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Journal of Infection and Public Health 14 (2021) 193–200

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Characteristics and outcomes of coronavirus disease 2019 (COVID-19) in critically ill pediatric patients admitted to the intensive care unit: A multicenter retrospective cohort study

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ARTICLE INFO

Article history:
Received 15 October 2020
Received in revised form
23 November 2020
Accepted 3 December 2020

Keywords:
Children
Intensive care
SARS-CoV-2
Mortality

ABSTRACT

Background: Characteristics of critical Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) infection in children is not well understood. This study described the clinical characteristics of children admitted to intensive care units (ICU) and explored factors associated with the need for invasive ventilation or mortality.

Methods: A multicenter, retrospective, cohort study was conducted over eight medical centers, including all patients younger than 18 years of age and admitted to the ICU due to a direct consequence of coronavirus disease 2019 (COVID-19). Patients who were admitted to the ICU for any alternate reason and tested positive for SARS-CoV-2 by screening test, and patients who were admitted due to multi-inflammatory syndrome in children, were excluded. Demographic, laboratory, imaging, and clinical data were collected. Descriptive statistics were used to compare survivors and non-survivors. Fine and Gray's hazard model was used to estimate the association between clinical variables and ICU death.

Results: During the study period, 25 pediatric COVID-19 patients received care in the ICUs. The median age was 2.78 years (IQR 0.21–8.51), and 60% were male. Only three patients were reported to be previously healthy at admission. Nine (36%) patients required invasive mechanical ventilation, including two were on extracorporeal membrane oxygenation. Four (16%) patients died during ICU care. In univariate analysis, the presence of comorbidity (HR 0.0001; 95%CI 0.00001–0.00016), platelets count (HR 0.99; 95% CI 0.98–0.99), elevated procalcitonin (HR 1.05; 95%CI 1.016–1.09), and circulatory compromise (HR 16.34; 95%CI 1.99–134.35), all at the time of ICU admission, were associated with in-ICU mortality.

Conclusion: Our findings suggest that children admitted to the ICU with SARS-CoV-2 infection, generally, have a favorable outcome. Low platelets count, elevated procalcitonin, presence of comorbidity, and shock at the time of ICU admission were associated with death. This study may shed more light on the disease dynamics of critical pediatric COVID-19.

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https://doi.org/10.1016/j.jiph.2020.12.010
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Introduction

Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) was first recognized in December 2019. Since then, it has caused a pandemic of respiratory illness, coronavirus disease 2019 (COVID-19), which causes a wide range of illness severity, including acute respiratory distress syndrome (ARDS) and respiratory failure. In older adults, SARS-CoV-2 infection is associated with high morbidity and mortality. About one-third of hospitalized adults require care in the intensive care unit (ICU) [1,2].

Children, in general, develop milder COVID-19 compared to adults [3]. National-level studies showed that pediatric COVID-19 cases represent less than 8% of all confirmed cases [3–5]. Among infected children, the proportion with severe or critical illness has ranged between 3.3%–8% [6–8]. Due to the relative rarity of pediatric critical SARS-CoV-2 infection, the exact proportion of pediatric COVID-19 cases needing care in an ICU and estimates of case fatality rate in children are difficult to ascertain. In a large European multicenter study that included 582 SARS-CoV-2-infected children, 8% required ICU admission, 4% were mechanically ventilated, and four patients died [8]. The Centers for Disease Control and Prevention (CDC) reported 2572 cases of COVID-19 in children, of which 15 were admitted to the ICU, and three died; however, hospitalization status was missing in 71% of subjects [9].

Risk factors for developing a critical disease in children are still not well understood. A mathematical model by Pathak et al. estimated that 0.6% of the detected pediatric COVID-19 cases would need ICU care [10]. The highest estimates were observed in children younger than one year of age [10,11]. Among 345 confirmed COVID-19 pediatric cases for whom data on underlying conditions were not missing, the most commonly reported underlying conditions were chronic lung disease (11.6%), cardiovascular disease (7.2%), and immunosuppression (2.9%) [9]. In a multicenter study that collected data from North American pediatric ICUs, 48 pediatric (<21 years) patients required ICU admission. Of those, 40 were admitted as a direct consequence of SARS-CoV-2, and two died [12].

