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Mortality audit of COVID-19 infection among children

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***Background & objectives*: As severe COVID-19 and mortality are not common in children, there is a scarcity of data regarding the cause of mortality in children infected with SARS-CoV-2. This study was aimed to describe the all-cause mortality and COVID-19 death (disease-specific mortality) in children with SARS-CoV-2 infection admitted to a paediatric COVID facility in a tertiary care centre.**

***Methods*: Data with respect to clinical, epidemiological profile and causes of death in non-survivors (0-12 yr old) of SARS-CoV-2 infection admitted to a dedicated tertiary care COVID hospital in north India between April 2020 and June 2021 were retrieved and analyzed retrospectively.**

***Results*: A total of 475 SARS-CoV-2–positive children were admitted during the study period, of whom 47 died [18 neonates, 14 post-neonatal infants and 15 children (1-12 yr of age)]. The all-cause mortality and COVID-19 death (disease-specific mortality) were 9.9 per cent (47 of 475) and 1.9 per cent (9 of 475), respectively. Underlying comorbidities were present in 35 (74.5%) children, the most common being prematurity and perinatal complications (n=11, 24%) followed by congenital heart disease (n=6, 13%). The common causes of death included septic shock in 10 (21%), COVID pneumonia/severe acute respiratory distress syndrome in nine (19%), neonatal illnesses in eight (17%), primary central nervous system disease in seven (15%) and congenital heart disease with complication in six (13%) children.**

***Interpretation & conclusions*: Our results showed a high prevalence of underlying comorbidities and a low COVID-19 death (disease-specific mortality). Our findings highlight that mortality due to COVID-19 can be overestimated if COVID-19 death and all-cause mortality in children infected with SARS-CoV-2 are not separated. Standardized recording of cause of death in children with SARS-CoV-2 infection is important.**

Key words Audit - comorbidities - COVID-19 - mortality - paediatric - SARS-CoV-2

Globally, risk factors and mortality in hospitalized adults with COVID-19 are well described. The overall case-fatality rate in early reports from China was 2.3 per cent, which increased to nearly three times (7%) in hospitalized patients[1,2]. Subsequent meta-analyses reported a much higher mortality of 17-18 per cent in hospitalized adults[3,4]. However, it was observed that severe disease due to SARS-CoV-2 was uncommon in children. Some of the postulated reasons included age-related variation in expression of angiotensin converting enzyme 2 receptors, difference in lymphocyte and natural killer cell abundance, stronger

innate immune response and higher chances of prior infection with seasonal human coronaviruses that can elicit cross neutralizing antibodies to SARS-CoV-2 virus[5,6]. Expectedly, data regarding case-fatality rates and risk factors for mortality in children with COVID-19 are limited. Data from the USA, Italy, France, UK, Germany, Spain and South Korea showed that mortality due to COVID-19 in children was 0.17 per 100,000 population, which comprised less than 0.5 per cent of estimated all-cause mortality in a normal year[7]. A multicentre study of children with SARS-CoV-2 from Southeast Asia, Japan and China had reported an overall mortality rate of 2.3 per cent[8].

With this background, this study was undertaken to describe the clinico-epidemiological characteristics and cause of death in children between 0 and 12 yr of age who were admitted to a tertiary level-dedicated paediatric COVID facility and succumbed to their illness.

Material & Methods

This study was conducted in the Advanced Paediatrics Centre, Postgraduate Institute of Medical Education & Research, Chandigarh, India. Case records of 47 non-survivors (0-12 yr of age) admitted to the dedicated tertiary level paediatric COVID facility between April 2020 and June 2021 were retrieved from the electronic medical records after approval from the Institute Ethics Committee. SARS-CoV-2 infection was diagnosed based on a positive reverse transcription - polymerase chain reaction (RT-PCR) and/or Gene Xpert test. COVID-19 death was defined as a death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, unless there was a clear alternative cause of death that could not be related to COVID-19 disease (*e.g.* trauma) as given by the World Health Organization[9]. Guidelines given by the Indian Council of Medical Research-National Centre for Disease Informatics and Research (ICMR-NCDIR) were used for recording of COVID-19–related deaths[10]. When in doubt, the cause of mortality to be assigned was discussed and reviewed by clinician in-charge and COVID Committee Chair (MJ) following which a consensus was made.

