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Letter to the Editor

Differences between children with severe acute lower respiratory infection with or without SARS-CoV-2 infection



Dear Editor,

It has been known that severe acute lower respiratory infection (ALRI) is a major cause of hospital admission in young children.¹ The COVID-19 pandemic due to SARS-CoV-2 has changed the epidemiology of ALRIs, resulting in a high demand for inpatient hospital services that has stretched healthcare systems to their capacity. We read with interest the article by Dr. Melé M and colleagues² where 110 children admitted with acute lower respiratory disease with (29%) or without (9%) SARS-CoV-2 infection were transferred to Paediatric Intensive Care Unit (PICU) ($P = 0.145$). It is not clear if children admitted with severe ALRI with or without SARS-CoV-2 infection differ between them. We evaluated patients with severe ALRI admitted to PICU and compared the clinical features and outcome of cases with or without SARS-CoV-2 infection. Patients were enrolled from April 2020 to April 2021 in a public tertiary care unit for infectious diseases assistance in Salvador, Brazil.

Inclusion criteria comprised children (under 17-years-old) admitted due to severe ALRI with investigation of SARS-CoV-2 infection. Severe ALRI includes any of the following criteria:³ (1) increased respiratory rate: ≥ 70 times/min (< 1 year), ≥ 50 times/min (≥ 1 year) (after ruling out the effects of fever and crying); (2) oxygen saturation $< 92\%$; (3) hypoxia: assisted breathing (moans, nasal flaring and three concave sign), cyanosis, intermittent apnea; (4) disturbance of consciousness: somnolence, coma, or convulsion; (5) food refusal or feeding difficulty, with signs of dehydration. Tachypnoea was defined as respiratory rate ≥ 60 times/min (< 2 months), ≥ 50 times/min ($\geq 1 - 11$ months), ≥ 40 times/min ($1 - 4$ years),⁴ ≥ 30 times/min (≥ 5 years).⁵ Investigation of SARS-CoV-2 infection was performed by real-time reverse-transcription PCR (RT-PCR) of nasopharyngeal sample collected by swab. Two RT-PCR kits were used during this study period: Allplex™ 2019-nCoV Assay, Seegene, Seoul, South Korea, and Kit Molecular Sars-Cov-2 (E/RP), Bio-Manguinhos, Rio de Janeiro, Brazil. Children whose medical charts were not available were excluded from the study.

All patients were managed at the discretion of the assistant physician. Clinical data, findings on physical examination performed upon PICU admission, treatment, and outcome data were collected through a review of medical charts and were recorded in standardized forms. Patients were categorized by with or without SARS-CoV-2 infection. Outcomes were death and invasive mechanical ventilation (IMV). This study was approved by the institutional ethical research committee.

Overall, 210 patients were included, out of which 120 (57.1%) were male. Median age (IQR) was 2.8 years (7.1 months–6.2 years). The most frequent complaints were difficulty breathing ($n = 206$; 98.1%), cough ($n = 144$; 68.6%), and fever ($n = 121$; 57.6%)

and the most frequent findings were oxygen saturation $< 92\%$ ($n = 154$; 73.3%), assisted breathing ($n = 131$; 62.4%), and dehydration ($n = 83$; 39.5%). Underlying illness was reported for 72 (34.3%) patients, being the most common ones chronic lung disease ($n = 39$; 18.6%), neurological diseases besides epilepsy ($n = 15$; 7.1%) and epilepsy ($n = 11$; 5.2%). IMV was used in 33 (15.7%; 95%CI 11.3–21.1%) patients. Eight (3.8%; 95%CI 1.8–7.1%) cases died. Almost one third of the patients ($n = 62$; 29.5%) tested positive for SARS-CoV-2.

Table 1 compares the baseline characteristics and outcomes of patients with and without SARS-CoV-2 infection. Male gender (67.7% vs. 52.7%, $P = 0.045$) and sickle cell disease (SCD) (6.5% vs. 0%, $P = 0.007$) were associated with SARS-CoV-2 infection. Wheezing upon admission was more common in patients without SARS-CoV-2 infection (38.5% vs. 21.0%, $P = 0.01$). IMV was more frequent among patients with SARS-CoV-2 infection (25.8% vs. 11.5%, $P = 0.009$) as well as death (8.1% vs. 2.0%, $P = 0.05$). Out of 62 cases with SARS-CoV-2 infection, 5 (8.1%) died, out of which 3 had underlying illness: 2 boys (9- and 12-years-old) had cerebral palsy and 1 girl (7-months-old) had floppy infant syndrome. Two boys (1-month-old and 12-years-old) had no previous underlying illness.

