

# The Effect of COVID-19 Pandemic on Patients with Primary Immunodeficiency: A Cohort Study

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## What's Known

- As appropriate innate and adaptive immune responses are essential for SARS-CoV-2 eradication, some epidemiological studies have investigated the relationship between primary immunodeficiency diseases and the fatal risk of COVID-19.
- Recent studies suggests that patients with primary immunodeficiency in antiviral innate immune signaling or combined immunodeficiency may be predisposed to the severe form of COVID-19 infection.

## What's New

- Individuals with combined immunodeficiency are more susceptible to the severe form of COVID-19 infection than patients with other types of primary immunological deficiencies.
- Some primary immunodeficiency patients require more attention due to their age, category, and additional comorbidities.

## Abstract

Both adaptive and innate immune responses are essential for an effective defense against the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection. We aimed to investigate the effect of the coronavirus disease 2019 (COVID-19) pandemic on patients with primary immunodeficiency (PID). This study was performed on patients who were diagnosed with PID by immunologist specialists and referred to Imam Reza Clinic of Asthma and Allergy, affiliated with Shiraz University of Medical Sciences, (Shiraz, Iran) for regular check-ups. The patients were enrolled in this cohort study and followed for any sign of COVID-19 from March 2020 to May 2021. COVID-19 infection was confirmed using a real-time polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs. Among the 90 PID patients under study, nine patients (10%) were diagnosed positive for COVID-19 infection. Five out of these nine patients belonged to the combined immunodeficiency (CID) category, while four patients were categorized as having primary antibody deficiencies (PADs). Eight patients with COVID-19 were required to be admitted to the hospital, and three patients died after hospitalization due to COVID-19 infection. It seems that patients with CID are at a higher risk of mortality, due to COVID-19 infection, than other types of PID.

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**Keywords** • COVID-19 • Mortality • Primary immunodeficiency diseases

## Introduction

Currently, the world has encountered the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup> This virus can induce respiratory tract infection accompanied by cold, sneezes, pneumonia, and coughs.<sup>2</sup> Some conditions, such as obesity, old age, hypertension, male gender, cancer, diabetes, chronic lung disease, and heart conditions are considered as risk factors predisposing individuals to a severe form of the disease.<sup>3</sup> An orchestrated adaptive and innate immune responses is essential for an effective defense against SARS-CoV-2 infection without the negative side effects of a hyper-immune response.<sup>4</sup> In this regard, it is expected that patients with primary immunodeficiency (PID) may be more susceptible to developing the severe form of COVID-19.<sup>5</sup> Some studies have investigated

the effect of the COVID-19 pandemic on patients with PID.<sup>6, 7</sup> It seems that PID patients with deficiency in antiviral innate immune signaling or combined immunodeficiency (CID) may be linked to the severe form of COVID-19 infection.<sup>8</sup> In this study, we aimed to investigate the rate and outcomes of COVID-19 infection among the cases diagnosed with PID.

**Patients and Methods**

This study was conducted on patients with PID living in Fars province and some neighboring provinces, who were referred to Imam Reza Clinic of Asthma and Allergy, affiliated with Shiraz University of Medical Sciences, (Shiraz, Iran). The diagnosis and management of PID patients were performed by immunologist specialists in this clinic according to the criteria of the European Society for Immunodeficiencies (ESID).<sup>9</sup> All patients were followed from March 2020 to May 2021 for any sign of COVID-19, including fever, dry coughs, dyspnea, and gastrointestinal (GI) symptoms. The COVID-19 test was performed on patients with the clinical triad of coughs, fever, and dyspnea using a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs. Informed consents were obtained from all the participants. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.845). The data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA, V. 21.00).

**Results**

The age of the 90 PID patients who were included in the study, ranged from 4.4 months to 48 years, with a mean age of 147.9±106.5 months. This study included 36 (40%) female and 54 (60%) male patients. During the follow-up period, fever, dry coughs, dyspnea, and GI symptoms were recorded for 16.6, 8.8, 6.6, and 5.5 percent of the total patients, respectively. A positive RT-PCR test for SARS-CoV-2 was verified in nine PID patients (10%), and all cases had a history of exposure to another COVID-19-infected family member. The demographic parameters and clinical state of these patients prior to COVID-19 infection are summarized in table 1. Six out of nine PID patients (66.6%) with COVID-19 infection fully recovered, while three patients (33.3%) died from the disease. All patients had symptoms of COVID-19 infection, such as fever, coughing, respiratory distress, and dyspnea. In certain cases, GI symptoms, myalgia, and anosmia were observed. One case (P5) experienced allergic symptoms, such as a runny nose and sneezing. Eight patients showed the severe form of the disease and were required to be hospitalized. Intravenous immune globulin (IVIG) and anti-viral therapy were used for all patients during the infection. The clinical data after COVID-19 infection and the outcomes of the treatment strategy of PID patients are presented in table 2.

