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International Journal of Infectious Diseases 107 (2021) 78–85

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Mortality in children with positive SARS-CoV-2 polymerase chain reaction test: Lessons learned from a tertiary referral hospital in Indonesia

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ARTICLE INFO

Article history:
Received 3 December 2020
Received in revised form 5 April 2021
Accepted 7 April 2021

Keywords:
COVID-19
SARS-CoV-2
Outcome
Children
Indonesia

ABSTRACT

Background: The incidence of coronavirus disease 2019 (COVID-19) is still increasing rapidly, but little is known about the prevalence and characteristics of fatal cases in children in Indonesia. This study aimed to describe the characteristics of children with COVID-19 with fatal outcomes in a tertiary referral hospital in Indonesia.
Methods: This cross-sectional study used data collected from the medical records of patients with COVID-19 admitted to Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia from March to October 2020.
Results: During the study period, 490 patients were admitted and diagnosed with suspected and probable COVID-19. Of these patients, 50 (10.2%) were confirmed to have COVID-19, and 20 (40%) had a fatal outcome. The fatality rate was higher in patients aged ≥10 years, categorized with severe disease upon admission, PaO_2/FiO_2 ratio ≤300 mmHg and chronic underlying diseases. The most common clinical manifestations were generalized symptoms, while acute respiratory distress syndrome (8/20) and septic shock (7/20) were the two most common causes of death. Increased procalcitonin, D-dimer, lactate dehydrogenase and presepsin levels were found in all fatal cases. One patient met the criteria of multisystem inflammatory syndrome in children.
Conclusion: Our work highlights the high mortality rate in paediatric patients with positive SARS-CoV-2 polymerase chain reaction test. These findings might be related to or co-incided with COVID-19 infection. Further studies are needed to improve understanding of the role of severe acute respiratory syndrome coronavirus-2 in elaborating the mechanisms leading to death in children with comorbidities.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in Wuhan, Hubei Province, China in December 2019. The disease caused by this virus later became known as coronavirus disease 2019 (COVID-19) (World Health Organization, 2020a). Most reports have indicated that children and adolescents comprise a small proportion of confirmed cases, and that these populations are less likely to be severely affected than adults (Castagnoli et al., 2020; Dong et al., 2020a; Ludvigsson, 2020; Rodriguez-Morales et al., 2020). Furthermore, studies have reported a good health status in children with underlying chronic conditions and those on immunosuppressive treatment (Nicastro et al., 2020; Di Giorgio et al., 2021). One study reported 80 deaths in children aged 0–14 years in a population of 137,047,945, resulting in a mortality rate of 0.06 per 100,000 population (Bhopal et al., 2020).

However, in early May 2020, an increasing amount of evidence emerged from the UK, the USA and Europe of a different manifestation of COVID-19 in paediatric patients, namely

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https://doi.org/10.1016/j.ijid.2021.04.019

hyperinflammatory shock with multi-organ involvement (Riphagen et al., 2020). This condition is interchangeably referred to as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 (Centers for Disease Control and Prevention, 2020; Royal College of Paediatrics and Child Health, 2020; World Health Organization, 2020b). The clinical manifestations of MIS-C and PIMS-TS are both distinct from and similar to other inflammatory syndromes in children, such as Kawasaki disease, Kawasaki disease shock syndrome and toxic shock syndrome (World Health Organization, 2020b).

Systematic reviews have shown that among 662 patients who fulfilled the MIS-C criteria, only 11 deaths (1.7%) were reported (Ahmed et al., 2020; Jiang et al., 2020). However, as of 20 July 2020, the Indonesian Pediatrician Society had reported 2,712 confirmed paediatric cases of COVID-19 with 51 deaths (1.9%) (Pulungan, 2020). There are limited data on the clinical characteristics of paediatric cases with COVID-19. More reliable data are needed to determine the disease burden to create better screening and intervention strategies for the Indonesian paediatric population. For these reasons, this study aimed to describe the characteristics of paediatric patients with fatal outcomes with positive COVID-19 and/or MIS-C tests admitted to a tertiary referral hospital in Indonesia.

Materials and methods

Patients, clinical data and sample collection

This is a cross sectional study wtih data collected from the medical records of suspected and confirmed paediatric cases of

Table 1
Demographic data of the confirmed paediatric cases of coronavirus disease 2019 (n = 20) at Dr. Cipto Mangunkusumo National Central Hospital, Indonesia, 2020.

