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Original Article

COVID-19 in children with inborn errors of immunity: clinical scenarios

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Abstract: The new emerging virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a huge burden of morbidity and mortality worldwide. One of the predisposing factors which might increase the infection susceptibility and its complications can be the Inborn Errors of Immunity (IEI). One hundred and seventeen primary immunodeficient (PID) pediatric patients were monitored from March to December 2020 for any signs and symptoms of SARS-CoV-2 infection. Among them twenty-eight children were symptomatic and nineteen out of the twenty-eight patients took the coronavirus PCR test. Out of them, the PCR test results of 9 patients were positive. Herein, we report the nine cases of pediatric patients with IEI who were also infected with SARS-CoV-2 with a positive PCR test. We observed a variation in clinical manifestations, clinical courses, and outcomes among IEI pediatric patients affected with COVID-19. In our survey, prompt diagnosis and appropriate monitoring for possible complications were shown to be effective in reducing the mortality rate of the SARS-CoV-2 affected patients with IEI. Although there is no approved treatment for SARS-CoV-2 infection, supportive treatment might reduce the complications and lead to better outcomes. This study received approval from the Research Ethics Committee of Mashhad University of Medical Science with the ethics code of IR.MUMS.REC.1399.155. (https://ethics.research.ac.ir/EthicsProposalViewEn.php?id=129963).

Keywords: Inborn errors of immunity, COVID-19, SARS-CoV-2, pediatric patients

Introduction

Since December 2019, millions of people have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and this new highly infectious virus with rapid distribution imposes a huge burden of morbidity and mortality worldwide [1]. The severity of COVID-19 and mortality from the disease are associated with the elderly and the elderly patients usually experience a more severe presentation and worse outcomes [2]. Meanwhile, the comorbidities of the disease are also associated with the Inborn Errors in Immunity (IEI) and its relevant immune system suppression in patients. Thus, children-especially those with preexisting conditions- are susceptible. Recently, a newly emerging multisystem inflammatory syndrome in children (MIS-C) with high mortality and morbidity was reported and assumed to have an association with SARS-CoV-2 [3-5]. Coronavirus disease 2019 (COVID-19) presentations in children with IEI may vary widely, and sometimes can be severe [6]. In a report of hospitalized patients with the pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PIMS-TS), it was demonstrated that a wide spectrum of manifestations and disease severity exists,

Table 1. Demographic characteristics of patients with IEI who are monitored in Akbar hospital

	predominantly antibody deficiencies	combined immune deficiency	combined immune deficiency with SYNDROME features	congenital defects of phagocytes	defects in INTRINSIC and innate immunity
patients					
total	33	20	35	25	4
alive	30	10	30	20	4
dead	1	10	5	5	0
unknown	2	-	-	-	-
sex (male:female)	23:10	8:12	14:21	16:9	3:1
mean age (years)	11	4	6	4	7
mean age of symptom presentation (months)	9	8	12	9	12
mean duration of follow-up (years)	10	4	4	4	5
treatment	IVIG Cotrimoxazole	IVIG	IVIG Cotrimoxazole	Cotrimoxazole	Interferon gamma, Cotrimoxazole

IEI: Inborn Errors of Immunity, IVIG: Intravenus Immunoglobulin.

ranging from fever, shock, and development of coronary artery aneurysms [7]. In other reports of SARS-CoV-2 in patients with IEI, the leading risk factors to severity and mortality of the disease in the general population was shown to affect younger patients with IEI too, but the Case Fatality Ratio (CFR) was higher than in the general population [8-10].

A diagnosis of SARS-CoV-2 infection in patients with inborn errors of immunity may improve their outcome, due to immediate management and regular monitoring for possible complications in patients [11]. Until now, the only drug which gets the approval of the U.S. Food and Drug Administration (FDA) for adults and certain pediatric patients with COVID-19 who are sick enough to need hospitalization is the antiviral drug Veklury (remdesivir) [12], whereas there was no approved treatment for COVID-19 infection at the time of our patients' admission [13]. In Iran, there are more than 3000 patients with IEI from which more than one hundred are under the observation of Mashhad University of Medical Sciences (MUMS) [14]. Herein, we reported nine IEI affected patients with SARS-CoV-2 manifestations who were referred to Akbar hospital, one of the most important referral pediatric medical centers in Northeastern Iran.

