Clinical Course and Characteristics of COVID-19 in Patients With Inborn Errors of Immunity: A Retrospective Multicenter Experience From Iran

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Abstract

Purpose

This study aimed to assess the effect of COVID-19 on patients with IELs, the potentially at-risk population, regarding the clinical course, complications, severity, and outcomes.

Methods

This two-phase study was conducted on patients from three referral immunodeficiency centers in Iran. At phase one, 98 IEL patients with COVID-19 infection were evaluated by telephone follow-up (TFU). At phase two, the demographic, clinical, and laboratory records of clinically confirmed 33 IEL patients with COVID-19 infection were collected and analyzed.

Results

At phase one, 16.3% represented COVID-19 infection without any report of pediatric intensive care unit (PICU) admission or death. During the second phase, combined immunodeficiency (CID) (42.4%) and predominantly antibody deficiencies (PADs) (33.3%) were the predominant immune defects. Atopy (27.3%) and lung disorders (27.3%) were the frequent pre-existing comorbidities. Organomegaly ($p=0.030$) and renal disorders ($p=0.033$) were significantly associated with the development of respiratory insufficiency. Cyanosis, tachypnea, intercostal retraction, and seizure were the chief complaints of patients who were more likely to progress respiratory insufficiency ($p<0.05$), being admitted to the PICU ($p<0.05$), and/or deceased ($p<0.05$). Laboratory evaluation revealed a marked positive correlation between D-Dimer ($p=0.045$), prothrombin time ($p=0.045$), C-reactive protein ($p=0.041$), proteinuria ($p=0.013$), ferritin ($p=0.020$), metabolic acidosis ($p=0.003$), and troponin ($p=0.049$) level with mortality. We detected a significant association between the chest X-ray pattern of COVID-19 infection with PICU admission ($p=0.023$) and death ($p=0.046$).

Conclusion

In the current study, patients with CID and PAD were introduced as patients at high risk of COVID-19 infection, who may need extra protective and therapeutic measurements.

I. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first diagnosed in December 2019 in Wuhan, China, and introduced as a pandemic in March 2020 by World Health Organization (1). The SARS-CoV-2 virus belongs to β -Coronaviruses and infects human cells by binding to the angiotensin-converting enzyme 2, expressed predominantly by lungs and intestinal epithelial cells, alveolar cells, and vascular endothelial cells (2). SARS-CoV-2 spreads within the human population mainly through droplet transmission and as of May 2021, 171,448,311 individuals have been infected with this virus, causing more than 3,714,831 deaths worldwide (3).

Risk factors associated with severe COVID-19 disease include advancing age (especially >65 years), obesity (body mass index >30), diabetes mellitus, chronic pulmonary diseases, cardiovascular diseases, chronic renal diseases, smoking, malignancies, chronic allergic diseases, and primary or secondary immunodeficiency (4). Among others, the clinical impact of the latter risk factor in COVID-19 infection has not been yet precisely determined.

Patients with inborn errors of immunity (IEIs) can be considered as prototypes of immune defects. IEIs form a heterogeneous group of inherited disorders caused by specific gene mutations that impact immune system development and function (5). To date, more than 430 monogenic IEIs have been reported (5, 6) and the global prevalence of IEIs has been estimated to be 1:8500 – 1:100000 for symptomatic patients (7). Since most IEL patients have defects in humoral and/or cellular components of immunity, they have susceptibility to viral and bacterial infections (5). Recent studies have shown that innate immune cells and specific immune pathways such as interferon (IFN) pathways have protective roles against certain viruses and a normal response to SARS-CoV-2 may depend on an intact innate immunity (8). Mutations in genes expressing IFN receptors (IFNAR1 and IFNAR2) and IFN regulatory factors (IRF7, IRF9, IFIH1) have been suggested as variants associated with severe COVID-19 disease (8, 9).

There are reports of increased frequency and severity of some IEIs during the COVID-19 pandemic, such as common variable immune deficiency (CVID) (10). In contrast, a complete absence of B cells as seen in the cases of X-linked agammaglobulinemia (XLA) may have protective effects for COVID-19 infection, probably due to prevention of inflammation development (11). However, there are still concerns about the COVID-19 severity and clinical consequences in the IEL population. This study aimed to assess the effect of SARS-CoV-2 infection on patients with IEIs, regarding the clinical course, complications, severity, and outcomes.

II. Methods

This retrospective study was conducted on patients from three referral immunodeficiency centers located in Mofid children's hospital and Masih Daneshvari hospital in Tehran and Namazi hospital in Shiraz provinces from March 2020 to May 2021.

All three participating centers in this study had access to national guidelines and necessary laboratory equipment for clinical and immunological evaluations of IEL patients. Moreover, the clinical diagnosis of the IEL patients was based on the diagnostic criteria of the European Society for immunodeficiencies (ESID)

working party (12).

