

## COVID-19 in transplant recipient children: An Iranian referral hospital-based study

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**Abstract.** To our knowledge, there is still very limited information on the severity, mortality, laboratory, and radiologic findings of COVID-19 infection in transplant patients, particularly children. In this study, we reported 7 transplant recipients with laboratory-confirmed COVID-19 infection. The median age was 7.5 years (IQR: 31month-10 years), and 71% of the patients were male. All cases presented with a fever. The median duration of fever before admission was 2 days (IQR:1-8 days). Five patients (71%) experienced cough and dyspnea. Lymphocytopenia (Median of 0.6 (IQR: 0.14-2.0× 10<sup>9</sup> cells per L) and thrombocytopenia (Median of 65 (IQR: 49-201× 10<sup>9</sup> cells per L) were the most common CBC findings (both seen in 5 out of the 7 patients. Among 4 of the patients who underwent CT scans, 2 had ground glass opacity and consolidations. The mean number of lobe involvement in our patients was 3 (0-5), and 75% of the cases showed bilateral lung involvement in the imaging. In 4 patients (51%) the disease course manifested severely, and 2 patients are now deceased (28.6%). In conclusion, immunocompromised pediatric subgroups may experience higher rates of disease severity and mortality in comparison with the immunocompetent pediatric population. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Keywords:** COVID-19, SARS-CoV-2, immunocompromised, transplant, children

### Introduction

COVID-19, caused by novel corona virus of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in late December of 2019 in Wuhan. It then spread across China and throughout the world. The daily report of the World Health Organization reports 35,109,317 confirmed cases of COVID-19 globally and 1,035,341 deaths before October 5<sup>th</sup>, 2020. From January 3<sup>rd</sup> to October 5<sup>th</sup> 2020 in Iran, there have been 471,772 confirmed cases of COVID-19 with 26,957 deaths (1).

COVID-19 is accompanied by a variety of clini-

cal presentations and different degrees of severity. Pulmonary disease is a notable contributing feature of elevated mortality rates. There is increasing evidence that there is an inflammatory condition due to cytokine storm and hypercoagulability responsible for the pathophysiology of a systemic disorder, rather than a respiratory infection (2-4). The incidence, severity, and prognosis of this disease are likely to be different in children compared to adults (5). While there is evidence that shows children may be less vulnerable to infection or may have milder manifestations upon infection (6), rare and novel manifestations are also reported (7, 8). It is suggested that children are less sus-

ceptible to COVID-19 because of several factors. One has been found to be the different configurations and binding capacity of Angiotensin Converting Enzyme II (ACE2), the main gate for SARS-CoV-2 infection. Furthermore, higher levels of antibodies against respiratory infection viruses, including respiratory syncytial virus (RSV), and various immune reactions to pathogens in contrast with adults might be another possible explanation (9). The mechanisms responsible for such differences in clinical manifestations between children and adults remain unclear though (10).

In this report, we present 7 patients admitted for COVID-19 with past histories of either bone marrow transplantation (6 cases) or liver transplantation (1 case). We discuss their symptoms, laboratory and radiologic findings, and their outcomes.

## Materials and Methods

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1399.060). Signed informed consent was obtained from all patients who participated in the study. In cases where patients did not have the legal capacity to provide informed consent or had not reached the age of consent, their parents/legal guardians provided it for them.

This study was performed at the Children's Medical Center, the primary center for pediatric medicine and research in Iran. More than 35,000 outpatients and 2500 inpatients are admitted to our hospital monthly. From February 13<sup>th</sup> to September 23<sup>th</sup> 2020, 7 patients who had undergone bone marrow (6 patients) and liver transplantation (1 patient) were entered into the study. The presence of SARS-CoV-2 was detected by the real-time reverse transcription polymerase chain reaction (RT-PCR) method using a nasopharyngeal swab, as previously described (10). If either radiologic studies or RT-PCR tests showed positive results for a patient, he/she was excluded from the survey.

The data gathered consists of demographic information, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings, radiologic evaluations, severity of disease, treatment, and mortality.