Parameter	Results
Sex (n = 20)	
Male	10
Female	10
BMI, median (range) (n = 15)	17.1 (11.2–29.9)
Severely underweight and underweight	3
Normal weight	9
Overweight and obese	3
Age in years, median (range) (n = 20)	11.3 (1.0–17.92)
<1	0
1–5	5
5–10	5
>10	10
Rapid antibody tests (n = 20)	
IgM positive	0
IgG positive	2
Negative	7
Not tested	11
Source of RT-PCR samples (n = 20)	
Naso-oropharyngeal	19
Sputum	1
Ct values (N gene Cq), median (range)	
First sample (n = 9)	33.2 (21.41–36.26)
Second sample (n = 6)	33.8 (22.78–38.1)
Third sample (n = 3)	31.3 (22.4–32.47)
Fourth sample (n = 2)	30.0 (20.05–35.88)
Clinical manifestations	
Generalized symptoms	12
Respiratory symptoms	9
Gastrointestinal symptoms	8
Neurologic symptoms	3
Comorbidities	
Kidney diseases	8
Cardiovascular diseases	6
Malignancy	6
Neurological diseases	4
Overweight and obesity	3
Underweight	3
Burn injury	2
Systemic lupus erythematosus	2
Deep vein thrombosis	1
Acute appendicitis with generalized peritonitis	1
Biliary atresia	1
Intestinal tuberculosis	1
Number of comorbidities	
Single	4
Multiple (two or more)	16
Exposure to healthcare facilities or professionals (n = 20)	18
History of contact with suspected or confirmed cases (n = 20)	2
Shock (n = 20)	
Septic	9
Not in shock	7
Hypovolaemic	4

BMI, body mass index; RT-PCR, reverse transcriptase polymerase chain reaction; Ct, cycle threshold.

COVID-19 admitted to Dr. Cipto Mangunkusumo National Central Hospital, Jakarta, a tertiary referral hospital in Indonesia, from March 2020 (when the first Indonesian case of COVID-19 was announced) to October 2020 (World Health Organization, 2020c). Before the pandemic, Dr. Cipto Mangunkusumo National Central Hospital was a general hospital that serves pediatric and adult patients with 1001 beds capacity. During the pandemic, the new pediatric unit was converted into a COVID-19 isolation unit that serves 237 beds (13 beds for family-centered wards, eight beds for children only, eight beds for paediatric intensive care unit (PICU), and eight beds for neonatal intensive care unit (NICU) isolation room). The total bed capacity was reduced to 888 beds due to a lack of personnel. In 2020, 31,075 patients across all ages visited the emergency department, with 1373 (4.41%) patients confirmed as positive for COVID-19. Demographic data (age, sex, weight and height), COVID-19 status [rapid antibody test results, reverse transcriptase polymerase chain reaction (RT-PCR) results, cycle threshold (Ct) values], signs and symptoms (such as fever and lethargy), respiratory symptoms, gastrointestinal symptoms, and neurological symptoms, comorbidities, PICU status, cause of death and laboratory data were obtained. We also obtained the length of stay in PICU and the total length of stay from admission to discharge or death.

This study included all paediatric patients (0–18 years old) who had tested positive for COVID-19 infection using RT-PCR from any sample involving a swab or other specimen and had a fatal outcome. Probable cases were excluded from this study. We used WHO's guideline to define probable cases as (1) a suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the resultof the test reported by the laboratory); or (2) a suspect case for whom testing could not be performed for any reasons (WHO, 2020d).

Patients were classified according to their clinical presentation upon admission as: (1) asymptomatic (absence of signs and symptoms associated with COVID-19, normal clinical imaging, but positive ribonucleic acid SARS-CoV-2 test); (2) mild [presence of symptoms limited to upper respiratory tract (including fever, fatigue, myalgia, cough, sore throat, runny nose or nasal congestion) or gastrointestinal symptoms (including nausea, vomiting and abdominal pain, with normal lung auscultation)]; (3) moderate (presence of symptoms mentioned in the mild category together with clinical signs and symptoms of pneumonia but without hypoxaemia); (4) severe (presence of signs and symptoms mentioned above together with dyspnoea, central cyanosis and oxygen saturation of <92%); and (5) critical (presence of acute respiratory distress syndrome, respiratory failure, encephalopathy, myocardial injury, coagulation dysfunction and acute kidney injury) (Dong et al., 2020b).

The Centers for Disease Control and Prevention (CDC) criteria for MIS-C associated with COVID-19 was used in this study. The

Table 2
Evolution of patients during hospital admission (n = 20).