The study was performed in two phases:

- The phase 1 study was performed in Mofid children's hospital and Masih Daneshvari hospital in Tehran during the early months of the COVID-19 epidemic, from March 2020 to mid-July, 2020. Inclusion criteria were; 1) Patients with an established diagnosis of IELs, 2) COVID-19 patients who tested positive for nucleic acid, 3) COVID-19 patients whose clinical stages were sorted based on currently accepted clinical stages. Patients who refused to cooperate were excluded. A questionnaire was surveyed by a phone interview to collect patient's demographic data, the clinical manifestation of COVID-19, probable transmission route, and measures taken against COVID-19.

- The phase 2 study was a retrospective cross-sectional study performed in three above-mentioned centers, and all IELs patients with COVID-19 infection from March 2020 to May 2021, were included. A questionnaire inquired multiple variables including demographic data such as age and sex of patients, IEL type and category, age at onset of immunodeficiency disease and age of its diagnosis, presence of comorbidities, past drug history (e.g. prophylactic antibiotics, immunoglobulin replacement therapy, current immunosuppressive therapy, etc.), clinical manifestations and laboratory data of COVID-19 infection, suspicion of COVID-19 infection or its confirmation by reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal samples, need for outpatient care or hospitalization or intensive care unit admission, types of treatment required, COVID-19 complications and outcomes.

All analyses were implemented using SPSS software (Version 26.0, Chicago, IL) and continuous quantitative variables were summarized with mean, standard deviation (SD), median, and interquartile range (IQR), whereas categorical and qualitative variables were recorded with frequencies and percentages. Statistical analysis was provided by using Mann-Whitney, Chi-square, and Fisher exact tests. P values less than 0.05 were considered statistically significant.

This study received approval from the Ethics Committee of the Shahid Beheshti University of Medical science (Approval code: IR.SBMU.RICH.REC.1400.025). Written informed consent was obtained from all patients and/or their parents.

III. Results

III.A. Demographic and clinical features of COVID-19 in patients with inborn errors of immunity – Phase 1

At the beginning of COVID-19 pandemic, 93 IELs patients [with gender distribution of 60.2% male and 39.8% female] were evaluated by telephone follow-up (TFU) including 22 (23.6%) CVID, 18 (19.35%) combined immunodeficiency (CID), 11 (11.82%) chronic granulomatous disease (CGD), 8 (8.6%) hyper IgM syndrome (HIGM), 7 (7.52%) Mendelian susceptibility to mycobacterial diseases (MSMD), 5 (5.37%) cyclic neutropenia (CN), 4 (4.3%) Wiskott–Aldrich syndrome (WAS), 4 (4.3%) ataxia telangiectasia, 4 (4.3%) IgA deficiency (IgAD), 3 (3.22%) XLA, 3 (3.22%) hyper IgE syndrome, and autoimmune lymphoproliferative syndrome (ALPS), familial Mediterranean fever (FMF), Chédiak–Higashi Syndrome (CHS), and leukocyte adhesion deficiency (LAD) each in 1 (1.07%) patient.

All patients implemented basic measures against COVID-19, including hand wash, avoiding busy places, keeping distance, and using sanitary products to surface. Most patients (n=74, 79.5%) wore facial mask.

Among 93 PID patients, 16 patients (17.2%) including 3 HIGM, 3 CVID, 3 CID, 1 IgAD, 1 CN, 1 WAS, and 1 XLA patients developed COVID-19 symptoms. 3 out of 16 patients were PCR-confirmed cases and the others were diagnosed clinically. The most commonly reported signs and symptoms were fever (10 cases), diarrhea (6 cases), cough (3 cases), otalgia, sore throat, and cervical lymphadenopathy (3 cases collectively), respiratory distress (2 cases), and rash (1 case). Four patients (25%) required hospitalization, though they were in stable condition in the general ward and only received supportive care. There was no pediatric intensive care unit (PICU) admission. No death was reported in this phase.

III.B. Demographic and clinical features of COVID-19 in patients with inborn errors of immunity – Phase 2

A. Demographic and clinical features of COVID-19 in patients with inborn errors of immunity

A total of 33 patients, 57.6% male (n=19) and 42.4% female (n=14), with an established diagnosis of IEL were enrolled in this study. Based on the latest IUIS phenotypical classification (13), most of the patients were categorized into combined immunodeficiency (CID) (n=14, 42.4%) and predominantly antibody deficiencies (n=11, 33.3%), followed by less common categories of congenital defects of phagocyte number and function (n=3, 9.1%), severe combined immunodeficiency (SCID) (n=2, 6.1%), diseases of immune dysregulation (n=2, 6.1%), and defects in intrinsic and innate immunity (n=1, 3.0%) (Table 1 and Figure 1). According to geographical distribution of IELs proposed by Iranian Primary Immunodeficiency Registry (IPIDR) (ref), more than half of the patients were referred from high PID incidence (>50/million) (n=19, 57.6%), and then from moderate PID incidence (10-50/million) (n=12, 36.4%), and low PID incidence (<10/million) (n=2, 6.1%).