Data collection: Data with respect to epidemiology, demographics, presence of comorbidities, presenting complaints, organ dysfunction scores, laboratory parameters, management, duration of hospital stay and cause of death of non-survivors were entered in a structured proforma and analyzed retrospectively. Non-survivors were further stratified into age groups of less than one month (neonatal), one month to one year (post-neonatal infants) and >1-12 yr (child).

Statistical analysis: The data were summarized and analyzed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA) and expressed as median, interquartile range (IQR) and numbers and percentages wherever appropriate. Kruskal Wallis test was used to compare the non-parametric continuous variables, while Chi square and Fisher's exact tests were applied for inter-group comparison between categorical variables.

Results & Discussion

A total of 475 children aged between 0 and 12 yr and tested positive for SARS-CoV-2 were admitted to the dedicated paediatric COVID facility during the study period (April 2020 to May 2021). Of these, 170 were neonates, 95 were post-neonatal infants and 210 were children (>1-12 yr of age). Of these, 47 children died and were included for final analysis. The all-cause mortality was 9.9 per cent (47 of 475). The overall mortality was 10.6 per cent (18 of 170) in neonates, 14.7 per cent (14 of 95) in post-neonatal infants and 7.1 per cent (15 of 210) in children 1-12 yr of age (P=0.112). The COVID-19 death rate was 1.9 per cent (9 of 475 children); three each in the neonatal (1.8%), post-neonatal infants (3.2%) and children 1-12 yr (1.4%) group died due to COVID-19.

Baseline characteristics of non-survivors: There were 24 (51%) male and 23 (49%) female children, giving male to female ratio of 1.0:0.95. Fever (16/47; 34%), cough (5/47; 11%), respiratory distress (32/47; 68%) and gastrointestinal symptoms (9/47; 19%) were common presenting symptoms. Nearly three fourth (n=35; 74.4%) of non-survivors had underlying comorbidity, the most common being prematurity and perinatal complications (n=11, 24%) followed by congenital heart disease (n=6, 13%), malignancy and haematological causes (n=4, 9%), neurological causes (n=3, 6%), Down syndrome (n=3, 6%), post-surgical cases (n=3, 6%), chronic liver disease (n=2, 4%), chronic kidney disease (CKD, n=2, 4%) and pulmonary tuberculosis (n=1, 2%). Nine children had COVID-19 pneumonia among whom six (66.7%) had underlying comorbidities.

Among non-survivors (n=47), 19.1 per cent (n=9) had severe COVID-19 illness. Among survivors

(n=428), COVID-19 illness was mild in 84.8 per cent (n=363), moderate in 9.1 per cent (n=39) and severe in 6.1 per cent (n=26). The median (IQR) PRISM score of non-survivors was 11 (7.5-17.5). Respiratory failure in 21 (44.6%), primary brain dysfunction in 11 (23.4%), respiratory distress in eight (17.0%) and hypotensive shock in four (8.5%) children were the common physiological decompensations at the time of presentation. Respiratory failure in five (10.6%), respiratory distress in two (4.3%) and hypotensive shock in two (4.3%) children were attributable to COVID-19. Organ dysfunction was measured using the Goldstein diagnostic criteria[11]. Thirty eight (80.9%) children developed multiple organ dysfunction syndrome (MODS) during hospital stay, and eight (17.2%) had MODS attributable to COVID-19.

