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Original Research Article

Clinical characteristics and predictive mortality risk factors in hospitalised children with COVID-19 illness during the first and second wave: single centre experiences from a tertiary paediatric hospital in Mumbai

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) pandemic has affected both adults and children alike. It presented in cluster of cases in short period of time all across the world. In India, there were two such clusters called as first and second wave. World over mortality was more in adults than in children. But, few children also had severe disease during these waves. Also, some presented with inflammatory state secondary to COVID-19 infection which is called as Multisystem Inflammatory syndrome in children (MIS-C). As major population affected with severe disease were older people this disease in initial phases was most studied in this population. It is thus necessary to observe and analyse disease manifestations, pattern and risk factors in children and also contrast these variables between the two waves. The objectives of the study was to compare and contrast clinico-demographic parameters and outcome predictors in children admitted with COVID-19 during the first and second waves.
Methods: This is a retrospective analytical study comparing aforementioned parameters of children (with and without co-morbidity) admitted with COVID-19 infection between the two waves of pandemic in a tertiary care public pediatric hospital in Western Maharashtra.
Results: First wave had 176 cases admitted over six months while the second wave had 185 cases over only three months. While proportion of cases with pneumonia requiring ICU stay was significantly higher in wave 2, those with MIS-C requiring inotropes was higher in wave 1. There was no difference in other clinico-demographic parameters of these cases irrespective of co-morbidity. Pneumonia, severe disease, hypoxia, need for inotropes or ICU care predicted poor outcome in both the waves.
Conclusions: Though the pattern of presentation was different, the clinico-demographic variables and predictors of mortality were comparable between the two waves.

Keywords: COVID -19, Co-morbidities, Mortality, First wave, Second wave, Severity

INTRODUCTION

Coronavirus disease 2019 (COVID-19), is a global pandemic, and has gripped the entire world, paralysing the human race in its entirety. India has experienced two waves of the corona virus disease (COVID-19) pandemic since the emergence of the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) in March 2020. Interestingly, total numbers of symptomatic pediatric cases lag behind adult cases suggesting a protective effect

of age according to international data.[1,2] Recent Chinese hospital-based data showed that the proportion of pediatric cases had increased from 4.2 per cent in the first wave to 5.8 per cent in the second.[3,4] Mumbai in Maharashtra continued to be an epicentre. Mumbai has 38, 45,481 under 18 population that could be largely asymptomatic or unexposed. We present this retrospective analytical study of children with COVID-19 positivity in the first and second waves at our centre, which is one of largest tertiary multispecialty referral children hospital in Western India.

With this study we aim to compare and contrast demographic, clinical and outcome predictors amongst the children affected with COVID-19 disease in the two waves. This study is intended to observe if there were any similarities or differences in pattern of presentation and predictors of mortality between the two waves. Thus, it will help us prepare better for any upcoming resurgence of the disease. To our knowledge, no studies have compared pediatric data between the two waves from India except for a few adult studies.[5-7]

METHODS

This is a retrospective analytical study conducted at Bai Jerbai Wadia Hospital for Children, Mumbai, India. Institutional ethics committee approval was sought prior to commencement of the study. Review of medical records of all COVID-19 positive children, aged <18 years admitted between March 2020 and May 2021 to the COVID care ward was done.

This study included children admitted with SARS CoV-2 during two wave periods viz. between March to October 2020 (Wave 1) and March 2021 to May 2021 (Wave 2) (Figure 1). Those children admitted outside the mentioned time frame were excluded from the study. Also, cases with MIS-C without concurrent COVID-19 infection were excluded. Thus, the total number of cases included were 361 of which 176 were during wave 1 and remaining 185 were during wave 2. The epidemiological characteristics and outcome of children admitted early between March 2020 and August 2020 was published previously.[8] These children were classified into those with co-morbidities (Group I) and those without (Group II). Co-morbidities consisted of hemato-oncological conditions, tuberculosis, nephrotic spectrum, endocrine, gastroenterohepatic, cardiac, surgical, neurological, and neonatal disorders.

For the study, cases were classified as "severe" on fulfillment of one or more of the following criteria: respiratory distress with the need for invasive or non-invasive mechanical ventilation, oxygen saturation (SpO2) of <90 % at room air, acute kidney injury, fluid refractory shock and encephalopathy or status epilepticus. Moderate cases were classified as those with respiratory distress with oxygen saturation between 90-94% on room air and requiring supplemental oxygen. Standard definitions for Multisystem Inflammatory syndrome in children (MIS-C) and Kawasaki Disease were adhered to.[9]

Study aimed at comparing parameters as represented in Table 1 between the cases during the two waves. Sub-analysis was done between Group I and Group II of the two waves separately. Parameters as represented in Table 2 compared the predictors of mortality. Also, assessment of predictors of mortality of all the deaths was done using regression analysis.