Parameter	Results
Days to worsening clinical manifestations since the first day of admission, median (range) (n = 20)	3 (0–50)
Days to worsening clinical manifestations since the onset of first clinical manifestations occurred, median (range) (n = 20)	5.5 (0–55)
Days to intubation since the first day of admission, median (range) (n = 10)	2.5 (0–50)
Days to ICU admission since the first day of admission, median (range) (n = 16)	2.5 (0–50)
Days spent in ICU, median (range) (n = 16)	1.5 (0–11)
Days to death since the first day of admission, median (range) (n = 20)	7 (0–51)
Days to death since the onset of first clinical manifestations, median (range) (n = 20)	8 (1–65)
Dialysis (n = 20)	
Yes	4
No	16
Fluid resuscitation (n = 20)	
Yes	8
No	12
Medications (n = 20)	
Vasopressors	19
Antibiotics	18
Steroids	6
IVIG	2
Enoxaparin	1
Lopinavir + ritonavir	1
Ventilator use (n = 20)	
Yes	10
No	10
PaO_2/FiO_2 ratio (n = 16)	
≤300	10
>300	6
Clinical condition upon admission (n = 20)	
Mild	0
Moderate	2
Severe	11
Critical	7
Cause of death (n = 20)	
Acute respiratory distress syndrome	8
Septic shock	7
Hypovolaemic shock	1
Encephalopathy sepsis	1
Medical and surgical bleeding	1
Pulmonary thrombosis	1
Multi-organ dysfunction syndrome	1
MIS-C (n = 20)	
Present	1
Absent	19

ICU, intensive care unit; IVIG, intravenous immunoglobulin; MIS-C, multisystem inflammatory syndrome in children.

criteria classified patients as having MIS-C if: (1) they were aged <21 years; (2) they had a fever and elevated inflammatory markers were present; (3) they had a clinically severe illness requiring hospitalization and had multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological or neurological); (4) other plausible alternative diagnoses had been excluded; and (5) they had a positive RT-PCR, serology or antigen test or COVID-19 exposure within 4 weeks preceding the onset of symptoms (Centers for Disease Control and Prevention, 2020). The CDC criteria were chosen because they were released earlier than the World Health Organization criteria. However, later on, our national guideline adopted the World Health Organization criteria of MIS-C.

Detection of COVID-19 infection

All naso-oropharyngeal and sputum/endotracheal tube aspirate samples were tested for the presence of SARS-CoV-2, and the N gene Cq was used as the parameter for the RT-PCR target. The standard protocol for obtaining the samples was via naso-oropharyngeal swabs with a minimum of two samples within a 1-day interval. If the samples were positive, subsequent samples were obtained every 5–7 days until conversion was achieved. Ct values >40 (detection limit) were reported as negative, while Ct values <37 were considered positive (He et al., 2020). A medium load (Ct value 37–40) requires confirmation via at least one repeat sample in the study institution.

Statistical analysis was done using IBM SPSS 22.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). The normality test was carried out using the Kolmogorov-Smirnov method, and if the p-value is greater than 0.05, the data were considered to have a normal distribution. The data would be presented in mean and standard deviation if the distribution was normal, while median and range would be used if it was not normal.

Results

In total, 490 paediatric cases were categorized as suspected or probable COVID-19. Of these, 50 (10.2%) cases were confirmed by RT-PCR. Among the confirmed cases, 20 patients (40%) died and were included in this analysis. The mortality rate in confirmed cases of COVID-19 in children was 40%.

There was no difference in mortality between males and females in patients positive for COVID-19 (Table 1). Most (18/20) of the patients had previous exposure to healthcare facilities or professionals. The highest mortality rate was seen in patients aged >10 years and those placed in the severe category upon admission. Most (12/20) patients presented with generalized or systemic symptoms such as fever, malaise, myalgia and fatigue. Kidney diseases, such as nephritic lupus with secondary hypertension, acute kidney failure and chronic kidney disease, were the most common comorbidities, found in eight patients, with four patients requiring dialysis. Three of these patients were previously on chronic dialysis, while one of them was receiving continuous renal replacement therapy regularly before their COVID-19 diagnosis.

Septic shock was the most common type of shock (9/20) seen among subjects, and acute respiratory distress syndrome was the most common cause of death (8/20). On average, it took 3 days from admission and 5.5 days from the onset of the first clinical manifestations of COVID-19 for their conditions to worsen (Table 2). Of the 20 patients who died, 16 required admission to the intensive care unit (ICU), with the median number of days from hospital admission to ICU admission being 2.5 days (range 0–50). Vasopressors (19/20) and antibiotics (18/20) were the two most common medications used during hospitalization, while mechanical ventilation was needed in half of the patients. According to national and hospital guidelines, patients were given antibiotics and antivirals according to the clinical severity of their symptoms. Most notably, one of the patients met the MIS-C criteria.

