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## Clinical presentation of pediatric patients with COVID 19 admitted in pediatric intensive care unit (PICU) in Iran

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000715
Article Type:	Original research
Date Submitted by the Author:	13-May-2020
Complete List of Authors:	Saeed, Amir shorafa, eslam; Shiraz University of Medical Sciences, sanaeidashti, anahita kadivar, mohammad rahim
Keywords:	Health services research, Virology, Mortality

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## Clinical presentation of pediatric patients with COVID 19 admitted in pediatric intensive care unit (PICU) in Iran

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Word count: 1522

**Key word:** COVID19; coronavirus; Wegener; PICU

## Abstract

**Objectives:** To describe clinical characteristics and laboratory data of pediatric patients who were admitted in pediatric intensive care unit (PICU) with the impression of COVID-19.

**Design:** A cross sectional study

**Setting and participants:** Ten pediatric patients admitted in PICU from 16<sup>th</sup> of March, 2020 to 21<sup>th</sup> of April, 2020, were enrolled in this study

**Main outcome measures:** Clinical and para clinical characteristics and outcome of the patients

**Result:** The median age was 7.9 year, the youngest was 4 months old and the oldest was 16 years old and two of them were female. The most common symptoms were; fever and cough. The most common reason for PICU admission was respiratory failure (in 9 patients). In half of patients, there was a history of contact to confirmed or suspicious people, six patients had pre-existing medical condition. Most of the patients had hypotension and received inotrope and six patients needed norepinephrine infusion added to dopamine and epinephrine.

Of all, 5 patients died and the most common cause of it, was refractory cardiac arrhythmia

**Conclusion:** COVID-19 can be fatal in pediatric patients especially in those who have a comorbidity or underlying disease and those who have delayed medical referral and or management.

It seems prudent to choose a more valid stricter triage criteria for pediatric emergency rooms and educate the physicians and nurses involving in pediatric care to better and early diagnose COVID 19 cases in this age group.

What is known about the subject?

- ▶ COVID -19 infection in is less frequent and severe in pediatric patients than adult patients.
- ▶ The main symptom is fever and few pediatric patients need mechanical ventilation or inotrope support.

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What this study adds?

- ▶ COVID -19 infection could be fatal pediatric patients especially in those who have comorbidities.
- ▶ The main respiratory problems in severe cases are oxygenation failure and in cardiovascular; hypotensive state necessitating inotropes.
- ▶ The main causes of mortality in our study were cardiac arrhythmia and refractory hypoxemia.

## Introduction

In December 2019, a cluster of acute respiratory illness occurred in Wuhan, Hubei Province, China by novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). On 3<sup>rd</sup> of January 2020, the 2019 novel coronavirus (2019-nCoV) was identified in samples of bronchoalveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of that (2).

The current outbreak of infections with SARS-CoV-2 is termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) (3). The disease has rapidly spreads from Wuhan to other areas and worldwide so that world health organization (WHO) in 11<sup>th</sup> march 2020 announces COVID-19 outbreak a pandemic (4).

The 2019-nCoV has close similarity to bat coronaviruses, and it has been assumed that bats are the primary source. While the origin of the 2019-nCoV is still being investigated, current evidence suggests spread to humans occurred via transmission from wild animals illegally sold in the Huanan Seafood Wholesale Market.

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3 The rate of infection with covid-19 in children is low and the first pediatric case  
4 was reported on January 20, 2020; was a 10-year-old Chinese boy, whose family  
5 had visited Wuhan City (4). A retrospective study was done in 366 children  
6 whose ages were  $\leq 16$  years old and were hospitalized for respiratory infections  
7 between January 7 and 15, 2020, COVID-19 was confirmed in 6 (1.6%) children  
8 whose onset of illness occurred between January 2 and 8, 2020. This study results  
9 suggests that COVID-19 infections in children were occurring early in the  
10 epidemic (5) One reason of low incidence rate in children in China is that;  
11 children were rarely tested for the virus in earlier phase of the outbreak, especially  
12 in Hubei province, where the most patients were confirmed so we have a limited  
13 data on the prevalence of COVID-19 in children (6).  
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21 In Iran, the first cases detected in February 2020 in Qom city and from there, the  
22 disease spread to whole country. In critically ill pediatric patients, also there are  
23 a few reports.  
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26 In this article we want to describe the characteristics of pediatric patients with  
27 COVID-19 admitted in pediatric intensive care unit (PICU) of Namazi hospital  
28 in Shiraz, Iran.  
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### 32 **Patients and Method**

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34 From March 16<sup>th</sup> to April 21<sup>th</sup>, the patients admitted in PICU of Namazi hospital  
35 in Shiraz, Iran (Namazi Hospital ;the largest hospital in south of Iran with 750  
36 beds is located in Shiraz city that is the main tertiary referral center in south of  
37 Iran which has 18 beds general PICU and 9 beds surgery PICU);and those whom  
38 with laboratory data and Chest CT scan COVID-19 confirmed for them or  
39 according to clinical presentation and chest CT scan were highly suspicious to  
40 COVID-19, included in this study. A laboratory confirmed case of Covid-19 was  
41 defined by a positive result on a reverse transcriptase–polymerase chain-reaction  
42 (RT-PCR) assay of a specimen collected on an oropharyngeal swab,  
43 nasopharyngeal swab or bronchoalveolar lavage. The patients whose ages were  
44 between one month to 18 year old included in this study. The patients younger  
45 than one month and older than 18 year old excluded from this study.  
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### 54 **Patient involvement**

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56 Patients were not directly involved in the design of this study.  
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## Ethics statement

This study was approved by the ethics committee of Shiraz University of Medical science (IR.sums.med.rec.1399.40). Written informed consent was obtained the parents guardians and sent to the ethics committee.

## Results

From 16<sup>th</sup> of march to 21<sup>th</sup> of April, 2020, ten patients admitted in PICU and COVID-19 diagnosed for them by RT-PCR or laboratory data and chest CT scan findings (Figure 1,2). In those, six patients had positive RT-PCR for COVID-19 and others had positive chest CT Scan findings and laboratory data in favor of COVID-19. The median age was 7.9 years and the youngest was four months old and the oldest was 16 year old. Eight patients were male. Six patients had underlying disease and four were healthy children before the PICU admission. Five patients had positive history of contact to confirmed or suspicious persons. The main symptoms were: fever, cough, abdominal pain, lethargy and encephalopathy. Four patients developed with convulsion during PICU stay (patients number: 2, 3,4 and 6) and in two patients, brain CT scan revealed severe brain edema (patients number: 2 and 3).

Unfortunately five of 10 patients expired (patients number:1, 2, 6, 9 and 10) ; of those, four patients had comorbidity before admission and in three patients cardiac arrhythmia was the cause of death (patients number 2, 6 and 9), and the last two was due to refractory hypoxia(case number 1,10).

The median time (day) from the presentation of symptoms to PICU admission was 4.7days, the minimum was 3 days and maximum was 8 days and that was in a patient who due to fear of COVID-19 infection, refused to go to hospital.

Four patients (cases number:2, 4, 6 and 9) developed with cardiac arrhythmia so that in three patients(patients number:2, 6, and 9) were refractory to medical therapy and resulted in cardiac arrest .

All patients had PaO<sub>2</sub>/Fio<sub>2</sub> less than 300 and of all ,nine patients needed intubation and mechanical ventilation, and in one patient(patient number:8) despite of decreased o<sub>2</sub> saturation and PaO<sub>2</sub>;47 mmhg ,he responded to o<sub>2</sub> via non rebreathing mask, in the others whom were intubated , their main problem was severe hypoxia but although they needed low peak pressure(by decreasing peak inspiratory pressure(PIP ) for enough tidal volume, and respiratory rate(unlike the usual cases we have seen in ARDS), o<sub>2</sub> saturation could not reach



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3 85 so that needed increasing peak expiratory pressure(PEEP) up to 18 and prone  
4 positioning.  
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7 Of nine patients admitted only two patients didn't have hypotension and of eight  
8 patients developed with hypotension six patients had vasoplegic shock, so that  
9 needed infusion of high dose norepinephrine.  
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12 In one patient (patient number 4) in order to close and continuous monitoring of  
13 hemodynamic and volume status of patient, in addition to bedside  
14 echocardiography that was done for all patients, arterial line inserted and  
15 monitored by proAQT device.  
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19 In all patients broad spectrum antibiotic started in addition to hydroxychloroquine  
20 and kaletra (lopinavir/ritonavir), but in 7 patients intravenous globulin (IVIG)  
21 (except cases no: 8 and 10) was given. In hypotensive patients, hydrocortisone,  
22 ascorbic acid and thiamine started.  
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26 In all of the patients, blood culture, tracheal aspirate culture and urine culture  
27 (especially for patient number 2 that was done two times) were negative, and also  
28 PCR for influenza A and B, in all patients were negative (Table 1, 2).  
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32 In patient number 6; the patient presented with fever, abdominal pain and  
33 tachypnea (both of his parents had fever and cough and in our center RT-PCR  
34 was done for them and both were positive). His symptoms progressed to lethargy  
35 so admitted in a hospital in Babol(a city in north of Iran which in that time had a  
36 surge in COVID-19 infection) seven days prior to our center's PICU admission  
37 and in that hospital, his condition deteriorated and developed icter so with the  
38 diagnosis of acute liver failure transferred to our center. On arrival, due to  
39 decreased o2 saturation and decreased level of consciousness, he was intubated  
40 and transferred to PICU. On PICU arrival, the patient had hypotension, fever and  
41 in chest CT scan had patchy infiltration. All lab data could be related to COVID-  
42 19 except high bilirubin that has not seen as high as our patient was (total bilirubin  
43 was 35) in COVID-19 (The patient tested negative for hepatitis A, B, C, EBV,  
44 CMV and serum ceruloplasmin was in normal range).  
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52 In patient number 2, abdominal sonography revealed no abscess formation or  
53 collection.  
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COVID Real-time	positive						negative			
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**Table 1:** Epidemiologic & Clinical findings of the patients

Patient number	1	2	3	4	5	6	7	8	9	10
Age(years)	4 months	1	1.5	3	3	11	13	15	16	16
Sex	male	male	female	female	male	male	male	male	male	male
Hypotension	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Tachycardia on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tachypnea on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chief complaint(s)	Fever & Letharginess	Fever & Letharginess	Fever & cough	Fever & cough	Fever & cough	Fever & abdominal pain & decreased LOC	Fever & Letharginess	Fever & cough	Fever & cough	Fever & cough
Previous illness	Cerebral Shunt	UPJO• with nephrostomy	negative	Immuno deficiency	negative	negative	Cerebral palsy	negative	wegener granulomatosis	Cerebral palsy
Convulsion	Yes	No	Yes	Yes	No	Yes	No	No	No	No
Decreased LOC*	negative	negative	negative	negative	negative	positive	positive	negative	negative	negative
Mechanical ventilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
ARDS# classification	Severe	Severe	moderate	Severe	moderate	Severe	Severe	Moderate	Severe	Severe
History of contact	negative	negative	positive	positive	positive	positive	negative	positive	negative	negative
Died	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes

