D-Dimer, CPK, troponin T, interleukin-6), cultures, abnormal radio imaging, test for SARS-COV 2 infection confirmation. Nasal and pharyngeal swab specimens of suspected cases were taken and maintained in viral transport medium and

confirmed by detection of COVID-19 using quantitative polymerase chain reaction (RT PCR) test in the microbiology laboratory of the hospital, one of the sentinel laboratories of the country. In some children, rapid antigen test (RAT) and COVID-19 antibody tests (immunoglobulin G to SARS-COVID-19) were performed when the tests were available and the suspicion was very high, and the RT-PCR tests were negative.

A confirmed case is defined as a patient in whom the patient has a positive test for COVID-19 infection (RTPCR, RAT or COVID antibody test).

Confirmed COVID-19 disease have been categorised as for the severity of illness according to 1 of 5 categories: asymptomatic, mild, moderate, severe, and critical disease.[4,11]

Asymptomatic: Without any clinical symptoms and signs; the chest imaging is normal, while COVID-19 test is positive.

Mild disease: Symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows congestion of the pharynx and no auscultatory abnormalities. Some cases may have no fever or have only digestive symptoms such as nausea, vomiting, poor feeding, lethargy, abdominal pain, and diarrhea. Laboratory investigations and chest imaging are normal.

Moderate disease: Fever, cough, wheeze but no obvious hypoxemia such as shortness of breath, and/or chest imaging consistent with SARS-CoV-2 pneumonia which is subclinical and no change from baseline requirements if receiving long-term respiratory support.

Severe disease: Fever, dyspnoea, may be accompanied by gastrointestinal symptoms, chest imaging consistent with SARS-CoV-2pneumonia, with new or increased supplemental oxygen requirement or central cyanosis with oxygen saturation, is <92%, and/or ventilatory support requirement.

Critical disease: Acute-respiratory distress syndrome, respiratory failure requiring mechanical ventilation, encephalopathy, shock, myocardial injury or heart failure, systemic inflammatory response syndrome, and/or multiorgan failure. Diagnosis of MISC has followed the WHO criteria.[13]

Ethical approval

For the retrospective medical record review and retrieval of patient's data, institutional review board (474(108/2020)/IEC/ABVIMS/RMLH) approval have been obtained with waiver of the patient consent form.

Statistical methods

Data of these children have been extracted from their medical records, entered in the predesigned proforma in excel sheet. Data cleaning have been performed, cross-checked, and analysed by two independent researchers involved in the study. For baseline characteristic analysis, all patients have been grouped into two non-severe and severe groups. Critical and severe cases are included in severe groups and others (asymptomatic, mild, and moderate) are considered as non-severe. Results are descriptive and presented as absolute numbers and percentages or as medians and interquartile ranges, as appropriate. Analysis was performed using excel version 16.16.21 (Microsoft).

RESULTS

Sixty-two SARS-COV 2 positive children and adolescents were included in the study. Descriptive analysis is described below.

Demographic profile of children

Children in the age group 11-18 years of age constituted the most affected population. The median age of the patients was 11 year (IQR-3-16 years), the youngest 18 days and the eldest was 18 years. There was no gender difference (31 male and 31 female). The 19% of children had a positive history of contact with close family members, while no clustering of the case was noted in the family or close vicinity. The 87.09% of children were hailing to the state with 12.9% other states. None of the children had a history of recent foreign nation travel. The median duration of hospital stay was 10 days. Co-morbidity was present in 33% (21/62). Among the comorbidities pre-existing CNS disease was common (39%) (Table 1).

Clinical features of COVID-19

Fever (>38 ^{0} C) was the most common presenting feature (74%) followed by features related to the involvement of the respiratory (58%), gastrointestinal (27%), and CNS system (14%). Cough, throat pain, breathlessness, chest pain were the most common respiratory symptoms and chest crackle, rhonchi, use of accessory muscle and low oxygen level were the most common signs noted in children presented with involvement of lower respiratory tract. Syn-pneumonic pleural effusion (n=2) and pneumothorax (n=1) were the least common presentation. Abdominal pain, diarrhea, vomiting were the common gastrointestinal manifestations of the illness. Headache followed by worsening of neurological deficits of pre-existing illness were the common neurological features. In the circulatory system sinus tachycardia and cardiogenic shock (Acute circulatory failure) were common findings and, ST-segment changes were noted in one child (Table 1).