A collaboration between eight pediatric intensive care units in Kuwait and the Kingdom of Saudi Arabia (KSA) was established to better understand the dynamics of critical pediatric COVID-19 and to improve the quality of care to those patients. Our objective was to describe the clinical characteristics, disease dynamics, and outcomes of critical pediatric COVID-19 cases admitted to one of the participating centers. Moreover, we evaluated predictors of mortality and intubation in this cohort of patients.

Materials and methods

A retrospective cohort, multicenter study was conducted in eight pediatric centers across Kuwait and the Kingdom of Saudi Arabia (KSA) between March 1st and August 1st, 2020. All centers combined provide medical service to around 12 million people. We included children aged less than 18 years with symptomatic newly diagnosed SARS-CoV-2 infection that leads to ICU admission. On the other hand, excluded subjects were patients with asymptomatic SARS-CoV-2 infection detected during a screening PCR test upon ICU admission, and patients who were admitted due to post-infectious complications of COVID-19, including multisystem inflammatory syndrome in children (MIS-C) [13].

Patients were identified through querying admission and discharge records from ICUs in six participating centers from Kuwait (Adan Hospital, Farwaniya Hospital, Jaber Al-Ahmad Hospital, Jahra hospital, Mubarak Al-Kabeer Hospital, and Sabah Medical Specialized Area), representing all pediatric ICUs in Kuwait, and two from KSA (Prince Sultan Military Medical City and King Saud University Medical City). As the pediatric age group differed between centers, records from both adult and pediatric ICUs were reviewed to ensure the inclusion of all patients less than 18 years of age. Ethics board approval from the Ministry of Health of Kuwait and each respective center in KSA were obtained.

Medical charts were reviewed to obtain demographic data, pre-existing comorbidities, clinical and laboratory information related to COVID-19 admission. Information also included the clinical course in relation to the date of admission and discharge, symptoms at admission, maximum respiratory support (Low-flow oxygen therapy, non-invasive ventilation including high flow nasal cannula, mechanical ventilation, and extracorporeal membrane oxygenation), the reason for respiratory support, nature of organ dysfunction, therapies received (antimicrobial, inotropic, bronchodilators, immunomodulatory therapies, and blood product transfusion). Patient outcome at discharge was recorded and categorized as full recovery, discharge with sequela, or death.

Disease severity was evaluated based on the classification suggested by the World Health Organization (WHO) [14]. Clinical and laboratory data required for the Pediatric Risk of Mortality Score (PRISM III) were also collected [15]. Organ dysfunction (cardiovascular, respiratory, neurological, hematological, renal, and hepatic dysfunction) was defined based on previously published consensus [16]. Physiological variables related to the pediatric risk of mortality score (PRISM) that occurred between two hours prior to ICU admission to four hours after were collected [15,17]. Reasons for ICU admission were categorized into respiratory failure, neurological disorder, or circulatory compromise. Patients were considered to have respiratory failure if they presented with acute hypoxemia, hypercarbia, or clinical respiratory distress requiring non-invasive or invasive respiratory support. Neurological disorder referred to any acute change of mental status or new neurological symptom not explained by low perfusion status or hypoxemia. Circulatory compromise is considered if the patient is presented with impaired perfusion, hypotension, or if started on vasoactive medication [18].

Statistical analysis was performed using R version 3.6.3. Counts and percentages were used to summarize categorical variables. Continuous variables were summarized using mean ± standard deviation (SD) or median and interquartile range (IQR) for normal and non-normal variables, respectively. Chi-square and Fisher-exact tests were used to assess the association between categorical clinical or laboratory parameters and study outcomes (survival or mechanical ventilation). Mann-Whitney test and unpaired t-test were used to determine the association of continuous non-normal and normal variables, respectively, with the study outcomes.

Fine and Gray's sub-distribution hazard model was used to assess the univariate association between clinical or laboratory data and mortality in the ICU. Survival, in days, was calculated as the time from ICU admission to in-ICU death, ICU discharge, or last follow-up date if the patient was not discharged from the ICU by the end of follow-up. Discharge from the ICU (alive) was considered a competing risk. Univariate analysis p-values were corrected for false discovery rate to avoid the inflation of the type I error. Multivariate analysis was not attempted due to the small sample size. Hypothesis testing was performed at 5% level of significance.

