ORIGINAL ARTICLE

Predictors of mortality in children admitted with SARS-CoV-2 infection to a tertiary care hospital in North India

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Aim: To compare the demographic, clinical, laboratory and radiological parameters of patients with different clinical outcomes (death or discharge) and analyse them to find out the potential predictors for mortality in children hospitalised with SARS-CoV-2 infection.

Methods: Retrospective chart review of all patients less than 18 years of age with laboratory-confirmed SARS-CoV-2 infection and requiring hospital admission between 16 April 2020 and 31 October 2020.

Results: Of 255 children with SARS-CoV-2 infection, 100 patients (median age 62.5 months, 59% males, 70% with moderate to severe disease) were hospitalised, of whom 27 died (median age 72 months, 59% males and 30% severely underweight). The subgroup with comorbidities ($n = 14$) was older (median age 126 months) and had longer duration of stay (median 10 days). Fever and respiratory symptoms were comparable while gastrointestinal symptoms were more common among non-survivors. Hypoxia at admission (odds ratio (OR) 5.48, $P = 0.001$), multi-organ dysfunction (OR 75.42, $P = 0.001$), presence of acute kidney injury (OR 11.66, $P = 0.001$), thrombocytopenia (OR 4.40, $P = 0.003$) and raised serum C-reactive protein (CRP) (OR 4.69, $P = 0.02$) were independently associated with mortality. The median time from hospitalisation to death was 3 days. The deceased group had significantly higher median levels of inflammatory parameters and a higher incidence of complications (myocarditis, encephalitis, acute respiratory distress syndrome and shock).

Conclusions: Hypoxia at admission, involvement of three or more organ systems, presence of acute kidney injury, thrombocytopenia and raised serum C-reactive protein were found to be independently associated with increased odds of in-hospital mortality in children admitted with SARS-CoV-2 infection.

Key words: child; COVID-19; critical illness; hospital mortality; risk factor; SARS-CoV-2.

What is already known on this topic

1 COVID-19-associated illness in children is usually mild and hospitalisation and death is uncommon.

2 Apart from fever and respiratory symptoms, gastrointestinal symptoms are frequent and sometimes the sole manifestation of COVID-19 in children.

3 Younger age, male sex, raised inflammatory markers and underlying comorbidities have been reported as possible risk factors for severe COVID-19 in children in some studies.

What this paper adds

1 The present study adds to the growing knowledge about clinical and laboratory characteristics of life threatening and fatal forms of paediatric SARS-CoV-2 infection.

2 Hypoxia at admission, multiorgan system involvement, renal injury at admission, thrombocytopenia and raised serum C-reactive protein increase the risk of mortality in children.

3 COVID-19 can be severe in underweight infants and in children older than 10 years of age with pre-existing comorbidities or acute co-infections.

The coronavirus (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global health and economic catastrophe of unprecedented magnitude. Global data from various countries show that, compared to adults with COVID-19, children and adolescents have a much lower incidence of symptomatic infection (1–5%), hospitalisation rates (0.9–3.6%) and mortality (0–0.23%).[1–3] Nevertheless, the rising numbers of infected cases world-wide, atypical presentations and multisystem involvement manifesting as paediatric multisystem inflammatory syndrome (MIS-C) has presented a unique challenge in the management of paediatric population infected with SARS-CoV-2.[4,5]

Despite a large number of studies focussing on risk factors for mortality in adults with COVID-19,[6,7] similar literature from paediatric populations is lacking. To the best of our knowledge, we could not find any study delineating the risk factors for fatal disease in children with COVID-19. Some studies have reported an association between COVID-19 severity and younger age, male

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sex, raised inflammatory markers and underlying comorbidities.[8–15] Clinical and laboratory risk factors for fatal illness need to be elucidated in order to plan appropriate management in resource limited settings like ours. Hence, we aimed to compare the demographic, clinical, laboratory and radiological parameters of patients with different clinical outcomes (death or discharge) and analyse them to find out the potential predictors for mortality in children hospitalised with SARS-CoV-2 infection.