Laboratory profile of COVID-19 children

In laboratory profile, leucocytes counts were in the normal range in a major proportion of children, leucopenia was found in only one child 1.6% (Children with severe disease had higher leukocyte counts for age with a higher neutrophil/leucocyte ratio. Anemia was a consistent finding in 60% (n=33) children which could be attributed to multiple factors. None of the children had thrombocytosis and thrombocytopenia 9% (n=5) was the finding in critically ill children.

Derangement in liver function tests and kidney function tests were noted only in children with a severe and critical illness. Hyperbilirubinemia was the finding in 5.4% (n=3) patients while SGOT and SGPT were deranged in 30.9% (n=17) and 16.3% (n=9) patients respectively. Blood urea was deranged in 45.6% of children with no derangement in creatinine.16% of children (n=10) were found to have deranged CPK-MB but none of them had troponin T positivity. It had been found that children who were found to have persistent tachycardia and circulatory failure had more derangement of CPK-MB (Table 3).

CRP was significantly raised in the severe group compared to children with non-severe disease (p=0.017) and there was no significant difference in N/L ratio, leucocyte counts, platelets between the two groups (Table 4).

In radiological imaging, 7 children (11%) did not have any radiological abnormality. These were the children who either did not have any respiratory symptoms or had mild symptoms. The 32 (50%) children had either focal consolidation of one lung lobe (<25% lung lobe involvement) or increase perihilar vascular marking. 19 (30%) children had involvement of more than one lung lobe in form of focal consolidation or lobar consolidation. Involvement of all lung fields with associated complications was found only in four children (6.4%). Among these children, 2 children had pleural effusion and bilateral pneumothorax was documented in one child. One child was found to have a miliary pattern on X-ray imaging which turn out to be ground-glass opacities with peripheral subpleural blebs formation on CT imaging (Table 3).

Outcome and intervention of COVID-19 children

Fifty percent (n=31) children had mild, 9.6% (n=6) moderate, 11.2% (n=7) severe and 22% (n=14) critical COVID-19 illness. In 6% of children, COVID positivity was an accidental finding which was done before some surgical procedure or part of contact tracing in admitted children. 14.5% (n=9) children were mechanical ventilated and 19.3% had need for vasoactive substances. 82% (n=51) of children had been discharged without any deficits and need of oxygen support at the home. Among 14% children (n=9) who succumbed to death, five had underlying comorbidities (1-TBM,1-pulmonary kochs,1-GDD with the seizure disorder as well as the 1-ACHD with CHF, 1- primary pulmonary hypertension) and two children had developed MISC with the multiorgan failure in the non-co-morbidity group. We could not find any correlation between the nutritional status and the outcome (Table 2).

Table 1: Presentation and demographic characteristics of 62 children of coronavirus disease 2019 (COVID-19), (n=62).

Characteristic	Number (%)
Age categories (Years)	
<1year	10 (16)
1-5 years	13 (20)
5-10	7 (11)
11-18	32 (51)
Age median (IQR) (months)	132 (36-192)
Sex	
Male	31 (50)
Female	31 (50)
Presentation	
Asymptomatic	4 (6)
Fever	43(74.14)
Respiratory	34(58.62)
Fever + respiratory	27(46.55)
Gastrointestinal	16(27.59)
Circulatory	10(18.1)
Neurological	14(24.14)
others	10 (17.24)
History of contact	12 (19)
Clustering of cases	0
History of travel	0
Resident within city	54 (87.09)
Resident outside the city	8 (12.9)
Nutritional status (weight/age)	
<3rd centile	17 (30.9)
3rd to 10th centile	38 (69.1)
Comorbidities (n=21)	21 (33.8)
CVS (RHD-2, ACHD-1, CCHD-1)	4 (17)
CNS (TBM-5, inflammatory granuloma-1, brain abscess-1, GBS-1, seizure disorder-1)	9 (39)
Type 1 diabetes	1 (4)
Renal (Re-curent UTI-1, UTI-1)	2 (8)
Respiratory (chronic lung disease with pulmonary hypertension-1, asthama-1)	2 (8)
Haematological (megaloblastic anaemia-2)	2 (8)
Gastrointestinal (HCV-1)	1 (4)
Septic knee arthritis	1 (4)

Table 2: Clinical course and outcomes of children with coronavirus disease 2019, (COVID-19).

