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Original Article

Clinical Presentation of Children with COVID-19 admitted to Pediatric Intensive Care Unit: Single Center Experience

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Abstract:
Background: Coronavirus disease of 2019 (COVID-19) infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) among children is mostly a mild disease yet it may cause life threatening direct histopathological lung injury and indirect immune dysregulation with hyperimmune response that causes multi inflammatory disease.
Aim of work: to study the clinical presentation, indication of admission to pediatric intensive care unit (PICU), complications and outcome in children with COVID-19 infection.
Material and Methods: Our prospective observational study included children with COVID-19 admitted to PICU of Fayoum University Hospital, Egypt between January and March 2021.
Results: The study included 35 children admitted with severe SARS-Cov-2, diagnosed by CT chest and positive antibodies against SARS-CoV-2, of them 20 (57.1%) were males and 15 (42.9%) females. Their mean ± SD age was 9 ± 8 months (range: 1 month to 10 years). The symptoms were heterogeneous; with fever 29 (82.9%) and cough 29 (82.9%) being the most frequent. The indication of admission to PICU was respiratory failure in 29 patients (80%), pediatric multisystem inflammatory syndrome – temporally associated with SARS- CoV-2 (PMIS-TS) in 5 (14.2%); 3 shocked, 2 of them with Kawasaki-like syndrome and 1 patient with liver cell failure (2.9%). The frequencies of lymphopenia and thrombocytopenia were (80% and 29.4%, respectively). Inflammatory markers, D-dimer, and cardiac enzymes were elevated in 28 (80%) patients. Complications included myocarditis in 8 (22.9%) cases and vascular thrombosis in 4 (11.4%). Intravenous immunoglobulin was prescribed exclusively for myocarditis, 31 (88.6%) of the patients received steroids and 19 (54.2%) received anticoagulants. Eight (22.9%) died; 6 with respiratory failure, 1 with liver cell failure and 1 with PMIS-TS and shock. Four (11.4%) patients were discharged with impaired cardiac function following myocarditis. Thrombocytopenia was found in 7 cases (29.4%) and was associated with mortality among the patients studied (p=0.014).
Conclusion: Severe COVID-19 in children presented with pulmonary and non-pulmonary affection. It was complicated by serious complications as myocarditis and vascular thrombosis. PMIS-TS clinically manifested as Kawasaki disease and/or shock syndrome. Thrombocytopenia was a risk factor of mortality in the studied patients.

Level of Evidence of Study: IV (*1*)**.**
Keywords: lymphopenia; thrombocytopenia; myocarditis; pediatric; COVID-19; PMIS-TS
Abbreviations: ACE2: angiotensin-converting enzyme 2; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKMB: creatine kinase-myoglobin binding; COVID-19: Coronavirus disease-2019; CRP: C-reactive protein; CT: Computed Tomography; IL: interleukin; INR: International Normalized Ratio; IVIG; intravenous immunoglobulins; PICU: pediatric intensive care unit: PMIS-TS: pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2; SARS-Cov-2: severe acute respiratory syndrome coronavirus 2.

Introduction

During the 2019, the rapid global spread of the novel severe acute respiratory syndrome coronavirus (COVID-19) has subdued the world. On March 11, 2020, the World Health Organization declared the disease caused by the novel virus a pandemic health emergency for the first time since the 2009 swine flu (H1N1) (*2*). Hospitals in areas affected by the COVID-19

pandemic continued to face challenges due to the rapid spread of infection and the lack of accurate knowledge regarding the efficacy of available treatments. Since many patients developed severe complications, the availability of intensive level of care was critical. Compared to adults, severe pediatric COVID-19 infection has been less frequently reported (*3*). A small proportion of children develop severe acute COVID-19 disease, only 0.0048% require hospitalization because of complications as respiratory compromise or multisystem inflammatory syndrome in children (*4*). The spectrum of clinical and laboratory data of children admitted to pediatric intensive care units (PICUs) with COVID-19 was variable with a better outcome than in adults (*5*). Subclinical and mild COVID-19 infection in children is the commoner presentation, yet, it can present by an aggressive serious multisystem inflammatory syndrome with COVID 19 (MISC); also named –pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS) which might be fatal (*6*). The clinical manifestations of this hyperinflammatory syndrome are similar to Kawasaki disease and/or toxic shock syndrome, presenting with persistent fever, multiorgan dysfunction and elevated inflammatory markers. We aimed to study the clinical presentation, indication of admission to pediatric intensive care unit (PICU), complications and outcome in children with COVID-19 infection.