Results

During the study period, 43 pediatric patients were admitted to the ICU with positive SARS-CoV-2 molecular test. Of those, 25 children with acute COVID-19, admitted to five of the participating ICUs, were included in the analysis (Fig. 1). Excluded subjects include 9 patients fulfilled MIS-C criteria, 2 duplicate entries, and 7 subjects had alternate reason for ICU admission and were identified to be SARS-CoV-2-infected by a routine screening. Thirteen patients

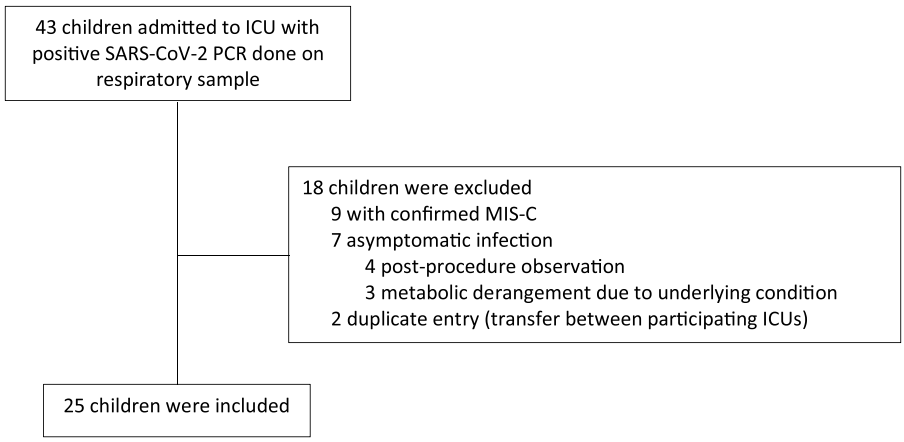

Fig. 1. Flow diagram of patients included in the study.

were admitted to one of three participating centers in Kuwait, and 12 were admitted to two centers in KSA.

The median age of subjects was 2.8 years (IQR 0.2–8.5 years), and 60% were male (Table 1). Most (88%) patients had underlying comorbidities. Six (24%) patients had an underlying neurological disease, five (20%) had hematological malignancies, and four (16%) had congenital heart disease. Noteworthy, three patients were not known to have any comorbidities at the time of ICU admission. By August 31st, 2020, 80% of patients were discharged home, of which two patients required home oxygen therapy. One patient is still admitted with a stable clinical condition. Four (16%) of the critical pediatric COVID-19 cases died. Median hospital and ICU length of stay were 16.5 (IQR 9.5–23.5) and 5 (IQR 3.75–21) days, respectively.

Fever and cough, were the most common presenting symptoms at the time of ICU admission (Table 2). Fever was present in 84% of subjects and lasted for a median of 4 days (IQR 1–7 days). The duration of fever was similar in survivors (median 4 days, IQR 1–7 days) and non-survivors (median 4 days, IQR 1–14.5 days, p = 0.9). Respiratory failure was the most common reason for ICU admission among survivors (95.2% in survivors vs. 50% in non-survivors, p = 0.057). Around 10% of the survivors presented with circulatory compromise compared to 75% of non-survivors (p = 0.016).

During ICU stay, nine patients were managed with non-invasive ventilation, nine required endotracheal intubation, of which two needed extracorporeal membrane oxygenation (ECMO). Hypoxic respiratory failure was the most common reason for requiring respiratory support, and it was observed more frequently in patients requiring invasive ventilation (88.9% vs. 60%, p = 0.19). One-third (32%) of the cohort, and all patients on invasive mechanical ventilation, received vasoactive agents (Table 3). Most (60%) patients requiring invasive ventilation had bilateral infiltrate or diffuse ground-glass opacities on chest radiographs.

In univariate analysis, the presence of comorbidity, low platelets count, high procalcitonin, and circulatory compromise, all at the time of ICU admission, were associated with death during the ICU stay (Fig. 2). Elevated levels of D-dimer (≥500 ng/dl) were observed in 24 (96%) of patients, and it was higher in survivors (mean: 3612 vs. 1086 ng/mL, p = 0.017 using unpaired t-test). However, in univariate Fine-Gray analysis, D-dimer levels were not significantly associated with in-ICU mortality (HR 0.99, adjusted p = 0.08). Low levels of absolute lymphocytic count were associated with mortality (HR 0.46; 95% CI 0.21–0.98); however, this association was not statistically significant after p-value adjustment.

Co-infection was uncommon in the studied cohort. Three (12%) patients had bloodstream infections: one with *Klebsiella pneumoniae,* one with *Staphylococcus lugdunensis,* and one patient had polymicrobial bloodstream infection (*K. pneumoniae* and *Escherichia coli*). In the latter, similar organisms were isolated from a concomitant urine culture. Of all included patients, seven (28%) had an upper respiratory sample tested negative for a respiratory virus, other than SARS-CoV-2, by a molecular assay. However, the targeted viruses varied by centers and included, as minimum, influenza, and respiratory syncytial virus (RSV).

