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Original Research Article

Predictors of invasive mechanical ventilation in children with severe COVID-19

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ABSTRACT

Background: To compare the demographic characteristics, clinical symptoms, laboratory findings, and comorbidities of hospitalized children with the Coronavirus disease (COVID-19) who required invasive mechanical ventilation (IMV) and analyse them to find out potential predictors for requirement of mechanical ventilation.
Methods: Study design was of single centre, retrospective record review. Settings were tertiary care hospital in New Delhi, India, between April, 2020 to October, 2020
Results: 100-laboratory confirmed COVID-19 cases were admitted during the study period. Thirty-five patients required IMV. Median age of ventilated patients was 65 (10.5, 126) months and median weight was 15 (8.5, 23.3) kg. Forty-three percent (43%) of patients were underweight (p=0.46) while 40% had chronic co-morbidity (p=0.015). Gastrointestinal symptoms (p<0.05), altered sensorium at presentation (p<0.001) and hypoxia at admission (p<0.00) were significantly greater in those who required ventilation. A statistically significant difference was also noted in inflammatory markers between ventilated and non-ventilated patients. Acute kidney injury (p=0.003) and transaminitis (p=0.05) at admission were 26 and 32% respectively in ventilated patients. The most common indicators for ventilation need were primary respiratory disease (35%) followed by shock (31%) and low Glasgow coma scale (23%). Nearly 70% of these were intubated within 48 hours of hospital admission. Multivariate analysis highlighted that presence of low SpO_2 at admission (adjusted OR, 6.9; 95% CI, 1.3-36.6) was significantly associated with need of IMV.
Conclusions: Study highlights important characteristics of paediatric population from developing country with COVID-19 who required IMV. Presence of low oxygen saturation at admission significantly associated with need of IMV.

Keywords: COVID-19, SARS-CoV-2, IMV, Children, Hypoxemia

INTRODUCTION

On March 11th2020, COVID-19, the novel coronavirus was declared as a pandemic by the world health organization. More than 200 countries witnessed its rapid and dramatic spread.[1] As of January, 2023 there are more than 44 Million confirmed cases of COVID-19 with 0.53 Million deaths including children in India.[2] While the virus affected people of all age groups and demographics, the data on children with severe COVID-19 infection from developing countries is still sparse.[3-6] Epidemiological studies suggest that infants and children infrequently experience severe disease with hospitalization rates of 0.6-20% and mortality ranging from 0-4% which is significantly lower than that in adults.[7-10] While the existing pool of knowledge about severe paediatric COVID-19 is increasing, studies exploring predictors and indications for the use of IMV in

children with COVID-19 are scarcer.[8,10-13] COVID-19 has already exhausted the healthcare resources in the previous waves. Now with the resurgence of newer variants of coronavirus and increasing number of COVID-19 cases across the globe, we will face unique challenges not only in children with severe and critical COVID-19 disease but also in those critically sick children who have co-infections and other chronic comorbidities. In these cases, it will be imperative to determine the timely requirement of ventilation for planning and allocation of the limited resources to improve outcome. COVID-19 is still a global emergency with the potential to crash our existing healthcare system so its urgently needed to identify the potential risk factors for requirement for ventilation in children with severe disease. The purpose of this study, therefore, is to elucidate the factors which can predict the need for requirement of IMV by analysing the clinical and laboratory parameters along with the impact of the presence of co-morbidities, severity of disease, duration of ventilation, therapeutic interventions and resultant short-term outcome of patients who required mechanical ventilation. The outcomes of this study will thereby inform and supplement the existing knowledge and best practices-across the world-in our fight against the coronavirus; especially where children are concerned and data on severe COVID-19 is scarce.