Methods

Study settings and care protocol

The study was conducted as a single centre retrospective chart review at a tertiary care paediatric centre in Indian capital of New Delhi. The study included patients admitted from 16 April 2020 to 31 October 2020 with clinical outcome monitored till 15 November 2020, the last defined date of follow up. All children <18 years of age with acute history of fever and any one sign/symptom of respiratory disease or contact with Covid positive case in home or hospital settings were tested for Covid-19 infection as per the prevailing Government guidelines (Appendix S4, Supporting Information). All consecutive patients with laboratory-confirmed SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction/cartridge-based nucleic acid amplification testing (RTPCR/CBNAAT) and requiring hospital admission were included in the study. The study was approved by institutional ethical committee of Lady Hardinge Medical College (LHMC/IEC/2020/97) as minimal risk research using data collected for routine clinical practice and waived the requirement for informed consent.

As part of public health response to COVID-19, a specific isolated area was created for the management of confirmed COVID-19 patients. Admission and discharge criteria were modified periodically as per the latest guidelines issued by the government of India (Appendix S4, Supporting Information). After the issuance of policy of home isolation for mild/asymptomatic cases, the predominant patient population of our hospital comprised moderate to severe cases. All included patients were investigated at admission to Covid ward using standard protocol with blood counts (total leucocyte count, differential leucocyte count, neutrophil to lymphocyte ratio (NLR)), liver and kidney function tests, serum C-reactive protein (CRP)) and chest X-ray. In addition, inflammatory markers (D-dimer, ferritin, fibrinogen, serum triglycerides), cardiac markers (creatinine phosphokinase (CPK), Troponin T), sepsis workup (blood and body fluid cultures, procalcitonin), tuberculosis work up (gastric aspirate for acid-fast bacilli and CBNAAT) and relevant serological tests (dengue serology and WIDAL) were also performed wherever indicated. Respiratory viral polymerase chain reaction panel could not be done due to in house unavailability. All patients were managed symptomatically with periodic vital monitoring, adequate respiratory support (oxygen/ventilation), appropriate nutritional and fluid management and other supportive therapy.

Data collection

The hospital case records of all confirmed COVID-19 patients were reviewed and data were collected on a predesigned proforma. Data regarding demographic characteristics; presence of comorbidities; clinical symptoms at presentation; clinical course during hospital stay including presence of any complications (Appendix S3, Supporting Information), number of organ systems involved, and presence of MIS-C; treatment received including need for oxygen, non-invasive and mechanical ventilation, antibiotics, inotropes, steroids, intravenous immunoglobulin (IVIG); laboratory parameters at admission; radiological findings and final outcome (death or discharge and duration of stay) was recorded on data collection forms. A comparative analysis of all these factors was done between those who survived and those who died using various statistical methods to identify the potential risk factors for mortality in SARS-CoV-2 infected children.

Case definitions

- Confirmed case: A confirmed case was defined as patient in whom SARS-CoV-2 was detected in nasopharyngeal sample by RT-PCR/CBNAAT testing. Testing was done as per the Government guidelines in place at that time and included children presenting with acute fever with respiratory symptoms or contact with SARS-CoV-2 positive case in home or hospital.
- Duration of symptoms was defined as time between the first symptom or sign or positive SARS-CoV-2 test if asymptomatic and the time of hospital visit.
- Hypoxia: defined as pulse oximeter oxygen saturation $SpO_2 < 94\%$ in room air. An SpO_2 reading <90% constituted severe hypoxia and was categorised as severe disease.
- Severity of illness: The patients were categorised as mild, moderate and severe as per the criteria in Appendix S1 (Supporting Information).
- Organ system involvement: was defined on basis of clinical and laboratory involvement of various organs during the course of illness (cardiovascular, central nervous system, respiratory, gastrointestinal, haematological or renal) (Appendix S2, Supporting Information).[5]
- MIS-C: Multisystem inflammatory syndrome related to Covid-19 was defined as per WHO definition.[5]

Statistical analyses

The data collected were analysed using software STATA (version 14.2 (StataCorp LLC, College Station, TX, USA). The data being non-normally distributed, descriptive statistics were described as median and IQR for continuous variables and count and percentages for categorical data. The comparison between the groups was done using two sum Wilcoxon rank Sum (Mann Whitney) test for continuous and χ^2 and fisher exact test for categorical variables as appropriate. Univariate and multivariable binary logistic regression were used to assess the potential risk factors associated with death in COVID-19 patients. A two tailed *P* value less than 0.05 was regarded as statistically significant.