Table 1
Summary of demographic data, clinical manifestations and outcomes

Pt ID	City of residence	Sex	Age of admission (Months)	IEI type	Comorbidities	Drug history	COVID19 Manifestations	COVID-19 PCR (#attempt)	In-hospital Medications
1	Varamin	M	163	Bruton	None	Prophylactic AB, IVIg	Fever, Dry cough, runny nose/sneezing, Dyspnea	Positive (1st)	Clindamycin Amikacin, IV
2	Garme	M	107	Hyper IgM	None	IVIg	Fever, Wet cough, GI symptoms, Convulsion	Positive (1st)	Meropenem, Vancomycin Metronidazole IVIg
3	Ghianddasht	M	112	Ataxia telangiectasia	None	IVIg	Fever, runny nose/sneezing, GI symptoms, Myalgia	Positive (1st)	Meropenem, Vancomycin IVIg
4	Shahriar	F	48	BCGosis	Fanconi syndrome, GI disorder	IVIg, IS, Favipiravir	Fever, Dry cough, Tachypnea, Hypotension, Retraction, Respiratory distress, GI symptoms, Myalgia	Positive (1st)	Meropenem, Cotrimoxazole Corticosteroids
5	Varamin	M	1.5	CID	Severe pneumonia, GI disorder, after COVID-19 seizure and pericardial effusion	Prophylactic AB, IVIg	Fever, Dry cough, Dyspnea, GI symptoms	Positive (1st)	Meropenem, Vancomycin Amikacin, Nystatin, Fluconazole, Corticosteroids
6	Ghazvin	M	6.5	SCID	Atopy, Organomegaly	IVIg, Ganciclovir	Fever, Dyspnea, Tachypnea, Hypotension, Retraction, Respiratory distress	Positive (3rd)	Vancomycin Meropenem, Cotrimoxazole Rifampin, IN Ethambutol, Clotrimazole Corticosteroids IVIg
7	Qom	F	179.7	CVID	Appendicitis	Prophylactic AB, IVIg, Acyclovir	Fever, GI symptoms, Myalgia	Positive (1st)	Cotrimoxazole Clindamycin Fluconazole, IVIg
8	Kordestan	M	13	CID	Allergic colitis	Prophylactic AB, IVIg, IS, Chloroquine	GI symptoms	Positive (1st)	Ceftriaxone, Corticosteroids IVIg
9	Babol	F	32.2	Gaucher, Neutropenia	Organomegaly	IVIg, Chloroquine	Fever, Dry cough, GI symptoms	Negative	Ceftriaxone, Vancomycin
10	Jajrood	F	231.7	SLE, Scleroderma, MCTD	SLE, Scleroderma, RTA, seizure, lung disease	IVIg, Remdesivir	GI symptoms, Convulsion, LOC	Positive (1st)	Meropenem, Vancomycin Corticosteroids IVIg
11	Qom	F	18	Early onset IBD/IL10R defect	Early onset IBD, Food allergy	-	-	Positive (2nd)	Clindamycin Amikacin, Meropenem, Vancomycin Azithromycin Corticosteroids
12	Meygoon	M	33.2	CID	None	Prophylactic AB, IVIg, IS	Fever, Hypotension, GI symptoms, LOC	Negative	Meropenem, Vancomycin Fluconazole
13	Eslamshahr	M	7.7	Ataxia telangiectasia	Hodgkin lymphoma, Pericardial effusion	IVIg, Ganciclovir	Dyspnea, Tachypnea, Hypotension, Retraction, Respiratory distress	Negative	Meropenem, Vancomycin Voriconazole Cotrimoxazole IVIg, Corticosteroids
14	Shahriar	F	81.2	CVID	None	IVIg	Fever, Dry cough, GI symptoms	Positive (1st)	Ceftriaxone, Vancomycin