METHODS

We conducted a retrospective medical record review of pediatric patients admitted with laboratory confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during first COVID wave from 16th April 2020 to 30th October 2020 in Kalawati Saran Children's hospital COVID PICU, New Delhi, India. All consecutive patients with COVID-19 infection and requiring hospital admission were included in the study. None were excluded. Data was collected in a pre-designed Performa and included demographic details, mode of presentation, presence of co-morbidities, laboratory parameters, and therapeutic interventions including type of respiratory support, clinical course, and eventual outcomes in terms of discharge or in-hospital mortality. Patients who required IMV were compared with those who did not required ventilation.

A confirmed case was defined where SARS-CoV2 was detected by a nasopharyngeal sample using real-time reverse transcriptase polymerase chain reaction (RT-PCR) or cartridge based nucleic acid amplification test testing. Testing was done as per the prevailing government of India guidelines issued at that time.[14] Duration of symptom onset was defined as the day when first symptom or sign occurred till the time of hospital visit. Oxygen saturation reading less than 90% constituted severe hypoxia and was categorized as severe disease. The patients were categorized as mild, moderate, and severe.[4] Multisystem inflammatory syndrome (MIS-C) related to COVID-19 was defined as per the WHO definition.[15] Acute respiratory distress syndrome (ARDS) was defined using recommendations from the pediatric acute lung injury consensus conference group.[16]

The study was reviewed and approved by the institutional ethical committee (IEC) with a waiver for consent on data collection (LHMC/IEC/2020/97).

Statistical analysis

Clinical data is presented as counts and percentages, means and standard deviations (SDs), and medians with inter quartile ranges (IQRs). Comparison of means and medians has been performed using the 2-sample student T test and the Wilcoxon Rank Sum test, respectively. Categorical data are compared using Chi square or Fishers exact test. All tests were 2-tailed with the threshold level of significance at $p<0.05$. Statistical analysis has been performed using STATA 14.2. We employed both univariate and multivariate logistic regression methods to explore the impact (odds) of the risk factors associated with requirement of ventilation.

RESULTS

Demographic and epidemiological features

A total of 100 SARS-CoV-2 positive pediatric patients were included in study. Out of these fifty-four patients needed some form of respiratory support, including 35 patients who finally required IMV during their course of illness. Baseline epidemiological and demographic characteristics of ventilated and non-ventilated patients are presented in Table 1. Out of those who required IMV, 19 (54%) were male. The median age was 65 (10.5, 126) months and median weight 15 (8.5, 23.3) kg. Fifteen (43%) patients were underweight out of which 23% were severe underweight. Among patients who required ventilation 14 had underlying chronic comorbidity for which they were receiving some immunosuppressive therapy (2-Aplastic anaemia, 7-Haematological malignancy, 1-nephrotic syndrome and 2-connective tissue diseases-systemic upus Erythematosus and systemic onset juvenile idiopathic arthritis) and two had co-infection (one each of tuberculosis and disseminated *Staphylococcal* sepsis). Only 3 of these patients had a positive history of contact with COVID-19 positive case. On univariate analysis presence of chronic co-morbidities was significantly higher in those who required IMV as compared to those who did not require IMV ($p=0.013$).

Clinical presentation

Gastrointestinal symptoms ($p<0.05$), altered sensorium at presentation ($p<0.01$), presence of hypoxia at admission ($p<0.01$) and high PRISM III ($p=0.01$) score were significantly greater in those who needed IMV (Table 2). The difference in median time between onset of symptom to hospitalization was 2 days lesser in patients who required IMV suggesting rapid progression of disease.

Presence of 2/more organ involvement at presentation was associated with increased chances of IMV. Cardiovascular system involvement at admission was present in 30 (86%) children who required IMV. Seven children were diagnosed with MIS-C in ventilated group and 5 in non-ventilated group (p<0.014). Majority of children, 25 (70%) required IMV within 48 hours of admission; out of these 12 children required IMV at admission only.