Thirty three of the 47 children (70.2%) developed shock during hospital stay, of whom 18 had septic, seven had cardiogenic, five had neurogenic and three had obstructive shock. Of these 33 children, 31 (94%) required inotropic support while two (6%) children were managed with fluid boluses alone. Acute kidney injury (AKI) developed in 10 (21.2%) children, of whom two patients required renal replacement therapy in the form of peritoneal dialysis. Shock in eight (17%) and AKI in one (2.1%) were attributable to COVID-19. Eight children required nasal prong oxygen, 12 needed continuous positive airway pressure (CPAP), one needed high flow nasal cannula (HFNC), three required non invasive ventilation (NIV) and 23 required intubation and ventilation at admission. One child aged eight years fulfilled the criteria for multisystem inflammatory syndrome in children (MIS-C) and was also positive for SARS-CoV-2 infection by RT-PCR. COVID-19 specific treatment which included remdesivir and systemic corticosteroids were given in 10 (21.2%) and 11 (23.4%) children, respectively. Systemic steroids were given to children with severe or critical COVID-19 as defined by the guidelines given by the Ministry of Health and Family Welfare, Government of India[12]. Dexamethasone was given to children with COVID-19 pneumonia and hypoxia, while methylprednisolone was given to the child with MIS-C. Majority (43, 91.4%) had received antimicrobials which included antifungal agents in five (10.6) patients. The Table shows the cause of death among COVID-19–positive children.

The detailed age-specific analysis of mortality is as follows.

Table. Causes of death among COVID-19–positive children

Cause of death	Number, n (%)
Septic shock	10 (21)
COVID pneumonia/ARDS	9 (19)
Primary CNS disease	7 (15)
Acute meningoencephalitis	2
TBM with hydrocephalus	1
Aplastic anaemia with I/C bleed	1
Polytrauma with I/C bleed	1
ALL with CNS relapse	1
Burkitt lymphoma with hypertensive emergency	1
Neonatal illness	8 (17)
Congenital heart disease with complication	6 (13)
Acute kidney injury and complications secondary to	
Anorectal malformation with CAKUT	4 (9)
Cystinosis	1
Acute gastroenteritis with severe dehydration	12
Fulminant liver failure	
Viral hepatitis	3 (6)
Chronic liver disease with decompensation	11
Autoimmune hepatitis	1
Total	47 (100)

ARDS, acute respiratory distress syndrome; CNS, central nervous system; TBM, tuberculous meningitis; ALL, acute lymphoblastic leukaemia; CAKUT, congenital anomalies of the kidney and the urinary tract; I/C, intracranial

Neonatal deaths: Only three of 18 neonatal deaths (16.6%) were COVID-19 deaths. The predominant manifestation of COVID-19 in all the three neonates was pneumonia and severe ARDS, and among these, two had underlying comorbidities (prematurity and Down syndrome, respectively). Causes of death in the rest (n=15) included prematurity and related complications (n=8), congenital anomalies (n=3), acute gastroenteritis with hypernatremic dehydration (n=2), late-onset neonatal sepsis (n=1) and congenital heart disease (n=1).

Post-neonatal infant deaths: Three of 14 deaths in infants were due to COVID-19 pneumonia. Two of them had underlying comorbidity which included global developmental delay (n=1) and Down syndrome (n=1). Among the rest (n=11), five died of complications related to congenital heart disease, two due to underlying neurological illness, two due

to post-surgical complications and one each due to chronic liver and CKD.

Mortality in children: Among the 15 (29.4%) deaths in this age group, three were COVID-19 deaths, with COVID-19 pneumonia and severe ARDS in two children and MIS-C with MODS in the third. Of the two children with COVID-19 pneumonia, one was a known case of pulmonary tuberculosis on treatment, while the second had autoimmune hepatitis and was on immunosuppressive therapy. In the rest (n=12), five had underlying comorbidity [haematological malignancy (n=4) and CKD (n=1)], three had acute meningoencephalitis with raised intracranial pressure and one each of liver abscess, burns with sepsis, acute liver failure and polytrauma.