SARS-CoV-2 RNA was detected in a sputum sample/endotracheal tube aspirate in one patient and naso-oropharyngeal swab specimens in the remaining patients. The median first-sample Ct value was 33.2, with a range of 21.41–36.26.

All patients were admitted with increased procalcitonin, D-dimer, lactate dehydrogenase and presepsin levels. White blood cell (WBC) count, platelet count, lactic acid, prothrombin time and creatinine levels were normal in most patients on Days 1 and 3 (Table 3).

Detailed clinical characteristics of each subject are described in Table 4. Two cases were asymptomatic (Cases 1 and 9), as they were initially admitted for severe burns affecting body surface areas of 59% and 45%, respectively, and were later diagnosed with COVID-19 by RT-PCR testing. Notably, sixteen out of twenty patients had more than one comorbidity. Echocardiography was performed on one patient (Case 5) and showed pericardial effusion with an ejection fraction of 77%. Two cases presented with moderate illness (Cases 3 and 10) and passed away due to surgical complications related to bleeding. The preliminary findings showed that increments in creatinine levels between Day 1 and

Table 3
Interpretation of laboratory findings.

Parameter	Normal value	Median (range)	Elevated, *n*	Normal, *n*	Decreased, *n*
Haemoglobin (g/dL) (*n* = 20)	12.0–15.0	10.2 (3.7–17.6)	2	5	13
White blood cells (10^3/μL) (*n* = 20)	4.0–10.0	12.7 (1.22–246.03)	8	9	3
Platelets (10^3/μL) (*n* = 20)	150–410	274 (1–818)	1	12	7
CRP (mg/L) (*n* = 17)	<5.0	25.6 (5–472.5)	16	1	N/A
Procalcitonin (ng/mL) (*n* = 18)	<0.05	3.1 (0.1–481.3)	18	0	N/A
Fibrinogen (mg/dL) (*n* = 10)	200–400	447.5 (44–1118)	5	2	3
D-dimer (μg/L) (*n* = 9)	<440	5490 (1120–6820)	9	0	N/A
Ferritin (ng/mL) (*n* = 7)	20–200	1411.4 (1–28,740.1)	5	1	1
SGOT (U/L) (*n* = 17)	10–40	69 (14–3173)	10	6	1
SGPT (U/L) (*n* = 17)	5.9–37	41 (10–1095)	9	8	0
Lactic acid (mmol/L) (*n* = 10)	0.7–2.5	1.6 (0.6–8.6)	2	7	1
Prothrombin time (s) (*n* = 18)	9.8–12.6	13.2 (10.1–120)	9	9	0
Activated partial prothrombin time (s) (*n* = 18)	31.0–47.0	50.4 (26.9–180)	10	7	1
Lactate dehydrogenase (B) (U/L) (*n* = 2)	125–220	713.5 (364–1063)	2	0	0
Presepsin (pg/mL) (*n* = 2)	<300	2274.5 (1257–3292)	2	0	N/A
Creatinine (Day 1) (mg/dL) (*n* = 19)	0.22–0.59	0.6 (0.2–5)	9	10	0
Creatinine (Day 3) (mg/dL) (*n* = 9)	0.22–0.59	0.7 (0.1–4.9)	4	5	0

CRP, C-reactive protein.

Table 4
Clinical characteristics of paediatric and adolescent patients with confirmed coronavirus disease 2019 (COVID-19) and fatal outcome.