Results

During the defined study period, a total of 255 children tested positive for SARS-CoV-2 infection at our hospital, of which 148 were managed as outpatient/home isolation due to asymptomatic/mild disease and 5 were referred to other hospital. Two children were brought dead to our emergency who were found SARS-CoV-2 positive on *post mortem* sampling. One hundred

Table 1 Comparison of demographic profile of Covid-19 among survivors and non-survivors

Characteristics	Total (*n* = 100)	Survivors (*n* = 73)	Non-survivors (*n* = 27)	*P* value
Age, months, median (IQR)	62.5 (16.75–120)	60 (24–120)	72 (10.5–126)	0.85
Age group, years, *n* (%)				
<1	24 (24)	16 (22)	8 (29.6)	0.42
1–5	26 (26)	23 (31.5)	3 (11)	0.08
5–10	25 (25)	18 (24.6)	7 (26)	0.89
>10	25 (25)	16 (22)	9 (33)	0.24
Sex, males, *n* (%)	59 (59)	43 (59)	16 (59)	0.97
Weight, kg, median (IQR)	15 (8.55–23.33)	15 (9–22)	16 (6.75–28.35)	0.77
Undernutrition (weight for age), *n* (%)				
Underweight (*Z* score < −2)	38 (38)	26 (35.6)	12 (44.4)	0.42
Severe underweight (*Z* score < −3)	18 (18)	10 (13.6)	8 (29.6)	0.06
Contact with Covid 19 positive case in family, *n* (%)	12 (12)	9 (12.3)	3 (11.1)	0.67
Comorbidities, *n* (%)				
Total present	59	45 (61.6)	14 (51.85)	0.38
Acute co-infection				
Liver abscess	6	6 (8.2)	0	0.18
Dengue	4	3 (4.1)	1 (3.7)	0.92
Disseminated staphylococcal sepsis	4	3 (4.1)	1 (3.7)	0.92
Pre-existing comorbidities				
Pulmonary TB	12	9 (12.3)	3 (11.1)	0.86
Extrapulmonary TB	7	4 (5.4)	3 (11.1)	0.38
Aplastic anaemia	2	1 (1.3)	1 (3.7)	0.45
Haematological malignancy	13	11 (15)	2 (7.4)	0.50
Rheumatological	2	0	2 (7.4)	0.07
Cerebral palsy	2	1 (1.3)	1 (3.7)	0.45
Nephrotic syndrome	2	2 (2.7)	0	0.53
Others†	5	5 (6.8)	0	0.19

†Others include: one patient each of congenital cystic adenomatoid malformation, surgical conditions like abdominal cystic mass and perforation peritonitis, DM type 1 and Tay Sach disease.

IQR, interquartile range; TB, tuberculosis.

children with predominantly moderate to severe disease were admitted to COVID block of our hospital and were included in the study. As on 15 November 2020, 27 of these died and 73 were discharged from the hospital.

Epidemiologic and demographic characteristics

Among the deceased cohort, 59% were males with median age 72 months (IQR 10.5–126 months), and median weight for age *Z* score as −1.8 (IQR −3.35 to −0.39). Thirty percent children (*n* = 8) were severely underweight. Fourteen children (51%) had underlying comorbidities out of which 12 had pre-existing disease (tuberculosis, haematological, rheumatological and neurological illnesses) and 2 patients presented with acute co-infections (1 each of severe dengue and disseminated staphylococcal sepsis). Three patients had a family history of contact with positive case and three children turned COVID positive after >7 days of hospitalisation for non-respiratory illness. The comparison of epidemiological and demographic characteristics among survivors and non-survivors is presented in Table 1. An important observation was that in the present cohort, patients with comorbidities

were equally represented between survivors and non-survivors (*P* value = 0.38).

Clinical characteristics, complications and primary management

Fever was the most prevalent symptom at disease onset in both deceased (70%) and recovered patients (84%). (Table 2) The proportion of patients presenting with respiratory symptoms (cough and fast breathing) was comparable in both groups. Hypoxia, diarrhoea and alteration of sensorium were significantly more common among those who died compared to survivors (*P* value = 0.001, 0.03 and 0.003, respectively). The majority of patients had moderate (26%) to severe (44%) disease, with all deceased patients belonging to the severe category at admission. A higher proportion of non-survivors had severe hypoxia and involvement of three or more organ system at the time of hospital admission. MIS-C was diagnosed in five (6.8%) survivors and five (19%) of those who died according to WHO definition (*P* = 0.08). The median time from onset of symptoms to hospital visit was comparable but the duration of hospital stay was significantly shorter among non-survivors.