Methods

One hundred and seventeen pediatric patients with IEI are currently monitored in the pediatric allergy and clinical immunology department of Akbar Hospital. They were diagnosed and classified as primary immune deficient (PID) patients through symptom observation and routine primary workups according to the criteria of the European Society for Immunodeficiencies [15]. Genetic studies were performed in about 10% of the patients. The male to female ratio is 64:53. The demographic characteristics of the patients are described in **Table 1**.

We monitored all 117 PID patients from March to December 2020 for any signs and symptoms of SARS-CoV-2 infection. The routine follow-up was done by phone calls to ask the parents if the PID patients have experienced symptoms such as fever, respiratory symptoms, gastrointestinal manifestations, malaise, or any exacerbation in their preexisting symptoms. Any patient who had at least one of the above-mentioned complaints was referred to the hospital for more evaluation. In addition, our registered patients who had routine follow-ups and had received monthly intravenous immunoglobulin (IVIG) administrations were also checked for any infection signs and symptoms.

In clinical evaluation of the symptoms, the body temperature of the nine patients was checked and recorded. The respiratory, gastrointestinal and other symptoms were assessed with clinical observation. Rhinorrhea, sneezing, coughing, rhonchi, respiratory distress, cyanosis, chest pain, and tachypnea were the respiratory manifestations observed in patients. Gastrointestinal observations included decreased appetite, vomiting, diarrhea, stool incontinence, nausea, and abdominal distension. Other symptoms in patients were bruising in

extremities, tonic colonic seizure, chill, bone pain, poor feeding, and irritability.

Samples of symptomatic children were collected by a nasal swab and were tested by reverse transcriptase-polymerase chain reaction (RT-PCR) in the Laboratory of Akbar hospital for further analysis. In addition, a routine evaluation chest X-ray (CXR) was also requested in the symptomatic phase of COVID-19 positive PID patients. We had admitted the IEI pediatric patients during the SARS-CoV-2 pandemic and since there was no approved treatment for SARS-CoV-2 infection for children during the period of admission and follow-up, all the patients were prescribed to receive symptomatic treatments. Due to the pre-existing immunocompromised conditions in the patients, we also prescribed parenteral antibiotics. Intravenous Meropenem, intravenous Vancomycin, intravenous Ceftazidime, intravenous Tazocin, intravenous Ciprofloxacin, intravenous Acyclovir, intravenous IFN-gamma, intravenous Cotrimoxazole, intravenous vitamin C, intravenous Immunoglobulin (IVIG), Hydroxichloroquin tablet, Ofluxacin tablet, Famotidine tablet, Furosemide tablet, Sildenafil tablet, Dexamethasone tablet, Milrinone and Epinephrine drip, Zinc syrup, anti-seizure treatments, pulse therapy of methylprednisolone, Ceftriaxone ampule, and vitamin C ampule were the prescribed medications. Details of presentations, treatments, drug history, and outcomes of each patient are listed in **Table 2**.

This study received approval from the Research Ethics Committee of Mashhad University of Medical Science (ethics code: IR.MUMS.REC.1399.155) and informed consent forms were signed by the parents of all children.

Results

Among one hundred and seventeen PID patients, twenty-eight (24%) patients had at least one of the mentioned complaints, from which only nineteen (16%) patients were visited by a physician and referred to the laboratory to receive the RT-PCR test. Nine patients (7.6%) who had mild and transient symptoms were not visited by a physician. Among those who performed RT-PCR, only nine (7.6%) patients (one female and eight males) with IEI had positive results for SARS-CoV-2. The mean age of the SARS-CoV-2 positive IEI patients was 47 months. Five confirmed SARS-CoV-2 patients had combined immunodeficiency, one had primary antibody deficiency, one had Mendelian susceptibility to mycobacterial diseases (MSMD), one had ataxia telangiectasia, and one had chronic granulomatous disease (CGD). The presentations and outcomes of all nine patients are described in detail in **Table 2**.