All patients in the cohort received antibiotics (Table 3). Third-generation cephalosporins (56%) and beta lactam-beta lactamase inhibitors (44%) were the most commonly prescribed antibiotic classes. Four patients received antifungals, of which three had proven or suspected pulmonary invasive fungal infection. The use of targeted antiviral therapy against SARS-CoV-2 was uncommon. However, almost two-thirds (60%) of subjects received immunomodulator therapy, of which low- and high-dose steroids were prescribed in 80% of those patients. There was no difference in the use of immunomodulator therapy between survivors and non-survivors, and between those with invasive ventilation and non-invasive ventilation.

Discussion

Critical SARS-CoV-2 infection in children is uncommon. In this multicenter, retrospective cohort study, we report the clinical characteristics and disease dynamics in 25 pediatric COVID-19 who required ICU care. We observed that the presence of comorbidities, low platelets count, high procalcitonin, and circulatory compromise on admission are associated with death in ICU. The D-dimer level was elevated in most patients admitted to ICUs; however, non-survivors had a lower rise in D-dimer levels when compared to survivors. In this study, 4 (16%) ICU-admitted children died. Our mortality, based on death-to-ICU admissions ratio, is higher than what was reported by Shekerdemian et al. [12]. This might be explained by our strict study inclusion criteria. We only included patients who were admitted to the ICU due to direct consequence of SARS-CoV-2 infection. This may be responsible for relatively inflating our reported COVID-19 ICU deaths. National-level data suggest a death-to-ICU admission ratio of 8–20% [8,9]. Furthermore, there were a total of 7934 SARS-CoV-2-infected children in Kuwait at the end of the our study, including 13 (0.16%; 95% CI 0.09–0.28%) ICU admissions part of this cohort, and three deaths (case fatality rate 0.04%, 95% CI 0.01–0.12%), which is lower than other reports [8,9].

Thrombocytopenia is commonly seen in critically ill SARS-CoV-2-infected patients. Our finding was consistent with what was described in adults with severe COVID-19 [19,20]. Many theories attempted to explain the association between severe COVID-19

Table 1
Demographic data of the study population.

Variables	Total (n = 25)	Survivors (n = 21)	Non-survivors (n = 4)	*p*-Value
Age (median, IQR)	2.78 [0.21;8.51]	2.13 [0.21;7.3]	10.3 [5.47;13.4]	0.458
Male (%)	15 (60%)	12 (57.1%)	3 (75%)	0.626
Routine vaccination status				1
Fully vaccinated	9 (36%)	8 (38.1%)	1 (25%)	
Missed vaccine	7 (28%)	6 (28.6%)	1 (25%)	
Unknown	9 (36%)	7 (33.3%)	2 (50%)	
Comorbid conditions				
Autoimmune disease	2 (8.0%)	2 (9.5%)	0 (0.0%)	1
Chronic lung disease	1 (4.0%)	1 (4.8%)	0 (0.0%)	1
Congenital heart disease	4 (16%)	4 (19.0%)	0 (0.0%)	1
Hematological Malignancy	5 (20%)	4 (19.0%)	1 (25%)	1
Medically complex[a]	3 (12%)	2 (9.5%)	1 (25%)	0.422
Neurological disease	6 (24%)	4 (19.0%)	2 (50%)	0.234
None	3 (12%)	3 (14.3%)	0 (0.0%)	1
Obesity	2 (8%)	2 (9.5%)	0 (0.0%)	1
Prematurity	4 (16%)	3 (14.3%)	1 (25.0%)	0.527
Sickle cell disease	3 (12%)	3 (14.3%)	0 (0.0%)	1
MRSA colonization	1 (4%)	0 (0.0%)	1 (25%)	0.16
Medical Center:				0.635
1	8 (32%)	6 (28.6%)	2 (50.0%)	
2	11 (44%)	10 (47.6%)	1 (25.0%)	
3	4 (16%)	3 (14.3%)	1 (25.0%)	
4	1 (4%)	1 (4.76%)	0 (0.00%)	
5	1 (4%)	1 (4.76%)	0 (0.00%)	
Hospital length of stay (median, IQR) (n = 18)	16.5 [9.5;23.5]	17.5 [11.5;23.5]	5.50 [4.25;12.5]	0.121
ICU length of stay (median, IQR) (n = 24)	5 [3.75;21]	4.5 [3.75;21]	5.5 [4.25;11.8]	0.969
Outcomes				< 0.001
Full recovery	18 (72%)	18 (85.7%)	0 (0.0%)	
Discharged with sequelae	2 (8%)[b]	2 (9.5%)	0 (0.0%)	
Still Hospitalized	1 (4%)	1 (4.76%)	0 (0.0%)	
Death	4 (16%)	0 (0.0%)	4 (100%)	