Pt ID	City of residence	Sex	Age of admission (Months)	IEI type	Comorbidities	Drug history	COVID19 Manifestations	COVID-19 PCR (#attempt)	In-hospital Medications
15	Shiraz	F	31	STIM1 deficiency	Vasculitis, Nephrotic syndrome, Myopathy, Autoimmune anemia and thrombocytopenia	IVIg, IS	Fever, Dry cough, Dyspnea, Cyanosis, Tachypnea, Retraction, Respiratory distress	Positive (2nd)	Vancomycin Tazocin, Meropenem, Corticosteroid IVIg
16	Darab	F	6	SCID	Atopy, Otitis media, Organomegaly, Lymphadenopathy, VSD, DCM, Convulsion	Prophylactic AB, IVIg, IS, Acyclovir	Fever, Dry cough, Dyspnea, Cyanosis, Tachypnea, Retraction, Convulsion, LOC	Positive (1st)	Clindamycin Meropenem, fluconazole, Corticosteroid IVIg
17	Shiraz	M	217	ICF syndrome	Organomegaly, Cirrhosis	IVIg, Remdesivir	Fever	Positive (1st)	Vancomycin Tazocin, Corticosteroid IVIg
18	Shiraz	M	324	Bruton	Bronchiectasis	IVIg	Fever, Dry cough, Myalgia, Anosmia	Positive (1st)	Azithromycin IVIg
19	Shiraz	M	264	Bruton	Hip Dysplasia, Poliomyelitis	IVIg, Remdesivir	Fever, Dry cough, Runny nose/Sneezing, Myalgia	Negative	Vancomycin Tazocin, Corticosteroid IVIg
20	Tehran	F	62.5	CID	Organomegaly, Rheumatologic disorder, Autoimmunity	Prophylactic AB, IVIg, IS, Chloroquine, Valganciclovir, ASA	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Tachypnea, Hypotension, Retraction, GI symptoms, Myalgia	Negative	AB, Fluconazole, Corticosteroid IVIg, Convalescer plasma
21	Tehran	M	86.5	CID	Atopy	Prophylactic AB, IS	Fever, Dry cough, Myalgia	Negative	AB, IVIg
22	Khoramabad	M	103	CGD	Liver, ENT, Lung disorder, Bronchiectasis, Atopy	Prophylactic AB, IS	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Cyanosis, Tachypnea, Hypotension, Retraction, Myalgia	Negative	AB, Fluconazole, Corticosteroid Monoclonal antibody
23	Varamin	M	6	MSMD	Lung disorder, Bronchiectasis, ENT disorder, Organomegaly	Prophylactic AB, IVIg	Fever, Dry cough, Runny nose/Sneezing, Cyanosis, Dyspnea, Tachypnea, Hypotension, Myalgia	Negative	AB, Amphotericin IVIg
24	Tehran	M	6.8	CID	Bronchiectasis, Atopy	Prophylactic AB, IVIg, Chloroquine	Fever, Dry cough	NP	AB, IVIg
25	Tehran	F	224.7	CVID	Atopy, Autoimmunity	Prophylactic AB, IVIg, IS	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Cyanosis, Tachypnea, Retraction, Myalgia	Negative	AB, Corticosteroid IVIg
26	Lahijan	Male	51.7	CID	ENT disorder	Prophylactic AB, IVIg, IS	Fever, Dry cough, Tachypnea,	NP	Voriconazole AB, IVIg

Pt ID	City of residence	Sex	Age of admission (Months)	IEI type	Comorbidities	Drug history	COVID19 Manifestations	COVID-19 PCR (#attempt)	In-hospital Medications
27	Maragheh	F	16.4	CID	Neurologic disorder	Prophylactic AB, IVIg, IS, Chloroquine, Naproxen	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Tachypnea, Hypotension, Retraction, GI symptoms, Myalgia	Negative	AB, Corticosteroids, IVIg, Fluconazole
28	Tehran	F	84.3	Neutropenia	None	Prophylactic AB, Acyclovir	Fever, Dry cough, Dyspnea, Cyanosis, Tachypnea, Hypotension, Retraction, GI symptoms, Myalgia	NP	AB, Fluconazole
29	Sari	M	139.7	CVID	ENT disorder, Lung disorder, Bronchiectasis, Atopy, Autoimmunity	Prophylactic AB, IVIg, Chloroquine	Fever, Dry cough, runny nose/sneezing, Dyspnea, Cyanosis, Tachypnea, Retraction, Myalgia	NP	AB, Voriconazole, IVIg
30	Ardebil	F	19.3	CID	Atopy, Heart disease, Hydrocephalus, Renal disorder	Prophylactic AB, IVIg, IS, Acyclovir	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Cyanosis, Tachypnea, Retraction, GI symptoms, Myalgia, Convulsion	Positive (1st)	AB, Voriconazole, Corticosteroids, IVIg
31	Esfahan	F	250	Autosomal recessive Agammaglobulinemia	ENT disorder, Lung disorder, Bronchiectasis, Neurologic disorder	IVIg, IS, Chloroquine, Remdesivir, Naproxen	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Myalgia	Positive (1st)	AB, Caspofungin, Corticosteroids, IVIg
32	Golpayegan	M	316	Bruton	Lung disorder, Bronchiectasis	IVIg, IS, Remdesivir, Naproxen	Fever, Dry cough, runny nose/sneezing, Dyspnea, Myalgia	Positive (1st)	AB, Corticosteroids, IVIg
33	Tehran	M	516.7	CVID	GI disorder, Heart disease, ENT disorder, Lung disorder, Bronchiectasis, Organomegaly	IVIg, IS, Chloroquine, Remdesivir, Favipiravir, Naproxen	Fever, Dry cough, Runny nose/Sneezing, Dyspnea, Cyanosis, Tachypnea, Hypotension, Retraction, GI symptoms, Myalgia	Positive (1st)	AB, Corticosteroids, IVIg
<i>IEI; inborn errors of immunity, COVID-19; Coronavirus disease 2019, ICU; Intensive Care Unit, IVIg; Intravenous immunoglobulin, GI; Gastrointestinal, AB; Antibiotic, Ear nose throat, CID; Combined immunodeficiency, CVID; Common variable immunodeficiency, SCID; Severe combined immunodeficiency, IBD; Inflammatory bowel disease, Mendelian susceptibility to mycobacterial disease, ICF syndrome; Immunodeficiency with centromeric instability and facial anomalies, STIM1; Stromal interstitial granulomatous disease, NP; not performed, DIC; disseminated intravascular coagulation</i>									