A seven-year-old patient with MSMD had been admitted to the hospital with salmonellosis several times. Her manifestations were abdominal pain, fever, and bruising in the extremities. In her recent admission, she presented with fever, flu-like symptoms, and petechial lesions on her lower limbs. She had also two episodes of epistaxis. After a comprehensive examination by her physician, the COVID-19 RT-PCR test was requested and the result was positive. After receiving 7 days of parenteral antibiotics, she was discharged in good condition. Her condition was monitored for six months.

A three-month-old infant with Omenn syndrome passed away after 36 hours of hospitalization. The patient had respiratory, gastrointestinal, and neurological symptoms. In his chest radiography, cardiomegaly was detected and in laboratory results, elevated cardiac enzymes were revealed. Despite aggressive treatment, he passed away after 36 hours. His clinical course was described in an article published in 2020 [16].

An eight-year-old boy with primary antibody deficiency presented to the pediatrician with fever, mild clear rhinorrhea, and a modest increase in his preexisting cough. In auscultation, rhonchi were heard in the right lung. Due to the exacerbation of his symptoms, the RT-PCR for SARS-CoV-2 were performed and the result was positive. After 7 days of receiving parenteral antibiotics, the symptoms were cleared and he was discharged. The case report of this patient was published in 2020 [17].

A seventeen-year-old Ataxia-telangiectasia patient had weeklong gastrointestinal symptoms and fever. Although there may be concerns about the risk of radiation, chest radiography with low radiation dose was performed considering clinical indications [18]. Despite the absence of respiratory symptoms, the patient was evaluated by chest X-ray. Fortunately, his radiograph showed hyper lucent and no emphy-

Table 2. Presentations and outcomes of the nine IEI patients confirmed to have COVID-19

PATIENT (#number)	diagnosis	age	sex	presentation				drug history and prophylaxis	treatment	duration of admission	outcome	follow-up result
				fever	respiratory symptoms	GI symptoms	other					
# 1	MSMD	7 yrs.	female	yes	Rhinorrhea, sneezing, chest pain	Decreased appetite	Bruising in extremities	Interferon γ (2 times per week, SC), Cotrimoxazole (5 mg/kg/day)	Intravenous Meropenem, Tab Famotidine	7 days	Discharged with good condition	Good condition after 6 months
# 2	Omenn synd.	3 mo.	male	yes	Respiratory distress, cyanosis	Vomiting	Tonic colonic seizure	Cotrimoxazole (5 mg/kg/day), anti-tuberclusis medications*, and IVIG (0.4 gr/kg/month)	Milrinone and Epinephrine drip, Furosemide, Intravenous Meropenem and Intravenous Vancomycin, anti-seizure treatment, IVIG	36 hours	death	none
# 3	PAD	8 yrs.	male	yes	Rhinorrhea, sneezing, modest increase in wet cough, rhonchi	none	none	Nebulized aminoglycoside and short acting bronchodilator, IVIG (0.4 gr/kg/month)	Intravenous Meropenem, Hydroxichloroquin, Ofluxacin, IVIG	7 days	Discharged with good condition	Good condition during 8 months of follow-up, with no additional complications
# 4	AT	17 yrs.	male	yes	none	Diarrhea, vomiting, stool incontinence	none	IVIG (0.4 gr/kg/month)	Amp. ceftriaxone, Syr. Zinc, IVIG	7 days	Discharged with good condition	No complaint after 9 months
# 5	CID	4 yrs.	male	yes	Respiratory distress, tachypnea, rhonchi			Cotrimoxazole (5 mg/kg/day), And IVIG (0.4 gr/kg/month)	Intravenous Meropenem, Vancomycin Tab furosemide, Tab Sildenafil, IVIG and pulse therapy of methylprednisolone	6 days	death	none
# 6	SCID	8 mo.	male	yes	Respiratory distress, tachypnea	vomiting	none	Cotrimoxazole (5 mg/kg/day), IVIG (0.4 gr/kg/month) and anti-tuberclusis medications*	Tab Dexamethasone, Amp vitamin C, Intravenous Ciprofloxacin, Intravenous Ceftazidime, IVIG	15 days	Discharged with good condition	Good condition during a 5 months follow-up. He was admitted again with similar symptoms and Was discharged in good condition. In the next 2 months he was ok
# 7	SCID	8 mo.	male	yes	Respiratory distress, tachypnea	none	none	Cotrimoxazole (5 mg/kg/day), IVIG (0.4 gr/kg/month) anti-tuberclusis medications*	Tab Dexamethason, Intravenous vitamin C, Intravenous Ciprofloxasin, Intravenous Ceftazidime, IVIG	15 days	Discharged with good condition	Good condition during 8 months follow-up
# 8	SCID	4 yrs.	male	yes	Cough	Nausea	Chill, bone pain	Cotrimoxazole (5 mg/kg/day), And IVIG (0.4 gr/kg/month)	Intravenous Meropenem, Vancomycin Tab vitamin C	5 days	Discharged with good condition	He has no problems after 2 months
# 9	CGD	22 days	male	yes	none	abdominal distention	Poor feeding, irritability	-	In first admission, Intravenous Vancomycin and Cefotaxim and azithromycin. In second admission, Tazocin, vancomycin, Acyclovir, IFN-gamma, and Cotrimoxazole	3 days in first admission, after one week he was admitted again for 16 days	Discharged with good condition	Good condition during 2 months of follow-up