ICU: intensive care unit.
[a] Defined as technically dependent children or those diagnosed with genetic or metabolic syndrome.
[b] All required home oxygen therapy.

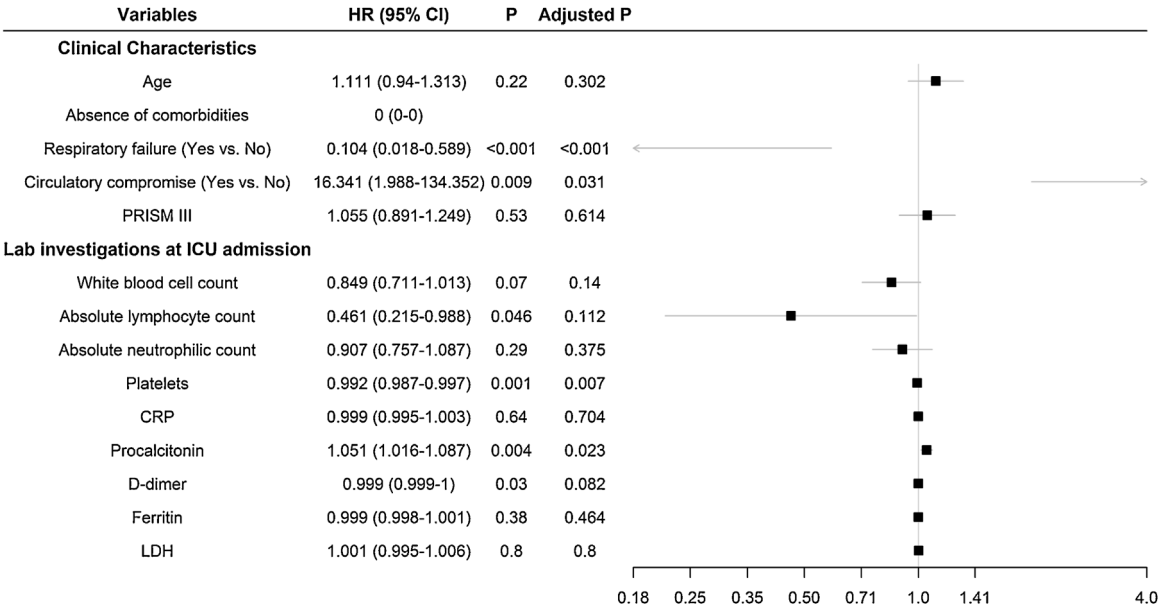

Fig. 2. Forest plot diagram demonstrating unadjusted hazard ratio for factors associated with ICU mortality due to SARS-CoV-2 infection in children.

and thrombocytopenia. Direct platelet destruction, either due to increased thrombosis or disseminated intravascular coagulation (DIC), and reduced platelet production were postulated as causes for thrombocytopenia in severe cases [19,20]. In our cohort, five patients (20%, one died) were diagnosed with hematological malignancy were infected with SARS-CoV-2 at different points of their treatment phase. It is difficult to assess if the underlying diseases contributed to the association between thrombocytopenia and mortality observed in this study. However, low platelet count was also observed in other patients that were supposed to have normal platelet counts. More studies are needed in children with SARS-CoV-2 infection to confirm this association. Once proven, we think that thrombocytopenia could be used as a marker to predict the unfavorable course of COVID-19 in children.

Table 2
Clinical characteristics of the study population.