No	PCR-positive sample		Age (years)	Mean Ct values	Rapid test	Clinical manifestations associated with COVID-19	Comorbidities	Shock	Mechancal ventilation	Fluid resuscitation	Medications	Laboratory findings	Clinical condition upon admission	Days in PICU	Days to intubation	Days to death	Cause of death
	Naso-oropharyngeal	Sputum/ ETT															
1 (M)	-	+	7.83	NA	IgG +	Asymptomatic	Superficial to full-thickness burn with 59% of body surface area affected, multi-organ dysfunction syndrome, overweight	Hypovolaemic	Yes	Yes	Epinephrine, dopamine, antibiotics	↑WBC, neutrophil count, PCT, CRP, SCr, ALT; ↓ lymphocyte count; metabolic acidosis	Critical	0	0	0	MODS
2 (F)	+	-	6.7	35.7	IgG +	Fever, fatigue, myalgia	Neuroblastoma stage IV, bilateral hydronephrosis, hypertensive kidney disease with kidney failure, underweight	No	No	No	Dobutamine	↑SCr, serum ureum, ALT, PCT, PT, APTT, INR, magnesium, phosphate; ↓Hb, platelets, WBC, lymphocyte count, fibrinogen, calcium, albumin; ΔSCr: 0,4	Severe	1	4	20	Septic shock
3 (M)	+	-	14.7	34.5	Neg	Fever, malaise, nausea, vomiting	Acute lymphoblastic leukaemia, agranulocytosis, moderate protein-energy malnutrition, anaemia, thrombocytopenia, cardiomyopathy, gastroenteritis, toxic liver disease	No	No	Yes	Epinephrine, norepinephrine, antibiotics	↑Lymphocyte count, uric acid, SCr, serum ureum, bilirubin, triglyceride, ALT, AST, CRP, PCT, D-dimer, lactic acid; ↓Hb, platelets, neutrophil count, sodium, potassium, albumin, phosphate, calcium, fibrinogen, LDL, HDL; metabolic alkalosis; ΔSCr: 0,1	Moderate	1	50	51	Medical and surgical bleeding
4 (F)	+	-	14.8	NA[a]	Not done	Fever	Suspected deep vein thrombosis and unspecified severe protein-energy malnutrition	No	No	No	None	↑CRP, PCT, WBC, D-dimer, APTT; ↓sodium, serum ureum	Severe	-	-	2	Pulmonary thrombus
5 (F)	+	-	15.1	30.025	Not done	Fever, dyspnoea, rash, mucosal changes	ARDS, nephritic lupus grade III	No	Yes	No	Epinephrine, norepinephrine, antibiotics	↑SCr, Hb, serum ureum, phosphate, neutrophil count, thrombocyte, ferritin, CRP, PCT, D-dimer, fibrinogen, CK-MB; ↓sodium, albumin, lymphocyte count, lactic acid, calcium, potassium; metabolic alkalosis; echocardiography: pericardial effusion with 77% EF; ΔCr: 0,6	Severe	2	2	4	ARDS due to COVID-19
6 (F)	+	-	1.1	38.1	Not done	Diarrhoea, altered mental status	Hepatic failure, intrahepatic cholestasis, CMV infection, prolonged diarrhoea coagulation defects, metabolic encephalopathy	Hypovolaemic	Yes	No	Epinephrine, norepinephrine, dobutamine, antibiotics, steroid	↑Ammonia, CRP, PCT, potassium, magnesium, bilirubin, ALT, AST, PT, APTT, lactic acid, neutrophil count, lymphocyte count, ferritin; ↓sodium, calcium, phosphate, fibrinogen, albumin; metabolic acidosis; ΔSCr: -0,2	Critical	5	7	8	Septic shock
7 (M)	+	-	13.3	33.16	Not done	Fever, cough, dyspnoea	Chronic kidney failure, essential hypertension, anemia, delirium, obesity	No	Yes	No	Epinephrine, antibiotics, steroid, IVIG	↑Ferritin, APTT, neutrophil count, WBC; ↓Hb metabolic acidosis	Critical	0	2	2	ARDS due to COVID-19
8 (F)	+	-	3.3	34.245	Not done	Diarrhoea, vomiting,	Haematemesis due to rupture of oesophageal varices, biliary atresia, acute diarrhoea with mild–moderate dehydration, hyperammonaemia, marasmus, hyperbilirubinaemia, hyponatraemia, anaemia, severely underweight	No	Yes	No	Epinephrine, norepinephrine, hydrocortisone, antibiotics	↑PCT, bilirubin, PT, APTT, neutrophil count, lymphocyte count, WBC, ammonia, SCr, serum ureum, ALT, AST; ↓ Hb, sodium; metabolic acidosis	Severe	1	1	2	Septic shock
9 (M)	+	-	1.8	36.26	Neg	Asymptomatic	Superficial dermal to mid-dermal burn with 45% of body surface area affected, haematemesis due to stress ulcer	No	No	Yes	Epinephrine, antibiotics	↑PCT, WBC; ↓sodium, PT, albumin, Hb; metabolic alkalosis	Severe	-	-	7	Hypovolaemic shock
10 (F)	+	-	17.8	21.225	Neg	Cough, dyspnoea	Polyserositis tuberculosis, ascites, obstruction of bile duct, protein-energy malnutrition	Hypovolaemic	Yes	No	Epinephrine, norepinephrine, dobutamine, antibiotics, steroid, lopinavir + ritonavir	↑CRP, PCT, PT, APTT, bilirubin, WBC, neutrophil count, D-dimer, SCr, serum ureum, potassium, presepsin, lactic acid, LDH (B), ferritin; ↓sodium, total protein, albumin, globulin, CD3+, CD4+, CD8+, CD45+, lymphocyte count, LDL, HDL, total protein; metabolic alkalosis; ΔSCr: 0,1	Moderate	10	41	51	Septic shock
11 (F)	+	-	13.7	27.18	Neg	Cough (haemoptysis), nasal congestion, dyspnoea	ARDS, SLE, chronic kidney failure, supraventricular tachycardia, septic encephalopathy	No	Yes	No	Epinephrine, norepinephrine, antibiotics, steroids, IVIG, enoxaparin	↑ PCT, SCr, serum ureum, CRP, ALT, neutrophil count, WBC, ferritin, D-dimer, fibrinogen, LDH (B), PT, APTT; ↓ albumin, sodium, lymphocyte count, Hb; metabolic alkalosis; ΔSCr: 2,6	Critical	11	0	11	ARDS due to COVID-19
12 (F)	+	-	1.7	NA	Not done	Fever, diarrhoea, altered mental status, seizure	Septic encephalopathy, underweight	Hypovolaemic	No	Yes	Epinephrine, antibiotics	↑ PCT, AST, CRP, PT, neutrophil count, lymphocyte count; ↓ sodium, albumin, Hb; respiratory alkalosis	Critical	8	8	8	Septic encephalopathy
13 (M)	+	-	9.1	NA	Neg	Fever, abdominal pain	Acute myeloid leukaemia, febrile neutropenia, respiratory failure	Septic	No	No	Norepinephrine, antibiotics	↑ PCT, CRP, bilirubin, GGT, PT, APTT; ↓ albumin, AST, ALT, Hb, thrombocyte, WBC, neutrophil count, lymphocyte count; respiratory alkalosis; ΔSCr: -0,1	Severe	4	41	45	ARDS due to COVID-19
14 (M)	+	-	14.6	NA	Not done	Cough, dyspnoea, lymphadenopathy	Leukaemia, toxic liver disease, cardiomegaly	Septic	No	No	Norepinephrine, antibiotics	↑ PCT, CRP, WBC, uric acid, PT, bilirubin, ALT, AST; ↓ Hb, thrombocyte, albumin, sodium, calcium; metabolic alkalosis; ΔSCr: 0	Severe	-	-	19	Septic shock
15 (F)	+	-	9.3	NA	Not done	Cough, dyspnoea	SLE	Septic	No	No	Epinephrine, antibiotics, steroid	↑ Neutrophil count, lymphocyte count, WBC; ↓sodium, albumin; respiratory alkalosis	Severe	-	-	3	ARDS due to COVID-19
16 (M)	+	-	17.9	NA	Not done	Fever, cough, nasal congestion, nausea, vomiting	Rhabdomyosarcoma, hypospadia, acute kidney failure, encephalopathy, hydronephrosis, urosepsis, respiratory failure	Septic	No	Yes	Norepinephrine, antibiotics	↑ SCr, serum ureum, WBC, ALT, PT, PCT, CRP; ↓ Hb, sodium; metabolic acidosis; ΔSCr: -0,1	Critical	1	1	2	ARDS due to COVID-19
17 (M)	+	-	1	NA	Neg	Fever, cough, nasal congestion, dyspnoea, diarrhoea	Encephalopathy, gastroenteritis	Septic	No	No	Epinephrine, antibiotics	↑CRP, PCT, SCr, ALT, AST, WBC, presepsin; ↓ Hb, sodium, albumin, thrombocyte	Severe	0	7	7	Septic shock due to *Klebsiella pneumoniae*