Mortality predictor in Covid-19 children

Table 2 Comparison of Clinical characteristics among survivors and non-survivors

Characteristics	Total (n = 100)	Survivors (n = 73)	Non-survivors (n = 27)	P value
Presenting symptoms, n (%)				
Fever	80 (80)	61 (84)	19 (70)	0.14
Cough	35 (35)	29 (40)	6 (22)	0.10
Fast breathing	47 (47)	32 (44)	15 (54)	0.35
Myalgia	11 (11)	9 (12)	2 (7)	0.72
Headache	11 (11)	7 (10)	4 (15)	0.48
Nausea and vomiting	34 (34)	21 (29)	13 (48)	0.07
Abdominal pain	27 (27)	17 (23)	10 (37)	0.17
Diarrhoea	11 (11)	5 (7)	6 (22)	0.03
Altered sensorium	13 (13)	5 (7)	8 (30)	0.003
Rash	9 (9)	7 (10)	2 (7)	1.0
Low SpO$_2$ at admission (<95%)	45 (45)	25 (34)	20 (74)	0.001
Severe hypoxia (<90%)	19 (19)	6 (8)	13 (48)	<0.001
Median time between onset of symptoms to hospital visit, days, median (IQR)	4 (2–7)	4 (2–7)	3 (2–7)	0.90
Severity of illness at admission, n (%)				
Mild	30 (30)	30 (41)	0	0.0001
Moderate	26 (26)	26 (35.6)	0	0.0001
Severe	44 (44)	17 (23)	27 (100)	0.001
Organ system involvement during stay, n (%)				
One system	49 (49)	48 (66)	1 (3.7)	0.00
Two systems	20 (20)	18 (25)	2 (7.4)	0.09
Three systems	17 (17)	5 (6.8)	12 (44)	<0.001
Four or more systems	14 (14)	2 (3)	12 (44)	<0.001
Complications during stay†, n (%)				
Shock	35 (35)	8 (11)	27 (100)	<0.001
Pneumonia	46 (46)	30 (41)	16 (59)	0.11
ARDS	10 (10)	3 (4.1)	7 (26)	0.003
Encephalitis	15 (13)	7 (7)	8 (29.6)	0.001
Myocarditis	9 (9)	2 (3)	7 (26)	<0.001
Acute kidney injury	12 (12)	3 (4)	9 (33)	<0.001
Haematological	66 (66)	46 (63)	20 (74)	
Anaemia	46 (46)	38 (52)	8 (30)	0.04
Leucopenia	11 (11)	9 (12)	2 (7)	0.72
Thrombocytopenia	37 (37)	21 (29)	16 (59)	0.003
DIC	19/40 (48)	8/24 (33)	11/16 (69)	0.03
Transamnitis	19 (19)	8 (11)	11/26 (42)	<0.001
MIS-C, n (%)	10 (10)	5 (7)	5 (19)	0.08
Treatment				
Respiratory support, n (%)				
None	46 (46)	46 (63)	0	<0.001
Oxygen	54 (54)	27 (37)	27	<0.001
Non-invasive ventilation (CPAP/HHFNC)	11 (11)	9 (12)	2 (7)	0.72
Mechanical ventilation	35 (35)	8 (11)	27 (100)	<0.001
Vasoactive support/inotrope, n (%)	32 (32)	7 (10)	25 (93)	<0.001
Pharmacotherapy, n (%)				
Antibiotics	99 (99)	72 (99)	27 (100)	1.0
Azithromycin	27 (27)	21 (29)	6 (22)	0.51
Antivirals/Oseltamivir	9 (9)	7 (10)	2 (17)	1.0
IVIG	17 (17)	7 (10)	10 (37)	0.001
Methylprednisolone	9 (9)	5 (7)	4 (15)	0.25
HCQS	4 (4)	4 (5)	0	0.57
Anticoagulants	4 (4)	2 (3)	2 (7)	0.29
Length of hospital stay, days, median (IQR)	7 (4–12.25)	8 (5–13)	3 (1.65–10)	0.003

†Definitions as per Appendix S3 (Supporting Information).