Variables	Total (n = 25)	Survivors (n = 21)	Non-survivors (n = 4)	*p*-value
Symptoms at hospital presentation				
Abdominal pain	2 (8%)	2 (9.5%)	0 (0.0%)	1
Chest pain	3 (12%)	3 (14.3%)	0 (0.0%)	1
Cough	15 (60%)	13 (61.9%)	2 (50%)	1
Cutaneous	3 (12%)	2 (9.52%)	1 (25%)	0.422
Diarrhea	6 (24%)	5 (23.8%)	1 (25%)	1
Fever	21 (84%)	17 (81%)	4 (100%)	1
Duration of fever [median; IQR]	4 [1;7]	4 [2;6]	4 [1;14.5]	0.891
Headache	4 (16%)	4 (19%)	0 (0.0%)	1
Loss of appetite	8 (32%)	7 (33.3%)	1 (25%)	1
Myalgia	6 (24%)	5 (23.8%)	1 (25%)	1
Rhinorrhea	6 (24%)	5 (23.8%)	1 (25%)	1
Seizure	2 (8%)	1 (4.76%)	1 (25%)	0.3
Sore throat	4 (16%)	4 (19%)	0 (0.0%)	1
Vomiting	14 (56%)	12 (57.1%)	2 (50%)	1
The main reason for ICU admission				
Respiratory failure	22 (88%)	20 (95.2%)	2 (50%)	0.057
Neurological compromise	2 (8%)	2 (9.5%)	0 (0.0%)	1
Circulatory compromise	5 (20%)	2 (9.5%)	3 (75%)	0.016
Diseases Severity				0.081
Severe pneumonia/ARDS	17 (68%)	16 (76.2%)	1 (25%)	
Sepsis/septic shock	8 (32%)	5 (23.8%)	3 (75%)	
Clinical characteristics at ICU admission				
PRISM III (median, IQR)	12 [9;17]	12 [9;16]	15 [8.25;21.8]	0.766
GCS (median, IQR)	13 [11;15]	15 [11;15]	12 [9.75;13.5]	0.305
Resuscitation within 24 hours	2 (8%)	1 (4.76%)	1 (25%)	0.3
Hypotension	4 (16%)	3 (14.3%)	1 (25%)	0.527
Highest respiratory support				0.042
None	1 (4%)	1 (4.8%)	0 (0.0%)	
Low flow oxygen	6 (24%)	6 (28.6%)	0 (0.0%)	
HFNC	4 (16%)	4 (19.0%)	0 (0.0%)	
CPAP-BIPAP	5 (20%)	5 (23.8%)	0 (0.0%)	
Intubation	7 (28%)	3 (14.3%)	4 (100%)	
ECMO	2 (8%)	2 (9.5%)	0 (0.0%)	
Reason for resp support				0.52
Hypoxic respiratory failure	17 (70.8%)	14 (70%)	3 (75%)	
Hypercarbic respiratory failure	4 (16.7%)	4 (20%)	0 (0.0%)	
Mixed respiratory failure	1 (4.2%)	1 (5%)	0 (0.0%)	
Hemodynamic instability	2 (8.3%)	1 (5%)	1 (25%)	
Type of organ failure				
Respiratory	19 (76%)	15 (71.4%)	4 (100%)	0.54
Cardiac	12 (48%)	8 (38.1%)	4 (100%)	0.039
Renal	2 (8%)	1 (4.8%)	1 (25%)	0.3
Hepatic	3 (12%)	2 (9.5%)	1 (25%)	0.422
Hematological	4 (16%)	3 (14.3%)	1 (25%)	0.527
Neurological	3 (12%)	1 (4.8%)	2 (50%)	0.057

BiPAP: bilevel positive pressure ventilation, CPAP: continuous positive airway pressure, ECMO: extracorporeal membrane oxygenation, GCS: Glasgow coma scale, HFNC: high-flow nasal canula, PRISM III: The pediatric risk of mortality III score.

Reduction of lymphocyte and neutrophil counts in peripheral blood was observed in other respiratory virus infections in children, including influenza [21]. In SARS-CoV-2-infected adults, studies found that leukopenia is associated with a severe illness [22]. We found that non-survivors had lower mean white blood cell (4.75 vs 11 $\times$ 10^9/L, p = 0.05), lymphocyte (0.77 vs 3.04 $\times$ 10^9/L, p = 0.005) and neutrophil counts (3.7 vs 6.62 $\times$ 10^9/L, p = 0.263) than survivors. However, none were statistically significant in the univariate hazard model. Both groups have elevated D-dimer levels. Interestingly, we found that the degree of increase in D-dimer was significantly lower in the non-survival group (mean: 3612 vs 1086 ng/dl, p = 0.003). The reason for this difference between the two groups is not clear. This finding is not in keeping with a larger cohort of severe adult COVID-19 patients [23]. A possible explanation for our finding could be that non-survivors had rapid progression of refractory circulatory instability that did not allow sufficient time for the rise of D-dimer, as an increasing trend of D-dimer may associate with disease worsening [24]. In addition, the observed difference can be related to the unmeasured confounding effect. For instance, age-dependent normal ranges in D-dimer serum concentration is not fully described [25].