\*LOC: level of consciousness

#ARDS: Acute respiratory distress syndrome

• UPJO: urethropelvic junction obstruction

PCR										
Patient	1	5	6	7	8	9	2	3	4	10
Ferritin (ng/ml) M: 22.81-275 F: 4.63-204	580	1235	954	5701	750	1310	3489	1067	651	*
Typical Chest CT finding	positive	positive	positive	positive	positive	#	positive	positive	positive	positive
White blood cells(count/ml)	26100	9800	7100	11300	7500	22000	14000	12000	3800	12000
Lymphocyte	2088	1470	710	1017	1100	1100	6380	2400	760	480
Procalcitonin ≤ 0.3	0.24	30.5	10.1	1.36	0.6	*	1.8	73	0.2	*
C- reactive protein <6 (mg/L)	32	90	50	150	37	5	3	85	3	3
Creatine phosphokinase (U/L) M: < 171 F:< 145	37	1769	950	374	557	264	88	220	163	140
Lactate dehydrogenase (U/L) < 480	640	635	5660	1820	1350	1350	1150	786	1670	938
Troponin (ng/ml) < 19	32	29.2	3343	2029	1.5	450	27	68	35	1.5
D-Dimer (ng/ml) < 500	1924	540	10000	9232	1296	638	5135	9536	1296	10000
Total bilirubin 0.1-1.2	0.7	0.3	35	0.6	0.4	0.2	*	0.3	0.6	*
Direct bilirubin < 0.3	0.3	0.1	21	0.1	0.2	0.1	*	0.1	0.1	*
Aspartate transaminase (U/L) M: < 37 F: < 31	1020	36	2030	51	40	97	*	77	68	*
Alanine aminotransferase (U/L) M: < 41 F: < 31	52	14	690	37	33	13	*	28	34	*
Creatinine M: 0.8 - 1.3 F: 0.6 - 1.2	13	0.5	0.1	0.5	0.9	4.8	0.5	0.4	0.4	3.3
Blood urea nitrogen (mg/dl) 8 - 20	0.9	11	113	13	14	53	9	3	19	62

**Table 2:** Para clinical findings on day one of admission

M: male/F: female

# did not performed due to his unstable condition

\*did not checked

## Discussion

The overall case fatality rate as per China Centre for Disease Control and Prevention (CDC) is 2.3%, which is much lower compared to SARS (9.6%) and MERS (34%) but significantly higher compared to the latest H1N1 influenza pandemic (0.001 – 0.007%) (7). However, as per WHO, the global case.

Fatality rate is as high as 4.4% with absolute number of deaths already higher than the total fatality of SARS and MERS combined (8). The case fatality reported from Italy is 7.2% which has gone up to 9.8% as per WHO (as on March 26, 2020) (9).

In pediatric patients admitted in PICU, we have limited data, The case fatality rate in our PICU was 50% and in adult patients admitted in ICU is about 50% (10,11,12) but in limited data we have; in Madrid, Spain, in a study there was no mortality(13) and in a Chinese study one patient(14). In a cohort study in Wuhan children hospital; three patients admitted in PICU and one of three (33%) died and all the patients had comorbidities (15). In another study in Wuhan one patient without comorbidity admitted in PICU and survived (5).

In our study, all patients were febrile and 70% had cough but in some studies done in non-critical pediatric patients were less than 50 % ( 5, 14, 15).

In our study, 60% patients had positive RT-PCR FOR COVID-19, that there are some reasons for that; first is in the first day we tested the patients via oropharyngeal swab and the other possibility is that the patients arrived PICU had severe disease and were in terminal stage of disease.

It has been shown that in coronavirus infection (SARS, MERS and even;COVID-19)liver can be damaged and we see increased Alanine aminotransferase (ALT) , decreased albumin and increased serum bilirubin levels but have seen mild to moderate elevation(16,17,18,19) in one of our patient(number:6) , we saw increased ALT and bilirubin, but they were much more than the other patients . So there are some possibilities for that: acute liver failure with COVID-19 infection, rare complications of COVID-19...

## Conclusion

There is a general conception that pediatric patients infected by COVID-19, it has less severe symptoms and better outcome but we should consider the group that has comorbidity has a higher risk of infection and worse outcome and in this people, we should consider routine screening test and education of warning signs and symptoms and using personal protective equipment. Even in general pediatric population whom taken to emergency rooms and physician, we should consider a stricter triage for screening the ill pediatric patients.

**Conflict of interest:** none

**Funding:** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Authors' Contributions:** A.S. planned the study and wrote the manuscript. E.S. gathered patients' data and submitted the manuscript. A.S.D. data interpretation. A.S.D. and M.R.K. edited the manuscript and were scientific consultant. All authors discussed the results and contributed to the final manuscript.

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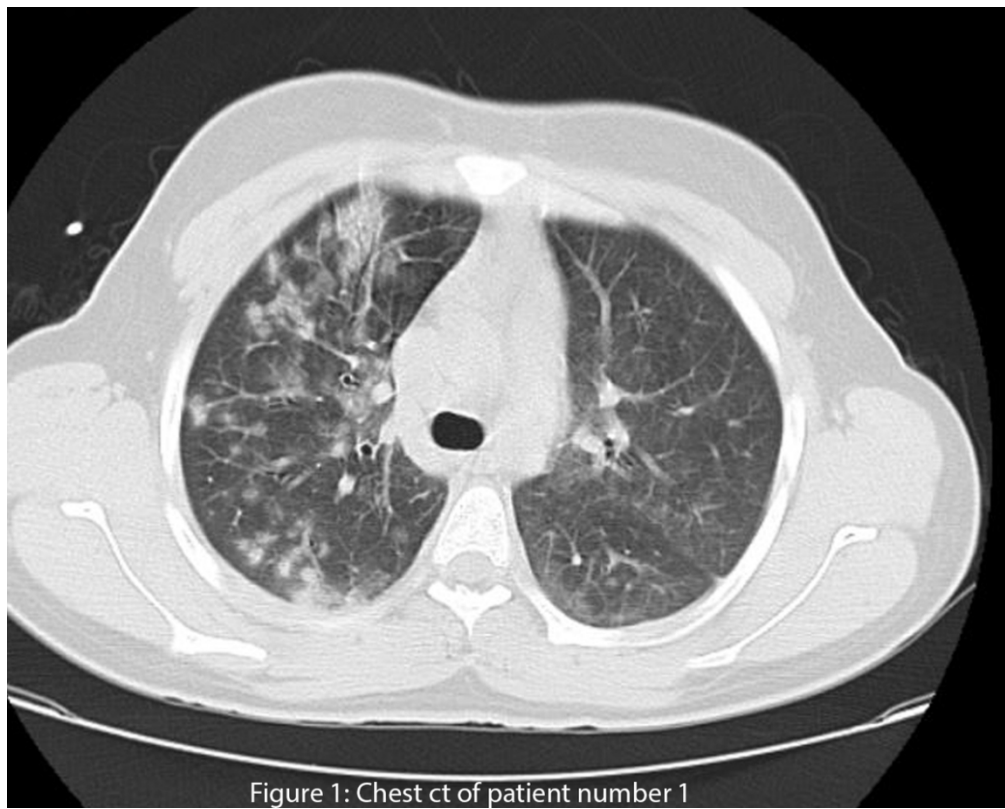
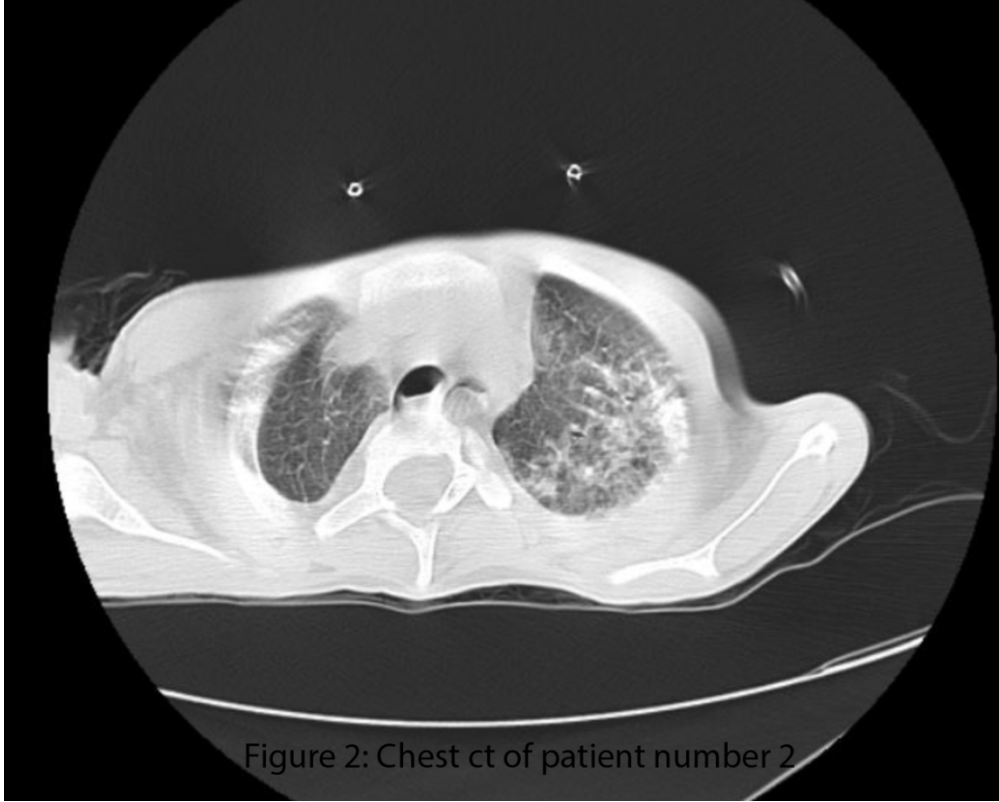


Figure 1: Chest ct of patient number 1

99x79mm (300 x 300 DPI)



99x79mm (300 x 300 DPI)

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# BMJ Paediatrics Open

## Clinical presentation of pediatric patients with COVID 19 admitted in a single pediatric intensive- care unit (PICU) in Iran

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000715.R1
Article Type:	Original research
Date Submitted by the Author:	08-Jul-2020
Complete List of Authors:	Saeed, Amir; Shiraz University of Medical Sciences Medical School, Pediatrics shorafa, eslam; Shiraz University of Medical Sciences, sanaeidashti, anahita; Shiraz University of Medical Sciences, department of pediatrics kadirvar, mohammad rahim; Shiraz University of Medical Sciences, department of pediatrics
Keywords:	Health services research, Virology, Mortality

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## Clinical presentation of pediatric patients with COVID 19 admitted in a single pediatric intensive care unit (PICU) in Iran

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Word count: 1522

**Keywords:** COVID 19; SARS coronavirus 2 , Wegener , child, PICU

## Abstract

**Objectives:** To describe the clinical manifestation, disease course, complications, co-morbidities, organ involvements apart from the lungs, outcome, and paraclinical characteristics of pediatric patients admitted in a single pediatric intensive care unit (PICU) in Iran with the impression of COVID-19

**Design:** A cross-sectional study

**Setting and participants:** Ten pediatric patients who were admitted in PICU from March 16 to April 21, 2020 . were enrolled in this study

**Main outcome measures:** Clinical and para-clinical characteristics, complications, and outcome of the patients

**Result:** The participants' median age was 7.9 years. The youngest one was 4 months old and the oldest 16 years old; two of them were female. The most common symptoms were fever and cough. Also, the most common reason for PICU admission was respiratory failure (in nine patients). In half of the patients, there was a history of contact to confirmed or suspicious COVID 19 cases. Six patients had a pre-existing medical condition. Most of the patients had hypotension on admission and received inotrope; six of them received norepinephrine infusion added to dopamine and epinephrine. Of them, 5 patients died and its most common cause was refractory cardiac arrhythmia.