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; DIC, disseminated intravascular coagulopathy; HCQS, hydroxy chrloroquine sulphate; HHFNC, humidified high flow nasal cannula; IQR, interquartile range; IVIG, intravenous immunoglobulin; MIS-C, multisystem inflammatory syndrome.

Table 3 Comparison of laboratory parameters at admission between survivors and non-survivors in children admitted with Covid-19

Characteristics	n	Total (n = 100)	Survivors (n = 73)	Non-survivors (n = 27)	P value
Hb, gm/dL, median (IQR)	100	9 (7.6–11.4)	9 (7.6–11.02)	9.6 (7.45–12.5)	0.48
Total leucocyte, count, /cu mm, median (IQR)	100	11 300 (7750–18 550)	10 140 (6475–16 975)	14 600 (9450–26 700)	0.03
Leucocytosis, >11 000/cu mm, n (%)	100	50 (50)	34 (46.5)	16 (59.2)	0.26
Absolute neutrophil count, /cu mm, median (IQR)	89	6600 (3496–10 700)	5500 (3327–9843)	7000 (4100–15 110)	0.19
Absolute lymphocyte count, /cu mm, median (IQR)	89	3240 (1598–5838)	2963 (1517–4878)	4150 (1840–7632)	0.13
Lymphopenia, <1500/cu mm, n (%)	89	25/89 (28)	19/64 (30)	6/25 (24)	0.59
Neutrophil to lymphocyte ratio, median (IQR)	89	1.83 (0.72–4.16)	1.73 (0.74–4.06)	1.97 (0.69–4.64)	0.91
Platelets, /cu mm, median (IQR)	100	220 (85–414)	246 (114–442)	110 (72–322)	0.08
ESR, mm, median (IQR)	10	55.5 (45–59.5)	45 (39.5–60)	58 (55.5–58)	0.73
CRP, mg/L, median (IQR)	100	41.5 (5–145.75)	24.9 (4.2–110)	121.7 (40.4–200)	0.001
Raised CRP, >6 mg/L, n (%)	100	70	46 (63)	24 (88.8)	0.02
Trop T positive, n (%)	18	7 (39)	2/11 (18)	5/7 (71)	0.05
CPK-MB, median (IQR)	29	69 (30–249)	43 (24.7–120)	223.5 (64.54–1259.25)	0.01
Raised CPK MB, >25 IU/L, n (%)	29	22	11/17	11/12	0.18
INR, median (IQR)	32	1.3 (1.18–1.6)	1.2 (1.07–1.3)	1.6 (1.45–1.68)	<0.001
D-Dimer, ng/mL, median (IQR)	33	1032 (542–1050)	687.50 (365.25–1050)	1050 (1042–1050)	0.01
Raised D-dimer, >510 ng/mL, n (%)	33	26 (79)	12/19 (63)	14/14 (100)	0.013
Fibrinogen, mg/dL, median (IQR)	14	318 (168.75–392)	367.50 (266.2–491.5)	202 (153.75–316.25)	0.09
Low fibrinogen, <250 mg/dL, n (%)	14	6/14 (43)	2/8 (25)	4/6 (67)	0.27
Ferritin, ng/mL, median (IQR)	13	579 (335–1128)	454.5 (276.25–936.75)	1128 (579–1298)	0.10
High ferritin, >500 ng/mL, n (%)	13	7/13 (76)	4/8 (50)	3/5 (60)	1.0
Triglycerides, mg/dL, median (IQR)	17	249 (157–342)	241 (158.25–288.25)	341 (157–354.5)	0.56
High triglyceride, >150 mg/dL, n (%)	17	13/17 (76)	8/10 (80)	5/7 (71)	1.0
Urea, mg/dL, median (IQR)	100	27 (19.08–50.8)	25.1 (19–39)	36 (22–72.45)	0.07
S creatinine, mg/dL, median (IQR)	100	0.33 (0.24–0.6)	0.30 (0.23–0.46)	0.6 (0.3–1.35)	0.005
SGOT/AST, IU/L, median (IQR)	95	47 (30.75–94.18)	45.0 (31.5–57)	75 (30–284)	0.06
SGPT/ALT, IU/L, median (IQR)	95	28 (19.35–58.9)	27.0 (19.25–45.85)	52.35 (20.75–148.75)	0.07
Total protein, g/dL, median (IQR)	65	6.1 (5.26–6.8)	6.17 (5.45–6.84)	5.80 (4.5–6.5)	0.28
Serum albumin, g/dL, median (IQR)	64	3.03 (2.38–3.60)	3.20 (2.4–3.6)	2.67 (2.07–3.5)	0.23
Hypoalbuminaemia, <2.5 g/dL, n (%)	64	20/64 (31)	13/46 (28)	7/18 (39)	0.41
Chest X-ray abnormal, n (%)	66	40/66 (61)	24/39 (60)	16/27 (59)	0.42