The median (IQR) age of study population was 81 (28-198) months. Pre-existing comorbidities included atopy (n=9, 27.3%), lung disorders (n=9, 27.3%), neurologic disorders (n=8, 24.2%), bronchiectasis (n=8, 24.2%), organomegaly (n=7, 21.2%), ear-nose-throat disorders (n=7, 21.2%), gastrointestinal disorders (n=6, 18.2%), autoimmunity (n=5, 15.2%), cardiovascular disorders (n=5, 15.2%), rheumatologic disorders (n=4, 12.1%), renal disorders (n=4, 12.1%), liver disorders (n=2, 6.1%), and malignancy (n=1, 3.0%). Among these comorbidities, organomegaly ($p=0.030$) and renal disorders ($p=0.033$) were significantly associated with the development of respiratory insufficiency.

Before COVID-infection, all IEI patients were stable on the standard of care treatment. Twenty-nine of 33 IEI patients (87.9%) received monthly intravenous immunoglobulin (IVIg) substitution as standard therapy. Seventeen patients (51.5%) were on prophylactic antibiotic therapy and fifteen patients (45.5%) received immunosuppressive agents.

The most common chief complaints at the presentation were fever (n=29, 87.9%), cough (dry: 23 (69.7%), wet: 1 (3.0%)), dyspnea (n=17, 51.5%), myalgia (n=17, 51.5%), gastrointestinal symptoms (n=15, 45.5%), runny nose/sneezing (n=15, 45.5%), tachypnea (n=15, 45.5%), intercostal retraction (n=13, 39.4%), hypotension (n=10, 30.3%), cyanosis (n=9, 27.3%), seizure (n=4, 12.1%), and loss of consciousness (n=3, 9.1%). In addition, 26 patients were hypoxic with in-room O₂ saturation of less than 90% (n=16, 48.5%), or 90-95% (n=10, 30.3%).

Patients with cyanosis ($p=0.047$), tachypnea ($p=0.003$), intercostal retraction ($p=0.003$), and seizure ($p=0.033$) at presentation were significantly more likely to progress respiratory insufficiency. In addition, tachypnea, intercostal retraction, hypotension, and hypoxia were significantly correlated with PICU admission ($p=0.022$, $p=0.019$, $p=0.007$, and $p=0.039$) and death outcome ($p=0.027$, $p=0.036$, $p=0.005$, and $p=0.027$), respectively.

All except one patient were hospitalized. One patient with X-linked Agammaglobulinemia (XLA) had mild disease and was treated as outpatient. During hospitalization, patients received antibiotics for potential bacterial co-infection or superinfections (n=33, 100%), hydroxychloroquine/chloroquine (n=8, 24.2%), antivirals (n=14, 42.4%), non-steroidal anti-inflammatory drugs (NSAIDs) (n=5, 15.2%), antifungals (n=15, 45.5%), steroids (n=20, 60.6%), monoclonal antibody (n=1, 3.0%), and convalescent plasma (n=1, 3.0%). Twenty-four patients (72.7%) continued to receive IVIG during hospitalization.

Almost half of patients (n=17, 51.5%) required PICU admission due to respiratory distress (n=12), septic shock (n=3), bradycardia (n=1), and loss of consciousness (n=1). Progression to respiratory insufficiency occurred in 15 patients (45.5%).

At the end of the survey, thirteen patients (39.4%) died following cardiorespiratory arrest (n=4), septic shock (n=3), disseminated intravascular coagulation (n=3), pulmonary hemorrhage (n=1), acute respiratory distress syndrome (n=1), and hemophagocytic lymphohistiocytosis (n=1). Of note, the most lethal COVID-19 infection among IEI entities was observed in patients with CID (6 of 13, 46.2%), followed by SCID (2 of 13, 15.4%), PADs (2 of 13, 15.4%), congenital defects of phagocytes (2 of 13, 15.4%), and diseases of immune dysregulation (1 of 13, 7.7%). However, the exact course of COVID-19 related deaths in these IEI patients is unknown. 69.2% (9 out of 13) of patients with IEI who succumbed to SARS-CoV-2 infection had pre-existing co-morbidities.