This was a retrospective audit of the clinico-epidemiological characteristics, underlying comorbidities and causes of mortality among non-survivors of COVID-19 admitted to a tertiary level-dedicated paediatric COVID-19 facility in north India. Public reporting regarding mortality or hospitalization due to COVID-19 was based mainly on the detection of SARS-CoV-2 virus (RT-PCR/Gene Xpert/RAT positive) rather than the presence of clinical symptoms compatible with COVID-19, and hence leading to overestimation of the impact of COVID-19 in children. In two large single-centre paediatric studies, SARS-CoV-2 infection was found to be incidental in around 40-45 per cent of the hospitalizations[13,14]. Studies from adults with underlying comorbidities and SARS-CoV-2 infection demonstrated that in the majority, the mortality was directly related to COVID-19 rather than the co-existing comorbidity[15].

The mortality rate in SARS-CoV-2-positive children (n=255) reported from another centre in India was 11.4 per cent; however, this study did not specify the attributable mortality rates due to COVID-19[16]. In another study from north India which included over 400 children hospitalized with SARS-CoV-2 infection, the mortality was around 3.2 per cent (13 of 402 children). All the 13 children had underlying comorbidities[17]. The mortality rates reported from hospitalized children infected with SARS-CoV-2 from paediatric intensive care units (PICUs) of developed economies ranged from 2.8 to 4 per cent[18,19]. Various studies from the PICUs of Italy, Spain and the United States have reported high prevalence of comorbidities ranging from 63 to 83 per cent in the hospitalized COVID-19 children[19-22]. A large cross-sectional study including over 40,000 children with SARS-CoV-2 infection concluded that children with underlying comorbidities were 3-7 times more likely to be hospitalized and 2-3 times more likely to have severe COVID-19[23].

The reasons behind increased severity of COVID-19 in children with associated comorbidities are not known. Abnormal muscle tone, defects in mucociliary clearance, abnormal craniofacial structures and delayed recognition of illness in children with genetic syndromes and neurological illness can increase the risk of decompensation in pulmonary infections[24]. In our study, the most common comorbidities were prematurity and perinatal complications, followed by congenital heart diseases, haematological malignancies, Down syndrome and congenital malformation. Prematurity as a risk factor for severe COVID-19 has been described in several studies[20,22,23,25]. Age less than one year and more than 10 yr is known to aggravate the risk of severe disease due to COVID-19 in children, a phenomenon described as U-shaped curve of severity[26]. Mortality due to COVID-19 was higher in children under one year of age (neonates and post-neonatal infants) at 2.3 per cent compared to those over one year of age (1.4%) in our study.

Our study had certain limitations. Being a single-centre study, the generalizability of findings may be difficult. COVID-19 death was decided based on the presence of severe pneumonia and ARDS and raised inflammatory biomarkers.

In conclusion, our study revealed a high prevalence of underlying comorbidities and a low COVID-19 mortality in hospitalized children. Standardized recording of cause of death in children with SARS-CoV-2 infection is important. Data thus generated will help measure the public health impact of COVID-19, plan interventions and allocate health resources.

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References

1. Epidemiology Working Group for NCIP Epidemic Response. Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; *41* : 145-51.
2. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, *et al.* COVID-19 patients' clinical characteristics, discharge

rate, and fatality rate of meta-analysis. *J Med Virol* 2020; *92* : 577-83.