Procalcitonin, the precursor of the hormone calcitonin, synthesis can be triggered by inflammatory cytokines in response to severe bacterial infection. However, this response is not specific and was observed in severe respiratory viral infections [26]. Similarly, procalcitonin was found to be a predictor for ICU admission and mortality in adult patients with COVID-19 [27,28]. Our findings were in-line with these reports. We found that procalcitonin, done at the time of ICU admission, was associated with mortality.

The reason for ICU admission and type of organ dysfunction could be associated with patients' outcome. Circulatory failure was significantly associated with pediatric death in our cohort despite the small number of patients. A similar finding was observed in a study evaluating severe SARS-CoV-2 infection in adults by Zhou et al. Acute cardiac injury and heart failure were significantly associated with in-hospital death [23]. Significant expression of angiotensin-converting enzyme 2 (ACE2) receptor, the protein required for viral attachment, on the myocardial

Table 3
Laboratory investigation and therapies provided to the study population.

Variables	Total (n = 25)	Survivors (n = 21)	Non-survivors (n = 4)	*p*-value
Laboratory investigations within 24 h of ICU admission (mean, SD)				
Creatinine	33.7 (17.3)	30.8 (12.9)	50.3 (32)	0.400
White blood cells	10.0 (8.8)	11.0 (9.1)	4.75 (4)	0.050
Absolute lymphocyte count	2.68 (2.5)	3.04 (2.6)	0.77 (0.8)	0.005
Absolute neutrophil count	6.16 (6.2)	6.62 (6.5)	3.70 (3.9)	0.263
Hemoglobin	111 (34.5)	112 (35.8)	108 (30.8)	0.821
Platelets	243 (167)	268 (169)	107 (56.4)	0.003
INR	1.30 (0.5)	1.25 (0.2)	1.53 (1.1)	0.627
D-dimer	3106 (3491)	3612 (3750)	1086 (306)	0.017
Ferritin	1229 (1689)	1358 (1807)	587 (796)	0.277
Lactate dehydrogenase	518 (224)	515 (226)	546 (288)	0.903
Troponin	24.7 (37.3)	24.7 (37.3)	0 (0)	NA
C-reactive protein	84.7 (107)	86.3 (116)	74.7 (22.3)	0.699
Procalcitonin	10.2 (21.2)	5.36 (14.0)	33.0 (35.7)	0.220
Erythrocyte sedimentation rate	35.4 (25.9)	29.8 (22.4)	58.0 (35.4)	0.451
Alkaline phosphatase	152 (78.2)	151 (81.7)	156 (68.7)	0.900
Alanine transferase	40.3 (67.6)	44.2 (74.0)	21.8 (11.3)	0.223
Albumin	33.3 (7.6)	34.3 (7.1)	28.8 (9.5)	0.336
pCO2	6.52 (2.2)	6.78 (2.3)	5.20 (1.3)	0.1
pH	7.29 (0.1)	7.30 (0.1)	7.27 (0.2)	0.843
Chest X-ray				0.84
Normal	1 (4.2%)	1 (4.8%)	0 (0.0%)	
Increased BV marking	2 (8.3%)	2 (9.5%)	0 (0.0%)	
Unilateral infiltrate	6 (25.0%)	6 (28.6%)	0 (0.0%)	
Bilateral infiltrate	9 (37.5%)	7 (33.3%)	2 (66.7%)	
Diffuse ground-glass opacities	6 (25.0%)	5 (23.8%)	1 (33.3%)	
Positive microbiological investigation				
Blood culture	3 (12%)	3 (14.3%)	0 (0.0%)	1
Urine culture	1 (4%)	1 (4.8%)	0 (0.0%)	1
Antibiotics				
Penicillins	4 (16%)	3 (14.3%)	1 (25%)	0.527
Third-generation cephalosporins	14 (56%)	12 (57.1%)	2 (50%)	1
Macrolides	4 (16%)	3 (14.3%)	1 (25%)	0.527
Lincosamides	3 (12%)	1 (4.8%)	2 (50%)	0.057
Beta lactam-beta lactamase inhibitor (anti-pseudomonal)	11 (44%)	8 (38.1%)	3 (75%)	0.288
Glycopeptides	11 (44%)	10 (47.6%)	1 (25%)	0.604
Carbapenems	5 (20%)	3 (14.3%)	2 (50%)	0.166
Aminoglycosides	2 (8%)	1 (4.8%)	1 (25%)	0.3
Trimethoprim-sulfonamide combinations	2 (8%)	1 (4.8%)	1 (25%)	0.3
Fluroquinolones	1 (4%)	1 (4.8%)	0 (0.0%)	1
Imidazoles	1 (4.2%)	1 (5%)	0 (0.0%)	1
Antifungals	4 (16%)	3 (14.3%)	1 (25%)	0.527
Antivirals				
Lopinavir/ritonavir	1 (4%)	1 (4.8%)	0 (0.0%)	1
Favipiravir	3 (12%)	3 (14.3%)	0 (0.0%)	1
Immunomodulators				
Tocilizumab	6 (24%)	5 (23.8%)	1 (25%)	1
High dose steroids	3 (12%)	3 (14.3%)	0 (0.0%)	1
Low dose steroids	9 (36%)	6 (28.6%)	3 (75%)	1
Intravenous immunoglobulin	5 (21.7%)	4 (21.1%)	1 (25%)	1
Convalescent plasma	2 (8%)	1 (4.8%)	1 (25%)	1
Anticoagulation	10 (43.5%)	8 (42.1%)	2 (50%)	1
Vasoactive agents				
Epinephrine	4 (16%)	2 (9.5%)	2 (50%)	0.106
Norepinephrine	5 (20%)	3 (14.3%)	2 (50%)	0.166
Dopamine	3 (12%)	2 (9.5%)	1 (25%)	0.422
Dobutamine	3 (12%)	2 (9.5%)	1 (25%)	0.422
Milrinone	2 (8%)	1 (4.8%)	1 (2%)	0.3