B. Laboratory and Imaging Findings:

SARS-CoV-2 infection was determined by RT-PCR (n=19, 57.6%) or computed tomography (CT) scan pattern (n=26, 78.8%) or chest x-ray (CXR) pattern (n=21, 63.6%). The first PCR test was positive in 16 (55.2%) and negative in 13 (44.8%) out of 29 evaluated patients. Three negative PCR tests turned positive within a median of 6 (3–10) days after the first result.

A summary of laboratory results is presented in Table 2. The complete blood count was consistent with leukocytosis (n=13, 40.6%), leukopenia (n=12, 37.5%), neutrophilia (n=10, 32.3%), lymphocytopenia (n=14, 45.2%), and thrombocytopenia (n=11, 34.4%). High inflammatory markers including ESR and CRP were high in 20 (62.5%) and 23 (71.9%) patients, respectively.

Table 2
– Comparative analysis between survived and deceased patients

Parameter	Total	Alive	Deceased	P-value
White blood cell $\times 10^3$ (cell/ μ L), median (IQR)	8.8 (3.8-15.0)	9.0 (5.5-13.4)	5.8 (2.0-13.5)	0.552
Absolute neutrophils count $\times 10^3$ (cells / μ L), median (IQR)	4.1 (1.9-10.8)	4.1 (2.2-10.8)	4.4 (1.0-10.5)	0.685
Absolute lymphocytes count $\times 10^3$ (cells / μ L), median (IQR)	1.3 (0.8-3.0)	1.3 (0.8-3.0)	1.1 (0.6-4.1)	0.655
Hemoglobin (g/dl), median (IQR)	9.7 (8.1-11.8)	10.6 (8.8-12.3)	9.3 (7.6-10.2)	0.053
Platelets $\times 10^3$ (cells / μ L), median (IQR)	247 (96.25-335.75)	279 (106-336)	203 (80-332)	0.527
Erythrocyte sedimentation rate (mm/hour), median (IQR)	38.5 (15.2-69.5)	33.0 (15.0-65.0)	49.0 (14.0-82.5)	0.478
C-Reactive Protein (CRP) (mg/L), median (IQR)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	3.0 (3.0-30.0)	0.041
Lactic Acid Dehydrogenase (U/L), median (IQR)	692 (520-780)	653 (534-752.7)	770 (414-1108)	0.183
Creatinine level (mg/dL), median (IQR)	0.6 (0.4-0.7)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.630
Urea (mmol/L), median (IQR)	10.3 (6.7-15.0)	8.0 (6.2-14.0)	12.0 (8.5-20.0)	0.102
Serum sodium (mEq/L), median (IQR)	135.0 (130.0-138.0)	135.0 (132.0-138.0)	131.0 (126.5-139.0)	0.239
Serum potassium (mEq/L), median (IQR)	3.8 (3.5-4.3)	3.9 (3.5-4.5)	3.7 (3.4-4.1)	0.743
Serum calcium (mg/dL), median (IQR)	8.4 (8.0-8.9)	8.5 (7.9-8.9)	8.4 (8.0-9.1)	0.936
Serum phosphorus (mmol/L), median (IQR)	3.4 (3.0-4.0)	3.2 (2.7-3.9)	3.4 (3.0-4.6)	0.201
Serum magnesium (mmol/L), median (IQR)	1.9 (1.7-2.0)	1.8 (1.7-2.0)	2.0 (1.7-2.1)	0.184
Venous Blood gases PH (U), median (IQR)	7.35 (7.20-7.40)	7.40 (7.35-7.43)	7.20 (7.15-7.28)	0.003
Venous Blood gases HCO ₃ (mmol/L), median (IQR)	21.6 (15-25.0)	22.5 (19.4-24.7)	15 (12.0-25.2)	0.216
Venous Blood gases PCO ₂ (mmHg), median (IQR)	44.5 (29.0-54.7)	41.5 (32.2-49.5)	49.4 (25.2-77.5)	0.643
Prothrombin time (seconds), median (IQR)	14.0 (12.0-18.6)	12.7 (12.0-15.0)	16.0 (13.3-22.0)	0.045
Partial thromboplastin Time (seconds), median (IQR)	35.0 (29.6-47.5)	35.0 (27.7-39.5)	35.0 (30.1-60.0)	0.509
International normalized ratio (INR), median (IQR)	1.2 (1.0-1.8)	1.0 (1.0-1.4)	1.3 (1.1-2.2)	0.053
Creatine phosphokinase (U/L), median (IQR)	54.5 (44.7-117.0)	53.5 (45.5-115.0)	74.0 (36.5-130.7)	0.895
AST (U/L), median (IQR)	52.0 (34.2-71.2)	41.0 (31.5-66.5)	64.0 (33.5-82.0)	0.379
ALT (U/L), median (IQR)	26.5 (19.0-75.5)	23.0 (19.0-72.0)	31.0 (19.0-79.2)	0.531
ALP (U/L), median (IQR)	319.0 (225.0-652.0)	299.5 (233.0-619.0)	325.0 (172.0-982.0)	0.844
Total Bilirubin (μ mol/L), median (IQR)	1.0 (0.6-1.2)	0.9 (0.7-1.0)	1.1 (0.6-6.2)	0.235
Direct Bilirubin (μ mol/L), median (IQR)	0.2 (0.1-0.6)	0.2 (0.2-0.5)	0.3 (0.1-3.6)	0.581
Troponin (ng/mL), median (IQR)	0.01 (0-0.002)	0 (0-0.01)	0.01 (0-111.7)	0.049
Ferritin (μ g/L), median (IQR)	413 (95-1500)	125 (78-413)	800 (800-2037)	0.020
Fibrinogen (g/L), median (IQR)	200 (100.2-236.7)	197.0 (88.7-203.5)	231.5 (103.7-336.5)	0.143
D-Dimer (ng/mL), median (IQR)	200 (140-200)	190 (86.5-200)	200 (200-748)	0.045