Laboratory and radiological findings

We observed significant difference in laboratory findings between the two groups (Table 3). Values of C-reactive protein were significantly higher in ventilated group as compared to non-ventilated group (p<0.05). A statistically significant difference was also noted in inflammatory markers– high fibrinogen, d-dimer, creatine kinase MB and ferritin values between ventilated and non-ventilated patients. Acute kidney injury (AKI) (p=0.01) and increased transaminases (p=0.01) at admission was seen in nine (26%) and eleven (32%) patients respectively in the ventilated group. Abnormal chest radiograph was seen in eighteen children in the ventilated group, out of which four had unilateral lung opacities and ten showed bilateral non homogeneous lung opacities. Two patients had pleural effusion.

Table 1: Comparison of demographic profile of COVID-19 amongst ventilated as well as non-ventilated groups, (n=100).

Characteristics	N	Ventilated, (n=35) (%)	Non-ventilated, (n=65) (%)	P value
Age (Months)*	62.5 (16.75-120)	65 (10.5-126)	60 (24-120)	0.46
Age group # (Years)				
< 1	22	9 (26)	13 (20)	0.43
1-5	28	8 (23)	20 (31)	0.40
5-10	27	9 (26)	18 (28)	0.39
>10	23	9 (26)	14 (22)	0.27
Sex, male #	59	19 (54)	40 (62)	0.48
Weight*	15 (8.5-23.3)	151 (6.7-28.3)	16 (9-22)	0.89
Underweight	20	7 (20)	13 (20)	0.463
Severe underweight	18	8 (23)	10 (15.3)	0.35
Contact with severe COVID-19 positive case	7	3 (8)	4 (6)	0.65
Co-infections	34	2 (5)	32 (49)	0.00
Chronic comorbidity	25	14 (40)	11 (17)	0.015

*Expressed as median (IQR), # expressed as percentage.

Table 2: Comparison of clinical characteristics amongst ventilated and non-ventilated groups, (n=100).

Characteristics	N	Ventilated, (n=35) (%)	Non ventilated, (n=65) (%)	P value
Clinical features				
Fever	80	26 (74)	54 (83)	0.29
Cough	35	9 (26)	26 (40)	0.15
Fast breathing	37	15 (43)	22 (34)	0.37
Myalgia	11	4 (11)	7 (11)	0.92
Headache	11	4 (11)	7 (11)	0.92
Vomiting	34	16 (46)	18 (28)	0.07
Abdominal pain	27	15 (43)	12 (18)	0.01
Diarrhoea	11	7 (20)	4 (16)	0.04
Altered sensorium	13	10 (29)	3 (5)	0.01
SpO_2 at admission (<94%)	45	26 (74)	19 (29)	0.00
Severe hypoxia (<90%)	19	14 (40)	5 (8)	0.00
Median time from onset of symptoms to hospital visit	4 (2-7)	3 (2-7)	5 (2-9)	0.38
Severity of illness				
Mild disease	29	0	29 (45)	0.00
Moderate disease	27	4 (12)	23 (35)	0.004
Severe disease	44	31 (88)	13 (20)	0.00
Complications				

Continued.

Characteristics	N	Ventilated, (n=35) (%)	Non ventilated, (n=65) (%)	P value
Shock	35	30 (86)	5 (8)	0.00
Pneumonia	46	20 (57)	26 (40)	0.10
Encephalitis	15	12 (34)	3 (5)	0.00
Myocarditis	9	8 (23)	1 (2)	0.001
AKI	12	9 (26)	3 (5)	0.003
ARDS	10	10 (29)	0	0.00
MIS-C	10	7 (20)	3 (8)	0.014
Respiratory support				
None	46	0	46 (71)	0.00
Oxygen only	54	35 (100)	19 (29)	0.00
Non-invasive ventilation (NIV)*	11	2 (6)	9 (14)	0.32
Mechanical ventilation	35	35 (100)	0	0.00
Vasoactive support/inotrope	32	28 (80)	4 (6)	0.00
PRISM III score	8 (7-15)	13 (9-18)	9 (6-10)	0.01
Length of hospital stay (days)	7 (4-12.25)	8 (4-12)	5 (2-15)	0.17

AKI-Aacute kidney injury, ARDS-Acute respiratory distress syndrome, MIS-C-Multisystem inflammatory syndrome, NIV-CPAP-Continuous positive airway pressure and HFNC-High flow nasal cannula, PRISM-Pediatric risk of mortality score.