**Conclusion:** COVID-19 can be fatal in pediatric patients, especially in those with a comorbidity or underlying disease and those who have delayed medical referral and or management.

What is known about the subject?

- ▶ COVID -19 infection is less frequent and severe in pediatric patients than adult patients.
- ▶ The main symptom is fever and few pediatric patients need mechanical ventilation or inotrope support.

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What this study adds?

- ▶ COVID-19 infection could be fatal in pediatric patients, especially in those with comorbidities.
- ▶ The main respiratory problems in severe cases are oxygenation failure and a hypotensive state necessitating inotropes.
- ▶ The main causes of mortality in our study were cardiac arrhythmia and refractory hypoxemia.

## Introduction

In December 2019, a cluster of acute respiratory illness occurred in Wuhan, Hubei Province, China by a novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). On the 3<sup>rd</sup> of January 2020, the virus was identified in the samples of bronchoalveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of the disease (2).

The current outbreak of infections with SARS-CoV-2 was termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) (3). The disease rapidly spread from Wuhan to other areas of the world, so that the world health organization (WHO) announced Covid-19 outbreak as a pandemic on March 11, 2020 (4).

The 2019-nCoV is closely similar to bat coronaviruses, and it has been assumed that bats are the primary source. While the origin of the 2019-nCoV is still being investigated, the current evidence suggests that spread to humans occurred from wild animals illegally sold in the Huanan Seafood Wholesale Market.

The rate of infection with covid-19 in children is low and the first pediatric case was reported on January 20, 2020, who was a 10-year-old Chinese boy, whose family had visited Wuhan City (4). A retrospective study on 366 children aged

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3 under 16 years old and hospitalized for respiratory infections between January 7  
4 and 15, 2020, confirmed COVID-19 infection in six (1.6%) of them. This study  
5 suggests that COVID-19 infections in children occurred early in the epidemic  
6 (5). One reason for the low frequency of the disease in children in China could  
7 be the fact that children were rarely tested for the virus in the earlier phase of  
8 the outbreak, especially in Hubei province, where most of the patients were  
9 confirmed, so there are a limited data on the prevalence of COVID-19 in  
10 children (6). The virus can produce a Kawasaki-like illness in children. World  
11 health organization (WHO) developed a preliminary case definition for this  
12 condition which was later named 'multisystem inflammatory disorder' in  
13 COVID-19 (MIS-C). The syndrome should be considered in children with  
14 features of typical or atypical Kawasaki disease or toxic shock syndrome.  
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23 Preliminary case definition:

24 Children and adolescents 0-19 years of age with fever > 3 days

25 AND two of the following:

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30 a) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation  
31 signs (oral, hands, or feet)  
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34 b) Hypotension or shock  
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36 c) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary  
37 abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)  
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40 d) Evidence of coagulopathy (by PT, PTT, and elevated d-Dimers)  
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43 e) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)  
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45 AND

46 Elevated markers of inflammation such as ESR, C-reactive protein, or  
47 procalcitonin  
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53 No other obvious microbial cause of inflammation, including bacterial sepsis,  
54 staphylococcal or streptococcal shock syndromes  
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Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19(7).

Herein, we describe the patients with COVID-19 presenting with multi-system inflammatory syndrome. In Iran, the first COVID-19 cases were detected in February 2020 in Qom city. There are a few reports from critically ill pediatric patients in the country. In this article, we describe the characteristics of pediatric patients with COVID-19 admitted in pediatric intensive care unit (PICU) of Namazi hospital in Shiraz, Iran.

## Patients and Method

From March 16 to April 21, the patients who were admitted in PICU of Nemazi hospital in Shiraz, Iran, were enrolled in the study. Nemazi educational hospital is the largest and the main tertiary referral center in the south of Iran with more than one thousand beds. The medical PICU of this hospital has 18 beds with two separate sections, one of which was devoted to COVID 19 cases from the beginning of the outbreak and those with suspicious or confirmed COVID-19 were admitted in this ward. A confirmed case of Covid-19 was defined by a positive result on a reverse transcriptase–polymerase chain-reaction (RT-PCR) assay of a specimen collected on an oropharyngeal swab, nasopharyngeal swab or bronchoalveolar lavage. The tests were performed using an Applied Biosystem Step One plus real-time PCR machine (Applied Biosystem, CA, USA). Amplification of N and ORF1b took place in a 20 $\mu$ L single-tube, and Superscript III Platinum one-step quantitative RT-PCR system (Invitrogen, Carlsbad, CA). Reactions contained 10.0  $\mu$ L of 2X RT/PCR reaction mix, 1  $\mu$ L primers/prob mix, 0.4  $\mu$ L Superscript III RT/Platinum Taq mix, 0.4  $\mu$ L ROX reference dye, and 5  $\mu$ L of extracted sample RNA or serially diluted previously confirmed patients' positive control. The cycling conditions consisted of one cycle at 50°C for 10 min, one cycle at 95°C for 2 min, 45 cycles at 95°C for 5 s, and 60°C for 30 min)(8).

A suspicious case of COVID 19 was defined as a patient with clinical, laboratory findings (9) and chest CT findings consistent with COVID 19 infection (10), but negative PCR result. The patients whose ages were between one month to 18-years old who were admitted in PICU were enrolled in this study. The patients younger than one month and older than 18 years old were excluded from the study.

## Patient involvement

The patients were not directly involved in the design of this study.

### **Ethics statement**

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.sums.med.rec.1399.40). Written informed consents were obtained from the parents and sent to the ethics committee.

### **Results**

From March 16 to April 21, 2020, ten patients were admitted in PICU with the impression of COVID-19 (Tables 1,2). Nine of them had been admitted in pediatric wards with impressions other than COVID-19 before transfer to PICU and only one of them was transferred from emergency room (ER) with the impression of COVID-19. From them, six patients had positive RT-PCR for COVID-19 and the others were suspicious with COVID-19. The median age was 7.9 years; the youngest one was four and the oldest was 16 years old. Eight patients were male. Also, six patients had underlying disease (Table 1) and four were already healthy children. Five patients had a positive history of contact to confirmed or suspicious persons (3 patients had contact to positive RT-PCR cases) or suspicious persons with fever and cough. The main symptoms were fever, cough, abdominal pain, lethargy and encephalopathy.

Four patients developed convulsion during PICU stay (patients number: 3, 7, 8 and 9) and brain CT of two of them revealed severe brain edema (patients number: 7 and 8); (other possible causes of decreased level of consciousness and convulsion, such as trauma, poisoning, electrolyte imbalance, etc. were evaluated and ruled out).

Unfortunately, five out of 10 patients passed away (patients number: 1,3, 6,7, and 10); of them, four patients had comorbidity before admission and in three patients cardiac arrhythmia was the cause of death (patients number 3,6 and 7). The median time from the presentation of symptoms to PICU admission was 4.7 days; the minimum was 3 days and maximum was 8 days ( occurring in a patient who refused to come to hospital due to fear of COVID-19 infection (case 6) ).

Four patients (cases: 3,6,7 and 9) developed cardiac arrhythmia that was refractory to medical therapy and resulted in ventricular fibrillation and cardiac arrest; patients number 3 and 6 had severe hypoxia ( $po_2 < 50$ ) at the presenting time of cardiac arrhythmia.

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3 All patients had PaO<sub>2</sub>/Fio<sub>2</sub> less than 300 and nine patients needed intubation and  
4 mechanical ventilation (all were intubated due to respiratory failure outside the  
5 PICU). One patient (number 5) responded to oxygen supplementation via non-  
6 rebreathing mask despite decreased O<sub>2</sub> saturation and PaO<sub>2</sub> of 47 mmHg. In  
7 other intubated patients, the main problem was severe hypoxia. Although they  
8 needed a low peak inspiratory pressure (PIP) for acceptable tidal volume, their  
9 oxygen saturation could not reach 85% , so peak expiratory pressure (PEEP)  
10 was increased even up to 18 and prone positioning was ordered to increase the  
11 oxygen saturation. (cases number 4 and 6). It should be mentioned that we do not  
12 have extracorporeal membrane oxygenation (ECMO) in our center.  
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19 For close and continuous monitoring of hemodynamic and volume status, the  
20 arterial line was inserted in one patient (patient number 9) and monitored by  
21 proAQT device. Besides, echocardiography was done for all patients. Of ten  
22 patients admitted, only two patients did not have hypotension and of eight patients  
23 with hypotension, six had vasoplegic shock, so infusion of high dose  
24 norepinephrine was added due to hypotension that was refractory to  
25 epinephrine/dopamine infusion; also, in patient number 9, Systemic Vascular  
26 Resistance Index (SVRI) was low (673)(dyn\*s/cm<sup>5</sup>\*m<sup>2</sup>) (reference range 1700-  
27 2400 according to proAQT device normal range). Enoxaparin was started with  
28 the aim of antithrombotic prophylaxis in all the patients.  
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35 In all patients broad spectrum antibiotics (meropenem and vancomycin) were  
36 started in addition to hydroxychloroquine (EKG was taken first and all had  
37 normal QTC; equal to or less than 0.40s) and kaletra (lopinavir/ritonavir), and  
38 intravenous immune globulin was given (IVIG) to 8 patients due to severe septic  
39 shock (except for cases number 5 and 10). In hypotensive patients,  
40 hydrocortisone, ascorbic acid, and thiamine were started.  
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46 In all of the patients, blood culture, tracheal aspirate, urine culture, and PCR for  
47 influenza A and B were negative (Table 1, 2).  
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50 Patient number 3 presented with fever, abdominal pain and tachypnea in Babol  
51 (a city in the north of Iran which had a surge in COVID-19 cases at that time).  
52 He had been admitted in Babol city hospital seven days prior to admission in our  
53 center. During the hospital stay, his condition deteriorated and he developed  
54 icterus, so he was taken by his parents' vehicle to our center (it's about 14  
55 hours from our center) with the diagnosis of acute liver failure (Nemazi hospital  
56 is the referral center for liver transplant in Iran). On arrival, he was intubated due  
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3 to decreased o2 saturation and decreased level of consciousness. He had  
4 hypotension, fever and patchy ground glass infiltrations in the chest CT scan.  
5 Surprisingly, the serum bilirubin level was very high (total bilirubin was 35);  
6 the other lab data in addition to alkaline phosphatase:387 and Gamma-glutamyl  
7 transferase (GGT) was:45 are shown in Table 1. The patient tests for hepatitis A,  
8 B, C, EBV, HSV, the and CMV were negative and serum ceruloplasmin level  
9 and LKM Ab were in normal range; he had a negative history of taking  
10 medications or substance abuse. His parents had fever and cough and their  
11 nasopharyngeal RT-PCR for COVID 19 turned positive in both.  
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18 In patient number 7, abdominal sonography revealed no abscess formation or  
19 collection.  
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**Table 1:** Epidemiologic and clinical findings of the patients