Statistical analysis

Data was analyzed using statistical software STATA, version 10.1 (Stata Corp.). For fulfilling the objectives of the paper bivariate and multivariate analysis was carried out. Pearson Chi-square test was used for assessing the association between independent and dependent variables. Mean was calculated for continuous variable and if the data was not normally distributed median was calculated for the same. Binary logistic regression model was applied to identify predictors of mortality accounting for the role of various factors, wherein adjusted odds ratio (OR) and 90% Confidence Intervals (CI) were estimated. A $p<0.1$ was considered statistically significant.

RESULTS

Of 10,890 children requiring admission, 4,895children were screened at in house facility with RT-PCR test. During the first wave the positivity rate was 8.8% (176/1997) while in the second wave it was 15% (185/1231) (Figure 1). The profiles of 361 out of 384 children who were admitted during the two waves were analyzed. Figure 1 shows distribution of cases and deaths with respect to the mentioned time frame. Wave 1 happened over six months while wave 2 occurred only over 3 months.

The median age at presentation was 2 years (5.3) versus 3 years (7.6) in first and second wave respectively. Nine children had MIS-C during the first wave versus three in the second wave. MIS-C in COVID 19 negative children were not included in this study and have been published earlier.[10] During wave 1, 22 (12.5%) had pneumonia as compared to 32 (17.4%) in wave 2. Thus, there were statistically more cases with MIS-C in wave 1 and those with pneumonia in wave 2 ($p=0.09$). The need for intensive care was 17.6% versus 25.9% in first and second waves respectively which was statistically significant ($p=0.056$). Overall, inotropes was required in 13.6% (14/176) in wave 1 versus 5.4 % (10/185) in wave 2 which was statistically significant ($p=0.016$). 17% cases required hospital stay for >9 days during wave 1 as compared to 15% in wave 2 which was statistically significant ($p=0.01$). There was no discernible difference between age distribution, symptoms at presentation, disease severity and chest radiograph findings between the two waves. Most cases were either asymptomatic or

had a mild disease and had a normal chest radiograph during both the waves (Table 1).

Table 1: Comparison of Clinical, demographic and disease outcome parameters between wave 1 and wave 2.

Parameters	All Children n (% of total)	Wave 1 n (% of total)	Wave 2 n (% of total)	P value
Gender - Male	213 (59.0)	101 (57.4)	112 (60.5)	0.542
Age				
<1 year	134 (37.1)	73 (41.5)	61 (33.0)	0.252
>1-5 years	102 (28.3)	49 (27.8)	53 (28.6)	
>5-10 years	85 (23.5)	39 (22.2)	46 (24.9)	
>10 years	40 (11.1)	15 (8.5)	25 (13.5)	
Symptoms at presentation				
Asymptomatic	64 (17.7)	38 (21.6)	26 (14.1)	0.298
Fever	76 (21.1)	35 (19.9)	41 (22.2)	
Upper respiratory	36 (10.0)	13 (7.4)	23 (12.4)	
Lower repiratory	54 (15.0)	29 (16.5)	25 (13.5)	
Gastrointestinal	62 (17.2)	28 (15.9)	34 (18.4)	
Seizures	44 (12.2)	23 (13.1)	21 (11.4)	
Others	25 (6.9)	10 (5.7)	15 (8.1)	
Abnormal chest radiograph	70 (19.4)	33 (18.8)	37 (20.0)	0.764
Disease severity				
Mild	226 (62.6)	104 (59.1)	122 (65.9)	0.300
Moderate	81 (22.4)	41 (23.3)	40 (21.6)	
Severe	54 (15.0)	31 (17.6)	23 (12.4)	
Need for intensive care	79 (21.9)	31 (17.6)	48 (25.9)	0.056
Respiratory support				
None	266 (73.7)	126 (71.6)	140 (75.7)	0.678
Supplemental oxygen	57 (15.8)	30 (17.0)	27 (14.6)	
Non-invasive / invasive ventilation	38 (10.5)	20 (11.4)	18 (9.7)	
Vasoactive drugs used	24 (8.3)	14 (13.6)	10 (5.4)	0.016
Outcome				
Discharge	339 (93.9)	166 (94.3)	173 (93.5)	0.226
Death	19 (5.3)	10 (5.7)	9 (4.9)	
Discharge against medical advise	3 (0.8)	0 (0.0)	3 (1.6)	
MISC / Pneumonia				
None	294 (81.7)	145 (82.4)	149 (81.0)	0.094
Pneumonia	54 (15.0)	22 (12.5)	32 (17.4)	
MIS-C	12 (3.3)	9 (5.1)	3 (1.6)	
Length of stay				
Hospital stay ≤9 d	316 (87.5)	146 (83.0)	170 (91.9)	0.01
Hospital stay >9 d	45 (12.5)	30 (17.0)	15 (8.1)	

Table 2: Distribution of death according to baseline characteristics and clinical profile in wave 1 and wave 2.