GI: gastrointestinal, MSMD: Mendelian susceptibility to mycobacterial disease, Synd: syndrome, PAD: primary antibody deficiency, AT: Ataxia Telangiectasia, CID: combined immune deficiency, SCID: severe combined immune deficiency, IVIG: intravenous immunoglobulin, SC: subcutaneous, yrs: years, mo.: months, Amp: Ampule, Syr: Syrup, Tab: Tablets. *, Anti-tuberculosis medications: Tab INH, Tab Etambutol, Tab vitamin B6, and Syrup Clarithromycin.

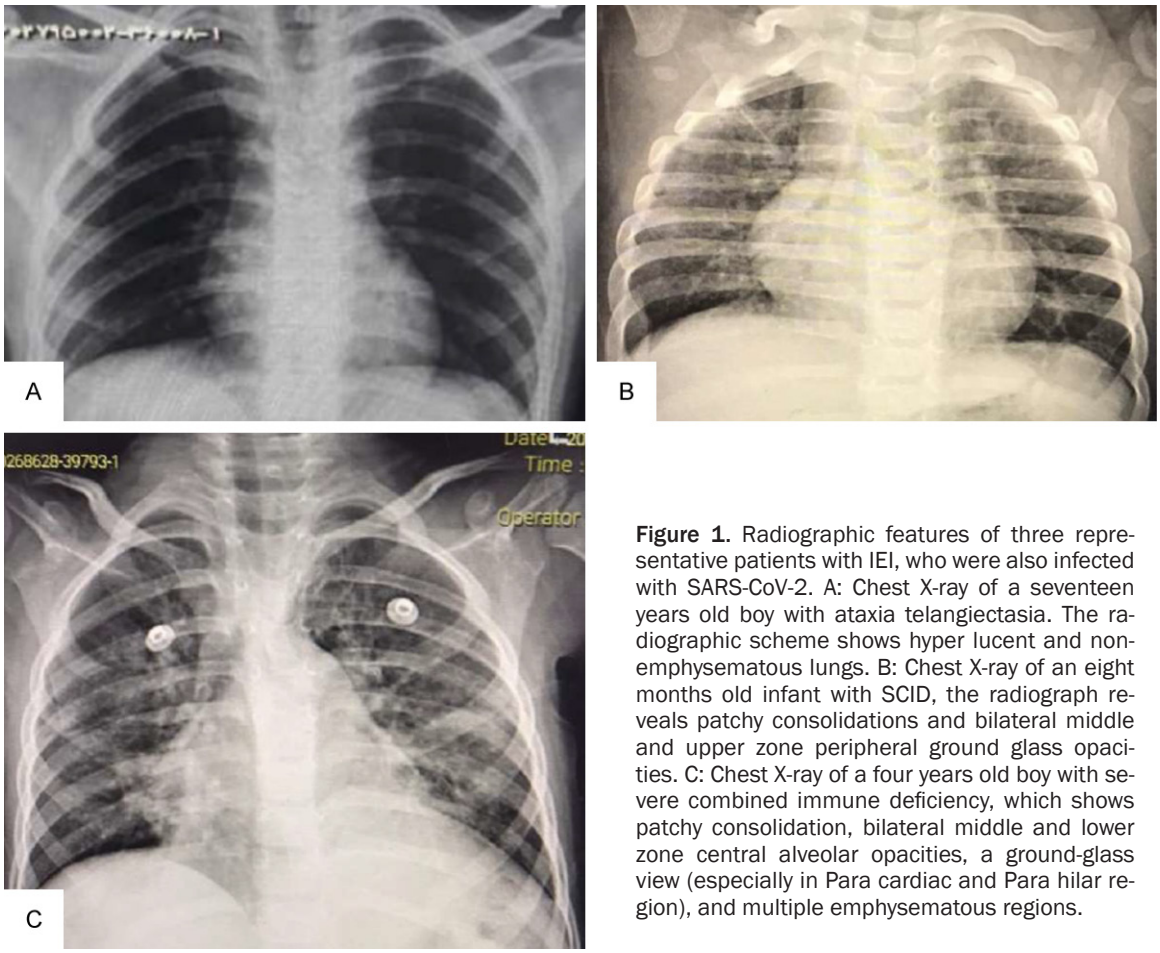

Figure 1. Radiographic features of three representative patients with IEI, who were also infected with SARS-CoV-2. A: Chest X-ray of a seventeen years old boy with ataxia telangiectasia. The radiographic scheme shows hyper lucent and non-emphysematous lungs. B: Chest X-ray of an eight months old infant with SCID, the radiograph reveals patchy consolidations and bilateral middle and upper zone peripheral ground glass opacities. C: Chest X-ray of a four years old boy with severe combined immune deficiency, which shows patchy consolidation, bilateral middle and lower zone central alveolar opacities, a ground-glass view (especially in Para cardiac and Para hilar region), and multiple emphysematous regions.

sematous pattern. The graph was shown in **Figure 1A**. He had gastrointestinal symptoms for two weeks before admission. He was discharged in a good condition after 7 days of receiving ceftriaxone. During his nine month follow-up, he showed no further signs. The information of the three above-mentioned PID cases have been previously published [19].

A four year old boy with combined immunodeficiency passed away after six days of admission. Since he was diagnosed with chronic lung disease and because of modestly exacerbation of preexisting tachypnea, widespread rhonchi, and also O_2 saturation of about 85% without O_2 therapy, he was subjected to more evaluation. In lab tests, the acute phase reactants were elevated. He received Meropenem and Vancomycin, then he was transferred to the intensive care unit (ICU) ward and received broad-spectrum antibiotics. After two days, his condition worsened and, despite high dose IVIG and corticosteroid, he passed away.