CPK-MB, creatinine phosphokinase - MB; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalised ratio; IQR, interquartile range; SGPT/ALT, Serum glutamic pyruvic transaminase/alanine transaminase; SGOT/AST, Serum glutamic oxaloacetic transaminase/aspartate aminotransferase

Among the deceased patients, cardiac complications like shock and myocarditis were most common followed by renal, hepatic and haematological complications including disseminated intravascular coagulopathy. Respiratory complications of severe pneumonia and acute respiratory distress syndrome were seen in 56 and 26% patients, respectively. All patients received mechanical ventilation which was initiated within first 48 h of admission for >75% patients. Two patients received non-invasive ventilation before progressing to invasive ventilation. More deceased patients were given IVIG and steroids considering MIS-C and potential cytokine storm in these patients.

Laboratory and radiological parameters

We observed substantial differences in laboratory findings between the two groups. (Table 3) The median total leucocyte count was significantly higher and median platelet count lower among non-survivors, with a significant difference in incidence of thrombocytopenia ($P = 0.003$). No significant difference was observed in absolute lymphocyte count and NLR between the

Fig 1 Chest X-ray showing bilateral lung opacities with pneumonia in non-survivor COVID-19 patient without any associated comorbidities

Table 4 Subgroup analysis of non-survivors among children hospitalised with COVID-19 with and without comorbidities

Parameter	With comorbidities (*n* = 14)	Without comorbidities (*n* = 13)	*P* value
Median age, months, median (IQR)	126 (87–153)	9 (2–42)	<0.001
Age distribution, *n* (%)			
<1 year (*n* = 8)	0	8 (100)	0.001
1–10 year (*n* = 10)	5 (50)	5 (50)	1.00
>10 years (*n* = 9)	9 (100)	0	0.01
Male sex (*n* = 16), *n* (%)	6 (37.5)	10 (62.5)	0.12
Severe underweight (*n* = 8), *n* (%)	1 (12.5)	7 (87.5)	0.01
Severe hypoxia at admission (*n* = 13), *n* (%)	6 (46.1)	7 (53.8)	0.70
MODS at admission (*n* = 24), *n* (%)	11 (45.8)	13 (54.1)	0.25
MIS-C (*n* = 5), *n* (%)	2 (40)	3 (60)	0.68
Duration of hospital stay, days, median (IQR)	10 (1.08–19.75)	3 (2–3)	0.04
Requirement of ventilation, *n* (%)			
At admission (*n* = 10)	4 (40)	6 (60)	0.44
Within 48 h of admission (*n* = 11)	5 (45.45)	6 (54.5)	0.70
>48 h after admission (*n* = 6)	5 (83.3)	1 (16.6)	0.19
Timing of death, *n* (%)			
Within 24 h of admission (*n* = 6)	4 (66.67)	2 (33.33)	1.0
Within 24–72 h of admission (*n* = 9)	1 (11.11)	8 (88.8)	0.04
>72 h after admission (*n* = 12)	9 (75)	3 (25)	0.04

IQR, interquartile range; MIS-C, multisystem inflammatory syndrome; MODS, multi organ dysfunction syndrome.

Table 5 Unadjusted and adjusted† logistic regression model for death among children with COVID-19

Parameter	Unadjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Age < 1 year	1.5	0.55–4.05	0.42			
Presence of comorbidities	0.56	0.23–1.38	0.20			
Severe underweight	2.65	0.91–7.67	0.07			
Low SpO$_2$ at admission	5.48	2.04–14.72	0.001	1.43	0.22–8.98	0.70
>2 organ system involvement	75.42	18.03–315.48	<0.001	361.78	21.7–6622.4	<0.001
Acute kidney injury	11.66	2.86–47.57	0.001	11.67	1.27–107.27	0.03
Thrombocytopaenia	4.40	1.68–11.51	0.003	1.08	0.13–9.10	0.06
Leucocytosis	1.67	0.68–4.08	0.26			
Raised CRP	4.69	1.29–17.07	0.02	1.32	0.16–10.50	0.79
Lymphopaenia	0.74	0.25–2.16	0.59			
MIS-C	3.09	0.81–11.68	0.09			

†Adjusted for factors with univariate *P* value <0.05.
CI, confidence interval; CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome; OR, odds ratio.

two groups. Concentrations of cardiac markers like CPK-MB, inflammatory markers like CRP, markers of coagulopathy including international normalised ratio and d-dimer and serum creatinine values were significantly higher among those who died.