Subjects and Methods

The current study was a prospective observational study conducted at the PICU of Fayoum University Hospital, Egypt. The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Fayoum University, Egypt (R177). Adequate measures have been taken to safeguard data confidentiality.

Participants

The study included 35 consecutive children (1 month to 10 years of age) with severe COVID-19 or PMIS-TS who were admitted to PICU between January and March 2021.

Methods

We collected all data relevant to history and clinical examination. Severity of pulmonary COVID 19 was assessed according to: (1) the need for invasive or noninvasive mechanical ventilation; (2) impending respiratory failure; (3) sustained peripheral oxygen saturation (SPO_2) < 92% on inspired mechanical ventilation oxygen > 50%; (4) signs of shock; and (5) altered mental status [5, 6]. The diagnosis of COVID 19 was made by presence of positive IgM and IgG antibodies against SARS-CoV-2 using COVID antibody test (Artron Laboratories Inc. Canada) and by non-contrast chest Computed Tomography (CT) studies (160 MDCT Toshiba Machine, Japan). The scan was obtained at the end inspiration from the base of the neck down to the diaphragm with a suitable field of view. CT scans were analyzed by an expert in the chest radiology**.**

PMIS-TS diagnosis relied upon the criteria of American Academy of Pediatrics (2020) (*7*): An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness, with multisystem (≥2) organ involvement (cardiac, renal, hematologic, respiratory, gastrointestinal, dermatologic, or neurological); AND positive for current or recent SARS-CoV-2 (COVID-19) infection by reverse transcription polymerase chain reaction (RT-PCR), serology, or antigen test with exclusion of alternative plausible diagnoses.

All enrolled children underwent the following lab investigations CBC ,C reactive protein (CRP), cardiac enzymes, liver enzymes and D-dimer and imaging using 2D and M mode echocardiography (GE Vivid 5 echo machine, USA) to assess the cardiac function, pulmonary hypertension and exclusion of pericardial effusion. Other investigations and imaging were individualized according to clinical judgment.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 26 for Windows (IBM Corp., Armonk, N.Y., USA). Categorical variables were described as frequencies and percentages, and continuous variables were described as medians and interquartile ranges (IQRs). Comparisons between groups were carried out using the chi-squared test or Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. A multivariable logistic regression model was used to assess the association of the covariates with the more severe forms of the disease characterized by mortality.

Results

Clinical presentation and indication of admission to PICU

We enrolled 35 COVID-19 children admitted to the Pediatric Intensive Care Unit of Fayoum University Hospital. All patients fulfilled the criteria of severe COVID-19, of them 20 (57.1%) were males and 15 (42.9%) females. The majority were younger than one year with mean± SD of 9 months ± 8 months. Symptoms were heterogeneous, fever was present in 29 (82.9%) and cough in 29 (82.9%) children. The indication of admission to PICU was pulmonary causes in the form of respiratory failure in 29 (80%) patients and non-pulmonary causes in 6 (17.1%); 5 (14.2%) with PMIS-TS and one (2.9%) with liver cell failure. (Table 1). Variable comorbidities were present in 14 patients (40%); the most common comorbidity was underlying congenital heart disease in 7 (20%) of them 2 (5.7%) patients had trisomy 21 associated with congenital heart disease.

Seven (20%) of the 35 patients had bacterial respiratory coinfection (Figure 1). Thirteen (37.14%) children had neurological symptoms in the form of altered mental state and convulsions; however, three of them had underlying neurological diseases. One with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome due to MTTL1 A3243G mutation, he presented by disturbed conscious level and convulsions, during the PICU admission his condition was complicated by shock. He received inotropes, steroids, anticonvulsant and he improved. Another had Kearns-Sayre disease, he presented by cyanosis, and disturbed conscious level, during the PICU admission his condition was complicated by respiratory failure, shock and he died. The third suffered from cerebral palsy, she presented by respiratory failure, and severe dehydration. During the PICU admission her condition was complicated by shock and she improved.