Another two patients were twins with combined immunodeficiency. Their presentations were relatively milder, and both of them had normal O_2 saturations at first admission. Both of them were evaluated by computed tomography (CT) scan on the second day of admission. Ground-glass opacification was seen in the scan of one of the twins, who presented with fever, vomiting, and respiratory distress. However, his brother with almost the same medical history and physical examination (although milder), had a normal CT scan. They received antibiotics, Dexamethasone, and vitamin C. RT-PCR test for COVID-19 was repeated within one week for both. The second test results were negative. After two weeks, they were discharged in good condition. The first mentioned twin was admitted again with fever, exacerbated cough, and diarrhea after five months. His O_2 saturation was 85% without O_2 therapy. In auscultation assessment, diffuse crackles in both lungs were heard. In chest X-ray, there was a suspected pattern of pneumocystis jiroveci pneumonia

or COVID-19. Ciprofloxacin, Dexamethasone, Cotrimoxazole, Amikacin, Ethambutol, Isoniazid, and vitamin B6 were started. In high-resolution CT (HRCT), peripheral patchy consolidations with the ground-glass pattern were seen. Due to clinical and radiological manifestations, lymphopenia (WBC=4640 per microliter, with 16% lymphocyte), and high C-reactive protein (CRP) level in the blood test, he was admitted to the COVID-19 intensive care unit despite negative SARS-CoV2 RT-PCR. After 16 days, he was discharged in good condition. His twin had mild symptoms, which improved with outpatient care. Both of them were in stable situations during their 8 month follow-up.