Characteristics	Numbers (%)
Severity of illness	
Asymptomatic	4 (6.4)
Mild	31 (50)
Moderate	6 (9.6)
Severe	7 (11.2)
Critical	11 (22.5)
MISC	3 (4.8)
Invasive respiratory support	9 (14.5)
Vasoactive support	12 (19.3)
Length of hospital stay (Days)	18±14 with median 10
Pharmacotherapy	
Steroid (dexa-4, methylpred-3)	7 (11.2)
Azithromycin	28 (45.1)
Oseltemavir	12 (19.3)
Remdesivir	1
Ivermectin	1 (1.6)
HCQ	1 (1.6)
Blood products	
Outcome	10 (16.1)
Discharged	51 (82.25)
Died	9 (14.51) (with comordidity-5, without comorbidity-4)

Table 3: Laboratory profile of 62 of children with coronavirus disease 2019, (COVID-19).

Characteristics	Number (%)
Hb (gm/L)	33 (60%)
TLC	Mean: 10192±4219×10^3/mm^3, Range: 1700-40100×10^3/mm^3
Increases (>11×10^9/L)	9 (16.06)
Decreased (<4×10^9/L)	1 (1.6)
N/L ratio	4.3 (SD±2.9)
Thrombocytosis (>500×10^9/L)	None
Thrombocytopenia (<150×10^9/L)	5(9.1)
Average platelets count	2.8±0.96x10^5/mm^3
Total bilirubin (>1 mg/dl)	3 (5.4)
SGOT (>50 U/L)	17 (30.9)
SGPT (50U/L)	9 (16.3)
Urea (>40 mg/dl)	25 (45.4)
Creatinine (>1.2 mg/dl)	0 (0)
CPK-MB (n=10 >25 U/L)	10 (16.1%)
LDH (n=20, >400 U/L)	15 (27.2%) (689±339)
CRP (n=32, 10 mg/L)	29.68 (Mean)
Ferritin (n=12, 250 ng/dl)	6 (9.6)
D-dimer (n=7, 250 ng/dl)	2335.85±1692.56
Radio imaging (Chest x-ray-62, CT-1)	Mild-32, moderate-19, severe-4

Table 4: Laboratory profile of children (non-severe and severe) with coronavirus disease 2019 (COVID-19).

Variables	Total, (n=62)	Non-severe, (n=41)	Severe, (n=21)	Statistic test
Age (Months)	111.60±77.15	108.68±80.26	111.53±77.79	t=-0.45, p=0.65
Sex (M:F)	31/31	19/22	12/9	X^2=0.48, cv=3.84, p=0.42
Comorbidity	23/39	11/30	12/9	X^2=5.46, cv=18.30, p=0.01
Contact history, (n=49)	12/37	10/24	2/13	X^2=1.45, cv=3.84, p=0.22
TLC	10192/mm^3	9366/mm^3	12907/mm^3	T stat: 1.8321, p (T ≤t) 0.9999

Continued.

Variables	Total, (n=62)	Non-severe, (n=41)	Severe, (n=21)	Statistic test
N/L	2.78	2.83	2.73	T stat: 0.3109, p (T ≤t) 0.75
Platelet	2.78×103±0.97×103/mm^3	2.81×103/mm^3	2.77×103/mm^3	t stat: 0.1024, p (T ≤t) 0.9188
CRP, (n=32)	17.33±19.91	8.71±9.16	25.94±15.71	t=2.51, t critical=2.045, p=0.017

DISCUSSION

In our study children, 10-18 years of age constituted 50% of the affected population. This could be because of more exposure of the adolescent population to the adult population or the asymptomatic, milder nature of the disease in the younger population. There was no sex predilection of the disease which was consistent with the previous studies.[3,4] Fever (74.14%) was the most common presenting symptom followed by symptoms related to the involvement of the respiratory tract system (58.62%) (cough, sore throat, difficulty in breathing) and gastrointestinal system (27.59%) (pain abdomen, diarrhea, vomiting). These findings were consistent with the previously reported literature.[14] Latif et al did a systemic review of 2228 children including new-borns and infants and found that dry cough (91%) and fever (96%) were the most common presenting symptoms.[15]

In our study, fifty percent children had mild disease with a better prognosis and outcomes. Published literature across the globe has shown that up to 96% of children had mild to moderate disease, <6% of children manifested severe disease with the critical disease in only 1%.[16-18]