SARS-CoV-2 infection was tested through the RT-PCR method, using a nucleocapsid gene. RNase P (RP) was used as an internal control (11). Nasopharyngeal swab samples were collected into a collection tube with 150 $\mu$ L of virus preservation solution to extract SARS-CoV-2 RNA from patients with suspected infection. The RT-PCR assay was done under the following conditions: 95 °C for 3 min, followed by 45 cycles of 95 °C for 3 s, and 58 °C for 30 s. A cycle threshold value (Ct value) of less than 37 was defined as a positive test result. Radiologic investigations including chest radiography and CT scan were done, and all laboratory testing was performed according to the clinical care needs of the patient. Laboratory evaluations consist of a complete blood count (CBC), blood chemical analysis, coagulation testing, assessment of liver and renal function, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR).

## Statistical Analysis

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 13.0 software (SPSS Inc.). Categorical variables were described as frequency rates and percentages, and continuous variables were described using median and interquartile range (IQR) values.

## Results

### *Demographic and clinical presentation*

During a 7-month study period, 7 patients who had undergone transplantations (6 with bone marrow transplantation and 1 with liver transplantation) with a positive SARS-CoV-2 RT-PCR, were included in the study. Bone marrow transplantations were due to Acute Lymphoblastic Leukemia (ALL), Acute Myelocytic Leukemia (AML), Fanconi Anemia (FA) and Aplastic Anemia (AA).

The median age of the patients was 8 years (IQR: 4-10). Five patients (71%) were male. All the patients were ethnically Iranian. Three children (42.8%) had a documented adult family member or household contact with symptoms associated with COVID-19 or a confirmed case of COVID-19. All patients presented

with a fever. The median duration of fever before admission was 2 days (1-8 days). Five out of 7 patients (71%) experienced cough and dyspnea, and 4 patients (57.14%) suffered from tachypnea. None of the patients experienced chest pain, and only one had pleural effusion. The median O<sub>2</sub> saturation upon admission was 92% (IQR 85-98%). Headache, myalgia, diarrhea and skin rash were all seen in only one patient. Sore throat, rhinorrhea, conjunctivitis, mucosal involvement, abdominal pain, vomiting, and confusion were not observed in any of the patients. The physical examination revealed no lymphadenopathy, hepatomegaly, splenomegaly, ascites, or extremity edema.

#### Laboratory findings

Lymphocytopenia (Median of 0.6 (IQR: 0.14-2.0 × 10<sup>9</sup> cells per L) and thrombocytopenia (Median of 65 (IQR: 49-201 × 10<sup>9</sup> cells per L) were the most common CBC findings (both seen in 5 out of the 7 patients). Elevated inflammatory tests, especially CRP and ESR, were noticeable in the patients. Creatine phosphokinase and Creatine kinase-MB were tested in 2 patients and found to be in the normal range.

The levels of venous blood gas were also either found to be normal or showed signs of mild respiratory

alkalosis. The median value of PCO<sub>2</sub> and HCO<sub>3</sub> levels was 30.45 (IQR: 25.37-37.6) and 18.45 (IQR: 17.27-19.35), respectively. The median levels of PO<sub>2</sub> and O<sub>2</sub> saturation were 44.65 (IQR: 35.7-60.65) and 81.15% (62.7-93.1), respectively. Prothrombin time (PT) and International normalized ratio (INR) were prolonged in only one of the patients after bone marrow transplantation. Hematuria was not seen in any of the patients, but sterile pyuria and proteinuria were found in 2 patients (28.5%). A single patient had dysentery and an abnormal stool exam (RBC:10-12, WBC:40-45).

All blood and urine cultures appeared negative. At the time of admission, four of the patients had a SARS-Cov-2 serology test. Only one was positive for combined IgG and IgM ELISA.

#### Imaging

For three of the patients, normal radiography was found in the chest X-rays. Spiral CT scans were done for the other 4 patients. Ground glass opacity and consolidation were reported in 2 of the CT scans. The mean number of lobe involvement in our patients was 3 (0-5). Seventy five percent had bilateral lung involvement found in imaging. Seventy five percent also had peripheral findings, rather than central, and 50% were affected diffusely in their lung parenchyma. Seventy-five percent of CT scans illustrated pulmonary nodules. None of the patients showed evidence of empyema, lymphadenopathy and fibrosis.

#### Treatment

All patients received hydroxychloroquine. Three of the patients additionally received oseltamivir in their regimen. Four out of 7 required Lopinavir/ Ritonavir kaletra. Azithromycin was used for 4 patients. Four patients received corticosteroids, and only one patient was treated by Intravenous Immunoglobulin (IVIG). Three of the patients needed Meropenem and Vancomycin. Trimethoprim/Sulfamethoxazole and acyclovir were prescribed for 5 patients (71%). Cef-tazidime was administered to 3 patients. Voriconazole seemed essential for 4 of our patients. Likewise, liposomal Amphotricin appeared necessary for a single patient. Immunosuppressive drugs and prednisolone were continued in almost all our patients.