Other neurologic findings were as follows: 2 (5.7%) patients had stroke with convulsions in one, 2 patients (5.7%) had electrolyte disturbances and 6 cases (17.1%) were diagnosed as viral encephalitis secondary to COVID.

The 5 (14.2%) cases with PMIS-TS presented with fever, shock and had laboratory evidence of inflammation in the form of high CRP (in four cases), erythrocyte sedimentation rate, ferritin and cardiac enzymes. Two of them fulfilled the criteria of Kawasaki with myocarditis, impaired myocardial function and coronary dilation in one of them that improved after receiving IVIG and steroids for four weeks. Among the other three PIMS cases, two had myocarditis with improvement in one and the other died.

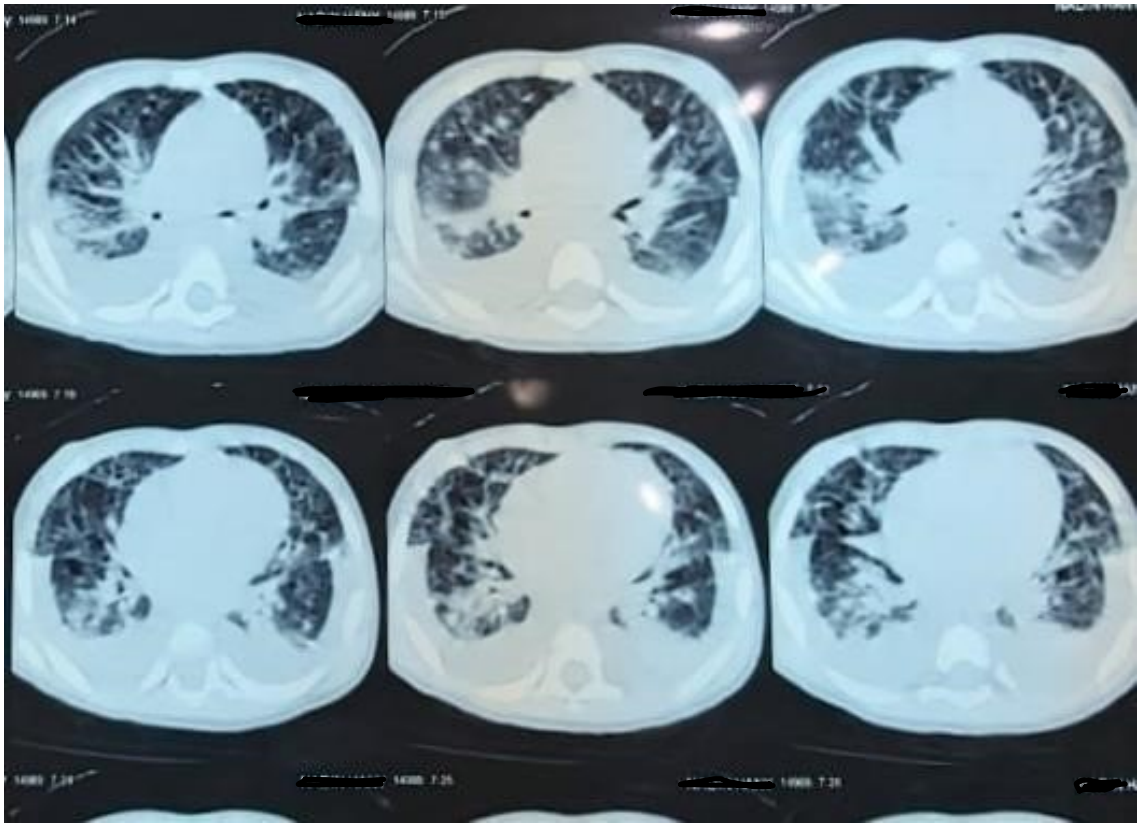

Figure 1. Computed Tomography scan chest of a patient with COVID-19 and respiratory coinfection showing pulmonary changes and pleural effusion