18 (F)	-	+	14.2	NA[a]	Neg	Fever, abdominal pain, nausea, vomiting	Acute appendicitis with generalized peritonitis	Septic	Yes	No	Norepinephrine, epinephrine, antibiotics	↑CRP, PCT, ALT, AST, APTT, neutrophil count, serum ureum, SCr, bilirubin, WBC, D-dimer, fibrinogen; ↓sodium, albumin, lymphocyte count, thrombocyte; respiratory acidosis	Critical	2	0	2	Septic shock
19 (M)	+	-	9.3	34.05	Neg	Fever, dyspnoea, vomiting, seizure	Obesity	Septic	Yes	No	Epinephrine, norepinephrine, dobutamine, hydrocortisone, antibiotics	↑Neutrophil count, magnesium; ↓lymphocyte count, calcium, sodium, and potassium; respiratory alkalosis	Severe	0	3	3	ARDS due to COVID-19
20 (M)	+	-	14.08	22.3	Not done	Fever, cough, dyspnoea	Acute myeloid leukaemia	No	Yes	Yes	Epinephrine, steroid, antibiotics	↑Lymphocyte count, CRP, PCT, ureum; ↓Hb, sodium, potassium, ureum; respiratory alkalosis	Severe	5	2	7	ARDS due to COVID-19