The four-year-old male patient with combined immunodeficiency (CID) was presented with fever, chills, cough, and bone pain. The laboratory exams showed severe anemia and thrombocytopenia. He received irradiated packed red blood cells and platelets, IVIG, and appropriate antibiotics and then was discharged in good condition. His symptoms were improved completely, and in his follow-up after 6 months, his general condition was very well.

Finally, a twenty-two days old infant from Afghanistan who lives in Mashhad, Iran was admitted to the hospital at the age of 10 days with fever, poor feeding, and irritability. His oxygen saturation was 94% at admission time. The result of the SARS-CoV2 RT-PCR test was positive, thus he received antibiotics and supportive care. His general condition became better, but unfortunately, after three days of medical care in the hospital, his parents discharged him despite the physician's recommendations. A week later, he was returned with poor feeding and abdominal distention. In a comprehensive examination, hepatomegaly, fever, and normal oxygen saturation were observed. Vancomycin, Acyclovir, and Tazocin were started. Due to hepatomegaly and multiple abscess formations in the liver, a primary immune deficiency evaluation was performed. The Nitro blue tetrazolium (NBT) test result was below 5%, thus chronic granulomatous disease (CGD) was diagnosed. In the second admission, the SARS-Cov2 RT-PCR result was negative. After sixteen days, he was discharged in good condition. Prophylactic Cotrimoxazole (5 mg/kg/day) and subcutaneous IFN-gamma were prescribed. In his follow-up after 2 months, he was well.

Overall, radiographic features of chest X-rays among all nine SARS-Cov2 positive PID patients showed varieties. Some cases had normal chest X-rays, and some showed prominent abnormalities, while those with more severe respiratory symptoms had more abnormalities in their chest X-ray. **Figure 1** shows chest radiographs of three representative patients.

Since we had admitted the IEI pediatric patients during the SARS-CoV-2 pandemic, and also because there was no approved treatment for SARS-CoV-2 infection for children during the period of admission and follow-up, all of our pediatric patients with IEI, who were affected by COVID-19 too, received symptomatic treatments. Because of the pre-existing immunocompromised condition, fever, respiratory and/or gastrointestinal symptoms in all patients, we prescribed parenteral antibiotics. Fortunately, their response to treatment was acceptable. After a few days, seven patients out of nine (77%) were discharged in good condition. Only three of our patients needed ICU admission, although finally, two of them passed away.

Discussion

All of our patients except two (the patients with Omenn syndrome and MSMD) were first admitted to receiving their monthly IVIG. The symptoms were mostly mild and manifested as the exacerbation of preexisting symptoms. After getting a detailed medical history and a comprehensive physical examination, the patients were suspected to be infected with SARS-CoV-2. Hence, the sooner an IEI patient is diagnosed as a COVID-19 patient, the higher their survival rate might be.

It was reported that the presentations of COVID-19 in children tended to be milder than adults [6]. However, recently due to ever-increasing reports of MIS-C, there are concerns about COVID-19 affected children. According to a recently published meta-analysis, more than half of COVID-19 associated MIS-C patients showed evidences of cardiogenic shock and needed to use vasopressor. The reported children had multiple organ dysfunction, and relatively more morbidity and mortality [4]. We had a three-month-old infant with Omenn syndrome who passed away after 36 hours of hospitalization despite aggressive treatment. Respiratory, gastrointestinal, and neurologic symptoms

were detected in early examinations. Moreover, cardiomegaly in his chest radiography and elevated cardiac enzymes in laboratory results could be assumed as the signs of cardiogenic shock. Unfortunately his parents admitted him to the hospital after a significant delay, so treatments were inefficient.