Patient number	1	2	3	4	5	6	7	8	9	10
Age(years)	4 months	3	11	13	15	16	1	1.5	3	16
Sex	male	male	male	male	male	male	male	female	female	male
Hypotension	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Tachycardia on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tachypnea on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chief complaint(s)	Fever & Letharginess	Fever & cough	Fever & abdominal pain & decreased LOC	Fever & Letharginess	Fever & cough	Fever & cough	Fever & Letharginess	Fever & cough	Fever & cough	Fever & cough
Previous illness	Cerebral Shunt	negative	negative	Cerebral palsy	negative	wegener granulomatosis	UPJO• with nephrostomy	negative	Immunodeficiency <sup>∞</sup>	Cerebral palsy
Convulsion	Yes	No	Yes	No	No	No	No	Yes	Yes	No
Decreased LOC*	negative	negative	positive	positive	negative	negative	negative	negative	negative	negative
Mechanical ventilation	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
ARDS# classification	Severe	moderate	Severe	Severe	Moderate	Severe	Severe	moderate	Severe	Severe
History of contact	negative	positive	positive	negative	positive	negative	negative	positive	positive	negative
Died	Yes	No	Yes	No	No	Yes	Yes	No	No	Yes

\*LOC: level of consciousness

#ARDS: acute respiratory distress syndrome

• UPJO: urethropelvic junction obstruction

∞ Immunodeficiency-10 is an autosomal recessive primary immunodeficiency characterized by the onset of recurrent infections in childhood due to defective T- and NK-cell function although the severity is variable (11).

Table 2: Paraclinical findings on day one of admission

COVID Real-time PCR	positive						negative			
Patient	1	2	3	4	5	6	7	8	9	10
Ferritin (ng/ml) M: 22.81-275 F: 4.63-204	580	1235	954	5701	750	1310	3489	1067	651	*
Typical Chest CT finding	positive	positive	positive	positive	positive	#	positive	positive	positive	positive
White blood cells(count/ml)	26100	9800	7100	11300	7500	22000	14000	12000	3800	12000
Lymphocyte	2088	1470	710	1017	1100	1100	6380	2400	760	480
Procalcitonin ≤ 0.3	0.24	30.5	10.1	1.36	0.6	*	1.8	73	0.2	*
C- reactive protein <6 (mg/L)	32	90	50	150	37	5	3	85	3	3
Creatine phosphokinase (U/L) M: < 171 F:< 145	37	1769	950	374	557	264	88	220	163	140
Lactate dehydrogenase (U/L) < 480	640	635	5660	1820	1350	1350	1150	786	1670	938
Troponin (ng/ml) < 19	32	29.2	3343	2029	1.5	450	27	68	35	1.5
D-Dimer (ng/ml) < 500	1924	540	10000	9232	1296	638	5135	9536	1296	10000
Total bilirubin 0.1-1.2	0.7	0.3	35	0.6	0.4	0.2	*	0.3	0.6	*
Direct bilirubin < 0.3	0.3	0.1	21	0.1	0.2	0.1	*	0.1	0.1	*
Aspartate transaminase (U/L) M: < 37 F: < 31	1020	36	2030	51	40	97	*	77	68	*
Alanine aminotransferase (U/L) M: < 41 F: < 31	52	14	690	37	33	13	*	28	34	*
Creatinine M: 0.8 - 1.3 F: 0.6 - 1.2	0.9	0.5	0.1	0.5	0.9	4.8	0.5	0.4	0.4	3.3
Blood urea nitrogen (mg/dl) 8 - 20	13	11	113	13	14	53	9	3	19	62

M: male/F: female

# was not performed due to his unstable condition

\*did not checked

## Discussion

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The reported overall case fatality rate is 2.3% according to China Centre for Disease Control and Prevention (CDC) which is much lower than SARS (9.6%) and MERS (34%), but significantly higher compared to the latest H1N1 influenza pandemic (0.001 – 0.007%) (12). However, WHO reported the global case fatality rate as high as 4.4% with absolute number of deaths already higher than the total fatality of SARS and MERS combined (13). The case fatality reported from Italy is 7.2%, which increased to 9.8% (WHO as on March 26, 2020) (14).

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There are few studies regarding pediatric patients admitted in PICU. The case fatality rate in our PICU was 50%. It was also about 50% in adult patients admitted in ICU (15,16,17). However, pediatric data from Madrid, Spain, reported no mortality (18), and in a Chinese study there was only one case (19). In a cohort study in children hospital in Wuhan, three pediatric patients were admitted in the PICU, all with comorbidities and one case (33%) died (20). In another study from Wuhan, one patient without comorbidity was admitted in PICU and survived (5).

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In our study, all patients were febrile and 70% had cough, but in some studies non-critical pediatric fever was present in less than 50% (5, 19, 20).

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In our study, 60% of patients had positive RT-PCR FOR COVID-19. There are some reasons for that; we tested the patients via oropharyngeal swab only and nasopharyngeal swab was not done. The other possibility is that the patients arrived in the PICU in terminal stages of the disease, so the viral shedding was low at that time.

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Moreover, in a study on 48 pediatric patients with COVID-19 admitted in 46 North American PICUs, 83% had significant pre-existing comorbidities, 73% presented with respiratory symptoms, 38% required invasive ventilation, and 23% had failure of 2 or more organ systems. The mortality rate was 4% in their study (up to the time of the report). Three patients were intubated, one patient was taking extracorporeal membrane oxygenation (ECMO), and only 25% needed vasoactive support (21).

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In the beginning of the pandemic, it was assumed that the main organ involvement in COVID-19 was respiratory system, but several studies reported Kawasaki-like syndrome MIS-C later (22).

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3 DeBiasi et al. described a 177 pediatric patients series in the Washington, DC  
4 metropolitan region; among them, 9 cases required critical care, 8 needed  
5 respiratory support, and one had Kawasaki-like shock syndrome(23).  
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9 Another report mentioned 8 pediatric patients with hyperinflammatory shock,  
10 showing features similar to atypical Kawasaki disease, Kawasaki disease shock  
11 syndrome, or toxic shock syndrome, all of which had negative test for severe  
12 acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on arrival, but clinical  
13 and laboratory findings were in favor of the disease. Two patients' tests for  
14 SARS-COV-2 was positive on discharge. Seven patients needed norepinephrine  
15 infusion, and one passed away according to their report (24).  
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21 In our study, some of our severely infected patients had elevated troponin level  
22 (especially in patients number 3,4,6), but despite fulfilling the criteria for MIS-  
23 C on arrival to PICU, they were hypotensive; this may explain those high levels,  
24 but could not rule out MIS-C.  
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28 Also, in the present study, six patients needed norepinephrine in addition to  
29 dopamine/epinephrine infusion due to refractory shock. In patient number 9, low  
30 amount of SVRI was the reason of norepinephrine infusion.  
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34 It has been shown that coronavirus infection (SARS, MERS and even; COVID-  
35 19) could damage the liver, and mild to moderate elevation of Alanine  
36 aminotransferase (ALT); decreased albumin and increased serum bilirubin levels  
37 occur frequently (25,26,27,28), but extremely high ALT and bilirubin levels in  
38 patient number 3 was noteworthy with some probable explanation like acute  
39 liver failure caused by COVID-19 or a rare complication of the disease (29).  
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44 In patient number 3, BUN and serum creatinine levels were disproportionate; it  
45 should be noted that the patient was hypotensive and oliguric, but in a day after  
46 PICU admission, as the patient's blood pressure became stable and the patient  
47 had normal urination, BUN decreased to 85 and creatinine turned to 0.5. This  
48 could be explained by hypotension,, altered liver function and hepatorenal  
49 syndrome.  
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54 This was our first experience toward COVID-19 patients. As the time passed, we  
55 became more familiar with characteristics of the disease, and the ways to better  
56 diagnose, and manage it. Through reporting the characteristics of our patients,  
57 we aimed to share our experience regarding COVID 19 patients and highlight  
58 some dark points of the disease. It is suggested that a more valid and strict  
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3 triage criteria should be chosen for pediatric emergency rooms and the physicians  
4 and nurses engaged in pediatric care should be educated to better diagnose  
5 COVID 19 cases in this age group.  
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## 10 **Conclusion**

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13 There is a general conception that pediatric patients infected by COVID-19 have  
14 less severe symptoms and better outcomes, but severe and fatal cases occur as  
15 well.  
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19 **Conflict of interest:** none

20  
21 **Funding:** The authors did not receive a specific grant for this research from any  
22 funding agency in the public, commercial or not-for-profit sectors.  
23  
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25 **Authors' Contributions:** A.S. planned the study and wrote the manuscript. E.S.  
26 gathered patients' data and submitted the manuscript. A.S.D. did the data  
27 interpretation. A.S.D. and M.R.K. edited the manuscript and were scientific  
28 consultant. All authors discussed the results and contributed to the final  
29 manuscript.  
30  
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32