Table 3: Laboratory parameters in ventilated and non-ventilated groups, (n=100).

Characteristics	N	Ventilated, (n=35) (%)	Non ventilated, (n=65) (%)	P value
Hemoglobin (g/dl*)	9 (7.6-11.4)	9 (7.45-11.6)	9.1 (7.6-10.9)	0.739
Total leucocyte count*, (per mm^3)	11300 (77500-18550)	14500 (9450-26650)	10100 (6475-16975)	0.02
Absolute lymphocyte count,* (per mm^3) (89)	3240 (1598-5838)	3726 (1767-7353)	3004 (1487-4878)	0.28
Neutrophil to lymphocyte ratio* (89)	1.83 (0.7-4.1)	2.41 (1.14-4.6)	1.6 (0.7-3.5)	0.27
Platelets*, (per mm^3)	2.2 (0.8-4.1)	1.66 (0.8-3.7)	2.46 (1-4.2)	0.32
CRP*, (mg/L)	41.5 (5-145)	111.5 (37.6-214)	23 (4-101)	0.0006
Troponin T positive # (%)	7 (18) (39)	6 (9) (67)	1 (9) (11)	0.016
CPK-MB * (29)	69 (30-249)	116.5 (49.3-604.7)	42 (24-120)	0.023
Raised CPK MB# (>25 IU/L)	22	15	7	0.013
INR * (32)	1.3 (1.17-1.6)	1.55 (1.2-1.6)	1.2 (0.9-1.3)	0.008
Raised D dimer # (>500 ng/ml) (%)	26 (33)	17 (18) (74)	9 (15) (60)	0.016
Low fibrinogen # (<250 mg/dl) (%)	6 (14) (43)	5 (8) (63)	1 (6) (17)	0.086
Ferritin*, (ng/ml) (13)	579 (335-1128)	903 (576-1213)	315 (236.75-862.25)	0.11
High ferritin# (>500 mg/dl) (%)	7 (13) (54)	5 (7) (71)	2 (6) (33)	0.017
High triglycerides (>150 mg/dl) (%)	13 (17) (76)	6 (8) (75)	7 (9) (78)	0.893
Serum creatinine* (mg/dl)	0.33 (0.23-0.60)	0.50 (0.29-0.98)	0.30 (0.23-0.44)	0.008
AST* IU/L (95)	47 (30-94)	68 (32-244)	45 (30-57)	0.05
ALT* IU/L (95)	28 (19.3-58.9)	40.7 (20-115)	26 (19-46)	0.07
Hypo-albuminemia # (<2.5 g/dl) (%)	20 (64) (31)	10 (24) (42)	10 (40) (25)	0.164
Abnormal chest x-ray # (66) (%)	40 (66)	18 (35) (51)	22 (31) (33.8)	0.239

In first column ( ) denotes total number sampled, * median (IQR), # frequency (percentage), AST-aspartate aminotransferase, CRP-C reactive protein, CPK-Creatinekinase ALT-Alanine aminotransferase, INR-International normalized ratio.

Table 4: Details of IMV in hospitalized children with COVID-19, (n=35).

Attributes	N (%)
Indication for ventilation	
Primary respiratory disease	12 (35)
Shock	11 (31)
Poor GCS ^	8 (23)
Time of initiation of respiratory support	

Continued.

Attributes	N (%)
At admission	12 (34)
Initial 48 hours of admission	15 (43)
After 48 hours of admission	8 (23)
Duration of respiratory support (Mean days)	4.7±7.4
Pre-existing lung disease	
Tuberculosis	3
Pleural effusion	2
Congenital cystic adenomatoid malformation	1
Abnormal chest X- ray at admission	18 (51)
Outcome	
Death	8 (23)
Discharge	27 (77)

^ Poor GCS defined as GCS < 8.