Our results showed that pediatric patients admitted to the PICU with severe ALRI infected with SARS-CoV-2 more frequently required IMV (25.8% vs. 11.5%, $P = 0.009$) and died (8.1% vs. 2.0%, $P = 0.05$). To the best of our knowledge, these are original findings. Additionally, male gender and SCD were baseline characteristics associated with SARS-CoV-2 infection among those patients.

About one quarter of our SARS-CoV-2 positive cases required IMV. This is in line with the results from an American study which enrolled 394 children admitted to PICU with SARS-CoV-2 infection and 23.1% needed IMV.⁶ Conversely, a British study reported that 57.5% of 73 SARS-CoV-2 infected children admitted to PICU needed IMV.⁷ Those authors acknowledged different thresholds for intubation as possible cause for such high rate (57.5%); they compared their results with data from PICU admitted children with influenza in 2019 and reported no difference in IMV use (57.5% vs. 66.3%). This finding contradicts our finding. However, we concomitantly included patients with and without SARS-CoV-2 infection whereas the British study used an historical group for comparison, which may have biased their results.

Noteworthy, SCD was associated with SARS-CoV-2 infection among our cases. Considering that all cases had severe ALRI, it is possible to observe that patients with SCD infected with SARS-CoV-2 are prone to evolve severely. A recently published review pointed out that pediatric SCD patients with SARS-CoV-2 infection need more intensive care than the global pediatric population.⁸ It means that as soon as COVID-19 vaccination is approved for the pediatric population, children with SCD should be in high priority groups.

Interestingly, wheezing was associated with absence of SARS-CoV-2 infection. Among patients with pneumonia, in which bac-

Table 1

Frequency and comparison of baseline characteristics between children admitted with severe acute lower respiratory infection with or without SARS-CoV-2 infection in a Pediatric Intensive Care Unit in Salvador, Brazil.