**Discussion**

In this study, nine patients were tested positive

**Table 1:** Demographic and clinical data of patients with primary immunodeficiency before COVID-19 infection

ID	Age (month)	Sex	PID diagnosis	Medical problems	IVIG-RT	Other treatment
P1	5	F	SCID	HM, DCM, VSD, OM, BCGitis, Convulsion, Rash and scaring	Yes	Prednisone
P2	32	F	CID-STIM1 deficiency	AIHA, ITP, Viscosities, Nephritic syndrome, Myopathy	Yes	Acyclovir, Co-trimoxazole, Isoniazid, Rifampin, Prednisone, Levetiracetam, Fluconazole
P3	18	M	ICF syndrome	SM, Cirrhosis	Yes	Levetiracetam, Ursobil
P4	124	F	Ataxia-telangiectasia	None	No	None
P5	22	M	Bruton agammaglobulinemia	DDH, Poliomyelitis	Yes	None
P6	27	M	Bruton agammaglobulinemia	Bronchiectasis	Yes	None
P7	72	F	CVID	Anemia, SMG,	No	
P8	480	F	CVID	SM, OM, Pneumonitis	Yes	Cefixime, Coamoxyclave, Levofloxacin
P9	204	F	Hyper IgE	Dermatitis, Pneumonitis, Arthritis	Yes	Acyclovir, Vancomycin, Meropenem, Cromolyn

PID: Primary immunodeficiency; CID: Combined immunodeficiency; SCID: Severe combined immunodeficiency; ICF: Facial anomalies syndrome; CVID: Common variable immunodeficiency; HM: Hepatomegaly; DCM: Dilated Cardiomyopathy; VSD: ventricular Septal Defect; AIHA: Autoimmune hemolytic anemia; ITP: Immune thrombocytopenic purpura; SM: Systemic mastocytosis; DDH: Developmental dysplasia of the hip; SMG: Splenomegaly; OM: Otitis media; CID-STIM1: Combined immunodeficiency due to STIM1 deficiency; P: Patient; M: Male; F: Female

**Table 2:** Clinical data after COVID-19 infection and outcome of treatment strategy in 9 patients with primary immunodeficiency

ID	Age (month)	Sex	PID diagnosis	COVID-19 related symptoms	Treatment strategy	Medication	Outcome/Cause of death
P1	5	F	SCID	Fever, Cough, Dyspnea, Respiratory distress	Hospitalized	IVIg, Acyclovir, Clindamycin, Meropenem, Fluconazole, Steroid	Death/ARDS
P2	32	F	CID-STIM1 deficiency	Fever, Cough, Dyspnea, Respiratory distress, retraction, hypotension, tachypnea	Hospitalized / ICU	IVIg, Vancomycin, Meropenem, Piperacillin/tazobactam, steroid	Death/Sepsis, Cardiorespiratory arrest
P3	18	M	ICF syndrome	Fever	Hospitalized/ ICU	IVIg, Acyclovir, Vancomycin, Piperacillin/tazobactam, steroid	Recovery
P4	124	F	Ataxia-telangiectasia	-	Hospitalized	IVIg,	Recovery
P5	22	M	Bruton agammaglobulinemia	Fever, Cough, Runny nose and sneezing, myalgia	Hospitalized	IVIg, Acyclovir, Vancomycin, Piperacillin/tazobactam, steroid	Recovery
P6	27	M	Bruton agammaglobulinemia	Fever, Cough, Myalgia, Anosmia	No	IVIg, Azithromycin	Recovery
P7	72	F	CVID	Fever, Cough, Dyspnea, GI symptom	Hospitalized	IVIg,	Recovery
P8	480	F	CVID	Fever, Respiratory distress, GI symptom, Anosmia	Hospitalized	IVIg, Meropenem, Tocilizumab, Steroid, Ceftriaxone	Recovery
P9	204	F	Hyper IgE	Fever, Respiratory distress	Hospitalized, ICU	IVIg, Cefixime, Cetirizine	Death/ARDS