Serum creatinine and BUN were high in 18 (56.3%) and 6 (18.8%) and based on the KDIGO criteria were in the stage 1 AKI range in three patients. Evidence of proteinuria (n=11, 35.5%) and/or hematuria (n=9, 29%) was observed in 13 patients (41.9%). The most common electrolyte abnormalities included hyponatremia (n=14, 43.8%), hypokalemia (n=5, 15.6%), hypocalcemia (n=17, 54.8%), hypophosphatemia (n=23, 79.3%), and hypomagnesemia (n=15, 55.6%). Half of the patients with evaluated VBG (10 of 20) had normal acid-base state, while metabolic acidosis (n=5, 25%), respiratory acidosis (n=4, 20%), and respiratory alkalosis (n=1, 5%) were also reported.

High serum levels of LDH (21 of 27, 77.8%), PT (10 of 29, 34.5%), PTT (9 of 29, 31%), INR (13 of 29, 44.8%), CPK (4 of 22, 18.2%), AST (18 of 30, 60%), ALT (10 of 30, 33%), ALK-P (2 of 27, 7.4%), bilirubin (total: 6 of 18, 33.3%, direct: 5 of 18, 27.8%), troponin (2 of 13, 15.4%), ferritin (13 of 19, 68.4%), fibrinogen (1 of 20, 5%), D-dimer (9 of 13, 69.2%) were also observed. 8 out of 11 (72.7%) patients evaluated for serum vitamin D level were insufficient or deficient.

The mortality rate was correlated with high ferritin ($p=0.018$), proteinuria ($p=0.056$), leukopenia ($p=0.150$), high troponin ($p=0.192$), high BUN ($p=0.194$), hypocalcemia ($p=0.171$), high PT ($p=0.064$), high D-dimer ($p=0.105$), high Alk-P ($p=0.157$), total bilirubin ($p=0.141$) and death outcome. Furthermore, there was a significant correlation between hyponatremia ($p=0.011$) and proteinuria ($p=0.013$) and the need for PICU admission. Thrombocytopenia ($p=0.108$),

hematuria ($p=0.113$), and high serum levels of LDH ($p=0.077$), PT ($p=0.126$), AST ($p=0.176$), and total bilirubin ($p=0.141$) were also correlate with the rate of PICU admission, although not statistically significant.

Positive PCR and COVID-19 evidence in CT scan were not associated with PICU admission ($p=0.579$ and $p=0.654$) or death outcome ($p=0.727$ and $p=0.361$), respectively. However, evidence of COVID-19 in CXR was significantly associated with the need for PICU admission ($p=0.023$) and death ($p=0.046$).

IV. Discussion

COVID-19 is a worldwide concern affecting millions of people globally and Iran is a hot zone area for this disease within the middle-east (14). Patients suffering from IEI are regarded as potentially at-risk cases during the current pandemic (15). However, the impact of SARS-CoV-2 on patients with primary immunodeficiency is not yet fully understood. Therefore, we retrospectively studied the clinical course and characteristics of COVID-19 in a number of Iranian patients with IEI. Up to this point, studies showed a higher incidence of COVID-19 in IEIs considering their underlying immunological defects (16), whereas, some others pointed out a fewer risk of severity among these patients (15, 17). Similarly, in phase one of this study, we detected a prevalence of 16.3% for SARS-CoV-2 infection in patients with IEI through TFU which was higher than the estimated prevalence of COVID-19 among the Iranian population (18).