Characteristics	Yes <i>n</i> = 62	No <i>n</i> = 148	<i>p</i>	All patients <i>n</i> = 210
Age (median [IQR])	2.8y (7.1 mo–6.1 y)	2.6y (6.9 mo–6.3 y)	0.7	2.8y (7.1 mo–6.2 y)
Age range	41 days – 14.7 y	32 days – 16.4 y		32 days – 16.4 y
Aged under 1 year	18 (29.0)	47 (31.8)	0.7	65 (31.0)
Male gender	42 (67.7)	78 (52.7)	0.045	120 (57.1)
Mixed race (self-reported)	61 (98.4)	145 (98.0)	1.0	206 (98.1)
History				
Duration of symptoms on admission (days) (median [IQR])	5 (2 – 7)	4 (2.3 – 6)	0.4	4 (2 – 7)
Admission >5 days after symptom onset	22 (35.5)	44 (29.7)	0.4	66 (31.4)
Complaints				
Difficulty breathing	62 (100)	144 (97.3)	0.3	206 (98.1)
Cough	40 (64.5)	104 (70.3)	0.4	144 (68.6)
Fever	39 (62.9)	82 (55.4)	0.3	121 (57.6)
Vomiting	5 (8.1)	26 (17.6)	0.08	31 (14.8)
Diarrhoea	5 (8.1)	11 (7.4)	1.0	16 (7.6)
Myalgia	4 (6.5)	10 (6.8)	1.0	14 (6.7)
Poor oral intake	3 (4.8)	8 (5.4)	1.0	11 (5.2)
Cutaneous rash	2 (3.2)	7 (4.7)	1.0	9 (4.3)
Cyanosis	4 (6.5)	5 (3.4)	0.5	9 (4.3)
Convulsion	4 (6.5)	4 (2.7)	0.2	8 (3.8)
Headache	2 (3.2)	3 (2.0)	0.6	5 (2.4)
Anosmia	1 (1.6)	0	0.3	1 (0.5)
Findings on admission				
Oxygen saturation < 92%	48 (77.4)	106 (71.6)	0.4	154 (73.3)
Assisted breathing	35 (56.5)	96 (64.9)	0.3	131 (62.4)
Dehydration ^a	24 (38.7)	59 (39.9)	0.9	83 (39.5)
Tachypnoea ^b	23 (37.1)	47 (31.8)	0.5	70 (33.3)
Wheezing	13 (21.0)	57 (38.5)	0.01	70 (33.3)
Rhonchi	20 (32.3)	44 (29.7)	0.7	64 (30.5)
Crackles	18 (29.0)	31 (20.9)	0.2	49 (23.3)
Somnolence	5/55 (9.1) ^c	8/141 (5.7) ^c	0.5	13/196 (6.6) ^c
Fast breathing ^d	3 (4.8)	8 (5.4)	1.0	11 (5.2)
Nasal flaring	3 (4.8)	8 (5.4)	1.0	11 (5.2)
Moans	2 (3.2)	7 (4.7)	1.0	9 (4.3)
Underlying illness^e				
Chronic lung disease	23 (37.1)	49 (33.1)	0.6	72 (34.3)
Neurological diseases besides epilepsy ^f	8 (12.9)	31 (20.9)	0.2	39 (18.6)
Epilepsy	7 (11.3)	8 (5.4)	0.1	15 (7.1)
Congenital heart disease	6 (9.7)	5 (3.4)	0.09	11 (5.2)
Sickle cell disease	1 (1.6)	4 (2.7)	1.0	5 (2.4)
Obesity	4 (6.5)	0	0.007	4 (1.9)
Down Syndrome	3 (4.8)	1 (0.7)	0.08	4 (1.9)
Diabetes mellitus type 1	1 (1.6)	3 (2.0)	1.0	4 (1.9)
Floppy infant syndrome	1 (1.6)	2 (1.4)	1.0	3 (1.4)
Floppy infant syndrome	1 (1.6)	0	0.3	1 (0.5)
Alpha thalassemia	0	1 (0.7)	1.0	1 (0.5)
Outcomes				
Invasive mechanical ventilation	16 (25.8)	17 (11.5)	0.009	33 (15.7)
Death	5 (8.1)	3 (2.0)	0.05	8 (3.8)

Results are expressed as absolute number and percentage if not otherwise specified.

None reported ageusia/dysgeusia.

^a Dehydration was observed by the treating physician who prescribed intravenous fluid bolus.

^b Respiratory rate ≥ 60 times/min (<2 months), ≥ 50 times/min ($\geq 1 - 11$ months), ≥ 40 times/min (1 – 4 years), ≥ 30 times/min (≥ 5 years).

^c The denominator was not 210 because patients admitted using sedation and invasive mechanical ventilation were excluded.

^d Respiratory rate ≥ 70 times/min (<1 year), ≥ 50 times/min (≥ 1 year) after ruling out the effects of fever and crying.

^e Some patients had more than one underlying illness.

^f Neurological diseases besides epilepsy comprise: cerebral palsy (*n* = 11), hydranencephaly (*n* = 2), congenital hydrocephalus (*n* = 1) and congenital microcephaly (*n* = 1).

terial and viral infections were thoroughly investigated, wheezing was associated with viral infection.⁹ Our finding suggests that SARS-Cov-2 is not among the wheezing trigger viruses.

It is worth mentioning that even during COVID-19 pandemic, about two-thirds of our patients were admitted with severe ALRI without SARS-CoV-2 infection. In 2016, 3 years before the beginning of the current COVID-19 pandemic, ALRI was estimated to cause 652 572 deaths among children younger than 5 years all over the world.¹⁰ Therefore, besides SARS-CoV-2, other causative agents remain causing severe ALRI.

In conclusion, children with severe ALRI infection with SARS-CoV-2 need IMV more frequently than those without it. Children

with SCD should be prioritized for COVID-19 vaccination, as soon as possible.

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CRedit authorship contribution statement

Vivian Botelho Lorenzo: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Cristiana M Nascimento-Carvalho:** Conceptualization, Formal analysis, Writing – review & editing, Writing – original draft.

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