Parameters	Wave 1 death	P value	Wave 2 death	P value
Gender				
Male	8 (7.9)	0.136	4 (3.6)	0.588
Female	2 (2.7)	0.136	5 (6.8)	
Age				
< 1 year	5 (6.8)	0.655	3 (4.9)	0.795
>1-5 years	2 (4.1)		2 (3.8)	
>5-10 years	3 (7.7)		2 (4.3)	
>10 years	0 (0.0		2 (8.0)	

Continued.

Parameters	Wave 1 death	P value	Wave 2 death	P value
Symptoms at presentation				
Asymptomatic	0 (0.0)	0.008	0 (0.0)	0.298
Fever	2 (5.7)		2 (4.9)	
Upper respiratory	0 (0.0)		2 (8.7)	
Lower respiratory	6 (20.7)		3 (12.0)	
Gastrointestinal	2 (7.1)		12 (5.9)	
Seizures	0 (0.0)		0 (0.0)	
Others	0 (0.0)		0 (0.0	
Chest radiograph				
Normal	4 (2.8)	0.001	2 (1.4)	0.000
Abnormal	6 (18.2)		7 (18.9)	
Disease severity				
Mild	1 (1.0)	0.000	0 (0.0)	0.000
Moderate	2 (4.9)		1 (2.4)	
Severe	7 (22.6)		8 (44.4)	
Need for intensive care				
Yes	7 (22.6)	0.000	9 (18.8)	0.000
No	3 (2.1)		0 (0.0)	
Respiratory support				
None	0 (0.0)	0.000	0 (0.0)	0.000
Supplemental oxygen	3 (10.0)		2 (7.4)	
Non-invasive/ invasive ventilation	7 (35.0)		7 (38.9)	
Vasoactive drugs used				
Yes	6 (42.9)	0.000	4 (40.0)	0.000
No	4 (4.5)		5 (2.9)	
Co-morbidities				
Yes	6 (7.6)	0.322	5 (6.4)	0.475
No	4 (4.1)		4 (3.7)	
MISC/ Pneumonia				
None	7 (4.8)	0.189	2 (1.3)	0.000
Pneumonia	3 (13.6)		7 (21.9)	
MIS-C	0 (0.0)		0 (0.0)	
Length of stay				
Hospital stay ≤9 d	10 (6.8)	0.127	9 (5.3)	0.568
Hospital stay >9 d	0 (0.0)		0 (0.0)	

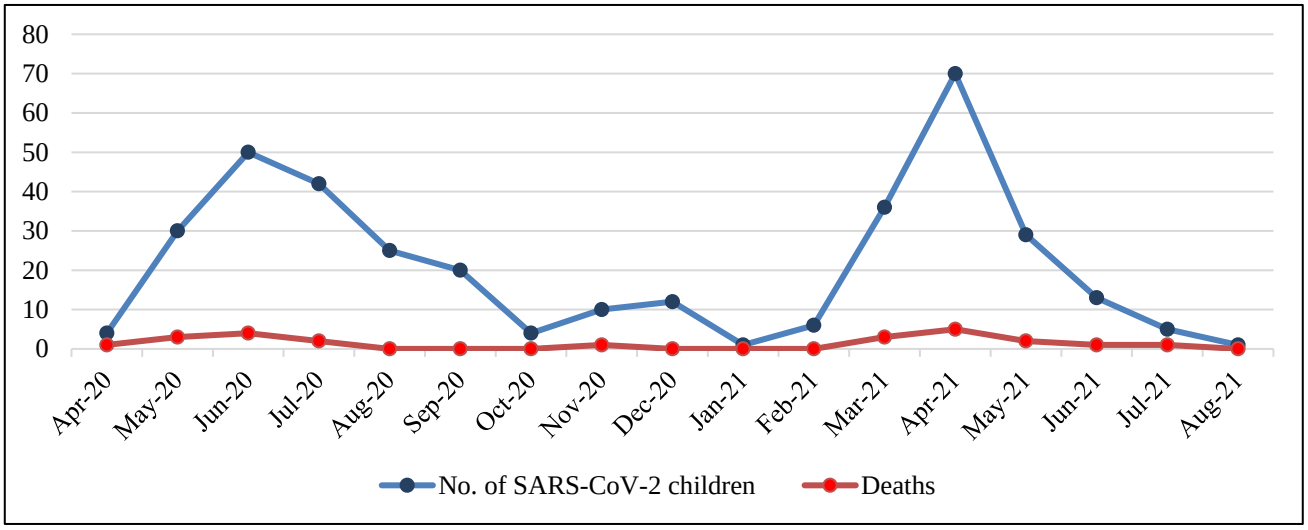

Figure 1: Distribution of cases and deaths during the defined wave 1 and wave 2.