33 **Acknowledgements:** The authors would like to thank Shiraz University of Medical Sciences,  
34 Shiraz, Iran and also Center for Development of Clinical Research of Namazi Hospital and Dr. Nasrin  
35 Shokrpour for editorial assistance.  
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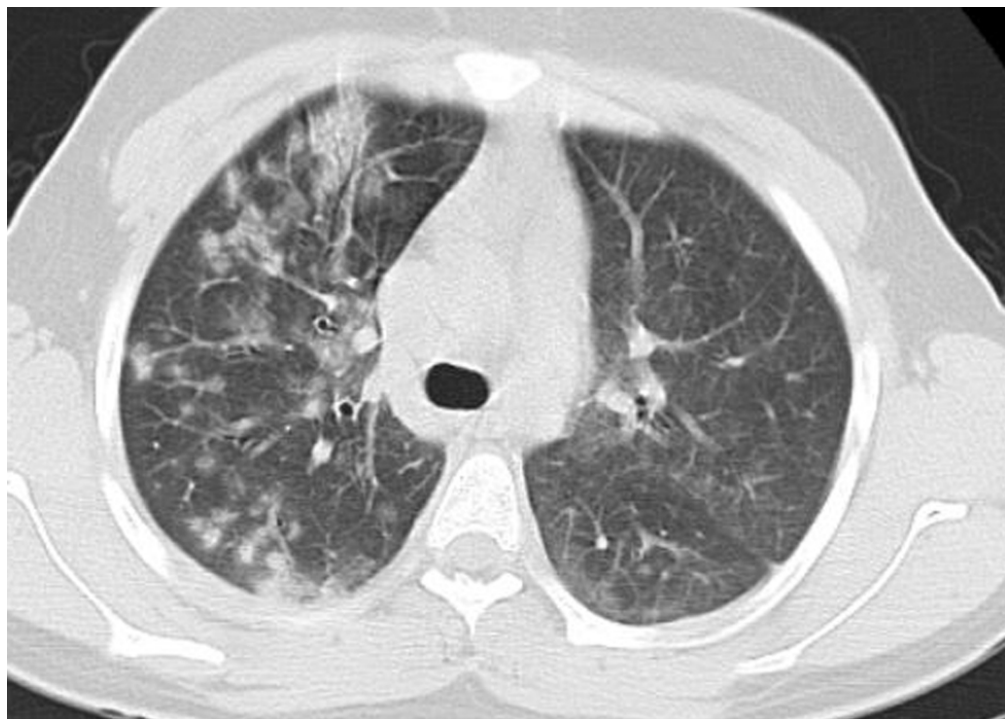
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# BMJ Paediatrics Open

## Clinical presentation of pediatric patients with COVID 19 admitted to a single paediatric intensive care unit (PICU) in Iran

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000715.R2
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2020
Complete List of Authors:	Saeed, Amir; Shiraz University of Medical Sciences Medical School, Pediatrics shorafa, eslam; Shiraz University of Medical Sciences, sanaeidashti, anahita; Shiraz University of Medical Sciences, department of pediatrics kadirvar, mohammad rahim; Shiraz University of Medical Sciences, department of pediatrics
Keywords:	Health services research, Virology, Mortality

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## Clinical presentation of pediatric patients with COVID 19 admitted to a single paediatric intensive care unit (PICU) in Iran

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Word count: 1522

**Keywords:** COVID 19; SARS coronavirus 2 , Wegener , child, PICU

## Abstract

**Objectives:** To describe the clinical characteristics of pediatric patients admitted to a single pediatric intensive care unit (PICU) in Iran with COVID-19

**Methods:** A cross-sectional study of pediatric patients who were admitted to a COVID dedicated PICU from March 16 to April 21, 2020 with COVID-19.

**Results:** Six children had confirmed COVID-19 and four had suspected COVID-19. Six had pre-existing chronic medical conditions. Nine had respiratory failure and needed ventilation. Five children, of whom four had chronic medical conditions, died. Four had cardiac arrhythmias. Clinical presentation included fever and cough.

**Conclusion:** COVID-19 can be fatal in pediatric patients, especially in those with a chronic medical condition.

What is known about the subject?

- ▶ COVID -19 infection is less frequent and severe in pediatric patients than adult patients.
- ▶ The main symptom is fever and few pediatric patients need mechanical ventilation or inotrope support.

What this study adds?

- ▶ COVID-19 infection may be fatal in pediatric patients, especially in those with chronic medical conditions.
- ▶ The main respiratory problems in severe cases are oxygenation failure and a hypotensive state necessitating inotropes.
- ▶ The main causes of mortality in our study were cardiac arrhythmia and refractory hypoxemia.

## Introduction

In December 2019, a cluster of acute respiratory illness occurred in Wuhan, Hubei Province, China by a novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). On the 3<sup>rd</sup> of January 2020, the virus was identified in the samples of bronchoalveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of the disease (2).

The current outbreak of infections with SARS-CoV-2 was termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) (3). The disease rapidly spread from Wuhan to other areas of the world, so that the world health organization (WHO) announced Covid-19 outbreak as a pandemic on March 11, 2020 (4).

The 2019-nCoV is closely similar to bat coronaviruses, and it has been assumed that bats are the primary source. While the origin of the 2019-nCoV is still being investigated, the current evidence suggests that spread to humans occurred from wild animals illegally sold in the Huanan Seafood Wholesale Market.

The rate of infection with covid-19 in children is low and the first pediatric case was reported on January 20, 2020, who was a 10-year-old Chinese boy, whose family had visited Wuhan City (4). A retrospective study on 366 children aged under 16 years old and hospitalized for respiratory infections between January 7 and 15, 2020, confirmed COVID-19 infection in six (1.6%) of them. This study suggests that COVID-19 infections in children occurred early in the epidemic (5). One reason for the low frequency of the disease in children in China could

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3 be the fact that children were rarely tested for the virus in the earlier phase of  
4 the outbreak, especially in Hubei province, where most of the patients were  
5 confirmed, so there are a limited data on the prevalence of COVID-19 in  
6 children (6). The virus can produce a Kawasaki-like illness in children. World  
7 health organization (WHO) developed a preliminary case definition for this  
8 condition which was later named 'multisystem inflammatory disorder' in  
9 COVID-19 (MIS-C). The syndrome should be considered in children with  
10 features of typical or atypical Kawasaki disease or toxic shock syndrome (7).  
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16 Herein, we describe the patients with COVID-19 presenting with multi-system  
17 inflammatory syndrome. In Iran, the first COVID-19 cases were detected in  
18 February 2020 in Qom city. There are a few reports from critically ill pediatric  
19 patients in the country. In this article, we describe the characteristics of pediatric  
20 patients with COVID-19 admitted in pediatric intensive care unit (PICU) of  
21 Namazi hospital in Shiraz, Iran.  
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## 24 25 26 27 **Methods**

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29 Nemazi hospital in Shiraz, is the largest and the main tertiary referral center in  
30 the south of Iran with more than one thousand beds. The medical PICU of this  
31 hospital has 18 beds with two separate sections, one of which was devoted to  
32 COVID 19 cases from the beginning of the outbreak and those with suspected or  
33 confirmed COVID-19 were admitted in this ward. All children aged one month  
34 to 18 years admitted to the COVID-19 PICU between March 16 and 21 April  
35 were included.  
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41 A confirmed case of Covid-19 was defined by a positive result on a reverse  
42 transcriptase–polymerase chain-reaction (RT-PCR) assay of a specimen collected  
43 on an oropharyngeal swab, nasopharyngeal swab or bronchoalveolar lavage. The  
44 tests were performed using an Applied Biosystem Step One plus real-time PCR  
45 machine (Applied Biosystem, CA, USA). Amplification of N and ORF1b took  
46 place in a 20µL single-tube, and Superscript III Platinum one-step quantitative  
47 RT-PCR system (Invitrogen, Carlsbad, CA). Reactions contained 10.0 µL of 2X  
48 RT/PCR reaction mix, 1 µL primers/prob mix, 0.4 µL Superscript III  
49 RT/Platinum Taq mix, 0.4 µL ROX reference dye, and 5 µL of extracted sample  
50 RNA or serially diluted previously confirmed patients' positive control. The  
51 cycling conditions consisted of one cycle at 50°C for 10 min, one cycle at 95°C  
52 for 2 min, 45 cycles at 95°C for 5 s, and 60°C for 30 min)(8).  
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A suspected case of COVID 19 was defined as a patient with clinical and laboratory findings (9) (table 1) plus chest CT findings consistent with COVID 19 infection (10)(figure 1,2) and history of close contact, but negative PCR result.

Table 1: laboratory and clinical findings in favor of COVID19 infection

Laboratory findings			clinical manifestation
increased		decreased	
CRP ESR AST,ALT procalcitonin LDH	D.dimer ferritin	Albumin lymphocytes	fever, cough, sore throat, headache, shortness of breath, nausea, vomiting, abdominal pain
			Sepsis and organ failure

### Patient involvement

Patients were not directly involved in the design of this study.

### Ethics statement

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.sums.med.rec.1399.40). Written informed consent was obtained from the parents and sent to the ethics committee.

### Results

From March 16 to April 21, 2020, six patients were admitted with confirmed COVID-19 and four had suspected COVID-19 (Tables 2,3). Only one of them was transferred from the Emergency Department (ER) with suspected COVID-19. Nine were transferred from other wards with other suspected diagnoses. The median age was 7.9 years. Eight patients were male. Six patients had chronic medical conditions (Table 2). The other four were previously healthy.

Five patients had a positive history of contact to confirmed or suspected cases (3 patients had contact to positive RT-PCR cases) or possible cases with fever and cough. The main symptoms were fever, cough, abdominal pain, lethargy and encephalopathy. The median time from the presentation of symptoms to PICU admission was 4.7 days (range 3-8 days).

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3 All the children had tachypnoea and tachycardia on admission to the PICU. All  
4 patients had PaO<sub>2</sub>/Fio<sub>2</sub> less than 300 and nine patients needed intubation and  
5 mechanical ventilation (all were intubated due to respiratory failure outside the  
6 PICU). One patient responded to oxygen supplementation via non-rebreathing  
7 mask despite decreased o<sub>2</sub> saturation and PaO<sub>2</sub> of 47 mmHg.  
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11 In other intubated patients, the main problem was severe hypoxia. Although they  
12 needed a low peak inspiratory pressure (PIP) for acceptable tidal volume, their  
13 oxygen saturation could not reach 85% , so peak expiratory pressure (PEEP)  
14 was increased even up to 18 and prone positioning was ordered to increase the  
15 oxygen saturation. (cases number 4 and 6). Extracorporeal membrane  
16 oxygenation (ECMO) was not available in our center.  
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20 Unfortunately, five patients died. Four of the five had chronic medical conditions.  
21 Cardiac arrhythmias occurred in three of the children who died.  
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28 Nine/Ten children had hypotension. Six children received high dose of  
29 norepinephrine(more than 0.3 micro/kilogram/minutes) in addition to other  
30 inotropes. Enoxaparin was started with the aim of antithrombotic prophylaxis in  
31 all the patients. In all patients broad spectrum antibiotics (meropenem and  
32 vancomycin) were started in addition to hydroxychloroquine (EKG was taken  
33 first and all had normal QTC; equal to or less than 0.40s) and kaletra  
34 (lopinavir/ritonavir), and intravenous immune globulin was given (IVIG) to 8  
35 patients due to severe septic shock (except for cases number 5 and 10). In  
36 hypotensive patients, hydrocortisone, ascorbic acid, and thiamine were started.  
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40 In all of the patients, blood culture, tracheal aspirate, urine culture, and PCR for  
41 influenza A and B were negative (Table 2,3).  
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46 Patient number 3 presented with fever, abdominal pain and tachypnea. he was  
47 transferred by his parents to our center with the diagnosis of acute liver failure  
48 (Nemazi hospital is the referral center for liver transplant in Iran). On arrival, he  
49 was intubated due to decreased o<sub>2</sub> saturation and decreased level of  
50 consciousness. He had hypotension, fever and patchy ground glass infiltrations  
51 in the chest CT scan. Surprisingly, the serum bilirubin level was very high (total  
52 bilirubin was 35); the other lab data in addition to alkaline phosphatase:387 and  
53 Gamma-glutamyl transferase (GGT) was:45 are shown in Table 3. The patient  
54 tests for hepatitis A, B, C, EBV, HSV and CMV were negative and serum  
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ceruloplasmin level and LKM Ab were in normal range; he had a negative history of taking medications or substance abuse. His parents had fever and cough and their nasopharyngeal RT-PCR for COVID 19 turned positive in both.