**Table 1.** The demographic and laboratory findings of the patients

Parameter	Median (IQR)
Median Age (year)	8 (4-10)
Median weight (kg)	24 (13-30)
<b>Laboratory findings</b>	
White blood cell count (× 10 <sup>9</sup> cells per L)	8.0 (2.7-12.5)
Hemoglobin (g/dL)	11.7 (8-15.2)
Platelets (× 10 <sup>9</sup> cells per L)	65 (49-201)
Neutrophil count (× 10 <sup>9</sup> cells per L)	5.0 (0.47-6.3)
Lymphocyte count (× 10 <sup>9</sup> cells per L)	0.6 (0.14-2.0)
C-reactive protein (mg/L)	40 (11-125)
Erythrocyte sedimentation rate (mm/h)	59(15-67)
Lactate dehydrogenase (U/L)	532.5 (457.5-1538.5)
Aspartate aminotransferase (U/L)	25(14.25-93)
Alanine aminotransferase (U/L)	27.5(19.75-319.25)
Urea (mmol/L)	10(8.5-48.25)
Creatinine (μmol/L)	0.55(0.2-1.175)
Albumin (g/dl)	4.1(3.55-4.15)

### *Admission Outcome*

The mean number of admission days was 15 (IQR: 4-30) days. Five patients (71.4%) had a severe form of the disease. Three patients (42.8%) were admitted to the ICU subsequently, from which one patient was intubated, and 3 (42.8%) needed ventilation. Four of the patients (57%) required oxygen therapy.

### *Mortality*

Two of our patients passed away due to COVID-19 during our study.

The first was a 7-year-old boy with Fanconi Anemia who had undergone bone marrow transplantation on February 24<sup>th</sup> of 2020. He was admitted to the post-transplant ward following a 15-minute seizure with jaw locking without fever or loss of consciousness. After his transplant, he received Cellcept (Mycophenolate mofetil), Cyclosporin, Folic Acid, Livregol and Folic Acid. Graft Versus Host Disease (GVHD) had also occurred after his transplantation. After admission on April 12<sup>th</sup> of 2020, cyclosporine was discontinued, and Tacrolimus was started. Levetiracetam was prescribed for seizure control. In his CT scan, evidence of ventriculomegaly was observed. Due to his restlessness and delirium, vitamin B6 was administered. An MRI was performed which illustrated cortical lesions, subcortical lesions, and viral encephalitis pattern. In the second MRI, meningoencephalitis and Posterior Reversible Encephalopathy Syndrome (PRES) were propounded. A rise in urea and creatinine levels was obvious at admission. In the ICU, the patient lost consciousness due to ineffective respiration and was intubated. His peripheral blood stream suggested Hemolytic Uremic Syndrome/ Thrombotic Thrombocytopenic purpura (TTP/HUS). He was treated with IVIG and plasmapheresis afterwards. Furosemide, dobutamine and dopamine infusion were performed for the Ejection Fraction (EF) improvement. Due to encephalopathy, urea, and creatinine elevation, peritoneal dialysis was also performed. A lumbar puncture sample was attained and appeared normal. Due to encephalitis, the patient remained unconscious. His brain stem reflexes were gone, and the Glasgow Coma Scale (GCS) became 3 out of 15. Unfortunately, cardiopulmonary arrest induced by COVID-19 encephalitis leads to the patient's death.

The second case was a 4.5-year-old boy with XLP (X-linked lymphoproliferative disease) who had undergone bone marrow transplantation on January 12<sup>th</sup> of 2020. He was admitted as a result of vomiting, food intolerance and having diarrhea five times. He had received prednisolone, cyclosporine, ofloxacin, voriconazole, valganciclovir and tranexamic acid beforehand. Oral oseltamivir, hydroxychloroquine, Acyclovir and intravenous meropenem, vancomycin and dexamethasone were then ordered. His pulmonary infection worsened due to immunodeficiency, and bacterial superinfections added onto the COVID-19 involvement. He passed away after 2 months due to septic shock from disseminated pulmonary infection.