ALT, alanine transaminase; APTT, activated partial prothrombin time; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; CK-MB, creatinine kinase-MB; CMV, cytomegalovirus; CRP, C-reactive protein; Ct, cycle threshold; EF, ejection fraction; ETT, endotracheal tube; GGT, gamma-glutamyl transferase; Hb, haemoglobin; HDL, high-density lipoprotein; IgG, immunoglobulin G; INR, international normalized ratio; LDL, low-density lipoprotein; LDH (B), lactate dehydrogenase B; MODS, multiple organ dysfunction syndrome; neg, negative; PCR, polymerase chain reaction; PCT, procalcitonin; PICU, paediatric intensive care unit; PT, prothrombin time; SCr, serum creatinine; SLE, systemic lupus erythematosus; WBC, white blood cell.

[a] Samples were positive from referring hospital, and Ct values are not available.

Day 3 led to prolonged hospitalization, except for one case (Case 13). This patient showed a decrease in creatinine level, although no association or significance can be inferred.

Discussion

The clinical and laboratory characteristics of paediatric patients with COVID-19 with fatal outcomes were studied. The proportion of COVID-19-associated deaths in this study is higher than the COVID-19 case fatality rate in 42 states in the USA, which reported mortality rates of 0–0.23% as of 22 October 2020 (American Academy of Pediatrics, 2020). It is also higher than the 1.9% nationwide case fatality rate reported in Indonesia (Pulungan, 2020). As the study centre is a national tertiary referral hospital, patients often present with one or more pre-existing underlying chronic diseases that will affect their prognoses and mortality. Nearly all of the patients in this study had at least one comorbidity, with the most common being kidney disease (8/20 cases), followed by malignancy and cardiovascular disease (6/20 cases each). Chronic kidney disease is associated with a poorer prognosis due to disturbances in the innate and adaptive immune responses, rendering such patients more susceptible to all infections (Gagliardi et al., 2020). The present findings differ from those of another study which reported that 86% of patients had at least one comorbidity, with the most prevalent pre-existing conditions being medically complex conditions (40%), immunosuppression or malignancy (23%), and obesity (15%). There were two deaths reported in this study, and both of the patients who died had comorbidities (Shekerdemian et al., 2020).

Obesity and overweight are the two comorbidities frequently mentioned as risk factors for mortality in COVID-19 or MIS-C in children (Ahmed et al., 2020; Jiang et al., 2020). However, underweight is a comorbidity that has not been discussed in detail to date, especially in children. Studies performed in adult populations show conflicting results; one study found that underweight individuals tended to trend towards increased risk of contracting COVID-19, but this trend was not significant (Jung et al., 2020). Another retrospective cohort study of 2466 hospitalized adults found that underweight individuals had a borderline significant association with increased risk of death or intubation (Anderson et al., 2020).

Another reason accounting for the high mortality rate seen in this study is the severity of clinical manifestations upon presentation. One review found that non-mild disease, defined as pneumonia or need for hospitalization, accounted for 33.3% of cases. In contrast, more severe illness accounted for 9.1% of cases, which contrasts with the 55% and 35% rates, respectively, that were observed in the present study (Anderson et al., 2020). Among 58 patients in three studies, 35 required invasive mechanical ventilation (60.3%) (Belhadjer et al., 2020; Escosa-García et al., 2020; Toubiana et al., 2020). While this number is slightly lower in the present study (10/20), it is lower because six parents signed 'do not resuscitate' forms, making treatment suboptimal for these patients. Other reasons that could explain the high mortality rate in the present study are overcrowding in the hospital wards due to the sudden surge of new cases of COVID-19, delayed presentation of chronic patients to the hospital and coupled with the lack of human resources to combat the pandemic initially.

The median first-sample Ct value in this study was 33.2, similar to the results from a study in China that examined 10 paediatric patients (median Ct value of 33.5) (He et al., 2020). Low SARS-CoV-2 Ct values were associated with the increased likelihood of progression to more severe disease, increased mortality, and the presence of biochemical and hematological markers (Rao et al., 2020). According to one study, the median Ct value of the present

study is classified as a low viral load (30–39.9) (Karahasan et al., 2020).