In our study cohort, chest X-ray was done only in those with clinical suspicion of pneumonia. Among the deceased patients, 59% (*n* = 16) had abnormal findings which included nine patients with bilateral lung opacities; three with unilateral consolidation, two with pleural effusion, one with pneumothorax and one with mediastinal lymphadenopathy. In six of these cases, investigations came positive for other infections as well – five had evidence of tuberculosis and one patient had blood culture

positive for *Staphylococcus aureus*. In the remaining patients without comorbidities, the X-ray pattern showed pneumonia, as in Figure 1.

Subgroup analysis

The subgroup of deceased patients with one or more comorbidities (*n* = 14) was significantly older (median age 126 months) with about two-third of them above 10 years of age (Table 4). In contrast, 60% patients without comorbidities (*n* = 13) were infants (*n* = 8), were severely underweight (*n* = 7) and had shorter median duration of stay (3 vs. 10 days).

Risk factors associated with death

On univariate logistic regression analysis, hypoxia at admission, involvement of three or more organ system, presence of acute kidney injury, thrombocytopenia and raised serum CRP were independently associated with increased odds of in-hospital mortality in children admitted with severe COVID-19. (Table 5) The multivariate logistic regression model included patients with complete data for all variables and *P* value <0.05 on univariate analysis. It showed that involvement of three or more organ systems at admission (adjusted odds ratios (ORs) 361.78, 95% confidence interval (CI) 21.7–6622.4, *P* value <0.001) and presence of acute kidney injury (adjusted ORs 11.67, 95% CI 1.27–107.27, *P* value = 0.03) were significantly associated with risk of death.

Discussion

The present study describes the clinical and laboratory characteristics of 100 children hospitalised with SARS-CoV-2 infection, comparing survivors and non-survivors. To the best of our knowledge, this is the first study from India which comprehensively describes the major differences in demographic, clinical and laboratory features between children who died with SARS-CoV-2 infection and those who recovered. It also identifies the presence of multiorgan system involvement and acute kidney injury as significant risk factors for mortality in children with SARS-CoV-2 infection.

Almost half the cases in our study belonged to the severe category, unlike previous studies where the prevalence of severe disease in children is reported to be around 2–20%.[14–18] Possible explanations are selective admission of children and adolescents requiring tertiary care and/or patients being referred at a late or advanced stage of disease. The high case fatality in our cohort is in contrast to case fatality rates <1% seen in most paediatric studies.[10] This is attributable to a skewed denominator excluding the large percentage of mild/asymptomatic cases managed at home, more severe burden of disease at presentation, as well as high rate of associated acute and chronic comorbidities which complicated their course of disease. A recent study by Oualha *et al.* also highlights a high death rate of 18% among children admitted to a French paediatric intensive care unit (PICU) with severe COVID-19.[15]

The age subgroup analysis in our study also revealed that most non-survivors belonged to children older than 10 years of age (*n* = 9, 33%) or younger than 1 year (*n* = 8, 30%). Infants with COVID-19 infection were without any pre-existing co-morbidities but were underweight and their time to death was much shorter compared to older children with comorbidities (median 3 vs. 10 days). Our findings correspond to published literature which shows young infants to have a higher proportion of severe and critical disease with age <1 year being a significant risk factor for PICU admission.[10,19] The presence of one or more comorbid illness in all children aged >10 years who succumbed, suggest that presence of comorbidities complicate the clinical course in this subset of population. This is in accordance with findings from multicentric studies from USA and Europe, which described the presence of comorbidities in 50–80% of children with severe disease and need for PICU admission.[15,16,20] The spectrum of comorbid illnesses in our cohort was substantially different from developed countries, with infections (particularly tuberculosis) and haematological malignancy being the commonest. It is difficult to delineate the impact of COVID-19 disease on