**Table 2:** clinical details of the patients

Patient number	1	2	3	4	5	6	7	8	9	10
Real-time PCR	+	+	+	+	+	+	-	-	-	-
Age(years)	4 months	3	11	13	15	16	1	1.5	3	16
Sex	male	male	male	male	male	male	male	female	female	male
Hypotension	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Tachycardia on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tachypnea on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chief complaint(s)	Fever & Letharginess	Fever & cough	Fever & abdominal pain & decreased LOC	Fever & Letharginess	Fever & cough	Fever & cough	Fever & Letharginess	Fever & cough	Fever & cough	Fever & cough
Previous illness	Cerebral Shunt	negative	negative	Cerebral palsy	negative	wegener granulomatosis	UPJO• with nephrostomy	negative	Immunodeficiency <sup>∞</sup>	Cerebral palsy
Convulsion	Yes	No	Yes	No	No	No	No	Yes	Yes	No
Decreased LOC*	negative	negative	positive	positive	negative	negative	negative	negative	negative	negative
Mechanical ventilation	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
ARDS# classification	Severe	moderate	Severe	Severe	Moderate	Severe	Severe	moderate	Severe	Severe
History of contact	negative	positive	positive	negative	positive	negative	negative	positive	positive	negative
Died	Yes	No	Yes	No	No	Yes	Yes	No	No	Yes

\*LOC: level of consciousness

#ARDS: acute respiratory distress syndrome

• UPJO: urethropelvic junction obstruction

∞ Immunodeficiency-10 is an autosomal recessive primary immunodeficiency characterized by the onset of recurrent infections in childhood due to defective T- and NK-cell function although the severity is variable (11).



Table 3: laboratory results on day one of admission

COVID Real-time PCR	positive						negative			
Patient	1	2	3	4	5	6	7	8	9	10
Ferritin (ng/ml) M: 22.81-275 F: 4.63-204	580	1235	954	5701	750	1310	3489	1067	651	*
Typical Chest CT finding	positive	positive	positive	positive	positive	#	positive	positive	positive	positive
White blood cells(count/ml)	26100	9800	7100	11300	7500	22000	14000	12000	3800	12000
Lymphocyte	2088	1470	710	1017	1100	1100	6380	2400	760	480
Procalcitonin ≤ 0.3	0.24	30.5	10.1	1.36	0.6	*	1.8	73	0.2	*
C- reactive protein <6 (mg/L)	32	90	50	150	37	5	3	85	3	3
Creatine phosphokinase (U/L) M: < 171 F:< 145	37	1769	950	374	557	264	88	220	163	140
Lactate dehydrogenase (U/L) < 480	640	635	5660	1820	1350	1350	1150	786	1670	938
Troponin (ng/ml) < 19	32	29.2	3343	2029	1.5	450	27	68	35	1.5
D-Dimer (ng/ml) < 500	1924	540	10000	9232	1296	638	5135	9536	1296	10000
Total bilirubin 0.1-1.2	0.7	0.3	35	0.6	0.4	0.2	*	0.3	0.6	*
Direct bilirubin < 0.3	0.3	0.1	21	0.1	0.2	0.1	*	0.1	0.1	*
Aspartate transaminase (U/L) M: < 37 F: < 31	1020	36	2030	51	40	97	*	77	68	*
Alanine aminotransferase (U/L) M: < 41 F: < 31	52	14	690	37	33	13	*	28	34	*
Creatinine M: 0.8 - 1.3 F: 0.6 - 1.2	0.9	0.5	0.1	0.5	0.9	4.8	0.5	0.4	0.4	3.3
Blood urea nitrogen (mg/dl) 8 - 20	13	11	113	13	14	53	9	3	19	62

M: male/F: female

# was not performed due to his unstable condition

\*did not checked

## Discussion

There are few studies regarding pediatric patients admitted in PICU. Pediatric data from Madrid, Spain, reported no mortality, but described one child who needed mechanical ventilation and two who needed non-invasive ventilation(12). In a Chinese study there was only one case who needed mechanical ventilation (13). In a cohort study in children hospital in Wuhan, three pediatric patients were admitted in the PICU, all with comorbidities and one case died (14). In another study from Wuhan, one patient without comorbidity was admitted in PICU and survived (5).

In our study, all patients were febrile and 70% had cough, but in some studies non-critical pediatric fever was present in less than 50%( 5, 13, 14).

In a study on 48 pediatric patients with COVID-19 admitted in 46 North American PICUs, 83% had significant pre-existing comorbidities, 73% presented with respiratory symptoms, 38% required invasive ventilation, and 23% had failure of 2 or more organ systems. The mortality rate was 4% in their study (up to the time of the report). Three patients were intubated, one patient was taking extracorporeal membrane oxygenation(ECMO), and only 25% needed vasoactive support (15).

In the beginning of the pandemic, it was assumed that the main organ involvement in COVID-19 was respiratory, but several studies have reported Kawasaki- like syndrome MIS-C later (16).

DeBiasi et al. described a 177 pediatric patients series in the Washington, DC metropolitan region; among them, 9 cases required critical care, 8 needed respiratory support, and one had Kawasaki-like shock syndrome (17).

In our study, some of our severely infected patients had elevated troponin level and fulfilling the criteria for MIS-C on arrival to PICU. Also hypotension and organ hypo perfusion, can explain the etiology of high level of troponin.

It has been shown that coronavirus infection (SARS, MERS and even; COVID-19) could damage the liver, and mild to moderate elevation of Alanine aminotransferase (ALT); decreased albumin and increased serum bilirubin levels occur frequently (18,19,20,21), but extremely high ALT and bilirubin levels in patient number 3 was noteworthy with some probable explanation like acute liver failure caused by COVID-19 or a rare complication of the disease (22).

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3 Through reporting the characteristics of our patients, we aim to share our  
4 experience regarding COVID 19 patients.  
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7 There is a general conception that pediatric patients infected by COVID-19 have  
8 less severe symptoms and better outcomes, but severe and fatal cases occur as  
9 well.  
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12 **Conflict of interest:** none  
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14  
15 **Funding:** The authors did not receive a specific grant for this research from any  
16 funding agency in the public, commercial or not-for-profit sectors.  
17  
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19 **Authors' Contributions:** A.S. planned the study and wrote the manuscript. E.S.  
20 gathered patients' data and submitted the manuscript. A.S.D. did the data  
21 interpretation A.S.D. and M.R.K. edited the manuscript and were scientific  
22 consultant. All authors discussed the results and contributed to the final  
23 manuscript.  
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26  
27 **Acknowledgements:** The authors would like to thank Shiraz University of Medical Sciences,  
28 Shiraz, Iran and also Center for Development of Clinical Research of Namazi Hospital and Dr. Nasrin  
29 Shokrpour for editorial assistance.  
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35 Figure legends:  
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37 Figure 1: chest CT of patient number 5  
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39 Figure 2: chest CT of patient number 10  
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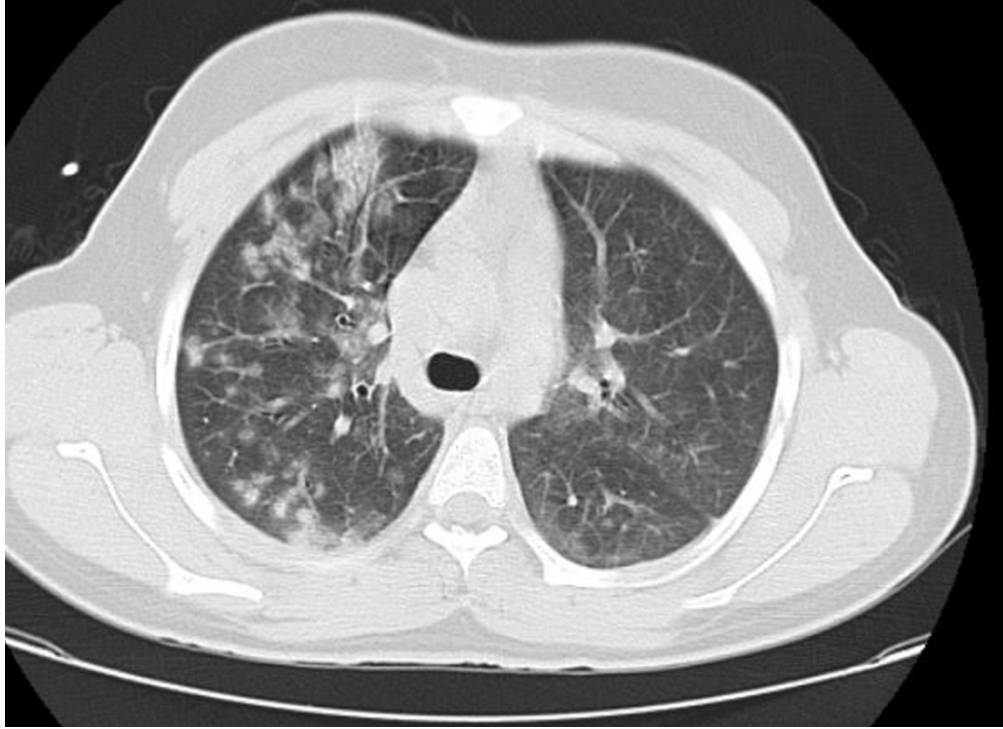


Figure 1: chest CT of patient number 5

99x72mm (300 x 300 DPI)



Figure 2: chest CT of patient number 10

99x68mm (300 x 300 DPI)

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# BMJ Paediatrics Open

## Clinical presentation of pediatric patients with COVID 19 admitted to a single paediatric intensive care unit (PICU) in Iran

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000715.R3
Article Type:	Original research
Date Submitted by the Author:	29-Aug-2020
Complete List of Authors:	Saeed, Amir; Shiraz University of Medical Sciences Medical School, Pediatrics shorafa, eslam; Shiraz University of Medical Sciences, sanaeidashti, anahita; Shiraz University of Medical Sciences, department of pediatrics kadirvar, mohammad rahim; Shiraz University of Medical Sciences, department of pediatrics
Keywords:	Health services research, Virology, Mortality

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## Clinical presentation of pediatric patients with COVID 19 admitted to a single paediatric intensive care unit (PICU) in Iran

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Word count: 1522

**Keywords:** COVID 19; SARS coronavirus 2 , Wegener , child, PICU

## Abstract

**Objectives:** To describe the clinical characteristics of pediatric patients admitted to a single pediatric intensive care unit (PICU) in Iran with COVID-19

**Methods:** A cross-sectional study of pediatric patients who were admitted to a COVID dedicated PICU from March 16 to April 21, 2020 with COVID-19.