Table 5: Unadjusted and adjusted odds ratios for IMV.

Variables	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Low SpO_2 at admission	7 (2.76-17.7)	0.00	6.88 (1.3-36.6)	0.02
Chronic co-morbidity present	3.273 (1.2-8.3)	0.01	0.36 (0.13-1.05)	0.06
AKI	7.15 (1.8-28.6)	0.00	2.7 (0.22-32.8)	0.43
Thrombocytopenia	2.4 (1.0-5.67)	0.04	1 (0.12-8.6)	0.97
MIS-C	5.1 (1.24-21.47)	0.00	1.9 (0.19-19.6)	0.57
High CRP	5.1 (1.63-16.4)	0.00	3.2 (0.62-16.4)	0.16

AKI-Acute kidney injury, MIS-C-Multisystem inflammatory syndrome, CRP-C reactive protein.

Mechanical ventilation and clinical outcomes

Out of the 35 children who required IMV, 31(88%) were admitted with severe disease. The most common indication was respiratory illness in 12 (35%) followed by shock in 11 (31%) and low Glasgow coma scale (GCS) in remaining 8 (23%). Nearly 25 patients (71%) were intubated within 48hrs of hospital admission and their mean duration of ventilation was 4.7±7.4 day. One patient developed pneumothorax at 48 hours of admission. Out of 35 ventilated patients only 8 were successfully weaned and discharged (Table 4). Median duration of hospital stay was 8 days (4-12 days) in ventilated and 5 days (2-15 days) in non-ventilated patients (Table 2). When we compared the age wise outcome of patients who required IMV on basis of presence and absence of co-morbidities, we observed that subgroup of ventilated patients with co-morbidities were older (>10 years); 2 out of these had acute underlying co-infection and 7 were immunosuppressed. Out of the total nine children aged more than 10 years, eight developed multiple organ dysfunction syndrome (MODS), seven had features of acute respiratory distress syndrome (ARDS) and only two were discharged. On other hand there were ten infants who required IMV without an underlying co-morbidity; five required continuous positive airway pressure (CPAP) or heated humidified high flow nasal cannula (HHHFNC) support but later because of worsening hypoxemia and shock, needed IMV.

Multivariate analysis showed that presence of low SpO_2 at admission (adjusted OR, 6.9; 95% CI, 1.3-36.6) was significantly associated with need of IMV (Table 5).

DISCUSSION

In our cohort of 100 hospitalized COVID-19 patients, 44%children were admitted with severe disease whereas in previous studies the incidence of severe COVID -19 in children is documented to be low and ranged from 1.7-20%.[10,17-20] Though information on paediatric COVID-19 is increasing, very few studies have described the characteristics and outcome of patients who required IMV.[10,21] A recent meta-analysis on clinical features and outcome of SARS-CoV-2 infection in children showed that only 2.1% of hospitalized COVID-19 patients required intensive care and out of them only 0.7% required IMV.[7] Similarly in a study from North India which included forty children suffering from multisystem inflammatory syndrome in children (MIS-C), the highest level of respiratory support received were nasal prong oxygen (40%), non-invasive ventilation (22.5%), invasive ventilation (22.5%), and HHHFNC (2.5%).[20] In another multicentric study, which enrolled 402 children, majority had mild disease, and about 10% had moderate to severe disease. The respiratory support included oxygen therapy in 11 (8.4%), NIV in 2 (2.9%), HHHFNC in 3 (4.4%) and IMV in 14 (6%) cases.[21] But both these studies did not discuss the outcome of children who required IMV. This exercise marks one of the first attempts to extract and analyse preliminary data of children with COVID-19 who required IMV from low-income countries with resource

constraint set-ups along with increased burden of acute co-infections and chronic background illnesses.