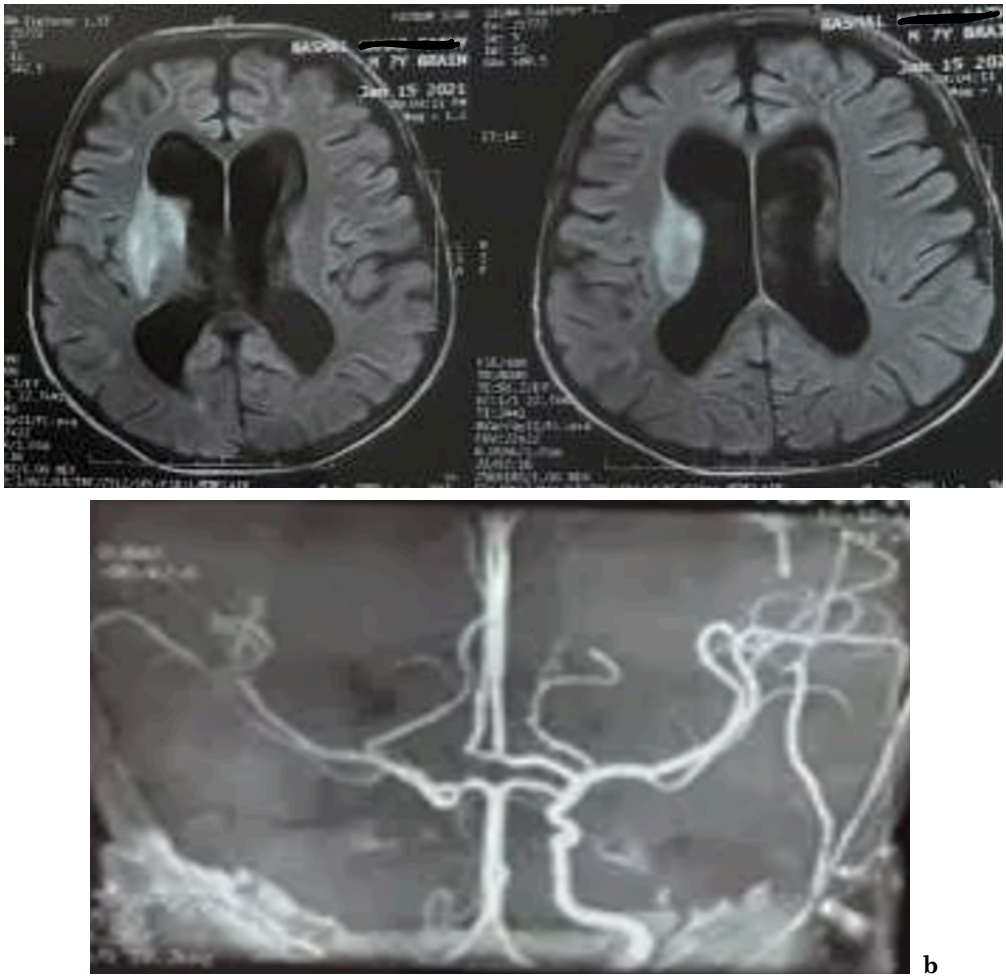

Figure 2. Imaging of a 9 years- old boy with COVID-19. (a) Magnetic resonance brain showing right parietal recent infarction and moderate ventriculomegaly. (b) Magnetic resonance showing non visualized right internal carotid and middle cerebral artery suggested to be thrombosed. Patient had myocarditis with impaired function thrombus in the left ventricle and hemiplegia. He received anticoagulant, IVIg, anti-failure measures and steroids with improvement neurologically regarding stroke but discharged with impaired left ventricular function.

Complications

Eight (22.9%) patients had gastrointestinal symptoms associated with cardiac manifestations and were diagnosed as myocarditis with impaired cardiac functions. Of them 4 (11.4%) had respiratory failure and the other 4 (11.4%) fulfilled the criteria PMIS-TS.

One patient with respiratory failure and elevated cardiac enzymes with normal cardiac function deteriorated and X-ray revealed flask shaped heart. Urgent echo done showed massive pericardial effusion and cardiac tamponade. Pericardiocentesis was done and the child improved. Two of the patients had also thrombus in the left ventricle and developed stroke.

Four patients (11.4%) developed thrombosis; on the second and third days of the illness, two patients developed vascular stroke associated with myocarditis with elevated cardiac enzymes and impaired cardiac function on echocardiography. Another two patients developed deep venous thrombosis of on the fourth to the sixth day of the illness, which manifested by swelling, pain, warmth, and redness in the leg.