On the other hand, since IEI patients are more prone to infectious diseases, it is reasonable to assume that they might experience a more aggressive episode of COVID-19, and due to preexisting complications, their outcomes might be worse. Some reports suggested that because of impaired immunologic responses in IEI patients, hyperinflammatory states may be absent [16, 20]. Our four years old boy with combined immunodeficiency who was diagnosed with bronchiectasis had experienced an exacerbation of his preexisting tachypnea, widespread rhonchi, and low O_2 saturation without O_2 therapy. Elevated levels of acute-phase reactants were also shown in his laboratory tests. Although he was transferred to the intensive care unit (ICU) ward and received broad-spectrum antibiotics, his condition worsened in two days and, despite high dose IVIG and corticosteroid, he passed away. Although elevated levels of acute-phase reactants in the blood can be an indication of inflammatory state, we suggest that it is better to include other proinflammatory markers of blood such as Interleukin-6 (IL-6) and D-dimer in patients' laboratory tests to help the physician through a prompt and accurate decision. Ho He *et al.* have also reported sixteen patients with IEI and SARS-CoV-2 infection in New York City. Their median age was 44.5 years old and most of them (n=14) had humoral immune deficiency [nine with common variable immunodeficiency (CVID) and three with Bruton tyrosine kinase (*BTK*) mutations]. They concluded that patients with humoral immunodeficiency had poorer outcomes and preexisting autoimmune/inflammatory complications, lung disease, or additional comorbidities, and exhibited higher proinflammatory responses (Four of them died, two with CVID, one with hypogammaglobulinemia, and one with IgA-IgG2 deficiency while two of them had chronic lung disease due to IEI [21].

In another report by Meyts *et al.* in September 2020, ninety-four IEI patients infected by SARS-CoV-2 were described. The patients were from 25 to 34 years old. More than half of them had antibody deficiency and about 15% had combined immunodeficiency. Nine of the ninety-four patients passed away. However, most of them had preexisting comorbidities, and their exact etiology of death was unknown [22]. Maheshvari et al. reported a four-month-old infant with severe multisystem manifestations and associated HLH. The child developed hemodynamic instability although he was on mechanical ventilation. His situation was worsened through an irreversible shock and he died after 27 days of admission. The genetic workup confirmed a JAK-3 Mutation causing SCID. They conclude the necessity of a rigorous evaluation of comorbidities in infants presenting with unusually severe multisystem manifestations of SARS CoV2 infection was concluded [23]. On the lines of the aforementioned surveys, we prescribed parenteral antibiotics for our nine patients with PIDs. Although the overall response rate was acceptable (77%), two out of nine patients passed away despite of intensive care. Hereby, we have to reemphasize the necessity of more investigations to illuminate the risk factors and effective comorbidities that make young IEI patients more prone to death during their SARS-CoV2 infection episode.

Recently, nineteen Iranian patients with a median age of 106 months were reported to have IEI and a confirmed SARS-CoV-2 infection. Among them, ten patients (52%) had combined immunodeficiencies without hematopoietic stem cell transplantation. We also reported nine IEI patients with a confirmed COVID-19 infection while 5 of them were diagnosed as CID patients (55%). The predominance of combined immunodeficiency in both reports is obvious. Moreover, because of poor cellular immunity, it can be predicted that the severity of the disease and the mortality rate to be higher in combined immunodeficient patients than in patients with humoral defects. In the above-stated report, eight patients (four patients out of ten with combined immunodeficiencies (40%)) passed away [19]. In our article we reported two deceased patients (one with omenn syndrome and one with CID, two out of five CID patients (40%); no patient with other IEI). Although the higher mortality rate in combined immunodeficient patients is reported in our survey too, the data is not enough to vali-

date the hypothesis. It is recommended to evaluate and compare the mortality rate in bigger groups of SARS-Cov-2 infected patients with IEI.

Conclusion

It seems that there is a wide variation in clinical manifestations, clinical courses, and outcomes among IEI pediatric patients affected with COVID-19. Performing a prompt initial assessment and follow-up, as well as informing parents about the risks of delay in diagnosis are suggested. Moreover, requesting for other proinflammatory markers such as IL-6 and D-dimer in laboratory tests is suggested to help the physician through a better understanding and decision-making process. Considering the fact that at the time of writing this article (July 2021) there is just one FDA approved drug (Remdesivir) for SARS-CoV-2 infection, case management and supportive treatments according to each patient's condition are recommended to alleviate complications.

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Disclosure of conflict of interest

None.

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