PID: Primary immunodeficiency; CID: Combined immunodeficiency; SCID: Severe combined immunodeficiency; ICF: Facial anomalies syndrome; CVID: Common variable immunodeficiency; IVIG: Intravenous immunoglobulin; ARDS: Acute respiratory distress syndrome; P: Patient; M: Male; F: Female

for COVID-19 infection, and the mortality rate was 33.3% among these patients. All COVID-19 cases belonged to the categories of CID and primary antibody deficiencies (PAD), with a higher fatality rate among patients with CID. Similarly, in a study performed by Delavari and colleagues, CID was the main PID entity among COVID-19-positive cases, followed by humoral immunodeficiencies.<sup>6</sup> In this context, several recent studies have found that lymphopenia with prominent decreased T cell counts (especially CD8<sup>+</sup> cells) is associated with the severe course of COVID-19 infection. Guang Chen and colleagues reported decreased CD4<sup>+</sup> and CD8<sup>+</sup> T cell counts, as well as interferon gamma (IFN- $\gamma$ ) production by CD4<sup>+</sup> T cells, in severe cases of COVID-19 infection.<sup>10</sup> Another study performed by Fan Wang and colleagues showed that total lymphocytes, CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, and natural killer (NK) cells decreased in COVID-19 patients, and severe cases had lower levels than mild ones. They also indicated a significant association between these cells and inflammatory status in COVID-19, especially for CD8<sup>+</sup> T cells and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio.<sup>11</sup> Reduced T cell counts (CD4<sup>+</sup> T cells, CD8<sup>+</sup> T

cells) associated with increased serum levels of interleukin IL-6, IL-10, tumor necrosis factor (TNF)- $\alpha$  concentration, and T cell exhaustion were seen in COVID-19 patients requiring intensive care unit (ICU) admission.<sup>12</sup> On the other hand, a multinational cohort study on 94 PID patients with COVID-19 infection revealed that older patients with CID manifested a milder course of COVID-19 infection than those of our study.<sup>13</sup> Primary antibody deficiencies were identified as another dominant PID category with four COVID-19 cases, all of whom recovered after hospitalization. According to Quinti and colleagues, patients with agammaglobulinemia showed a milder course of the disease than the patients with common variable immunodeficiency (CVID) who were characterized by dysfunctional B cells.<sup>14</sup> As B cells are considered to be one of the main sources of IL-6 production, which enhances the level of inflammatory responses, the lack of B cells in agammaglobulinemia might be considered as an advantage, since they help avoiding the development of inflammatory responses and cytokine storms.<sup>5</sup> However, in our study, the clinical course of the disease resembled that of CVID and agammaglobulinemia

categories. These observations, along with other reports, either show that T cell response is more important against the virus or emphasize the role of B cells in the inflammation caused by SARS-CoV-2. Two out of the three PID patients died from COVID-19 infection, were under the age of three. In contrast with the results that show the mild form of the disease in children and adolescents to be due to the low expression of angiotensin-converting enzyme-2 (ACE-2) receptor and functional adaptive immunity, a fraction of them with PID who suffer from other comorbidities, may develop the severe course of the disease requiring hospital admission and even suffer a fatal outcome. In this regard, more caution should be exercised for complicated PID patients during the COVID-19 pandemic, and this should be taken into account by all physicians.

### Conclusion

In conclusion, it seems that patients with CID are at a higher risk of mortality, due to COVID-19 infection, than other types of PID. More attention should be paid to some PID patients regarding their age, the PID categories, especially CID, and further comorbidities. Future studies may confirm the individual risk of different PID diseases, and clarify the potential need for preventative measures for specific subsets of PID patients, who are at a high risk for a critical course of COVID-19.

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### Authors' Contribution

M.B: Conceptualization, Methodology, Formal analysis and investigation, original draft preparation, Supervision; Z.K: Formal analysis and investigation, original draft preparation, revise and editing; N.S: Formal analysis and investigation, original draft preparation; S.A: Conceptualization, revise and editing, funding acquisition, Resources, Supervision; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

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