Lab and echo findings

Patients were subjected to frequent laboratory testing. Common findings were lymphopenia 28 patient (80%) as well as elevated inflammatory markers and D-dimer. Elevated cardiac enzymes were present in 20 (57.1%) cases. (Table 2).

All patients had normal echocardiographic measurements appropriate to their age except the 8 (22.9%) patients with myocarditis who had impaired systolic function. Another 13 (37.1%) patients had reversible mild pulmonary hypertension secondary to chest condition which improved in the surviving patients after 2 weeks. ECHO proved beneficial in assessment of coronary artery which was dilated in one child with Kawasaki.

Table 1. Clinical presentations and comorbidities of the studied children with severe COVID19 admitted to Pediatric Intensive Care Unit

Mean PICU stay: 7 days (Range 3-40 days)			Outcome			
	N	%	Resolved	improved	stationary	death
Pulmonary symptoms	29	82.9	18	5		6
Non pulmonary symptoms	5	14.2	2	1	1	1
Fever	29	82.9	21			8
Cardiovascular symptoms	16	45.7	5	4 had congenital heart disease	4 discharged with impaired cardiac function	3 with congenital heart disease died (one was Down syndrome).
Gastrointestinal symptoms	8	22.9	6			2
Hematological symptoms	6	17.1	4			2
Mucocutaneous symptoms	2	5.7	1	1		
Neurological symptoms	13	37.1	5	2	5 patients were discharged with neurological sequalae; 2 with hemiplegia and 3 with convulsions	1
Thrombosis	4	11.4		2 cases with DVT improved	2 patients discharged with hemiplegia	
Indication of PICU admission						
Respiratory failure	28	80.0	17	5		6
Shock	21	60.0	17			3 died with severe COVID and respiratory failure and 1 case died with PMIS-TS
Acute hepatic failure	1	2.9				1
Presence of comorbidities						
Bronchial asthma	2	5.7		2		
Congenital heart disease	6	17.1		4		2
Congenital heart disease, Down syndrome	2	5.7		1		1
Underlying neurological disease mitochondrial disease cerebral palsy	3 2 1	8.6 5.7 2.9		1 1		 1
Chronic liver disease	1	2.9				1
Cleft lip, palate	1	2.9		1		
Associated complications						
Thrombosis: deep venous thrombosis stroke	4 2 2	11.4 5.7 5.7		2	2	
Myocarditis with impaired cardiac function	8	22.8	3		4	1
Arrythmia	1	2.9		1		
Liver cell failure*	1	2.9				1

* Child had underlying chronic liver disease.

Treatment

All subjects with pulmonary manifestations required respiratory support, and 31(88.6%) required assisted ventilation with an average duration of six days.

Antibiotics and corticosteroids were used in 36 (100%) and 31 (88.6%) cases and respectively but not hydroxychloroquine. Intravenous immunoglobulin was prescribed exclusively for myocarditis with impaired cardiac function in 8 (22.9%) children, vasoactive infusions in the form of noradrenaline and dopamine in 21 (60%) and 13 child (37.1%) respectively, and 19 children (54.2%) received anticoagulants according to the Egyptian guidelines of COVID (Table 3). All cases of myocarditis with impaired function received intravenous immunoglobulins without significant improvement followed by steroids with improvement in 3 cases.

Table 2. Laboratory findings of studied cohort with severe COVID-19 correlated to mortality

	Number	%	Normal value	Mortality				P value
				Died		Survived		
				Number	%	Number	%	
Lymphopenia	28	80.0		7	25.0	21	75.0	1.000
Neutrophilia	8	22.9		1	12.5	7	87.5	0.648
Thrombocytopenia	10	29.4		5	50.0	5	50.0	0.014*
Anemia	23	65.7		7	30.4	16	69.6	0.216
Variable	Median	IQR						
D-dimer (µ/mL)	1.6	0.4-4.8	< 0.4					0.304
CRP	20	5-29	< 6	3	23.1	10	76.9	1.000
Ferritin (ng/mL)	300	78-3629	-50 to 200 for 2- 5 months old -7 to 140 for children 6 months - 15 years					0.458
CKmb	130	12-800	5 to 25 IU/L					0.32
INR	1.2	1-3.8	1-1.2					0.521
ALT	62.5	14-275	10-40					0.633
AST	80.5	15-480	10-50					0.563
Labs normalize in surviving cases (days)	7	4-30						

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKmb: creatine kinase-MB; CRP: C-reactive protein; INR: International Normalized Ratio.