**Results:** Six children had confirmed COVID-19 and four had suspected COVID-19. Six had pre-existing chronic medical conditions. Nine had respiratory failure and needed ventilation. Five children, of whom four had chronic medical conditions, died. Four had cardiac arrhythmias. Clinical presentation included fever and cough.

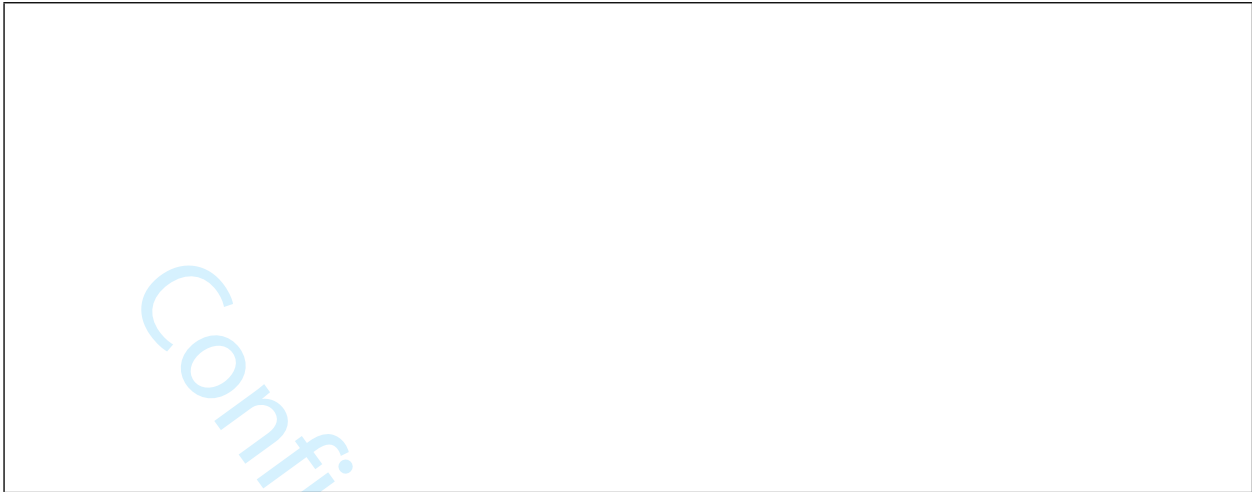
**Conclusion:** COVID-19 can be fatal in pediatric patients, especially in those with a chronic medical condition.

What is known about the subject?

- ▶ COVID -19 infection is less frequent and severe in pediatric patients than adult patients.
- ▶ The main symptom is fever and few pediatric patients need mechanical ventilation or inotrope support.

What this study adds?

- ▶ COVID-19 infection may be fatal in pediatric patients, especially in those with chronic medical conditions.
- ▶ The main respiratory problems in severe cases are oxygenation failure and a hypotensive state necessitating inotropes.
- ▶ The main causes of mortality in our study were cardiac arrhythmia and refractory hypoxemia.



## Introduction

The coronavirus pandemic originated in Wuhan, China<sup>1 2</sup>. The current outbreak of infections with coronavirus 2 (SARS-CoV-2) was termed Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO)<sup>3</sup>. The disease rapidly spread from Wuhan to other areas of the world, so that the WHO announced that the outbreak was a pandemic in March 2020<sup>4</sup>.

The first paediatric case was a 10-year-old Chinese boy, whose family had visited Wuhan City<sup>4</sup>. A retrospective study on 366 children hospitalized for respiratory infections in January 2020 confirmed COVID-19 infection in six (1.6%) of them. This study suggests that COVID-19 infections in children occurred early in the epidemic<sup>5</sup>. Children were rarely tested for the virus in the earlier phase of the outbreak, so there are limited data on the prevalence of COVID-19 in children<sup>6</sup>. The virus can produce a Kawasaki-like illness in children. WHO developed a preliminary case definition for this condition which was later named 'multisystem inflammatory disorder' in COVID-19 (MIS-C)<sup>7</sup>.

In Iran, the first COVID-19 cases were detected in February 2020 in Qom city. There are a few reports from critically ill pediatric patients in the country. In this article, we describe the characteristics of pediatric patients with COVID-19 admitted in pediatric intensive care unit (PICU) of Namazi hospital in Shiraz, Iran.

## Methods

Namazi hospital in Shiraz, is the largest and the main tertiary referral center in the south of Iran with more than one thousand beds. The medical PICU of this hospital has 18 beds with two separate sections, one of which was devoted to COVID 19 cases from the beginning of the outbreak and those with suspected or confirmed COVID-19 were admitted in this ward. All children aged one month to 18 years admitted to the COVID-19 PICU between March 16 and 21 April were included.

A confirmed case of Covid-19 was defined by a positive result on a reverse transcriptase–polymerase chain-reaction (RT-PCR) assay of a specimen collected on an oropharyngeal swab, nasopharyngeal swab or bronchoalveolar lavage. The tests were performed using an Applied Biosystem Step One plus real-time PCR machine (Applied Biosystem, CA, USA). Amplification of N and ORF1b took place in a 20µL single-tube, and Superscript III Platinum one-step quantitative RT-PCR system (Invitrogen, Carlsbad, CA). Reactions contained 10.0 µL of 2X RT/PCR reaction mix, 1 µL primers/prob mix, 0.4 µL Superscript III RT/Platinum Taq mix, 0.4 µL ROX reference dye, and 5 µL of extracted sample RNA or serially diluted previously confirmed patients' positive control. The cycling conditions consisted of one cycle at 50°C for 10 min, one cycle at 95°C for 2 min, 45 cycles at 95°C for 5 s, and 60°C for 30 min)<sup>8</sup>.

A suspected case of COVID 19 was defined as a patient with clinical and laboratory findings<sup>9</sup> (table 1) plus chest CT findings consistent with COVID 19 infection<sup>10</sup> (figure 1,2) and history of close contact, but negative PCR result.

Table 1: laboratory and clinical findings in favor of COVID19 infection

Laboratory findings			clinical manifestation
increased		decreased	
CRP	D.dimer	Albumin	fever, cough, sore throat, headache, shortness of breath, nausea, vomiting, abdominal pain
ESR	ferritin	lymphocytes	
AST,ALT			Sepsis and organ failure
procalcitonin			
LDH			

## Patient involvement

Patients were not directly involved in the design of this study.

## Ethics statement

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.sums.med.rec.1399.40). Written informed consent was obtained from the parents and sent to the ethics committee.

## Results

From March 16 to April 21, 2020, six patients were admitted with confirmed COVID-19 and four had suspected COVID-19 (Tables 2,3). Only one of them was transferred from the Emergency Department (ER) with suspected COVID-19. Nine were transferred from other wards with other suspected diagnoses. The median age was 7.9 years. Eight patients were male. Six patients had chronic medical conditions (Table 2). The other four were previously healthy.

Five patients had a positive history of contact to confirmed or suspected cases (3 patients had contact to positive RT-PCR cases) or possible cases with fever and cough. The main symptoms were fever, cough, abdominal pain, lethargy and encephalopathy. The median time from the presentation of symptoms to PICU admission was 4.7 days (range 3-8 days).

All the children had tachypnoea and tachycardia on admission to the PICU. All patients had PaO<sub>2</sub>/Fio<sub>2</sub> less than 300 and nine patients needed intubation and mechanical ventilation (all were intubated due to respiratory failure outside the PICU). One patient responded to oxygen supplementation via non-rebreathing mask despite decreased O<sub>2</sub> saturation and PaO<sub>2</sub> of 47 mmHg.

In other intubated patients, the main problem was severe hypoxia. Although they needed a low peak inspiratory pressure (PIP) for acceptable tidal volume, their oxygen saturation could not reach 85% , so peak expiratory pressure (PEEP) was increased even up to 18 and prone positioning was ordered to increase the oxygen saturation. (cases number 4 and 6). Extracorporeal membrane oxygenation (ECMO) was not available in our center.

Unfortunately, five patients died. Four of the five had chronic medical conditions. Cardiac arrhythmias occurred in three of the children who died.

Nine children had hypotension. Six children received high dose of norepinephrine (more than 0.3 micro/kilogram/minutes) in addition to other

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3 inotropes. Enoxaparin was started with the aim of antithrombotic prophylaxis in  
4 all the patients. In all patients broad spectrum antibiotics (meropenem and  
5 vancomycin) were started in addition to hydroxychloroquine (ECG was taken  
6 first and all had normal QTC; equal to or less than 0.40s) and kaletra  
7 (lopinavir/ritonavir), and intravenous immune globulin was given (IVIG) to 8  
8 patients due to severe septic shock (except for cases number 5 and 10). In  
9 hypotensive patients, hydrocortisone, ascorbic acid, and thiamine were started.  
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12 In all of the patients, blood culture, tracheal aspirate, urine culture, and PCR for  
13 influenza A and B were negative (Table 2,3).  
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15 Patient number 3 presented with fever, abdominal pain and tachypnea. he was  
16 transferred by his parents to our center with the diagnosis of acute liver failure  
17 (Namazi hospital is the referral center for liver transplant in Iran). On arrival, he  
18 was intubated due to decreased o2 saturation and decreased level of  
19 consciousness. He had hypotension, fever and patchy ground glass infiltrations  
20 in the chest CT scan. Surprisingly, the serum bilirubin level was very high (total  
21 bilirubin was 35); the other lab data in addition to alkaline phosphatase:387 and  
22 Gamma-glutamyl transferase (GGT) was:45 are shown in Table 3. The patient  
23 tests for hepatitis A, B, C, EBV, HSV and CMV were negative and serum  
24 ceruloplasmin level and LKM Ab were in normal range; he had a negative history  
25 of taking medications or substance abuse. His parents had fever and cough and  
26 their nasopharyngeal RT-PCR for COVID 19 turned positive in both.  
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40 **Table 2:** clinical details of the patients  
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Patient number	1	2	3	4	5	6	7	8	9	10
Real-time PCR	+	+	+	+	+	+	-	-	-	-
Age(years)	4 months	3	11	13	15	16	1	1.5	3	16
Sex	male	male	male	male	male	male	male	female	female	male
Hypotension	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Tachycardia on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tachypnea on admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chief complaint(s)	Fever & Letharginess	Fever & cough	Fever & abdominal pain & decreased LOC	Fever & Letharginess	Fever & cough	Fever & cough	Fever & Letharginess	Fever & cough	Fever & cough	Fever & cough



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Previous illness	Cerebral Shunt	negative	negative	Cerebral palsy	negative	wegener granulomatosis	UPJO• with nephrostomy	negative	Immuno deficiency <sup>∞</sup>	Cerebral palsy
Convulsion	Yes	No	Yes	No	No	No	No	Yes	Yes	No
Decreased LOC*	negative	negative	positive	positive	negative	negative	negative	negative	negative	negative
Mechanical ventilation	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
ARDS# classification	Severe	moderate	Severe	Severe	Moderate	Severe	Severe	moderate	Severe	Severe
History of contact	negative	positive	positive	negative	positive	negative	negative	positive	positive	negative
Died	Yes	No	Yes	No	No	Yes	Yes	No	No	Yes

\*LOC: level of consciousness

#ARDS: acute respiratory distress syndrome

• UPJO: urethropelvic junction obstruction

<sup>∞</sup> Immunodeficiency-10 is an autosomal recessive primary immunodeficiency characterized by the onset of recurrent infections in childhood due to defective T- and NK-cell function although the severity is variable<sup>11</sup>.