### **Discussion**

The first confirmed pediatric case of SARS-CoV-2 infection was reported in a familial cluster in Shenzhen on January 20<sup>th</sup> of 2020 (12). As the COVID-19 outbreak spread, the first infant case was reported from Xiaogan, Hubei province. The patient was a 3-month-old female with a one day fever admitted on January 26<sup>th</sup> of 2020 (13). As the pandemic progressed worldwide, the number of pediatric patients increased concomitantly (14). Several studies suggested that the signs and symptoms of pediatric COVID-19 are similar to adults. However, pediatric infection is considered to be milder in severity in comparison with adults (15-18).

The clinical features and outcomes of COVID-19 among immunosuppressed patients, who are presumed to be at risk for a more critical form of the disease, are not fully identified. Adult patients with cancer and solid organ transplantation recipients may be at higher risk for more serious COVID-19 disease. There is evidence suggesting that patients taking biologic drugs may not be at elevated risk. However, whether they are actually at lower risk for severe forms of COVID-19 or not remains unclear (19). The few publications so far indicate very low incidence of complications in immunocompromised children infected by SARS-Cov-2 (20). There is still very limited knowledge of COVID-19 infection in the transplant population, particularly children. In this study, we reported 7 transplant

recipients with laboratory-confirmed COVID-19 infection.

Our study indicates slightly higher degree of disease severity (5 out of 7) and mortality (2 out of 7) in post bone marrow or organ transplant children in comparison with immunocompetent children. Therefore, we should not underestimate the risk of immunosuppressive drugs causing children to develop a more severe form of COVID-19. An important issue is that harsh preventive measures should not lead to medical follow-up postponements or obstruct their specific treatment (21). Respiratory viruses are historically concerning for patients with a previous history of bone marrow transplantation, solid organ transplantation, and cancer given their association with higher risk of morbidity. Our preliminary concentration should remain on disease prevention, infection control procedures, isolation precaution, and avoidance of contact with suspected individual with COVID-19 (22).

In a meta-analysis focusing on clinical characteristics of COVID-19 in children, 49 studies were reviewed. The most common symptoms presented were fever and cough (23). Dyspnea and tachypnea were additionally prevalent symptoms among our patients. Four patients (57%) needed oxygen therapy, and in 4 patients the disease course was preceded by severe manifestation of symptoms.

Routine laboratory tests, like many other viral infections, may not indicate any specific or significant changes (24). In a meta-analysis, lymphocyte count was below normal in 15% of pediatric cases, less than what is observed in adults. CRP was increased in 22% of cases (25). Lymphocytopenia and thrombocytopenia were found in 71% of the patients, higher than our previous studies (10, 26). Elevated inflammatory tests, especially CRP and ESR, were noticeable in our study, inconsistent with our previous studies (10, 11, 26).

Ground glass opacities were previously introduced as the most common finding in the CT scans of infected children (24, 25, 27). Only 2 patients (out of 4 patients who had undergone CT scan) illustrated such involvement, and the other 2 had pulmonary consolidations. It has been reported that ground-glass opacities and consolidations are the most common CT abnormalities (61.5%). Most studies found

peripheral and lower-lobe distribution as a prominent imaging finding (28). In our study, peripheral lesions in both lungs located in different lobes, as well as pulmonary nodules, were remarkable.

This study, to our knowledge, is the first to introduce 7 pediatric cases among the post bone marrow or organ transplantation population. Detecting positive cases among immunosuppressed children is of great importance for adducing the most common documented clinical, laboratory and imaging characteristics. However, due to our limited samples in this case series, many objectives for precise diagnosis and management alternatives remain unrevealed.

Further targeted studies on progression of COVID-19 in the pediatric immunocompromised subgroup are highly recommended. Clinical practitioners should also consider the special features of pediatric involvement to develop more accurate approaches to the disease. Moreover, policy makers are responsible for coordinating detailed diagnosis criteria and treatment guidelines for children.

In conclusion, immunocompromised pediatric subgroups may experience higher degrees of disease severity and mortality in comparison with the immunocompetent pediatric population. The majority of children diagnosed with SARS-CoV-2 infection were of school age. Fever was detected in all of our patients. Cough and dyspnea were determined as the most common clinical symptom. Lymphocytopenia, thrombocytopenia, and elevated inflammatory markers, particularly CRP and ESR, were the most significantly observed laboratory findings. The most common pattern found in CT scans was involvement of peripheral sections by ground glass opacities or consolidations including both lungs and pulmonary nodules.

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