Outcome

Sixteen (45.7%) patients were discharged without complications. Four (11.4%) patients were discharged with impaired cardiac function following myocarditis, and five patients were discharged with neurological insults; two of them with hemiplegia following myocarditis and impaired cardiac function (Figure 2), and the others had seizures but they were known to have underlying neurological diseases.

Four patients were discharged with impaired cardiac function following myocarditis, and five patients were discharged with neurological insults; two of them with hemiplegia following myocarditis and impaired cardiac function, and the others had seizures but they were known to have underlying neurological diseases.

The mortality rate was 22.9% (eight children died); 6 cases with respiratory failure (3 males and 3 females with mean± SD age of 6 ± 6 months), 1 case with liver cell failure (male patient 1 year old with underlying chronic hepatitis) and 1 with PMIS-TS and shock (male patient 2 year old). Three of the patients who died had congenital heart diseases in the form of large ventricular septal defect, patent ductus arteriosus and complete atrioventricular canal in a patient with Down syndrome. The other 3 patients who died were previously healthy. All the patients who died received inotropes, invasive mechanical ventilation, steroids and anticoagulants (except the patient with liver cell failure) without improvement.

Thrombocytopenia was associated with higher mortality in patients with severe COVID-19 ($p = 0.014$). (Table 4). The other comorbidities were not associated with higher mortality; congenital heart disease and Down syndrome ($p= 0.5$), myocardial dysfunction ($p= 0.7$), respiratory failure ($p= 0.1$), neurological disease/complications ($p= 0.6$) and vascular involvement ($p= 0.5$).

The duration of PICU stay ranged from 3 to 40 days with mean 7± 8 days. Mean ± SD duration of admission was 9 ± 8 days and 10 ± 9 days for those with COVID 19 complicated with bacterial infection and those with myocardial dysfunction (p= 0.23). There was no significant difference in PICU stay regarding gender (p= 0.48), neurological complications (p= 0.36), history of bronchial asthma (p= 0.28) or with congenital heart diseases (p= 0.21).

Table 3. Treatment and outcome of studied cohort with severe COVID-19 correlated to mortality

	Median	**IQR**	**Correlation to Mortality P value**
Duration of PICU stay, days	7	3-40	0.5
Duration of ventilation, days	6	0-14	0.362
	Number	**%**	
Vasopressor support			
Did not need vasopressor	4	11.4	0.543
Needed vasopressor	31	88.6	
Intravenous immunoglobulin			
Did not receive intravenous immunoglobulin	27	77.1	0.611
Received intravenous immunoglobulin	8	22.9	
Anticoagulant			
Did not receive anticoagulant	16	45.7	0.328
Received anticoagulant	19	54.2	
Corticosteroids			
Did not receive corticosteroids	4	14.3	0.543
Received corticosteroids	31	88.6	
Assisted Ventilation			
Did not need assisted ventilation	4	11.4	0.543
Needed assisted ventilation	31	88.6	
Anti-IL-6 receptor antagonist			
Did not receive anti IL-6 receptor antagonist	31	88.6	0.437
Received anti IL-6 receptor antagonist	4	11.4	
Cardiac function on discharge			
Normal cardiac function	23	85.2	0.564
Impaired cardiac function	4	14.8	
Neurological insult			
No neurological insult	22	81.5	0.431
Neurological insult	5	18.5	
Mortality			
Died	8	22.9	
Survived	27	77.1	

Discussion

COVID-19 is a viral contagious disease. Transmission occurs through infected persons or asymptomatic carriers. The main transmission routes include respiratory droplet, contact, and may be the digestive tract, with an incubation period ranging from 1 to 24 days (*8*). In Egypt, the disease spectrum of disease COVID-19 included asymptomatic, mild, moderate and severe disease necessitating PICU admission (*9*). Medical comorbidities (associated with developmental delay and/or genetic abnormalities), congenital heart disease, neurological disease, chronic lung disease, oncological or hematological diseases, immunosuppressant use, and prematurity are common in pediatric patients with severe COVID-19 (*5*).