Table 3: laboratory results on day one of admission

COVID Real-time PCR	positive						negative			
Patient	1	2	3	4	5	6	7	8	9	10
Ferritin (µg/L) M: 22.81-275 F: 4.63-204	580	1235	954	5701	750	1310	3489	1067	651	*
Typical Chest CT finding	positive	positive	positive	positive	positive	#	positive	positive	positive	positive
White blood cells(count/ml)	26100	9800	7100	11300	7500	22000	14000	12000	3800	12000
Lymphocyte	2088	1470	710	1017	1100	1100	6380	2400	760	480
Procalcitonin ≤ 0.3(µg/L)	0.24	30.5	10.1	1.36	0.6	*	1.8	73	0.2	*
C- reactive protein <6 (mg/L)	32	90	50	150	37	5	3	85	3	3
Creatine phosphokinase (µkat/L) M:< 2.86 F:< 2.4	0.62	29.5	15.8	6.2	9.3	4.4	1.4	3.6	2.7	2.3
Lactate dehydrogenase (µkat/L) < 8	10.6	10.6	94.5	30.3	22.5	22.5	19.2	13.3	27.8	15.6
Troponin (µg/L)< 19	32	29.2	3343	2029	1.5	450	27	68	35	1.5
D-Dimer (nmol/L) < 2738	10535	2957	54760	50554	7096	3993	28119	52219	7096	50554
Total bilirubin (µmol/L)5.1-17	11.9	5.1	598.6	10.2	6.8	3.4	*	5.1	10.2	*
Direct bilirubin (µmol/L)3.4-12.0	5.1	1.7	359	1.7	3.4	1.7	*	1.7	1.7	*
Aspartate transaminase (µkat/L) M: < 0.62 F: < 0.52	17	0.6	33.9	0.85	0.67	1.6	*	1.2	1.1	*
Alanine aminotransferase (µkat/L) M: < 0.68 F: < 0.52	0.8	0.2	11.5	0.62	0.55	0.22	*	0.47	0.57	*
Creatinine (µmol/L) M: 53-106 F: 44-97	79.5	44.2	8.8	44.2	79.5	424.3	44.2	35.3	35.3	291.7
Blood urea nitrogen (mmol/L) 3.6-7.1	4.6	3.9	40.3	4.6	5	18.9	3.2	1	6.7	22.1

M: male/F: female

# was not performed due to his unstable condition

\*did not checked

## Discussion

There are few studies regarding pediatric patients admitted in PICU. Pediatric data from Madrid, Spain, reported no mortality, but described one child who needed mechanical ventilation and two who needed non-invasive ventilation<sup>12</sup>. In a Chinese study there was only one case who needed mechanical ventilation<sup>13</sup>. In a cohort study in children hospital in Wuhan, three pediatric patients were admitted in the PICU, all with comorbidities and one case died<sup>14</sup>. In another study from Wuhan, one patient without comorbidity was admitted in PICU and survived<sup>5</sup>.

In our study, all patients were febrile and 70% had cough, but in some studies non-critical pediatric fever was present in less than 50%<sup>5 13 14</sup>.

In a study on 48 pediatric patients with COVID-19 admitted in 46 North American PICUs, 83% had significant pre-existing comorbidities, 73% presented with respiratory symptoms, 38% required invasive ventilation, and 23% had failure of 2 or more organ systems. The mortality rate was 4% in their study (up to the time of the report). Three patients were intubated, one patient was taking extracorporeal membrane oxygenation (ECMO), and only 25% needed vasoactive support<sup>15</sup>.

In the beginning of the pandemic, it was assumed that the main organ involvement in COVID-19 was respiratory, but several studies have reported Kawasaki-like syndrome MIS-C later<sup>16</sup>.

DeBiasi et al. described a 177 pediatric patients series in the Washington, DC metropolitan region; among them, 9 cases required critical care, 8 needed respiratory support, and one had Kawasaki-like shock syndrome<sup>17</sup>.

In our study, some of our severely infected patients had elevated troponin level and fulfilling the criteria for MIS-C on arrival to PICU. Also hypotension and organ hypo perfusion, can explain the etiology of high level of troponin.

It has been shown that coronavirus infection (SARS, MERS and even; COVID-19) could damage the liver, and mild to moderate elevation of Alanine aminotransferase (ALT); decreased albumin and increased serum bilirubin levels occur frequently<sup>18-21</sup>, but extremely high ALT and bilirubin levels in patient

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2  
3 number 3 was noteworthy with some probable explanation like acute liver  
4 failure caused by COVID-19 or a rare complication of the disease<sup>22</sup>.  
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7 Through reporting the characteristics of our patients, we aim to share our  
8 experience regarding COVID 19 patients.  
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11 There is a general conception that pediatric patients infected by COVID-19 have  
12 less severe symptoms and better outcomes, but severe and fatal cases occur as  
13 well.  
14  
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16 **Conflict of interest:** none  
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18  
19 **Funding:** The authors did not receive a specific grant for this research from any  
20 funding agency in the public, commercial or not-for-profit sectors.  
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23 **Authors' Contributions:** A.S. planned the study and wrote the manuscript. E.S.  
24 gathered patients' data and submitted the manuscript. A.S.D. did the data  
25 interpretation A.S.D. and M.R.K. edited the manuscript and were scientific  
26 consultant. All authors discussed the results and contributed to the final  
27 manuscript.  
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31 **Acknowledgements:** The authors would like to thank Shiraz University of Medical Sciences,  
32 Shiraz, Iran and also Center for Development of Clinical Research of Namazi Hospital and Dr. Nasrin  
33 Shokrpour for editorial assistance.  
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Figure legends:

Figure 1: chest CT of patient number 5

Figure 2: chest CT of patient number 10

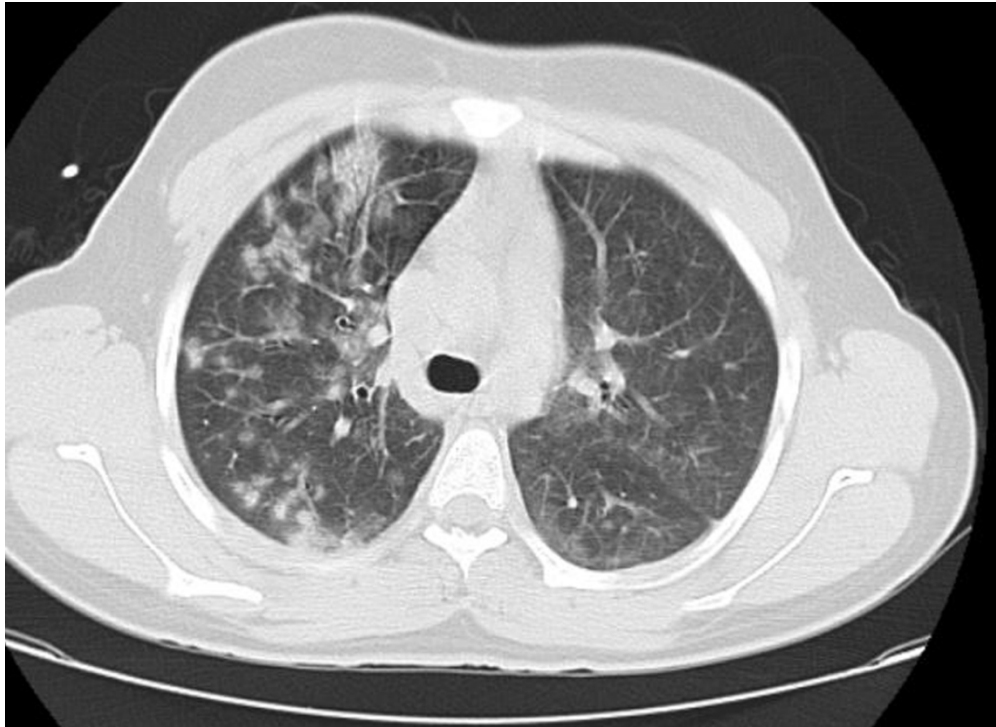


Figure 1: chest CT of patient number 5

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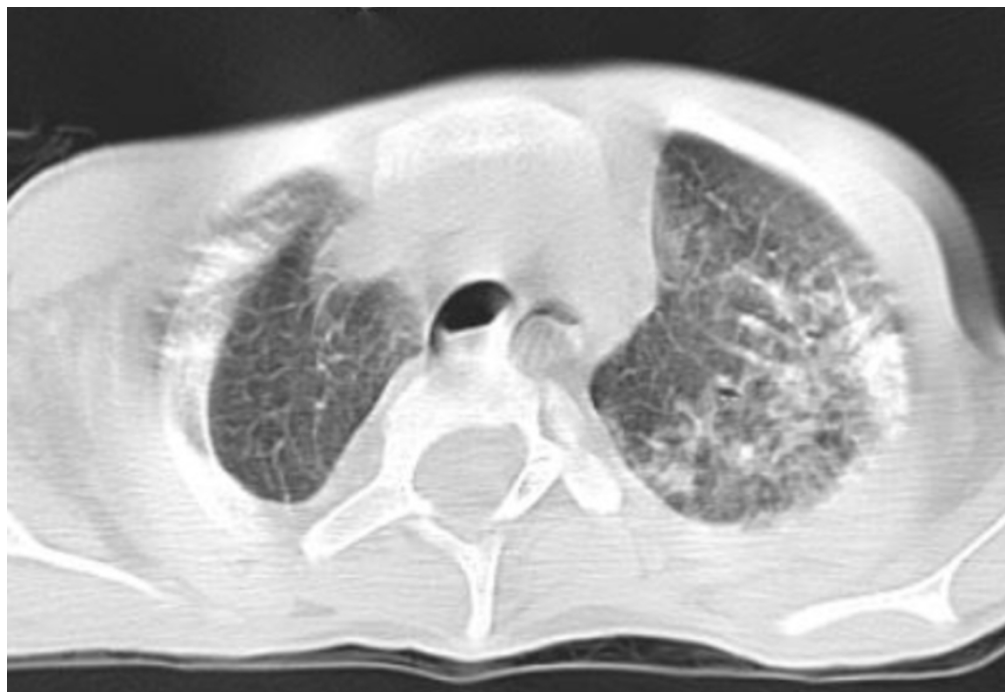


Figure 2: chest CT of patient number 10