3. Noor FM, Islam MM. Prevalence and associated risk factors of mortality among COVID-19 patients: A meta-analysis. *J Community Health* 2020; *45* : 1270-82.
4. Macedo A, Gonçalves N, Febra C. COVID-19 fatality rates in hospitalized patients: Systematic review and meta-analysis. *Ann Epidemiol* 2021; *57* : 14-21.
5. Cristiani L, Mancino E, Matera L, Nenna R, Pierangeli A, Scagnolari C, *et al.* Will children reveal their secret? The coronavirus dilemma. *Eur Respir J* 2020; *55* : 2000749.
6. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. *Turk J Med Sci* 2020; *50* : 592-603.
7. Bhopal SS, Bagaria J, Olabi B, Bhopal R. Children and young people remain at low risk of COVID-19 mortality. *Lancet Child Adolesc Health* 2021; *5* : e12-3.
8. Wong JJM, Abbas Q, Chuah SL, Malisie RF, Pon KM, Katsuta T, *et al.* Comparative analysis of pediatric COVID-19 infection in Southeast Asia, South Asia, Japan, and China. *Am J Trop Med Hyg* 2021; *105* : 413-20.
9. World Health Organization. *Estimating mortality from COVID-19* . Available from: *https://www.who.int/news-room/commentaries/detail/estimating-mortality-from-covid-19*, accessed on March 18, 2022.
10. Indian Council of Medical Research. National Centre for Disease Informatics and Research. *NCDIR e-Mortality Software (NCDIR e-Mor)*. Available from: *https://ncdirindia.org/e-mor/*, accessed on March 14, 2022.
11. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; *6* : 2-8.
12. Ministry of Health & Family Welfare, Government of India. *Guidelines for management of COVID-19 in children (below 18 years).* Available from: *https://www.mohfw.gov.in/pdf/GuidelinesforManagementofCOVID19inCHILDREN18June2021final.pdf*, accessed on March 7, 2022.
13. Webb NE, Osburn TS. Characteristics of hospitalized children positive for SARS-CoV-2: Experience of a large center. *Hosp Pediatr* 2021; *11* : e133-41.
14. Kushner LE, Schroeder AR, Kim J, Mathew R. "For COVID" or "with COVID": Classification of SARS-CoV-2 hospitalizations in children. *Hosp Pediatr* 2021; *11* : e151-6.
15. Elezkurtaj S, Greuel S, Ihlow J, Michaelis EG, Bischoff P, Kunze CA, *et al.* Causes of death and comorbidities in hospitalized patients with COVID-19. *Sci Rep* 2021; *11* : 4263.
16. Singh P, Attri K, Mahto D, Kumar V, Kapoor D, Seth A, *et al.* Clinical profile of COVID-19 illness in children-experience from a tertiary care hospital. *Indian J Pediatr* 2022; *89* : 45-51.
17. Jat KR, Sankar J, Das RR, Ratageri VH, Choudhary B, Bhat JI, *et al.* Clinical profile and risk factors for severe disease in 402 children hospitalized with SARS-CoV-2 from India: Collaborative Indian pediatric COVID study group. *J Trop Pediatr* 2021; *67* : fmab048.
18. Derespina KR, Kaushik S, Plichta A, Conway EE Jr., Bercow A, Choi J, *et al.* Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr* 2020; *226* : 55-63.e2.
19. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, *et al.* Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric Intensive Care Units. *JAMA Pediatr* 2020; *174* : 868-73.
20. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A, Díaz-Rubio F, Piñeres-Olave BE, Fernández-Sarmiento J, *et al.* Pediatric critical care and COVID-19. *Pediatrics* 2020; *146* : e20201766.
21. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, *et al.* Severe coronavirus disease-2019 in children and young adults in the Washington, DC, Metropolitan Region. *J Pediatr* 2020; *223* : 199-203.e1.
22. Williams N, Radia T, Harman K, Agrawal P, Cook J, Gupta A. COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: A systematic review of critically unwell children and the association with underlying comorbidities. *Eur J Pediatr* 2021; *180* : 689-97.
23. Kompaniyets L, Agathis NT, Nelson JM, Preston LE, Ko JY, Belay B, *et al*. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open* 2021; *4* : e2111182.
24. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, *et al.* Multicenter interim guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. *J Pediatric Infect Dis Soc* 2021; *10* : 34-48.
25. Parri N, Magistà AM, Marchetti F, Cantoni B, Arrighini A, Romanengo M, *et al.* Characteristic of COVID-19 infection in pediatric patients: Early findings from two Italian Pediatric Research Networks. *Eur J Pediatr* 2020; *179* : 1315-23.
26. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: A systematic review and meta-analysis. *Arch Dis Child* 2021; *106* : 440-8.

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