In children with severe disease the mean SpO2 on admission in wave 1 was statistically less than in wave 2 (90% versus 93%) (p=0.002). Similarly, the mean neutrophil: lymphocyte ratio (N/L) was statistically more in cases during wave 2 (6.36) compared to wave 1 (5.94).

On sub-analysis between Group 1 and Group 2 the only statistical difference found was for higher use of inotropes (p=0.01) and hospital stay of more than 9 days (p=0.008) during wave 1 in Group 2. Similarly, cases with pneumonia (p=0.03) and need for PICU care was higher during wave 2 in Group 1 (p=0.013).

The mortality rate in admitted patients was 5.7% (10/176) versus 4.9% (9/185) in the two waves respectively. Overall higher mortality was observed in children with co-morbidity with 60% (6/10) and 55.6% (5/9) in both the waves respectively. In the bivariate analysis, presence of lower respiratory tract infection, abnormal chest radiograph, need for respiratory support, inotropes, intensive care and severe disease were associated with mortality in both the waves (Table 2). On regression analysis, severe disease, SpO2 of <94%, need for respiratory support and inotropes were significantly associated with mortality.

DISCUSSION

Some viral illnesses have difference in patterns of presentations and demographic characteristics in different waves of disease example- dengue. This study aimed at ascertaining similar differences with COVID-19 infection in children between the two waves.

A total of 17.7% (64/361) had asymptomatic infection with 21.6% and 14.1% in first and second wave respectively. Fever, respiratory and gastrointestinal symptoms were most common symptoms in both the waves. None of children above 8 years of age complained of anosmia which is a common adult symptom.

In our study, 15% had severe illness and the difference was not significant between the two waves. Results of a population-based study from China by Dong et al suggested presence of severe disease in 6% of pediatric population. 4 The difference can be explained on the basis that our study was carried out at a referral center.

We found 157/361 (43.4%) children had comorbid conditions and the proportion of these cases was not different between the two waves. The most common co-morbidities were hemato-oncological disorders, surgical disorders, gastrointestinal disorders in that order. In the study by Kapoor et al 62 (51.7%) children had co-morbidities, wherein, tuberculosis (32.3%) followed by other infections (27.4%) and hematological (19.4%) conditions were most common.[11] Tsankov et al, in their meta-analysis reported the most common co-morbidity was obesity. Significantly higher number of children without comorbidity required inotropes in wave 1 than in wave 2 as compared to those with co-morbidity.[12] This is in contrast to study by Kapoor D et al who found no association with any of outcome variables between co-morbid children and non-comorbid children.[11] This difference is attributable to presence of more MIS-C cases with shock in wave 1 in Group II.

Proportion of severe cases was comparable between the two waves. Thus, neither SpO2 on admission nor N/L ratio predicts the severity outcome as significantly more children in wave 2 had higher mean oxygen saturation and mean N/L ratio than in wave 1. This is in contradiction to the findings that higher N/L ratio is associated with severe disease.[13]

The overall mortality rate was 5.3%. It is higher than in the meta-analysis by Yadav et al, presumably due to referral bias as our centre is the largest referral multispecialty hospital.[14]

In the bivariate analysis, presence of lower respiratory tract infection, abnormal chest radiograph, need for respiratory support, vasoactive drugs, intensive care and severe disease were associated with mortality in both the waves. On regression analysis, severe disease, oxygen saturation of <94%, need for respiratory support and inotropes were significantly associated with mortality. Cases needing inotropes were at 4.3 times higher odds of mortality. Mortality in second wave was statistically significant in those with pneumonia.

Strengths of the study are that it is a single centre experience of a relatively large cohort and compares both the waves. This will help us to predict that third wave, if it comes, may not be very different in presentations and severity.

Our study had limitations of being retrospective and no follow-up. Despite these shortcomings, this study provides preliminary data of the spectrum, presentations and outcomes of children, which was not greatly different in two waves that have hit the city and comparable even if children had underlying co-morbidity. There may be referral bias and might underestimate the disease as mild and moderate disease are managed at primary hospital and only severe get referred to higher centre.

In conclusion, this study highlights that clustering of cases in children follows same graph as that in adults. Like in adults most children have asymptomatic or mild symptomatic disease. Those children with underlying medical/surgical disorders are at higher risk of severe disease and death. There was a change in pattern of presentation with regards to severe disease between the two waves; second wave had more COVID-19 pneumonia though this did not affect the outcome as mortality was comparable between the two waves. Presence of lower respiratory tract infection, abnormal chest radiograph, need for respiratory support, inotropes, intensive care and severe disease were associated with

mortality in both the waves. Thus, this study would be helpful in triaging and early intervention of those cases who are at higher risk of severe disease or death during the local upsurge of the pandemic.

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