In the present study, mortality also tended to be higher in patients with PaO_2/FiO_2 ratios ≤300 mmHg, in line with other studies performed in Europe (Wendel et al., 2020). The present study produced results similar to those of other meta-analyses (Elshazli et al., 2020; Henry et al., 2020) and one review study (Letícia et al., 2020), which reported that increased D-dimer, fibrinogen, procalcitonin, CRP and ferritin levels, as well as low haemoglobin levels were associated with severe disease and mortality. Although increased WBC counts were consistently cited as one of the significant predictors for severe disease (Elshazli et al., 2020; Henry et al., 2020; Letícia et al., 2020), nine of the patients in the present study had normal WBC counts, which might be explained by the inclusion of six patients with haematological malignancies with the potential to impair WBC count.

One patient (Case 18) met the CDC criteria for MIS-C, meaning that a positive RT-PCR, serology or antigen test or COVID-19 exposure within 4 weeks preceding the onset of symptoms was required (Ahmed et al., 2020; Jiang et al., 2020). Although two patients presented as IgG-positive on serologic testing, they did not meet the other criteria, as one presented with severe burns and no COVID-19-related symptoms (Case 1). In contrast, the other case (Case 2) presented with a high Ct value, indicating recent infection. There was limited knowledge concerning MIS-C early in the pandemic; therefore, limited data were available on its physical manifestations, such as Kawasaki-like symptoms, and diagnostic SARS-CoV-2 serology, cardiac markers and echocardiography, which may have led to the underdiagnosis of MIS-C in the study patients.

Patients were managed conservatively, as almost all paediatric guidelines recommend mainly supportive treatment. Most patients present with presumed sepsis and/or pneumonia as evidenced by clinical manifestations and elevated inflammatory markers. Hence, empirical antibiotics were given until PCR or culture and sensitivity results came back. The practice of prescribing empirical antibiotics follows the national and hospital guidelines which recommend administering antibiotics according to clinical severity (Kementerian Kesehatan Republik Indonesia, 2020). Antivirals were also given to some patients due to underlying comorbidities resulting in immunocompromised conditions. As the knowledge of COVID-19 is always evolving, knowledge about the use of intravenous immunoglobulin, steroids and low-molecular-weight heparin for prophylaxis of thrombosis was not widespread early in the pandemic. It hence reflected the lack of specific treatments for COVID-19. This study also shows that most patients were exposed to healthcare facilities. This highlights the urgent need for infection prevention education protocols, especially for children with chronic medical conditions necessitating multiple hospital visits.

This study has several limitations. First, as Dr. Cipto Mangunkusumo Hospital is a referral hospital for managing patients with COVID-19, especially those with comorbidities, the mortality rate for paediatric cases of COVID-19 reported in this study cannot be extrapolated to other hospitals, cities or regions in the country. Secondly, the authors could not establish significant associations between several of the variables mentioned above and mortality as well as MIS-C. Thirdly, the authors could not determine whether the cause of death was attributable to COVID-19 or underlying comorbidities. Finally, several laboratory panels, such as interleukins and other cytokines, were not checked to measure the severity of COVID-19. Nevertheless, despite these limitations, this study revealed a high mortality rate in paediatric patients with COVID-19. To the authors' knowledge, this study is the first to describe the clinical characteristics of an Indonesian population.

Conclusion

This study described cases of mortality in paediatric patients with positive tests for COVID-19. A higher proportion of deaths was observed in patients aged >10 years with severe manifestations upon admission, and with PaO_2/FiO_2 ratios ≤300 mmHg. This is the first study in Indonesia to highlight the mortality-related or coincidental to SARS-CoV-2. However, further multicentre studies and better intervention and management studies are required to optimize public health measures, especially for paediatric patients with severe and critical COVID-19. Further studies are also needed to improve understanding of the role of SARS-CoV-2 in supporting the mechanisms leading to mortality in children with associated comorbidities.

Author contributions

Conceptualization and study design: NDP, RD, NK, TT, MRJ, HAP, AH.

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Funding acquisition: NDP, MMD, AH.

Clinical data collection: NDP, TT, MRJ, HAP, RM, HAP, RD, NK, MRK, DBS, AHP, MMD, AP, WI, YP, HAS, ELH, DM, NWP, RM, AR, IY, AS, SH.

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Ethical approval

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia approved this study (Ref. 596/UN2.F1/ETIK/PPM.00.02/2020).

Funding

This study was funded by a research grant from Cipto Mangunkusumo Hospital.

Conflict of interests

None declared.

Acknowledgements

The authors wish to thank the Director of Cipto Mangunkusumo Hospital, all patients and their families, paediatric residents of the University of Indonesia, and the Kiara Ultimate medical team for their help and support.

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