patients with pre-existing comorbidities as most of them had underlying immunosuppression. However, in most of our non-survivors with co-morbidities (*n* = 12), there was an acute deterioration in clinical status including respiratory parameters when they acquired SARS-CoV-2 infection. Even in cases with acute co-infection (*n* = 2), the contributory role of SARS-CoV-2 towards poor outcome cannot be negated completely. To date, no literature evidence is available on the impact of co-infections on the clinical course of paediatric COVID-19, especially in developing countries where the background infection rate is high. In the present study, both age <1 year and presence of comorbidities was not found to be a significant risk factor for mortality on univariate analysis. This could be ascribed to the relatively small sample size of the study with equal distribution of comorbidities among survivors and non-survivors and selection bias.

The predominant clinical features at presentation essentially consisted of fever and respiratory symptoms, as in other documented adult and paediatric studies.[19–22] However, gastrointestinal symptoms in the form of diarrhoea were significantly more common among those who died. Recent studies have described gastrointestinal symptoms as being frequent and sometimes the sole manifestations of COVID-19 in children.[9,17] The higher prevalence of gastrointestinal symptoms in the MIS-C group and late identification of GI symptoms alone as COVID-19 manifestations could possibly account for this difference between the two groups.[17,23,24] Presence of low oxygen saturation, involvement of three or more organ systems at admission and presence of acute kidney injury were significant predictors of mortality in this study population. This again corresponds to a more critical presentation of disease as reflected by the majority requiring ventilation within 48 h of admission (*n* = 21, 77%). The median duration of time between admission to death was 3 days, with about one quarter of deaths occurring within 24 h of admission.

The overall incidence of MIS-C was 10% and was comparable between the two groups. To date, no specific therapy has been proven to be effective in paediatric COVID-19 and hence supportive organ protective strategies remain the mainstay of management. Most of our study population received antibiotics and antivirals. However, the deceased population received more immunomodulatory therapy in the form of IVIG and methylprednisolone for possible severe pneumonia, myocarditis and cytokine storm.

On comparing the laboratory parameters, it was found that leucocytosis, thrombocytopenia, raised levels of inflammatory and cardiac markers (CRP, CPK-MB, D-dimer), deranged serum creatinine and liver enzymes were significantly more common among the non-survivors. Thrombocytopenia and raised serum CRP were found to be independently associated with risk of mortality on univariate analysis. These findings are similar to published systematic reviews on predictors of adult mortality in COVID-19[6,7] and risk factors for PICU admission among the paediatric population.[14,17,18] Leucopenia, lymphopenia, NLR and serum albumin were not found to be significantly different between the two groups, unlike some paediatric studies which have shown their association with a complicated disease course.[14,17]

The present study has several limitations. Firstly, the study design is retrospective with a limited sample size, including a few patients not admitted primarily with COVID-19 manifestations. Secondly, there is a selection bias as only the patients admitted to our hospital with moderate to severe disease were studied and our results and conclusions do not reflect the overall spectrum of

COVID-19 in Indian children which is predominantly mild/asymptomatic. Thirdly, inflammatory markers could not be measured on all patients due to hospital policy on indications for testing and non-availability of timely resources, so could not be compared between the two groups sufficiently. Lastly, computed tomography scan of the chest could not be performed for any of the patients to differentiate typical features of COVID-19 pneumonia from other pulmonary infections. Despite these limitations, this study has the merit of focussing on the severe form of paediatric COVID-19 and contributes relevant information on early identification of patients at risk of complications and mortality.

Conclusions

The present study adds to the growing knowledge about life threatening and fatal forms of paediatric COVID-19 infection. We found that apart from known predictors of severity like younger age and presence of comorbidities, hypoxia at admission, multi-organ system involvement, renal injury at admission, hematologic derangements and raised inflammatory markers increase the risk of mortality and influence the overall outcome of Covid-19 disease in children. Early risk stratification and appropriate treatment strategies would help in optimising the outcome and making informed decisions regarding allocation of health-care resources and personnel during the Covid-19 pandemic.

Acknowledgements

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Severity of illness adapted from MOHFW guidelines.
Appendix S2. Definitions used for organ system involvement.
Appendix S3. Clinical definitions for complications.
Appendix S4. Policy for admission and discharge of patients with Covid-19.