In our study, the proportion of children who had severe (11%) and critical disease (22%) was high with subsequent higher mortality (14%). Earlier pediatric studies from China had reported severe in 5.2 %, critical disease in 0.6% children with mortality extremely rare.[4] The prevalence of severe and critical disease was proportionate to younger age and with only 1.8% required intensive care and all of those had underlying diseases. In our study, 29% of children had severe and critical disease and 14% requires invasive ventilator support and vasoactive support (19%) with an overall fatality rate of 14%. Probably this could be because our institute is a tertiary level referral institute that admitted sicker children with underlying comorbidities and almost all the deaths were noted in the Critically sick children. This high mortality rate in our study is a reflection of comorbidities, late referral and poor availabilities of resources during the pandemic. In our study, only three children were noted to have features suggestive of MISC-TS. This may be due to inclusion of COVID-19 antibody positive cases with multiorgan involvement as MISC and exclusion of COVID-19 infection with positive RT-PCR, and acute or hyperacute inflammatory reaction as severe and critical COVID-19 infection.[19] These children had persistence of fever, acute gastrointestinal symptoms, rash, derangement of hepatic and cardiac functions. Laboratory parameters showed higher values of CRP, serum ferritin, derangement in coagulation function with negative culture positivity. Coronaries involvement (giant aneurism) in ECHO was seen in one child.

In our study, twenty-one (33%) children had some form of underlying comorbidities which showed worsening course with COVID-19 infection with subsequent poor outcomes in three. A study done in a pediatric intensive care setting in the USA and Canada (48 children) found that comorbidities were prevalent in more than 80% of the infants and children hospitalized with serious illness from COVID-19.[20] Hence, children have a milder disease with a good prognosis but those with underlying comorbidities related to neurological, cardiac, and lungs are observed to have poor outcome.[21]

Hematological profiles of adult COVID-19 patients have demonstrated leucopenia with associated neutrophilia, lymphopenia, eosinopenia, and thrombocytopenia. Also, higher NLR, LMR, and PLR have been associated with severe disease and used for prognostication.[22] Lymphopenia was not the finding in children as seen in the adult population. In our study majority of children had normal leukocyte counts, only 1% were found to have lymphopenia. Small proportion of severely infected children had lymphocytosis with raised neutrophil/leucocyte ratio which was not statistically significant in the severe and non-severe group. In our study, we have found that a large proportion of children have anemia 33 (60%) which was not reported in other studies. Microcytic hypochromic and megaloblastic anemia were the predominant findings in the peripheral smear. This could be because of higher prevalence of unrecognised anemia in the population. In adult studies values of CRP were synonymous with the COVID-19 disease severity. In our study, CRP values were significantly raised in the severe group compared to children with non-severe disease (p=0.017). Children with severe and critical illness had a multiorgan failure with derangement in organ-specific enzymes.[23,24]

In our study, 58% of children had respiratory system involvement while radiological abnormalities were present in 88% of children. Preponderance of radiological abnormalities were also observed in other studies. Patchy lesions in 21.0% and ground-glass opacities in 32.9% of patients were depicted in lung radiograph and computed tomography.[12] A study involving 171 children done by Liu et al reported 15.8% of children did not have symptoms of infections or radiological features of pneumonia. A clinical diagnosis of pneumonia was made in 64.9% of the children. Only a small subset of children had radiological abnormality including 33% had ground-

glass opacity, 18.7% and 12.3% patients had local or bilateral patchy shadowing on CT imaging.[25]

Our study has some limitations. COVID-19 children with positive RT PCR were managed in SARI and COVID ward. Children with MISC diagnosis and COVID antibody positivity were managed in Pediatric Intensive Care.

CONCLUSIONS

Even though it seems the morbidity and mortality associated with SARS-CoV-2 infection in pediatric population miniscule, the infection definitely causes significant illness in the subgroup who requires hospitalisation and carries significant mortality with those with comorbidity. Our data lends credence to the fact that children and adolescents can have fatal outcomes if appropriate rescue measures are not taken in time. The inflammation associated with the active infection and post infection manifesting as MISC contributes to the morbidity and mortality associated with the COVID-19 disease. Rise in CRP can be used as a biochemical marker for predicting severity of COVID-19 illness. The hyperacute inflammation called cytokine storm in both active and post infection state may need to be managed in pediatric intensive care facilities with monitoring facilities and appropriate organ support with antivirals (Remdesvir), anti-inflammatory steroids (Dexamethasone/ methyl prednisolone), intravenous immunoglobulin and immunosuppressives (Toclizumab) for an optimal outcome in a subgroup of high-risk pediatric population.

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