A large proportion of our patients in phase two had combined immunodeficiency and antibody deficiency being stable on the standard of care treatment. The pre-existing comorbidities as important determinants of poor outcome were present in 69.2% of the patients who succumbed to SARS-CoV-2 infection. Atopy and lung disorders were the main comorbidities detected in our patients. However, the presence of organomegaly and renal disorder was strongly correlated with the development of respiratory insufficiency, which may be considered as a severity index and a high risk of death. This relationship between chronic renal disorders and COVID-19 severity has been previously described in both the general populace (19, 20) and patients with IEIs (21).

Although a majority of clinical symptoms encompassing fever (87.9%), dry cough (69.7%), dyspnea (51.5%), myalgia (51.5%), and gastrointestinal symptoms (45.5%) in our patients overlapped the general population, the frequency of atypical complaints including seizure (12.1%) and loss of consciousness (9.1%) was more prominent than the general population and previous IEI study (22–24). Severe symptoms such as cyanosis, tachypnea, intercostal retraction, hypotension, and seizure were accompanied by a higher rate of respiratory insufficiency leading to PICU admission and death. Similar to *Delavari S et al.* study (16), the mortality rate (39.4%) was considerably greater than the general population, of those, cases with CID were accounted for most. It should also be noted that our cases were predominantly diagnosed with CID.

The rate of false-negative first SARS-CoV-2 PCR test was 10.3% in our patients that is slightly higher than the results of a study conducted in Canada (25). Consistent with former publications that exhibited an association between increased inflammatory markers and worse prognosis in COVID-19 (26, 27), we found a remarkable positive correlation between D-Dimer, PT, CRP, proteinuria, ferritin, metabolic acidosis, and troponin level with mortality and poorer outcome. Similar to other studies in SARS-CoV-2 infection (28), hyponatremia (43.8%) was one of the prevalent electrolyte imbalances leading to increased risk of PICU admission ($p=0.011$).

We further tracked the radiographic evidence of COVID-19 in CXR and chest CT scans of the patients. Conforming to the reports of *Colman J et al.* (29), CXR patterns unlike chest CT scan and positive PCR test were significantly associated with ICU admission ($p=0.023$) and death ($p=0.046$). On the other hand, this skewing might be the result of higher demand for CXR in critically ill patients due to its portability and inability to reveal slight changes of lung fields compared to chest CT scans.

Interestingly, SARS-CoV-2 was the triggering factor that prompted to X-linked Hyper-IgM syndrome diagnosis in one of our patients who was a 7 months old boy who presented with pneumonia and cervical lymphadenopathy. He had lymphopenia, low CD4+ cell, CD8+ cell, natural killer (NK) cell counts along with low immunoglobulin level, as described previously in hospitalized COVID-19 patients (30). Three other novel cases with agammaglobulinemia (two X-linked and one autosomal recessive) represented prolonged disease and PCR- positivity for SARS-CoV-2 infection. Thus, a recommendation for prolonged treatment of patients with IEI, particularly agammaglobulinemia, might be of benefit.

In summary, we studied the course of COVID-19 in 33 patients with IEI. Our data revealed that pre-existing organomegaly and renal disorder along with severe SARS-CoV-2-related symptoms including cyanosis, tachypnea, intercostal retraction, hypotension, and seizure were the predisposing factors to PICU admission and mortality. Additionally, radiographic evidence of COVID-19 in CXR was remarkably associated with a worse prognosis in COVID-19. We also reported prolonged disease duration and PCR-positivity for SARS-CoV-2 infection in agammaglobulinemic patients and introduced SARS-CoV-2 as the triggering factor prompting IEI appearance. However, future studies should be conducted to provide further evidence for this conclusion.

V. Declarations

Funding: The authors received no specific funding for this research.

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Availability of data and material: Not applicable.

Code availability: Not applicable.

Ethics approval: The present study was conducted according to the principles expressed in the Helsinki Declaration and the ethics committee of Pediatric Infections Research Center and Research Institute for Children's Health of Shahid Beheshti University of Medical Sciences (Approval code: IR.SBMU.RICH.REC.1400.025).

Consent to participate: The informed consent was obtained from all individual participants (their parents) included in the study.

Consent for publication: Informed consent for publication was obtained from the parents of the patient prior to being included in the study.

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Figures

Figure 1

Distribution of IEI groups composed of 33 patients with a diagnosis of SARS-CoV-2 infection. Combined immunodeficiency (n=14); predominantly antibody deficiencies (n=11); Congenital defects of phagocyte number or function (n=3); Immune dysregulation syndrome (n=2); Severe combined immunodeficiency (n=2); Defect in intrinsic and innate immunity (n=1).