Out of 54 children who required respiratory support, 41 children were aged less than 10 years. This is also in contrast to other paediatric studies where children >11 years more frequently required PICU admission.[10,21] This difference can be explained by the fact that in our country background incidence of acute respiratory infections is much higher in younger age group who were routinely screened for COVID-19 as per the prevailing Government guidelines whereas in other studies from high income countries only symptomatic children were screened.[14]

In paediatric studies, co-morbidities have been described as predictors for severe disease in children with COVID - 19 representing nearly 50-80% of PICU admissions.[20-24] However, data about co-morbidity profile from underdeveloped countries is limited.[3-7] Our study overcomes this data limitation as nearly 46% patients who required IMV had associated co-morbidity (co-infection and/or chronic diseases). The spectrum of these co-morbidities in our cohort is somewhat different from other countries, tropical infections and haematological disorders being the most common whereas obesity, neuromuscular disease and developmental delay were commonly associated with severity of illness in other studies.[10,21,22] The presence of co-morbidity in >10 year age ventilated patients was associated with poor outcome. Univariate analysis showed that presence of chronic co-morbidities had unadjusted OR, 3.2 (95% CI,1.2-8.3; p=0.013) showing that presence of chronic co-morbidities is associated with higher risk for requiring invasive ventilation however, this significance is lost on multivariate analysis. To bring out the true effect probably larger multicentre study from developing countries is needed to identify the impact of co-morbidities and co-infections on severity of disease and outcome in children with COVID-19.

These children who required IMV had higher prevalence of gastrointestinal symptoms, altered sensorium and hypoxia at admission. Predominance of these symptoms in critically sick children requiring IMV highlights the importance of suspicion of SARS-CoV-2 infection in children presenting with non-respiratory symptoms. When lab parameters were compared, it was found that high total leucocyte count (TLC), low platelets and high inflammatory markers were significantly high in ventilated group when compared with non-ventilated group. Our findings are similar to other studies where similar parameters were associated with severe disease requiring intensive care.[10,21,23]

The incidence of AKI in children who required ventilation was higher as compared to non-ventilated children (26% vs 5%). It is likely that development of AKI in these children further complicated the course of disease. This is comparable to incidence of AKI (26.9%) observed in pediatric study involving critically sick patients admitted in PICU.[25] But this is in contrast to the results from a multicentric point prevalence study where they observed a relatively higher occurrence of AKI in children with COVID-19-44%.[26]

The need for IMV in our patients was significantly higher and was associated with lower survival as compared to the previous studies.[10,21,22] But our results are similar to a recent multinational pediatric study including low and middle income countries which also showed that 41% hospitalized children required invasive ventilation and over half of young children intubated on day 1 also suffered cardiac arrest.[27] This finding may bear serious implication for decision to intubate early or late in children with COVID-19. Moreover, the clinical profile of children from high income countries cannot be compared and applied to children in low-income countries where multiple other factors can affect the clinical outcome including availability of resources and medical personnel. Our study also highlights the fact that the primary indication for IMV was not only respiratory involvement and worsening hypoxia seen in 35% cases, but also hemodynamic instability at presentation and poor neurological status. In our study ARDS was reported in 30% cases as compared to 71% in Brazilian PICU and 67% in New York PICU.[10,21] This again reiterate the finding that most of the children who required IMV in our cohort had multiorgan involvement at presentation. The presence of low SpO_2 at admission was independently associated with requirement of IMV but other factors associated with poor outcome in these patients needs further evaluation.

The present study has few limitations. Firstly, this was a retrospective data. Secondly, we did not test for other respiratory organisms which could have contributed to the severity of illness. It is therefore difficult to interpret how much COVID-19 contributed to severity of pneumonia or vice versa. However, our study highlights some of the important facts pertaining to COVID-19 in children from developing countries requiring IMV.

CONCLUSION

We describe important characteristics of the paediatric population from low-income countries with COVID-19 who required IMV. Presence of low SpO_2 at admission was significantly associated with need of IMV. With the origin of newer mutating variants, larger multicentre experiences highlighting all potential risk factors is needed to identify the predictors for requirement of IMV in severe paediatric COVID-19.

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