ICU: intensive care unit, INR: international normalized ratio, pCO2: carbon dioxide partial pressure.

cells is believed to play a role in the increased cardiac morbidity in COVID-19 [29,30]. Also, cytokine release syndrome triggered by SARS-CoV-2 infection may contribute the circulatory failure [31].

This multicenter study has several limitations. The study is limited to its retrospective nature. Clinical data were dependent on the healthcare workers' accuracy in recording daily medical information. In addition, since the severe and critical disease is uncommon in children, number of the study subjects was limited. For that reason, we were not able to accurately define all predictors for mortality during the ICU stay. Finally, study centers had variable supportive services. Not all ICUs were part of a tertiary pediatric center or had an ECMO service. Whether this contributed to patient mortality is unclear although patient transferring to another, more equipped, ICU was possible. Finally, study centers may have different laboratory assays with distinct test performance. This may contribute to some differences in laboratory results. However, there was insignificant differences in overall laboratory results among the study centers between the two patient groups. Also, all centers used commercial and verified assays. Finally, long-term follow-up

for the discharged patients to assess the potential long-term effect of ICU admission was not possible.

Conclusions

Our findings showed that children admitted to the ICU with SARS-CoV-2 infection, generally, have a favorable outcome. Also, low platelet counts and circulatory compromise at the time of ICU admission were associated with death. Due to the small study population in this paper, larger prospective studies are needed to confirm our findings and better understand SARS-CoV-2 infection in children.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Ethics board approval from the Ministry of Health of Kuwait and each respective center in KSA were obtained.

CRediT authorship contribution statement

Abdulla Alfraij: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. **Abdulrahman A. Bin Alamir:** Conceptualization, Investigation, Writing - review & editing. **Abdulnasir M. Al-Otaibi:** Conceptualization, Investigation, Writing - review & editing. **Danah Alsharrah:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Abdulrahman Aldaithan:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Ahmed M. Kamel:** Methodology, Data curation, Formal analysis. **Muna Almutairi:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Salman Alshammari:** Conceptualization, Investigation, Writing - review & editing. **Mohammed Almazyad:** Conceptualization, Investigation, Writing - review & editing. **Jara Mia Macarambon:** Conceptualization, Investigation, Writing - review & editing. **Mohammad Alghounaim:** Conceptualization, Methodology, Data curation, Writing - original draft, Supervision.

Acknowledgement

We thank Dr Sarah Al Youha, MD, PhD, for her help with initial statistical analysis.

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