In our study, a quarter of the children with severe COVID-19 admitted to our PICU had comorbidities, and the most common comorbidity was congenital heart disease in eight cases (22.9%) and most of the patients were below the age of 1 year. It seems that COVID- 19 in those less than one year are more susceptible to need PICU admission (*10*) especially if associated with comorbidities. We did not study the frequency of COVID-19 among the population to estimate the need for PICU admission, yet, in case of being admitted to PICU, younger age seems to be a risk factor to develop a more severe form of COVID-19. Mortality rate in the current study was 22.9% (8 cases) with almost two thirds having comorbidities, namely congenital heart diseases in the form of large ventricular septal defect, patent ductus arteriosus and complete AV canal in a patient with Down syndrome, one patient with Kearns-Sayre disease and one patient had chronic liver disease. It seems that the presence of underlying disease is a risk factor, that was not confirmed statistically in our study. It might be attributed to the small sample size in our study. This conflicting evidence suggests that, the

presence of comorbidities is not the only factor capable of favoring the worsening of the clinical manifestations and developing complications. Those patients with underlying heart diseases seem to be a vulnerable population at high risk as three of the patient died had congenital heart diseases.

Several centers reported that significant proportions of critically ill children required mechanical ventilation which was attributed to the rapid deterioration of other systems that needed emergency support, and accounted for the high mortality rate (*11*). In the current study we did not find the ventilatory support predictive of mortality. It might be attributed to the multisystem affection in our studied cohort, rendering a single cause for morbidity unlikely.

There is scarcity of data on cardiac affection in children with severe COVID-19. COVID - 19 presenting as classic Kawasaki disease was reported (*6*), yet studies describe myocardial dysfunction and arrhythmias in pediatric patients with MIS-C, but these changes are less common in patients with severe COVID-19 (*12*). Myocarditis with reduced left ventricular systolic function was the most common cardiac complication in the studied group. Thrombus in the left ventricle, cardiac tamponade, arrhythmia and coronary dilatation were also encountered. Shock was multifactorial not limited to cardiogenic shock in our studied cohort.

Low-dose corticosteroids have reduced mortality in adult patients with severe or critical COVID-19 without increasing adverse events. The use of anti-inflammatory drugs such as corticosteroids could be beneficial (*13*). This is similar to the finding we observed as most of the patients improved clinically and laboratory after using corticosteroids even the patients with myocarditis; cardiac enzymes decreased and function improved after using steroids not IVIg. The long-term consequences of cardiac involvement in COVID-19 are unknown but we had four cases discharged with impaired cardiac function to be followed-up in a cardiomyopathy clinic, and one case developed arrhythmia and was discharged on antiarrhythmic medications. patient with dilated coronary artery received intravenous immunoglobulins and steroids with improvement of coronary artery diameter and cardiac function after 1 month.

Thrombocytopenia was found in 29.4% of the cases and was associated with mortality among the studied patients. It seems to be a red flag among children admitted to PICU with severe COVID-19.

Conclusion

Pediatric patients with severe COVID can present with severe pulmonary and extrapulmonary complications at any age especially if they had comorbidities and if less than 1 year. Respiratory failure was the leading cause of PICU admission and in children with severe COVID-19. (PMIS-TS) presented with severe manifestations, clinically similar to Kawasaki disease or shock syndrome. Myocarditis stroke, arrythmia and cardiac tamponade are life-threatening complications of severe COVID=19 or PMIS-TS.

To appropriately manage severe pediatric COVID-19 cases, greater attention should be paid to infants under the age of one year especially if they have comorbidities. Furthermore, assessment of the cardiac function and coronaries in critically ill children with COVID-19 should be considered to identify any cardiac complication and prevent poor prognosis. Close follow-up is needed in these young individuals with cardiac affection.

Author Contributions:

SI conceived, conceptualized and designed the survey. SI and MI collected and analyzed the data. SI wrote the manuscript. MI reviewed the imaging and reviewed the manuscript. Both authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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